JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER INC.

VOL. 64, NO. 18, 2014
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2014.07.985

Platelet Activation Is Associated With Myocardial Infarction in Patients With Pneumonia

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ABSTRACT

BACKGROUND Troponins may be elevated in patients with pneumonia, but associations with myocardial infarction (MI) and with platelet activation are still undefined.

OBJECTIVES The aim of this study was to investigate the relationship between troponin elevation and in vivo markers of platelet activation in the early phase of hospitalization of patients affected by community-acquired pneumonia.

METHODS A total of 278 consecutive patients hospitalized for community-acquired pneumonia, who were followed up until discharge, were included. At admission, platelet activation markers such as plasma soluble P-selectin, soluble CD40 ligand, and serum thromboxane B_2 (TxB_2) were measured. Serum high-sensitivity cardiac troponin T levels and electrocardiograms were obtained every 12 and 24 h, respectively.

RESULTS Among 144 patients with elevated high-sensitivity cardiac troponin T, 31 had signs of MI and 113 did not. Baseline plasma levels of soluble P-selectin and soluble CD40 ligand and serum TxB_2 were significantly higher in patients who developed signs of MI. Logistic regression analysis showed plasma soluble CD40 ligand ($p < 0.001$) and soluble P-selectin ($p < 0.001$), serum TxB_2 ($p = 0.030$), mean platelet volume ($p = 0.037$), Pneumonia Severity Index score ($p = 0.030$), and ejection fraction ($p = 0.001$) to be independent predictors of MI. There were no significant differences in MI rate between the 123 patients (45%) taking aspirin (100 mg/day) and those who were not aspirin treated (12% vs. 10%; $p = 0.649$). Aspirin-treated patients with MIs had higher serum TxB_2 compared with those without MIs ($p = 0.005$).

CONCLUSIONS MI is an early complication of pneumonia and is associated with in vivo platelet activation and serum TxB_2 overproduction; aspirin 100 mg/day seems insufficient to inhibit thromboxane biosynthesis. (MACCE in Hospitalized Patients With Community-acquired Pneumonia; NCT01773863) (J Am Coll Cardiol 2014;64:1917–25) © 2014 by the American College of Cardiology Foundation.

Community-acquired pneumonia (CAP) is the most common infection leading to hospitalization in intensive care units and the most common cause of death associated with infectious diseases (1). Epidemiological studies have shown that respiratory tract infections are associated with an increased risk for the development of acute cardiovascular events (2). This link is further

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Manuscript received April 18, 2014; revised manuscript received June 17, 2014, accepted July 8, 2014.

ABBREVIATIONS AND ACRONYMS

ASA = acetylsalicylic acid

CAP = community-acquired pneumonia

CHD = coronary heart disease

COPD = chronic obstructive pulmonary disease

hs-cTnT = high-sensitivity cardiac troponin T

IQR = interquartile range

MI = myocardial infarction

MPV = mean platelet volume

PAD = peripheral arterial disease

PSI = Pneumonia Severity Index

sCD40L = soluble CD40 ligand

sP-selectin = soluble p-selectin

T2DM = type 2 diabetes mellitus

TxB_2 = thromboxane B_2

supported by studies indicating that influenza vaccination is associated with reduced risk for hospitalization for pneumonia, heart disease, cerebrovascular disease, and the risk for death from all causes during influenza seasons in elderly patients (3).

A prospective study (4) focused attention on the association of pneumonia with elevations of cardiac enzymes (e.g., creatine kinase-MB) and signs of myocardial ischemia, suggesting that myocardial infarction (MI) may be a complication of pneumonia in the early phase of clinical presentation. More recently, Chang et al. (5) showed elevated serum troponins (a more sensitive marker of cardiac damage than creatine kinase-MB) in patients with pneumonia, but the relationship with MI was not investigated. Furthermore, the mechanism of MI in patients with pneumonia is still elusive.

Platelets play a key role in the occurrence of MI, as shown by interventional trials showing that acetylsalicylic acid (ASA), which inhibits platelet thromboxane A_2 production via irreversible acetylation of COX-1 (6), lowers cardiovascular events in patients with acute or chronic coronary heart disease (CHD) (7). In patients with pneumonia or other infections, previous studies showed in vivo elevation of platelet activation biomarkers, suggesting potential interplay between platelet overactivation and cardiovascular events during pneumonia. Thus, we speculated that in pneumonia, differences in platelet activation might be detected in patients with and without signs of MI. For this purpose, we performed a prospective study in which the relationships between in vivo markers of platelet activation were analyzed in the early phase of hospitalization of patients affected by CAP. Markers analyzed included plasma levels of soluble CD40 ligand (sCD40L) (8) and soluble P-selectin (sP-selectin) (9); serum levels of thromboxane B_2 (TxB_2), which reflects maximal platelet formation of thromboxane A_2 (10–12); and serum levels of high-sensitivity cardiac troponin T (hs-cTnT).

METHODS

PATIENT SELECTION. The study was conducted at 4 centers of the University Hospital Policlinico Umberto I (Rome, Italy). All patients with CAP admitted to the 4 units through the emergency department from October 2011 to April 2013 were prospectively recruited and followed up. After they gave written informed consent, we enrolled 278 consecutive patients who fulfilled the following criteria in the study: 1) age ≥ 18 years; 2) clinical presentation of an acute illness with one or more of the following signs or symptoms suggesting CAP: presence of rales, rhonchi, bronchial breath sounds, dullness, increased fremitus and egophony, fever (>38.0°C), tachycardia, chills, dyspnea, coughing (productive or unproductive cough), and chest pain; and 3) presence of new consolidation(s) on chest x-ray. Pneumonia was considered CAP if it was diagnosed on hospitalization and the patient had not been discharged from an acute care facility within 14 days preceding the clinical presentation.

Patients were excluded from the study if any of the following criteria applied: radiographic evidence of preexisting infiltrates, severe sepsis or immunosuppression (human immunodeficiency virus infection, chemotherapy, high doses of immunosuppressive agents such as prednisone), presence of malignancy, pregnancy or breastfeeding, documented severe allergy to antibiotics, and health care–associated pneumonia (13).

BASELINE ASSESSMENT. Data on demographic characteristics and comorbidities were collected. Severity of illness at presentation was quantified by the Pneumonia Severity Index (PSI), a validated prediction score for 30-day mortality in patients with CAP (14). Immediately after diagnosis of CAP, routine blood laboratory tests including platelet count and mean platelet volume (MPV), serum hs-cTnT and high-sensitivity C-reactive protein, serum TxB_2, and arterial blood gas test, were performed. Thereafter, serum hs-cTnT was assessed every 12 h, and 12-lead electrocardiography was repeated every 24 h. M-mode and 2-dimensional color Doppler echocardiography was performed within 2 days of hospital admission. Ejection fraction was measured using the modified Simpson's rule.

Type 2 diabetes mellitus (T2DM), hypertension, history of CHD, dyslipidemia, peripheral arterial disease (PAD), and chronic obstructive pulmonary disease (COPD) were defined as previously described (15–17). Baseline treatments were defined according to patients' pharmacological histories. Patients already treated with ASA before admission were categorized as ASA users. Compliance with ASA and other medications was monitored daily.

This study was conducted according to the principles stated in the Declaration of Helsinki. The institutional review board approved this prospective, observational study, which was registered at ClinicalTrials.gov (NCT01773863).

STUDY ENDPOINTS. The primary study end point was the occurrence of MI during the hospital stay.