

ques) varies significantly; positive biopsies can be acted on quickly, but a negative biopsy does not lay the issue to rest.

Much effort has been expended on developing biomarkers that could be used to screen high-risk populations for lung cancer. These include sputum cytology, exhaled breath analysis, gene promoter methylation in sputum or blood, chromosomal aneusomy in sputum or bronchial epithelium, gene expression patterns in bronchial brushings, proteomic analysis of blood (or potentially, bronchoalveolar lavage), and antibodies to tumor antigens (11–16). Tests based on sputum are promising but appear to be more useful for central airway cancers than peripheral nodules (11, 12). Whether the performance of these tests can be improved by enrichment for epithelial cells or the use of techniques to obtain more distal pulmonary secretions is unknown. The necessary test characteristics for screening asymptomatic high-risk populations are highly stringent, but in the setting of an indeterminate lung nodule, lower degrees of sensitivity and specificity may be clinically useful either in reassuring patients and physicians that “watchful waiting” is appropriate or in accelerating the pace of the diagnostic workup. It is likely that biomarker-based tests will initially be applied to the management of lung nodules, rather than mass screening. CT screening trials, such as the Pittsburgh Lung Screening Study and the NLST, have incorporated blood and sputum collection, which should be invaluable in evaluating the performance of biomarker based tests in the setting of indeterminate pulmonary nodules in high-risk subjects.

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Is the Cardiovascular System the Primary Target of Obstructive Sleep Apnea?

Obstructive sleep apnea (OSA) syndrome is defined by the occurrence of five or more episodes of obstructive apneas and/or hypopneas per hour of sleep (apnea-hypopnea index [AHI]) in conjunction with hypersomnolence or related problems in daytime function (1). The prevalence of OSA syndrome among the middle-aged male and female population is 4 and 2%, respectively (1). When the necessity of daytime complaints is not included in the definition, the prevalence of OSA in males and females leaps to 24 and 9%, respectively (1). Therefore, only one

out of approximately five subjects with elevated AHI complains of excessive daytime sleepiness in population studies. However, the exact significance of this large number of nonsleepy subjects with elevated AHI is not completely understood. In addition to daytime symptoms, it is now recognized that OSA triggers a cascade of biological reactions, including increased sympathetic activity, systemic inflammation, oxidative stress, and metabolic alterations that are potentially harmful to the cardiovascular system (2).

The most well-established link between OSA and cardiovascular disease is between OSA and hypertension. Epidemiological studies show a clear dose–response relationship between AHI and the risk of developing hypertension (3). This independent association was not corrected for the presence or absence of daytime symptoms (3). In addition, the treatment of OSA with continuous positive airway pressure (CPAP) in patients with coexisting hypertension produced a significant decrease in blood pressure (4). Among patients with established cardiovascular disease, including heart failure (5), implanted pacemaker (6), and metabolic syndrome (7), OSA is frequently not accompanied by complaints of hypersomnolence. Two independent studies found no significant effects of CPAP on blood pressure in nonsleepy OSA patients over a period of 4 to 6 weeks (8, 9). These results gave rise to the question whether elevated AHI in non-sleepy patients really indicated the need for treatment (10). One possible explanation for the negative results relies on the fact that the two studies included several patients with controlled blood pressure at study entry (11). Another possibility is that the detrimental cardiovascular effects of OSA also occur through other mechanisms not related to blood pressure.

One tempting unifying hypothesis is that OSA accelerates atherosclerosis progression. In this case, the association between OSA with poor cardiovascular outcome (and the reversion with CPAP) would become clear only over prolonged periods of time. The 18-year mortality follow-up on the population-based Wisconsin Sleep Cohort showed that untreated subjects with high AHI at baseline were at increased risk of cardiovascular mortality, irrespective of symptoms of sleepiness (12). The authors concluded that the treatment of OSA should not be contingent on daytime sleepiness symptoms (12).

In this issue of the *Journal* (pp. 984–988), Kohler and colleagues (13) provide important insights into cardiovascular morbidity in this large group of patients with elevated AHI but no self-reported daytime sleepiness. The authors studied endothelial function and arterial stiffness in 64 nonsleepy OSA patients and 15 well-matched controls. Despite similar cardiovascular risk profiles, well-established markers (14) of early vascular damage were abnormal in nonsleepy OSA patients compared with controls. The study of Kohler and colleagues therefore suggests that these nonsleepy OSA patients are, in fact, exposed to increased cardiovascular risk.

This study has potential limitations. Kohler and colleagues did not monitor the quality or duration of sleep, and the average oxygen desaturation index (>4%) was 23 ± 15 per hour, suggesting that except for overt daytime symptoms, several patients would be classified as having moderate or even severe OSA. As acknowledged by the authors, this was an association study that indicates the necessity of future randomized trials involving treatment intervention. On the other hand, these results are in line with the findings of early signs of atherosclerosis, as evaluated by increased arterial stiffness, carotid intima media thickness, and carotid diameter in a subset of apparently healthy patients with OSA that were nonsmokers and free of comorbidities (15). Moreover, CPAP was able to reverse these early signs of atherosclerosis independent of changes in blood pressure (16). Considering all these potential limitations, the studies collectively suggest that the harmful effects of OSA do not seem to spare patients who do not complain of daytime symptoms or individuals who are otherwise apparently healthy.

The potential implications of the study of Kohler and colleagues should not be underestimated. If daytime symptoms are not necessary to define the disease, the prevalence of OSA in the general population is extremely high. Even adopting a rather conservative threshold of AHI greater than 15 events per hour,

the prevalence of OSA in middle-aged men and women remains 9 and 4%, respectively (1). No matter how we look at the problem, OSA is a leading health burden with major cardiovascular implications.

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