Regression of Collateral Function After Recanalization of Chronic Total Coronary Occlusions

A Serial Assessment by Intracoronary Pressure and Doppler Recordings

Gerald S. Werner, MD; Ulf Emig, MD; Oliver Mutschke, MD; Gero Schwarz, MD; Philipp Bahrmann, MD; Hans R. Figulla, MD

Background—Collaterals can maintain myocardial function or preserve viability in chronic total coronary occlusions (CTOs). It is unknown whether and to what extent collaterals regress after successful recanalization of a CTO.

Methods and Results—In 103 patients with successful recanalization of a CTO collateral function was assessed by intracoronary Doppler and pressure recordings before and after recanalization, and again after 5.0±1.3 months. Doppler (CFI) and pressure-derived collateral function indexes (CPI) and collateral (RColl) and peripheral resistance indexes (RP) were calculated. In 10 patients with reocclusion, all without myocardial infarction during follow-up, collateral function had reached a similar level as before the first recanalization. In the other 93 patients with or without restenosis, collateral function was attenuated during follow-up. CPI had decreased by 23% immediately after recanalization (P<0.001) and decreased further by another 23% at follow-up (P<0.001). The RColl increased immediately after recanalization by 82% (P<0.001) and by a further 273% at follow-up (P<0.001). In contrast, RP increased only by 22% after recanalization (P<0.001) and by an additional 12% at follow-up (P<0.05). The initial size of the collaterals but not the incidence of a restenosis influenced the collateral regression. Only 18% of patients at follow-up had collaterals with a CPI >0.30, presumably sufficient to prevent ischemia during acute occlusion.

Conclusions—Collateral function regresses during long-term follow-up, especially in collaterals with a small diameter. In the majority of patients, collaterals are not readily recruitable in the case of acute occlusion. However, collaterals have the potential to recover in the case of chronic occlusion. (Circulation. 2003;108:2877-2882.)

Key Words: collateral circulation • occlusion • hemodynamics • angioplasty

Coronary collaterals in humans develop during gradual progression of coronary lesions or after an acute occlusion and can completely or partially preserve myocardial function. However, even well-developed collaterals may not fully substitute normal coronary flow, and surgical or percutaneous revascularization is often indicated. The incidence of acute myocardial infarction (MI) after recanalization of a chronic total coronary occlusion (CTO) suggests that collaterals that are no longer required to uphold myocardial perfusion may regress after revascularization. However, there is also anecdotal evidence that collaterals remain recruitable, especially during a gradual reocclusion.

Studies in dogs have shown a regression of collaterals after restored perfusion and a capacity to recover during a prolonged reocclusion. The applicability of these data to human pathophysiology is not yet proven, but the advent of direct measurement of collateral function in humans with miniaturized sensors of coronary flow and pressure provides a means to test the experimental data in humans. Applying these invasive methods in CTOs, we had recently shown a loss of collateral function within 30 minutes after recanalization. The present study should assess whether collaterals regress or remain preserved several months after recanalization. Possible clinical determinants of collateral regression could be diabetes mellitus, the regional left ventricular (LV) function and prior MI or angiographic factors such as collateral anatomy and size, and the incidence of restenosis or reocclusion.

Methods

Patients

One hundred nineteen consecutive patients with successful recanalization of a CTO were enrolled and underwent an invasive assessment of collateral function. The principal inclusion criterion was that this assessment was possible before the first balloon inflation. Other inclusion criteria were a duration of the occlusion >2 weeks; TIMI grade 0 coronary flow; spontaneously visible collaterals; and no ventricular aneurysm supplied by the occluded artery. The study protocol had been approved by the institutional ethics committee.

The analysis presented here is based on 103 patients who had both a baseline assessment of collateral function and a reassessment...
during a follow-up angiography. Of the initial 119 patients, 3 patients had died and 2 patients had declined a repeat angiography. Another 11 patients (9 with reocclusion, 2 with high-grade restenosis) had no reassessment because they did not undergo a repeat angioplasty. They were referred to surgery (n=8) or were treated medically (n=3).

**Baseline Study**

All patients received a bolus of 10 000 IU of heparin; they received aspirin (100 mg) and clopidogrel (75 mg) for 4 weeks. After the lesion was crossed by a 0.014-inch guide wire, an over-the-wire catheter was advanced distal to the occlusion to allow the exchange for a Doppler wire (FloWire, Endosonics Corporation) and a pressure wire (PressureWire, RADI Medical Systems) as previously described. After flow velocity and pressure recordings, the angioplasty commenced with stent implantation.

The measurement of baseline collateral flow was done before antegrade flow could occur that was ascertained by proximal contrast injection without affecting the distal Doppler signal. Nitroglycerin (0.1 mg) was injected locally before the Doppler recording. The Doppler wire was moved within a range of 10 mm to obtain a maximum flow velocity signal. After exchange for the pressure wire, 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 (\(P_a\)) from the guiding catheter. Mean pressures were used for computation. Examples are shown in Figure 1.

From the Doppler flow signals distal to the occlusion, the average peak velocity (APV\(_{\text{oct}l}\)) was obtained. A Doppler-derived collateral flow index (CFI) was calculated as the ratio of APV\(_{\text{oct}l}\)/APV\(_{\text{ante}l}\). The antegrade APV\(_{\text{ante}l}\) was recorded at the same position where the collateral flow signal had been recorded at the end of the recanalization procedure. A pressure-derived collateral pressure index (CPI) was calculated as \((P_d - \text{CVP})/(P_a - \text{CVP})\), where CVP is the central venous pressure. CVP was measured invasively in 41 patients (10±3 mm Hg) and substituted for by 10 mm Hg in the remaining patients. A collateral resistance index was calculated as \(R_{\text{col}} = \) \(P_a - P_d\)/APV\(_{\text{oct}l}\) and a peripheral resistance index was calculated as \(R_{\text{per}} = P_a/\text{APV}_{\text{ante}l}\).

In 80 patients, the immediately recruitable collateral flow velocity and distal coronary pressure were recorded at the end of the procedure (31±19 minutes after the baseline recording) during a final balloon inflation of 3 minutes.

**Follow-Up Study**

In 10 of 19 patients with reocclusion and in 39 of 41 patients with restenosis, collateral function was reassessed during a repeat therapeutic angioplasty. In 54 patients without restenosis, collateral function was reassessed during a balloon recollateralization within the stent, using inflation pressures of 2 to 4 atm. The procedure was done with over-the-wire balloon catheters of the same size used for the stent implantation during recanalization. After injecting 0.1 mg of nitroglycerin, the Doppler wire was introduced to the identical site of the baseline measurement and moved within a range of 10 mm to achieve an optimum signal. The occlusion was held for 3 minutes or until chest pain was reported. The procedure was repeated after exchange for a pressure wire to record distal pressure. In patients with a recollateralization and repeat recanalization, the procedure was the same as at baseline, that is, collateral function was assessed before the first balloon inflation.

**Angiographic Analysis**

Coronary angiograms of the collateral connections were obtained using a 7-inch field size. The view with the least foreshortening was selected for analysis. The size of collaterals was graded as previously described as CC0 (no direct connection visible between donor and recipient branch; CC1 (continuous thread-like connection); and CC2 (continuous small side branch–like connection). In the case of several pathways per lesion, the largest one was considered for further analysis.

**Statistics**

Data are given as mean values ±SD, unless otherwise indicated. Changes of parameters from baseline to subsequent measurements were evaluated by a t test for paired data. Differences between two groups were analyzed by Student’s t test or Fisher’s exact test when appropriate. One-way ANOVA with Bonferroni correction for multiple comparisons and repeated-measures ANOVA to compare changes of parameters between groups during follow-up were
In contrast, the RP increased only by 22% after recanalization after recanalization by 82% and by a further 273% at follow-up. Individual values and an immediate decrease from 0.41/11006 to 0.15 after recanalization, with no further decrease at follow-up (Figure 2).

Recruitable collateral function 5 months after recanalization

During Follow-Up

Collateral Function After Recanalization and During Follow-Up

Recruitable collateral function 5 months after recanalization in 93 patients without (n=54) or with a nonocclusive restenosis (n=39) was considerably lower than at baseline (Table 2). In 80 patients with assessment of the immediately recruitable collateral function, R_{coll} increased from baseline to the recording after recanalization by 82% and by a further 273% at follow-up. In contrast, the R_{p} increased only by 22% after recanalization and by a further 12% at follow-up (Figure 2).

The Doppler-derived CFI showed a wide variability of individual values and an immediate decrease from 0.41±0.33 to 0.22±0.15 after recanalization, with no further decrease at follow-up (0.21±0.31). The pressure-derived CPI decreased by 23%, from 0.39±0.12 to 0.30±0.13 after recanalization, with a further decrease of 23% to 0.21±0.12 at follow-up (Figure 2).

Neither CPI nor CFI increased during the course of the 3-minute balloon occlusion.

Collaterals in the Case of Reocclusion at Follow-Up

In 10 patients with reocclusion, the collateral function determined before the first balloon inflation at follow-up was not significantly different from that obtained before the recanalization at baseline. The collateral function had recovered from an immediate loss after recanalization (Table 3).

Collateral Regression in Chronic Occlusions

Table 1. Clinical Characteristics of 103 Patients With CTO

<table>
<thead>
<tr>
<th>Age, y</th>
<th>63±10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male gender, %</td>
<td>75</td>
</tr>
<tr>
<td>No. of diseased arteries (1/2/3), %</td>
<td>44/38/18</td>
</tr>
<tr>
<td>Occluded coronary artery (right/LAD/LCX), %</td>
<td>59/37/4</td>
</tr>
<tr>
<td>Previous MI, %</td>
<td>68</td>
</tr>
<tr>
<td>Duration of occlusion ≥3 mo, %</td>
<td>49</td>
</tr>
<tr>
<td>Angina pectoris (CCS class 0 to IV), %</td>
<td>0/3/43/53/1</td>
</tr>
<tr>
<td>Heart failure (NYHA class 0 to IV), %</td>
<td>2/40/14/0</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>76</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>72</td>
</tr>
<tr>
<td>History of smoking, %</td>
<td>47</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>57.5±18.9</td>
</tr>
<tr>
<td>Wall motion severity index (SD/chord)</td>
<td>−1.96±1.35</td>
</tr>
</tbody>
</table>

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

A level of P<0.05 was considered significant. All calculations were done with SPSS for Windows (Version 10.05, SPSS Inc).

Results

Baseline Clinical Characteristics and Follow-Up

The clinical data are summarized in Table 1. During follow-up, the LV ejection fraction increased from 57±19% to 65±16% (P<0.001), and the WMSI improved from −1.96±1.35 SD/chord to −1.34±1.35 SD/chord (P<0.001). In 114 patients with angiographic follow-up, a reocclusion was observed in 16.5% and a restenosis was observed in 35.7%. One patient with reocclusion had a late subacute stent thrombosis 4 weeks after recanalization with acute MI; all other reocclusions were clinically silent. During a subsequent follow-up of 2.1±1.1 years, no clinical event occurred that could be attributed to the experimental protocol during repeat angiography.

Collateral Function After Recanalization and During Follow-Up

Table 2. Changes of Collateral Function During Follow-Up in CTOs Without Reocclusion

<table>
<thead>
<tr>
<th>Collateral Function</th>
<th>At Baseline (n=93)</th>
<th>Recruitable After Recanalization (n=72)</th>
<th>Recruitable at Follow-Up (n=93)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDP, mm Hg</td>
<td>15±8</td>
<td>16±7</td>
<td></td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>68±12</td>
<td>69±12</td>
<td>66±13</td>
</tr>
<tr>
<td>APV_{occl}, m/s</td>
<td>10.7±5.9</td>
<td>6.2±3.8*</td>
<td>4.7±4.9*</td>
</tr>
<tr>
<td>Pa mean, mm Hg</td>
<td>107±17</td>
<td>106±15</td>
<td>107±16</td>
</tr>
<tr>
<td>P_{p} mean, mm Hg</td>
<td>45±14</td>
<td>35±14*</td>
<td>22±15*</td>
</tr>
<tr>
<td>CPI</td>
<td>0.39±0.12</td>
<td>0.30±0.13*</td>
<td>0.21±0.12*</td>
</tr>
<tr>
<td>CFI</td>
<td>0.41±0.33</td>
<td>0.22±0.15*</td>
<td>0.21±0.31*</td>
</tr>
<tr>
<td>R_{coll}, mm Hg/cm per second</td>
<td>9.1±10.3</td>
<td>16.6±12.7*</td>
<td>41.4±41.2*</td>
</tr>
<tr>
<td>R_{p}, mm Hg/cm per second</td>
<td>6.3±7.1</td>
<td>7.7±5.9†</td>
<td>8.5±8.3</td>
</tr>
</tbody>
</table>

APV indicates average peak velocity; CFI, collateral flow index; CPI, collateral pressure index; LVEDP, left ventricular end-diastolic pressure; Pa, mean, distal pressure; P_{p}, mean, aortic pressure; R_{coll}, collateral resistance index; and R_{p}, peripheral resistance index.

Comparison with column to the left: *P<0.001; †P<0.05.

Collaterals in the Case of Reocclusion at Follow-Up

In 10 patients with reocclusion, the collateral function determined before the first balloon inflation at follow-up was not significantly different from that obtained before the recanalization at baseline. The collateral function had recovered from an immediate loss after recanalization (Table 3).

Figure 2. Changes of Doppler and pressure-derived collateral function indexes (A) and collateral and peripheral resistance indexes (B) before and after recanalization of a CTO and at follow-up (excluded are patients with reocclusion). Data are mean±SEM. *P<0.001; †P<0.05 for comparison with previous time point.
Determinants of Collateral Regression During Follow-Up

In patients without reocclusion, possible determinants of recruitable collateral function at follow-up were assessed. The increase of $R_{\text{Coll}}$ from baseline to follow-up was evaluated by repeated-measures ANOVA. The incidence of a nonocclusive restenosis, the presence of regional ventricular dysfunction (WMSI $\leq -2$ SD/chord), diabetes mellitus, a history of prior MI, and the collateral connection size (CC0 to CC2) were entered as between-subject effects. Only the collateral connection size was a significant predictor of the increase of $R_{\text{Coll}}$ during follow-up. Collateral function was best preserved in larger collaterals of grade CC2, both immediately after recanalization and at follow-up, whereas the greatest functional regression occurred with CC0 collaterals (Figure 3).

Patients With Preserved Recruitable Collateral Function

At baseline, 79% of patients had a CPI $\geq 0.3$, which is considered sufficient to prevent acute ischemia. Immediately after recanalization, this rate dropped to 46% and decreased further at follow-up to 18% (Figure 4). Patients with a CPI $\geq 0.3$ less frequently had angina during balloon occlusion at follow-up than patients with a CPI $<0.3$ (21% versus 63%; $P<0.05$). Patients with a CPI $\geq 0.3$ at follow-up were also those who more often had CC2 collaterals at baseline (69%; $P<0.01$). The CPI at follow-up in patients with and without a nonocclusive restenosis was not correlated with the degree of restenosis ($r=0.05$; $P=0.7$).

Discussion

This is the first prospective study in humans to evaluate long-term changes of collateral function after recanalization of a CTO by direct assessment of collateral hemodynamics. Immediately after restoration of antegrade flow, collateral function is attenuated, with a further regression during a follow-up of 5 months. This functional regression is not influenced by the degree of restenosis, but in the case of a complete reocclusion, collaterals have the potential to recover completely to the level before recanalization. This indicates that a functional but not an anatomical regression occurred after recanalization.

Clinical Observations on Collateral Regression and Recurrence

The question arising from clinical observations is whether a patient with coronary artery disease will remain protected by collaterals after removing the obstruction in the collateralized artery or whether collaterals regress and lose their functional capacity. The incidence of MI in the case of reocclusion after a successful recanalization in recent prospective studies is evidence for a collateral regression.4,5 However, the rate of MI was smaller than the incidence of reocclusion. This could be explained by a potential for collateral recruitment or persistent collateral channels in some patients.9–11 In our study, only one MI was observed at follow-up, which suggests that most reocclusions may have occurred gradually.

Collateral Regression and Recovery After Recanalization of a CTO

In humans, collaterals supplying CTOs showed a functional loss immediately after recanalization.20,24 The present study enhances this observation by the systematic assessment of collateral function during a long-term follow-up by demonstrating a further functional regression. The complete recov-

![Figure 3. Changes of APV (A), CPI (B), and $R_{\text{Coll}}$ (C) from baseline before recanalization to reocclusion immediately after PTCA and at follow-up in patients with different collateral connection grades (CC0 to CC2) (excluded are patients with reocclusion). $P<0.001$ for comparison of CC0 with CC2 at the specified time point; $P<0.05$ for comparison of CC2 with CC1 at the specified time point; $P<0.05$ for comparison of CC2 with CC0; $P<0.05$ for comparison of CC1 with CC0.]
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Figure 4. Distribution of individual values of the collateral pressure index at baseline, after recanalization, and at follow-up. Line indicates a threshold of 0.3, sufficient to prevent ischemia during balloon occlusion.18

evory observed in patients with reocclusion suggests that collaterals remain recruitable during recurrence of an occlusion and do not disappear completely after recanalization.

These data are in agreement with several studies in dogs that showed a regression of collaterals after removal of an obstruction. Recovery of collateral function in the case of a reocclusion occurred not instantaneously25 but within a few minutes to 1 hour.12–14 It is obvious that we could not perform a long-lasting reocclusion in humans, and within the planned 3-minute duration, the balloon occlusion had to be relieved prematurely in some patients because of angina. Therefore, we cannot estimate a time interval required for a full functional recovery in humans, but it appears to be longer than in the animal model. In the case of an acute occlusion, collateral recovery would take too long to prevent ischemia in most patients, as only 18% of patients had a CPI ≥0.3 at follow-up.18

The mechanisms involved in collateral regression and recovery probably are flow-dependent changes of the collateral vascular tone.13 This is documented in our study by the increase of Rcoll at baseline, the microvascular arterioles and collaterals would be maximally dilated, and both Rcoll and Rp are low. After recanalization the peripheral arteriolar tone increases as a consequence of the autoregulatory potential of the microvasculature to respond to the improved perfusion, and Rp increases. The much steeper increase in Rcoll indicates that an increased tone may even lead to a collapse of collateral connections after the removal of the pressure gradient between donor and recipient artery. A longer-lasting reocclusion would again increase the pressure gradient and lead to a reopening of the collateral connections.

Determinants of Collateral Regression

No clinical determinant (presence of diabetes, prior MI) of collateral regression could be detected. There was even no correlation of the degree of restenosis with the recruitable collateral function. The latter is in agreement with an earlier study that used the less sensitive angiographic grading of collaterals and ECG signs of ischemia during balloon occlusion as measures of collateral function.26 Only patients with subtotal restenosis and reduced TIMI flow showed recruitable collaterals at follow-up, similar to our observation of collateral recovery only in the case of reocclusion.

The immediate loss of collateral function is related to the size of the collateral connections.22 Also, after several months, the well-developed collaterals remain those with the greatest potential for functional recovery. The various diameters of collateral connections represent the human analogy to the different developmental stages of collaterals observed in animal studies.27 In humans, rudimentary collateral connections are prevalent in the first 2 to 4 weeks after a persistent occlusion, and further “maturization” with increasing collateral diameters is observed within about 12 weeks.22

Limitations

Even though the invasive approach is superior to the widely used angiographic assessment of collateral function,16,28 some limitations must be kept in mind. The calculation of the Doppler parameters is not based on flow volume but on flow velocity, which is sensitive to changes of the vessel diameter. To minimize this influence, nitroglycerin was given frequently during the procedure. The recording of the Doppler signal is very critical to the sensor tip location, and despite the special care taken to record at identical points during the follow-up study, an inaccuracy is inherent in this approach. As the observation of collateral regression was likewise observed for the pressure-derived indexes, the observed changes can be considered genuine.

In the calculation of CPI, the CVP was inversely measured in 41 of 103 patients and in the remaining patients substituted by a fixed value. This brings about a source of inaccuracy but does not affect the observed changes during follow-up. Furthermore, CVP might also influence Rp and is included in the numerator of the formula as (Pd – CVP) instead of Pd alone, but the widely used formula omits CVP.17 The inclusion of CVP would lead to a 22% lower Rp, but it would not influence the main observation that Rp increased only moderately during follow-up in contrast to the steep increase of Rcoll.

The increase of Rcoll and Rp after recanalization could be the consequence of distal embolization. However, this would cause either an increase of both indexes or rather a predominant increase of Rp. The >10-fold increase of Rcoll as compared with Rp indicates that there occurs a specific change in collateral resistance during follow-up.

Clinical Implications

Collateral function in patients with CTOs regresses after recanalization, but with the potential for functional recovery in the case of a probably gradual occlusion. Only one fifth of patients with a patent artery at follow-up would be protected from ischemia in the case of an acute occlusion by immediately recruitable collaterals. It is notable that this rate of preserved collaterals is in the same range as the rate of preformed functional collaterals observed during balloon occlusion of nonstenotic arteries.29 It may be speculated that the patients with well-preserved collaterals after recanala-
tion might have been those with preformed arterial connections.

**References**

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