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EDITORIAL

Recent updates in autonomic research: orthostatic hypotension in prodromal synucleinopathy; longitudinal morbidity and mortality in orthostatic hypotension with and without supine hypertension; a cardiac vagal sensory system underlying reflex syncope

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Prevalence of orthostatic hypotension in isolated REM sleep behavior disorder in the NAPS2 cohort

Isolated rapid eye movement (REM) sleep behavior disorder (iRBD) is a prodromal condition, with iRBD demonstrating a propensity to phenoconvert to synucleinopathies, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and multiple system atrophy (MSA) [1]. In parallel, orthostatic hypotension (OH) stands out as a prevalent non-motor manifestation within the spectrum of synucleinopathies [2]. Despite the close association and the prodromal significance, a paucity of large prospective investigations has hindered the determination of OH prevalence in iRBD.

The North American Prodromal Synucleinopathy (NAPS) consortium systematically enrolled individuals with polysomnography-confirmed RBD across nine centers in the USA and Canada. A recent study of the NAPS cohort has contributed pivotal insights into the prevalence of OH in iRBD [3]. Among the 361 participants in the cohort, 340 underwent assessment of orthostatic vitals (5-min supine rest, 3-min active standing). Employing consensus criteria for classical OH [2], a sustained drop of 20 mm Hg in systolic blood pressure (SBP) or 10 mm Hg in diastolic blood pressure (DBP) within 3 minutes of upright posture, 93 participants (27%) met criteria for OH. Notably, within the OH cohort, 72 individuals (21.1%) had evidence of impaired heart rate (HR) augmentation, suggestive of a neurogenic cause of OH ($\Delta HR/\Delta SBP \leq 0.5$). In addition, a noteworthy observation was the presence of supine hypertension (SH, $SBP \geq 140$ mmHg and/or $DBP \geq 90$ mmHg [4]) in 72% of OH patients. Strikingly, in comparing iRBD participants with and without OH, there was no significant difference in autonomic symptoms reported in daily life, including in the cardiovascular domain, as assessed by total and domain subscores of the Scales for Outcomes in Parkinson's Disease-Autonomic Function (SCOPA-AUT).

This study contributes substantial epidemiological insights into OH prevalence in iRBD. A quarter of iRBD patients exhibit OH of any kind, with one-fifth demonstrating bedside evidence of neurogenic OH. Use of the consensus definition may underestimate OH prevalence, considering the recognition of delayed OH occurring beyond 3 min of upright posture [5]. Given the longitudinal objective of understanding pathways of phenoconversion to specific synucleinopathies, the identification of individuals with delayed OH assumes significance, given the eventual emergence of classical OH in most patients with delayed OH and the association of combined presence of RBD and OH (of any type) increasing odds of motor phenoconversion in patients with pure autonomic failure [6]. Exploring emerging biomarkers such as cardiac sympathetic neuroimaging, alpha-synuclein oligomer conformation or presence/distribution on skin biopsy, and neurofilament light chain levels in cerebrospinal fluid will be pivotal in gaining deeper perspectives on phenoconversion in individuals with RBD and OH [7–9, 10]. Furthermore, the high incidence of SH in the OH cohort and the degree of asymptomatic OH in the current study underscore the intricate challenges associated with OH management, as emphasized in a recent viewpoint [11]. Subsequent studies are expected to delve into these crucial

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matters, offering clarification in the realm of management considerations.

Standing low and lying high—do we have our priorities straight?

Supine hypertension (SH) occurs in ~ 50% of individuals with neurogenic orthostatic hypotension (OH) [4]. While SH in autonomic failure is often quite severe, clinical treatment (and research) prioritization traditionally favors OH, due to presumed greater acute risks of syncope and falls [12].This approach has been called into question by some due to findings of poorer long-term outcomes in patients with concurrent neurogenic OH and SH [13]. A recent study by Earle and colleagues in the journal *Hypertension* [14] thickens the plot and further raises questions about clinical and research prioritization related to concurrent OH and SH.

The authors analyzed data from the Atherosclerosis Risk in Communities (ARIC) prospective cohort study, which, starting in the late 1980s, followed middle-aged (45–64-year-old) adults for over 30 years in four U.S. regions. Using data from this cohort, the longitudinal consequences of SH vs. standing hypotension (mean standing SBP or DBP of ≤ 105/65 mmHg) were compared in individuals with and without baseline OH. *Note*: This review only highlights study findings related to OH. Expert panel-adjudicated outcomes of interest were cardiovascular (heart disease, stroke, heart failure), non-cardiovascular (falls, syncope), and all-cause mortality. The analysis included 546 individuals with OH (56% female; mean age 57.5 years) of whom 58% had SH, 21% had standing hypotension, and 7.5% had both. Covariate-adjusted Cox hazard ratio (HR) models first compared outcome risks of SH to standing hypotension and second tested outcome risk for each OH phenotype (e.g., with or without SH, or standing hypotension). The authors found that those with OH and SH, compared to OH with standing hypotension, had a greater risk of heart disease (HR 1.28 vs. 0.87; $p = 0.028$), heart failure (HR 1.71 vs. 1.06; $p < 0.001$), and all-cause mortality (HR 1.42 vs. 1.07; $p = 0.018$). Interestingly, falls and syncope were equally likely between those with OH and SH and individuals with OH and standing hypotension. In computing outcome risk among individual OH phenotypes, those with OH and SH, but no standing hypotension, had the greatest magnitude of cardiovascular risk (heart disease HR = 2.09, heart failure HR = 2.74, stroke HR = 2.65), though OH with standing hypotension did raise risk of heart disease (HR = 1.49) and heart failure (HR = 1.93). For non-cardiovascular risks, OH with SH, without standing hypotension, was the only OH phenotype conferring fall risk (HR = 1.57) and had the highest magnitude risk of syncope (HR = 1.89). All-cause mortality risk was greatest in those with all three phenotypes (OH, SH, and standing hypotension; HR = 2.12).

This study provides further evidence that SH, when concurrent with OH, contributes heavily to poor cardiovascular outcomes, increases mortality risk, and equally raises risk of falls and syncope, compared to OH with standing hypotension. However, these findings do not immediately generalize to patients with autonomic failure. The OH cohort was 'younger' at baseline than typical autonomic failure patients and OH was not defined as a *sustained* blood pressure fall. In addition, while mean SBP falls were not reported, comparisons of supine and standing measures suggest they were likely lower in magnitude than what typically occurs in neurogenic OH. Nevertheless, these findings are strikingly similar to a pivotal study by Palma et al. [13], who found neurogenic OH with SH was associated with greater target organ damage, cardiovascular risk, and earlier death than OH alone. Further replication of these converging findings is necessary to better inform this treatment dilemma. Ultimately, trials investigating differential or combined interventions on neurogenic OH and SH are imperative.

Old reflex, new tricks—vagal sensory neurons and neurally mediated syncope

Syncope is a transient loss of consciousness and postural tone associated with systemic hypotension and cerebral hypoperfusion that rapidly resolves with recumbency. Almost half of all individuals will experience syncope at least once, and it is an incredibly common reason for emergency room visits and/or referrals to cardiology or autonomic clinics [15]. Neurally mediated syncope (NMS), the most common type, typically involves a paroxysmal fall in both heart rate and blood pressure due to reflex withdrawal of sympathetic vasomotor tone and increased parasympathetic cardioinhibition [16]. Despite its clinical importance, the neurophysiologic mechanisms underlying NMS are poorly understood.

The best-known mechanistic theory for NMS, the Bezold–Jarisch Reflex (BJR), came about from experiments done in the mid-late 1800s and 1930s, whereby intravenous veratrum alkaloid injections caused a triad of bradycardia, hypotension, and respiratory suppression [17]. Crucially, the reflex requires a functional central and peripheral cardiovagal system. The BJR is proposed to result from impaired cardiac filling, perhaps from venous pooling, that causes a hypercontractile state and activation of stretch-sensitive afferent vagal sensory neurons (VSNs) that *somehow* mediate an NMS event. Lovelace and colleagues, in the journal *Nature* [18], present a *tour-de-force* characterization not only of the entire BJR neuroanatomical arc but also provide tantalizing evidence of a central, subcortical circuit mediating

syncope induction and duration *in parallel* with cerebral hypoperfusion.

Using a pre-existing database of RNA sequenced murine nodose ganglia, the team first uncovered a transcriptomic cluster related to neuropeptide Y receptor Y2 (NPY2R) separate from those related to PIEZO2 baroreceptors. Tract tracing studies led to discovery of NPY2R vagal afferents originating in cardiac ventricles that, in contrast to afferent aortic arch VSNs, project to the area postrema far more than the solitary nucleus. In addition, this system was anatomically separate from other VSNs projecting from the aorta, lung, and gut. A complicated series of experiments involving optogenetics, echocardiography, and laser Doppler flowmetry of the brain showed that stimulating the NPY2R system reproduced the BJR triad, reduced cardiac output, caused cerebral hypoperfusion, and after ~5 s led to behaviors consistent with syncope (e.g., loss of tone, pupillary dilation, eye roll). Ablation of NPY2R vagal neurons abolished these responses without affecting resting physiology. Intravenous atropine administration coincident with NPY2R stimulation delayed onset of the BJR physiology, improved cerebral perfusion, and delayed syncope. Scalp EEG and a novel, large-scale neural depth recording system (>20 cortical and subcortical sites) showed that NPY2R stimulation caused a transient increase in neural activity followed by profound suppression. A notable exception was the hypothalamic periventricular zone, which *increased* its activity earlier than any other structure and was tonically active during NP2YR stimulation. Inhibiting activity of the periventricular zone prolonged syncope, while increasing its activity sped up recovery and generally increased global neural activity. Authors speculate that this structure, in conjunction with brainstem viscerosensory integration sites and the area postrema, monitors ongoing peripheral autonomic activity to induce cerebral inactivation and the state of syncope during periods of cerebral hypoperfusion. In other words, there appears to be a subcortical circuit that induces and maintains the cerebral state of syncope *apart* from, but *in relation to*, cerebral hypoperfusion.

This work did not demonstrate that the NPY2R afferents system acts as mechanosensitive sensors of ventricular hypercontractility, as proposed by hypotheses related to the BJR. In addition, this pathway would not explain isolated bradycardic or vasodepressor variations of NMS. However, this study lays ground for further research evaluating whether the NPY2R vagal sensory system or central structures involved in mediating the 'syncope brain state' could be intervened upon to treat what is often a debilitating condition.

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