Morning Surge in Blood Pressure Is Associated With Reactivity of the Sympathetic Nervous System

Elisabeth A. Lambert,1,2 Kanella Chatzivlastou,3 Markus Schlaich,4,5 Gavin Lambert,1,5 and Geoffrey A. Head2,3

BACKGROUND
An exaggerated morning surge in blood pressure (BP) closely relates to target organ damage and cardiovascular risk, but whether the causative mechanism involves greater reactivity of the sympathetic nervous system (SNS) is unknown. We determined whether the response of the SNS to a cold pressor test predicted the BP morning surge.

METHODS
Ambulatory BP recordings were obtained from 14 men and 19 women (age = 41 ± 4 years), and the amplitude (day-night difference), rate of rise (RoR), rate by amplitude product (BPPower), and morning BP surge (MBPS; post-awake minus pre-awake) of morning mean arterial pressure (MAP) were determined. The reactivity of the SNS to CPT was assessed by recording of muscle sympathetic nerve activity (MSNA).

RESULTS
CPT induced a marked increase in MAP and all parameters of MSNA, including burst amplitude. Log-normalized BPPower positively correlated with the overall average CPT-induced increases in total MSNA (r = 0.38; P = 0.04) and burst amplitude (r = 0.43; P = 0.02) but was not related to the increase in MSNA frequency. Furthermore, a strong positive linear trend in the CPT-induced changes in burst amplitude across tertiles of BPPower and RoR was observed. BPPower and RoR were not related to CPT-induced hemodynamic changes. The MBPS did not correlate with any of the CPT-induced changes in vascular or MSNA variables.

CONCLUSIONS
These results suggest that the central nervous system mechanisms influencing the increase in MSNA burst amplitude during arousal may also be fundamental in determining the rate and power of BP rise during the morning period.

Keywords: ambulatory blood pressure; blood pressure; cold pressor test; double logistic equation; hypertension; microneurography; morning blood pressure surge; sympathetic nervous system.

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An exaggerated surge in morning blood pressure (BP) is recognized as an independent risk factor for cardiovascular (CV) events.1 In particular, it has been found that an enhanced morning surge in BP is independently associated with an increased risk of stroke in elderly hypertensive individuals2 and is associated with increased left ventricular mass3 and with increased risk of CV complications in untreated hypertensive patients.4 However, at variance with these findings, a recent large outcome study following >3,000 untreated patients with hypertension concluded that a greater morning BP surge did not predict a greater CV risk and, unexpectedly, the risk of CV events was increased in patients with a blunted BP surge.5 At present, the mechanisms underlying an exaggerated morning surge in BP remain unclear. The sympathetic nervous system (SNS) is the major effector system associated with the arousal circadian rhythm. It has been shown in healthy subjects that there is a circadian rhythm in basal vascular tone, which is related to greater alpha-adrenoceptor vasoconstrictor activity in the morning.6 These findings are further supported by the demonstration that α1-adrenoceptor antagonist administration in mild hypertensive subjects resulted in reduction in BP during the morning hours and that centrally acting sympatholytic agents effectively suppressed the morning surge in BP in hypertensive patients with poorly controlled morning BP.7 There is also evidence suggesting that the morning rise in BP is controlled by direct sympathetic neural input to the heart and vasculature in response to activity and posture changes rather than by the intrinsic fluctuations of plasma catecholamines.8 Although these findings suggest that an
exaggerated morning surge in BP may be mediated by an overactive SNS, recent data failed to demonstrate an association between resting muscle sympathetic nerve activity (MSNA) and the morning BP surge in patients with essential hypertension.6 However, sympathetic “reactivity” may be more likely than baseline sympathetic tone to predict the morning surge in BP. Acute physical and psychological stressors are known to elevate BP and can trigger acute CV events.7 Furthermore it has been demonstrated that changes in plasma catecholamines during mental arithmetic and cold pressor tests (CPTs) contribute substantially and significantly to the prediction of future systolic blood pressure.8

We have recently developed a new measure of the morning surge in BP known as the BPPower, which is the product of the rate and the amplitude of the BP morning surge.9 BPPower is 2.5-fold greater in hypertensive subjects than matched normotensive patients and may therefore represent more effectively the impact of the morning surge.10 We have also recently found that the rate of morning rise in BP is an independent predictor of myocardial infarction and stroke.11 To our knowledge, the relationship between the reactivity of the SNS to arousal stimuli and the rate, power, and amplitude characteristics of the morning surge in BP has yet to be examined. The main objective of this study was therefore to determine whether the diurnal amplitude, rate, and/or power of the morning rise in BP are positively associated with the reactivity of the SNS to a cold pressor arousal stimulus.

METHODS

Subjects

Thirty-three subjects participated in the study; the clinical characteristics of the subjects are summarized in Table 1. Subjects were included if they were aged ≥18 and <90 years and excluded if they suffered from a psychiatric or neurological disorder. Other exclusion criteria included severe illness such as cancer and having suffered from a severe CV event in the previous 6 months. Body weight was measured in light indoor clothes without shoes using a digital scale, and body mass index was measured as weight in kilograms divided by height in centimeters squared. The study protocol conformed to relevant guidelines of the National Health and Medical Research Council of Australia and was approved by the Alfred Hospital Human Research Ethics Committee. All participants gave written informed consent before their participation.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 33)</th>
<th>Tertile of BPPower</th>
<th>P between tertiles</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>I (n = 11)</td>
<td>II (n = 11)</td>
<td>III (n = 11)</td>
</tr>
<tr>
<td>Age, years</td>
<td>40.6 ± 4.0</td>
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<td>Male sex, %</td>
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<td>36</td>
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<tr>
<td>Height, cm</td>
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<td>166.4 ± 3.4</td>
<td>169.0 ± 1.9</td>
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<td>Weight, kg</td>
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<td>69.3 ± 3.2</td>
<td>77.1 ± 3.6</td>
</tr>
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<td>BMI, kg/m²</td>
<td>25.9 ± 0.7</td>
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<td>27.1 ± 1.4</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
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<td>Fasting blood glucose, mmol/L</td>
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<td>Supine SBP, mm Hg</td>
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<td>114 ± 6</td>
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<td>Supine DBP, mm Hg</td>
<td>71 ± 3</td>
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<td>3 (27)</td>
</tr>
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<td>8 (24)</td>
<td>4 (36)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Other medication, no. (%)</td>
<td>8 (24)</td>
<td>1 (9)</td>
<td>4 (36)</td>
</tr>
</tbody>
</table>

Values are presented as either mean ± SEM or as the valid total or percentage of the corresponding valid total (%). Abbreviations: BMI, body mass index; BPPower, power of the morning rise of blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Study protocol

Ambulatory BP. Ambulatory BP was recorded on a typical day using SpaceLabs Medical 90207 oscillometric devices (SpaceLabs Medical, Redmond, WA), which were programmed to automatically measure BP at 30-minute intervals over a 24–26-hour period. Subjects were also provided with a patient diary where they recorded their activities, including sleep and awake times, and rated their quality of sleep. Subjects who obtained <35 successful readings, had large chunks of data missing (≥22.5 hours or ≥5 consecutive readings), or who reported having severely impaired sleep were either excluded or asked to have a repeat assessment.

MSNA and hemodynamic measurements. Recordings of multiunit postganglionic MSNA were made in the fasting state in the morning (between 9:00 and 11:30 AM). A tungsten microelectrode (FHC, Bowdoinham, ME) was inserted directly into the right peroneal nerve at the fibular head. A subcutaneous reference electrode was positioned 2–3 cm away from the recording site. The recording electrode was adjusted until a satisfactory MSNA signal was obtained. The nerve signal was amplified (×50,000), filtered (bandpass, 700 to 2,000 Hz), amplified...
and integrated. Beat-to-beat BP was measured in the finger using a Finometer (model 2300, Datex-Ohmeda, Louisville, KY) device, and brachial BP was assessed every 5 minutes (Dinamap model 1846SX; Critikon, Tampa, FL) to ensure correct readings. Heart rate (HR) was derived from continuous 3-lead electrocardiogram recordings. Blood pressure, electrocardiogram, and MSNA signals were digitized at 1,000 Hz (PowerLab, model ML 785/85P; ADI Instruments, New South Wales, Australia). Resting measurements were recorded over a 15-minute period. A CPT was then performed, which involved subjects immersing their left hand up to the wrist in a bucket of ice water for 2 minutes, as described previously. This test was preferred over mental stress testing because the latter does not produce a robust increase in MSNA compared with the CPT. Hemodynamic variables were recorded during the CPT and for at least 7 minutes after the stimulus. Cardiac output (CO) was estimated from the Finometer pressure waveform, and total peripheral resistance (TPR) was estimated from the BP and CO measurements using the following formula: TPR = mean arterial pressure (MAP)/CO.

Data analysis

**Ambulatory BP Monitoring.** Using a computer program written in Labview, ambulatory BP recordings were modeled to a 6-parameter, double logistic equation, as described previously:

\[
\hat{y} = P1 + \frac{P2}{1 + e^{P3(P4-x)}} + \frac{P2}{1 + e^{P3(P6-x)}}
\]

where \(P1\) represents the night-time plateau, \(P2\) is the difference between daytime and nighttime plateaus (i.e., amplitude of the morning rise in BP) and was taken as the diurnal range or degree of dipping, \(P3\) indicates the rate of transition from day to night, \(P5\) indicates the rate of transition from night to day, and \(P4\) and \(P6\) indicate the midpoint of these transition periods. The power of the morning rise in BP (BPPower) was calculated as \(P5 \times P2\) and the rate of rise (RoR) in BP was taken as \(P6\).

Additional analysis included the assessment of the established measure of the morning blood pressure surge (MBPS) as the post-awake 2-hour period minus the pre-awake 2-hour period, as defined by Kario and colleagues, as well as measures of BP variability (SD) during the day and night for comparison.

**Sympathetic and hemodynamic analysis.** MSNA was analyzed manually by visual inspection of the neurogram using the Chart computer program (version 5.5.5, ADI Instruments). MSNA was expressed as burst frequency (bursts/minute), total MSNA (bursts/minute x amplitude), units/minute, and burst amplitude (%). For burst amplitude, MSNA was normalized using the largest burst detected at rest designated as 100. Burst amplitude was expressed as a percentage of this value. Average values of MSNA and hemodynamic variables were calculated over each 30-second interval of the 2-minute CPT, over 1.5–2 minutes during a control rest period before the CPT, and during a recovery period 5 minutes after the stimulus.

Assessment of spontaneous arterial baroreflex control of MSNA. Over a 5–8-minute resting period, diastolic blood pressures of individual heart beats were grouped in intervals of 2 mm Hg, and, for each interval, the percentage of diastoles associated with a sympathetic burst was plotted against the mean of the pressure interval. Muscle sympathetic bursts were advanced by 1.3 seconds to compensate for baroreflex delay. The sensitivity of the sympathetic baroreflex gain was defined as the slope of the regression line and was expressed as bursts per 100 heartbeats/mmHg.

Assessment of spontaneous cardiac baroreflex function. The sequence method as described by Parati et al. was used to estimate baroreflex sensitivity. The spontaneous sequences of ≥3 consecutive beats in which systolic BP progressively rose and cardiac interval progressively lengthened (type 1 sequences) or systolic BP progressively fell and cardiac interval progressively shortened (type 2 sequences), with a lag of 1 beat, were calculated. For each sequence, the linear correlation coefficient between cardiac interval and systolic BP was computed, and the sequence was validated for \(r > 0.85\). The slope between cardiac interval and systolic BP was calculated for each validated sequence and expressed as msec/mmHg.

**Data preparation and statistical analysis.** BPPower and RoR parameters are non-normally distributed and were therefore normalized using log_{10} transformation. MSNA is known to increase with increasing age and body mass index (BMI), and all MSNA variables measured were therefore adjusted by both age and BMI using the following formula:

\[
Y_a = y - b_1(x - x_{\bar{x}}) - b_2(x - x_{\bar{x}}) - \ldots - b_p(x - x_{\bar{x}}),
\]

where \(y\) and \(x\) are data points of the original linear regression with slope \(b_i\), and where \(x\) is the mean of variable \(x\) and \(Y_a\) represents the adjusted value for variable \(y\). Statistical analysis was performed using Microsoft Excel 2000. The relationship between variables was determined using Pearson correlation for continuous variables. A split plot analysis of variance was performed to characterize the MSNA and hemodynamic changes elicited by the CPT using the absolute values of these variables at each 30-second interval of the stimulus. Between-group variance in the average overall change in burst amplitude was also analyzed in tertiles based on the distribution of BPPower and RoR using the change in burst amplitude from rest for each 30-second interval of the CPT. All statistical tests of significance were two-tailed, with a \(P < 0.05\) considered significant.

**RESULTS**

**Ambulatory BP characteristics**

Subjects were subdivided according to the tertiles of BPPower distribution, as determined using ambulatory recordings of MBP. Subject characteristics, such as age, BMI, cholesterol, fasting glucose, and clinic BP, were similar across the BPPower tertiles (Table 1). Similarly, there was no difference in 24-hour, day, or night MBP across BPPower
tertiles (Table 2). As expected there were marked differences across tertiles for BPPower in MBP (P < 0.001) (Table 2; Figure 1). By contrast, the RoR in HR and the rate of nocturnal decline in MBP and HR were similar across BPPower tertiles (Figure 1). Moreover, the lower BPPower showed a pronounced asymmetrical pattern for the circadian changes in MAP (P < 0.001), with a more rapid reduction rather than rise in BP. The upper BPPower tertile also showed an asymmetrical circadian pattern in MBP (P < 0.05) but with a more rapid rise rather than decline in BP; whereas the upper RoR tertile did not (Figure 1). Importantly, the day–night difference in MAP (range) was similar across the tertiles of BPPower (Table 2), suggesting that the main factor influencing the differences was the RoR. Indeed, when the subjects were divided according to tertiles of RoR, very similar findings were observed in the pattern of 24-hour MAP recordings (Figure 1), with the only exception being a larger day–night difference in MAP in the lower RoR tertile compared with the upper RoR tertile.

Responses to CPT

The CPT produced a marked increase in MBP (+21%; F1,155 = 106; P < 0.001), TPR (+23%; P < 0.001), and MSNA (+115%; P < 0.001) and a modest increase in HR (+10%; P < 0.001) but no change in CO (−3%). Mean BP and all parameters of MSNA, including burst amplitude, showed an immediate response within the first 30 seconds of the CPT and then reached a stable plateau within the 2-minute period (Figure 2). This was represented statistically by a significant linear and curvilinear component (e.g., for MAP: F1,155 linear = 10; F1,155 curvilinear = 7; P = 0.01). HR also increased within the first 30 seconds of the CPT and then, in contrast with the changes in MSNA, decreased with a linear trend throughout the remainder of the intervention (F1,155linear = 7; P = 0.009). MSNA, BP, CO, and HR all returned toward basal levels 5 minutes after the CPT (Figure 2).

The average change in MAP positively correlated with the percentage average changes in total MSNA (r = 0.481; P < 0.01) and in burst frequency (r = 0.370; P =0.03) but was not related to the percentage average change in burst amplitude.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 33)</th>
<th>Tertile of BPPower</th>
<th>P between tertiles</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>I (n = 11)</td>
<td>II (n = 11)</td>
</tr>
<tr>
<td>24-hour MBP, mm Hg</td>
<td>88 ± 2</td>
<td>85 ± 3</td>
<td>89 ± 3</td>
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<tr>
<td>Mean daytime MBP, mm Hg</td>
<td>93 ± 2</td>
<td>90 ± 2</td>
<td>94 ± 3</td>
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<tr>
<td>Mean nighttime MBP, mm Hg</td>
<td>81 ± 2</td>
<td>79 ± 3</td>
<td>82 ± 3</td>
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<td>Log, RoR MBP</td>
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<td>0.42 ± 0.05</td>
<td>0.81 ± 0.06</td>
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<td>RoR MBP, mm Hg/h</td>
<td>7.7</td>
<td>2.8</td>
<td>7.0</td>
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<tr>
<td>Log, BPPower MBP</td>
<td>2.14 ± 0.06</td>
<td>1.78 ± 0.05</td>
<td>2.15 ± 0.03</td>
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<tr>
<td>BPPower MBP, mm Hg²/h</td>
<td>178.3</td>
<td>64.0</td>
<td>144.5</td>
</tr>
<tr>
<td>Range, mm Hg</td>
<td>24.4 ± 1.4</td>
<td>23.8 ± 2.2</td>
<td>23.6 ± 2.8</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SEM.
Abbreviations: BPPower, power of the morning rise of blood pressure; MBP, mean blood pressure; RoR, rate of rise.

Relationship between morning BP surge parameters and the changes in MSNA elicited by the CPT

Log-normalized BPPower was positively related to the average overall change in total MSNA (r = 0.38; P = 0.04) and burst amplitude (r = 0.43; P = 0.02) but was not associated with the average overall change in burst frequency (r = 0.03; P = 0.90) (Figure 3). The same was observed for log-normalized RoR, except that in this case there was a trend toward a positive relationship with the average overall change in total MSNA (r = 0.33; P = 0.07) (Figure 3). However, the diurnal range and the MBPS were not associated with the CPT-induced responses in any of the MSNA parameters (Figure 3). The regression correlations of BPPower and burst amplitude were strongly influenced by 1 particular subject who showed both a large rise of burst amplitude in response to the CPT as well as a rapid and large surge in BP during waking.

A split pot analysis of variance was also undertaken with the CPT-induced responses in burst amplitude across tertiles of RoR and BPPower. The CPT-induced changes in burst amplitude showed a positive linear trend across the RoR (F1,96 = 4.5; P = 0.04) and BPPower tertiles (F1,96 = 8.7; P = 0.004), confirming the results of the correlation analysis (Figure 4).

Relationship between BP variability and the changes in MSNA and hemodynamic variables elicited by the CPT

The SDs during the day, night, and over 24 hours (8.6 ± 0.4; 10.4 ± 0.6; and 11.6 ± 0.4 mm Hg, respectively) were used as a measure of BP variability. SD at night was negatively correlated with average change in burst frequency (r = 0.44; P = 0.01) and change in TPR (r = 0.38; P = 0.04) to the CPT. There was no relationship between any other MSNA or hemodynamic variables with measures of variability.

Relationship of the morning surge in BP parameters with baroreflex sensitivity

Correlation analyses were also carried out to determine whether there was a relationship between baroreflex
sensitivity and the circadian range, rate, and BPPower of the morning surge in BP. Sympathetic burst incidence showed a strong negative correlation with the changes in DAP, with an average value of \( r = 0.93 \) (\( P < 0.001 \)) observed in the 18 subjects for which sympathetic baroreflex threshold was analyzed. Sympathetic baroreflex sensitivity was found to be associated with fasting blood glucose levels and waist circumference but not with age or any other demographic and baseline clinical characteristics. In this case, there was no adjustment made to the sympathetic baroreflex values. Cardiac baroreflex sensitivity correlated strongly with age and height and was therefore adjusted for by both of these parameters. The adjusted cardiac baroreflex sensitivity did not reveal a statistically significance relationship with the circadian range, log RoR, or log BPPower.

**DISCUSSION**

The morning surge in BP is influenced by many factors, including hypertension, aging, and psychological and physical stress. In this study, we examined whether the reactivity of the SNS to acute arousal stimuli was associated with the morning surge in BP as determined using ambulatory BP monitoring. Our major findings support the hypothesis of an association between the surge in BP and the degree of SNS responsiveness to an arousal stimulus, in this case the CPT. Importantly, the morning surge, as estimated by both BPPower and RoR, showed a strong positive relationship with the average overall change in burst amplitude, whereas neither were related to burst frequency. Moreover, a highly significant positive linear trend in the change in burst amplitude was observed across both BPPower and RoR tertiles, suggesting that findings obtained by the correlation analysis were not biased by outlying values. By contrast the commonly used measure, MBPS, which compares the pre-awake and post-awake period differences, was not associated with any of the MSNA changes produced by the CPT. The reason for this discrepancy is uncertain but may reflect the importance of the rate of rise component of the morning power function, which is not a characteristic of the traditional method that more closely reflects the amplitude of the rise. In a study of 340 individuals, we were able to show that the rate of the morning surge in systolic BP was the leading risk factor for acute myocardial infarction and stroke independent of age and BP, indicating that our method of analysis may be useful in studies of the risk of cardiovascular diseases.

We suggest that mechanisms underlying the central nervous system pathways that are involved in influencing sympathetic burst amplitude in response to an arousal stimulus may be one of the critical factors engaged in the exaggerated morning BP surge.

The effects of a CPT on hemodynamic and sympathetic responses have been previously described and used by our group in previous studies. In general, responses include a marked rise in BP, TPR, HR, plasma noradrenaline concentrations, and muscle sympathetic burst frequency. In
agreement with the study of Victor,\textsuperscript{23} we also found that the average MBP response to the CPT was directly related to the percentage change in MSNA when expressed in burst frequency (data not shown). Hemodynamic and sympathetic responses to a CPT are complex, involving both central neural and peripheral reflex mechanisms. Furthermore, MSNA responses to CPT may vary in terms of frequency and amplitude depending on individuals.\textsuperscript{24,25} The key to the association of the MSNA response to the CPT and the BPower and RoR measured during the ABP assessment lies in the central pathways influencing MSNA burst amplitude rather than frequency. This finding further highlights the separate control

Figure 2. Time course of hemodynamic and muscle sympathetic nerve activity (MSNA) responses to the cold pressor test (CPT) in all subjects. Dots represent average absolute values, and error bars are ± SEM. ○: rest period before CPT (1.5–3 minute average); ●: CPT intervention (30 second average); ★: recovery period 5 minutes after CPT (1.5–3 minute average); n = 26–33. All MSNA variables measured were adjusted by both age and body mass index. Abbreviations: CO, cardiac output; hb, heartbeat; HR, heart rate; MAP, mean arterial pressure; TPR, total peripheral resistance. ***P < 0.001 for effect of CPT averaged over 2 minutes.
Figure 3. Relationship between the morning surge parameters, including the morning blood pressure surge (MBPS) and the overall average 2-minute cold pressor–induced changes in total activity, sympathetic burst frequency, and burst amplitude. All muscle sympathetic nerve activity (MSNA) variables measured were adjusted by both age and body mass index. r Values are Pearson correlation coefficients. Abbreviations: BPPower, power of the morning rise of blood pressure; RoR, rate of rise.
of the amplitude and the frequency of sympathetic bursts, which has been previously investigated in animal studies. Burst frequency is strongly driven by sympathetic baroreflex control and can be modulated by direct stimulation of the rostroventrolateral medulla. On the other hand, burst amplitude, which reflects the number of active fibers, seems to be modulated independently by chemoreceptor afferents. The concept that the burst amplitude and burst frequency can be independently modulated by different reflexes has also been proposed in humans. One of the main reasons for using the CPT in this study is that it produces a rapid and marked increase in both MSNA frequency and amplitude and hence total MSNA. Using functional magnetic resonance imaging, CPT evokes marked activation of the amygdala, insular and frontal cortex, and ventral and dorsal pons with a delayed activation of the hippocampus. Activation of these regions is strongly associated with psychosocial stress in humans and animals. Interestingly, a similar pattern of activation of the amygdala and hypothalamus is observed in mice just after the transition to the active period. Thus there is a close association between the central mechanisms influencing SNA activated during the CPT and the morning arousal. Taking these animal and human studies together, it appears that the association between the morning surge (BPPower and RoR) and the activation of the amplitude of the MSNA observed during the CPT lies in the individual’s propensity to activate specific but common stress/arousal pathways in the forebrain.

A surprising finding perhaps was that this study did not reveal any relationship between the changes in BP induced by the CPT and the morning surge in BP. This may indicate that the acute rise in BP to stress (minutes) and the mechanisms governing the slower rise in BP during the morning period, which takes hours, are quite unrelated. Presumably, the acute effects involve the vascular neuroeffector mechanisms and vascular compliance, whereas the rapidity of the increase in BP in the morning is more related to the degree of SNA activity activation and possibly hormonal actions related to circadian patterns.

Sympathetic and cardiac baroreflex functions are thought to contribute to diurnal hemodynamic variables and may therefore play a role in the morning BP surge. Cardiac baroreflex sensitivity tends to increase during sleep and subsequently reaches a minimum level in the morning after awakening. It has been suggested that the combination of the decreasing cardiac and suppressed sympathetic baroreflex sensitivities in the morning may contribute considerably to the morning surge in BP by lessening the buffering capacity of the autonomic nervous system. Indeed, a recent study showed that sympathetic baroreflex function was inversely related to the morning surge in elderly hypertensive patients. Reduced baroreflex sensitivity has been associated

Figure 4. Average cold pressor test–elicited changes in burst amplitude of subjects divided into tertiles of the (a) rate of rise (RoR) and (b) the power of the morning rise of blood pressure (BPPower). Lower tertile (LT): white; n = 9–10. Mid tertile (MT): gray; n = 9. Upper tertile (UT): black; n = 8–9. All muscle sympathetic nerve activity (MSNA) variables measured were adjusted by both age and body mass index. Error bars are ± SEM. ** P < 0.01, * P < 0.05 for linear trend between tertiles.
with exaggerated pressor responses to mental and physical stimuli, which also implies that the morning surge in BP may be influenced by baroreflex function. Although it may have been expected that low baroreflex sensitivity may increase the impact of the morning surge, sympathetic and cardiac baroreflex function did not relate to the morning surge of BP; therefore arguing against a role of the baroreflex function in the morning surge in BP. We also noted that MSNA burst frequency, but not amplitude CPT-induced changes, was negatively related to SD, particularly at night. Because MSNA frequency is strongly influenced predominantly by baroreflex mechanisms, a greater inhibition of the baroreflex during the CPT might indicate greater baroreflex gain in these individuals, which might also explain the reduced variability. However, this result should be interpreted with caution because baroreflex functions were investigated on 1 occasion only, during the awake time, which may not necessarily reflect their function during the awakening period.

Limitations include that the study population was small and included younger and older subjects, some of whom were hypertensive or on antihypertensive treatment. Because age and BMI are known to influence resting levels of MSNA, all measurements of MSNA were adjusted for by age and BMI to eliminate the influence of age and BMI on the study findings. Nevertheless, it was expected that if the rate and power of the rise in BP were strongly influenced by the reactivity of the SNS, then this relationship would be apparent across a wide range of subjects. We do acknowledge that our findings are strongly influenced by a small number of the participants. Another limitation of the study is the variability observed in the measurement of the morning surge in BP. Head et al. have reported that the coefficient of variation for the RoR in BP is high (118%). On the other hand, they found that the RoR is highly reproducible within subjects. A further limitation is that this article uses a novel mathematical approach to characterize the changes in BP in the morning period. This was developed because the morning period is recognized as a time of increased risk of cardiovascular events due in part to the associated surge in BP. Although our approach may be more refined than the traditional methods and can independently predict cardiovascular events, its applicability in very large population cohort studies remains unknown.

The study suggests that the morning surge in BP may be positively related to the responsiveness of the SNS to an arousal stimulus. The central nervous system mechanisms influencing the increase in MSNA burst amplitude during arousal may also be fundamental in determining the rate of BP rise during the morning period.

ACKNOWLEDGMENTS

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DISCLOSURE

Professor Schlaich serves on scientific advisory boards for Abbott (formerly Solvay) Pharmaceuticals and Novartis Pharmaceuticals and Medtronic and has received honoraria and travel support from Abbott, Servier, Novartis, and Medtronic. Professor Lambert has acted as a consultant for Medtronic and has received honoraria or travel support for presentations from Pfizer, Wyeth Pharmaceuticals, Servier, and Medtronic. The laboratories of Professors Schlaich and Lambert currently receive research funding from Medtronic, Servier Australia, Abbott, and Allergan. The funding organizations played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript. The investigators report no conflicts of interest with regards to this article.

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