

ORIGINAL RESEARCH

Infarct-Related Artery as a Donor of Collaterals in ST-Segment–Elevation Myocardial Infarction With Concomitant Chronic Total Occlusion: Challenge of the Double-Jeopardy Thesis

Matthias Scholz , MD; Thomas Meyer , MD, PhD; Lars S. Maier , MD*; Karl Heinrich Scholz , MD*

BACKGROUND: In ST-segment–elevation myocardial infarction (STEMI), a concomitant chronic total occlusion (CTO) in a non-infarct-related artery (NIRA) is associated with adverse outcome. In the case of the infarct-related artery (IRA) as a donor vessel for collaterals to the CTO, the IRA occlusion may lead to an acute threat to both the immediate IRA and the collaterally supplied CTO area, which has been described as a double-jeopardy effect.

METHODS AND RESULTS: We investigated the role of preformed intercoronary collaterals to the CTO originating from either the IRA or NIRA. Data were obtained from 2 hospitals participating in the prospective FITT-STEMI (Feedback Intervention and Treatment Times in ST-Segment Elevation Myocardial Infarction) study. From a total cohort of 2102 patients with acute STEMI, 93 patients had single-vessel CTO in an NIRA and well-developed intercoronary collaterals to the CTO. In-hospital mortality differed significantly with respect to the origin of the collaterals. Mortality was 15.2% with collaterals originating from the NIRA, 29.4% with a collateral origin from the IRA proximal to the acute STEMI occlusion, and 3.3% with a collateral origin from the IRA distal to the acute occlusion ($P=0.044$). A multivariate regression model confirmed that a proximal collateral origin had a significant higher mortality compared with a branching in the distal position from the acute STEMI occlusion ($P=0.027$; odds ratio = 20.8 [95% CI, 1.4–304.1]).

CONCLUSIONS: In STEMI with CTO in an NIRA, a CTO collateralization from the IRA distal to the acute occlusion is associated with a better prognosis. This finding challenges the double-jeopardy assumption as the main cause of adverse outcome in STEMI with CTO in an NIRA.

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Key Words: collaterals ■ CTO ■ infarct-related artery ■ STEMI

A preexisting chronic total occlusion (CTO) in a non-infarct-related artery (NIRA) is a known predictor of adverse clinical outcome in patients with acute ST-segment–elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).^{1–3} Reasons for the poorer prognosis in patients with STEMI

and CTO are likely to be multifactorial. In general, the myocardium distal to the CTO lesion is supplied by a particular network of collaterals with a wide variety of patterns of ipsi- and contralateral collateralization.^{4,5} Besides beneficial effects, for example, on left ventricular function,⁶ especially during stress, the functional collateral supply

Correspondence to: Matthias Scholz, MD, Department of Diagnostic and Interventional Radiology, University Medical Center Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany. Email: matthias.scholz1@med.uni-goettingen.de

*L. S. Maier and K. H. Scholz contributed equally.

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CLINICAL PERSPECTIVE

What Is New?

- Analyzing the prognostic impact of preformed chronic total occlusion (CTO) collaterals in patients with ST-segment-elevation myocardial infarction and a concomitant CTO in a non-infarct-related artery, we found no prognostic difference between patients with collaterals originating from the infarct-related artery versus patients with collaterals originating from the non-infarct-related artery.
- In patients with an infarct-related artery as the collateral donor, a collateral origin in distal position to the acute ST-segment-elevation myocardial infarction occlusion was associated with a better short-term survival compared with a collateral origin proximal to the culprit lesion.
- Our findings challenge the double-jeopardy hypothesis as a main cause of adverse outcome in patients with ST-segment-elevation myocardial infarction with CTO in a non-infarct-related artery.

What Are the Clinical Implications?

- The collateral status in relation to the acute thrombotic occlusion is a key to the short-term prognostic assessment in ST-segment-elevation myocardial infarction.
- Previous studies have not shown an overall benefit from an additional CTO-percutaneous coronary intervention within 1 week of primary percutaneous coronary intervention, but subgroup analysis suggested that some patients may benefit.
- The predescribed beneficial hemodynamic effects of a CTO recanalization also on the collateral donor vessel may be of particular importance in the identified high-risk group with an infarct-related donor artery and a collateral origin in proximal position to the acute occlusion.

Nonstandard Abbreviations and Acronyms

CC	collateral connection
CC-IRA-D	patients with a collateral connection to the chronic total occlusion originating from the infarct-related artery in distal orientation to the acute occlusion
CC-IRA-P	patients with a collateral connection to the chronic total occlusion originating from the infarct-related artery in proximal orientation to the acute occlusion

CTO	chronic total occlusion
IRA	infarct-related artery
NIRA	non-infarct-related artery
TIMI	Thrombolysis in Myocardial Infarction

in patients with CTO is limited.⁷ Data about the impact of a collateralization in the specific setting of STEMI with CTO are rare. Perfusion through a well-developed coronary collateral circulation to the CTO area already preexistent at the onset of acute myocardial infarction could contribute to the preservation of jeopardized myocardial tissue. This possibly exerts beneficial effects on the regional and global ventricular wall motion and is associated with an increased ejection fraction⁸ and improved long-term survival.⁹ In particular, the interplay between the acute infarct-related artery (IRA) and the CTO vessel via a direct collateral connection (CC) could be of great hemodynamic importance.

Some authors describe the double-jeopardy effect as the main cause of the poor outcome in STEMI with CTO in an NIRA.^{1,10,11} According to this hypothesis, an acute occlusion in proximal orientation to the collateral branching leads to a sudden interruption of the previously developed CC to the CTO area and, thus, poses an acute threat to both the immediate IRA area and the collaterally supplied CTO area, resulting in a larger infarct size. A few studies support this hypothesis showing a higher short-term mortality in patients with collaterals distal to the acutely occluded segment.^{9,12,13} Others, in contrast, could not confirm a prognostic impact of the IRA in the case of a collateral donor.^{14,15}

Our investigation aimed to analyze the impact of angiographically visible collaterals to the CTO area on mortality in patients with STEMI and CTO in an NIRA. In particular, we compared the prognostic influence of collaterals originating from the IRA versus the NIRA. With regard to the double-jeopardy hypothesis, we additionally investigated the clinically relevant research question as to whether a CC to the CTO originating either proximal or distal from the culprit lesion differs with respect to survival in acute STEMI.

METHODS

The data that support the findings of this study are available from the corresponding author on reasonable request.

Study Design

All consecutive patients with acute STEMI who underwent primary PCI between March 2008 and February 2014 were prospectively enrolled from 2 study sites

(Göttingen and Hildesheim) of >50 centers participating in the FITT-STEMI (Feedback Intervention and Treatment Times in ST-Segment Elevation Myocardial Infarction) study. This ongoing multicenter trial recruits PCI-capable hospitals throughout Germany for assessment of the prognostic impact of a standardized feedback-driven quality management initiative for improvement of treatment times and mortality in local STEMI treatment networks. Details of the study protocol of the FITT-STEMI trial have been published, including predefined outcome measures, such as in-hospital mortality, cardiopulmonary resuscitation, and cardiogenic shock.^{16,17} The 2 participating PCI centers collected data for this analysis by prospectively enrolling all consecutive patients with STEMI who presented within 24 hours after the onset of symptoms of myocardial infarction. Clinical data including the assessment of treatment times were recorded. The participants gave informed consent, and the FITT-STEMI protocol was approved by the ethics committee of the Medical Faculty at the University of Göttingen. The study was conducted in accordance with the Declaration of Helsinki.

Coronary Angiographic Parameters

Coronary angiography and primary PCI were performed via a transfemoral and only rarely via a transradial approach. Once the culprit lesion in the IRA had been identified, balloon angioplasty and intracoronary stent implantation were performed at the discretion of the responsible operator. Blood flow in the IRA was determined before and after the primary PCI procedure according to the angiographic flow criteria of the TIMI (Thrombolysis in Myocardial Infarction) study group with 0=no perfusion, 1=penetration without perfusion, 2=partial perfusion, and 3=complete perfusion.¹⁸ Cineangiograms for the left and right coronary arteries were routinely obtained in at least 2 projections (Figure 1). In each patient, coronary angiograms before and after PCI were analyzed by 2 investigators at both study sites followed by a joint assessment of the collateral status (M.S. and K.H.S. at St. Bernward-Hospital Hildesheim; M.S. and L.S.M. at University Medical Center Göttingen). The investigators were blinded to the clinical data. With reference to the EuroCTO club, a concomitant CTO in an NIRA was defined as an occluded segment with a TIMI 0 flow and an estimated existence of >3 months.¹⁹

Coronary collateral flow to the CTO was graded on angiograms before and after primary PCI using the well-validated, qualitative classification scheme by Rentrop.²⁰ All patients with a visible collateralization to the CTO area in either the pre- or post-PCI angiograms were assigned to the group of patients with CC. Patients with at least a partial collateral filling of the

recipient artery exceeding a Rentrop grade of 1 were included in this analysis. If there was a relevant CC to the CTO area, it was classified either as an ipsilateral connection from the CTO vessel itself (including bridging collaterals) or as a contralateral connection with intercoronary course from the 2 remaining non-CTO arteries, depending on the donor vessel. Patients with an intercoronary collateralization of the CTO were divided in 2 groups: those with a CC from the IRA versus those with a CC to the CTO from the NIRA (CC-NIRA). If multiple intercoronary connections with origins from both the NIRA and IRA were present, these patients were assigned to the group with collateral involvement of the IRA. This latter cohort was finally subdivided according to the collateral origin in relation to the culprit lesion into either a proximal (CC-IRA-P) or distal (CC-IRA-D) group (Figure 2). Patients with left-main coronary artery occlusion, preexisting coronary artery bypass grafts, and multiple CTOs were excluded from the analysis. The latter group with 3 occluded vessels (including the STEMI lesion) was excluded because of the additional altered hemodynamics with consecutive difficult collateral assessment and an extremely high early mortality.

Assessment of Clinical Data

For each patient, clinical data were obtained on comorbid diagnoses, medical history, blood pressure, heart rate, numbers of coronary arteries narrowed, infarct localization, coronary artery dominance, and the origin of collaterals. The TIMI risk score for STEMI was used as a well-validated prognostication scheme categorizing the patient's risk of death.²¹ In addition, treatment times including the time of arrival on the scene of the emergency medical service, the transport duration from the scene to the PCI hospital, the intrahospital transfer to the catheterization laboratory, and the times to puncture and first balloon inflation of the culprit lesion were documented. In patients with hemodynamic instability, clinical signs of cardiogenic shock were assessed.

Statistical Analysis

Individual treatment time intervals from first medical contact at the scene to balloon inflation were determined from raw data. To compare the 3 separated groups of patients with a defined collateralization from the NIRA (CC-NIRA) and the IRA in proximal (CC-IRA-P) and distal (CC-IRA-D) position to the culprit lesion, χ^2 tests were calculated for categorical variables and ANOVA for continuous variables. Categorical variables were reported as number (percentage) and continuous data as mean $\pm$ SD. Odds ratios (ORs) and their 95% CIs for in-hospital mortality were calculated in patients with a CC to the CTO. A logistic regression

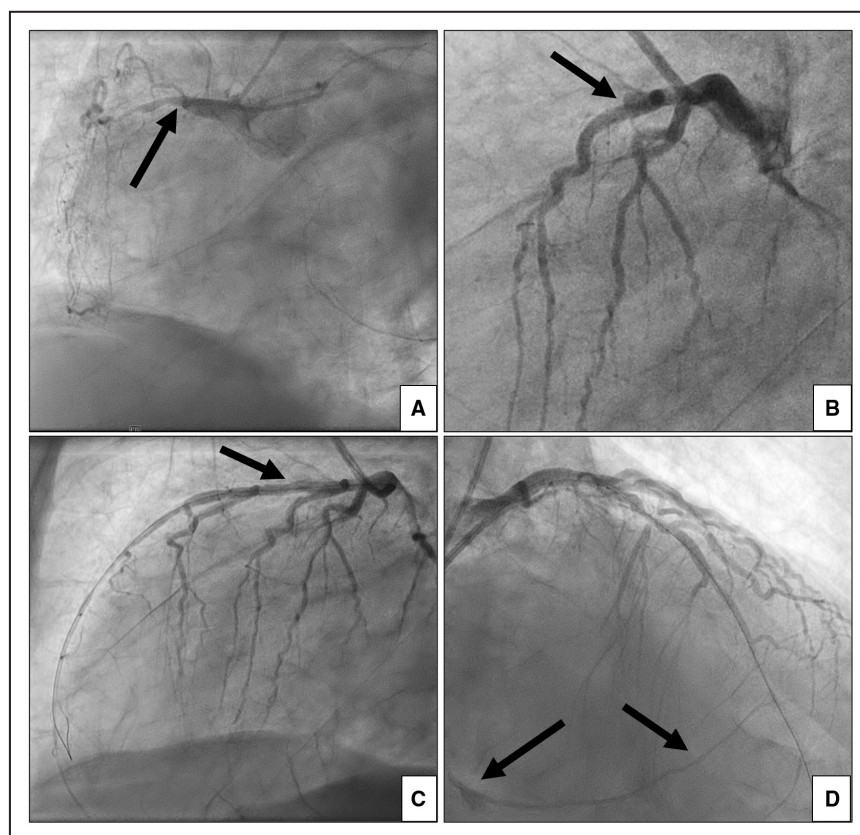


Figure 1. Angiographic images of an acute ST-segment-elevation myocardial infarction with a chronic total occlusion in a non-infarct-related artery and a collateral connection originating distal from the culprit lesion in the infarct-related artery to the chronic total occlusion.

A, Chronic total occlusion in the proximal right coronary artery (black arrow) with multiple ipsilateral collateral pathways. **B,** Culprit lesion in the proximal left anterior descending artery (black arrow). **C,** Recanalization of the proximal left anterior descending artery (black arrow). **D,** Detection of a Rentrop score of 3 collateral connection (black arrows) from the left anterior descending artery as the infarct-related artery to the chronically occluded right coronary artery following successful recanalization.

model was created with mortality as a dependent variable and CC groups as independent variables. This model was adjusted to clinical confounders that were significantly associated with mortality in univariate analyses. The reported *P* values are all 2-sided, and *P* values of <0.05 were considered statistically significant. Because of the experimental character and the small sample size of this pilot study, no formal adjustment for multiple testing was carried out. Statistical analyses were performed on a personal computer using the software program SPSS version 22 (IBM).

RESULTS

Characterization of the Study Cohort

During the study period of 6 years, a total of 2102 patients with STEMI and symptom onset of <24 hours agreed to participate in this study and were enrolled (Figure 2).

Patients without primary PCI ($n=398$) and with previous coronary artery bypass graft ($n=72$) were excluded from the analyses, as were patients with multiple CTOs ($n=12$) and left main coronary artery occlusion ($n=8$). Of the remaining patients with STEMI, 123 patients had a concomitant CTO in an NIRA, of whom 93 patients were identified as having an angiographically visible intercoronary CC to the CTO area with a Rentrop score ≥ 2 .

Of the latter study cohort, 46 patients had a CC originating from the nonoccluded NIRA to the CTO (CC-NIRA), and 47 patients had a CC originating from the IRA to the CTO. This group was further separated into 17 patients with an intercoronary CC originating proximal to the localization of the culprit lesion (CC-IRA-P) and 30 patients with a collateral origin in distal position (CC-IRA-D). There were no significant differences between the 3 groups (CC-NIRA, CC-IRA-P, and CC-IRA-D) in terms of sex, age, comorbidities, and the electrocardiographically determined infarction

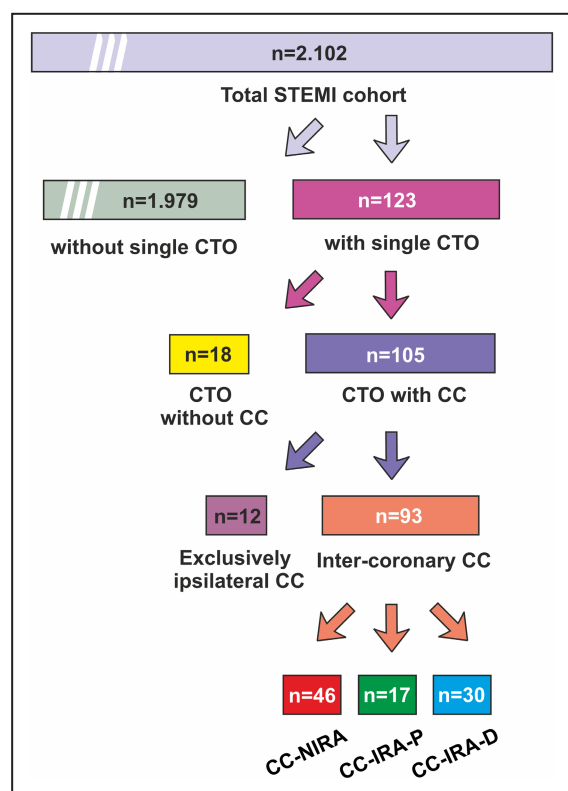


Figure 2. Flowchart.

CC indicates collateral connection; CC-IRA-D, patients with a CC to the CTO originating from the infarct-related artery in distal orientation to the acute occlusion; CC-IRA-P, patients with a CC to the CTO originating from the infarct-related artery in proximal orientation to the acute occlusion; CC-NIRA, patients with a CC to the CTO from the non-infarct-related artery; CTO, chronic total occlusion; and STEMI, ST-segment-elevation myocardial infarction.

site, except for body mass index and the CTO vessel (Table 1). Similarly, treatment times and proportion of patients with direct transportation to the catheterization laboratory bypassing the emergency department did not significantly differ between the groups. Furthermore, there was no significant difference in the percentage of coronary artery dominance. The proportion of patients with a TIMI angiographic flow grade in the IRA of ≤ 1 before PCI was higher in the CC-NIRA (89%) and CC-IRA-P (94%) groups than in the CC-IRA-D group (73%); however, this difference did not reach significance ($P=0.086$). After the PCI procedure, a TIMI angiographic flow grade ≥ 2 was achieved in $>90\%$ of all patients, indicating a successful and similar recanalization rate in all 3 CTO groups.

Outcome Data With Respect to CTO Group

In-hospital mortality in the overall group of patients with STEMI and a single CTO in an NIRA was 17.1% compared with only 8.3% in the group of patients with STEMI and multivessel disease without CTO in an NIRA

($P=0.002$). Patients with STEMI with an existing CC to the CTO area ($n=105$) had a lower in-hospital mortality compared with patients without relevant angiographically visible collateralization ($n=18$, 13.3% versus 38.9%, $P=0.008$; Figure 3). The mortality did not differ between patients with exclusive ipsilateral CC and no angiographical indication of a contralateral collateralization (8.3%) compared with patients with intercoronary collaterals (14%, $P=0.583$). In the presence of an intercoronary connection ($n=93$), there was no relevant prognostic difference between a collateral origin from the IRA ($n=47$) or from the remaining NIRA (CC-NIRA; $n=46$), as the in-hospital mortality rates were 12.8% and 15.2%, respectively ($P=0.733$).

Patients with IRA as collateral donor were further grouped with respect to the collateral origin in relation to the culprit lesion into either a proximal (CC-IRA-P, $n=17$) or distal (CC-IRA-D, $n=30$) group. Notably, in-hospital mortality differed significantly between the CC-NIRA, CC-IRA-P, and CC-IRA-D groups ($P=0.044$; Table 1). In the CC-NIRA group, there were 7 deaths (15.2%), whereas there were 5 deaths in the group of patients with a collateral branching in proximal orientation to the acute occlusion (CC-IRA-P, 29.4%) compared with only 1 patient in the distal group (CC-IRA-D, 3.3%). Although the proportion of cardiogenic shock was highest in CC-IRA-P group (29.4%), this difference did not reach statistical significance ($P=0.577$).

Variables Associated With Mortality in Patients With an Intercoronary Collateralization

Next, we identified clinical and angiographic variables associated with mortality in patients with an intercoronary CC to the CTO vessel ($n=93$), irrespective of whether the collaterals were originating from either the NIRA or IRA. In an univariate logistic regression model, the CC-IRA-P group had a >12 -fold higher OR for in-hospital mortality compared with the CC-IRA-D group (OR, 12.1 [95% CI, 1.3–114.6]; $P=0.030$), whereas the CC-IRA-D and CC-NIRA groups did not differ significantly with respect to survival ($P=0.133$; Table 2). Furthermore, a history of myocardial infarction (OR, 4.4 [95% CI, 1.2–16.0]; $P=0.026$) and previous PCI (OR, 6.5 [95% CI, 1.7–25.4]; $P=0.007$) were both linked to a higher mortality. In addition, cardiogenic shock was significantly associated with reduced survival (OR, 8.2 [95% CI, 2.3–29.2]; $P<0.001$). All other tested parameters showed no significant association with mortality (Table 2).

Finally, we performed a multivariate regression model with in-hospital mortality as the dependent variable and the assignment to the 3 groups as independent variable. This model was adjusted to all confounding factors that were identified to be significantly associated with mortality in the univariate analysis. After adjustment,

Table 1. Demographic, Clinical, and Angiographic Characteristics of Patients With STEMI With a CTO and Intercoronary CC to the CTO From the NIRA and IRA Stratified by the Localization of the Collateral Branch in Relation to the Culprit Lesion in Proximal and Distal Groups

	All CTO with intercoronary CC (n=93)	CC-NIRA (n=46)	CC-IRA-P (n=17)	CC-IRA-D (n=30)	P value
Demographic data					
Male sex	71 (76.3)	36 (78.3)	14 (82.4)	21 (70.0)	0.576
Age, mean±SD, y	65.0±12.4	65.4±11.8	64.3±14.4	64.8±12.4	0.951
Clinical data					
Body mass index, kg/m ²	27.8±3.6	28.6±3.8	26.0±3.6	27.6±3.0	0.047*
Hypertension	59 (63.4)	30 (65.2)	10 (58.8)	19 (63.3)	0.896
Diabetes	27 (29.0)	14 (30.4)	7 (41.2)	6 (20.0)	0.294
Prior angina pectoris	28 (30.1)	14 (30.4)	6 (35.3)	8 (26.7)	0.823
Hyperlipidemia	27 (29.0)	17 (37.0)	3 (17.6)	7 (23.3)	0.229
Family history	23 (24.7)	13 (28.3)	2 (11.8)	8 (26.7)	0.386
Current smoker	37 (39.8)	20 (43.5)	7 (41.2)	10 (33.3)	0.671
Renal failure	9 (9.7)	5 (10.9)	2 (11.8)	2 (6.7)	0.790
Previous MI	15 (16.1)	8 (17.4)	4 (23.5)	3 (10.0)	0.455
Previous angioplasty	12 (12.9)	5 (10.9)	2 (11.8)	5 (16.7)	0.753
Cardiogenic shock	21 (22.6)	11 (23.9)	5 (29.4)	5 (16.7)	0.577
ECG, STEMI site					
Anterior	38 (40.9)	16 (34.8)	10 (58.8)	12 (40.0)	0.513
Inferior	47 (50.5)	25 (54.3)	6 (35.3)	16 (53.3)	
Lateral	8 (8.6)	5 (10.9)	1 (5.9)	2 (6.7)	
Procedural data					
Door-to-balloon time, min	48.7±24.5	45.3±26.1	58.3±26.0	48.3±20.0	0.176
Contact-to-balloon time, min	128.0±85.3	138.7±111.2	124.0±44.8	113.6±49.0	0.459
Direct transfer to catheterization laboratory	67 (72)	35 (76)	12 (71)	20 (67)	0.663
Off-hours admission	65 (70)	32 (70)	12 (71)	21 (70)	0.997
Angiographic data					
CTO					
LAD	20 (22)	6 (13)	3 (18)	11 (37)	0.010*
RCA	48 (52)	22 (48)	13 (77)	13 (43)	
LCX	25 (27)	18 (39)	1 (6)	6 (20)	
IRA					
LAD	37 (40)	16 (35)	9 (53)	12 (40)	0.158
RCA	35 (38)	16 (35)	4 (24)	15 (50)	
LCX	21 (23)	14 (30)	4 (24)	3 (10)	
Left coronary artery dominance	13 (14)	5 (11)	2 (12)	6 (20)	0.511
TIMI angiographic flow grade before PCI					
Scores 0 to 1	79 (85)	41 (89)	16 (94)	22 (73)	0.086
Scores 2 to 3	14 (15)	5 (11)	1 (6)	8 (27)	
TIMI angiographic flow grade after PCI					
Scores 0 to 1	3 (3)	2 (4)	1 (6)	0 (0)	0.456
Scores 2 to 3	90 (97)	44 (96)	16 (94)	30 (100)	
Treatment and outcome					
In-hospital mortality	13 (14.0)	7 (15.2)	5 (29.4)	1 (3.3)	0.044*

Data are presented as mean±SD or number (percentage). P values refer to the comparisons between the following 3 groups: CC-NIRA, CC-IRA-P, and CC-IRA-D. CC indicates collateral connection; CC-IRA-D, patients with a CC to the CTO originating from the IRA in distal orientation to the acute occlusion; CC-IRA-P, patients with a CC to the CTO originating from the IRA in proximal orientation to the acute occlusion; CC-NIRA, patients with a CC to the CTO from the NIRA; CTO, chronic total occlusion; IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; NIRA, non-infarct-related artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*indicates statistical significance ($P<0.05$).

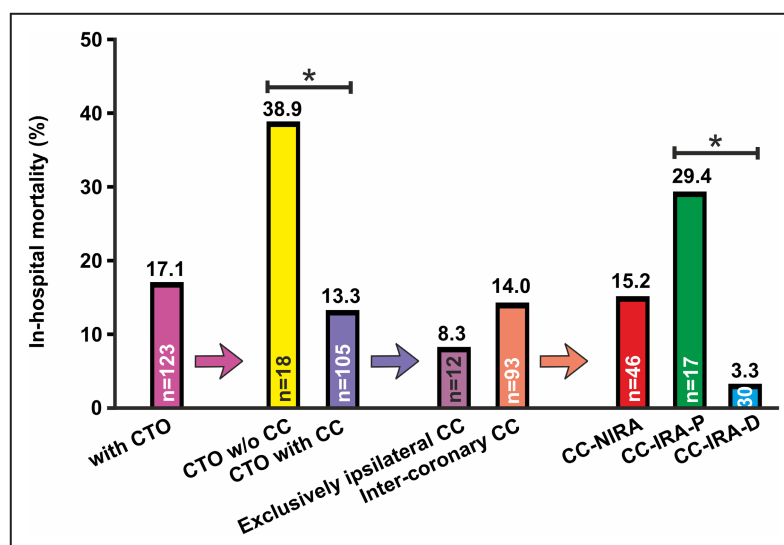


Figure 3. In-hospital mortality in the subgroups of ST-segment-elevation myocardial infarction with a CTO in an NIRA and different patterns of CC.

*indicates statistical significance ($P < 0.05$). CC indicates collateral connection; CC-IRA-D, patients with a CC to the CTO originating from the infarct-related artery in distal orientation to the acute occlusion; CC-IRA-P, patients with a CC to the CTO originating from the infarct-related artery in proximal orientation to the acute occlusion; CC-NIRA, patients with a CC to the CTO from the non-infarct-related artery; and CTO, chronic total occlusion.

a distal branching of the collaterals in relation to the newly developed STEMI occlusion (CC-IRA-D group) remained associated with a better outcome compared with a proximal origin (CC-IRA-P group; OR, 20.8 [95% CI, 1.4–304.1]; $P = 0.027$) (Table 2). Other independent predictors for mortality were previous PCI (OR, 31.5 [95% CI, 2.0–490.2]; $P = 0.014$) and cardiogenic shock (OR, 16.7 [95% CI, 2.9–97.1]; $P = 0.002$).

DISCUSSION

Whereas the presence of collaterals has beneficial effects in patients with both acute myocardial infarction^{22,23} and chronic occlusion,^{6,24} the role of the collateral circulation in the more complex setting of an acute STEMI with concomitant CTO in an NIRA remains unclear. With 2 occluded main coronary arteries, patients with STEMI and a CTO in an NIRA have only 1 remaining unaffected donor artery for immediate collateral supply to the newly infarcted area, giving the preformed CC to the CTO a particular importance. In this study, we focused on the role of intercoronary collaterals in the setting of STEMI with a concomitant CTO in an NIRA and noted 3 main findings.

Protective Role of Preexisting Collaterals in STEMI With CTO in an NIRA

First, a well-developed, preexisting collateral supply (Rentrop ≥ 2) of the CTO area is associated with a

significant reduction in short-term mortality compared with those patients with STEMI and a CTO in an NIRA and no relevant collateral circulation (13.3% versus 38.9%). This finding is consistent with data from Elias and colleagues suggesting that a preexisting coronary collateral network to the CTO area has beneficial effects for the perfusion in the acutely infarcted area.⁹ This is most probably based on a preserved microcirculation in the infarct border zone, thereby preventing hemodynamic instability and the consecutive development of cardiogenic shock.

Similar Mortality Rates in Patients With IRA Versus NIRA as Collateral Donor Vessels

Second, in patients with STEMI and collaterals to the CTO area, there was no prognostic difference between patients with collaterals originating from the IRA compared with the remaining unaffected NIRA as the main donor vessel. This indicates that a collateral supply from the IRA is not necessarily per se associated with a higher mortality.

Better Prognosis Attributed to Collateralization From a Distal Position to the Culprit Lesion

Third, and most important, we found that patients with a collateral origin distal from the acute IRA occlusion

Table 2. Predictors for In-Hospital Mortality. Results From a Set of Univariate and Multivariate Logistic Regression Models in Patients With STEMI and Intercoronary Collaterals to the CTO (n=93)

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Demographic data						
Male sex	1.833	0.374–8.984	0.455			
Age	1.016	0.968–1.067	0.513			
Clinical data						
Body mass index	0.996	0.842–1.177	0.959			
Hypertension	1.350	0.382–4.768	0.641			
Diabetes	1.101	0.308–3.936	0.882			
Prior angina pectoris	2.260	0.684–7.471	0.181			
Hyperlipidemia	1.101	0.308–3.936	0.882			
Family history	0.511	0.105–2.497	0.407			
Current smoker	0.938	0.281–3.124	0.916			
Renal failure	3.700	0.797–17.176	0.095			
Previous MI	4.375	1.193–16.038	0.026*	0.836	0.077–9.124	0.883
Previous angioplasty	6.518	1.673–25.397	0.007*	31.510	2.026–490.160	0.014*
Cardiogenic shock	8.246	2.326–29.229	<0.001*	16.674	2.864–97.063	0.002*
ECG (STEMI site)						
Anterior	4.552	1.136–18.242				
Lateral	2.095	0.190–23.087	0.073			
Inferior	Reference	Reference				
Procedural data						
Door-to-balloon time, min	0.991	0.963–1.018	0.502			
Contact-to-balloon time, min	1.001	0.994–1.007	0.870			
Direct transfer to catheterization laboratory	0.968	0.240–3.896	0.963			
Off-hours admission	0.443	0.134–1.463	0.181			
Angiographic data						
CTO						
LAD	0.481	0.094–2.459				
LCX	0.377	0.075–1.897	0.384			
RCA	Reference	Reference				
IRA						
LAD	2.489	0.589–10.519				
LCX	1.778	0.324–9.744	0.449			
RCA	Reference	Reference				
TIMI angiographic flow grade before PCI						
Score ≤1 vs ≥2	0.971	0.191–4.938	0.971			
TIMI angiographic flow grade after PCI						
Score ≤1 vs ≥2	3.250	0.273–38.662	0.351			
CC groups						
CC-NIRA	5.205	0.606–44.672	0.133	6.770	0.650–70.513	0.110
CC-IRA-P	12.083	1.274–114.639	0.030*	20.801	1.423–304.130	0.027*
CC-IRA-D	Reference	Reference	Reference	Reference	Reference	Reference

The multivariate model with in-hospital mortality as dependent variable and the assignment to the CC groups as the independent variable were adjusted to all confounders, which in univariate analysis were significantly associated with mortality.

CC indicates collateral connection; CC-IRA-D, patients with a CC to the CTO originating from the IRA in distal orientation to the acute occlusion; CC-IRA-P, patients with a CC to the CTO originating from the IRA in proximal orientation to the acute occlusion; CC-NIRA, patients with a CC to the CTO from the NIRA; CTO, chronic total occlusion; IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; MI, myocardial infarction; NIRA, non-infarct-related artery; OR, odds ratio; PCI, percutaneous coronary intervention; RCA, right coronary artery; STEMI, ST-segment-elevation myocardial infarction; and TIMI, Thrombolysis in Myocardial Infarction.

*indicates statistical significance ($P<0.05$).

had a significantly better prognosis compared with patients with a proximal origin of the collaterals in relation to the culprit lesion. This unexpected finding is in contrast to results from previous assumptions and challenges the double-jeopardy hypothesis, which suggests that an acute occlusion proximal to the collateral origin poses a threat to both the immediate IRA area and the collaterally supplied CTO area, leading to the high mortality in STEMI with CTO in an NIRA.^{1,9,11,12} Hemodynamically, the double-jeopardy hypothesis may be plausible if a CTO is assumed to be supplied by only a singular CC (Figure 4). However, because CTO-dependent myocardial areas are known to be usually supplied by a collateral network via a wide variety of pathways,^{4,5} a more complex hemodynamic interaction must be considered. Our finding of favorable effects of collaterals originating distal from the culprit lesion in the IRA can be explained by 2 putative pathophysiological mechanisms.

1. The acute thrombotic occlusion in an IRA with a collateral origin in a distal position to the culprit lesion results in an abrupt interruption of the collateral flow from the newly occluded vessel to the CTO area. With a preexisting multilateral network of CTO collaterals and thus a maintained perfusion of parts of the CTO area, this may lead to an inversion of the pressure gradient from the CTO area toward the newly developed infarct area with a

flow reversal in the preexisting CTO-IRA CC. Accordingly, a protective residual perfusion of the acutely infarcted area, especially in the microcirculation of the infarct border zone, may be obtained (Figure 5, scenario 2). As a result, patients with STEMI and a CTO in an NIRA with a distal origin of their collaterals would experience less severe clinical events with a lower rate of cardiogenic shock and death, as shown in this study.

2. In the opposite case of collaterals originating proximal, the acute occlusion in the IRA could lead to an increased blood outflow via the CC proximal to the occlusion, thereby further depriving the acute infarct area of a blood supply (Figure 5, scenario 3). Our observation of a higher proportion of patients with a low TIMI flow rate (0–1) in the IRA before PCI in this group (94%) compared with patients with a distal collateralization (73%) supports this hypothesis. This proposed variant of coronary steal may have a negative impact on the microcirculation in the ischemic peri-infarct area, resulting in a higher rate of complications, including shock and death.

Our findings may have therapeutic implications. The randomized EXPLORE (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Elevation Myocardial Infarction) trial has not shown overall beneficial effects

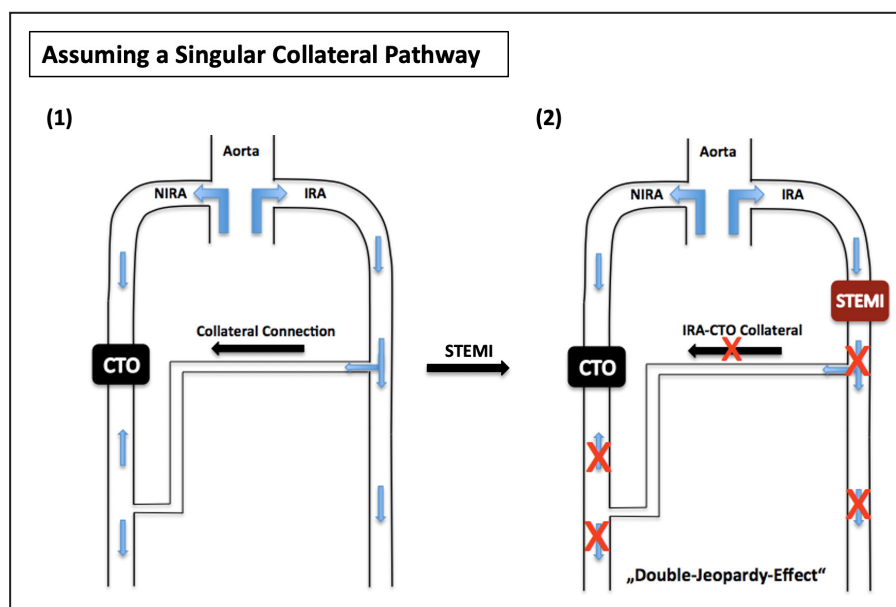


Figure 4. Proposed flow patterns in patients with a CTO before (scenario 1) and after de novo occlusion of the IRA (scenario 2) when assuming a singular collateral connection with a double-jeopardy effect leading to an increased infarct size. CTO indicates chronic total occlusion; IRA, infarct-related artery; NIRA, non-infarct-related artery; and STEMI, ST-segment-elevation myocardial infarction.

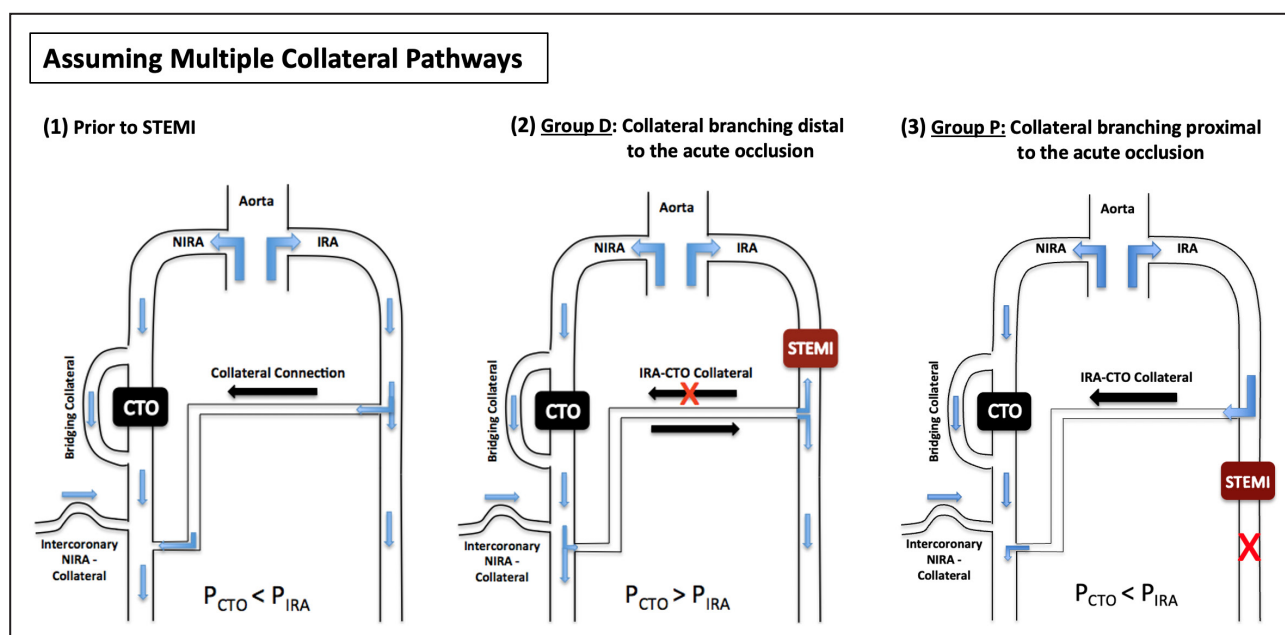


Figure 5. Hypothetical flow patterns in patients with a CTO before (scenario 1) and after de novo occlusion of the IRA in preexisting multiple collateral pathways with a distal (scenario 2) and proximal branching (scenario 3) of the collateral vessel in relation to the culprit lesion.

Note the inversion of the flow direction in scenario 2 and the blood outflow via the collateral connection, which may lead to a reduced blood supply in the acute infarct zone in scenario 3. CTO indicates chronic total occlusion; IRA, infarct-related artery; NIRA, non-infarct-related artery; P, intravascular perfusion pressure; and STEMI, ST-segment-elevation myocardial infarction.

from additional early CTO PCI within 1 week of primary PCI in patients with STEMI and concomitant CTO in an NIRA,²⁵ but a subgroup analysis may suggest that some patients will indeed benefit from this intervention. Considering our novel findings, future studies should incorporate the collateral status as well as identify subgroups of patients who may benefit from additional CTO PCI. The predescribed positive hemodynamic effects of a CTO recanalization also on the collateral donor vessel may be of particular importance in this context,^{26,27} especially if the donor artery is infarct related.

Limitations

The main limitation of the present study is its retrospective analysis in an ongoing clinical registry that mainly investigates the effects of STEMI management on treatment times and survival in patients with STEMI. Despite an initially large STEMI population, the sample size of the cohort with additional CTO in an NIRA and collateralization was relatively small. Because of the high number of patients who died early or were critically ill, no meaningful quantitative data on infarct size or ejection fraction were available. Given the limiting resolution of coronary angiography, only a small part of the collateral network is generally captured. In addition, in patients with shock, collateral detection may be difficult by the reduced coronary perfusion. However, Rockstroh and

Brown observed that the 2 or 3 largest collaterals provide the main supply to an occluded area.²⁸ Therefore, we focused on the assessment of the major intercoronary CCs to the CTO area using a Rentrop score ≥ 2 .

CONCLUSIONS

In summary, our results highlight the complexity of collateral networks in the event of an infarct-related sudden change in blood pressure throughout the coronary system. Depending on the anatomical localization of the CC in the relation to the newly developed occlusion, both adverse and favorable effects on patient outcome occur. Our findings demonstrate that the individual coronary status in these patients who are critically ill is the key to a prognostic assessment in the short-term course and that generally not every patient with STEMI and concomitant CTO in an NIRA has a reduced prognosis. Preformed collaterals originating distal from the acute STEMI occlusion may have protective effects, potentially because of a preserved perfusion of the acutely infarcted area with a consecutive better prognosis. In contrast, collaterals originating proximal in relation to the acute occlusion are associated with a significantly poorer outcome. These results challenge the double-jeopardy hypothesis as the main cause of adverse outcome in patients with STEMI and CTO in an NIRA.

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Affiliations

Department of Diagnostic and Interventional Radiology (M.S.) and Department of Psychosomatic Medicine and Psychotherapy (T.M.), University Medical Center Göttingen, Göttingen, Germany; German Centre for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany (M.S., T.M.); Department of Internal Medicine II, University Hospital Regensburg, Regensburg, Germany (L.S.M.); and Department of Cardiology and Intensive Care, St. Bernward Hospital, Hildesheim, Germany (K.H.S.).

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