Influence of coronary collateral flow on coronary diagnostic parameters: An in vitro study

Srikara Viswanath Peukhanna, Lloyd H. Back, Rupak K. Banerjee

Department of Mechanical Engineering, University of Cincinnati, Cincinnati, OH, United States
Jet Propulsion Laboratory, California Institute of Technology, Pasadena, CA, United States
Department of Biomedical Engineering, University of Cincinnati, Cincinnati, OH, United States

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Abstract

Functional severity of coronary stenosis is often assessed using diagnostic parameters. These parameters are evaluated from the combined pressure and/or flow measurements taken at the site of the stenosis. However, when there are functional collaterals operating downstream to the stenosis, the coronary flow-rate increases, and the pressure in the stenosed artery is altered. This effect of downstream collaterals on different diagnostic parameters is studied using a physiological representative in vitro coronary flow-loop.

The three diagnostic parameters tested are fractional flow reserve (FFR), lesion flow coefficient (LFC), and pressure drop coefficient (CDP). The latter two were discussed in recent publications by our group (Banerjee et al., 2007, 2008, 2009). They are evaluated for three different severities of stenosis and tested for possible misinterpretation in the presence of variable collateral flows. Pressure and flow are measured with and without downstream collaterals. The diagnostic parameters are then calculated from these readings.

In the case of intermediate stenosis (80% area blockage), FFR and LFC increased from 0.74 to 0.77 and 0.58 to 0.62, respectively, for no collateral to fully developed collateral flow. Also, CDP decreased from 47 to 42 for no collateral to fully developed collateral flow. These changes in diagnostic parameters might lead to erroneous postponement of coronary intervention. Thus, variability in diagnostic parameters for the same stenosis might lead to misinterpretation of stenosis severity in the presence of operating downstream collaterals.

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1. Introduction

Left coronary artery (LCA) stenosis or left anterior descending (LAD) stenosis is often one of the main causes of heart failure and ischemia. Anatomic (angiography) endpoints are being widely used to assess the severity of the stenosis, but these often fail to delineate the functional (hemodynamic) severity of the stenosis (White et al., 1984). Functional diagnostic parameters are used to give a better assessment of the severity of coronary stenosis (Pijls et al., 1993; Spaan et al., 2006; Kern et al., 2006). They are calculated from pressure and flow measurements performed in the coronary arteries.

Three diagnostic parameters were evaluated in this study. The first one, fractional flow reserve (FFR), defined as the ratio of pressures distal and proximal to the stenosis at hyperemia (flow through artery at maximum vasodilation), is currently being used in clinical practice. Based on widely held clinical trials, a cut-off value of 0.75 was established for single vessel coronary stenosis (Pijls et al., 1993, 1995a, b; Lederman et al., 1997) to make decisions on coronary interventions. Studies have shown that FFR < 0.75 is specific for ischemia, whereas FFR > 0.80 essentially rules out significant ischemia. The decision to use a cut-off point of 0.80, instead of the traditional 0.75 for coronary intervention, is based on the clinical scenario suggesting ischemia (Fearon et al., 2007; Silber et al., 2005; Pijls, 2003). For single vessel coronary stenosis, if FFR < 0.75, coronary intervention is recommended, and if FFR > 0.75, a coronary intervention is deferred. The other two parameters, pressure drop coefficient (CDP) and lesion flow coefficient (LFC), are formulated based on fundamental fluid dynamic principles. These two diagnostic parameters have been published and are being investigated for clinical use (Banerjee et al., 2007, 2008, 2009; Sinha Roy et al., 2008).

However, these studies did not account for the effect of different resistances present in the coronary circuit, e.g. existence of downstream collateral flows, on the diagnostic parameters.
1.1. Coronary collaterals

Collateral arteries are small interconnections between a healthy and stenosed artery. They are normally either non-existent or non-functional, but become functional when there is a recurrent or severe stenosis in primary coronary arteries such as LCA, LAD, left circumflex (LCX) and right coronary artery (RCA). Functional collaterals supply blood and reperfuse the microvasculature downstream to the stenosed artery (Rentrop et al., 1988; Sasayama and Fujita, 1992; Rockstroh and Brown, 2002; Koerselman et al., 2003; Fujita and Tambara, 2004).

The increase in downstream flow causes an elevation in the pressure downstream to the stenosis. The increased pressure, in turn, causes a change in the diagnostic parameters. This often leads to a misinterpretation of the functional severity of the coronary stenosis and could lead to misdiagnosis. The extent of possible misinterpretation is evaluated in three different stenosis severities, in combination with three different diameters of downstream collaterals, using an in vitro experimental set-up.

2. Methods

To evaluate the effect of collaterals on the diagnostic parameters, a physiological representative in vitro experimental flow-loop is used to obtain pressure and flow readings for different collateral flows and different stenosis severities.

2.1. Experimental set-up

For this study, the flow-loop used in our previous studies (Ashtekar et al., 2007; Banerjee et al., 2008) is modified to include the collateral flow. The selection of collateral diameters and the flow-loop is based on previous in vitro experimental studies on coronary network involving collaterals (Pijls et al., 1993, 1995a, b; Kern et al., 1995; Seiler et al., 1998, 1999; Wahl et al., 2000; Pohl et al., 2001; Werner et al., 2001; Billinger et al., 2002).

Three different degrees of blockages made of Lexan material representing true stenosis geometry are used: 90% area blockage (severe stenosis), 80% area blockage (intermediate stenosis) and 64% area blockage (moderate stenosis). To represent various levels of collateral flow, three different diameters of collaterals are used, 3 mm diameter: fully developed (FD)-collateral, 2 mm diameter: intermediately developed (ID) collateral and 1.5 mm diameter: partially developed (PD)-collateral. Each stenosis severity is tested for four conditions: no collateral flow (NC), PD, ID and FD conditions.

The in vitro experimental set-up is shown in Fig. 1A. The flow-loop is similar to the coronary flow network having LCA, LCX and LAD. Non-Newtonian blood analog fluid, a mixture of 35% glycerin, 65% water and 0.035% Xanthum gum, with a density of 1.05 g/cm$^3$ is used to mimic the shear-thinning properties of blood. A Harvard apparatus pulsatile pump, representing left ventricle, is used to impart the required hyperemic (maximum) flow-rate ($\sim$200 ml/min) and desired heart-rate. A conduit representing the aorta originates from the pump; it bifurcates into two arteries: one supplying fluid for systemic circulation and the other to the LCA. The LCA bifurcates into the LCX and the LAD. The three stenosis (severe, intermediate, and moderate) test sections are evaluated in the LAD, with downstream collaterals operating from the LCX to the LAD. Latex rubber tubing was used for all coronary arteries. A compliance chamber is used before the LCA-bifurcation to maintain pressure levels similar to the physiological values.

![Fig. 1.](A) In vitro experimental flow-loop showing physiologic representation of coronary artery set-up. (B) Schematic diagram showing the flow through stenotic and collateral conduits.)
total flow (by an ultrasound flow-cuff before the collateral from the LCX joins the LAD; and after the collateral from the LCX joins the LAD. Collateral flow transducers, placed as shown in Fig. 1B. Sixteen pressure readings are taken in the LAD: flow through the stenosed artery ($Q_s$), obtained by an ultrasound flow-cuff before the collateral from the LCX joins the LAD; and total flow ($Q_T$), measured by a transit-time ultrasound internal flow meter (Transonics Inc.) after the collateral from the LCX joins the LAD. Collateral flow ($Q_c$) is computed as the difference between $Q_T$ and $Q_s$, i.e., $Q_c = Q_T - Q_s$.

To check the uniqueness and consistency of the input flow pulse, the flow meter is connected to the LAD before the stenosis section (Fig. 2A). Two flow pulses are recorded, with the collateral channel closed and with the fully developed operating collateral (Fig. 2B). The flow profiles in Fig. 2B for both the cases are identical, which shows that a consistent input flow pulse is maintained for all test conditions.

### 2.3. Diagnostic parameters

The flow and pressure values measured experimentally are post-processed using Microsoft Visual Basic macros and analyzed in Microsoft Excel. Distal (3 cm downstream of stenosis; Port no. 1) and proximal pressures (3 cm upstream of stenosis; Port no. 1) are selected from the sixteen pressure values obtained across the stenosis. The three parameters FFR, CDP, and the LFC are computed based on the formulae mentioned below.

#### 2.3.1. FFR

The FFR is defined as the ratio of distal pressure to the proximal pressure in the stenosis at hyperemia (maximum vasodilation) (Pijls et al., 1995a, b):

$$\text{FFR} = \frac{P_d - P_v}{P_d - P_m}$$

at hyperemia

$P_d$ is the pressure proximal to the stenosis; $P_v$, the venous pressure $\approx 0$ mmHg; and $P_m$ the pressure distal to the stenosis.

As the severity of the blockage increases, the pressure value distal to the stenosis decreases and hence FFR decreases. As mentioned previously, a cut-off value of 0.75 differentiates between severe and moderate blockages. If FFR $> 0.75$, the blockage is considered to be moderate, and coronary intervention is deferred. If FFR $< 0.75$, the blockage is considered severe, and a coronary intervention is recommended. Indecision might result when the value of FFR is near the cut-off value of 0.75, which normally occurs in the case of intermediate stenosis, particularly if microvascular disease coexists.

#### 2.3.2. CDP

The CDP and the LFC are defined based on the fundamental fluid dynamics. The functional parameter CDP depends on trans-stenotic pressure drop and velocity value in the proximal region of the stenosis for assessing the stenosis severity. (Fig. 3, Banerjee et al., 2007). CDP is defined as:

$$\text{CDP} = \frac{\Delta p}{0.5 \rho U_m^2}$$

where $\Delta p$ is the pressure drop across the stenosis, dynes/cm$^2$; $U_m = Q_c/A_t$, the velocity proximal to the stenosis, cm/s; $A_t$ the proximal lumen area, cm$^2$; and $\rho$ the density of the fluid, gm/cm$^3$.

As stenosis severity increases, the value of distal pressure as well as flow (velocity) decreases, and thus, $\Delta p$ increases. So, an increase in the value of CDP is expected as stenosis severity increases.

#### 2.3.3. LFC

The LFC (Banerjee et al., 2007) is a normalized parameter with values ranging from 0 to 1 and could also be useful, like CDP, under clinical setting. It combines the lesion geometry (Fig. 3), i.e. anatomical endpoints (Wilson et al., 1988; Banerjee et al., 2003), and pressure and flow measurements, i.e. functional endpoints. It is defined using the velocity value in the throat region:

$$\text{LFC} = \frac{1 - k}{\sqrt{\Delta p/(0.5 \rho U_m^2)}}$$

where $k = A_m/A_t$, $A_m$ is the stenosis throat area, cm$^2$ and $U_m = Q_c/A_t$, the velocity in the throat region, cm/s.

The value of LFC is expected to increase as the severity of the stenosis increases.

### 3. Results

The effect of collateral flow on pressure and flow readings is analyzed first. Then the diagnostic parameters computed from these readings are checked for misinterpretation. All the flow, pressure, and diagnostic parameter values are time-averaged from transient quantities obtained from three data sets for hyperemic flow condition.

#### 3.1. Effect of collaterals on flow and pressure

As the diameter of the collateral conduit increases, the value of collateral flow ($Q_c$) increases. This increase in $Q_c$ causes an increase in total flow, $Q_T = Q_s + Q_c$. Increased flow downstream of the stenosis leads to a decrease in the pressure drop ($\Delta p$) across the stenosis. The effect of increasing collateral diameters on $Q_c$ and $Q_T$ for the three degrees of stenosis is shown in Fig. 4A and B, respectively. The effect of different collateral flows on $\Delta p$ is shown in Fig. 5. The details of the effect of collateral flows in each degree of stenosis are discussed below.
3.1.1. Severe stenosis

The hyperemic flow value \( Q \) when there is no collateral flow \( (Q_c=0) \) is 116 ml/min. The collateral flow elevates from 12 to 32 ml/min, a 2.7 fold increase, as the diameter of the collateral conduit increases from partially developed \( (D=1.5 \text{ mm}; \text{PD}) \) to fully developed \( (D=3.0 \text{ mm}, \text{FD}) \) condition (Fig. 4A). Increase in \( Q \) contributes to the total out-flow in the artery. So, the value of \( Q \) elevates from 128 to 147 ml/min, a 15% increase, as the collateral flow increases from PD to FD state (Fig. 4B). Increased downstream pressure due to elevated flow leads to a reduction in \( \Delta p \) across the stenosis. The \( \Delta p \) value decreases from 51 to 46 mmHg, an 11% decrease, as the collateral flow increases from PD to FD state (Fig. 5).

3.1.2. Intermediate stenosis

The hyperemic flow value when \( Q_c=0 \) is 148 ml/min. The value of \( Q \) increases from 6 to 17 ml/min, a 3 fold increase, as the collateral conduit increases from PD to FD condition (Fig. 4A). Thus, the value of \( Q \) elevates from 154 to 165 ml/min, a 7% increase, as the collateral flow increases from PD to FD state (Fig. 4B). Similarly, as the collateral flow elevates from PD to FD state, the value of \( \Delta p \) decreases from 24 to 22 mmHg, a 9% decrease (Fig. 5).

3.1.3. Moderate stenosis

The hyperemic flow value when \( Q_c=0 \) is 178 ml/min. As the collateral conduit increases from PD to FD condition, the collateral flow value increases from 2 to 6 ml/min, a 3 fold increase (Fig. 4A). So, the value of \( Q \) correspondingly increases from 179 to 184 ml/min as the collateral flow elevates from PD to FD condition, a 3% increase (Fig. 4B). The value of \( \Delta p \), therefore, decreases from 11 to 10 mmHg as the collateral flow elevates from PD to FD state, a 10% decrease (Fig. 5).

3.2. Effect of collaterals on diagnostic parameters

The trend followed by the parameters is dependent upon the way they are defined. In a particular stenosis, with increasing downstream collateral flow, the values of FFR and LFC increase while the value of CDP decreases.

3.2.1. Effect of collaterals on FFR

3.2.1.1. Severe stenosis.

The effect of increasing downstream collateral flow on FFR is shown in Fig. 6. The value of FFR when \( Q_c=0 \) is 0.49. This value increases to 0.51 and 0.55, respectively, as the collateral flow elevates from PD \( (D=1.5 \text{ mm}) \) to FD \( (D=3 \text{ mm}) \) state. This increase in parameter value in the presence of downstream collaterals may not lead to a misinterpretation of stenosis severity, as the FFR values are less than the cut-off value of 0.75.

3.2.1.2. Intermediate stenosis.

The value of FFR when \( Q_c=0 \) is 0.74. It increases to 0.75 and further to a value of 0.77 as the collateral flow increases. Cut-off value of FFR is 0.75.
flow elevates from PD to FD condition. The values, as shown, vary along the cut-off value of 0.75. This might lead to a possible misdiagnosis, as the clinician might defer coronary intervention based on the fully developed collateral value of 0.77 while the severity of the stenosis remains the same.

3.2.1.3. Moderate stenosis. The value of FFR when $Q_c=0$ is 0.87. This value increases to 0.88 and 0.89 as the collateral flow elevates from PD to FD state. However, this increase might not lead to a misinterpretation as the values are all above the cut-off value of 0.75.

3.2.2. Effect of collaterals on CDP and LFC

CDP and LFC are computed using the pressure, flow, and lesion geometry values (known for stenosis test sections). Cut-off values for these parameters have yet to be determined as clinical evaluation is under investigation. Fig. 7 shows the change in CDP, and Fig. 8 shows the variation of LFC in the presence of varying collateral flows.

3.2.2.1. Severe stenosis. The value of CDP decreases as the collateral flow increases. The typical value of CDP when $Q_c=0$ is 177. It decreases to 166 and then to 149 as the collateral flow changes from PD to FD condition. The value of LFC, on the other hand, elevates as the collateral flow increases. The no collateral flow value is 0.61. It increases to 0.63 and then to 0.67 as the collateral flow elevates from PD to FD condition.

3.2.2.2. Intermediate stenosis. The typical value of CDP when $Q_c=0$ is 47. It decreases to 46 and then to 42, as the collateral flow increases from PD to FD state. Similarly, the value of LFC for no collateral flow is 0.58. It increases to 0.59 and then to 0.63 as the collateral flow increases from PD to FD condition.

3.2.2.3. Moderate stenosis. When $Q_c=0$, the value of CDP is 15.4. As the collateral flow increases from PD to FD state, the value decreases from 14.9 to 13.3. Also, the value of LFC when $Q_c=0$ is 0.47. This value increases from 0.48 to 0.51 as the collateral flow elevates from PD to FD condition. The above results show that a misinterpretation might result even in the case of the CDP and LFC. Table 1 shows the % change in diagnostic parameters with variable collateral flow and % area stenosis.

4. Discussion

The values of FFR, CDP, and LFC with no collateral, obtained in this study were compared with the previous works (Pijls et al., 1995a, b; Sinha Roy et al., 2008; Banerjee et al., 2008). These previous studies do not consider the effect of downstream collateral flow on the diagnostic parameters. Hence, the present study focuses on the effect of downstream collaterals on FFR, CDP, and LFC in an in vitro set-up.

The variation of diagnostic parameters in the presence of collaterals might lead to some misinterpretation in the case of intermediate stenosis unless a prior knowledge of collateral flow is available. A lack of knowledge of collateral conduits and its effect on FFR might wrongly lead to the postponement of coronary interventional procedures, particularly in patients with intermediate stenosis. Further, the variability in CDP and LFC might also lead to misinterpretation of stenosis severity due to the presence of downstream collaterals.

Other resistances, such as abnormal microvasculature, are difficult to simulate in an in vitro set-up. Similarly, guidewire obstruction effect (Back et al., 1996; Banerjee et al., 1999, 2008 and Roy et al., 2005) and the eccentricity of guidewires and catheters also influence pressure and flow measurements. In addition, dynamic factors, such as the heart-rate, contractility, and left ventricular pressure of the patient might also influence the diagnostic parameters. The above-mentioned factors, which cannot be simulated in an in vitro set-up, need to be evaluated under clinical setting for better diagnosis of coronary stenosis.

This study assumes the existence of single collateral of variable sizes, a priori. The collateral growth and development is a complex phenomenon involving diverse biological factors and pathways. Many factors such as the severity and recurrence of stenosis influence collateral development and growth in humans (Rentrop et al., 1988; Carmeliet, 2000; Fujita and Tambara, 2004; Schaper and Ito, 1996; D’Amore and Thompson, 1987). Such factors have not been considered in this study. There might be multiple operating collaterals, which could further elevate the collateral flow. These factor needs to be further studied in a bench top and clinical setting.

If extended for in vivo and clinical evaluation, assessment of the effect of collateral flow on diagnostic parameters might aid in better diagnosis of coronary stenosis. There are a few methods available for quantification of coronary collaterals under clinical setting. Coupled with myocardial contrast echocardiography (Sabia et al., 1992; Vogel et al., 2006) or Thallium-201 SPECT imaging data (Verani, 1992; Chouraqi et al., 2003), the diagnostic parameters discussed here might help in better understanding of...
the effect of downstream collaterals; thus reducing misinterpre-
tation.

5. Conclusion

The FFR, CDP, and LFC changed in the presence of functional
downstream collaterals. CDP decreased, whereas FFR and LFC
increased as the collateral flow increased, for the same severity
of stenosis. In the case of intermediate stenosis, a higher value of FFR
in the presence of collateral flow (value of 0.77) could result in
misinterpretation and possible misdiagnosis based on the cut-off
value of 0.75. Clinical evaluation of the influence of downstream
collateral flow on diagnostic parameters will aid in improved
determination of coronary stenosis severity.

Conflict of interest statement

The authors have no conflict of interest.

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