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- (CFlD) and pressure-derived collateral flow indices (CFIP), as well as indices of collateral (Rcoll) and peripheral resistance (RP). Patients with normokinesia had lower Rcoll (4.9±2.5 versus 11.8±8.2 mm Hg·cm⁻¹·s⁻¹; P=0.033) and lower RP (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 Rcoll and RP, whereas those with akinesia and a longer TCO duration had similar collateral function as patients with normokinesia. After PTCA, CFlD and CFIP 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 Rcoll of 139±128% (P<0.001) and RP 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 Rcoll and RP. (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...
Doppler wire positioning. Nitroglycerine (0.1 mg) was injected into the catheter was performed to identify major side branches and assist in the Doppler signal of collateral flow occurred during contrast injection. The baseline measurement of collateral flow was performed before the occlusion during proximal contrast injection. No alteration of the antegrade flow to the collateralized vascular bed had started. After PTCA, the recruitable collateral function is determined during balloon inflation (right).

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 Groups
The regional 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) 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 duration of the occlusion was based on the date of the MI. In patients without MI, the onset or sudden worsening of angina pectoris determined the time of occlusion. According to the duration of occlusion, patients were divided into two groups: those with duration of ≤3 months and those with duration of >3 months.

Study Protocol
Figure 1 depicts the study concept, which is based on an electric analog model of serial and parallel resistances.17

Angioplasty Procedure
The recanalization was performed via the femoral approach using 7F guiding catheters. All patients received a bolus of 10 000 IU of heparin and were taking aspirin (100 mg) and clopidogrel (75 mg) for 4 weeks. All patients were on oral nitrate or molsidomine, which was continued on the day of the procedure. After the lesion was crossed by a 0.014-inch guidewire, an over-the-wire exchange catheter (Transit, Cordis) was advanced distal to the occlusion in 38 patients, and a low-profile, over-the-wire balloon catheter (Ranger, Scimed) was advanced distal to the occlusion in 12 patients. The initial guidewire was exchanged first for the Doppler wire (FloWire, EndoSonics Corporation), and then for the pressure wire (PressureWire, RADI Medical Systems), and the Doppler and pressure recordings were taken. After exchange for a support wire, angioplasty with stenting was performed.

Intracoronary Doppler Velocimetry
The baseline measurement of collateral flow was performed before the antegrade flow to the collateralized vascular bed had started. A leakage of antegrade flow along the exchange catheter was excluded by the absence of contrast medium passage to the segment distal of the occlusion during proximal contrast injection. No alteration of the Doppler signal of collateral flow occurred during contrast injection. Contrast opacification of the distal segment through the exchange catheter was performed to identify major side branches and assist in Doppler wire positioning. 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 (Pd) was recorded together with the aortic pressure (Pao) that was obtained through the guiding catheter. Mean pressures were used for computation. The recruitable collateral function was assessed by recording Pd 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,16 and the maximum velocity (MV) and average peak velocity (APV) were obtained. A Doppler-derived collateral flow index (CFID) was calculated as the ratio of APV distal to the occlusion to antegrade APV. A pressure-derived CFIP was calculated as (Pd−CVP)/(PAo−CVP), where CVP is the central venous pressure, for which 5 mm Hg was substituted.4,5 Resistance indices were calculated assuming steady laminar flow and constant vessel diameters.18 Because flow velocity was used instead of flow volume, the unit of measure was mm Hg · cm/s. The collateral resistance index was calculated as Rcoll=(Pao−Pd)/APV, and the peripheral resistance index as Rp=Pdf/APV.15

Angiographic Assessment of Collateral Flow
The collateral supply was graded angiographically.2 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

Figure 2. Examples of anatomic collateral pathways between the left anterior descending artery (LAD) and the right coronary artery (RCA). Intramyocardial pathways (arrowheads) from LAD to the posterior descending branch of the RCA (arrow) (A), and from RCA to LAD (B). Epicardial pathways (arrowhead) around the apex from LAD to RCA (C), and via right ventricular branches (arrowheads) from RCA to LAD (D).
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 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 normokinesia and TCO ≤3 months (\( P = 0.001 \)). R\(_c\) showed a similar relation (\( P = 0.007 \)) (Figure 3).

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>0/1/14/1/3</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>0.24</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.

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). \( R_{coll} \) was comparably low in patients with normokinesia and akinesia with TCO >3 months, but was higher in patients with akinesia and TCO ≤3 months (\( P = 0.001 \)). \( R_p \) 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; \( P = 0.002 \)). \( P_0 \) was considerably higher with epicardial collaterals (57 ± 16 versus 43 ± 10 mm Hg; \( P = 0.006 \)), leading to a higher CFI\(_p\) (0.53 ± 0.08 versus 0.41 ± 0.10; \( P < 0.001 \)), whereas CFI\(_d\) was not different (0.39 ± 0.21 versus 0.33 ± 0.21; \( P = 0.38 \)). \( R_{coll} \) 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 \( R_p \) 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 Recanulation

The measurement of recruitable collateral function during a final balloon reoclusion 44 ± 15 minutes after baseline measurement showed a significant reduction of APV and MV and a decrease of \( P_0 \) in patients with and without regional dysfunction (Table 2). Both CFI\(_d\) and CFI\(_p\) decreased significantly (Figure 4). None of the patients experienced chest pain or ECG changes during the reoclusion of 3 minutes. The resistance indices increased, but this result was more...
pronounced for \( R_{\text{Coll}} \) than for \( R_F \) (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 \( R_F \) 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 (CFIP)\(^4,19\) or Doppler recordings (CFID).\(^5\) 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 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.\(^11\) 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>Normokinetic</th>
<th></th>
<th>AkinetiC</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Occlusion After PTCA</td>
<td>Baseline</td>
<td>Occlusion After PTCA</td>
</tr>
<tr>
<td>( APV_{\text{ooc}} ), cm/s</td>
<td>13.0±5.5*</td>
<td>6.9±2.9§</td>
<td>9.0±5.4</td>
<td>5.9±5.2§</td>
</tr>
<tr>
<td>( MV ), cm/s</td>
<td>30.9±14.9†</td>
<td>19.4±11.2§</td>
<td>17.4±8.8</td>
<td>15.2±9.5</td>
</tr>
<tr>
<td>Antegrade ( APV ), cm/s</td>
<td>28.0±14.5</td>
<td></td>
<td>30.3±13.8</td>
<td></td>
</tr>
<tr>
<td>Mean ( P_{Ao} ), mm Hg</td>
<td>106±15</td>
<td>107±14</td>
<td>106±21</td>
<td>106±16</td>
</tr>
<tr>
<td>Mean ( P_c ), mm Hg</td>
<td>49±13</td>
<td>39±11§</td>
<td>45±14</td>
<td>38±13§</td>
</tr>
<tr>
<td>( CFIP )</td>
<td>0.47±0.11</td>
<td>0.36±0.09§</td>
<td>0.43±0.11</td>
<td>0.36±0.13§</td>
</tr>
<tr>
<td>( CFID )</td>
<td>0.44±0.21†</td>
<td>0.25±0.13§</td>
<td>0.29±0.18</td>
<td>0.19±0.17§</td>
</tr>
<tr>
<td>( R_{\text{Coll}} ), mm Hg · cm(^{-1}) · s(^{-1})</td>
<td>5.11±2.24*</td>
<td>11.23±4.67§</td>
<td>10.57±9.53</td>
<td>21.41±17.04§</td>
</tr>
<tr>
<td>( R_F ), mm Hg · cm(^{-1}) · s(^{-1})</td>
<td>4.51±2.31†</td>
<td>6.24±2.84§</td>
<td>7.17±5.18</td>
<td>10.63±6.94‡</td>
</tr>
</tbody>
</table>

Difference between normokinetic and akinetiC group: *\( P<0.05 \); †\( P<0.001 \). Significant changes between basal and recruitable collateral flow: ‡\( P<0.05 \); §\( P<0.001 \).
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 recollection. 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 recanalization. 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. Epicardial 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.

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, nitroglycerine 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 the consequence of distal embolization. As shown in patients with acute MI, distal embolization would cause a reduced antegrade APV, 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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