Cerebral blood flow modulations during proactive control in chronic hypotension

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Abstract

In addition to complaints including fatigue, mood disturbance, dizziness or cold limbs, chronic low blood pressure (hypotension) is associated with reduced cognitive performance. Deficiencies in cerebral blood flow regulation may contribute to this impairment. This study investigated cerebral blood flow modulations during proactive control in hypotension. Proactive control refers to cognitive processes during anticipation of a behaviourally relevant event that allow optimization of readiness to react. Using functional transcranial Doppler sonography, bilateral blood flow velocities in the middle cerebral arteries were recorded in 40 hypotensive and 40 normotensive participants during a precued Stroop task. Hypotensive participants exhibited smaller bilateral blood flow increases during response preparation and longer response time. The group differences in blood flow and response time did not vary by executive function load, i.e. congruent vs. incongruent trials. Over the total sample, the flow increase correlated negatively with response time in trials with a higher executive function load. The findings indicate reduced cerebral blood flow adjustment during both the basic and more complex requirements of proactive control in hypotension. They also suggest a general deficit in attentional function and processing speed due to low blood pressure and cerebral hemodynamic dysregulations rather than particular impairments in executive functions.

Key words: Hypotension, blood pressure, cerebral blood flow, proactive control, transcranial Doppler sonography

Introduction

Chronic hypotension refers to a persistent state of low blood pressure independent of the occurrence of other pathological conditions (De Buyzere et al., 1998). Associated complaints include fatigue, reduced drive, impaired mood, dizziness, and cold limbs (Duschek et al., 2017a; Pilgrim, 1994; Rosengren et al., 1993). According to WHO (1978) criteria, hypotension is diagnosed when systolic blood pressure falls below 100 mmHg in women and 110 mmHg in men. The prevalence of this condition has been estimated at 2-3% in the general population, with younger women being especially affected (Duschek & Schandry, 2004). Aberrances in autonomic cardiovascular control have been well-established in chronic hypotension suggesting involvement of autonomic nervous system dysregulations in its etiology (Covassin et al., 2013; Duschek et al., 2008a).

In addition to bodily symptoms and mood disturbance, there is evidence of cognitive impairment in chronic hypotension. Various studies have documented prolonged simple reaction times (Duschek et al., 2006), as well as deficits in attentional functions such as tonic and phasic alertness or selective, divided and sustained attention (Duschek et al., 2005; Costa et al., 1998). Memory impairment has been suggested by lower recall performance of verbal material (Costa et al., 1998). In contrast, higher cognitive domains, i.e. executive functions, have barely been investigated in hypotension. Moreover, the available studies revealed mixed results. While one study documented reduced task switching ability (Weisz et al., 2002), both positive and negative results were seen for working memory updating (Duschek et al., 2005, 2017b; Sarlo et al., 2013). Further studies failed to find differences between individuals with low and normal blood pressure in performance on arithmetic tasks (Duschek & Schandry, 2006; Covassin et al., 2013).

Disturbance in cerebral blood flow regulation has been considered to mediate cognitive impairments in chronic hypotension (Duschek & Schandry, 2004; Sarlo et al., 2013). Due to the close coupling of neural activity and brain metabolism, cerebral activation processes are accompanied by transient increases in cerebral blood flow (Iadecola, 2017). In hypotension, this mechanism may not be sufficient to ensure optimal perfusion. Research concerning this hypothesis has been conducted in the field of preparatory cognitive processing using a cued reaction time task (Duschek & Schandry, 2004). Paradigms of this type focus on the attentional function of phasic arousal, namely a short-term increase in attentional tone the anticipation of a significant event (Johnson & Proctor, 2004; Posner & Rafal, 1987). Using functional transcranial Doppler sonography (fTCD), blood flow modulations in the middle cerebral arteries (MCA) of both hemispheres were recorded during the task. A right-dominant blood flow increase was seen, which was far smaller in individuals with hypotension than in those with blood pressure in the normal range. This has been interpreted as indicative of insufficient adjustment of brain perfusion to cognitive demands. Moreover, longer response times arose in hypotensive individuals, as well as a positive correlation between reaction speed and the magnitude of blood flow increase, which underlines the significance of hemodynamic adjustment in task performance (Duschek et al., 2008b, 2010).

Though phasic alertness such as addressed by cued reaction time tasks is doubtlessly crucial in everyday life, it is important to note that response preparation commonly involves more complex cognitive processes. These processes have been conceptualized as proactive control and may include the maintenance of goal-relevant information, response selection or inhibition of inappropriate behavior (Aron, 2011; Braver, 2012; Connolly et al., 2002). Complex preparatory processes and the psychophysiological mechanisms involved therein have not yet been investigated in chronic hypotension. To address this research gap, we studied cerebral blood flow modulations during preparation of responses in the Stroop task (MacLeod, 1991). In the Stroop task, the subject has to name the font colour of different colour words, while ignoring the word meaning. The font colour may match the word meaning (congruent condition) or differ from word meaning (incongruent condition). During the incongruent condition, interference occurs between font colour and word meaning, which is associated with increased cognitive load and longer response time. In the present study, a precued Stroop task was applied to study cerebral blood flow modulations during complex preparatory processes in chronic hypotension. In a Stroop task, proactive control especially implies interference anticipation and prevention (Manard et al., 2017). Considering the required overriding of the dominant response of word reading, proactive inhibition is also likely to be involved, that is, control mechanisms preventing an inappropriate response from occurring in an anticipated situation (Ballanger, 2009).

Evidence from fMRI studies suggests that, on a neural level, proactive control is mainly represented in the lateral prefrontal cortex (Braver, 2012; Chambers et al., 2009). In addition, precued tasks involve substantial load on phasic alertness, which is associated with a network including the lateral prefrontal and inferior parietal cortex, in addition to the reticular formation (Paus et al., 1997). The previously documented deficiencies in cerebral blood flow adjustment during cognition in chronic hypotension may also emerge during complex preparatory processes, resulting in suboptimal task performance (Duschek & Schandry, 2004; Sarlo et al., 2013). In contrast to incongruent trials of the Stroop task, the preparation of congruent trials is widely restricted to basic attentional processing. As such, comparison between both types of trials allows evaluation as to the degree to which the expected differences between hypotensive and normotensive individuals in cerebral blood flow and performance vary according to task difficulty, as well as the involvement of executive functions. Though available knowledge executive functions cognition in hypotension is still scarce, as a working hypothesis, we predicted that both the reduction in cerebral blood flow adjustment and reaction speed are greater for incongruent trials, indicating reduced proactive control of interference.

In the study, fTCD was applied to measure blood flow velocities in the MCA of both cerebral hemispheres. This technique enables continuous recording at a high temporal resolution, which in turn allows analysis of distinct periods of the hemodynamic response (Duschek & Schandry, 2003; Schuepbach et al., 2007, 2009; c.f. Wecht et al., 2002 for application of fTCD during a Stroop paradigm). fTCD studies using precued tasks revealed biphasic courses of blood flow modulations, with the first component associated with response preparation and the second with response execution (Duschek & Schandry, 2004, Duschek et al., 2010; Montoro et al., 2015). However, based on previous observations, we presently hypothesized that only the magnitude of the first component varies according to blood pressure and is linked to task performance (Duschek & Schandry, 2004; Duschek et al., 2008b, 2010; Montoro et al., 2015).

This study investigated cerebral blood flow modulations during proactive control in chronic hypotension. Cerebral blood flow modulations may be relevant at the interface between cardiovascular regulation, neural activity and cognition, where cognitive impairments may be mediated by insufficient neural activation associated with reduced blood flow adjustment. The following hypotheses were tested: (1) Individuals with chronic hypotension exhibit smaller bilateral MCA blood flow increases during the preparation of congruent and incongruent trials of the Stroop task than those with normal blood pressure. (2) Moreover, hypotensive participants show longer response times in both types of trials. (3) The magnitude of the preparatory blood flow increase is positively associated with response speed. (4) In the entire sample, incongruent trials are associated with stronger MCA blood flow increases during response preparation and longer response times than congruent trials. (5) Finally, as a result of greater color word interference in hypotension, differences in the preparatory blood flow increase and response speed between both conditions are larger in hypotensive than in normotensive participants.

Methods

Participants

In total, 40 individuals with hypotension according to WHO criteria (WHO, 1978) and 40 normotensive control persons participated. The sample included five men (two in the hypotensive sample, three in the control group). Participants were recruited via e-mail distribution lists of the local universities that addressed students and their friends and families. Persons suffering from a relevant physical disease or mental disorder were excluded from participation. Health status was assessed by means of an anamnestic interview and a questionnaire covering diseases of the cardiovascular, respiratory, gastro-intestinal and uro-genital systems, the thyroid and liver, and metabolic diseases and psychiatric disorders. In addition, none of the participants used any kind of medication affecting the cardiovascular or central/peripheral nervous system. In both groups, 34 participants were university students; the remaining participants were in the workforce. Seventy-six subjects were right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971) (38 in both groups); 17 participants were smokers (six in the hypotensive group, 11 in the control group). Table 1 provides information about age, body mass index (BMI), extent of education, physical activity, and blood pressure and heart rate (as recorded at the beginning of the experimental procedure).

Table 1

Cognitive task

The Stroop task was presented on a standard desktop computer using Experimental Builder software (SR Research Ltd., Ottawa, Canada). In the center of the screen, a white cross (height and width 1.3 cm) was displayed for 35 s, acting as a fixation point. A trial began with an acoustic cue (warning tone, 400-Hz, 500 ms duration). Five seconds after the onset of the tone, one of three color words (red, blue or yellow, height 1.8 cm, width 3.8 to 4.8 cm), written in one of these colors, appeared for 1000 ms. In each trial the participant had to press a color-button corresponding to the color of the word, ignoring the word meaning. For this purpose, three keys on the computer keyboard (arrow keys) were marked with colored stickers. The arrangement of the keys (red, blue or yellow in the middle) was randomized across participants. Participants were instructed to respond as quickly and as accurately as possible. After disappearance of the word, the white cross was shown again for 35 s. This relative long inter-trial interval was chosen to ensure complete return of MCA blood flow velocities to baseline level after the behavioral response (c.f. Duschek & Schandry, 2004, 2016; Montoro et al., 2015).

The task consisted of two blocks, one of which comprised 18 congruent trials (match between word color and word meaning) and the other 18 incongruent trials (mismatch between word color and word meaning). The two blocks were separated by a 1 min break. Half of the participants started with the congruent trials, and the other half with the incongruent trials. Participants used their dominant hand for task execution.

Task performance was indexed by mean response time for congruent and incongruent trials. In addition, an interference score was computed as the difference in mean response times between incongruent and congruent trials. As participants made very few mistakes in the task (M=0.31, SD=0.63, range 0 to 3 for congruent trials; M=0.49, SD=0.76, range 0 to 3 for incongruent trials in the entire sample), mistakes were not factored into the analysis.

Recording and processing of cerebral blood flow

A commercially available Doppler sonography device (Multidop L2; DWL Elektronische Systeme, Sipplingen, Germany) was used for cerebral hemodynamic assessment. Blood flow velocities were recorded simultaneously in the MCA of both hemispheres. The recordings were obtained through the temporal bone windows using two 2-MHz transducer probes. Insonation of the MCA took place at a depth between 48 and 52 mm. The MCA were identified according to the flow direction of the blood stream towards the ultrasonic probe and their depth of approximately 50 mm. Following vessel identification, the probes were fixed to the head using a head harness. The spectral envelope curves of the Doppler signal were stored at a rate of 28 samples per second (for the insonation technique and validation of fTCD, see Duschek & Schandry, 2003).

The envelope curves revealed by fTCD were analyzed offline using AVERAGE software (Deppe et al., 1997). Blood flow velocities were represented by a time- and intensity-weighted mean flow velocity index. This score is the least susceptible to artifacts and demonstrates the highest correlation with blood volume flowing through a vessel (Duschek & Schandry, 2003). Flow velocities were integrated over each cardiac cycle and averaged, time locked to the cuing tone. The mean flow velocity during the 10 seconds prior to the cue served as a baseline (FV_{bas}). Relative (percent) changes in flow velocity during task execution (dFV) were calculated for the left and right MCA using the formula $dFV=[FV(t)-FV_{bas}]X100/FV_{bas}$, where FV(t) represents the flow velocity over time. Following this, the data were resampled at 5 Hz. Trials involving erroneous responses of a participant were excluded from the analysis.

Visual inspection of the data revealed two clear-cut flow velocity modulation components during the task in both MCA (see Figures 2a and 2b): the first component was associated with response preparation and arose during the interval between the cuing tone and the appearance of the word; the second component was related to the participants´ response and occurred after word presentation. The amplitudes of the two components were defined as dependent variables. They were expressed by the individual maximum of dFV within the interval between the cuing tone and appearance of the word (preparation component), and as the maximum during the 10 s period after word presentation (response component) (see Montoro et al., 2015).

Procedure

Assignment of subjects to the two study groups was carried out on the basis of blood pressure readings that were taken in a screening session conducted at least 1 week prior to the main experiment, and again at the beginning of the experimental session. For this purpose, after a rest period of 10 min, three sphygmomanometric blood pressure measurements were taken in a sitting position using an automatically inflating blood pressure monitor (Omron M400; Omron Healthcare, Lake Forest, IL). Blood pressure readings were separated by 5-min rest intervals. The mean value of the three measurements was used for group assignment. Females with a mean systolic blood pressure of less than 100 mmHg, and males with a mean value below 110 mmHg, were assigned to the hypotensive group. Subjects with systolic blood pressure between 115 and 140 mmHg were included in the control group. The criteria had to be fulfilled at both the screening and experimental sessions. In total 329 potential participants were screened during sample acquisition (234 for the hypotensive group, 95 for the control group).

Data were acquired in a silent, dimly-lit room. The subject was placed at a distance of approximately 60 cm in front of the computer screen. Participants were requested not to drink alcohol or beverages containing caffeine for 3 hours prior to the screening and experimental sessions. They received a financial remuneration of 30 EUR. The study was approved by the Board for Ethical Questions in Science of the University of Innsbruck, Austria, and all participants provided written informed consent.

Statistical analysis

Statistical analysis of cerebral blood flow data was based on ANOVA models with the two within-subjects factors of condition (congruent vs. incongruent trials) and hemisphere (left vs. right MCA), and the between-subjects factor of group (hypotension vs. control group). Separate models were computed for the amplitudes of the two blood flow components (preparation and response). For response time, an ANOVA with the within-subjects factor of condition (congruent vs. incongruent trials) and the between-subjects factor of group was computed.

Relationships between physiological and performance parameters were quantified in the entire sample using Pearson correlations. Systolic and diastolic blood pressure, amplitudes of the first blood flow component (preparation), response times for congruent and incongruent trials and the interference score were included in this analysis. High correlations were seen between the amplitudes of the preparation component in the left and right MCA ($r=.95$ for congruent trials, $r=.89$ for incongruent trials); therefore, amplitudes aggregated across both hemispheres were used in this analysis. Alpha was set at .05 in all analyses.

Results

Figure 1 depicts the response times of the two study groups for congruent and incongruent trials of the Stroop task. The hypotensive group exhibited longer response times than the control group under both conditions. Moreover, in both groups, response times were longer under the incongruent than the congruent condition; the size of the difference between the conditions was similar in both groups. The ANOVA revealed significant group and condition effects (group: F[1,78]=5.20, p=.025, η_p^2=.063; condition: F[1,78]=77.18, p<.001, η_p^2=.50). The group by condition interaction was not significant (F[1,78]=0.005, p=.95, η_p^2<.001).

Figure 1

The time courses of the relative blood flow velocity changes in the left and right MCA during execution of congruent and incongruent trails of the Stroop task are presented in the Figures 2a and 2b (grand averages). In both hemispheres, and under both task conditions, blood flow increases were overall smaller in the hypotensive group than in the control group. While the amplitude of the first blood flow component (preparation component) was markedly lower in hypotensive participants than controls, only a minor difference arose for the second component (response component). The group difference in the preparation component was somewhat greater for incongruent than congruent trials. Hemispherical differences were rather small under both task conditions. The ANOVA showed a group effect for the preparation component (F[1,78]=8.05, p=.006, η_p^2=.094) but not the response component (F[1,78]=0.71, p=.40, η_p^2=.009). Neither the condition factor (preparation component: F[1,78]=0.13, p=.72, η_p^2=.002; response component: F[1,78]=0.61, p=.44, η_p^2=.008) nor the hemisphere factor (preparation component: F[1,78]=1.34, p=.25, η_p^2=.017; response component: F[1,78]=0.045, p=.83, η_p^2=.001) showed significant effects. The same was true for all interaction effects (all p≥.43 in both models).

Figure 2a

Figure 2b

Correlation analysis showed inverse associations between blood pressure and response times (systolic blood pressure: congruent trials, r=-.24, p=.016, incongruent trials, r=-.23, p=.020; diastolic blood pressure: congruent trials, r=-.20, p=.038, incongruent trials, r=-.23, p=.018). The amplitude of the first (preparation) blood flow component (aggregated across both MCA) correlated negatively with response time during incongruent (r=-.23, p=.018) but not congruent trials (r=-.14, p=.11). No significant associations between physiological parameters and the interference score reached significance (all p>.20).

Discussion

This study aimed to investigate cerebral blood flow modulations during proactive control in chronic hypotension based on a precued Stroop task. Individuals with hypotension exhibited smaller blood flow increases in the MCA of both hemispheres during anticipation of congruent and incongruent trials of the task than those with blood pressure in the normotensive range. Response times were longer in hypotensive than in normotensive participants in both types of trials; however, contrary to our hypothesis, the magnitude of color word interference, indexed by the difference in response time between congruent and incongruent trails, did not differ between groups. Over the total sample, the flow velocity increase during the anticipatory interval correlated negatively with response time in the incongruent condition.

Our fTCD recordings suggest reduction of cerebral blood flow adjustment in chronic hypotension during basic and more complex conditions of proactive control. This replicates the previous observation of a diminished bilateral MCA blood flow response during a phasic alertness task (Duschek & Schandry, 2004). However, as a novel aspect, results from the precued Stroop task indicates that this deficit is not confined to basic attentional function, but also emerges during more sophisticated preparatory processes such as interference anticipation, response selection and proactive inhibition.

Peculiarities in cerebral hemodynamics in hypotension may be discussed in the context of flow metabolism coupling and cerebral autoregulation (Duschek & Schandry, 2004; Sarlo et al., 2013). Neurovascular coupling is a regulatory mechanism that enables adjustment of local cerebral blood flow to neural activity through vasomotor changes in cerebral arterioles and capillaries (Guerra et al., 2018; Iadecola, 2004, 2017). It ensures sufficient supply with oxygen and nutrients to the increased demands of neural activity. Neurovascular coupling involves the interplay between neurons, astrocytes, endothelial cells and smooth muscle cells, which altogether are referred to as the neurovascular unit (Iadecola, 2017). Some neurotransmitters (e.g., acetylcholine, catecholamines or neuropeptides) exhibit vasoactive properties, their release causing dilation of cerebral microvessels (Iadecola, 2004). Moreover, astrocytes, which are functionally linked to neurons, produce powerful vasodilators including CO, K+ and adenosine (Harder et al., 2002). Agonists from neurons and astrocytes may also activate vasoactive agents like NO and CO in the endothelium (Golding et al., 2002). The chemical signals originating from neurons, astrocytes and endothelial cells exert their influence on the smooth muscle cells through altering intracellular Ca^{++} concentration in and phosphorylation state of light chain myosin (Iadecola, 2004). Based on the assumption that vasodilation during neural activity occurs to the same degree in both a hypotensive and normotensive context, it may be argued that, in hypotension, blood pressure is insufficient to enable adequate blood flow adjustment during neural activity (Duschek & Schandry, 2004).

Cerebral autoregulation refers to physiological mechanisms that keep brain perfusion constant by buffering systemic blood pressure oscillations (Folino, 2007). In order to stabilize blood flow, cerebral resistance vessels constrict during increases, and dilate during reductions, in blood pressure (Paulson, 2002). Multiple physiological mediators are also involved in this regulatory system (Yang & Liu, 2017): a myogenic mechanism is assumed, where changes in transmural pressure are directly responded by compensatory adjustment of vascular tone. Moreover, similar as in neurovascular coupling, vasoactive agents derived from all components of the neurovascular unit trigger changes in the vasculature during fluctuations in perfusion pressure. Finally, vascular tone is highly sensitive to changes in CO_2 partial pressure during increases and decreases in cerebral perfusion (Iadecola, 2004; Yang & Liu, 2017). Autoregulation is supposed to ensure virtual independence of cerebral blood flow from systemic blood pressure in a large blood pressure range, i.e. mean arterial pressures between 50 and 160 mmHg (Paulson, 2002). However, this doctrine has been challenged, for example by findings of reduced MCA flow velocities at rest in chronic hypotension (Duschek & Schandry, 2004), in addition to increased dependence of blood flow modulations on changes in systemic blood pressure in this group (Duschek & Schandry, 2006; Sarlo et al., 2013). This is in line with the present finding confirming the notion of deficient cerebral blood flow regulation as a relevant characteristic of chronic hypotension.

On a behavioral level, the reduction in cerebral blood flow modulation in hypotension was accompanied by slower task execution. However, the correlation between the magnitude of the preparatory blood flow increase and response time only reached significance in incongruent trials, which may possibly be ascribed to the lower difficulty of the congruent condition resulting in smaller response time variance. The finding replicates associations between task-induced MCA blood flow responses and performance on cued reaction time and arithmetic tasks in previous hypotension studies (Duschek & Schandry, 2004, 2006). As stated above, flow modulations during mental activity reflect a perpetual adjustment to the changing metabolic demands of neural processing. In particular, the high rate of aerobic metabolism in the neural tissue requires a constant and sufficient supply of oxygen and glucose (Iadecola, 2004). It therefore has been argued that diminished blood flow responses result in suboptimal functional conditions impeding cognitive performance (Duschek & Schandry, 2004; Duschek et al., 2010; Sarlo et al., 2013). By definition, this causal interpretation cannot be made unambiguously. In terms of an alternative explanation, one could attribute the association between blood flow modulation and performance to different magnitudes of neural activation. From this perspective, lower performance in the case of smaller blood flow increase would only constitute an epiphenomenon of lower nerve-cell activity. This view is challenged by the results of experimental manipulation of brain perfusion in hypotension (Duschek et al., 2007). Blood flow increase due to pharmacological blood pressure elevation led to enhanced attentional performance, where the magnitude of the blood flow increase correlated positively with cognitive facilitation. The hypothesis of cognitive impairment due to reduced brain perfusion can therefore be retained.

In addition to the initial blood flow increase, fTCD revealed a second bilateral peak during the response interval after presentation of the color word. The first peak may relate to adjustment of attentional tone (i.e., phasic alertness) and, in the case of incongruent trials, more complex proactive control processes. Proactive control mainly is commonly associated with anticipatory activity of the dorsolateral prefrontal and inferior parietal cortex (Aron, 2011; Braver, 2012). Moreover, event-related fMRI studies investigating proactive inhibition based on precued antisaccade tasks suggested the involvement of a larger network, including the frontal eye fields and anterior cingulate, in addition to dorsolateral prefrontal and parietal regions (Connolly et al., 2002; DeSouza et al., 2003; Ford et al., 2005). Regarding the control of attentional tone, a neural network has been identified, which arises in the reticular formation and projects to the lateral prefrontal cortex and, thereafter, to further cortical areas, in particular the inferior parietal lobe (Pardo et al. 1991; Paus et al., 1997; Posner & Peterson, 1990). Except for the reticular formation and anterior cingulate, all of the mentioned structures form part of the perfusion territory of the MCA (Haines, 2007); as such, the first blood flow component may be ascribed to their activity. The second flow increase may reflect behaviors including processing of the colour words, interference resolution, decision-making and inhibition of the inappropriate response of word reading. Neuroimaging studies have demonstrated activity in a network of frontoparietal structures during the classical Stroop task, which may underlie this component (Manard et al., 2017; Matsumoto & Tanaka, 2004). Regarding response inhibition, a key role of the dorsolateral prefrontal cortex has been suggested by studies using fMRT, rTMS and intracranial EEG, as well as lesion studies (Aron et al., 2003; Chambers et al., 2006, 2009; Chikazoe et al 2009; Swann et al., 2009). It is important to note that difference between hypotensive and normotensive participants was restricted to the first blood flow component.

This accords with a previous finding (Duschek & Schandry, 2004), and underlines the relevance of proactive control in task performance and hypotension-related impairment.

Our hypothesis pertaining to increased MCA blood flow response during preparation of incongruent as opposed to congruent trials in the entire sample was not confirmed. Though in terms of behavior the higher cognitive load due to color word interference was expressed by a longer response time during the incongruent condition, this effect was not reflected in cerebral blood flow. This is in contrast to a recent fTCD study investigating complex preparatory processes in healthy individuals using a precued antisaccade task (Duschek et al., 2017c). That study revealed stronger MCA blood flow increase during preparation of antisaccadic than prosaccadic eye movements. This was ascribed to higher mental load during proactive control of antisaccades, particularly proactive inhibition of automatized saccadic responses (Ballanger, 2009). It may be hypothesized that the cortical resources required therein exceed those of proactive interference control in a Stroop task.

Another unexpected result pertains to the lack of lateralization of the blood flow responses. The application of precued tasks in previous fTCD research revealed stronger flow increases in the right MCA (Duschek et al., 2007, 2008b, 2010), which were ascribed to the dominance of the right hemisphere in arousal regulation (Posner & Peterson, 1990). The divergence of the present finding may at least partly be explained by cerebral activity related to motor processing. While in the aforementioned studies motor responses were carried out half-and-half with both hands, 76 of the 80 participants in the present study used the right hand for the entire task. Anticipation of the movement of the right hand may have boosted left hemispheric blood flow increase.

In contrast to our á priori hypothesis, the difference in the preparatory blood flow response and response time between congruent and incongruent Stroop task trials was not larger in hypotensive than normotensive participants, which suggests a similar magnitude of color word interference in both groups. This may be relevant to the characterization of the cognitive impairment related to chronic hypotension. Performance on the classical Stroop task reflects the executive function of inhibition, which refers to the ability to deliberately override dominant or automatic behaviors (Miyake et al., 2000). Regarding this function, a distinction between the three interrelated processes of inhibiting a prepotent response, stopping an ongoing response and interference control has been drawn (Barkley, 1997; van Mourik et al., 2005). In overcoming the prepotent response of word reading and resolving color word interference, the Stroop task is most closely related to inhibition of a prepotent response and interference control. During quantification of these domains, congruent trials with reduced executive function load serve as a control condition (MacLeod, 1991). Considering this, the lack of a difference between hypotensive and normotensive individuals in color word interference contradicts the assumption of impaired inhibition in chronic hypotension. Instead, the prolonged response times under both task conditions, and the linear association between blood pressure and task speed, reflect globally slowed information processing and thus more basic attentional impairment in the context of low blood pressure.

The assumption of cognitive slowing in chronic hypotension accords with a number of previous observations, including prolonged cued and non-cued reaction times (Duschek et al., 2005, 2006; Duschek & Schandry, 2004), longer response times in tasks measuring selective, divided and sustained attention (Duschek et al., 2005), as well as poorer performance on attention tasks placing a high load on processing speed, like the Number Connection Test (Oswald & Roth, 1987), Test d2 (Attentional Performance Test; Brickenkamp, 1994) and the Course of Concentration Test (Abels, 1954) (Costa et al., 1998; Richter-Heinrich et al., 1971). In our Stroop task, the reduction in mental speed in hypotension occurred independently of task difficulty and seemed to affect both basic and more complex processes. While mental slowness may also impede performance on tasks involving higher cognitive functions, the available evidence of a particular executive function deficit in hypotension is not strong. While two studies revealed higher error rates in n-back tasks measuring working memory updating (Duschek et al., 2005, 2017b), no such deficit arose in another study (Sarlo et al., 2013). Controversial results have also been reported for tests addressing the executive function of mental set shifting (Duschek et al., 2017b; Weisz et al., 2002); and serial subtraction tasks quantifying arithmetic abilities did not reveal differences between individuals with low and normal blood pressure (Duschek & Schandry, 2006; Covassin et al., 2013).

In conclusion, this study revealed evidence of deficient cerebral blood flow regulation during basic and complex conditions of proactive control in chronic hypotension. The reduction of blood flow adjustment during response preparation was accompanied by lower processing speed, which arose during both task conditions (and thus irrespective of executive function load). The lack of an effect of blood pressure on colour word interference contradicts the notion of specific impairments in the executive functions of inhibition and interference control. Instead, low blood pressure and cerebral hemodynamic dysregulations may predominantly affect cognitive performance via a more general deficit in basic attentional function and diminished processing speed.

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Table 1. Sample characteristics

	Hypotension		Control group	
	M	*SD*	*M*	*SD*
Systolic blood pressure (mmHg)	93.68	5.21	120.05	5.43
Diastolic blood pressure (mmHg)	61.82	4.08	77.57	6.26
Heart rate (beats/min)	71.54	10.97	86.46	12.02
Age (years)	22.95	3.07	23.10	4.04
Body mass index (kg/m^2)	20.52	2.14	21.93	2.48
Length of education (years)	15.73	2.74	15.98	9.49
Physical activity (hours/week)	5.61	3.56	3.89	2.76

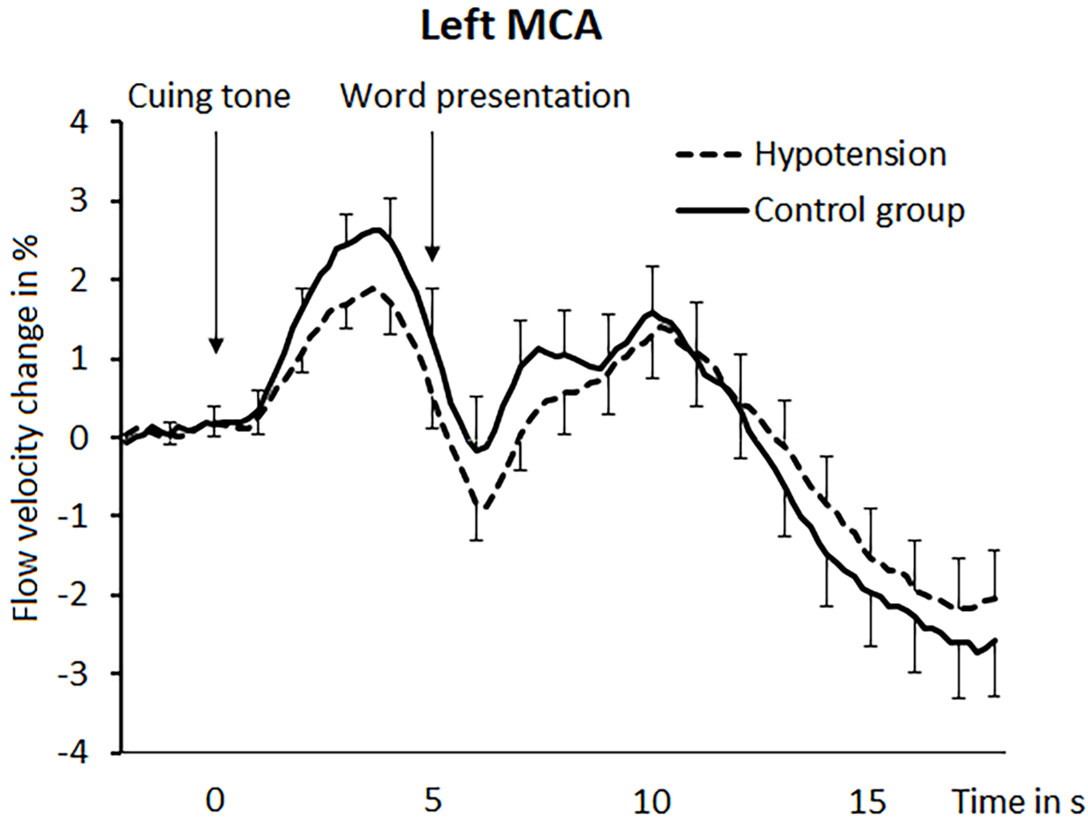
Figure captions

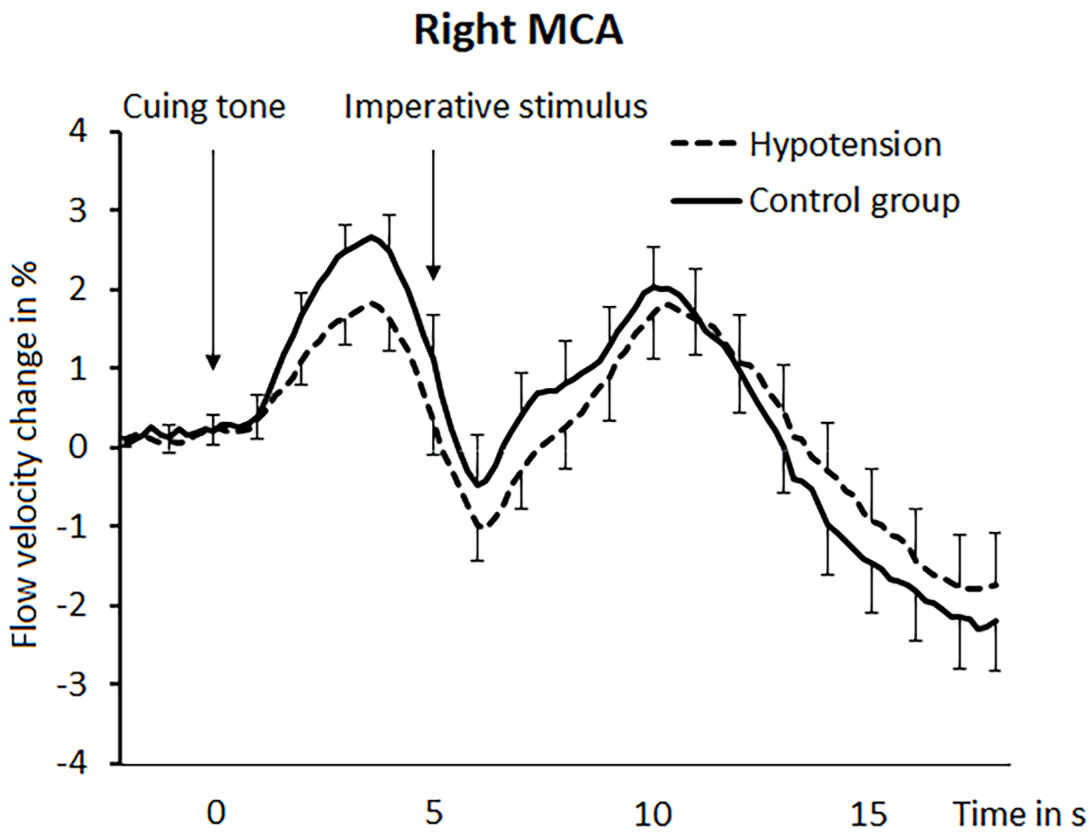
Figure 1. Response times for congruent and incongruent trials (bars denote standard errors of the mean)

Figure 2a. MCA blood flow modulations during execution of congruent trials of the Stroop task (grand average, bars denote standard errors of the mean)

Figure 2b. MCA blood flow modulations during execution of incongruent trials of the Stroop task (grand average, bars denote standard errors of the mean)

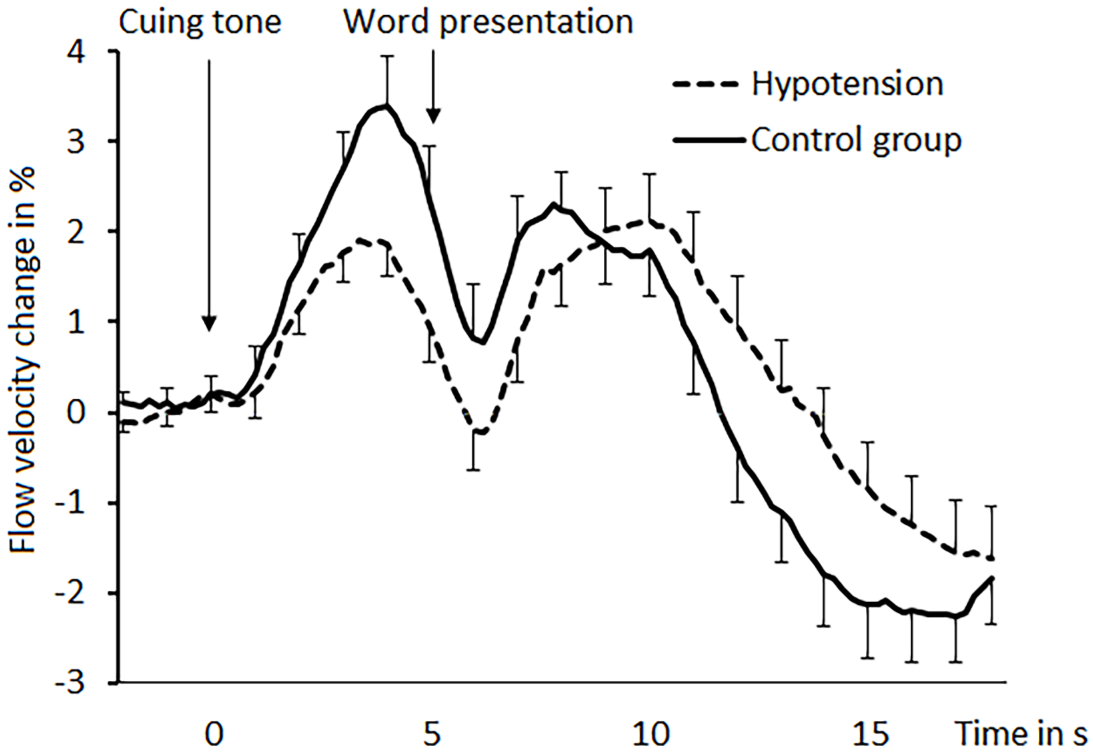
Stroop task: Congruent trials





Stroop task: Incongruent trials

Left MCA



Right MCA