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Determinants of Target Vessel Failure in Chronic Total Coronary Occlusions After Stent Implantation

The Influence of Collateral Function and Coronary Hemodynamics

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OBJECTIVES The goal of this study was to assess the influence of collateral function, coronary hemodynamics, and the angiographic result on the risk of target vessel failure (TVF) after recanalization of a chronic total coronary occlusion (CTO).

BACKGROUND Collaterals may have an adverse effect on TVF.

METHODS In 111 consecutive patients, a CTO (duration >2 weeks) was successfully recanalized with stent implantation. Collateral function was assessed by intracoronary Doppler flow velocity and pressure recordings distal to the occlusion. Baseline collateral function was determined before the first balloon inflation, and recruitable collateral function after stenting during a balloon reocclusion. Finally, the coronary flow velocity reserve (CFVR) and the fractional flow reserve (FFR) were measured.

RESULTS Angiographic follow-up after 5 $\pm$ 1.4 months in 106 patients showed a reocclusion in 17% and a restenosis in 36%. The major determinants of TVF were the stent length ($p < 0.01$) and number of implanted stents ($p < 0.01$). No difference was observed in baseline or recruitable collateral function between patients with and without TVF; 52% of patients had a CFVR $\geq$2.0, and only 18% a CFVR $\geq$2.5 after percutaneous transluminal coronary angioplasty, but neither cutoff-value predicted TVF. A low FFR discriminated patients with reocclusion (0.81 $\pm$ 0.07 vs. 0.86 $\pm$ 0.08, $p < 0.05$) but not with restenosis (0.87 $\pm$ 0.06).

CONCLUSIONS This study showed that there is no relation between a well-developed collateral supply and the risk of TVF in recanalized CTOs. This was rather determined by the stented segment length. There was also no adverse effect of the frequently observed impaired CFVR on TVF, whereas a low FFR was associated with a higher risk of reocclusion. (J Am Coll Cardiol 2003;42: 219–25) © 2003 by the American College of Cardiology Foundation

The rationale for recanalizing a chronic total coronary occlusion (CTO) is to relieve symptoms of angina and improve impaired left ventricular (LV) function (1–3) with a favorable effect on survival (4). However, the angioplasty of CTOs is hampered by a higher recurrence rate than in nonocclusive lesions (5,6), especially a higher rate of reocclusion, which is uncommon in nonocclusive lesions (7). The routine use of coronary stents in CTOs reduces but does not abolish these specific features of lesion recurrence (8–11). Possible explanations for this high recurrence rate could be the specific morphology of occluded lesions (12–16), the presence of a concurrent flow via residual collaterals after recanalization (17–20), or the impairment of coronary flow by a high prevalence of microvascular dysfunction (21,22).

The relevance of procedural parameters such as stent length and the angiographic result had been shown to be major determinants of target vessel failure (TVF) in CTOs (23). However, the potential influence of collateral and coronary hemodynamics had not been assessed previously. This can be done through the application of microsensor wires to assess intracoronary flow and pressure before and during percutaneous transluminal coronary angioplasty (PTCA) (24). The present study should test the hypothesis of a possible confounding effect of collateral function and coronary hemodynamics on restenosis and reocclusion in a nonselected, prospective consecutive series of successfully recanalized CTOs.

METHODS

Patients. All consecutive CTOs of a major coronary branch (diameter $\geq$2.5 mm) scheduled for PTCA between January 1999 and April 2002 at the University Hospital at Jena, Germany, were included in this study if the duration of the occlusion was >2 weeks and if there were spontaneously visible collaterals. The duration of CTOs was 0.5 to 337 months (median 4 months). The indication for PTCA was either chest pain related to the CTO or persistent occlusion after a prior myocardial infarction (MI). Of 138 CTOs, 117 were successfully recanalized, and 111 could be studied according to the study protocol described below. Angiographic follow-up was available in 106 patients, who constitute the study group. The study was approved by the university's ethics committee, and written informed consent obtained.

Angioplasty procedure. The recanalization was done as previously described (25). All patients were being treated with aspirin (100 mg) and received clopidogrel (75 mg) for

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Abbreviations and Acronyms

APV	=	average peak velocity
CFVR	=	coronary flow velocity reserve
CPI	=	collateral pressure index
CTO	=	chronic total coronary occlusion
CVP	=	central venous pressure
FFR	=	fractional flow reserve
LV	=	left ventricular
MI	=	myocardial infarction
MLD	=	minimum lumen diameter
P_{Ao}	=	mean aortic pressure
P_D	=	mean pressure distal to the lesion
P_{Occl}	=	mean pressure distal to the occlusion
PTCA	=	percutaneous transluminal coronary angioplasty
TVF	=	target vessel failure

four weeks starting on the day of the procedure. After the lesion was crossed by a guidewire, an exchange catheter (Transit, Cordis, Miami, Florida) or a low profile over-the-wire balloon catheter (Bandit, Scimed, Boston Scientific Corporation, Natick, Massachusetts) was advanced distal to the occlusion. Then the guidewire was exchanged for a 0.014-inch Doppler guidewire (FloWire, Endosonics/Jomed, Rancho Cordova, California) to record Doppler flow velocity distal to the occlusion. Then the Doppler wire was exchanged for a 0.014-inch pressure wire (PressureWire, RADI Medical Systems AB, Uppsala, Sweden) to record coronary pressure distal to the occlusion (P_{Occl}).

After the Doppler and pressure recordings, the occlusion was dilated and treated by stent implantation. The stent expansion was optimized according to angiographic criteria with a balloon-to-artery ratio of at least 1.1.

Protocol for intracoronary Doppler and pressure recordings of collateral flow. The angiographic anatomy distal to the occlusion was visualized by a contrast injection through the exchange catheter to aid the positioning of the sensor wires. The Doppler wire was advanced 1 to 2 cm distal to the occlusion in a segment without a focal stenosis to a position where a clearly defined and stable velocity signal could be recorded. These Doppler recordings of baseline collateral flow were done before the first balloon inflation. The absence of antegrade flow was ascertained by lack of distal opacification after proximal contrast injection and no interference with the distal Doppler signal. All Doppler flow signals were measured manually as described before (25,26). Depending on the relative position of the Doppler wire to the collateral inflow, the detected flow could be antegrade, retrograde, or bidirectional, and, therefore, the absolute values were used for further computation of the average peak velocity (APV).

For the pressure recording, care was taken to position the transducer at the same spot where the Doppler wire tip had been located. The mean pressure of P_{Occl} and the aortic pressure (P_{Ao}), which was obtained through the fluid filled 6F or 7F guiding catheter, were used for further computation. A collateral pressure index (CPI) was calculated (27). The formula includes the central venous pressure (CVP): $CPI = (P_{Occl} - CVP)/(P_{Ao} - CVP)$. In most patients CVP was not measured directly and substituted in the formula by 10 mm Hg. This was based on 24 patients with invasive measurement of CVP of 10 ± 3 mm Hg, which did not change significantly during balloon reocclusion.

In 85 patients, recruitable collateral function was reassessed at the end of the PTCA during a balloon inflation, with the last balloon used for the stent expansion. The identical location of the Doppler wire for all recordings was ascertained by fluoroscopy on two orthogonal planes with only minimal variations allowed to optimize the Doppler signal. Likewise, the pressure recording was repeated during a balloon reocclusion.

Functional assessment by Doppler and pressure recordings after recanalization. After the PTCA, the Doppler wire was positioned distal to the stented site with a distance to side branches of at least 5 mm. At this position the antegrade APV was recorded. When the Doppler signal was stable, 20 to 40 μg of adenosine were injected rapidly, intracoronary, and the maximum increase of flow velocity was recorded to calculate the coronary flow velocity reserve (CFVR) as the ratio of hyperemic and baseline antegrade APV. The adenosine injection was repeated three times and averaged for further analysis.

Finally, the pressure wire was used to calculate the fractional flow reserve (FFR) at the end of the PTCA (28). The wire was positioned about 1 cm distal to the stented lesion. Intracoronary distal pressure (P_D) and P_{Ao} were recorded on an identical scale at a speed of 10 mm/s. Particular care was taken to avoid artifacts by the guiding catheter, the pressure transducer position, and the selective intracoronary injection of 20 to 40 μg of adenosine (29). A simplified formula for myocardial $FFR = P_D/P_{Ao}$ was used (30). The measurement of FFR was repeated three times and averaged for further analysis.

Quantitative coronary angiography. The collateral supply was graded according to Rentrop et al. (31). Preinterventional angiograms showed either collateral flow grade 2 (partial epicardial filling of the occluded artery) or 3 (complete epicardial filling of the occluded artery). The LV function at baseline and at follow-up was analyzed using a standard software program (LVA 4.0, PieMedical Imaging, Maastricht, the Netherlands). The centerline method was used to assess regional LV function in the territory of the recanalized artery by the regional wall motion severity index (SD/chord) (32).

The final result of stent implantation (reference diameter, minimum lumen diameter [MLD], residual stenosis, and lesion length) was assessed by quantitative angiography using the smallest diameter from two orthogonal planes (QCA 4.0, PieMedical Imaging, Maastricht, the Netherlands). Quantitative angiography was repeated at follow-up, and a restenosis was defined as an MLD in the recanalized artery of <50% of the reference diameter.

Table 1. Comparison of Patients With CTOs With and Without TVF

	No TVF n = 50	Restenosis n = 38	Reocclusion n = 18	p Value
Age (yrs)	63.6 ± 9.0	62.4 ± 11.5	65.1 ± 9.5	0.63
Male gender (%)	74	76	67	0.74
Number of diseased arteries (1/2/3) (%)	40/42/18	37/45/18	39/44/17	1.0
Duration of occlusion (<3 months) (%)	56	42	67	0.19
Previous myocardial infarction (%)	66	68	56	0.64
CCS (1/2/3/4) (%)	2/40/56/2	5/34/61/0	4/40/56/0	0.78
NYHA (0/1/2/3/4) (%)	0/38/46/16/0	5/40/42/13/0	0/50/28/22/0	0.45
Diabetes (%)	30	37	50	0.32
Hypertension (%)	68	76	67	0.65
Hypercholesterolemia (%)	68	84	78	0.21
History of smoking (%)	44	47	39	0.84
Ejection fraction (%)	55.8 ± 19.2	58.7 ± 17.3	61.8 ± 18.8	0.48
Wall motion severity index (SD/chords)	−1.96 ± 1.44	−2.00 ± 1.24	−1.82 ± 1.19	0.89
Reference diameter (mm)	2.74 ± 0.56	2.73 ± 0.55	2.62 ± 0.37	0.70
MLD (mm)	2.29 ± 0.58	2.21 ± 0.45	2.08 ± 0.44	0.32
Diameter stenosis (%)	17 ± 10	18 ± 12	21 ± 10	0.39
Number of stents	1.6 ± 0.9	2.1 ± 0.9	2.2 ± 1.2	0.009
Stent length (mm)	20.0 ± 10.4	29.1 ± 17.2	26.4 ± 11.4	0.006

Data are mean (SD) or number (%).
CCS = Canadian Cardiovascular Society; CTO = chronic total coronary occlusion; LAD = left anterior descending; LCX = left circumflex; MLD = minimum luminal diameter; NYHA = New York Heart Association; TVF = target vessel failure.

Statistics. Data are given as the mean value ± SD if not indicated otherwise. Group differences of continuous variables were evaluated by analysis of variance (ANOVA) and, in case of a significant result followed, by an LSD post-hoc test. Group differences of categorical variables were tested by a chi-squared test. A paired *t* test was used to compare changes of LV function during follow-up. A logistic regression analysis was done to assess determinants of TVF. A level of $p < 0.05$ was considered significant. All calculations were done with SPSS for Windows (Version 10.05, SPSS Inc., Chicago, Illinois).

RESULTS

Clinical follow-up. Of 111 patients entered in this study, two patients died suddenly one and three weeks after PTCA with open stents confirmed by autopsy; one patient had a subacute stent thrombosis; and two patients without clinical symptoms of recurrent angina declined a repeat angiography. Repeat angiography after 5.0 ± 1.4 months in the remaining 106 patients showed a reocclusion in 17.0% and a restenosis in 35.8%. The TVF was 52.8%. Target lesion revascularization was 50.9% with repeat PTCA in 43.4% and bypass surgery in 7.5%. Clinical symptoms of angina and heart failure were improved in 78%, unchanged in 15%, and deteriorated in 7%—the latter in patients with reocclusion at follow-up. There were no differences in clinical baseline parameters among patients with and without TVF (Table 1).

Quantitative angiography and TVF. Of the angiographic parameters, the reference diameter and the MLD were similar in patients with and without TVF (Table 1), but there was a significantly higher number of stents and a longer stented segment in patients with restenosis and reocclusion (Fig. 1). In 43 patients with only one stent, the TVF was 34.9% with 11.6% reocclusions, whereas, with >2 stents, the TVF increased to 71.4% with 19% reocclusion (Fig. 2).

Collateral function and TVF. Both Doppler and pressure parameters of collateral function measured before recanalization were similar in patients with and without TVF (Table 2). The parameters of recruitable collateral function assessed 47 ± 13 min after the baseline measurement showed also no significant difference in Doppler and pressure recordings. The distribution of CPI with and without TVF is shown in Figure 3.

Coronary hemodynamics and TVF. After recanalization, the CFVR did not differ between patients with and without TVF (Table 2). An impaired CFVR <2.0 after PTCA was observed in 48%. Both a CFVR <2.0 and an FFR ≥0.75

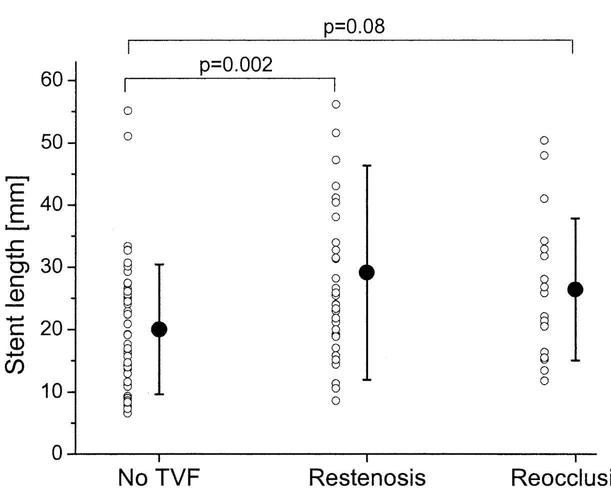

Figure 1. Difference in stent length among patients with and without target vessel failure (TVF) after recanalization of a chronic total coronary occlusion. Individual data points and mean ± SD are shown. The p values represent the post-hoc analysis of the analysis of variance (p = 0.006).

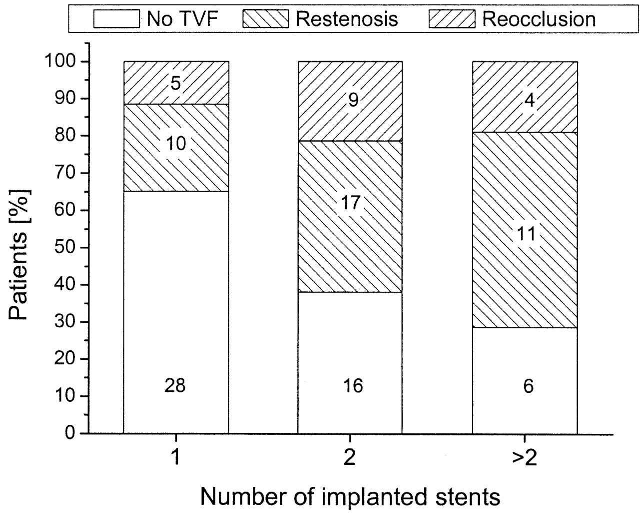

Figure 2. The difference in recurrence rate after recanalization of chronic total coronary occlusions depending on the number of implanted stents. The relative distribution is shown; the numbers indicate the absolute number of patients. Chi-squared test for the difference between groups: p = 0.037. TVF= target vessel failure.

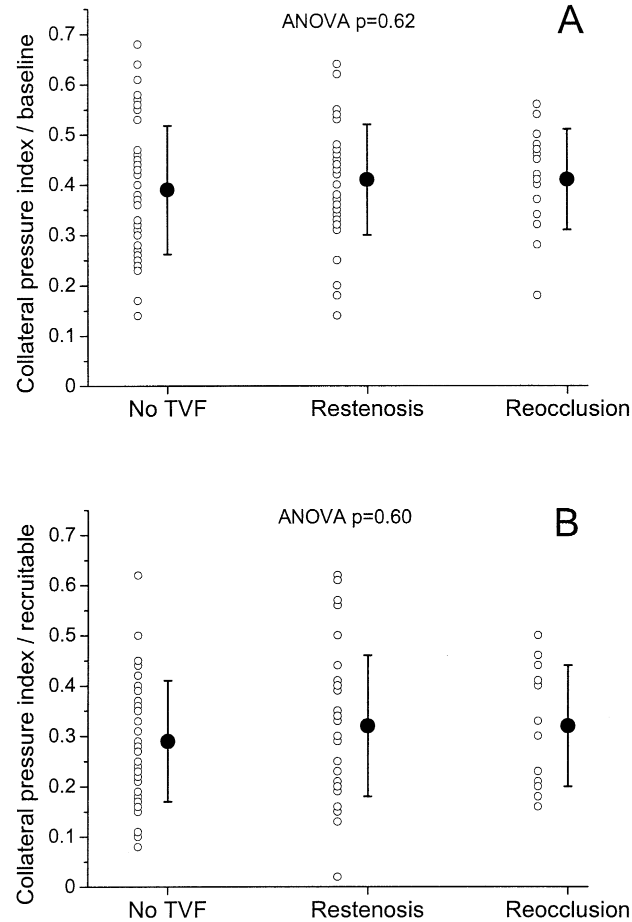

Figure 3. Collateral pressure index before (baseline) **(A)** and after (recruitable) **(B)** recanalization of a chronic total coronary occlusion with no significant difference between groups. Individual data points and mean ± SD. ANOVA = analysis of variance; TVF = target vessel failure.

was observed in 44%, indicating the presence of microvascular disease. Both a reduced CVR and FFR was observed in 4% as evidence of diffuse atherosclerosis. Patients with microvascular disease had a TVF of 47%, which was even slightly but insignificantly lower than the TVF of 58% in patients with a CFR ≥2.0 and an FFR ≥0.75 ($p = 0.51$).

A high CFVR ≥2.5 was observed in only 18% of patients with a TVF of 56%, which was similar to the TVF of 51% in patients with a CFVR <2.5 ($p = 0.93$). There was also no difference in CFVR with respect to patients with reocclusion. In contrast, the FFR was significantly lower in patients with a reocclusion, but there was no difference between patients with and without restenosis (Fig. 4). An FFR ≥0.9 was observed in 41% of patients. These patients had a similar TVF of 55.6% but a lower reocclusion rate (5.6%) than patients with an FFR <0.9, a TVF of 53.8%, but a reocclusion rate of 21.2%. An FFR ≥0.95 was achieved in only 12.5% of patients, none of whom had a reocclusion, with a TVF of 36%, compared with 53% in patients with an FFR <0.95 ($p = 0.25$).

Predictors of TVF. In a logistic regression analysis to determine predictors of TVF, we included quantitative angiographic parameters (stented segment length, stent number, reference diameter, and MLD), collateral function

Table 2. Collateral and Coronary Hemodynamic Assessment in Patients With CTOs

	No TVF n = 50	Restenosis n = 38	Reocclusion n = 18	p Value
Rentrop grade 3 (%)	76	79	77	0.94
APV_{Occl} baseline (cm/s)	10.4 ± 5.7	10.7 ± 5.4	10.7 ± 7.1	0.98
APV_{Occl} recruitable (cm/s)	5.8 ± 3.4	7.1 ± 4.2	7.3 ± 6.4	0.32
P_{Occl} baseline (mm Hg)	45 ± 15	44 ± 15	47 ± 13	0.78
P_{Occl} recruitable (mmHg)	35 ± 13	36 ± 15	36 ± 13	0.97
CPI baseline	0.39 ± 0.13	0.41 ± 0.11	0.41 ± 0.10	0.62
CPI recruitable	0.29 ± 0.12	0.32 ± 0.14	0.32 ± 0.12	0.60
Baseline APV (cm/s)	31.4 ± 16.5	27.8 ± 12.6	31.3 ± 17.3	0.54
Hyperemic APV (cm/s)	57.1 ± 28.0	54.5 ± 21.1	62.6 ± 34.7	0.61
CFVR	1.95 ± 0.61	2.07 ± 0.52	2.06 ± 0.59	0.59
FFR	0.86 ± 0.08	0.87 ± 0.06	0.81 ± 0.07	0.027

Data are mean ± SD or (%).

APV = average peak velocity; APV_{Occl} = average peak velocity distal to occlusion; CFVR = coronary flow velocity reserve; CPI = collateral pressure index; CTO = chronic total coronary occlusion; FFR = fractional flow reserve; P_{Occl} = mean coronary pressure distal to occlusion; TVF = target vessel failure.

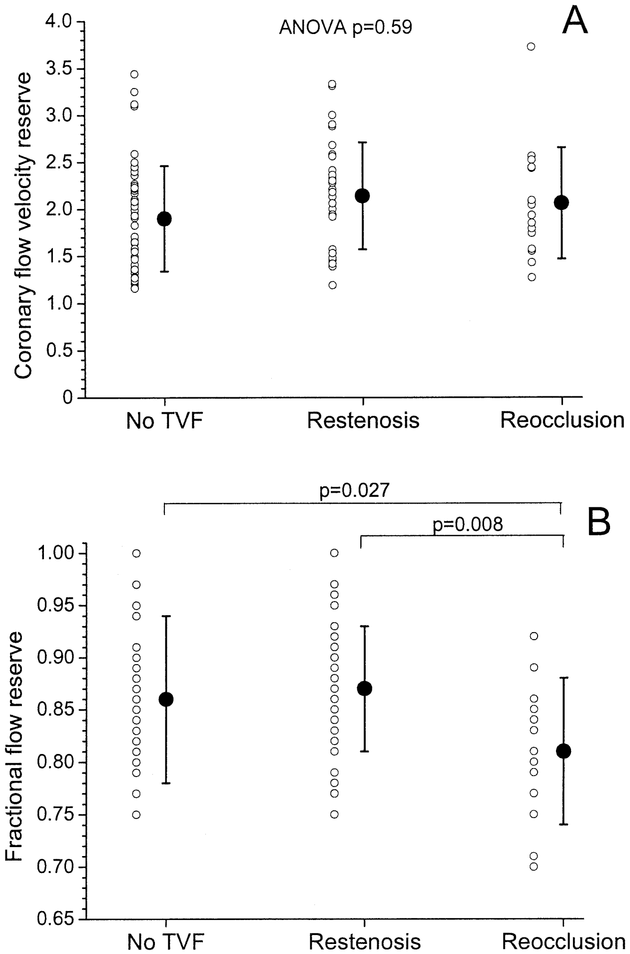

Figure 4. Coronary flow velocity reserve (CFVR) **(A)** and fractional flow reserve (FFR) **(B)** among patients with and without target vessel failure (TVF) after recanalization of a chronic total coronary occlusion. Individual data points and mean ± SD are shown. The p values represent the analysis of variance (ANOVA) result for CFVR and the post-hoc analysis of the ANOVA for FFR (p = 0.027).

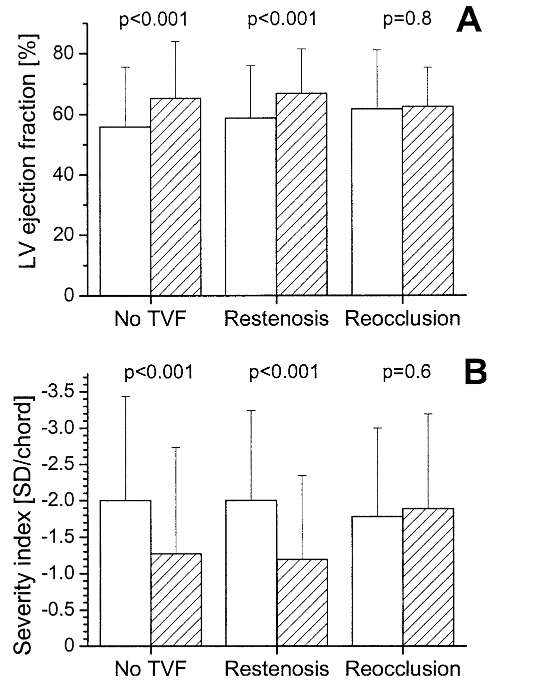

Figure 5. Global **(A)** and regional **(B)** left ventricular (LV) function before recanalization and at follow-up in patients with and without target vessel failure (TVF). There were no differences at baseline, with improvement during follow-up in all patients except those with reocclusion. p values for paired *t* test. **Open bars** = baseline; **hatched bars** = follow-up.

parameters, CFVR, and FFR. None of the functional parameters had a significant influence on TVF. The stented segment length remained the best predictor (p = 0.007), followed by the MLD (p = 0.015).

Relation between LV function and TVF. The baseline global and regional LV function was not significantly different in patients with and without TVF. Despite the high rate of restenosis, both the LV ejection fraction and regional wall motion severity index improved similarly in patients with restenosis and without TVF. However, LV function did not improve in patients with reocclusion (Fig. 5).

DISCUSSION

The present study is the first to investigate the influence of directly assessed collateral function and coronary flow reserve on the risk of TVF after the recanalization of a CTO. Neither good collateral function at baseline nor an impaired coronary flow reserve after PTCA were predictors of TVF. The major predictor of TVF was the length of the stented segment. Furthermore, the risk of reocclusion was predicted by a low FFR after PTCA. The FFR appeared superior to CFVR in assessing the angioplasty result in CTOs.

TVF in chronic occlusions. This study was done in an unselected cohort of consecutive patients with a successful recanalization of a CTO. Despite the routine use of stents, the TVF was high compared with some of the randomized studies in CTOs. However, most of these studies had applied exclusion criteria regarding reference vessel diameter (>2.5 mm), and technical feasibility, which resulted in the exclusion of more than 50% of the screened patients (8,9,11,33). One study with less restrictive inclusion criteria had similar recurrence rates (10). Furthermore, the length of the lesion was no exclusion criterion, and the number of stents used was consequently high. Lesions treated with a single stent had a lower TVF than those treated with multiple stents and were comparable to the results of the aforementioned randomized studies (8,9,33).

Collaterals and the risk of TVF. Previous reports suggested that well-preserved collaterals are one of the factors responsible for the high TVF in CTOs (17,18). This was explained by an increased distal coronary pressure and concurrent flow via persistent collaterals in analogy to observations after bypass surgery of a progress in lesion severity in the native bypass receiving coronary artery (34,35). With native collaterals, however, concurrent collateral flow is much lower than that provided by a bypass graft. Previous studies that suggested an adverse effect of collaterals on TVF used the angiographic appearance of collaterals as a criterion of collateral function, and they compared nonocclusive and occlusive lesions (17,18). There is no doubt that CTOs have a better collateral supply, which may serve as an explanation for the high TVF rate, but there are also considerable differences in the morphology of a CTO lesion with higher plaque load than a nonocclusive lesion, which may influence the risk of TVF (13–15).

Therefore, we looked exclusively at CTOs with a wide variability of collateral supply to study the influence of concurrent flow via collaterals on the risk of restenosis and reocclusion as demonstrated by the invasive assessment of collateral flow and pressure. We assessed both baseline and recruitable collateral function, the latter being the relevant source of concurrent flow after recanalization. Despite the use of a physiologic measure of collateral supply, which is superior to angiographic methods for the assessment of collaterals (36,37), we observed no adverse effect of a well-developed collateral system on TVF in CTOs.

Collateral function after recanalization of CTOs. Collateral function is lost after recanalization of CTOs (25,26), which becomes clinically evident with an MI rate of up to 6% within six months after PTCA (8–11). As this rate is lower than the actual incidence of reocclusion, either some CTOs remain protected from ischemic events by a residual collateral function (38) or collaterals recover during a gradual reocclusion. In our study the high rate of reocclusion was not associated with MI, but with recurrence of clinical symptoms in half of the patients with reocclusion. This is indirect evidence that the reocclusion occurred gradually and allowed for recruitment of collaterals sufficient to prevent an MI (39).

Coronary flow reserve and FFR and the risk of TVF. In nonocclusive lesions an impaired CFVR after PTCA identified patients with a high TVF and adverse event rate during long-term follow-up, but it was unclear whether it was of similar relevance in CTOs (22,40). The incidence of microembolization during PTCA is a potential cause for this observation (41). However, we could recently demonstrate that the incidence of troponin and creatinine kinase increase after recanalization of a CTO was <10% and did not account for the impaired CFVR in almost half of all patients (42). The impaired CFRV was not associated with a higher risk of TVF in CTOs. Thus, criteria based on CVFR for the guidance of balloon angioplasty for nonocclusive lesions are not applicable to CTOs with routine stenting (22).

In contrast, the recording of the FFR provided information that could be relevant for the PTCA. A low FFR after recanalization was associated with a high risk of reocclusion. As a reocclusion impedes LV recovery, every effort should be made to reduce its incidence, and FFR might be a valuable tool for this purpose. In a recently reported large registry of nonocclusive lesions, an FFR ≥0.90 predicted a low incidence of major adverse cardiac events (43). In CTOs we achieved an FFR ≥0.90 in only 41% of patients, with no difference in TVF. However, an FFR ≥0.95 in 12.5% of patients tended to be associated with a lower TVF. Even though this was not a significant effect, it may indicate that a more "aggressive optimization" guided by FFR should be tried to further improve the outcome. Whether this is a feasible approach, given the often diffuse atherosclerosis of the occluded artery, remains to be proven by a future study.

Study limitations. Studies in CTOs often contain a limited number of patients because CTOs constitute <10% of all patients undergoing a PTCA and the primary success rate is about 70%. The present study represents a large single-center series of CTOs with the additional strength of a prospective and consecutive patient inclusion and a sole exclusion criteria of a reference diameter <2.5 mm. Despite the limited number of patients, the high percentage of TVF provides a statistical power for a meaningful analysis.

Limitations of the invasive assessment of collateral function in CTOs by Doppler and pressure wires had been discussed in detail before (25,26). In principal, vascular flow is assessed by Doppler velocimetry, not by volume flow measurement. Specific care was taken for exact positioning of the pressure and Doppler wire under fluoroscopic control using angiographic landmarks. Furthermore, the CPI, which as a pressure-derived index is less sensitive to the exact wire tip position, also showed no difference between patients with and without TVF, further corroborating the Doppler findings.

Clinical implications. The presence of well-developed collaterals and the high prevalence of a low CFVR after PTCA does not influence the risk of lesion recurrence after recanalization of CTOs and should not prevent us from attempting a recanalization. The improvement of LV function can be considerable despite the frequent incidence of restenosis, which might be targeted successfully by drug-eluting stents (44). Still, the incidence of reocclusion is a specific problem of CTOs that impedes LV recovery. Target vessel failure may be reduced by limiting the number of stents, and FFR might be useful for the guidance of the angioplasty to avoid reocclusions. Such an FFR-guided approach with the goal of limiting the number of stents should be tested prospectively.

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