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Impact of chronic total occlusion in a non-infarct-related coronary artery on myocardial injury assessed by cardiac magnetic resonance imaging and prognosis in ST-elevation myocardial infarction

Mohammed Saad [a,b], Thomas Stiermaier [a,b], Georg Fuernau [a,b], Janine Pöss [a,b], Steffen Desch [c], Holger Thiele [c], Ingo Eitel [a,b,*]

[a] Medical Clinic II, University Heart Center Lübeck, Lübeck, Germany
[b] German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany
[c] University of Leipzig – Heart Center, Department of Internal Medicine/Cardiology, Leipzig, Germany

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ABSTRACT

Background: Mechanisms underlying increased mortality in patients with chronic total occlusion (CTO) of a non-infarct-related artery (non-IRA) are unknown. Cardiac magnetic resonance (CMR) is uniquely suited to provide important mechanistic and pathophysiological information on myocardial damage and reperfusion injury. Aim of this study was to investigate the association of a CTO in a non-IRA with myocardial damage assessed by CMR in patients with ST-elevation myocardial infarction (STEMI).

Methods: STEMI patients ($n = 791$) were stratified according to the presence of single-vessel disease (SVD), multivessel disease (MVD) without a CTO and MVD with a concomitant CTO in a non-IRA. CMR parameters of myocardial injury and clinical outcome after 12 months (major adverse cardiac events [MACE]: death, re-infarction, readmission for heart failure) were compared between groups.

Results: A CTO in a non-IRA was present in 74 patients (9%), whereas 372 (47%) had MVD without a CTO and 345 (44%) had SVD. Patients with a CTO in a non-IRA had significantly larger infarcts, a lower myocardial salvage index and lower left ventricular ejection fraction as compared to patients with SVD or MVD without a CTO. MACE rates were significantly higher in patients with MVD and concomitant non-IRA CTO (9.7%) versus MVD patients without CTO (6.5%) and SVD patients (4.1%) ($p = 0.015$). MVD with non-IRA CTO was a significant independent predictor of clinical outcome [hazard ratio 2.06, 95% confidence interval 1.11–3.82, $p = 0.021$].

Conclusion: In patients with acute reperfused STEMI, the presence of a CTO in a non–IRA was associated with larger myocardial damage and increased MACE rates.

1. Introduction

In patients with ST-elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PPCI) the incidence of a chronic total occlusion (CTO) in a non-infarct-related artery (non-IRA) ranges from 7 to 21% [1,2]. Several studies have shown that the presence of such a concurrent CTO in a non-IRA is one of the most important factors for an unfavorable outcome in patients with STEMI [3–6]. A recent meta-analysis including >14,000 patients underlined these findings with a threefold increase in long-term all-cause mortality of patients with a non-IRA CTO compared with those without a non-IRA CTO [7]. However, the exact mechanisms underlying the increased mortality in patients with CTO of non-IRA are unknown. It has been speculated that a lower residual left ventricular ejection fraction (LVEF) and/or less collateral flow to the IRA with subsequent larger infarcts may be responsible [5,8].

Cardiac magnetic resonance (CMR) is a useful tool to assess all relevant pathophysiological consequences of myocardial ischemia and reperfusion after STEMI [9,10]. To the best of our knowledge, there are no CMR data evaluating the morphological, functional, and microvascular sequelae of a concomitant CTO in a non-IRA in STEMI patients undergoing PPCI. Aim of this study was therefore to investigate and comprehensively evaluate the association of a CTO in a non-IRA with myocardial damage assessed by CMR in patients with STEMI treated by PPCI.

Abbreviations: AIDA STEMI, Abciximab Intracoronary versus intravenously Drug Application in ST-elevation myocardial infarction; CI, Confidence interval; CMR, Cardiac magnetic resonance; CTO, Chronic total occlusion; LVEF, Left ventricular ejection fraction; MACE, Major adverse cardiac events; MVD, Multi-vessel disease; Non-IRA, Non-infarct-related artery; PPCI, Primary percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; SVD, Single-vessel disease.

* Corresponding author at: Medical Clinic II, University Heart Center Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany.
E-mail address: ingoeitel@gmx.de (I. Eitel).

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2. Methods

2.1. Study population and protocol

This study was performed as a predefined substudy of the *Abciximab Intracoronary* versus *intravenously Drug Application in ST-elevation myocardial infarction* (*AIDA STEMI*; NCT00712101) trial that compared intravenous versus intracoronary abciximab application in patients with STEMI and did not show a difference in infarct size, reperfusion injury, and clinical outcome between the treatment groups. Study design, 90-day, and 1-year follow-up results of the AIDA STEMI trial and its CMR substudy have been reported previously [11–14]. In short, AIDA STEMI was a randomized, open-label, multicenter trial. Patients presenting with STEMI in the first 12 h after symptom onset were randomly assigned in a 1:1 ratio to intracoronary versus intravenous abciximab bolus (0.25 mg/kg bodyweight) during PPCI with a subsequent 12 h intravenous infusion at 0.125 μg/kg per minute (maximum 10 μg/min). Patients were enrolled at 22 sites in Germany, with a final enrolled trial population of 2065 patients (intracoronary abciximab [$n = 1032$] and intravenous abciximab [$n = 1033$]). The study was conducted according to the Declaration of Helsinki. National regulatory authorities and ethics committees of participating centers approved the study. All patients provided written informed consent.

The CMR substudy enrolled 795 consecutive patients undergoing CMR imaging within 10 days after infarction at 8 sites with proven expertise in infarct CMR imaging [14]. For the purpose of the current predefined CTO substudy patients enrolled in the AIDA STEMI CMR study were divided according to the presence of single-vessel disease (SVD), multivessel disease (MVD) without a CTO and MVD with concomitant CTO in a non-IRA. MVD was defined as the presence of at least one lesion with diameter stenosis ≥50% in at least two major epicardial coronary arteries, as determined by the angiographic core laboratory. A CTO in a non-IRA was defined as the presence of TIMI 0 flow grade in a non-treated vessel not related to the acute infarct episode with antegrade or retrograde filling through collateral vessels [15]. The primary clinical endpoint of the study was the occurrence of major adverse cardiac events (MACE: death, re-infarction, re-admission for heart failure) within 12 months after the index event.

2.2. Cardiac magnetic resonance

According to study protocol, CMR was performed between day 1 and day 10 after the index event [14]. CMR images were sent to an experienced CMR core laboratory for blinded assessment (University of Leipzig - Heart Center, Leipzig, Germany). Certified

Table 1
Patient characteristics.

Variable	SVD $n = 345$ (44%)	MVD without CTO $n = 372$ (47%)	MVD with CTO $n = 74$ (9%)	*p*-Value
Age (years)	58 (49–69)	64 (54–73)	64 (53–70)	<**0.001**
Male sex: *n* (%)	258/345 (75%)	282/372 (76%)	60/74 (81%)	0.52
Cardiovascular risk factors: *n* (%)				
Current smoking	159/316 (50%)	143/336 (43%)	35/71 (49%)	0.12
Hypertension	206/343 (60%)	275/371 (74%)	56/74 (76%)	<**0.001**
Hypercholesterolemia	115/341 (34%)	154/368 (41%)	34/74 (46%)	**0.034**
Diabetes mellitus				
Any	49/344 (14%)	94/372 (25%)	16/74 (22%)	**0.001**
Insulin requiring	20/344 (6%)	45/372 (12%)	9/74 (13%)	**0.010**
BMI (kg/m^2)	27.5 (24.9–30.1)	27.1 (24.8–30.4)	27.1 (25.2–30.7)	0.46
Anterior infarction: *n* (%)	163/327 (50%)	196/358 (55%)	35/69 (51%)	0.39
Times (min)				
Symptom onset to PCI hospital admission	165 (104–296)	180 (110–290)	233 (123–404)	0.18
Door-to-balloon-time	30 (21–41)	30 (22–43)	29 (23–44)	0.63
Killip-class on admission: *n* (%)				0.25
1	308/345 (89%)	325/372 (87%)	62/74 (84%)	
2	28/345 (8%)	24/372 (7%)	7/74 (10%)	
3	6/345 (2%)	11/372 (3%)	3/74 (4%)	
4	3/345 (1%)	12/372 (3%)	2/74 (3%)	
Number of diseased vessels: *n* (%)				<**0.001**
1	345/345 (53%)	0/372 (0%)	0/74 (0%)	
2	0/345 (0%)	258/372 (69%)	43/74 (58%)	
3	0/345 (19%)	114/372 (31%)	31/74 (42%)	
Infarct related artery: *n* (%)				<**0.001**
Left anterior descending	164/345 (48%)	146/372 (39%)	35/74 (45%)	
Left circumflex	38/345 (11%)	53/372 (14%)	5/74 (12%)	
Right coronary	143/345 (41%)	169/372 (45%)	31/74 (50%)	
Left main	0/345 (0%)	4/372 (1%)	1/74 (0%)	
Bypass graft	0/345 (0%)	0/372 (0%)	2/74 (3%)	
TIMI-flow before PCI: *n* (%)				0.12
TIMI-flow 0	213/345 (62%)	188/372 (51%)	42/74 (57%)	
TIMI-flow I	40/345 (12%)	54/372 (15%)	9/74 (12%)	
TIMI-flow II	46/345 (13%)	68/372 (18%)	14/74 (19%)	
TIMI-flow III	46/345 (13%)	62/372 (17%)	9/74 (12%)	
Stent implanted: *n* (%)	335/345 (97%)	368/372 (99%)	72/74 (97%)	0.23
Thrombectomy: *n* (%)	96/345 (28%)	76/372 (20%)	18/74 (24%)	0.068
TIMI-flow post PCI: *n* (%)				0.67
TIMI-flow 0	6/344 (2%)	4/372 (1%)	2/74 (3%)	
TIMI-flow I	9/344 (3%)	8/372 (2%)	2/74 (3%)	
TIMI-flow II	21/344 (6%)	35/372 (9%)	6/74 (8%)	
TIMI-flow III	308/344 (89%)	325/372 (87%)	64/74 (87%)	
Intraaortic balloon pump: *n* (%)	8/341 (2%)	21/365 (6%)	4/70 (6%)	0.066
Peak CK (μmol/l*s)	27 (12–46)	25 (11–45)	27 (12–45)	0.52
ST-segment resolution (%)	55 (24–80)	55 (23–77)	46 (18–68)	0.35
Concomitant medications: *n* (%)				
ß-blockers	334/345 (97%)	350/371 (94%)	71/73 (97%)	0.21
ACE-inhibitors/AT-1-antagonist	325/345 (94%)	357/372 (96%)	69/73 (95%)	0.43
Aspirin	345/345 (100%)	371/371 (100%)	73/73 (100%)	
Clopidogrel, prasugrel or both	345/345 (100%)	371/371 (100%)	73/73 (100%)	
Statins	328/345 (95%)	353/371 (95%)	69/73 (95%)	0.98
Aldosterone antagonist	33/345 (10%)	50/371 (14%)	8/73 (11%)	0.26
Completion of abciximab infusion	325/345 (94%)	350/371 (94%)	69/74 (93%)	0.93

Continuous data are presented as median and interquartile range.
ACE = angiotensin-converting enzyme, AT-1 = angiotensin1, BMI = body mass index, CK = creatine kinase, CMR = cardiac magnetic resonance, CTO = chronic total occlusion, MVD = multivessel disease, PCI = primary percutaneous coronary intervention, SVD = single vessel disease, TIMI = Thrombolysis in Myocardial Infarction.