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Letter to the Editor

Smoker's paradox in ST-elevation myocardial infarction: Role of inflammation and platelets

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Cigarette smoking is an established risk factor for coronary artery disease, known to be associated with an increased chronic inflammatory state;[1-2] nevertheless, it has been associated with a better prognosis in the setting of acute coronary syndromes in several studies.[3-4] This phenomenon, ("smoker's paradox") has several potential explanations including the lower platelet reactivity observed in smokers, irrespective of the type of P2Y12 inhibitor drug used.[5] Moreover, a higher inflammatory status has been shown to increase platelet reactivity in patients with acute coronary syndromes.[6] As acute inflammation plays a key role in the pathophysiology of STEMI, contributing to microvascular dysfunction,[7-8] we sought to assess whether it could be mitigated by the chronic inflammatory status due to smoking[2] in these patients.

We analyzed a large single-center cohort of 2958 consecutive patients with STEMI treated by pPCI during 2005-2017 in our University Hospital. The inflammatory response was evaluated using an established acute inflammatory index, Neutrophil-to-Lymphocyte Ratio (NLR), calculated the first day after reperfusion.[9] Microvascular reperfusion was assessed using ST resolution (STR), defined according to previous literature.[10] Continuous variables were expressed as median [p25%-p75%] and compared by the Mann-Whitney test, whereas categorical variables were expressed as percentages and compared by the Fisher exact test. Mortality analysis was performed by generating Kaplan-Meier curves and logistic regression models.

Overall, 62.9% of our population were smokers; they were younger, more frequently men and less frequently diabetics and hypertensive, and had a lower CK peak (all $p < 0.001$, see Table 1). Systolic blood pressure did not show significant difference in smokers at admission, while diastolic blood pressure and heart rate were statistically higher (80 [70-95] vs. 80 [70-90] mmHg, $p = 0.003$ and 76 [66-88] vs. 75 [65-86] bpm, $p = 0.006$, respectively). ST resolution occurred more frequently in smokers: 72.5% vs. 65.2% ($p = 0.001$) and NLR was lower in smokers: 4.6 [2.6-7.7] vs 5.1 [2.8-8.5] ($p < 0.001$). In the whole population, all-cause mortality was 4.5% in hospital and 5.4% at 30 days. Thirty-day mortality was higher in nonsmokers than in smokers (10% vs. 2.5%, $p < 0.001$) [see Figure 1]. The association of previous smoking with a better prognosis was confirmed at multivariable analysis

Table 1
Associations between smoking and variables

Characteristics of the population	Smoking		p-value
	No (n = 37.2%)	Yes (n = 62.8%)	
Age (years, median [p25-p75])	69 [51-75]	59 [61-82]	<0.001
Male sex (%)	66.4%	84.2%	<0.001
Diabetes mellitus (%)	19.9%	15.1%	0.001
Killip class ≥2 (%)	22.9%	14.7%	<0.001
Left ventricular ejection fraction (%, mean [±SD])	43.1 ± 10	44.7 ± 9.7	0.001
Creatinine kinase peak (MU/L, median [p25-p75])	1.44 [0.79-2.66]	1.43 [0.71-2.66]	<0.001
Intra-aortic balloon pump use (%)	10.3%	6.3%	<0.001
Three-vessel coronary disease (%)	30.8%	23.9%	<0.001
Final TIMI flow<3 (%)	12.4%	7.3%	<0.001
Previous use of statins (%)	10.9%	11.5%	0.659
Hypertension (%)	64.8%	49.7%	<0.001
Systolic Blood Pressure at admittance median [p25-p75])	135 [120-150]	130 [120-150]	0.220
Diastolic Blood Pressure at admittance median [p25-p75])	80 [70-90]	80 [70-95]	0.003
Heart rate at admittance median [p25-p75])	75 [65-86]	76 [66-88]	0.006

List of abbreviations: TIMI = thrombosis in myocardial infarction.

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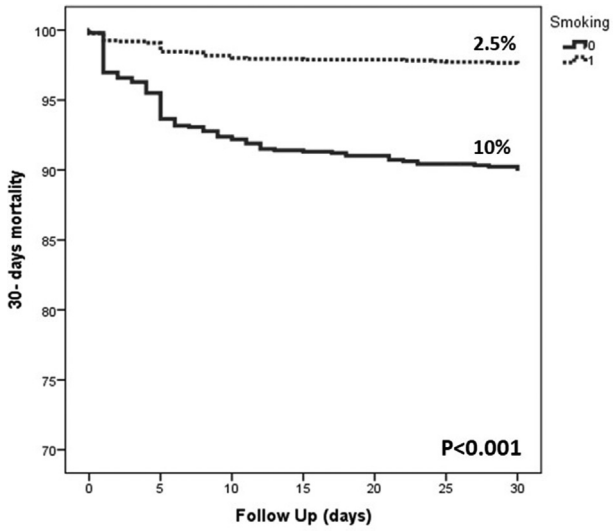

Figure 1. Kaplan-Meier curves for 30-day survival.

for all cause 30-day mortality (adjusted for sex, diabetes, baseline eGFR, age, Killip class ≥2, three-vessel disease, CK peak, and basal hemoglobin), with a protective hazard ratio of 0.55 [95% CI 0.33-0.91, p = 0.019].

In conclusion, our analysis showed that among patients with STEMI treated by pPCI, smokers showed a decreased acute inflammatory response, confirming previous data,[4] and a lower degree of microvascular dysfunction, two phenomena potentially associated with lower mortality. Accordingly, we found a significant association between smoking and lower short-term mortality, both at univariate and multivariable analyses, confirming the existence of a smoker's paradox in our population. Because of the retrospective and epidemiological nature of the study, we cannot exclude the presence of selection bias or confounding/reporting bias; another limitation is the lack of data on platelet reactivity in the present cohort. Despite this, we hypothesize that the chronic inflammatory status due to smoking[2] could play a protective role in the acute inflammatory setting of a STEMI, providing a sort of "inflammatory preconditioning," thereby reducing the activation of platelets and chemotaxis of inflammatory cells in coronary capillaries and the degree of microvascular dysfunction. Further studies assessing the interaction between acute inflammatory response and platelet reactivity in this subset of patients are needed.

Declarations of interest

None.

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