The increasing use of ambulatory blood pressure monitoring (ABPM) devices in the investigation of hypertension has allowed detailed study of the circadian rhythm of blood pressure variability, the assessment of resistant hypertension, and the syndrome of “white coat” hypertension. The relevance of ABPM to target-organ damage and the complications of hypertension, such as heart attacks and strokes, has only recently gained prominence. There are more than 30 cross-sectional studies that have linked ABPM to hypertensive target-organ damage, including left ventricular hypertrophy (LVH), microalbuminuria, hypertensive retinal changes, and cerebrovascular disease. The majority of these studies have consistently reported that patients with an absent or reduced fall in blood pressure at night (referred to as “nondippers”) have more severe target-organ damage, including LVH and cerebrovascular disease, when compared with patients who demonstrate a normal nocturnal fall in blood pressure. For example, Verdecchia et al, in a prospective cohort of over 1100 hypertensive patients, reported higher mortality rates both in nondippers and “reverse dippers” and higher cardiovascular morbidity rates in female nondippers compared with dippers. In addition, Yamamoto et al recently reported that progressive cerebrovascular disease, including silent ischemic lesions and symptomatic stroke, was associated with a reduced nocturnal blood pressure fall in patients with a history of lacunar infarction. In a cross-sectional study of patients admitted with acute stroke (ictus <12 hours), Lip at al reported that such patients could generally be classed as nondippers, with higher blood pressures recorded using ABPM (but not using casual manual measurements) in black/Afro-Caribbean patients and also in patients with hemorrhagic stroke. These studies therefore suggest the potential usefulness of ABPM in epidemiological, cohort, or cross-sectional studies and the assessment of ethnic differences, stroke subtypes, and prognosis.

A nondipper status on ABPM may thus appear to be a potential predictor of cardiovascular or cerebrovascular morbidity and mortality. There are a number of potential problems that may complicate such an assumption. Vascular disease itself could impair nocturnal blood pressure falls through impairment of cardiovascular reflexes. Furthermore, it remains uncertain whether this nondipper status genuinely reflects a greater daily blood pressure “load” or whether it merely means that the patient did not sleep soundly, having been disturbed by the inflation of the blood pressure cuff. This may particularly be the case in an acutely unwell stroke patient who is unable to sleep immediately after hospital admission. The association between nocturnal blood pressure and the progression of cerebrovascular disease could be complicated by the potential exacerbation of cerebral ischemia by excessive falls in nocturnal blood pressure leading to reduced cerebral blood flow or the reduction of nocturnal blood pressure with antihypertensive therapy.

Blood pressure alterations following acute stroke, particularly a reduction in the day-night difference and a transient elevation in blood pressure after stroke, have been reported in a number of studies. The interpretation of the reduced day-night difference or nondipping is, however, complicated by two factors. First, 20% of hypertensive patients exhibit nondipping, which has also been described in medical conditions as diverse as renal disease, diabetes with autonomic neuropathy, heart failure, Cushing’s disease, and severe pre-eclampsia. Second, many studies have relied on arbitrary, fixed thresholds for the definition of day and night, failing to account for variable sleep patterns and the appreciable arousal from sleep in some patients. Nevertheless, one plausible explanation for the reduced day-night variation in poststroke patients is the influence of stroke subtype (that is, cerebral infarct or hemorrhage) and the extent or topographical location of the cerebral lesion, perhaps with altered autonomic regulation leading to pathological activation of the sympathetic nervous system.

Activation of the autonomic nervous system is well recognized as being present in humans with essential hypertension. Indirect markers of sympathetic tone, such as plasma norepinephrine, are elevated in essential hypertension, and sympathetic nerve activation to the skeletal muscle circulation is increased in borderline hypertensive individuals and further increased according to the severity of the hypertension. Such sympathetic activation may lead to alterations in cardiac and vascular structure that are independent of the blood pressure elevation, and this may be an important factor in nondippers, who continue to demonstrate heightened nocturnal sympathetic tone. Some experimental evidence also suggests that increased α-1 adrenergic receptor stimulation may contribute to the persistently elevated blood pressure levels in nondippers. Animal studies, rat models in particular, have significantly contributed to our understanding of
autonomic modulation in acute stroke. For example, middle cerebral artery occlusion (MCAO) in rats leads to consistent focal cerebral ischemia, and this has proved to be a valuable model for studying autonomic dysfunction and other cardiovascular abnormalities in acute stroke. Many studies have shown that MCAO leads to an increase in renal sympathetic nerve discharge, an increase in circulating norepinephriners, and associated myocardial ischemia, subendocardial congestion, or subendocardial hemorrhage. Indeed, the sympathetic activation is more marked after right MCAO, with involvement of the insular cortex and amygdala. Because the latter mediates cardiovascular responses to stress, the neurochemical changes in the amygdala may thus be responsible for stroke-induced cardiovascular disturbances.

Human studies have also attempted to determine the influence of stroke subtype, the topographical location, the extent and laterality of the infarction or hemorrhage, and the involvement of structures such as the insular cortex on sympathetic nervous system activation. For example, Sander and Klingelhofer reported reduced day-night blood pressure changes in patients with thromboembolic cerebral infarction and that involvement of the insular cortex was associated with reverse dipping and increased plasma norepinephrine levels. Right hemisphere lateralization of autonomic control has also been demonstrated in humans, with a reduction in ipsilateral parasympathetic innervation after right hemisphere stroke. It has even been postulated that this relative increase in sympathetic tone could account for the differential effects of cerebral infarction on cardiac rhythm.

Although the majority of clinical studies have not specifically addressed the role of stroke subtype on the 24-hour blood pressure profile, differential responses have been observed in a number of studies. For example, Lip et al. reported a reduced day-night difference in all types of stroke, with a trend toward reverse dipping in patients with primary intracerebral hemorrhage (PICH). Similarly, Yamamoto et al. reported a significant reduction in the proportional nighttime blood pressure fall in subcortical and brain stem strokes, particularly after PICH. In this issue of Stroke, the Leicester group report a study using 24-hour ABPM to assess the diurnal blood pressure variation in 98 stroke patients within 48 hours of ictus. Fifty patients had cortical infarcts, 29 subcortical infarcts, and 19 PICH. Their patients with cortical infarcts and PICH had significantly reduced diurnal variation in systolic blood pressure, whereas subcortical infarcts demonstrated only reduced percentage differences. Mean diurnal differences in diastolic blood pressure were, however, significantly reduced in all stroke groups.

This article therefore attempts to address the effect of stroke subtype on diurnal changes in blood pressure, with the suggestion that autonomic regulation of blood pressure is damaged, especially in cortical infarction and PICH, leading to nondipping on ABPM. However, the numbers in each subgroup are probably too small to draw precise conclusions about the effect of the extent and laterality of the infarction or hemorrhage and the involvement of structures involved in autonomic control. For example, it would have been interesting to ascertain whether patients with right MCAO, with involvement of the insular cortex and amygdala, have more sympathetic activation, as was seen in animal studies.

The cynic would argue that the clinical and prognostic implications of ABPM findings in acute stroke are unclear. The suggestion that nondipping is associated with a poorer prognosis after stroke seems plausible in view of the associations with target-organ damage and complications of hypertension; however, if nondipping is detected in a stroke patient in present-day clinical practice, our management is still unlikely to differ. The use of cusums analysis is an attempt to avoid the problems of day-night definition with ABPM studies, but the clinical application of this complex statistical method to clinical practice is uncertain; indeed, how many of us would base our patient management on a cusum plot?

Perhaps nondipping may merely reflect a (very) large area of brain damage following a stroke, whether ischemic or hemorrhagic. A larger and more comprehensive series of well-characterized patients is therefore needed, in which the analysis of the effect of different stroke subtypes on blood pressure variation as a surrogate of autonomic function would not only prove some clinical relationship to previous animal work but also allow greater understanding of brain anatomy and function and provide information on the prognostic value of such measurements.

References

Ambulatory Blood Pressure Monitoring and Stroke: More Questions Than Answers
Gregory Y. H. Lip, Christopher R. Gibbs and D. Gareth Beevers

Stroke. 1998;29:1495-1497
doi: 10.1161/01.STR.29.8.1495

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1998 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/29/8/1495