

# Time-Dependent Myocardial Necrosis in Patients With ST-Segment–Elevation Myocardial Infarction Without Angiographic Collateral Flow Visualized by Cardiac Magnetic Resonance Imaging: Results From the Multicenter STEMI-SCAR Project

Simon Greulich, MD; Agnes Mayr, MD; Steffen Gloekler, MD; Andreas Seitz, MD; Stefan Birkmeier, MD; Tim Schäufele, MD; Raffi Bekeredjian, MD; Christine S. Zuern, MD; Peter Seizer, MD; Tobias Geisler, MD; Karin A. L. Müller, MD; Patrick Krumm, MD; Konstantin Nikolaou, MD; Gert Klug, MD; Sebastian Reinstadler, MD; Mathias Pamminer, MD; Martin Reindl, MD; Andreas Wahl, MD; Tobias Traupe, MD; Christian Seiler, MD; Bernhard Metzler, MD; Meinrad Gawaz, MD; Stephan Windecker, MD; Heiko Mahrholdt, MD

**Background**—Acute complete occlusion of a coronary artery results in progressive ischemia, moving from the endocardium to the epicardium (ie, wavefront). Dependent on time to reperfusion and collateral flow, myocardial infarction (MI) will manifest, with transmural MI portending poor prognosis. Late gadolinium enhancement cardiac magnetic resonance imaging can detect MI with high diagnostic accuracy. Primary percutaneous coronary intervention is the preferred reperfusion strategy in patients with ST-segment–elevation MI with <12 hours of symptom onset. We sought to visualize time-dependent necrosis in a population with ST-segment–elevation MI by using late gadolinium enhancement cardiac magnetic resonance imaging (STEMI-SCAR project).

**Methods and Results**—ST-segment–elevation MI patients with single-vessel disease, complete occlusion with TIMI (Thrombolysis in Myocardial Infarction) score 0, absence of collateral flow (Rentrop score 0), and symptom onset <12 hours were consecutively enrolled. Using late gadolinium enhancement cardiac magnetic resonance imaging, the area at risk and infarct size, myocardial salvage index, transmural index, and transmural grade (0–50%, 51–75%, 76–100%) were determined. In total, 164 patients (aged  $54 \pm 11$  years, 80% male) were included. A receiver operating characteristic curve (area under the curve: 0.81) indicating transmural necrosis revealed the best diagnostic cutoff for a symptom-to-balloon time of 121 minutes: patients with >121 minutes demonstrated increased infarct size, transmural index, and transmural grade (all  $P < 0.01$ ) and decreased myocardial salvage index ( $P < 0.001$ ) versus patients with symptom-to-balloon times  $\leq 121$  minutes.

**Conclusions**—In MI with no residual antegrade and no collateral flow, immediate reperfusion is vital. A symptom-to-balloon time of >121 minutes causes a high grade of transmural necrosis. In this pure ST-segment–elevation MI population, time to reperfusion to salvage myocardium was less than suggested by current guidelines. (*J Am Heart Assoc.* 2019;8:e012429. DOI: 10.1161/JAHA.119.012429.)

**Key Words:** cardiac magnetic resonance imaging • coronary artery disease • ST-segment–elevation myocardial infarction • necrosis

Ischemic heart disease is the most common cause of death worldwide.<sup>1</sup> Despite major advances in both interventional medical treatment/secondary prevention, mortality and morbidity in patients with ST-segment–elevation myocardial

infarction (STEMI) remain substantial. Mortality is affected by various factors including Killip class, local emergency logistics, number of diseased coronary vessels, left ventricular (LV) ejection fraction, and time to treatment.<sup>1</sup> In cases of acute

From the Department of Cardiology and Cardiovascular Diseases (S.G., P.S., T.G., K.A.L., M.G.) and Department of Radiology (P.K., K.N.), University of Tübingen, Germany; Department of Radiology (A.M., M.P.), and Department of Cardiology (G.K., S.R., M.R., B.M.), University of Innsbruck, Austria; Department of Cardiology, Inselspital, Bern University Hospital, University of Bern, Switzerland (S.G., A.W., T.T., C.S., S.W.); Department of Cardiology, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany (S.G.); Department of Cardiology, Robert Bosch Medical Center, Stuttgart, Germany (A.S., S.B., T.S., R.B., H.M.); Department of Cardiology, Universitätsspital Basel, Switzerland (C.S.Z.).

**Correspondence to:** Heiko Mahrholdt, MD, Robert-Bosch-Medical Center, Auerbachstrasse 110, 70376 Stuttgart, Germany. E-mail: heiko.mahrholdt@rbk.de

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## Clinical Perspective

### What Is New?

- In patients with first-time acute ST-segment-elevation myocardial infarction presenting with complete occlusion of the culprit coronary artery and no coronary collaterals, cardiac magnetic resonance imaging visualized time-dependent transmural infarction with a cutoff of 121 minutes, which seems much lower than reported for viable myocardium.

### What Are the Clinical Implications?

- This study highlights the therapeutic priority of reducing ischemic times of patients presenting with ST-segment-elevation myocardial infarction during emergency care because in this pure ST-segment-elevation myocardial infarction population, time to reperfusion to salvage myocardium was less than suggested by current guidelines.

and complete coronary occlusion, besides area at risk (AAR), protecting collateral flow, and ischemic preconditioning, time to reperfusion is the most important factor in the treatment of STEMI patients. The wavefront concept of myocardial infarction (MI) states that myocardial necrosis is a time-dependent ischemic process beginning from the endocardial layers and moving up to the epicardium without essential lateral extension<sup>2</sup>: A prolonged occlusion of the infarct-related artery (IRA) will result in a high amount of myocardial necrosis and a low amount of myocardial salvage. To limit myocardial necrosis of the myocardium supplied by the IRA, the AAR, blood flow to the IRA has to be restored as soon as possible.<sup>3</sup> Without protecting collateral flow, sustained ischemia will result in progressive transmural expansion of the myocardial necrosis with the loss of myocardial salvage, portending adverse prognosis.<sup>4–6</sup> Thus, current guidelines recommend primary percutaneous coronary intervention (PCI) as the preferred reperfusion strategy in patients with STEMI within 12 hours of symptom onset, provided it can be performed within 120 minutes from STEMI diagnosis (the time at which the ECG of a patient with ischemic symptoms is interpreted as presenting ST-segment elevation).<sup>1</sup> However, despite major advances in treatment and emergency medical care, a substantial number of STEMI patients have transmural infarction with adverse prognosis.<sup>7–9</sup>

Late gadolinium enhancement cardiac magnetic resonance imaging (LGE-CMR) can determine ischemic scar with high diagnostic accuracy compared with histology.<sup>10–12</sup>

By visualizing the ischemic wavefront process, the AAR, infarct size (IS), and myocardial salvage are determined.<sup>11,13,14</sup> Most CMR studies assessing the extent of MI in STEMI patients are performed in patients with a symptom-to-balloon time of

>180 minutes.<sup>15</sup> Furthermore, most studies also included initial TIMI (Thrombolysis in Myocardial Infarction) antegrade flow  $\geq 1$  and patients with visible retrograde collateral flow (Rentrop grade  $\geq 1$ ).<sup>15</sup> However, both of the latter conditions mitigate the time-dependent progress of the ischemic wavefront after total occlusion of a coronary artery.

We sought to investigate the time-dependent ischemic wavefront process in a “pure” STEMI population lacking the mentioned limitations by using a dedicated LGE-CMR protocol in STEMI patients with the following characteristics: (1) single-vessel disease only, (2) complete absence of antegrade flow (TIMI 0), (3) complete absence of visible retrograde collateral flow (Rentrop grade 0), and (4) presentation within 12 hours of symptom onset.

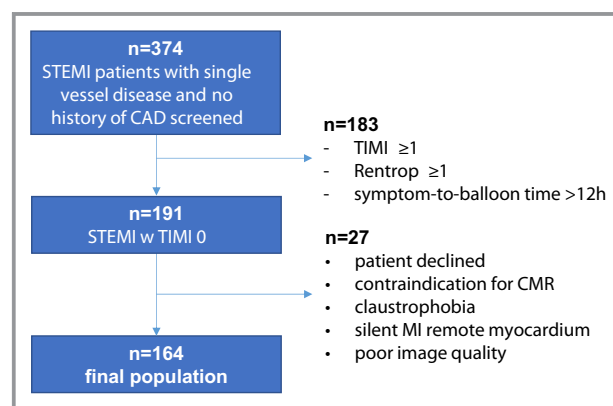
## Methods

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

## Patient Population

Patients admitted with first-time STEMI, no preinfarction angina, and no prior cardiac history treated with primary PCI at one of the 4 institutions (Stuttgart and Tübingen, Germany; Innsbruck, Austria; Bern, Switzerland) were eligible for study participation if they had STEMI according to the European Society of Cardiology/American College of Cardiology committee redefinition<sup>16</sup> and had onset of symptoms <12 hours.

Patients with (1) initial antegrade flow of TIMI >0, (2) retrograde collateral flow of Rentrop >0, (3) multivessel



**Figure 1.** Flowchart demonstrating the study population. CAD indicates coronary arterial disease; CMR, cardiac magnetic resonance; MI, myocardial infarction; STEMI, ST-segment-elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction.

**Table 1.** Baseline Characteristics

	Entire Group (n=164)	≤121 min (n=64)	>121 min (n=100)	P Value
Age, y	53.7±10.8	53.8±10.0	53.5±11.3	0.70
Sex (female)	33 (20)	16 (25)	17 (17)	0.22
Symptom-to-balloon, min	133 (103–196)	95 (77–110)	180 (137–249)	<0.001*
CAD risk factors				
Diabetes mellitus	17 (10)	5 (8)	12 (12)	0.48
Hypertension	74 (45)	33 (52)	41 (41)	0.31
Smoking <sup>†</sup>	48 (29)	14 (22)	34 (34)	0.11
Hyperlipidemia	70 (43)	34 (53)	36 (36)	0.04*
Family history of CVD	64 (39)	28 (44)	36 (36)	0.33
BMI, kg/m <sup>2</sup>	27±4.5	27.2±3.8	26.8±4.9	0.40
Hemodynamics				
Systolic BP, mm Hg	130±26	130±27	130±26	0.79
Diastolic BP, mm Hg	81±16	83±16	80±16	0.13
Medication				
Statins	28 (17)	9 (14)	19 (19)	0.52
β-Blockers	33 (20)	14 (22)	19 (19)	0.69
Aspirin	28 (17)	10 (16)	18 (18)	0.83
Clopidogrel	7 (4)	4 (6)	3 (3)	0.43
ARB	31 (19)	10 (16)	21 (21)	0.42
Biomarkers				
CK	2668 (1431–4950)	2210 (1227–3509)	2912 (1606–5467)	0.02*
Coronary angiography				
LAD	100 (61)	34 (53)	66 (66)	0.10
RCA	39 (24)	20 (31)	19 (19)	0.09
RCX	25 (15)	10 (16)	15 (15)	1.0
DES	144 (88)	54 (84)	90 (90)	0.33
Number of stents	1.3±0.6	1.3±0.6	1.3±0.6	0.85
Femoral approach	139 (85)	54 (84)	85 (85)	0.98
TIMI 1 after PCI	1 (1)	...	1 (1)	...
TIMI 2 after PCI	14 (9)	5 (8)	9 (9)	1.0
TIMI 3 after PCI	149 (91)	59 (92)	90 (90)	0.78
MBG 0–1	23 (14)	10 (16)	13 (13)	0.65
MBG 2	49 (30)	20 (31)	29 (29)	0.86
MBG 3	92 (56)	34 (53)	58 (58)	0.63

Values are n (%), mean±SD, or median (interquartile range). ARB indicates angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CK, creatine kinase; CVD, cardiovascular disease; DES, drug-eluting stent; LAD, left anterior descending; MBG, myocardial blush grade; PCI, percutaneous coronary intervention; RCA, right coronary artery; RCX, right circumflex artery; TIMI, Thrombolysis in Myocardial Infarction

\*Statistically significant *P*-values (*P*<0.05).

<sup>†</sup>Current smokers.

disease (presence of >50% stenosis in >1 large epicardial coronary artery according to coronary angiography during primary PCI), (4) contraindications for CMR, (5) presence of

silent MI in remote myocardium, or (6) poor CMR image quality were excluded (Figure 1). At each participating site, the respective institutional review board approved the

research protocol, and informed consent was obtained from the participants. Since analyses were performed in STEMI patients, visualizing myocardial scar by CMR, the project was called STEMI-SCAR.

## Primary PCI and Angiographic Analysis

Primary PCI was performed by experienced interventional cardiologists. Pre- and post-PCI coronary angiographies were performed, with the same projections permitting offline evaluation of (1) TIMI flow before and after PCI (range: 0–3), (2) the Rentrop collateral grade (range: 0–3), and (3) the myocardial blush grade (range: 0–3) at the final angiogram by 2 independent interventional cardiologists (S.G., T.S.). Symptom-to-balloon times (ie, time from onset of symptoms to first balloon inflation) were precisely reported for each patient.

## CMR Protocol

ECG-gated CMR was performed in breath hold using a 1.5-T Magnetom Symphony, Magnetom Sonata, Magnetom Avanto, or Magnetom Aera (Siemens Healthcare) in line with Society for Cardiovascular Magnetic Resonance recommendations.<sup>12</sup> Both cine and LGE short-axis CMR images were prescribed every 10 mm (slice thickness: 6 mm) from base to apex. Cine CMR was performed using a steady-state free-precession sequence. LGE images were acquired on average 10 minutes after contrast administration, using segmented inversion recovery gradient echo constantly adjusting inversion time. The contrast dose (gadodiamide, gadopentetate dimeglumine, or gadobutrol) was 0.15 mmol/kg.

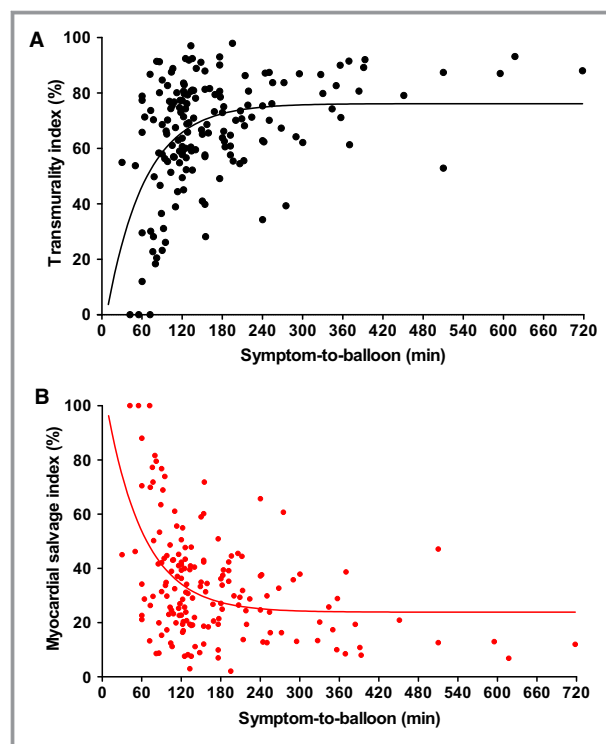
## CMR Analysis

Image postprocessing was performed using dedicated software (Argus [Siemens] and Mass [Medis], respectively). Cine and contrast images were evaluated by experienced observers (A.M., S.B., A.S., S.G.), as described elsewhere,<sup>17</sup> and any differences were resolved by consensus. In brief, endocardial and epicardial borders were outlined on the short-axis cine images. Volumes and LV ejection fractions were derived by summation of epicardial and endocardial contours. LV mass was calculated by subtracting endocardial from epicardial volume at end-diastole and multiplying by 1.05 g/cm<sup>3</sup>. AAR was drawn in LGE images indicating MI, as previously described.<sup>11</sup> AAR, IS, and microvascular obstruction (MVO) were assessed using the Mass analysis software, and the results were expressed as percentage of myocardial LV mass. LGE was defined of an image intensity level  $\geq 2$  SD above the mean of remote myocardium.<sup>18</sup> MVO was defined as a persisting area of hypoenhancement within regions of LGE.<sup>19</sup>

Furthermore, myocardial salvage index (MSI), equal to  $(\text{AAR} - \text{IS}) / \text{AAR} \times 100$ , and transmural index  $(100 - \text{MSI})$  were derived. In addition, infarct transmural index was graded visually by quarters: <25%, 25% to 50%, 51% to 75%, and 76% to 100% indicating transmural infarction.<sup>8,20</sup> Analyses were made blinded to clinical and angiographic parameters.

## Statistical Analysis

Absolute numbers and percentages were computed to describe the patient population. Categorical variables were expressed as counts and percentages. Continuous variables were expressed as mean  $\pm$  SD or median (interquartile range), as appropriate. Variables were tested for normal distribution applying the D'Agostino–Pearson normality test. Comparisons between groups were made using the Student *t* test for normally distributed variables and the Mann-Whitney *U* test for nonnormal distribution. Dichotomous variables were compared using the Fisher exact test.  $P < 0.05$  (2-tailed) was considered significant. The Youden index was used to depict the optimal cutoff value from the receiver operating characteristic curve. Statistical analyses were performed using GraphPad software or SPSS 22.0 (IBM Corp).



**Figure 2.** Transmurality index and myocardial salvage index: time-dependent parameters. **A**, Transmurality index increased, with longer symptom-to-balloon time (minutes) mirroring the ischemic wavefront. **B**, In contrast, the myocardial salvage index decreased, with longer symptom-to-balloon time (minutes) indicating progressive loss of myocardial salvage.

**Table 2.** CMR characteristics

	Entire Group	≤121 min	>121 min	P Value
	(n=164)	(n=64)	(n=100)	
Days to CMR	4 (2–6)	4 (2–5)	4 (2–8)	0.82
LVEF, %	50±10	51±10	49±10	0.24
LVEDV, mL	159±48	157±45	160±51	0.56
LVESV, mL	84±39	79±34	88±42	0.15
LVSV, mL	78±21	80±21	77±20	0.50
LV mass, g	130.7±31.8	130.1±35.5	131.9±30.2	0.75
AAR mass, g	48.4±25.8	44.6±27.8	50.8±25.1	0.10
Area at risk, %	36.9±17.7	34.0±19.4	38.4±16.7	0.17
Infarct mass, g	33.0±22.0	27.1±23.2	37.1±20.5	0.001*
Infarct size, %	26.0±16.0	20.8±16.9	29.2±14.7	0.003*
MSI, %	32.4±18.2	39.4±20.0	27.7±14.0	<0.001*
Transmurality index, %	67.6±18.2	60.6±20.0	72.3±14.0	<0.001*
Transmurality				
0–50%	12 (7)	12 (19)	...	...
51–75%	15 (9)	11 (17)	4 (4)	0.01*
76–100%	137 (84)	41 (64)	96 (96)	<0.001*
MVO				
Patients	105 (64)	34 (53)	71 (71)	0.03*
Mass, g	3.9±6.2	3.4±6.5	4.3±6.0	0.04*
% LV mass	3.2±4.5	2.8±4.7	3.4±4.4	0.09
% Infarct	9.2±10.9	9.1±12.8	9.3±9.5	0.20

Values are n (%), mean±SD, or median (interquartile range). AAR indicates area at risk; CMR, cardiac magnetic resonance; LV, left ventricular; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVSV, left ventricular stroke volume; MSI, myocardial salvage index; MVO, microvascular obstruction. \*Statistically significant *P*-values (*P*<0.05).

## Results

### Patient Characteristics

Of the 374 screened patients, 164 were included in the final study cohort (Figure 1). Patients were aged 53.7±10.8 years and predominantly male (80%); median symptom-to-balloon time was 133 minutes (Table 1). The left anterior descending artery was the most frequent IRA. TIMI 3 flow after PCI was achieved in >90% of patients.

### CMR Characteristics

CMR was performed after a median of 4 days after STEMI. LV ejection fraction was moderately reduced (50±10%). Patients demonstrated a low MSI (32.4±18.2) and, consequently, a high transmural index (67.6±18.2), which increased further by prolonged symptom-to-balloon time (Figure 2). Among the 12 patients (7%) demonstrating a transmural grade <50%, 3 patients (2%) showed no myocardial scar at all. Among those,

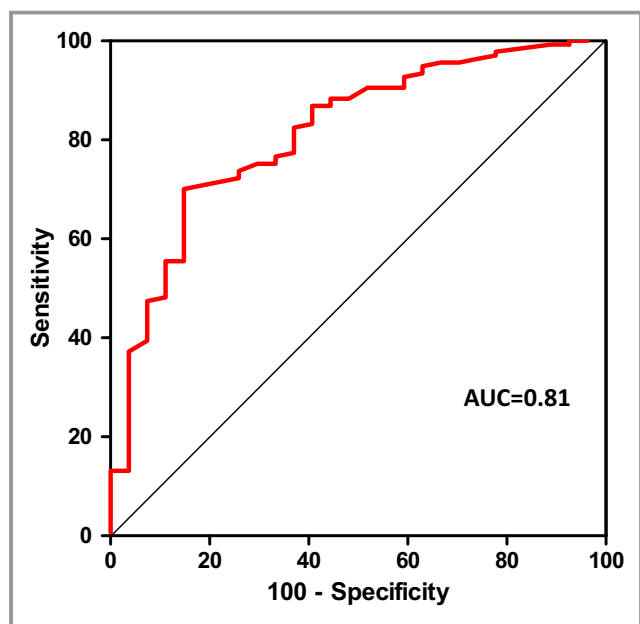
the mean symptom-to-balloon time was 56±15 minutes, whereas the mean symptom-to-balloon time for all 12 patients demonstrating a transmural grade <50% was 77±29 minutes. Conversely, the majority of patients (n=137; 84%) showed a high transmural grade (76–100%) for the AAR. Moreover, 64% of the patients demonstrated MVO, indicating severe myocardial injury (Table 2).

### Symptom-to-Balloon Time Cutoff for Imminent Transmural Myocardial Necrosis

The receiver operating characteristic curve (area under the curve: 0.81) indicating transmural myocardial necrosis revealed the best diagnostic cutoff with a symptom-to-balloon time of 121 minutes (Figure 3).

Dichotomous interpretation identified 64 patients with a symptom-to-balloon time of ≤121 minutes (median: 95 minutes) and 100 with a symptom-to-balloon time of >121 minutes (median 180 minutes; *P*<0.001). Beside the symptom-to-





**Figure 3.** ROC curve: cutoff of 121 minutes. ROC curve (AUC: 0.81; 95% CI, 0.73–0.90;  $P<0.0001$ ) indicating transmural myocardial necrosis revealed the best diagnostic cutoff for a symptom-to-balloon time of 121 minutes. AUC indicates area under the curve; ROC, Receiver operating characteristic.

balloon time, hyperlipidemia, and the serum creatine kinase level ( $P=0.02$ ), both groups showed similar baseline characteristics (Table 1). However, CMR in patients with a symptom-to-balloon time  $>121$  minutes revealed a larger infarct mass and IS, a higher grade of transmural infarction (ie, a higher transmural index), and a lower MSI compared with patients with a symptom-to-balloon time  $\leq 121$  minutes (all  $P\leq 0.01$ ; Table 2). Consequently, in patients with a symptom-to-balloon time  $>121$  minutes, no patient showed a transmural grade of  $<50\%$  compared with 12 (19%) patients in the group with a symptom-to-balloon time of  $\leq 121$  minutes (Figure 4). The relationship between symptom-to-balloon time and the occurrence of transmural necrosis is illustrated in Figure 5. Plausibly, MVO was more frequent in patients with a symptom-to-balloon time  $>121$  minutes ( $P=0.03$ ; Figure 6).

## Discussion

This study is the first to evaluate the time-dependent progress of myocardial necrosis in a relatively pure model of STEMI in patients with acute total occlusion of the IRA with completely abolished antegrade flow (TIMI 0) and without mitigation by visible retrograde collateral flow (Rentrop 0). Current guidelines recommend primary PCI as the preferred reperfusion strategy in STEMI patients within 12 hours of symptom onset (class 1 indication), and an absolute time from STEMI diagnosis to mechanical reperfusion within 120 minutes.<sup>1</sup> However, in our more strictly defined STEMI cohort, a symptom-to-balloon time

$>121$  minutes caused a high grade of transmural infarction (and low MSI), underscoring the paramount importance of the symptom-to-balloon time in the wavefront of myocardial ischemia in patients not protected by a certain extent of residual myocardial blood flow from ante- or retrograde.

## Patient Characteristics

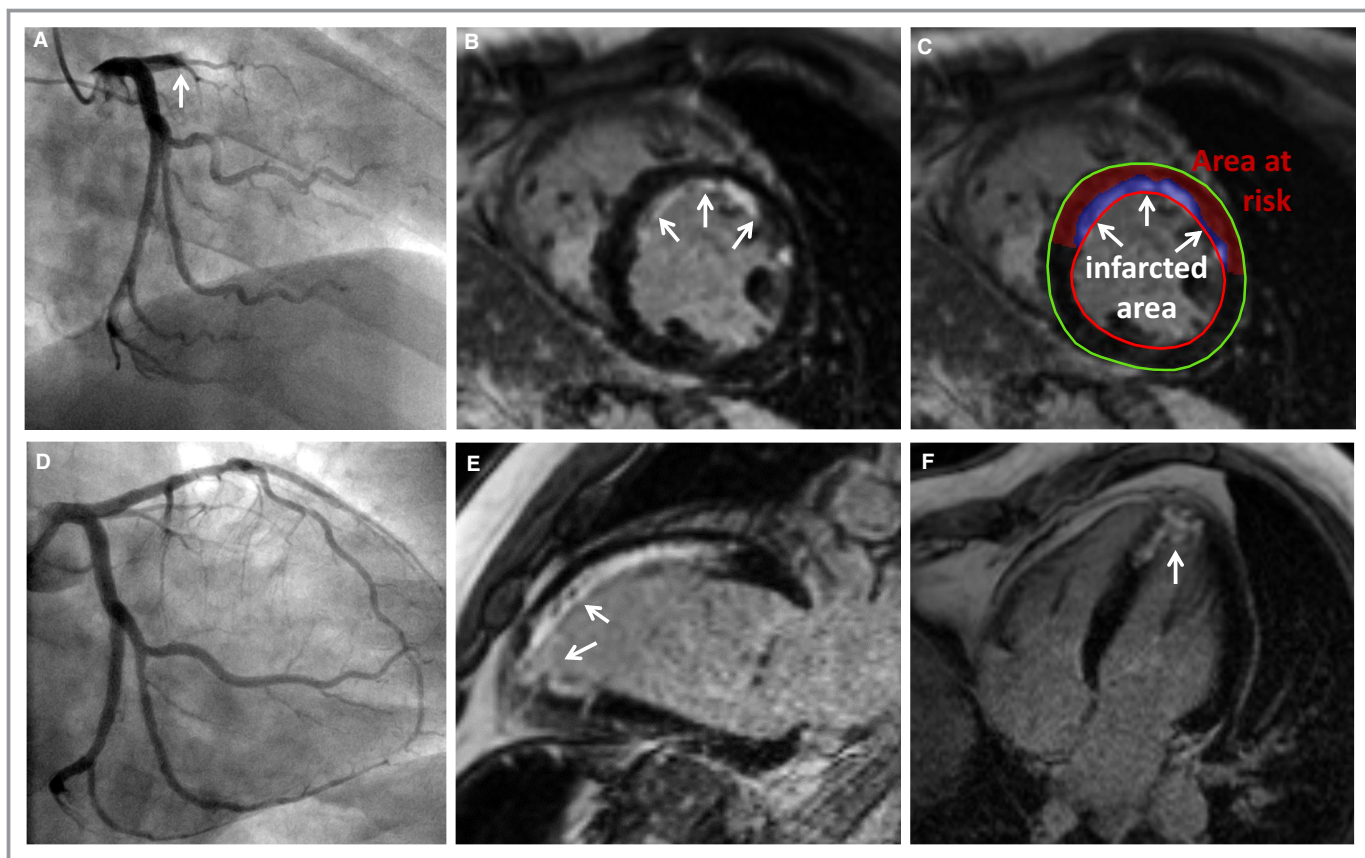
Consistent with previous findings from STEMI registries, patients were relatively young and predominantly male<sup>1,21</sup>; median symptom-to-balloon time was 133 minutes, which was much shorter than in other STEMI trials.<sup>15</sup> TIMI 3 after PCI could be achieved in  $>90\%$  of the patients, similar to previous STEMI studies.<sup>22</sup>

## CMR Characteristics

LV ejection fraction was moderately reduced ( $50\pm 10\%$ ), in line with previous data.<sup>23,24</sup> Overall, patients demonstrated low MSI ( $32\pm 18\%$ ) and a consistently high transmural index ( $68\pm 18\%$ ), which proceeds at sustained occlusion (longer symptom-to-balloon time; Figure 2). Time dependency of transmural index is further illustrated in the small subset of patients with  $<50\%$  transmural index: Of these, mean symptom-to-balloon time increased from  $56\pm 15$  minutes in the 3 patients (2%) with no necrosis to  $77\pm 29$  minutes for all 12 patients (7%), demonstrating a degree of transmural index  $<50\%$ . In this relatively pure model of STEMI, these remarkably short time intervals underscore the need for urgent restoration of flow in the IRA to prevent transmural wavefront expansion. However, even in this patient cohort with relatively short symptom-to-balloon times, the vast majority ( $n=137$ ; 84%) had a high transmural index grade (76–100%). Consequently, the current recommendation of reperfusion in STEMI patients presenting within 12 hours of symptom onset and 120 minutes from the STEMI diagnosis to primary PCI<sup>1</sup> may apply only to a mixed all-comers STEMI population with partly residual antegrade- and retrograde collateral flow slowing the ischemic wavefront to a certain extent.

## Symptom-to-Balloon Time of 121 Minutes: The Cutoff for Imminent Transmural Necrosis

Receiver operating characteristic curve analysis (area under the curve: 0.81) indicating transmural myocardial necrosis revealed the best diagnostic cutoff for a symptom-to-balloon time of 121 minutes (Figure 3). CMR revealed larger infarct mass and IS, higher grade of transmural infarction, and increased transmural index and lower MSI in the subgroup with a symptom-to-balloon time  $>121$  minutes versus patients with a symptom-to-balloon time  $\leq 121$  minutes (all  $P\leq 0.01$ ; Table 2). Although previous studies support the



**Figure 4.** Symptom-to-balloon time of 106 minutes: subendocardial necrosis. A 46-year-old man presenting with chest pain and ST-segment elevation in the anterior leads. Coronary angiography revealed TIMI 0 occlusion of the LAD (A, arrow); primary PCI with stent implant was performed, resulting in TIMI 3 flow after PCI (D). Symptom-to-balloon time was 106 minutes. CMR revealed a preserved global left ventricular ejection fraction (56%) with mild hypokinesia in the anteroseptal and apical wall. Late gadolinium enhancement CMR images revealed subendocardial necrosis (arrows) in the anteroseptal wall (B, C, E) and the apex (E, F), consistent with the region supplied by the infarct-related artery (LAD). CMR indicates cardiac magnetic resonance; LAD, left anterior descending; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

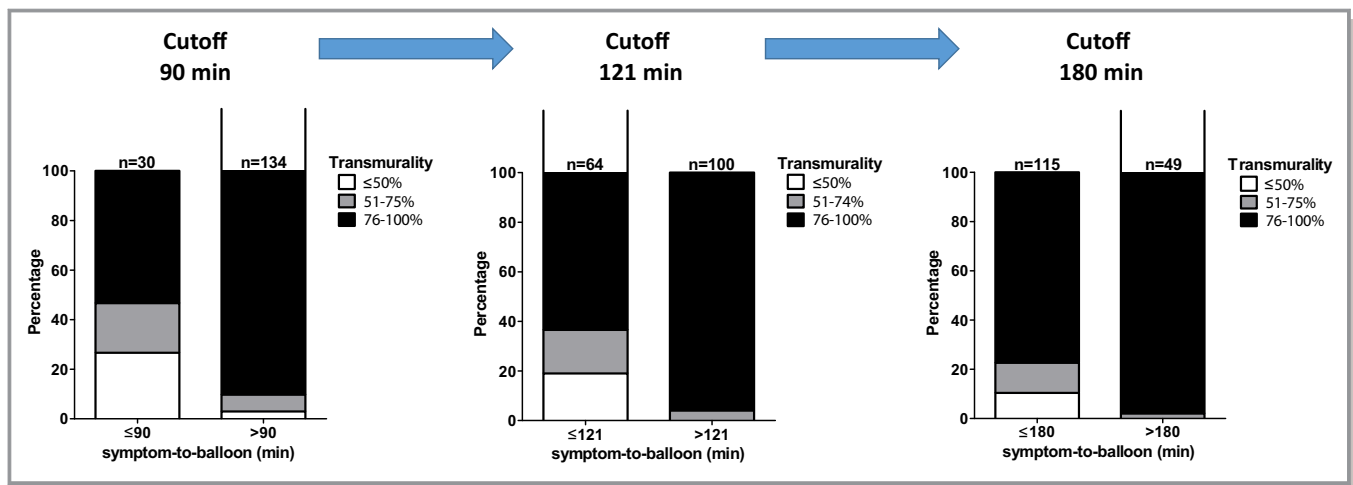
finding that late PCI resulted in larger IS and smaller MSI,<sup>23,25</sup> it is important to note that the IS is rather determined by the IRA; for example, in the AAR of an occluded left circumflex artery, IS may be rather small despite a high transmural index. Conversely, rapid recanalization of an occluded large left anterior descending artery (with a large AAR) may reveal a relatively large IS despite a relatively low transmural index and high MSI, respectively.

A meta-analysis of 2632 STEMI patients demonstrated that IS measured by CMR or single-photon emission computed tomography early after PCI was strongly associated with 1-year hospitalization for heart failure and all-cause mortality,<sup>9</sup> underscoring the high prognostic value of a distinct evaluation of the IS in STEMI patients. In addition, LGE-CMR-derived MSI is considered a more sensitive measure than IS alone because it normalizes the IS to the AAR, which shows tremendous interindividual variation.<sup>26</sup>

Beek et al demonstrated that the transmural extent is relevant in predicting myocardial functional recovery: The

likelihood of complete functional recovery of segments without LGE was 3.8, 11.1, and 50 times higher than that of segments with 26% to 50%, 51% to 75%, and >75% LGE, respectively ( $P<0.001$ ).<sup>27</sup> Other studies demonstrated a significant association with the extent of ischemic LGE and mortality in patients with coronary arterial disease.<sup>7-9</sup>

The link between symptom-to-balloon time and the occurrence of transmural necrosis can be viewed in Figure 5. After a 180-minute cutoff of symptom-to-balloon time, most patients had irreversible transmural necrosis. Corroborating this result, a pooled analysis revealed that IS was large when the first balloon inflation was performed >180 minutes from symptom onset, with little impact of further delays beyond 180 minutes, suggesting a kind of plateau (or “flat” part) of the transmural index and MSI curves.<sup>25</sup> However, few patients demonstrate substantial myocardial salvage in stages at >180 minutes of symptom-to-balloon time, suggesting some other potential mechanisms to salvage myocardium (Figure 2).



**Figure 5.** Grade of transmurality at different symptom-to-balloon times. The left bar (cutoff: 90-minute symptom-to-balloon time) demonstrates a significant percentage of subendocardial MI at  $\leq 90$  minutes of symptom-to-balloon time. The middle bar (cutoff: 121 minutes) demonstrates a smaller but still substantial percentage of subendocardial MI  $\leq 121$  minutes. The right bar (cutoff: 180 minutes) shows further reduction in the percentage of subendocardial MI  $\leq 180$  minutes. MI indicates myocardial infarction.

Successful recanalization of the IRA per se does not guarantee the normalization of myocardial perfusion which is impaired in 30% to 75% of patients due to MVO of various extents.<sup>28</sup> MVO refers to the inability to reperfuse the intramyocardial microcirculation in an ischemic region despite restoring flow in the epicardial vessel and is accurately displayed by LGE-CMR.<sup>11</sup> These patients have a higher prevalence of early postinfarct complications, adverse LV remodeling, recurrent hospitalizations for heart failure, and mortality.<sup>15,24,29–31</sup> The high prevalence of MVO in our population (64%) is similar to those in other reports showing rates of MVO up to 60% in patients receiving primary PCI for acute STEMI (Table 2).<sup>24,32</sup> MVO was more common in patients with longer symptom-to-balloon time (Figure 6), which is consistent with previous data in STEMI patients.<sup>33,34</sup>

Aside from major logistic advancements (eg, preannounced STEMI, direct handoff from ambulances to catheterization laboratories), improved patient awareness may play a crucial role in the reduction of the symptom-to-balloon time. A prospective multicenter study of STEMI patients revealed time intervals from onset of symptoms to first medical contact far beyond the symptom-to-balloon time that seemed to be desirable in STEMI patients as suggested by this study.<sup>35</sup>

## Limitations

Although the wavefront concept of myocardial ischemia is well accepted, there might be some lateral extent of MI, leading to a certain inaccuracy in the definition of the AAR (and its components). However, these potential inaccuracies might be negligible.<sup>14</sup>

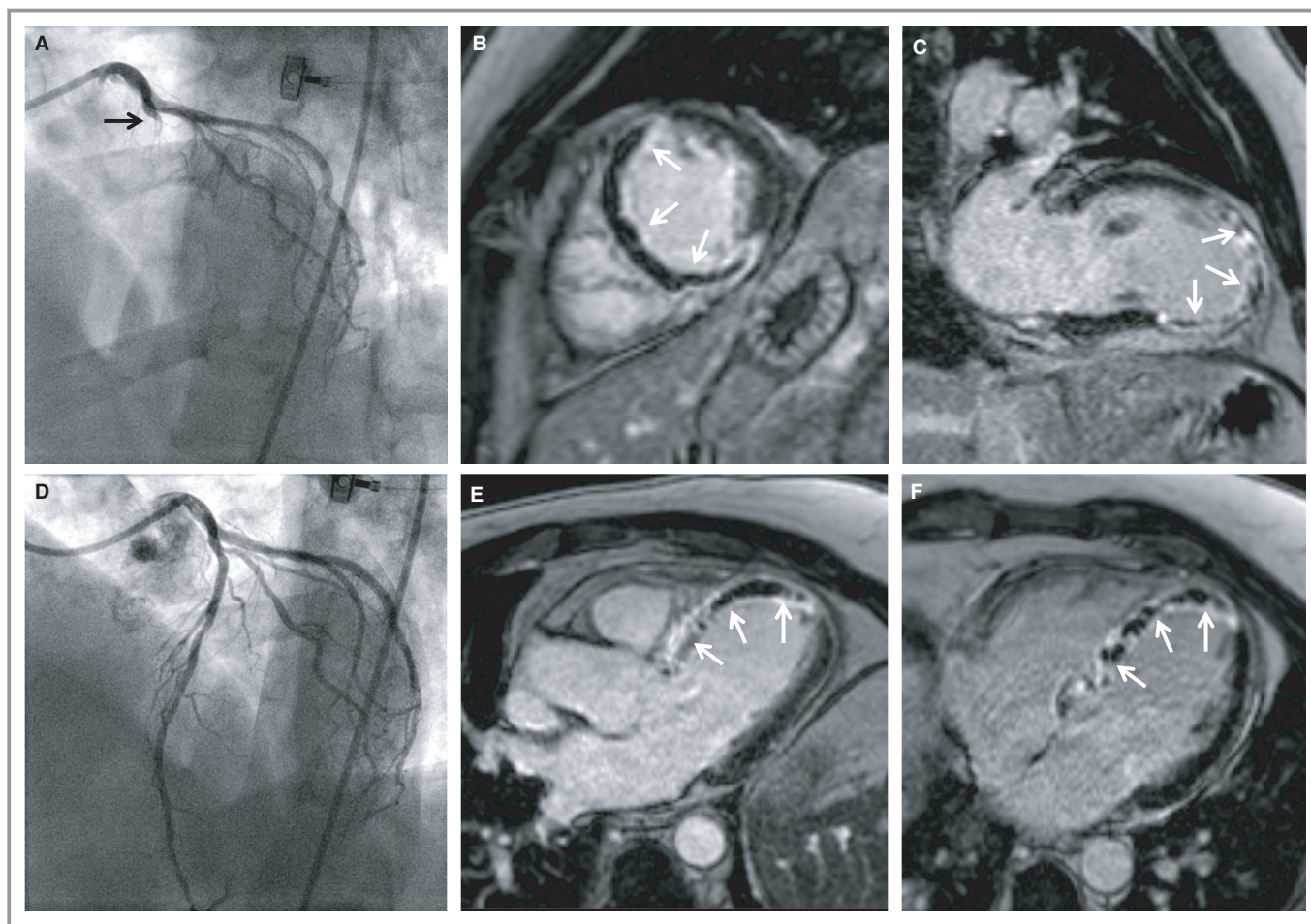
Myocardial blush grade did not differ significantly between patients with a symptom-to-balloon time  $>121$  versus  $\leq 121$  minutes, but CMR-derived MVO was more common in patients with a symptom-to-balloon time  $>121$  minutes ( $P=0.03$ ). Symptom-to-balloon time does not necessarily imply time to reperfusion because in some cases TIMI 3 flow cannot be achieved or, very rarely, the myocardial blush grade is 0/1. Nevertheless, neither TIMI flow after PCI nor myocardial blush grade was significantly different between groups (Table 1).

T2-weighted images were not consistently performed. Those images were used in some studies to delineate the AAR.<sup>36,37</sup> However, image quality is often impaired and prone to artifacts, and T2-weighted images are problematic on many levels.<sup>11, 38</sup> Moreover, post-MI edema in patients is not stable but follows a bimodal pattern that affects CMR estimates of the AAR by T2-weighted images.<sup>39</sup> Furthermore, Kim et al clearly demonstrated that T2-weighted CMR does not depict the AAR.<sup>14</sup>

Although coronary angiography is a commonly used method for evaluation of collateral circulation, and visible retrograde collateral flow was systematically excluded from the present study, smaller, invisible, but functionally present and beneficial collateral vessels may have been missed.<sup>40,41</sup>

CMR mapping sequences were not performed. However, despite the promising results of T1 mapping in STEMI for measuring IS without the use of contrast agent, studies have been small and from single centers.<sup>42,43</sup> Larger multicenter studies are required to investigate the clinical value of mapping techniques before they can be more widely adopted.





**Figure 6.** Symptom-to-balloon time of 141 minutes: transmural necrosis and extensive MVO. A 48-year-old man presenting with chest pain and ST-segment elevation in the anterior leads. Coronary angiography revealed TIMI 0 occlusion of the LAD (A); primary PCI with stent implantation was performed, resulting in TIMI 3 flow after PCI (D). Symptom-to-balloon time was 141 minutes. CMR revealed impaired left ventricular ejection fraction (38%) with akinesia in the anteroseptal, septal, and apical wall. Late gadolinium enhancement CMR images revealed extensive transmural necrosis with concomitant MVO (arrows) in the anteroseptal and septal wall (B, C, E) and the apex (E, F), consistent with the region supplied by the infarct-related artery (large LAD). CMR indicates cardiac magnetic resonance; LAD, left anterior descending; MVO, microvascular obstruction; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction.

## Conclusions

In MI not mitigated by either residual antegrade flow through incomplete coronary occlusion or visible retrograde collateral flow, immediate reperfusion is vital. A symptom-to-balloon time >121 minutes causes a high grade of transmural necrosis. In this pure STEMI population, time to reperfusion to salvage myocardium was less than suggested by current guidelines.

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## Disclosures

None.

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