White Coat Hypertension and Sleep Apnea
Is There a Link?

The potential role of sleep apnea in the pathogenesis and complications of cardiovascular disorders is a notion that recently has gained support. More specifically, several studies have been performed in order to analyze the association of hypertension in patients with sleep apnea and the potential importance of obstructive sleep apnea as a secondary and possible treatable cause of hypertension. In this issue of CHEST, García-Rio et al report on the prevalence of “white coat hypertension” in patients with obstructive sleep apnea. They demonstrate that the prevalence of white coat hypertension in patients with sleep apnea is 33% (15 patients). Before discussing their findings, we will briefly summarize our knowledge regarding the association of sleep apnea and hypertension, and the clinical significance of white coat hypertension.

Sleep Apnea and Hypertension
Epidemiology
The association of sleep apnea and hypertension also has been the focus of epidemiologic studies. Observations from epidemiologic studies point toward an association between obstructive sleep apnea and hypertension, independent of age, obesity, or other confounding factors. Thus, the Sleep Heart Health Study demonstrated an independent association between obstructive sleep apnea and hypertension in a cross-sectional analysis of 6,132 subjects. The prevalence of hypertension increased with increasing apnea-hypopnea index (AHI) values. A cross-sectional analysis of 1,069 subjects who underwent polysomnography in the Wisconsin Sleep Cohort Study demonstrated that there was a significant linear increase in daytime BP with increasing AHI. The association between obstructive sleep apnea and hypertension was stronger in this study, with an adjusted odds ratio for hypertension of 3.1 (95% confidence interval, 1.7 to 5.7) associated with an AHI of > 30. Furthermore, a prospective follow-up of 893 of those subjects for more than 4 to 8 years demonstrated that the odds ratio for the new onset of hypertension at follow-up, associated with the presence of obstructive sleep apnea at baseline, was 2.89 (95% confidence interval, 1.46 to 5.64).

Clinical Significance
Although the mechanisms by which obstructive sleep apnea promotes hypertension are not known, evidence from experimental and human studies had pointed toward the roles of intermittent hypoxia and activation of the sympathetic nervous system. The clinical significance of obstructive sleep apnea in the development of hypertension has been the focus of several studies. Not only does obstructive sleep apnea cause an increase in nocturnal BP, but also the normal nocturnal fall of BP (ie, 15% below daytime levels [patients called dippers]) is attenuated or absent, defining the majority of patients with obstructive sleep apnea as nondippers. Interestingly, it is possible that many patients who are nondippers may have undiagnosed sleep apnea. In this regard, Portaluppi et al reported the presence of unsuspected obstructive sleep apnea in 10 of 11 patients with hypertension, but in none of 10 nondipping patients with hypertension. These results lead to the conclusion that the nondipping phenomenon is probably related to sleep apnea in many patients with essential hypertension. Since the higher risk of cardiovascular complications is associated with the lack of nocturnal decrease in BP (nondipping) independent of the daytime BP level, the dispute about whether obstructive sleep apnea is a factor in the development of daytime hypertension may be less significant.

What Is White Coat Hypertension?
The alerting response to the physician’s visit has been shown to precipitate an increase in BP, which is regarded as white coat effect. This event has often been associated with a clinical condition that is characterized by a constantly high BP in the doctor’s office and a constantly normal BP at other times, which is a condition that is commonly referred to as isolated office hypertension or white coat hypertension.
It was Sir George Pickering\textsuperscript{11} who introduced the concept of diurnal variation of BP. He recorded 24-h BP intraarterially in one of his young assistants and demonstrated that BP was low during sleep, rose suddenly while he ran to catch the bus, decreased again when he fell asleep after rounds, and raised remarkably when the head sister stuck him with a pin to awaken him.

The term white coat syndrome was formulated in 1983, when Mancia et al.\textsuperscript{12} reported, on the basis of continuous intraarterial BP recording, that systolic and diastolic pressures rose on average by 27 and 15 mm Hg, respectively, and heart rate increased by 16 beats/min when a doctor entered the patient’s hospital room.

The prevalence of white coat hypertension has ranged between 20\% and 60\%, depending on the criteria utilized for its diagnosis.\textsuperscript{10} The clinical interest in white coat hypertension stems from the potential clinical consequences of patients carrying this diagnosis. However, several studies regarding the prognosis and target organ damage of white coat hypertension have proven to be controversial. The Ambulatory BP Monitoring and Treatment of Hypertension Trial\textsuperscript{13} demonstrated that white coat hypertension carried a significantly better prognosis for patients experiencing cardiovascular events compared to those with established hypertension. Khattar et al.\textsuperscript{14} have shown that patients with isolated office hypertension have a lower risk of developing left ventricular hypertrophy. Conversely, other studies have shown that target organ damage in patients with white coat hypertension was very similar to the damage found in patients with established hypertension.\textsuperscript{15–17} In addition, it has been reported\textsuperscript{16,19} that patients with white coat hypertension progress to develop established hypertension and that patients with white coat hypertension share the same metabolic abnormalities of patients with established hypertension.

White Coat Hypertension and Sleep Apnea

The relationship between obstructive sleep apnea and white coat hypertension has not been clearly delineated. The study by García-Río et al in this issue of \textit{CHEST} is the first attempt to analyze this association. The authors designed a very simple study in which 99 patients with obstructive sleep apnea were divided into groups according to their BP status: normotensive subjects, patients with white coat hypertension, and patients with sustained hypertension. All these patients underwent several laboratory tests such as 24-h BP monitoring and urinary catecholamine measurement, while at the same time a polysomnographic study was performed. García-Río et al demonstrate that the prevalence of white coat hypertension in patients with sleep apnea is 33\% (15 patients) and that these patients have higher values of sleep-onset latency and waking after sleep onset.

In addition, in a logistic regression model gender, age, smoking, diabetes, sleep-onset latency, and waking after sleep onset were predictors of white coat hypertension. Although the data are interesting, there are many questions and limitations that arise from this study. First, the difference in the sleep patterns between patients with white coat hypertension and hypertension do not have any clinical meaning, since we certainly do not know the characteristics of sleep in patients with white coat hypertension. It would have been more consequential to perform polysomnographic studies in patients with white coat hypertension and to define the sleep pattern of these patients. The latter has never been explored. It is possible that one of the reasons that patients had white coat hypertension is the fact that they have undiagnosed sleep apnea. Interestingly, in this article a great proportion of patients with sleep apnea and white coat hypertension consists of non-dippers (73\%). Second, will these data allow us to treat these patients differently? Third, should the conclusion of the article be applied just to patients with sleep apnea or just to patients with white coat hypertension? In other words, we do not know how many patients with white coat hypertension have sleep apnea. Finally, it seems that the authors propose to use ambulatory BP monitoring to assess the prevalence of white coat hypertension in patients with sleep apnea. Many of the patients with sleep apnea have hypertension, as the epidemiologic data have demonstrated, whether white coat or established, thus the sleep-breathing disorders should be treated, regardless, in order to improve cardiovascular complications and quality of life in these patients.

In summary, we believe that further longitudinal studies are needed to delineate the clinical significance of sleep-breathing disorders in patients with white coat hypertension. In addition, it would be interesting to assess the impact of therapy for obstructive sleep apnea in the control of BP in patients with white coat hypertension.

\textbf{Hector O. Ventura, MD}\textbf{\hspace{1cm}Mandeep R. Mehra, MD}\textbf{\hspace{1cm}New Orleans, LA}

Drs. Ventura and Mehra are affiliated with the Cardiomyopathy and Heart Transplantation Center, Ochsner Clinic Foundation. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (e-mail: permissions@chestnet.org). Correspondence to: Hector O. Ventura, MD, Ochsner Clinic Foundation, 1514 Jefferson Hwy, New Orleans, LA 70121; e-mail: heventura@ochsner.org
D-dimer for Suspected Pulmonary Embolism

Whom Should We Test?

After > 10 years of intensive research, plasma d-dimer measurement is increasingly accepted as a first-line test in patients with suspected pulmonary embolism. Adoption of d-dimer was faster in suspected deep venous thrombosis, probably because clinicians are less fearful of a false-negative result in that context than when a potentially fatal disease such as pulmonary embolism is suspected. Nevertheless, as carefully reviewed in a recent editorial in CHEST by Kelly and Hunt, and in a recent review of outcome studies in suspected pulmonary embolism, the evidence is now convincing: highly or even less sensitive d-dimer assays combined with clinical probability assessment are safe instruments to rule out pulmonary embolism. However, it is now well recognized that d-dimer assays are not a homogeneous group and exhibit vastly different characteristics: they recognize different epitopes of d-dimer and use different technologies (latex, enzyme-linked immunosorbent assay [ELISA], immunoturbidimetry) that impact on the diagnostic characteristics and performance of each individual assay. The safety of ruling out pulmonary embolism based on a d-dimer concentration below the predefined cutoff value depends on the sensitivity of the test, ie, the proportion of patients with pulmonary embolism in whom d-dimer is elevated. Indeed, if that proportion approaches 100% (the true figure lies between 96% and 99% for ELISA and immunoturbidimetric assays), the probability of a false-negative test result is very low, and a negative test result is strong evidence that the patient does not have pulmonary embolism. However, although d-dimer is highly specific for cross-linked fibrin, fibrin is generated and degraded in a wide variety of clinical situations. Therefore, the specificity of highly sensitive d-dimer assays for pulmonary embolism is only approximately 40% in outpatients. This has two consequences. First, a d-dimer result above the threshold value is of no clinical usefulness of the test. Consider a prevalence of pulmonary embolism of 20%, a usual figure in the published literature. In a hypothetical cohort of 100 patients, 20 patients would not have the disease. If the specificity of d-dimer is 40%, d-dimer will be negative in 32 patients. Therefore, the number of

References