The International Journal of Cardiovascular Imaging (2019) 35:1079–1087
https://doi.org/10.1007/s10554-019-01556-2

ORIGINAL PAPER

Impact of smoking on cardiac magnetic resonance infarct characteristics and clinical outcome in patients with non-ST-elevation myocardial infarction

Hans-Josef Feistritzer[1,2] · Ingo Eitel[3,4] · Alexander Jobs[1,2,4] · Suzanne de Waha-Thiele[3,4] · Thomas Stiermaier[3,4] · Mohamed Abdel-Wahab[1,2] · Philipp Lurz[1,2] · Sebastian J. Reinstadler[5] · Martin Reindl[5] · Gert Klug[5] · Bernhard Metzler[5] · Steffen Desch[1,2,4] · Holger Thiele[1,2]

Received: 29 November 2018 / Accepted: 7 February 2019 / Published online: 15 February 2019

Abstract

Data derived from several studies suggest a better survival in smokers with acute myocardial infarction, a phenomenon referred to as the 'smoker's paradox'. We aimed to investigate the association of smoking with cardiac magnetic resonance (CMR) imaging determined infarct severity and major adverse cardiac events (MACE) defined as the occurrence of death, reinfarction, and congestive heart failure at 12 months in patients with non-ST-elevation myocardial infarction (NSTEMI) reperfused by early percutaneous coronary intervention (PCI). In this multicenter, registry study 311 NSTEMI patients underwent CMR imaging 3 (interquartile range [IQR] 2–4) days after PCI. Myocardial salvage index (MSI), infarct size (IS), and microvascular obstruction (MVO) as well as MACE rate were compared according to admission smoking status. Approximately one-third of patients were current smokers (n = 122, 39%). Smokers were significantly younger and less likely to have hypertension as compared to non-smokers (all $p < 0.05$). The extent of MSI (63.2, IQR 28.9–85.4 vs. 65.6, IQR 42.2–82.9, $p = 0.30$), and IS (7.2, IQR 2.3–15.7%LV vs. 7.0, IQR 2.2–12.4%LV, $p = 0.27$) did not differ significantly between smokers and non-smokers. Despite similar prevalence of MVO, MVO (%LV) was higher in smokers compared to non-smokers (2.0, IQR 0.9–4.7%LV vs. 1.2, IQR 0.7–2.2%LV, $p = 0.03$). MACE rates at 12 months were comparable in smokers and non-smokers (5.7% vs. 7.4%, $p = 0.65$). In NSTEMI patients, smoking is neither associated with increased myocardial salvage nor less severe myocardial damage. Clinical outcome at 12 months was similar in smokers and non-smokers. *Trial registration* NCT03516578.

Keywords Smoking · Smoker's paradox · Non-ST-elevation myocardial infarction · Cardiac magnetic resonance imaging · Prognosis

Introduction

The high risk for acute ischemic events associated with cigarette smoking might be due to several predisposing factors including endothelial dysfunction, oxidative stress and inflammatory processes [1, 2]. During the last three decades several studies observed lower mortality rates in smokers with acute myocardial infarction (AMI), a phenomenon referred to as the 'smoker's paradox' [3–7]. Less severe myocardial injury in smokers was thought to be a possible underlying cause of this phenomenon [8, 9]. However, the majority of these studies was generated in the thrombolytic era and included mainly patients with ST-elevation myocardial infarction (STEMI).

✉ Hans-Josef Feistritzer
Hans-Josef.Feistritzer@medizin.uni-leipzig.de

1 Department of Internal Medicine/Cardiology, Heart Center Leipzig at University of Leipzig, Strümpellstr. 39, 04289 Leipzig, Germany

2 Leipzig Heart Institute, Leipzig, Germany

3 Department of Cardiology, Angiology and Intensive Care Medicine, University Heart Center Lübeck, University Hospital Schleswig-Holstein, Lübeck, Germany

4 German Center for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Lübeck, Germany

5 University Clinic of Internal Medicine III, Cardiology and Angiology, Medical University of Innsbruck, Innsbruck, Austria

In patients after AMI, cardiac magnetic resonance (CMR) imaging is regarded as the reference technique to assess myocardial function, morphology as well as myocardial and microvascular injury [10–16]. Moreover, quantification of myocardial salvage visualizes the effect of reperfusion therapy [17, 18]. However, studies using CMR to observe the impact of smoking on myocardial injury following AMI had been lacking for a long time. Recently, in patients with STEMI no association was observed between smoking status and CMR-derived infarct size (IS), microvascular obstruction (MVO) and myocardial salvage [19, 20]. Moreover, in these studies smoking was not related with clinical outcome after multivariable adjustment. These data challenge the existence of a smokers paradox in contemporary STEMI patients treated with PCI.

To date, however, no studies addressed the impact of smoking on CMR-determined infarct characteristics and clinical outcome in patients with non-ST-elevation myocardial infarction (NSTEMI) reperfused with primary percutaneous coronary intervention (PCI). Therefore, the present study aimed (1) to investigate the association of smoking with infarct characteristics assessed by CMR and (2) to determine the prognostic significance of smoking on clinical outcome in patients with NSTEMI reperfused with early PCI.

Materials and methods

Study design

The present study was a analysis from a prospective, multicenter, registry study, investigating clinical and angiographic determinants as well as the prognostic significance of CMR-derived infarct characteristics in NSTEMI patients. Patients were included if they had: (1) ischemic symptoms in accordance with a possible NSTEMI diagnosis; (2) elevated cardiac troponin levels above the 99th percentile; and (3) an identifiable culprit lesion during early invasive coronary angiography with performed PCI. Patients with STEMI, cardiogenic shock, no identifiable culprit lesion or culprit lesion ineligible for PCI, indication for acute bypass surgery, age < 18 years or > 90 years, pregnancy and contraindications for CMR (e.g. claustrophobia, implanted pacemakers or internal cardioverter defibrillators, intracranial metallic implants, allergy to gadolinium based contrast agents and creatinine clearance < 30 mL/min) were excluded. Posterior ECG-leads were routinely performed to exclude posterior STEMI.

Smoking status was assessed at admission and patients were categorized as current smokers or non-current smokers. The clinical endpoint of the study was the incidence of major adverse cardiac events (MACE), defined as a composite of all-cause death, reinfarction and new congestive heart failure at 12 months after index infarction. Clinical endpoints were assessed by a telephone interview and verified by reviewing hospital or general practitioner records. The local Ethics Committees approved the study. Informed consent was obtained from all individual participants included in the study.

Image acquisition and analysis

CMR imaging was performed on 1.5 or 3.0 T scanners using a standardized scan protocol described in detail previously [21]. Myocardial edema/area at risk (AAR) was derived from T2-weighted triple-inversion recovery turbo spin-echo images (repetition time 2 × R-R interval; echo time 80 ms; flip angle 180°; voxel size 0.71 × 0.71 × 8.0 mm) (Fig. 1) [22]. Stacks of short axis images were acquired from base to apex with a slice thickness of 8 mm (gap 0 mm). IS and MVO were analyzed from T1-weighted inversion recovery turbo gradient-echo sequences (repetition time 2.8 ms; echo time 1.1 ms; flip angle 15°; typical spatial resolution 1.8 × 1.8 × 5 mm) approximately 15 min after administration of 0.2 mmol/kg body weight gadobutrol (Gadovist, Bayer-Schering, Germany) [22]. Left ventricular (LV) function and volumes were assessed using a standard steady-state free precession sequence with short axis slices covering the whole ventricle. LV endocardial and epicardial borders were traced manually at end-diastole and end-systole. All participating centers proved longstanding expertise in performing CMR examinations in patients with myocardial infarction [15, 16, 18, 23–26]. CMR images acquired at the Heart Center Leipzig and the University Heart Center Lübeck were analyzed at the CMR core laboratory at the Heart Center Leipzig—University Hospital, providing excellent reproducibility as well as inter-observer and intra-observer variability for IS and myocardial salvage assessment [17, 27]. CMR images acquired at the Medical University of Innsbruck were analyzed at the University Clinic of Internal Medicine III, Medical University of Innsbruck by well experienced observers. The standardized imaging protocol used at the Medical University of Innsbruck recently allowed the participation in a multicenter study in STEMI patients [28]. Certified CMR evaluation software (cmr^{42}, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada; IMPAX, Agfa HealthCare, Bonn, Germany; ARGUS, Siemens, Erlangen, Germany) was used for image analysis. The area of abnormal signal intensity was measured in the T2-weighted images and in the corresponding delayed enhancement images in each of the short axis slices. AAR was defined as signal intensity of > 2 standard deviations of remote myocardium, infarcted myocardium as > 5 standard deviations of remote myocardium [22]. Data for myocardial salvage, IS and MVO were expressed as percentage of LV myocardial

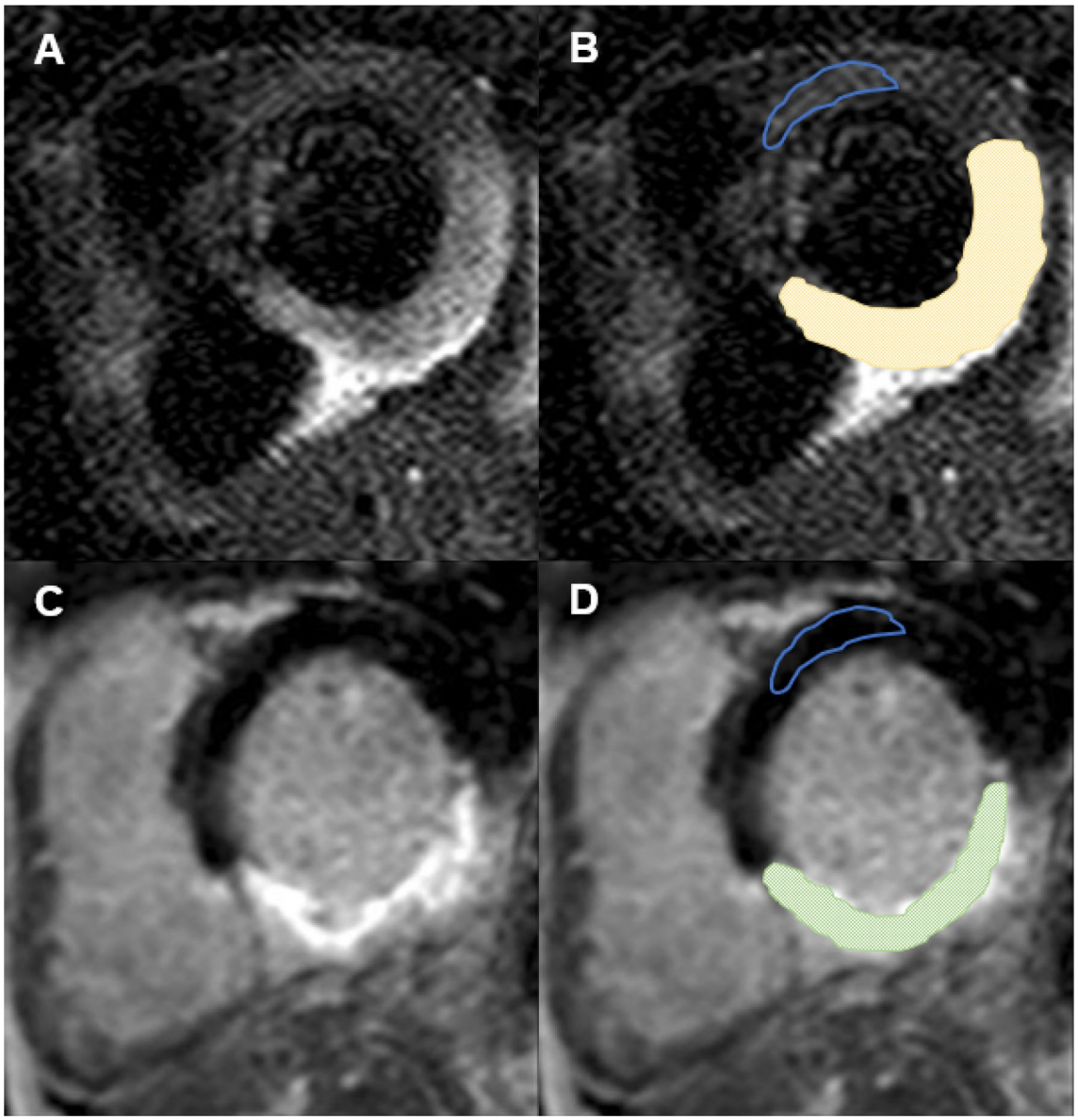

Fig. 1 **a** T2-weighted image in short axis orientation showing high signal intensity of the inferolateral segments indicating myocardial edema. **b** The yellow overlay indicates a signal intensity > 2 standard deviations above remote myocardium (blue contour). **c** Contrast-enhanced image showing high signal intensity inferolateral reflecting myocardial necrosis. **d** The green overlay indicates a signal intensity > 5 standard deviations above remote myocardium (blue contour)

mass (%LV). Additionally, MVO was expressed as percentage of IS (%IS). As previously described, myocardial salvage was calculated as AAR minus IS. Myocardial salvage index (MSI) was calculated as (AAR minus IS)/AAR [17].

Statistical analysis

We used SPSS 20.0.0 (IBM, Armonk, New York) for statistical analysis. All continuous variables are expressed as median and interquartile range (IQR). Categorical variables are displayed as frequencies and corresponding percentages. To test for group differences the Mann–Whitney *U* (for continuous variables) or Chi square (for categorical variables) test was used. Outcome analysis was performed using Kaplan–Meier curves with the log-rank test for group comparison. Furthermore, the prognostic significance of smoking was tested in Cox regression analysis. All tests were 2-tailed and p-values < 0.05 were considered statistically significant.

Results

Baseline patient characteristics

CMR datasets were available in 314 patients. Three patients were excluded from final analysis due to missing outcome data. Baseline clinical and angiographic characteristics of the total study cohort and their association with smoking status are shown in Table 1. One hundred twenty-two (39%) patients were current smokers. Smokers were significantly younger ($p < 0.001$) and less likely to have hypertension ($p = 0.002$) compared to non-smokers. Pre-PCI TIMI flow grade was lower in smokers compared to non-smokers ($p = 0.03$). Moreover, pre-PCI ($p < 0.001$) and post-PCI ($p = 0.005$) TIMI flow grades were significantly lower in patients with presence of MVO compared to those without MVO. Pain-to-balloon time did not differ significantly between patients with and without MVO (14, IQR 7–26 h vs. 20, IQR 7–34 h; $p = 0.18$).

Smoking and CMR findings

CMR scans were performed 3 (IQR 2–4) days after PCI. CMR characteristics of the total study cohort and after stratification for smoking status are shown in Table 2. Data on myocardial edema was missing in 16 (5%) patients. Late gadolinium enhancement (LGE) was present in 270 (87%) patients, showing no significant difference between smokers and non-smokers (n = 107, 88% vs. n = 163, 86%; $p = 0.74$). IS was significantly higher in patients with MVO compared to those without MVO in the entire cohort (15.5, IQR 10.6–20.5%LV vs. 4.1, IQR 1.1–7.7%LV), as well as after stratification for smoking status (all $p < 0.001$). The prevalence of MVO (n = 45, 37% vs. n = 57, 30%, $p = 0.22$) as well as MVO (%IS) ($p = 0.18$) did not differ significantly between smokers and non-smokers (Table 2). However, MVO (%LV) was significantly higher in smokers compared to non-smokers ($p = 0.03$). Furthermore, LV end-diastolic ($p = 0.005$) and end-systolic ($p = 0.01$) volumes were significantly higher in smokers compared to non-smokers.

After exclusion of patients with a history of prior myocardial infarction, prior PCI and coronary artery bypass surgery, no significant differences in CMR derived infarct characteristics could be observed between smokers and non-smokers (all $p > 0.17$).

Clinical outcome

Twenty-one (6.8%) patients developed MACE at 12 months after index infarction. Patients with a history of prior myocardial infarction, prior PCI or coronary artery bypass surgery showed a higher MACE rate at 12 months (n = 6, 14.6% vs. n = 15, 5.6%; $p = 0.04$). MACE rates were similar in smokers and non-smokers (n = 7, 5.7% vs. n = 14, 7.4%; $p = 0.65$), even after exclusion of patients with a history of prior myocardial infarction, prior PCI or coronary artery bypass surgery (n = 3, 2.7% vs. n = 12, 7.6%; $p = 0.11$). Accordingly, smoking status was not a significant predictor of MACE in univariable Cox regression analysis in the entire cohort (HR 0.78, 95% confidence interval (CI) 0.31–1.92, $p = 0.58$), and after exclusion of patients with a history of prior myocardial infarction, prior PCI or coronary artery bypass surgery (HR 0.35, 95% confidence interval (CI) 0.10–1.23, $p = 0.10$). Multivariable analysis was therefore abandoned. Kaplan–Meier curves of MACE-free survival stratified by smoking status are shown in Fig. 2 without a significant difference between groups (log-rank: $p = 0.58$).

Discussion

This is the first multicenter registry study with a relevant patient number evaluating the impact of admission smoking status on CMR-derived myocardial salvage and irreversible myocardial damage as well as its prognostic value in NSTEMI patients undergoing early PCI. The major findings are as follows: (1) myocardial salvage, IS and presence of MVO were similar between smokers and non-smokers; (2) MVO (%LV) and LV volumes were higher in smokers; and (3) admission smoking status was not associated with the risk for MACE at 12 months. Consequently, these findings challenge the existence of a "smoker's paradox" in contemporary NSTEMI patients referred for early PCI therapy.

Smoking status and clinical characteristics

In the present study, smokers were about 10 years younger compared to non-smokers and had a more favorable cardiovascular risk profile, particularly regarding the presence of hypertension. These findings are in accordance with data derived from recent studies in STEMI patients [19, 29]. Since heart rate, Killip class and presence of ST-segment deviation were similar in smokers and non-smokers, the lower GRACE risk score observed in smokers is primarily attributable to the younger age.

According to pre-PCI TIMI flow grade complete occlusions were more frequently observed in smokers than in non-smokers, which might be due to prothrombotic effects of cigarette smoking [2]. Interestingly, an association between smoking status and complete coronary artery occlusions was not reported in STEMI patients [19, 29]. One explanation for this diverging finding in NSTEMI and STEMI patients might be, that the prothrombotic effects of smoking are masked in

Table 1 Baseline characteristics of the total study cohort and after stratification for smoking status

Baseline characteristics	Total study (n = 311)	Smokers (n = 122)	Non-smokers (n = 189)	p-value
Age, years	66 (55–74)	58 (51–68)	70 (61–77)	**< 0.001**
Male sex, n (%)	234 (75)	104 (85)	130 (69)	**0.001**
Cardiovascular risk factors, n (%)				
Hypertension	234 (75)	80 (66)	154 (82)	**0.002**
Hypercholesterolemia	120 (39)	49 (40)	71 (38)	0.72
Diabetes mellitus	85 (27)	28 (23)	57 (30)	0.19
BMI, kg/m^2	27.4 (24.9–30.1)	27.8 (25.2–29.9)	27.2 (24.8–30.4)	0.82
Medical history, n (%)				
Previous infarction	27 (9)	7 (6)	20 (11)	0.15
Previous PCI	25 (8)	6 (5)	19 (10)	0.14
Previous CABG	9 (3)	2 (2)	7 (4)	0.49
Systolic blood pressure, mmHg	140 (120–158)	134 (119–150)	145 (125–160)	**0.002**
Heart rate, beats/min	76 (66–85)	78 (66–87)	75 (66–85)	0.49
ST-segment deviation on admission ECG, n (%)	147 (47)	55 (50)	92 (52)	0.72
GRACE risk score	134 (107–155)	122 (98–151)	137 (114–160)	**0.002**
Killip class on admission, n (%)				0.66
1	290 (93)	115 (94)	175 (93)	
2	20 (6)	7 (6)	13 (7)	
3	1(0)	0 (0)	1 (1)	
4	0 (0)	0 (0)	0 (0)	
Number of diseased vessels, n (%)				0.88
1	140 (45)	57 (47)	83 (44)	
2	104 (33)	39 (32)	65 (34)	
3	67 (22)	26 (21)	41 (22)	
Pain-to-balloon time, hours	16 (7–32)	18 (7–31)	16 (6–32)	0.48
Anterior infarction, n (%)	108 (35)	37 (30)	71 (38)	0.22
Infarct-related artery, n (%)				0.09
Left anterior descending artery	108 (35)	37 (30)	71 (38)	
Left circumflex artery	125 (40)	49 (40)	76 (40)	
Right coronary artery	74 (24)	36 (30)	38 (20)	
Left main coronary artery	0 (0)	0 (0)	0 (0)	
Bypass graft	4 (1)	0 (0)	4 (2)	
TIMI flow grade pre-PCI, n (%)				**0.03**
0	127 (41)	59 (48)	68 (36)	
1	28 (9)	11 (9)	17 (9)	
2	84 (27)	22 (18)	62 (33)	
3	72 (23)	30 (25)	42 (22)	
TIMI flow grade post-PCI, n (%)				0.07
0	7 (2)	1 (1)	6 (3)	
1	6 (2)	0 (0)	6 (3)	
2	30 (10)	15 (12)	15 (8)	
3	268 (86)	106 (87)	162 (86)	
hs-cTnT, ng/L	916 (329–2373)	1008 (328–2576)	892 (326–2231)	0.55

Bold values indicate statistical significance (p-value < 0.05)

BMI body mass index; *PCI* percutaneous coronary intervention; *CABG* coronary artery bypass graft; *ECG* electrocardiogram; *GRACE* global registry of acute coronary events; *TIMI* thrombolysis in myocardial infarction; *hs-cTnT* high-sensitivity cardiac troponin T

Table 2 Cardiac magnetic resonance imaging derived markers of the total study cohort and after stratification for smoking status

CMR parameters	Total study (n = 311)	Smokers (n = 122)	Non-smokers (n = 189)	p-value
Area at risk (edema), %LV	20.4 (15.1–25.4)	19.9 (13.8–25.1)	20.7 (15.3–25.6)	0.58
Infarct size, %LV	7.0 (2.3–13.5)	7.2 (2.3–15.7)	7.0 (2.2–12.4)	0.27
Myocardial salvage, %LV	11.2 (6.7–16.7)	10.5 (5.4–15.6)	11.9 (7.4–17.0)	0.12
Myocardial salvage index	65.2 (36.7–82.9)	63.2 (28.9–85.4)	65.6 (42.2–82.9)	0.30
MVO present, n (%)	102 (33)	45 (37)	57 (30)	0.22
MVO, %LV	1.6 (0.8–3.1)	2.0 (0.9–4.7)	1.2 (0.7–2.2)	**0.03**
MVO, %IS	14.1 (7.1–21.6)	15.0 (7.9–28.9)	13.1 (6.5–21.0)	0.18
LV ejection fraction, %	51 (45–58)	50 (44–57)	51 (45–58)	0.16
LV end-diastolic volume, ml	135 (113–166)	144 (122–172)	131 (107–162)	**0.005**
LV end-systolic volume, ml	65 (52–87)	69 (54–96)	63 (47–83)	**0.01**

Bold values indicate statistical significance (p-value < 0.05)

LV left ventricular; *MVO* microvascular obstruction

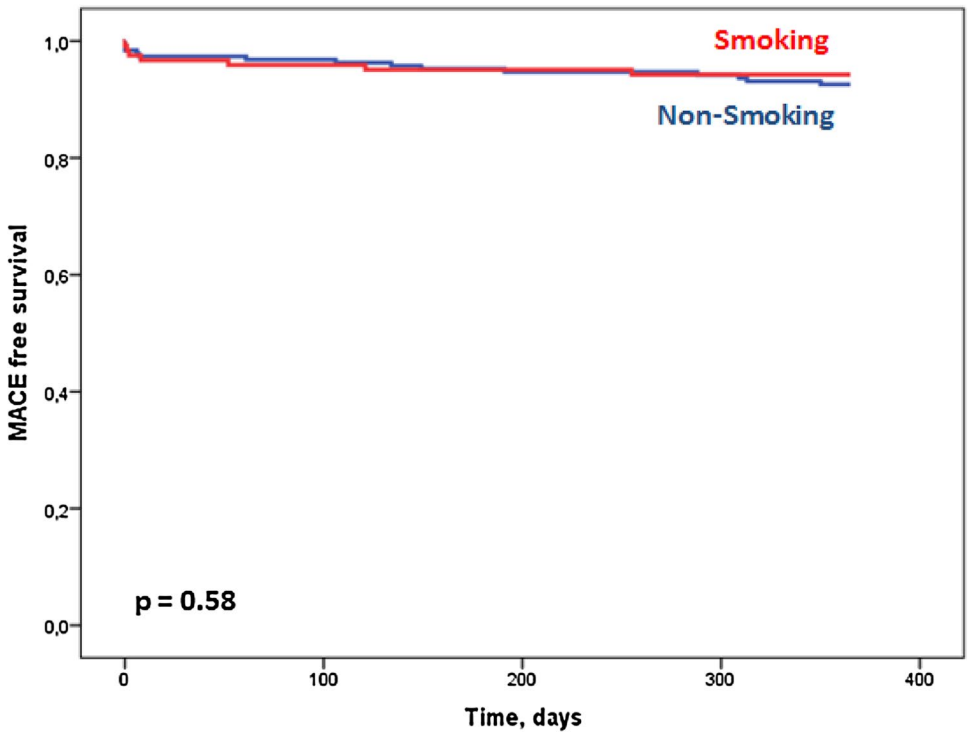

Fig. 2 Kaplan–Meier curves of MACE-free survival, stratified by smoking status. MACE = major adverse cardiac events

the setting of early administered potent antiplatelet agents, as recommended by current STEMI guidelines [30].

Association of smoking with myocardial damage and prognosis

Several studies in patients with AMI suggested favorable clinical outcome in smokers compared to non-smokers. However, the majority of data suggesting these paradoxical effects of smoking were generated in the thrombolytic era primarily including STEMI patients [3–7]. Subsequent studies in STEMI patients demonstrated that the favorable prognostic effects seen in smokers are primarily due to differences in clinical risk characteristics and do not longer exist after multivariable adjustment [31–34]. Accordingly, no independent prognostic benefit of smoking could be detected by two recent trials in STEMI patients reperfused by primary PCI [19, 20].

So far, studies observing the prognostic significance of smoking in NSTEMI patients undergoing early PCI are lacking. In the present study, no association of smoking status with clinical outcome at 12 months was observed. These discrepancies compared to several STEMI cohorts might be due to differences in clinical characteristics including age, risk profile and comorbidities [35]. Considering the about 10 years younger age of smokers in the present study, a similar

MACE rate compared to non-smokers may even indicate a bad sign. This finding might suggest worse outcome in the smoking group in the long run.

The pathophysiological mechanism linking smoking status to clinical outcome is controversially discussed. Some studies in STEMI patients suggested increased myocardial salvage and less severe myocardial damage in smokers [8, 9, 36]. However, none of these studies used CMR imaging, which is nowadays the undisputed reference technique to quantify myocardial injury after myocardial infarction [10–13, 16]. Recently, two studies did not show an association between smoking status and CMR-derived myocardial salvage, IS and microvascular injury in STEMI patients [19, 20]. For the first time, the present study analyzed the association of smoking with CMR-derived infarct characteristics in mechanically reperfused NSTEMI patients. Similar to data derived from STEMI cohorts, we could not detect significant differences in myocardial salvage and IS with regard to smoking status. Controversial findings exist regarding the presence and extent of MVO. Whereas the prevalence of MVO was similar, the extent of MVO (%LV) was larger in smokers than in non-smokers. However, this finding should be interpreted with caution. First, MVO was present in only 33% of patients. Second, the association of smoking and MVO did not longer exist if expressed as percentage of IS (MVO %IS). Considering the higher IS in patients with MVO, this finding theoretically suggests also an association of smoking and IS. However, IS and myocardial salvage were similar in smokers and non-smokers. Another finding of the present study was that LV end-diastolic and end-systolic volumes were higher in smokers compared to non-smokers. Interestingly, similar findings were recently published for STEMI patients [29]. While the pathophysiological mechanism for this association is unknown so far, higher LV volumes might reflect the development of post-infarction LV remodeling, which however cannot be addressed by the present study.

Limitations

Several limitations must be taken into consideration. First, the present study was a subanalysis of a registry study and consequently, common limitations of registry studies are also applicable to the present analysis. Second, patients could only be categorized as current smokers and non-current smokers at the time of hospital admission. Data regarding smoking history, habits and pack years were not available in the present study. Therefore, a larger study, allowing for a more detailed patient characterization, should be performed in the future. Third, this registry study also included patients with a history of prior myocardial infarction, prior PCI and coronary artery bypass surgery. Not surprisingly, these patients showed a higher MACE rate 12 months after index infarction compared to those without prior coronary events. However, associations between smoking status and CMR derived infarct characteristics as well as clinical outcome did not change after exclusion of these patients. Fourth, in the present study CMR imaging was restricted to a single time-point at baseline precluding the assessment of LV remodeling as previously described in STEMI patients [29]. This important issue should be further investigated in future trials. Furthermore, the missing effect of smoking status on clinical outcome in the present study should be interpreted aware of the limited event rate. Therefore, to confirm our findings larger studies are needed in the future.

Conclusions

In this prospective, multicenter, registry study of NSTEMI patients undergoing early PCI, active smoking at the time of hospital admission was neither associated with increased myocardial salvage nor less severe myocardial damage. Clinical outcome at 12 months was similar in smokers and non-smokers.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Camici PG, Crea F (2007) Coronary microvascular dysfunction. N Engl J Med 356(8):830–840
2. Barua RS, Ambrose JA (2013) Mechanisms of coronary thrombosis in cigarette smoke exposure. Arterioscler Thromb Vasc Biol 33(7):1460–1467
3. Molstad P (1991) First myocardial infarction in smokers. Eur Heart J 12(7):753–759
4. Barbash GI, White HD, Modan M, Diaz R, Hampton JR, Heikkila J et al (1993) Significance of smoking in patients receiving thrombolytic therapy for acute myocardial infarction. Experience gleaned from the International Tissue Plasminogen Activator/Streptokinase Mortality Trial. Circulation 87(1):53–58
5. Grines CL, Topol EJ, O'Neill WW, George BS, Kereiakes D, Phillips HR et al (1995) Effect of cigarette smoking on outcome after thrombolytic therapy for myocardial infarction. Circulation 91(2):298–303
6. Barbash GI, Reiner J, White HD, Wilcox RG, Armstrong PW, Sadowski Z et al (1995) Evaluation of paradoxic beneficial effects of smoking in patients receiving thrombolytic therapy for acute myocardial infarction: mechanism of the "smoker's paradox" from the GUSTO-I trial, with angiographic insights. Global Utilization of Streptokinase and Tissue-Plasminogen Activator for Occluded Coronary Arteries. J Am Coll Cardiol 26(5):1222–1229
7. Ruiz-Bailen M, de Hoyos EA, Reina-Toral A, Torres-Ruiz JM, Alvarez-Bueno M, Gomez Jimenez FJ et al (2004) Paradoxical effect of smoking in the Spanish population with acute

myocardial infarction or unstable angina: results of the ARIAM Register. Chest 125(3):831–840
8. Albertal M, Cura F, Escudero AG, Thierer J, Trivi M, Padilla LT et al (2008) Mechanism involved in the paradoxical effects of active smoking following primary angioplasty: a subanalysis of the protection of distal embolization in high-risk patients with acute myocardial infarction trial. J Cardiovasc Med 9(8):810–812
9. Verouden NJ, Haeck JD, Kuijt WJ, Meuwissen M, Koch KT, Henriques JP et al (2010) Clinical and angiographic predictors of ST-segment recovery after primary percutaneous coronary intervention. Am J Cardiol 105(12):1692–1697
10. Kim RJ, Fieno DS, Parrish TB, Harris K, Chen EL, Simonetti O et al (1999) Relationship of MRI delayed contrast enhancement to irreversible injury, infarct age, and contractile function. Circulation 100(19):1992–2002
11. Wu KC, Zerhouni EA, Judd RM, Lugo-Olivieri CH, Barouch LA, Schulman SP et al (1998) Prognostic significance of microvascular obstruction by magnetic resonance imaging in patients with acute myocardial infarction. Circulation 97(8):765–772
12. Wagner A, Mahrholdt H, Holly TA, Elliott MD, Regenfus M, Parker M et al (2003) Contrast-enhanced MRI and routine single photon emission computed tomography (SPECT) perfusion imaging for detection of subendocardial myocardial infarcts: an imaging study. Lancet 361(9355):374–379
13. de Waha S, Desch S, Eitel I, Fuernau G, Zachrau J, Leuschner A et al (2010) Impact of early vs. late microvascular obstruction assessed by magnetic resonance imaging on long-term outcome after ST-elevation myocardial infarction: a comparison with traditional prognostic markers. Eur Heart J 31(21):2660–2668
14. Bellenger NG, Davies LC, Francis JM, Coats AJ, Pennell DJ (2000) Reduction in sample size for studies of remodeling in heart failure by the use of cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2(4):271–278
15. Eitel I, Kubusch K, Strohm O, Desch S, Mikami Y, de Waha S et al (2011) Prognostic value and determinants of a hypointense infarct core in T2-weighted cardiac magnetic resonance in acute reperfused ST-elevation-myocardial infarction. Circ Cardiovasc Imaging 4(4):354–362
16. Eitel I, de Waha S, Wohrle J, Fuernau G, Lurz P, Pauschinger M et al (2014) Comprehensive prognosis assessment by CMR imaging after ST-segment elevation myocardial infarction. J Am Coll Cardiol 64(12):1217–1226
17. Desch S, Engelhardt H, Meissner J, Eitel I, Sareban M, Fuernau G et al (2012) Reliability of myocardial salvage assessment by cardiac magnetic resonance imaging in acute reperfused myocardial infarction. Int J Cardiovasc Imaging 28(2):263–272
18. Eitel I, Desch S, Fuernau G, Hildebrand L, Gutberlet M, Schuler G et al (2010) Prognostic significance and determinants of myocardial salvage assessed by cardiovascular magnetic resonance in acute reperfused myocardial infarction. J Am Coll Cardiol 55(22):2470–2479
19. Reinstadler SJ, Eitel C, Fuernau G, de Waha S, Desch S, Mende M et al (2017) Association of smoking with myocardial injury and clinical outcome in patients undergoing mechanical reperfusion for ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging 18(1):39–45
20. Gennaro G, Brener SJ, Redfors B, Kirtane AJ, Genereux P, Maehara A et al (2016) Effect of smoking on infarct size and major adverse cardiac events in patients with large anterior ST-elevation myocardial infarction (from the INFUSE-AMI trial). Am J Cardiol 118(8):1097–1104
21. de Waha S, Eitel I, Desch S, Scheller B, Bohm M, Lauer B et al (2013) Thrombus Aspiration in ThrOmbus containing culpRiT lesions in Non-ST-Elevation Myocardial Infarction (TATORT-NSTEMI): study protocol for a randomized controlled trial. Trials 14:110
22. Stiermaier T, Eitel I, de Waha S, Poss J, Fuernau G, Thiele H et al (2017) Myocardial salvage after primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction presenting early versus late after symptom onset. Int J Cardiovasc Imaging 33(10):1571–1579
23. Klug G, Mayr A, Schenk S, Esterhammer R, Schocke M, Nocker M et al (2012) Prognostic value at 5 years of microvascular obstruction after acute myocardial infarction assessed by cardiovascular magnetic resonance. J Cardiovasc Magn Reson 14:46
24. Mayr A, Pedarnig K, Klug G, Schocke M, Pachinger O, Jaschke W et al (2012) Regional functional recovery after acute myocardial infarction: a cardiac magnetic resonance long-term study. Int J Cardiovasc Imaging 28(6):1445–1453
25. Mayr A, Klug G, Feistritzer HJ, Reinstadler SJ, Reindl M, Esterhammer R et al (2017) Myocardial edema in acute myocarditis: relationship of T2 relaxometry and late enhancement burden by using dual-contrast turbo spin-echo MRI. Int J Cardiovasc Imaging 33(11):1789–1794
26. Feistritzer HJ, Klug G, Reinstadler SJ, Grober MT, Mair J, Kirchmair R et al (2015) Fetuin-A is related to infarct size, left ventricular function and remodelling after acute STEMI. Open Heart 2(1):e000244
27. Thiele H, Kappl MJ, Conradi S, Niebauer J, Hambrecht R, Schuler G (2006) Reproducibility of chronic and acute infarct size measurement by delayed enhancement-magnetic resonance imaging. J Am Coll Cardiol 47(8):1641–1645
28. Reinstadler SJ, Stiermaier T, Reindl M, Feistritzer HJ, Fuernau G, Eitel C et al (2019) Intramyocardial haemorrhage and prognosis after ST-elevation myocardial infarction. Eur Heart J Cardiovasc Imaging 20(2):138–146
29. Symons R, Masci PG, Francone M, Claus P, Barison A, Carbone I et al (2016) Impact of active smoking on myocardial infarction severity in reperfused ST-segment elevation myocardial infarction patients: the smoker's paradox revisited. Eur Heart J 37(36):2756–2764
30. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H et al (2018) 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 39(2):119–177
31. Gottlieb S, Boyko V, Zahger D, Balkin J, Hod H, Pelled B et al (1996) Smoking and prognosis after acute myocardial infarction in the thrombolytic era (Israeli Thrombolytic National Survey). J Am Coll Cardiol 28(6):1506–1513
32. Andrikopoulos GK, Richter DJ, Dilaveris PE, Pipilis A, Zaharoulis A, Gialafos JE et al (2001) In-hospital mortality of habitual cigarette smokers after acute myocardial infarction; the "smoker's paradox" in a countrywide study. Eur Heart J 22(9):776–784
33. Weisz G, Cox DA, Garcia E, Tcheng JE, Griffin JJ, Guagliumi G et al (2005) Impact of smoking status on outcomes of primary coronary intervention for acute myocardial infarction–the smoker's paradox revisited. Am Heart J 150(2):358–364
34. Allahwala UK, Murphy JC, Nelson GI, Bhindi R (2013) Absence of a 'smoker's paradox' in field triaged ST-elevation

myocardial infarction patients undergoing percutaneous coronary intervention. Cardiovasc Revasc Med 14(4):213–217
35. Park HW, Yoon CH, Kang SH, Choi DJ, Kim HS, Cho MC et al (2013) Early- and late-term clinical outcome and their predictors in patients with ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction. Int J Cardiol 169(4):254–261
36. Wakabayashi K, Romaguera R, Laynez-Carnicero A, Maluenda G, Ben-Dor I, Sardi G et al (2011) Impact of smoking on acute phase outcomes of myocardial infarction. Coron Artery Dis 22(4):217–222