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Evaluation of lesion flow coefficient for the detection of coronary artery disease in patient groups from two academic medical centers

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ABSTRACT

Background. In this study, lesion flow coefficient (LFC: ratio of % area stenosis [%AS] to the square root of the ratio of the pressure drop across the stenosis to the dynamic pressure in the throat region), that combines both the anatomical (%AS) and functional measurements (pressure and flow), was assessed for application in a clinical setting.

Methods and Results. Pressure, flow, and anatomical values were obtained from patients in 251 vessels from two different centers. Fractional flow reserve (FFR), Coronary flow reserve (CFR), hyperemic stenosis resistance index (HSR) and hyperemic microvascular index (HMR) were calculated. Anatomical data was corrected for the presence of guidewire and the LFC values were calculated. LFC was correlated with FFR, CFR, HSR, HMR, individually and in combination with %AS. The p < 0.05 was used for statistical significance.

LFC correlated significantly when the FFR (pressure-based), CFR (flow-based), and anatomical measure %AS were combined (r = 0.64; p<0.05). Similarly, LFC correlated significantly when HSR, HMR, and %AS were combined (r = 0.72; p<0.05). LFC was able to significantly (p < 0.05) distinguish between the two concordant and the two discordant groups of FFR and CFR, corresponding to the clinically used cut-off values (FFR=0.80 and CFR=2.0). The LFC could also significantly (p < 0.05) distinguish between the normal and abnormal microvasculature conditions in the presence of non-significant epicardial stenosis, while the comparison was borderline significant (p = 0.09) in the presence of significant stenosis.

Conclusion. LFC, a parameter that combines both the anatomical and functional end-points, has the potential for application in a clinical setting for CAD evaluation.
INTRODUCTION

Ischemic heart disease (IHD) is a multi-level condition that involves the epicardial coronary arteries and the coronary microvasculature, as well as the myocardium. In current clinical practice, the diagnosis of IHD is focused on assessing epicardial stenosis severity as the evaluation of microvascular disease has been a challenge\(^1\textsuperscript{-3}\), particularly in the presence of concomitant epicardial and microvascular disease. Therapeutic decision-making for treatment of IHD is therefore generally based on visual assessment of severity of the stenosis, but visually ambiguous stenoses are often further assessed for their functional severity\(^4\textsuperscript{,5}\). Currently, the functional significance of such intermediate stenosis is mostly assessed using the coronary pressure-based fractional flow reserve,\(^6\textsuperscript{-8}\) which aims to address the epicardial contribution to IHD, and occasionally using the flow-based coronary flow reserve (CFR), which depicts the combined contribution of the epicardial and microvascular compartments.

However, the hemodynamics of IHD involve a complex interplay between pressure and flow variations due to the presence of microvascular dysfunction and the epicardial stenosis\(^9\). Therefore, diagnostic parameters that combine both coronary pressure and flow\(^10\textsuperscript{,11}\) have been introduced. These include the hyperemic stenosis resistance index (HSR), a stenosis-specific parameter, and the hyperemic microvascular resistance index (HMR), a microcirculation-specific parameter. Although providing additional insight into the origin of IHD, their combined assessment may yield difficulties in clinical decision-making. Hence, a single parameter that can simultaneously account for the presence of epicardial stenosis and microvascular disease could provide important diagnostic advantages.

In view of the above shortcomings, two non-dimensional parameters based on fundamental fluid dynamics principles have been introduced. The first one, pressure drop coefficient (CDP),
the ratio of trans-stenotic pressure drop to distal dynamic pressure, combines both pressure and flow measurements. It has a wider range of 0 ~ 1000 and has been extensively validated in pre-clinical trials\textsuperscript{12-18}. In a recent study, CDP has been evaluated for clinical application\textsuperscript{19} and cut-off values for delineation of epicardial and microvascular impairments have been proposed\textsuperscript{20}.

The second parameter, the focus of this study, is the lesion flow coefficient (LFC), the ratio of \% area stenosis (\%AS) to the square root of CDP at the throat region (CDP\textsubscript{m}), that combines both the anatomical and functional measurements. LFC is a normalized parameter with a range from 0 ~ 1, similar to FFR. LFC has also been evaluated \textit{in vitro}\textsuperscript{16-18,21} and \textit{in vivo}\textsuperscript{12-15,22} for the successful assessment of the functional severity of epicardial stenosis. Further, LFC has also been shown to simultaneously distinguish the presence of epicardial stenosis with concomitant microvascular disease\textsuperscript{23} in animal model. In a recent pilot clinical study, LFC was assessed for clinical application in relation to the current diagnostic parameters\textsuperscript{24}.

Therefore, in this study with a larger sample size, the \textit{patient-level} pressure, flow, and anatomical data from two centers were used to evaluate the LFC in a clinical scenario. The hypothesis was that the LFC would prove to be a clinical parameter that could diagnose both the epicardial and microvascular diseases involved in the CAD. To this effect, LFC was correlated with existing parameters. Further, group mean comparisons were performed between: i) the 75\% AS groups, ii) the two concordant and the two discordant groups of FFR and CFR, and iii) the normal and abnormal microvasculature groups, in the presence of significant and non-significant epicardial stenosis.
METHODS

Patient population. The population consisted of patient-level pressure, flow, anatomical details from 251 vessels. Eighty-four vessel data was obtained from the clinical protocol approved by the Institutional Review Board at the University of Cincinnati and the research and development committee at the Cincinnati Veteran Affairs Medical Center. One hundred and sixty seven data points were obtained from the study by van de Hoef et al., 2012, based on a similar protocol approved by the institutional ethics committee at Academic Medical Center-Amsterdam.

Patients of 18 years or above with an abnormal stress test indicating reversible ischemia were considered for enrollment into the study. Patients with by-pass grafts, baseline serum Creatinine > 2.5 mg/dl, pregnant women, and significant co-morbid conditions that incapacitated the patients from the consent process were excluded from the study.

Cardiac catheterization and functional measurements. Patients consented to participate in the study underwent the standard-of-care cardiac catheterization. Unfractionated heparin was administered using a weight-based protocol. Using a 5 or 6 French diagnostic catheter, the coronary arteries were visually assessed for blockages through coronary angiography. According to the standard of care, angiographically moderate to borderline severe lesions were further assessed using functional measurements at rest and at adenosine induced maximal arterial dilatation (hyperemia).

The aortic pressure ($p_a$) and ECG tracings were continuously recorded through Combomap® system (Volcano Therapeutics Inc., CA) or on a personal computer. Pressure and flow readings were obtained using a combination of 0.014” pressure and flow wires (167 points) or a 0.014” dual-sensor tipped Combowire (84 points) with a flow sensor at its tip and pressure sensor at 1.5 cm offset. The Combowire (or pressure-wire) was set at zero, calibrated, advanced through the guiding catheter and normalized to aortic pressure ($p_a$) at the coronary ostium. Following this,
the wire was advanced distal to the stenosis and placed at a location downstream to the stenosis and before any side branches to obtain pressure and flow data under baseline conditions. Subsequently, hyperemia was induced using Adenosine, infused intravenously (140 μg/kg/min) or intracoronary (20-140 µg) to obtain pressure and flow data under hyperemic conditions. Anatomical data, the vessel diameter ($D_v$) and diameter at the stenosis ($D_m$), was then obtained using quantitative coronary angiography (QCA), as described below.

Quantitative coronary angiography. The angiographic images taken during the procedure were reviewed. The frames representing the best view of the stenosed artery were selected. Most of the frames were auto calibrated and were ready for analysis. For those needing manual calibration, the size of the guide catheter was used as a reference. Lesion contour was carefully drawn to get the best possible measurements. Using automatic edge-detection techniques available in the GE centricity software, vessel diameter ($D_v$), stenosis diameter ($D_m$), and lesion length were obtained. To check for consistency, QCA values were obtained from three different frames using blinded review. The %AS was calculated based on these diameter values. The averaged values were used for the analyses. For some stenoses, the stenosis parameters obtained from a single frame were used.

**Diagnostic parameters.** The FFR, CFR, HSR, and HMR were calculated based on their formula provided below.

$$\text{FFR} = \frac{P_d}{P_a}, \text{ at hyperemia,}$$

$$\text{CFR} = \frac{APV_h}{APV_b}, \text{ APV = average peak velocity; subscripts “b” = baseline, “h” = hyperemic,}$$

$$\text{HSR} = \frac{\Delta p}{APV_h}, \text{ \Delta p is the pressure drop across the stenosis,}$$
\[ HMR = \frac{p_d}{APV_h} \]

**LFC calculation.** LFC combines the lesion geometry (%AS) and pressure and flow measurements. It is defined as the ratio of the % area obstruction to the square root of CDP\(_m\), which is the CDP calculated at the throat region of the stenosis:

\[ LFC = \frac{(1-k) \cdot \% AS}{\sqrt{CDP_m}}, \quad k = \left( \frac{A_m-A_g}{A_v-A_g} \right). \]

In the above equation, the numerator \(1 - k\) is the %AS; in other words, \(k\) is the area ratio \(A_m/A_v\), where \(A_m\) and \(A_v\) are area of the throat and vessel obtained from QCA (cm\(^2\)). On a similar note, the CDP\(_m\) in the denominator is \(\Delta p/0.5 \times \rho \times APV_m^2\), where \(\Delta p\) is the pressure drop across the stenosis, \(p_a\) (Aortic pressure) - \(p_d\) (downstream pressure measured from Combowire), \(\rho\) is the density of the blood (1.05 g/cm\(^3\)), \(APV_m\) is the mean velocity in the throat region, and \(A_g\) is the area of the guidewire \((= \pi \times 0.3556^2 = 0.099 \text{ mm}^2)\). The \(APV_m\) is calculated from the measured distal \(APV\) (cm/sec) obtained using the Combowire. Based on the mass conservation principle, the following formula was used:

\[ (A_m-A_g)APV_m = (A_v)APV, \]

where \(A_m\) is the throat area calculated from minimal luminal diameter obtained using the QCA, \(A_g\) is the area of guidewire, and \(A_v\) is the area of the vessel calculated based on the diameter of vessel obtained from QCA.

**Statistical analysis.** The LFC values obtained using the above-mentioned formula were first correlated with the FFR, CFR, and %AS solitarily, as well as with a combination of these data. Similarly, LFC values were correlated individually with HSR and HMR, and in combination with %AS. The correlation equations along with regression coefficients (r-values) and the p-values obtained using the regression analysis of LFC with FFR, CFR, and %AS are summarized.
in Table 2. The correlation equations, r-value and p-value of LFC with HSR and HMR are summarized in Table 3.

This was followed by ANOVA mean comparison of LFC groups for the 75% AS cut-off value (4,5). A comparison of the LFC values between the concordant (FFR < 0.80 and CFR < 2; FFR > 0.80 and CFR > 2) and discordant (FFR > 0.80 and CFR < 2; FFR < 0.80 and CFR > 2) groups of FFR and CFR was also performed. Subsequently, a comparison was performed between the normal (CFR > 2) and abnormal microvasculature (CFR < 2) groups in the presence of significant epicardial stenosis (FFR < 0.8) and non-significant epicardial stenosis (FFR > 0.80). The p < 0.05 was used for statistical significance for the correlations and ANOVA comparisons. All the values were reported as mean ± standard error (SE).

RESULTS

The mean values of the LFC, CFR, FFR, %AS, HSR and HMR, along with their corresponding ranges are summarized in Table 1. The correlations of the LFC with FFR, CFR, and %AS are reported in Table 2. The correlations of the LFC with HSR, HMR, and %AS are presented in Table 3.

Correlation analyses

Correlation of LFC with FFR, CFR, and %AS. FFR showed a near significant (p = 0.06) linear correlation with LFC with a r-value of 0.12 (Figure 1A). When the LFC was correlated with CFR, the r-value significantly (p = 0.0002), and had a better correlation value of 0.22 (Figure 1B). When LFC was correlated with the anatomical measure %AS, there was a significant corre-
lation (p < 0.001) with an r-value of 0.57 (Figure 2). When LFC was correlated in combination with FFR, CFR, and %AS, the r-value significantly (p < 0.001) increased to 0.68.

**Correlation of LFC with HSR, HMR, and %AS.** There was a significant (p = 0.01) correlation between HSR and LFC with the r-value being 0.17 (Figure 3A). Similarly, there was a significant correlation (p = 0.03) between LFC and HMR, with the r-value being 0.14 (Figure 3B). Interestingly, when the LFC was correlated simultaneously with HSR, HMR, and %AS, the r-value considerably increased (r = 0.69) with a strong statistical significance (p < 0.001).

**ANOVA comparisons**

%AS groups. A comparison of mean LFC values between the %AS < 75% and %AS > 75% groups is presented in Figure 4. LFC was able to distinguish between the two intermediate stenosis groups. The mean value of LFC significantly (p < 0.05) increased from 0.38 ± 0.02 for the %AS < 75% group to a value of 0.60 ± 0.02 for the %AS > 75% group.

Discordant and concordant FFR and CFR groups. Figure 5A presents the comparisons made between the group mean of LFC values in the two concordant FFR and CFR groups ([i] FFR < 0.80 and CFR < 2; [ii] FFR > 0.80 and CFR > 2). The group mean value of LFC in the FFR < 0.80 and CFR < 2 group was 0.44 ± 0.03, which increased significantly to 0.54 ± 0.03, for the FFR > 0.80 and CFR > 2 group (Figure 4A). Hence, LFC was able distinguish between the two concordant FFR and CFR groups.

The comparisons of group mean LFC values between the two discordant FFR and CFR groups ([i] FFR < 0.80 and CFR > 2; [ii] FFR > 0.80 and CFR < 2) were also presented in Figure 4A. The mean LFC value for the FFR < 0.80 and CFR > 2 group was 0.52± 0.03. This value significantly (p < 0.05) decreased to 0.38 ± 0.04 for the FFR > 0.8 and CFR < 2 group. Hence, LFC was able to distinguish between the two discordant FFR and CFR groups.
**Epicardial and microvascular groups.** In addition to above, group mean comparisons of LFC were also performed in order to check the ability of LFC to distinguish between normal (CFR>2) and abnormal (CFR<2) microvasculature status in the significant (FFR<0.8) and non-significant (FFR>0.8) epicardial stenosis groups (Figure 4B). In the non-significant epicardial stenosis group, LFC could significantly (p<0.05) distinguish the normal microvasculature (0.54±0.03) and abnormal microvasculature (0.38±0.04) levels (Figure 4B). In the significant epicardial stenosis group, the LFC value decreased from 0.52±0.03 to a value of 0.44 ± 0.03 for the abnormal microvasculature group. However, this decrease was marginal (p=0.09; Figure 4B).

**ROC analysis for cut-offs of epicardial and microvascular diseases.** For the delineation of significant and non-significant epicardial stenoses, 75% AS value corresponding to the intermediate stenosis defined by the AHA/ACC guidelines was used. CFR cut-off value of 2.0 was used to determine the microvascular impairment. Using the current data, a LFC value of 0.36 was obtained as the optimum value to differentiate between significant and non-significant epicardial stenosis, corresponding to the %AS<75% and %AS>75% groups, respectively. Hence, a value of LFC < 0.36 indicated non-significant stenosis and a value of LFC > 0.36 indicates the presence of significant stenosis (AUC=74%, p<0.001; Sensitivity=84; Specificity=59).

In the presence of non-significant stenosis (%AS<75%), a value of LFC < 0.30 (AUC=71%, p <0.001; Sensitivity=67; Specificity=69) indicates normal microvasculature (CFR>2.0) while a value of LFC > 0.30 indicates abnormal microvasculature (CFR<2.0). In the presence of significant stenosis (%AS>75%), a value of LFC < 0.54 (AUC=66%, p<0.001; Sensitivity=59; Specificity=75) indicated normal microvasculature (CFR>2.0) while a value of LFC > 0.54 indicated abnormal microvasculature (CFR<2.0).
DISCUSSION

To our knowledge this is the first comprehensive study using patient-level information of anatomical and functional (intracoronary pressure and flow) measurements from two different centers to assess the LFC in relation to current diagnostic parameters.

The main results from the study are that the proposed parameter, LFC, correlates significantly when the anatomical (%AS) and functional (pressure-based FFR and flow-based CFR) indices are combined. It also correlated well when the indices HSR (defined for epicardial stenosis alone) and HMR (defined for microvascular resistance alone) were combined with the anatomical index, %AS. LFC could significantly distinguish between %AS groups based on the intermediate stenosis cut-off of 75%AS. It was also able to distinguish between the two concordant and the two discordant groups of FFR and CFR. Further, LFC was also able to delineate normal (CFR>2) and abnormal (CFR<2) microvasculature groups in the presence of non-significant epicardial stenosis (FFR>0.80) while the values remained borderline significant in the presence of significant epicardial stenosis (FFR<0.80). A brief discussion of the study results is provided below.

LFC in relation to current parameters. There was a borderline significant correlation (p=0.06) between FFR and LFC. This can be explained by the fact that pressure-based FFR is an epicardial-specific parameter, while LFC combines functional (pressure and flow) and anatomical (%area stenosis; %AS) measurements. While LFC can account for the variations in flow due to the presence of concomitant microvascular disease, FFR being a pressure-based parameter tends to be overestimated in such scenarios\textsuperscript{26}. Therefore, the variability of FFR in the presence of microvascular disease might also be the reason for the lack of good correlation between LFC and FFR.
LFC showed a statistically significant correlation with low r-values with the epicardial specific parameter, HSR (r=0.17) and microvascular specific parameter, HMR (r=0.14). The lower correlation coefficient could be due to the combination of the anatomical and functional measurements involved in the LFC. Further, most of the lesions assessed in this study were non-diffuse lesions in the intermediate stenosis range. It is expected that the strength of the correlation between the LFC and FFR, HSR, HMR will increase with the inclusion of a wider range of disease combinations with a larger sample size.

Concordant and Discordant groups of FFR and CFR. Johnson et al., 2012, reported that the discordant values of FFR > 0.8 and CFR < 2.0 were observed in the presence of a predominant diffuse stenosis compared to focal stenosis or in the presence of concomitant microvascular disease (Figure 3 of Johnson et al., 2012). Similarly, values of FFR < 0.8 and CFR > 2 were attributed to the presence of primarily focal stenosis compared to diffuse stenosis.

Recently, in a 10-year clinical outcome study, Van de Hoef et al., 2014 showed that the discordant group of normal FFR and abnormal CFR resulted in major adverse outcomes in comparison to the concordant normal FFR and CFR group. It was also reported that the clinical outcomes remained similar in the discordant group of abnormal FFR and normal CFR and the concordant group of normal FFR and CFR. In the current study, LFC was able to distinguish between the two concordant groups of FFR and CFR and the two discordant groups of FFR and CFR. These statistically significant differences in the LFC values between various concordant and discordant groups demonstrate the possible potential of LFC for diagnostic application in a clinical setting.

Clinical application of LFC. In a catheterization laboratory, the numerator %AS in the LFC is obtained from imaging methods discussed below. The denominator, CDP_m is obtained
through functional measurements. The current technology available to evaluate %AS are QCA, IVUS \(^{29,30}\), and OCT \(^{31-33}\). The method used in our study is the QCA obtained using angiograms, which does not require any additional time or procedure. On the other hand, IVUS and OCT may provide more accurate area measurement but require the insertion of an additional catheter, adding time and expense to the standard-of-care procedure. However, the importance of IVUS and OCT for accurate anatomical measurements is gaining popularity both for stenosis assessment and for stent placement \(^{34-36}\). The introduction of 0.014” dual-sensor tipped Combowire\(^\circledR\) (Volcano therapeutics Inc., CA) has made it easier to obtain both pressure and flow readings with a single wire. Therefore, the ease of application of LFC is evident from the fact that it can be computed using the data obtained from a 0.014” guidewire and QCA evaluation of standard angiographic images. Neither the Combowire measurements nor the QCA analysis adds any extra time to the standard of care measurements.

Further, the new s5 imaging system\(^\circledR\) (Volcano Therapeutics Inc., CA) is the first step towards the integration of anatomical measurements (using IVUS) and functional measures (currently, FFR) in the catheterization laboratory. It is expected that such integration will further improve the use of combined functional and anatomical assessment in cardiac catheterization lab.

In addition to the ease of measurement, LFC can have separate cut-off values to indicate the severity of epicardial stenosis alone, microvascular disease alone, and concomitant epicardial stenosis with microvascular disease. Using a single index, such as LFC, a cardiologist may get a comprehensive knowledge about the relative contribution of each of the epicardial and microvascular resistances. This will allow for better therapeutic decision-making. Therefore, \(LFC\) is a
potential parameter for clinical application because of its 1) ease of application in a catheterization lab; and 2) the possible ability to delineate epicardial and microvascular disease.

Limitations.

APV. LFC, developed from fundamental fluid dynamics principles, has been defined based on the average velocity rather than APV obtained using a Combowire. For a flow waveform, the APV or peak velocity is always higher than the average velocity. Therefore, the LFC values might be somewhat higher when the APV is used instead of average velocity. In other words, LFC values would be somewhat lower if computed using the average velocity. The current technology allows for the acquisition of APV only. It is expected that the trend of LFC is not affected by the measurement of APV as opposed to the average velocities.

QCA. QCA is limited by the fact that a 3-dimensional vessel is being analyzed in a 2-dimensional plane. There might be some inaccuracies in the LFC values due to the 2D area measurements. Blinded QCA measurements were performed on multiple frames to reduce observer bias and obtain average diameter and area. The technology to obtain better anatomical details is emerging rapidly, mainly by using either IVUS or OCT techniques. The main roadblock for these emerging technologies is that they are not yet cost- and time-effective. Therefore, using the standard-of-care technology available in the catheterization laboratory, we presented the best possible LFC values. The LFC calculation can be further improved with the advancement in the technology.

Variations of CAD. This parameter needs to be further tested in patient sub-groups for application to left main disease, complex and diffuse lesions, and particularly, in patients with known microvascular disease.
**Future directions.** LFC still needs to be tested in a larger patient population in order to increase the sensitivity and specificity of the LFC cut-off values for delineating epicardial and microvascular diseases. Further, the plan is to perform a multi-center clinical trial to test the diagnostic efficacy of the LFC cut-off values for decision-making in the catheterization laboratory. To obtain better anatomical measurements for more accurate LFC values, clinical trials using IVUS and/or OCT are also being planned. Further, a prospective clinical trial specifically designed to evaluate the positive and negative predictive ability of LFC relative to the non-invasive imaging modality positron emission tomography (PET) is also being planned.

**CONCLUSION**

LFC, a futuristic parameter that combines both the anatomical and functional readings, correlated significantly, when FFR, CFR, and %AS were combined as well as when HSR, HMR, and %AS were combined. LFC could significantly distinguish between the two discordant and the two concordant groups of FFR and CFR. Further, LFC was able to delineate between the presence and absence of microvascular disease in the presence of non-significant epicardial stenosis. LFC values remained marginally significant between the normal and abnormal microvasculature status in the presence of significant epicardial stenosis. Therefore, LFC holds the potential to become a comprehensive diagnostic parameter for delineating the epicardial stenosis and microvascular diseases involved in the CAD.
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Figure Captions

1. Figure 1: Scatter plots along with the regression lines for the correlation analyses between
   a. LFC and FFR
   b. LFC and CFR

2. Figure 2: Scatter plots along with the regression lines for the correlation analyses between LFC and %AS.

3. Scatter plots along with the regression lines for the correlation analyses between
   a. LFC and HSR
   b. LFC and HMR

4. Bar-plots summarizing the group mean comparisons of LFC values between the %AS < 75% group and the %AS > 75% group.

5. Bar-plots summarizing the group mean comparisons of LFC values between:
   a. The two concordant groups of FFR and CFR: Normal FFR and CFR; Abnormal FFR and CFR. The discordant groups of FFR and CFR: Abnormal FFR and normal CFR; Normal FFR and abnormal CFR.
   b. The normal and abnormal microcirculation groups in the presence of significant and non-significant epicardial stenosis.

6. Summary of the results from the ROC analysis. Diagnostic cut-off values of LFC were assessed for significant and non-significant epicardial stenosis groups based on the %AS = 75% cut-off. Similarly, the LFC cut-off values were assessed for the normal and abnormal microvasculature groups based on the CFR = 2 cut-off.
Table 1: Mean values and range of various diagnostic parameters (n = 251)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SE</th>
<th>Range</th>
</tr>
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<tbody>
<tr>
<td>FFR</td>
<td>0.79 ± 0.01</td>
<td>0.28 – 0.98</td>
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<tr>
<td>CFR</td>
<td>2.2 ± 0.04</td>
<td>0.9 – 5.4</td>
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<tr>
<td>%Area stenosis (1-k)</td>
<td>74 ± 0.7</td>
<td>31 - 96</td>
</tr>
<tr>
<td>LFC</td>
<td>0.49 ± 0.02</td>
<td>0.04 – 1.0</td>
</tr>
<tr>
<td>HSR</td>
<td>0.65 ± 0.04 mmHg/cm/s</td>
<td>0.03 – 1.0</td>
</tr>
<tr>
<td>HMR</td>
<td>2.1 ± 0.05 mmHg/cm/s</td>
<td>0.68 – 4.4</td>
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Table 2: Correlation of LFC with FFR, CFR, %AS, individually and in combination

<table>
<thead>
<tr>
<th>LFC correlation</th>
<th>Equation</th>
<th>r</th>
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<tbody>
<tr>
<td>FFR</td>
<td>0.25 × FFR + 0.29</td>
<td>0.12</td>
<td>0.06</td>
</tr>
<tr>
<td>CFR</td>
<td>0.08 × CFR + 0.29</td>
<td>0.22</td>
<td>0.0002</td>
</tr>
<tr>
<td>%AS</td>
<td>0.01 × %AS - 0.39</td>
<td>0.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>FFR, CFR, %AS</td>
<td>0.89 × FFR + 0.07 × CFR + 0.02 × %AS – 1.66</td>
<td>0.68</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table 3: Correlation of LFC with HSR, HMR, %AS, individually and in combination

<table>
<thead>
<tr>
<th>LFC correlation</th>
<th>Equation</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSR</td>
<td>-0.06 × HSR + 0.53</td>
<td>0.17</td>
<td>0.01</td>
</tr>
<tr>
<td>HMR</td>
<td>-0.05 × HMR + 0.59</td>
<td>0.14</td>
<td>0.03</td>
</tr>
<tr>
<td>HSR, HMR, %AS</td>
<td>-0.18 × HSR - 0.04 × HMR + 0.02 × %AS - 0.69</td>
<td>0.69</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>
Figure 1
Figure 2
Figure 3
Figure 4
Figure 5

A

Concordant groups

\[ p = 0.02 \]

Discordant groups

\[ p = 0.01 \]

B

Significant epicardial stenosis

\[ p = 0.09 \]

Insignificant epicardial stenosis

\[ p = 0.001 \]
**%AS = 75% cut-off**
- LFC = 0.36
- AUC = 74%, $p < 0.0001$
- Sensitivity = 84
- Specificity = 59

<table>
<thead>
<tr>
<th>LFC = 0.30</th>
<th>LFC = 0.36</th>
<th>LFC = 0.54</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR &gt; 2</td>
<td>CFR &gt; 2</td>
<td>CFR &lt; 2</td>
</tr>
<tr>
<td>No microvascular disease</td>
<td>No microvascular disease</td>
<td>Microvascular disease</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>Non-significant epicardial stenosis</td>
<td>Significant epicardial stenosis</td>
</tr>
</tbody>
</table>

- LFC = 0.30
  - AUC = 71%, $p < 0.0001$
  - Sensitivity = 67
  - Specificity = 69

- LFC = 0.54
  - AUC = 66%, $p < 0.001$
  - Sensitivity = 59
  - Specificity = 75
Acknowledgements

The authors regret the untimely death of our co-author Dr. Paul Succop. The authors would like to thank Gary Henry, Sherri Rosser and Mary Colleen–Rogge at the VA medical center, Ginger Conway, Rachel Mardis, Cindy Werner, and Cindy Mulcahy at the UCMC for help with the patient consent process. We would also like to thank all the nurses and technicians at the VA medical center and UCMC catheterization laboratories for their help during the procedures. We also acknowledge the nursing staff of the cardiac catheterization laboratory at AMC (Head: MGH Meesterman) for their skilled assistance.
Highlights

- In this study, a new parameter lesion flow coefficient (LFC) that combines both the anatomical (%AS) and functional measurements (pressure and flow), was assessed for application in a clinical setting.
- LFC correlated significantly when the FFR (pressure-based), CFR (flow-based), and anatomical measure %AS were combined (r = 0.64; p<0.05).
- LFC was able to significantly (p < 0.05) distinguish between the two concordant and the two discordant groups of FFR and CFR, corresponding to the clinically used cut-off values (FFR=0.80 and CFR=2.0).
- Probable cut-off values for LFC to diagnose of epicardial stenosis and microvascular disease were proposed.
- LFC, a parameter that combines both the anatomical and functional end-points, has the potential for application in a clinical setting for CAD evaluation.