Pressure-Derived Collateral Flow Index as a Parameter of Microvascular Dysfunction in Acute Myocardial Infarction

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OBJECTIVES

The goal of this study was to examine the implications of the pressure-derived collateral flow index (CFIp) in acute myocardial infarction (AMI).

BACKGROUND

Higher CFIp is associated with less severe myocardial ischemia during angioplasty in the non-infarcted heart. It remains unknown whether CFIp also identifies collateral function in AMI patients with and without no-reflow phenomenon.

METHODS

The study population included 48 patients with a first AMI. After successful percutaneous transluminal coronary angioplasty (PTCA) stent, we measured mean aortic pressure (Pa), central venous pressure (Pv) and coronary wedge pressure (Pcw) of the infarct-related artery to calculate: CFIp = (Pcw – Pv)/(Pa – Pv). Myocardial contrast echocardiography (MCE) was performed with the intracoronary injection of microbubbles to assess myocardial perfusion. Left ventriculograms at days 1 and 28 were provided for the measurement of the regional wall motion (RWM, SD/chord).

RESULTS

There was no difference in CFIp among subsets based on angiographic collateral grades (grade 0, 1, 2, 3; 0.28 ± 0.07, 0.27 ± 0.09, 0.27 ± 0.08, 0.23 ± 0.08, p = NS). The CFIp was significantly higher in patients with MCE no-reflow (n = 16) than in those with MCE reflow (n = 32) (0.34 ± 0.07 vs. 0.23 ± 0.06, p < 0.01). There was a significant inverse correlation between the extent of functional improvement (∆RWM[28 d–1 d]) and CFIp (r = 0.56, p < 0.01), implying that higher CFIp is associated with worse functional improvement.

CONCLUSIONS

In AMI, CFIp is unlikely to reflect collateral function but seems to increase with the severity of microvascular dysfunction. Because higher CFIp was associated with poorer functional recovery, it provides a simple and useful estimate of clinical outcomes in AMI. (J Am Coll Cardiol 2001;38:1383–9) © 2001 by the American College of Cardiology

Coronary reperfusion therapy with thrombolysis and/or percutaneous coronary intervention (PCI) has brought beneficial clinical outcomes in patients with acute myocardial infarction (AMI). The beneficial impact of coronary reperfusion, however, varies among patients (1–5). Several factors have been postulated to account for the variation, which include age, elapsed time from symptom onset to reperfusion, preinfarction angina and collateral channels (3–8). Collateral channels are usually assessed with coronary angiography, but we may not necessarily evaluate most collateral networks in the myocardium (9). Recently, several studies have reported that the intracoronary pressure measurements with pressure wire allow us to assess collateral function in the non-infarcted heart (10–13). Pressure-derived collateral flow index (CFIp) is hypothesized to increase with an increase in collateral flow, and the higher CFIp is associated with the less severe myocardial ischemia during PCI. Likewise, higher CFIp in TIMI (Thrombolysis In Myocardial Infarction trial)-3 flow AMI patients was associated with better functional outcomes (14). These findings were not identified in patients with AMI with no-reflow or TIMI-2 reflow despite much evidence showing that the microvascular dysfunction is common in patients with AMI (15–21).

This study was designed to assess whether CFIp reflects collateral function in patients with AMI under the presence of microvascular dysfunction. We assessed the severity of microvascular dysfunction with both myocardial contrast echocardiography (MCE) and TIMI flow grade and studied the relation between no-reflow phenomenon and CFIp. Finally, we assessed the clinical value of the new pressure-derived index in assessing functional outcomes in patients with reperfused AMI.

METHODS

Study population. We prospectively studied 52 patients with first AMI, referred to our hospital between January 2000 and October 2000, who met the following criteria: 1) chest pain >30 min in duration and presentation ≤24 h after the symptom onset; 2) ST segment elevation ≥2 mm in at least two electrocardiograph (ECG) leads; 3) >3-fold increase in serum creatine kinase; 4) TIMI-0 or -1 flow at baseline study; 5) successful coronary reflow (residual diameter stenosis <25%) after the primary PCI; and 6) under-
going MCE study shortly after PCI. Exclusion criteria were the presence of cardiogenic shock, previous bypass surgery, moderate-to-severe valvular lesions, atrial fibrillation and recurrent ischemic events during the follow-up period. Four patients were excluded: three because of severe congestive heart failure and one because of reinfarction during follow-up. Thus, 48 patients were enrolled in this study. The study protocol was approved by the ethics committee of our hospital, and written informed consent was obtained from all patients before cardiac catheterization by one of the investigators.

**Protocols.** We gave aspirin (243 mg) to each patient. Following intravenous (IV) heparin (100 U/kg), we performed left and right coronary angiography and left ventriculography (right anterior oblique view) using the right femoral approach with the Judkins technique. We performed primary PCI according to the protocol of our hospital to achieve residual diameter stenosis of <25%. A 0.0014-in. (0.036 cm) fiber optic pressure monitoring guide wire (Wave Wire, Endo Sonics, Rancho Cordova, California) was set at 0 calibrated, advanced through the guiding catheter and positioned distal to the culprit lesion. After intracoronary injection of 0.3 mg nitroglycerin, the culprit lesion was occluded by the inflated balloon to measure distal coronary pressure. We simultaneously measured mean aortic pressure (Pa) (mm Hg, via the guiding catheter), the distal coronary artery wedge pressure during balloon occlusion (Pcw) (mm Hg) and central venous pressure (Pv). The CFIp (unitless) was calculated as (Pcw−Pa)/Pv.

At a mean of 16 min after PCI, we injected 2 ml of sonicated Ioxaglate (Hexabrix-320, Tanabe) containing microbubbles of a mean size of 12 µm into the right or left coronary artery, whichever included the infarct lesion, to study the contrast reperfusion pattern (19–21). Echocardiograms were monitored using a mechanical sector scanner (SONOS100, Agilent Technologies, carrier frequency of 3.5 MHz). The MCE images were recorded on SVHS videotape (AG-6300, Panasonic); MCE images included the parasternal short-axis view at the mid-papillary muscle level and the apical two-chamber and four-chamber views. Coronary angiography and left ventriculography were also performed at a mean of 28 days after PCI.

**Evaluation of angiographic data.** Angiographic collateral grade was determined by two independent observers according to Rentrop’s classification (22). These observers also evaluated TIMI flow grade of the infarct-related artery at days 1 and 28 (23). The global left ventricular ejection fraction (LVEF) was measured with the area–length method and regional wall motion (RWM) with the centerline method all by the same physician, who had no knowledge of the patient’s data (24). Both ALVEF and ARWM were calculated as the difference of the values at day 28 minus those at day 1.

**Assessment of myocardial perfusion abnormalities.** Echocardiograms were analyzed with a commercially available off-line computer system (Color Cardiology Workstation, TomTec Imaging). The details of analysis were described elsewhere (19–21). An operator who did not know the patients’ data analyzed the MCE images. We used the apical two-chamber view and the parasternal short-axis view for an anterior wall AMI and for an inferior or posterior wall AMI, respectively. The area at risk was defined as an area of akinesia or dyskinesia at baseline study. Myocardial reperfusion in the risk area was considered incomplete (MCE no-reflow) when the endocardial length of contrast perfusion defect exceeded a quarter of that of the risk area. In the other cases, we considered myocardial reperfusion adequate (MCE reflow). Areas showing contrast defect were always successfully defined, and measurements of the size of contrast defects were highly reproducible (21). Statistical analysis. Statistical analysis was performed using StatView 5.0 for Macintosh. Continuously distributed variables were expressed as mean ± SD. The one-way analysis of variance (ANOVA) with the Fisher PLD test was used to compare continuous variables, and the chi-square test was used to compare categorical variables. Receiver operating characteristic curves were constructed to study the feasibility of parameter for predicting MCE no-reflow. Multiple regression analysis was performed to identify independent factors those were related to CFIp. A p value <0.05 was considered statistically significant.

**RESULTS**

**Angiographic collateral grade and CFIp.** There was no difference in CFIp among those with collateral grades of 0 to 3 (grades 0, 1, 2, 3; 0.28 ± 0.07, 0.27 ± 0.09, 0.27 ± 0.08, 0.23 ± 0.08, p = NS), and there was no relation between CFIp and the collateral grade (Fig. 1). There was also no difference in CFIp between the patients with no or poor collateral (grade 0 or 1) and those with well-developed collateral (grade 2 or 3) (0.28 ± 0.08 vs. 0.26 ± 0.08, p = NS).

**The CFIp and microvascular injury.** The study population was divided into two groups according to contrast reperfusion pattern: MCE no-reflow (n = 16) and MCE reflow (n = 32) (Table 1). The MCE reflow group had better angiographical collateral than those with MCE no-reflow. There were no differences in other baseline charac-
among collateral grades (0, 1, 2, 3; 0.28 among angiographical collateral grades. There was no difference in CFIp variables. Values are expressed as mean ± SD.

Characteristics between the two groups. There was also no difference in hemodynamic variables between the two groups except for left ventricular end-diastolic pressure (LVEDP), which was higher in the MCE no-reflow group than in the MCE reflow group.

The CFIp was significantly higher in the MCE no-reflow than in the MCE reflow group. Although Pa and Pv were comparable between the two groups, the mean Pcw was significantly higher in the MCE no-reflow than in the MCE reflow group. Thus, the elevation of mean Pcw seems in part to explain an increase in CFIp in the MCE no-reflow patients. Figure 2 compares the instantaneous waveform of Pcw in patients with MCE no-reflow and those with MCE reflow. Diastolic Pcw showed comparable values, but systolic Pcw was higher in patients with MCE no-reflow than in patients with MCE reflow. Although there was no difference in end-diastolic Pcw between the two groups, peak systolic Pcw was significantly higher in the MCE no-reflow than in the MCE reflow group (Fig. 3). These findings clearly show that an increase in mean Pcw is attributable mainly to an increase in systolic Pcw in MCE no-reflow.

Multiple regression analysis was performed to identify the factors that are closely related to CFIp. These included heart rate, LVEDP, LVEF, RWM, angiographical collateral grade, infarct-related artery, time interval from the symptom onset to reperfusion, heart rate and the presence or absence of MCE no-reflow. Among these factors, MCE no-reflow and LVEDP are the independent factors related to CFIp (r value 4.5 vs. 2.4, p value <0.01 vs. <0.05, respectively), and MCE no-reflow showed the strongest relationship to the CFIp. Receiver operating characteristic analysis documented that we can estimate MCE no-reflow with sensitivity of 93% and specificity of 75% by CFIp of ≥0.26.

The CFIp and functional outcomes. All patients showed patent infarct-related artery without restenosis and also showed TIMI flow grade 3 (Table 2). Peak creatine phosphokinase was significantly higher in the MCE no-reflow than in the MCE reflow group. The values for LVEF and RWM at both days 1 and 28 were significantly higher in the MCE reflow group than in the MCE no-reflow group, and ΔLVEF and ΔRWM were also higher in the MCE reflow group than in the MCE no-reflow group. We compared the relation between CFIp and magnitude of improvement in left ventricular function. The CFIp significantly correlated with ARWM (r = 0.42, p < 0.01), implying the higher CFIp is associated with worse func-

![Figure 1](image-url)  
**Figure 1.** Comparison of pressure-derived collateral flow index (CFIp) among angiographical collateral grades. There was no difference in CFIp among collateral grades (0, 1, 2, 3; 0.28 ± 0.07, 0.27 ± 0.09, 0.27 ± 0.08, 0.23 ± 0.08, p = NS), and a correlation was not found between the two variables. Values are expressed as mean ± SD.

**Table 1.** Patient Characteristics and Coronary Hemodynamic Variables

<table>
<thead>
<tr>
<th>MCE Findings</th>
<th>No Reflow (n = 16)</th>
<th>Reflow (n = 32)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>62 ± 9</td>
<td>58 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>14 (88)</td>
<td>26 (81)</td>
<td>NS</td>
</tr>
<tr>
<td>Anterior wall AMI</td>
<td>14 (88)</td>
<td>17 (53)</td>
<td>NS</td>
</tr>
<tr>
<td>Onset-reperfusion time (h)</td>
<td>6.8 ± 6.3</td>
<td>5.6 ± 5.0</td>
<td>NS</td>
</tr>
<tr>
<td>Good collaterals</td>
<td>5 (31)</td>
<td>25 (70)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>% Diamter stenosis after PTCA</td>
<td>10 ± 8</td>
<td>10 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>10 (63)</td>
<td>20 (63)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>7 (44)</td>
<td>15 (47)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (31)</td>
<td>7 (22)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (37)</td>
<td>14 (44)</td>
<td>NS</td>
</tr>
<tr>
<td>Pa, mm Hg</td>
<td>90 ± 21</td>
<td>95 ± 13</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>85 ± 14</td>
<td>79 ± 14</td>
<td>NS</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>17 ± 6</td>
<td>11 ± 5</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pv, mm Hg</td>
<td>7 ± 3</td>
<td>5 ± 3</td>
<td>NS</td>
</tr>
<tr>
<td>Pcw, mm Hg</td>
<td>35 ± 9</td>
<td>26 ± 5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>CFIp</td>
<td>0.34 ± 0.07</td>
<td>0.23 ± 0.06</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Parameters are expressed as mean ± SD and number (percent).  
CFIp = pressure-derived collateral flow index; good collateral = Rentrop grade 2 or 3; Pa = mean aortic pressure; Pcw = coronary wedge pressure; Pv = central venous pressure.
tional improvement. All patients with MCE reflow had TIMI-3 reflow. Among 16 patients with MCE no-reflow, 10 patients showed TIMI-2 reflow, and six patients showed TIMI-3 reflow. When CFIp and ΔRWM were compared with each other in the selected patients with MCE reflow or TIMI-3 reflow, there was no relation among the patients with MCE reflow, but there was a weak inverse correlation among those with TIMI-3 reflow (MCE reflow; \( r = 0.32, p = \text{NS} \), TIMI-3 reflow; \( r = 0.50, p < 0.01 \)).

Because a good correlation existed between CFIp and ΔRWM in the patients with AMI, we derived a simple parameter that does not require the measurement of \( P_v \) to estimate functional outcomes: \( P_{cw}/P_a \). This parameter was significantly lower in the MCE reflow group than in the MCE no-reflow group (0.28 ± 0.04 vs. 0.39 ± 0.07, \( p < 0.01 \)). The receiver operating characteristics curve documented that MCE no-reflow could be recognized with sensitivity of 100% and specificity of 78% by \( P_{cw}/P_a \) of \( \geq 0.30 \). There was a close inverse relation between \( P_{cw}/P_a \) and ΔRWM (Fig. 4B).

**DISCUSSION**

Our study documented that pressure-derived collateral flow index (CFIp) does not necessarily reflect collateral function in patients with AMI. In other words, the higher CFIp does not imply the presence of angiographically well-developed collateral channels nor is it associated with better functional improvement. The CFIp was even higher in patients with MCE no-reflow than in those with MCE reflow, and the higher CFIp was associated with worse functional improvement. Thus, the CFIp is significantly influenced by the presence and severity of ischemic microvascular dysfunction in AMI, and the higher CFIp is associated with no-reflow phenomenon and with the worse functional outcomes.

**Figure 2.** Waveforms of aortic pressure (\( P_a \)) and coronary wedge pressure (\( P_{cw} \)) in patients with MCE reflow (A) and with MCE no-reflow (B). Although \( P_{cw} \) shows comparable value in diastole, \( P_{cw} \) was extremely higher in systole in a case of MCE no-reflow than in a case of MCE reflow.

**Figure 3.** Comparison of peak systolic \( P_{cw} \) (A) and end-diastolic \( P_{cw} \) (B) between the patients with MCE reflow and those with MCE no-reflow. There was no difference in end-diastolic \( P_{cw} \) between the two groups, but peak systolic \( P_{cw} \) was significantly higher in patients with MCE no-reflow than in those with MCE reflow (end-diastolic pressure: 22 ± 10 vs. 18 ± 4, NS; peak systolic pressure: 59 ± 11 vs. 40 ± 13, \( p < 0.01 \)). Abbreviations as in Figure 2. Values are expressed as mean ± SD.
The CFIp and microvascular dysfunction in AMI. Our result is different from the previous observation that implies the CFIp parallels the functional significance of total collateral channels in the non-infarcted heart (10–13). This difference is explained by the presence of the microvascular dysfunction in the infarct zone. In the non-infarcted heart, the pressure signals obtained distal to the occluded coronary artery almost invariably originated from collateral channels. Hence, an increase in Pcw is caused mainly by collateral flow, and thus, CFIp is a likely index to express the amount of flow to the vascular region of interest as a fraction of the flow via the collateral channels. Acute myocardial infarction is a different case. The higher CFIp is not associated with well-developed collateral channels. From the analysis of instantaneous waveform of Pcw, we found that the elevation of systolic Pcw seems to be a main reason for an increase in mean Pcw.

Increase in systolic Pcw, especially in patients with reperfused but no-reflow AMI, may be explained by the congested blood flow in coronary microvasculature. In the non-infarcted heart, intramyocardial blood is smoothly squeezed into the venous circulation in systole, but this convection of blood to the venous system should be impeded owing to the extensive microvascular obstruction in the infarct zone. Because of this congestion, intramyocardial blood pressure should increase extremely in systole with an increase in myocardial wall stress. Another possible explanation of the increase in systolic Pcw in MCE no-reflow is that the systolic pressure wave comes from open collaterals entering the infarct vessels distally of the balloon and proximally to the microvessels. Because of the congestion of the distal infarct vessels, collateral flow may experience a no-reflow problem. These open collaterals, not visible angiographically, could be the reason for an elevated systolic post-balloon pressure. Thus, an increase in systolic Pcw and CFIp is hypothesized to be dependent on the increase in the impedance of the microvasculature. In fact, these variables were higher in the MCE no-reflow than in MCE reflow group. In this sense, CFIp can be regarded as an alternate means of estimating microvascular dysfunction and functional outcomes in AMI.

**Difference from previous studies.** Choel et al. (14) studied the clinical implications of CFIp in patients with reperfused AMI and documented the better functional outcomes associated with higher CFIp. However, in the no-reflow AMI group, the higher CFIp was associated with the lower RWM, implying the worse functional outcomes. Significant correlation was also found between ΔRWM and Pcw/Pa (B). This correlation coefficient seems to be better than that between CFIp and ΔRWM. Solid circles indicate patients with MCE no-reflow, and open circles represent patients with MCE reflow. Δ = the difference of the values at day 28 minus those at day 1. Other abbreviations are the same as before.
associated with patients with higher CFIp. Their result was different from our observations. Their study population included only patients with TIMI-3 reflow after successful percutaneous transluminal coronary angioplasty. In contrast, our study included patients with successful coronary recanalization irrespective of TIMI flow grades. Among our patients, 33% and 21% showed MCE no-reflow and TIMI-2 reflow, respectively. Therefore, their finding is exclusively based on patients with only minimally damaged microvasculature, rather than on common AMI patients.

We compared CFIp and ΔRWM in selected patients with TIMI-3 reflow, but we found only a weak inverse correlation between the two variables. Although the number of patients was small compared to the Choel et al. study, this result should indicate that the microvascular dysfunction cannot be negligible even in patients with TIMI-3 reflow. Our previous study demonstrated that 16% of patients with reperfused and TIMI-3 reflow AMI showed sizable no-reflow phenomenon (18). Our MCE study also documented that contrast intensity in the risk area, which parallels functional microvasculature, decreased in patients with AMI (19). Thus, CFIp seems to be affected by the microvascular dysfunction even in patients with reperfused and TIMI-3 reflow AMI.

Study limitations. Our findings are derived from a selected population of AMI patients who were successfully treated with primary PCI. Patients with shock, hemodynamically instability or recurrent myocardial infarction were excluded from the study because the CFIp is difficult to obtain. Hence, our results may not be generalizable to all patients receiving reperfusion therapy.

We evaluated collateral status after PCI, although angiography for evaluating collateral status was done before PCI. Microembolization with obstruction of the peripheral microvasculature may possibly occur with PCI (25). Hence, collateral channels angiographically proven before PCI might disappear after PCI because of the congestion of blood flow within the no-reflow zone. Thus, evaluated collateral status before PCI does not necessarily correspond with functional state after PCI is performed.

Based on our data, we hypothesized that the higher Pcw is caused by extensive microvascular dysfunction. The higher Pcw, however, is likely to reflect simply larger infarctions associated with no-reflow, higher LVEDP and poor contractile function rather than being specific for microvascular dysfunction. Experimental studies are required to reveal the relation between Pcw and the severity of microvascular dysfunction.

Clinical implications. The method described in the present study can be routinely applied in clinical practice with standard equipment and with minimal prolongation of the procedural time. For calculating CFIp, only an additional central venous catheter is required; but the measurement of central venous pressure is not necessary to assess functional outcomes. Pcw/Pa shows a reasonable correlation with functional improvement. The procedure to measure Pcw/Pa is easy and safe, and thus, Pcw/Pa provides a useful estimate of functional outcomes in patients with reperfused AMI.

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