Orthostatic hypotension (OH) is associated with cognitive impairment in otherwise healthy individuals as well as among those with neurodegenerative diseases. There is much current interest in the OH–cognitive impairment connection.1–4 OH and cognitive impairment are both common in Parkinson disease and can lower quality of life. Nonpharmacologic and pharmacologic treatments for OH are readily available, while treatments to modify the course of neurodegenerative cognitive impairment are nil. If the association between OH and cognitive impairment is causal and OH damages the brain, a promising window of therapeutic opportunity suggests itself. Alternately, OH and cognitive impairment are simply markers of a shared pathologic substrate.

In this issue of Neurology®, Centi et al.3 provide compelling proof of principle evidence for causality. This well-designed and executed study demonstrates reversible decline in cognition in Parkinson disease (PD) by testing cognition on a tilt table with patients first supine, then upright, and then supine again. Domains assessed included areas characteristically problematic in PD: attention/executive function, memory, and visuospatial skills. PD is characterized by decreased cortical perfusion, mainly in the frontal and posterior regions, both of which are associated with executive function and visuospatial skills. The magnitude of the perfusion decrement increases with cognitive impairment and disease progression.5 Cognitive problems in PD have been characterized as a disconnection syndrome involving interruptions in lateralized cortical and subcortical loops.6

In this study, participants with PD without OH (PD), participants with PD and OH (PDOH), and controls were given a battery of neurocognitive tests. All groups were without dementia, normotensive, and matched for age, sex, and education. Patient groups were additionally matched for disease stage, symptom severity, and levodopa equivalent doses. Patients had mild to moderate PD. Notably, not all patients with OH were symptomatic. Thus, they would not have been detected by standard clinical interview alone. None had severe symptoms on tilt table testing. A total of 55 people were enrolled. Patients with PDOH showed greater supine cognitive deficits as well as greater declines in test performance in the upright position than did controls. These were manifest in PD-specific as well as overall cognitive domains. PD and PDOH participants did not differ in supine test performance. However, in upright position, patients with PD performed intermediate to controls and PDOH groups. Cognitive decrements were reversed with return to the supine position. Tight temporal linkage between postural change and cognitive performance suggests that the blood pressure drops themselves impair cognition.

The authors point out that the consequences of orthostatically worsened cognition may be easy to miss in the office despite playing an important role in public settings in daily life. Walking is always upright and seating is not always available. Problems with visual scanning may impair balance, navigation, and visual search. Daily activities such as counting change, tracking conversations, and shopping may present challenges, create anxiety, and lead to social withdrawal. In clinical practice, symptomatic screening for OH is generally limited to questions about dizziness and lightheadedness. Time-consuming orthostatic blood pressures are not typically checked in the absence of these symptoms. Neuropsychological testing is usually not undertaken.

The final common pathway of OH is the failure of activation of adrenergic receptors on arterial muscles. While the final common pathway of OH is peripheral, the final common pathway of cognitive changes is cerebral. Cerebrovascular circulation is autoregulated. The incompletely understood neural circuitry controlling cerebral blood flow involves interconnected systems confined entirely to the brain as well as systems that loop through peripheral and spinal nuclei of the autonomic nervous system (ANS).7 Multiple neurotransmitters and peptides are involved; not only neurons, but also glial cells, play a key role.

The disconnection syndrome in PD may include not only disruptions in the normal connections between cortical and subcortical structures, but may involve...
other more far-flung networks. Extensive coordination among overlapping but distinct systems is required to maintain cerebrovascular homeostasis. These include central and peripheral nervous and vascular systems, sympathetic and parasympathetic limbs of the ANS, cerebral and systemic transmitter-mediated vascular control, and coupling of cerebral blood flow and metabolism. Furthermore, both CNS and ANS functions lateralize, and PD is often asymmetric. Improved understanding of underlying mechanisms between systemic blood pressure and cognitive function is needed, and spans subspecialty disciplines of clinical and basic research, a challenge in an age of silos.

Limitations of the present study include size of the sample studied, use of repeated measures, possible motoric confounds of cognitive testing, and use of neurocognitive tests of unknown ecologic validity/applicability to daily life. While all participants were normotensive at baseline, at least some were on antihypertensive or antihypotensive medications. These may present confounds. Additionally, tilt table positioning is not equivalent to standing up.

Replication and further study await. If generalizable, the implications are potentially far-reaching: OH is a commonplace among the elderly. Of note, this study also found a surprisingly high rate (over 25%) of supine hypertension (systolic blood pressure >135 mm Hg or diastolic blood pressure >100) across all study groups, including controls. This is an important observation and serves as a check on interventions that can cause or exacerbate supine hypertension, itself a risk factor for cognitive decline as well as cardiocerebral disease. Nonetheless, it may be appropriate to consider less aggressive blood pressure targets among patients with PD. It is early for a quick reach to the prescription pad in daily practice. Perhaps, however, it may not be early for greater awareness of the range of symptoms of OH and thoughtful consideration of empirically tailored intervention.

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DISCLOSURE
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REFERENCES