The natural circadian rhythm of blood pressure (BP) typically includes a nocturnal decrease of 10% to 20% in BP compared with daytime, awake values. However, in as many as 25% to 35% of hypertensive patients, there is a moderate-to-marked loss of this decline in nocturnal BP, a phenomenon that has been associated with excessive cardiac, renal, and cerebrovascular target organ damage. In addition, patients with hypertension who exhibit a nocturnal BP increase compared with daytime BP (so-called “risers”) have the worst prognosis for future stroke and cardiac events. In contrast, there is also some evidence that patients with marked nocturnal BP declines (so-called “extreme dippers”) are at greater risk for ischemic strokes and silent myocardial ischemia than patients whose decline in BP during sleep is normal.

Both the etiologies and the consequences of an elevated nocturnal BP are diverse. Since Shimada et al first reported a study evaluating ambulatory BP monitoring in older patients with hypertension using MRI 15 years ago, there has been an ongoing issue with our general understanding of BP variability and the brain as a target organ, because most studies have had small sample sizes and have been performed in homogenous populations. In this issue of Hypertension, Schwartz et al have provided us with a large cross-sectional study from Minnesota and Mississippi of 263 black and 343 white subjects who underwent clinic and ambulatory monitoring of the BP and MRI of the brain to assess the relations among the various BP measures and white matter lesion volumes. In both black and white subjects, BP during sleep and the nocturnal decline in BP (ie, the dip in the 24-hour curve) were associated with white matter lesion volume; in contrast, 24-hour mean and daytime awake BP values were associated with white matter lesions in black patients but not in white patients.

In comparison to cardiac or renal target organ involvement in patients with hypertension, there is far less information on age- and gender-normalized data for MRI-derived white matter lesions in older patients with hypertension. These lesions, also referred to as leukoaraiosis or small-vessel ischemic disease, may be multifocal or progress to confluence over time. White matter lesion volumes increase with age and multiple risk factors, including elevated homocysteine levels. Studies over the past several years have reported that white matter hyperintensity lesions are associated with increased risk of primary and recurrent stroke, gait and balance disorders, and dementia; hence, the potential for clinical importance seems established. These findings are not surprising, because there are good correlations between neuropathologic subcortical vascular disease and the brain imaging abnormalities. In addition, it is now felt that the white matter lesions seen on T2-weighted MRI are different from lacunar infarctions, because they are hyperintense throughout the lesion rather than hypointense with a T2 hyperintense circumferenc. Nevertheless, as clinicians we still remain uncertain as to whether white matter lesion volumes of 5, 10, or 20 cm³ in an older, asymptomatic patient with hypertension have different predictive values for future stroke, dementia, or gait disorders.

The study by Schwartz et al demonstrates that subjects who have an elevated nocturnal BP have a greater burden of white matter lesions. Furthermore, this finding was independent of the clinic BP values and is present in a biracial population. The lack of a more robust finding relating 24-hour BP with the volume of white matter lesions in this large sample size is surprising but, as the authors noted, could be secondary to a 1-year lag time between performing the MRIs and the ambulatory BP recordings or to the high rate of use of long-standing antihypertensive therapies. I would bet on the latter, because ambulatory BP monitoring is quite robust and highly reproducible over 1 to 2 years and probably did not play a major role in the weak association with 24-hour mean values and white matter lesion volume. Schwartz et al do not provide follow-up data of the subjects, and we know little about the progression of white matter lesions over time in patients with hypertension. In one longitudinal study by Goldstein et al, 155 healthy men and women, aged 55 to 79 years, were followed for 5 years with two 24-hour ambulatory BP studies and MRIs to quantify hyperintensities and total brain volumes. During the 5 years between studies, only 10 subjects started antihypertensive therapy, and the average awake and sleep ambulatory systolic BP increased by 6 mm Hg in the population. The best predictors of increases in white matter lesion volume corrected by total brain volume were age, an elevated awake systolic BP at both time points, and the volume of the white matter lesions itself. In fact, for each millimeter of mercury increase in awake systolic BP, there was a 4.6% increased risk of severe white matter lesions 5 years later. For each millimeter of mercury of sleep BP
variability, there was a 16.3% risk of development of severe
brain atrophy.

Thus, it is relatively clear that the relationships among
casual (or clinic), awake, and sleep BP and vascular disease
in the brain are varied according to the patient population
studied, the methodology used to evaluate the white matter
lesion volumes, and the presence or absence of antihypertensive
drug therapy. This entire field from the perspective of a
hypertension specialist is in its infancy. In the study by
Goldstein et al., ischemic lesions in the insular subcortex
were related to levels of the patients’ casual systolic BP. The
insular subcortex is an area of the brain that is associated with
increased heart rate variability and hyperglycemia in patients
with stroke. It is unknown whether ischemic damage to this
area of the brain begets hypertension or vice versa. Fortu-
nately, studies have shown that patients taking antihyperten-
sive drugs and who have controlled BP have a reduced risk of
severe white matter lesions. Dufoi et al. performed a 3-year
MRI substudy of the Perindopril Protection Against Recur-
rent Stroke Study to measure the presence of volume of
incidental white matter lesions in 225 patients with previous
stroke or transient ischemic attacks. The results demonstrated
that well-controlled patients on 2 drugs (an angiotensin-
converting enzyme inhibitor and diuretic) who had white
matter lesions at baseline were not likely to experience an
increase in lesions over 3 years. These results need to be
extended to patients who have not yet had a stroke and may
have different rates of progression of vascular injury. In the
future, these studies should obtain BP measurements during
sleep if we are to understand the impact of an intervention
that may or may not control BP over a full 24-hour period.

Sources of Funding
This work was supported in part by funding from the National
Institutes of Health grant R01 AG022092-01 and a Community
and Clinical Research Award from the Catherine Weldon and
Patrick Donaghue Medical Research Foundation (Hartford, Conn).

Disclosures
None.

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The Riskiest Time for the Brain: Could the Nighttime Be the Right Time for Intervention?

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Hypertension. 2007;49:1215-1216; originally published online April 2, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.089060

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/49/6/1215

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