

# Neurocardiovascular Instability and Cognition

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Neurocardiovascular instability (NCVI) refers to abnormal neural control of the cardiovascular system affecting blood pressure and heart rate behavior. Autonomic dysfunction and impaired cerebral autoregulation in aging contribute to this phenomenon characterized by hypotension and bradyarrhythmia. Ultimately, this increases the risk of falls and syncope in older people. NCVI is common in patients with neurodegenerative disorders including dementia. This review discusses the various syndromes that characterize NCVI including hypotension, carotid sinus hypersensitivity, postprandial hypotension and vasovagal syncope and how they may contribute to the aetiology of cognitive decline. Conversely, they may also be a consequence of a common neurodegenerative process. Regardless, recognition of their association is paramount in optimizing management of these patients.

## INTRODUCTION

Neurocardiovascular instability (NCVI) represents abnormal neural control of the cardiovascular system [1]. This affects blood pressure (BP) and heart rate behavior, predominantly resulting in hypotension and bradyarrhythmia with abnormal baroreflex function manifesting as supine hypertension and exaggerated BP variability. Older adults are more susceptible to NCVI because of age-related physiological changes in the cardiovascular system, autonomic nervous system, cerebral blood flow, and humoral system.

Clinically, NCVI manifests as fatigue, falls, presyncope and syncope. These presentations are complicated and exacerbated by comorbidity and polypharmacy. Dysautonomic syndromes such as or-

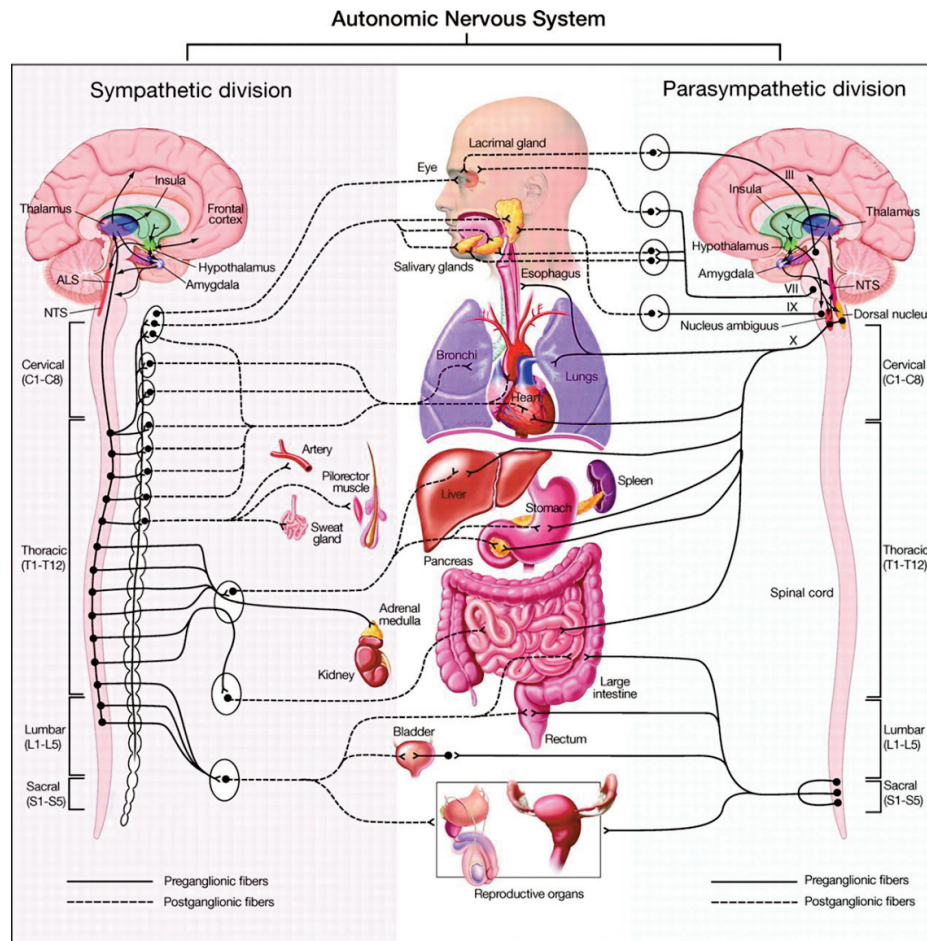
thostatic hypotension (OH), carotid sinus hypersensitivity (CSH), postprandial hypotension (PPH), and vasovagal syncope (VVS) characterize NCVI. It is common in patients with neurodegenerative disorders including established dementias. OH and CSH occur predominantly, with a combined frequency of 40 percent in patients with Alzheimer's dementia and 50 percent in patients suffering from dementia with Lewy bodies [2].

Understanding the mechanism of NCVI and its possible causative association with cognitive decline and dementia may help us target prevention and therapeutic strategies for a poorly understood, but well-established and burdensome disease. Similarly, recognition and management of NCVI in dementia patients can direct us in falls prevention,

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†Abbreviations: NCVI, neurocardiovascular instability; BP, blood pressure; OH, orthostatic hypotension; CSH, carotid sinus hypersensitivity; PPH, postprandial hypotension; VVS, vasovagal syncope; ANS, autonomic nervous system; ACh, acetylcholine; NE, norepinephrine; PPD, Parkinson's disease dementia; CBF, cerebral blood flow; CA, cerebral autoregulation; HTN, hypertension; MCI, mild cognitive impairment; AD, Alzheimer's dementia; VaD, vascular dementia; APOE, Apolipoprotein E; DLB, dementia with Lewy bodies; ChEI, Cholinesterase Inhibitor; SBP, systolic blood pressure; WML, white matter lesions; ATP, Adenosine Triphosphate; DBP, diastolic blood pressure; REAL-FR, French Research Programme on AD; OI, orthostatic intolerance; TILDA, The Irish Longitudinal Study on Aging; HRV, heart rate variability; PD, Parkinson's Disease; MMSE, Mini-Mental State Exam; MSA, Multi-System Atrophy; CSM, carotid sinus massage; CSS, carotid sinus syndrome; MRI, Magnetic-Resonance Imaging

Keywords: neurocardiovascular instability, autonomic dysfunction, cognitive impairment, dementia, hypotension, orthostatic hypotension, carotid sinus syndrome, postprandial hypotension, syncope



**Figure 1:** Schematic representation of the autonomic nervous system divisions and the systemic anatomical structures each innervate [150]. Roman numerals III, VII, IX and X (vagus) represent cranial nerves. ALS = anterolateral system  
NTS = nucleus tractus solitarius.

and thus reduce morbidity, institutionalization, and mortality in this physiologically vulnerable cohort.

## PATHOPHYSIOLOGY

The autonomic nervous system (ANS) is responsible for control of the body's visceral functions, maintenance of homeostasis, and adaptation to changing conditions. The baroreceptor reflex is the key regulatory mechanism for short-term control of systemic BP. Arterial baroreceptors are stretch receptors in the walls of the carotid sinuses and aortic arch. Afferent sensory input from these receptors travel via cranial nerves IX and X, and the carotid sinus nerve to the brainstem. This information is subsequently relayed to the hypothalamus, cerebellum, *substantia nigra*, and cerebral hemispheres [3].

Efferent limbs of the ANS consist of sympathetic and parasympathetic fibers to the heart, as well as sympathetic fibers to the smooth muscles in the peripheral blood vessels (Figure 1). Pre-ganglionic sympathetic nerves release acetylcholine (ACh) and post-ganglionic nerves release norepinephrine (NE), with the exception of sweat glands. ACh is the primary neurotransmitter of pre- and post-ganglionic para-sympathetic nerves.

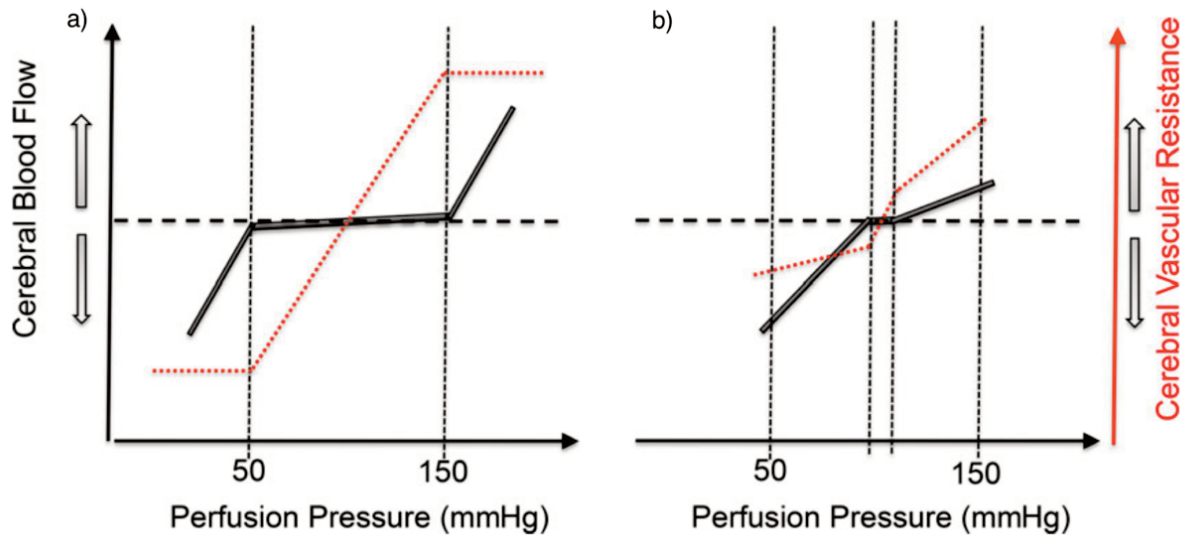
In healthy individuals, sympathetic activation is initiated in response to low BP, resulting in increased heart

rate, cardiac contractility, and vasomotor tone to restore BP and maintain an adequate cardiac output for systemic and cerebral perfusion. Autonomic dysfunction occurs in all common dementias, but is especially prominent in Parkinson's disease dementia (PDD) [4].

With age, there is dysregulation of a number of neurohumoral systems contributing to NCVI: decreased baroreflex sensitivity; diminished heart rate responses to orthostatic change and other stress responses; impaired  $\alpha$ -adrenergic vasoconstriction — particularly in the splanchnic system, which is responsible for one-third of venous pooling during standing; decreased parasympathetic tone, resulting in less cardioacceleration and vagal withdrawal on standing; proneness to dehydration due to impaired thirst response; inability of the kidney to conserve salt and water during times of relative dehydration; reduction in plasma renin; angiotensin and aldosterone levels; elevation in natriuretic peptides; an increase in cardiac “stiffness” with impaired diastolic filling; and reduced stroke volume resulting in decreased venous return during standing.

Most of the symptomatic consequences of NCVI are due to these neurohumoral changes and usually present during orthostatic change and mobilization.

Cerebral blood flow (CBF) is regulated by the effect of blood gases and neuronal metabolism, the ANS, and cerebral autoregulation [5]. Brain perfusion is highly



**Figure 2:** Stylized representation of the (a) classical and (b) contemporary relationships between mean arterial pressure and cerebral blood flow — i.e. autoregulation [5].

a) Classical view of cerebral autoregulation by Lassen et al. [7].

b) Contemporary view of cerebral autoregulation by Tan et al. [8].

sensitive to changes in PaCO<sub>2</sub>, and increased PaCO<sub>2</sub> produces smooth muscle relaxation and increased flow. Cerebral autoregulation (CA) refers to the delicate process of maintaining stable cerebral perfusion against changes in systemic BP [6].

Lassen [7] constructed a plot of average BP and total blood flow from seven studies involving 11 different BP levels and this revealed a plateau wherein CBF remains relatively unchanged within the mean arterial BP range of 60 to 150 mmHg. Recent data [8] shows a smaller plateau indicating a more pressure-passive CBF than conventionally believed, with evidence that the brain defends more effectively against acute hypertension (HTN) than hypotension (Figure 2) [5].

With aging, there is a progressive reshaping of the CA curve from a sigmoid curve to a straight line, implying that any abrupt change in BP will result in an appreciable change in CBF [9]. Sub-threshold BP may lead to cerebral hypoperfusion and consequently ischemia, resulting in cerebral damage and vascular cognitive impairment [10].

## COGNITIVE IMPAIRMENT AND DEMENTIA

The majority of adults experience some decline in cognitive function over the course of their lifetime. Mild cognitive impairment (MCI) is defined as cognitive function worse than normative data for a set age and educational level, yet not severe enough to meet the criteria defining dementia [11]. Functional ability remains preserved, thus differentiating it from dementia, in which there is functional impairment.

Although patients with MCI have a greater risk of developing dementia compared with the general population, studies report substantial variability [12]. Reported annual rates of MCI conversion to dementia span from less than 5 percent [13] to 12 to 20 percent [14], depending on the country and population studied.

Our studies have shown that patients with MCI have a higher prevalence of NCVI and autonomic dysfunction than controls, and that the presence of NCVI at least doubles conversion rates to dementia [15]. The two most common forms of dementia are Alzheimer's dementia (AD) and vascular dementia (VaD).

AD is classified as a progressive neurodegenerative disorder with histopathological hallmarks of amyloid plaques, neurofibrillary tangles of hyperphosphorylated tau, and cerebral amyloid angiopathy [16]. Other mechanisms might contribute to sporadic AD, such as those suggested by the vascular hypothesis that states that cardiovascular diseases are important causal or contributing factors in AD, with HTN regarded as the most powerful vascular risk factor for AD [17,18]. Cognitive features of early AD include anterograde memory loss, visuo-spatial dysfunction and mild anomia.

VaD occurs as a result of cerebrovascular insults in cortical and subcortical areas responsible for memory and executive function. However, there are no neuropathological criteria to indicate the extent of vascular changes on imaging required to make a diagnosis [16]. Cerebrovascular ischemic abnormalities are often found in conjunction with pathological changes of AD [16]. This co-occurrence of the two disorders is commonly referred to as mixed dementia [19,20].

Certain polymorphisms of the Apolipoprotein E (APOE) gene are associated with both dementia subtypes. Its presence increases the incidence of VaD in post-stroke patients and is a risk factor for cerebral amyloid angiopathy in AD [21].

Dementia with Lewy bodies (DLB) is a progressive, degenerative dementia characterized by the deposition of Lewy bodies in the cerebral cortex. It is characterized by deficits in attention and visuospatial function, fluctuating cognition, recurrent visual hallucinations, and motor features of Parkinsonism. PDD occurs in the setting of well-established Parkinsonism and shares clinical and histopathological features with DLB.

Common to the major types of dementia is a deficit in cholinergic activity in the basal ganglia and neocortex, secondary to loss of cholinergic neurons. This is the focus of conventional pharmacotherapy, which aims to increase the levels of available ACh by inhibiting acetylcholinesterase.

A recent systematic review showed that cholinesterase inhibitors (ChEIs) produced small, short-lived improvements in cognitive function in mild to moderate AD and DLB, but no significant benefit in VaD [22]. ChEIs can exacerbate NCVI as they augment parasympathetic activity causing cardioinhibition and bradyarrhythmia [23]. They also increase the risk of syncope [24].

## HYPERTENSION AND COGNITION

The association of BP with cognitive decline and dementia is complex, and systematic reviews have suggested that this association varies considerably with age and duration of follow-up [25,26]. Overall, the association is more evident in studies with a long follow-up and with BP measured in midlife [27]. Several longitudinal studies have reported an adverse effect of midlife HTN on late-life-related cognitive impairment and dementia [28-35]. In contrast, studies with a short follow-up or cross-sectional studies on BP measured in late life are less consistent [27].

In these studies, HTN does not seem to be associated with an increased risk of dementia and some studies reported a protective effect of hypertension [34,36-42]. It is of note, however, associations with late-life BP measurements may be modified by survival bias due to the premature death of individuals exposed to high BP levels [27]. Other studies report a "U-shaped" relationship between systolic blood pressure (SBP) and cognitive function, such that both low (SBP < 130 mmHg) and high SBP (SBP > 160 mmHg) are associated with cognitive impairment and dementia [43-46].

HTN is an important risk factor for progression of cerebral small vessel disease, markers of which include white matter lesions (WMLs), covert brain infarcts, microbleeds, and dilated perivascular spaces [27]. According to a meta-analysis in 2010 [47], increasing WML burden is associated with a two- to three-fold in-

creased risk of stroke and dementia (mainly VaD), and also predicts an increased risk of cognitive decline and MCI. Cerebral small vessel disease ultimately results in cerebral hypoperfusion, and hypoxia driven pathways may potentiate cerebral amyloid accumulation and tau protein phosphorylation [48].

Chronic HTN also causes vascular remodeling and hypertrophy with loss of arterial elasticity and compliance. This results in increased myogenic tone affecting cerebral autoregulation and necessitating higher perfusion pressures to maintain the same level of CBF [49]. This diminished autoregulatory capacity means the brain is more vulnerable to ischemic insults when SBP dips below a critical threshold for maintaining perfusion [10].

Given the association between midlife HTN and cognitive decline, it is a reasonable hypothesis that the use of antihypertensive drugs would reduce this risk. Certain anti-hypertensives, including calcium channel blockers, have neuroprotective properties that may even reduce the risk of AD, independent of their effects on BP [50]. The target BP in later life that ensures adequate perfusion while preventing cognitive decline is less clear [51].

Recent research has suggested considerably lower goals in target BP than previously recommended [52]. However, there is evidence that antihypertensive drug therapy needs to be individualized to each person and that not only chronological age, but also biological age, needs to be taken into account, as well as the existing degree of systemic and cerebrovascular damage [53].

Excessive BP lowering in older patients with cognitive impairment and dementia may even be harmful as shown by Mossello et al. [54], who found that low daytime SBP was independently associated with greater progression of cognitive decline in these patients on antihypertensive drugs. Tinetti et al. additionally showed that antihypertensive drugs are associated with an increased risk of serious fall injuries [55].

## HYPOTENSION AND COGNITION

Chronically low BP in elderly people can result in fatigue, dizziness, and falls. Essential hypotension refers to a chronic condition of inappropriately reduced BP independent of the presence of any other pathological factors [56], and may be secondary to low fluid intake or low body weight. Hypotension contributing to cerebral hypoperfusion may also be secondary to reduced cardiac output mediated by left ventricular dysfunction, arrhythmias, or valvulopathies [57].

As mentioned previously, CA does not necessarily protect the brain from chronic low BP in aging. Highly metabolically active neurons in the hippocampus are particularly vulnerable to impaired CBF not meeting energy demands and undergo oxidative and endoplasmic reticulum stress, resulting in decreased adenosine triphosphate (ATP). This compromises brain cell survival and results in progressive cognitive decline [57].

**Table 1: Studies investigating hypotension and cognitive impairment**

Author and study setting	Participants and follow-up	Main conclusions
Mossello et al. [54] 2015	172 memory clinic patients of mean age 79 followed up for nine months	Patients with low daytime SBP treated with antihypertensive drugs had greater progression of cognitive decline.
Waldstein et al. [38] 2005 Baltimore Longitudinal Study of Aging	847 people of mean age 70 followed up for 11 years	Both high and low DBP was associated with poorer performance on tests of executive function and confrontation naming.
Kahonen-Vare et al. [58] 2004 Helsinki Aging Study	650 people aged 75 to 85 followed up for 10 years	Low MMSE scores were associated with low BP at baseline.
Pandav et al. [59] 2003 The Indo-US Cross National Dementia Epidemiology Study	4,810 people aged >55	In both Indian and the United States' samples, lower DBP was inversely related to cognitive impairment, although not significantly in the latter.
Bohannon et al. [45] 2002 Duke Established Populations for Epidemiological Studies of the Elderly	2,260 African-American and 1,876 white people aged 65 to 105 followed up for three years	Decline in cognitive function was associated with extremes of SBP (<110 mmHg and >165 mmHg) in older white people.
Zhu et al. [60] 1998 Kungsholmen Project	924 people aged ≥75 followed up for three years	There was a correlation between SBP reduction and cognitive decline in women, which was not accounted for by other factors.
Guo et al. [43] 1997 Kungsholmen Project	1,736 people ages 75 to 101 followed up for three years	Individuals with a baseline SBP <130 mmHg had odds ratio 1.88 for cognitive impairment (MMSE <24) compared with those with SBP 130-159 mmHg.

Numerous studies [38,43,45,54,58-60] have provided convincing evidence for the association of hypotension with cognitive impairment (Table 1), especially with regards to memory and attention [56].

Several longitudinal population studies [61-72] have identified that lower BP values may be a risk factor for later-life dementia (Table 2). A systematic review and meta-analysis of population studies examining this relationship concluded that the pooled estimates from included studies demonstrated an increased risk for AD with lower diastolic blood pressure (DBP) values in later life [73].

While low DBP is a risk factor for dementia, overall low BP may also occur as a secondary phenomenon to disease progression. In the French Research Programme on AD (REAL-FR), Hanon et al. [74], noted a significant decrease in both SBP and DBP from baseline to follow-up a year later, and patients with the worst cognitive impairment showed a larger decrease in BP. The retrospective study by Burke et al. [75] on autopsy-proven patients with AD found sustained BP

reduction beginning in the third to fourth year after diagnosis. The authors postulate that BP is altered in AD as a consequence of neuronal degeneration. It may also be related to diet changes and weight loss associated with dementia, or a deficit in central neurotransmitters that regulate BP [76].

## ORTHOSTATIC HYPOTENSION AND COGNITIVE IMPAIRMENT

Classical OH is defined by consensus statement as a sustained reduction in SBP of at least 20 mmHg and/or DBP of 10 mmHg within 3 minutes of standing [77]. Prevalence of OH varies widely depending on the population characteristics (e.g. age range, institution, use of concomitant medications) and the methodology used. It has a prevalence of 16.2 percent in those older than age 65 living in the community [78], and its incidence increases exponentially with age, most commonly affecting men [79,80] and patients in institutions such as nursing homes.

**Table 2: Longitudinal studies investigating hypotension and dementia**

<b>Author and study setting</b>	<b>Participants and follow-up</b>	<b>Main conclusions</b>
Joas et al. 2012 [61] Prospective Population Study of Women in Gothenburg	1,462 women of mean age 45 followed up for 37 years	A decline in SBP during later part of study was observed in those who developed dementia regardless of anti-hypertensive drugs.
Qiu et al. 2009 [62] Kungsholmen Project, Sweden	422 people aged >75 followed for nine years	Low DBP (<70 mmHg) was associated with a multiaadjusted hazard ratio of 2.13 for dementia and 2.16 for AD. BP declined substantially over about three years before dementia became evident.
Stewart et al. 2009 [63] Honolulu Heart Program/Honolulu-Asia Aging Study	1,890 Japanese-American men followed up for 32 years of mean age 83 at end of study	Men who developed dementia had a greater increase, followed by a greater decrease in SBP. Both were modified by antihypertensive drugs.
Razay et al. 2009 [64] The OPTIMA Longitudinal Study	477 people followed up for five years	High (110 mmHg) and low (60 mmHg) DBP levels were related to faster cognitive decline in AD patients.
Nilsson et al. 2007 [65] OCTO-Twin Study, Sweden	599 people aged ≥80 followed up for four years	Low SBP and DBP were associated with a higher incidence of AD.
Qiu et al. 2003 [66] Kungsholmen Project, Sweden	1,270 people aged >75 followed up for six years	Both very low DBP (≤65 mmHg) and very high SBP are associated with an increased risk of AD and dementia.
Qiu et al. 2003 [67] Kungsholmen Project, Sweden	966 people aged >75 years followed up for six years	APOE-4 allele, high SBP (>140 mm Hg), and low DBP (<70 mmHg) were associated with an increased risk of AD.
Verghese et al. 2003 [68] Bronx Aging Study, US	488 community volunteers aged ≥75 followed up to 21 years with a mean follow-up of 6.7 years	Individuals with a DBP (< 70 mmHg) were twice as likely to develop AD when compared to those with a DBP (>90 mmHg).
Ruitenbergh et al. 2001 [69] Rotterdam Study and Gothenberg H-70 Study	6,668 people aged ≥55 from Rotterdam Study and 382 people aged 85 from Gothenburg H-7 Study followed up for an average of 2.1 years	There was an inverse association between BP and dementia risk in elderly persons on antihypertensive drugs. Persons demented at baseline had stronger BP decline during follow-up than those who were not demented.
Morris et al. 2001 [70] East Boston Study, US	378 people aged ≥65 followed up for four years	DBP (<70 mmHg) was associated with an increased risk of AD.
Guo et al. 1999 [71] Kungsholmen Project	304 people aged 75 to 96 followed up for three years	Those with SBP (≤140 mmHg) had a significantly higher risk of dementia and AD.
Skoog et al. 1999 [72]	382 people aged 70 to 75 followed for 15 years	BP declined in the years preceding onset of dementia and was similar to, or lower than, that in non-demented patients.

The above definition is based on auscultatory and oscillometric BP measurement, but recently more accurate phasic beat-to-beat measurement using digital photoplethysmography has been used. This allows the further identification and possible classification of initial OH, a transient BP decrease ( $> 40$  mmHg SBP and/or  $> 20$  mmHg DBP) within 15 seconds of standing, with symptoms of cerebral hypoperfusion [81].

In contrast to initial OH, delayed OH — symptomatic OH that occurs 3 minutes after standing — is characterized by a late drop in BP [82]. Symptoms of OH include lightheadedness, weakness, presyncope, visual and hearing disturbances, neck pain, chest pain, falls, and syncope. Orthostatic intolerance (OI), or subclinical OH, is defined as a systolic drop less than 20 mmHg, or a diastolic drop less than 10 mmHg, with a variety of orthostatic symptoms such as those named above [78].

Neurogenic, hypovolemic, and drug-induced OH comprise the major subtypes of OH. Neurogenic OH is caused by primary dysautonomia or can be secondary to hereditary, inflammatory, infectious, or metabolic diseases. OH is associated with a significant increased risk for overall mortality [83]. Patient education regarding aggravating factors, increased fluid and salt intake and physical counter maneuvers are imperative in the management of OH. Failing this, pharmacological options include midodrine, pyridostigmine, droxidopa, and fludrocortisone [84].

While OH is common in patients with a diagnosis of dementia, the association between OH and cognitive decline and impairment is less clear and their causal relationship remains controversial [85]. It is not clear whether OH and cognitive impairment coexist owing to underlying neurodegeneration at multiple neural domains, or whether cardiovascular dysautonomia exerts negative effects on cognitive outcome through hypotensive and hypertensive peaks, which in turn increase the risk of brain ischemia [86].

A number of studies [15,87-98] (Table 3) have investigated the association, although results have been mixed, which may be because of small sample size [15,90,91,95,97], variable age range of sample [91,93], lack of adjustment for potential confounding factors [91,92], or use of cognitive tests with low sensitivity and specificity [87,90,94-96].

OH can be associated with supine HTN [99], representing extremes of BP variability and baroreceptor dysfunction. In a longitudinal study of aging in Ireland (TILDA), we have shown that OH, coupled with supine HTN, is associated with poorer performance on cognitive tasks [88]. Nocturnal hypertension refers to reversal of physiological BP circadian rhythm [86]. It is common in PD patients [100], especially those with OH, and may be secondary to sympathovagal disruption [101].

Collins et al. [102] demonstrated that patients with MCI had significant autonomic dysfunction compared with controls. This was predominantly parasympathetic as

evidenced by deficits in heart rate responses to cardiovascular reflex tests and reduced high frequency on heart rate variability (HRV). Sympathetic activity was also somewhat reduced and patients with MCI demonstrated a significantly greater orthostatic fall in SBP than controls.

HRV was independently associated with poor global cognitive performance in a large representative population sample of community-dwelling, non-demented persons older than 50 [103]. This further strengthens the relationship between autonomic dysfunction and cognitive disorders. The concept of orthostatic HTN, an elevation in BP on standing [104], has not been studied so well. It has, however, been associated with greater leukoariosis and silent infarction on MRI brain imaging [98,105].

## ORTHOSTATIC HYPOTENSION AND DEMENTIA

Autonomic dysfunction is common in all of the dementia subtypes [106,107], but particularly in PDD and DLB [106,108]. It is the second-most common dysautonomic feature after urinary dysfunction [109,110].

In AD, it has been hypothesized that the deficit in cholinergic function could lead to autonomic dysfunction [111]. There is evidence that cortical perivascular cholinergic nerve terminals are largely lost resulting in impaired vasodilation and reduced CBF; the cholinergic-vascular hypothesis [112,113]. Also, various central nervous system structures affected in AD are implicated in ANS regulation, such as the hypothalamus, locus coeruleus, cerebral neocortex, insular cortex, and brainstem [114].

Braak [114] speculated that these structures may be affected by neurodegeneration in a preclinical stage and that autonomic dysfunction may be present before the onset of clinical symptoms of AD. It has also been suggested that the presence of autonomic cardiac dysfunction in AD patients might be due to a cholinergic deficit in the peripheral ANS, as HRV showed a significant correlation with blood levels of acetylcholinesterase activity [115].

A meta-analysis in 2011 reported a prevalence of OH in 30 percent of Parkinson's disease (PD) patients [116], and it has been reported in up to 50 percent of DLB patients [117]. Most epidemiological studies probably underestimate the prevalence of cardiovascular autonomic dysfunction as they are based on clinical symptoms of OH, rather than more accurate measurements of SBP or DBP change with standing [86].

Involvement of the sympathetic nervous system in PDD and DLB is likely related to both CNS damage as well as postganglionic sympathetic lesions [118]. Lewy body deposits have neurotoxic effects on high metabolic rate neurons [119]. This dual involvement could account for the abnormal failure to release appropriate amounts of norepinephrine on standing,

**Table 3: Studies investigating orthostatic hypotension and cognitive impairment**

<b>Author</b>	<b>Study design</b>	<b>Number of participants</b>	<b>Main conclusions</b>
Hayakawa et al. [15] 2015	LS	225	OH is more common and more prolonged in MCI. People with MCI and a SBP deficit >30 percent 30 seconds after standing are twice as likely to convert to dementia.
Elmstahl et al. [87] 2014	Cohort	1,480	OH and OI are risk factors for cognitive decline.
Frewen et al. [89] 2014	CS	5,936	OH is associated with poorer global cognitive function and memory independent of potential confounders in women.
Frewen et al. [88] 2014	CS	4,690	OH coupled with supine HTN is associated with lower cognitive performance.
Schoon et al. [90] 2013	Retrospective cohort	184	Cognitive impairment was not more prevalent in patients with hypotensive syndromes.
Czajkowska et al. [91] 2010	CS	74	Poor BP regulation in response to orthostasis was associated with decreased verbal memory and decreased concentration.
Mehrabian et al [92] 2010	CS	495	Subjects with OH showed poorer cognitive function.
Rose et al. [93] 2010	LS	12,702	OH was associated with less-favorable cognitive function, but this was largely attributable to demographic and cardiovascular risk factors.
Yap et al. [94] 2008	CS and LS	2,321	There was no significant association of OH with cognitive impairment. Hypotensive people with OH were more likely to have cognitive impairment.
Bendini et al. [95] 2007	CS	36	There was no strong causal relationship between OH and cognitive impairment.
Viramo et al. [96] 1999	LS	1,159	OH did not predict cognitive decline during a two-year follow-up.
Elmstahl et al. [97] 1997	LS	33 women	OH is a risk factor for cognitive decline. Elderly women who developed dementia tended to have a larger drop in BP.
Matsubayashi et al. [98] 1997	CS	334	OH was associated with poorer scores on neurobehavioral function tests and more advanced leukoaraiosis on MRI.

- a) CS = Cross sectional study  
b) LS = Longitudinal study



resulting in OH due to pooling of blood in the lower limbs and splanchnic circulation [118].

Sympathetic dysfunction may precede cognitive decline in DLB [120,121] and there appears to be a more significant and prolonged drop of SBP in DLB patients, compared to AD and controls [122].

In general, studies on the relation between cognitive impairment and OH in PD patients reported no differences in global function, but significant differences in single tasks, especially executive tasks. As reported for elderly and demented patients, PD patients with OH were generally older than patients without, and this may contribute to a decline in cognitive function. Despite different disease duration and motor disability, the Mini-Mental State Exam (MMSE) scores were similar in PD patients with and without OH [85].

WMLs in alpha-synucleinopathies (PD, Multi-System Atrophy (MSA) and DLB) have been correlated with more severe NCVI. This raises the question of whether WML are the consequence of chronic alternate hypotensive and hypertensive stress or, alternatively, whether WML involving autonomic networks may cause future development and/or worsening of cardiovascular autonomic failure [86].

## CAROTID SINUS HYPERSENSITIVITY

Carotid sinus hypersensitivity is diagnosed when carotid sinus massage (CSM) of 10 seconds produces either a ventricular pause lasting >3 seconds (cardioinhibitory CSH) or a decrease in SBP of >50 mmHg (vasodepressor CSH) [123], or a combination of both (mixed CSH). It is caused by an abnormal baroreceptor reflex involving cardioinhibition via the vagus nerve and vasodepression secondary to sympathetic withdrawal [124].

CSH may present clinically as falls, presyncope, and syncope in older people, more commonly males [125]. Precipitating factors may include sudden movement of the head and neck [126], e.g. when shaving or compression of the carotid sinus by a tight collar, or less frequently by a neck tumor.

Symptomatic CSH is believed to be secondary to impaired cerebral autoregulation [127]. When CSH is associated with syncope it is known as carotid sinus syndrome (CSS). Syncope in CSS typically has little or no prodrome [124], and is associated with appreciable morbidity [1]. It frequently coexists with other dysautonomic hypotensive disorders such as OH and VVS, making its diagnosis elusive and impeding appropriate intervention.

While dual chamber pacing is indicated for cardioinhibitory CSS, treatment for vasodepressor CSS is less satisfactory. Similar to OH, first-line management includes reduction in antihypertensive drugs and advice on increased fluid intake. Failing this, pharmacological treatment may be considered.

CSH is associated with neurodegenerative dementias including AD, DLB and PDD [128-131]. The prevalence of cardioinhibitory CSH is particularly high in DLB — up to 32 percent compared with 11.1 percent in AD, and 3.2 percent in case controls. In addition, patients with DLB have greater heart rate slowing (>2 seconds) and decreases in SBP (>20 mmHg) than those with AD or controls during CSM [129].

Miller et al. [132] found increased tau accumulation in baroreflex associated medullary nuclei in CSH patients, and suggested that this accumulation may be involved in the pathogenesis of CSH and precipitation of CSH symptoms. This is of particular interest as the selective degeneration of medullary autonomic nuclei is implicated in the pathogenesis of PDD, DLB, and AD. Alpha-synuclein accumulates in autonomic nuclei in early asymptomatic stages of PD and DLB [133], while medullary autonomic and reticular formation nuclei show a selective vulnerability to tau and amyloid plaques in AD [134,135].

Also of note, the density of deep WMLs on Magnetic-Resonance Imaging (MRI) correlate with the degree of hypotension induced during CSM in patients with DLB, supporting a causal link between episodic hypotension and cerebral small vessel damage [136].

CSS is an important diagnosis in unexplained falls in the elderly, especially in patients with cognitive impairment, when frequently the history is unreliable, or there is retrograde amnesia for the loss of consciousness and there is lack of a witness [137].

## POSTPRANDIAL HYPOTENSION

Classically, PPH has been defined as a decrease in SBP of  $\geq 20$  mmHg or a decrease below 90 mmHg from a pressure of  $\geq 100$  mmHg within two hours after a meal [138]. Studies have shown the prevalence in institutionalized elders is about 25 to 38 percent [139-141]. PPH in older nursing home residents was associated at long-term follow-up with a higher incidence of falls, syncope, new coronary events, new stroke, and total mortality [142]. It is also associated with asymptomatic cerebrovascular damage in hypertensive patients [143], and is a risk factor for asymptomatic lacunar infarction [144].

Risk factors include polypharmacy, diuretics, carbohydrate-rich meals, hot meals, diabetes, PD, and HTN [145]. PPH appears to result from an inadequate sympathetic response to the normal physiologic post-meal decrease in BP rather than to an exaggerated amount of splanchnic pooling [145]. Vasodilator effects of insulin and other gut peptides, namely neurotensin and VIP, contribute to postprandial BP drops [146].

Preliminary cross-sectional studies reported PPH in 48 percent of dysautonomic PD patients [147], but Idiaguez et al. [148] reported no consistent association between OH or PPH and cognitive deficits in PD. In another small study by the same author, seven out of 10

patients with AD were found to have PPH, compared to six out of 23 controls [149].

Conflicting evidence regarding episodic hypotension and cognitive impairment was reported by Schoon [90], who investigated the association of OH, PPH, and CSH with cognitive impairment in 184 elderly patients presenting with falls.

It was found that patients with one or more hypotensive syndromes were not likely to have cognitive impairment, thus contradicting current data that hypotension is associated with cognitive decline.

## VASOVAGAL SYNCOPE

Syncope is defined as a sudden loss of consciousness due to transient global cerebral hypoperfusion characterized by rapid onset, short duration, and spontaneous complete recovery [123]. As mentioned above, OH, PPH, and CSH may cause syncope if cerebral blood flow is sufficiently compromised.

VVS, also known as the “common faint,” is a type of reflex syncope that is usually triggered by emotion or by orthostatic stress. In the presence of hypertension and atherosclerotic cerebrovascular disease, excessive loss of baroreflex sensitivity leads to dysautonomic responses during prolonged orthostasis (in which blood pressure and heart rate decline steadily over time), and patients become susceptible to VVS [1]. It is the cause of syncope in 20 to 30 percent of older patients with single or recurrent presyncope or syncope [150].

Similar to CSH, the responses in VVS can be inhibitory or vasodepressor or both. It is diagnosed using a head-up tilt test with continuous blood pressure and heart rate monitoring.

The European Society of Cardiology has recommended that syncope be considered causal in patients with unexplained falls [123], a frequent presentation in elderly people causing major mortality and morbidity [151]. Syncope and unexplained falls were shown to be independently associated with poorer cognitive performance among individuals aged  $\geq 50$  in the TILDA cohort [152].

## CONCLUSION

There is a discernible and intricate association between NCVI, the aging brain and cognition. The direction of causality is less apparent. Given the above evidence, it is possible that NCVI contributes to cognitive decline. Equally, NCVI may be a consequence of a neurodegenerative process; indeed they may even be parallel age-related pathological processes. Future research should focus on a deeper understanding of phenotypes to better guide treatment of HTN and other clinical components of NCVI in patients with cognitive impairment and dementia.

Regardless of the direction of causality, recognition of their coexistence is important particularly in relation to prescribing in older adults with dementia. The use of

ChEIs should be carefully considered and initiated in the appropriate patient group, while concomitantly minimizing risk of syncope. Similar caution should be adopted with antihypertensive drugs, tailoring suitability, and avoiding excessive BP lowering, which contributes to falls risk and exacerbates cognitive decline.

In summary, enhanced understanding of the link between NCVI and cognition will improve overall management of these patients with disrupted homeostatic adaptive capacity and vulnerability to physiological stress.

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