Clin Auton Res (2012) 22:99–107
DOI 10.1007/s10286-011-0145-3

REVIEW ARTICLE

A review of orthostatic blood pressure regulation and its association with mood and cognition

Lawrence C. Perlmuter · Garima Sarda · Vanessa Casavant · Kimberly O'Hara · Mariah Hindes · Patrick T. Knott · Aron D. Mosnaim

Received: 11 December 2010 / Accepted: 24 August 2011 / Published online: 25 September 2011

Abstract
Aims This paper will review literature that examines the psychological and neuropsychological correlates of orthostatic blood pressure regulation.
Results The pattern of change in systolic blood pressure in response to the shift from supine to upright posture reflects the adequacy of orthostatic regulation. Orthostatic integrity involves the skeletal muscle pump, neurovascular compensation, neurohumoral effects and cerebral flow regulation. Various physiological states and disease conditions may disrupt these mechanisms. Clinical and subclinical orthostatic hypotension has been associated with impaired cognitive function, decreased effort, reduced motivation and increased hopelessness as well as dementia, diabetes mellitus, and Parkinson's disease. Furthermore, inadequate blood pressure regulation in response to orthostasis has been linked to increased depression and anxiety as well as to intergenerational behavioral sequalae.
Conclusions Identifying possible causes and consequences of subclinical and clinical OH are critical in improving quality of life for both children and older adults.

Keywords Orthostasis · Subclinical orthostatic hypotension · Blood pressure regulation · Affective disorders · Cognition

L. C. Perlmuter (✉) · V. Casavant
Department of Psychology, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Rd, North Chicago, IL 60064, USA
e-mail: lawrence.perlmuter@rosalindfranklin.edu

G. Sarda · K. O'Hara · M. Hindes
Chicago Medical School, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Rd, North Chicago, IL 60064, USA

P. T. Knott
Physician Assistant Program, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Rd, North Chicago, IL 60064, USA

A. D. Mosnaim
Department of Cellular and Molecular Pharmacology, Rosalind Franklin University of Medicine and Science, 3333 Green Bay Rd, North Chicago, IL 60064, USA

Introduction

Orthostatic hypotension (OH), broadly defined as a drop in systolic blood pressure (SBP) upon assuming upright posture after being supine, is diagnosed as *clinical* OH when SBP declines at least 20 mmHg within a minute of standing. This change may be accompanied by a decrease in diastolic blood pressure (DBP) of about 10 mmHg [1]. Similar to most pathological processes such as pre-diabetes and glucose intolerance, there are likely to be *subclinical* patterns of OH expression that also can result in measurable sequalae. Response to a subclinical (<20 mmHg change) reduction in SBP may vary from one of little relevance [2] to the onset of symptoms ranging in severity from lightheadedness to confusion, dizziness or even syncope [3, 4]. Subclinical changes in OH may be joined by a variety of behavioral and emotional sequelae that may not be innocuous [5].

OH is an increasingly important topic in the biomedical and psychological fields as a result of an increasing aging population [6] as well as certain medications. Specifically, agents routinely used to control high blood pressure (BP), as well as to treat various common diseases such as pure autonomic failure and diabetes mellitus, increase one's risk

of OH [2, 7]. Furthermore, OH has come to be associated with other frequent medical and behavioral conditions such as depression and anxiety [2]. The successful treatment of patients with OH is a challenge faced by many clinicians due to the variety of underlying causes, symptoms and associated co-morbidities [7].

Of primary interest to our work is whether subsyndromal OH, is associated with the usual cognitive and affective sequalae of clinical OH. Our studies have revealed that a measurable but asymptomatic response to an orthostatic challenge may be associated with a variety of negative psychological and neuropsychological consequences [5, 8–11]. In this paper, we will review the autonomic, neurohumoral, and cardiovascular mechanisms associated with orthostasis and examine the relationships between clinical and subsyndromal OH and cognition and affective disorders. PubMed and Google Scholar were used to locate relevant research; key words included OH, bp, bp regulation, orthostasis, cognition, depression, and anxiety. Articles were selected for inclusion if they were relevant to the comprehensive review of OH and neuropsychological factors.

Causes of orthostatic hypotension

There are a variety of medical conditions, of both neurogenic and non-neurogenic origin, with widely different etiologies as well as associated pathophysiologies that have been shown to increase the risk for both subclinical and clinical OH [12]. Some conditions are typically chronic or irreversible such as cardiac failure, diabetes mellitus, Parkinson's disease (PD), adrenal insufficiency, pure autonomic failure and multiple system atrophy [2], while others are acute or reversible such as dehydration. Risk of OH is also associated with certain medications, particularly agents routinely used to control high bp. Side effects arising from the use of drugs like antidepressants, antipsychotics, beta-blockers, diuretics, sedatives and vasodilators, to name a few, include autonomic dysfunction and can also result in OH [12]. These agents can be classified as secondary neurogenic causes [4] as they may interrupt autonomic function directly (beta-blocking agents) or may produce a neuropathy, resulting in OH.

OH may also result from alterations in venous pooling and reduced intravascular volume [2]. In addition, there is evidence that relatively tall individuals (such as in Marfan syndrome [13]) with poorly developed musculature or those suffering from anorexia nervosa may also exhibit inadequate postural adjustment. OH is often seen during pregnancy, or following various non-related events such as rigorous physical exertion, space flight, prolonged bed rest, gastrectomy, and marijuana use. Finally, and very importantly, OH is associated with aging, partly because the autonomic nervous system may become less functional [12].

Mechanism of OH

Heart function, neurovascular compensation, selective release of neurotransmitters, hormones, and cerebral autoregulation are primary systems responsible for maintaining normal orthostatic blood flow [3]. In assuming an upright position, about 500–700 ml of blood are redistributed such that it may be pooled in the lower extremities, splanchnic bed and pulmonary circulation resulting in decreased venous return to the heart and cardiac output (CO) [2]. Primary defense against blood pooling in the legs is a skeletal muscle pump that forces blood from the legs and gluteal muscles to the heart through the venous system thus increasing venous return pressure in the dependent limbs [3]. The neurovascular adjustments, initiated by the arterial baroreceptor reflex, include pressure-sensing areas in the carotid sinus, intima of the aortic arch, and heart chambers. A significant drop in bp (as a result of decreased venous return and cardiac output) triggers a decrease in the firing of the arterial baroreceptors. The baroreceptor afferent pathway travels through cranial nerves IX, X and the carotid sinus nerve, and terminates in the caudal area of the solitary nucleus and the paramedian nucleus of the reticular formation in the brainstem, subsequently relaying information to the hypothalamus, cerebellum, substantia nigra and cerebral hemispheres. Efferent outflow from the brainstem is multisynaptic, and these efferent sympathetic fibers reach the spinal cord and travel through the intermediolateral gray column, eventually leaving the spinal cord via thoracolumbar spinal nerves [12] ultimately releasing norepinephrine (NE) thereby stimulating alpha-adrenergic receptors that in turn cause vasoconstriction [12]. Vasoconstriction in the lower extremities and splanchnic bed leads to a rapid change in vessel tone limiting blood flow to these areas and enhancing venous emptying [4]. Under "normal physiological" conditions vasoconstriction in the periphery causes blood to shift toward the central venous system increasing blood flow into the left ventricle. The baroreceptor reflex, along with complex events involving muscle sensors, high- and low-pressure receptors, and changes in circulating catecholamines cause the heart rate to increase in response to orthostasis [12]. The normal immediate physiological response to hypotension is tachycardia (heart rate >100 beats per minute) [14].

Hormonal reaction in response to orthostasis includes changes in the renin–angiotensin–aldosterone system, promoting sodium and water retention and ultimately

increasing blood volume, along with the release of other peptides and active neuroamines such as vasopressin and epinephrine whose effects are seen within the minutes of orthostasis [4]. Vasopressin release from the posterior pituitary in response to minimal changes in blood volume is initiated by stimulation of the atrial stretch receptors and arterial baroreceptors [12]. Figure 1 provides an overview of orthostasic mechanisms.

Together with these defense mechanisms cerebral autoregulation, is estimated to occur within seconds following orthostasis and is designed to maintain cerebral blood flow in response to the change from supine to standing. It protects the brain by causing increased cerebral resistance in response to high bp and decreased resistance in response to low bp. Researchers examining the relationship between orthostatic stress and a disruption in cerebral autoregulation report that following an orthostatic stress-head-upright-tilt test, patients with recurrent syncope experienced vasoconstriction in the middle cerebral artery, instead of the normal vasodilation that occurs when blood flow to the brain is reduced. These findings suggested that as a result of an abnormal baroreceptor response, cerebral flow regulation was disrupted, resulting in vasovagal syncope [15].

Recent evidence also shows a possible association between OH and changes in cerebral blood flow (CBF) as measured with PET scanning techniques. Blood flow levels were significantly increased in the cerebellar vermis and visual cortical areas of the brain of healthy individuals during orthostatic stress. These areas, which are important for motor coordination and control over voluntary standing are especially relevant to balance and falls in the elderly [16]. CBF in the frontal and parietal cortices tends to decrease as subjects move from a supine to a standing

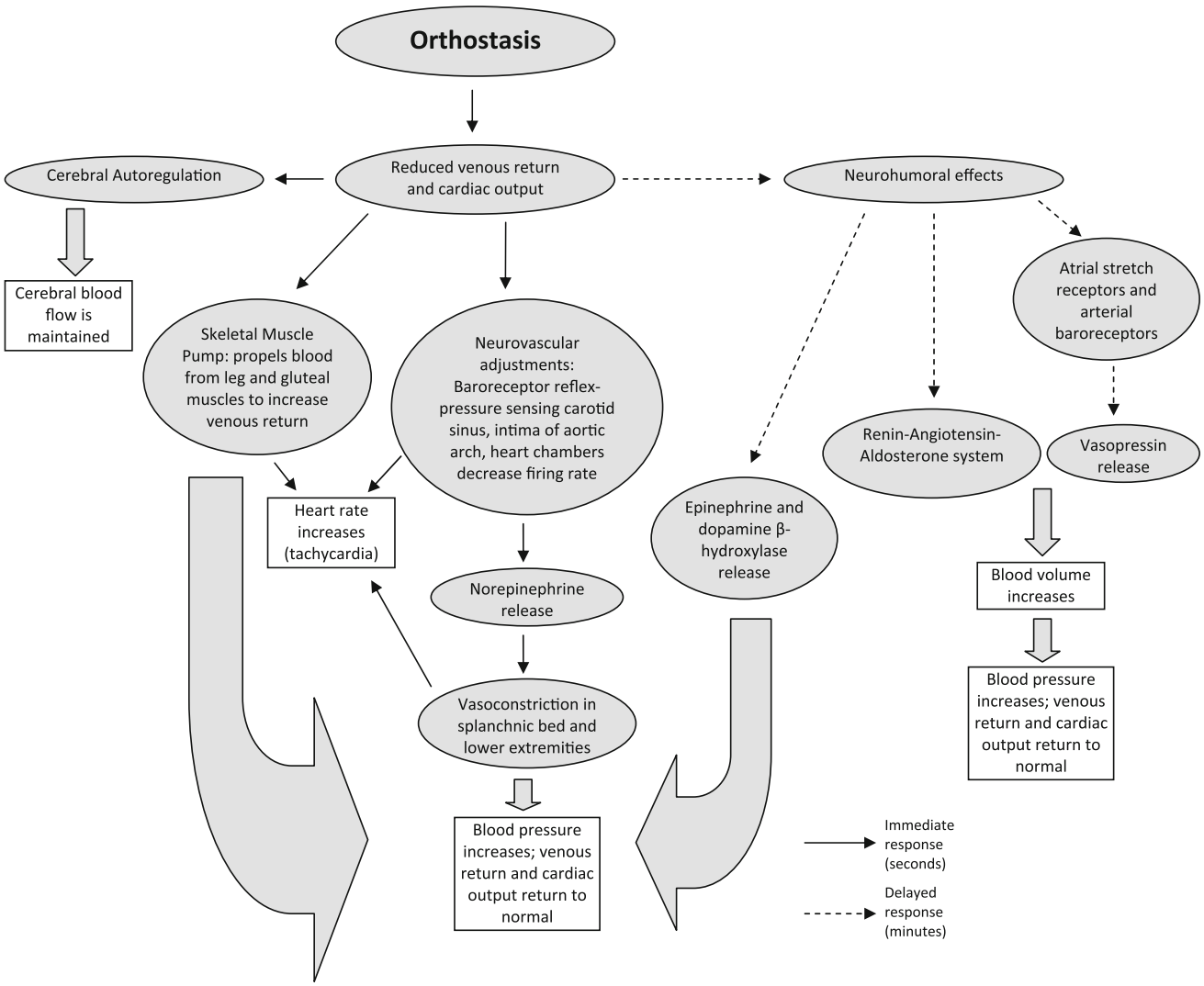

Fig. 1 Overview of the mechanism of orthostasis (figure summarizes [2–4, 12, 14, 25])

position [16]. Similar results had been reported using a transcranial Doppler ultrasound flow in patients with OH [17]. These authors [17] also found that postural cerebral hypoperfusion in patients with OH was localized to the frontal areas of the brain as a result of an inadequate vascular response during orthostasis.

Three measures, decreased NE levels, decreased systemic arterial pressure and reduced pulse rate, were associated with an increased likelihood of exhibiting OH after standing. In contrast, individuals relatively free of OH tended to show increased NE levels, along with elevated systemic arterial pressure and increased pulse rate thereby providing some support for the hypothesis that the observed decrease in NE levels reflect a withdrawal of sympathetic nervous tone to the vasculature potentially causing hypotension during a vasodepressor reaction [18]. The mechanism supporting orthostatic regulation is disrupted in individuals presenting with primary chronic autonomic failure, multiple system atrophy, and autonomic failure associated with PD. These patients often express reduced sympathetic activity during orthostasis, so their increase in sympathetic action is not sufficient to compensate for the decreased venous return to the heart that occurs upon standing [19]. In addition, evidence suggests that patients with PD as well as OH have diffuse sympathetic innervation throughout the left ventricle of the heart that could potentially cause or contribute to the OH [19].

OH in older adults

A number of physiological changes and medical conditions associated with increasing age such as abnormal sympathetic activity, altered hormone levels and denervation impact the ability of the body to compensate for an orthostatic challenge and may lead to the development of OH. Along with a variety of age-related changes including a decline in autonomic function [6, 12] there is an increase in OH prevalence from 15 to 26% during the years of 65–69 to 85 years or older [2]. In addition, while there are a number of age-related events that could be associated with increasing number of falls among the elderly, OH could secondarily contribute to this outcome via usage of beta blockers. That is, with standing, the baroreceptor response may become impaired with age and older patients may experience a large decrease in blood volume along with inadequate cardiovascular compensation [2]. Further, it is known that arterial stiffness, resulting in decreased elastic and contractile force, increases with age and a positive correlation was found between increased upper limb arterial stiffness in elderly patients and OH [20]. Parenthetically, it has been shown that increased arterial stiffening is associated with an elemental psychological process that is identified as hopelessness. Hopelessness serves as an entry process that can be a marker for a number of strongly negative sequelae such as depression and morbidity [21].

Aging is also associated with generalized neuronal loss, fewer beta receptors with decreased functionality, and a weaker response to catecholamines—all of which are potential factors contributing to the development of OH [12]. Finally, OH is implicated in cerebral hypoperfusion among elderly individuals [22]. With age, blood vessels become narrow, calcified, elongated and tortuous thereby preventing effective vasodilation and curtailing cerebral perfusion, especially in periventricular white matter, basal ganglia, hippocampus, and regions of the brain that have more than one source of blood supply. When these areas develop lesions, the prefrontal-basal ganglia circuits may become disrupted, impairing cognition and memory, and thereby increasing the likelihood of vascular dementia [22].

OH and cognition

The relationship between cognition and BP regulation has been the subject of a good amount of research. Although most studies have found a relationship between effective OH regulation and stable cognitive performance, variability of reported findings may reflect varied patient populations as well as the difficulties in comparisons of results obtained from various cognitive tests.

While some authors [23] have proposed a curvilinear relationship between OH and cognition within a small maximal range, others have suggested that the changes in cognitive functioning observed following postural changes are rather unpredictable. In a two and a half year follow-up study of prospective memory among elderly with and without OH, this condition was not associated with significant alterations in cognitive performance [8]. However, the cognitive test data were based on scores from the mini mental status exam in which a difference of a single point determines the level of cognitive functioning. Even so, mild cognitive impairments are widely accepted as recognizable patterns and symptoms of OH [24].

Various reports point to potential connections between areas of the brain, cognitive functioning and OH. Dusheck et al. [25] suggested that hypotension affects cortical activity via the cardiovascular system and the prefrontal cortex. The autonomic nervous system is controlled by the hypothalamus, which in turn is controlled by limbic structures including the cingulate gyrus. The degeneration of the anterior cingulate gyrus provokes hypothalamic dysfunction, which projects to various cortical and subcortical structures contributing to autonomic effects evident in various disorders [26].

Current literature on brain perfusion and cognitive performance indicates that in individuals with *chronic hypotension*, BP is inadequate at maintaining perfusion of a large part of the brain despite autoregulation [25]. Consequently, blood flow in the middle cerebral artery, in particular, is substantially reduced in hypotensive subjects. In order to maintain cognition, the middle cerebral artery supplies regions that are directly related to subcortical areas, large fractions of the frontal and parietal lobes and the temporal lobes. Therefore, lack of perfusion in this major cerebral artery contributes to difficulties in cognitive performance [25].

Significantly impaired motor speed, attention and executive functioning among patients with autonomic failure have been identified; these findings may be consequences of cerebral hypoperfusion via systemic hypotension [27]. Román [22] postulated that hypoperfusion may initiate risks of cognitive impairments among elderly with OH, suggesting that anatomical changes in the aging brain leave certain regions, such as the basal ganglia and hippocampus more susceptible to ischemic hypoperfusion that in turn can impact cognitive and memory functioning. In a separate study, community dwelling elderly participants with poor orthostatic BP regulation exhibited significantly inferior scores on measures of activities of daily living relative to participants without orthostatic problems [9]. Whereas some elderly patients with either postural hypotension or hypertension had more advanced leukoaraiosis (changes in white matter) and/or periventricular hyperintensities (areas of high intensity seen on magnetic resonance imaging scans; [9]), others showed leukoaraiosis associated cognitive and motor impairments [28] and poor prognosis among individuals with cerebrovascular disease [29].

In some clinical studies, patients diagnosed with various types of dementia showed an increased OH prevalence, some of which may be associated with impaired autonomic function [30]. OH was reported in 69% of Lewy body patients with dementia and in 42% of Alzheimer's disease dementia patients compared to only 13% of controls [31]. Elderly women who developed dementia during a 5-year longitudinal study tended to have a larger drop in BP during an orthostatic challenge and low beta activity (or a lower state of active awareness) compared to participants who remained dementia-free [32]. A study showing OH contributing to significant declines in sustained attention, visual memory and visual perception led to suggestions that this condition might also contribute to cognitive decline among patients with PD who also suffer from dementia [33]. In a related work, it was reported that OH, frequent among PD patients with dementia, exhibited exacerbated attention problems [34].

Comparing brain perfusion among PD patients with or without OH showed that bilateral activity in the anterior cingulate gyrus played a role in autonomic failure. The anterior cingulate gyrus was significantly less perfused in the participants with OH [26]. It is generally accepted that reduced CBF may account for the increased prevalence of OH among patients with dementia. Furthermore, it has been suggested that the neurocardiovascular instability caused by *chronic hypotension* commonly observed among dementia patients may exacerbate their cognitive decline [35].

OH may also be related to motivation. The anterior cingulate has been identified as an area that mediates effort and motivation [36]. Reduced stimulation in this area is associated with the effectiveness of orthostatic blood pressure regulation of anterior cingulate activity as observed by both experimental research and in clinical studies primarily in individuals with PD. Those with PD along with OH showed reduced levels of activity in the anterior cingulate while those with only PD but free of OH showed no diminution of activity in the anterior cingulate. In an experimental study, participants who were instructed to respond with maximum effort on a simple reaction time test exhibited not only significantly faster reaction time responses, but also significantly greater activity in the cingulate than those without the additional instructions [36].

While the majority of the literature focuses on clinical OH and cognitive impairments, there are a few studies that have specifically examined the effect of *subclinical* levels of OH. In a controlled study involving 181 type 2 diabetes mellitus patients and 43 normal individuals, the presence of *asymptomatic* subclinical OH was positively correlated with diminished cognitive performance. That is, relative to the supine systolic values, as orthostatic SBP decreased, poorer learning, memory and slower reaction times were evident in patients and controls [5]. Apparently, those older individuals with relatively poor orthostatic BP regulation are at risk for a variety of cognitive problems. None of these individuals were symptomatic for OH and none of them had exhibited clinical values of OH.

Such cognitive effects are not limited to older individuals, even those who are asymptomatic and exhibit subclinical levels of OH. Children with untreated orthostatic dysregulation have shown significantly smaller amplitudes in early, late, and total contingent negative variation (a measurement associated with cognitive processes and is used to assess attention and motivation/hypodynamia) [37].

To examine the possibility that OH may be related to cognitive effects in the young, school age and pre-school age samples were studied. In relatively healthy children (ages 6–9), less effective BP regulation in response to orthostatic challenge was reflective of poorer performances on several neuropsychological measures [10]. Specifically, smaller increases in SBP or pulse pressure (defined as the

difference between systolic and diastolic BP) following orthostasis were predictive of decreased verbal memory scores and poor prospective memory, respectively [10]. On the other hand, improved BP compensation following a postural change (increases in SBP, even subclinical) was associated with enhanced cognitive functioning [10]. Similarly, a study with pre-schoolers of self-reported Hispanic American heritage displayed improved performance on a standardized developmental screening measure (Speed-DIAL-III). As SBP increased upon standing, scores in the domains of language and concept formation also increased [11]. In a double-blind study, teachers' yearlong evaluations of effort in 45 students were positively correlated with higher levels of systolic orthostatic BP regulation [38].

OH and anxiety and mood

Depression and anxiety disorders have been associated with cardiovascular morbidity and impaired autonomic functioning [39, 40]. Depression is associated with altered autonomic regulation as evidenced by reduced heart rate variability [39, 41]. Mood states such as increased depressive symptoms have been related to greater vascular resistance, and even subclinical levels of depression appear to be associated with cardiovascular functioning [40]. Researchers have examined connections between blood pressure regulation and mood and anxiety symptoms. Dopamine levels are implicated in depression and also play an important role in effective OH regulation [42].

Recent studies have shed some light on the nature of orthostatic responses to a variety of anxiety disorders including panic disorder, general anxiety and social phobias. Lorenz et al. [43] not only reported a positive relationship between mother and child anxiety scores, but also between maternal anxiety and child BP regulation in response to orthostatic challenge. That is, as mother's chronic, or *trait* anxiety increased, children exhibited poorer SBP responses to orthostasis. This is the first study to suggest that not only anxiety is associated with poor SBP regulation, but also has an inter-generational impact in nonclinical samples. In comparison to anxiety patients, panic disorder patients showed a greater DBP overshoot immediately following standing which supports the suggestion of an increased sympathetic baroreceptor function, which in turn can have significant negative health effects [44]. Using an isometric hand-grip test, which measures strength and effort while raising BP and heart rate, Yeragani et al. [45] measured BP during postural change. Results suggested that the increase in adrenergic tone among panic disorder patients was significantly elevated compared to controls. In related studies, a significantly higher heart rate has been reported in response to an orthostatic challenge among panic disorder patients compared to healthy controls and social phobics. This latter group of individuals had increased circulating NE levels during the supine and standing position when compared to controls and panic disorder patients [46]. In patients suffering from orthostatic panic, a recently described phenomenon observed primarily in Southeastern Asian refugees, participants reported catastrophic cognitions (e.g. fear of having a heart attack) occurring after a change from supine to standing position. The presence of OH is associated with autonomic changes that may be reflected as dizziness, palpitations, anxiety, fear and catastrophic cognitions, a constellation of symptoms referred to as the "multiplex model of panic attack." In addition to cultural specific somatic worries, participants also experienced orthostatic-induced flashbacks, similar to those with post-traumatic stress disorder [47, 48]. Thus, among this spectrum of anxiety disorders, these findings further emphasize previous suggestions that BP regulation functions differently in response to orthostasis.

Relationships have also been documented in children. Those children who exhibited subclinical BP dysregulation or decreased pulse pressure in response to orthostatic challenge displayed a variety of psychological sequelae including elevated anxiety and/or increased depression, poor mood, lowered self-esteem and perceived lack of competence [10]. In addition, reports of depressive states were correlated with less efficient SBP changes following orthostasis [10].

Changes in CBF and circulating NE levels may contribute to and help to explain the association between affect (including anxiety and depression) and orthostatic BP regulation. There is some evidence supporting a relationship between the presence of panic disorder and regulation of blood flow to the brain. When compared to healthy controls, panic disorder patients, either of recent onset or in full remission, exhibited decreased blood velocity in the middle cerebral artery and presented with sudden drops in blood flow following a change in position from supine to standing. When compared to controls or unipolar depressed patients, circulating supine NE levels were lower in bipolar patients. However, after an orthostatic challenge, amine levels increased significantly for both depressed patient groups (close to 100% over controls) [49]. Related reports showed depressed and panic disorder individuals as having significantly increased circulating NE levels during supine and standing position while bipolar patients had significantly lower amine levels during supine posture [50]. Higher plasma NE levels were positively related to self-reported anxiety [51] and combat veterans have been described as displaying "hemodynamic abnormalities" of the NE system [52]. Many have suggested an important

link between NE and affective disorders and BP regulation, but other neurotransmitters such as serotonin and acetylcholine may also play a significant role [53].

Clinical relevance

OH impacts individuals of all ages, and its occurrence is associated with a variety of diseases of widely different etiologies. In fact, diabetes mellitus, PD and various conditions affecting the cardiovascular and central nervous system are known to increase the risk for developing OH. A better understanding of the relationship between these conditions and BP regulation may help to elucidate the processes leading to OH [2]. It is generally accepted that there is an association of OH with the presence of a variety of behavioral and emotional disorders Additional research on the mechanisms relating OH to cognition and affective disorders will hopefully provide physicians and other health practitioners with new tools for better treatment of these patients.

Although OH is not routinely assessed, chronic orthostatic difficulties is an increasing reason for primary care referrals as its severity and impact on daily life can be disabling and patients are often unable to hold jobs or attend school. Fainting also poses the risk of fractures and skull injuries, especially in the elderly [54, 55]. In addition, OH and BP dysregulation has been connected with altered affective states including anxiety and depression, thus significantly reducing the quality of life.

At least in one study, birth weight was shown to predict subclinical OH in children (10- to 12-year old). That is, as birth weight increased from 4 to 10 pounds, the effectiveness of the SBP response to an orthostatic challenge also increased [56].

In summary, identifying early predictors of BP regulation, such as birth weight, may help in monitoring for signs of various problems associated with affect and cognition. Even in nonclinical samples, when OH is subclinical, decreased mood, poor self-esteem, decreased self-efficacy, somatic complaints, worry, fatigue and pessimism all have been linked to orthostatic BP inadequacy in response to orthostatic challenge among children and adults across various cultures, irrespective of the presence of comorbidities. Most importantly, these nonclinical samples provide increased external validity for the findings.

Final comments

Even though this review of the literature is not exhaustive, we have broadened the examination by focusing on clinical and subclinical aspects of OH, and its possible and hitherto unrecognized sequelae. We emphasize that OH has many implications including decreased cognitive function, attention deficits, increased incidence of depression and heightened feelings of anxiety across the lifespan. Although most of the research in this area has focused on clinical OH, the subclinical manifestation of this condition is becoming an increasingly important area of interest, especially in children, as OH measurements are generally overlooked in the clinical setting. Orthostatic measurements should be implemented into routine physical examinations to possibly prevent the progression of subclinical OH, and also to identify insidious influences on cognitive and affective disorders as well as to design rational behavioral and pharmacotherapeutic treatments for this condition.

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