Functionaland Anatomical Diagnosis of Coronary Artery Stenoses

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Background. Functional/physiological evaluation of coronary artery stenoses may be more important than anatomical measurements of severity. Optimization of thresholds for stenosis intervention and treatment endpoints depend on coupling functional hemodynamic and anatomical data. We sought to develop a single prognostic parameter correlating stenosis-specific anatomy, pressure gradient, and velocities that could be measured during catheterization.

Materials and methods. In vivo experiments were performed in six swine (41 ± 3 kg). The lumen area of the left anterior descending coronary artery was measured with intravascular ultrasound. An angioplasty balloon was inflated to create the desired intra luminal area obstructions. Fractional flow reserve (FFR), coronary flow reserve (CFR), and hyperemic-stenosis-resistance index were measured distal to the balloon at peak hyperemia with 10 mg intracoronary papaverine. A functional index: pressure drop coefficient (CDP) and a combined functional and anatomical index: lesion flow coefficient (LFC) were calculated from measured hyperemic pressure gradient, velocity, and percentage area stenosis. \( P < 0.05 \) was considered statistically significant.

Results. The CDP and LFC correlated linearly and significantly with FFR and CFR. The CDP (\( R^2 = 0.72, P < 0.0001 \)) correlated better than LFC (\( R^2 = 0.19, P < 0.003 \)) with hyperemic-stenosis-resistance index. When LFC was correlated simultaneously with FFR and CFR, \( R^2 \) improved to 0.82 (\( P < 0.0001 \)). Inclusion of percentage area stenoses concurrently with FFR and CFR marginally improved the correlation with LFC.

Conclusions. A dimensionless parameter combining measured pressure gradient, velocity, and area reduction data can optimally define the severity of coronary stenoses based on our preliminary results and could prove useful clinically. © 2008 Elsevier Inc. All rights reserved.

Key Words: coronary circulation; fractional flow reserve; coronary flow reserve; hemodynamics

INTRODUCTION

Severity of stenoses within coronary and peripheral arteries affected by atherosclerotic occlusive disease has historically been determined by angiographic measurement of diameter or area luminal reduction. Functional assessment of impaired distal perfusion caused by occlusive lesions is better described by hemodynamic parameters (pressure drop/gradient, flow rate, velocity) rather than anatomical measures. Currently, coronary flow reserve (CFR) and fractional flow reserve (FFR) are used to gauge the functional severity of coronary stenoses and the success of percutaneous interventions (e.g., angioplasty). FFR is the ratio of mean pressure distal to a stenosis to the mean proximal pressure (or the aortic pressure) at peak vasodilation (hyperemia). CFR is the ratio of peak hyperemic flow to basal (or resting) flow, both measured distal to the stenosis. Hyperemia can be induced by one of the following methods: (1) by injecting bolus dose of adenosine or papaverine; (2) administering intravenous adenosine. While FFR is measured only during hyperemia, CFR requires velocity measurement at both basal and hyperemic flow. FFR and CFR increase as the stenosis severity decreases such as after balloon angioplasty. The FFR and CFR allow comparison of abnormal state of the vessel to a normal state when blood flow is no longer severely impaired. The FFR has
a lower and upper bound of 0 and 1 for no obstruction and complete vessel occlusion, respectively. If FFR < 0.75 [1–7], angioplasty of the target coronary vessel is recommended. No such threshold value for intervention exists for CFR.

However, both CFR and FFR are affected not only by stenosis severity but also by distal microvascular flow resistance [1–5] that can be increased by left ventricular hypertrophy, chronic or acute ischemia or infarct, diabetes mellitus, and other disease conditions. If microvascular resistance is above normal, then CFR tends to decrease while FFR tends to increase. Under such a scenario, longer stenoses length, diffuse (nonfocal), lower grade stenoses have been associated with borderline abnormal FFR values (0.75–0.80) [5–7], where optimal lesion management (angioplasty or surgery) remains unclear. These limitations of current functional measures indicate the need to better couple pressure gradient, blood flow derangement, and lesion anatomy/geometry to define stenosis severity.

To offset these issues, the simultaneous assessment of pressure gradient and blood flow is recommended for the differential diagnosis of epicardial (proximal) coronary artery stenoses and altered distal microcirculation [2, 4, 8, 9]. While current diagnostic indices use only pressure and blood flow information, an index that combines hemodynamic pressure gradient (dp) [8, 9], blood flow velocity (u) [8, 9], as well as coronary area blockage (usually expressed as percentage area stenosis) for assessing the severity of coronary stenoses, is currently lacking [10, 11]. Recently simultaneous assessment of pressure gradient and flow were included in a hyperemic stenosis flow index (HSR) defined as the ratio of hemodynamic pressure gradient (dp) [8, 9], blood flow velocity (u) [8, 9], as well as coronary area blockage (usually expressed as percentage area stenosis) for assessing the severity of coronary stenoses, is currently lacking [10, 11]. Recently simultaneous assessment of pressure gradient and flow were included in a hyperemic stenosis flow index (HSR) defined as the ratio of hemodynamic pressure gradient (dp) [8, 9], blood flow velocity (u) [8, 9], as well as coronary area blockage (usually expressed as percentage area stenosis) for assessing the severity of coronary stenoses, is currently lacking [10, 11].

Recently hemodynamic assessments have also been used to describe functional implications of stenoses in peripheral vessels such as the renal artery. Selecting patients for successful intervention of renal artery stenosis and improvement of renal-mediated hyperten-

The animal protocol was approved by the University of Cincinnati's Institutional Animal Care and Use Committee. All measurements were made in the left anterior descending (LAD) coronary artery of the animal at basal flow and after induction of peak hyperemia. Six Yorkshire swine (mean wt. 41 ± 3 kg) were premedicated with intramuscular xylazine (2 mg/kg), telazol (7 mg/kg), and atro-

During the experiment, anesthesia was main-
tained with 2% isoflurane, and supplemental oxygen was given by endotracheal intubation. Intravenous saline was administered to maintain euvolemia and normotensive conditions during coronary studies. A sheath was introduced into the right carotid artery. A 6-F guiding catheter was introduced. An intravenous bolus dose of 300 U/kg of heparin was administered. First, an intravascular ultrasound (2.5-F, 40-MHz intravascular ultrasound (IVUS); Boston Scientific Corp., MA) catheter was introduced into the LAD to measure its lumen cross-sectional area. Continuous monitoring of the location of the IVUS within the LAD was maintained by X-ray fluoroscopy. Then, the IVUS catheter was withdrawn, and a 0.014-inch Doppler flow wire (Volcano Therapeutics Inc., San Diego, CA) was introduced via the 6-F catheter. Based on the artery size, a Voyager angioplasty balloon of rapid exchange type (Guidant Inc., IN) and appropriate size was introduced over the Doppler flow wire. For all measurements, only balloons of nominal diameters of either 2.25 or 2.5 mm were used. The lengths of the balloons were either 13 or 15 mm. The balloon was insufflated to different pressures to create intraluminal obstructions of varying severity. This procedure is similar to the study conducted by MacCarthy et al. [21]. Linear variation of diameter with change in inflation pressure for individual balloon, as per manufacturer’s data sheet (Voyager balloons, Guidant Inc.), was used to calculate the percentage area intraluminal obstructions. The inflation pressure for each balloon did not exceed the recommended pressure range. A 0.014-inch pressure wire (Volcano Therapeutics Inc.) was inserted adjacent and distal to the balloon (Fig. 1). Since the Doppler wire was used to guide the balloon catheter, the tip of the wire was positioned distal to the balloon. For FFR, aortic pressure was recorded via the 6-F guiding catheter by an external pressure sensor (Edwards Lifeiences, Irvine, CA).
The velocity root in the above equation was added to simplify the definition of calculated as the ratio of inches, \( A_e \) aortic pressure (and guiding catheter, respectively. The ratio of distal pressure (\( \text{ub} \)) was calculated as CFR. The distal pressure (\( P_d \)) and aortic pressure (\( P_a \)) at peak hyperemia were recorded by the pressure wire and guiding catheter, respectively. The ratio of distal pressure (\( P_d \)) to aortic pressure (\( P_a \)) at peak hyperemia was calculated as FFR.

From Fig. 1, the percentage area stenosis \( = (1 - \kappa) \times 100 \) can be calculated. The \( (1 - \kappa) \) is given by: \( (1 - \kappa) = (A_{ba}^{\text{h}} + A_{ba}^{d})(A' - A_{ba}^{\text{h}} - A') \), where \( A_{ba}^{\text{h}} \) = balloon cross-sectional area obtained from the manufacturer's calibration chart for different inflation pressures, \( A' = \) guidewire cross-sectional area based on a diameter of 0.014 inches, \( A' = \) intraluminal area of the vessel measured by IVUS (proximal to the balloon), and \( A_{ba}^{d} = \) cross-sectional area of balloon shaft available as per manufacturer specifications. In the above equation for \( (1 - \kappa) \), the area available for blood flow proximal to the inflated balloon (Fig. 1) was used to calculate the percentage area stenosis.

The LFC is calculated as: \( \text{LFC} = (1 - \kappa)^{[\text{CDP}]^{0.5}} \), where CDP is the pressure drop coefficient [18, 19, 23]. The CDP is a function of hyperemic \( dp_h \) (in dyn/cm²); 1 dyn/cm² = 7.495 \times 10^{-3} \text{ mmHg}) and \( u_h \) (in cm/s), where \( u_h \) is the peak hyperemic velocity adjacent to the balloon (or at the site of the balloon as shown in Fig. 1). The square root in the above equation was added to simplify the definition of LFC as described in Banerjee et al. [18]. To calculate CDP and \( u_h \), the following relations were used, respectively (Fig. 1): \( \text{CDP} = dp_h / [0.5 \times \rho (u_h^2)] \) and \( u_h = u_a \times A'/A' - A_{ba}^{\text{h}} - A') \), where \( \rho = 1.05 \text{ g/cm}^3 \) is the density of blood. In the above relations, flow rate balance between the distal section and the site of balloon obstruction was used, i.e., \( \rho \times \text{velocity} \times \text{area} = \text{flow rate} \). Since the Doppler flow wire measures the velocity \( u_a \) distal to the balloon, the distal lumen area was used to calculate \( u_a^{\text{h}} \). To calculate \( u_a^{\text{h}} \), the distal lumen area was assumed to be the same as proximal lumen area \( A' \). To explain the procedure of calculation of LFC from measurements made across a balloon obstruction, a set of hyperemic hemodynamic and anatomical measurements for an inflated balloon should be considered (Table 1).

Using the data from Table 1, we obtain LFC as follows from steps (a) to (d):

\[
1 - \kappa = \frac{2.59^2 + 0.35^2}{3.44^2 - 0.35^2 - 0.79^2} = 0.616 \text{ or 61.6% area stenosis (a)}
\]

\[
u_h^2 = \frac{25 \times 3.44^2}{3.44^2 - 2.59^2 - 0.35^2} = 59.1 \text{ cm/sec (b)}
\]

\[
\text{CDP} = \frac{27 \times 13.6 \times 98.1}{0.5 \times 1.05 \times 59.1} = 19.6 \text{ (c)}
\]

\[
\text{LFC} = \frac{1 - \kappa}{(\text{CDP})^{0.5}} = 0.139 \text{ (d)}
\]

Further, the values of LFC will always lie between 0 and 1, similar to FFR [18, 23]. Fig. 2A shows an angiographic image of the LAD without (left) and with (right) the inflated balloon. Fig. 2B shows an IVUS measurement of the intraluminal area of the LAD. Fig. 3 shows a sample screen capture of the pressure-flow measuring instrument. The yellow and pink color waveforms in the top half of the figure represent the arterial pressure proximal (Proximal MAP in the figure) and distal (Distal MAP in the figure) to the balloon. The bottom half of Fig. 3 shows the Doppler spectrum of the LAD flow with a mean APV (or \( u_h \)) of 39 cm/s. The heart rate was 125 beats per minute.

### TABLE 1

A Set of Hemodynamic and Anatomic Measurements Made Using a 2.5-mm Nominal Diameter Balloon of Length 13 mm Inflated to a Pressure of 10 atm

<table>
<thead>
<tr>
<th>( A' )</th>
<th>( A_{ba}^{\text{h}} )</th>
<th>( A' )</th>
<th>( A_{ba}^{d} )</th>
<th>( \text{dp}_h )</th>
<th>( v_h )</th>
<th>( u_h )</th>
</tr>
</thead>
<tbody>
<tr>
<td>9.29 mm²</td>
<td>5.27 mm²</td>
<td>0.1 mm²</td>
<td>0.49 mm²</td>
<td>27 mmHg</td>
<td>25 cm/s</td>
<td>59.1 cm/s</td>
</tr>
<tr>
<td>(diameter = 3.44 mm)</td>
<td>(diameter = 2.59 mm)</td>
<td>(diameter = 0.35 mm)</td>
<td>(diameter = 0.79 mm)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. At 10 atm, the rated diameter of the inflated balloon was 2.59 mm.
Statistical Analysis

The mean values of FFR, CFR, (1 − κ), HSR, CDP, and LFC were calculated along with their ±SD. Analysis of variance was used to analyze the data and assess any significant linear correlations among CDP, LFC, FFR, CFR, HSR, and (1 − κ). A probability value $P < 0.05$ was considered statistically significant.

RESULTS

A total of 46 measurements (around 6 to 10 measurements per swine) were made for each parameter: the FFR, CFR, (1 − κ), HSR, CDP, and LFC in six swine. The mean proximal internal vessel diameter (used to calculate $A$) was 3.37 ± 0.25 mm. Mean proximal aortic pressure ($P_a$) at hyperemia was 59 ± 13 mmHg (range: 44–83), which was similar to recently reported hyperemic coronary pressure measured in swine under acute obstruction [22]. The mean values of CFR, FFR, HSR, (1 − κ), CDP, and LFC are reported in Table 2.

Fig. 4 shows the results of linear correlation: (i) CDP versus FFR ($R^2 = 0.66$, $P < 0.0001$); (ii) CDP versus

FIG. 2. (A) Angiographic image of the LAD. The figure on the left shows only the LAD with contrast injected. The figure on the right shows the inflated balloon introduced into the LAD via the guiding catheter. (B) An IVUS measurement of the intraluminal area of the LAD. The white box on the bottom left side of the figure encloses the measured area ($A_1$) in mm².
CFR \( (R^2 = 0.37, P < 0.0001) \). As stenosis severity decreases, CDP and HSR decrease, whereas FFR and CFR increase. This is consistent with fluid dynamic behavior of coronary stenoses. A similar correlation between CDP and \( \frac{1}{(1 - \kappa)} \) yielded a weak correlation with marginal statistical significance (CDP = 24.064 \( \times (1 - \kappa) + 8.173; R^2 = 0.09, P = 0.05 \)). Similar to this finding, in the recent past, correlations of FFR and CFR with percentage area stenoses have been reported to be less significant \[3, 24\].

![FIG. 3. A sample screen capture of the pressure-flow measuring instrument. The yellow and pink color waveforms in the top half of the figure represent the arterial pressure proximal (Proximal MAP in the figure) and distal (Distal MAP in the figure) to the balloon. The bottom half of the figure shows the Doppler signal of the LAD flow with a mean APV (or \( \tilde{u}_h \)) of 39 cm/s. The heart rate was 125 beats/min. (Color version of figure is available online.)](https://example.com/figure3.png)

TABLE 2

| Mean Values of CFR, FFR, \( 1 - \kappa \), HSR, CDP, and LFC |
|-----------------|-----------------|
| Mean            | Range           |
| CFR             | 1.51 ± 0.36     | 1.08-1.88 |
| FFR             | 0.63 ± 0.09     | 0.42-0.81 |
| \( 1 - \kappa \) | 0.52 ± 0.09     | 0.40-0.68 |
| HSR             | 0.973 ± 0.368 mmHg/cm/s | 0.153-1.653 |
| CDP             | 20.59 ± 7.24    | 5.96-29.33 |
| LFC             | 0.13 ± 0.05     | 0.08-0.17 |
limited set of clinical data [20] could be attributed to limitations in accurate estimation of percentage area stenoses. Since CDP is a functional parameter and does not include percentage area stenoses, its correlations with FFR, CFR, and HSR remained significant. In the future, it is of interest to improve anatomical assessment techniques (such as using IVUS measurements across the stenotic region pre- and postintervention to get exact measures of percentage area stenosis) similar to functional assessment methods. The strong correlations for CDP and LFC suggest that a limiting value of these indices may be obtained based on FFR = 0.75 and CFR = 2 [1, 3, 8] from human studies and compared with sensitive noninvasive measures of degree of ischemia in humans for specificity, sensitivity, and accuracy (e.g., 8).

**DISCUSSION**

This baseline study has established a combined *in vivo* estimation of pressure gradient, blood flow velocity, and percentage area stenosis. The measurement of CDP and LFC uses standard techniques of pressure gradient and velocity measurements using 0.014-inch pressure and Doppler flow wire. Recent advances have introduced a dual sensor pressure and flow wire, which will further simplify the procedure of measuring CDP and LFC [2, 8]. The nonlinear form of CDP and LFC does not enable any linear correlation with $u_b$ and $dP_h$. Based on $P$ values, both the CDP and the LFC correlated significantly with FFR and CFR. Similarly, CDP correlated significantly with HSR. However, based on...
the $R^2$ value, the correlation of LFC (which combines $(1 - \kappa)$ with CDP) with HSR became less significant. Further, in vivo investigations are needed to address this difference.

In the past, it was concluded that wide variation in area parameter due to the above reason resulted in a low $R^2$ value for correlation between FFR and percentage area stenosis. This limited the use of percentage area stenosis alone for assessing the hemodynamic importance of epicardial coronary stenoses [3]. However, it was important to assess the correlation of CDP and LFC with the percentage area stenosis as it is a fundamental component of LFC [18]. Kern et al. [12] have discussed the usefulness of coronary hemodynamics in multivessel, serial, and diffuse stenoses. Further, quantitative angiographic (QA) measurements are often inaccurate [12], and this is also highlighted in the present study by the weaker correlation. For clinical application, the variability in CDP and LFC, with respect to standard QA and other techniques (e.g., ref.

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**FIG. 6.** Results of linear regression analysis: (i) LFC versus FFR; (ii) LFC versus CFR.

**FIG. 7.** A 3D plot of linear regression analysis of LFC versus FFR and CFR. The solid line shows the regressed equation.
needs to be tested in humans for both focal and diffuse stenoses. With these improved area measurement techniques such as QA, which the authors did not have an access to for animal experiments, it is expected that LFC could become a potential combined parameter for diagnostics of different types of lesions.

The CDP is a fundamental fluid dynamic parameter combining hyperemic pressure gradient and flow velocity measurements [18, 19]. However, it would be certainly useful if a more comprehensive index such as LFC that combines functional (hemodynamic) and anatomical information exists and is able to achieve significant correlation with functional indices. Further, delineation of severities of serial stenoses with existing functional indices is not trivial and, thus, the diagnosis of serial stenoses is based more on “judgment” [12]. It is also anticipated that assessment of serial stenoses may not be simplistic and will need further evaluation. Thus, combined use of functional and anatomical endpoints for assessing serial stenoses may have its own complexity; hence, identifying remedial measures for such conditions may be premature. A similar anatomical limitation also exists for diffuse stenoses. For diffuse stenoses, the proximal area, which is expected to be smaller than the healthy vessel area, can again be used as a measure of reference lumen area. It may be noted that change in proximal vessel area will also affect FFR, CFR, and HSR. Similar to the existing hemodynamic indices, LFC cannot account for arterial remodeling when lumen diameter is unchanged, although there is expansion of adventitia/intima.

Additionally, the use of balloons in this study created the flow dynamics seen within a diffuse stenosis as compared to focal lesions of length <10 mm. McCarthy et al. [21] demonstrated correlation between pressure-derived CFR and flow-based CFR in a set of patients with diffuse stenoses, which was similar to the correlation in another set of patients with normal vessels obstructed by inflated angioplasty balloon. Thus, balloon obstructions are more similar to diffuse stenoses. In contrast, focal stenoses also provided significant but different correlations between pressure-derived CFR and flow-based CFR [26]. In other words, slopes of correlations were different for the diffuse and focal stenoses [21, 26]. Thus, the effect of focal stenoses needs to be investigated in vivo and compared with our past findings.

The thermodilution-based CFR cannot be used as it does not provide any velocity data [9]. The Doppler technique can measure velocity immediately distal to the stenosis. The thermodilution method requires substantial distance (~6 cm) between the proximal and distal temperature sensor for measurement of mean transit time. The two wires along with the balloon shaft created additional resistance to flow in this study. However, the formulation of (in the normalization term) LFC was able to accurately account for this impairment as discussed in the Materials and Methods section. For CDP, correction for guidewire obstruction does not exist as both pressure drop and velocity are guidewire-measured values [13]. The use of a single wire will definitely reduce the flow impairment [27–29].

As future work, this study needs to be extended to obtain values of CDP and LFC combined with measures of degrees of ischemia, such as stress test under the condition of disrupted microcirculation to provide comprehensive evidence about its clinical applicability. Further, the effect of collateral circulation along with varying hemodynamic conditions (heart rate, contractility, blood pressure) need to be tested as the native coronary circulation of swine has minimal collateral flow.

**STUDY LIMITATIONS**

The less significant correlation with $(1 - \kappa)$ could be attributed to limitation in accurate edge detection and measurement of lumen diameter, which gets magnified in area calculation. This is because area includes the square of diameter, and the LFC is a function of percentage area stenosis but not the percentage diameter stenosis. Any error in diameter measurements gets magnified as a square term for area calculation. Such an error also exists in clinical evaluation and supports the fact that pressure and flow measurements were more accurate than anatomical endpoint measures in the study. The assumption of stable proximal vessel diameter following the IVUS measurement could have resulted in discrepancies in the calculation of $(1 - \kappa)$. In clinical measurements, $(1 - \kappa)$ is usually measured under basal flow conditions. Thus, the CDP has an advantage over LFC as it is a purely hyperemic hemodynamic or functional parameter. The LFC incorporates both hemodynamic and anatomical information. As discussed previously, these indices need to be evaluated carefully with QA techniques to achieve more efficient patient diagnosis.

In this study, the repeated use of IVUS prior to balloon inflation would have required withdrawal of the balloon from the vessel. This excessive handling of the coronary vessel results in cardiac arrhythmias and vessel spasm. Thus, the authors refrained from repeated IVUS insertions into the target coronary vessel. Instead the variation of diameter with change in inflation pressure for individual balloon, as per the manufacturer’s data sheet, was used to calculate the of area intraluminal obstructions. The serial use of IVUS could be more beneficial in determining area available for blood flow before and after intervention. The study also needs to be expanded to a wider range of stenoses.
severities as the sizes of the balloons relative to the vessel size restricted the maximum percentage area stenosis to ~70%. Although the stenoses created were anatomically not significant, the low FFR and CFR values suggest that the stenoses created were more similar to diffuse obstructions (long stenosis length) compared to focal obstructions as observed by other researchers [6, 21, 26].

The proposed indices use Doppler velocity measurements, which are inherently limited by practical difficulties associated with obtaining high-quality velocity signals. In the present study, the presence of a balloon catheter and a wire over the balloon resulted in significantly lower values of CFR. However, the low values of distal pressure due to the flow impairment did not result in any significant loss of the coronary vasodilatory reserve as was also reported recently by Fearon et al. [22]. In actual stenosed coronary vessels, the flow impairment will be much smaller as only a single wire can make both pressure and flow measurements.

CONCLUSION

These analyses support the concept that functional/physiological evaluation may be more important than isolated anatomical endpoints in evaluating stenoses severity. Improvements in area measurement (potentially provided by repeated intraprocedural use of IVUS) are needed to optimize accuracy of measurements of pressure gradient, blood flow, and percentage area stenosis used in calculation of a novel prognostic dimensionless parameter coupling hemodynamics and anatomy.

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