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Letter to the Editor

Black carbon exposure, oxidative stress markers and major adverse cardiovascular events in patients with acute coronary syndromes

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Cardiovascular morbidity and mortality have been associated with particulate matter (PM) air pollution in numerous epidemiological studies [1–4]. Several pathways have been proposed to explain these associations, including increased oxidative stress and systemic inflammation [5]. Black carbon (BC) is a traffic-related particle produced as a combustion by-product and has been associated more strongly than fine PM [aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$)] with a number of cardiovascular endpoints [6].

We hypothesize that patients with acute coronary syndromes (ACS) may be especially vulnerable to BC exposure. One potential pathway is the oxidative stress which may play a role. This study examines whether oxidative stress is associated with BC exposure and predicts major adverse cardiovascular events (MACE) at 30 days in patients with ACS.

Our study participants were selected from AIRACOS (AIR and Acute COronary Syndrome) study, details of which have been published previously [7]. We included 307 consecutive ACS patients admitted into a tertiary care hospital. The research protocol was approved by the ethics committee of our institution and all patients gave written informed consent for inclusion in the study. This study has been registered at ClinicalTrials.gov no. NCT01799148.

Peripheral venous blood samples were obtained from all patients at hospital admission. Serum malondialdehyde (MDA) levels, a stress marker, were measured using the thiobarbituric acid-reactive substance (TBARS) method as described by Kikugawa et al. [8]. The detection limit of this assay was 0.079 nmol/ml. Coefficients of variation were 1.82% and 4.01% for intra- and inter-assays, respectively. The serum concentration of MDA was expressed in nmol/ml. MDA determination was performed by a laboratory technician blinded to all clinical data. We determined the average concentrations of different sizes of PM_{10}, $PM_{2.5}$ and BC, the concentrations of gaseous pollutants (sulfur dioxide, nitrogen dioxide, ozone, benzene, toluene and xylene) and meteorological parameters from 1 day up to 7 days prior to admission. The atmospheric pollutants were measured in an urban background monitoring station using reference methods [9].

Patients were clinically followed during 30 days and the occurrence of clinical events was registered in all patients. MACE was defined as the combined result of cardiovascular death, non-fatal myocardial infarction or re-admission for unstable angina.

Analysis of normality of the continuous variables was performed with the Kolmogorov–Smirnov test. Results for normally distributed continuous variables are expressed as the mean value + standard deviation (SD), and continuous variables with non-normal distribution are presented as median values (interquartile intervals). Logistic regression was used to assess the univariate associations between continuous baseline characteristics and the combined endpoint, and χ^2 testing was used for discrete variables. We assessed independent predictors of MACE using a binary logistic regression analysis. Logistic regression analysis parameters were obtained with the Wald test. Backward stepwise selection was used in all multivariate models to derive the final model for which significance levels of 0.1 and 0.05 were chosen to exclude and include terms, respectively. Variables included in multivariate analyses were age, gender and also those which showed a correlation in univariate analysis that was significant at the 5% significance level (BC, MDA levels and beta-blocker treatment). Differences were considered to be statistically significant if the null hypothesis could be

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rejected with .95% confidence. The SPSS 20.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used for all calculations.

Baseline characteristics of patients classified according to the presence or absence of events during the 30 day follow-up period are shown in Table 1. Eight patients (2.6%) showed MACE. There were no significant differences between groups regarding age, gender, body mass index, ACS type, cardiovascular risk factors, coronary artery disease extension, left ventricular ejection fraction and medications at discharge, except for the use of beta blockers, which were more frequent in patients without events. In relation to biochemical results, MDA levels were higher in patients who developed MACE compared to patients who did not (Table 2).

There were no significant differences (Table 3) regarding the gaseous pollutants and meteorological data when we compared patients with and without events. However, in the atmospheric particles, we found statistically significant differences in BC, with higher concentration in patients with MACE compared to patients without MACE. Multivariate analysis showed that BC (OR: 1.007, 95% CI: 1.002–1.011, P = 0.004) and serum malondialdehyde (OR: 4.25, 95% CI: 1.99–9, P < 0.001) were significant predictors of MACE at 30 day follow–up.

The major and original finding of our study is that in patients admitted to hospital due to ACS, BC concentration averaged the 7 days preceding and MDA levels on admission were associated with MACE at 30 days follow-up. The current study is one of the few studies aiming to assess the relation between BC and MACE at 30 days in patients with ACS. BC is a traffic-related particle, and our finding of a relation between BC and MACE, if further confirmed in other trials, may have important clinical implications because of widespread exposure to traffic emissions across the population.

Although many of the estimates were imprecise owing to a limited sample size, the overall trend of the point estimates was positive, consistent with recent epidemiological findings from other populations. BC is associated with increased risk of emergency myocardial infarction hospitalization [10]. Mordukhovich et al. demonstrated that a 1-SD increase in BC concentration was associated with a 1.5 mm Hg increase in systolic blood pressure and a 0.9 mm Hg increase in diastolic blood pressure [11]. Other studies suggest that the association between BC and inflammatory mechanisms may explain the increased risk of air pollution-associated cardiovascular events among patients with diabetes [12,13]. Moreover, other studies [14,15] showed that exposure of BC alters autonomic function, particularly among high-risk subjects.

Potential mechanisms through which PM may increase the risk of ischemia in vulnerable patients with coronary artery disease have been reviewed [6]. Mechanisms considered include decreased myocardial oxygen supply related to either vasoconstriction or transient thrombus formation, possibly resulting from systemic or local inflammation, oxidative stress, endothelial dysfunction, and/or autonomic dysfunction [6].

Some potential mechanism has been considered to explain the relationship between high BC concentrations and increased 30 day MACE in ACS patients. In vitro studies provide evidence that nanosized BC exposure activates endothelial cells and generates oxidative stress, which is associated with vasomotor dysfunction [16]. In our study, high MDA levels were also predictive of MACE at 30 days. This association remained significant even after adjustment for clinically relevant covariates.

Traffic exposure, which likely represents a complex combination of local pollution exposures, independently adds to risk incurred by the background of regional pollution. Susceptible populations such as individuals with coronary artery disease should be considered when setting

Table 1
Patients classified according to the presence or absence of events during the 30 day follow-up period.

	With Events (n = 8)	Without events (n = 299)	P value
Age, years	64.7 ± 10.4	63.6 ± 12.1	0.8
Male gender, n (%)	5 (62.5)	229 (76.6)	0.4
BMI, kg/m^2	31.4 ± 5.3	27.9 ± 4.4	0.1
Stroke, n (%)	0 (0)	13 (4.3)	0.5
Clinical condition and revascularization			
STEMI ACS, n (%)	4 (50)	134 (44.8)	0.7
Non-STEMI ACS, (%)	4 (50)	165 (55.2)	0.7
Revascularization, (%)	5 (62.5)	253 (84.6)	0.12
Cardiovascular risk factors			
Hypertension, n (%)	7 (87.5)	166 (55.5)	0.14
Smoking habit, n (%)	2 (33.3)	127 (42.5)	0.5
Dyslipidemia, n (%)	4 (50)	183 (61.2)	0.7
Diabetes mellitus, n (%)	5 (62.5)	93 (31.1)	0.12
Medications			
Aspirin	8 (100)	299 (100)	1
Clopidogrel, n (%)	5 (62.5)	239 (79.9)	0.2
Beta blockers, n (%)	5 (62.5)	268 (89.6)	0.04
ACE inhibitors/ARB, n (%)	8 (100)	209 (69.9)	0.11
Statins, n (%)	8 (100)	299 (100)	1
Antidiabetic medication, n (%)	5 (62.5)	93 (31.1)	0.11
Coronary angiogram			0.8
Non-obstructive CAD, n (%)	0 (0)	15 (5)	
One vessel disease, n (%)	4 (50)	146 (48.8)	
Two vessel disease, n (%)	2 (25)	86 (28.8)	
Three vessel disease, n (%)	2 (25)	52 (17.4)	
Left ventricular ejection fraction, %	56.4 ± 9.3	57.2 ± 10.2	0.8

ACE: angiotensin-converting-enzyme; ARB: angiotensin II receptor antagonist; BMI: body mass index; STEMI: ST-elevation myocardial infarction; ACS: acute coronary syndrome; CAD: Coronary artery disease.

Table 2
Biochemical results in patients classified according to the presence or absence of events during the 30 day follow up period.

	With events (n = 8)	Without events (n = 299)	P value
Hemoglobin, mg/dL	13 ± 2.2	14.5 ± 7.5	0.12
Hematocrit, %	38.8 ± 6	41.6 ± 4.6	0.2
Leukocytes, 10^9/L	11.9 ± 3.6	11 ± 3.8	0.5
Neutrophils, 10^9/L	7.2 ± 1.5	7 ± 1.3	0.7
Creatinine, mg/dL	1 ± 0.5	0.88 ± 0.46	0.5
Troponin I, ng/mL	57.2 ± 34.2	30.4 ± 31.8	0.12
NT-ProBNP, pg/mL	1680 [666–2280]	483 [169–1520]	0.055
Total cholesterol, mg/dL	165.5 [133.25–180]	175.5 [147–202]	0.6
Triglycerides, mg/dL	176.5 [90–237.8]	135 [107.25–173]	0.2
Hs-CRP, mg/L	8.85 [3.6–52.2]	8.3 [5–17]	0.7
MDA, nmol/ml	4.3 [2.1–5.4]	2.2 [1.7–2.8]	0.045

MDA: malondialdehyde; CRP: C-reactive protein.

Table 3
Data on atmospheric pollution in ambient air and meteorological variables between the previous day and the 7 days prior to admission in patients classified according to the presence or absence of events during the 30 day follow-up period.

	With events (n = 8)	Without events (n = 299)	P value
Meteorological variables			
Wind speed (m/s)	3 ± 0.5	3.1 ± 0.4	0.6
Temperature (°C)	21 ± 2.7	21.5 ± 2.7	0.5
Relative humidity (%)	59.9 ± 2.8	59.9 ± 4.6	0.9
Pressure (mbar)	1000.75 ± 3.15	999.1 ± 2.7	0.2
Gaseous pollutants			
SO_2 (μg/m^3)	7 ± 1.7	7.4 ± 2.3	0.5
NO_2 (μg/m^3)	5 ± 1.9	4.7 ± 1.2	0.7
O_3 (μg/m^3)	65.6 ± 7.6	66.7 ± 7.8	0.7
C_6H_6 (μg/m^3)	0.25 ± 0.46	0.19 ± 0.54	0.7
C_7H_8 (μg/m^3)	1 ± 0.53	1 ± 0.34	0.8
C_8H_{10} (μg/m^3)	0.25 ± 0.46	0.24 ± 0.44	0.9
Atmospheric particles			
PM-10 (μg/m^3)	19.25 ± 5	17.2 ± 5.5	0.3
PM-2.5 (μg/m^3)	9.75 ± 2	8.7 ± 2	0.2
Black carbon (μg/m^3)	1077.1 ± 253.3	859 ± 196.1	0.045

C_6H_6, benzene; C_7H_8, toluene; C_8H_{10}, xylene; NO_2, nitrogen dioxide; O_3: ozone; SO_2, sulfur dioxide. PM, particulate material with an aerodynamic diameter [PM_{10}, $PM_{2.5}$].

national policies and regulations to control levels of PM air pollution and traffic [6].

Our study has some limitations. We did not use time series analysis in our study to examine the short-term relationship between the variations in PM and ACS. This was because daily variations in the pollutants during the 7 days prior to admission were small enough to allow us to exclude the time series analysis [17]. We believe that the results of our study are hypothesis generating and should be interpreted with caution, as the MACE rate and sample size are low.

In conclusion, this study demonstrates in ACS patients that high BC exposure and oxidative stress marker levels are independently associated with MACE at 30 days.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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