A Bullet in Search of the Smoking Gun

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A search of Medline from 1966 to the present reveals more than 200 manuscripts that are categorized by the combination of the following terms: ‘cardiovascular diseases’ and ‘sleep apnea syndromes’ or ‘sleep apnea, obstructive’. Over the past 10 years, publication of these studies has moved from journals devoted exclusively to sleep medicine to more mainstream venues. The general medical community now accepts that obstructive sleep apnea is much more prevalent and relevant than previously thought. Despite the proliferation of articles that cite the association between sleep-disordered breathing and myocardial infarction, heart failure, hypertension, and stroke, the proof that sleep apnea leads to the development of cardiovascular disease remains the ‘Holy Grail’ that continues to elude investigators of sleep disorders.

In this issue of *Respiration*, by investigating the association of the apnea hypopnea index (AHI) and the highly sensitive assay of C-reactive protein (hs-CRP) levels, Zouaoui Boudjeltia et al. [1] attempt to provide ‘a bullet’ that explains this association (‘the smoking gun’) of obstructive sleep apnea and cardiovascular disease. Clearly, prior studies have demonstrated that elevated hs-CRP levels are an independent risk factor for developing cardiovascular disease. Evidence suggests that hs-CRP may be the strongest predictor of future myocardial infarction and sudden cardiac death [2].

There has been a lack of consistency among prior studies examining the relationship of sleep-disordered breathing to an elevation of hs-CRP. As such, the conclusion

that the inflammatory response putatively associated with obstructive sleep apnea is the cause of cardiovascular disease has remained in doubt. As Zouaoui Boudjeltia et al. [1] point out, the prior investigations that failed to find an association have either examined children [3, 4] or have utilized a patient population characterized by a narrow range of AHIs [5]. Unlike these prior studies, the investigation in the current issue has studied patients referred to a sleep center for evaluation of a suspicion of obstructive sleep apnea. In contradistinction to the prior studies [5], this group of patients had a wide range of AHIs. The present investigation considers confounders that may have contributed to the observed elevations of CRP. Strict criteria were developed to define airway obstruction/chronic obstructive pulmonary disease and diabetes. Other variables associated with elevated levels of hs-CRP and inflammation, such as obesity and leukocyte and monocyte counts, were also evaluated. Using hs-CRP as the dependent variable, multivariate regression analysis identified AHI as the only variable directly associated with hs-CRP levels. The authors suggest that the short duration of the obstructive symptoms may explain the lack of association of the level of AHI and hs-CRP observed in young children.

The study by Zouaoui Boudjeltia et al. [1] is intriguing but alas inconclusive. It provides some evidence to define the cause of cardiovascular disease in patients with sleep-disordered breathing; however, questions remain. The authors failed to find an association between CRP levels

and body mass index and other clinical conditions usually associated with elevated levels of hs-CRP. The investigators studied a relatively small number of patients and the study seems to be underpowered to reliably detect these expected associations. Perhaps the greatest strength

of this study is that it may help us to frame a large, properly powered, prospective, case-controlled multicenter evaluation to determine which patient characteristics, including severity of sleep-disordered breathing, may lead to the development of cardiovascular disease.

References

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