Immediate Changes of Collateral Function After Successful Recanalization of Chronic Total Coronary Occlusions

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**Background**—Coronary collaterals are essential to maintain myocardial function in chronic total coronary occlusions (TCOs). The aim of the present study was to assess the collateral circulation in TCOs before coronary angioplasty and to determine the recruitable collateral perfusion after recanalization by use of intracoronary Doppler flow velocimetry.

**Methods and Results**—In 21 patients with TCOs (duration >4 weeks), Doppler recordings of basal collateral flow were obtained before the first balloon inflation. Angioplasty was performed with stent implantation in all lesions. At the end of the procedure, recruitable collateral flow was measured during a repeat balloon inflation. The collateral flow index (CFI) was calculated from the velocity integral during the occlusion/velocity integral of antegrade flow. In 17 of 21 patients, angiography was repeated after 24 hours, and CFI was reassessed. Average peak velocity of collateral flow was 10.9 ± 5.6 cm/s with a predominantly systolic flow (diastolic/systolic velocity ratio <0.5) compared with antegrade flow (diastolic/systolic velocity ratio >1.5). After recanalization, the average peak velocity of recruitable collateral flow dropped by >50% to 4.7 ± 2.5 cm/s. CFI fell from 0.48 ± 0.25 to 0.21 ± 0.16 (P < 0.001). There was no further change of CFI during the following 24 hours. CFI was higher in patients with preserved regional ventricular function than in those with akinetic myocardium (0.57 ± 0.23 versus 0.38 ± 0.12, P < 0.05).

**Conclusions**—Collateral circulation in TCO provided 50% of antegrade coronary flow. A considerable fraction of ischemia. Some studies on the function of collaterals during PTCA of nonocclusive coronary lesions as a model of coronary collateral circulation. Many studies were carried out enabled a more direct approach in the assessment of the sors to monitor coronary flow and pressure in humans radionuclide studies. The availability of miniaturized senors to monitor coronary flow and pressure in humans enabled a more direct approach in the assessment of the coronary collateral circulation. Many studies were carried out during PTCA of nonocclusive coronary lesions as a model of ischemia. Some studies on the function of collaterals included patients with TCOs, but no distinction was made between nonocclusive and occlusive lesions. Because the recurrence of TCOs after PTCA often leads to clinical symptoms, including myocardial infarction, we assumed that the collateral function in TCO would change after reopening of the artery. The present study should assess these changes during the first 24 hours after recanalization by use of Doppler flow velocimetry.

**Methods**

**Patients**
The study group consisted of 21 consecutive patients with a successful PTCA of a TCO. The TCO was defined as follows: (1) duration of the occlusion >4 weeks, as determined from a previous angiogram, the date of a prior infarction, or the onset of symptoms, and (2) Thrombolysis in Myocardial Infarction (TIMI) grade 0 coronary flow. Indications for the recanalizations were (1) evidence of ischememia (exercise bicycle test or scintigraphy) related to the occlusion, (2) viable myocardium detected by PET using fluorodeoxyglucose in an akinetic segment, (3) spontaneously visible collaterals, and (4) written informed consent. The median duration of the occlusion was 2.7 months (range 1 to 87 months).

**Angioplasty Procedure**
The femoral approach and 7F guiding catheters were used. All patients received a bolus of 10 000 IU heparin, and they were on aspirin (100 mg) and clopidogrel (75 mg) for 4 weeks. All patients were on oral nitrate or molsidomine, which was continued during the
day of the procedure. An over-the-wire exchange catheter (Transit, Cordis) was used in all cases. When the lesion was crossed by a 0.014-in guidewire, the exchange catheter was passed through the occlusion. When this was not possible in 5 lesions, a low-profile over-the-wire balloon catheter (Bandit, Scimed) was used instead.

No patient was included if a predilatation was required to cross the lesion for the following measurements. After positioning of the catheter tip distal to the occlusion, the guidewire was exchanged for the Doppler wire, and the Doppler recording was performed. The PTCA was continued with a support wire, and a balloon was selected according to the operator’s estimation of the vessel size. In small vessels of ≥3.0-mm diameter (8 patients), the dilatation was optimized by intracoronary ultrasound as described previously. All TCOs received stents, with multiple stents in 33% of the lesions.

Protocol of Intracoronary Doppler Velocimetry

The baseline measurements of collateral flow were performed before the first balloon inflation. The distal coronary bed was visualized by injecting contrast media through the exchange catheter to identify major branches and to assist positioning of the Doppler wire (FloWire, Endosonics Corp) distal to the occlusion. Nitroglycerin (0.1 mg) was injected through the catheter before the Doppler wire was inserted. The wire position was documented on cine film. A potential problem of the basal collateral flow recording could be an unaccounted contribution of antegrade flow along the exchange catheter within the occlusive lesion. This could be ruled out in all patients by lack of contrast passage during proximal contrast injection into the recanalized artery while the exchange catheter was in place. The continuously recorded Doppler signal of collateral flow did not change during this injection.

After the stent implantation was completed, 0.1 mg nitroglycerin was again applied, and the Doppler wire was reintroduced to the previously documented position to record the antegrade coronary flow. The final balloon was reinflated within the stent, and the recruitable collateral flow was recorded. Specific care was taken to keep the wire at an identical position relative to vessel side branches, which was ascertained by fluoroscopy of the wire tip on 2 orthogonal planes. In all cases, the recording was repeated 3 times with the Doppler wire moved within a range of 10 mm to obtain the recording with the maximum flow velocity integral to be used for quantification.

A repeat angiography after 20 to 24 hours was performed in 17 of the 21 patients. None of the patients had an early reocclusion. A Doppler wire was advanced through the stented lesion. The antegrade flow at a position identical to the one of the prior examination was recorded. Subsequently, a balloon catheter of the identical size of the one used on the previous day was inflated within the stent, and the recruitable collateral flow distal to the occlusion was recorded as described above.

Analysis of Intracoronary Flow Velocity

The Doppler guidewire was connected to a console (FloMap, Endosonics Corp). Coronary flow velocity signals were recorded on
Super VHS tape. In case of correct detection of the systolic and diastolic phase of the signal and the outline of the velocity signal, the automated measurement algorithm of the console was used. When this algorithm failed because of artifacts, the measurements were performed manually. The manual tracing was performed in a blinded fashion by 1 investigator who averaged the velocity signals of 3 cardiac cycles. The comparison of automated and manual measurements in 10 patients showed a difference for the quantitative values of the same recordings of <3%. All collateral flow signals were measured manually to eliminate the wall motion artifacts from the automated algorithm (Figure 1). For manual measurements, printouts of the Doppler flow were scanned into a PC and measured with the use of SigmaScan Pro (SPSS Inc).

The following parameters were obtained: the velocity integral during systole and diastole, the total velocity integral (TVI), the duration of systole and diastole, the average peak systolic and diastolic velocities (ASV and ADV, respectively), and the relative duration of collateral flow/cardiac cycle. Depending on the relative position of the Doppler wire to the collateral inflow, the detected flow could be antegrade, retrograde, or bidirectional; therefore, the absolute values were used for further computation. The calculations of average peak velocity (APV), ASV, ADV, and the diastolic to systolic velocity ratio (DSVR) were performed with a standard worksheet program. A collateral flow index (CFI) was calculated as the ratio of TVI before reopening of the occluded artery and TVI of the antegrade flow after PTCA at the same location. The recruitable CFI was obtained at the end of the recanalization procedure and after 24 hours during reocclusion with a balloon catheter.

**Angiographic Assessment of Collateral Flow**

The collaterals to the occluded coronary artery were assessed by contrast injection of the donor artery and were graded according to the classification of Rentrop et al. As an inclusion criterion, preinterventional collateral flow was of grade 2 (partial epicardial filling of the occluded artery) or 3 (complete epicardial filling of the occluded artery). The anatomic pathway of the collaterals was categorized as epicardial, as intramyocardial, and as undefinable. This assessment was repeated at the end of the PTCA procedure and on the next day. The grading was performed independently by 2 experienced investigators, and in case of discordance, consensus was obtained with a third investigator.

**Statistical Analysis**

Data are given as the mean ± SD. Changes of parameters between baseline and subsequent measurements were evaluated by a paired t test. A Student unpaired t test, or a χ² test when appropriate, was used to analyze differences between patient groups. A probability level of P < 0.05 was considered significant. The calculations were performed on a PC with use of the statistical software program Statistica for Windows (Version 5, StatSoft Inc).

**Results**

**Clinical and Angiographic Characteristics**

Characteristics of patients are shown in (Table 1). Fifteen patients had a history of myocardial infarction. Akinesia in the area supplied by the occluded artery was observed in 10 patients, and no or only moderate hypokinesia was observed in 11 patients. The collaterals were of angiographic grade 2 in 24% and grade 3 in 76% of the patients. An epicardial collateral pathway was found in 33% of the patients.

**Specific Features of Collateral Flow in TCOs**

A retrograde collateral flow signal was found in 7 patients, and both retrograde and antegrade flows were found in 8 patients. The collateral flow profile showed 2 basic patterns: (1) a predominantly systolic flow with only minor or no diastolic flow in 11 patients and (2) a biphasic systolic and diastolic flow with marked diastolic contribution in 10 patients. Examples are shown in Figure 1. Mean arterial pressure at the beginning of the procedure was 102 ± 20 mm Hg; it dropped to 94 ± 21 mm Hg after intracoronary nitroglycerin administration.

**Changes of Collateral Flow After Recanalization**

The recruitable collateral flow was recorded 48 ± 17 minutes after the baseline recording. An example is shown in Figure 2. The APV dropped from 10.9 ± 5.6 to 4.7 ± 2.5 cm/s (P < 0.001). The systolic flow contribution was higher in basal and recruitable collaterals of the right compared with the left coronary artery (Table 2). There were also qualitative changes of the flow pattern. In 11 patients with a predominantly systolic flow, the diastolic flow contribution was further reduced. In 5 of 10 patients with a biphasic collateral flow, it changed to a predominantly systolic flow. Only in 5 patients did the pattern remain similar to that during baseline but with a reduced relative diastolic contribution. In 17 patients with a repeat measurement after 23.7 ± 11.7 hours, the collateral flow showed no further significant changes (Figure 3).

**Antegrade Coronary Flow After Recanalization**

The flow pattern in both left and right coronary arteries was predominantly diastolic with a higher DSVR compared with the collateral flow signal (Figure 4). ASV was higher in the right coronary artery compared with the left coronary artery (Table 2). The parameters of antegrade flow did not change significantly within 24 hours.

**CFI Before and After Recanalization**

CFI was 0.48 ± 0.25 before the recanalization, and 81% of the patients had a CFI > 0.30. After PTCA, CFI dropped to 0.21 ± 0.16 (P < 0.001), with no further change within 24 hours (CFI 0.19 ± 0.15, Figure 5). One patient had a basal CFI

| TABLE 1. Clinical Characteristics of Patients With Chronic TCOs |
|----------------------|--------------------|
| Age, y               | 66.8 ± 5.3         |
| Sex (M/F)            | 14/7               |
| Diseased arteries (1/2/3) | 5/9/7              |
| Occluded artery (right/LAD/LCX) | 11/8/2         |
| Duration of occlusion (</>) (mo) | 10/11          |
| Previous myocardial infarction (yes/no) | 15/6                          |
| Angina pectoris score (CCS 0–4) | 2.5 ± 0.6          |
| Heart failure classification (NYHA 0–4) | 2.0 ± 0.8          |
| Diabetes (yes/no)    | 8/13               |
| Hypertension (yes/no) | 10/11              |
| Ejection fraction, % | 48 ± 18            |
| Regional wall motion (normal/hypokinetic/akinetin) | 5/5/11          |
| Rentrop classification of collateral flow (0–3) | 2.8 ± 0.4          |
| Anatomic collateral localization (epicardial/intramyocardial) | 7/14              |

Values are mean ± SEM or No. of patients. LAD indicates left anterior descending; LCX, left circumflex; CCS, Canadian Cardiovascular Society; and NYHA, New York Heart Association.
1 recorded in the distal circumflex artery with an epicardial collateral; the CFI dropped after PTCA but remained the highest among all individuals. There was only 1 patient with an increase of CFI on day 1, but the recording was affected by tachyarrhythmia of 170 bpm. After recanalization, only 20% of the patients retained a CFI >0.30. During the balloon reocclusion of 3 minutes, no increase in recruitable collateral flow over time could be detected. No collaterals were visible by angiography after PTCA and after 24 hours.

Factors With Possible Influence on Collateral Flow in TCO
Patients with a prior myocardial infarction did not show any difference in basal or recruitable collateral flow. Likewise, none of the following parameters had an influence on collateral flow: history of hypertension, diabetes mellitus, sex, duration of occlusion ≤3 months or >3 months, left ventricular ejection fraction ≤0.48 or >0.48, or intramyocardial or epicardial collateral pathway.

The influence of regional ventricular function was assessed by comparing patients with akinesia or severe hypokinesia (n=10) with those with moderate or no regional dysfunction (n=11). The basal CFI was higher with normal regional function (0.57±0.23 versus 0.38±0.12, P<0.05), and a similar difference was observed for recruitable CFI (0.31±0.19 versus 0.14±0.07, P<0.05) (Figure 6).

Discussion
Collateral Function in TCOs
The collateral circulation can be assessed by recording pressure and flow distal to an occluded artery. Pijls and colleagues\textsuperscript{7,26} calculated a pressure-derived CFI, and a similar
qualitative changes of collateral flow with a reduction of the diastolic flow contribution (see Figure 2). The duration of basal collateral flow of 87% of the cardiac cycle dropped to 60%. A long flow duration was considered to be an indicator of sufficient collateralization. The reduced flow duration of recruitable collaterals indicated a reduced collateral function (Table 2).

Collateral flow is determined by the resistance of the collateral vessel and of the vascular bed distal to the occlusion. The underlying mechanism of an immediate change in collateral function could be an increase of collateral and/or peripheral resistance. The improved perfusion by antegrade flow may induce these hemodynamic changes, which were not immediately reversed during balloon recollection. It is possible that the collateral function would gradually improve during persistent recollection. There is anecdotal evidence that collaterals in TCO remain instantaneously recruitable even several years after successful revascularization. In a small study of 8 patients with TCOs, 25% suffered from myocardial infarction during follow-up with no reappearance of collaterals. Recent trials of stenting in TCO report infarction rates up to 6% during a follow-up period of 6 months. Thus, not all TCOs remain protected from ischemic events by a well-developed collateral circulation after PTCA. This is supported by our direct observation of immediate changes of collateral flow after PTCA.

Possible Determinants of Collateral Flow

The major determinant for CFI appeared to be the extent of regional dysfunction distal to the occluded artery, whereas CFI was independent of a history of hypertension, diabetes mellitus, prior myocardial infarction, global left ventricular function, or duration of the occlusion. CFI was higher in lesions that supplied a myocardial area with normal or moderate regional dysfunction compared with an akinetic myocardial area. This difference was also evident after PTCA, indicating that collateral supply for normokinetic myocardium remained superior to that for akinetic myocardium (Figure 5).

Changes in Collateral Function

After recanalization, the recruitable CFI during reocclusion dropped below 50% of its baseline value. There were also

Table 2. Collateral Flow in Chronic TCOs Before and After Recanalization

<table>
<thead>
<tr>
<th></th>
<th>LCA Collateral Flow</th>
<th>RCA Collateral Flow</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Recruitable</td>
</tr>
<tr>
<td>APV, cm/s</td>
<td>9.4±4.4</td>
<td>3.8±2.0†</td>
</tr>
<tr>
<td>ADV, cm/s</td>
<td>6.9±4.9</td>
<td>3.2±2.8†</td>
</tr>
<tr>
<td>ASV, cm/s</td>
<td>13.8±5.8*</td>
<td>5.3±2.1†</td>
</tr>
<tr>
<td>DSVR</td>
<td>0.49±0.33</td>
<td>0.68±0.58</td>
</tr>
<tr>
<td>TVI, cm</td>
<td>9.5±5.0</td>
<td>4.0±2.9†</td>
</tr>
<tr>
<td>DVI, cm</td>
<td>5.2±4.2</td>
<td>2.1±1.7†</td>
</tr>
<tr>
<td>SVI, cm</td>
<td>4.2±1.6</td>
<td>2.1±1.8§</td>
</tr>
<tr>
<td>MV, cm/s</td>
<td>23.5±17.6</td>
<td>11.7±4.9</td>
</tr>
<tr>
<td>Flow duration, %</td>
<td>81±26</td>
<td>58±27†</td>
</tr>
</tbody>
</table>

Values are mean±SEM. LCA indicates left coronary artery; RCA, right coronary artery; DVI, diastolic velocity integral; SVI, systolic velocity integral; and MV, maximum velocity.

*P<0.01, †P<0.05, and ‡P<0.005 for difference between LCA and RCA; †P<0.001, ‡P<0.005, and §P<0.01 for changes between basal and recruitable collateral flow.
In 81% of our patients, the CFI was higher than the level considered to protect from ischemia during PTCA. However, this level of CFI does not protect from exercise ischemia and can lead to regional myocardial dysfunction even in the absence of infarction. Most of the patients with TCOs had a history of infarction despite a high CFI, which indicates that the collaterals were not yet fully developed at the time of infarction. Similar observations of a large proportion of prior myocardial infarction in patients with well-developed collaterals were made in previous studies.

Study Limitations
With Doppler flow velocimetry, 2 sets of data are comparable only at identical sites of measurement and with constant vessel diameters. These prerequisites were addressed by exact positioning of the Doppler wire under fluoroscopic control and by applying vasodilators. Still, a change of the distal coronary diameter before recanalization compared with the diameter during balloon occlusion cannot be ruled out. The value of CFI may be affected by a flow-mediated increase in vessel diameter after recanalization. Because of a larger vessel cross section or an increase in the perfused vascular bed (ie, a reduced peripheral resistance), the antegrade flow velocity would be lower but represent a higher flow than the collateral flow, and the CFI would be overestimated.

The difference in basal and recruitable collateral flow could be due to difficulties in obtaining high-quality signals during reocclusion. Aside from careful and repeated sampling, the qualitative changes of the systolic and diastolic phase of the collateral flow signal at baseline and during reocclusion and the similarity of the recordings immediately and 24 hours after recanalization indicate that the observed changes in collateral flow were genuine.

Conclusions
The physiological role of collaterals in TCO is to preserve ventricular function. This is supported by our observation of a high collateral flow in the presence of a preserved regional function. The immediate loss of a large fraction of collateral flow after recanalization indicates that TCOs do not necessarily remain protected from future ischemic events by recruitable collaterals. Therefore, one should limit the attempt to recanalize a well-collateralized occluded coronary artery to those patients with clinical signs and symptoms of ischemia. Further studies with long-term follow-up in a larger patient group are needed to establish whether the recruitable collateral function would determine the risk of future ischemic events after recanalization.

References


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