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Impaired cerebral and systemic hemodynamics under cognitive load in young hypotensives: a transcranial Doppler study

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Abstract Reduced sympathetic outflow and deficits in cerebral hemodynamics have been considered as possible factors mediating the impaired cognitive performance in essential hypotension. However, the relationship between systemic blood pressure (BP), cerebral blood flow and cognitive functioning is still poorly understood. The present study was aimed at clarifying the physiological processes underlying cerebral and systemic hemodynamics in young hypotensives during cognitive engagement. Doppler sonography blood flow velocities in both middle cerebral arteries were measured from 17 hypotensives and 15 normotensives during a working memory task. Impedance cardiographic and BP measures were also recorded continuously. Lower increases in systolic and diastolic BP were observed in hypotensives. However, no evidence of lower sympathetic control was found for this group, as assessed by pre-ejection period. Flow velocity in middle cerebral arteries showed a lower increase in hypotensives throughout the task. Moreover, significant positive correlations between BP changes and blood flow velocities in middle cerebral arteries during the task were obtained for this group only, suggesting a less effective cerebral autoregulation. No difference was found between groups in task performance. Results suggest that during cognitive challenge hypotensives show impaired hemodynamic adjustments, both central and peripheral. However, such alterations do not directly affect cognitive performance, at least under moderate cognitive load.

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Introduction

Essential hypotension has been defined as a chronic condition of low blood pressure, with systolic reading below 100 mmHg in females and below 110 mmHg in males, regardless of the diastolic reading (World Health Organization, 1978). Symptoms include fatigue, lack of motivation, poor concentration, visual disturbances, and cardiovascular symptoms such as palpitations, cold limbs, headache, dizziness, and habitual paleness (Pilgrim et al., 1992). Even when regarded as extremes of the normal population (such as in the United States and United Kingdom), many hypotensive individuals receive treatment for low blood pressure, thus the economic cost for health care and the social cost in terms of work-loss days should not be underestimated (Pilgrim, 1994). Most importantly, there is evidence suggesting that hypotension is associated with cognitive decline and dementia in elderly population, possibly by affecting cerebral perfusion (Launer et al., 1995; Suter et al., 2002; Qiu et al., 2004). In addition, several studies have demonstrated poorer working memory performance, reduced sustained attention and lower arithmetic skills even in young adult hypotensives compared with normotensives (Costa et al., 1998; Duschek et al., 2005; Duschek & Schandry, 2007). Crucially, such a reduction in cognitive performance was found to be associated with lower cortical activation, as measured by slow brain potentials (Costa et al., 1998; Weisz et al., 2002; Duschek et al., 2006) and spontaneous electroencephalographic alpha activity (Duschek et al., 2006).

The close relationship between neural activity and cerebral blood flow (i.e., neurovascular coupling) is well established (Villringer & Dirnagl, 1995; Logothetis et al., 2001) and has been explored through many different brain imaging techniques. Transcranial Doppler sonography provides a non-invasive and real-time estimation of relative changes in cerebral blood flow by measuring blood flow velocity in the basal cerebral arteries with a high temporal resolution (i.e., on a beat-to-beat basis) (Aaslid et al., 1982). Given its characteristics, this technique has proven to reliably detect selective circulatory changes during cognitive activity (Kelley et al., 1992). Recent studies employing transcranial Doppler sonography demonstrated reduced cerebral blood flow velocity in young hypotensives as compared with normotensives both at rest and during cognitive activity (for a review, see Duschek & Schandry, 2007). Such an alteration has been often called into question as a possible link between low blood pressure, symptoms of fatigue, or lack of energy, and reduction in cognitive performance (Duschek & Schandry, 2004). This view, however, presents a challenge to the traditional notion of cerebral autoregulation, according to which cerebral blood flow is assumed to be maintained relatively constant over a wide range of mean arterial pressure (Wahl & Schilling, 1993; Folino, 2007), usually between 60 and 150 mmHg (Paulson et al., 1990). An alternative hypothesis is that reduced sympathetic outflow plays a significant role in determining both dampened cardiovascular reactivity and impaired cognitive performance in hypotensives (Duschek et al., 2005), particularly in the light of the recent controversial debate over the sympathetic neural regulation of cerebral blood flow (see Ainslie & Tzeng, 2010).

Within this framework, the present study aimed at clarifying the mechanisms underlying the association between chronically low blood pressure and reduced cognitive performance by investigating the relationship between systemic and cerebral hemodynamic changes during a cognitive task involving working memory load. Reduced sympathetic outflow and deficits in cerebral autoregulation have been considered as possible mediating factors. The combined use of transcranial Doppler sonography, impedance cardiography, and continuous blood pressure measurement allowed a reliable noninvasive assessment of the main hemodynamic parameters involved in the emerging response.

Method

Participants

Seventeen hypotensive female students (mean age = 23.8 ± 3.2 years, range = 20–31 years) and 15 healthy female controls (mean age = 23.9 ± 2.3 years, range = 20–29 years) participated in the study.

The screening session was conducted at least 1 week prior to the experimental session. After a resting period of 10 min, three blood pressure measurements were taken in a seated position, separated by 5 min rest intervals. BP measurements were taken by a well-trained research assistant using a standard mercury sphygmomanometer. Individuals with a mean SBP <100 mmHg were assigned to the hypotensive group (mean SBP = 98.42 ± 1.8; mean DBP = 65.58 ± 2.6). Normotensive subjects were required to have a mean SBP between 115 and 130 mmHg (mean SBP = 121.13 ± 3.5; mean DBP = 73.68 ± 2.5). The results of the BP-screening were confirmed by repeating this measurement procedure right before the beginning of the experimental session.

All participants were non-smokers, free of cardiovascular, immune, or metabolic disorders, and took no medications known to affect the autonomic nervous system. Participants were requested not to eat or drink alcohol or beverages containing caffeine for 3 h prior to screening and testing. Subjects were paid €25 for participation. The study was approved by the local Ethics Committee and conformed with the principles outlined in the Declaration of Helsinki. All volunteers gave written consent prior to participation.

Cognitive task

The N-back task was presented on a computer using E-Prime 1.1 software (Psychology Software Tools, Inc.). A series of white-colored alphabetic letters were presented on a grey background at the centre of the screen. Participants were required to press the spacebar with both forefingers whenever the letter presented on the screen matched the one presented 2 trials previously. The task is assumed to place great cognitive load on working memory processes (Owen et al., 2005).

Each letter was presented for 250 ms with an interstimulus interval of 1,550 ms. The task consisted of three 3-min blocks, each including 100 stimuli (30 target and 70 non-target). Each block was preceded and followed by 1-min blank screen. The stimuli were randomly presented within each block. The version of the N-back task employed in the present study was based on previous relevant investigations of working memory (e.g., Segalowitz et al., 2001; Wintink et al., 2001; Mendrek et al., 2005). The interstimulus interval was slightly modified to obtain an overall duration of 3 min per block.

Data acquisition and processing

The electrocardiogram (EKG) was recorded using a Grass Model 7E Polygraph (Grass Instrument Co., W. Quincy,

MA). Ag/AgCl surface electrodes (1 cm diameter) were composed in a Lead II configuration. The signal was filtered 5–300 Hz and digitized at a sampling rate of 500 Hz. A digital trigger detecting R-waves was applied to the EKG signal to obtain interbeat intervals, which were then converted to heart rate.

Beat-to-beat systolic (SBP) and diastolic (DBP) blood pressure were measured noninvasively from the subject's middle finger of the left hand using a photoplethysmograph cuff (Finapres 2300, Ohmeda, Englewood, CO). This method has been validated in a variety of settings and has the advantage to provide continuous measurements of peripheral arterial pressure. On the other hand, it is acknowledged that characteristic alterations of the blood pressure waveform occur with distal propagation, with a significant increase particularly in the systolic component (e.g., McAuley et al., 1997). Therefore, the limited accuracy of finger blood pressure does not allow the assessment of absolute blood pressure levels (Imholz et al., 1998). Even so, the *t* test analysis performed in the present study on mean resting Finapres SBP values confirmed a significant difference between normotensives and hypotensives ($Ms = 137.19$ and 113.44 mmHg, respectively; $t(30) = 4.80$, $p < .0001$).

A tetrapolar band electrode configuration was employed for impedance signal acquisition. The inner two recording electrode bands were placed around the base of the neck and around the thorax over the tip of the xiphoid process. The outer two current electrode bands were placed at a distance of at least 3 cm from the recording electrodes, in accordance with established guidelines (Sherwood et al., 1990). A Minnesota Impedance Cardiograph Model 304 B (IFMInc., Greenwich, CT) was used, providing a 4-mA constant current source with 100-kHz frequency. Stroke volume (ml) was obtained by applying the Kubicek equation (Sherwood et al., 1990). Cardiac output (l/min) was derived by multiplying heart rate by stroke volume. Preejection period (ms) was assessed as an index of sympathetic influence on cardiac activity. It was derived from the impedance cardiogram by computing the time interval between the EKG Q wave and the dZ/d*t* B point. Total peripheral resistance (TPR) was derived from cardiac output (CO) and mean arterial pressure (MAP) by the formula TPR = (MAP/CO) * 80.

Mean flow velocities of right and left middle cerebral arteries were continuously recorded by means of transcranial Doppler sonography employing a Multidop X4 system (DWL Elektronische Systeme). Two dual 2-MHz transducers were fixed by an elastic headband and placed on the temporal bone windows. The highest signal was obtained at a depth ranging from 45 to 55 mm. The spectral envelope curves of the Doppler signal were recorded with a sample rate of 28 Hz. For technical details and applications of this technique, see Duschek and Schandry (2003).

Physiological signals were recorded continuously for 1 min immediately prior to task onset and throughout the task. For all the physiological measures, the time course of each response during task execution was analyzed by dividing the 3-min stimulus period into six 30-s epochs. Change scores between each epoch and the last 30-s baseline interval were analyzed. Percentage of mean flow velocity (MFV) changes were computed as follows: [(MFV during task execution − MFV during baseline)/MFV during baseline) × 100].

Statistical analysis

For each measure, mean change scores were entered into separate analyses of covariance (ANCOVAs) using baseline score as a covariate, Group (hypotensives vs. normotensives) as a between-subjects factor, and Block (1, 2, 3) and Time (six 30-s epochs) as within-subjects factors. Analysis of MFV changes included Hemisphere (left and right) as a further within-subjects factor. For all analyses, the Huynh–Feldt correction was applied when sphericity assumptions were violated. In these cases, the uncorrected degrees of freedom and the corrected probability levels are reported.

We also performed Pearson's correlation analysis separately for each group to explore the relationship between mean changes in systemic blood pressure and mean changes in cerebral blood flow velocity during cognitive load. Lastly, to investigate any possible effects of systemic and cerebral hemodynamic variables on cognitive performance, a backward stepwise regression analysis was conducted separately for each group using mean changes in systolic and diastolic blood pressure, cardiac output, and cerebral blood flow velocity as independent variables and performance accuracy rate as a dependent variable.

Results

Behavioral performance

No significant differences were found between hypotensives and normotensives in mean reaction times and accuracy during task execution (all $ps > .40$).

Cardiovascular measures

Significant Group × Time interactions were found for both SBP and DBP, $F(5,145) = 3.59$, $p < .03$, and $F(5,145) = 4.36$, $p < .004$, respectively. As supported by the significant Group × Time linear trends, $F(1,29) = 5.31$, $p < .03$, and $F(1,29) = 6.85$, $p < .02$, respectively, during cognitive

performance SBP and DBP increased to a significantly higher degree in normotensives than in hypotensives, particularly at the beginning of each block (Fig. 1).

However, no evidence of lower sympathetic control was found for hypotensives, as assessed by changes in pre-ejection period. Independent of group, a significant Block × Time interaction was found, $F(10,290) = 2.20$. $p < .05$. As supported by the significant Block × Time linear trend, $F(1,29) = 6.75$, $p < .02$, both groups showed a clear-cut sympathetic activation (as indexed by a shortening of pre-ejection period) only during the first block of the task, peaking within 60–90 s after task onset (see Fig. 2). No significant effects involving group were found for this measure, as well as for heart rate, cardiac output, and total peripheral resistance.

Blood flow velocity in middle cerebral arteries

Throughout the task, hypotensives showed significantly lower increases in mean flow velocity than normotensives in both middle cerebral arteries (Group main effect: $F(1,29) = 6.88$, $p < .02$). Moreover, a significant Group × Block × Time × Hemisphere interaction was found, $F(10,290) = 2.24$, $p < .03$). As supported by the significant Group × Block linear trend, $F(1,29) = 5.89$, $p < .03$), and Group × Block × Time × Hemisphere linear trend, $F(1,29) = 7.26$, $p < .02$), in normotensives the highest percentage increase was observed in the first two blocks compared with the third one in both hemispheres, whereas in hypotensives no difference in mean flow velocity changes was found across blocks, particularly in the left hemisphere (Fig. 3).

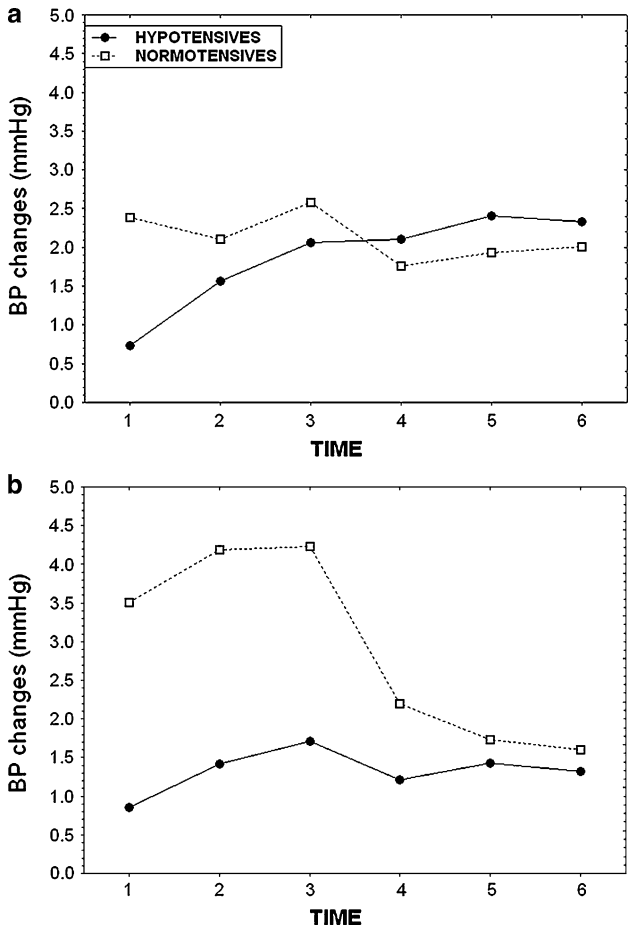

Fig. 1 Diastolic (**a**) and systolic (**b**) blood pressure (BP) changes from baseline in hypotensives and normotensives during the cognitive task. Time 1 = 1–30 s; 2 = 31–60 s; 3 = 61–90 s; 4 = 91–120 s; 5 = 121–150 s; 6 = 151–180 s

Flow-pressure relationship

Significant positive correlations were obtained in hypotensives between mean changes in cerebral blood flow velocity and mean changes in systolic and diastolic BP during the task, $r = .49$, $p < .04$, and $r = .62$, $p < .008$, respectively (Fig. 4), whereas no significant correlations emerged in normotensives (all ps $> .20$).

Exploratory regression analyses

The results of the backward stepwise regression analysis indicated that in hypotensives mean SBP changes during the first block of the task were positively related to the accuracy rate, whereas none of the other potential predictor variables showed significant associations. Mean flow velocity and cardiac output were sequentially removed from the model (all ps $> .38$), whereas SBP and DBP were retained in the final model, which accounted for 30% of the variance. However, only SBP was found to significantly predict the accuracy rate, $\beta = 0.78$, SE = 0.21, $t = 2.42$, $p < .03$, whereas the relationship between DBP and accuracy rate did not reach statistical significance, $\beta = -0.54$, SE = 0.51, $t = -1.69$, $p > .11$.

In normotensives, no significant associations were found, as all the regressors were sequentially excluded from the final model, which accounted for 18% of the variance (all ps $> .11$).

Discussion

The present study was aimed at investigating the interaction between systemic and cerebral hemodynamics during cognitive engagement in young hypotensives. By using impedance cardiography together with the continuous monitoring of blood pressure, we were able not only to assess changes in the main cardiovascular parameters, but also to obtain a reliable estimation of sympathetic

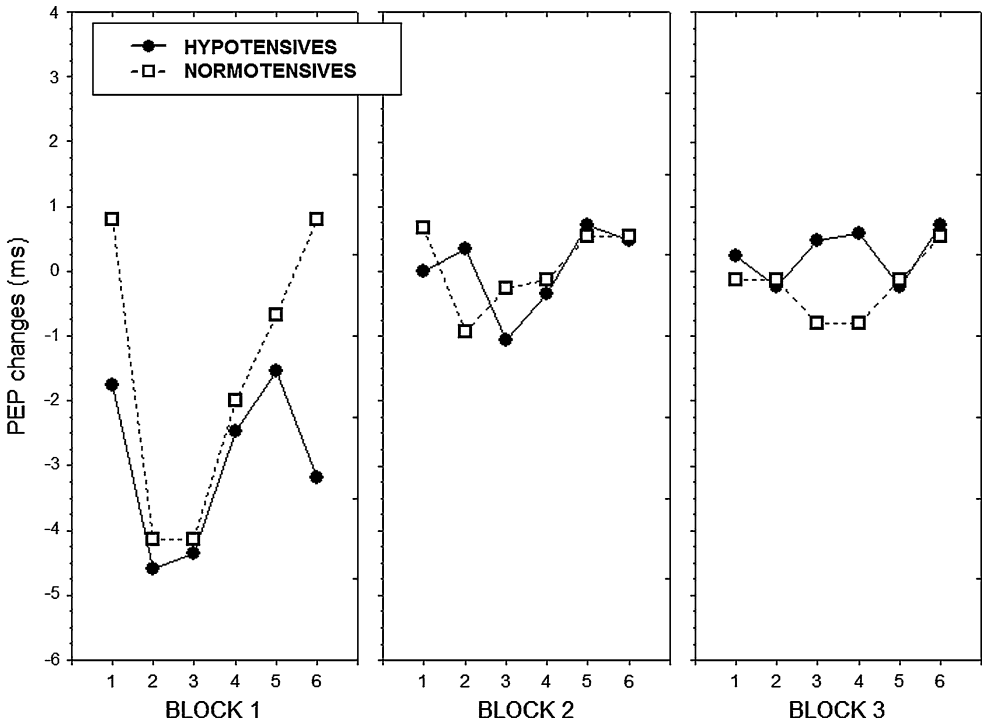

Fig. 2 Pre-ejection period (PEP) changes from baseline in hypotensives and normotensives across blocks during the cognitive task. Time 1 = 1–30 s; 2 = 31–60 s; 3 = 61–90 s; 4 = 91–120 s; 5 = 121–150 s; 6 = 151–180 s. Note that no significant differences were found between groups

beta-adrenergic activation. Crucially, the concurrent use of transcranial Doppler sonography allowed the evaluation of cognitively induced changes in mean flow velocity of both middle cerebral arteries in relation with systemic hemodynamic adjustments.

Three main findings were obtained. First, lower systolic and diastolic BP increases were found in hypotensives as compared with normotensives during the execution of the working memory task. These cardiovascular changes were not simply a function of reduced sympathetic cardiac activation, as demonstrated by a lack of differences in pre-ejection period changes between groups. Second, flow velocities in middle cerebral arteries showed significantly lower increases in hypotensives as compared to normotensives throughout the task, indicating reduced cerebral perfusion. Third, and most importantly, the linear relationship found in hypotensives between changes in systemic blood pressure and changes in blood flow velocities suggests impaired cerebral autoregulation in these individuals.

Previous research has demonstrated in young hypotensives reduced attentional and memory performance (Costa et al., 1998; Duschek et al., 2005; Duschek & Schandry, 2007), associated with decreased cortical activity (Costa et al., 1998; Weisz et al., 2002; Duschek et al., 2006) and reduced adjustment of brain perfusion to cognitive demands (Duschek & Schandry, 2004, Duschek & Schandry, 2007). In the present study, despite normal levels of task performance, evidence of alterations were found in both systemic and cerebral hemodynamic adjustments to effortful cognitive processing.

During the working memory task, systolic BP increased to a significantly lower degree in hypotensives than in normotensives, particularly in the first half of each block. This was associated with a less pronounced increase in diastolic BP at the beginning of each block. While on the one hand such a blunted reactivity in hypotensives may play a protective role against the development of cardiovascular disease during exposure to aversive stressors, on the other hand it might directly and negatively affect their cognitive performance. Indeed, systolic BP reactivity during the first block significantly predicted accuracy rate in hypotensives but not in normotensives. Therefore, even a marginal reduction in blood pressure responsivity might result in increased number of errors during demanding cognitive activities. This result complements and extends previous work showing positive relations between BP *levels* and cognitive performance in young hypotensives (Wharton et al., 2006) by demonstrating that systolic BP *reactivity* is a critical determinant of accuracy performance during a working memory task.

Previous studies have reported lower BP (Duschek et al., 2005; Duschek & Schandry, 2006; Duschek et al., 2009) reactivity to cognitive activity in essential hypotension. In those studies, a general reduction in sympathetic outflow has been hypothesized as a possible underlying mechanism; however, no indices of sympathetic activation were provided. In the present study, no evidence of reduced cardiac sympathetic outflow was found in hypotensives, as assessed by changes in pre-ejection period during the task. Instead, pre-ejection period substantially shortened during the first block of the task in both groups, indicating

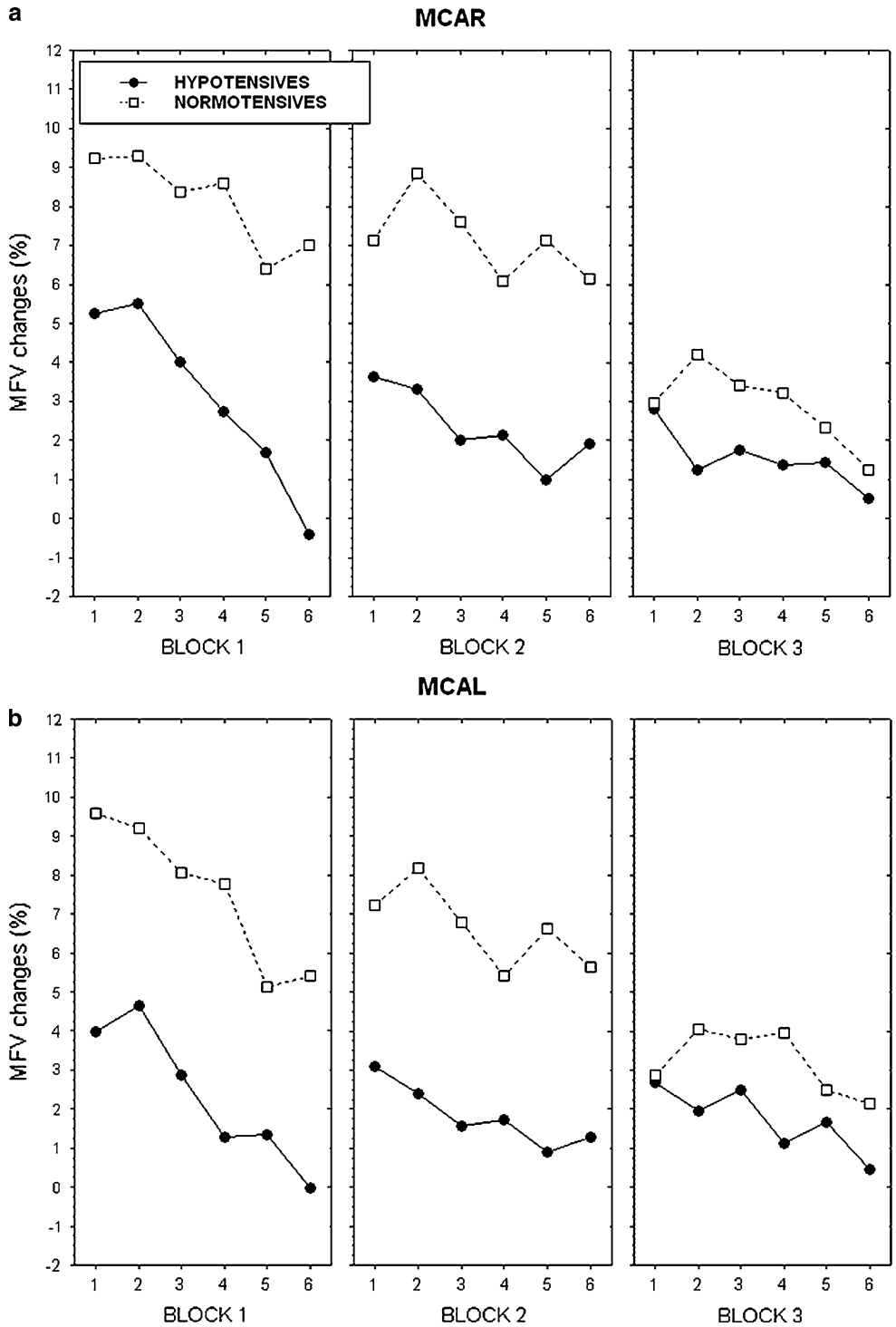

Fig. 3 Mean cerebral blood flow velocity (MFV) changes from baseline in the *right* (**a**) and *left* (**b**) middle cerebral arteries in hypotensives and normotensives across blocks during the cognitive task. Time 1 = 1–30 s; 2 = 31–60 s; 3 = 61–90 s; 4 = 91–120 s; 5 = 121–150 s; 6 = 151–180 s

comparable sympathetic beta-adrenergic activation. Furthermore, the lack of differences between groups in total peripheral resistance changes during the task makes it unlikely that a diminished vascular tone due to reduced alpha-adrenergic activity determined the blunted BP reactivity observed in hypotensives.

Among the alternative mechanisms underlying such changes, a crucial role might be played by an impairment

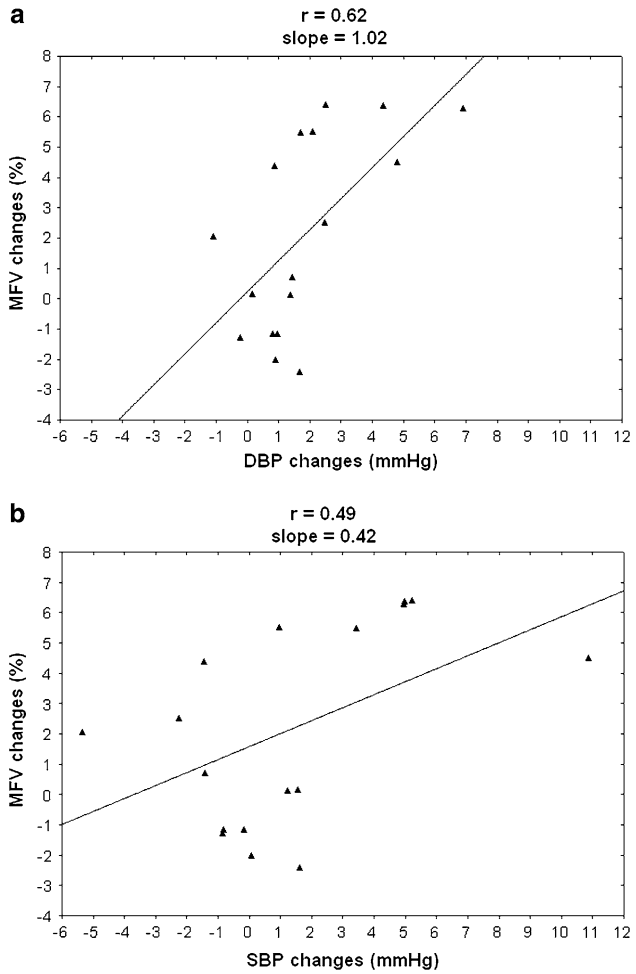

Fig. 4 Association between changes in mean cerebral blood flow velocity (MFV) and corresponding changes in **a** diastolic blood pressure (DBP) and **b** systolic blood pressure (SBP) in hypotensives ($n = 17$) during the cognitive task. The regression line is shown

in baroreflex regulation. This issue has been recently addressed by Duschek et al. (2008a), who demonstrated increased sensitivity of such neural feedback mechanism in chronic hypotensives both at rest and during mental stress, associated with lower increases of BP and stroke volume under stress. Moreover, the administration of an alpha-adrenergic agonist led to BP enhancement while not reducing but even amplifying baroreflex sensitivity, as a result of autonomic counter-regulation (Duschek et al., 2009). Taken together, these results suggest that in essential hypotension increased baroreflex sensitivity entails overcompensatory alterations of phasic blood pressure increases, with a possible resetting of the system to lower blood pressure levels. An altered baroreflex regulation might therefore support reduced BP levels and reactivity without involving a reduction in sympathetic outflow.

Another major finding of the present study regards the relationship between systemic and cerebral hemodynamics. Throughout the task, hypotensives showed significantly lower increases in mean flow velocity than normotensives in both middle cerebral arteries, consistent with what was observed by Duschek and Schandry (2004) using a simple attentional task. In addition, in contrast with normotensive controls, hypotensives showed no modulation of cerebral blood flow across blocks, suggesting a less effective adjustment of brain perfusion to the current neural metabolic demands.

The hypothesis of an alteration in cerebral perfusion is strongly supported by the finding of a linear positive relationship between changes in systolic and diastolic BP and changes in blood flow velocities of both middle cerebral arteries during the cognitive task in hypotensive individuals. In contrast, no significant relationship between the two variables emerged in normotensive controls. Similar results have been obtained by Duschek and Schandry (2006) when employing a mental arithmetic task.

The fact that changes in systemic blood pressure can induce in hypotensives parallel changes in cerebral blood flow might indicate an impairment in cerebral autoregulation. Autoregulation implies that cerebral blood flow is maintained relatively constant over a wide range of systemic mean arterial pressure, which is generally assumed between 60 and 150 mmHg (Paulson et al., 1990). However, the lower autoregulatory limit has been recently questioned by a number of evidence suggesting considerably higher values (Drummond, 1997; Duschek & Schandry, 2004), up to between 73 and 88 mmHg (Olsen et al., 1995; Olsen et al., 1996), with a large interindividual variability (Waldemar et al., 1989). It is therefore possible that, in individuals with chronic hypotension, changes in systemic blood pressure are not effectively compensated by autoregulatory processes, thus affecting cerebral perfusion. This, in turn, might result in inadequate hemodynamic adjustments to cognitive demands.

Some limitations of the present study need to be mentioned. First, as resting blood pressure values are known to vary markedly across circumstances, multiple measurements in different screening sessions would have provided a more accurate assessment of essential hypotension in our sample. Secondly, a relationship between changes in blood flow velocity and cognitive performance might have been revealed by analyzing the early time frames of the hemodynamic response, as shown by recent relevant studies (Schuepbach et al., 2007; Duschek et al., 2008b). Differently, by averaging blood flow velocities over 30-s time windows, we did not make full use of the high temporal resolution of transcranial Doppler sonography. This choice was due to the need of comparing cerebral and systemic hemodynamics during task execution. Indeed, in order to avoid respiratory artifacts producing distortions of the dZ/d*t* signal, impedance cardiography requires averaging

values over multiple cardiac cycles encompassing three or four respiratory cycles (Sherwood et al., 1990). This led us to employ relatively long time windows for analyses. It is also possible that the 2-back task has been insufficiently demanding to highlight differences in performance between young hypotensives and normotensives. The choice of a working memory task was motivated by the considerations that this function is involved in many cognitive operations and is strongly associated with the attentional system (Baddeley, 1986), and that essential hypotension proved to be accompanied by deficits primarily in the domains of memory and attention (Stegagno et al., 1996; Costa et al., 1998; Weisz et al., 2002; Duschek & Schandry, 2003, Duschek et al., 2005). Indeed, when working memory was assessed within a battery of several specific cognitive tasks, lower accuracy was found in hypotensives as compared with normotensives even using a 1-back task (Duschek et al., 2005). We therefore suggest that in our study the lack of significant differences in performance between groups might be attributable to the execution of a single cognitive task divided in three blocks and performed in isolation, which is less challenging than a similar task performed in a context of sustained cognitive effort. On a different but related note, we also acknowledge the limited generalizability of our findings in the light of the use of only one cognitive task involving working memory.

In conclusion, our findings indicate cardiovascular hyporeactivity associated with reduced cerebral perfusion during cognitive challenge in young hypotensive individuals. Such a hemodynamic response pattern suggests an impairment in cerebral autoregulation in which changes in systemic blood pressure directly affect cerebral blood flow and cognitive performance. Further research employing ambulatory BP monitoring is needed to better elucidate the hemodynamic alterations involved in chronic hypotension in both research and clinical settings.

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Conflict of interest The authors report no biomedical financial interests or potential conflicts of interest pertaining to the subject of this manuscript.

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