Collateral Function in Chronic Total Coronary Occlusions Is Related to Regional Myocardial Function and Duration of Occlusion

Gerald S. Werner, MD; Markus Ferrari, MD; Stefan Betge, MD; Oliver Gastmann, MD; Barbara M. Richartz, MD; Hans R. Figulla, MD

**Background**—Collateral circulation can maintain myocardial function and viability in chronic total coronary occlusion (TCO). The present study evaluates the relation of myocardial function and duration of occlusion to collateral function.

**Methods and Results**—A total of 50 patients underwent a successful recanalization of a TCO (>4 weeks’ duration). Collateral function was assessed by intracoronary Doppler and pressure recordings before the first balloon inflation and after PTCA had been completed. Collateral function was assessed by Doppler- (CFI_D) and pressure-derived collateral flow indices (CFI_P), as well as indices of collateral (R_Coll) and peripheral resistance (R_P). Patients with normokinesia had lower R_Coll (4.9±2.5 versus 11.8±8.2 mm Hg · cm⁻¹ · s⁻¹; P=0.033) and lower R_P (3.8±1.9 versus 6.1±4.1 mm Hg · cm⁻¹ · s⁻¹; P=0.031) than those with akinesia. Patients with akinesia and a TCO duration of ≤3 months had the highest R_Coll and R_P, whereas those with akinesia and a longer TCO duration had similar collateral function as patients with normokinesia. After PTCA, CFI_D and CFI_P decreased from 0.37±0.20 to 0.21±0.17 (P<0.001) and from 0.44±0.12 to 0.36±0.11 (P<0.001), respectively, with an increase in R_Coll of 139±128% (P<0.001) and R_P by 65±99% (P=0.003). This attenuation of collateral function was less pronounced with epicardial collaterals than with intramyocardial collaterals.

**Conclusions**—Collateral function was better in patients with TCO and normal regional function than in those with impaired regional function. In the latter group, collateral function improvement was time dependent. After recanalization, the recruitable collateral function was attenuated because of an increase of R_Coll and R_P. (Circulation. 2001;104:2784-2790.)

**Key Words:** collateral circulation • occlusion • hemodynamics • angioplasty

The collateral circulation has been studied in experimental animal models with certain limitations on their applicability to humans. The in vivo assessment of collateral function in humans developed from a qualitative anatomic evaluation by angiography to a physiological assessment by microsensors recording coronary flow velocity and pressure during cardiac catheterization. Most of these studies were done in selected patients with single vessel disease, nonocclusive lesions, and normal ventricular function.

Little is known of the prominent role of collaterals in chronic total coronary occlusions (TCOs). In TCOs, the collaterals are capable of complete preservation of myocardial function or of providing a minimum perfusion for hibernating myocardium. Both the extent of preserved regional function and the duration of the occlusion would be likely determinants of collateral function. However, the angiographic evaluation of collaterals supplying the myocardium with normal or impaired function did not show any differences.

The present study assesses the relation of collateral and regional myocardial function, as well as the influence of the occlusion duration, by measuring the intracoronary flow velocity and pressure distal to the occlusion. Indices of collateral and microvascular resistance were used, which are superior to the angiographic assessment of collaterals. A considerable attenuation of recruitable collateral flow had been observed after recanalization of a TCO. Therefore, the present study also evaluates whether this result was due to changes in collateral resistance after restoration of antegrade perfusion.

**Methods**

**Patients**

In 50 of 56 consecutive patients with a successful PTCA of a proximal TCO, collateral flow could be measured before the first balloon inflation and before antegrade flow was reestablished. These patients formed the study population. The inclusion criteria were an occlusion duration of >4 weeks as determined from a previous angiogram, the date of a prior myocardial infarction (MI), or the
Nitroglycerine (0.1 mg) was injected into the catheter to identify major side branches and assist in the positioning of the Doppler wire. During contrast injection, a Doppler signal of collateral flow occurred. No alteration of the proximal contrast injection was observed, and the leakage of antegrade flow along the exchange catheter was excluded.

Intracoronary Doppler Velocimetry

The collateral flow was analyzed by Doppler velocimetry after the recanalization. After PTCA, the Doppler wire was moved within a range of 10 mm to obtain the recording with the maximum flow velocity integral.

The recruitable collateral flow velocity was recorded at the end of the PTCA during a final balloon inflation of 3 minutes’ duration. Finally, 0.1 mg nitroglycerine was injected, and the Doppler wire was reintroduced to the previous position to record the antegrade coronary flow.

Intracoronary Pressure Recording

Care was taken to place the pressure transducer exactly at the previous Doppler transducer position. The distal coronary pressure ($P_D$) was recorded together with the aortic pressure ($P_{Ao}$) that was obtained through the guiding catheter. Mean pressures were used for computation. The recruitable collateral function was assessed by recording $P_D$ during the final balloon occlusion.

Data Analysis

Intracoronary Flow and Pressure Recordings

The Doppler flow signals distal to the occlusion were analyzed as previously described, and the maximum velocity (MV) and average peak velocity (APV) were obtained. A Doppler-derived collateral flow index ($CFL_D$) was calculated as the ratio of APV distal to the occlusion to antegrade APV. $CFL_D$ was calculated as $(P_{Ao} - CVP)/(P_{Ao} - CVP)$, where CVP is the central venous pressure, for which 5 mm Hg was substituted. Resistance indices were calculated assuming steady laminar flow and constant vessel diameters. Because flow velocity was used instead of flow volume, the unit of measure was mm Hg $\cdot$ cm$^{-1}$ $\cdot$ s$^{-1}$.

Angiographic Assessment of Collateral Flow

The collateral supply was graded angiographically. The anatomic pathway of the collateral supply was categorized as epicardial (collateral filling via connections on the epicardial surface) or intramyocardial (collateral channels through the myocardium, often locally before the Doppler recording of collateral flow. The Doppler wire was moved within a range of 10 mm to obtain the recording with the maximum flow velocity integral.

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via the intraventricular septum). Examples are shown in Figure 2. The angiographic assessment was done independently by two blinded investigators, and in case of disagreement a consensus was obtained.

**Statistics**

Data are given as mean±SD. Changes of parameters from baseline to subsequent measurements were evaluated by a paired t test. Differences between two groups were analyzed by a Student’s t test or a Fisher’s exact test when appropriate. One-way ANOVA with Bonferroni correction was applied for multiple comparisons. Repeated-measures ANOVA was used to compare changes of parameters between groups before and after PTCA. P<0.05 was considered significant. All calculations were performed with SPSS for Windows (Version 10.05, SPSS Inc).

**Results**

The median duration of TCOs was 5.4 months (range, 1 to 152 months). Patients with akinesia distal to the TCO had a lower global ventricular function and more severe heart failure compared with those with normokinesia (Table 1). The former more often had a history of MI and diabetes. All collaterals were angiographically grade 3 in patients with normokinesia and akinesia with TCO >3 months, but was higher in patients with akinesia and TCO ≤3 months (P=0.001). Rr showed a similar relation (P=0.007) (Figure 3).

**Anatomic Pathway of the Collaterals**

Epicardial collaterals were observed in 14 patients (28%). These patients had a higher diastolic/systolic velocity ratio than did patients with intramyocardial pathways (1.34±0.74 versus 0.68±0.60; P=0.002). Rr was considerably higher with epicardial collaterals (57±16 versus 43±10 mm Hg; P=0.006), leading to a higher CFIr (0.53±0.08 versus 0.41±0.10; P<0.001), whereas CFIp was not different (0.39±0.21 versus 0.33±0.21; P=0.38). Rcoll tended to be lower with epicardial collaterals (5.44±2.20 versus 9.56±8.99 mm Hg · cm⁻¹ · s⁻¹; P=0.10), but Rr was similar (5.90±2.09 versus 6.17±5.10 mm Hg · cm⁻¹ · s⁻¹; P=0.88).

**Immediate Change of Collateral Function After Recanalization**

The measurement of recruitable collateral function during a final balloon reocclusion 44±15 minutes after baseline measurement showed a significant reduction of APV and MV and a decrease of Pr in patients with and without regional dysfunction (Table 2). Both CFIp and CFIr decreased significantly (Figure 4). None of the patients experienced chest pain or ECG changes during the reocclusion of 3 minutes. The resistance indices increased, but this result was more

### Table 1. Clinical Characteristics of Patients With Chronic Total Coronary Occlusions

<table>
<thead>
<tr>
<th></th>
<th>Normokinetic Patients</th>
<th>Akinetik Patients</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=21)</td>
<td>(n=29)</td>
<td></td>
</tr>
<tr>
<td>Age, y (mean±SD)</td>
<td>63.4±11.7</td>
<td>62.7±9.6</td>
<td>0.82</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>17 (81)</td>
<td>28 (97)</td>
<td>0.15</td>
</tr>
<tr>
<td>Number of diseased arteries (1/2/3), n</td>
<td>8/9/4</td>
<td>11/10/8</td>
<td>0.72</td>
</tr>
<tr>
<td>Occluded coronary artery (right/LAD/LCX), n</td>
<td>10/8/3</td>
<td>16/12/1</td>
<td>0.46</td>
</tr>
<tr>
<td>Duration of occlusion &gt;3 mo, n (%)</td>
<td>14 (67)</td>
<td>16 (55)</td>
<td>0.56</td>
</tr>
<tr>
<td>Previous Q-wave MI, n (%)</td>
<td>8 (38)</td>
<td>25 (86)</td>
<td>0.001</td>
</tr>
<tr>
<td>Angina pectoris (CCS 0/1/2/3/4), n</td>
<td>0/0/8/13/0</td>
<td>0/1/14/13/1</td>
<td>0.58</td>
</tr>
<tr>
<td>Heart failure (NYHA 0/II/III/IV), n</td>
<td>1/14/6/0/0</td>
<td>0/6/18/5/0</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>2 (10)</td>
<td>12 (42)</td>
<td>0.024</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (71)</td>
<td>20 (69)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>18 (86)</td>
<td>20 (69)</td>
<td>0.20</td>
</tr>
<tr>
<td>History of smoking, n (%)</td>
<td>10 (48)</td>
<td>11 (38)</td>
<td>0.57</td>
</tr>
<tr>
<td>Ejection fraction, % (mean±SD)</td>
<td>71.5±10.6</td>
<td>48.3±16.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVEDP, mm Hg (mean±SD)</td>
<td>10.3±4.6</td>
<td>16.6±7.8</td>
<td>0.003</td>
</tr>
<tr>
<td>Angiographic grading of collaterals (2/3), n</td>
<td>0/21</td>
<td>4/25</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Values are mean±SD, number (percentage), or number of patients.

CCS indicates Canadian Cardiovascular Society classification of chest pain; LAD, left anterior descending; LCX, left circumflex; NYHA, New York Heart Association classification of heart failure, and LVEDP, left ventricular end-diastolic pressure.

**Regional Function and Collateral Flow**

APV and MV measured distal to the occlusion before recanulation were higher in patients with normokinesia compared with patients with akinesia. Pressure values did not differ significantly except for systolic Pr (Table 2). CFIp was lower in the akinetik group, whereas CFIp was similar. Rcoll and Rp were significantly higher in the akinetik group (Table 2). Left ventricular end-diastolic pressure was correlated with APV (r=−0.39; P=0.006), Rcoll (r=0.41; P=0.004), and Rp (r=0.40; P=0.005), and was higher in the akinetik group.

**Duration of TCO**

Patients with normokinesia were compared with patients with MI and impaired regional function, with the latter divided according to the duration of TCO (>3 months and ≤3 months). Rcoll was comparably low in patients with normokinesia and akinesia with TCO >3 months, but was higher in patients with akinesia and TCO ≤3 months (P=0.001). Rp showed a similar relation (P=0.007) (Figure 3).
pronounced for \( R_{\text{Coll}} \) than for \( R_P \) (139±128% versus 65%±99%; \( P=0.003 \)). The increase was observed both in patients with normokinesia and with akinesia (Figure 5).

The differences between epicardial and intramyocardial pathways became more distinct for recruitable collateral function compared with baseline. The increase of \( R_{\text{Coll}} \) was less pronounced with epicardial collaterals. The increase of \( R_P \) was independent of the anatomic pathway (Figure 6).

**Discussion**

The feature specific to the present study is the assessment of collateral function in TCO before restored antegrade flow changed hemodynamics distal of the occlusion. The majority of previous studies on collateral function were performed during balloon occlusion in nonocclusive lesions, or, when TCOs were included, the assessment was performed after an initial balloon inflation.\(^3,6,7,13,14\) Collateral function can be quantified by calculation of a collateral flow index on the basis of either pressure recordings (\( \text{CFI}_P \))\(^4,19\) or Doppler recordings (\( \text{CFI}_D \))\(^5\). In addition, we calculated a collateral resistance index by simultaneous pressure and flow recording.\(^12,14,15\) A good collateral function was characterized by a high \( \text{CFI}_P \) and \( \text{CFI}_D \) and a low \( R_{\text{Coll}} \).

**Determinants of Collateral Function**

Collateral function is better in patients with normal regional function than in those with impaired regional function. This result would be expected but was not shown previously using angiographic methods.\(^11\) In patients with preserved ventricular function, collaterals must have developed before the actual occlusion, and no exact occlusion date can be given. How-
ever, in patients with akinesia and MI, the occlusion date could be well defined. Collateral function was least developed in patients with a TCO/3 months in duration, whereas patients with TCO/3 months in duration had a collateral function comparable to patients with normokinesia. This finding extends previous observations that newly developing collaterals become visible by angiography in 10 days after a persistent acute occlusion, 20 but these early collaterals are not yet fully developed, and further functional maturation occurs within 12 weeks. This idea is in accordance with animal studies, in which collateral development required 8 weeks. 21,22 However, the exact time course of collateral development in humans remains uncertain because the collateral status at the incidence of occlusion is not known.

Collateral supply through epicardial pathways was better than through intramyocardial pathways, which confirms a previous study using Doppler velocimetry. 6 However, many of the patients with epicardial pathways have coexistent intramyocardial pathways, and the impact of epicardial collaterals on the long-term outcome in TCO remains to be established.

The myocardial perfusion distal to an occlusion is determined not only by the collateral perfusion but also by the microvascular resistance. R_P was lower in patients with normokinesia as compared with those with akinesia. This finding pointed to either a higher vascular tone or a restricted number of perfused arterioles in the group with impaired ventricular function. Another factor contributing to the difference of resistance indices between both groups was the higher left ventricular end-diastolic pressure in patients with akinesia.

Changes in Collateral Function After Recanalization
Animal studies have shown a regression of collaterals after restored perfusion and a capacity to recover during a gradual and prolonged recocclusion. 23,24 Despite the limited transferability of these studies, there are observations of a similar behavior of collaterals in humans. The majority of collaterals regress after PTCA and may not be available to prevent ischemia in case of acute reocclusion, 25,26 but there is also anecdotal evidence that collaterals are recruitable, 27,28 especially when a reocclusion occurred gradually. 29

In TCO, an immediate attenuation of collateral function was observed after recanalization. 16 Such a phenomenon was not observed in nonocclusive lesions with a stable collateral flow during repeated balloon occlusions. 4,30 In TCOs, the myocardium depends completely on collateral perfusion, and the restored antegrade flow changed hemodynamics considerably with an increase of R_Coll and a moderate increase of R_P. At baseline, microvascular arterioles and collaterals would be maximally dilated, but after recanalization, the arteriolar tone increases as a consequence of the autoregulatory potential of the coronary vascular bed. Our observations with regard to R_Coll indicate an autoregulatory capacity of collateral conduits. In patients with preserved regional function, recruitable collateral function remained better than in those with regional dysfunction; however, in some patients the level of recruitable collateral perfusion may drop below a threshold that protects from ischemic events. 4,19 This result explains the incidence of MI in reocclusions after successful recanalizations. 31 However, during a gradual reocclusion, dormant collaterals may recur. 29 Notably, the recruitable collateral function was better preserved with epicardial collaterals as compared with intramyocardial collaterals.

Limitations
The flow and pressure recorded distal to an occlusion are approximations of collateral function, inasmuch as they assess only that part of collateral perfusion that can be detected distal to the occlusion. Collateral perfusion through
intramyocardial pathways may be underestimated. Anatomic pathways of collaterals vary widely, with a considerable variability of collateral flow patterns.\(^\text{3,6,7,16}\) Epididymal collaterals seem to provide a flow pattern that is closer to the physiological diastolic coronary flow, whereas with intramyocardial collaterals it was predominantly systolic. Despite the imperfections of the distal flow measurement, it seems to be a feasible way to assess collaterals in humans, with a higher spatial resolution than noninvasive techniques provide.\(^\text{32}\)

The calculation of resistance indices is simplified by assuming steady rather than pulsatile flow.\(^\text{18}\) These calculations were based on flow velocimetry and not volumetric flow. To minimize the influence of diameter changes, nitroglycerine was given.\(^\text{12,13,15}\) Another simplification is the fact that more than one epicardial and intramyocardial pathway coexist, and thus collateral resistance is found distal to a coronary occlusion in both serial and parallel order.

The increase of \(R_{\text{Coll}}\) and \(R_{\text{P}}\) after recanalization could be the consequence of distal embolization. As shown in patients with acute MI, distal embolization would cause a reduced antegrade APV,\(^\text{33}\) whereas antegrade APV in TCOs with 30 cm/s was high. This fact makes distal embolization an unlikely cause of reduced collateral function.

**Clinical Implications**

Collateral function in patients with TCO and normal regional function was better than in those with impaired regional function. In the latter group, however, collateral function had the potential to improve considerably within 12 weeks of occlusion duration. The recruitable collateral function immediately after recanalization was attenuated and may not be sufficient during an acute reocclusion.

**References**


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