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REVIEW ARTICLE

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Reduced brain perfusion and cognitive performance due to constitutional hypotension

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Abstract This review article includes a systematic evaluation of the empirical data concerning deficits in mental ability, brain perfusion, and cerebral functioning due to chronically low blood pressure. A number of studies have provided strong evidence for reduced cognitive performance in hypotension, particularly in the domains of attention and memory. EEG studies have demonstrated that the hypotension-related poorer mental ability is also reflected in diminished cortical activity. Contrary to convention, more recent research has suggested a deficient regulation of cerebral blood flow in persons with low blood pressure. In addition to reduced tonic brain perfusion, studies demonstrated insufficient adjustment of blood flow to cognitive requirements. Altogether, these findings suggest that more attention should be allocated to chronic hypotension in both research and clinical practice.

Key words blood pressure · hypotension · cerebral blood flow · cognitive · autonomic nervous system

Introduction

Chronically low blood pressure is accompanied by a variety of complaints including fatigue, reduced drive, faintness, dizziness, headaches, palpitations, and increased pain sensitivity [1–4]. In addition, hypotensive individuals report cognitive impairment, above all deficits in attention and memory. Nevertheless, it is generally the case that in research, as well as in clinical practice, relatively little importance is ascribed to hypotension. One reason for this is that, despite mental symptoms, cerebral dysfunction generally is not taken into account [1]. This is a consequence of the current doctrine that low systemic blood pressure is compensated by autoregulatory processes which prevent reduced blood perfusion of the brain [5, 6].

Some recent findings challenge this doctrine: reduced cognitive performance in hypotension has been demonstrated by neuropsychological testing, and EEG studies have revealed diminished cortical activity. Moreover, the assumption of unimpaired brain perfusion in hypotension no longer holds. In the present review the necessity of a reappraisal concerning hypotension is discussed in light of the relationship between blood pressure and cerebral functioning.

Constitutional hypotension

Hypotension has been defined by the World Health Organization (WHO) [4] as a low blood pressure with a systolic reading below 110 mmHg in males and below 100 mmHg in females, regardless of diastolic

blood pressure. The concept of constitutional hypotension refers to a chronic condition of inappropriately reduced blood pressure independent of the presence of further pathological factors. Both secondary hypotension (e.g. due to blood loss or medication) and orthostatic hypotension (caused by circulatory problems when assuming an upright position) are distinguished from the constitutional form [1, 6].

Constitutional hypotension is relatively widespread in the general population. In a representative German sample of more than 7,000 subjects approximately 3% fulfilled the criteria of the WHO [c.f. 1]. In contrast to elevated blood pressure, which constitutes a significant risk factor for cardiovascular disease, hypotension is commonly not regarded as a severe condition. Nevertheless, its impact on personal well-being and quality of life has been shown in several epidemiological studies. For instance, Wessely et al. [7], as well as Pilgrim et al. [3] demonstrated impaired physical and mental health in the case of low blood pressure. Reduced health-related quality of life [8] and a heightened degree of depressiveness [9] were also reported by hypotensive individuals.

Chronic hypotension has been identified as a major risk factor in pregnancy [10]. Moreover, several studies focusing on the elderly population have reported associations between low blood pressure and the prevalence and incidence of Alzheimer's and vascular dementia [c.f. 11–14]. Whilst a few longitudinal studies examining this relationship have been published [15, 16], the causal role of low blood pressure in degenerative brain disorders has thus far not been proven [e.g. 13].[1]

Concerning the etiology of hypotension, reduced liquid intake and low body weight may be considered [c.f. 1, 17]. A dysregulation of the autonomous nervous system may additionally be of significance. Various findings on reduced electrodermal activity [18] and increased heart rate variability [19] reflect diminished sympathetic tone and habitually heightened parasympathetic activity in persons with low blood pressure values. This is corroborated by findings on the effects of sympathomimetic drugs [20, 21]. In mixed samples of persons with constitutional and orthostatic hypotension, α and β adrenergic substances were shown to lead to blood pressure elevation accompanied by a reduction of subjective symptoms. A malfunction of the arterial baroreceptor system was postulated as a further etiological factor [22]. Responding to mechanical stretch of the vessel walls, the baroreceptors form part of a negative feedback loop ("baroreflex") compensating phasic blood pressure fluctuations [23]. Increased sensitivity of the baroreceptor system may result in stabilizing blood pressure at a lower level. In addition to findings in animals [24], this hypothesis is supported by a still unpublished study of our own group which yielded increased baroreflex sensitivity in the case of low blood pressure.

[1]The cited findings [3, 7–9, 11–16] were revealed in large epidemiological studies. All included samples across the total blood pressure spectra and did not explicitly define hypotension according to the WHO criteria [4].

Cognitive deficits in constitutional hypotension

Table 1 presents the most relevant studies devoted to cognitive functioning in hypotension. In addition to the main results, the table includes information concerning the respective samples and assessment instruments.

A pioneering study investigating the relationship between blood pressure and cognitive abilities was conducted by Richter-Heinrich et al. [18]. They showed reduced performance of individuals with both lowered and elevated blood pressure on a test of concentration. A more comprehensive assessment was carried out by Stegagno et al. [26], in which poorer performances of hypotensive subjects on a verbal memory test and on an arithmetic task, as well as prolonged reaction times to acoustic stimuli were observed. Costa et al. [29] found reduced scores on two standard German paper–pencil tests assessing selective attention and cognitive speed. Moreover, as in the Stegagno et al. [26] study, impaired verbal memory performance was documented.

Weisz et al. [22] reported that female hypotensive subjects performed significantly worse than controls on a computer-based test measuring attentional flexibility [36]. Subjects with only a moderately decreased blood pressure were assessed by Duschek et al. [37]. In this sample, reduced attentional performance and prolonged reaction times were again found as compared to normotensive controls.

Duschek et al. [38] investigated the relationship between low blood pressure and attentional abilities through the application of a multidimensional diagnostic approach. They presented their subjects with a battery of six computer-based tasks [39] focusing on tonic and phasic alertness, selective, divided and sustained attention, as well as working memory. Additionally, in order to control for possible confounders, a test battery examining fine motor abilities [40] and a mood questionnaire [41] were presented. Reduced performance of hypotensives was evident in each of the six cognitive tests. The significant differences between hypotensive and control subjects persisted even when the effects of motor performance and mood were controlled.

Table 1 Studies on cognitive performance in hypotension (SBP, systolic blood pressure; DBP, diastolic blood pressure)

Authors	Main focus	Samples	Assessment instruments	Main results
Richter-Heinrich et al. [18]	Attentional performance in hypotension and hypertension	30 hypotensives (SBP < 106 mmHg); 40 hypertensives (SBP > 140 mmHg); 31 normotensive controls; age 16–40 years	Konzentrations-Verlaufs-Test (course of concentration test) [25]	Reduced attentional performance in the case of both lowered and elevated blood pressure
Stegagno et al. [26]	Attentional, memory and arithmetic performance in hypotension	17 female hypotensives (SBP < 100 mmHg); 19 normotensive controls; mean age 23 years	Reaction times to acoustic stimuli; digit span [27]; recall of word lists [28]; serial subtractions	Prolonged reaction times, poorer performance on the verbal memory and arithmetic tasks in hypotension, no effect for digit span
Costa et al. [29]	Attentional and memory performance in hypotension	26 female hypotensives (SBP < 105, DBP < 65 mmHg), 22 normotensive controls; mean age 29 years	Aufmerksamkeits-Belastungs-Test (attentional strain test) [30]; Zahlen-Verbindungs-Test (trail making test) [31]; recall of word lists [28]	Poorer attentional and memory performance on each of the three tests in hypotension
Morris et al. [32]	Relationship between blood pressure and cognitive performance in elderly persons	Representative population sample covering the total spectrum of blood pressure (n = 5,816; age over 64 years)	East Boston Memory Test [33]; Symbol Digit Modalities Test [34]; Mini-Mental State Examination [35]	Weak U-shaped relationship between blood pressure and cognitive performance
Weisz et al. [22]	Attentional performance in hypotension	25 female hypotensives (mean SBP = 102 mmHg); 25 normotensive controls; age 19–44 years	Attentional and Cognitive Efficiency Battery [36]	Reduced performance on a subtest assessing cognitive flexibility in hypotension
Duschek et al. [37]	Attentional performance in moderate hypotension	26 borderline hypotensives (mean SBP = 112 mmHg); 29 normotensive controls; mean age 26 years	Reaction times to acoustic stimuli; Aufmerksamkeits-Belastungs-Test (attentional strain test) [30]; Zahlen-Verbindungs-Test (trail making test) [31]	Prolonged reaction times and poorer performance on the "Aufmerksamkeits-Belastungs-Test" in moderate hypotension, no effects for the "Zahlen-Verbindungs-Test"
Duschek et al. [38]	Attentional and working memory performance in hypotension with motor performance and mood controlled	40 hypotensives (SBP < 105 mmHg in women, SBP < 110 mmHg in men); 40 normotensive controls; age 19–45 years	Testbatterie zur Aufmerksamkeitsprüfung (battery for the assessment of attention) [39]; Motorische Leistungsserie (motor performance series) [40]; Befindlichkeitsskala (mood scale) [41]	Poorer performance on six tests assessing tonic and phasic alertness, selective, divided and sustained attention as well as working memory in hypotensives with fine motor performance and mood controlled

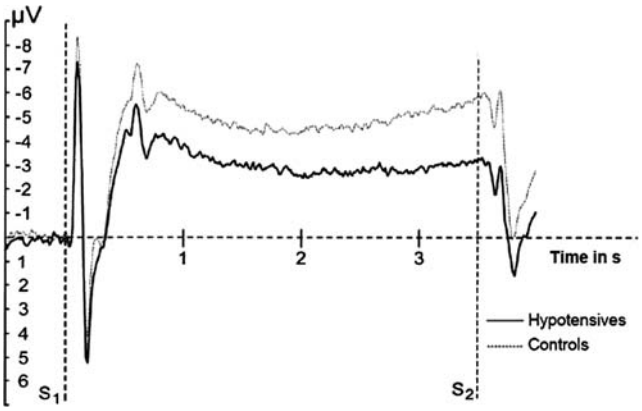

Fig. 1 The CNV occurs during the period between a warning signal (S1) and a second stimulus (S2) demanding a motor, verbal or cognitive response. As can be seen in the figure, its amplitude was found to be reduced in hypotensive subjects ($N = 40$) as compared to normotensive controls ($N = 40$); modified from [47]

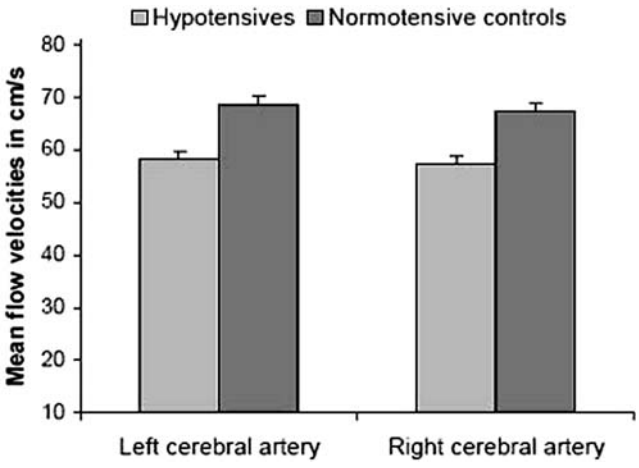

Fig. 2 Mean flow velocities in the left and right middle cerebral arteries under resting conditions in hypotensive ($N = 40$) and control subjects ($N = 40$); bars represent standard errors [65]

Altogether, the existing data provide strong evidence for cognitive deficits related to constitutional hypotension, especially in the domains of attention and memory. The reduced performance seems to be a direct consequence of low blood pressure rather than an effect of impaired well-being related to this state. Up to now there have been no empirical data concerning specific effects of hypotension-related deficits on everyday life. Nonetheless, these findings raise concern regarding the impact of the deficits on attention-demanding activities (e.g. professional or academic), including public health-related functions (e.g. traffic safety) [42].

It would appear that both extremes of the blood pressure spectrum are accompanied by a decrease in cognitive ability. A number of studies concerned with elevated blood pressure showed reduced performance on various cognitive tests [43, 44]. This is in line with epidemiological studies reporting an inverted U-shaped relationship between blood pressure and cognitive performance in elderly persons [c.f. 11, 13, 32, 45, 46]. Therefore, it may further be hypothesized that there is a relatively small range of normal blood pressure in which the brain exerts its optimal function.

Neuroelectrophysiological correlates of hypotension-related cognitive deficits

Cognitive deficits in low blood pressure states are also reflected in decreased cortical activity. In accordance with earlier results [22, 29], Duschek et al. [47] found the amplitude of the contingent negative variation (CNV) to be reduced in a hypotensive sample defined according to the WHO criteria [4] (c.f. Fig. 1).

The CNV is an evoked potential which is generally viewed as a neuroelectrophysiological correlative of attentional processing [48]. This is supported by pharmacological studies showing that the effects of various stimulant and sedative drugs on attention involve an increase or decrease, respectively, of the CNV amplitude [49, 50]. Moreover, attentional deficits due to brain lesions and psychiatric diseases are associated with a reduced CNV [51, 52]. In the Duschek et al. [47] study, the amplitude of the CNV proved to be negatively correlated with reaction time, which in turn was prolonged in the hypotensive group. This highlights that the CNV constitutes a brain electrical correlate of an aspect of cognitive functioning which is affected in hypotension.

The relationship between blood pressure and cortical activity is also reflected in a negative correlation between blood pressure and α wave activity in the spontaneous EEG [47]. This suggests that low blood pressure is associated with a reduced tonic cortical arousal [53]. On the behavioral level, higher degrees of α activity are known to be associated with generally diminished vigilance and preparedness to react [54].

Considering the physiological processes mediating the relationship between blood pressure and brain function, it must be taken into account that blood pressure can influence cortical activation processes via afferent projections [47, 55–57]. The brain continuously receives information about the state of the cardiovascular system by means of viscero-afferent fibers [23]. These afferent signals enter the brain via brainstem nuclei. From there, ascending pathways continue via hypothalamic and thalamic regions to cortical areas such as the anterior cingulate, the insula and the prefrontal lobe [58]. The latter areas, in particular the prefrontal cortex and the anterior cingulate

are of crucial importance in the regulation of cortical arousal, as well as for attentional processes [59, 60]. Thus, these brain structures may represent functional interfaces between cardiovascular activity and attention [42].

Also neurochemical mediators should be regarded in the relationship between blood pressure and cortical activity. Noradrenaline is involved in the control of cortical arousal and attentional processes, as well as in the genesis of the CNV [59, 61]. Catecholamines are also of great influence in the regulation of blood pressure [62]. Bearing this in mind, one could speculate on the neurochemical level about a specific role of noradrenaline linking cardiovascular and cortical activation.

Cerebral blood perfusion in constitutional hypotension

It is generally assumed that in healthy individuals processes of autoregulation keep the cerebral blood flow constant within a wide range of arterial pressure. In order to ensure stable perfusion, cerebral resistance vessels constrict during increases and dilate during reductions in systemic blood pressure [5]. Autoregulation is considered to be a protective mechanism which prevents brain ischemia during blood pressure decrease, and guards against capillary damage and edema formation during periods of elevated blood pressure.

Under normal conditions the limits within which cerebral blood flow is assumed to be constant are approximately between a mean arterial pressure (MAP) of 60 and 150 mmHg [5, 63, 64]. If blood pressure is outside of this range, cerebral blood flow rises or falls with respective increases or decreases in blood pressure. Slight reductions of blood pressure below the lower limit of autoregulation can be compensated by an increase of the extraction coefficient of oxygen from the blood. Further reductions are accompanied by symptoms such as pallor and dizziness and ultimately lead to irreversible brain damage [5].

MAP in individuals with constitutional hypotension usually does not decrease beyond the assumed lower MAP limit of autoregulation (60 mmHg). In light of this, low blood pressure in these subjects should be compensated, and cerebral blood flow should not be affected. This assumption was challenged by Duschek and Schandry [65]. They recorded blood flow velocities by means of transcranial Doppler sonography in both middle cerebral arteries (MCA) in hypotensive individuals, defined according to the WHO [4], and in normotensive control subjects. Contrary to the current doctrine, MCA blood flow at rest was found to be substantially bilaterally reduced in hypotensives (c.f. Fig. 2).

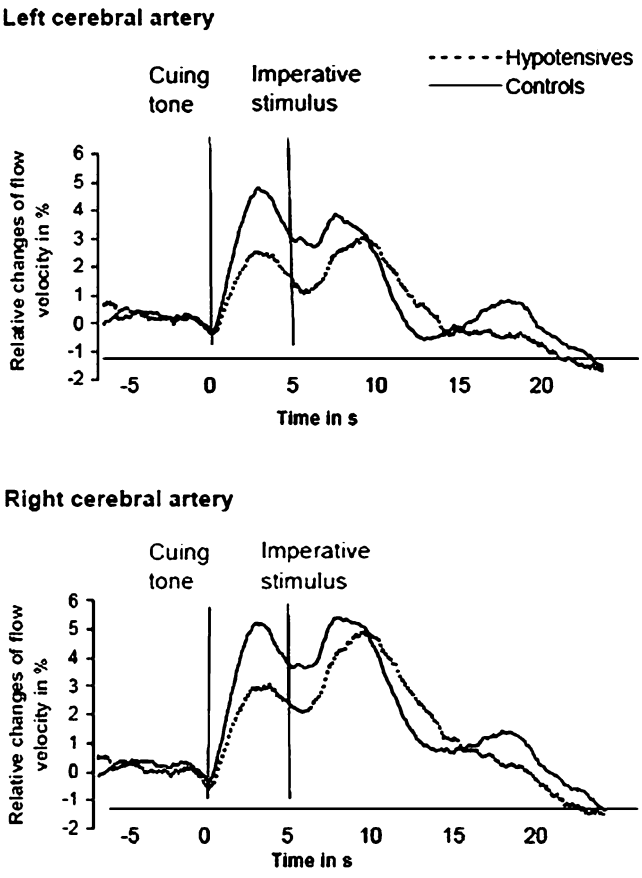

Fig. 3 Changes of blood flow velocities in the left and right MCA during the execution of an attentional task in hypotensives ($N = 40$) and controls ($N = 40$). The subjects had to press a key in response to a visual imperative stimulus which was announced by a cuing tone. In both MCA the rise in flow velocity which occurred during the anticipation of the imperative stimulus was substantially less pronounced in hypotensives. A second flow velocity maximum visible after the motor reaction was also slightly reduced in hypotensives [65]

The perfusion territory of the MCA includes subcortical areas, large fractions of the frontal and parietal lobes, as well as the temporal lobes [66]. Thus, the latter finding demonstrated that, despite autoregulation, blood pressure in subjects with constitutional hypotension is not sufficient in maintaining the perfusion of a large part of the brain at the level of normotensive individuals [see also 67].

In explaining this unexpected result, it must be noted that the determination of the lower limit of autoregulation was exclusively based on the experimental manipulation of blood pressure employing pharmacological methods, as well as head up-tilt [68–71]. However, such a transient reduction of blood pressure is most certainly not comparable to conditions of chronic hypotension. Additionally, in all of these studies global cerebral blood flow was assessed by means of the oxygen difference method according to Lennox and Gibbs [72], which may be less sensitive to perfusion changes than Doppler sonography.

Nevertheless, more recent findings suggest values for the lower MAP limit of autoregulation to be considerably higher than 60 mmHg [73–75]. In a critical review of the literature, Drummond [76] postulated an average lower limit of no less than 70 mmHg. Moreover, the limit seems to vary strongly across individuals. Waldemar et al. [77], for instance, reported an inter-individual range between 53 and 103 mmHg. In accordance with Duschek and Schandry's [65] data, the doctrine of stable cerebral perfusion down to the limit of a MAP of 60 mmHg can no longer be supported by the current state of research.

A further important aspect of cerebral hemodynamics concerns the continuous adjustment of brain perfusion to current requirements. Due to the close coupling of neural activity and brain metabolism, cerebral activation processes are accompanied by changes in cerebral blood flow [78]. Neurovascular coupling is based on the contraction and dilation of small resistance vessels, resulting from the changing metabolic demands of neuron populations in the vicinity [64].

With regards to hypotension-related cognitive deficits, the extent of blood flow adjustment to mental activity was also tested in the Duschek and Schandry [65] study. Subjects were presented with a simple attentional task (motor reactions to visual stimuli cued by acoustic signals). During task execution blood flow velocities in the MCA of both hemispheres were recorded by means of functional transcranial Doppler sonography (for technical details see [66]).

As expected, mental activity was accompanied by a substantial increase of MCA perfusion. In control subjects, however, this increase was approximately 70% stronger than in hypotensives (c.f. Fig. 3). It would seem that blood pressure in the latter group was not sufficient to enable adjustment of brain perfusion to cognitive demands, as seen in normotensives. Moreover, hypotensive participants showed prolonged reaction times, and a positive correlation was found between reaction speed and the extent of blood flow increase. This finding corroborates the significance of hemodynamic adjustment for optimal cognitive functioning.

Final comments

There is strong evidence suggesting that chronically low blood pressure is accompanied by diminished cognitive performance, primarily involving attention and memory [26, 29, 38]. Recent research has provided an insight into the psychophysiological mechanisms of action underlying these deficits: EEG studies have demonstrated that the weaker cognitive performance is associated with reduced cortical activity [22, 29, 47]. Furthermore, deficient regulation of cerebral blood flow must be assumed in hypotension. In addition to diminished tonic brain perfusion, reduced adjustment of brain perfusion to cognitive demands was documented [65]. It stands to reason that, as a consequence of this situation, a diminished metabolic supply of the brain tissue accounts for the cognitive deficits.

The cognitive deficits can widely affect the every day life of hypotensive persons, and more attention should therefore be allocated to this topic within basic and clinical research, as well as in clinical practice [1, 17]. This finally leads to the issue of the treatment of hypotension. Empirical knowledge concerning the effectiveness of antihypotensive therapy continues to be scant. A variety of treatment strategies such as physical training, increase of liquid intake and pharmacological measures have been suggested [1]. In two clinical trials the administration of sympathomimetics was found to result in a reduction of subjective hypotensive symptoms [20, 21]. Recent data of our own group suggest that cognitive performance may also be enhanced by pharmacological blood pressure elevation [79]. Based on a placebo controlled design, the vasopressor agent midodrine was shown to raise cerebral blood perfusion as well as performance on a test assessing selective attention [30] in hypotensive subjects, defined according to the WHO [4]. The results of these pioneering studies are promising. Further research would appear worthwhile and should aim to establish precise guidelines which enable chronic hypotension to be efficiently and effectively dealt with in practice.

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