Cardiovascular down-regulation in essential hypotension: Relationships with autonomic control and sleep

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Abstract

In this work, we aimed to clarify the autonomic involvement in the cardiovascular down-regulation in essential hypotension. The relationships between cardiovascular response and sleep quality were also examined. Thirteen female hypotensives and 13 female normotensives performed a stress task followed by polysomnography. Measures derived from blood pressure monitoring, impedance cardiography, and heart rate variability were collected. Hypotensives exhibited lower cardiovascular and autonomic activation than controls during the task. While a better sleep quality (i.e., higher sleep efficiency and lower nocturnal wakefulness) correlated with a reduced reactivity in normotensives, the opposite pattern occurred in hypotensives. The results suggest that a blunted response in both autonomic branches underlies the cardiovascular hypoactivation in hypotension. Further, good sleep seems to be associated with optimal levels of physiological reactivity.

Descriptors: Autonomic system, Cardiovascular reactivity, Heart rate variability, Hypotension, Impedance cardiography, Sleep

Essential (or constitutional) hypotension is a condition of chronic low blood pressure (BP), with systolic BP (SBP) lower than 110 mmHg in men and 100 mmHg in women and diastolic BP (DBP) lower than 60 mmHg (Pemberton, 1989; Pschyrembel, 1990). Unlike orthostatic or secondary hypotension, it occurs in the absence of any identifiable pathological factors.

Essential hypotension has been estimated to affect 2–3% of the general population (Duschek & Schandry, 2006a; Pemberton, 1989) and to be prevalent in young females, as it has been described in up to 10–20% of women aged 20–40 years (Baenkler, Fritze, & Füeßl, 1999). The spectrum of symptoms experienced by hypotensives is heterogeneous and includes fatigue, dizziness, headache, breathing difficulties, and loss of appetite. Cold hands and feet, paleness, and sweating are also commonly reported (Parati, Di Rienzo, Coruzzi, & Castiglioni, 2013; Pilgrim, 1994; Wessely, Nickson, & Cox, 1990). In addition to somatic symptoms, hypotensive sufferers often complain of cognitive disturbances, with deficits being particularly prominent in the areas of attention and memory (Duschek, Matthias, & Schandry, 2005; Stegagno, 2006b). A more comprehensive cardiovascular assessment has been carried out by Duschek and colleagues (Duschek, Dietel, Schandry, & Reyes Del Paso, 2008). Similar to the prior investigation, hypotensive participants exhibited a less marked rise in both SBP and DBP in comparison with controls under a stress task, largely mediated by a milder increase in cardiac output (CO). These findings were later replicated in a further study (Duschek, Heiss, Buechner et al., 2009). In addition, measures of central hemodynamics have been found to be in accordance with peripheral findings, as a diminished acceleration in cerebral blood flow velocity under stimulation has been recorded in hypotensives (Sarlo, de Zambotti, Gallicchio, Devigili, & Stegagno, 2013; Stegagno, Patritti, Duschek, Herbert, & Schandry, 2007).

Multiple evidence points towards a hypoactivation of the cardiovascular system in essential hypotension. By measuring BP changes during task execution, a lower surge in BP compared with resting values has been observed in essential hypotensive participants than in normotensives (Duschek, Matthias, & Schandry, 2005; Duschek & Schandry, 2006b). A more comprehensive cardiovascular assessment has been carried out by Duschek and colleagues (Duschek, Dietel, Schandry, & Reyes Del Paso, 2008). Similar to the prior investigation, hypotensive participants exhibited a less marked rise in both SBP and DBP in comparison with controls under a stress task, largely mediated by a milder increase in cardiac output (CO). These findings were later replicated in a further study (Duschek, Heiss, Buechner et al., 2009). In addition, measures of central hemodynamics have been found to be in accordance with peripheral findings, as a diminished acceleration in cerebral blood flow velocity under stimulation has been recorded in hypotensives (Sarlo, de Zambotti, Gallicchio, Devigili, & Stegagno, 2013; Stegagno, Patritti, Duschek, Herbert, & Schandry, 2007).

The cardiovascular down-regulation described in essential hypotension has been advanced to reflect abnormalities in the neurovegetative system. Particularly, a sympathetic withdrawal has been proposed as underlying this condition (Akahoshi et al., 2006; Duschek & Schandry, 2007; Fredrikson et al., 1990). In addition to the evidence of reduced cardiovascular reactivity, this assumption relies on the finding of a more accelerated electrodermal response habituation in a hypotensive group compared with normotensives and hypertensives (Fredrikson et al., 1990). Further support ensues from the efficacy of sympathomimetic agents in alleviating hypotensive symptoms in this population (Duschek, Hadjamu, &...
The concept of sympathetic hypoactivation associated with essential hypotension has been questioned by a recent report (Sarlo et al., 2013), which failed to find diminished sympathetic drive in hypotensives. By examining the systemic and cerebral hemodynamic changes during a cognitive task, the authors found an attenuated increase in cardiovascular parameters such as BP and cerebral blood flow velocity in hypotensive individuals. Nevertheless, they did not detect group differences in the pre-ejection period (PEP), a metric inversely related to the sympathetic beta-adrenergic activity (Cacioppo et al., 1994; Kelsey, 2012; Sherwood, 1993). On the contrary, we documented a reduced PEP shortening during cognitive testing in hypotensives as compared with normotensives (de Zambotti, Covassin, Cellini, Sarlo, & Stegagno, 2012), thus giving strength to the above-discussed hypothesis. Moreover, the mentioned study illustrated lower vagal withdrawal in hypotensive participants by measuring heart rate variability (HRV), which also suggests a parasympathetic involvement in the autonomic dysregulation associated with this state. The lack of consistency between these studies is conceivably dependent on the tests administered. Although both investigations employed a similar cognitive task (i.e., the N-back test), the difficulty of the test diverged. Particularly, de Zambotti and coworkers (2012) employed a more demanding version that entailed higher cognitive load than did Sarlo and colleagues (2013). It is broadly agreed that cardiovascular reactivity augments with the increase in task demand (e.g., Gendolla, 1998; Gendolla, Richter, & Silvia, 2008; Smith, Baldwin, & Christensen, 1990). Given that a highly challenging task evokes an enhanced physiological activation, it is also more likely to unmask abnormalities in cardiovascular autonomic regulation. Furthermore, different tasks elicit various cardiovascular patterns mediated by different autonomic contributions (e.g., Hurwitz et al., 1993).

The cardiovascular reactivity to a stress task is widely accepted as a marker of health. Abnormal responses in terms of either exaggerated hyperactivation or hypoactivation have been linked to augmented risk of cardiovascular and noncardiovascular outcomes such as coronary heart disease, stroke, depression, and obesity (Carroll, Lovallo, & Phillips, 2009; Everson et al., 2001; Lovallo & Gerin, 2003; Treiber et al., 2003).

In this context, whereas it has long been known that resting elevated cardiovascular values and sleep disturbances are related (Nieto et al., 2000; Owens & Matthews, 1998), knowledge regarding the association with cardiovascular response to stress is lacking. However, converging evidence is suggestive of a relationship between cardiovascular reactivity and sleep. An extensive literature documents heightened cardiovascular excitation in hypertension sufferers (for a review, see Manuck & Krantz, 1986), also displaying disrupted sleep in terms of decreased slow wave sleep and increased arousals (Mansoor, 2002; Pedulla et al., 1995). An abnormal cardiovascular activation has been described in sleep disorders such as obstructive sleep apnea. Particularly, apneic patients compared with healthy subjects have been shown to exhibit more elevated resting cardiac contractility and reduced increase in cardiac beta-adrenergic drive when exposed to a stress task (Nelesen et al., 1996, 2001). Moreover, sleep deprivation has been shown to alter hemodynamic response, mainly affecting vascular functions (Franzen et al., 2011; James & Gregg, 2004; Sauvet et al., 2010). Within healthy conditions, cardiovascular reactivity has been consistently found to augment with aging (Jennings et al., 1997; Uchino, Holt-Lunstad, Bloor, & Campo, 2005; Uchino, Uno, Holt-Lunstad, & Flinders, 1999), when a higher incidence of sleep disturbances such as insomnia, sleep-disordered breathing, and periodic limb movement during sleep also occurs (for a review, see Wolkove, Elkholy, Baltzan, & Falayew, 2007). Given these data, an association between cardiovascular hyperreactivity and sleep disturbances can be postulated.

On the other hand, some findings suggest that the opposite relation is plausible as well. Indeed, according to this hypothesis, a better sleep might be expected in conditions exhibiting reduced activation under stress, such as hypotension. However, recent work targeted at exploring sleep objectively by means of polysomnography (PSG) did not find any differences in sleep between hypotensives and normotensives (de Zambotti, Covassin, Cellini, Sarlo, Torre, & Stegagno, 2012). In this context, case-control studies assessing the reactivity in chronic fatigue syndrome, a condition frequently associated with hypotension, have documented diminished cardiovascular response to a variety of stressful tests in these patients (LaManca et al., 2001; Soetekouw, Lenders, Bleijenberg, Thien, & van der Meer, 1999). Interestingly, patients with chronic fatigue syndrome have been reported to show decreased sleep efficiency and augmented wake time after sleep onset, together with subjective complaints of sleep difficulties (Morris et al., 1993). Likewise, sleep problems are often endorsed by individuals with addictions such as smoking (Cohrs et al., in press; Jaehne et al., 2012; Nakata et al., 2008) and alcoholism (Colrain, Turlington, & Baker, 2009; Redwine, Dang, Hall, & Irwin, 2003; Zhabenko, Wojnar, & Brower, 2012), which also exhibit hyporeactivity to stress tests. Indeed, attenuated BP and heart rate (HR) responses to acute psychological stress have been documented in smokers when compared to nonsmokers (al’Absi, Wittmers, Erickson, Hatsuami, & Crouse, 2003; Phillips, Der, Hunt, & Carroll, 2009). Blunted HR stress reactivity occurs also in alcoholics (Pankin, Dickensheets, Nixon, & Lovallo, 2002). Taking into account these considerations, the relation between cardiovascular activation and sleep quality appears complex to describe.

The purpose of the current study was twofold. First, we aimed at elucidating the autonomic pathway underlying cardiovascular stress reactivity in essential hypotension. In order to achieve this goal, we administered a mental arithmetic test, a task well known to trigger a substantial cardiovascular activation mediated by both neurovegetative divisions (e.g., Allen & Crowell, 1989; Berntson et al., 1994; Berntson, Cacioppo, & Fieldstone, 1996). Along with a thorough hemodynamic evaluation, the PEP and the high-frequency (HF) HRV indices were derived to characterize the sympathetic and vagal influences on cardiac activity, respectively. As a second purpose, we were interested in investigating the relation between cardiovascular activation and sleep. To explore whether a higher magnitude of reactivity is related to either poor sleep or good sleep, an overnight PSG was performed, and the associations between sleep measures and cardiovascular responses under stress were examined.

Method

Participants

Participants were 13 essential hypotensives ($M = 23.1$, $SE = 0.4$ years) and 13 normotensives ($M = 22.3$, $SE = 0.5$ years). All sub-
subjects were enrolled by way of advertisements posted at the University of Padova. Given the sharp female preponderance of low BP (Baenkler et al. 1999), the sample was limited to women.

Screening
A screening protocol consisting of multiple BP measurements was conducted 1 week prior to the experimental session to identify eligible individuals. Three sessions were run across different days and different times in order to account for the day-to-day variability and circadian fluctuations of BP values: 9–10 a.m., 1–2 p.m., 5–6 p.m. Each individual underwent all sessions in a randomized order.

Subjects were required to refrain from drinking alcohol for 24 h and from eating, smoking, and taking caffeine for at least 3 h prior to each appointment for BP measure. After 10 min of resting, three BP readings were taken 3 min apart by way of a sphygmomanometer, with the subject in sitting position. SBP and DBP were identified by I and V Korotkoff sounds, respectively. The first measurement of each triplicate reading was rejected to account for alerting reactions; thus, the mean screening BP values were defined by averaging six readings.

Subjects showing both a mean SBP lower than 100 mmHg and a mean DBP lower than 60 mmHg were selected as hypotensives. In addition, a positive history of disturbances associated with hypotensive condition (e.g., dizziness, fainting, and fatigue) was ascertained before recruitment. Individuals with a mean SBP between 110 and 130 mmHg regardless of DBP were assigned to the normotensive group.

The screening protocol also included the administration of the Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989), a 19-item questionnaire providing an evaluation of sleep quality. The total score varies from 0 to 21, with high scores reflecting poor sleep. To rule out the presence of sleep disorders, a cut-off of ≥5 was applied. Moreover, the Morningness–Eveningness Questionnaire (MEQ; Horne & Ostberg, 1976) was administered in order to identify the circadian typology. The MEQ consists of 19 items addressing the timing of sleep habits and preferred times of physical and mental performance, yielding a total score ranging from 16 to 86 on the eveningness–morningness scale. Individuals scoring either <31 or ≥69 were excluded as they were classified as extreme evening types or extreme morning types, respectively.

Additional exclusion criteria were body mass index (BMI) >30, somatic or psychiatric diseases, excessive tobacco, alcohol, or caffeine consumption, and usage of medications. All subjects had normal or corrected-to-normal vision.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Padova. A written informed consent was obtained from each subject, and a compensation of 100 euros was provided for participating in the experiment.

Measures

Mental arithmetic task. The mental arithmetic task consisted of a serial subtraction test. The task was initiated by the presentation of a randomly generated 3-digit number on a computer screen. Participants were required to count backwards by 17s from the starting number for a period of 3 min. Subtractions were performed mentally with answers spoken aloud, and subjects were instructed to perform them as quickly and accurately as possible. The percentage of correct answers (accuracy; %) was computed as a measure of performance.

Subjective state measures. The State-Trait Anxiety Inventory-Y1 (STAI-Y1; Spielberger, Gorsuch, Luschene, Vagg, & Jacobs, 1983) consists of 20 items assessing the levels of state anxiety, with responses ranging from 1 (not at all) to 4 (very much).

The Stanford Sleepiness Scale (SSS; Hoddes, Zarcone, Smythe, Phillips, & Dement, 1973) is a 7-grade scale asking the subject to rate current sleepiness. A score of 1 indicates maximum alertness while a score of 7 indicates maximum somnolence.

Cardiovascular recording. Beat-to-beat BP was recorded continuously using the Finapres device (Finapres 2300, Ohmeda, Englewood, CO). A photoplethysmographic cuff of proper size was fitted to the second phalanx of the subject’s middle digit of the left hand. The hand was kept at the heart level during acquisition.

Data were checked for artifacts, and mean arterial pressure (MAP) was derived as follows: DBP + [(SBP − DBP)/3] to compute for total peripheral resistance (TPR) (see below).

Electrocardiogram (ECG) was registered in a modified lead II configuration. ECG signal was amplified, band-pass filtered (1–100 Hz), and digitized at 500 Hz. The interbeat intervals (IBIs) were derived from the ECG recording by applying an automated algorithm for R-wave detection. IBI data were first edited automatically, then visually inspected and manually corrected where necessary. After resampling, an autoregressive model was employed to quantify the spectral power in the HF band (0.15–0.4 Hz; ms²).

The Kubios HRV Analysis Software 2.0 (MATLAB, Kuopio, Finland) was used for analysis. Since respiration is known to affect HRV (e.g., Grossman, Karemaker, & Wieling, 1991; Grossman & Kollai, 1993), respiratory rate was also calculated from respiratory effort belts.

The impedance signal (Z0) and the derivative of the impedance signal (dZ/dt) were acquired by Impedance Cardiograph Minnesota model 304 B (IFM Inc., Greenwich, CT). In accordance with guidelines (Sherwood et al., 1990), a tetrapolar band electrode disposition was adopted. Two inner (voltage) bands were positioned around the base of the neck and around the thorax, over the xiphisternal junction. Two outer (current) bands were placed to encompass the neck and the thorax, at least 3 cm above each of the recording bands. The outer electrodes transmitted a 4-mA AC at 100 kHz, and Z0 and dZ/dt signals were registered from the inner electrodes and digitized at 500 Hz. Impedance signals were acquired and processed by the COP-WIN software system (BIT Inc., Chapel Hill, NC), which uses an ensemble averaging procedure to generate 30-s samples after filtering out movement and respiratory artifacts. The positions of the B (i.e., the beginning of the left-ventricular ejection) and the X (i.e., the closure of the aortic valve) points on the dZ/dt waveform and the Q wave on the ECG were automatically marked. Each cardiac cycle was visually scanned and edited when the algorithm failed to detect these points. HR (bpm) was defined as the number of heart beats per minute. Stroke volume (SV; ml) was derived by the Kubicek equation (Kubicek, Karnegis, Patterson, Witsoe, & Mattson, 1966). CO (l/min) was calculated as HR × SV. PEP (ms) was identified as the time interval between the Q wave on the ECG signal and the B point on the dZ/dt signal. TPR (dyn × sec/cm²) was computed as (MAP/CO) × 80.

PSG. A standard PSG recording was conducted using the Siesta system (Compumedics, Melbourne, Australia), including
electroencephalography (EEG: C3-A2, C4-A1, F3-A2, F4-A1, O1-A2, O2-A1), bilateral electrooculography (EOG: right EOG-A1, left EOG-A2), and submental electromyography (EMG). Sleep was manually scored in 30-s epochs in accordance with current criteria (Iber, Ancoli-Israel, Chesson, & Quan, 2007), and the following sleep variables were derived: total recording time (TTR; min), total sleep time (TST; min), sleep onset latency (SOL; min), wake after sleep onset (WASO; min), sleep efficiency (SE; %; computed as [(TST/TRT) x 100]), and amount of rapid eye movement (REM) and non-REM (nREM) sleep stages (min). Because the TRT was set to be identical for both groups (i.e., 480 min; see the Procedure section for details), TST and SE were redundant; hence, only the former measure was considered for analysis.

Procedure
The study was run in a quiet, soundproof, temperature-controlled room in the Psychophysiology Laboratory at the University of Padova.

Participants spent two consecutive nights at the sleep lab. An adaptation night was assigned the day before the experimental night in order for them to become familiar with the lab environment. Participants had to abstain from tobacco, alcohol, and caffeine consumption and from naps the day before and during the days of the scheduled appointment.

Subjects were invited to the lab at 8 p.m. and electrodes for physiological recording were attached, then they relaxed quietly for 10 min to allow physiological parameters to stabilize. After acclimatization, the participants filled out the STAI-Y1 and the SSS. A 3-min resting period (baseline) preceded the mental arithmetic task. Cardiovascular monitoring was continuous throughout the baseline and the task execution. After task completion, subjects were allowed to engage in nonarousing activities such as reading books, watching television, or listening to music. The sleep period was set from midnight to 8 a.m. After awakening, PSG equipment was removed, and subjects were debriefed.

Data Reduction and Statistical Analyses
Cardiovascular measures were averaged for 1 min across the baseline and the task. Because of skewed distribution, PEP, TPR, and HF variables were log-transformed prior to the analysis.

As pointed out by previous research (Imholz, Wieling, Van Montfrans, & Wesseling, 1998; Larkin, Manuck, Jennings, & Stewart, 1994), while the Finapres device may overestimate BP levels resulting in limited accuracy in assessing absolute values, reliability in tracking BP changes has been established. Given these considerations, only change scores were considered for analysis. Reactivity scores (Δ) were calculated for each cardiovascular measure by subtracting the last minute of baseline value from each 1-min task value.

Unpaired t tests were computed over screening and subjective measures as well as on task performance and sleep variables to evaluate group differences. Cardiovascular reactivity was analyzed by applying on each index a mixed model analysis of covariance (ANCOVA) with group (hypotensives, normotensives) as between-subjects factor, time (three 1-min intervals; T1, T2, T3) as within-subjects factor, and baseline as covariate. To control for potential respiratory confounding, the respiratory rate was included as further covariate for HRV analysis. The Greenhouse-Geisser correction was performed where appropriate, but original degrees of freedom are reported. Bonferroni correction was used for post hoc comparisons. Partial eta squared (η²) is reported as estimate of effect size.

Lastly, Pearson’s correlations were run to examine the relationship between reactivity cardiovascular measures and sleep variables. A p < .05 was considered as significant.

Results

Screening
Hypotensives reported significantly lower screening SBP and DBP (as expected, as it was used as criterion to select participants; both ps < .001) (Table 1). No group differences were observed with regard to age, BMI, MEQ score, and PSQI score.

Subjective State Measures
Hypotensive and normotensive participants did not differ with respect to anxiety and sleepiness levels as assessed before testing (Table 1).

PSG
Sleep parameters were found to be comparable between groups, as listed in Table 1.

Cardiovascular Reactivity
The ANCOVAs performed on BP reactivity scores disclosed a lower increase under stress in both ΔSBP, F(1,23) = 16.36,
p < .001, $\eta^2_p = 0.41$, and $\Delta DBP$, $F(1,23) = 8$, $p = .009$, $\eta^2_p = 0.25$, in hypotensives than in normotensives. The significant time main effect indicated a sustained buildup in $\Delta SBP$, $F(2,46) = 11.39$, $p < .001$, $\varepsilon = 0.74$, $\eta^2_p = 0.32$, and $\Delta DBP$, $F(2,46) = 19.02$, $p < .001$, $\varepsilon = 0.86$, $\eta^2_p = 0.44$, over task execution. However, the interaction Group $\times$ Time ($\Delta SBP$: $F(2,46) = 8.49$, $p = .002$, $\varepsilon = 0.74$, $\eta^2_p = 0.26$; $\Delta DBP$: $F(2,46) = 4.49$, $p = .016$, $\varepsilon = 0.86$, $\eta^2_p = 0.16$) revealed a progressive increase only in normotensive individuals, while BP reactivity did not vary in hypotensives across the execution (Figure 1).

As illustrated in Figure 2, hypotensive participants exhibited lower $\Delta HR$ acceleration, $F(1,23) = 5.1$, $p = .033$, $\eta^2_p = 0.18$, than did normotensives. $\Delta HR$, $F(2,46) = 17.99$, $p < .001$, $\varepsilon = 0.84$, $\eta^2_p = 0.43$, and $\Delta CO$, $F(2,46) = 17.36$, $p < .001$, $\varepsilon = 0.65$, $\eta^2_p = 0.42$, showed a maximum increase at the first minute of the task (T1) and gradually declined with the task progression in both groups. In contrast, $\Delta TPR_{log}$ elevation peaked at T2, then stabilized, $F(2,46) = 29.51$, $p < .001$, $\varepsilon = 0.73$, $\eta^2_p = 0.55$ (Figure 3). Moreover, a reduced $\Delta TPR_{log}$ rise, $F(1,23) = 4.67$, $p = .041$, $\eta^2_p = 0.16$, was detected in hypotensives compared with normotensive individuals. No significance was observed with regard to $\Delta SV$.

A group main effect was found for $\Delta PEP_{log}$, $F(1,23) = 4.34$, $p = .048$, $\eta^2_p = 0.15$, and $\Delta HF_{log}$, $F(1,23) = 5.94$, $p = .023$, $\eta^2_p = 0.21$, revealing that hypotensives displayed a diminished decrease in both variables than normotensives (Figure 3). The drop in $\Delta PEP_{log}$ peaked at the beginning of the task and progressively recovered throughout the performance in all participants, $F(2,46) = 15.03$, $p < .001$, $\varepsilon = 0.94$, $\eta^2_p = 0.39$, as depicted in Figure 3.

**Correlations between Sleep and Cardiovascular Measures**

As summarized in Table 2, Pearson's correlations run on cardiovascular change scores revealed that the PSG sleep variables were related with $\Delta HR$ and $\Delta CO$ in the normotensive group: the higher the $\Delta HR$, the lower the SE and the amount of REM sleep, and the

Figure 1. Mean (SE) changes in systolic blood pressure (SBP; upper panel) and diastolic blood pressure (DBP; lower panel) from baseline over the task. T1 = 1–60 sec; T2 = 61–120 sec; T3 = 121–180 sec.

Figure 2. Mean (SE) changes in heart rate (HR; upper panel), stroke volume (SV; central panel) and cardiac output (CO; lower panel) from baseline over the task. T1 = 1–60 sec; T2 = 61–120 sec; T3 = 121–180 sec.
more prolonged the WASO. Similar results were obtained with respect to the relation between ΔCO and SE and WASO. Both ΔPEPlog and ΔHFlog were also positively associated with SE and REM sleep and were negatively associated with WASO in normotensives. Lastly, a positive correlation was found between ΔHFlog and nREM sleep in this group.

In hypotensives, the amount of REM sleep increases with the augmentation in ΔHR and ΔCO. Moreover, ΔHR was positively associated with SE and was negatively associated with WASO in this group.

Correlations were also performed between PSQI scores and cardiovascular reactivity measures, but no significant relationships were observed.

Discussion

In the current study, we carried out a comprehensive hemodynamic and autonomic examination seeking to explore the cardiovascular reactivity and the underlying mechanisms in essential hypotension. In agreement with previous investigations (Duschek et al., 2008; Duschek, Heiss, Buechner et al., 2009; Duschek, Matthias, & Schandry, 2005; Duschek & Schandry, 2006b), the magnitude of cardiovascular activation displayed throughout the mental arithmetic task was overall reduced in the essential hypotensive group in comparison with normotensive participants. Hypotensives exhibited lower acceleration in HR and lower elevation in TPR, which in turn resulted in diminished BP surge. The finding of reduced surge in peripheral resistance is somehow novel, since previous research failed to find differences over this parameter between hypotensives and normotensives (Duschek et al., 2008; Duschek, Heiss, Buechner et al., 2009; Sarlo et al., 2013), leading to the assumption that a primary cardiac hypoactivity underlies this condition. Conversely, our results suggest that a more complex pattern involving down-regulation in both myocardial and vascular functions occurs in essential hypotension. Further corroboration with the evidence of blunted cardiovascular reactivity in essential hypotension ensues from the analysis of the temporal course of the response. Whereas normotensives displayed a progressive buildup in BP levels throughout the task execution, a flattened response was detected in hypotensives. It should be remarked that subjective states such as sleepiness and anxiety were comparable across groups before the task. Likewise, the blunted cardiovascular reactivity found in hypotensives cannot be attributed to differences in task performance as the groups performed similarly for the task.

Because the mental arithmetic task is known to elicit a cardiovascular response that reflects a mixed autonomic pattern, in terms of both sympathetic activation and vagal withdrawal (e.g., Allen & Crowell, 1989; Berntson et al., 1994, 1996), the evaluation of neurovegetative indices may provide an avenue for a better understanding of the mechanisms mediating the reduced cardiovascular response in essential hypotension. The PEP represents a measure of myocardial contractility as it represents the isovolumic contraction time. As the ventricles are mainly innervated by sympathetic fibers, it is regarded as being an index of beta-adrenergic influences on the heart (Cacioppo et al., 1994; Kelsey, 2012; Sherwood, 1993): the shorter the PEP, the higher the cardiac sympathetic output. The assessment of changes in PEP over task performance revealed a lower reduction in hypotensives compared with normotensives, thus indicating a decreased cardiac sympathetic activation in hypotensive individuals. On the other hand, the diminished cardiac pumping observed in this population is likely to be modulated by the vagal system as well. Indeed, the group comparisons performed over HF values disclosed heightened reduction in normotensives compared to hypotensives. Since it is broadly agreed that the HF fluctuations in HRV are a reliable indicator of the parasympathetic control on the sinoatrial node (e.g., Berntson et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996), these results suggest a milder vagal withdrawal in the latter subjects. Taken together, a less marked autonomic reactivity in both cardiac sympathetic and parasympathetic drives is exhibited in hypotensives, which is reasonable to account for the blunted cardiovascular response in hypotension.
Table 2. Pearson’s Correlation Coefficients Between Sleep Parameters and Cardiovascular Reactivity Data

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<th>Hypotensives</th>
<th>Normotensives</th>
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<td></td>
<td>SE</td>
<td>WASO</td>
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<td>Cardiovascular change scores</td>
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<td>ΔSBP</td>
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<td>ΔDBP</td>
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<td>ΔHFlog</td>
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Note. CO = cardiac output; DBP = diastolic blood pressure; HF = high-frequency; HR = heart rate; NREM = nonrapid eye movement sleep; PEP = pre-ejection period; REM = rapid eye movement sleep; SBP = systolic blood pressure; SE = sleep efficiency; TPR = total peripheral resistance; WASO = wake after sleep onset.
*p < .05. **p < .01.

response. Thus, our study provides corroboration to the hypothesis of autonomic dysregulation advanced in essential hypotension (Akahoshi et al., 2006; Duschek & Schandry, 2007; Fredrikson et al., 1990). In particular, we replicated our prior findings (de Zambotti, Covassin, Cellini, Sarlo, & Stegagno, 2012) illustrating decreased activation in both autonomic divisions during cognitive test in this condition. As hypothesized, the administration of an effortful, highly demanding task appears to be more adequate to evoke a physiological activation and thus more sensitive to reveal clear-cut differences in response. Within this framework, the result of less pronounced elevation in TPR gives further strength to the proposed sympathetic hypoactivation. As the modulation of peripheral resistance can be mainly ascribed to the sympathetic system, a diminished sympathetic drive toward vasculature seems to affect the essential hypotension. However, it should be remembered that the TPR is a nonspecific metric of peripheral resistance as it reflects both alpha- and beta-adrenergic influences (e.g., Guyton & Hall, 2006). Thus, whether these results originate from a milder increase in alpha-mediated vasoconstriction or a lower decrease in beta-mediated vasodilation or a combination of both processes is unknown. Pharmacological trials employing beta- and alpha-blockers may help to discriminate such contributions.

In agreement with our hypothesis, results of interest were disclosed with regard to the relationship between cardiovascular reactivity and sleep. Specifically, sleep quality (as indexed by sleep parameters such as SE and WASO) was found to worsen with the augmentation in HR acceleration in response to stress in normotensives. A lower decrease in cardiac autonomic metrics (i.e., ΔPEP and ΔHF HRV) was also consistently related to more time spent sleeping and diminished nocturnal wakefulness, thus indicating that the lower the cardiovascular and autonomic activation under stress, the better the sleep quality in controls. Interestingly, the associations between change scores and sleep were observed as being reversed in hypotensives. Indeed, sleep was found to improve (higher SE and REM sleep and lower WASO) when higher HR acceleration occurred in this population, thereby suggesting that, unlike normotensives, good sleep is related to enhanced reactivity in hypotensives. Notably, abnormalities in sleep cannot account for these findings, since PSG revealed similar sleep in both groups.

Given that in our previous report we observed similar trends for the relationship between screening BP values and sleep (i.e., better SE associated with lower SBP in normotensives and with higher SBP in hypotensives; see de Zambotti et al., 2012), taken together these data yield the intriguing hypothesis that an optimal level of both cardiovascular activity and reactivity located between the upper limit of hypotension and the lower limit of normotension promotes a good sleep quality. Bearing in mind that sleep can be defined as a reversible state of perceptual disengagement from and reduced responsiveness to both internal and external stimulation (Carskadon & Dement, 2011), an enhanced physiological activation under stress may reflect a difficulty in the process of inhibition that aids a good sleep. Nevertheless, when the hypoactivation is exaggerated, impairment in modulating promptly and dynamically the physiological functions may occur, which in turn may compromise the physiological deactivation. Thereby, we can surmise that a curved rather than a linear relationship may better account for the association disclosed between sleep and cardiovascular regulation across the entire BP range. Support of this speculation is provided by the evidence of a J-shaped relation between BP values and risk of adverse outcomes (Carroll et al., 2009; Farnett, Mulrow, Linn, Lucey, & Tuley, 1991; van der Giezen et al., 1990). However, this is tentative as firm conclusions cannot be drawn in the context of a small sample cross-sectional study. Large sample examinations tailored at testing this theory by examining the full BP spectrum from the hypotensive limit to the hypertensive threshold are warranted.

The application of a screening procedure consisting of multiple BP readings provided a careful group selection. A positive history of symptoms related to the hypotensive condition as well as the exclusion of secondary forms was ensured prior to the recruitment of hypotensive participants. Moreover, the use of the PSG technique allowed us to obtain objective measures of sleep quality and quantity. However, a number of weaknesses have to be acknowledged. The major limitation of the current work is the small sample size, which may have reduced our statistical power. In spite of the level of anxiety being evaluated before the task completion, no post-task measures were collected. Although we cannot exclude that the task triggered a different extent of anxiety in hypotensives and normotensives, thereby affecting the outcomes, this event seems to be unlikely as the literature on essential hypotension consistently suggests independence of the performance from the mood in this population (Duschek et al., 2005, 2007a, 2007b). Since we tested females only, the results we obtained may not extend to the entire hypotensive population. Research on sex differences over cardiovascular reactivity yielded inconsistent findings. Some studies revealed various patterns of reactivity in males and females (Allen, Stoney, Owens, & Matthews, 1993; Stroud, Niaura, & Stoney, 2001), while others did not observe such effect (Gerin & Pickering, 1995; van Doormen, 1986). In order to clarify
whether the gender influences the reactivity in essential hypotension, future investigations are needed.

In spite of more convincing evidence suggesting no effect of the menstrual phase on cardiovascular reactivity (Colverson, James, & Gregg, 1996; Litschauer, Zauchner, Huemer, & Kafka-Lutzow, 1998; Pico-Alfonso et al., 2007), the lack of hormonal control should also be recognized as a further limitation in the present study.

Aside from reflecting changes in the sympathetic control on the heart, as discussed above, the PEP can be also affected by variations in preload or afterload (e.g., Lewis, Leighton, Forester, & Weisssler, 1974). Increases in ventricular filling may lead to higher preload resulting in shorter PEP. A shortening in PEP can also stem from a decrease in afterload due to a fall in peripheral resistance. Nonetheless, when the concurrent reactivity in other cardiovascular parameters is taken into account for the evaluation of variations in PEP, these potential influences can be reasonably disentangled (Sherwood et al., 1990). Particularly, TPR can be regarded as an index directly related to afterload, while HR is thought as being inversely related to preload. Considering the response to the task, a shortening in PEP was seen in the context of HR acceleration and TPR surge, thus suggesting a decrease in preload and a surge in afterload, respectively. Given that PEP decrease was accompanied by the opposite patterns to those expected when it is driven by the mentioned parameters, our data converge to indicate that changes in PEP truly reflected variations in cardiac sympathetic beta-adrenergic output. Comparable considerations apply when group differences in PEP are examined.

Since the HF fluctuations of HRV are synchronous with breathing, respiration may alter the interpretation of this variable as an index of vagal tone (Grossman et al., 1991; Grossman & Kollai, 1993). However, we can conceivably exclude that this confounder had a substantial impact on our findings as we controlled for respiration in our analysis. In addition, it should be noted that HR data are consistent with the interpretation of changes in HF in terms of changes in vagal activity as HR accelerated while HF decreased.

It is well established that the cardiovascular activation is modulated by the circadian pacemaker (for a review, see Rüger & Scheer, 2009). However, the literature on the influence of the time of the day on cardiovascular reactivity is inconsistent (Nebel et al., 1996; van Eekelen, Houtven, & Kerkhof, 2004; Willis, O’Connor, & Smith, 2005). On the other hand, more compelling findings support the relationship between chronotype and cardiovascular response to stress (Nebel et al., 1996; Willis, O’Connor, & Smith, 2005). Thereby, in order to rule out potential confounding effects deriving from different circadian typology, we excluded from our study individuals exhibiting extreme chronotypes as assessed through the MEQ.

To summarize, in the current investigation we found a reduced cardiovascular activation in response to a stress task in hypotensives compared with normotensives. Since the cardiovascular down-regulation occurred in the context of a cardiac autonomic hypoactivation, our results corroborate the theory of autonomic dysregulation in essential hypotension. Moreover, the associations we found between cardiovascular change scores and PSG parameters suggest the likelihood of a complex relationship between the physiological reactivity and sleep across the BP spectrum, an appealing hypothesis that future studies are encouraged to address.

References


Cardiovascular reactivity and hypotension


