Cognition and Hopelessness in Association With Subsyndromal Orthostatic Hypotension

Jadwiga Czajkowska, Stanislav Ozhog, Earl Smith, and Lawrence C. Perlmuter

Department of Medicine, Chicago Medical School, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois.
Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois.

Address correspondence to Lawrence C. Perlmuter, PhD, Department of Psychology, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois. Email: lawrence.perlmuter@rosalindfranklin.edu

Background. The move from lying to standing is typically associated with a variety of physiological and neurohumoral changes, most especially a slight increase in systolic blood pressure (SBP). Decreased efficacy of the various mechanisms that control orthostatic blood pressure (BP) regulation may result in lightheadedness, dizziness, syncope, and cerebral hypoperfusion. The lack of effective orthostatic BP regulation is a symptom for various problems, including fatigue, depression, anxiety, and reduced attention.

Methods. This study examined men and women (N = 74) who were aged 30–75 years and asymptomatic for clinical orthostatic hypotension.

Results. Relatively poor BP regulation in response to orthostasis was associated with decreased verbal memory, decreased concentration, and higher hopelessness scores.

Conclusions. Individuals who exhibited less effective SBP regulation even to a subsyndromal degree in response to an orthostatic challenge may be at increased risk for cognitive and affective problems. The relationship between orthostatic BP regulation is best described as curvilinear.

Key Words: Subclinical orthostatic hypotension—Cognition—Hopelessness.

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Upon changing position from lying to standing or from sitting to standing, systolic blood pressure (SBP) is expected to show a slight increase. Thus, orthostasis is accompanied by a slight increase in SBP along with approximately 500–700 mL of blood displacement from central circulation into splanchnic and pulmonary circulation. The requirement for upward blood flow is challenged by gravity and may result in some degree of cerebral hypoperfusion along with the pooling of blood in the lower extremities. To correct the reduction in SBP, the sympathetic nervous system surges to restore normal blood circulation. Various factors influence regulation of BP, including baroreceptor firing, cardiac output, release of neurotransmitters, and increased vascular fitness. In addition, norepinephrine and dopamine involved in the signaling of depressive states are also associated with the adequacy of the response to an orthostatic challenge.

The spectrum of events occurring in response to orthostasis includes suppression of parasympathetic control along with reflexive sympathetic innervations and increased systole. Decreased parasympathetic activity along with vagal inhibition lead to increased heart rate, strengthened sympathetic tone, and vasoconstriction followed by increased total peripheral resistance.

SBP is the maximum pressure during ventricular contraction and diastolic pressure is the lowest arterial pressure during ventricular filling. Clinical orthostatic hypotension is defined by the American Autonomic Society and the American Academy of Neurology (1996) as a 20 mmHg or more decrease in SBP within 1 minute of standing after sitting or supine posture and a 10 mmHg decrease in diastolic BP. The present study focuses on subsyndromal orthostatic hypotension that is defined by a subclinical reduction of SBP within 1 minute of standing after being supine.

It has been shown that orthostatic hypotension can lead to cerebral hypoperfusion and with repeated episodes, cerebral structural deterioration could impair cognitive function and degrade affective status. In addition, affective problems such as hopelessness can reciprocally exacerbate structural problems by increasing arterial wall thickening. However, it is unlikely that such gradually impaired structural changes fully account for these cognitive, behavioral, and affective problems because these relationships are evident even in children as young as 3–5 years of age.

In adults, neuropsychological testing has demonstrated that slower reaction times, tracking difficulties, compromised serial list learning, decreased attention and concentration, prospective memory difficulties, poorer learning of...
new materials, and even slight elevations in somatic depression are evidenced in individuals who exhibit a subsyndromal drop in SBP in response to orthostatic challenge (8–10). In addition to increased affective disturbances (11) and behavioral problems (12), subsyndromal orthostatic hypotension is associated with decreases in motivation, volition, and concentration (13). Furthermore, in adults aged 75 years and older, a moderate SBP increase in response to orthostatic challenge was associated with higher levels of cognitive performance, whereas lesser or greater increases were associated with poorer performance, thereby indicating an overall curvilinear relationship between the magnitude of the systolic response to an orthostatic challenge (9).

Contributors to orthostatic BP regulation include: baroreceptor signaling in the aortic arch, carotid sinuses, and autonomic nervous system activity associated with the release of neurotransmitters, such as norepinephrine and dopamine (2,3). Interestingly, poor orthostatic BP regulation and decreased levels of norepinephrine and dopamine also affect depressive status (14,15). Additionally, norepinephrine receptor blockade has been involved in affective and cognitive problems (2,3,16). In the aggregate, these biologic changes in signaling are not only associated with poorer orthostatic hypotension responsibility but also play a role in cognitive and affective difficulties. Thus, poor orthostatically mediated SBP regulation is unlikely to serve as a causal factor for affective and cognitive problems. More likely, it provides a marker for defects in neurohumoral problems. In turn, neurohumoral changes appear to be associated with decreased cerebral and behavioral activities in the anterior cingulate (17) and orbitofrontal cortices (18).

The goal of this study was to evaluate cognition and affective status in individuals exhibiting mild or subsyndromal orthostatic hypotension in response to standing. We hypothesized that, a moderate increase in SBP regulation would result in the best level of performance and affective status, whereas lesser or greater increases were associated with poorer performance, thereby indicating an overall curvilinear relationship between the magnitude of the systolic response to an orthostatic challenge (9).

METHODS

Participants

There were 74 participants in the study of whom about 10% had less than high school training, 58% had graduated high school, and 32% had some college experience. Participants ranged in age from 30 to 75 years, with about 75% recruited from the outpatient primary care clinic at an inner city hospital in a major mid-Western city. The remainder was recruited from inpatient general medical floors with relatively minor complaints, such as foot infection. With only a few exceptions, all who were approached agreed to participate. Participants were invited to volunteer and were given a $5 monetary gift as a token of appreciation for participation in the study. All participants signed a consent form and were provided an option to withdraw from the study for any reason without sacrificing their monetary gift.

Exclusions included those with BMI more than 30 owing to possible mobility restrictions; previous diagnosis of orthostatic hypotension; or currently receiving treatment for psychiatric problems; limb amputations; Parkinson’s or Alzheimer’s disease; deafness; or inability to read or write or altered mental status.

Procedure

Half of the participants were instructed to lie supine for 5 minutes. An appropriate sized cuff was loosely fitted to their left arm that was positioned parallel to their body. After 5 minutes, BP and pulse were measured by auscultation. Then, they were instructed to stand up unassisted for 1 minute after which BP and pulse were measured again. The experimenter was positioned adjacent to the participant to prevent any untoward events. Next, while seated, participants completed a series of tests measuring cognition and mood. Following test completion, participants once again were outfitted with a loosely fitted cuff on the left arm and laid prone for 5 minutes, and BP measurements were repeated. Finally, participants stood upright for 1 minute and the BP procedure was repeated. Half of the participants began with the prone procedure and the remainder with the supine procedure. Because the prone to standing measurements did not yield any significant outcomes, these measures were not included in the article. For all participants, only the supine to standing measurements are reported in this study.

Testing

Information regarding age, race, height, weight, and current medical problems such as diabetes mellitus had been obtained from medical records. Before the cognitive tests were administered, all participants reported their handedness, and then, they successfully completed the Mini-Mental Status Examination (19). Next, the following tests were given: the Controlled Oral Word Association (COWA) Test; the Trail Making Test (TMT) part A and part B; Zung Self-Rating Depression Test (20); an adaptation from the two-item Hopelessness Test (21); and lastly the State and Trait Test for anxiety (22). All tests were taken in the same sequence.

The COWA Test assessed verbal fluency (23). Participants were asked to recite as many words as possible starting with the letter “F” within 60 seconds, and subsequently, they recited as many words as possible starting with the letter “S” (24). The experimenter recorded the words as recited. By instructions, repeated words, variations of the same word (eg, short, shorter or stand, standing, stood), and proper nouns were not permitted and were not scored.
The TMT parts A and B were given sequentially. TMT part A involves sequential connection of a series of encircled numbers written haphazardly across the page with the goal to complete this test with speed and accuracy. TMT part B measures skills involved in sequencing and attention. TMT part B requires connecting a series of circled numbers and circled letters in an alternating sequence (eg, first 1 and then A and then 2 etc.). TMT part B measures mental flexibility, planning, and visual–perceptual processing speed. In both parts, A and B, participants were instructed not to lift their writing instrument from the paper (25). Time to complete each part of TMT was measured with a stopwatch. Higher scores on TMT are indicative of slower performance. In order to further assess participants’ mental flexibility independent of the motor component, the difference between the TMT part B and TMT part A was calculated, thereby removing the motor component from TMT part B (26,27). Finally, depression and anxiety tests were also administered.

**Statistical Analyses**

Categorical variables were evaluated with chi-square tests, whereas continuous variables were examined with analyses of variance. Lastly, stepwise multiple regression models were utilized to evaluate the relationship between orthostatic BP regulation and performance after accounting for potential confounders, including age and gender.

**RESULTS**

Means and standard deviations for the primary demographic and outcome variables are displayed in Table 1.

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>BMI</th>
<th>Trail A (s)*</th>
<th>Trail B (s)*</th>
<th>Total depression*</th>
<th>Hopelessness*</th>
<th>Trait anxiety*</th>
<th>State anxiety*</th>
<th>Word generation</th>
<th>Systolic STD (mmHg)</th>
<th>Diastolic STD (mmHg)</th>
<th>Pulse STD (BPM)</th>
<th>Systolic SUP (mmHg)</th>
<th>Diastolic SUP (mmHg)</th>
<th>Pulse SUP (BPM)</th>
<th>Relative systolic BP difference (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>54.63</td>
<td>27.83</td>
<td>70.93</td>
<td>211.08</td>
<td>38.32</td>
<td>3.12</td>
<td>38.31</td>
<td>41.60</td>
<td>16.18</td>
<td>115.69</td>
<td>70.76</td>
<td>81.73</td>
<td>121.35</td>
<td>70.27</td>
<td>75.07</td>
<td>−5.66</td>
</tr>
</tbody>
</table>

**Correlations among study variables (age, gender, education, standing systolic, and supine SBP) are displayed in Table 2. Categorical variables were evaluated with Spearman rho and continuous variables with Pearson r.**

Figure 1 displays the difference measured in millimeters of mercury between standing and supine BP divided by the average of the standing minus lying difference scores.

To determine whether the linear and quadratic expressions of orthostatic BP regulation were predictive of affective status and cognition, multiple regression analyses were developed examining hopelessness; depression; and performance on Trail A, Trail B, Trail B–A, and word retrieval (COWA). Covariates were entered on the initial steps of the regression, including gender, age, and education. Next, to enter was the linear expression of the systolic difference score, and last to enter was the curvilinear expression of the systolic difference score (Table 3).

**Hopelessness.—** Each of the 4-point questions measuring hopelessness from “never” to “most of the time” was used (Figure 2). The curvilinear expression of the SBP difference
score indicated that up to a maximum, improved BP regulation was associated with decreasing hopelessness, but on either side of the maximum, BP regulation in response to orthostasis was associated with increased levels of hopelessness.

**Word Production**

With word retrieval as the dependent variable and gender, age, and education as covariates, increasing age was associated with poorer performance. With respect to orthostatic difference scores, up to a point, increasing SBP (quadratic) was associated with higher word retrieval scores.

**Trails A and B**

Although performance on Trail A was not significantly correlated with orthostatic BP changes, performance on Trail B (Figure 3) improved as the curvilinear expression of SBP regulation reached a maximum. To evaluate performance on Trail B after correcting for the motor speed component, as reflected in Trail A, the Trails B–A (Figure 4) difference measure showed improvement as SBP regulation went through a maximum. Apparently, the curvilinear component of SBP regulation affects attention processes, even after controlling for the simple speed measures, as reflected in performance on Trail A.

**Depression and Its Subscales**

Surprisingly, in this study, depression scores, including independent analyses of its somatic and affective components were not predicted by either the linear or quadratic components of SBP regulation.

**Discussion**

In response to orthostatic challenge, even minor or subsyndromal SBP problems were associated with increased

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**Table 3. Multiple Regression Models: Standardized Beta and \( R^2 \) Change**

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Stand. Beta</th>
<th>( R^2 ) change</th>
<th>Stand. Beta</th>
<th>( R^2 ) change</th>
<th>Stand. Beta</th>
<th>( R^2 ) change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DV = hopelessness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>−.14</td>
<td>.01</td>
<td>.11</td>
<td>.01</td>
<td>−.03</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>.01</td>
<td>.00</td>
<td>.20</td>
<td>.02</td>
<td>.14</td>
<td>.03</td>
</tr>
<tr>
<td>Education</td>
<td>−.17</td>
<td>.04</td>
<td>.06</td>
<td>.00</td>
<td>−.13</td>
<td>.02</td>
</tr>
<tr>
<td>Systolic difference</td>
<td>.48</td>
<td>.16**</td>
<td>.21</td>
<td>.04</td>
<td>−.01</td>
<td>.00</td>
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<tr>
<td>Systolic difference Sq.</td>
<td>.32</td>
<td>.09**</td>
<td>.04</td>
<td>.00</td>
<td>.21</td>
<td>.04</td>
</tr>
<tr>
<td><strong>DV = Zung total depression</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>.14</td>
<td>.00</td>
<td>.14</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>.20</td>
<td>.04</td>
<td>.20</td>
<td>.04</td>
<td>−.22</td>
<td>.06*</td>
</tr>
<tr>
<td>Education</td>
<td>−.02</td>
<td>.00</td>
<td>.03</td>
<td>.00</td>
<td>.06</td>
<td>.00</td>
</tr>
<tr>
<td>Systolic difference</td>
<td>.16</td>
<td>.00</td>
<td>.20</td>
<td>.01</td>
<td>.12</td>
<td>.03</td>
</tr>
<tr>
<td>Systolic difference Sq.</td>
<td>.42</td>
<td>.16**</td>
<td>.44</td>
<td>.18**</td>
<td>−.25</td>
<td>.05*</td>
</tr>
<tr>
<td><strong>DV = Trail A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>.14</td>
<td>.00</td>
<td>.14</td>
<td>.01</td>
<td>.01</td>
<td>.01</td>
</tr>
<tr>
<td>Age</td>
<td>.20</td>
<td>.04</td>
<td>.20</td>
<td>.04</td>
<td>−.22</td>
<td>.06*</td>
</tr>
<tr>
<td>Education</td>
<td>−.02</td>
<td>.00</td>
<td>.03</td>
<td>.00</td>
<td>.06</td>
<td>.00</td>
</tr>
<tr>
<td>Systolic difference</td>
<td>.16</td>
<td>.00</td>
<td>.20</td>
<td>.01</td>
<td>.12</td>
<td>.03</td>
</tr>
<tr>
<td>Systolic difference Sq.</td>
<td>.42</td>
<td>.16**</td>
<td>.44</td>
<td>.18**</td>
<td>−.25</td>
<td>.05*</td>
</tr>
</tbody>
</table>

Notes: Relative supine systolic = the difference between standing BP/(the sum of standing BP and supine BP/2).

BP = blood pressure; COWA = Controlled Oral Word Association; Sq = squared; DV = dependent Variable; Stand. = standardized.

*p < .05; **p < .001.

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**Figure 2.** Hopelessness as a function of quadratic expression of systolic blood pressure change.

**Figure 3.** Trail B as a function of quadratic expression of systolic blood pressure change.
hopelessness. This relationship was exhibited both with respect to the linear and quadratic expressions of systolic orthostatic change. Poorer word retrieval (COWA) (23) was evidenced with respect to the quadratic expression of problems with systolic regulation. Poorer performance on Trail B was evidenced in the presence of minor problems in SBP regulation, as reflected in the quadratic expression. On the TMT, orthostatic BP regulation had no impact on the time to complete Part A of the test, suggesting that simple motor speed is spared by subsyndromal changes in orthostatic BP regulation. However, on Part B of the TMT, the relation between orthostatic BP regulation and time to task completion was evident, even after controlling for more elemental motor speed scores, as indicated in Trail A. Depression and its subscales appeared to be spared. However, no causal connections can be imputed in this cross-sectional study between orthostatic BP regulation and either affect or cognitive performance.

Many of the identified associations between orthostatic BP regulation and cognition, attention, and affective status were curvilinear. The curvilinear nature of this relation has been evidenced in several studies (Matsubayashi and colleagues; Stress and colleagues) (9,1), suggesting that either a relatively weak or an overly vigorous increase in SBP in response to an orthostatic challenge is associated with compromised performance on selected cognitive tasks and aspects of affect.

In older individuals with orthostatic hypotension or orthostatic hypertension, there is evidence showing deep white matter lesions called leukoaraiosis that had probably developed over time as a result of cerebral hypoperfusion (9). However, it is unlikely that a similar process would have had sufficient time to develop in 7- to 11-year-old children (7), many of whom displayed difficulty with cognitive function (1), reduced effort (17), and affective problems (7) in association with less effective orthostatic BP regulation. Moreover, the presence of either orthostatic hypotension or orthostatic hypertension in association with cognitive and affective problems suggests that the explanations are of necessity more complicated than merely reduced SBP. Thus, reduced levels of SBP provide only a marker for underlying mediating processes, such as reduction of dopamine, adrenergic changes, and other variables, like norepinephrine, which control BP regulation, also playing a role in cognition and affective status, as reflected by increased hopelessness.

It is well known that in response to a relatively quick postural shift from lying to standing, a series of processes are immediately required to maintain sufficient blood flow to the brain. Additionally, reduced cerebral blood flow, as in cerebral vascular accidents, results in selective deterioration in cognitive status (16). Schroeder and colleagues (16) showed that selective norepinephrine transporter blockade creates a phenotype that resembles idiopathic orthostatic intolerance, supporting the hypothesis that malfunctioning norepinephrine uptake mechanisms could also contribute to cardiovascular disease. Additionally, norepinephrine transporter inhibition has been used to decrease vasovagal reactions (16), contributing to various neuropsychological and neurobehavioral outcomes.

Further importance of the interaction between neurotransmitters and prefrontal cortex (PFC) are illustrated in studies, focusing on attention-deficit hyperactivity disorder (ADHD). Specifically, neuropsychological and imaging studies indicate that ADHD is associated with alterations in PFC and its connections to striatum and cerebellum. Research in animals along with observations of patients with cortical lesions have shown that the PFC is critical for the regulation of behavior and attention, using representational knowledge. Additionally, the PFC is important for sustaining attention over a delay, inhibiting distraction, and dividing attention, whereas more posterior cortical areas are essential for perception and the allocation of attentional resources. Also, the PFC in the right hemisphere is especially important for behavioral inhibition. Lesions to the PFC produce a profile of distractibility, forgetfulness, impulsivity, poor planning, and locomotor hyperactivity. Finally, the PFC is very sensitive to its neurochemical environment, and either too little or too much catecholamine release in PFC weakens cognitive control of behavior and attention, suggesting a curvilinear relationship (28).

Recent electrophysiological studies in animals suggest that norepinephrine enhances “signals” through postsynaptic alpha2A adrenoceptors in PFC, whereas dopamine decreases “noise” through modest levels of D1 receptor stimulation. Alpha2A-Adrenoceptor stimulation strengthens the functional connectivity of PFC networks, whereas blockade of alpha2 receptors in the monkey PFC recreates the symptoms of ADHD, resulting in impaired working memory, increased impulsivity, and locomotor hyperactivity.
Furthermore, genetic alterations in catecholamine pathways may contribute to deregulation of PFC circuits in the ADHD. Medications may have many of their therapeutic effects by optimizing stimulation of α2A-adrenoceptors and D1 receptors in the PFC, thus strengthening PFC regulation of behavior and attention (28).

Neurogenic orthostatic hypotension results from failure to release norepinephrine, the neurotransmitter of sympathetic postganglionic neurons, appropriately upon standing. In double-blind, cross-over placebo-controlled trials, administration of droxidopa, a synthetic amino acid that is decarboxylated to norepinephrine by the enzyme L-aromatic amino acid decarboxylase, increases standing BP, ameliorates symptoms of orthostatic hypotension, and improves standing ability in patients with neurogenic orthostatic hypotension due to degenerative autonomic disorders. The pressor effect results from conversion of droxidopa to norepinephrine outside the central nervous system, both in neural and nonneural tissue. This stop mechanism of action makes droxidopa effective in patients with central and peripheral autonomic disorders (29). The effectiveness of variables, such as dopamine and norepinephrine, which help to maintain blood flow to the brain, despite gravitational effects, also plays a key role in supporting cognitive function and affective status. Dopamine and norepinephrine are widely used as first-line agents to correct hypotension in patients with acute circulatory failure. There has been considerable debate in recent years, as to whether one is better than the other. Even though both drugs can increase BP in shock states, norepinephrine seems to be more powerful. However, dopamine can increase cardiac output more than norepinephrine along with increasing renal and hepatopancreatic blood flow (30).

It has been hypothesized that cerebral hypoperfusion may be related to assuming an upright posture from the supine position and may be associated with failure to maintain sufficient BP, as a consequence of blood pooling in the lower extremities (1,27). Poor BP regulation forecasts possible cognitive and affective problems. The upright posture may result in a modest subsyndromal decrease in BP that, in turn, is also predictive of reduced cognitive function and increased levels of depression and anxiety. Relatively poor SBP adjustment to orthostatic challenge was associated with higher depression scores in older women (31,32). Furthermore, increased depression has been associated with decreased likelihood of successfully fulfilling a future or prospective cognitive task (31,32). Surprisingly, in the present study, neither overall depression values nor somatic or affective components of depression were associated with orthostatic BP regulation. However, overall performance on attention processes (Trail B) was most strongly correlated with a moderate increase in SBP. Similarly, word production and hopelessness scores benefited with modest increase in SBP in response to the orthostatic challenge.

Some of the limitations in the present study included limited sample size, N = 75, and the inability to objectively measure cerebral blood flow. In conclusion, these results point to the role of subsyndromal orthostasis as a potential risk factor for cardiovascular problems, reduced cognitive function and increased hopelessness. The routine assessment and identification of orthostatic hypotension may provide an opportunity to reduce the risk for cognitive and affective decline through medication and physical exercise.

Acknowledgments

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References