The morning blood pressure surge: a dynamic and challenging concept
Paolo Palatini\textsuperscript{a} and Guido Grassi\textsuperscript{b}

Journal of Hypertension 2011, 29:2316–2319

\textsuperscript{a}Dipartimento di Medicina Clinica e Sperimentale, Università di Padova, Padua and \textsuperscript{b}Clinica Medica, Dipartimento di Medicina Clinica, Prevenzione e Biotecnologie Sanitarie, Università Milano-Bicocca, Ospedale San Gerardo, Monza, Italy

Correspondence to Professor Paolo Palatini, Department of Clinical and Experimental Medicine, University of Padova, via Giustiniani 2, 35128 Padua, Italy
Tel: +39 049 821 2278; fax: +39 049 875 4179; e-mail: palatini@unipd.it

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Many hypertensive patients display an exaggerated increase in blood pressure (BP) levels in the morning, referred to as the morning BP surge, a phenomenon that is known to increase the risk of cardiovascular events [1–5]. Indeed, a number of studies have shown that the onset of acute events, including sudden death, myocardial infarction and stroke peak in the first 4–6 h after awakening [6,7]. The pathogenesis of the morning surge is not well known and understanding the mechanisms responsible for this abnormal increase in BP, particularly in hypertensive patients, might be of help for identifying new therapeutic strategies. Two main definitions of the morning surge in BP are currently used in the literature [8,9]. One is called the ‘sleep-through morning surge’ and is defined as the difference between the morning pressure during the first 2 h after awakening and the average of the lowest nighttime BP. The second definition is the ‘preawakening morning surge’ and is calculated as the difference between the morning BP during the first 2 h after awakening and the BP during the first 2 h before awakening. The level of the morning BP surge at which the risk appears to become excessive is not well known. Kario \textit{et al.} [10] in their seminal description of the impact of the morning BP surge on stroke events used the 55 mmHg threshold level (top decile of sleep-through morning surge). In the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome that analyzed 5645 people from eight countries, the top decile for the two definitions of morning BP surge was 37 and 28 mmHg, respectively [11]. Using both definitions, the authors suggested that a systolic morning BP surge less than 20 mmHg is unlikely to be associated with increased risk. In a study by Marfella \textit{et al.} [12], the morning BP surge was defined as a rise in SBP of at least 50 mmHg (90\% percentile of normotensive patients) and/or DBP of at least 22 mmHg during the early morning (0600–1000 h), compared with the mean BP during the night. According to Suzuki \textit{et al.} [13], there are even two types of morning surge, the mechanisms of which may differ. The BP rise occurring immediately after waking up is more common in older hypertensive individuals, and is probably related to augmented arousal response in BP, whereas the morning surge beginning gradually during sleep is more common in younger hypertensive individuals and is characterized by reaching basal BP earlier at night.

Several studies performed in the past decade have found significant relations among the early morning BP surge and target-organ damage in hypertension. Kuwajima \textit{et al.} [14] reported a significant association between the increase in SBP after arising from bed and left ventricular mass index. Gosse \textit{et al.} [15] found that left ventricular mass index and wall thickness were better correlated with the SBP on arising than with office BP. Similar results were found by Marfella \textit{et al.} [12], who found that morning BP surge was significantly positively correlated with left ventricular posterior wall thickness and left ventricular internal diastolic diameter. Some authors have found significant relations of the early morning BP surge also with vascular disease [16] or white matter lesions of the brain [10,17]. In a group of individuals with exaggerated morning BP surge, Marfella \textit{et al.} [12] observed that increased sympathetic activity in the morning led to prolonged QTc dispersion, a harbinger of ventricular arrhythmias and sudden death. Prospective studies in Japan and Europe have demonstrated a longitudinal association of the early morning BP surge with cardiovascular events. In older hypertensive individuals, Kario \textit{et al.} [10] showed that a higher morning BP surge was a main predictor of stroke risk independently of the nocturnal BP decline. In this study, for each 10-mmHg increase in the morning BP surge, the risk of stroke increased by 22\%. In the Ohasama study, an exaggerated early morning BP surge was associated with the development of hemorrhagic stroke [18]. These results are consistent with those obtained in a French population in which a higher cardiovascular morbidity and mortality rate was observed in the patients with the highest morning BP surge compared with those in the lowest morning BP surge group [19]. In a recent analysis of the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcome, the morning BP surge was associated with a 30–45\% increase in hazard for cardiovascular events [11]. Some studies, however, failed to confirm morning surge as an independent predictor of cardiovascular events. This is the case for the evidence collected in the general population sample of the
Dramatis that exaggerated morning surge found no significant differences between et al., only a BP surge of at least 55.0 mmHg was an et al. Journal of Hypertension. Adapted from [12].

Given the detrimental effect of an exaggerated morning surge on the cardiovascular system, it is important to unveil the mechanisms responsible for this hemodynamic phenomenon. According to most authors [1,2,22–24], the sympathetic nervous system is a key regulator of the morning BP surge and a sudden activation of the sympathetic nervous system, particularly the \( \alpha \)-adrenergic component, is thought to be the primary mediator of the morning rise in BP. A significant rise both in epinephrine and norepinephrine has been found to be responsible for the morning increase in BP in normal individuals [25,26].

In this issue of the Journal of Hypertension, Hering et al. [27] investigated the relationship between the morning BP surge and sympathetic activity through microneurographic assessment of sympathetic nerve traffic to blood vessels. Muscle sympathetic nerve activity (MSNA) was measured during undisturbed supine rest in 68 untreated hypertensive patients. In a multivariate analysis, taking into consideration age, BMI and sex, they found that MSNA was independently related to both daytime (\( P = 0.006 \)) and night-time heart rate (\( P = 0.02 \)), but not to the morning surge of BP, either calculated as the difference between the morning BP and the preawakening BP or the morning BP minus mean BP during the 1 h that included the lowest sleep BP. They concluded that sympathetic neural mechanisms are unlikely to contribute to the morning BP surge in recently diagnosed essential hypertensive patients. According to Hering et al. [27] the lack of relationship between the morning surge and MSNA in their study might be attributed to the relatively small average preawakening SBP morning surge present in their group (19 mmHg) compared with previous reports. In the study by Li et al. [11], only a morning BP surge exceeding 37.0 mmHg at least was a significant and independent predictor of mortality and cardiovascular events. In the prospective clinical study by Kario et al. [10], a BP surge of at least 55.0 mmHg was an independent risk factor involved in stroke events in elderly hypertensive individuals. However, the lack of correlation between morning hemodynamics and MSNA measured in resting conditions may not be surprising. As the authors themselves point out, patients were studied in the supine position using direct measurements of MSNA from the peroneal nerve during daytime and not upon awakening. For obvious technical reasons, measurement of MSNA was not available during sleep (very few are the studies performed so far recording MSNA during sleep) and, thus, direct calculation of the change in sympathetic nervous system activity from night to day was not possible. The results obtained by Marfella et al. [12] with spectral analysis of heart rate variability in two groups of hypertensive individuals, one with exaggerated BP morning surge and one with normal BP rise, may reconcile the apparently conflicting results of the study by Hering et al. with those by other investigators. In keeping with the results by Hering et al., Marfella et al. found no significant differences between the two morning surge groups for the low-frequency/high-frequency power ratio (LF/HF), an indirect index of sympathetic activity, during the daytime or the nighttime period (Fig. 1) [12]. However, the morning LF/HF ratio was significantly higher in the individuals with exaggerated morning surge than in the rest of the group. In addition, a relative decrease in the high-frequency

![Fig. 1](image_url)

**Fig. 1**

Low frequency/high frequency ratio (LF/HF) from spectral analysis of heart rate variability in a group of hypertensive individuals with exaggerated morning BP peak (+) and a group with normal BP peak (−). Adapted from [12].
component and a significant increase in LF/HF ratio was observed in the individuals with exaggerated BP surge during the morning period. Also, diurnal and nocturnal plasma catecholamine concentrations, other well-recognized markers of sympathetic activity, did not differ according to the amplitude of the morning surge [12]. However, in the individuals with large morning BP surge, both urinary epinephrine and norepinephrine outputs during the morning period were significantly greater than that in individuals with normal BP rise. These data confirm that autonomic nervous system activity measured in steady-state basal conditions may be normal in patients with increased BP morning surge. However, the greater morning increase in LF/HF ratio and urinary catecholamine levels observed in people with morning BP peaks indicate that sympathetic reactivity is a key determinant of the morning rise in BP. According to Kario et al. [28], an exaggerated morning BP surge may be present in extreme dippers that may be closely associated with morning sympathetic activation. These authors found that 24% of extreme dippers had an exaggerated morning BP surge, which was accompanied by orthostatic increases in BP and plasma norepinephrine levels that were selectively abolished by an α-adrenergic blocker.

On the basis of the background information provided by the experimental studies discussed above, it is reasonable to hypothesize that the α-adrenergic vasoconstrictor response of small resistance vessels, and a progressive remodeling of the small vessels with time, would contribute to the BP rise upon awakening chiefly in predisposed individuals. Risk factors for a profile of excessive early morning hypertension include excessive alcohol use and tobacco consumption, older age, longer sleep times and later awakening times [1,2]. Data by Modesti et al. [29] showed that cold weather was significantly associated with increased morning BP surge in elderly individuals, which may partly account for the increased number of cardiovascular events observed in the morning during the winter season.

Several other mechanisms have been postulated to explain the morning BP surge. Different functional alterations of the circulation can variably combine in individual patients and account for the heterogeneous pathophysiological mechanisms of the morning rise in BP. The renin–angiotensin–aldosterone system (RAAS) is also activated in the morning and could contribute to the high BP reactivity in the morning [1,2]. In addition to circulating factors, it was shown that tissue RAAS also exhibits diurnal variation, possibly in relation to a clock gene [30]. Reduced endothelial function could contribute to the exaggerated increases in vascular resistance and peaks of pressure during the morning hours [31,32]. Even in healthy individuals, flow-mediated dilatation of the brachial artery was reduced in the early morning when compared with other periods of the day [31], and the degree of attenuation in endothelial function in the morning in healthy normal individuals was very similar to the attenuation of brachial artery reactivity found in high-risk patients [32]. Marques et al. [33] recently studied the genes responsible for exaggerated circadian variation of BP in the Schlager hypertensive mouse, a model that exhibits a similar morning BP surge as seen in human essential hypertension. These authors identified 212 hypothalamic genes whose expression differed between ‘peak’ and ‘trough’ BP in the hypertensive strain. These included genes with known roles in the expression of hormones implicated in the regulation of BP such as vasopressin, oxytocin and thyrotropin-releasing hormone. In summary, several potential causes of exaggerated morning BP surge have been described in hypertension, suggesting different, and variously concurrent, pathogenetic mechanisms in individual patients, which can account for the described heterogeneous pathophysiological features of this hemodynamic phenomenon. These mechanisms may variously involve a transient increase in neurohumoral vasoconstrictor activity and a background of increased susceptibility to vasoconstrictor agents.

Although the morning BP surge may be seen as a physiological phenomenon in the hypertensive patients, it is an independent risk factor for the development of atherosclerosis and target-organ damage and a potential trigger of cardiovascular events. Thus, in addition to strict BP control, it seems reasonable to consider targeting this time of day with appropriate antihypertensive drug therapy. As suggested by some investigators [34], α-adrenergic blockade at bedtime may be an effective means to reduce the morning BP rise in patients with uncontrolled ‘morning hypertension.’ Also, renin–angiotensin-blocking agents that maintain pharmacodynamic effects into the early morning period may be of help in individuals with exaggerated rise in morning BP [35]. These two classes of drugs would favorably act on the two main mechanisms that regulate BP during this period of the day. Future research should appropriately focus on the effect of a therapy targeting BP and heart rate in the early morning to evaluate whether reduction of the morning surge will reduce cardiovascular morbidity and mortality.

**Acknowledgement**

**Conflicts of interest**

There are no conflicts of interest.

**References**

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