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EDITORIAL COMMENT

The Sum of Two Evils

Pneumonia and Myocardial Infarction: Is Platelet Activation the Missing Link?*

Carlos G. Santos-Gallego, MD, Juan J. Badimon, PhD

Community-acquired pneumonia (CAP) affects >5 million adults, causes 1.1 million hospital admissions, and is responsible for >60,000 deaths each year in the United States (1). Recent studies connected CAP with cardiovascular disease (CVD), the leading cause of death worldwide (2), and its most feared complication, myocardial infarction (MI). In this issue of the *Journal*, Cangemi et al. (3) add a new piece to the puzzle of this relationship.

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Although traditionally regarded as confined to the lungs, all severities of acute pneumonia infection affect the cardiovascular system. Several recent retrospective clinical observations and meta-analyses found increased MI incidence after CAP (see Corrales-Medina et al. [1] for a comprehensive summary). Analysis of a prospective multicenter cohort of 2,344 unselected patients with CAP confirmed these data (4). In this cohort, 30-day incidences of heart failure, arrhythmia, and MI were 21%, 10%, and 3%, respectively, with risks peaking in the first 2 days of hospitalization. Even after adjusting for baseline risk, MI was independently associated with a 60% increase in short-term mortality risk. These findings suggest that prevention of cardiac complications may improve CAP outcomes.

This increased MI risk is not limited to CAP. Large retrospective epidemiological studies found increased MI risk after acute respiratory infections (5), and retrospective studies (6) and clinical trials (7) showed an association between influenza vaccination and reduced risk for MI and stroke. Additionally, early treatment of influenza in patients with CVD was associated with a 60% decrease in MI risk (8).

Despite this robust association, its potential mechanisms of action are not well understood, although several hypotheses have been postulated. Atherosclerosis is an inflammatory disease; acute infections, such as CAP, not only elicit systemic inflammatory responses but can also have direct inflammatory effects on atherosclerotic plaques, increasing their vulnerability. In atherosclerotic apolipoprotein E-knockout mice, influenza virus infection promotes acute inflammation in the atheromata (infiltration of plaques with macrophages and T lymphocytes) and superimposed fibrin deposition, similar to unstable plaques after MI (9). Coronary artery tone abnormalities may also be involved, as increased vasoconstrictive responses were observed in animals injected with staphylococcal α-toxins (10). Other factors may likely contribute: tachycardia shortens diastole (when coronary perfusion occurs), decreased central blood pressure (as in severe sepsis) impairs myocardial perfusion through stenotic coronary segments, and hypoxemia and increased cardiac metabolic demands (secondary to tachycardia and catecholamine release) can contribute to the development of myocardial ischemia.

The work of Cangemi et al. (3) is a prospective study in which 278 consecutive patients with CAP at 4 different hospitals were recruited and followed until discharge, including periodic cardiac (high-sensitivity cardiac troponin T [hs-cTnT]) and in vivo platelet activation marker measurement. Although up to 52% of patients with CAP had high hs-cTnT levels, 11% of them showed signs of MI (increased hs-cTnT concentrations and electrocardiographic changes or symptoms). Thus, in the 41% of patients without

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electrocardiographic changes, increased hs-cTnT is probably not secondary to ischemia. Other possibilities include stress-induced cardiomyopathy or nonspecific toxic effects on cardiomyocytes, leading to biomarker leakage. The 11% MI rate was higher than in previous reports, probably explained by the use of hs-cTnT instead of creatine kinase (4), a less sensitive myocardial injury biomarker, and because hs-cTnT levels were measured every 12 h, not only at hospital admission (4). The main clinical take-home message is that patients with previous CVD or severe CAP (both independently associated with MI) should be monitored daily with hs-cTnT and electrocardiographic assessment to detect MI, especially during the first 2 days of hospitalization, because MI was asymptomatic and increased the risk for death.

This paper's importance stems from its suggestion that high platelet activation may provide a mechanistic explanation for increased MI risk in CAP. In vivo platelet activation markers (soluble CD40 ligand, soluble P-selectin, and thromboxane B_2 levels) at admission were increased in patients who subsequently developed MIs, suggesting that CAP increases platelet activation, which may in turn cause MI. Previous studies highlighted the contribution of infection to platelet activation. Kreutz et al. (11) found increased platelet reactivity in patients affected by viral respiratory infections compared with healthy controls. Modica et al. (12) found more pronounced platelet aggregation and increased aspirin nonresponsiveness in patients with MIs with concurrent infection than in uninfected patients with MIs. Several mechanisms were proposed to explain these findings. Gram-positive bacteria induce platelet aggregation and the formation of platelet-neutrophil complexes (13). Additionally, in response to lipopolysaccharide from Gram-negative bacteria, platelets bind more avidly to fibrinogen under flow conditions in a Toll-like receptor 4-dependent manner (14). Surprisingly, Cangemi et al. (3) found no difference in the MI rate between aspirin-treated and untreated patients.

A limitation of the present study is that the role of platelet function is not fully understood. Platelet aggregation may be either a risk factor (it correlates with the disease, and treatment reduces the incidence of the disease) or a risk marker (it correlates with the disease, but treatment does not affect the incidence of the disease because it is merely a surrogate indicator of disease severity). Platelet aggregation seems to behave as a risk marker. In the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay—Impact on Thrombosis and Safety) (15) and ARCTIC (Double Randomization of a Monitoring Adjusted Antiplatelet Treatment Versus a Common Antiplatelet Treatment for DES Implantation, and Interruption Versus Continuation of Double Antiplatelet Therapy; NCT00827411) (16) clinical trials, tailored pharmacological antiplatelet therapy aiming to decrease platelet aggregation did not reduce CVD events. Therefore, increased platelet activation in CAP may be a marker of disease severity but not a causal link, and antiplatelet therapy would not reduce MI. That aspirin-treated patients did not show reduced MI risk in this population supports this notion, as does the lack of a statistically significant reduction in MI among aspirin-treated patients with CAP in previous observational studies (17,18). Alternatively, because platelet aggregation involves many different agonists (arachidonic acid/thromboxane A_2 receptors, adenosine diphosphate/$P2Y_{12}$ receptors, von Willebrand factor/glycoprotein Ib, collagen/glycoprotein VI, glycoprotein IIb/IIIa, thrombin/thrombin receptor), specific inhibition of a single pathway (thromboxane A_2, with aspirin) may be insufficient to mitigate MI risk. An open question is whether patients with CAP should be treated prophylactically with more potent antiplatelet therapy.

The study by Cangemi et al. (3) confirms high MI incidence during CAP (silent MI in the first 2 days of hospitalization, especially in patients with severe CAP or previous CVD) and suggests CAP-mediated increased platelet activation as the mechanistic explanation but still leaves some questions unanswered. Future studies are needed for confirmation of the mechanism and to delineate the best therapy (e.g., antiplatelet agents, vaccines) to reduce MI risk.

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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 supported by studies indicating that influenza vaccination is associated with reduced risk for

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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

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.

MI criteria were those of the third universal definition of MI: the detection of an increase in cardiac troponin with at least 1 value above the 99th percentile upper reference limit, associated with at least 1 of the following: 1) chest pain; 2) detection of new or presumably new significant ST-segment-T-wave changes or new left bundle branch block; 3) development of pathological Q waves on electrocardiography; 4) de novo imaging evidence of viable myocardium loss or regional wall motion abnormality; 5) identification of an intracoronary thrombus by angiography or autopsy; and 6) cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic electrocardiographic changes or new left bundle branch block (18).

ST-segment elevation MI and non–ST-segment elevation MI were defined as previously reported (18). Therapeutic treatment at admission and during the hospital stay were registered.

Adjudication of cardiovascular events was performed by a committee of cardiologists (C.C. and A.C.) who did not participate in patient recruitment and follow-up and were unaware of any patient's clinical and laboratory characteristics.

PLASMA LEVELS OF sCD40L, sP-SELECTIN, AND SERUM TXB_2. Blood samples to measure biomarkers of platelet activation were obtained within 24 h of admission and at the end of hospitalization. Samples with or without 3.8% sodium citrate were taken without stasis from patients who had fasted for at least 12 h.

After withdrawal of a first blood sample, 1-ml serum aliquots were immediately transferred into glass tubes and allowed to clot at 37°C for 1 h. Serum was separated by centrifugation and frozen at −80°C until assayed. Serum TxB_2 was measured using an enzyme-linked immunosorbent assay commercial kit (R&D Systems, Inc., Minneapolis, Minnesota) and expressed as nanograms per milliliter. Intra- and interassay coefficients of variation for the TxB_2 assay kit were 5.9% and 8.9%, respectively.

Citrated samples were centrifuged to separate plasma, which was frozen at −80°C until assayed. Plasma sCD40L and sP-selectin levels were measured with a commercial immunoassay (Tema Ricerca, Castenaso, Italy). Intra- and interassay coefficients of variation were 5% and 7% for sCD40L and 4.3% and 6.1% for sP-selectin.

SERUM HS-cTNT MEASUREMENT. Hs-cTnT levels were measured with the Elecsys 2010 (Roche Diagnostics, Indianapolis, Indiana) at a dedicated core laboratory. According to the manufacturer, the 99th-percentile cutoff point for hs-cTnT is 0.014 μg/l, and a coefficient of variation of <10% is achieved at 0.013 μg/l (19).

STATISTICAL ANALYSIS. Categorical variables are reported as counts and percentages and continuous variables as mean ± SD or medians and interquartile ranges (IQRs). Differences between percentages were assessed by chi-square or Fisher exact tests. Student unpaired *t* tests and analysis of variance were used for normally distributed continuous variables. Appropriate nonparametric tests (Mann-Whitney, Kruskal-Wallis, and Spearman rank correlation tests) were used for all other variables.

To better define the relationships between TxB_2, sCD40L, and sP-selectin levels and cardiovascular events, we grouped these continuous marker measurements into 4 categories, with cutoffs on the basis of quartiles of the observed measurements.

The bivariate and multivariate effects of prognostic factors and treatments on the primary and secondary endpoints were assessed by means of logistic regression models. Wald confidence intervals and tests for odds ratios and adjusted odds ratios were computed on the basis of the estimated standard errors. In addition to TxB_2, sCD40L, and sP-selectin levels, possible independent variables considered were age, sex, body mass index, PSI score, ejection fraction, history of CHD or stroke, T2DM, hypertension, renal failure, COPD, chronic or paroxysmal atrial fibrillation, dyslipidemia, PAD, high-sensitivity C-reactive protein, and use of statins and ASA.

For multivariate models, model selection was performed using forward stepwise regression on the basis of the Akaike information criterion.

Variance inflation factors were computed to assess collinearity for each predictor in the final multivariate model, with a variance inflation factor < 2.5 considered safe. The variance inflation factor criterion was satisfied in all reported models, hence there were no collinearity issues.

TxB_2, sCD40L, and sP-selectin levels evaluated at the end of hospitalization were compared with baseline levels by Wilcoxon rank sum tests.

Only p values <0.05 were regarded as statistically significant. All tests were 2-tailed, and analyses were performed using computer software packages (R version 2.15.2, R Development Core Team, Vienna, Austria).

Sample size. The minimum sample size was computed considering 1) an expected rate of MI of 5% (20–24); 2) a relevant difference in TxB_2 levels to be detected between groups of $|\delta| \geq 50$ ng/ml; 3) a SD between the groups of 35 ng/ml; and 4) type I error probability of $\alpha = 0.05$ and power of $1 - \beta = 0.90$.

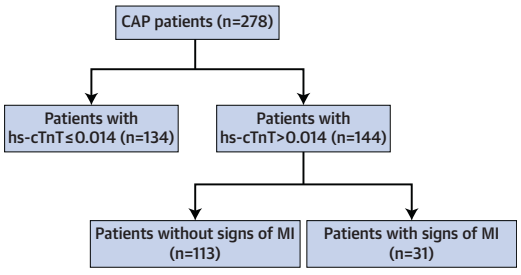


FIGURE 1 Study Flow Diagram

CAP = community-acquired pneumonia; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction.

This resulted in a sample size of 220 patients. The expected event rate and TxB_2 levels were obtained by analyzing data from previous studies (25).

TABLE 1 Patient Characteristics

Variable	CAP With hs-cTnT ≤0.014 μg/l (n = 134)	CAP With hs-cTnT >0.014 μg/l Without MI (n = 113)	CAP With hs-cTnT >0.014 μg/l and MI (n = 31)	p Value
Age, yrs	61.8 ± 16.6	77.3 ± 10.2	79.2 ± 8.9	<0.001
Men	62	65	58	0.742
BMI, kg/m^2	26.4 ± 4.1	26.6 ± 3.8	26.8 ± 3.6	0.875
Ejection fraction, %	56.4 ± 6.2	49.7 ± 10.4	43.9 ± 8.6	<0.001
Pre-existing comorbid conditions				
History of CHD	21	45	65	<0.001
Previous stroke	11	9	23	0.104
T2DM	16	31	32	0.015
Hypertension	58	79	84	0.001
Renal failure	4	33	29	<0.001
COPD	25	48	36	0.017
PAF	9	16	16	0.281
CAF	8	25	16	0.002
Peripheral artery disease	2	10	13	0.018
Dyslipidemia	17	24	29	0.231
ASA	37	52	48	0.069
Statins	32	36	37	0.776
hs-CRP, ng/ml	5.9 (2.7–12.8)	6.0 (3.3–12.7)	6.3 (3.5–11.6)	0.955
PSI score	75 ± 27	104 ± 25	120 ± 29	<0.001
Platelet count	223 (173–319)	238 (180–274)	237 (173–249)	0.767
MPV, fl	8.3 (7.5–8.8)	8.6 (7.7–9.5)	9.4 (8.2–10.4)	0.001
sCD40L, ng/ml	3 (2.2–4.0)	3.2 (2.4–6.0)	10 (9.5–13)	<0.001
sP-selectin, ng/ml	15 (11–19)	22 (16–30)	37 (28–48)	<0.001
TxB_2, ng/ml	108 (60–200)	106 (50–180)	200 (100–352)	0.004

Values are mean ± SD, %, or median (interquartile range).

ASA = acetylsalicylic acid; BMI = body mass index; CAF = chronic (persistent or permanent) atrial fibrillation; CAP = community-acquired pneumonia; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; hs-CRP = high-sensitivity C-reactive protein; hs-cTnT = high-sensitivity cardiac troponin T; MI = myocardial infarction; MPV = mean platelet volume; PAD = peripheral artery disease; PAF = paroxysmal atrial fibrillation; PSI = Pneumonia Severity Index; sCD40L = soluble CD40 ligand; sP-selectin = soluble P-selectin; T2DM = type 2 diabetes mellitus; TxB_2 = thromboxane B_2.

RESULTS

We recruited 278 patients hospitalized for CAP (173 men, 105 women; mean age 70.0 ± 15.7 years). Most of the patients had arterial hypertension (68%). Histories of CHD were present in 36% of patients, previous strokes in 12%, T2DM in 24%, COPD in 35%, PAD in 7%, and dyslipidemia in 21%. Histories of paroxysmal atrial fibrillation were present in 12% of patients, while 16% were affected by chronic (persistent or permanent) atrial fibrillation, and 18% had severe renal failure (i.e., glomerular filtration rate <30 ml/min). Among the entire population, 123 patients (47%) were treated with ASA 100 mg/day.

Elevated serum levels of hs-cTnT (>0.014 μg/l; median 0.042 μg/l; IQR: 0.024 to 0.116 μg/l) were found in 144 of the patients with CAP (52%). Of these 144 patients, 113 had isolated hs-cTnT elevations, and 31 showed signs of MI (Figure 1). MI generally occurred within 48 h of pneumonia clinical presentation. Most MIs were non-ST-segment elevation MIs (n = 26), 2 were ST-segment elevation MIs, 3 were fatal, and all but 2 had no chest pain.

Clinical characteristics of patients with CAP without hs-cTnT elevation (median 0.010; IQR: 0.007 to 0.011 μg/l), patients with hs-cTnT elevation (median 0.033; IQR: 0.023 to 0.060 μg/l) without signs of MI, and patients with troponin hs-cTnT elevation (median 0.299; 0.165 to 0.556 μg/l) and signs of MI are summarized in Table 1. Patients with hs-cTnT elevation (whether or not they developed MIs) were older and had a higher prevalence of COPD, chronic atrial fibrillation, PAD, renal failure, and T2DM than patients without hs-cTnT elevation.

Baseline plasma levels of sCD40L and sP-selectin, serum TxB_2, and MPV were significantly higher in patients who developed signs of MI. Furthermore, plasma sP-selectin levels were higher in patients with isolated hs-cTnT but without signs of MI ($p < 0.001$) (Table 1). When ASA users and nonusers were considered separately, both sCD40L and sP-selectin were significantly correlated with serum TxB_2 in ASA users (Rs = 0.440; $p < 0.001$, and Rs = 0.214; $p = 0.020$, respectively) and nonusers (Rs = 0.269; $p = 0.001$, and Rs = 0.258; $p = 0.001$, respectively).

No significant differences in platelet count were observed in patients with normal or elevated hs-cTnT. Platelet count also did not correlate with markers of platelet activation or serum TxB_2 (not shown).

To better define the magnitude of the relationship between markers of platelet activation and MI, patients with CAP were stratified into sCD40L,

sP-selectin, and TxB_2 quartiles (Figure 2). The largest number of MIs occurred in the upper quartiles of all 3 variables, corresponding to sCD40L >6.0 ng/ml, sP-selectin >26 ng/ml, and TxB_2 >200 ng/ml.

In univariate analysis, age ($p < 0.001$), PSI score ($p < 0.001$), ejection fraction ($p < 0.001$), history of CHD ($p < 0.001$), previous stroke ($p = 0.040$), hypertension ($p = 0.044$), sCD40L >6.0 ng/ml ($p < 0.001$), sP-selectin >26 ng/ml ($p < 0.001$), TxB_2 >200 ng/ml ($p = 0.003$), and MPV ($p = 0.001$) were associated with MI occurrence. By multivariate analysis, sCD40L, sP-selectin, serum TxB_2, MPV, PSI score, and ejection fraction were independently associated with MI (Table 2).

ASA AND THROMBOXANE. Among the 278 patients, 123 (45%) were treated with ASA 100 mg/day. The rate of MI was 10% in ASA-untreated patients and 12% in ASA-treated patients ($p = 0.649$). Patients with long-term ASA use showed lower serum TxB_2 levels than non-ASA-treated patients (median 61 ng/ml [IQR: 20 to 100 ng/ml] vs. 160 ng/ml [IQR: 106 to 247 ng/ml]; $p < 0.001$). Among ASA-untreated patients; serum TxB_2 levels were higher in those who experienced MIs compared with those who did not ($p = 0.001$). Similar findings were detected in ASA-treated patients; ASA-treated patients with MIs had higher serum TxB_2 values than ASA-untreated patients ($p = 0.005$) (Figure 3). Only 9 patients had serum TxB_2 <10 ng/ml, corresponding to full COX1 inhibition (26).

FOLLOW-UP OF PLATELET ACTIVATION BIOMARKERS. Analyses of plasma sCD40L and sP-selectin levels and serum TxB_2 were repeated at the end of hospitalization (within approximately 10 days of hospital admission). Compared with baseline values, all of the variables significantly decreased, independent of ASA use (Figure 4).

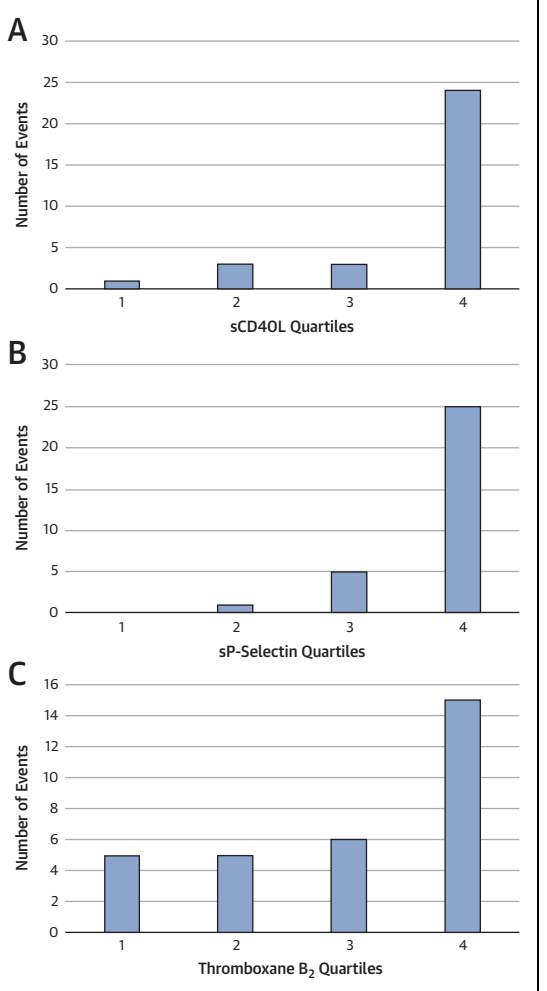


FIGURE 2 Intrahospital MI According to In Vivo Platelet Activation Markers

Number of patients with CAP with intrahospital MI stratified according to soluble CD40 ligand (sCD40L) **(A)**, soluble P-selectin (sP-selectin) **(B)**, and thromboxane B_2 **(C)** quartiles. Other abbreviations as in Figure 1.

DISCUSSION

In this study, we prospectively analyzed the incidence of MI in patients hospitalized for CAP. The novel findings of the study are as follows: 1) in the early phase of pneumonia (within 48 h of presentation), patients showed elevated hs-cTnT, which may be either isolated or MI associated; 2) MI was not associated with chest pain in the majority of cases; 3) the severity of pneumonia, as assessed by PSI score and ejection fraction, was independently associated with MI; 4) in vivo platelet activation and overproduction of serum TxB_2 formation were independently associated with MI; and 5) ASA 100 mg/day seemed insufficient for preventing serum TxB_2 overproduction.

Previous studies showed that pneumonia is complicated by elevated hs-cTnT values, indicating an association between infectious disease and myocardial injury. Notably, Chang et al. (5) recently reported that 19% of patients with pneumonia have elevated hs-cTnT values at admission. We found that elevated hs-cTnT was even more prevalent in our population; hs-cTnT was elevated in >50%. This difference may be because we measured hs-cTnT levels not only at baseline but also every 12 h during the first days of hospitalization. Increased hs-cTnT was detectable up to 48 h from hospital admission,

TABLE 2 Adjusted ORs for MI According to Selected Variables on the Basis of Logistic Regression Analysis

Variable	OR	95% CI Lower	95% CI Upper	p Value	VIF*
sCD40L >6.0 ng/ml	1.234	1.147	1.327	<0.001	1.129
sP-selectin >26 ng/ml	1.233	1.142	1.330	<0.001	1.217
TxB_2 >200 ng/ml	1.084	1.008	1.166	0.030	1.035
MPV	1.025	1.002	1.048	0.037	1.056
Ejection fraction	0.994	0.991	0.998	0.001	1.150
PSI score	1.001	1.001	1.002	0.030	1.254

After adjusting for age, sex, BMI, history of CHD, previous stroke, T2DM, hypertension, renal failure, COPD, CAF, PAF, PAD, dyslipidemia, platelet count, hs-CRP, use of statins, and ASA. *Given that all VIFs are well below the cutoff, the parameters can be directly interpreted, and there are no collinearity issues.

CI = confidence interval; OR = odds ratio; VIF = variance inflation factor; other abbreviations as in Table 1.

indicating that myocardial damage should be investigated in the early phase of hospitalization.

Among patients with elevated hs-cTnT, 31 were diagnosed as affected by MI, yielding an 11% intrahospital incidence of MI. Although previous studies showed that pneumonia may be complicated by MI (2), those were mostly retrospective studies, and the rate of MI ranged from as low as 0.8% to as high as 10.7% (21-24). In the only prospective study reported thus far, Corrales-Medina et al. (4) found a 3.6% rate during a follow-up period of 7 days. In the present study, we found a higher MI rate, likely because we measured hs-cTnT, a more sensitive marker of myocardial necrosis, and because we monitored hs-cTnT values daily, along with electrocardiography. Moreover, our hospitalized patients were older, had a higher prevalence of comorbidities, and had higher PSI scores.

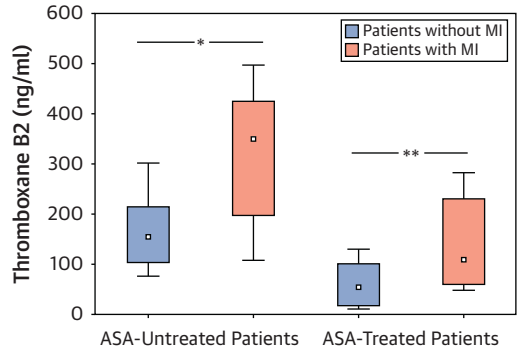


FIGURE 3 Thromboxane B_2 Levels in ASA-Untreated and ASA-Treated Patients Who Did or Did Not Experience MIs

*p = 0.001; **p = 0.005. ASA = acetylsalicylic acid; MI = myocardial infarction.

MI usually occurred within 48 h of clinical presentation, consistent with the study by Corrales-Medina et al. (2), who found that more than 50% of cardiovascular complications occurred within 24 h of presentation. The peculiarity of our methodological approach turned out to be particularly useful, because almost all patients with pneumonia had silent MIs; without daily monitoring of cardiac troponins and electrocardiography, it would not be possible to fully appreciate the occurrence of MI. Among the clinical variables analyzed, age, PSI score, ejection fraction, history of CHD, previous stroke, and hypertension were associated with MI. However, in multivariate analysis, only PSI and ejection fraction were independently associated with MI. Of note, patients with a mean PSI score of 120 were at higher risk for MI. Our observation of an association between MI and history of CHD in 65% of patients who experienced MI is also interesting and suggests that patients with underlying CHD are more susceptible to MI after pneumonia.

Few studies have analyzed platelet behavior in pneumonia. Patients with MI complicated by pneumonia displayed platelet hyperaggregation and nonresponse to ASA more than patients with MI without pneumonia, suggesting that lung infection could trigger platelet activation (27,28). Additionally, Kreutz et al. (29) found higher platelet aggregation in patients affected by viral upper respiratory tract infections compared with controls. The interplay between platelet activation and MI in a population affected by pneumonia had never been examined. We report for the first time that in vivo platelet activation, as assessed by plasma levels of sCD40L and sP-selectin, was independently associated with MI. TxB_2 overproduction accompanied in vivo platelet activation, which was also independently associated with MI. Even if this suggests a role for COX1 activation in enhancing platelet activation, platelet TxB_2 overproduction is unlikely to be the only mechanism for platelet activation, as serum TxB_2 was only weakly correlated with sCD40L and sP-selectin.

Previous studies demonstrated that an increased platelet count was more predictive of clinical outcomes in patients with CAP than leukocyte count abnormalities (30). However, we did not observe any differences in platelet count between patients with or without MIs; conversely, MPV was both significantly higher in patients with MIs and an independent predictor, consistent with previous studies showing that MPV is independently associated with MI (31).

Bacteria may activate platelets; thus, the association between pneumonia and in vivo platelet

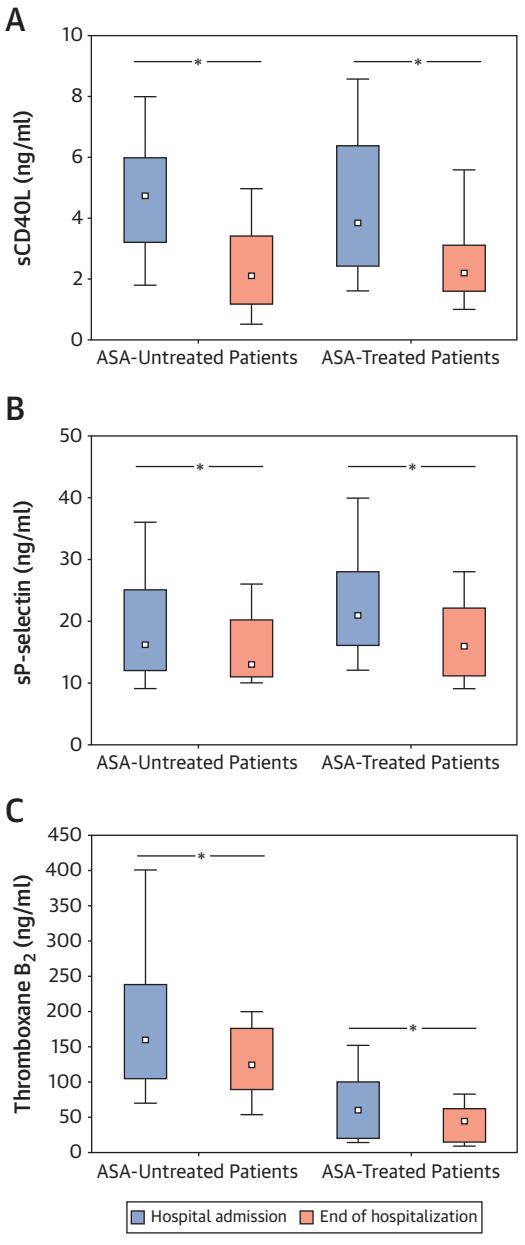
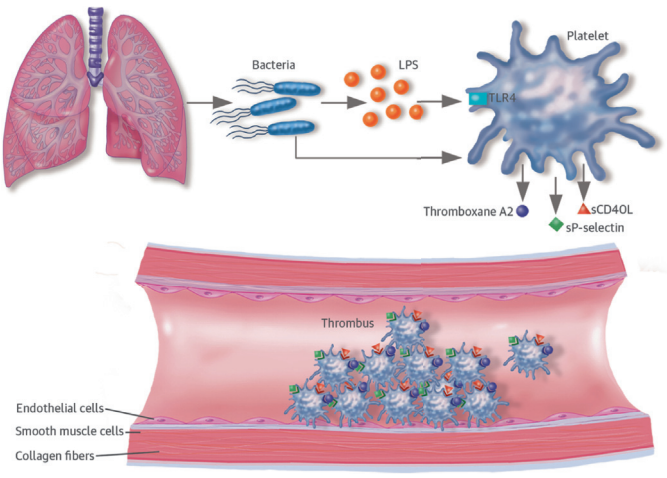


FIGURE 4 In Vivo Platelet Activation Markers at Hospital Admission and at the End of Hospitalization

Plasma levels of soluble CD40 ligand (sCD40L) **(A)**, soluble P-selectin (sP-selectin) **(B)**, and serum thromboxane B_2 **(C)** at hospital admission and at the end of hospitalization in acetylsalicylic acid (ASA)–untreated and ASA-treated patients. *p <0.001.



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CENTRAL ILLUSTRATION Potential Mechanisms for Platelet Activation During Pneumonia

Platelets can interact directly with bacteria or with lipopolysaccharide (LPS) (an endotoxin) on the surface of Gram-negative bacteria by a Toll-like receptor 4 (TLR4)-mediated mechanism; this results in platelet activation and aggregation and, eventually, thrombus formation. sCD40L = soluble CD40 ligand; sP-selectin = soluble P-selectin.

activation is biologically plausible. In particular, bacteria-platelet interaction may occur via bacteria binding to platelets, either directly, through a bacterial surface protein, or indirectly by a plasma-bridging molecule linking bacterial and platelet surface receptors (28). However, whether either a specific agent or the infection burden is implicated in platelet activation and, eventually, coronary thrombosis remains to be explored (28). In this context, the role of endotoxins should be examined, as there is evidence to support a role for endotoxins as platelet stimulators via Toll-like receptor 4 (32,33) (**Central Illustration**). An intriguing finding of the present study was that although patients on ASA treatment showed lower serum TxB_2 compared with nonusers, serum TxB_2 in ASA-treated patients was persistently elevated, suggesting that low-dose ASA was insufficient to fully inhibit COX1. Accordingly, many patients on ASA had values of serum TxB_2 >10 ng/ml, while optimal long-term ASA treatment is usually associated with serum TxB_2 <10 ng/ml (26). Furthermore, ASA-treated patients who experienced MIs had significantly higher serum TxB_2 than ASA-treated patients who did not experience MIs.

Among the whole study population, 113 patients (41%) displayed elevated hs-cTnT not associated with electrocardiographic changes, which were considered isolated hs-cTnT elevation. Isolated elevation of hs-cTnT can be detected in several clinical settings not associated with MI, including infections and sepsis, and is usually considered a specific marker of

myocardial injury (34). Even if elevated hs-cTnT is a marker of poor prognosis (35), its use for diagnosis and management in settings unrelated to acute coronary syndrome is still evolving (34). Of note, with the exception of a weak correlation with sP-selectin, neither sCD40L nor serum TxB_2 was correlated with isolated hs-cTnT.

STUDY LIMITATIONS. The study had limitations and implications. Because CAP affected our population, the data cannot be extrapolated to other types of pneumonia. The mechanism accounting for platelet activation is not fully clarified by the present study; however, the correlation between serum TxB_2 and the 2 markers of platelet activation suggests that platelet TxB_2 overproduction might play a role. We also did not investigate if pneumonia was of bacterial or viral origin or if specific pathogens or systemic inflammation were responsible for platelet activation and platelet TxB_2 overproduction. However, acute infection per se is likely to be implicated, as in vivo platelet activation and serum TxB2 significantly decreased at hospital discharge, independent of ASA use. Finally, we have no explanation for MI being silent in patients with pneumonia, and further study should be done to clarify this phenomenon. We cannot exclude that an imbalance between myocardial oxygen supply and demand was the primary cause of MI in many of our critically ill patients (i.e., MI type 2 according to the universal definition [18]). Therefore, further study in an even larger population is needed to better appreciate the rate of MI in this setting.

An important implication of this study is that in patients with severe pneumonia, such as those with PSI scores of approximately 120, corresponding to classes IV and V (14), or prior CHD, daily monitoring of cardiac troponins and electrocardiography is necessary to detect MI, as MI was rarely associated with chest pain. Such monitoring should be done immediately after pneumonia diagnosis, as MI generally occurred within 48 h of presentation. Another important issue raised by this study is the inefficacy of ASA 100 mg/day in completely preventing serum TxB_2 formation in patients with pneumonia, suggesting that this dosage does not fully inhibit COX-1. In other clinical settings, it is becoming evident that because of accelerated platelet turnover, a dose of 100 mg ASA twice daily is more effective than ASA 100 mg/day to fully prevent platelet TxB_2 (36). We cannot exclude that a similar phenomenon may also occur in pneumonia and that another ASA regimen should therefore be adopted in this clinical setting. However, we cannot exclude that the persistent platelet TxB_2 elevation, despite ASA treatment, observed at baseline, may result from lowered ASA bioavailability or poor compliance (37).

CONCLUSIONS

We provide evidence that >50% of patients with pneumonia had hs-cTnT elevation, which was isolated or associated with MI in about 11% of cases. Because MI was silent in the majority of cases, daily monitoring of troponins and electrocardiography is needed for detection. Platelet activation was significantly associated with MI, suggesting a role for platelets in triggering coronary thrombosis. Daily 100-mg doses of ASA were unable to prevent platelet TxB_2 formation. Future studies should be done to identify a more appropriate ASA dose to fully block COX1, thus preventing serum TxB_2 overproduction in patients with pneumonia.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Elderly patients are at risk for developing myocardial ischemia and infarction early in the course of CAP. Elevated platelet activation markers and thromboxane A_2 generation in these patients suggest that platelets play a role in the pathogenesis of these cardiac events.

TRANSLATIONAL OUTLOOK: Future studies should address the safety and efficacy of administering ASA or other antiplatelet drugs to patients presenting with acute CAP.

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