Nocturnal Cardiovascular Activity in Essential Hypotension: Evidence of Differential Autonomic Regulation

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Objective: Essential hypotension represents a form of chronic low blood pressure (BP) not explained by medical or orthostatic conditions. The pathogenesis of essential hypotension may involve sympathetic hypoactivation and other forms of autonomic dysregulation. The aim of the current study was to investigate autonomic and cardiovascular activity during sleep in individuals with essential hypotension. **Methods:** A case-control study was conducted in 14 individuals with essential hypotension (mean [standard error] = 23.4 [0.6] years, all women) and 14 controls (mean [standard error] age = 22.2 [0.4] years, all women). The following measures were collected over a night of sleep: BP, heart rate (HR), stroke volume, cardiac output (CO), preejection period (PEP), total peripheral resistance, and time-domain measures of HR variability. **Results:** Hypotensive participants had consistently lower BP, HR, and CO than did normotensives. Cardiac autonomic variables revealed enhanced parasympathetic tone (proportion of adjacent normal-to-normal intervals that differed in length by more than 50 milliseconds = 40.8 [6.3] versus 23.4 [4.5], $p = .03$) and reduced sympathetic drive in hypotensives (PEP = 99.4 [3.6] versus 86.1 [4.3], $p = .02$). Analysis of temporal profiles showed that HR, stroke volume, and CO decreased throughout the night in both groups, whereas PEP and HR variability increased. Unlike controls, BP remained essentially unchanged in hypotensives, as the decrease in CO was counterbalanced by a parallel rise in total peripheral resistance. **Conclusions:** These findings suggest that nocturnal cardiac sympathetic withdrawal combined with vagal hyperactivity is a characteristic of the autonomic regulation in essential hypotension. **Key words:** autonomic nervous system, blood pressure, heart rate variability, hypotension, impedance cardiography.

BMI = body mass index; **BP** = blood pressure; **CO** = cardiac output; **DBP** = diastolic blood pressure; **ECG** = electrocardiogram; **EOG** = electrooculogram; **HR** = heart rate; **HRV** = heart rate variability; **ICG** = impedance cardiography; **MBP** = mean blood pressure; **NN** = normal-to-normal intervals; **PEP** = preejection period; **pNN50** = proportion of adjacent NN intervals that differed in length by more than 50 milliseconds; **PSG** = polysomnography; **PSQI** = Pittsburgh Sleep Quality Index; **RMSSD** = squared differences between consecutive NN intervals; **RR** = respiratory rate; **SBP** = systolic blood pressure; **SE** = standard error; **SNS** = sympathetic nervous system; **SV** = stroke volume; **TPR** = total peripheral resistance; **ANOVA** = analysis of variance.

INTRODUCTION

According to the World Health Organization, hypotension is defined as a condition of systolic blood pressure (SBP) below 110 mm Hg in men and below 100 mm Hg in women (1). Essential hypotension refers to a form of chronic low blood pressure (BP) that is not caused by a primary medical disease (i.e., secondary hypotension) or a response to upright posture (i.e., orthostatic hypotension) but occurs in the absence of any identified pathological factors. In addition to SBP values defined by the World Health Organization, a concomitant diastolic BP (DBP) lower than 60 mm Hg has also been proposed for diagnosis (2,3).

Epidemiological data suggest that essential hypotension affects 2% to 3% of the general population (4,5). The prevalence has been found to be higher in women and in the young (6,7), occurring in up to 10% to 20% of the female population aged 20 to 40 years (8).

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As documented by large population-based studies, people with essential hypotension frequently complain of fatigue, dizziness, faintness, headache, cold limbs, and mood disturbances (9–12). Other clinical features are decreases in cerebral blood flow (13–15), cortical activity (16–18), and body temperature (6,19) as well as cognitive impairment (for a review, see Ref. (20)), thus resulting in reduced subjective well-being and quality of life (10–12). Despite subjective complaints, there is compelling evidence that steady low BP carries a protective effect, reducing the mortality risk for both cardiovascular and noncardiovascular deaths in the general population (21–23).

Little is known about the etiology of essential hypotension, unlike essential hypertension, which has been extensively investigated, yielding considerable knowledge about the pathogenetic processes involved (for a review, see Ref. (24)). An autonomic dysregulation has been hypothesized as the mechanism underlying this condition (6,14,25). Indeed, decreased heart rate (HR), stroke volume (SV), and cardiac output (CO) (6,26) as well as enhanced baroreflex sensitivity (27) have been described in hypotensive individuals compared with normotensive individuals both at rest and in response to stress tasks. These findings have been interpreted as suggestive of a sympathetic hypoactivation (6,25). The effectiveness of sympathomimetic agents in providing relief from acute symptoms and in improving cognitive functions in people with hypotension provided further support to this hypothesis (28–30). However, it should be noted that neither cardiac nor vascular pure sympathetic indexes have been measured in the studies mentioned. Furthermore, an augmented parasympathetic tone could also be involved in the pathophysiology of essential hypotension.

HR variability (HRV) is commonly used as a noninvasive and validated method to estimate autonomic modulation of the heart. Traditionally, HRV can be assessed in either time or spectral domains, providing information on autonomic balance. The high-frequency oscillations spectrum reflects the vagal drive, whereas the low-frequency cyclic fluctuations are regarded to be mediated by both the parasympathetic and the sympathetic

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branches (31,32). Thus, the pure sympathetic influence is difficult to assess by means of HRV analysis. An alternative sympathetic nervous system (SNS) index is the preejection period (PEP), which corresponds to the time interval from the onset of ventricular depolarization to the opening of semilunar valves. Because the ventricular myocardium is mainly innervated by SNS fibers, this measure, derived by impedance cardiography technique, is considered to be inversely related to sympathetic β-adrenergic activity (33–35).

Sleep is a condition relatively free of external disturbances that can influence physiological measurements during wakefulness (e.g., emotional status and degree of cooperation). In addition, the autonomic system is known to play a key role in modulating the cardiovascular activity during sleep (for a review, see Ref. (36)). Thus, the analysis of the hemodynamic and neurovegetative pattern during sleep in essential hypotension may provide relevant insights into this condition.

To the best of our knowledge, the cardiovascular evolution throughout the night has yet to be investigated in essential hypotension. Also, whether hypotensive individuals have a different autonomic regulation during sleep compared with normotensive individuals is unknown.

The aim of the present study was to explore the overnight profile of cardiovascular activity during sleep in essential hypotension by means of a wide range of measures. To clarify the postulated autonomic imbalance in hypotensive participants, we sought to examine the nocturnal cardiac autonomic regulation by assessing the involvement of both neurovegetative divisions. In particular, for this latter purpose, the PEP and vagal-related time-domain measures of HRV were estimated as noninvasive markers of cardiac sympathetic and parasympathetic drives, respectively. We hypothesized that the nocturnal autonomic pattern in essential hypotension is characterized by both sympathetic hypoactivation and vagal hyperactivity, resulting in blunted hemodynamics overnight in hypotensive participants compared with normotensive participants.

METHODS

Participants

Fourteen essential hypotensive participants (mean [standard error], or M [SE], age = 23.4 (0.6) years, range = 21–29 years) and 14 normotensive participants (M [SE] age = 22.2 (0.4) years, range = 19–25 years) participated in this study. All subjects were recruited through advertisements placed in the University of Padova. Given the extremely low rate of essential hypotension in men (4,6–8), the sample was restricted to women.

By considering the high circadian and day-to-day variability in BP (37–39), the following screening procedure including multiple office BP readings was applied 1 week before the experiment. Three sessions were carried out in the following timetables: 9 to 10 AM, 1 to 2 PM, and 5 to 6 PM. Each participant underwent all three BP measurement sessions in a randomized order. All subjects abstained from alcohol for 24 hours and from food, tobacco, and beverages containing caffeine for at least 3 hours before each BP measurement. After a resting period of 10 minutes, three readings were taken with 3-minute interval in between. BP was measured in sitting position by using a mercury sphygmomanometer, with a standard cuff fitted to the nondominant upper arm. Korotkoff phases I and V were used to identify, respectively, SBP and DBP values, with a deflation rate of 2 mm Hg/s.

Overall, 9 BP measurements were collected for each participant. To account for alerting reactions to the measurement procedure (40), the first reading of each session was discarded; thus, the screening SBP and DBP values were derived by averaging six measurements. Participants were classified as hypotensive if the mean SBP level was lower than 100 mm Hg and the mean DBP level was lower than 60 mm Hg. Participants reporting a mean SBP level of at least 110 mm Hg, regardless of DBP, were defined as normotensive.

A positive history of hypotensive symptoms (e.g., dizziness, faintness, and fatigue) was ensured before enrolling hypotensive participants. Screening procedures also included the administration of the Pittsburgh Sleep Quality Index (PSQI; (41)) to assess sleep quality. A cutoff of 5 or more was applied to identify sleep disturbances. Lastly, participants also filled out a questionnaire to collect medical and psychiatric anamnesis and investigate habits with regard to smoking, alcohol, caffeine, and drugs consumption. In addition, data about weight and height were collected to allow calculation of body mass index (BMI; in kilograms per meter squared). Exclusion criteria for both groups were as follows: a BMI of at least 30 kg/m^2; a score of 5 or more on the PSQI; excessive tobacco, alcohol, or caffeine consumption; assumption of drugs or medications known to affect cardiovascular or nervous system; and medical or psychiatric diseases.

The experimental protocol was approved by the Ethics Committee of the University of Padova. Each participant signed an informed consent form before commencement of the study and received 100 Euros for participation. Data were collected between September 2010 and February 2011.

Polysomnography

Full polysomnography (PSG) included electroencephalograms (O1-A2, O2-A1, C3-A2, C4-A1, F3-A2, F4-A1), electrooculograms (EOGs; right EOG-A1, left EOG-A2), electromyogram (submentalis muscle), electrocardiogram (ECG; precordial II lead), thoracic and abdominal respiratory belts, oronasal thermistor, and pulse oximeter. PSG data were recorded using a computerized system (Siesta; Compumedics, Melbourne, Australia). ECG signals were amplified, band-pass filtered (1-100 Hz), and digitized at 500 Hz.

Sleep was manually 30-second scored according to standard criteria (42), to obtain the following parameters: sleep onset latency (minutes), wake after sleep onset (minutes), sleep efficiency (%), amount of rapid eye movement and non–rapid eye movement sleep (minutes). For the purposes of the study, the first occurrence after lights of at least 3 consecutive 30-second epochs scored as sleep was used to identify sleep onset.

BP Monitoring

BP measurements were collected during PSG by means of an automated oscillometric system (Spacelabs 90217; SpaceLabs Medical, Inc., Issaquah, WA), with a cuff of appropriate size fitted to the nondominant upper arm. The device was set to take BP readings at 10-minute intervals. The monitor was previously calibrated against a mercury sphygmomanometer to ensure accuracy.

Systolic BP, DBP, and mean BP (MBP) were derived, and all recorded measurements were manually checked for artifacts.

Impedance Cardiography

The impedance signal (Z_0) and the first derivative of pulsatile impedance (dZ/dt) were measured by Impedance Cardiograph Minnesota model 304 B (IFM Inc., Greenwich, CT) through standard tetrapolar band electrode configuration, according to guidelines (43). The two inner (recording) bands were placed around the base of the neck and around the thorax over the tip of the xiphoid process. The two outer (current) bands were positioned around the neck and thorax, at least 3 cm away from each of the recording electrodes. A 4-mA alternating current at 100 kHz was transmitted through the two outer electrodes, and Z_0 and dZ/dt signals were recorded from the two inner electrodes and digitized at 500-Hz sampling rate. The samples were 30-second ensemble averaged by a software system (COP-WIN software Bio-Impedance Technology, Chapel Hill, NC) that summed the digitized beat-by-beat waveforms, time synchronized to the R wave of the ECG, and divided by the number of cardiac cycles, filtering respiratory, and movement artifact. The positions of the B point (i.e., the onset of the left ventricular ejection) and the X point (i.e., the closure of the aortic valve) in the dZ/dt signal and the Q wave in the ECG were automatically detected. Moreover, each cardiac cycle was visually inspected and edited offline when the algorithm failed to correctly detect these points.

HR (beats per minute) was calculated as the number of heart beats per minute. SV (ml) was derived using the Kubicek equation (44). CO (l/min) was computed as HR × SV. PEP (milliseconds) was defined as the time interval between the Q wave on the ECG signal and the B point on the dZ/dt signal. Total peripheral resistance (TPR; dynes s/cm^5) was calculated as (MBP/CO)* 80.

HRV Time-Domain Analysis

An automated algorithm was applied to detect the R waves on the ECG and compute the interbeat intervals. Isolated artifacts and missed and ectopic beats were identified and replaced with interpolated interbeat interval data.

According to HRV guidelines (32), overall HRV was assessed by computing the standard deviation of normal-to-normal (NN) intervals (milliseconds). High-frequency variability was determined as the square root of the mean of the squared differences between consecutive NN intervals (RMSSD; milliseconds) and the proportion of adjacent NN intervals that differed in length by more than 50 milliseconds (pNN50; %). The Kubios HRV Analysis Software 2.0 (Matlab, Kuopio, Finland) was used for the HRV analyses.

Given the impact of respiration on HRV (e.g., Refs. (45,46)), the respiratory rate (RR; Hz) was also computed.

Study Design

After the screening procedure, participants were scheduled to undergo two consecutive overnight PSGs in the Psychophysiology Sleep Laboratory of the Department of General Psychology at the University of Padova. The first night allowed for adaptation, and no data were analyzed. Participants were required to refrain from smoking, drinking beverages containing alcohol or caffeine, and taking naps the day before and during the day of scheduled PSGs. They were admitted to the laboratory at 8 PM, and electrodes and monitoring equipment were placed. They were allowed to engage in quiet activities (e.g., reading, watching television, or listening to music) before lights out. Sleep period was set from 12 PM to 8 AM (time of scheduled awakening).

Cardiovascular data were collected continuously throughout the night.

Data Analysis and Statistics

The first 7 hours after sleep onset were considered for the analyses of physiological measures, selecting only stable sleep periods. Epochs of either wakefulness or sleep disturbances as arousal or body movements were therefore discarded, the latter accounting for 8% or less of the recording time. Values were then averaged and analyzed in fourteen 30-minute intervals.

All data are expressed as M (SE).

Demographic, screening, and PSG data were compared by group using unpaired t tests. To control for type I error, a multivariate analysis of variance was run over the mean values of the night including all cardiovascular measures. To assess the cardiovascular and autonomic activity as a function of time, mixed-design analyses of variance (ANOVAs) consisting of group by time were performed on physiological variables. Bonferroni post hoc comparisons were performed on the significant effects, and the Greenhouse-Geisser correction was applied where appropriate, with adjusted significance levels and nonadjusted degrees of freedom reported. Partial eta-squared (η^2p) was computed as a measure of effect size. A p value less than .05 was considered significant for all statistical analyses.

RESULTS

Demographic, Screening, and PSG Measures

Comparisons on demographic, screening and PSG data between groups are provided in Table 1.

Because BP values were used as the selection criteria for each group, as expected, significantly lower screening SBP ($t = -15.49$, $p < .001$), DBP ($t = -6.59$, $p < .001$), and MBP ($t = -10.35$, $p < .001$) were recorded in hypotensive participants compared with normotensive participants, whereas groups were comparable with regard to age, BMI, and PSQI score. Likewise, hypotensive and normotensive participants did not differ with respect to any of the sleep parameters.

BP Variables

The multivariate analysis of variance conducted over the mean cardiovascular values of the night revealed a significant difference between hypotensive participants and controls across all variables combined (omnibus $F(11,16) = 4.05$, $p = .006$, η^2p = 0.74).

Results of ANOVAs performed on all cardiovascular measures are summarized in Table 2.

As shown by the significant main effects of group, ANOVAs revealed lower SBP ($F(1,26) = 20.43$, $p < .001$, η^2p = 0.44),

TABLE 1. Demographic, Screening, and Polysomnographic Data

	Hypotensive Participants (n = 14)	Normotensive Participants (n = 14)	t	p
Demographics				
Age, y	23.4 (0.6)	22.2 (0.4)	1.61	.12
BMI, kg/m^2	21.6 (0.7)	23 (0.6)	−1.52	.14
PSQI	3.5 (0.3)	3.1 (0.3)	0.75	.46
Screening BP				
SBP, mm Hg	88.8 (1.1)	114.3 (1.2)	−15.49	<.001
DBP, mm Hg	56.3 (1.2)	68.5 (1.5)	−6.59	<.001
MBP, mm Hg	67.1 (1)	83.8 (1.3)	−10.35	<.001
PSG				
SOL, min	13 (2.3)	17.1 (5.3)	−0.72	.48
WASO, min	30.2 (6.3)	40 (7)	−1.04	.31
SE, %	91 (1.5)	88.1 (2.2)	1.11	.28
NREM sleep amount, min	333.3 (7.7)	333.5 (7.4)	−0.02	.98
REM sleep amount, min	103.5 (7.2)	89.4 (6.2)	1.49	.15

BMI = body mass index; PSQI = Pittsburgh Sleep Quality Index; BP = blood pressure; SBP = systolic BP; DBP = diastolic BP; MBP = mean BP, as DBP + 1/3(SBP − DBP); PSG = polysomnography; SOL = sleep onset latency; WASO = wake after sleep onset; SE = sleep efficiency; NREM = non–rapid eye movement sleep; REM = rapid eye movement sleep.
Values are means (standard error). Degrees of freedom = 26.

TABLE 2. ANOVA Results for BP, ICG, and HRV Measures

			Group			Time			Group × Time		
	Hypotensive participants (n = 14)	Normotensive participants (n = 14)	F	P	η^2p	F	p	η^2p	F	p	η^2p
BP											
SBP, mm Hg	91 (1.5)	104.6 (2.6)	20.43	<.001	0.44	1.98	.04	0.07	1.55	.12	0.06
DBP, mm Hg	54.9 (1.5)	60.6 (2)	5.35	.03	0.17	1.69	.09	0.06	2.1	.02	0.07
MBP, mm Hg	68.1 (1.4)	75.8 (1.9)	10.63	.003	0.29	1.99	.03	0.07	2.68	.003	0.09
ICG											
HR, beats/min	63.8 (1.8)	72.7 (2.6)	7.66	.01	0.23	5.83	<.001	0.18	1.06	.39	0.04
SV, ml	92.8 (4.1)	94.7 (2.4)	0.16	.7	0.01	13.45	<.001	0.34	1.39	.2	0.05
CO, l/min	5.9 (0.3)	6.9 (0.3)	5.25	.03	0.17	14.4	<.001	0.36	1.59	.09	0.16
TPR, dynes s/cm^5	969.2 (53)	913.3 (38.2)	0.73	.4	0.03	8.9	<.001	0.25	2.06	.04	0.07
PEP, ms	99.4 (3.6)	86.1 (4.3)	5.72	.02	0.18	5	<.001	0.16	1.52	.15	0.06
HRV											
SDNN, ms	92.6 (11)	72.2 (10.1)	1.87	.18	0.07	3.62	<.001	0.12	1.06	.39	0.04
RMSSD, ms	86.2 (15)	62.2 (14.5)	1.32	.26	0.05	2.08	.04	0.07	0.39	.89	0.01
$RMSSD_{log}$	1.82 (0.06)	1.62 (0.06)	5.98	.02	0.19	2.69	.01	0.09	0.99	.44	0.04
pNN50, %	40.8 (6.3)	23.4 (4.5)	5	.03	0.16	2.48	.01	0.09	0.92	.5	0.03
RR, Hz	0.26 (0.01)	0.26 (0.01)	0.07	.79	0.01	1.58	.12	0.05	0.925	.51	0.03

BP = blood pressure; ICG = impedance cardiography; HRV = heart rate variability; η^2p = partial eta-squared; SBP = systolic BP; DBP = diastolic BP; MBP = mean BP; HR = heart rate; SV = stroke volume; CO = cardiac output; TPR = total peripheral resistance; PEP = preejection period; SDNN = standard deviation of normal-to-normal (NN) intervals; RMSSD = square root of the mean of the squared differences between consecutive NN intervals; pNN50 = proportion of adjacent NN intervals that differed in length by more than 50 milliseconds; RR = respiratory rate.

Values are means (standard error). Nighttime means are averages of the first 7 hours of sleep after sleep onset. Degrees of freedom for F statistics: group = 1, 26; time = 13, 338; group × time = 13, 338.

DBP (F(1,26) = 5.35, p =.02, η^2p = 0.17), and MBP (F(1,26) = 10.63, p = .003, η^2p = 0.29) in hypotensive participants compared with normotensive participants throughout the night. The SBP also decreased in both groups from sleep onset through out the night (F(13,338) = 1.98, p = .04, ϵ = 0.76, η^2p = 0.07). A time effect was found also for MBP (F(13,338) = 1.99, p = .03, ϵ = 0.84, η^2p = 0.07), as well as a significant interaction group × time (F(13,338) = 2.68, p = .002, ϵ = 0.84, η^2p = 0.09), revealing that normotensive participants exhibited a marked drop in MBP from sleep onset across the night, followed by a rise approaching morning, whereas the values remained unchanged in hypotensive individuals over time. The interaction group × time observed in DPB (F(13,338) = 2.1, p = .02, ϵ = 0.81, η^2p = 0.07) displayed the same profile as that of MBP. Nocturnal temporal courses of BP values by group are depicted in Figure 1.

Impedance cardiography Variables

As illustrated in Figure 2, hypotensive participants had a significantly lower HR than did normotensive participants (F(1,26) = 7.66, p = .01, η^2p = 0.23). Time effect also indicated a progressive reduction in HR in the night in all participants (F(13,338) = 5.83, p < .001, ϵ = 0.42, η^2p = 0.18). CO exhibited a similar pattern, as it was reduced in the essential hypotension group (F(1,26) = 5.25, p = .03, η^2p = 0.17) and continuously decreased during sleep in both groups (F(13,338) = 14.4, p < .001, ϵ = 0.41, η^2p = 0.36). Regarding SV, a marked fall from sleep onset over time was detected in all participants (F(13,338) = 13.45, p < .001, ϵ = 0.66, η^2p = 0.34). TPR, however, augmented during the night (F(13,338) = 8.9, p < .001, ϵ = 0.64, η^2p = 0.25), but the interaction group × time showed that although the controls reported a nonsignificant increase, hypotensive participants displayed a significant progressive rise (F(13,338) = 2.06, p = .04, ϵ = 0.64, η^2p = 0.07). Lastly, PEP was found to be higher in hypotensive than in normotensive participants (F(1,26) = 5.72, p = .02, η^2p = 0.18) and to enhance throughout the night in both groups (F(13,338) = 5, p < .001, ϵ = 0.64, η^2p = 0.16).

HRV Variables

Considering HRV measures, as seen in Figure 3, a significant time main effect characterized by a gradual increase over the sleep period in both groups was observed for all variables (standard deviation of NN interval, F(13,338) = 3.62, p < .001, ϵ = 0.59, η^2p = 0.12; RMSSD, F(13,338) = 2.08, p = .04, ϵ = 0.55, η^2p = 0.07; pNN50, F(13,338) = 2.48, p = .01, ϵ = 0.61, η^2p = 0.09). The pNN50 was also found to be significantly more elevated in hypotensive participants in comparison with the controls (F(1,26) = 5, p = .03, η^2p = 0.16). Because of the high dispersion in the unstandardized RMSSD values, we calculated the log-transformed RMSSD ($RMSSD_{log}$). In addition to the time effect (F(13,338) = 2.69, p = .01, ϵ = 0.57, η^2p = 0.09), a significant

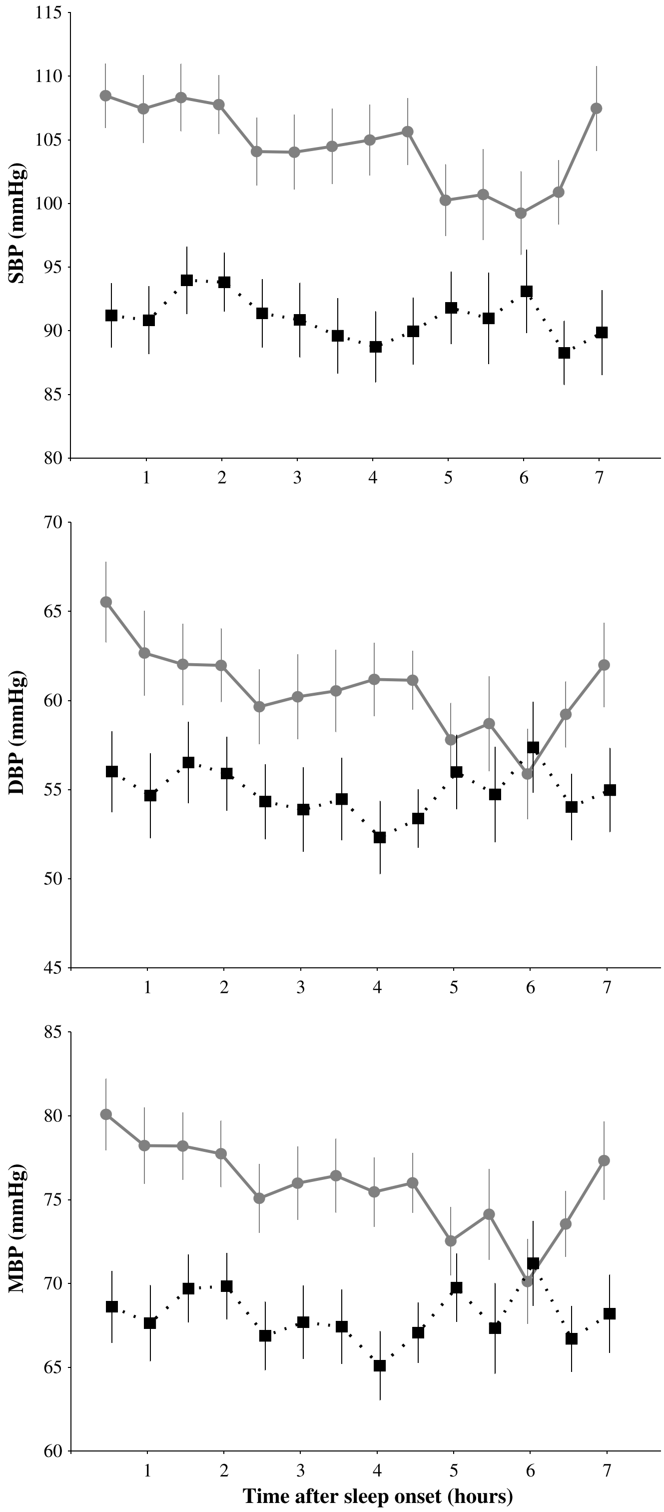

Figure 1. Nocturnal temporal profiles of blood pressure (BP) data in hypotensive and normotensive participants. Values are means (standard error). Data are 30-minute averages of the first 7 hours after sleep onset. Solid lines represent normotensive participants; dashed lines represent hypotensive participants. SBP = systolic BP; DBP = diastolic BP; MBP = mean BP.

group effect was revealed for the RMSSDl$_{og}$ ($F(1,26) = 5.98$, $p = .02$, $\eta^2p = 0.19$).

No significant effects were observed with regard to the RR.

DISCUSSION

In the current study, we investigated the cardiovascular and autonomic activity during sleep in essential hypotension by applying a wide range of measures to obtain a deeper insight into the pathophysiology of this condition. Hemodynamic measurements displayed markedly diminished cardiovascular activity in hypotensive participants compared with normotensive participants during sleep. In addition, analyses of cardiac autonomic functions revealed that hypotensive individuals exhibited enhanced cardiac parasympathetic drive associated with reduced sympathetic tone.

Regarding the cardiovascular pattern, as expected, hypotensive participants reported markedly lower BP than did the controls. Because TPR did not differ between groups, lowered BP values are likely caused by the decreased CO, which resulted, in turn, by diminished HR. These findings are in accordance with previous studies that assessed hemodynamics in essential hypotension at rest, reporting decreased HR (6,26) and CO and no differences in TPR (26) in comparison with the normotensive condition. The abnormally low CO may lead to insufficient organ perfusion, thereby accounting for the decreased body temperature and cold limbs often reported by essential hypotension individuals (6,12,19).

As expressed by augmented PEP values, a reduced cardiac sympathetic output was recorded in hypotensive participants: the longer the PEP, the lower the cardiac SNS tone. Because PEP measures the velocity of isovolumic myocardial contraction, it also reflects cardiac contractility, which was thereby reduced in this sample. On the other hand, vagal-related HRV indexes (i.e., pNN50 and $RMSSD_{log}$) also revealed heightened cardiac vagal tone in hypotensive participants compared with normotensive participants throughout the night, suggesting that the parasympathetic system is also affected in essential hypotension.

It is also noteworthy that the different physiological pattern we observed between groups is unlikely to be ascribed to differences in sleep because their PSG parameters were found to be comparable. More sophisticated analysis (e.g., cyclic alternating pattern or spectral electroencephalographic investigation) may unmask subtle group differences.

Unlike the other forms of hypotension (i.e., orthostatic and secondary hypotension), there is a paucity of data about the chronic condition. Prior investigations reported reduced cardiovascular and electrodermal activity in hypotensive individuals at rest and in response to stress tasks (6,25,26), ascribing these data to a sympathetic hypoactivation. Results from pharmacological trials aimed at examining the effect of sympathomimetic agents in reducing hypotensive symptoms are in line with this interpretation (28–30).

Our findings support and extend the postulated autonomic dysfunction in essential hypotension, yielding further information about the physiological mechanisms associated with this condition. By examining the cardiac autonomic modulation during sleep, we observed not only a sympathetic withdrawal but also a parasympathetic hyperactivity in hypotensive participants, which likely led to their diminished cardiac activity.

Regarding the overnight time course, all participants exhibited the typical nocturnal cardiac autonomic regulation, with a progressive shift from sympathetic toward parasympathetic prevalence. Indeed, all time-domain HRV measures augmented gradually through the night, including the indexes that reflect vagal tone (i.e., RMSSD and pNN50). The enhanced cardiac parasympathetic drive was combined with a parallel sympathetic withdrawal shown by lengthening in PEP, in agreement with the prior investigations (47–50). Consistently, HR and SV fell continuously from sleep onset throughout the sleep period in both groups, leading to a reduction in CO (47–49,51,52).

Nonetheless, analysis of temporal profile also revealed interesting differences between groups. The BP trend observed in normotensive participants is in accord with the literature (53–55), showing a progressive decrease over time and a rise in the latter part of the night before awakening. As previously reported (51,52,56), the expected fall in BP was conceivably caused by a drop in CO because TPR showed no significant changes in the night. On the contrary, hypotensive participants displayed a blunted reduction only in SBP, whereas DBP and MBP remained unchanged during sleep. The loss of nocturnal variation in BP in essential hypotension seems to be owned by both CO and TPR changes. In hypotensive individuals, unlike with normotensive individuals, as CO decreased throughout the night, TPR increased, counterbalancing the fall in CO to maintain BP at steady values. We can speculate that the parallel rise in TPR occurred as a compensatory response for the progressive drop in CO, which otherwise might have resulted in an excessive and thus potentially harmful nocturnal fall in BP. The augmentation in TPR needs further examination. Keeping in mind the progressive lowering in cardiac sympathetic drive during the night, this effect seems discrepant. Although a consistency in discharge over targets can be assumed, sympathetic and parasympathetic outputs have been demonstrated to vary substantially at different organ sites (31,57–59). Therefore, the reduction in the heart SNS tone we observed might not have occurred likewise on vasculature. Beyond the direct sympathetic modulation, it should be taken into account that several factors are involved in regulating the vasculature, such as baroreflexes, chemoreflexes, blood viscosity, blood volume, vessels length, nitric oxide, renin-angiotensin-aldosterone system, and central inputs (60–65). In particular, as prior reports have shown an enhanced baroreflex sensitivity in essential hypotension (27), an overresponsivity of this reflex could have contributed to BP regulation by rising the TPR to contrast the decrease in CO (62). This finding also challenges the hypothesis recently advanced by Duschek and coworkers (26) that the

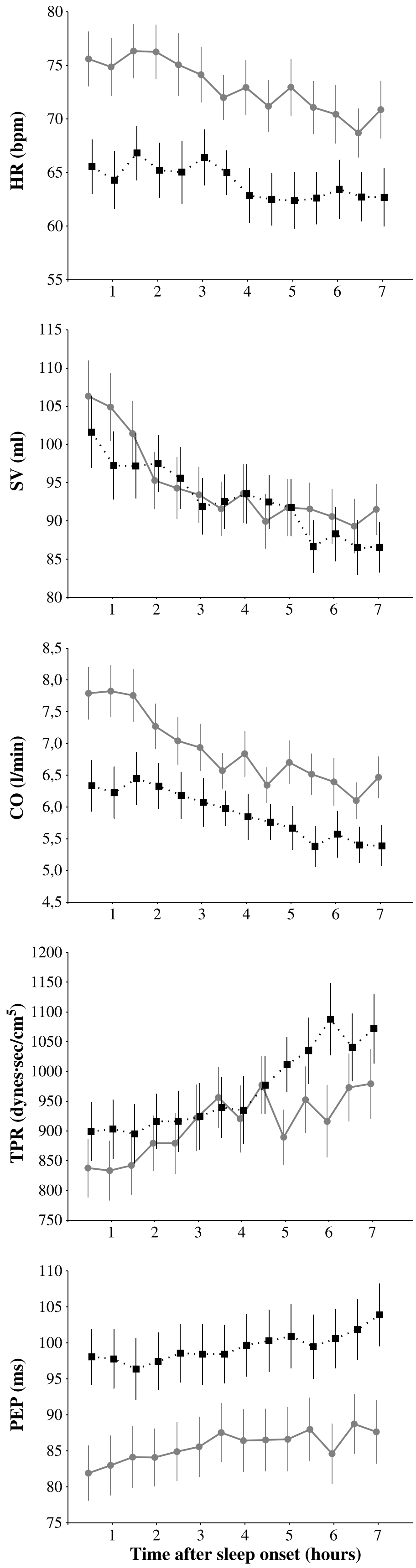

Figure 2. Nocturnal temporal profiles of impedance cardiography data in hypotensive participants and normotensive participants. Values are means (standard error). Data are 30-minute averages of the first 7 hours after sleep onset. Solid lines represent normotensive participants; dashed lines represent hypotensive participants. HR = heart rate; SV = stroke volume; CO = cardiac output; TPR = total peripheral resistance; PEP = preejection period.

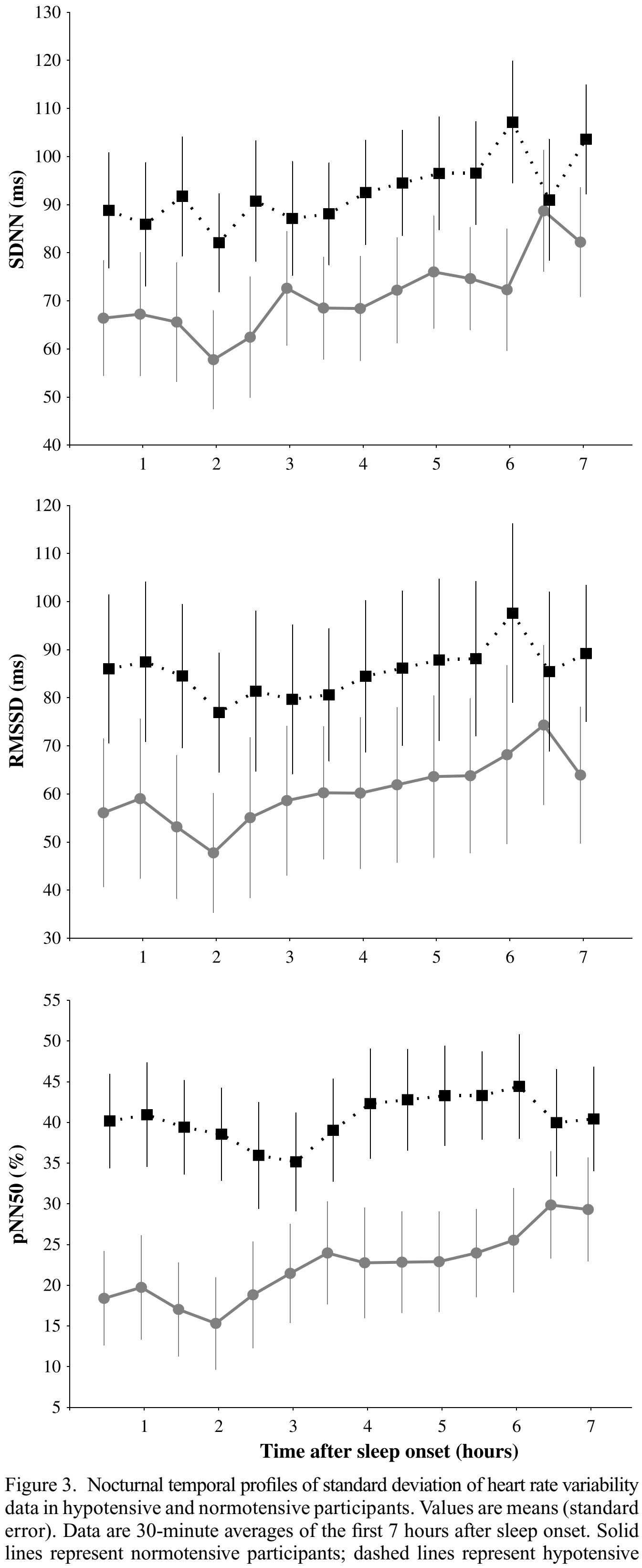

Figure 3. Nocturnal temporal profiles of standard deviation of heart rate variability data in hypotensive and normotensive participants. Values are means (standard error). Data are 30-minute averages of the first 7 hours after sleep onset. Solid lines represent normotensive participants; dashed lines represent hypotensive participants. SDNN = normal-to-normal (NN) intervals; RMSSD = square root of the mean of the squared differences between consecutive NN intervals; pNN50 = proportion of adjacent NN intervals that differed in length by more than 50 milliseconds.

nature of essential hypotension primarily involves the cardiac activity rather than the vascular one, postulated by observing a diminished CO in the absence of differences in TPR. Indeed, despite a lack of group differences in TPR, a contribution of vascular factors cannot be completely ruled out because hypotensive participants showed an involvement of this variable in modulating BP throughout the night. However, only speculative interpretation can be advanced because the role played by these mechanisms cannot be directly addressed within the context of the present analysis.

In the current study, we performed an accurate sample selection by means of multiple BP measurements. Particular attention was paid to enroll only hypotensive individuals in which the chronic low BP was primary, thus carefully excluding secondary forms. Nonetheless, some limitations should be addressed. The main limitation of this investigation is that the sample consisted of women only. Because there is some evidence of sex differences in autonomic functions (66,67), we cannot rule out that this might have influenced our findings. However, because the results we found in normotensive participants are consistent with the literature (see earlier discussion), we can reasonably assume that the reliability and generalizability of our data are not reduced by the sample selection. The relatively small sample size might also have reduced our statistical power in detecting significance (for instance, with regard to the group difference in the BMI).

Concerns may arise when considering PEP to estimate sympathetic influences on heart. Although several investigations have documented this measure as inversely related to cardiac sympathetic β-adrenergic activity (33–35), it can also be affected by variations in afterload (i.e., rise in BP may lead to augmentation in PEP) (43). The lengthening in PEP throughout the night might have reflected the increase in time required to overcome the more elevated external pressure caused by the heightening in BP, rather than a decrease in SNS output. Nonetheless, because BP fell during sleep in normotensive participants and remained substantially unchanged in hypotensive participants, we can reasonably exclude that changes in BP contributed significantly to the augmentation in PEP values we detected in both groups. Moreover, the finding of higher PEP in hypotensive participants, which also exhibited lower BP, gives further strength to this interpretation.

Similarly, although HRV analysis is widely recognized as a reliable method to assess cardiac autonomic control (31,32), the effect exerted by respiration cannot be overlooked because it may bias the relationship between HRV and cardiac vagal tone (45,46). Given the respiratory residual vagal activity, further caution is needed when considering between-individual differences (45). To account for respiratory confounds, we analyzed the breathing pattern over the night. Unlike from HRV indexes, RR did not vary significantly either throughout the sleep period or between groups. In addition, it is noteworthy that the HR data mirrored the HRV results, both between-group and within-condition comparisons. Hence, the interpretation of changes in vagal-related HRV indexes in terms of modifications in cardiac vagal drive seems justified.

Despite reduced subjective well-being in individuals (11,68), there is broad evidence demonstrating that low BP represents a benign risk factor, reducing the likelihood of cardiovascular events and enhancing overall life expectancy in the general population (21–23). Taken together, our findings support this association between hypotension and reduced mortality and morbidity. In fact, the pattern we detected in hypotensive participants, characterized by decreased HR, low cardiac contractility, and heightened vagal tone, in addition to reduced BP, has been documented by several epidemiological investigations to reflect diminished health risk (32,57,69,70). However, because our results have been obtained from a relatively small sample and in a cross-sectional study, large prospective examinations targeted at identifying the variables accounting for this relationship are warranted.

In sum, we observed a diminished cardiovascular activity during sleep in essential hypotensive participants compared with normotensive participants, which reflected a decreased sympathetic drive combined with an augmented vagal tone, thus leading support to the autonomic dysfunction postulated in essential hypotension. Whether both neurovegetative divisions are primarily affected or the dysregulation occurring in one branch leads, in turn, to the dysfunction in the other is still unknown. This issue requires further investigations to be clarified, as well as the role played by each autonomic system in eliciting the symptoms complained by hypotensive individuals. A systematic comparison of subjective disturbances between hypotensive and normotensive individuals would be of interest. In addition, given the evidence for altered autonomic cardiac control in hypotensive individuals and the involvement of peripheral resistance in setting nocturnal BP, it would also be worthwhile to assess vascular activity and, particularly, sympathetic α-adrenergic drive to obtain a more comprehensive insight into this condition. In this context, additional measures of neurovegetative outflows over different organ sites aside from the cardiovascular system, such as the pupil or the airway smooth muscles, should be used to support the generalizability of the results to the entire autonomic system.

REFERENCES

1. World Health Organization. Arterial hypertension. Geneva: WHO, 1978. Contract No. 628.
2. Quadri R, Valentini M, Chiandussi L. Ipotensione arteriosa: aspetti nosografici, fisiopatologici e clinici. Fed Med 1992;4:37–44.
3. Weiß B, Donat K. Arterielle hypotonie. Fortschr Med 1982;30:1396–9.
4. Duschek S, Schandry R. Antriebsschwäche und beeinträchtigte Hirnleistungen: neue Perspektiven zum chronisch niedrigen Blutdruck. Dtsch Med Wochenschr 2006;131:272–7.
5. Pemberton J. Does constitutional hypotension exist? BMJ 1989;298:660–2.
6. Akahoshi M, Hida A, Imaizumi M, Soda M, Maeda R, Ichimaru S, Nakashima E, Seto S, Yano K. Basic characteristics of chronic hypotension cases: a longitudinal follow-up study from 1958 through 1999. Hypertens Res 2006;29:1–7.
7. Donner-Banzhoff N, Kreienbrock L, Baum E. Hypotension—does it make sense in family practice? Fam Pract 1994;11:368–74.
8. Baenkler HW, Fritze D, Füeßl HS. Innere Medizin. Stuttgart, DE: Thieme; 1999.
9. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. J Epidemiol Community Health 2007;61:53–8.
10. Pilgrim JA, Stansfeld S, Marmot M. Low blood pressure, low mood? BMJ 1992;304:75–8.
11. Rosengren A, Tibblin G, Wilhelmsen L. Low systolic blood pressure and self perceived wellbeing in middle aged men. BMJ 1993;306:243–6.
12. Wessely S, Nickson J, Cox B. Symptoms of low blood pressure: a population study. BMJ 1990;301:362–5.
13. Duschek S, Schandry R. Cognitive performance and cerebral blood flow in essential hypotension. Psychophysiology 2004;41:905–13.
14. Duschek S, Schandry R. Reduced brain perfusion and cognitive performance due to constitutional hypotension. Clin Auton Res 2007;17:69–76.
15. Stegagno L, Patritti D, Duschek S, Herbert B, Schandry R. Cerebral blood flow in essential hypotension during emotional activation. Psychophysiology 2007;44:226–32.
16. Costa M, Stegagno L, Schandry R, Ricci Bitti PE. Contingent negative variation and cognitive performance in hypotension. Psychophysiology 1998;35:737–44.
17. Duschek S, Meinhardt J, Schandry R. Reduced cortical activity due to chronic low blood pressure: an EEG study. Biol Psychol 2006;72:241–50.
18. Weisz N, Schandry R, Jacobs AM, Mialet J-P, Duschek S. Early contingent negative variation of the EEG and attentional flexibility are reduced in hypotension. Int J Psychophysiol 2002;45:253–60.
19. Stegagno L, Angrilli A, Costa M, Palomba D. Deficit cognitivi e ipotensione arteriosa: un'indagine cronopsicofisiologica. G Ital Psicol 1996; 23:837–59.
20. Duschek S, Weisz N, Schandry R. Reduced cognitive performance and prolonged reaction time accompany moderate hypotension. Clin Auton Res 2003;13:427–32.
21. Glynn RJ, Field TS, Hebert PR, Taylor JO, Hennekens CH, Rosner B. Evidence for a positive linear relation between blood pressure and mortality in elderly people. Lancet 1995;345:825–9.
22. Phillipp T. Chronische arterielle hypotonie. In: Rieger H, editor. Angiologie, Hypotonie, Hypertonie. 20th ed. Munich, DE: Urban & Schwarzenberg; 1993:305–13.
23. Robbins JM, Korda H, Shapiro MF. Treatment for a nondisease: the case of low blood pressure. Soc Sci Med 1982;16:27–33.
24. Carretero OA, Oparil S. Essential hypertension: part I: definition and etiology. Circulation 2000;101:329–35.
25. Fredrikson M, Edman G, Levander SE, Schalling D, Svensson J, Tuomisto M. Electrodermal responsivity in young hypotensive and hypertensive men. Psychophysiology 1990;27:649–55.
26. Duschek S, Heiss H, Buechner B, Werner N, Schandry R, Reyes del Paso GA. Hemodynamic determinants of chronic hypotension and their modification through vasopressor application. J Physiol Sci 2009;59:105–12.
27. Duschek S, Dietel A, Schandry R, Reyes Del Paso GA. Increased baroreflex sensitivity and reduced cardiovascular reactivity in individuals with chronic low blood pressure. Hypertens Res 2008;31:1873–8.
28. Duschek S, Hadjamu M, Schandry R. Dissociation between cortical activation and cognitive performance under pharmacological blood pressure elevation in chronic hypotension. Biol Psychol 2007;75:277–85.
29. Duschek S, Hadjamu M, Schandry R. Enhancement of cerebral blood flow and cognitive performance following pharmacological blood pressure elevation in chronic hypotension. Psychophysiology 2007;44:145–53.
30. Duschek S, Heiss H, Werner N, Reyes del Paso GA. Modulations of autonomic cardiovascular control following acute alpha-adrenergic treatment in chronic hypotension. Hypertens Res 2009;32:938–43.
31. Berntson GG, Thomas Bigger J, Eckberg DL, Grossman P, Kaufmann PG, Malik M, Nagaraja HN, Porges SW, Saul JP, Stone PH, Van Der Molen MW. Heart rate variability: origins, methods, and interpretive caveats. Psychophysiology 1997;34:623–48.
32. Task Force of the European Society of Cardiology and North American Society of Pacing and Electrophysiology. Heart rate variability: standards of measurement, physiological interpretation, and clinical use. Circulation 1996;93:1043–65.
33. Cacioppo JT, Berntson GG, Binkley PF, Quigley KS, Uchino BN, Fieldstone A. Autonomic cardiac control. II. Noninvasive indices and basal response as revealed by autonomic blockades. Psychophysiology 1994; 31:586–98.
34. Sherwood A, Allen MT, Obrist PA, Langer AW. Evaluation of beta-adrenergic influences on cardiovascular and metabolic adjustments to physical and psychological stress. Psychophysiology 1986;23:89–104.
35. Sherwood A. Use of impedance cardiography in cardiovascular reactivity research. In: Blascovich J, Katikin E, editors. Cardiovascular Reactivity to Psychological Stress and Disease. Washington, DC: American Psychological Association; 1993:157–99.

36. Trinder J. Cardiac activity and sympathovagal balance during sleep. Sleep Med Clin 2007;2:199–208.
37. Casiglia E, Palatini P, Colangeli G, Ginocchio G, Menza GD, Onesto C, Pegoraro L, Biasin R, Canali C, Pessina C. 24 h rhythm of blood pressure and forearm peripheral resistance in normotensive and hypertensive subjects confined to bed. J Hypertens 1996;14:47–52.
38. Furlan R, Guzzetti S, Crivellaro W, Dassi S, Tinelli M, Baselli G, Cerutti S, Lombardi F, Pagani M, Malliani A. Continuous 24-hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. Circulation 1990;81:537–47.
39. Mancia G, Sega R, Bravi C, Vito GD, Valagussa F, Cesana G, Zanchetti A. Ambulatory blood pressure normality: results from the PAMELA study. J Hypertens 1995;13:1377–90.
40. Shapiro D, Jamner LD, Lane JD, Light KC, Myrtek M, Sawada Y, Steptoe A. Blood pressure publication guidelines. Psychophysiology 1996;33:1–12.
41. Buysse DJ, Reynolds III CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
42. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology, and Technical Specifications. Westchester, IL: American Academy of Sleep Medicine; 2007.
43. Sherwood A, Allen MT, Fahrenberg J, Kelsey RM, Lovallo WR, van Doornen LJ. Methodological guidelines for impedance cardiography. Psychophysiology 1990;27:1–23.
44. Kubicek WG, Karnegis JN, Patterson RP, Witsoe DA, Mattson RH. Development and evaluation of an impedance cardiac output system. Aerosp Med 1966;37:1208–12.
45. Grossman P, Kollai M. Respiratory sinus arrhythmia, cardiac vagal tone, and respiration: within- and between-individual relations. Psychophysiology 1993;30:486–95.
46. Ritz T, Dahme B. Implementation and interpretation of respiratory sinus arrhythmia measures in psychosomatic medicine: practice against better evidence? Psychosom Med 2006;68:617–27.
47. Burgess HJ, Penev PD, Schneider R, Van Cauter E. Estimating cardiac autonomic activity during sleep: impedance cardiography, spectral analysis, and Poincare plots. Clin Neurophysiol 2004;115:19–28.
48. Burgess HJ, Trinder J, Kim Y. Cardiac autonomic nervous system activity during presleep wakefulness and stage 2 NREM sleep. J Sleep Res 1999; 8:113–22.
49. Burgess HJ, Trinder J, Kim Y, Luke D. Sleep and circadian influences on cardiac autonomic nervous system activity. Am J Physiol Heart Circ Physiol 1997;273:H1761–8.
50. Monti AM, Medigue CM, Nedelcoux HN, Escourrou PE. Autonomic control of the cardiovascular system during sleep in normal subjects. Eur J Appl Physiol 2002;87:174–81.
51. Drager LF, Ueno LM, Lessa PS, Negrão CE, Lorenzi-Filho G, Krieger EM. Sleep-related changes in hemodynamic and autonomic regulation in human hypertension. J Hypertens 2009;27:1655–63.
52. Khatri IM, Freis ED. Hemodynamic changes during sleep. J Appl Physiol 1967;22:867–73.
53. Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. Lancet 1978;311:795–7.
54. Sayk F, Becker C, Teckentrup C, Fehm H-L, Struck J, Wellhoener JP, Dodt C. To dip or not to dip. Hypertension 2007;49:1070–6.
55. Wiinberg N, Høegholm A, Christensen HR, Bang LE, Mikkelsen KL, Nielsen PE, Svendsen TL, Kampmann JP, Madsen NH, Bentzon MW. 24-h ambulatory blood pressure in 352 normal Danish subjects, related to age and gender. Am J Hypertens 1995;8:978–86.
56. Imai Y, Abe K, Munakata M, Sakuma H, Hashimoto J, Imai K, Sekino H, Yoshinaga K. Circadian blood pressure variations under different pathophysiological conditions. J Hypertens 1990;8:S125–32.
57. Malpas SC. Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. Physiol Rev 2010;90:513–57.
58. Schächinger H, Weinbacher M, Kiss A, Ritz R, Langewitz W. Cardiovascular indices of peripheral and central sympathetic activation. Psychosom Med 2001;63:788–96.
59. Ritz T. Studying noninvasive indices of vagal control: the need for respiratory control and the problem of target specificity. Biol Psychol 2009; 80:158–68.
60. Di Rienzo M, Castiglioni P, Iellamo F, Volterrani M, Pagani M, Mancia G, Karemaker JM, Parati G. Dynamic adaptation of cardiac baroreflex sensitivity to prolonged exposure to microgravity: data from a 16-day spaceflight. J Appl Physiol 2008;105:1569–75.
61. Du Y-H, Chen AF. A "love triangle" elicited by electrochemistry: complex interactions among cardiac sympathetic afferent, chemo-, and baroreflexes. J Appl Physiol 2007;102:9–10.
62. Guyton A. The relationship of cardiac output and arterial pressure control. Circulation 1981;64:1079–88.
63. Ray CA. Interaction of the vestibular system and baroreflexes on sympathetic nerve activity in humans. Am J Physiol Heart Circ Physiol 2000; 279:H2399–404.
64. Somers VK, Mark AL, Abboud FM. Interaction of baroreceptor and chemoreceptor reflex control of sympathetic nerve activity in normal humans. J Clin Invest 1991;87:1953–7.
65. Iellamo F, Di Rienzo M, Lucini D, Legramante JM, Pizzinelli P, Castiglioni P, Pigozzi F, Pagani M, Parati G. Muscle metaboreflex contribution to cardiovascular regulation during dynamic exercise in microgravity: insights from mission STS-107 of the space shuttle Columbia. J Physiol 2006; 572:829–38.
66. Convertino VA. Gender differences in autonomic functions associated with blood pressure regulation. Am J Physiol Regul Integr Comp Physiol 1998; 275:R1909–20.
67. Evans JM, Ziegler MG, Patwardhan AR, Ott JB, Kim CS, Leonelli FM, Knapp CF. Gender differences in autonomic cardiovascular regulation: spectral, hormonal, and hemodynamic indexes. J Appl Physiol 2001;91:2611–8.
68. Mann A. Psychiatric symptoms and low blood pressure. More evidence for an association. BMJ 1992;304:64–5.
69. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. Am J Hypertens 2000;13:112S–22S.
70. Palatini P, Julius S. Heart rate and the cardiovascular risk. J Hypertens 1997;15:3–17.