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COMMENT

Orthostatic hypotension with nondipping: phenotype of neurodegenerative disease

Michiaki Nagai[1] · Masaya Kato[1] · Keigo Dote[1]

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More than 40 years ago, Jim Rafferty and his group at Northwick Park Hospital in London and John Floras and Peters Sleight at John Radcliffe Hospital in Oxford conducted a series of studies using direct intra-arterial ambulatory blood pressure (BP) monitoring (ABPM) for 24 h [1]. In 1982, Pickering regarded that variation in normal circadian BP was characterized by higher levels during daytime and 10 to 20% reduction during sleep [2]. In 1988, since O'Brien et al. first coined the term "dipping", it has been shown that patients with a fall in nocturnal BP ("dipper") and those with sustained elevation of nocturnal BP ("nondipper") have different cardiovascular outcomes [1]. The pathophysiology remains poorly understood.

The paper by Patteta et al. [3] in this issue provides several new insights into the relationship between orthostatic hypotension (OH) and night-time dipping patterns in the 425 geriatric outpatients. OH was observed in 38.1% of patients, who had a significantly higher prevalence of abnormal circadian BP patterns of nondipper and riser than those without OH. In multivariate analysis, orthostatic change in systolic BP (SBP) was significantly inversely associated with day-night SBP change, specifically in patients over 80 years [3]. In an earlier study, abnormal diurnal BP variation was closely associated with abnormal postural BP change in hypertension in the elderly, and there was a significant negative correlation between orthostatic SBP change and the sleep/awake ratio of SBP [4]. The daytime upright position can reduce daytime BP in nondippers and cause partially abnormal diurnal BP variation.

Upon standing, gravitational forces produce a blood volume shift of ~500–800 ml, with venous blood pooling in the lower part of the body. Thus, venous return and stroke volume decrease, and BP consequently falls [5]. In response to this stress, arterial baroreflex buffering mechanisms send afferent information to the brainstem to activate the sympathetic vasoconstrictor response to raise BP and to inhibit cardiovagal outflow to increase the heart rate [5, 6].

On the other hand, elevated BP activates baroreceptors in the carotid sinus [6]. The afferent signal is transmitted via the glossopharyngeal nerve (IX) and activates the solitary tract nucleus (NTS) of the brain stem. This activates caudal ventrolateral medulla (VLM) neurons, which provide inhibitory input to the rostral medulla oblongata ventrolateral area, the region where sympathetic nerve activity occurs. This reduces sympathetic tone carried through the preganglionic fibers in the medial lateral column of the spinal cord, decreases the function of the postganglionic efferent fibers that innervate the heart and blood vessels, and normalizes BP [6]. Baroreceptors relay information to the NTS and VLM for further processing in the higher-order autonomic nervous network, including the insular cortex, cingulate cortex, and amygdala [7].

Synucleinopathy is a neurodegenerative disorder characterized by abnormal intracellular deposition in specific areas of the central and/or peripheral nervous system and aggregation of the misfolded form of the protein α-synuclein [5, 6]. In the spectrum of Lewy body diseases, which include Parkinson's disease (PD) and dementia with Lewy bodies (DLB), autonomic failure is due to degeneration of peripheral postganglionic noradrenergic nerve fibers. In multiple system atrophy (MSA), α-synuclein deposits form glial cytoplasmic inclusions and cause neuronal degeneration in central autonomic pathways [5].

In PD and DLB, neurogenic OH is primarily caused by denervation of the peripheral sympathetic nerves; in MSA, degeneration of the central autonomic pathway is thought to

✉ Michiaki Nagai
nagai10m@r6.dion.ne.jp

[1] Department of Cardiology, Hiroshima City Asa Hospital, Hiroshima, Japan

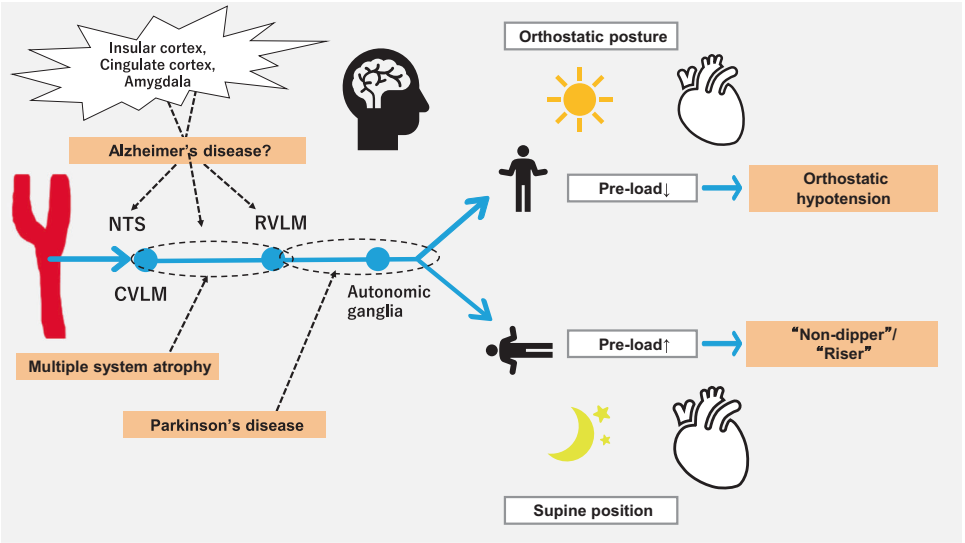

Fig. 1 A possible pathway for the relationship between orthostatic hypotension, nondipping pattern and neurodegenerative diseases. NTS nucleus tractus solitarius, RVLM rostral ventrolateral medulla, CVLM caudal ventrolateral medulla. Reproduced from Biaggioni et al. [3] with permission from the manufacturer

lead to neurogenic OH [8]. Neurogenic OH is the consequence of impaired sympathetic vasoconstriction due to defective norepinephrine release from postganglionic neurons. Patients with PD, DLB, and MSA show supine hypertension associated with neurogenic OH. ABPM helps in detecting daytime BP fluctuations, hypotension, and nighttime nondipper or riser patterns [5]. Preload increases with the supine position at night, and BP rises as cardiac output increases. However, in these neurodegenerative patients, BP continues to rise even during sleep due to impaired central and peripheral autonomic compensation (Fig. 1). Although no neurological assessments were performed in the study reported by Patteta et al. [3], OH patients with nondipper or riser patterns may share the pathophysiology associated with synucleinopathy.

In the Jichi Medical School ABPM study Wave 2 Core, ambulatory BP was an independent indicator of cerebral atrophy and cognitive function in hypertension in elderly subjects. Those with a nondipper phenotype appeared to have a small brain volume and diminished cognitive function [9]. Alzheimer's disease and vascular dementia are the two most common forms, but there is considerable overlap, and mixed patterns are not uncommon. Both of these forms are associated with hypertension. DLB is the second most common degenerative form, though its association with hypertension remains unclear [10]. Recently, the proportions of hypertension in PD, DLB, and MSA were reported to be 23.7% [11], 74.9% [12], and 28.7% [13], respectively. Furthermore, hypertension was significantly associated with the incidence of PD [14], and it appears that differences in orthostatic BP change and nocturnal BP dipping occurred depending on the prognosis of MSA patients [13]. In recent years, reports of OH and nondipper patterns in patients with Alzheimer's disease have accumulated [15]. In addition to the nucleus in the brain stem being associated with the autonomic nervous system, the relationship between the higher-order autonomic nervous network and OH and nondipper patterns will be clarified.

To date, there have been few reports assessing relationships of nocturnal BP dipping patterns and orthostatic BP changes with neurodegenerative diseases. The data presented in the study by Patteta et al. [3] thus make an important contribution, provided that the results are considered within the context of the precise pathophysiology underlying neurodegenerative diseases. It is possible that some, if not all, nondipping patterns are caused by neurodegenerative diseases, and future research is expected to elucidate the pathophysiology of nondipping, which has been unresolved until now.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

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