ABSTRACT: Objectives and Background. Functional assessment of coronary lesion severity during cardiac catheterization is conducted using diagnostic parameters like fractional flow reserve (FFR; pressure derived) and coronary flow reserve (CFR; flow derived). However, the complex hemodynamics of stenosis might not be sufficiently explained by either pressure or flow alone, particularly in the case of intermediate stenosis. CDP (ratio of pressure drop across a stenosis to distal dynamic pressure), a non-dimensional index derived from fundamental fluid dynamic principles based on a combination of intracoronary pressure and flow, may improve the functional assessment of coronary lesion severity. 

Methods. We performed a meta-analysis of seven studies, retrieved from MEDLINE and PubMed, comparing the results of FFR and CFR of the same lesions. Two studies reported functional measurements (pressure and flow) obtained in individual patients. Five studies reported two-dimensional plots of FFR vs CFR. The FFR and CFR data were digitized and corresponding functional measurements were extracted using the reported mean values of hemodynamic data from each of the five studies. The receiver operating characteristic (ROC) curve was used to identify the optimal cut-off point of CDP, which corresponds to the clinically used cut-off values (FFR = 0.80, FFR = 0.75, and CFR = 2.0).

Results. CDP correlated significantly with FFR (r = 0.78; P < .001) and had significant diagnostic efficiency (area under the ROC curve = 89%), specificity (83% and 85%), and sensitivity (81% and 76%) at FFR <0.8 and FFR <0.75, respectively. The corresponding cut-off value for CDP to detect FFR <0.80 and FFR <0.75 was at CDP >27.1 and CDP >27.9, respectively.

Conclusions. CDP, a functional parameter based on both intracoronary pressure and flow measurements, has close agreement (area under the ROC curve = 89%) with FFR, the most frequently used method for evaluation of coronary stenosis severity.

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Key words: coronary disease, FFR, CFR, catheterization, meta-analysis

Coronary angiography is the current standard for detecting epicardial coronary artery disease (CAD). However, coronary angiography frequently fails to accurately identify the functional significance of intermediate coronary stenoses. Invasive functional studies from the past 15 years have demonstrated favorable outcomes for decision making in patients with intermediate stenoses, including single, multivessel, left main, bifurcation, and ostial lesions. Thus, integrating angiography and invasive coronary physiology provides unique functional information (pressure and flow) that complements anatomic (angiographic) evaluation, and facilitates optimal decision making for treatment of CAD in the catheterization laboratory.

Assessment of functional coronary lesion severity, using sensor-equipped guidewires, has emerged as a standard diagnostic modality to provide objective evidence of myocardial ischemia during cardiac catheterization. Coronary diagnostic indices, fractional flow reserve (FFR; pressure derived), and coronary flow reserve (CFR; flow derived) showed a high agreement with non-invasive stress testing.

FFR is an established invasive clinical parameter used for assessing physiological significance of epicardial disease. FFR, defined as the ratio of pressures distal and proximal to a stenosis measured at maximal hyperemia, has a lower bound of ‘0’ representing complete vessel obstruction and an upper bound of ‘1’ representing no obstruction and normal flow. Based on extensive clinical trials, a cut-off value of 0.75-0.80 for FFR was shown to indicate hemodynamic significance of coronary stenosis. Some limitations of FFR include the assumption of zero central venous pressure, as well as its dependence on achieving maximal hyperemia. Failure to achieve peak hyperemia may result in not achieving minimal constant microvascular resistance, leading to underestimation of pressure drop and overestimation of FFR across a stenosis.

CFR, defined as the ratio of flow at hyperemia to flow at rest, was found to have excellent agreement with non-invasive stress testing at a cut-off value of 2.0. An abnormal CFR (<2.0) corresponded to reversible myocardial perfusion defects with high sensitivity and specificity. It should be noted that CFR can give the combined effect of epicardial stenosis and microvascular dysfunction, but cannot delineate between the two.

Because these indices, FFR and CFR, are based on either intracoronary pressure or flow, they do not differentiate between hemodynamic status of the epicardial stenosis and microvasculature. To overcome these issues, parameters were proposed based on simultaneous measurements of pressure drop and velocity. However, these parameters were defined for detection of either epicardial stenosis, namely, hyperemic stenosis resistance index (HSR; ratio of pressure drop across the stenosis to the distal velocity during hyperemia); or for the detection of microvascular dysfunction,
namely, hyperemic microvascular resistance index (HMR; ratio of mean distal pressure and velocity during hyperemia).\textsuperscript{13} While FFR and CFR are ratios and do not have any units, HSR and HMR are dimensional quantities with units of mm Hg/cm/s.

Recently, for simultaneous detection of epicardial stenosis and microvascular dysfunction using a single diagnostic parameter, we introduced the functional index, the pressure drop coefficient CDP, the ratio of transstenotic pressure drop ($\Delta p$) to distal dynamic pressure ($\frac{1}{2} \times \text{blood density} \times \text{APV}^2$), where APV (average peak flow velocity) is measured under maximal hyperemia.\textsuperscript{14} This parameter is a non-dimensional ratio, derived from fundamental fluid dynamic principles that incorporate a simultaneous assessment of pressure drop ($\Delta p$) and flow (APV) in its formulation. The functional measurements ($\Delta p$ and APV) necessary for the evaluation of CDP can be readily obtained during routine cardiac catheterization procedures using a dual-sensor tipped guidewire.

The CDP was validated in \textit{in vivo},\textsuperscript{14,15} and \textit{in vitro} animal studies\textsuperscript{14-20} to delineate between epicardial stenosis and microvascular dysfunction. Furthermore, in a recent clinical trial,\textsuperscript{21} CDP has been evaluated in a target patient population to distinguish between stenosis severities. However, a quantitative evaluation of CDP to correctly predict the epicardial disease and microvascular dysfunction using the preexisting cut-off values of the currently used diagnostic parameters, FFR and CFR, is needed. Thus, we conducted a meta-analysis of the available data from studies reporting both intracoronary pressure (FFR) and flow (CFR) information to determine the limiting value of CDP that can distinguish between patients with epicardial and microvascular dysfunction. We hypothesize that CDP, an index based on combined pressure and flow measurements, has adequate diagnostic accuracy for functional assessment of coronary lesion severity.

**Methods**

**Study eligibility.** All English-language studies that have performed both the invasively measured FFR and CFR evaluation for the same coronary lesions were eligible for this analysis. Studies were considered regardless of the clinical setting (asymptomatic, stable angina, unstable angina, after early myocardial infarction [MI], other) and regardless of whether they addressed native coronary arteries or arteries that had undergone PCI (not bypass grafts). Studies with evaluations of the extent of coronary stenosis, only by visual inspection, were deemed ineligible.

**Search strategy.** We performed a literature search using PubMed, MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Google Scholar, and Internet-based sources of information on clinical trials (www.clinicaltrials.gov, www.tctmd.com, and www.cardiosource.com) for studies written in English from 1990 to 2013 (last updated March 2013). We used the following medical subject headings and search terms: fractional flow reserve; coronary flow reserve; coronary flow; and coronary pressure; in combination with the exploded term “coronary artery disease.” Titles and abstracts were examined, and potentially eligible studies were scrutinized in full text. We reviewed the reference lists of identified articles for additional leads, and selected papers
published before 1990 were also considered. Bibliographies of relevant studies and the “related articles” link in PubMed was also used to identify additional studies. We reviewed all eligible reports for potential overlap in the study populations to retain only the largest of the overlapping studies.

Data extraction. For each eligible study, we documented the first author, journal, year of publication, and number of patients evaluated with FFR and CFR. Data pertaining to intracoronary pressure and velocity were extracted from text, tables, and figures. Some studies reported individual hemodynamic data of intracoronary pressure and flow information and the data were directly documented from these studies. Alternatively, some studies reported the two-dimensional plots of FFR vs CFR data. In such scenarios, the corresponding FFR and CFR data were digitized from the published graphs. The corresponding intracoronary pressure (distal to stenosis) and flow (at hyperemia) information was evaluated using the above-mentioned digitized values and the reported mean values of hemodynamic information (mean pressure proximal to stenosis and mean flow at rest) in each study. The hemodynamic information, pressure and flow, thus evaluated, were used to calculate CDP (pressure drop coefficient).

Calculation of CDP. CDP has been previously described in detail in the literature. Briefly, CDP is defined as the ratio of transstenotic pressure drop ($\Delta p = p_0 - p_f$) to distal dynamic pressure. The product of blood density ($\rho$), the square of average peak flow velocity ($APV$) and a constant value of 0.5, i.e., $0.5 \times \rho \times APV^2$, is calculated to obtain distal dynamic pressure, measured at hyperemia. Blood density, $\rho$, does not change significantly at hyperemia, and thus can be assumed to have a constant value (1.05 g/cm$^3$). Thus,

$$CDP = \frac{\Delta p}{0.5 \times \rho \times APV^2}$$

(a dimensionless parameter; where $\Delta p = p_0 - p_f$)

where $p_0$ and $p_f$ are mean pressures measured proximal and distal to the stenosis at hyperemia, respectively.

Analysis. We examined the diagnostic concordance of CDP vs FFR; CDP vs CFR; and CDP vs FFR and CFR, using receiver operating characteristic (ROC) curve analysis. FFR and CFR will be considered “positive” for values of <0.80 and <2.0, respectively, in the main analysis. Analysis was also performed using a threshold of FFR <0.75.

Statistical analysis. Continuous variables are summarized as mean ± standard error. Analysis of variance was used to analyze the data and assess any significant linear correlations, summarized using both the Pearson ($r$) and Spearman ($\rho$) correlation coefficients among CDP, FFR, and CFR. Multiple linear regression analysis was also conducted to compare simultaneous correlations among hemodynamic parameters.

Sensitivity and specificity estimates for each analysis are independently combined across all the studies using random effects that allow for the possibility that sensitivity and specificity estimates may differ across studies.

The standardized mean difference (SMD) was calculated for effect size based on sample size and 95% confidence intervals (CIs) for each study, and for the pooled studies using variance analysis. Weighted mean difference (WMD) and 95% confidence intervals (CIs) were calculated for continuous data. To assess heterogeneity across the different studies, we used the Cochran Q-test. Heterogeneity was also assessed by means of $I^2$ statistic, as proposed by Higgins et al, thus determining the variance across groups as a result of heterogeneity instead of chance. Based on $I^2$ statistic, values of 25%, 50%, and 75% were considered as yielding low, moderate, and high heterogeneity, respectively.

ROC curve analysis was used to compare the diagnostic performance of CDP with FFR and CFR. ROC curves were generated, and the area under the curve (AUC) was calculated (MedCalc, version 10.2.0.0). The AUC summarizes the accuracy of a diagnostic test. An area of 1 represents a perfect test, while an area of 0.5 represents a bad test. Accuracy of the CDP to correctly predict the outcome of FFR and CFR was calculated for predefined and clinically used cut-off values (CFR = 2.00; FFR = 0.75; and FFR = 0.80). Results were considered statistically significant when $P$-value was <.05.
Results

The initial search resulted in 157 titles. Seven studies were included after the review of abstract and examined full text for eligibility (studies reporting both invasively measured FFR and CFR) (Figure 1). Among these, two studies reported functional measurements (pressure and flow) obtained in individual patients, whereas five studies reported two-dimensional plots of FFR vs CFR. The hemodynamic information, ie, pressure and flow, was evaluated and then used to calculate CDP.

Combined CFR-FFR measurements. Seven studies matched the selection and search criteria, reporting combined CFR-FFR measurements. The corresponding values of CDP were evaluated from individual pressure drop and flow information. Table 1 summarizes the studies reporting invasive CFR and FFR, along with the number of patients in each study. Figure 2 displays all of the available combined invasive CFR and FFR values (n = 329) evaluated in this study. A significant, but modest, correlation exists between invasive CFR and FFR as a whole (r = 0.41 [95% CI, 0.32-0.50; P < .001]; ρ = 0.37 [95% CI, 0.27-0.46; P < .001]).

CDP correlations. Figure 3 shows the linear correlation of CDP with FFR and CFR. As shown in Figure 3A, CDP, when correlated with CFR, had a moderate but significant correlation (r = -0.56 [95% CI, -0.63 to -0.48; P < .001]; ρ = -0.65 [95% CI, -0.71 to -0.59; P < .001]). When correlated with FFR, CDP showed a linear and significant correlation (r = -0.78 [95% CI, -0.82 to -0.74; P < .001]; ρ = -0.81 [95% CI: -0.84 to -0.77; P < .001]), as shown in Figure 3B.

The functional index, CDP, when correlated simultaneously with FFR and CFR, was found to have a significant and improved correlation (r = 0.82; P < .001), and is shown in Figure 4. This is consistent with the definition of CDP, which is a functional parameter that includes both pressure (FFR) and flow (CFR) information.

Diagnostic characteristics of CDP based on FFR. The ROC curve was used to identify the optimal cut-off point of CDP corresponding to FFR < 0.80 and FFR < 0.75, as shown in Figure 5. Table 2 summarizes the ROC analysis for CDP to predict FFR < 0.75 and FFR < 0.80. There were 142 and 181 data points satisfying the criterion for FFR < 0.75 and FFR < 0.80, respectively.

The area under the ROC curve for CDP (Figure 5A), to predict FFR < 0.75, equals 0.89 (95% CI, 0.85-0.92; P < .001), with a sensitivity of 85.2% and specificity of 76.5%. The corresponding CDP value to predict FFR < 0.75 was 27.9. Similarly,
the area under the ROC curve for CDP (Figure 5B), to predict FFR <0.80, equals 0.89 (95% CI, 0.85-0.92; P <.001), with a sensitivity of 80.1% and specificity of 83.1%. The corresponding areas under the curve of the ROC curve for the subgroup analysis in FFR <0.75 and FFR <0.80 were significant at 0.93 and 0.90, respectively. In the subgroups of FFR >0.75 and FFR >0.80, the cut-off value to predict CDP <20 was 27.1. Notably, the ROC curve of CDP yielded a similar AUC for FFR <0.75 and FFR <0.80.

Subgroup analysis of CDP based on CFR. Table 3A shows the subgroup analysis of CDP to detect CFR <2.0 in the FFR <0.75 and FFR >0.75 groups, respectively. In the subgroup of FFR <0.75, the cut-off value to predict CFR <2.0 was CDP >57.9, with a sensitivity of 84.1% and specificity of 93.2%. Similarly, Table 3B shows the subgroup analysis of CDP to detect CFR <2.0 in the FFR <0.80 and FFR >0.80 groups, respectively. In the subgroup of FFR <0.80, the cut-off value to predict CFR <2.0 was CDP >57.9, with a sensitivity of 76.2% and specificity of 93.8%. The corresponding areas under the curve of the ROC curve for the subgroup analysis in FFR <0.75 and FFR <0.80 were significant at 0.93 and 0.90, respectively. In the subgroups of FFR >0.75 and FFR >0.80, the cut-off value to predict CFR <2.0 was a CDP >19.3, with a sensitivity of 63.4% (57.4%) and specificity of 74.1% (85.1%). The corresponding areas under the curve of the ROC curve for the subgroup analysis in FFR <0.75 and FFR <0.80 were significant at 0.75 and 0.76, respectively. Notably, this subgroup analysis (based on FFR) yielded similar cut-off points for CDP to detect CFR, as shown in Table 3. Consolidating the above results, Figure 6 shows the schematic representation of CDP to predict combined assessment of FFR and CFR.

Discussion

Invasive assessment of pressure drop and coronary flow can provide clinically useful information in patients with known or suspected ischemic heart disease. Recent advances in guidewire technology have introduced dual-sensor pressure and flow wires, which will further simplify the simultaneous assessment of pressure drop and flow. This study has established cut-off values for CDP, in order to predict the outcome of FFR and CFR. This study also showed that the fundamental fluid dynamic diagnostic parameter CDP, which incorporates both pressure drop and flow information in its formulation, correlates well with FFR, which is the most frequently used method for evaluation of coronary stenosis severity.

CDP cut-off points predicting the outcome of FFR and CFR. CDP is a fundamental fluid dynamic parameter based on pressure and flow information that can simultaneously distinguish between epicardial stenosis (FFR) and microvascular dysfunction (CFR). The CDP cut-off points to predict FFR <0.75 and FFR <0.80 are shown in Table 2. Similarly, the CDP...
Pressure Drop Coefficient: A Meta-Analysis

Table 1. Summary of studies used in the systematic review.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients / Data Points</th>
<th>Age (years)</th>
<th>Gender M / F</th>
<th>Clinical Setting</th>
<th>Diameter Stenosis</th>
<th>Hyperemia</th>
<th>FFR</th>
<th>CFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meuwissen et al 2008</td>
<td>19 / 16</td>
<td>61</td>
<td>15 / 4</td>
<td>Patients with deferred PCI based on noninvasive stress test</td>
<td>54 ± 9</td>
<td>IC adenosine</td>
<td>0.79 ± 0.02</td>
<td>2.30 ± 0.16</td>
</tr>
<tr>
<td>Di Mario et al 1996</td>
<td>21 / 16</td>
<td>62 ± 10</td>
<td>17 / 4</td>
<td>Patients undergoing PCI</td>
<td>86 ± 0.09</td>
<td>IC papaverine</td>
<td>0.63 ± 0.04</td>
<td>2.04 ± 0.18</td>
</tr>
<tr>
<td>Kolli et al 2013</td>
<td>27 / 27</td>
<td>60 ± 2</td>
<td>25 / 2</td>
<td>Patients undergoing elective angiography and angioplasty</td>
<td>68 ± 2</td>
<td>IV adenosine</td>
<td>0.80 ± 0.02</td>
<td>1.77 ± 0.07</td>
</tr>
<tr>
<td>Tron et al 1995</td>
<td>62 / 65</td>
<td>56 ± 13</td>
<td>55 / 7</td>
<td>Patients undergoing angiography</td>
<td>56 ± 15</td>
<td>IC adenosine</td>
<td>0.66 ± 0.02</td>
<td>1.93 ± 0.08</td>
</tr>
<tr>
<td>Akasaka et al 2003</td>
<td>31 / 30</td>
<td>65 ± 9</td>
<td>NS</td>
<td>Patients referred for elective angiography and angioplasty</td>
<td>51 ± 23</td>
<td>IV adenosine</td>
<td>0.78 ± 0.02</td>
<td>2.10 ± 0.12</td>
</tr>
<tr>
<td>Meuwissen et al 2001</td>
<td>126 / 147</td>
<td>61</td>
<td>NS</td>
<td>Patients with intermediate coronary lesions</td>
<td>61 ± 9</td>
<td>IC adenosine</td>
<td>0.75 ± 0.01</td>
<td>2.27 ± 0.06</td>
</tr>
<tr>
<td>Werner et al 2001</td>
<td>27 / 27</td>
<td>64 ± 8</td>
<td>NS</td>
<td>Repeat angiography</td>
<td>NS</td>
<td>IC adenosine</td>
<td>0.85 ± 0.07</td>
<td>1.91 ± 0.12</td>
</tr>
</tbody>
</table>

1 Patients with acute myocardial infarction (MI), valvular heart disease, and extreme tortuosity of vessel dilated were excluded in Di Mario et al (1996).28
2 Cross-sectional area of stenosis reported in Di Mario et al (1996).28
3 Percent area stenosis reported in Kolli et al (2013).31
4 Patients with previous MI, visible collateral supply, patent bypass graft to the studied vessel, left main coronary artery narrowing (>40% diameter stenosis) and lesions inaccessible to Doppler coronary guidewire were excluded in Tron et al (1995).29
5 Patients with acute MI, unstable angina, valvular heart disease were excluded in Akasaka et al (2003).30

NS = not stated.

Table 2. CDP cut-off based on FFR and CFR cut-off values individually.

<table>
<thead>
<tr>
<th></th>
<th>FFR &lt;0.75</th>
<th>FFR &lt;0.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive (n)</td>
<td>142</td>
<td>181</td>
</tr>
<tr>
<td>Negative (n)</td>
<td>187</td>
<td>148</td>
</tr>
<tr>
<td>Sensitivity (%)</td>
<td>85.2</td>
<td>80.1</td>
</tr>
<tr>
<td>Specificity (%)</td>
<td>76.5</td>
<td>83.1</td>
</tr>
<tr>
<td>CDP cut-off</td>
<td>27.9</td>
<td>27.1</td>
</tr>
<tr>
<td>Area under the curve</td>
<td>0.89 ± 0.02</td>
<td>0.89 ± 0.02</td>
</tr>
<tr>
<td>P-value</td>
<td>.001</td>
<td>.001</td>
</tr>
</tbody>
</table>

Meuwissen et al,30 where highly stenotic lesions were associated with normal CFR values. The values of CDP greater than 57.9 refer to the disease group of physiologically significant FFR and CFR (FFR <0.75 and CFR <2.0). This group can be explained by the presence of significant epicardial stenosis, but the concurrent presence of microvascular disease cannot be excluded. It may be noted that in current clinical practice, for the physiologically significant FFR and CFR disease group, we conclude the presence of microvascular disease in a sequential process of fixing the epicardial lesion and then evaluating whether the CFR is still less than 2. We believe that CDP will

cut-off points to predict CFR <2.0 in the positive and negative FFR subgroups are shown in Table 3. Consolidating the above results, Figures 6 and 7 show the schematic representation of four different disease combinations based on FFR (epicardial disease) and CFR (microvascular disease).

Considering the FFR cut-off of 0.75 as shown in Figure 6, the range of CDP to predict both physiologically insignificant CFR and FFR (FFR >0.75 and CFR >2.0) is between 0 and 19.3, whereas the range of CDP to predict physiologically insignificant FFR and significant CFR (FFR >0.75 and CFR <2.0) is between 19.3 and 27.9. Similarly, the range of CDP to predict physiologically significant FFR and insignificant CFR (FFR <0.75 and CFR >2.0) is 27.9 and 57.9. In this group, the expected physiological interpretation would be the presence of a significant epicardial stenosis (FFR <0.75) and a functionally preserved microcirculation (CFR >2.0). The explanation of the values in this group has to be further investigated, since theoretically CFR should also be affected by the significant epicardial stenosis and its value may not be greater than 2. However, a possible explanation is that some lesions can be detected by FFR, but missed by CFR, because unlike FFR, CFR has a large interindividual variability, influenced by heart rate, contractility, age, gender, and physical training among other factors.34,35

This hypothesis is supported by data from Wilson et al36 and
be able to diagnose this concomitant disease without adopting the sequential process.

For an FFR cut-off of 0.80, as shown in Figure 7, the range of CDP to predict both physiologically insignificant CFR and FFR (FFR >0.80 and CFR >2.0) is between 0 and 19.3, whereas the range of CDP to predict physiologically significant FFR and significant CFR (FFR >0.80 and CFR <2.0) is between 19.3 and 27.1. Similarly, the range of CDP to predict physiologically significant FFR and insignificant CFR (FFR <0.80 and CFR >2.0) is 27.1 and 57.9, whereas values of CDP >57.9 refer to the disease group of physiologically significant FFR and CFR (FFR <0.80 and CFR <2.0).

Thus, for the present patient population, cut-offs for CDP are obtained from pressure and flow measurements using meta-analysis, to delineate the epicardial disease and microvascular dysfunction.

**Heterogeneity of pooled analysis.** Pooled population (Table 1) from different studies might have heterogeneity. The results (for the endpoint FFR <0.80) of the different studies, and the overall standardized mean differences with 95% CIs are shown in the forest plot (Figure 8). The Q-value for the test of heterogeneity is 5.39 (degree of freedom = 6; \( P=0.49 \)). The heterogeneity was also assessed by means of \( I^2 \) statistic as proposed by Higgins et al\(^2\) (determining the variance across groups as a result of heterogeneity instead of random error). The index of inconsistency, \( I^2 \), represents the percentage of the total variation, which is due to variations between studies. There was no significant heterogeneity with respect to the endpoint of FFR <0.80 and FFR <0.75 (\( I^2 = 0\% ; P=0.43 \)).

**Combined measurement of pressure and flow.** We have also correlated another diagnostic parameter that combines pressure and flow measurements, HSR (hyperemic stenosis resistance: ratio of transstenotic pressure drop to the distal average peak velocity)\(^3\) in relation to CDP. It should be noted that CDP when correlated with HSR (Figure 9), a linearly significant correlation (\( r=0.97; P<0.001 \)) was observed. This is expected, since both CDP and HSR are measures of stenosis resistances as they are functions of both pressure and flow measurements.

**Advantages of pressure drop coefficient.** It should be noted that physiologically, the extent of reduction in maximal hyperemic flow due to microvascular dysfunction is higher than that due to epicardial stenosis. In such circumstances, the square of maximal hyperemic flow in the denominator of CDP magnifies this reduction, thus providing an increased resolving power for CDP. This allows improved delineation of the status of epicardial vessel and microcirculation simultaneously. Theoretically, the values of CDP range from zero to infinity. Furthermore, it should be noted that in the presence of microvascular dysfunction and submaximal hyperemia, pressure drop and blood flow are affected in the same direction. In such scenarios, as mentioned previously, diagnostic indices based on either pressure or flow alone can be affected significantly. CDP, however, is a diagnostic parameter based on both pressure and flow information, and is thus expected to be unaffected and show a similar trend. Thus, in the future, we plan to evaluate the effect of hyperemia on CDP by comparing the CDP measured under hyperemia and baseline conditions (without needing hyperemia).

**Study limitations.** Seven studies were included in this meta-analysis. Among these, two studies (group 1)\(^22,29 \) reported functional measurements (pressure and flow) obtained in individual patients; whereas five studies (group 2)\(^30-34 \) reported two-dimensional plots of FFR vs CFR, allowing digitization of FFR and CFR data from the published graphs. The corresponding intracoronary pressure (distal to stenosis) and flow (at hyperemia) information was evaluated using these digitized values and the reported mean values of hemodynamic information (mean flow at rest and mean pressure proximal to stenosis) in each study. However, to further compare the interpretation.

### Table 3. CDP cut-off based on subgroup analysis of FFR to detect CFR.

<table>
<thead>
<tr>
<th>Subgroup analysis with FFR cut-off of 0.75 and CFR cut-off of 2.0. Number of data points in parentheses.</th>
<th>FFR &lt;0.75 (142)</th>
<th>FFR &gt;0.75 (187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR &lt;2.0 (83)</td>
<td>CFR &gt;2.0 (59)</td>
<td>CFR &lt;2.0 (71)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>84.1%</td>
<td>63.4%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.2%</td>
<td>74.1%</td>
</tr>
<tr>
<td>CDP cut-off</td>
<td>57.9</td>
<td>19.3</td>
</tr>
<tr>
<td>AUC</td>
<td>0.93 ± 0.02</td>
<td>0.75 ± 0.04</td>
</tr>
<tr>
<td>( P )-value</td>
<td>.001</td>
<td>.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subgroup analysis with FFR cut-off of 0.80 and CFR cut-off of 2.0. Number of data points in parentheses.</th>
<th>FFR &lt;0.80 (181)</th>
<th>FFR &gt;0.80 (148)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFR &lt;2.0 (100)</td>
<td>CFR &gt;2.0 (81)</td>
<td>CFR &lt;2.0 (54)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76.2%</td>
<td>57.4%</td>
</tr>
<tr>
<td>Specificity</td>
<td>93.8%</td>
<td>85.1%</td>
</tr>
<tr>
<td>CDP cut-off</td>
<td>57.9</td>
<td>19.3</td>
</tr>
<tr>
<td>AUC</td>
<td>0.90 ± 0.02</td>
<td>0.76 ± 0.04</td>
</tr>
<tr>
<td>( P )-value</td>
<td>.001</td>
<td>.001</td>
</tr>
</tbody>
</table>
of this methodology, we evaluated the weighted average means of the flow values at rest and hyperemia between group 1 and group 2. There was no significant difference (P=0.05) in the mean values of the flow at rest (21.33 ± 6.71 cm/s in group 1 vs 20.03 ± 8.35 cm/s in group 2) and hyperemia (39.77 ± 9.47 cm/s in group 1 vs 42.22 ± 14.62 cm/s in group 2). Nonetheless, we believe that patient level meta-analysis of the trials reporting individual hemodynamic data could add to the current analysis.

Conclusion

This meta-analysis based on the available data from studies reporting both intracoronary pressure and flow information determined the diagnostic cut-off values of CDP that can differentiate between the hemodynamic status of epicardial stenosis and microvascular dysfunction. The combined pressure and flow diagnostic parameter, CDP, had a close agreement (area under ROC curve = 89%) with FFR and a good correlation with FFR and CFR. The present data also highlight the need for combined assessment of pressure and flow information for detecting CAD. Therefore, we believe that CDP by combining both velocity and pressure information might be more accurate than FFR or CFR in predicting functional significance of stenosis.

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References