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REVIEW SERIES

Diurnal blood pressure variation and sympathetic activity

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Blood pressure changes occurring over a 24-h period are under behavioral, humoral and reflex regulation. The sympathetic nervous system modulates blood pressure variation by affecting cardiac output and peripheral vascular resistance. This paper reviews evidence for the relationship between adrenergic neural drive and blood pressure as measured by direct and indirect approaches. This paper also reviews the sympathetic activity associated with increased 'in-office' and 'out-of-office' blood pressure, that is, the white-coat and the masked-hypertensive states. Finally, this paper examines altered neuroadrenergic influences on nocturnal blood pressure reduction and blood pressure variability.
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INTRODUCTION

Blood pressure undergoes considerable change during a 24-h period, showing both rapid fluctuations lasting a few cardiac cycles and prolonged variations, such as those distinguishing daytime from nighttime blood pressure.[1,2] Clinical evidence shows that both short- and long-term blood pressure variations occurring during a 24-h period increase progressively as subjects advance from normotensive to hypertensive.[3] Evidence also indicates that the prevalence and severity of end-organ damage from hypertension is closely related to the 24-h blood pressure average and blood pressure variability.[4–6] Finally, further studies unequivocally show that the magnitude of blood pressure variability has major prognostic relevance and predicts both nonfatal and fatal cardiovascular events.[4,7,8] Collectively, these studies emphasize the clinical importance of spontaneous blood pressure oscillations and validate this variability as a target of antihypertensive drug treatment.

Despite the vast accumulated information on the clinical relevance of blood pressure variation, the mechanisms responsible for blood pressure variability still remain largely undefined. This paper examines the mechanisms responsible for daytime blood pressure variation. Emphasis will be given to the influences from the sympathetic nervous system or 'neurogenic factors' involved in daytime blood pressure regulation.

MECHANISMS INVOLVED IN DIURNAL BLOOD PRESSURE VARIATIONS

Blood pressure recording using invasive or noninvasive devices permits measurement under various conditions, including static or dynamic exercise, daily living under stressful conditions, cigarette smoking and sleep. With the exception of sleep, all the above-mentioned conditions increase blood pressure, blood pressure variability and oscillations.[9] By contrast, sleep is associated with reduced blood pressure and reduced blood pressure variability, regardless of whether sleep takes place during the nighttime or daytime period.[9] Blood pressure changes have been ascribed to the so-called 'behavioral influences,' including environmental factors, response to physical or emotional stressors, as well as baroreflex and/or neural mechanisms that regulate cardiovascular responses to exogenous stimuli (Figure 1).

The wide range in 24-h (and particularly daytime) blood pressure variability among subjects may originate from varied baroreflex response.[9] This hypothesis is based on evidence that in experimental animals, sino-aortic denervation or the surgical ablation of carotid baroreceptors is accompanied by a three-fold increase in blood pressure variability.[10,11] However, diurnal blood pressure variation and circadian blood pressure rhythms depend on the influences of other factors, such as the renin–angiotensin system,[12,13] vasomotor tone[14] and cyclic variations in plasma norepinephrine and epinephrine, as shown previously in studies that measured catecholamines in cerebrovascular regions or in the plasma reservoir[12,15–17] (Figure 2). Direct recording of efferent postganglionic muscle sympathetic nerve traffic can now be accomplished using the microneurographic technique. This approach reveals new information on the role of sympathetic neural factors in diurnal blood pressure changes and the pathogenesis of human hypertension.[18]

SYMPATHETIC MECHANISMS AND DIURNAL BLOOD PRESSURE

Sympathetic neural mechanisms regulate the two main cardiovascular variables involved in the determination of blood pressure, that is,

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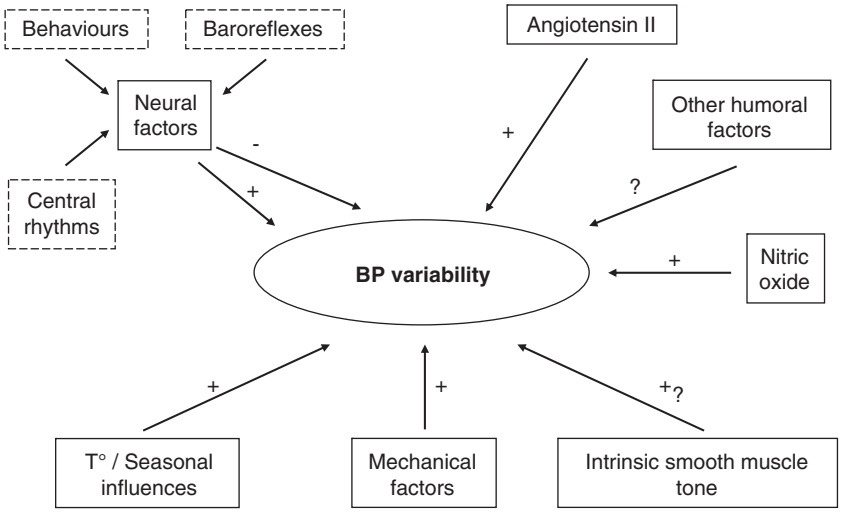

Figure 1 Schematic drawing illustrating the possible mechanisms involved in modulating blood pressure (BP) variability. The symbol (+) means excitatory influences increasing BP variability, whereas the symbol (−) means inhibitory influences reducing BP variability. Question marks refer to the influences not yet fully defined.

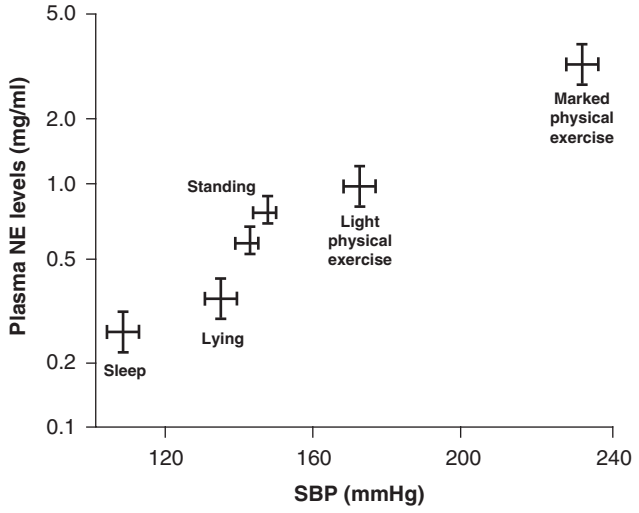

Figure 2 Changes in plasma norepinephrine (NE) and systolic blood pressure (SBP) as related to subject behavior and activity during a 24-h period. Figure modified from Watson *et al*.[16]

cardiac output and peripheral resistance.[18] High blood pressure is triggered by increased sympathetic influence on the heart and peripheral vessels that leads to hyperkinetic circulation and peripheral vasoconstriction, respectively.[18–20] The literature further supports that sympathetic neural factors exert a key role not only in the development and progression of hypertension but also in the pathogenesis of hypertension-related cardiovascular and renal end-organ damage.[18]

A number of studies have also examined whether and to what extent sympathetic neural mechanisms participate in two forms of hypertension of recent definition, that is, 'white-coat' and 'masked' hypertension. White-coat hypertension is characterized by elevated clinically measured blood pressure but normal ambulatory daytime blood pressure. Masked hypertension is characterized by normal clinically measured blood pressure but elevated ambulatory daytime blood pressure.[21] Direct and indirect approaches to assess human sympathetic function have been used to determine the sympathetic contribution to the above-mentioned conditions. For indirect approaches, power spectral analysis of the heart rate signal have shown that the low- to high-frequency ratio, considered as an index of sympathovagal balance, is increased in white-coat hypertension, which suggests increased sympathetic and decreased parasympathetic drive to the heart.[22–24] However, these studies did not provide information on systemic sympathetic activity, that is, of the adrenergic influences that modulate peripheral vasomotor tone and vascular resistance. This limitation can be circumvented by recording efferent postganglionic muscle sympathetic nerve traffic using the microneurographic approach that measures adrenergic outflow to peripheral vessels.[18] Two studies used this approach to determine the neurogenic contribution to white-coat hypertension and masked hypertension.[25,26] Results showed that white-coat hypertension was characterized by marked elevation in muscle sympathetic nerve traffic, both when assessed as sympathetic burst incidence over time and when corrected for heart rate (Figure 3). A similar phenomenon was detected in masked hypertension (Figure 3). Finally, the magnitude of adrenergic overdrive detected in both white-coat and masked hypertension appears similar to that of established hypertension, the condition with elevated clinically measured and daytime ambulatory blood pressure (Figure 3). Collectively, these findings suggest that several forms of hypertension share marked adrenergic overdrive that involves the cardiac district and the entire cardiovascular system.

MORNING BLOOD PRESSURE SURGE AND SYMPATHETIC ACTIVITY

As mentioned previously, plasma catecholamine levels undergo marked changes during a 24-h period, increasing in the early morning hours upon wakening.[12,15–17] Circadian variation in plasma adrenergic neurotransmitters supports the hypothesis that the morning surge in blood pressure has a neurogenic component that depends on sympathetic activation. Although intriguing, this hypothesis has received only indirect support from the markers of elevated plasma norepinephrine and heart rate. However, these two markers are not conclusive for sympathetic activation. Increased plasma norepinephrine may be ascribed not only to augmented sympathetic drive but also to reduced tissue clearance of norepinephrine due to altered tissue perfusion.[27] Similarly, increased heart rate does not necessarily imply increased cardiac sympathetic neural activity, given that the

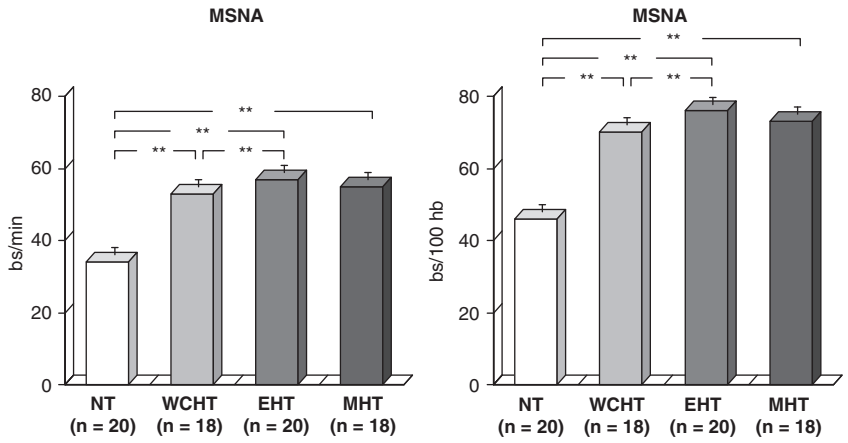

Figure 3 Mean values (±s.e.) of muscle sympathetic nerve traffic (MSNA), expressed as burst incidence over time (left panel) and corrected for heart rate values (right panel), in patients with white-coat hypertension (WCHT), established hypertension (EHT) or masked hypertension (MHT). Data collected in a group of normotensive subjects (NT) are also shown. Asterisks (**$P<0.01$) refer to the statistical significance between groups. Figure modified from Grassi *et al*.[26]

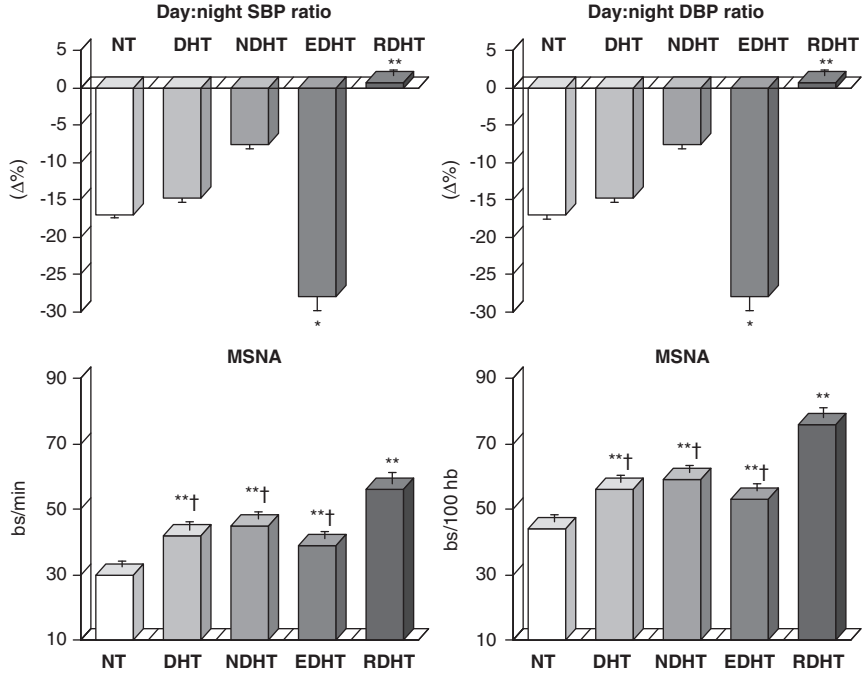

Figure 4 Upper panels. Day:night systolic and diastolic blood pressure (SBP and DBP, respectively) ratio in normotensive subjects (NT) and in hypertensive patients with a dipping hypertension (DHT), nondipping hypertension (NDHT), extreme dipping hypertension (EDHT) and reverse dipping hypertension (RDHT) profile. Data are shown as mean percentage values (±s.e.). Lower panels: values of muscle sympathetic nerve traffic (MSNA), expressed as bursts incidence over time (left panel) and corrected for heart rate values (right panel). Asterisks (*$P<0.05$ and **$P<0.01$) refer to the statistical significance between HT and NT groups. The symbol (†) refers to the statistical significance ($P<0.05$) between RDHT and the other HT groups. Data are shown as mean absolute values ± s.e. Figure modified from Grassi *et al*.[35]

reduced inhibitory drive by the parasympathetic nervous system may also trigger a tachycardic response.[28] The microneurographic approach may show increased sympathetic neural drive in the early morning hours. Abnormal increases in early morning blood pressure may be accompanied by increased sympathetic nerve activity.[29,30] The issue has important clinical and therapeutic implications because exaggerated morning blood pressure surge is associated with a greater risk of cerebrovascular and cardiovascular events.[30–33] Therapeutic implications could include the use of antihypertensive drugs that are capable of reducing adrenergic activation to achieve a better blood pressure control in the early morning hours.[34]

Two additional factors may affect sympathetic neural influence on diurnal and early morning blood pressure variation, blood pressure patterns during sleep and sleep apnea. The morning surge in blood pressure may depend on the magnitude of blood pressure reduction during sleep. Blood pressure change patterns during sleep described as dipping, nondipping, extreme dipping or reverse dipping are under profound sympathetic neural influence. A recent study conducted by our group assessed sympathetic activity in the peroneal nerve using the microneurographic approach in middle-age normotensive and hypertensive subjects showing patterns of dipping, nondipping, extreme dipping and reverse dipping.[35] The results in Figure 4 show

that sympathetic drive in hypertensive subjects is similar among dipper, nondipper and extreme dipper patterns, but is higher in the reverse dipper pattern. These findings again confirm that sympathetic activation is a major mechanism for determining the difference between day and evening blood pressure. Obstructive sleep apnea also impacts diurnal blood pressure variation and hypertension.[36] This effect depends on the marked adrenergic overdrive caused by abnormalities in the apnea/hypopnea index as measured by nighttime polysomnographic evaluation.[37,38]

BLOOD PRESSURE VARIABILITY AND SYMPATHETIC NEURAL FACTORS

Blood pressure variability is influenced by sympathetic factors. Originally documented in experimental animals,[39] this finding has also been confirmed in humans by spectral analysis of heart rate[40] and more recently by the direct microneurographic approach.[41,42] The results of these microneurographic studies can be summarized as follows. First, normotensive subjects with higher sympathetic nerve traffic display greater daytime blood pressure variability.[41] Second, normotensive subjects with higher sympathetic nerve traffic have more pronounced declines in nighttime blood pressure.[41] Finally, studies in elderly normotensive subjects showed that sympathetic neural factors modulate the cyclic components of blood pressure variability that significantly contribute to blood pressure variation. By contrast, noncyclic and residual components of blood pressure variability (that is, the erratic changes in blood pressure not regulated by specific mechanisms) do not display significant relationships with sympathetic neural factors.[42] Collectively, these findings suggest that sympathetic mechanisms regulate absolute blood pressure values and their variability throughout the 24-h period.

CONCLUSIONS

Increasing evidence supports the hypothesis that sympathetic neural mechanisms significantly contribute to diurnal blood pressure variation and to absolute blood pressure variability. It is likely that altered sympathetic neural influences interact with other humoral or reflex mechanisms and increase the complexity of the servo-control process regulating absolute blood pressure and diurnal blood pressure variation.

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