I, Ishan Goswami, hereby submit this original work as part of the requirements for the degree of Master of Science in Mechanical Engineering.

It is entitled:
Influence of geometric and flow variations on coronary diagnostic parameters: An in-vitro study

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Influence of geometric and flow variations on coronary diagnostic parameters: An In-vitro study

A thesis submitted to the
Graduate School
of the University of Cincinnati
in partial fulfillment of the
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Masters of Science

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of the College of Engineering and Applied Sciences

by

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Bachelor of Technology, Vellore Institute of Technology, India

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Committee Chair: Dr. Rupak K. Banerjee, Ph.D., P.E.
ABSTRACT

In current practice, diagnostic parameters, such as fractional flow reserve (FFR) and coronary flow reserve (CFR), are used to determine the severity of a coronary artery stenosis. These parameters are evaluated from pressure and/or flow information, using sensor-tipped guidewire advanced into an artery at maximal vasodilation (hyperemia) condition. FFR is defined as the ratio of hyperemic pressures distal and proximal to a stenosis. CFR is the ratio of flow at hyperemic and basal (resting) condition. In addition to these, new diagnostic parameters have been suggested to overcome the shortcomings of the conventional parameters. Three such parameters assessed in this study are pressure drop coefficient (CDP), lesion flow coefficient (LFC), and stenotic resistance index ($\tilde{R}_s$). CDP is defined as the ratio of the pressure drop across the stenosis to the upstream dynamic pressure. LFC is the ratio of pressure drop coefficient at high Reynolds number to the pressure drop coefficient based on pressure drop across stenosis and throat dynamic pressure. The $\tilde{R}_s$ is assessed by taking the ratio of hyperemic pressure drop to flow rate.

These parameters may be influenced by variations in geometric and flow conditions. This study investigated whether the newly developed parameters had an advantage in areas where FFR failed to diagnose stenosis severity. Four major issues were addressed. Firstly, the influence of native arterial diameter was investigated, followed by an assessment with variation in vasculature status. The latter is an important comparison, since it is a topic of current debate, and this analysis adds to the pool of data currently available. The impact of a newly designed guidewire on the diagnostic parameters was also tested. Another important aspect of this study was to present a proof-of-concept analysis for basal based parameters.
In-vitro experiment coupled with pressure-flow relationships from human clinical data was used to simulate pathophysiologic conditions in two representative arterial diameters, 2.5 mm (N1) and 3 mm (N2). With a 0.014” and newly designed 0.022” guidewire inserted separately, diagnostic parameters were evaluated for mild (~64% area stenosis (AS)), intermediate (~80% AS), and severe (~90%AS) stenosis for both N1 and N2 arteries, and between two conditions: with and without myocardial infarction (MI). From the obtained experimental data, diagnostic parameters were assessed at basal condition of 42 ml/min and 50 ml/min, for N1 and N2 respectively.

Arterial and guidewire diameter did not influence FFR for clinically relevant cases of mild and intermediate stenosis (difference< 5%). Newer parameters varied considerably, but had distinctive increasing trend, which allowed stenosis delineation. However, FFR was overestimated (mild: ~9%, intermediate: ~20%, severe: ~30%) for MI. Overestimation of FFR may affect clinical decision making. CDP had variation with vascular condition (mild: ~35%, intermediate: ~14%, severe: ~9%). The value of $\tilde{R}_s$ also showed similar variation (mild: ~30%, intermediate: ~25%, severe: ~14%). LFC varied somewhat (<8%) for intermediate and severe stenosis. All parameters delineated stenosis in presence of MI, overcoming the disadvantage of FFR. Of the three new parameters, CDP’s wide range allowed better delineation of stenosis severities irrespective of hyperemic or basal conditions.
ACKNOWLEDGEMENTS

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Nomenclature

Hyperemia
Condition of vasodilation

Basal
Resting condition

Perfusion
Process through which nutrients are exchanged in the tissue

Stenosis
Blockage

Epicardial
Related to bigger coronary arteries called epicardial arteries

Microvascular
Related to smaller arteries

Proximal
Upstream position to a stenosis

Distal
Downstream position to a stenosis

Throat
Region of minimum cross section area in a stenosis

Subscripts

h
Hyperemic value

b
Basal value

a
Value at aorta

r
Distal (downstream) value

e
Proximal (upstream) value

m
Value at throat

Superscript

\( \bar{A} \)
Value of A time-averaged over the cardiac cycle
Stenosed geometry terms

\( l_c \)  Converging length
\( l_m \)  Throat length
\( l_r \)  Diverging length
\( a_e \)  Proximal diameter
\( a_m \)  Throat diameter
\( A_e \)  Proximal cross sectional area
\( A_m \)  Throat cross sectional area

Fluid mechanics terms

\( \bar{p}_a \)  Proximal aortic pressure
\( \bar{p}_r \)  Distal/perfusion pressure
\( \bar{p}_{ro} \)  Zero-flow pressure; threshold perfusion pressure
\( \bar{u}_e \)  Proximal velocity
\( \bar{u}_m \)  Throat velocity
\( \rho \)  Density
\( \bar{\dot{Q}} \)  Flow rate
\( \dot{\gamma} \)  Shear rate
\( \mu_{\infty} \)  Dynamic viscosity at high shear rates
\( \mu_0 \)  Dynamic viscosity at zero shear rate
\( \lambda, n \)  Material constants of the Carreau viscosity model
### Diagnostic parameters

<table>
<thead>
<tr>
<th>Symbol</th>
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<td>FFR</td>
<td>Fractional flow reserve</td>
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<td>CFR</td>
<td>Coronary flow reserve</td>
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<td>CDP</td>
<td>Pressure drop coefficient</td>
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<td>LFC</td>
<td>Lesion flow coefficient</td>
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<tr>
<td>$\bar{R}_s$</td>
<td>Stenotic resistance index</td>
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<table>
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<td>$\bar{R}_{epi}$</td>
<td>Epicardial resistance</td>
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<tr>
<td>$\bar{R}_v$</td>
<td>Distal resistance</td>
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1 Introduction

According to a recent report by American Heart Association, one of every six deaths in United States for the year 2007 is due to coronary disease (Roger et al., 2011). An estimated 785,000 Americans are at risk with a coronary attack each year. A staggering 195,000 Americans have silent myocardial infarctions each year.

The heart acts like a pump, supplying blood to the different parts of our body. This pumping action is achieved through the heart muscle, which is composed of three layers, namely the endocardium (inner layer), myocardium (middle layer), and epicardium/pericardium (outer layer). These muscle layers themselves need nutrients for pumping. Nutrients to tissues are provided by blood through a process called perfusion. This process needs a specific pressure called the perfusion pressure. Therefore, the heart creates its own perfusion pressure, and blood is supplied to the three layers through the coronary arterial network (Figure 1.1). The Figure 1.1 shows the major branches of the coronary arteries only, and not the coronary veins.

Figure 1.1: The coronary arteries. A) Anterior view of heart B) Posterior view of heart
Larger epicardial arteries carry blood to the different epicardial regions of the heart, and smaller branches from these arteries supply blood to the inner layers of the heart muscle. This simplified model has been illustrated by Epstein et al. (Epstein et al., 1985) in their review of hemodynamics in coronary arteries, and a modified version is shown in Figure 1.2.

In a compartmentalized version, many investigators (Camici and Crea, 2007; Epstein et al., 1985) divide the network into two primary parts. The first compartment consists of the epicardial vessel and the second compartment consists of the smaller vessels namely the arterioles and capillary network (Figure 1.3). The resistance ($R_{\text{epi}}$) offered by the epicardial compartment is primarily due to friction and minor losses. The resistance offered by the smaller microvascular bed ($R_{\text{v}}$) depends on the metabolic demands of the heart muscle. In normal vessels, resistance ($R_{\text{epi}}$) offered by the epicardial compartment is negligible compared to microvascular resistance ($R_{\text{v}}$) (Epstein et al., 1985). The vascular water-fall theory suggests that
the arteries have a threshold pressure only above which perfusion can take place, and this pressure is called the zero-flow pressure \( \bar{p}_{ro} \) (Downey and Kirk, 1975). Hence, time averaged flow \( \bar{Q} \) in an epicardial artery may be related to the time averaged perfusion pressure \( \bar{p}_r \) by the simple relationship (Banerjee et al., 2003a):

\[
\bar{Q} = \frac{\bar{p}_r - \bar{p}_{ro}}{\bar{R}_v}
\]

In a normal vessel, \( \bar{p}_r \) is almost equal to the aortic pressure \( \bar{p}_a \) due to negligible value of epicardial resistance \( \bar{R}_{epi} \). In resting (basal) condition microvascular resistance \( \bar{R}_v \) is high, leading to low flow. In exercised state, the resistances in the network are lowered by dilating the bigger epicardial vessels (vasodilation) and decreasing \( \bar{R}_v \). This state is called hyperemia.

Figure 1.3: The arterial compartments

Epicardial resistance: \( \bar{R}_{epi} \)  Microvascular resistance: \( \bar{R}_v \)

\( \bar{R}_{epi} << \bar{R}_v \)
1.1 Influence of Epicardial Blockage

An area blockage (area stenosis, AS) leads to pressure drop across it, and therefore reduces the perfusion pressure available to the arteries downstream (distal) to it (Figure 1.4). In basal condition, this added resistance by stenosis ($\tilde{R}_s$) is compensated by a decrease in $\tilde{R}_v$ to allow for the demand of nutrients in the heart tissue. However, if the stenosis is very severe (> 94% AS), capacity of the microvascular bed to decrease $\tilde{R}_v$ gets exhausted, leading to reduced blood flow (Epstein et al., 1985; Gould et al., 1974).

In a normal vessel, the maximum hyperemic flow could be as much as four or five times of the basal flow (Hoffman, 1984; Klocke, 1987). With a stenosis, the added stenotic resistance ($\tilde{R}_s$) lowers the flow at hyperemia, thus reducing the blood supply to the tissues. Hence, patients with significant stenosis experience ischemia (blood deprivation), which may result in chest pain (angina) during exercise. A prolonged period of ischemia leads to coronary disease such as myocardial infarction (tissue death), microvascular dysfunction, hypertrophy etc.

\[
\begin{align*}
\tilde{p}_a & \quad \tilde{Q} \quad \tilde{p}_r = \tilde{p}_a - \Delta\tilde{p} \\
\text{Epicardial artery stenosis} \\
\text{Pressure drop across stenosis } \Delta\tilde{p} & \quad \text{Stenotic resistance } \tilde{R}_s = \Delta\tilde{p}/\tilde{Q}
\end{align*}
\]

Figure 1.4: Added stenotic resistance in the network
1.2 Diagnosis: Importance of Coronary Diagnostic Parameters

A simplified description of diagnosis of stenosis in a clinical setting is provided. A Patient with suspected cardiac problem is made to undergo a standard treadmill stress test. Electrocardiogram from the patient is checked for any possible abnormality. If there is any abnormality, non-invasive imaging of the heart is done. Imaging techniques include myocardial perfusion scintigraphy, stress echocardiography and angiography. Severe stenosis (> 90% AS) can be easily detected through angiography. However, stenosis of intermediate AS (~64%-90% AS) cannot be determined reliably through imaging techniques (Kern et al., 2006).

Initial attempts to overcome this problem included invasive measurement of pressure drop across stenosis using a sensor-tipped guidewire. However, technical difficulties, and insignificant relationship between ischemia and pressure drop, led to failure of this method (Hodgson et al., 1986; MacIsaac et al., 1989; Peterson et al., 1987). Clinicians turned towards the use of a flow based parameter, coronary flow reserve (CFR) (Hoffman, 1984; Klocke, 1987). CFR is defined as the ratio of the flows at hyperemic ($\bar{Q}_h$) and basal conditions ($\bar{Q}_b$). Hyperemia in patients is induced through drugs in the clinical setting (McGeoch and Oldroyd, 2008).

$$CFR = \frac{\bar{Q}_h}{\bar{Q}_b}$$

However, hyperemic flow in a patient varies with hemodynamic conditions such as presence of left ventricular hypertrophy, diabetes mellitus, microvascular impairment etc (Klein et al., 2003; Schafer et al., 2002; Strauer, 1990; Strauer et al., 1997). This limited the use of CFR. Thus, use of a modified version of CFR, rCFR (relative CFR), came into practice. rCFR is evaluated by taking the ratio of CFR values in a diseased and normal artery of a patient. However, this did not solve the problem of hemodynamic dependence completely (Kern, 2000).
A CFR value less than 2 indicates either an epicardial dysfunction or a microvascular impairment, or a combination of the two (Kern et al., 2006).

Pijls et al. (Pijls et al., 1995; Pijls et al., 1993) came up with a pressure based parameter called the fractional flow reserve (FFR). FFR is the ratio of the hyperemic pressures distal and proximal to a stenosis (Pijls et al., 1993):

\[ FFR = \frac{\bar{p}_{rh} - \bar{p}_v}{\bar{p}_{ah} - \bar{p}_v} \]

where, \( \bar{p}_{ah} \) is the time averaged hyperemic proximal pressure

\( \bar{p}_{rh} \) is the time averaged hyperemic distal pressure.

\( \bar{p}_v \) is the time averaged venous pressure (~ 0 mmHg)

Pijls et al. claimed that FFR, evaluated at maximum hyperemia, was an estimate of the coronary flow, and could evaluate the ischemic risk of a stenosis. The FFR value was also observed to be independent of hemodynamic parameters (de Bruyne et al., 1996). Hence, the current clinical practice involves the use of FFR and CFR. The FFR ranges from 0 (severe stenosis) to 1 (normal vessel). A FFR less than 0.75 leads to percutaneous coronary intervention (Kern et al., 2006).

1.2.1 Limitations of CFR and FFR

Despite FFR and CFR being widely used in clinical practice, these parameters do have shortcomings. In the following paragraph, few of the issues which hinder the proper evaluation of stenosis severity (Johnson et al., 2012; Pijls and Tonino, 2011; Tobis et al., 2007), are summarized.

Native arterial diameter varies in humans (Dodge et al., 1992), and so pressure drop across a stenosis and flow would vary in arteries. For a constant flow-rate, pressure drop across a
stenosis would increase in a smaller artery. This is due to higher wall shear stress. However, hyperemic flow is likely to be lower in a smaller artery due to higher resistance and auto-regulation, leading to reduced pressure drop. This would mean FFR and CFR could be functions of native arterial diameter. In the presence of vascular abnormalities, such as MI, hyperemia is limited even for mild stenosis. The reduced pressure drop due to lower flow leads to higher FFR, and could lead to misdiagnosis in intermediate stenosis (Tobis et al., 2007).

The introduction of a guidewire into the artery creates an additional blockage, and leads to reduced flow and increased pressure drop across the stenosis (Ashtekar et al., 2007; Kern, 2000; Kern et al., 2006; Sinha Roy et al., 2006). This obstruction effect may lead to a misdiagnosis. The proper evaluation of stenosis severity, using FFR and CFR, is dependent on inducing maximum hyperemia in the patient. However, inducing a reliable maximal hyperemia has technical difficulties (De Luca et al., 2011; Heusch, 2010; Nair et al., 2011; Pijls and Tonino, 2011). These factors point to the fact that FFR and CFR may not always be reliable under a clinical setting.

1.2.2 New Diagnostic Parameters

Considering limitations of FFR and CFR, there is a need to develop better diagnostic parameters. Our group has suggested two diagnostic parameters, pressure drop coefficient (CDP) and lesion flow coefficient (LFC). These parameters are based on basic fluid dynamics principles. Another parameter, stenotic resistance index ($\tilde{R}_s$), has been suggested by Siebes et al. as an improved diagnostic parameter (Siebes et al., 2004; van de Hoef et al., 2012a)
**Pressure Drop Coefficient (CDP).** It is defined as the ratio of the pressure drop across the stenosis to the upstream dynamic pressure (Banerjee et al., 2008). It has a wide range (0-1000), which allows high sensitivity to flow changes.

\[
CDP = \frac{\Delta \bar{\rho}_h}{0.5 \rho \bar{U}_e^2}
\]

where, \(\Delta \bar{\rho}_h\) is the mean hyperemic pressure drop across the stenosis \((\bar{p}_{ah} - \bar{p}_{rh})\), dynes/cm²

\(\bar{U}_e\) is the mean hyperemic velocity proximal to the stenosis, cm/sec

\(\rho\) is the density of fluid in gm/cm³

**Lesion Flow Coefficient (LFC).** It is defined as the ratio of pressure drop coefficient at high Reynolds number to the pressure drop coefficient based on pressure drop across stenosis and throat dynamic pressure (Banerjee et al., 2007; Rajabi-Jaghargh et al., 2011). It varies from 0 (normal) to 1 (severe).

\[
LFC = \left( \frac{\tilde{c}_{\Delta p \omega c}}{\tilde{c}_{\Delta p}} \right)^{0.5}
\]

The numerator of the above expression represents “Borda-Carnot” head loss (Banerjee et al., 2003a) and an expression for it may be derived analytically:

\[
\tilde{c}_{\Delta p \omega c} = \left( 1 - \frac{A_m - A_g}{A_e - A_g} \right)^2
\]

where, \(A_m\) is the minimum cross sectional area at site of the stenosis, cm²

\(A_e\) is the cross sectional area of the native artery, cm²

\(A_g\) is the cross sectional area of the guidewire, cm²

The denominator of the expression for LFC is calculated using the following equation

\[
\tilde{c}_{\Delta p} = \frac{\Delta \bar{\rho}_h}{0.5 \rho \bar{U}_m^2}
\]
where, $\Delta \bar{p}_h$ is mean hyperemic pressure drop across the stenosis ($\bar{p}_{ah} - \bar{p}_{rh}$), dynes/cm$^2$

$U_m$ is mean hyperemic velocity at the site of minimum cross sectional area, cm/sec

$\rho$ is density of fluid in gm/cm$^3$

Previous work have shown CDP and LFC to be independent of hemodynamic factors such as contractility, heart rate, and microvascular impairment (Kolli et al., 2012; Kolli et al., 2011; Peelukhana et al., 2009; Peelukhana et al., 2012). Cutoffs for both these parameters are under clinical investigation.

**Stenotic Resistance ($R_s$).** It is another new parameter undergoing clinical investigation (van de Hoef et al., 2012b; Verhoeff et al., 2005). It is defined as the ratio of the time-averaged hyperemic pressure drop and flow rate (Siebes et al., 2004).

$$R_s = \frac{\Delta \bar{p}_h}{\bar{Q}_h}$$

where, $\Delta \bar{p}_h$ is mean hyperemic pressure drop across the stenosis ($\bar{p}_{ah} - \bar{p}_{rh}$), dynes/cm$^2$

$\bar{Q}_h$ is mean hyperemic flow rate, cm$^3$/sec

### 1.3 Objective and Outline of Thesis

The objective of this study was to assess the influence of geometric and flow variations on diagnostic parameters. The hypothesis was that these variations have little influence on the diagnostic capability of the parameters. Specifically, the study investigated the variation of coronary diagnostic parameters with change in native arterial diameter, vasculature status, and guidewire diameter. Coronary diagnostic parameters were also assessed in basal condition, since flow conditions change.

The chapter 2 of this thesis focuses on the methodology used in this study. The chapter 3 focuses on influence of native arterial diameter and vasculature status on diagnostic parameters.
*In-vitro* experiment coupled with pressure-flow relationships from human clinical data was used to simulate pathophysiologic conditions in two representative arterial diameters, 2.5 mm and 3 mm. With a 0.014” guidewire inserted, diagnostic parameters were evaluated for mild (~64% AS), intermediate (~80% AS), and severe (~90% AS) stenosis for both arteries, and between two conditions: with and without some levels of myocardial infarction. The chapter 4 focuses on influence of guidewire diameter and flow conditions on diagnostic parameters. Guidewires of diameters 0.014” and 0.022” were inserted in stenosed sections, assessing pressure flow data one at a time. Using the same *in-vitro* experiment and methodology, the effect of guidewire diameter on diagnostic parameters, FFR, CDP, LFC, and $\tilde{R}_s$ was evaluated for non-myocardial infarction case. These diagnostic parameters were assessed at basal flow condition, to present a *proof-of-concept* of basal based parameters. The chapter 5 concludes the results obtained in the previous two chapters, and presents the scope of future work.
2 Methodology

An *in-vitro* experiment involves replicating a biological component or system using a mechanical setup. Test sections, using lexan material, were used to mimic stenosed arteries (Figure 2.1). These test sections had either a diameter of 2.5 mm (N1) or 3 mm (N2). These diameters represented unblocked diameter of the artery, or the native arterial diameter. Each diameter had three clinically representative area stenosis (AS): mild (~64% AS), intermediate (~80% AS), and severe (~90% AS). These stenosed test sections were attached, one at a time, in the experimental flow loop (Figure 2.2) to obtain pressure drops across the stenoses. Care was taken to obtain the recovery pressure after the stenosis, by having a minimum of ten static pressure ports after the stenosed section. The obtained time-averaged pressure drop ($\Delta \bar{p}$) and flow rate ($\bar{Q}$) measurements were used to build pressure drop-flow rate ($\Delta \bar{p}$-$\bar{Q}$) curves. These curves, coupled with pressure-flow relationship from human data, were used to obtain physiological hyperemic values of distal pressure and flow rate. From the obtained hyperemic values of pressure and flow, diagnostic parameters were calculated. In this chapter, a detailed experimental protocol of obtaining physiologic flow and pressure, and the description of materials and instruments is provided.
Figure 2.1: Typical stenotic geometry used. Subscripts e, c, m and r denote proximal, converging, throat and distal respectively for diameter (d) and lengths (l).

Table 2.1: Dimensions of stenotic geometries used. DS denotes diameter stenosis and AS denotes area stenosis.

<table>
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<th>lc</th>
<th>lm</th>
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<th>% AS</th>
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<td>(mm)</td>
<td>(mm)</td>
<td>(mm)</td>
<td>(mm)</td>
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<td>~89</td>
</tr>
<tr>
<td>Intermediate</td>
<td>6.35</td>
<td>0.95</td>
<td>1.62</td>
<td>1.32</td>
<td>~56</td>
<td>~81</td>
</tr>
<tr>
<td>Mild</td>
<td>6.96</td>
<td>3.15</td>
<td>1.79</td>
<td>1.75</td>
<td>~42</td>
<td>~66</td>
</tr>
</tbody>
</table>
Figure 2.2: The schematic of the experimental flow loop.

2.1 Experimental Setup

The stenotic test sections were fixed in a flow loop one at a time, as shown in Figure 2.2. The flow and pressure in a coronary artery is pulsatile in nature (Figure 2.3). Pulsatile flow was obtained using a pulsatile pump (Harvard apparatus pulsatile pump, Instech Labs Inc.), and physiologic flow and pressure were obtained by adjusting the compliance chambers (C1 and C2) and constriction resistances (R1 and R2) shown in Figure 2.2. The time period of flow pulse in all cases was approximately 0.8 seconds (cardiac cycle time) and the ratio of average to peak flow rate in a cycle varied in the range of 0.5 to 0.7. Proximal pressures were maintained in the physiological range of 80-90 mmHg. A steady head was provided to the pulsatile pump using a constant head tank. A reservoir tank and submersible pump were used to circulate the blood analogue fluid.
With the test section attached, and appropriate pulsatile flow achieved, a guidewire was advanced into the stenotic section and its pressure tip was placed distal to the stenosis, similar to clinical setting. In this study two guidewires were tested, one at a time. The first one was the conventionally used guidewire of 0.014” (0.35 mm) diameter. The second guidewire was a new design by ACIST Medical Systems, and had a diameter of 0.022” (0.55 mm). The 0.014” and 0.022” diameter guidewires is referred as G14 and G22 respectively, in this document.

Figure 2.3: Representative flow and pressure pulses obtained during the experiments.

Once the guidewire was inserted, pressure drops and pulsatile flow rates were measured simultaneously. Inlet flow rate was measured using an ultrasound flow meter console (Transonic TS410-ME4XN107). Each stenotic section had sixteen axial static wall ports which were connected to a pressure sensor array module (Scanivalve DSA3207: ±0.20% accuracy). For each of the stenosed sections, there were at least ten static ports downstream to capture the recovery pressure. Synchronization of data acquisition was done through a data acquisition
system (National Instruments cDAQ 9174) with analog voltage measurement unit (National Instruments 9205). Data was post-processed using user-defined macros in Microsoft Excel. Time averaged pressure drop ($\Delta \bar{p}$) was calculated by subtracting the recovered distal pressure ($\bar{p}_r$) from the proximal (or upstream) pressure ($\bar{p}_a$). For the recovered distal pressure, instantaneous pressure at the peak of the cardiac cycle flow was observed, and the port of recovered pressure was assessed (Figure 2.4). The pressure at this port of recovered pressure was used to calculate distal pressure time-averaged over the cardiac cycle period.

Pressure drop-flow ($\Delta \bar{p}$-$\bar{Q}$) curves were constructed for N1 and N2 at different stenotic severities using G14 and G22. These curves were constructed using experimental pressure drops, averaged over three repeated experimental dataset for each flow rate. Four to five flow rates were measured. Based on the Brown-Bolson-Dodge criterion for ischemia in subendocardium (Brown et al., 1984), pressure drop curves for pressure drop within 35 mmHg are shown. Discussion on results of $\Delta \bar{p}$-$\bar{Q}$ curves are presented in the following chapters.

![Figure 2.4: Example of instantaneous pressure at peak flow (left) and time-averaged pressure (right) obtained along the stenosis](image-url)
2.2 Stenotic Sections

Lexan models were used to replicate stenosed sections (Figure 2.1). Geometry consisted of five distinct regions – proximal, converging, throat, diverging, and distal (representative shown in Figure 2.1). Dimensions of N2 sections were based on angiographic images by Wilson et al. (Wilson et al., 1988), and were used in previous studies (Ashtekar et al., 2007; Banerjee et al., 2003a; Peelukhana et al., 2009; Roy et al., 2005). By using geometric similarity, the dimensions of the smaller diameter artery (N1) were obtained. Due to machining inaccuracies, the dimensions of the machined test sections varied from the theoretical values obtained from geometric similarity. The final dimensions after machining inaccuracies were obtained through a microscope. The validation of dimensions, obtained through the microscope, was done by Micro-CT image reconstruction for N2 arterial sections (Appendix). Dimensions of N1 and N2 arterial sections are reported in Table 2.1.

Static pressure ports were drilled radially into the section, and can be observed in the Figure 2.1. These ports comprised of two parts: the seat and the orifice hole (Figure 2.5). Various factors such as the orifice hole length (l) and diameter (d), and flow Reynolds number, affect the
accuracy of the pressure readings. To minimize the error in static pressure measurement, the l/d of the pressure ports were greater than 2, and orifice hole diameter were 0.25 mm for N1 and 0.3 mm for N2, based on the review of Chue (1975) and Shaw (1960). There were a minimum of two static pressure ports drilled at the proximal part of the test sections. There was one pressure port each in the converging, throat, and diverging section. A minimum of ten static pressure ports were drilled at the distal (downstream) region, to allow capture of recovery pressure.

2.3 Blood Analogue Fluid

Blood is a shear thinning fluid (Cho and Kensey, 1991), which means that the viscosity of blood decreases as shear rate is increased. Many models have been proposed to for this shear thinning behavior (e.g. Powell-Eyring, Cross, Carreau models) However, Carreau model is widely used to represent blood viscosity (Cho and Kensey, 1991). According to this model:

$$\mu = \mu_\infty + (\mu_0 - \mu_\infty) \times (1 + (\lambda \dot{\gamma})^2)^{0.5(n-1)}$$

Where,

$\mu$ is the dynamic viscosity

$\mu_\infty$ is the dynamic viscosity at very high shear rates

$\mu_0$ is the dynamic viscosity at zero shear rate

$\dot{\gamma}$ is the shear rate

$\lambda$ and $n$ are material constants

A blood analogue fluid composed of glycerin, water and xanthum gum was prepared. Approximate percentages by weight of glycerin, water, and xanthum gum were 20, 80, and 0.02 respectively based on study by Brookshier and Tarbell (1993) and previous studies (Ashtekar et al., 2007; Banerjee et al., 2008; Brookshier and Tarbell, 1993; Peelukhana et al., 2009).
Viscosity measurement was done using a concentric cylinder viscometer (DV-II+ PRO Digital Viscometer, Brookfield, MA). Due to the inherent uncertainty of the viscosity measurement by the viscometer at low and high shear rates, readings were used to perform a non-linear curve fitting for the Carreau model in Matlab. The fitted curve, experimental points averaged over 7 readings, and viscosity curve reported by Cho and Kensey (1991) are reported in Figure 2.3. Experimentally obtained values of viscosity were: $\mu_\infty = 2.4$ cP, $\mu_0 = 54.6$ cP, $\lambda = 4.3$, and $n = 0.5$. These values were comparable to values reported by previous literature (Ashtekar et al., 2007; Cho and Kensey, 1991).
2.4 Basal Flow Assumptions

The basal flow rate of 50 ml/min was based on clinical data (Bache and Schwartz, 1982; Hundley et al., 1996; Kessler et al., 1998) and was reported in previous studies by our group (Banerjee et al., 2000, 2003b). Based on the Reynolds similarity, basal flows of 42 ml/min and 50 ml/min were determined for N1 and N2 respectively.

2.5 Determination of Hyperemia

Hyperemic values of distal pressure ($\tilde{p}_{rh}$) and flow ($\tilde{Q}_h$) were determined by solving equations for distal bed resistance ($\tilde{R}_v$) and $\Delta \tilde{p} - \tilde{Q}$ curves. $\tilde{R}_v$ is defined as (Banerjee et al., 2003a):

$$\tilde{R}_v = (\tilde{p}_{rh} - \tilde{p}_{ro})/\tilde{Q}_h \quad \text{Equation 2.1}$$

The value of time-averaged zero-flow pressure ($\tilde{p}_{ro}$) was assumed to be 20 mmHg based on previous studies (Bache and Schwartz, 1982; Banerjee et al., 2003a; Van Herck et al., 2007). The values of $\tilde{R}_v$ were kept constant for each of the arterial diameters for a given condition of vasculature status.

Pressure drop across a stenosis follows a quadratic behavior $\Delta \tilde{p} = a\tilde{Q} + b\tilde{Q}^2$, where $a$ and $b$ are coefficients related to viscous and momentum losses respectively (Back et al., 1996). Using this expression for pressure drop, $\tilde{p}_{rh}$ can be expressed as a function of $\tilde{Q}_h$:

$$\tilde{p}_{rh} = \tilde{p}_a - a\tilde{Q}_h - b\tilde{Q}_h^2 \quad \text{Equation 2.2}$$

Equation 2.1 and 2.2 were solved for $\tilde{p}_{rh}$ and $\tilde{Q}_h$. Graphical solution may be represented using a CFR-$\tilde{p}_{rh}$ curve, also known as a maximal vasodilation-distal perfusion pressure plot. The obtained $\tilde{p}_{rh}$ and $\tilde{Q}_h$ were used to calculate the diagnostic parameters FFR, CDP, $\tilde{c}$, and $\tilde{R}_s$. Detailed results on CFR-$\tilde{p}_{rh}$ curves are provided in chapter 3.
3 Influence of Native Arterial Diameter and Vasculature Status

Native arterial diameter varies in humans (Dodge et al., 1992), and so pressure drop across a stenosis and flow would vary in arteries. For a constant flow-rate, pressure drop across a stenosis would increase in a smaller artery. This is due to higher wall shear stress. However, hyperemic flow is likely to be lower in a smaller artery due to higher resistance and auto-regulation, leading to reduced pressure drop. Since diagnostic parameters are dependent on pressure and flow information, it would be interesting to assess their dependence on arterial diameter. Previous works by our group on arterial stenosis and guidewire diagnostics were primarily based on the assumption of no microvascular dysfunction in a 3 mm diameter artery (Banerjee et al., 1999, 2000, 2003b; Roy et al., 2005). A stenosed artery leads to lower blood supply to the tissues. A prolonged reduction of blood supply leads to tissue death, also known as myocardial infarction (MI). In patients with MI, lower CFR values have been observed even after reopening the stenosed artery through intervention. This behavior of “no-reflow” has been attributed to increased microvascular resistance. Microvascular dysfunction is a complex phenomenon and is subject to ongoing studies (Aarnoudse et al., 2004; Camici and Crea, 2007; Chamuleau et al., 2003; Kloner et al., 1980; Marzilli, 2007; Patel and Fisher, 2010; Peelukhana et al., 2012). Meuwissen et al. (Meuwissen et al., 2001) has reported an ambiguity in distinguishing stenosis severity using conventional diagnostic parameters in 27% of the 41 patients due to variable microvascular resistance. Diagnostic parameters should be capable of delineating stenosis severity irrespective of the vascular condition. Hence, there is a need to study the variation of diagnostic parameters with native arterial diameter, as well as vascular condition.
Therefore, in this chapter the variation of FFR, CDP, LFC, and $\tilde{R}_s$ in N1 and N2 was assessed, using G14 guidewire. Each diameter had three clinically relevant levels of focal stenosis (mild, intermediate, and severe) as reported in previous chapter (Table 2.1). In addition, diagnostic parameters were evaluated at each of these severities for the two diameters between conditions with and without some levels of MI. This chapter reports only the values with G14 wire because it is the conventionally used guidewire.

3.1 Results

The pressure-flow characteristic curves obtained for G14 from the in-vitro experiment are first summarized, followed by estimation of hyperemic flow and assessment on diagnostic parameters with variation of native arterial diameter and vascular condition. The diagnostic parameters are compared for the two arterial diameters, and for the conditions with and without myocardial infarction (MI). Pressure drops measured from the experiments and the parameters calculated are summarized in Table 3.1.

3.1.1 Pressure-Flow Characteristic Curves

A pressure drop – flow rate ($\Delta\tilde{p}$-$\tilde{Q}$) relation across a stenotic section is a quadratic relation represented by $\Delta\tilde{p} = a\tilde{Q} + b\tilde{Q}^2$, where a and b are coefficients related to viscous and momentum losses respectively (Back et al., 1996; Brown et al., 1984). $\Delta\tilde{p}$-$\tilde{Q}$ characteristic curves measured with G14 inserted for different stenotic levels in N1 and N2 arteries, are reported in Figure 3.1. Curves are extrapolated for the case of intermediate stenosis and are shown with dotted lines (Figure 3.1).
Figure 3.1: $\Delta\tilde{p}$-$\tilde{Q}$ curves with 0.014” (G14) guidewire

Viscous components (units: mmHgml$^{-1}$min) were (reported for N1 vs. N2): mild: 0.034 vs. 0.021, intermediate: 0.065 vs. 0.036, and severe: 0.404 vs. 0.119. Higher viscous losses were observed for N1 when compared to N2.

Momentum components (units: mmHgml$^{-2}$min$^2$) were comparable for mild (N1: 0.0003 vs. N2: 0.0002), and intermediate (N1: 0.0014 vs. N2: 0.0010) stenosis cases. However, in the case of severe stenosis the coefficient increased from N2 (0.0029) to N1 (0.0134).
3.1.2 Estimation of Hyperemia

Based on the $\Delta\tilde{p} - \tilde{Q}$ curves obtained from the experiments, hyperemic flow rates for various combinations of arterial diameter, stenosis and vascular condition were obtained using the $CFR$-$\tilde{\rho}_{rh}$ plots (Figure 3.2).

Line 1 represents a $CFR$-$\tilde{\rho}_{rh}$ relationship for a 32 patient data reported by Wilson et al. (Wilson et al., 1988) undergoing percutaneous coronary angioplasty (PTCA) and having no microvascular dysfunction. This group of patients had no ventricular hypertrophy, no valvular heart disease, and had normal left ventricular ejection fraction. There was also no evidence of myocardial infarction, no stenosis in the parent branch, and no angiographically apparent collateral circulation. The x-intercept ($\tilde{\rho}_{ro}$) of this line was 20 mmHg. Such values of $\tilde{\rho}_{ro}$ (~18 mmHg) were reported for a dog by Bache et al. (Bache and Schwartz, 1982), and for a group of patients with stable angina pectoris by van Herck et al. (Van Herck et al., 2007).

The $CFR$-$\tilde{\rho}_{rh}$ line MI_1 and MI_2 had $\tilde{\rho}_{ro}$ of 20 mmHg and 30 mmHg respectively. These lines were developed using data from Claeys et al. (Claeys et al., 1996) for patients with MI undergoing PTCA. Patients had no valvular disease, congestive heart failure, and left ventricular hypertrophy. Also there was no angiographically apparent collateral supply, bypass graft, or ostial narrowing observed in this group. Values of $\tilde{\rho}_{ro}$ in the range of 20 mmHg to 40 mmHg were reported for MI patients by van Herck et al. (Van Herck et al., 2007).

Lines 1 through 3 represent constant distal bed resistance values for a native arterial diameter case. Line 1 represents $\bar{R}_v$ of 0.37 mmHgml$^{-1}$min (N1) and 0.30 mmHgml$^{-1}$min (N2). Line 2 represents $\bar{R}_v$ of 0.76 mmHgml$^{-1}$min (N1) and 0.63 mmHgml$^{-1}$min (N2). Line 3 represents $\bar{R}_v$ of 0.59 mmHgml$^{-1}$min (N1) and 0.49 mmHgml$^{-1}$min (N2).
Figure 3.2: CFR-$\tilde{p}_{rh}$ curves for two vascular conditions

A pressure drop – flow rate ($\Delta\tilde{p}$-$\tilde{Q}$) relation across a stenotic section is a quadratic relation represented by $\Delta\tilde{p} = a\tilde{Q} + b\tilde{Q}^2$, where $a$ and $b$ are coefficients related to viscous and momentum losses respectively (Back et al., 1996; Brown et al., 1984; Gould, 1978). Pressure drop ($\Delta\tilde{p}$) was measured in the in-vitro experiment, averaged over three repeated trials for each flow rate. A unique quadratic $\Delta\tilde{p}$-$\tilde{Q}$ characteristic curve was obtained for each stenosis model by curve fitting the experimentally-obtained $\Delta\tilde{p}$ for four to five flow-rates. Using these fitted polynomial characteristic curves, distal pressure ($\tilde{p}_{rh}$) may be obtained as a function of flow ($\tilde{Q}$) and proximal pressure ($\tilde{p}_{ah}$):

$$\tilde{p}_{rh} = \tilde{p}_{ah} - a\tilde{Q} - b\tilde{Q}^2$$
Table 3.1: Hemodynamic endpoints and corresponding diagnostic parameters for two native arteries and vascular condition

<table>
<thead>
<tr>
<th></th>
<th>CFR</th>
<th>Pressure drop (mm Hg)</th>
<th>FFR</th>
<th>CDP</th>
<th>LFC</th>
<th>$\bar{R}_s$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-MI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>N1</td>
<td>3.4</td>
<td>11.1</td>
<td>N1</td>
<td>11</td>
<td>0.61</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>3.5</td>
<td>9.8</td>
<td>N2</td>
<td>14</td>
<td>0.53</td>
</tr>
<tr>
<td>Int.</td>
<td>N1</td>
<td>2.7</td>
<td>24.6</td>
<td>N1</td>
<td>42</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>2.7</td>
<td>23.5</td>
<td>N2</td>
<td>56</td>
<td>0.63</td>
</tr>
<tr>
<td>Severe</td>
<td>N1</td>
<td>1.2</td>
<td>50.8</td>
<td>N1</td>
<td>458</td>
<td>0.72</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.9</td>
<td>38.8</td>
<td>N2</td>
<td>182</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>MI_1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>N1</td>
<td>1.9</td>
<td>4.6</td>
<td>N1</td>
<td>15</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.9</td>
<td>3.8</td>
<td>N2</td>
<td>19</td>
<td>0.46</td>
</tr>
<tr>
<td>Int.</td>
<td>N1</td>
<td>1.7</td>
<td>11.9</td>
<td>N1</td>
<td>49</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.7</td>
<td>10.7</td>
<td>N2</td>
<td>62</td>
<td>0.60</td>
</tr>
<tr>
<td>Severe</td>
<td>N1</td>
<td>1.0</td>
<td>38.1</td>
<td>N1</td>
<td>493</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.4</td>
<td>23.6</td>
<td>N2</td>
<td>201</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>MI_2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>N1</td>
<td>2.0</td>
<td>5.0</td>
<td>N1</td>
<td>15</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>2.0</td>
<td>4.2</td>
<td>N2</td>
<td>18</td>
<td>0.47</td>
</tr>
<tr>
<td>Int.</td>
<td>N1</td>
<td>1.8</td>
<td>12.6</td>
<td>N1</td>
<td>48</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.8</td>
<td>11.5</td>
<td>N2</td>
<td>62</td>
<td>0.60</td>
</tr>
<tr>
<td>Severe</td>
<td>N1</td>
<td>0.9</td>
<td>36.2</td>
<td>N1</td>
<td>500</td>
<td>0.69</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>1.4</td>
<td>23.6</td>
<td>N2</td>
<td>201</td>
<td>0.90</td>
</tr>
</tbody>
</table>

Proximal pressures ($\bar{p}_{ah}$) for mild, intermediate and severe stenoses were assumed to be 84 mmHg, 86 mmHg, and 89 mmHg, respectively, based on clinical evidence by Wilson et al. (Wilson et al., 1988). The unique $\bar{p}_{rh}$ for each stenotic model was plotted on the CFR-$\bar{p}_{rh}$ (Figure 3.2), and the intersection of these characteristic curves with CFR-$\bar{p}_{rh}$ constructed from clinical data (Lines 1-3) provided single pathophysiologic hyperemic values of CFR and $\bar{p}_{rh}$ for each stenotic model. For example, the intersection of the curve N1_Severe and line 1 (non-MI...
case) provides the hyperemic condition for an artery of 2.5 mm diameter (N1) with a severe stenosis and with no MI condition (Figure 3.2). The obtained CFR and $\tilde{p}_{rh}$ values were used to calculate the unique diagnostic parameter (FFR, CDP, LFC, $\tilde{R}_s$) values (Ashtekar et al., 2007; Banerjee et al., 2003a; Roy et al., 2005). The same procedure was applied to find unique values of diagnostic parameters for all stenoses cases, and hence diagnostic parameters are reported without any error bars (Table 3.1; Figures 3.3-3.11). Values reported for the MI case are based on the MI_1 line since the percent difference of diagnostic parameters were within 5% between the two lines of MI (MI_1 vs. MI_2). Using calculation methods reported in literature (Kline, 1953; Moffat, 1988), the uncertainty in diagnostic parameters due to measurement was calculated to be less than 1% (See Appendix for sample calculations).

3.1.3 Variation of Diagnostic Parameters with Diameter Change

The variation of diagnostic parameters with diameter under the two vascular conditions, MI and non-MI, for mild, intermediate, and severe stenoses cases is summarized in Table 3.2. The percent difference is defined as:

$$\left[\frac{(\text{Diagnostic parameter}_{N1} - \text{Diagnostic parameter}_{N2}) \times 100}{\text{Diagnostic parameter}_{N2}}\right]$$

**Table 3.2:** Variability of diagnostic parameters with diameter (reported as percentage deviation from 3mm case). Intermediate has been abbreviated as Int.
Negative values in Table 3.2 denote that the diagnostic parameters were lower in the smaller artery N1 as compared to N2. Similarly, positive values imply higher values for N1 compared to N2. The values of the parameters used to calculate the percentage difference are given in Table 3.1.

**CFR for non-MI condition.** CFR values for mild and intermediate stenosis for N1 and N2 under non-MI condition were within 5% difference (mild: 3.4 vs. 3.5; intermediate: 2.7 vs. 2.7). However, in the case of severe stenosis (N1: 1.2 vs. N2: 1.9), a percentage difference of greater than 30% was observed between CFR values (Figure 3.3).

**CFR for MI condition.** Difference in CFR values between diameters for mild and intermediate stenosis were negligible (mild: 1.9 vs. 1.9; intermediate: 1.7 vs. 1.7), whereas for severe case it was more than 25% (1.0 vs. 1.4).

![Figure 3.3: Variation of CFR with native diameter with non-MI vascular condition.](image)

**FFR for non-MI condition.** The variation in FFR with diameter is shown in Figure 3.4. FFR values for mild stenosis for N1 (0.87) and N2 (0.88) under non-MI condition were within 5% difference. A similar trend was observed for the intermediate stenosis case, with the difference in values of N1 (0.71) and N2 (0.73) being under 5%. However, there was a considerable percentage difference (> 20%) between two diameters at severe stenosis (0.43 vs. 0.56).
**FFR for MI condition.** Difference in FFR values between diameters N1 and N2 for mild and intermediate stenosis were minimal (< 5%; mild: 0.95 vs. 0.96; intermediate: 0.86 vs. 0.88), but was considerable (> 20%) for severe stenosis (0.57 vs. 0.73) case.

![Bar chart showing FFR variation with native diameter](image)

**Figure 3.4:** Variation of FFR with native diameter with non-MI vascular condition.

**CDP for non-MI condition.** The variation in CDP with diameter is shown in Figure 3.5. CDP values for the mild stenosis case for N1 (11) and N2 (14) were different by 21.4%. Similarly, in the case of intermediate stenosis, the CDP values of the N1 (42) and N2 (56) had a percentage difference of 25.0%. However, the CDP value for smaller artery N1 was one and a half times higher than N2 in case of severe stenosis (458 vs. 182). Although there was a higher variation in CDP with diameter, the distinct range of these values allowed easier delineation of the severities.

**CDP for MI condition.** CDP values for mild and intermediate stenosis were 21.1 % and 21.0 % lower in the smaller artery N1 (mild: 15 vs. 19; intermediate: 49 vs. 62), but was approximately one and a half times higher for N1 as compared to N2 for severe case (493 vs. 201).
Figure 3.5: Variation of CDP with native diameter with non-MI vascular condition.

_LFC for non-MI condition._ The variation in LFC with diameter is shown in Figure 3.6. LFC values for the mild stenosis case for N1 (0.61) and N2 (0.53) were different by 15.1%. Similarly, in the case of intermediate stenosis, the LFC values of the N1 (0.80) and N2 (0.63) had a percentage difference of 27.0%. However, the LFC values were lower in the smaller artery N1 by 23.4% in severe stenosis (N1: 0.72; N2: 0.94) due to flow limitation at severe AS.

_LFC for MI condition._ Values of LFC for mild and intermediate stenosis were 15.2% and 23.3% higher in the smaller artery N1 (mild: 0.53 vs. 0.46; intermediate: 0.74 vs. 0.60), but was lower by 22.2% for N1 for severe case (0.70 vs. 0.90).
Figure 3.6: Variation of LFC with native diameter with non-MI vascular condition.

$\tilde{R}_s$ for non-MI condition. The variation in $\tilde{R}_s$ with diameter is shown in Figure 3.7. $\tilde{R}_s$ values for the mild stenosis case for N1 (0.08) and N2 (0.06) were different by 33.3%. Similarly, in the case of intermediate stenosis, the $\tilde{R}_s$ values of the N1 (0.22) and N2 (0.17) had a percentage difference of 29.4%. The $\tilde{R}_s$ values in severe stenosis were higher in the smaller artery N1 by more than 2.5 times (N1: 1.05; N2: 0.40).

$\tilde{R}_s$ for MI condition. Values of $\tilde{R}_s$ for mild and intermediate stenosis were 50.0% and 41.7% higher in the smaller artery N1 (mild: 0.06 vs. 0.04; intermediate: 0.17 vs. 0.12). The $\tilde{R}_s$ was almost 3 times for N1 as compared to N2 for severe case (0.94 vs. 0.33).
Figure 3.7: Variation of $\tilde{R}_s$ with native diameter with non-MI vascular condition.

Table 3.3: Variability of functional parameters with vascular condition (Non-MI vs. MI reported as percentage deviation from Non-MI case). Intermediate has been abbreviated as Int.

<table>
<thead>
<tr>
<th></th>
<th>N1</th>
<th></th>
<th>N2</th>
<th></th>
<th>N2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild</td>
<td>Int.</td>
<td>Severe</td>
<td>Mild</td>
<td>Int.</td>
</tr>
<tr>
<td>CFR</td>
<td>-44.1</td>
<td>-37.0</td>
<td>-16.7</td>
<td>-45.7</td>
<td>-37.0</td>
</tr>
<tr>
<td>FFR</td>
<td>9.2</td>
<td>21.1</td>
<td>32.6</td>
<td>9.1</td>
<td>20.6</td>
</tr>
<tr>
<td>CDP</td>
<td>36.4</td>
<td>16.7</td>
<td>7.6</td>
<td>35.7</td>
<td>10.7</td>
</tr>
<tr>
<td>LFC</td>
<td>-13.1</td>
<td>-7.5</td>
<td>-2.8</td>
<td>-13.2</td>
<td>-4.8</td>
</tr>
<tr>
<td>$\tilde{R}_s$</td>
<td>-25.0</td>
<td>-22.7</td>
<td>-10.5</td>
<td>-33.3</td>
<td>-29.4</td>
</tr>
</tbody>
</table>
3.1.4 Variation with Vascular Condition

The variation of parameters with vascular condition for N1 and N2 for mild, intermediate, and severe cases is summarized in Table 3.3. The percent difference was defined as:

\[
\left(\frac{\text{Diagnostic parameter}_\text{MI} - \text{Diagnostic parameter}_\text{non-MI}}{\text{Diagnostic parameter}_\text{non-MI}}\right) \times 100
\]

Negative values in Table 3.3 denote that the diagnostic parameters were lower for the MI as compared to the non-MI. Similarly, positive values imply higher values for MI than non-MI. The values of the parameters used to calculate the percentage difference are given in Table 3.1.

**CFR for N1.** CFR values for N1 were 44.1%, 37.0%, and 16.7% lower for mild, intermediate, and severe stenosis respectively for the MI case as compared to non-MI condition (mild: 1.9 vs. 3.4; intermediate: 1.7 vs. 2.7; severe: 1.0 vs. 1.2).

**CFR for N2.** Lower values of CFR were measured for MI condition (mild: 1.9 vs. 3.5; intermediate: 1.7 vs. 2.7; severe: 1.4 vs. 1.9). These were 45.7%, 37.0% and 26.3% lower in mild, intermediate, and severe stenosis respectively. A trend of decreased CFR is shown in Figure 3.8.

**FFR for N1.** FFR values for N1 were 9.2%, 21.1%, and 32.6% higher in mild, intermediate, and severe stenosis respectively for the MI case as compared to the non-MI condition (mild: 0.95 vs. 0.87; intermediate: 0.86 vs. 0.71; severe: 0.57 vs. 0.43). This was primarily due to the reduced CFR value, which led to lower pressure drops across the stenosis.

**FFR for N2.** The variation of FFR with changing vascular condition for the N2 diameter is shown in Figure 3.8. It can be observed that there is an overestimation in the FFR values for the MI condition in comparison to the non-MI condition. The values of FFR were higher by 9.1%, 20.6 %, and 30.4% for the MI condition, in comparison to the non-MI condition for the mild (0.96 vs. 0.88), intermediate (0.88 vs. 0.73), and the severe stenoses (0.73 vs. 0.56), respectively.
Figure 3.8: Variation of CFR (left) and FFR (right) with vascular conditions shown for 3mm diameter (N2) artery.

CDP for N1. CDP values for N1 were 36.4%, 16.7%, and 7.6% higher in mild, intermediate, and severe stenosis respectively, for the MI case as compared to the non-MI condition (mild: 15 vs. 11; intermediate: 49 vs. 42; severe: 493 vs. 458).

CDP for N2. The variation of CDP with changing vascular condition for the N2 diameter is shown in Figure 3.8. The values of CDP were higher by 35.7%, 10.7%, and 10.4% for the MI condition, in comparison to the non-MI condition for the mild (19 vs. 14), intermediate (62 vs. 56), and the severe stenosis (201 vs. 182) respectively. It can be stated that unlike FFR, which underestimates the severity in presence of infarction, CDP was able to distinguish the severities irrespective of the vascular condition.
Figure 3.9: Variation of CDP with vascular conditions shown for 3mm diameter (N2) artery

LFC for N1. LFC values for N1 were 13.1%, 7.5%, and 2.8% lower in mild, intermediate, and severe stenosis respectively for the MI case as compared to the non-MI condition (mild: 0.53 vs. 0.61; intermediate: 0.74 vs. 0.80; severe: 0.70 vs. 0.72).

LFC for N2. The variation of LFC with changing vascular condition for the N2 diameter is shown in Figure 3.9. It can be observed that there is an underestimation in the LFC values for the MI condition in comparison to the non-MI condition. The values of LFC were lower by 13.2%, 4.8%, and 4.3% for the MI condition, in comparison to the non-MI condition for the mild (0.46 vs. 0.53), intermediate (0.60 vs. 0.63), and the severe stenoses (0.90 vs. 0.94), respectively.
Figure 3.10: Variation of LFC with vascular conditions shown for 3mm diameter (N2) artery

$\bar{R}_s$ for N1. $\bar{R}_s$ values for N1 were 25.0%, 22.7%, and 10.5% lower in mild, intermediate, and severe stenosis respectively for the MI case as compared to the non-MI condition (mild: 0.06 vs. 0.08; intermediate: 0.17 vs. 0.22; severe: 0.94 vs. 1.05). This was primarily due to the reduced CFR value, which led to lower pressure drops across the stenosis.

$\bar{R}_s$ for N2. The variation of $\bar{R}_s$ with changing vascular condition for the N2 diameter is shown in Figure 3.10. It can be observed that there is an underestimation in the $\bar{R}_s$ values for the MI condition in comparison to the non-MI condition. The values of $\bar{R}_s$ were lower by 33.3%, 29.4%, and 17.5% for the MI condition, in comparison to the non-MI condition for the mild (0.04 vs. 0.06), intermediate (0.12 vs. 0.17), and the severe stenoses (0.33 vs. 0.40), respectively.
Figure 3.11: Variation of $R_s$ with vascular conditions shown for 3mm diameter (N2) artery

3.2 Assumptions and Limitations

Geometric parameters such as shape, length of stenosis, percent area stenosis, contraction and diverging angles, symmetry conditions, are few of the parameters expected to influence pressure drop across a stenosis (Back et al., 1996; Baumgartner et al., 1993; Seeley and Young, 1976). It has been widely reported that percent AS is the major geometric factor governing pressure drop in severe cases (Mates et al., 1978; Young, 1979). Due to the predominance of momentum loss over viscous loss in severe stenosis, the role of stenosis length on pressure drop has been reported to be negligible (May et al., 1963; Young, 1979). The pressure drop across a mild stenosis is very small, and hence geometric variations would not alter the distal pressure drastically for a focal stenosis. However, geometric parameters could be important for the case
of intermediate stenosis, and further investigation is necessary (Banerjee et al., 2008; Feldman et al., 1978).

*Rigid wall* of the stenosed geometry was assumed based on clinical observation (Drexler et al., 1989; Vita et al., 1989). Compliance reduces the pressure drop with increasing severity of stenosis (Konala et al., 2011). Hence, we believe a rigid wall approximation provides a conservative estimate of the pressure drop.

Non-Newtonian behavior of blood plays an important role in diseased arteries where reductions in area leads to formation of localized low shear rates recirculation downstream of stenosis (Banerjee et al., 2003b). *Blood viscosity changes* with many factors (Cho and Kensey, 1991) and such variations may have an impact on pressure drop due to viscous losses.

A pulsatile *flow wave pulse* was supplied to the stenotic section with ratio of average to peak flow in a cardiac cycle varying in the range of 0.5 to 0.7. This variability of ratio was assumed to be reasonable based on clinical observation in the left circumflex coronary arteries of dogs (Young, 1979).

*Concentricity of the guidewire* is not possible to detect or maintain in a clinical setting. Concentricity was not checked in this study and a concentrically placed guidewire will lead to marginally higher pressure drop across a stenosis compared to an eccentrically placed guidewire (Back et al., 1996; Daripa and Dash, 2002).

In this study, *estimates of distal bed resistances* were provided to quantify the difference between non-MI and MI data. These estimates were based on the assumption of linearity of $CFR - \tilde{p}_{rh}$ plots and a constant $\tilde{p}_{ro}$ of 20 mmHg (Bache and Schwartz, 1982; Van Herck et al., 2007). However, determining the value of $\tilde{p}_{ro}$ is complex in clinical studies, and is being
debated in the medical community (Dole, 1987; Gosselin and Kaplow, 1991; Nanto et al., 1996; van de Hoef et al., 2012b).

### 3.3 Discussion

*In-vitro* experiment coupled with pressure-flow relationships from human clinical data was used to simulate pathophysiologic conditions in two representative arterial diameters, 2.5 mm (N1) and 3 mm (N2). With a 0.014” (0.35 mm) guidewire inserted, diagnostic parameters were evaluated for mild (~64 % AS), intermediate (~80 % AS), and severe (~90 % AS) stenosis for both N1 and N2 arteries, and between two conditions: with and without myocardial infarction (MI). \( CFR_{rh} \) lines were used to determine the hyperemic flow rates and distal pressure. These lines were based on clinical human data. Three lines, one representing non-MI and two representing MI were used. The difference between the two MI lines (MI_1 vs. MI_2) was the use of different \( \rho_{ro} \). Values reported for the MI are based on the MI_1 line, since the percent difference of FFR and CDP were within 5% between the two lines of MI (MI_1 vs. MI_2).

\( CFR_{rh} \) is thought to be non-linear at very low coronary flow due to vascular waterfall mechanism (Downey and Kirk, 1975; van de Hoef et al., 2012b). In this study, flow rates were in the linear region and non-linearity was ignored (Bache and Schwartz, 1982).

Results obtained show native arterial diameter does not influence diagnosis of stenosis severity. However, vasculature status does influence diagnostic parameters. First, variation of diagnostic parameters with diameter is discussed followed by variation with vascular condition.

**Variation of Diagnostic Parameters with Diameter**

In a clinical setting, native arterial diameter varies between patients. Therefore, this effect has been assessed in the current study. For all severities, viscous components in the \( \Delta \rho - \bar{Q} \)
relationships were higher in the smaller diameter (N1) artery, and momentum components were comparable except for severe stenosis (Figure 3.1).

In case of severe stenosis for both vascular conditions, guidewire obstruction at the throat led to higher pressure drops and lower hyperemic flow in the N1 artery. This led to a difference of more than 20% in FFR values between N1 and N2. Lower pressure recovery due to guidewire obstruction led to higher (~2.5 times) CDP values for N1. The higher obstruction effect at the throat led to $\tilde{R}_s$ values in the N1 artery to be as much as 2.5 times as compared to values in N2 artery. The flow limiting condition in severe stenosis led to lower (~32%) flow rate, which reduced LFC by approximately 22% in N1.

For both vascular conditions, obstruction created by the guidewire in the arteries was comparable for the mild and intermediate stenoses. The marginal difference in pressure drops in these cases may be attributed to difference in viscous components. FFR varied little (<5%) between the two diameters but, CDP was 20-25% lower in N1 due to higher dynamic pressure. The $\tilde{R}_s$ value varied considerably in mild (>30%) and intermediate (>30%) stenosis. Similarly, the LFC values also had a high variability with diameter at mild (~15%) and intermediate stenosis (~25%). In clinical setup, functional assessment of stenosis is primarily done in cases of intermediate stenosis range. Since FFR varied little for mild to intermediate stenoses cases, variability of diameter will not influence diagnostic assessment. New diagnostic parameters, CDP, LFC, and $\tilde{R}_s$, had increasing trend with stenosis severity, and delineated stenoses severities despite high variability with diameter.
Variation of Diagnostic Parameters with Vascular Condition

A prolonged reduction of blood supply to the tissue leads to MI. Microvascular dysfunction has been observed in patients with stenosed arteries and infarcted tissue (Camici and Crea, 2007; Patel and Fisher, 2010). It leads to reduced hyperemic flows. Therefore, in this study flow limiting conditions in the presence of MI were also assessed. Decreased flow (17-46%) due to MI led to lower pressure drops (25-62%). This resulted in overestimation of FFR for both arterial diameters (mild: ~9 %, intermediate: ~20 %, severe: ~30 %). Higher FFR values for intermediate stenosis in the presence of MI meant the vascular condition may lead to misdiagnosis of stenosis severity.

The reduced contribution of dynamic pressure in the presence of MI led to higher values of CDP (mild: ~35 %, intermediate: ~14 %, severe: ~9 %) for both arterial diameters. In N1, presence of MI changed CDP from 11 to 16 (mild), 42 to 49 (intermediate), and 458 to 493 (severe) (Table 2.2). In N2, presence of MI changed CDP from 14 to 19 (mild), 56 to 62 (intermediate), and 182 to 201 (severe). For the combined pool of varying diameter and vascular condition, CDP varied from 11 to 19 (mild), 42 to 62 (intermediate), and 182 to 201 (severe).

The reduced flow implied reduced values of $\bar{R}_s$ (mild: ~29%; intermediate: ~25%; severe: ~14%). Hence, the $\bar{R}_s$ value was observed to be highly dependent on flow. LFC was reduced in presence of MI. This is the combined result of relatively lower pressure drop compared to reduction in flow rate. The reduction of LFC was lowest at severe case (~3%), and approximately 13% and 6% in mild and intermediate stenosis respectively. This proved that for a given arterial diameter LFC was able to detect stenosis severity irrespective of the vasculature status.
Claeys et al. (Claeys et al., 2001) reported FFR of 0.72 ± 0.10 (pre-intervention) and 0.84 ± 0.08 (post-intervention) for 19 non-infarct patients. These patients had diameter stenosis of 54 ± 10 % (AS 78 ± 10 %) before intervention and 40 ± 10 % (AS 64 ± 11 %) post intervention. These values were close to the values for ~80 % AS (N1: 0.71 and N2: 0.73) and ~64 % AS (N1: 0.87 and N2: 0.88) obtained in this study (Table 3.1). Studies have reported overestimation of FFR for intermediate stenoses in presence of MI (Tobis et al., 2007). Other studies have shown that FFR is capable of diagnosing severe stenosis irrespective of the vascular condition (McClish et al., 2004). A similar trend was seen in our study (Table 3.1). However, non-overlapping range of CDP allowed better delineation of the severities irrespective of variation in diameter or vascular condition. Therefore, we believe that CDP can be a potential diagnostic parameter for better estimation of functional severity of coronary stenosis.
4 Influence of guidewire diameter and flow conditions

The introduction of a guidewire creates an additional blockage, and leads to reduced flow and increased pressure drop across the stenosis (Sinha Roy et al., 2006; Ashtekar et al., 2007). Arteries with intermediate stenosis (~ 64-90% area stenosis, or AS) cannot be accurately determined through angiography alone (Kern et al., 2006). Hence, for intermediate range of stenosis, additional functional or hemodynamic assessment is recommended. However, for these cases, guidewire obstruction may lead to misdiagnosis. Another problem affecting clinical diagnosis of stenosis severity is the achievement of maximal hyperemia. Proper evaluation of stenosis severity using FFR and CFR depends on the level of maximal hyperemia. However, inducing a reliable maximal hyperemia has technical difficulties (De Luca et al., 2011; Heusch, 2010; Nair et al., 2011; Pijls and Tonino, 2011). Lately, a few investigators have proposed parameters based on basal condition. These include instantaneous wave-free ratio (Sen et al., 2012), stenosis resistance index (van de Hoef et al., 2012a), and ratio of distal and proximal pressures (Mamas et al., 2010). In the first part of this chapter, variability of FFR, CDP, LFC, and $\tilde{R}_s$ with guidewire diameter (G14 vs. G22) was assessed. The second part of this chapter reports FFR, CDP, LFC, and $\tilde{R}_s$ assessed in basal condition, to present a proof-of-concept analysis of basal-based parameters.

The same methodology used in the previous chapter had been used to obtain the results. The comparison of guidewire diameter was done for the non-MI case, since the variation will be same in the MI case. For the evaluation of basal based parameters, pressure drops at basal condition were obtained from $\Delta\bar{p}-\bar{Q}$ curves at flow rates of 42 ml/min (N1) and 50 ml/min (N2).
4.1 Results

The effect of guidewire diameter on Δ̃rh and CFR is analyzed first. Then FFR, CDP, LFC, and ̃Rh computed from obtained CFR-̃rh curves (Figure 4.2) is reported, followed by a summary of the diagnostic parameters analyzed at basal condition. The introduction of G22 guidewire in the smaller artery of 2.5 mm (N1) with severe stenosis leads to AS greater than 94%. Basal flow may reduce by 20%-80% for such AS (Epstein et al., 1985; Gould et al., 1974). Hence diagnostic parameters assessed for N1 diameter and severe AS may have significant uncertainty. For the same reason, basal parameters have not been reported for this case.

4.1.1 Effect of Guidewire Diameter on CFR, Pressure Drop, and ̃Rh

Pressure drop across a stenosis follows a quadratic behavior Δ̃ = ãQ + b̃Q², where a and b are coefficients related to viscous and momentum losses respectively (Back et al., 1996). The obtained Δ̃-Q curves are shown in Figure 4.1. CFR, Δ̃rh, and ̃Rh obtained are reported in Table 4.1. The variation of ̃Rh measured using G14 and G22 for different levels of AS in two native arterial diameters is shown in Figure 4.3.

Mild Stenosis. Viscous components (units: mmHgml⁻¹min × 10⁻⁴) were 343 (N1) and 208 (N2) with G14, and 353 (N1) and 321 (N2) with G22 (Figure 4.1). Momentum component (units: mmHgml⁻²min⁻² × 10⁻⁴) were 3 (N1) and 2 (N2) with G14, and 5 (N1) and 2 (N2) for G22. The CFR values were 3.4 (N1) and 3.5 (N2) with G14, and 3.2 (N1) and 3.4 (N2) with G22 (Table 4.1). The Δ̃rh values (units: mmHg) were 11.1 (N1) and 9.8 (N2) with G14, and 13.9 (N1) and 11.2 (N2) with G22. The introduction of G14 led to ̃Rh of 0.08 (N1) and 0.06 (N2), and increased to 0.10 (N1) and 0.07 (N2) with G22. The Δ̃rh value for the G22 was higher by 25% in N1 and 14% in N2, when compared with G14.
\[ \Delta P_{N1\_Mild} = 0.0003Q^2 + 0.0343Q \quad R^2 = 0.9970 \]

\[ \Delta P_{N2\_Mild} = 0.0002Q^2 + 0.0208Q \quad R^2 = 0.9985 \]

\[ \Delta P_{N1\_Int} = 0.0014Q^2 + 0.0653Q \quad R^2 = 0.9969 \]

\[ \Delta P_{N2\_Int} = 0.001Q^2 + 0.0358Q \quad R^2 = 0.9997 \]

\[ \Delta P_{N1\_Severe} = 0.0134Q^2 + 0.4039Q \quad R^2 = 1.00 \]

\[ \Delta P_{N2\_Severe} = 0.0029Q^2 + 0.1188Q \quad R^2 = 0.9996 \]

\[ \Delta P_{N1\_Mild} = 0.0005Q^2 + 0.0353Q \quad R^2 = 0.9999 \]

\[ \Delta P_{N2\_Mild} = 0.0002Q^2 + 0.0321Q \quad R^2 = 0.9995 \]

\[ \Delta P_{N1\_Int} = 0.0022Q^2 + 0.1265Q \quad R^2 = 0.9973 \]

\[ \Delta P_{N2\_Int} = 0.0013Q^2 + 0.0577Q \quad R^2 = 0.9999 \]

\[ \Delta P_{N1\_Severe} = 0.0622Q^2 + 1.5197Q \quad R^2 = 0.9998 \]

\[ \Delta P_{N2\_Severe} = 0.0054Q^2 + 0.2435Q \quad R^2 = 0.9997 \]

Figure 4.1: Pressure drop–flow rate curves with 0.014” (G14) guidewire (A) and 0.022” (G22) guidewire (B)
Figure 4.2: CFR-$\bar{p}_{rh}$ curves for G14 guidewire (A) and G22 guidewire (B)
### Table 4.1: Summary of CFR and $\Delta \tilde{p}_h$ (units: mmHg) obtained from the CFR-$\tilde{p}_{rh}$ curve. Also provided is the stenosis resistance $\bar{R}_s$ (units: mmHgml$^{-1}$min$^{-1}$)

<table>
<thead>
<tr>
<th></th>
<th>G14 guidewire</th>
<th>G22 guidewire</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CFR</td>
<td>$\Delta \tilde{p}_h$</td>
</tr>
<tr>
<td><strong>Case A - 2.5 mm (N1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3.4</td>
<td>11.1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.7</td>
<td>24.6</td>
</tr>
<tr>
<td>Severe</td>
<td>1.2</td>
<td>50.8</td>
</tr>
<tr>
<td><strong>Case A - 3.0 mm (N2)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>3.5</td>
<td>9.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2.7</td>
<td>23.5</td>
</tr>
<tr>
<td>Severe</td>
<td>1.9</td>
<td>38.8</td>
</tr>
</tbody>
</table>

**Intermediate Stenosis.** Viscous components (units: mmHgml$^{-1}$min$^{-1} \times 10^{-4}$) were 635 (N1) and 358 (N2) with G14, and 1265 (N1) and 577 (N2) with G22 (Figure 4.1). Momentum components (units: mmHgml$^{-2}$min$^{-2} \times 10^{-4}$) were 14 (N1) and 10 (N2) with G14, and 22 (N1) and 13 (N2) with G22. The CFR values were 2.7 for both N1 and N2 with G14, and 2.2 (N1) and 2.5 (N2) with G22 (Table 4.1). The $\Delta \tilde{p}_h$ values (units: mmHg) were 24.6 (N1) and 23.5 (N2) with G14, and 31.1 (N1) and 27.1 (N2) with G22. The introduction of G14 led to $\bar{R}_s$ of 0.22 (N1) and 0.17 (N2), and increased to 0.33 (N1) and 0.22 (N2) with G22. The $\Delta \tilde{p}_h$ value for the G22 was higher by 26% in N1 and 15% in N2, when compared with G14.

**Severe Stenosis.** Viscous components (units: mmHgml$^{-1}$min$^{-1} \times 10^{-4}$) were 4039 (N1) and 1188 (N2) with G14, and 15197 (N1) and 2435 (N2) with G22 (Figure 4.1). Momentum components (units: mmHgml$^{-2}$min$^{-2} \times 10^{-4}$) were 134 (N1) and 29 (N2) with G14, and 622 (N1)
and 54 (N2) with G22. The CFR values were 1.2 (N1) and 1.9 (N2) with G14, and 0.5 (N1) and 1.5 (N2) with G22 (Table 4.1). The $\Delta \bar{p}_h$ values (units: mmHg) were 50.8 (N1) and 38.8 (N2) with G14, and 61.1 (N1) and 46.6 (N2) with G22. The introduction of G14 led to $\bar{R}_s$ of 1.05 (N1) and 0.40 (N2), and increased to 2.85 (N1) and 0.64 (N2) with G22. The $\Delta \bar{p}_h$ value for the G22 was higher by 20% in both N1 and N2, when compared with G14.

The introduction of a larger diameter guidewire G22 led to increased $\bar{R}_s$ and flow obstruction. The difference between CFR with G14 and G22 introduced was highest in severe stenosis (N1: 58%; N2: 21%). In mild and intermediate stenoses, the maximum differences of CFR were 6% and 19% respectively. Although there was a flow reduction, the larger obstruction at throat with G22 wire led to increased $\Delta \bar{p}_h$ (14%-26%) in all levels of AS.

**Figure 4.3:** Comparison of $\bar{R}_s$, evaluated for different combinations of native arterial diameter and guidewire diameter. Also shown are the minimum differences between two AS levels. The superscript ‘**’ implies uncertainty in values due to high AS.
4.1.2 Effect of Guidewire Diameter on FFR, CDP and LFC

The variations of FFR, CDP, and LFC measured using G14 and G22 for different levels of AS are shown in Figures 4.4, 4.5, and 4.6, respectively. Also shown in these figures are the minimum differences between two AS levels. The superscript ‘*’ in these figures indicates the uncertainty in values due to high AS.

Mild Stenosis. The FFR values were 0.87 (N1) and 0.88 (N2) with G14, and 0.83 (N1) and 0.87 (N2) with G22 (Figure 4.4). Difference in FFR values between G14 and G22 were negligible (< 5%). The CDP values were 11 (N1) and 14 (N2) with G14, and 15 (N1) and 16 (N2) with G22 (Figure 4.5). Difference in CDP values between G14 and G22 was 36% in N1 and 14% in N2. The LFC values were 0.61 (N1) and 0.53 (N2) with G14, and 0.69 (N1) and 0.57 (N2) with G22 (Figure 4.6). Difference in LFC values between G14 and G22 was 13% in N1 and 7.5% in N2.

Intermediate Stenosis. The FFR values were 0.71 (N1) and 0.73 (N2) with G14, and 0.64 (N1) and 0.68 (N2) with G22 (Figure 4.4). Difference in FFR readings between G14 and G22 was 10% in N1 and 7% in N2. The CDP values were 42 (N1) and 56 (N2) with G14, and 70 (N1) and 75 (N2) with G22 (Figure 4.5). Difference in CDP values between G14 and G22 was 67% in N1 and 34% in N2. The LFC values were 0.80 (N1) and 0.63 (N2) with G14, and 1.02 (N1) and 0.74 (N2) with G22 (Figure 4.6). Difference in LFC values between G14 and G22 was 27.5% in N1 and 17.5% in N2.
Severe Stenosis. The FFR values were 0.43 (N1) and 0.56 (N2) with G14, and 0.31 (N1) and 0.48 (N2) with G22 (Figure 4.4). Difference in FFR readings between G14 and G22 was 28% in N1 and 14% in N2. The CDP values were 458 (N1) and 182 (N2) with G14, and 2633 (N1) and 370 (N2) with G22 (Figure 4.5). CDP values with G22 were more than 2 times when compared to values with G14. The LFC values were 0.72 (N1) and 0.94 (N2) with G14, and 1.60 (N2) with G22 (Figure 4.6). The LFC value with G22 was 1.7 times the value with G14.

**Figure 4.4:** Comparison of FFR, evaluated for different combinations of native arterial diameter and guidewire diameter. Also shown are the minimum differences between two AS levels.
Figure 4.5: Comparison of CDP evaluated at different native arterial diameter and guidewire size. A) CDP in mild and intermediate stenosis. B) CDP in intermediate and severe stenosis. Also shown, the minimum difference between two AS levels.
Figure 4.6: Comparison of LFC, evaluated for different combinations of native arterial diameter and guidewire diameter. Also shown are the minimum differences between two AS levels.

The higher $\Delta \tilde{p}_h$ with G22 led to appreciable difference (> 14%) between FFR values measured with G14 and G22 in severe AS. For intermediate AS, FFR values measured by both G14 and G22 were less than 0.75, and were within 10% difference. For mild stenosis, the FFR values measured by G14 and G22 were above 0.75 and were within 5% difference. FFR values of 0.72 ± 0.10 (pre-intervention) and 0.84 ± 0.08 (post-intervention) were measured in a pool of 19 non-infarct patients in a clinical study (Claeys et al., 2001). These patients had diameter stenosis of 54 ± 10% (AS 78 ± 10%) before intervention and 40 ± 10% (AS 64 ± 11%) post intervention. In this study, FFR measured with G14 for intermediate and mild stenoses were
0.72 and 0.88 respectively (Figure 4.4). Therefore, results of the present study and data reported by Claeys et al. were comparable.

The CDP values measured with G14 and G22 were more than 14% and 34% different in mild and intermediate AS, respectively. In severe AS, the CDP obtained with G22 was more than 2 times of the value obtained with G14. Apart from the higher $\Delta p_{h}$ with G22, the reduction of flow also contributed to the difference of CDP values between the two guidewires. The difference in values of LFC evaluated with G14 and G22 were greater than 8% and 17%, for mild and intermediate AS, respectively. In severe stenosis, the LFC with G22 was greater than 1.5 times the value obtained with G14. The higher values of LFC, in case of G22, are due to increased pressure drop. For the similar reason, the $R_s$ measured with G22 were more than values measured with G14 (mild: >16%; intermediate: >29%; severe: by more than 1.5 times).

4.1.3 Basal values of diagnostic parameters

Values of time averaged pressure drop ($\Delta p_{b}$), FFR$_b$, CDP$_b$, LFC$_b$ and $R_s$$_b$ assessed at basal flow (N1: 42 ml/min; N2: 50 ml/min) are summarized in Table 4.2. Subscript ‘b’ denotes basal values.
Table 4.2: Summary of parameters at basal condition

<table>
<thead>
<tr>
<th></th>
<th>G14 guidewire</th>
<th>G22 guidewire</th>
<th>G14 guidewire</th>
<th>G22 guidewire</th>
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<tbody>
<tr>
<td></td>
<td>Δp_b</td>
<td>CDP_b</td>
<td>FFR_b</td>
<td>R_sb</td>
</tr>
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<td><strong>Case A - N1</strong></td>
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<td>23</td>
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</tr>
<tr>
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<td>0.94</td>
<td>0.12</td>
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<tr>
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<td>0.97</td>
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<tr>
<td><strong>Case B - N2</strong></td>
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<tr>
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<td>27</td>
<td>0.98</td>
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<tr>
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<td>0.95</td>
<td>0.09</td>
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<tr>
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<td>233</td>
<td>0.86</td>
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*Mild Stenosis.* The Δp_b values (units: mmHg) were 2.0 (N1) and 1.5 (N2) with G14, and 2.4 (N1) and 2.1 (N2) with G22 (Table 3). The CDP_b values were 23 (N1) and 27 (N2) with G14, and 27 (N1) and 36 (N2) with G22. Difference in CDP_b values between G14 and G22 was 17% in N1 and 33% in N2. The FFR_b values with G14 and G22 were 0.98 and 0.97 respectively. The R sb values (units: mmHg ml⁻¹ min) were 0.05 (N1) and 0.03 (N2) with G14, and 0.06 (N1) and 0.04 (N2) with G22. The R sb values with G22 were more than 20% higher when compared to G14. The LFC_b values were 0.43 (N1) and 0.38 (N2) with G14, and 0.52 (N1) and 0.39 (N2) with G22. Difference in LFC_b values between G14 and G22 was 21% in N1 and 3% in N2.

*Intermediate Stenosis.* The Δp_b values (units: mmHg) were 5.2 (N1) and 4.3 (N2) with G14, and 9.2 (N1) and 6.1 (N2) with G22 (Table 3). The CDP_b values were 62 (N1) and 76 (N2) with G14, and 103 (N1) and 104 (N2) with G22. Difference in CDP_b values between G14 and G22 was 66% in N1 and 37% in N2. The FFR_b values were 0.94 (N1) and 0.95 (N2) with G14, and
0.89 (N1) and 0.93 (N2) with G22. The $\bar{R}_{sb}$ values (units: mmHgml$^{-1}$min) were 0.12 (N1) and 0.09 (N2) with G14, and 0.22 (N1) and 0.12 (N2) with G22. The $\bar{R}_{sb}$ values with G22 were more than 33% higher when compared to G14. The $LFC_b$ values were 0.65 (N1) and 0.54 (N2) with G14, and 0.84 (N1) and 0.63 (N2) with G22. Difference in $LFC_b$ values between G14 and G22 was 29% in N1 and 17% in N2.

Severe Stenosis. The $\Delta\bar{p}_b$ values (units: mmHg) were 40.6 (N1) and 13.2 (N2) with G14, and 25.7 (N2) with G22 (Table 3). The $CDP_b$ values were 484 (N1) and 233 (N2) with G14, and 435 (N2) with G22. $CDP_b$ measured by G22 was 1.8 times when compared to values with G14. The $FFR_b$ values were 0.54 (N1) and 0.86 (N2) with G14, and 0.71 (N2) with G22. The $\bar{R}_{sb}$ values (units: mmHgml$^{-1}$min) were 0.97 (N1) and 0.26 (N2) with G14, and 0.51 (N2) with G22. The $\bar{R}_{sb}$ was 2 times higher with G22 when compared to G14. The $LFC_b$ values were 0.70 (N1) and 0.83 (N2) with G14, and 1.48 (N2) with G22. The $LFC_b$ with G22 was approximately 1.8 times the value obtained with G14.

$CDP_b$ had a wide and non-overlapping range for different levels of AS (mild: 23-36; intermediate: 62-104; severe: >233). $\bar{R}_{sb}$ values were reduced in magnitude but had ranges (mild: 0.03-0.06; intermediate: 0.09-0.22; severe: >0.26) that were close to each other. $FFR_b$ also had ranges (mild: 0.97-0.98; intermediate: 0.89-0.95; severe: 0.54-0.86) that may be difficult to delineate. Due to its formulation based on fundamental fluid mechanics principle, the values of $LFC_b$ showed an increasing trend with increasing severity of stenosis (mild: 0.38-0.52; intermediate: 0.54-0.84; severe: >0.70). $FFR_b$, $LFC_b$, and $\bar{R}_{sb}$ values had very small differences between mild and intermediate AS, which could lead to diagnostic uncertainty. The $CDP_b$ values
varied considerably with guidewire (mild: >17%; intermediate: >36%; severe: by ~1.8 times). The $R_{sb}$ showed similar variation in values between G14 and G22 (mild: ~20%; intermediate: ~33%; severe: ~2 times). Values of $LFC_b$ also varied considerably between two guidewires (mild: <25%; intermediate: >17%; severe: by 1.8 times). Difference in $FFR_b$ evaluated with G14 and G22 were negligible (<5%) in mild and intermediate stenosis, and appreciable (17%) in severe stenosis. A recent study (van de Hoef et al., 2012a) reported a $\Delta p_b$ of 5 mmHg (range: 2–9 mmHg) for a pool of 210 patients with diameter stenosis of 52 ± 9 % (AS ~ 77 ± 9 %) using G14. A study on $FFR_b$ (Mamas et al., 2010) showed values less than 0.85 corresponded to $FFR < 0.75$. The results from these studies compared well with the results presented here.

4.2 Discussion

The results from the in-vitro experiment, coupled with pressure-flow relationship from human data, were used to analyze the effect of guidewire diameter on diagnostic parameters. Diagnostic parameters were also evaluated at basal condition. However, it must be realized that there is a limitation to the analysis at severe stenosis for G22 cases. This was because of the high obstruction at the throat, which could change basal flow rate and lend uncertainty to hyperemic results.

Variation of diagnostic parameters with guidewire diameter:

In severe stenosis, FFR values were considerably lower (~14%) in G22 than in G14 due to high obstruction effect. However, FFR values differed little (<10%) for mild and intermediate stenoses. FFR was below 0.75 for intermediate and severe stenoses, irrespective of the
guidewire used. A FFR lower than 0.75 leads to intervention. Hence, from a diagnostic point of view there was no difference between FFR measured by G14 and G22.

The lower CFR obtained with G22 coupled with higher \( \Delta \tilde{p}_h \) (~20%), led to an appreciable difference of CDP values measured with G14 and G22 (mild: >14%; intermediate: >34%; severe: >2 times). This may be attributed to the lower upstream dynamic pressure in an artery due to obstruction effect. The CDP values between two AS levels had a difference of order greater than 10, and had a wide range (mild: 11-16; intermediate: 42-75; severe: >182). Hence, CDP allowed better delineation of stenosis severity irrespective of native arterial diameter and guidewire size.

The LFC values varied with guidewire diameter (mild: >8%; intermediate: >17%; severe: by 1.5 times). Thus, LFC increased with stenosis severity for the clinically relevant cases of mild and intermediate stenosis. For example, LFC for 3mm (N2) diameter artery increased from 0.53 (mild) to 0.63 (intermediate) with G14, and 0.57 to 0.74 with G22. Similar trend was observed for 2.5 mm (N1) arterial model. Therefore, LFC showed an increasing trend from mild to intermediate stenosis severity.

The values of \( \tilde{R}_s \) also showed an increasing trend with stenosis severity. For example, \( \tilde{R}_s \) for 3 mm (N2) diameter artery increased from 0.06 (mild) to 0.17 (intermediate) with G14, and 0.07 to 0.22 with G22. Similar trend was observed in 2.5 mm (N1) arterial model. Hence, although the newer parameters show variability with guidewire diameter, they have an increasing trend with stenosis severity for the clinically relevant cases of mild and intermediate stenosis. The severe stenosis case is expected to be diagnosed through standard-of-care imaging method.
**Coronary diagnostic parameters at basal condition**

Basal parameters were evaluated at 42 ml/min (N1) and 50 ml/min (N2). However, basal blood flow varies with metabolic demand and factors such as age, anemia, contractility, hypertrophy etc. (Czernin et al., 1993; Hoffman, 1984; Klocke, 1987; Wilson et al., 1987). With variation of basal flow, $\Delta \bar{p}_b$ is also expected to vary. For $\bar{R}_{sb}$, LFC$_b$ and FFR$_b$, the differences between mild and intermediate AS were small, and could lead to diagnostic uncertainty. The CDP$_b$ values between two AS levels had a difference of order greater than 10, and had a wide range (mild: 23-36; intermediate: 62-104; severe: >233). Ranges of CDP evaluated at hyperemia and basal condition overlapped for a given AS, and allowed better delineation of stenosis severity. Thus, CDP could be used under basal condition and without hyperemia.
5 Conclusions

This study aimed at comparing conventional coronary diagnostic parameter FFR with newly developed parameters such as CDP, LFC, and $\tilde{R}_s$. The study investigated whether the newly developed parameters had an advantage in areas where FFR failed to diagnose stenosis severity. Four major issues were addressed. Firstly, the influence of diameter was investigated, followed by an assessment with variation in vasculature status. The latter is an important comparison, since it is a topic of current debate, and this analysis adds to the pool of data currently available. The impact of a newly designed guidewire on the diagnostic parameters was also tested. Another important aspect of this study was to present a proof-of-concept analysis for basal based parameters.

In chapter 3, coronary diagnostic parameters were investigated for variation with diameter and vascular condition in an in-vitro experiment. With a 0.014” (0.35 mm) guidewire inserted, the FFR values were similar between the two diameters N1 and N2 for the mild and intermediate stenosis. However, there was variability (> 20%) between N1 and N2 for severe cases. The variability of arterial diameter will not influence diagnosis since functional assessment of stenosis severity is done only for mild to intermediate cases.

A comparison of stenosis with and without presence of MI was investigated. Vascular condition altered the hyperemic flow and consequently affected the pressure drop across stenosis. Variability in vascular condition led to overestimation of FFR for MI (difference in values; mild: ~8 %, intermediate: ~20%, severe: ~30 %) due to reduction in flow. However, FFR remained below the clinical cutoff of 0.75 for severe stenosis. Findings confirm that the variability in vascular condition may affect clinical diagnosis of a stenosis.
CDP varied with both diameter and vasculature status. However, the non-overlapping ranges of CDP (mild: 11-19; intermediate: 42-62; severe: 182-201) allowed better classification of the stenosis severities irrespective of the variation in diameter and vasculature status. The LFC varied considerably between native arterial diameter (mild: ~15%; intermediate: ~25%; severe: ~22%), but somewhat (<10%) between vascular conditions in mild and intermediate AS for a given native arterial diameter. LFC maintained an increasing trend from mild to intermediate stenosis (mild: 0.46-0.61; intermediate: >0.60). Despite its variability with native arterial diameter and vasculature status, $\bar{R}_s$ maintained an increasing trend from mild to intermediate stenosis (mild: 0.04-0.08; intermediate: 0.12-0.22).

In chapter 4, assessment indicated that FFR is reliable for mild and intermediate stenosis even with a change in guidewire diameter. This was because the variation was within 10% between the two guidewire diameters. Although CDP varied considerably with guidewire diameter, it had a wide range (mild: 11-16; intermediate: 42-75; severe: >182), and delineated stenosis severities. Similarly, LFC and $\bar{R}_s$ showed considerable variability with guidewire diameter. However, an increasing trend with stenosis severity, for the clinically relevant cases of mild and intermediate stenosis, was observed for the two parameters.

Based on the findings from chapter 3 and 4, the diagnostic parameters’ ranges for a combined pool of varying native arterial diameter, guidewire size, and vasculature status may be evaluated. FFR ranges varied from 0.83-0.96 (mild), 0.64-0.86 (intermediate), and 0.31-0.73 (severe). The analysis provided in this study confirms the argument that FFR is sufficient to delineate severe stenosis irrespective of varying clinical scenarios. However, the analysis also demonstrates FFR’s shortcoming in intermediate stenosis cases. This is in line with observations by recent investigators.
The values of LFC followed the expected increasing trend from mild to intermediate stenosis for a given native diameter (mild: 0.46-0.69; intermediate: >0.06). This is because, with increasing stenosis severity, pressure drop coefficient reaches values close to “Borda-Carnot” head loss. With regards to diagnostic ability, a similar increasing trend from mild to intermediate stenosis, was observed in $\bar{R}_s$ (mild: 0.04-0.10; intermediate: 0.12-0.33). CDP’s formulation normalized change in arterial diameter, guidewire size, and vasculature status. For the combined pool, the CDP ranges were well segregated (mild: 11-19; intermediate: 42-75; severe: >182). The order of difference between two stenosis levels allowed better delineation of stenosis severities. Based on these findings, CDP holds promise for better functional assessment of stenosis severity in a clinical setting, and could overcome the shortcomings of conventional diagnostic parameters.

Chapter 4 contained analysis of parameters assessed at basal condition. For $\bar{R}_{sb}$, $\bar{c}_b$, and FFR$_b$, the differences between mild and intermediate AS were small, and could lead to diagnostic uncertainty. The CDP$_b$ values between two AS levels had a difference of order greater than 10, and had a wide range (mild: 23-36; intermediate: 62-104; severe: >233). There was an overlap between basal and hyperemic ranges for a given level of stenosis severity. Thus, CDP could be used under basal condition and without hyperemia.

Future work. The analysis provided in this study points to the possibility of CDP as a new tool, which could eliminate the disadvantages of present coronary diagnostic parameters. However, there are many more variations in clinical conditions. For example, the presence of multiple stenoses could be investigated (Pijls, 2003). Although in-vitro studies allow a controlled environment for analysis, it is by no means a substitute for clinical experiments. The
promising results using CDP, both at basal and hyperemic conditions, could be the basis for future clinical trials.
References


APPENDIX

Images of reconstructed test section geometry

**Figure A.1:** An example of images of a test section with a microscope (left), and micro-CT scan reconstruction (right).

**Figure A.2:** An example of stl image file from the reconstruction, used for measurement of dimensions in SolidWorks®. Image reconstruction software used: Mimics®.
Uncertainty Analysis of diagnostic parameters

Pressure measurements are taken using a DSA-3207 pressure scanner which directly collects data to an output file on the computer. Flow readings are taken using a Transonics inc. flow probe connected to a data acquisition system with a trigger that allows simultaneous collection of pressure and flow data. A sample calculation to find the uncertainty in FFR, CDP, LFC, and Rs is shown.

Once the stenosis test section is connected to the pressure ports, an initial data at resting condition, with zero flow, is taken. Any bias in the pressure readings and flow readings taken during the experiment was eliminated by subtracting these initial values from the final values. The only remaining uncertainty is due to the precision error of the pressure scanner and flow-meter. From the manufacturer’s data, the precision errors for pressure and flow measurement are 0.2%, and 4%, respectively.

Using uncertainty analysis from Moffat (1988), total uncertainty $U$ is given by:

$$U = (B_U^2 + P_U^2)^{1/2}$$

where $B$ is the bias error and $P$ is the precision error.

If the relationship between the experimental results, $r$, and measured quantities, $a_i$, is of the form $r = f(a_1, a_2, a_3, a_4 \ldots \ldots, a_n)$. The propagation of uncertainty to the calculated results can be determined by the following [Kline and McClintock, 1953]:

$$(\delta r)^2 = \sum_{i=1}^{n} \left[ \frac{\partial r}{\partial a_i} \delta a_i \right]^2$$

---------- (A)
Uncertainty calculation for CDP:

\[ CDP = \frac{(P_a - P_r) A_e^2}{0.5 \rho Q^2} \]  

(B)

Since, \( P_a \) is kept constant, using the equations (A) and (B), the precision error \( P_{CDP} \) would be

\[
\left( \frac{P_{CDP}}{CDP} \right)^2 = \left( \frac{\partial CDP}{\partial P_r} \right)_r^2 + \left( \frac{\partial CDP}{\partial Q} \right)_r^2 = \left( -\frac{1}{P_a - P_r} P_{Pr} \right)^2 + \left( -\frac{2}{Q} P_Q \right)^2
\]

Consider the following result:

Vascular condition: non-MI; Arterial diameter: 2.5 mm; Guidewire diameter: 0.014”;

Severity: Severe; Pressure drop: 50.77 mmHg

Substituting the values, we get,

\[
\left( \frac{P_{CDP}}{CDP} \right) = 0.0017
\]

Thus, the precision error \( P_{CDP} = 0.17\% \) CDP. Since the bias error is 0, uncertainty in CDP,

\[ U_{CDP} = \pm 0.17\% \]

The uncertainties in measurement for all the results reported were under 0.4%.

Uncertainty calculation for FFR:

\[ FFR = \frac{P_r}{P_a} \]  

(C)

Since, \( P_a \) is kept constant, using the equations (A) and (C), the precision error \( P_{FFR} \) would be

\[
\left( \frac{P_{FFR}}{FFR} \right)^2 = \left( \frac{\partial FFR}{\partial P_r} \frac{P_{Pr}}{FFR^2} \right)^2 = \left( \frac{1}{P_r} P_{Pr} \right)^2
\]
Consider the following result:

Vascular condition: non-MI; Arterial diameter: 2.5 mm; Guidewire diameter: 0.014”; Severity: Severe; Pressure drop: 50.77 mmHg

Substituting the values, we get,

\[
\left( \frac{P_{\text{FFR}}}{\text{FFR}} \right) = 5.2 \times 10^{-5}
\]

Thus, the precision error \( P_{\text{FFR}} = 0.005\% \) FFR. Since the bias error is 0, uncertainty in FFR, \( U_{\text{FFR}} = \pm 0.005\% \). The uncertainties in measurement for all the results reported were under 0.007%.

Uncertainty calculation for LFC:

\[
LFC = \frac{1 - k}{\sqrt{\frac{(P_a - P_r)A_m^2}{0.5 \rho Q^2}}}
\]

Since, \( P_a \) is kept constant, using the equations (A) and (D), the precision error \( P_{\text{LFC}} \) would be

\[
\left( \frac{P_{\text{LFC}}}{LFC} \right)^2 = \left( \frac{\partial LFC}{\partial P_r} P_r \right)^2 + \left( \frac{\partial LFC}{\partial P_Q} P_Q \right)^2 = \left( \frac{2}{P_a - P_r} P_P \right)^2 + \left( \frac{1}{Q} P_Q \right)^2
\]

Consider the following result:

Vascular condition: non-MI; Arterial diameter: 2.5 mm; Guidewire diameter: 0.014”; Severity: Severe; Pressure drop: 50.77 mmHg

Substituting the values, we get,
Thus, the precision error $P_{LFC} = 0.08\%$ LFC. Since the bias error is 0, uncertainty in LFC, $U_{LFC} = \pm 0.08\%$. The uncertainties in measurement for all the results reported were under 0.2%.

Uncertainty calculation for $R_s$:

\[
R_s = \frac{(P_a - P_r)}{Q} \quad (E)
\]

Since, $P_a$ is kept constant, using the equations (A) and (E), the precision error $P_{Rs}$ would be

\[
\left( \frac{P_{Rs}}{R_s} \right)^2 = \left( \frac{\partial R_s}{\partial P_r} \frac{P_r}{R_s^2} \right)^2 + \left( \frac{\partial R_s}{\partial Q} \frac{Q}{R_s^2} \right)^2 = \left( \frac{1}{P_a - P_r} P_r \right)^2 + \left( \frac{1}{Q} P_Q \right)^2
\]

Consider the following result:

Vascular condition: non-MI; Arterial diameter: 2.5 mm; Guidewire diameter: 0.014”;

Severity: Severe; Pressure drop: 50.77 mmHg

Substituting the values, we get,

\[
\left( \frac{P_{Rs}}{R_s} \right) = 0.0008
\]

Thus, the precision error $P_{Rs} = 0.08\%$ $R_s$. Since the bias error is 0, uncertainty in $R_s$, $U_{Rs} = \pm 0.08\%$. The uncertainties in measurement for all the results reported were under 0.1%.