NEW RESEARCH

JCSM
Journal of Clinical Sleep Medicine

COMMENTARY

Platelet Activity and Cardiovascular Risk in Obesity and Obstructive Sleep Apnea: Compelling Need for Interdisciplinary Research?

Commentary on Rahangdale S, et al. The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. *J Clin Sleep Med* 2011;7(2):172-178.

Yüksel Peker, M.D., Ph.D.

Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, University of Gothenburg & Sleep Medicine Unit, Skaraborg Hospital, Skövde, Sweden

Obstructive sleep apnea (OSA) is a common disorder with serious cardiovascular consequences.[1] Mechanisms which have been advanced to explain the relationship between OSA and cardiovascular disease (CVD) include increased sympathetic activity, intermittent hypoxemia, oxidative stress, inflammation, endothelial dysfunction, enhanced coagulability and platelet activation.[2] However, as also stated by the American Heart Association/American College of Cardiology, there is a paucity of data for a causal role of OSA in CVD,[3] which underlines the importance of well-done studies. In the current edition of *Journal of Clinical Sleep Medicine,* Rahangdale et al.[4] addressed the role of OSA on platelet function in a community-based sample of otherwise healthy obese individuals with and without OSA matched for body mass index (BMI) and statistically adjusted for age and gender. They found no association between OSA status (apnea-hypopnea index [AHI] $\geq$ 10 events/h) and platelet activation, but, in a post hoc analysis identified OSA subjects who spent $\geq$ 1 min/hour of sleep at oxygen saturations < 90% to demonstrate increased platelet activity. They concluded that the degree of hypoxemia in OSA, rather than flow-based apneic and hypopneic events, should be viewed as a possible marker for adverse atherothrombotic consequences of OSA, even in an otherwise healthy obese patient.

These findings are not surprising. As the pathways being affected by OSA are the same pathways that are affected by obesity, it has been suggested that the role of OSA on CVD may be dependent on the degree of obesity, and negative studies in extremely obese subjects cannot be generalized to those with lesser degrees of obesity.[5] On the other hand, the independent impact of obesity on platelet function has not yet been fully explored. Indeed, in a well-done work comprising 6319 individuals, the correlation between platelet count, platelet activation, and systemic inflammation in overweight, obese, and morbidly obese individuals was previously addressed.[6] Complete blood counts, high sensitivity C-reactive protein serum levels, and BMI were measured during routine checkups in all subjects, and platelet activation markers were further studied among 30 obese (BMI = 41 ± 8 kg/m^2) and 35 nonobese (BMI = 24 ± 3 kg/m^2) individuals. Interestingly, overweight, obese, and morbidly obese females had significantly elevated platelet counts compared with normal-weight females while no significant elevation of platelet counts was observed in the male subgroups. However, the flow cytometry analysis of platelets showed no significant differences in activation marker expression between nonobese and obese individuals, suggesting that obesity is not associated with increased platelet activation. In females, obesity was found to be associated with elevated platelet counts but not independently of chronic inflammation.[6] Though these findings were not adjusted for OSA, one may also speculate that the role of obesity on CVD may be dependent on the degree of OSA severity. In this context, the study of Rahangdale et al. highlighting the degree of hypoxemia as a predictor of platelet activity is an important observation. Moreover, as also reported in the paper, previous studies investigating the role of OSA in platelet function have recruited patients referred to sleep clinics, who are much more likely to have complaints of daytime sleepiness (and are generally sicker) compared to a community cohort. Thus, the prior literature, though largely uniform in demonstrating that OSA is associated with increased platelet activation, is limited by methodological issues, lack of control for major comorbidities, and probable lack of generalizability.[4]

However, it is not clear in the current paper if hypoxemia is important in itself or as simple as a reflection of increased severity of OSA, as 13 subjects with greater desaturations were also the ones with higher AHI. Although the authors point to the "relatively large sample size" of the study for a physiologic study, the findings should be interpreted cautiously as 13 subjects with the finding of interest is actually not that large. Moreover, it is also possible that not only glycoprotein (GP)1b, but also other markers of platelet activation including platelet surface P-selectin, platelet surface activated GPIIb/IIIa, platelet-monocyte aggregation, and platelet-neutrophil aggregation would be positive with a larger sample size. Though the case-controlled design as well as the relatively small sample size of the study limits interpretation of data regarding a causal relationship, the paper raises a number of important questions related to platelet activation and its potential as a mediator of cardiovascular complications of OSA in otherwise healthy obese individuals.

Single morning measurements of platelet activation also leaves open the question as to whether changes are due to chronic untreated OSA, or reflect only the acute and transient effects of overnight hypoxia. In that context, one much more interesting observation than the possibility that hypoxemia is the determinative metric for OSA-induced thrombotic risk, is the decrease in GP1b fluorescence, which apparently is longer lasting than the other measures and as such is ideally suited for the evaluation of persistent daytime changes resulting from a process occurring during the night.[7]

It is also known that silent brain infarction and platelet activity measures (serum levels of sCD40L and sP-selectin) are associated with an increased risk of cerebrovascular disease. Minoguchi et al.[8] studied silent brain infarction by brain magnetic resonance images in 50 male patients with OSA and 15 obese male control subjects who were free of comorbidities. In addition, the effects of 3 months of treatment with nasal continuous positive airway pressure (nCPAP) on serum parameters were studied in 24 patients with moderate to severe OSA. The authors found that the percentage of silent brain infarction as well as serum levels of sCD40L and sP-selectin were significantly higher in patients with moderate to severe OSA than in obese control subjects or patients with mild OSA. Moreover, nCPAP significantly decreased the markers of platelet activity in patients with moderate to severe OSA. Thus, there seems to be more evidence supporting the hypothesis that OSA, in the absence of obesity, can activate relevant pathways than the hypothesis that obesity, in the absence of OSA, can do the same. From the study of Rahangdale and coworkers, we do not have the answers to the challenging questions if platelet activation can be reduced by CPAP in the management of OSA, and if this will lower the frequency of cardiovascular events. Moreover, it should also be addressed if such a benefit of CPAP is additive to the effects of antiplatelet therapy, including aspirin and clopidogrel (especially in patients with known coronary artery disease). It is interesting that obese individuals in a large cohort of 2014 people have recently been reported to have greater native platelet reactivity and retain greater residual platelet function despite aspirin treatment compared with nonobese individuals.[9] Though the authors conclude that it remains unclear whether the currently recommended low-dose of aspirin therapy provides equivalent cardioprotection to obese and nonobese patients at risk for cardiovascular events, it is difficult to understand how a concomitant, untreated OSA in obese individuals can still be ignored in such a manuscript[9] in the year 2010 in this context. The global epidemic of obesity is no doubt associated with consequent increased prevalence of OSA, which may often be present even in nonsleepy individuals. As previously stated in a review article,[5] if CPAP lowers risk for cardiovascular events in high-risk individuals, the criteria for implementation of CPAP therapy may need to be expanded to include intervention for nonsleepy individuals, with OSA. Unfortunately, the current evidence, including the report from the study of Rahangdale et al.,[4] is not convincing enough to justify such therapeutic approaches. The need for a closer collaboration between experts in obesity, sleep apnea, and cardiology to perform larger controlled and randomized trials to test such treatment strategies continues to emerge.

REFERENCES

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230-5.
2. Celen YT, Peker Y. Cardiovascular consequences of sleep apnea – II: Cardiovascular mechanisms. *Anadolu Kardiyol Derg* 2010;10:168-75.
3. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease. An American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing Council. *Circulation* 2008;118:1080-111.
4. Rahangdale S, Yim SY, Novack V, et al. The influence of intermittent hypoxemia on platelet activation in obese patients with obstructive sleep apnea. *J Clin Sleep Med* 2011;7:172-8.
5. Pack AI, Gislason T. Obstructive sleep apnea and cardiovascular disease: a perspective and future directions. *Progress Cardiovasc Dis* 2009;5:434-451.
6. Samocha-Bonet D, Justo D, Rogowski O, et al. Platelet counts and platelet activation markers in obese subjects. *Mediators Inflamm* 2008; 2008:834153.
7. Michelson AD, Ellis PA, Barnard MR, Matic GB, Viles AF, Kestin AS. Downregulation of the platelet surface glycoprotein Ib-IX complex in whole blood stimulated by thrombin, adenosine diphosphate, or an in vivo wound. *Blood* 1991;77:770-9.
8. Minoguchi K, Yokoe T, Tazaki T, et al. Silent brain infarction and platelet activation in obstructive sleep apnea. *Am J Respir Crit Care Med* 2007;175:612-7.
9. Bordeaux BC, Qayyum R, Yanek LR, et al. Effect of obesity on platelet reactivity and response to low-dose aspirin. *Prev Cardiol* 2010;13:56-62.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2011
Accepted for publication March, 2011
Address correspondence to: Yüksel Peker, Department of Emergency and Cardiovascular Medicine, Sahlgrenska Academy, University of Gothenburg & Sleep Medicine Unit, Skaraborg Hospital, SE 54185 Skövde, Sweden; Tel: +46 500 431000; Fax: +46 500 431897; E-mail: yuksel.peker@lungall.gu.se

DISCLOSURE STATEMENT

Dr. Peker has participated in speaking engagements for ResMed and has received institutional research support from ResMed, Boehringer Ingelheim, Actelion and Pfizer.