Impact of Obstructive Sleep Apnea on Platelet Function Profiles in Patients With Acute Coronary Syndrome Taking Dual Antiplatelet Therapy

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Background—Obstructive sleep apnea (OSA) is a novel risk factor for acute coronary syndrome (ACS). Several studies have shown OSA to be associated with induced platelet reactivity. However, whether OSA have effects on platelet function profiles in ACS patients taking dual antiplatelet therapy remains unexplored.

Methods and Results—This was a cross-sectional observational study, in which ACS patients taking maintenance aspirin and clopidogrel therapy were included. OSA was defined as an apnea-hypopnea index ≥15 events/hour. The inhibitory rate of arachidonic acid or adenosine diphosphate pathway were assessed with thrombelastography and defined patients with high residual on-treatment platelet reactivity. Platelet indices were obtained from routine analysis of blood samples using an automated blood cell counter. A total of 127 ACS patients taking dual antiplatelet therapy were analyzed. Platelet volume indices, including mean platelet volume and platelet large cell ratio, were significantly increased in patients with OSA. Patients with OSA (n=68) had significantly lower inhibitory rate of adenosine diphosphate receptor pathway (P=0.028) compared with those without (n=59). After adjustment for potential confounders, patients with OSA were more likely to have high residual on-treatment platelet reactivity after clopidogrel therapy (adjusted odds ratio: 3.25, 95% confidence interval: 1.19–8.87, P=0.021).

Conclusions—In ACS patients taking dual antiplatelet therapy, OSA is associated with an increased level of platelet volume indices, reduced clopidogrel-induced antiplatelet effects and a greater prevalence of high residual on-treatment platelet reactivity. (J Am Heart Assoc. 2018;7:e008808. DOI: 10.1161/JAHA.118.008808.)

Key Words: acute coronary syndrome • dual antiplatelet therapy • obstructive sleep apnea

Obstructive sleep apnea (OSA) is characterized by repetitive upper airway obstruction during sleep, and is usually associated with a wide range of cardiovascular, metabolic, and neurocognitive disorders and may lead to increased morbidity and mortality.1,2 A prevalence of OSA up to 66% has been reported in the early phase of acute coronary syndrome (ACS).3 And about 50% of patients with percutaneous coronary intervention (PCI) suffer from OSA.4,5 Importantly, patients with OSA experience an increased risk of adverse outcomes after PCI.4,5 Recent findings from meta-analysis suggested that OSA appears to increase the risk of cardiac death, non-fatal myocardial infarction (MI), and coronary revascularization in patients after PCI.4 Outcomes in ACS patients with moderate/severe OSA have shown to be worse compared with normal or mild OSA patients.6

In fact, OSA can impact the platelet function.7,8 Gunbey et al have found that platelet aggregation was correlated with apnea-hypopnea index (AHI).9 The platelet distribution width (PDW) and mean platelet volume (MPV) of OSA patients were significantly increased.9 Rahangdale et al have reported that adenosine 5'-diphosphate (ADP)-induced platelet aggregation was markedly increased in OSA patients.7 In addition, platelet reactivity and MPV levels decreased significantly after continuous positive airway pressure (CPAP) therapy in
Clinical Perspective

What Is New?

- In acute coronary syndrome (ACS) patients taking maintenance aspirin and clopidogrel therapy, obstructive sleep apnea (OSA) is associated with increased level of platelet volume indices, reduced clopidogrel-induced antiplatelet effects and a greater prevalence of high residual on-treatment platelet reactivity.
- These findings may explain the elevated prevalence of ischemic complications among ACS patients with OSA.

What Are the Clinical Implications?

- This results suggest that OSA affects platelet function and pharmacodynamic profiles of antiplatelet drugs in ACS patients.
- These findings may explain why some ACS patients with OSA have worse clinical prognosis than others and suggest the potential need for further categorizing this already high-risk cohort of patients into those with and without OSA.
- This study enables a better understanding of individual risk profiles of patients with ACS and OSA, and suggests future development of targeted treatment strategies may be beneficial for these patients.

patients with OSA. Dual antiplatelet therapy (DAPT), consisting of the combination of aspirin and an oral inhibitor of the platelet P2Y12 receptor for ADP, is the cornerstone of drug therapy for post-PCI or ACS patients. However, it remains unclear whether OSA affects platelet function and pharmacodynamic profiles of antiplatelet drugs in patients taking DAPT.

The aim of the present study was to assess the impact of OSA on platelet function profiles in ACS patients taking DAPT.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Study Design and Subjects

This cross-sectional observational study is an ancillary study of the OSA-ACS Project (a prospective cohort study of NCT03362385 [Impact of Obstructive Sleep Apnea and Continuous Positive Airway Pressure Therapy on Outcomes in Patients with Acute Coronary Syndrome: The OSA-ACS Project]). The aim of that large-scale, prospective cohort study was to delineate the whole picture of the association of OSA with short- and long-term outcomes of patients with ACS and the effect of CPAP treatment on the incidence of new cardiovascular events. In this study, we evaluated patients consecutively admitted to Beijing Anzhen Hospital (Beijing, China) with a diagnosis of ACS from June 2015 to May 2017. ACS was defined according to ACS related guidelines. Patients were eligible for platelet function analyses if they were in their maintenance steady-state phase (at least 7 days) of DAPT with aspirin (100 mg/day) and clopidogrel (75 mg/day). After patients agreed to participate and the consent form was signed, all patients underwent an overnight sleep study to assess the presence of OSA.

Exclusion criteria included: patients aged >75 or <18 years; any previously diagnosed sleep disorder; known OSA on CPAP treatment; known allergies to aspirin or clopidogrel; dialysis; blood dyscrasia; active bleeding or bleeding diathesis; gastrointestinal bleed within last 6 months; hemodynamic instability; acute cerebrovascular event within 3 months; any malignancy; concomitant use of other antithrombotic drugs (oral anticoagulants, dipyridamole, cilostazol) or non-steroid anti-inflammatory drugs; life-limiting chronic disease; serious hepatorenal functional impairment; and hematocrit <25%; platelet count <100 (1000/mm³). The study complied with the Declaration of Helsinki, and was approved by the ethics committee of Beijing Anzhen Hospital.

All patients gave their informed written consent.

Overnight Sleep Study

All patients underwent an overnight sleep study after clinically stabilization during hospitalization, using a portable cardiorespiratory monitoring device (The ApneaLink, Resmed, Australia). Nasal airflow, arterial oxygen saturation, thoraco-abdominal movements, and snoring episodes were recorded. An obstructive apnea episode was defined by a complete cessation of airflow lasting ≥10 seconds. An episode of hypopnea was defined as a reduction in airflow lasting ≥10 seconds and is associated with oxygen desaturation. Oxygen desaturation is considered as a decrease in SaO₂ >4%. AHI was defined as the number of apneas and hypopneas per hour of sleep. All studies will be manually analyzed by an independent sleep technologist who is not aware of the patients’ clinical characteristics. To ensure the accuracy and consistency of analyzing, 50% of all studies will be audited by a masked investigator with expertise in sleep medical. Recruited patients were classified into OSA (AHI ≥15 events/hour) and non-OSA (AHI <15 events/hour) groups.5,13

Clinical Data Extraction

The following baseline demographic medical history and a detailed medication history were collected from the medical records of the recruited patients.
### The Thrombelastography Platelet Mapping Assay

Thrombelastography Platelet Mapping assay used 4 channels to detect effects of antiplatelet therapy with arachidonic acid and ADP activators. A detailed description of this method is outlined previously. Percentage platelet inhibition is defined by the extent of non-response of the platelet ADP (P2Y12) or thromboxane A2 receptor to the exogenous ADP and arachidonic acid as measured by maximum amplitude (MA). The percentage platelet aggregation to agonist can be calculated by: \( \frac{(MA_{ADP}/AA - MA_{Fibrin})}{(MA_{thrombin} - MA_{Fibrin}) \times 100} \). Percentage platelet inhibition is thus 100%—the percentage platelet aggregation (%). This calculation is performed by the Thrombelastography Platelet Mapping software. Similarly, the percentage inhibition resulting from the antiplatelets clopidogrel and aspirin can be calculated.

### Statistical Analysis

Continuous variables are expressed as the mean±SD or median (interquartile range) for data with a skewed distribution. Patients characteristics were compared using Student t test, analysis of variance, or the non-parametric Mann–Whitney test for skewed data. Categorical variables are presented as counts and percentages and were compared by means of the chi-square test or Fisher exact test. Spearman correlation analysis was performed for determination of correlation. A multivariable linear regression model was used to evaluate the independent contribution of the OSA and non-OSA groups to the inhibitory rate of ADP pathway. Control for potential confounders and analysis of independent correlates of high residual on-treatment platelet reactivity (HRPR) were performed with a logistic regression model including age, sex, body mass index, diabetes mellitus, hypertension, prior PCI, and estimated glomerular filtration rate (eGFR) as independent control variables and OSA as the independent study variable of interest. Odds ratio (OR) and 95% confidence interval (CI) were calculated. All tests were 2-sided, and a value of \( P<0.05 \) was considered statistically significant. Statistical analysis was performed with IBM SPSS Statistics, Version 22.0 (IBM Corp., Armonk, NY, USA).

### Results

#### Patient Population

A total of 127 ACS patients were studied. Baseline demographic data, clinical characteristics, and laboratory data of patients with (n=68) and without (n=59) OSA were described in Table 1. Of the participants, 88.2% were men; the mean age was 55.23±9.93 years. There were no differences in terms of age, sex, or prevalence of cardiovascular risk factors (hypertension, diabetes mellitus, dyslipidemia, prior MI and smoking) among all groups. Patients with OSA have higher body mass index (Table 1). Sleep information was shown in Table 2. AHI, oxygen desaturation index, minimum, and average oxygen saturation, and time of \( SaO_2 <90\% \) were significantly different between groups (\( P<0.001 \)).

### The Impact of OSA on Platelet Volume Indices in ACS Patients Taking DAPT

Platelet volume indices are indicator of platelet activation and play an important role in the pathophysiology of cardiovascular diseases. In the study, we found that patients with OSA have higher MPV and platelet large cell ratio values (Figure 1A and 1B). And PDW (%) in OSA group also tended to be higher than that in the non-OSA group (13.1±2.3 versus 12.4±1.9, \( P=0.07 \)), although this was not statistically significant (Figure 1C).

Additionally, correlation of MPV with parameters of sleep was noted. MPV weakly correlated with AHI (\( r=0.204, P=0.022 \)), oxygen desaturation index (\( r=0.216, P=0.023 \)), and minimum \( SaO2 \) (%) (\( r=-0.180, P=0.044 \) (Figure 2). These results suggested that OSA patients have higher MPV and platelet large cell ratio values and tend to have relatively increased platelet activation and atherothrombotic risk.

### The Impact of OSA on Pharmacodynamic Profiles of Antiplatelet Drugs

No significant difference in inhibitory rate of arachidonic acid pathway was observed between patients with OSA and those without (Figure 3A). Significant lower inhibitory rate of ADP pathway in patients with OSA compared with those without (Figure 3B). Additionally, correlation of the inhibitory rate of ADP pathway with parameters of sleep was analyzed by Spearman correlation analysis. The inhibitory rate of ADP pathway weakly correlated with mean \( SaO_2 \) (%) (\( r=0.188, P=0.034 \)) and total percentage of time \( SaO_2 <90\% \) (\( r=-0.198, P=0.038 \) (Figure 4).

Previous studies have demonstrated that suboptimal response to antiplatelet agents was affected by many factors. Simple linear regression analysis showed that the inhibitory rate of ADP pathway may be associated with age, sex, OSA, hypertension, eGFR, platelet counts and \( \beta \)-blockers (\( P<0.1 \) (Table S1)). To further examine the relationship OSA and the inhibitory rate of ADP pathway, we used a multivariable linear regression model to evaluate the independent contribution of the OSA and non-OSA groups to the inhibitory rate of ADP pathway after adjusting for age, sex, hypertension, eGFR,
platelet counts and β-blockers. These results showed that the presence or not of OSA significantly contributed to the inhibitory rate of ADP pathway ($\beta: -1.057, 95\% \text{ CI}: -19.68$ to $-1.45, P=0.023$) (Table 3), suggesting that OSA is associated with reduced clopidogrel-induced antiplatelet effects.

**OSA and HRPR**

In the overall study population, inhibitory rates of ADP pathway quartile cut points for the 25th, 50th, and 75th percentiles of the study population were 26.8%, 47.8%, and 66.9%, respectively. The lower quartile identified patients with

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**Table 1. Patients Characteristics**

| Variables             | All (n=127) | OSA Group (n=68) | Non-OSA Group (n=59) | P Value |
|-----------------------|-------------|------------------|----------------------|---------|
| Age, y                | 55.2±9.9    | 55.9±10.5        | 54.5±9.2             | 0.42    |
| Male                  | 112 (88.2)  | 62 (91.2)        | 50 (84.7)            | 0.29    |
| Diabetes mellitus     | 37 (29.1)   | 19 (27.9)        | 18 (30.5)            | 0.85    |
| BMI, kg/m²            | 26.6 [24.6, 28.7] | 27.7 [25.3, 29.3] | 25.9 [24.2, 27.7]    | 0.02    |
| Smoking               | 76 (59.8)   | 36 (52.9)        | 40 (67.8)            | 0.10    |
| Alcohol               | 53 (41.7)   | 33 (48.5)        | 20 (33.9)            | 0.10    |
| Medical history       |             |                  |                      |         |
| Hypertension          | 76 (59.8)   | 44 (64.7)        | 32 (54.2)            | 0.28    |
| Dyslipidemia          | 30 (23.6)   | 17 (25.0)        | 13 (22.0)            | 0.83    |
| Prior MI              | 16 (12.6)   | 6 (8.5)          | 10 (16.2)            | 0.28    |
| Prior PCI             | 20 (15.7)   | 14 (20.6)        | 6 (10.2)             | 0.14    |
| Prior CABG            | 2 (1.6)     | 1 (1.5)          | 1 (1.7)              | 1.00    |
| Prior stroke          | 11 (8.7)    | 8 (11.8)         | 3 (5.1)              | 0.22    |
| ACS category          |             |                  |                      |         |
| UA                    | 45 (35.4)   | 26 (38.3)        | 19 (32.2)            | 0.60    |
| NSTEMI                | 33 (26.0)   | 13 (19.1)        | 20 (33.9)            | 0.09    |
| STEMI                 | 49 (38.6)   | 29 (42.6)        | 20 (33.9)            | 0.41    |
| PCI                   | 100 (78.7)  | 55 (80.9)        | 45 (76.3)            | 0.66    |
| Medication            |             |                  |                      |         |
| PPIs                  | 107 (84.3)  | 56 (82.4)        | 51 (86.4)            | 0.63    |
| ACEI                  | 78 (61.4)   | 43 (63.2)        | 35 (59.3)            | 0.72    |
| ARB                   | 21 (16.5)   | 12 (17.6)        | 9 (15.3)             | 0.81    |
| Diuretics             | 5 (3.9)     | 3 (4.4)          | 2 (3.4)              | 1.00    |
| Statin                | 127 (100.0) | 68 (100.0)       | 59 (100)             | -       |
| β-blockers            | 111 (87.4)  | 58 (85.3)        | 53 (89.8)            | 0.59    |
| Calcium antagonists   | 17 (13.4)   | 11 (16.2)        | 6 (10.2)             | 0.44    |
| Laboratory data       |             |                  |                      |         |
| Platelet count, 1000/mm³ | 211.5 [179.8, 248.3] | 207.0 [172.0, 249.0] | 213.0 [185.0, 248.0] | 0.42    |
| Plateletcrit (%)      | 0.20 [0.18, 0.24] | 0.20 [0.18, 0.25] | 0.21 [0.18, 0.24]    | 0.88    |
| Hematocrit, %         | 41.94±3.63  | 41.82±3.43       | 42.08±3.88           | 0.68    |
| WBC, 1000/mm³         | 8.56±2.77   | 8.87±2.76        | 8.20±2.76            | 0.17    |
| HbA1c, %              | 6.58±1.37   | 6.55±1.29        | 6.60±1.46            | 0.85    |
| Creatinine, μmol/L    | 75.0 [88.0, 85.0] | 76.5 [71.0, 86.5] | 74.0 [66.0 83.0]     | 0.08    |
| eGFR, ml/min per 1.73 m² | 97.7 [83.8, 109.0] | 94.5 [83.0, 106.5] | 102.0 [85.4, 114.3]  | 0.14    |

Data given as n (%), mean±SD or median [IQR]. P value is moderate/severe OSA vs without or with mild OSA. ACEI indicates angiotensin-converting enzyme inhibitors; ACS, acute coronary syndrome; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; HbA1c, hemoglobin A1c; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PPIs, proton pump inhibitors; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; WBC, white blood cell counts.

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HRPR.\(^2\) As Figure 5 showed, patients with OSA were more likely to have HRPR than those non-OSA (33.8% versus 13.6%, \(P=0.012\)).

To further investigate the impact of OSA on HRPR, we classified the included patients into 2 groups (non-HRPR and HRPR) according to the inhibitory rates of ADP pathway. The characteristics and demographic variables of the patient groups are shown in Table S2. Logistic regression analysis showed that OSA significantly associated with HRPR (OR: 3.26, 95% CI: 1.33–8.01, \(P=0.010\)). After adjustment for potential confounders (age, sex, body mass index, diabetes mellitus, hypertension, prior PCI, and eGFR), OSA remained markedly associated with HRPR (adjusted OR: 3.25, 95% CI: 1.19–8.87, \(P=0.021\)).

### Discussion

The present study showed that in ACS receiving maintenance aspirin and clopidogrel therapy, the presence of OSA is associated with higher levels of MPV and L-PCR compared with patients with non-OSA. In particular, these patients with OSA also have higher degrees of platelet reactivity after clopidogrel therapy. Additionally, after adjustment for potential confounders, patients with OSA had a 3.25-fold increase in the likelihood of showing HRPR after clopidogrel therapy. Overall, these findings are indicative not only of the presence of a hyper-reactive platelet phenotype but also of dysfunctional ADP signaling mediated P2\(\text{Y}_{12}\) receptor. Therefore, these observations might explain the elevated prevalence of ischemic complications, including stent thrombosis, among CAD patients with OSA.

OSA is now considered a novel cardiovascular risk factor, according to the “European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (2012)”.\(^{21}\) Up to 66% of ACS patients have OSA and about 50% of patients with PCI suffer from OSA.\(^{3–5}\) Meta-analysis demonstrated that cardiac death is 2-fold higher in patients with OSA after successful PCI.\(^4\) The OSA patients also have more aggressive atherosclerotic disease and a greater risk of thrombotic complications, including stent thrombosis.\(^{22}\) The Sleep and Stent Study enrolled 1311 patients successfully treated with PCI, and >98% of these patients were treated with DAPT. The result of the study showed that OSA is independently associated with subsequent major adverse cardiac and cerebrovascular events, claiming the need for additional studies to evaluate therapeutic approaches to mitigate OSA-associated risk.\(^5\)

Interestingly, some clinical studies showed that severe OSA significantly increases the level of MPV and platelet reactivity, and CPAP therapy significantly reversed this effect.\(^7,9\) Rahangdale et al have previously reported in a small cohort ADP-induced platelet aggregation was markedly increased in OSA patients.\(^7\) However, it remains unclear whether OSA affects the clinical outcomes of CAD patients taking DAPT by influencing platelet function and antiplatelet agent efficacy.

Table 2. Sleep Information

| Variables                      | All (n=127) | OSA Group (n=68) | Non-OSA Group (n=59) | \(P\) Value |
|-------------------------------|------------|----------------|-----------------|-----------|
| AHI, events/h                 | 16.0 [8.0, 34.0] | 32.8 [24.0, 52.0] | 8.0 [4.0, 10.9] | <0.001    |
| ODI, events/h                 | 16.0 [7.0, 36.0] | 36.0 [22.5, 51.0] | 7.0 [4.0, 11.0] | <0.001    |
| Minimum Sa\(\text{O}_2\) (%)  | 85.0 [80.0, 88.0] | 83.0 [76.0, 86.0] | 88.0 [85.0, 89.0] | <0.001    |
| Mean Sa\(\text{O}_2\) (%)     | 94.0 [93.0, 95.0] | 93.0 [92.0, 94.0] | 95.0 [94.0, 96.0] | <0.001    |
| Total percentage of time of Sa\(\text{O}_2\) <90% | 1.0 [0.0, 8.0] | 6.0 [1.0, 17.5] | 0.0 [0.0, 1.0] | <0.001    |

Data given as median [IQR]. AHI indicates apnea-hypopnea index; IQR, Interquartile range; ODI, oxygen desaturation index; OSA, obstructive sleep apnea.

In patients with
ACS or undergoing PCI, HRPR is associated with ≈2- to 3-fold greater risk of recurrent ischemic events and about 1.5-fold greater risk of all-cause mortality.\textsuperscript{27–29} In particular, this study shows a broad variability platelet function profiles in patients receiving clopidogrel, and OSA is associated with reduced clopidogrel-induced antiplatelet effects and a greater likelihood of having HRPR. Our study findings might contribute to explain why some OSA patients have worse clinical prognosis than others and suggest the potential need for further categorizing this already high-risk cohort of patients into those with and without OSA. This might enable a better understanding of their individual risk profile and allow the future development of targeted treatment strategies for these patients.

The persistence of high-platelet reactivity despite adjunctive clopidogrel therapy underscores the need for more potent platelet inhibition strategies to reduce the risk of recurrence of ischemic events, including high dose of clopidogrel and

**Figure 1.** The impact of OSA on platelet volume indices in ACS patients taking DAPT. The level of MPV (A), P-LCR (B) and PDW (C) in patients with and without OSA. ACS indicates acute coronary syndrome; DAPT, dual antiplatelet therapy; MPV, mean platelet volume; OSA, obstructive sleep apnea; PDW, platelet distribution width; P-LCR, platelet large cell ratio.

**Figure 2.** Correlation between MPV and parameters of sleep. Correlation between MPV and AHI (A), ODI (B), and minimum SaO\textsubscript{2} (%) (C), mean SaO\textsubscript{2} (%) (D), and total percentage of time of SaO\textsubscript{2}<90% (E). AHI indicates apnea-hypopnea index; MPV, mean platelet volume; ODI, oxygen desaturation index.
new antiplatelet agents. The new P2Y₁₂ inhibitors (prasugrel and ticagrelor) have a more predictable response, greater potency and faster onset of characteristics, thus making them the treatment of choice in patients receiving clopidogrel therapy with HRPR. Nowadays, new oral P2Y₁₂ inhibitors have evidentially been recommended for the treatment of ACS, as

**Figure 3.** The impact of OSA on the inhibitory rate of arachidonic acid or ADP pathway. (A) No significant differences in inhibitory rate of arachidonic acid pathway was observed between patients with OSA and those without; (B) Patients with OSA had significantly lower inhibitory rate of ADP pathway compared with those without. The central box represents the values between the lower and upper quartiles, and the middle line is the median. AA indicates arachidonic acid; ADP, adenosine diphosphate; OSA, obstructive sleep apnea.

**Figure 4.** Correlation between inhibitory rate of ADP pathway and parameters of sleep. Correlation between inhibitory rate of ADP pathway and AHI (A), ODI (B), and minimum SaO₂ (%) (C), mean SaO₂ (%) (D), and total percentage of time of SaO₂<90% (E). ADP indicates adenosine diphosphate; AHI, apnea-hypopnea index; ODI, oxygen desaturation index.

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Table 3. Multivariable Linear Regression Analysis of the Inhibitory Rate of ADP Receptor Pathway (Presence or Not of OSA)

| Variables     | β (95% CI)   | P Value |
|---------------|-------------|---------|
| Age, y        | −0.03 (−0.58, 0.53) | 0.930   |
| Male          | 9.56 (5.36, 24.48)  | 0.207   |
| Group         |             |         |
| Non-OSA       | Reference   |         |
| OSA           | −10.57 (−19.68, −1.45) | 0.023   |
| Hypertension  | 5.09 (−4.02, 14.20)  | 0.271   |
| eGFR, mL/min per 1.73 m² | 0.24 (0.02, 0.47) | 0.035   |
| Platelet counts, 1000/mm³ | 0.08 (0.00, 0.16) | 0.043   |
| β-blockers    | −13.918 (−27.72, −0.12) | 0.048   |

ADP indicates adenosine diphosphate; CI, Confidence interval; eGFR, estimated glomerular filtration rate; OSA, obstructive sleep apnea.

they show a reduction in cardiovascular events compared with clopidogrel.11,12 However, it may be argued that high-platelet reactivity alone cannot be used as a good indicator for using more potent platelet inhibition, because if OSA also exists, then reducing the potential benefits of ischemic events may be offset by the bleeding rate. In fact, OSA is well-established to be associated with increased bleeding risk.30–32 Indeed, evaluating outcome data in OSA patients will provide more insights on the risk-benefit ratio of antithrombotic strategies, particularly with the introduction of novel and more potent agents.

Several limitations of this study should be noted. First, this is a cross-sectional observational study of independent groups and suffers from the apparent limitations of a non-randomized trial. In an attempt to account for these limitations, we also made comparisons that were adjusted for several clinical variables. Because of the large number of variables introduced, we cannot rule out a potential of overfitting models. Second, in the present study, we assessed the impact of OSA on pharmacodynamic profiles of antiplatelet drugs according to thrombelastography. No data (eg, glycoprotein IIb/IIIa activation and P-selectin expression) were available to evaluate platelet activation. Third, this study excluded elderly patients (aged ≥75 years), which could have included patients who exhibited the most severe OSA.

Conclusion

To the best of our knowledge, this is the first study providing a potential underlying mechanism to explain why OSA patients with CAD have worse outcomes. In ACS patients taking maintenance aspirin and clopidogrel therapy, OSA is associated with an increased level of platelet-volume indices, reduced clopidogrel-induced antiplatelet effects, and a greater prevalence of HRPR.

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Disclosures

None.

References

1. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep apnea and cardiovascular disease: lessons from recent trials and need for team science. Circulation. 2017;136:1840–1850.
2. Javaheri S, Barbe F, Campos-Rodriguez F, Dempsey JA, Khayat R, Javaheri S, Malhotra A, Martinez-Garcia MA, Mehrara M, Pack AI, Polotsky VY, Redline S, Somers VK. Sleep apnea: types, mechanisms, and clinical cardiovascular consequences. J Am Coll Cardiol. 2017;69:841–858.
3. Lee CH, Kho SM, Tai BC, Chong EY, Lau C, Than Y, Shi DX, Lee LC, Kailasam A, Low AF, Teo SG, Tan HC. Obstructive sleep apnea in patients admitted for acute myocardial infarction. Prevalence, predictors, and effect on microvascular perfusion. Chest. 2009;135:1488–1495.
4. Qiu H, Guo M, Zhang Y, Shi DZ. Obstructive sleep apnea increases the risk of cardiac events after percutaneous coronary intervention: a meta-analysis of prospective cohort studies. Sleep Breath. 2016;22:33–40.
5. Lee CH, Sethi R, Li R, Ho H, Hein T, Jim MH, Loo G, Koo CY, Gao XF, Chandra S, Yang XX, Furlan SF, Ge Z, Mundhekar A, Zhang WW, Uchida CH, Kharwar RB, Chan PF, Chen SL, Chan MY, Richards AM, Tan HC, Ong TH, Roldan G, Tai BC, Drager LF, Zhang JJ. Obstructive sleep apnea and cardiovascular events after percutaneous coronary intervention. Circulation. 2016;133:2008–2017.
6. Wu H, Yuan X, Wang L, Sun J, Liu J, Wei Y. The relationship between obstructive sleep apnea hypopnea syndrome and inflammatory markers and quality of life in subjects with acute coronary syndrome. Respir Care. 2016;61:1207–1216.

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7. Rahangdale S, Yeh SY, Novack V, Stevenson K, Barnard MR, Furman MI, Frelinger AL, Michelson AD, Malhotra A. The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. J Clin Sleep Med. 2011;7:172–178.

8. Toraldo DM, De Benedetto M, Scoditti E, De Nuccio F. Obstructive sleep apnea syndrome: coagulation anomalies and treatment with continuous positive airway pressure. Sleep Breath. 2016;20:457–465.

9. Gunby E, Karabulut I, Karabulut H, Zaim M. Impact of multilevel surgical treatment on mean platelet volume in patients with obstructive sleep apnea syndrome. J Craniofac Surg. 2015;26:1287–1289.

10. Varol E, Ozturk O, Yuceh H, Gonca T, Has M, Dogan A, Akkaya A. The effects of continuous positive airway pressure therapy on mean platelet volume in patients with obstructive sleep apnea. Platelets. 2011;22:552–556.

11. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, Bax JJ, Borger MA, Brozovic G, Chew DP, Gencer B, Hasenfuss G, Keldsen K, Lancellotti P, Landmesser U, Mehilli J, Mukherjee D, Storey RF, Windecker S, Baumgartner H, Gaemperli O, Achenbach S, Badimon L, Baigent C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cincotta T, Cifonelli D, Hagesko M, Hamm C, Hildick-Smith D, Huber K, Ilidromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosenman T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.

12. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cincotta T, Cifonelli D, Hagesko M, Hamm C, Hildick-Smith D, Huber K, Ilidromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosenman T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.

13. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5:136–143.

14. Collyer TC, Gray DJ, Sandhu R, Berridge J, Lyons G. Assessment of platelet inhibition secondary to clopidogrel and aspirin therapy in preoperative acute surgical patients measured by Thrombelastography Platelet Mapping. Br J Anaesth. 2009;102:492–498.

15. Hobson AR, Agarwala RA, Swallow RA, Dawkins KD, Curzen NP. Thrombelastography: current clinical applications and its potential role in interventional cardiology. Platelets. 2006;17:509–518.

16. Ozturk ZA, Dag MS, Kuyucu ME, Cam H, Yesil Y, Yilmaz N, Aydini M, Kadayifci A, Kepekci Y. Could platelet indices be new biomarkers for inflammatory bowel diseases? Eur Rev Med Pharmacol Sci. 2013;17:334–341.

17. Wasilewski J, Desperak P, Hawranek M, Cilak A, Osadnik T, Pyka Ł, Gawlita M, Bujak K, Niedziela J, Krawczyk M, Gąsior M. Prognostic implications of mean platelet volume on short- and long-term outcomes among patients with non-ST-segment elevation myocardial infarction treated with percutaneous coronary intervention: a single-center large observational study. Platelets. 2016;27:452–458.

18. Gurbel PA, Belden KP, Hiatt BL, O’Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation. 2003;107:2908–2913.

19. Zhang YJ, Li MP, Tang J, Chen XP. Pharmacokinetic and pharmacodynamic responses to clopidogrel: evidences and perspectives. Int J Environ Res Public Health. 2017;14:E301.

20. Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabaté M, Ferreira JL, Ueno M, Jimenez-Quevedo P, Alfonso F, Bach T, Macaya C, Fernandez-Ortiz A, Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Bugiardini R, Carerj S, Casselman F, Cincotta T, Cifonelli D, Hagesko M, Hamm C, Hildick-Smith D, Huber K, Ilidromitis E, James S, Lewis BS, Lip GY, Piepoli MF, Richter D, Rosenman T, Sechtem U, Steg PG, Vrints C, Luis Zamorano J. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.

21. Li Y, Yang S, Chen S, Guo X, Chen Y. Patients with symptoms and characteristics consistent with obstructive sleep apnea are at a higher risk for acute and subacute stent thrombosis after percutaneous coronary stent implantation: a single-center case-control study. BMC Cardiovasc Disord. 2017;17:226.

22. Nena E, Papanas N, Steiropoulos P, Zikidou P, Zarogoulidis P, Pita E, Constantiniou TC, Maltezos E, Mikhailidis DP, Bourou D. Mean platelet volume and platelet distribution width in non-diabetic subjects with obstructive sleep apnoea syndrome: new indices of severity? Platelets. 2012;23:447–454.

23. Pyo JS, Cho WJ. Mean platelet volume, platelet distribution width, and platelet count in varicocoele: a systematic review and meta-analysis. Cell Physiol Biochem. 2016;38:2239–2246.

24. Valenti R, Marcucci R, Capodanno D, De Luca G, Migliorini A, Gori AM, Parodi G, Giusti B, Barabba N, Panica A, Cantini G, Mammì M, Gensini GF, Abbate R, Antonucci D. Residual platelet reactivity to predict long-term clinical outcomes after clopidogrel loading in patients with acute coronary syndromes: comparison of different cutoff values by light transmission aggregometry from the responsiveness to clopidogrel and stent thrombosis 2-acute coronary syndrome study. J Thorac Thrombosis. 2015;40:74–82.

25. Nguyen TA, Diodati JG, Phan R. Resistance to clopidogrel: a review of the evidence. J Am Coll cardiol. 2005;45:1157–1164.

26. Breet NJ, van Werkum JW, Bouman HJ, Kelder JC, Ruijth FJ, Dal TMZ, Harmes JM, van der Heyden JA, Rensing B, Sutter MJ, Hackeng CM, ten Berg JM. Comparison of platelet function tests in predicting clinical outcome in patients undergoing coronary stent implantation. JAMA. 2010;303:754–762.

27. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antonucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA. 2011;306:1215–1223.

28. Aradi D, Kirtane A, Bonello L, Gurbel PA, Tantry US, Huber K, Freyhofer MK, ten Berg J, Janssen P, Angiolillo DJ, Siller-Matula JM, Marcucci R, Patti G, Mangiacapra F, Valgimigli M, Morel O, Palmerini T, Price MJ, Cuisset T, Kastrati A, Stone GW, Sibbing D. Bleeding and stent thrombosis on P2Y12-inhibitors: collaborative analysis on the role of platelet reactivity for risk stratification after percutaneous coronary intervention. Eur Heart J. 2015;36:1762–1771.

29. Pontes-Neto OM, Fernandes RM, Sander HH, da Silva LA, Mariano DC, Nobre F, Simão G, de Araujo DB, dos Santos AC, Leite JP. Obstructive sleep apnea is frequent in patients with hypertensive intracerebral hemorrhage and is related to perihematoma edema. Cerebrovasc Dis. 2010;29:36–42.

30. Hwang D, Shakir N, Limann B, Sison C, Kalra S, Shulman L, Souza Ade C, Greenberg B. Association of sleep-disordered breathing with postoperative complications. Chest. 2008;133:1128–1134.

31. Song TJ, Park JH, Choi KH, Chang Y, Moon J, Kim JH, Choi Y, Kim YJ, Lee HW. Moderate-to-severe obstructive sleep apnea is associated with cerebral small vessel disease. Sleep Med. 2017;30:36–42.
SUPPLEMENTAL MATERIAL
Table S1. Simple linear regression analysis of the inhibitory rate of ADP receptor pathway.

| Variables          | β (95% CI)         | P value |
|--------------------|--------------------|---------|
| Age                | -0.46 (-0.94, 0.25) | 0.063   |
| Male               | 13.71 (-1.15, 28.57) | 0.070   |
| BMI (kg/m²)        | -0.20 (-1.52, 1.13) | 0.770   |
| Smoking            | 7.94 (-1.87, 17.75)  | 0.112   |
| Alcohol            | 2.57 (-7.28, 12.41)  | 0.607   |
| **Medical history**|                    |         |
| Diabetes           | -4.10 (-14.77, 6.58) | 0.449   |
| Hypertension       | 8.92 (-0.86, 18.71)  | 0.074   |
| Dyslipidemia       | 1.97 (-9.46, 13.41)  | 0.733   |
| Prior MI           | -7.80 (-22.38, 6.78) | 0.292   |
| Prior stroke       | 6.81 (-10.43, 24.04) | 0.436   |
| **Diagnosis**      |                    |         |
| STEMI              | -0.56 (-10.55, 9.42) | 0.911   |
| **Sleep information**|               |         |
| AHI (events/hr)    | -0.21 (-0.45, 0.04)  | 0.099   |
| ODI (events/h)     | -0.23 (-0.49, 0.03)  | 0.086   |
| Minimum SaO₂ (%)   | 0.58 (0.03, 1.12)    | 0.039   |
| Mean SaO₂ (%)      | 1.97 (0.20, 3.74)    | 0.029   |
| Time of SaO₂<90%   | -0.16 (-0.59, 0.26)  | 0.445   |
| Moderate/severe OSA| -11.18 (-20.72, -1.64) | 0.022   |
| **Medication**     |                    |         |
| PPIs               | 4.15 (-9.18, 17.47)  | 0.539   |
| ACEI               | -1.36 (-11.34, 8.62) | 0.787   |
| ARB                | -3.40 (-16.46, 9.67) | 0.608   |
| Diuretics          | -3.43 (-28.41, 22.55) | 0.786   |
| β-blockers         | -13.87 (-28.30, 0.57) | 0.060   |
| **Calcium antagonists** | 0.49 (-13.78, 14.76) | 0.946 |
|-------------------------|-----------------------|-------|

**Laboratory data**

| **Platelet count (1,000/mm³)** | 0.99 (0.02, 0.18) | 0.015 |
|-------------------------------|------------------|-------|
| **Platelet crit (%)**         | 87.59 (3.11, 172.07) | 0.042 |
| **MPV (fl)**                  | -1.40 (-6.39, 3.60) | 0.580 |
| **PDW (%)**                   | 0.99 (-1.30, 3.27) | 0.394 |
| **P-LCR (%)**                 | 0.05 (-0.61, 0.70) | 0.889 |
| **HbA1C (%)**                 | 0.79 (-3.01, 4.61) | 0.678 |
| **Creatinine (μmol/l)**       | -0.02 (-0.29, 0.24) | 0.858 |
| **eGFR (ml/min/1.73m²)**      | 0.35 (0.14, 0.56) | 0.001 |

ACS indicates acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitors; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HRPR, high residual on-treatment platelet reactivity; MI, myocardial infarction; MPV, mean platelet volume; ODI, oxygen desaturation index; IQR, interquartile range; PCI, percutaneous coronary intervention; PDW, platelet distribution width; P-LCR, platelet large cell ratio; PPIs, proton pump inhibitors; SD, standard deviation; and STEMI, ST-segment elevation myocardial infarction.
Table S2. Characteristics of patients with non-HRPR and HRPR.

| Variables          | Non-HRPR (n=96)       | HRPR (n=31)       | P value |
|--------------------|-----------------------|-------------------|---------|
| Age, years         | 54.96±10.15           | 55.97±9.43        | 0.63    |
| Male               | 86 (89.58)            | 26 (83.87)        | 0.52    |
| BMI (kg/m²)        | 26.6 [24.5, 28.7]     | 27.0 [24.8, 29.4] | 0.65    |
| Smoking            | 60 (62.50)            | 16 (51.61)        | 0.30    |
| Alcohol            | 41 (42.71)            | 12 (38.71)        | 0.84    |
| **Medical history**|                       |                   |         |
| Diabetes           | 29 (30.21)            | 8 (225.81)        | 0.82    |
| Hypertension       | 61 (63.54)            | 15 (48.39)        | 0.15    |
| Dyslipidemia       | 24 (25.00)            | 6 (19.35)         | 0.63    |
| Prior MI           | 12 (12.50)            | 4 (12.90)         | 1.00    |
| Prior PCI          | 11 (11.56)            | 9 (29.03)         | 0.04    |
| Prior CABG         | 2 (1.50)              | 0 (0.00)          | 1.00    |
| Prior Stroke       | 8 (8.33)              | 3 (9.68)          | 0.73    |
| **Sleep information**|                      |                   |         |
| AHI (events/h)     | 13.50 [6.83, 32.95]   | 22.20 [15.00, 45.00] | 0.03    |
| ODI (events/h)     | 14.00 [6.00, 36.00]   | 22.00 [11.25, 43.75] | 0.05    |
| Minimum SaO₂ (%)   | 86.00 [79.25, 88.00]  | 85.00 [83.00, 87.00] | 0.45    |
| Mean SaO₂ (%)      | 94.00 [93.00, 95.00]  | 93.00 [92.00, 95.00] | 0.22    |
| Time of SaO₂<90%    | 1.00 [0.00, 5.75]     | 2.00 [0.00, 9.00]  | 0.19    |
| OSA                | 45 (46.88)            | 23 (74.19)        | 0.01    |
| **Diagnosis**      |                       |                   |         |
| Type of ACS (STEMI)| 35 (36.46)            | 14 (45.16)        | 0.40    |
| **Medication**     |                       |                   |         |
| PPIs               | 82 (85.42)            | 25 (80.65)        | 0.57    |
| ACEI               | 61 (63.54)            | 17 (54.84)        | 0.40    |
| ARB                | 13 (13.54)            | 8 (25.81)         | 0.16    |
| Diuretics          | 3 (3.13)              | 2 (6.45)          | 0.60    |
| Sartin             | 96 (100)              | 31 (100)          | —       |
| β-blockers         | 81 (84.38)            | 30 (96.77)        | 0.12    |
| Calcium antagonists| 13 (13.54)            | 4 (12.90)         | 1.00    |
| **Laboratory data**|                       |                   |         |
| Platelet count (1,000/mm³) | 212.00 [181.00, 249.00] | 201.00 [171.00, 246.00] | 0.49    |
| Platelet crit (%)  | 0.20 [0.17, 0.24]     | 0.20 [0.18, 0.25] | 0.66    |
| MPV (fl)           | 10.30±1.00            | 10.55±0.90        | 0.21    |
| PDW (%)            | 12.82±2.23            | 12.62±1.88        | 0.65    |
| P-LCR (%)          | 27.70±7.63            | 28.85±7.28        | 0.46    |
| HbA1C (%)          | 6.67±1.50             | 6.27±1.20         | 0.25    |
|                          | No. (%), mean ± SD or median [IQR] | P value | Non-HRPR vs. HRPR |
|--------------------------|-----------------------------------|---------|-------------------|
| Creatinine (μmol/l)      | 74.00 [67.00, 83.00]              | 0.06    |                   |
| eGFR (ml/min/1.73m²)     | 101.87 [85.83, 113.37]            | 0.02    |                   |

Data given as No. (%), mean ± SD or median [IQR]. P value is non-HRPR vs. HRPR. ACS indicates acute coronary syndrome; ACEI, angiotensin converting enzyme inhibitors; AHI, apnea-hypopnea index; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; HbA1C, hemoglobin A1c; HRPR, high residual on-treatment platelet reactivity; MI, myocardial infarction; MPV, mean platelet volume; ODI, oxygen desaturation index; IQR, interquartile range; PCI, percutaneous coronary intervention; PDW, platelet distribution width; P-LCR, platelet large cell ratio; PPIs, proton pump inhibitors; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.