Coronary Collaterals Remain Recruitable After Percutaneous Intervention

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Background—Rapid loss of collateral support has been reported after percutaneous coronary intervention (PCI), leaving the myocardium susceptible to subsequent infarction. However, well-developed collaterals have been found in normal hearts, suggesting that collaterals exist even in the absence of an ischemic stimulus. We assessed the plasticity and determinants of collateral supply after PCI.

Methods and Results—Collateral flow index (CFI) was calculated in 60 patients as \( (P_w - P_c)/(P_a - P_r) \) by measurement of aortic \( (P_a) \), central venous \( (P_c) \), and coronary wedge \( (P_w) \) pressures. CFI was reassessed during transient balloon occlusion 5 minutes and 24 hours after PCI in the first 29 patients and at 6 months in the subsequent 25 patients. We also evaluated the relationship between collateral supply, lesion characteristics, and circulating hemopoietic cells numbers before and after successful PCI. CFI at baseline was 0.23±0.10, with no change 5 minutes and 1 day later (0.21±0.12, \( P=0.62 \); and 0.22±0.11, \( P=0.96 \), respectively). At 6 months, CFI was 0.14±0.07 or 63±27% of the baseline value (\( P<0.001 \)). CFI was proportional to severity of the coronary lesion at baseline \( (r=0.63, P<0.0001) \) but not 6 months after PCI \( (r=−0.04, P=0.87) \). The number of circulating CD133+ and CD34+ cells was associated with CFI 6 months after PCI \( (CD133, r=0.59, P=0.035; CD34, r=0.63, P=0.037) \).

Conclusions—Coronary collateral flow remains undiminished for at least 24 hours after successful PCI. Functional collateral support subsequently declines but does not regress completely. (Circulation. 2007;115:2015-2021.)

Key Words: angiogenesis ■ angioplasty ■ collateral circulation ■ physiology ■ stem cells

The ability of collaterals to abrogate ischemia and limit infarct size1–3 has led to the belief that the collateral circulation develops in response to recurrent myocardial ischemia and that coronary artery disease is a necessary precondition for collateral growth.4 Similarly, relief of ischemia might be expected to lead to regression of collateral supply. Indeed, several recent studies have suggested a rapid loss of collateral function after percutaneous coronary intervention,5–8 rendering the myocardium susceptible to infarction in the event of subsequent coronary occlusion.9 It has been proposed that the apparent loss of collateral function is due to abolition of the pressure gradient across the collateral bed, which in turn is thought to be essential for the development and persistence of collateral vessels.4

Clinical Perspective p 2021

However, this assertion is called into question by the discovery of well-developed coronary collaterals in the presence of normal coronary arteries.10 One in 4 of these individuals was found to have sufficient collateral support to prevent ischemia on sudden balloon occlusion. Furthermore, anecdotal evidence11 and data from animal experiments12 suggest that coronary collaterals remain recruitable for a considerable time after resolution of ischemia. Such observations imply that collateral development may be dissociated from an ischemic stimulus and may reflect innate collateral-forming potential.

We have carried out a prospective study to evaluate the plasticity of the collateral circulation after successful percutaneous coronary intervention (PCI). We also have assessed the determinants of collateral supply before and after coronary revascularization.

Methods

Patients

Sixty patients with single-vessel coronary disease were studied during elective PCI. Patients with high-grade lesions or chronic total occlusions (CTOs) (duration ≥4 weeks, Thrombolysis In Myocardial Infarction grade 0 or 1 flow) and Canadian Cardiovascular Society class 2 or 3 exertional angina were eligible. Those who had undergone previous PCI or coronary bypass surgery were excluded from the study, as were any patients with a known malignancy or inflammatory disorder associated with neovascularization. The protocol was approved by the local research ethics committee, and written informed consent was obtained from each subject at enrollment and again at the 6-month follow-up.
Coronary Intervention

Coronary angiography and PCI were carried out via the femoral route with a 6F or an 8F guiding catheter. Patients were pretreated with aspirin and clopidogrel, and unfractionated heparin was administered to maintain an activated clotting time >250 seconds during the procedure. An intracoronary bolus of 1 mg isosorbide dinitrate was administered before diagnostic angiography, with further boluses given during the procedure. The lesion was crossed directly with a Pressurewire (Radi Medical Systems, Glostrup, Denmark) and a conventional guidewire, and the Pressurewire was inserted via an exchange catheter. Predilation, followed by stent deployment, was mandated by the protocol. Drug-eluting stent use was prohibited, so all patients received bare metal stents.

Quantification of Collateral Supply

After calibration and equalization to aortic pressure, the tip of a 0.014-in pressure-sensing guidewire (Pressurewire) was advanced beyond the lesion to measure distal coronary pressure. Collateral flow index (CFI) was measured as previously described by simultaneous measurement of aortic (P_a) and right atrial (P_v) pressures, where CFI = (P_w − P_v) / (P_a − P_v). P_w was assessed after at least 90 seconds of balloon occlusion, and abolition of antegrade flow was confirmed by contrast angiography. P_v was measured by the guide catheter; P_a was measured via the tip of a diagnostic catheter, which was inserted into the right atrium through the femoral vein. All measurements were carried out during maximal hyperemia induced by an intravenous infusion of adenosine at 140 μg · kg⁻¹ · min⁻¹.

Identification of Hemopoietic Progenitor Cells

Peripheral blood mononuclear cells were isolated by density-gradient centrifugation. Aliquots of 0.5 × 10⁶ peripheral blood mononuclear cells were incubated with monoclonal antibodies against CD133 (PharMingen, San Diego, Calif.), CD34 (Becton, Dickinson and Company, Franklin Lakes, NJ, for CD133 and CD34, respectively). After 20 minutes of incubation, the cells were washed and resuspended in PBS for immediate analysis or fixed in 1% paraformaldehyde (Sigma-Aldrich, Gillingham, Dorset, UK) and kept at 2°C to 8°C for a maximum of 3 days. Flow cytometric analysis was carried out on a Becton, Dickinson and Company FACScan flow cytometer incorporating CellQuestPro software (Becton, Dickinson and Company).

Study Protocol

Early collateral plasticity was assessed in 30 patients who had CFI measurements during PCI and 5 minutes and 24 hours later, with arterial and venous access sheaths left in situ between procedures. Creatine phosphokinase and troponin T levels were measured 12 to 24 hours after PCI. Late collateral plasticity was assessed in the next 30 patients who underwent systematic follow-up angiography and CFI assessment 6 months after the initial procedure or sooner in the event of recurrent symptoms. At this stage, CFI was estimated during recollection of the stented segment by low-pressure balloon inflation. Clopidogrel 75 mg was administered daily for 2 weeks after the 6-month CFI measurement to minimize the risk of thrombotic stent occlusion. The degree of restenosis at follow-up was characterized by quantitative coronary angiography, volumetric intravascular ultrasound, and fractional flow reserve measurement. Target vessel revascularization was based on the clinical status of the patient at follow-up. Hemopoietic progenitor cells were identified at the time of PCI in the late plasticity group as described above.

Statistical Analysis

Data are presented as mean±SD unless otherwise specified. CFI at different time points was analyzed by 1-way ANOVA with Bonferroni’s correction for multiple comparisons. Mann-Whitney or χ² tests (with Yates’ correction when appropriate) were used to compare baseline variables between groups at a significance level of 5%.

Results

Patients

Baseline CFI measurements were carried out in 60 patients 59±9 years of age. In the early plasticity group (n=30), CFI was reassessed 5 minutes and 20±2 hours after the baseline measurement in 29 patients (follow-up data on 1 patient could not be used for technical reasons). In the late plasticity group (n=30), CFI was measured 188±25 days after PCI in 25 patients (4 patients who were asymptomatic declined follow-up; 1 patient had undergone angiography at another center that revealed critical restenosis, and restudy for measurement of CFI was not considered appropriate). The demographic profile of the study population is summarized in the Table. No clinical events attributable to the follow-up procedures were detected during the study.

Early Change in Collateral Flow

CFI at baseline was 0.23±0.10 in the early plasticity group, with no significant change when measured 5 minutes and 1 day after PCI (0.21±0.12, P=0.62; and 0.22±0.11, P=0.96, respectively). On the basis of a CFI threshold of 0.25,1⁵ a

### Demographic Profile of Patients With Complete Follow-Up

<table>
<thead>
<tr>
<th></th>
<th>Early Plasticity (n=29)</th>
<th>Late Plasticity (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>61±8</td>
<td>0.17</td>
</tr>
<tr>
<td>Female, %</td>
<td>18</td>
<td>32</td>
<td>0.38</td>
</tr>
<tr>
<td>Risk factors, %</td>
<td></td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>18</td>
<td>8</td>
<td>0.52</td>
</tr>
<tr>
<td>Smoker, current/ex/non</td>
<td>25/32/43</td>
<td>12/68/20</td>
<td>0.03</td>
</tr>
<tr>
<td>Medication, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blocker</td>
<td>79</td>
<td>88</td>
<td>0.59</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>43</td>
<td>36</td>
<td>0.82</td>
</tr>
<tr>
<td>Statin</td>
<td>93</td>
<td>96</td>
<td>0.92</td>
</tr>
<tr>
<td>Serum cholesterol, mmol/L</td>
<td>4.4±0.9</td>
<td>4.1±1.0</td>
<td>0.24</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>66±11</td>
<td>62±13</td>
<td>0.32</td>
</tr>
<tr>
<td>CTOs, %</td>
<td>25</td>
<td>28</td>
<td>0.80</td>
</tr>
<tr>
<td>Pre-PCI diameter stenosis, %</td>
<td>81±16</td>
<td>82±16</td>
<td>0.87</td>
</tr>
<tr>
<td>Pre-PCI FFR, %</td>
<td>0.48±0.18</td>
<td>0.50±0.17</td>
<td>0.58</td>
</tr>
<tr>
<td>Stent diameter, mm</td>
<td>3.2±0.5</td>
<td>3.4±0.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Stent length, mm</td>
<td>21.5±13.3</td>
<td>23.4±14.6</td>
<td>0.62</td>
</tr>
<tr>
<td>Post-PCI diameter stenosis, %</td>
<td>7±11</td>
<td>11±9</td>
<td>0.11</td>
</tr>
<tr>
<td>Baseline CFI</td>
<td>0.23±0.10</td>
<td>0.23±0.13</td>
<td>0.72</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; LV, left ventricular; and FFR, fractional flow reserve. Data are mean±SD when appropriate.

McNemar’s test was used to assess differences in the proportion of patients with sufficient collaterals to prevent ischemia at different time points. Temporal changes in collateral flow in patients with CTOs and nonocclusive lesions were compared by repeated-measures ANOVA, allowing for random patient effects. Baseline variables found to correlate with 6-month CFI on univariate analysis (P<0.05) were assessed by a multiple linear regression model. Analyses were carried out with StatView 5.0 software (SAS Institute, Inc, Cary, NC).

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.
similar proportion of patients had sufficient collateral flow to prevent ischemia at baseline and 1 day after PCI (47% versus 45%; P = 1.00).

Late Change in Collateral Flow
CFI was found to have diminished significantly, from 0.23±0.13 at baseline to 0.14±0.07 at 6 months (P<0.001). Only 4% of patients had a CFI ≥0.25 at 6 months (P=0.001 versus baseline) (Figure 1A). Individual CFI plasticity was heterogeneous (Figure 2), and CFI at 6 months was 63±27% of the baseline value (P<0.001) (Figure 1B).

Restenosis and Clinical Events at Follow-Up
Twenty-four hours after PCI, neither creatinine kinase nor troponin T levels were found to be elevated above the reference limit in any of these patients. At 6 months, the degree of stent obstruction on volumetric intravascular ultrasound (neointimal volume/stent volume) was 21±10%, and fractional flow reserve across the stented segment was 0.84±0.08. No cases of death, myocardial infarction, or unstable angina occurred during the follow-up period. No target vessel revascularization took place in patients who underwent follow-up angiography at 6 months, although the overall 6-month target vessel revascularization rate was 6.6% in the cohort that was initially recruited.

Collateral Supply and Lesion Severity
CFI at baseline was proportional to the anatomic and hemodynamic severity of the coronary lesion, assessed as diameter stenosis on quantitative coronary angiography (r=0.63, P<0.0001) and fractional flow reserve (r=-0.42, P=0.001) (Figure 3A). However, at 6 months, CFI was not related to diameter restenosis on quantitative coronary angiography or stent obstruction on intravascular ultrasound (r=0.03, P=0.90; and r=0.27, P=0.23, respectively) (Figure 3B), and a modest inverse correlation existed with hemodynamic severity of the lesion (fractional flow reserve, r=0.50, P=0.02). Baseline CFI was a strong predictor of CFI at 6 months (r=0.71, P<0.0001), as was baseline stenosis severity (r=0.50, P=0.02). The decrease in CFI relative to the baseline value was greatest in patients with high baseline CFI and CTOs (r=0.51, P=0.02; and r=0.57, P=0.006, respectively). Patients with CTOs had a significantly higher CFI at baseline than those with nonocclusive lesions (0.33±0.07 versus 0.20±0.10; P<0.001), but absolute CFI at 6 months was similar in both groups (0.15±0.04 versus 0.13±0.08, respectively; P=0.56) (Figure 4). In the CTO group, CFI was 90±31%, 87±33%, and 44±6% of the baseline value at 5 minutes, 24 hours, and 6 months after PCI, whereas in the nonocclusive group, CFI was 97±40%, 127±95%, and

![Figure 1](http://circ.ahajournals.org/)
Figure 1. CFI after PCI. A, Change in absolute CFI after PCI (error bars=1 SD), B, CFI at 5 minutes, 24 hours, and 6 months after PCI in relation to baseline CFI (error bars=1 SEM).

![Figure 2](http://circ.ahajournals.org/)
Figure 2. Individual variation in collateral plasticity. The early plasticity of collateral supply was heterogeneous, but no overall change in CFI occurred at 5 minutes or 24 hours after PCI. CFI declines to 63% of baseline 6 months later.
75±26% at these intervals (P=0.02 for comparison of trend between groups).

Hemopoietic Progenitor Cells
FACS data were available in 20 patients in the late plasticity group. At PCI, 0.09±0.06% and 0.09±0.05% of cells in the lymphocyte gate were found to express CD133 and CD34, respectively. Baseline CFI was weakly related to the number of circulating CD133 cells (r=0.42, P=0.08) but unrelated to numbers of CD34 cells (r=0.09, P=0.74). In contrast, CFI 6 months after PCI clearly was associated with the number of cells expressing CD133 (r=0.59, P=0.035) and CD34 (r=0.63, P=0.037) (Figure 5). Neither CD133 nor CD34 cell numbers were related to lesion severity or any demographic features listed in the Table. In a multiple regression model incorporating baseline CD133 cell number, CD34 cell number, initial stenosis severity, and baseline CFI, only stenosis severity remained predictive of CFI at 6 months (P=0.02).

Discussion
Early Collateral Plasticity
Several previous investigators have reported rapid loss of collateral function after PCI. Using myocardial contrast echocardiography, Petronio et al6 demonstrated an early and progressive decline in collateral supply after PCI to chronic left anterior descending coronary artery occlusions, with virtually no detectable collateral perfusion within 12 hours. Similarly, Doppler-derived CFI has been shown to decrease by >50% within 12 hours of recanalization of CTOs.7 In a recent study, Zimarino et al8 reported complete loss of collateral support within minutes of recanalization of a CTO. However, many of these studies are limited by inaccuracies in assessment of collateral flow. Several investigators assessed spontaneously visible collateral perfusion,6,8,16 which clearly declines with restoration of antegrade flow in the target vessel and correlates poorly with collateral supply that is recruitable after coronary occlusion.15,17 Despite using coronary wedge pressure, Zimarino et al failed to induce systemic maximal hyperemia18 and did not measure right atrial (or central venous) pressure but assumed values of 0 and 10 in calculating “collateral pressure index” and “collateral fractional flow reserve,” respectively. We have previously shown that as-
suming fixed values of 0 and 10 for right atrial pressure leads to massive errors in CFI estimation (57±89% and −20±64%, respectively),14 which in turn could alter these results substantially.

Instantaneous involution or regression of a functional, well-developed collateral circulation seems biologically implausible. In addition to the methodological differences mentioned above, another source of the discrepancy between our observations and previously published work is distal embolization. Up to 40% of patients undergoing uncomplicated elective PCI are found to have a periprocedural rise in cardiac troponin levels, most of which is thought to be due to distal embolization.19 Distal embolization could account for some of the acute decrement in collateral supply that has previously been reported; it is worthy of note that no instances of troponin elevation appeared in the present study. In contrast, our prospective study has demonstrated for the first time that collateral function may reflect anatomic remodeling resulting from a reduction in sheer stresses and hypoxia, which in turn could alter these results substantially.

Late Collateral Plasticity

Long-term collateral regression in humans has not been studied until recently, and the limited available data are confusing. Werner et al21 have reported that, after an immediate and dramatic drop, the Doppler-derived CFI remains subsequently undiminished for several months. However, in the same study, the authors assessed an alternative index of collateral supply, which suggested a very different pattern of plasticity. The collateral pressure index had fallen by 23% immediately after PCI and a further 23% at follow-up. Direct comparison of this pressure index with CFI is difficult because the former was not assessed during maximal hyperemia, which leads to overestimation of the drop in collateral flow.18 Although abolition of the resting pressure gradient across the collateral bed had no immediate effect on CFI in our study, a degree of functional regression clearly does occur during subsequent weeks or months. The long-term decline in collateral function may reflect anatomic remodeling resulting from a reduction in sheer stresses and hypoxia, which in turn would be expected to follow a time scale similar to that observed in our study.22

Chronic Total Occlusions Versus Nonocclusive Lesions

The association between CTOs and their collateral support often has been considered unique,23 but few studies have directly compared CTOs with nonocclusive lesions. Pohl et al24 observed that patients with nonocclusive lesions tended to have increased CFI, whereas those with CTOs tended to have a lower CFI a few minutes after PCI. We did not find that CFI had changed significantly in either group 5 minutes after PCI. However, we did observe a small increase in CFI in the nonocclusive group 24 hours later that was not seen in the CTO group. The increase in CFI in the nonocclusive group may represent collateral recruitment after delivery of prolonged and repeated ischemic stimuli at the time of PCI, whereas CTOs are protected from acute ischemia by a well-developed collateral supply.

At 6 months, the decrease in collateral support relative to baseline was ≈2.5-fold greater in patients with CTOs than in those with nonocclusive lesions. Given that CFI was similar in both groups at 6 months despite appreciably higher initial CFI in the CTO group, the differential decline in collateral function may reflect regression to an intrinsic level of collateral support, which in turn is independent of the original coronary lesion. In this context, patients with CTOs may represent one end of a spectrum of collateral plasticity in that they are better able to develop and regress their collateral supply in response to metabolic and hemodynamic stimuli.

Determinants of Collateral Supply

In patients with significant coronary disease, the extent of collateral flow to the distal myocardium is best predicted by the degree of coronary stenosis or the duration of antecedent angina, which are both surrogate markers of the ischemic burden.25–28 In a study of 450 patients, Pohl and colleagues25 observed that percent diameter stenosis of a coronary artery was the only independent predictor of CFI in the corresponding territory, although the association was relatively weak (r=0.10). We have demonstrated an even stronger correlation between CFI and anatomic and functional stenosis severity at the time of PCI that supports the concept that collateral development may be promoted by chronic myocardial ischemia.

On the other hand, we have shown that the extent of residual collateral supply after PCI is no longer correlated with stenosis severity. Furthermore, given that CFI is maintained at ≈65% of its baseline state after PCI, these findings suggest that ischemia is not a prerequisite for maintenance of collateral supply. Our observations reinforce those of Wustmann and colleagues,10 who have found well-developed collateral circulations even in subjects with normal coronary angiograms. Allowing for differences in the populations studied, the CFI in these individuals without coronary disease (range, 0.04 to 0.36) was similar to our own measurements at a 6-month follow-up (range, 0.01 to 0.35) and may represent an intrinsic level of collateral support that is independent of an ischemic stimulus.

Transfused hemopoietic progenitor cells have been shown to contribute to vasculogenesis in the coronary collateral circulation of animals with myocardial ischemia.29 In clinical studies, hemopoietic progenitor cell transfusion after acute myocardial infarction has led to subsequent improvement in left ventricular function, which may in turn have been mediated by collateral growth.30,31 Furthermore, a recent study carried out in our unit32 demonstrated a direct correlation between circulating hemopoietic progenitor cell numbers
and the extent of collateral development in patients with critical coronary disease. Similarly, administration of granulocyte-macrophage colony-stimulating factor has been shown to promote collateral supply in the short term, providing indirect evidence for the role of bone marrow–derived progenitor cells in collateral formation.\(^{33,34}\) As such, we hypothesized that the heterogeneity of intrinsic collateral support also would be predicted by hemopoietic progenitor cell numbers. The strong independent correlation observed between the number of CD133\(^+\) cells at baseline and the level of collateral support after PCI supports this hypothesis. These findings, together with the observed uncoupling of lesion severity and CFI after PCI, suggest that circulating hemopoietic progenitor cell prevalence is a marker for intrinsic collateral support in the absence of myocardial ischemia. Development of a coronary stenosis appears to promote further development of the collateral circulation mediated by the consequent ischemic stimulus and potentially by the altered shear stresses across the microvascular bed.

**Study Limitations**
The sample size in our study was relatively small, although the constraints imposed by low numbers are ameliorated by the fact they were a carefully characterized population who represented a broad spectrum of collateral support. We have used a collateral regression model to evaluate the level of “intrinsic” or “background” collateral support. However, the correspondence between CFI after PCI and true intrinsic collateral development in normal hearts is largely unknown. Furthermore, for ethical reasons, we have not repeated CFI measurements after the 6-month assessment in any of our patients and cannot exclude a further decline in collateral support in subsequent months or years. Finally, because of the lack of accepted methods, we have not directly assessed the angiogenic potential of the hemopoietic progenitor cells identified in the present study.

**Conclusions**
Coronary collateral flow remains undiminished for at least 24 hours after PCI. Functional collateral support subsequently declines but does not regress completely, despite the lack of a persistent coronary lesion or ongoing ischemia. Circulating hemopoietic progenitor cell numbers correlate with the degree of intrinsic collateral support detectable after successful PCI.

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**Disclosures**
None.

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Coronary collaterals abrogate ischemia and limit infarct size after sudden closure of an epicardial coronary artery. It is widely held that collaterals disappear rapidly after percutaneous coronary intervention, rendering the myocardium susceptible to subsequent infarction in the event of acute stent occlusion. However, the recent demonstration of collaterals in normal hearts suggests that collateral formation may occur even in the absence of an ischemic stimulus. Using quantitative measurements based on intracoronary pressure recordings, this longitudinal study demonstrates that collaterals do not disappear after percutaneous coronary intervention and that the degree of collateral support remains undiminished for at least 24 hours. Collateral support eventually declines but remains detectable 6 months after PCI, even in patients without an ischemic substrate. This may reflect innate collateral-forming potential, and it is notable that the degree of intrinsic collateral support several months after percutaneous coronary intervention correlates with the frequency of circulating hemopoietic progenitor cells. Our findings suggest that there may be a basal level of innate collateral support in the human heart that is further stimulated by ischemia.

CLINICAL PERSPECTIVE
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