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\textsubscript{D}) and pressure-derived collateral flow indices (CFI\textsubscript{P}), as well as indices of collateral (R\textsubscript{Coll}) and peripheral resistance (R\textsubscript{P}). Patients with normokinesia had lower R\textsubscript{Coll} (4.9±2.5 versus 11.8±8.2 mm Hg·cm\textsuperscript{-1}·s\textsuperscript{-1}; \(P=0.033\)) and lower R\textsubscript{P} (3.8±1.9 versus 6.1±4.1 mm Hg·cm\textsuperscript{-1}·s\textsuperscript{-1}; \(P=0.031\)) than those with akinesia. Patients with akinesia and a TCO duration of ≤3 months had the highest R\textsubscript{Coll} and R\textsubscript{P}, whereas those with akinesia and a longer TCO duration had similar collateral function as patients with normokinesia. After PTCA, CFI\textsubscript{D} and CFI\textsubscript{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\textsubscript{Coll} of 139±128% (\(P<0.001\)) and R\textsubscript{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\textsubscript{Coll} and R\textsubscript{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.\textsuperscript{1} The in vivo assessment of collateral function in humans developed from a qualitative anatomic evaluation by angiography\textsuperscript{2} to a physiological assessment by microsensors recording coronary flow velocity and pressure during cardiac catheterization.\textsuperscript{3,4,5} 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).\textsuperscript{6,7,8} In TCOs, the collaterals are capable of complete preservation of myocardial function or of providing a minimum perfusion for hibernating myocardium.\textsuperscript{9,10} 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.\textsuperscript{11}

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.\textsuperscript{12–15} A considerable attenuation of recruitable collateral flow had been observed after recanalization of a TCO.\textsuperscript{16} 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 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.

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. A pressure-derived $CFl_P$ was calculated as $(P_D−CVP)/(P_A−CVP)$, 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 · cm$^{-1}$ · s$^{-1}$. The collateral resistance index was calculated as $R_{Coll}=P_D/P_A/D$, and the peripheral resistance index as $R_P=P_D/APV$.

**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

**Study Groups**

The angiographic function of the myocardium supplied by the occluded artery was graded as normokinetic (1), hypokinetic (2), akinetic (3), or dyskinetic (4), on the basis of a biplane left ventriculography by two blinded investigators; in case of disagreement, a consensus was reached. A group of 21 patients (normokinetic) with moderate or no impairment of regional function (grade 1.6±0.8) was compared with a group of 29 patients (akinetic) with akinesia or dyskinesia (grade 3.6±0.6). In patients with clinically documented Q-wave MI, the onset of symptoms; TIMI grade 0 coronary flow; evidence of ischemia related to the occlusion; viable myocardium in case of akinesia (as detected by PET with fluorodeoxyglucose); spontaneously visible collaterals; and written formal consent. The study protocol was approved by the university ethics committee.

**Study Protocol**

Figure 1 depicts the study concept, which is based on an electric analog model of serial and parallel resistances. The distal flow velocity ($APV_{Occl}$) and pressure ($P_{Occl}$) are determined by the $R_{Coll}$ and $R_P$ in serial order (left). $APV_{Coll}$ and $P_{Coll}$ are recorded before antegrade flow is reestablished. The aortic pressure ($P_Ao$) is recorded through the guiding catheter; the right atrial pressure (RA) and the epicardial resistance of the donor artery are neglected. After PTCA, the recruitable collateral function is determined during balloon inflation (right).
TABLE 1. Clinical Characteristics of Patients With Chronic Total Coronary Occlusions

<table>
<thead>
<tr>
<th></th>
<th>Normokinetic Patients (n=21)</th>
<th>Akinetic Patients (n=29)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<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/I/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.

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 akinesia; 4 of 29 patients with normokinesia had grade 2.

Regional Function and Collateral Flow
APV and MV measured distal to the occlusion before recanalization were higher in patients with normokinesia compared with patients with akinesia. Pressure values did not differ significantly except for systolic P0 (Table 2). CFIw was lower in the akinetic group, whereas CFIv was similar. Rcoll and Rp were significantly higher in the akinetic 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 akinetic 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).

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). P0 was considerably higher with epicardial collaterals (57±16 versus 43±10 mm Hg; P=0.006), leading to a higher CFIw (0.53±0.08 versus 0.41±0.10; P<0.001), whereas CFIv 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 Rp 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 P0 in patients with and without regional dysfunction (Table 2). Both CFIw and CFIv 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...
pronounced for \( R_{\text{Coll}} \) than for \( R_{\text{P}} \) (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 \( R_{\text{P}} \) 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.\(^1^,6^,7^,13^,14\) Collateral function can be quantified by calculation of a collateral flow index on the basis of either pressure recordings (CFIP)\(^4^,19\) or Doppler recordings (CFID).\(^5\) In addition, we calculated a collateral resistance index by simultaneous pressure and flow recording.\(^1^2^,14^,15\) A good collateral function was characterized by a high CFIP and CFID 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.\(^1^1\) In patients with preserved ventricular function, collaterals must have developed before the actual occlusion, and no exact occlusion date can be given. How-

### Table 2. Collateral Flow, Pressure, and Resistance Indexes in TCO Before and After Recanalization

<table>
<thead>
<tr>
<th></th>
<th>Normokineti</th>
<th>Akinetic</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Occlusion After</td>
</tr>
<tr>
<td></td>
<td>PTCA</td>
<td>PTCA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \text{APV}_{\text{coll}} ), cm/s</td>
<td>13.0±5.5*</td>
<td>6.9±2.9§</td>
</tr>
<tr>
<td>MV, cm/s</td>
<td>30.9±14.9†</td>
<td>19.4±11.2§</td>
</tr>
<tr>
<td>Antegrade ( \text{APV} ), cm/s</td>
<td>28.0±14.5</td>
<td>30.3±13.8</td>
</tr>
<tr>
<td>Mean ( P_{\text{Ao}} ), mm Hg</td>
<td>106±15</td>
<td>107±14</td>
</tr>
<tr>
<td>Mean ( P_{\text{ao}} ), mm Hg</td>
<td>49±13</td>
<td>39±11§</td>
</tr>
<tr>
<td>CFIP</td>
<td>0.47±0.11</td>
<td>0.36±0.09§</td>
</tr>
<tr>
<td>CFID</td>
<td>0.44±0.21*</td>
<td>0.25±0.13§</td>
</tr>
<tr>
<td>( R_{\text{coll}} ), mm Hg ( \cdot ) cm(^{-1} \cdot ) s(^{-1} )</td>
<td>5.11±2.24*</td>
<td>11.23±4.67§</td>
</tr>
<tr>
<td>( R_{\text{p}} ), mm Hg ( \cdot ) cm(^{-1} \cdot ) s(^{-1} )</td>
<td>4.51±2.31*</td>
<td>6.24±2.84§</td>
</tr>
</tbody>
</table>

*\( \text{P}<0.05 \); †\( \text{P}<0.001 \); ‡\( \text{P}<0.05 \); §\( \text{P}<0.001 \).

**Figure 3.** Comparison of \( R_{\text{Coll}} \) (A) and \( R_{\text{p}} \) (B) among patients with TCO and preserved regional ventricular function and those with impaired regional function and a TCO of \( \leq 3 \) or \( >3 \) months’ duration. P values are given for the intergroup comparison with Bonferroni correction.

**Figure 4.** Decrease of CFIP (A) and CFID (B) after recanalization of TCO.
ever, in patients with akinesia and MI, the occlusion date could be well defined. Collateral function was least developed in patients with a TCO / H11349 3 months in duration, whereas patients with TCO / H11022 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 / H11349 10 days after a persistent acute occlusion, 20 but these early collaterals are not yet fully developed, and further functional maturation occurs within / H11015 12 weeks. This idea is in accordance with animal studies, in which collateral development required / H11015 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. Rp 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 recocclusion, 25,26 but there is also anecdotal evidence that collaterals are recruitable, 27,28 especially when a recocclusion 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 Rcoll and a moderate increase of Rp. 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 Rcoll 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 recocclusions after successful recanalizations. 31 However, during a gradual recocclusion, 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. Epicardial collaterals seem to provide a flow pattern that is closer to the physiological diastolic coronary flow, whereas 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.

The calculation of resistance indices is simplified by assuming steady rather than pulsatile flow. These calculations were based on flow velocimetry and not volumetric flow. To minimize the influence of diameter changes, nitroglycerin was given. 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_coll and R_p after recanalization could be in the supply and receiving coronary arteries during angioplasty for total coronary occlusion. Simultaneous intracoronary blood flow velocity analysis in an angioplasty model. Proc Natl Acad Sci USA 1993;90:11005–11009.

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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