A Novel Flow-Based Parameter of Collateral Function Assessed by Intracoronary Thermodilution

Markus Lindner, Stephan B. Felix, MD, Klaus Empen, MD, Thorsten Reffelmann, MD

ABSTRACT: Background. Currently, many methods for quantitation of coronary collateral function are based on intracoronary pressure measurements distal of an occluded balloon, which do not fully account for the dynamic nature of collateral flow. Therefore, a flow-based parameter of coronary collateral function based upon principles of thermodilution was evaluated. Methods. In 26 patients with a high-grade coronary artery stenosis, intracoronary hemodynamics were analyzed by the RadiAnalyzer system (St Jude Medical), including fractional flow reserve (FFR), index of microcirculatory resistance (IMR), and the pressure-based collateral flow index (CFI) during balloon occlusion and hyperemia (intravenous adenosine). Moreover, immediately after an intracoronary bolus of room-temperature saline, the balloon was occluded and the intracoronary temperature distal to the balloon was analyzed over time. The slope of the temperature-time curve was calculated after logarithmic transformation as an index of collateral blood flow (CBFI). Results. The coefficient of variation between two measurements of CBFI amounted to 11 ± 2%. In patients with CFI ≥ two measurements of CBFI amounted to 11 ± 2%. In patients with CFI <0.25, CBFI amounted to 0.55 ± 0.09, whereas in those with CFI ≥0.25, CBFI was 0.37 ± 0.03. CBFI correlated significantly with CFI (r = 0.65; P < 0.001). Interestingly, in the subgroup with IMR below the median (<14.2 mm Hg • s), the slope of the linear regression for CBFI vs CFI was steeper than in individuals with higher IMR, which indicates more effective collateral flow for any given intracoronary pressure distal to the occluded balloon in the group with lower microvascular resistance. Conclusions. This novel index might be useful as a flow-based index of collateral function, and should be evaluated in further studies.


Key words: coronary collateral function, fractional flow reserve

To date, various angiographic indices as well as flow- and pressure-derived parameters are used for quantitation of coronary collateral function.1-4 Collateral flow index (CFI), originally introduced as collateral fractional flow reserve in 1993,2 measured as the difference between distal coronary occlusion pressure and central venous pressure during intracoronary balloon inflation divided by the difference between aortic pressure and central venous pressure, is presumed to be the “gold standard,” in particular when determined during maximum coronary vasodilation (eg, systemic adenosine infusion).2,4,6,7,9,10 However, this index does not fully take into account the dynamic aspect of coronary collateral flow: apart from pressure differences between the three compartments (aortic pressure, distal occlusion pressure, venous pressure), the resistance of the collateral circulation and the resistance of the myocardium supplied by the coronary arterial segment, which is occluded by the balloon, determine flow through the collateral network.2 In situations where distal myocardial resistance is increased (eg, due to vasoconstriction), CFI appears to be higher than expected, which led to the above-mentioned recommendation to measure CFI during maximum vasodilation (eg, 140 μg adenosine/kg/min intravenously).3,7,9,10 Even with fixed elevations of myocardial resistance, as it may occur downstream to a stenosis due to the no-reflow phenomenon resulting from previous myocardial infarction or coronary microembolization,11 apparently high CFI values may not only reflect low collateral resistance, but impeded outflow toward the venous vasculature.

Therefore, parameters estimating effective collateral flow rather than distal coronary pressure at steady state during balloon occlusion may be more suitable for quantifying the functional collateral capacity. In this pilot study, we present a novel flow-based parameter of collateral function in patients with coronary artery disease based upon principles of intracoronary thermodilution.

Methods

The study protocols are consistent with the principles of the Declaration of Helsinki and were approved by the Ethics Committee of the University of Greifswald.

Patient population and inclusion/exclusion criteria. Prior to angioplasty, informed consent was obtained from all patients. Patients 18-90 years old with a high-grade coronary artery atherosclerotic stenosis scheduled for percutaneous coronary intervention (PCI) were eligible for this study. Only stenoses within the proximal parts of the epicardial artery were included in order to ensure that the tip of the guidewire could be safely positioned in the distal artery at a site of sufficient luminal diameter. Exclusion criteria were: acute ST-segment elevation and non-ST-segment elevation myocardial infarction (within 48 hours), glomerular filtration rate <30 mL/min (estimated by the Modification of Diet in Renal Disease [MDRD] formula),12 stenoses with involvement of the left main stem, bifurcational stenosis, diffuse atherosclerotic lesions, lesions located in the distal third of the epicardial artery, and expectedly complex PCI procedures according to the physician’s discretion, eg, those requiring special guidewires or additional devices.

Study protocol. After taking the patient’s history (including atherosclerotic risk factors), blood pressure was measured, a 12-lead electrocardiogram (ECG) was performed, and standard laboratory parameters including blood count, electrolytes, creatinine, urea, thyroid stimulating hormone, cholesterol, low-density lipoprotein,
high-density lipoprotein, triglycerides, glucose, and coagulation parameters were taken. All patients scheduled for PCI received oral aspirin and clopidogrel prior to the intervention.

Coronary intervention and intracoronary measurements. All coronary interventions were carried out using standard procedures. Femoral arterial and venous access was obtained using the Seldinger technique. A pigtail catheter was advanced into the vena cava inferior to the right atrium junction to measure central venous pressure. After positioning the coronary guiding catheter a calibrated Radi PressureWire Certus (St Jude Medical) was advanced into the distal coronary artery. Only patients with a side branch of the coronary artery adjacent to the temperature sensor were included.

Fractional flow reserve (FFR; mean distal intracoronary pressure / mean aortic pressure [pressure at the tip of the guiding catheter]) and coronary flow reserve (CFR; ratio of mean transit time of an intracoronary cold bolus under baseline conditions to hyperemia [3 mL room temperature saline, three measurements each]) were determined. Hyperemia was induced by intravenous adenosine (140 µg/kg/min). The index of microcirculatory resistance (IMR) was calculated as the pressure distal to the stenosis multiplied by mean transit time. In patients with a chronic total occlusion, mean distal intracoronary pressure / mean aortic pressure during the first balloon inflation within the reopened coronary artery measured under adenosine was taken as an estimate of FFR.

According to the manufacturer, the pressure sensor of the Radi PressureWire Certus measures with an accuracy of ±1 mm Hg from -30 to 300 mm Hg with a sampling frequency of 0-25 Hz. In temperature mode, the sensor measures from 15-42 °C with an accuracy of at least 0.05 °C or 10% of ∆T, whichever is greatest, with a sampling rate of 0-7 Hz.

Measurement of the novel collateral blood flow index (CBFI). During the angioplasty procedure, the intracoronary temperature distal to the occluded balloon was registered via the Radi PressureWire Certus during each balloon inflation with a simultaneous intravenous infusion of adenosine (140 µg/kg/min). To ensure that the temperature sensor of the wire was positioned distally to the balloon, the tip of the wire was advanced more than 3 cm distally to the distal end of the balloon. During the first balloon inflation (without administration of room-temperature saline), distal temperature was recorded to evaluate whether the balloon inflation itself had any influence on measured distal temperature. Prior to the second balloon inflation, an intracoronary flush of room-temperature saline (approximately 3-5 mL) was given until intracoronary temperature

Figure 1. Typical temperature curve during collateral blood flow index (CBFI) measurement, as recorded by the RADI-analyzer. This figure shows the interface of the RADI-analyzer in temperature mode. At the top, mean pressure distal to the stenosis (Pd) and mean aortic pressure (Pa), as well as their ratio (FFR) are shown. In the bottom window, temperature is constantly recorded. After a flush of room-temperature saline, the temperature decreases, the balloon is occluded, and simultaneously, distal intracoronary pressure decreases. During occlusion, temperature returned to baseline. At the bottom right, the temperature curve is seen after logarithmic transformation. The slope of the linear regression equals CBFI.

Figure 2. Repeatability of collateral flow index (CFI; left) and collateral blood flow index (CBFI; right) between the first and second registration of the intracoronary temperature curve during balloon occlusion after a room-temperature bolus injection of saline (regression line and 95% confidence interval).
had dropped by at least 1-3 °C. Immediately after the temperature drop had occurred, the balloon was inflated and the flush of saline was stopped. The change in intracoronary temperature over time toward baseline temperature was recorded. To assess repeatability, the procedure was repeated during the next balloon inflation. When it was safe to advance the wire more distally, the measuring procedure was repeated with the wire tip more distal to estimate the influence of the wire position on the values of CBFI.

During these measurements, temperature asymptotically increased from the initial temperature drop back to baseline (Figure 1). Temperature-time curve analysis started once complete balloon occlusion was reached, as indicated by the reduction of intracoronary pressure. After logarithmic transformation, this curve was approximated by a linear equation. By the method of least squares, CBFI was calculated as the slope of its linear regression and multiplied by 1000 (Appendix 1).

Simultaneously, during each balloon occlusion, collateral flow index (CFI) was assessed as a ratio of pressure distal to the stenosis minus central venous pressure to mean aortic pressure minus central venous pressure.2-4

To calculate CBFI, recorded data were exported from the RADI analyzer into ASCII format with 100 time points per second. Further conversion by Microsoft Excel resulted in a temperature listing in °C to the third decimal place.

Quantitative coronary angiography (QCA). Vessel diameters, diameter stenosis, and the distance between the tip of the PressureWire and the distal end of the balloon were analyzed offline, using the QCA tool provided by the program Horizon Cardiology 11.1, with client TCS 3.2 service pack 6 (McKesson). The diameter and length of the stenosis were measured three times (renewed calibration each) and then averaged.

Statistical analysis. The statistical analysis was carried out using SigmaPlot 11.0 (Systat Software). For comparison between groups, unpaired t-test or one-way analysis of variance (ANOVA) was used. Correlation analysis was performed using Pearson’s model or Spearman rank order. Multiple linear regressions (least square method) were compared by analysis of covariance (ANCOVA). Results are expressed as mean ± standard error of the mean or percentages. The coefficient of variation was calculated as standard deviation divided by the mean (as percentage). A P-value <.05 was considered statistically significant.

Results
Exclusions. Out of 32 patients, 6 were excluded from final analysis due to the following reasons: 5 patients were not included because QCA showed that the wire was positioned in a small side branch and the vessel diameter was too small (<1.3 mm). In 1 patient, the tip of the wire was <3 cm distal to the balloon. Thus, the final study population consisted of 26 patients.

Patient characteristics. The risk profile and clinical data of the patients are presented in Table 1. Thirteen out of 26 patients had prior myocardial infarction (MI); 7 MIs had occurred in the area that was treated by angioplasty in this study. Four patients had a CTO of the treated coronary artery. Ten out of 26 patients had a CFI >0.25, which is assumed to be a marker for relevant collateral flow.

According to the Rentrop’s angiographic grading of collaterals, 3 patients were classified as Rentrop III, 1 patient as Rentrop II, and 22 as Rentrop 0. Table 2 illustrates hemodynamics as assessed by intracoronary pressure measurements and thermodilution.

Measurement of CBFI, feasibility, and repeatability. During the first balloon inflation without the initial flush of saline, measured
In coronary arteries with a diameter >1.3 mm at the sensor position, CBFI correlated significantly with CFI. Regarding patients with increased myocardial resistance within the coronary territory supplied by the occluded part of the coronary artery, an interesting observation could be made, ie, the flow-based parameter of collateral function indicated less flow for any given value of CFI in comparison to coronary arteries with lower myocardial resistance.

**Hemodynamics of collateral function.** Currently, CFI, originally introduced as collateral fractional flow reserve in 1993, is presumed to be the gold standard, in particular when determined during maximum coronary vasodilation (eg, intravenous adenosine infusion). However, collateral function is not only characterized by pressure differences between the three coronary compartments (aortic pressure, distal occlusion pressure, venous pressure), but also by the resistance of the collateral network as well as microvascular resistance of the myocardium supplied by the coronary arterial segment that is occluded by the balloon. Since flow over the collaterals to the coronary artery and flow from the coronary over the microvasculature toward the venous system are in series, both are equal during balloon occlusion. Therefore, provided there is no hemodynamically significant stenosis proximal to the origin of the collateral network, flow can be related to collateral and myocardial resistance (according to Ohm's law), using the following equations where \( \Delta p = \) aortic pressure, \( \Delta p_d = \) distal pressure, \( Z_{VD} = \) central venous pressure, and \( R = \) resistance:

\[
\text{Flow}_{\text{vascular}} = \frac{(\Delta p - \Delta p_d)}{R_{\text{collateral}}} = \frac{(\Delta p - \Delta V_{D})}{R_{\text{myocardial}}} = \frac{(\Delta p - \Delta V_{D})}{(R_{\text{collateral}} + R_{\text{myocardial}})}
\]

Therefore, CFI equals:

\[
\text{CFI} = \frac{R_{\text{myocardial}}}{(R_{\text{collateral}} + R_{\text{myocardial}})}
\]

As a consequence, pressure-derived CFI is influenced by the resistance of the collateral circulation (with high collateral resistance \( R_{\text{collateral}} \gg R_{\text{myocardial}} \) resulting in low CFI, and by the resistance of the myocardial circulation with high myocardial resistance \( R_{\text{myocardial}} \gg R_{\text{collateral}} \) resulting in a CFI near 1, even if collateral flow is low).

In situations where distal myocardial resistance is high (eg, due to vasconstriction), CFI appears to be higher than expected, which led to the above-mentioned recommendation to measure CFI during maximal vasodilation (eg, 140 \( \mu \)g adenosine/kg/min intravenously). By the same token, this may also be the case with fixed elevations of myocardial resistance, as it may occur downstream to a stenosis, eg, due to the no-reflow phenomenon. Apparently, high CFI values may not reflect low collateral resistance, but rather impeded outflow toward the venous vasculature.

Therefore, measurements of parameters related to effective collateral flow rather than resulting coronary pressure at steady state may be more suitable for characterizing the functional capacity of the collateral network. Another frequently used index for characterizing collateral flow is derived from measurements of blood flow velocities using an intracoronary Doppler flow wire. For this purpose, coronary flow velocities during complete balloon occlusion (measured distally to the occluded balloon) were divided by flow velocities at the same site after successful balloon angioplasty. Hereby, the average peak velocity, as assessed by intracoronary Doppler spectra during...
maximum vasodilation distal to the occluded balloon was divided by the average peak velocity at the same site after balloon dilatation. This approach assumes that flow after angioplasty is immediately restored to normal; even more importantly, it cannot account for the unpredictable direction of coronary flow during balloon occlusion (as the main collaterals may insert more distally or proximally to the tip of the flow wire).

**A novel flow-based index of collateral function.** Assuming that distal temperature (after coronary balloon occlusion) is predominately determined by convection, ie, collateral flow, and direct thermic conduction is negligible, which is presumed to be the case with sufficient vessel diameters, the temperature in the distal coronary segment should asymptotically increase back to zero after the initial temperature drop caused by the intracoronary saline flush. This equation is transformed logarithmically. The slope of the resulting linear equation is approximated by the method of least squares and taken for the amount of relative collateral blood flow, called CBFI. In order to standardize the procedure, the measurements should be undertaken during 140 µg/kg/min adenosine intravenously to ensure maximum coronary vasodilation. The distal tip of the wire should be at least >3 cm distal to the balloon to make sure the sensor is reliably outside of the balloon. In addition, a side branch of the coronary artery should exist adjacent to the temperature sensor.

The results of this pilot study indicate a good correlation between CBFI and CFI, as long as the vessel diameter is sufficient. Most importantly, this parameter appeared to reflect dynamic flow rather than static pressures as a marker of collateral function. This ties in well with the observation that the relation between CBFI and CFI tended to be higher when peripheral resistance was low in comparison to higher resistance in the myocardium supplied by the segment of the coronary artery treated by PCI. However, in the presence of a severe stenosis, IMR might overestimate myocardial resistance to a certain degree, which could slightly weaken this correlation. Moreover, given further specification of accuracy and validity of CBFI, the relationship between intracoronary pressure distal to the occluded balloon, central venous pressure, and CBFI might also be used as an index of microvascular resistance in the supplied myocardial territory. Notably, as shown in Figure 2, the two measurements of collateral function under identical conditions did not point to the recruitment of collateral function during two subsequent balloon occlusions in our setting, neither when CFI nor when CBFI was used as a measure of collateral function. This is in contrast to a 1999 study by Billinger et al, where subsequent balloon inflations over 2 minutes resulted in an increase in CFI from 0.13 ± 0.11 during the first inflation to 0.19 ± 0.10 during the third inflation. Apart from different study populations with different cardiovascular risk profile in Billinger’s study, there might be two reasons for this discrepancy between the studies. First, in our study an initial balloon inflation was performed to exclude any influence of balloon occlusion on distal temperature measurements. This first balloon occlusion might have had influence on subsequent measurements in our study. Second, the balloon inflations in Billinger’s study were carefully standardized to 2 minutes of occlusion each. In our study, the length of our balloon occlusions were left to the physician’s discretion because it was judged necessary to achieve an adequate PCI result. In our setting, with an average measuring time of 29 ± 2 s, no evidence for collateral recruitment was demonstrated.

### Table 1. Patient characteristics, medications, and angiographic findings.

<table>
<thead>
<tr>
<th>Patients</th>
<th>26 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male)</td>
<td>19 (73%)</td>
</tr>
<tr>
<td>Age</td>
<td>70 ± 1.6</td>
</tr>
<tr>
<td>Current smokers</td>
<td>11 (42%)</td>
</tr>
<tr>
<td>Hypertensives</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Dyslipoproteinemia</td>
<td>23 (88%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>30 ± 1.1</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>13 (50%)</td>
</tr>
<tr>
<td>Prior infarction in treated coronary artery</td>
<td>7 (27%)</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>14 (54%)</td>
</tr>
<tr>
<td>1-vessel coronary heart disease</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>2-vessel coronary heart disease</td>
<td>8 (31%)</td>
</tr>
<tr>
<td>3-vessel coronary heart disease</td>
<td>15 (58%)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>26 (100%)</td>
</tr>
<tr>
<td>Statin</td>
<td>25 (96%)</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>24 (92%)</td>
</tr>
<tr>
<td>ACE inhibitor/AT-II receptor antagonist</td>
<td>25 (96%)</td>
</tr>
</tbody>
</table>

*Data given as number (percentage) or mean ± standard error of the mean.*

### Table 2. Hemodynamics assessed by intracoronary pressure measurement and thermodilution in patients with collateral flow index (CFI) ≥0.25 and patients with CFI <0.25.

<table>
<thead>
<tr>
<th>CFI ≥0.25 (n = 10)</th>
<th>CFI &lt;0.25 (n = 16)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFI</td>
<td>0.39 ± 0.04</td>
<td>0.15 ± 0.01</td>
</tr>
<tr>
<td>CBFI</td>
<td>0.55 ± 0.09</td>
<td>0.37 ± 0.03</td>
</tr>
<tr>
<td>CFR</td>
<td>1.35 ± 0.10</td>
<td>1.45 ± 0.07</td>
</tr>
<tr>
<td>FFR</td>
<td>0.62 ± 0.06</td>
<td>0.77 ± 0.03</td>
</tr>
<tr>
<td>IMR (mm Hg • s)</td>
<td>19.14 ± 4.57</td>
<td>16.21 ± 1.60</td>
</tr>
<tr>
<td>Stenosis (%)</td>
<td>86.5 ± 5.1</td>
<td>79.9 ± 2.6</td>
</tr>
</tbody>
</table>

*CFI = collateral flow index (pressure-derived); CBFI = collateral blood flow index (thermodilution); CFR = coronary flow reserve; FFR = fractional flow reserve; IMR = index of microvascular resistance. P-values between groups; NS = not significant. ‘Four total coronary occlusions.*

### Study limitations. As demonstrated above, the measured CBFI value increased when the wire was further advanced into the coronary artery. Therefore, careful standardization of the measuring procedure is mandatory with the sensor position outside the occluded balloon and a coronary vessel of sufficient size. Only coronary arteries of sufficient size (>1.3 mm) and stenoses in the proximal to mid part of the arteries are eligible for these measurements. In smaller arteries, CBFI appeared to be inadequately high, probably due to direct thermal conduction. Furthermore, a marginal location of the wire within the coronary artery is likely to result in altered temperature measurements due to the proximity of the vessel wall. Repeatability of two subsequent measurements under identical conditions
was relatively good (coefficient of variation 11 ± 2%). Most importantly, the initial temperature drop, which substantially differed between two intracoronary injections of saline, had no consistent effect on CFI, which was measured as the slope of the temperature time curve after logarithmic transformation. This is in agreement with the high coefficient of determination ($R^2 = 0.97$) of the linear regression of these curves. Moreover, the time point, when complete balloon occlusion was achieved, which was the starting point for the measurements, could be easily defined from the intracoronary pressure measurements (compare Figure 1). Even if this parameter does not represent absolute collateral flow, it does appear to be closely related to it, since indices of myocardial resistance strongly influenced the relation between CFI and CBFI.

**Conclusion**

This novel parameter of collateral function might be validated in larger studies including other parameters of collateral flow (eg, scintigraphic techniques in total coronary occlusions). Our results suggest that this parameter may in part account for changes in distal myocardial microvascular resistance, therefore representing a flow-based parameter. If further validation is possible, and limitations of accuracy can be precisely defined, this parameter in conjunction with CFI might also be useful to estimate myocardial viability within the supplied coronary territory, as fixed total coronary occlusions. Our results suggest that this parameter may in part account for changes in collateral flow (eg, scintigraphic techniques for assessing function of coronary microcirculation).

Furthermore, collateral flow and myocardial viability may be closely linked in patients with recent myocardial infarction. Studies on temporal development of collateral function and pathophysiological determinants may also include a flow-based parameter to fully account for the dynamic nature of collateral flow.

**References**


**Appendix 1. Mathematical equations for calculation of collateral blood flow index (CFI).**

During the performed measurements temperature asymptotically increased from the initial temperature drop back to baseline (Figure 1). After logarithmic transformation, this curve was approximated by a linear equation. By the method of least squares, CFI was calculated from the slope of its linear regression:

Starting with a linear equation like

$$f(x) = a_0 + a_1 x$$

the approximation by the method of least squares provides:

$$a_1 = \frac{\sum_{i=1}^{n} (y_i - \bar{y})(x_i - \bar{x})}{\sum_{i=1}^{n} (x_i - \bar{x})^2}$$

with $\bar{x}$ measurement at timepoint $i$.

$$\text{with } T_i = \text{temperature at timepoint } i$$

and $T_0 = \text{temperature at the starting point it equals:}$

$$\text{(} y_i - \bar{y} \text{)} = \ln(T_i) - \ln(T_0) - \ln(T_0) - \ln(T_0)$$

With a negative temperature drop at the beginning, the final equation for CFI was:

$$\text{CFI} = \frac{\sum_{i=1}^{n} (x_i - x)^2}{\sum_{i=1}^{n} (x_i - \bar{x})^2}$$

$$\times 1000$$