Rapid Decline of Collateral Circulation Increases Susceptibility to Myocardial Ischemia

The Trade-Off of Successful Percutaneous Recanalization of Chronic Total Occlusions

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OBJECTIVES

We evaluated the time-behavior of changes in collateral circulation after successful percutaneous coronary intervention (PCI) with drug-eluting stents (DES) in chronic (>1 month) total occlusions (CTO), and assessed their relationship with myocardial ischemia.

BACKGROUND

It has been hypothesized that the immediate reduction of collateral flow after PCI of CTO could expose the patients to a higher risk of future ischemic events in the case of vessel reocclusion.

METHODS

In 42 patients with CTO, two consecutive balloon inflations and final DES deployment were performed after positioning of a pressure guidewire. Minimal lumen diameter (MLD), diameter stenosis (DS), angiographic collateral grading (Rentrop score), myocardial (FFRmyo), coronary (FFRcor), and collateral fractional flow reserve (FFRcoll) were evaluated. Chest pain and the sum of ST-segment elevation ($\Delta$ST) were analyzed to document the occurrence and extent of myocardial ischemia.

RESULTS

Percutaneous coronary intervention induced a progressive improvement of indexes of stenosis severity (MLD, DS, Thrombolysis in Myocardial Infarction flow, FFRmyo, and FFRcor) and a rapid reduction in collateral circulation (FFRcoll and Rentrop score). A progressive worsening of ischemia at each balloon inflation occurred, concomitant with the reduction of collateral circulation. At linear regression analysis, an inverse relationship of FFRcoll with $\Delta$ST ($R^2 = 0.352, p < 0.001$) and angina pain score ($R^2 = 0.247, p < 0.001$) was observed.

CONCLUSIONS

In CTO, collateral circulation, which provides most coronary flow at baseline, rapidly declines after successful stent implantation and the restoration of an antegrade flow. This rapid de-recruitment of collaterals is likely to put such patients at risk of future ischemic events. (J Am Coll Cardiol 2006;48:59–65) © 2006 by the American College of Cardiology Foundation

Coronary collateral circulation offers an alternative source of blood supply to the myocardium when the original vessel fails to provide sufficient blood flow (1–3). Collaterals limit myocardial ischemia during coronary occlusion (4), minimize the infarct area, and predict the presence of viable myocardium in patients with a history of myocardial infarction (5).

Contrast angiography has been the most widely used method to assess coronary collaterals in the past (6). The availability of miniaturized sensors to monitor coronary blood flow and pressure in humans now allows a more detailed evaluation of the collateral circulation during percutaneous coronary interventions (PCI) after guidewire crossing of the lesion (7).

Today, PCI of chronic total occlusions (CTO) is mostly performed with the use of drug-eluting stents (DES) (8,9). After successful recanalization, an immediate loss of a large fraction of collateral flow occurs. It has been hypothesized that these changes expose the patients to a higher risk of future ischemic events in the case of vessel reocclusion (10).

We aimed to investigate the time-course of collateral de-recruitment after restoration of antegrade flow with the deployment of DES in a chronically occluded artery, and to determine whether the reduction of collateral circulation would immediately reduce tolerance to ischemia during subsequent sudden occlusions of the main vessel.

METHODS

Study population. We studied 42 patients with stable coronary artery disease, who underwent successful DES deployment after recanalization of a CTO, with evidence of myocardial ischemia (at exercise electrocardiography or radionuclide stress perfusion imaging) attributed to the CTO and the presence of angiographically documented collaterals to an epicardial vessel estimated to be $\geq 2.5$ mm in diameter.

A CTO was defined as follows: 1) duration of the occlusion $>1$ month, as determined from a previous angiogram, the date of a previous infarction, or the onset of symptoms; and 2) a Thrombolysis In Myocardial Infarction (TIMI) coronary flow grade $\leq 1$ (11).
Abbreviations and Acronyms

- CPI = collateral pressure index
- CTO = chronic total occlusion
- DES = drug-eluting stent
- DS = percent diameter stenosis
- FFRColl = collateral fractional flow reserve
- FFRCor = coronary fractional flow reserve
- FFRMyo = myocardial fractional flow reserve
- MLD = minimal lumen diameter
- Pa = mean aortic pressure
- PCI = percutaneous coronary intervention
- Pd = coronary distal pressure
- Pv = central venous pressure
- Pw = coronary wedge pressure
- RefD = reference diameter
- TIMI = Thrombolysis In Myocardial Infarction

The study was approved by the local ethics committee, and written informed consent was obtained from all patients.

Study protocol. PCI and pressure recordings. Percutaneous coronary intervention was performed via the femoral approach using 7-F guiding catheters in 68 consecutive patients. All patients were on aspirin (100 mg/day) and ticlopidine (250 mg/twice a day) or clopidogrel (75 mg/day) started at least three days before the procedure and continued for six months thereafter. They all received a bolus of 10,000 IU of heparin at the beginning of PCI. In 19 patients (28%), we were unable to cross the lesion; PCI was successfully performed in 45 cases (71%). After CTO crossing with a 0.014-inch guidewire, a 2.5-F over-the-wire exchange catheter (Transit, Cordis, Warren, New Jersey, in 18 patients), or an over-the-wire 1.5-mm balloon catheter (Ninja, Cordis, in 27 patients) was advanced distal to the occlusion. The 0.014-inch pressure monitoring guidewire (PressureWire, Radi Medical Systems, Uppsala, Sweden) was calibrated, and advanced distal to the target lesion, taking care of positioning the pressure transducer in a disease-free, straight coronary segment. Three more patients were excluded from the study: one patient who received a bare-metal stent and two patients in whom the pressure wire was correctly positioned only after a predilation of the CTO. Therefore, the study population was comprised of 42 patients.

Percutaneous coronary intervention was performed with two subsequent balloon inflations (balloon/artery ratio 0.8 ± 1:1) at 8 and 12 atm and the deployment of a DES at 14 atm, with a balloon artery ratio 1.2:1 (Fig. 1). Mean aortic pressure (Pa), coronary wedge pressure (Pw) (both at baseline and during balloon inflations), and coronary distal pressure (Pd) (after balloon inflations) were obtained after a bolus intracoronary injection of adenosine 50 μg for the left coronary artery or 30 μg for the right coronary artery. In order to minimize coronary microvascular resistances, for baseline and occlusion measurements, adenosine was injected in the coronary artery that supported the collateral circulation to the occluded artery (12). We, therefore, injected adenosine in the contralateral coronary artery in 15 cases (vide infra: angiographic evaluation). Central venous pressure (Pv) was assumed in all cases to be 10 mm Hg (7).

Myocardial fractional flow reserve (FFRMyo) was calculated as the maximum myocardial blood flow in the presence of a narrowing, divided by the theoretical maximum blood flow in the absence of the narrowing: FFRMyo = (Pd − Pv)/(Pa − Pv). Coronary fractional flow reserve (FFRCor) was calculated as the maximum recruitable antegrade perfusion: FFRCor = (Pd − Pa)/(Pa − Pw). Collateral fractional flow reserve (FFRColl) was calculated as the collateral contribution to myocardial perfusion: FFRColl = FFR myo − FFRCor (13,14). In order to evaluate the instantaneous recruitability of the collateral circulation during coronary occlusion, the collateral pressure index (CPI) was calculated as: CPI = Pw/Pa (7).

Angiographic evaluation. Quantitative coronary angiography was performed using the guiding catheter for calibration. The diameter of the vessel proximal to the occlusion was taken as the reference diameter (RefD), and...
the minimal lumen diameter (MLD) was measured at the site of the lesion. Because a total occlusion was the admission criterion, the MLD was always made equal to 0 on the baseline angiogram. Percent diameter stenosis (DS) was determined as: DS (%) = \([1 - (\text{MLD}/\text{RefD})]\) · 100.

The culprit vessel flow was assessed by means of the TIMI flow grade, as: grade 0 = no antegrade flow beyond the point of occlusion; grade 1 = contrast medium passes beyond the area of obstruction but fails to opacify the entire coronary bed across the obstruction and opacifies the coronary artery distal to the obstruction in 3 beats; grade 3 = the bed distal to the obstruction is opacified in 3 beats (11).

Collaterals to the occluded coronary artery were assessed by contrast injection of the donor artery and graded according to the Rentrop's classification, as follows: grade 0 = no visible collateral vessels; grade 1 = faintly visible collateral vessels without filling of the occluded epicardial vessel; grade 2 = partial filling; grade 3 = complete filling of the occluded vessel (6). The diagnostic study had identified a contralateral collateral circulation in 15 cases (36%). In such cases a bilateral femoral approach was obtained, and separate injections of contrast medium were performed during the study at each session of measurements.

The anatomic pathway of the collateral supply was categorized as epicardial, when most collaterals were filled via connections on the epicardial surface, or intramyocardial, when collateral circulation was supplied through the myocardium.

The assessment was performed independently by two experienced investigators, and resolved by consensus with a third investigator in case of discordance.

**CLINICAL AND ELECTROCARDIOGRAPHIC ASSESSMENT OF ISCHEMIA SEVERITY.** At the end of each balloon inflation, the intensity of anginal pain was assessed using a visual analog scale, by asking patients to place a mark on a scale of 10 ranging from no pain (0) to the most severe pain ever experienced (10) (15).

A standard 12-lead surface electrocardiogram (ECG) was recorded at baseline and during 2 min of inflation (Fig. 1). The level of ST-segment displacement 80 ms after the J point was determined in each lead, and the sum of ST-segment elevation versus baseline in all 12 leads (ΣST) was calculated and expressed in mm (1 mm = 0.1 mV). All ECG measurements were performed by an experienced cardiologist blind to the study protocol.

**Follow-up.** Follow-up was performed by direct visit and exercise stress testing at one month and every six months thereafter. All patients were solicited to undergo repeat angiography at 12 months. Coronary angiography was prompted by the occurrence of cardiac ischemic events or in case of symptoms or signs of myocardial ischemia.

**Statistical analysis.** Categorical variables are expressed as absolute numbers and percent values or as median and range, as appropriate. Continuous variables are expressed as mean ± SD. Standard (baseline, post 1, post 2, and final) and occlusive (balloon 1, balloon 2, and stent) measurements were compared by the paired t test with the Bonferroni's correction for multiple comparisons. An interpatient comparison of the occurrence of myocardial ischemia (ECG modifications and/or angina) was performed by the McNemar's test. Linear regression analysis was performed by standard methods. Analyses were performed with the aid of the SPSS for Windows statistical software (release 11.5, SPSS Inc., Chicago, Illinois).

A value of p < 0.05 was considered significant for linear regression and McNemar’s test. For post-hoc multiple comparisons, we elected a preassigned value of p/number of comparisons (Bonferroni’s correction) as the threshold for significance, and, therefore, a p < 0.008 (0.05/6) and a p < 0.016 (0.05/3) were used as a definition of statistical significance for n = 6 and n = 3 comparisons, respectively.

**RESULTS**

**Procedural outcome.** Clinical and baseline angiographic characteristics of the 42 study patients are summarized in Table 1. Percutaneous coronary intervention was successfully performed with two balloon inflations and final DES deployment in all the study patients. The proximal RefD of the CTO was 2.86 ± 0.44 mm, balloon diameter was 2.48 ± 0.37 mm, and the balloon/artery ratio 0.87 ± 0.12; the diameter of the balloon used for the DES delivery was 3.13 ± 0.50 mm, and the stent/artery ratio 1.10 ± 0.08. Two overlapping DES were used in 16 patients (38%), and three DES were used in 9 cases (21%) to entirely cover the lesion. Overall, 76 DES were used, of the following types: 39 dexamethasone-eluting stents (Dexamet, Abbott Vascular Devices, Ns Ulestraten, Holland), 27 sirolimus-eluting

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>n = 42</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>62 (45–78)</td>
</tr>
<tr>
<td>Gender (M)</td>
<td>36 (86%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (52%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>23 (55%)</td>
</tr>
<tr>
<td>Smoking history</td>
<td>25 (60%)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>28 (67%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>7 (17%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Estimated duration of occlusion (months)</td>
<td>6 (3–83)</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>51 (31–65)</td>
</tr>
<tr>
<td>Multivessel CAD</td>
<td>18 (43%)</td>
</tr>
<tr>
<td>Occluded artery LAD/LCx/RCA</td>
<td>12/14/16</td>
</tr>
<tr>
<td>TIMI flow grade 0/1</td>
<td>36/6</td>
</tr>
</tbody>
</table>

Data are presented as median (range), number, or n (%) of patients.

CABG – coronary artery bypass grafting; CAD – coronary artery disease; LAD – left anterior descending; LCx – left circumflex; LVEF – left ventricular ejection fraction; MI – myocardial infarction; PCI – percutaneous coronary intervention; RCA – right coronary artery; TIMI – Thrombolysis In Myocardial Infarction.
As documented by the increase in deployment, a significant worsening of ischemia was observed, angina was reported by 27 patients (64%, \( p < 0.008 \) for all) accompanied by a concomitant reduction in collateral circulation, evaluated by the Rentrop’s grading and CPI (\( p < 0.016 \) for both). The behavior of FFR-based measurements is shown in Figure 2. Baseline myocardial perfusion was entirely due to the function of collaterals. With the re-establishment of antegrade flow, the coronary component becomes more and more responsible for the observed increase of myocardial perfusion, and fully accounts for the final result.

### Inducibility of ischemia.

During PCI, ST-segment changes were documented in 36 patients (86%), while angina was reported by 27 patients (64%, \( p < 0.001 \)).

During the subsequent balloon inflations and stent deployment, a significant worsening of ischemia was observed, as documented by the increase in \( \Sigma ST \)-segment elevation and angina pain score versus the first balloon inflation (\( p < 0.008 \) for both) (Table 2).

Electrocardiogram modifications were documented in all the 27 subjects complaining about angina during PCI. In this subgroup of patients, a \( \geq 1 \) mm \( \Sigma ST \)-segment elevation occurred earlier and for a concomitant higher FFRcoll (0.18 ± 0.10) and CPI (0.38 ± 0.13) compared with both FFRcoll (0.15 ± 0.06, \( p = 0.0217 \)) and CPI (0.34 ± 0.13, \( p = 0.0111 \)) calculated at the first occurrence of angina.

A representative example of angiograms, coronary pressures, and ECG findings in one patient is shown in Figure 3.

At linear regression analysis, an inverse relationship of collateral FFRcoll with both \( \Sigma ST \)-segment elevation \( (R^2 = 0.352, p < 0.001) \) and angina pain score \( (R^2 = 0.247, p < 0.001) \) was evident. Collateral pressure index had a lesser degree of correlation with both \( \Sigma ST \)-segment elevation \( (R^2 = 0.084, p = 0.012) \) and angina pain score \( (R^2 = 0.093, p = 0.006) \).

### Occlusion age and anatomic pathway of collaterals.

Baseline FFRcoll was similar among 14 patients (33%) with 1 ± 3 months CTO (0.41 ± 0.13) and in 28 subjects (67%) with >3 months CTO (0.40 ± 0.12, \( p = NS \)).

At linear regression analysis, no relationship was documented between age of CTO and baseline FFRcoll (\( p = NS \)), nor between age of CTO and CPI (\( p = NS \)).

A prevalent epicardial pathway of collateral circulation was identified in 16 patients (38%). Epicardial collaterals showed a trend toward a higher baseline FFRcoll (0.44 ± 0.12) and CPI (0.42 ± 0.11) versus intramyocardial collaterals (0.37 ± 0.13, \( p = 0.089 \), and 0.36 ± 0.12, \( p = 0.112 \), respectively). No differences were documented in FFRcoll or CPI at the occurrence of ECG modifications or angina according to the anatomic pathway of collaterals.

### Follow-up.

Late clinical follow-up was obtained in all patients at 17 ± 5 months. No patient died during this time period; three patients refused follow-up angiography. Thirty-nine subjects underwent repeat angiography at 11 ± 3 months. No deaths occurred. Major adverse cardiac events were documented in 7 patients (17%): 1 (2.4%) myocardial infarction and 6 (14.3%) target vessel revascularizations. Among the 39 subjects who underwent repeat angiography, reocclusion was identified in two cases (5.1%): 1 patient, who experienced a myocardial infarction, was treated with medical therapy, and 1 patient, who had recurrence of angina, underwent successful repeat PCI. Subocclusive re-

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**Table 2. Angiographic, Pressure-Derived, Electrocardiographic, and Clinical Variables During DES Implantation in Chronic Total Coronary Occlusions**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Balloon 1</th>
<th>Post 1</th>
<th>Balloon 2</th>
<th>Post 2</th>
<th>DES</th>
<th>Final</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD (mm)</td>
<td>0.1 ± 0.2</td>
<td>1.0 ± 0.5*</td>
<td>1.7 ± 0.4*</td>
<td>2.9 ± 0.4*</td>
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<tr>
<td>DS (%)</td>
<td>98 ± 5</td>
<td>65 ± 16*</td>
<td>40 ± 10*</td>
<td>−2 ± 7*</td>
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<tr>
<td>TIMI flow grade</td>
<td>0.1 ± 0.4</td>
<td>1.8 ± 0.8*</td>
<td>2.7 ± 0.6*</td>
<td>3 ± 0.2</td>
<td></td>
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</tr>
<tr>
<td>Rentrop</td>
<td>1.9 ± 0.8</td>
<td>1.3 ± 0.9†</td>
<td>0.7 ± 0.7†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>CPI</td>
<td>0.40 ± 0.13</td>
<td>0.33 ± 0.09†</td>
<td>0.27 ± 0.07†</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chest pain</td>
<td>0 ± 0.3</td>
<td>1.3 ± 1.1†</td>
<td>2.8 ± 2.1†</td>
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<tr>
<td>( \Sigma ST ) (mm)</td>
<td>0.7 ± 1.1</td>
<td>3.5 ± 2.6†</td>
<td>5.9 ± 3.1†</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

\( ^* p < 0.008 \) vs. previous measurement; \( ^† p < 0.016 \) vs. previous measurement.

CPI = collateral pressure index; DES = drug-eluting stent; DS = diameter stenosis; MLD = minimal lumen diameter; TIMI = Thrombolysis In Myocardial Infarction; \( \Sigma ST \) = sum of ST-segment elevation in all 12 leads.

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**Figure 2.** Modifications of fractional flow reserve (FFR) parameters: fractional flow reserve myocardial (FFRmyo), fractional flow reserve coronary reserve (FFRcor), and fractional flow reserve collateral (FFRcoll). Measurements were performed before (baseline), after the first balloon inflation (Post 1), after the second balloon inflation (Post 2), and after drug-eluting stent deployment (Final). Data are mean ± SD; \( p < 0.008 \) for each parameter versus the previous time point.
stenosis was identified in 5 subjects (13%) who underwent repeat PCI in 4 cases (10%) and bypass surgery in 1 case (2.6%). In no case was disease progression anywhere in the coronary epicardial vessels requiring revascularization documented.

**DISCUSSION**

We observed a rapid and progressive reduction of collateral function, evident soon after the restoration of antegrade flow, during PCI of CTO. The early “de-recruitment” of collateral circulation reduced tolerance to myocardial ischemia induced by subsequent balloon inflation.

Coronary collaterals in humans preserve myocardial function (1,3). Myocardial ischemia and the pressure gradient deriving from a high-grade stenosis are stimuli sufficient to induce the development of coronary collaterals through several biochemical signals, which include the release of angiogenic growth factors (1–4). Collateral circulation is more developed in patients with preserved myocardial function (10,16). Although exhibiting a residual vasodilatory capacity during moderate increases in myocardial oxygen demand, collateral circulation may, however, not fully provide a normal coronary flow (17).

Collateral modifications after PCI. Collateral function can be accurately measured by FFRcoll; it is directly related to—and a likely determinant of—myocardial perfusion of the territory supplied by the occluded artery (18). After the restoration of antegrade flow with successful PCI of CTO, a rapid decline of collateral function has been already documented (10); the regression is even more evident when the vessel is persistently patent at a five-month follow-up (19). Our findings confirm the rapid regression of collateral function after deployment of DES, but also add clinical relevance to these observations by documenting a contextual reduction in the tolerance to ischemia, here documented by us in >80% of cases by ECG modifications and in >60% by angina. Two pressure-derived parameters describe collateral function: FFRcoll expresses the collateral contribution to myocardial perfusion, while CPI evaluates the recruitability of collateral circulation during coronary occlusion. Values of FFRcoll <0.25 and of CPI <0.30 were previously found to be strongly associated with the presence of ischemia on the ECG during coronary artery occlusion (20,21). In our experience, ECG modifications were documented at a mean of FFRcoll 0.18 and a CPI of 0.38. Both indexes were inversely related to the inducibility of ischemia.

Figure 3. Angiographic findings, electrocardiographic and pressure measurements during recanalization of a chronic right coronary artery occlusion (black asterisk), with collateral circulation (white arrows) supported from the left coronary system at baseline. Measurements of mean aortic pressure (Pa) and coronary wedge pressure (Pw) documented a collateral pressure index (CPI) (collateral pressure index = Pw/Pa) of 0.61 during the first balloon inflation (Balloon 1). After the first balloon inflation (Post 1), the percentage diameter stenosis was 65% (white arrowhead). During the second balloon inflation (Balloon 2), CPI decreased to 0.46, and a slight ST-segment modification (black arrow) was evident on the electrocardiogram. A residual diameter stenosis of 42% (double white arrowheads) was documented by angiography (Post 2). During the drug-eluting stent (DES) deployment, collateral pressure index dropped to 0.33, the patient experienced chest pain (grade 4/10), and a marked ST-segment elevation (double black arrows) was evident on the electrocardiogram. Angiography showed an 8% residual diameter stenosis (Final).
elicited by balloon inflation, but FFRcoll showed a stronger relationship with both 2ST-segment elevation and angina pain score than CPI.

**Clinical implications.** Myocardial infarction may occur in up to about 12% of cases during the first six months after a successful percutaneous recanalization of a CTO (22–25). This observation suggests that previously developed collaterals do not systematically exert a protective effect in case of late reocclusion of the target vessel. The rapid “de-recruitment” of the collateral circulation may put the patient at risk of future ischemic events. An impaired acute recruitment of collaterals has been documented in diabetic patients with duration of CTO <3 months, and this finding has been advocated as a hypothetical cause of the increased adverse events after PCI among patients with diabetes (26).

Increased susceptibility to myocardial ischemia after the decline of collateral circulation is likely to become even more relevant with the current increasing use of DES. Stent thrombosis is a catastrophic event when it occurs without the protective role of a collateral circulation. Drug-eluting stents dramatically reduce the occurrence of restenosis (27,28), but there is concern that they might also be susceptible to very late (>1 year) thrombosis related to delayed endothelialization of the stent struts concomitant with the discontinuation of aspirin and/or clopidogrel (29). In our study population, adverse events were documented in 17% of patients; this rate appears to be considerably higher than reported in other studies, where <10% restenosis and <3% reocclusion rates were documented after sirolimus- or paclitaxel-eluting stent implantation (8,9). One explanation might be that a dexamethasone-eluting stent, likely not equivalent to sirolimus- or paclitaxel-eluting stents, was used in most of our patients (51%).

**Study limitations.** In the calculation of FFR, $P_v$ was substituted by a fixed value (10 mm Hg). This is a source of inaccuracy, but does not affect the observed changes during PCI of CTOs (10). Only pressure measurements were performed. A Doppler wire was not used, and, therefore, data on flow and resistances could not be calculated. However, FFRcoll has been shown to be extremely accurate in the quantitative assessment of collateral blood flow (30).

Data on regional myocardial function were not systematically available. However, the attenuation of collateral function, more pronounced in patients with akinesis in the myocardium supplied by the CTO, is evident also in patients with normal ventricular function (31).

For baseline and occlusion measurements, we injected adenosine in the coronary artery that supported the collateral circulation to the occluded artery. We acknowledge that a systemic adenosine infusion would have been preferable, because it would have minimized microvascular resistances distal to the lesion treated by PCI even in absence of antegrade flow. Selective adenosine infusion in one coronary artery may have changed peripheral resistances in a somewhat less predictable fashion. Despite this technical limitation, the observed trend of changes in FFR measurements was consistent throughout our study, fitted with pathophysiological predictions and, therefore, likely reflects our pathophysiological interpretation.

The functional significance of collateral vessels during coronary occlusion was judged by clinical and ECG monitoring only during brief periods of coronary occlusion, and the method was not expanded to include hemodynamic monitoring, metabolic alterations, or assessment of global or regional ejection fractions. The development of electrocardiographic signs of ischemia during coronary occlusion may be influenced by the relationship between the size of the myocardium “at risk” and the extent of collateral-dependent vascular bed, which were not assessed in the present study. During balloon occlusions, regional systolic and diastolic myocardial function modifications are directly related to the amount of collateral flow in the territory (32), and an echocardiographic evaluation would have allowed a more sensitive evaluation of the ischemic burden. These limitations, however, do not appear to hamper the directional trend and the temporal pattern of the phenomena observed.

We used three different types of DES in carrying out the present study. The choice was left at the operator’s discretion and varied upon market availability during the study period. There is no report on the effectiveness of dexamethasone-eluting stent in CTOs, and these devices probably cannot be rated as “equivalent” to sirolimus- and paclitaxel-eluting devices in terms of long-term outcome. When analyzed in subgroups according to the DES used, FFR modifications were, however, similar for all three DES types used. Exercise-induced vasoconstriction of the proximal and distal vessel segments adjacent to sirolimus-eluting stents has been recently documented, and endothelial dysfunction has been hypothesized as the underlying mechanism (33). In our study, it appears, however, very unlikely that any drug eluted by the stent would have any effect on the acute modifications of collateral circulation.

A long-term functional evaluation of collaterals was not systematically performed, and, therefore, no data are available on the recruitable of collateral circulation and its relationship to long-term tolerance to ischemia.

**Conclusions.** In CTO, collateral circulation, providing most coronary flow at baseline, rapidly declines, almost disappearing after successful stent implantation. The rapid “de-recruitment” of collaterals reduces myocardial tolerance to ischemia, which can be easily elicited in a predictable fashion during PCI. The quick changes of collateral circulation after the PCI resolution of a CTO may put the patient at risk of future ischemic events in case of spontaneous sudden reocclusion of the vessel. This suggests the use of a more aggressive antiplatelet therapy, with prolonged aspirin and clopidogrel administration, after recanalization of CTO and successful stent implantation.
REFERENCES


