Morning Blood Pressure Surge and the Risk of Stroke

To the Editor:

I read with great interest the important study of Kario et al1 in the March 18th issue about morning blood pressure surge and the risk of stroke. I would like to point out that the blood pressure surge does not occur solely on awakening in the morning. My colleagues and I2 as well as others3 have found that blood pressure surges also occur after the afternoon nap, also known as the siesta. As noted in the accompanying editorial, we have also described that practice of the siesta may be associated with doubled mortality in the elderly. More recently, two independent groups in Greece have found people in whom the siesta is prevalent and in whom a second peak of stroke corresponds to awakening from the siesta.3,5 The unaccounted-for siesta may be one cause of misclassification of dipping; another is nocturnal awakening, the siesta’s nocturnal mirror. Many older individuals such as the cohort of Kario et al, wake up at night, sometimes several times (especially men with prostatism). If their nocturnal awake blood pressure measurements were included in the nocturnal average, as occurs when such awakenings are not accounted for, major misclassification would occur.6 Such misclassification would bias the night’s blood pressure, lack of dipping (or extreme dipping), and the subsequent blood pressure surge on awakening. As this surge may be extremely important as pointed out by Kario et al, it should be appropriately evaluated. Until more precise tools are widely available, estimation by using patients’ diaries is a simple, easy, inexpensive, and universally available tool for such evaluation. Last but not least, it is well accepted by patients and increases their confidence in the analysis extracted from the little box.

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To the Editor:

We read with interest the report on morning surge of blood pressure by Kario et al and the editorial by Kaplan. For the recognition of the morning surge, the use of early morning home blood pressure measured by the patient him- or herself is suggested. From our own experience of ambulatory 24-hour monitoring (ABPM) and home blood pressure monitoring, we agree with the potential benefits of this approach.

We compared self-measured blood pressure and heart rate values with the respective values of ABPM in a group of 37 consecutively recruited hypertensives with poor blood pressure control despite antihypertensive medication (Mengden et al, unpublished data, 2000). Self-measurement of blood pressure was performed with the highly accurate Omron IC system (upper arm, oscillometric device). Patients were instructed to measure blood pressure after rising and before taking antihypertensive medication for a period of 2 weeks. As the Omron IC is a memory device with automatic storage of blood pressure/heart rate values together with the respective time of measurement, we were able to compare the trough values of self-measured home blood pressure with the respective trough values of ABPM (Spacelabs Medical 90207 recorder). We compared self-measurement (in the morning before intake of antihypertensive medication), the average of 3 ABPM recordings at the end of the dose interval (morning ABPM, trough value before intake of antihypertensive medication, measuring cycles 15 minutes), and the mean daytime readings of ABPM (6 AM to 10 PM).

The highest blood pressure values were observed with self-measurement of home blood pressure (163.0±20.0/10.0±10.0 mm Hg) as compared with morning ABPM values (151.1±20.1/88.0±10.9 mm Hg; P=0.0001 for systolic values). ABPM daytime values (148.4±14.9/89.3±9.4 mm Hg) did not differ significantly from morning ABPM values. Heart rate at the end of the dose interval was significantly lower for self-measurement as compared with ABPM readings (71.8±9.0 versus 76.9±14.6 and 77.2±12.0; P=0.01). In our patients, self-measurement delivered additional information about the early morning rise of blood pressure and heart rate that was different as compared with ABPM. The self-measured readings indicate the need for more effective, long-acting antihypertensive therapy (24-hour or longer efficacy). The significantly lower heart rate observed with self-measurement despite higher blood pressure values may indicate that activation of the sympathetic nervous system played a minor role in the morning surge. Home measurements can be used to recognize the morning surge of blood pressure. Given the well-known observer bias for the reporting of self-measured values, memory-equipped devices should be used to identify the exact measurement time with regard to rising and medication intake.

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To the Editor:

Kario et al1 report that a higher morning blood pressure surge (MBPS) is associated with stroke risk independent of ambulatory blood pressure (BP), nocturnal BP falls, and silent infarct in older hypertensives. The authors suppose that an excessive MBPS might trigger strokes through some hemodynamic mechanism such as increased shear stress on the atherosclerotic cerebral vessels, but there are several other factors that change during the morning hours. These include an increase of sympathetic nervous activity, particularly α-adrenergic activity,2 and other related acute risk factors such as platelet hyperactivity, hypercoagulability and hypofibrinolysis, blood viscosity, and increased vas-
cular spasm. We have recently reported\(^4\) that in never-treated subjects with essential hypertension, a rise in systolic BP ≥50 mm Hg and/or diastolic BP ≥22 mm Hg during the early morning (6:00 to 10:00 AM) is associated with the highest morning values of the ratio between low-frequency and high-frequency RR interval (considered as a marker of sympathetic overactivity), increased urinary catecholamine output, and left ventricular hypertrophy. The coexistence of sympathetic overactivity and left ventricular hypertrophy in patients with higher MBPS might contribute to their raised vascular risk and might explain the increase of cardiovascular accidents in early morning. The increase of sympathetic activity in the early morning is associated with some adverse modifications regarding heart rate, fibrinolytic activity, and platelet aggregability\(^5\) that may make the morning BP rise at most a pathophysiological cofactor in the determination of the increased morning rate of cardiovascular morbidity and fatal events.

**Response**

Dr Burszytyn pointed out that individual behavioral factors such as a siesta and nocturnal awakening are important modulators of the association between morning blood pressure (BP) surge and cardiovascular risk. Recently developed ambulatory BP monitors (ABPM) equipped with actigraphy\(^1\) could be used to assess the relationships between the morning- or siesta-associated BP surges and changes in physical activity.

Dr Mengden et al recommended using memory-equipped devices for self-measurement of morning BP (SMBP) to reduce observer bias and to demonstrate the marked differences between morning BP and pulse rate measured by SMBP and ABPM. They found that morning systolic BP was 12 mm Hg higher by SMBP than by ABPM, whereas morning pulse rate was 5 mm Hg lower by SMBP. This may indicate that self-monitoring per se might be stressful for some patients. In our Jichi Morning-Hypertension Research (J-MORE) Pilot Study of a total of 1027 consecutive hypertensives who were taking the same antihypertensive medication for at least 3 months, SMBP was conducted twice in the morning just before taking antihypertensive medication and in the evening just before going to bed for 3 consecutive days, using devices. In this study, the first BP reading of each pair of the 6 sets of measurements (morning and evening for 3 days) was consistently higher by 3.4 to 3.9 mm Hg systolic and by 1.1 to 1.7 mm Hg diastolic, whereas the difference between the first and the second pulse rates was <1.0 bpm. This suggests that some pressor response occurs during the first measurement of SMBP. To reduce the effects of this response, the second measurement may be preferable to assess morning BPs.

SMBP cannot directly assess the morning BP surge, but when evening BPs measured just before going to bed are combined with morning BPs, some additional information can be derived for clinical practice. When we analyzed data from the same 519 patients using the morning and evening BPs (ME) derived from the ABPM data, after controlling for baseline characteristics, both the ME average (morning systolic BP+evening systolic BP÷2) (10 mm Hg increase; relative risk=1.41 [95% CI=1.19 to 1.67], \(P=0.0001\)) and the ME surge (morning systolic BP−evening systolic BP) (10 mm Hg increase; relative risk=1.24 [95% CI=1.08 to 1.42], \(P=0.0025\)) were independently associated with the risk of stroke.

We agree with the opinion of Dr Marfella et al that other sympathetic activation–associated potentiation of risk factors, including heart rate and platelet/hemostatic factors,\(^3\) would augments the morning risk for cardiovascular events. In fact, in our recent study, the morning increase in platelet aggregation and in the plasma levels of von Willebrand factor and tissue-type plasminogen activator, 2 in vivo markers of endothelial cell stimulation, were significantly correlated with a higher morning BP surge in hypertensive patients (K. Kario MD, et al, Linkage between morning surge in blood pressure and acute risk factors for silent cerebrovascular disease in elderly hypertension, submitted for publication). To clarify the impact of morning BP surge from other confounders, we have just initiated the Japan Morning Surge-1 (JMS-1) Study, a randomized parallel control study, in which we attempt to study the effect of suppression of morning BP surge on target organ damage in treated hypertensives with high morning BPs.

We believe that the strict control of morning BP as well as morning-potentiated risk factors would achieve more effective prevention of cardiovascular events in hypertensive patients.

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Effect of the Asp\textsuperscript{298} Variant of Endothelial Nitric Oxide Synthase on Survival for Patients With Congestive Heart Failure

To the Editor:

McNamara et al\textsuperscript{1} recently reported a significant association between the Asp\textsuperscript{298} variant of endothelial NO synthase (NOS3) and poorer event-free survival in congestive heart failure (CHF) patients. This study was based on the premise that the Asp\textsuperscript{298} NOS3 variant would have a shorter half-life, thus implying a decreased in vivo generation of NO, which is deemed to play a protective role. To support their contention, the authors quoted a study that claimed the Asp\textsuperscript{298} variant to be more vulnerable to intracellular cleavage. However, this contention was subsequently disputed by a painstaking study that clearly demonstrated that the intracellular cleavage found in cells harboring the Asp\textsuperscript{298} NOS3 substitution was an in vitro artifact caused by the acidic pH used.\textsuperscript{2} According to both studies, the Asp\textsuperscript{298} replacement does not affect NOS3 biological activity.\textsuperscript{2,3}

Portantly, we also showed that this variant, and not the Asp,\textsuperscript{298} allele, binds a replication protein A1 that acts as a repressor of NOS3 transcription. Therefore, it is not surprising that this allele has been associated with a significant reduction in NOS3 gene promoter activity, with ensuing reduction in the rate of transcription of NOS3 in response to hypoxia and also with vasoconstrictor angina in Japanese patients. Thus, it remains controversial whether the Asp\textsuperscript{298} variant implies a blunted NOS3 activity; accordingly, the contention that the latter accounts for the poorer event-free survival in CHF observed by McNamara et al\textsuperscript{1} cannot be taken for granted.

At variance with the Asp\textsuperscript{298} variant, another single-nucleotide polymorphism located in the promoter region of the NOS3 gene, the T\textsuperscript{786}C substitution was shown to bear functional consequences. The C\textsuperscript{786} allele binds a replication protein A1 that acts as a repressor of NOS3 transcription. Therefore, it is not surprising that this allele has been associated with a significant reduction in NOS3 gene promoter activity, with ensuing reduction in the rate of transcription of NOS3 in response to hypoxia and also with vasospastic angina in Japanese patients.

We recently reported that the Asp\textsuperscript{298} NOS3 variant was in linkage disequilibrium with the T\textsuperscript{786}C substitution.\textsuperscript{4} More importantly, we also showed that this variant, and not the Asp,\textsuperscript{298} was associated with a blunted forearm blood flow response to acetylcholine in essential hypertensive patients\textsuperscript{5} and with multivessel coronary artery disease in the GENICA study.\textsuperscript{4} Therefore, we propose that the C\textsuperscript{786} variant, which was not determined in the study by McNamara et al,\textsuperscript{1} can be the most relevant one, both functionally and as predictor of events in CHF patients.

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Response

We appreciate the point emphasized by Drs Maiolino and Rossi that other common polymorphisms exist in the NOS3 gene, including the T\textsuperscript{786}C promoter polymorphism referenced in their recent studies. We also agree that there is much debate about the functional significance of both the T\textsuperscript{786}C and the Asp\textsuperscript{298}/Glu polymorphisms. Overall, clinical studies of these polymorphisms support the concept that genetic heterogeneity at the NOS3 locus influences both cardiovascular risk and clinical outcomes. Whether these specific mutations are causative, or in linkage disequilibrium with distinct and functionally more important polymorphisms, remains open to question.

Although not part of the published study, the impact of the T\textsuperscript{786}C polymorphism for heart failure outcomes has been investigated by M.B. in our laboratory. Although this analysis does confirm linkage disequilibrium between these 2 polymorphisms, the T\textsuperscript{786}C polymorphism does not appear to influence event-free survival. We cannot exclude the possibility raised by Drs Maiolino and Rossi that the impact of the Asp\textsuperscript{298} variant in our cohort was due to linkage to an additional polymorphism of NOS3. However, our data do not support the influential role for the T\textsuperscript{786}C polymorphism that they have proposed.

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