EDITORIAL

AUTONOMIC NEUROPATHY AND CARDIOVASCULAR DISEASE IN AGING

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Similar to any other systems in the human body, the nervous system undergoes functional decline with aging. These changes have been identified in both central and peripheral components of the nervous systems including the somatic and autonomic branches. Some of the well-known neurological deficits which are associated with aging are hyperopia, presbycusis, diminished sense of taste and smell, loss or impairment of vibratory sense in ankles, and toes, and reduced number of motor end units (1). The autonomic nervous system (ANS) is the nervous system which maintains homeostasis by regulating the function of the heart, the endocrine and exocrine glands, the abdominal viscera, the smooth muscles throughout the body, and the immune system (2) (Figure 1). The ANS is divided into two divisions: the sympathetic thoracolumbar chain outflow and parasympathetic craniosacral outflow (3). Multiple hypotheses have been proposed about changes which occur to the ANS secondary to aging. These appear to be predominantly due to a decline in receptor functionality (4, 5).

Orthostatic Hypotension

Orthostatic hypotension (OH) has been defined as drop in 20 mmHg $\leq$ in systolic blood pressure or 10 mmHg $\leq$ in diastolic blood pressure within 3 minutes of standing from supine position (6-10). It has been shown that orthostatic hypotension prevalence increases with age and it is present in 70% of institutionalized elderly individuals (11). The prevalence of OH among unselected elderly aged 70 $\leq$ is between 6 to 30% (12-14). The occurrence of OH is higher in females than males and more common in blacks than whites (15, 16).

Some long term outcomes of OH are syncope, falls, fracture, and motor vehicle accidents (17). A meta-analysis found that OH was associated with increased mortality (OR 1.5 (1.21-1.81) (18). The mortality increase was greater in those younger than 65 years. Orthostatic hypotension has been associated with chronic heart failure (19), neurodegenerative diseases (20), frailty (21), diabetes (22), hypertension (23), atrial fibrillation (22), coronary artery disease (24, 25), and ischemic stroke (26). OH may or may not be symptomatic, but it technically is different from what has been described as orthostatic intolerance (OI) which is defined as symptomatic hypotension upon upright position (27). Frailty is a common condition in older patients and has been shown to predict OI (OH yes) (26, 29, 30).

Although the majority of patients with OH are either asymptomatic or only experience very few non-specific symptoms, as a result of decreased cerebral hypoperfusion secondary to OH, some patients may experience visual blurring, lightheadedness, dizziness, nausea, fatigue, and syncope (30).

In a normal healthy individual, standing will result in decreased venous return and subsequently reduced stretch of the afferent baroreceptors in both carotid sinuses and aortic arch. These baroreceptors are electromechanical transducers (31). Decreased transmural pressure from the aortic baroreceptor is detected and the signal is transmitted through the vagus nerve (CN X) to the dorsal medullary nuclei bilaterally which are called nucleus tractus solitarius (NTS). Finally, inhibitory interneurons which extend from each NTS nucleus into the rostral ventrolateral medulla result in a vasoconstriction response (31).

Figure 1
Cardiovascular Syndromes Due to Autonomic Neuropathy in Older Persons

The etiology of orthostatic hypotension is divided in two main categories: neurogenic and cardiovascular. The neurogenic causes of OH can be central (also known as primary autonomic degenerative disorders) and peripheral disorders of autonomic nervous systems. Primary autonomic degenerative disorders which disrupt the autonomic portion of the central nervous system (CNS) are multiple-system atrophy, dementia with Lewy bodies, Parkinson's disease, and pure autonomic failure (7). Peripheral disorders of autonomic nervous systems are mainly due to malfunctioning of the small fibers of the peripheral nerves which is typically observed in amyloidosis, diabetes, immune-mediated neuropathies, inflammatory neuropathies, neurotoxins, infection induced neuropathies, paraneoplastic syndromes, porphyria and vitamin B12

Table 1
Medications used for the treatment of orthostatic hypotension

Medication	Mechanism of Action	Dosage Form	Dose & Frequency
Fludrocortisone	Potent mineralocorticoid	Tablet	0.1 - 0.4 mg daily
Midodrine	α 1-Adrenergic agonist	Tablet	5 mg daily
Octreotide	Increase splanchnic and peripheral vascular resistance	Subcutaneously	25 - 200 μ g daily
Pyridostigmine	Acetylcholinesterase inhibitor	Tablet	60 - 240 mg daily
Droxidopa	Precursor synthetic amino acid to norepinephrine	Capsule	100 - 600 mg three times a day
Atomoxetine	Selectively inhibitor of norepinephrine reuptake	Capsule	18 mg daily
Erythropoietin	Increase systemic blood pressure	Subcutaneously	25 - 75 U/kg daily
Desmopressin	V1 and V2 receptor agonist	Nasal spray	5 - 40 μ g daily
Yohimbine	α 2-Adrenergic antagonist	Capsule	5 mg four times a day

deficiency (7, 32).

Because OH is so common all patients over 65 years old and those younger with diabetes mellitus or being treated for hypertension should have their standing blood pressure measured at each visit. OH is only present on about half of the occasions it is measured and it is more common in the morning (33). Medications should also be carefully reviewed for medications that may cause OH (9, 34).

The Valsalva maneuver is a method of evaluation for sympathetic adrenergic dysfunction based on assessment of beat-to-beat blood pressure and heart rate responses to indirectly assess the sympathetic vasoconstrictor function (35, 36). The Valsalva maneuver has been shown to be a reliable assessment for evaluation of the baroreflex sensitivity (37). In a tilt table test the patient is placed in head up position on a tilt table and the table is elevated at an angle of 60 degrees or greater (38). It is rarely necessary to make the diagnosis of OH in older persons.

In the management of OH, the non-autonomic causes such as Addison disease, anemia, dehydration, and polypharmacy need to be examined and treated (23, 28, 39). Volume expansion is the initial step of the treatment. Daily fluid intake of 2 to 2.5 L in addition to sodium intake of 8 to 10 g has been recommended (6). Patient should be advised to avoid alcohol and have small frequent meals (6, 40).

The use of nonpharmacological methods of treatments such as biofeedback and upper body exercises have shown to be noneffective (41). Most commonly used medications for treatment of OH are listed in table I (6, 16, 17, 21, 42-54):

While the majority of these medications have little evidence supporting their use, fludrocortisone and Droxidopa have both been shown to be effective in treatment of OH (37, 49, 55).

Postural Tachycardia Syndrome (POTS)

POTS is orthostatic intolerance that leads to a tachycardia (pulse increase of >30 beats/min or >120/min within 10

minutes of standing) on standing (56,57). It is associated with dizziness, fainting, fatigue, palpitations, sweating, nausea and headaches. Patients with POTS have impairment of memory, attention deficits and executive function as well as anxiety and depressive symptoms (58). POTS is rarely reported in older persons with age of onset being prior to 50 years of age (59). However, it is found in concert with syncope in older persons due to orthostatic cerebral hypoperfusion syndrome (60). It is more common in diabetics with autonomic dysfunction and multiple sclerosis (61, 62). In general, POTS is due either to a decrease in blood return to the brain due to poor sympathetic innervation of peripheral blood vessels leading to sympathetic nervous system outflow leading to cardiac stimulation and tachycardia (63) (Figure 2). This can be aggravated by a decrease in peripheral blood volume. Treatment can be very difficult with the first choice being increasing salt intake, compression stockings, abdominal binding and a nonspecific beta blocker (e.g., propranolol) (64).

Postprandial Hypotension

Postprandial Hypotension (PPH) was initially described in 1977 by Seyer-Hansen as a case report in a patient with a Parkinson disease (65, 66). PPH is defined as 20 mmHg $\leq$ drop in systolic blood pressure within the first 2 hours of food intake or systolic blood pressure of 90 < mmHg within 2 hours of having a meal (if SBP prior to having a meal was above 100 mmHg) (67, 68). The prevalence of PPH among "healthy" older individuals is between 24% to 38% and it increases up to 91% in hospitalized elderly patients. (69,70). PPH has been associated with old age, autonomic dysfunction, falls, syncope, tabes dorsalis, Parkinson's disease, Alzheimer's disease, stroke, coronary artery disease, hypertension, diabetes mellitus, and increased frequency of all-cause mortality (1, 15, 71-76). Predisposing risk factors of PPH are polypharmacy, diuretics, hot meals (50 C <), rich carbohydrate diet, diabetes mellitus, autonomic dysfunction, Parkinson disease, end-stage renal

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disease on hemodialysis, hypertension, and fragile X mutation (77) (Figure 3).

Patients with PPH may present with lightheadedness, nausea, syncope, fall, chest pain (angina pectoris), or even transient ischemic attack (67). Symptoms are often most prominent in the morning and after breakfast (78,79).

Figure 2

Pathophysiology of the Postural Tachycardia Syndrome

Blood pressure should be measured at least after one meal that patient feels the worst symptoms (77). However, if more measurements are required, an ambulatory blood pressure monitoring (ABPM) for at least 24 hours is suggested (77, 79). Only one positive reading will be sufficient to diagnose PPH. It has been shown that measuring the patient's blood pressure in an upright posture (head-up tilt-table) specifically after consumption of a warm carbohydrate rich meal would exacerbate symptomatic hypotension which would be the ideal time to evaluate the patient for the PPH (80). It has also been demonstrated that in elderly individuals, the intensity of postprandial hypotension and orthostatic hypotension are additive; however, their magnitude is not synergistic (80). While it was originally believed that postprandial hypotension was due to increased blood flow to the gut it now seems more likely to be due to the release of calcitonin gene related peptide (CGRP) which causes peripheral vasodilation (64).

Nonpharmacological treatment of PPH could be initiated by drinking warm water prior to having a meal. It has been shown that drinking 480 mL of water (at room temperature) could prevent the drop in blood pressure as much as 20 mmHg

in patients with autonomic dysfunction (81). Some of the commonly used medications for treatment of PPH are listed in Table 2 (77, 78, 82):

The Role of Cardiac Autonomic Neuropathy in Syncope

Autonomic neuropathy from a variety of causes is a major reason for arrhythmias and sudden cardiac death (83). With aging autonomic neuropathy can occur at a level significant to cause arrhythmias (84). This is especially true in persons with diabetes mellitus (85, 86). There is also a high rate of autonomic neuropathy in persons with dementia (87). Twenty-four hour measurement of heart rate variability would appear to be the best method to determine if a patient has cardiac autonomic neuropathy (88, 89). Insertion of a loop recorder should be considered in all patients with cardiovascular autonomic neuropathy (90). In patients with cardiac syncope due to bradycardia or asystole, a dual chamber pacemaker can significantly reduce the recurrence of episodes (90).

Figure 3

Pathophysiology of Postprandial Hypotension

The most important step in evaluating a patient for neurally mediated syncope (also known as vasovagal syncope) is to exclude other diseases with similar presentations such as vertigo, seizures, pseudoseizures, cataplexy, hypoglycemia, fall secondary to gait abnormalities, leukoaraiosis, or polypharmacy (39, 91, 92). The etiology of syncope related to autonomic neuropathy can be due to bradyarrhythmias or arrhythmias and/or hypotension.

Table 2

Medications used for the treatment of postprandial hypotension

Medication	Mechanism of Action	Dosage Form
Liraglutide	Glucagon-like peptide-1 (GLP-1) slows gastric emptying	Subcutaneously
Acarbose/ miglitol	α -1-Glucosidase inhibitor – slows gastric emptying	Tablet
Guar gum	Slows gastric emptying	Powder
Octreotide	Increase splanchnic vascular resistance	Subcutaneously

The most common events which proceed to a syncopal episodes are stressful events, micturition, defecation, exercise, or pain (91). The typical prodromal symptoms are diaphoresis, nausea, and tunnel vision (93). The etiology of syncope could be divided in three categories: 1- autonomic dysfunction 2- cardiac induced syncope 3- vascular occlusion or stenosis (93). All three mechanisms have a common end result which is decrease blood perfusion to the brain and result in transient loss of consciousness.

Head-up tilt test is the widely used test to evaluate a patient for vasovagal syncope (94). According to the American College of Cardiology/American Heart Association guidelines published on 2017 for treatment of vasovagal syncope in patients with prolonged prodromal period, patient's education to practice physical counter-maneuvers such as limb and/or abdominal contraction, squatting, or leg crossing could be significantly effective (95). Midodrine has been suggested for medical treatment of patients with recurrent episodes of vasovagal syncope (96). Other medications such as Fludrocortisone, Beta-blockers (in patients 42 year <), or selective serotonin reuptake inhibitor could also be beneficial (95). In treatment of patients with cardiac syncope secondary to symptomatic bradycardia or asystole, a dual chamber pacemaker would significantly reduce the recurrence of episodes (97).

Carotid sinus syndrome is seen in a patient with an extreme response to baroreceptor-mediated reflex stimulation which result in symptomatic bradycardia and possibly hypotension (8). Carotid sinus syndrome occurs after a carotid sinus massage which results an asystole for longer than 3 seconds (37).

Conclusion

Autonomic neuropathy is common in older persons particularly if they have diabetes mellitus – It is commonly a cause of syncope. Clinicians caring for older persons should always consider cardiovascular disease due to autonomic neuropathy in older persons with syncope.

References

- Ropper, A. H. Adams and Vectors principles of neurology. New York: McGraw-Hill Education Medical, 2014.
- Cardinali, D. P. Autonomic Nervous System: Basic and Clinical Aspects. Cham: Springer International Publishing, 2018.
- Daroff, R. B. Bradley's neurology in clinical practice. London: Elsevier, 2016.
- Hotta, H., & Uchida, S. Aging of the autonomic nervous system and possible improvements in autonomic activity using somatic afferent stimulation. *Geriatrics & Gerontology International*, 2010;10. doi:10.1111/j.1447-0594.2010.00592.x
- Ko, D., Preis, S. R., Lubitz, S. A., McManus, D. D., Vasan, R. S., Hamburg, N. M. Mitchell, G. F. Relation of Orthostatic Hypotension With New-Onset Atrial Fibrillation (From the Framingham Heart Study). *The American Journal of Cardiology*, 2018;121(5), 596-601. doi:10.1016/j.amjcard.2017.11.036
- Benarroch, E. E. The clinical approach to autonomic failure in neurological disorders. *Nature Reviews Neurology*, 2014;10(7), 396-407. doi:10.1038/nrneurol.2014.88
- Freeman, R. Neurogenic Orthostatic Hypotension. *New England Journal of Medicine*, 2008;358(6), 615-624. doi:10.1056/nejmc074189
- Halter JB, Ouslander JG, Studenski S, High KP, Asthana S, Supiano MA, Ritchie C. eds. *Hazzard's Geriatric Medicine and Gerontology*, 7e New York, NY: McGraw-Hill
- Juraschek, S. P., Daya, N., Rawlings, A. M., Appel, L. J., Miller, E. R., Windham, B. G., Selvin, E. Association of History of Dizziness and Long-term Adverse Outcomes With Early vs Later Orthostatic Hypotension Assessment Times in Middle-aged Adults. *JAMA Internal Medicine*, 2017;177(9), 1316. doi:10.1001/jamainternmed.2017.2937
- Kasper, D. L., Fauci, A. S., Hauser, S. L., Longo, D. L., Jameson, J. L., & Loscalzo, J. *Harrisons principles of internal medicine*. New York: McGraw Hill Education, 2015.
- Freeman, R., Wieling, W., Axelrod, F. B., Benditt, D. G., Benarroch, E., Biaggioni, I., Dijk, J. G. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. *Clinical Autonomic Research*, 2011;21(2), 69-72. doi:10.1007/s10286-011-0119-5
- Foster-Dingley, J. C., Moonen, J. E., Ruijter, W. D., Mast, R. C., & Grond, J. V. Orthostatic hypotension in older persons is not associated with cognitive functioning, features of cerebral damage or cerebral blood flow. *Journal of Hypertension*, 2018;36(5), 1201-1206. doi:10.1097/hjh.0000000000001681
- Luukinen, H., Koski, K., Laippala, P., & Kivelä, S. Prognosis of Diastolic and Systolic Orthostatic Hypotension in Older Persons. *Archives of Internal Medicine*, 1999;159(3), 273. doi:10.1001/archinte.159.3.273
- Mader, S. L. Low Prevalence of Postural Hypotension Among Community-Dwelling Elderly. *JAMA: The Journal of the American Medical Association*, 1987;258(11), 1511. doi:10.1001/jama.1987.03400110093033
- Catz, A., Mendelson, L., & Solzi, P. Symptomatic postprandial hypotension in high paraplegia. Case report. *Spinal Cord*, 1992;30(8), 582-586. doi:10.1038/sc.1992.118
- Strogatz, D. S., Keenan, N. L., Barnett, E. M., & Wagner, E. H. Correlates of Postural Hypotension in a Community Sample of Elderly Blacks and Whites. *Journal of the American Geriatrics Society*, 1991;39(6), 562-566. doi:10.1111/j.1532-5415.1991.tb03593.x
- Kaufmann, H., Freeman, R., Biaggioni, I., Low, P., Pedder, S., Hewitt, L. A., Mathias, C. J. Droxidopa for neurogenic orthostatic hypotension: A randomized, placebo-controlled, phase 3 trial. *Neurology*, 2014;83(4), 328-335. doi:10.1212/wnl.0000000000000615
- Ricci F, Fedorowski A, Radio F, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: A meta-analysis of prospective observational studies. *Eur Heart J* 2015;36:1609-1617.
- Fedorowski, A., Engström, G., Hedblad, B., & Melander, O. (2010). Orthostatic Hypotension Predicts Incidence of Heart Failure: The Malmö Preventive Project. *American Journal of Hypertension*, 2010;23(11), 1209-1215. doi:10.1038/ajh.2010.150
- Goldstein, D. S. Dysautonomias: Clinical Disorders of the Autonomic Nervous System. *Annals of Internal Medicine*, 2002;137(9), 753. doi:10.7326/0003-4819-137-9-200211050-00011
- Ramirez, C. E., Okamoto, L. E., Arnold, A. C., Gamboa, A., Diedrich, A., Choi, L. Shihao, C. A. Efficacy of Atomoxetine Versus Midodrine for the Treatment of Orthostatic Hypotension in Autonomic Failure Novelty and Significance. *Hypertension*, 2014;64(6), 1235-1240. doi:10.1161/hypertensionaha.114.04225
- Krolewski, A. S., Warram, J. H., Cupples, A., Gorman, C., Szabo, A., & Christlieb, A. Hypertension, orthostatic hypotension and the microvascular complications of diabetes. *Journal of Chronic Diseases*, 1985;38(4), 319-326. doi:10.1016/0021-9681(85)90078-5
- Shihao, C., Lipsitz, L. A., & Biaggioni, I. Evaluation and treatment of orthostatic hypotension. *Journal of the American Society of Hypertension*, 2013;7(4), 317-324. doi:10.1016/j.jash.2013.04.006
- Mancia, G., & Grassi, G. Orthostatic hypotension and cardiovascular risk: Defining the epidemiological and prognostic relevance. *European Heart Journal*, 2009;31(1), 12-14. doi:10.1093/eurheartj/ehp389
- Rutan, G. H., Hermanson, B., Bild, D. E., Kittner, S. J., Labaw, F., & Tell, G. S. Orthostatic hypotension in older adults. The Cardiovascular Health Study. CHS Collaborative Research Group. *Hypertension*, 1992;19(6_Pt_1), 508-519.
- Phipps, M. S., Schmid, A. A., Kapoor, J. R., Peixoto, A. J., Williams, L. S., & Bravata, D. M. Orthostatic hypotension among outpatients with ischemic stroke. *Journal of the Neurological Sciences*, 2012;314(1-2), 62-65. doi:10.1016/j.jns.2011.10.031
- Frith, J., Ng, W., Day, C. P., Payne, B., Sheerin, N., Gorman, G. Newton, J. L. (2014). Orthostatic intolerance is common in chronic disease – A clinical cohort study. *International Journal of Cardiology*, 2014;174(3), 861-863. doi:10.1016/j.ijcard.2014.04.175
- Gupta, V., & Lipsitz, L. A. Orthostatic Hypotension in the Elderly: Diagnosis and Treatment. *The American Journal of Medicine*, 2007;120(10), 841-847. doi:10.1016/j.amjmed.2007.02.023
- Morley, J. E. Frailty, Falls, and Fractures. *Journal of the American Medical Directors Association*, 2013;14(3), 149-151. doi:10.1016/j.jamda.2012.12.009
- Ricci, F., Caterina, R. D., & Fedorowski, A. Orthostatic Hypotension. *Journal of the American College of Cardiology*, 2015;66(7), 848-860. doi:10.1016/j.jacc.2015.06.1084
- Boron, W. F., & Boulpaep, E. L. *Medical physiology*. Chapter 2017;20, 461-482.e2 Philadelphia: Elsevier, 2017.
- Dineen, J., & Freeman, R. Autonomic Neuropathy. *Seminars in Neurology*, 2015;35(04), 458-468. doi:10.1055/s-0035-1558983
- Kanjwal, K., George, A., Figueredo, V. M., & Grubb, B. P. Orthostatic hypotension. *Journal of Cardiovascular Medicine*, 2015;16(2), 75-81. doi:10.2459/01.

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- jcm.0000446386.01100.35
34. Low, P. A. Prevalence of orthostatic hypotension. *Clinical Autonomic Research*, 2008;18(S1), 8-13. doi:10.1007/s10286-007-1001-3
35. Goldstein, D. S., & Cheshire, W. P. (2017). Beat-to-beat blood pressure and heart rate responses to the Valsalva maneuver. *Clinical Autonomic Research*, 2017;27(6), 361-367. doi:10.1007/s10286-017-0474-y
36. Goldstein, D. S., & Sharabi, Y. Neurogenic Orthostatic Hypotension: A Pathophysiological Approach. *Circulation*, 2009;119(1), 139-146. doi:10.1161/circulationaha.108.805887
37. Sánchez-Ferro, Á, Benito-León, J., & Gómez-Esteban, J. C. The Management of Orthostatic Hypotension in Parkinson's Disease. *Frontiers in Neurology*, 2013;4. doi:10.3389/fneur.2013.00064
38. Jones, P. K., Shaw, B. H., & Raj, S. R. Orthostatic hypotension: Managing a difficult problem. *Expert Review of Cardiovascular Therapy*, 2015;13(11), 1263-1276. doi:10.1586/14779072.2015.1095090
39. Morley, J. E., Rolland, Y., Tolson, D., & Vellas, B. Increasing Awareness of the Factors Producing Falls: The Mini Falls Assessment. *Journal of the American Medical Directors Association*, 2012;13(2), 87-90. doi:10.1016/j.jamda.2011.11.002
40. Ci, W., & E, T. Syncope: Dietary advice to help manage the symptoms of syncope. *Integrative Food, Nutrition and Metabolism*, 2016;3(5). doi:10.15761/ifnm.1000165
41. Gillis, D. J., Wouda, M., & Hjeltnes, N. Non-pharmacological management of orthostatic hypotension after spinal cord injury: A critical review of the literature. *Spinal Cord*, 2008;46(10), 652-659. doi:10.1038/sc.2008.48
42. Arnold, A. C., & Shibao, C. Current Concepts in Orthostatic Hypotension Management. *Current Hypertension Reports*, 2013;15(4), 304-312. doi:10.1007/s11906-013-0362-3
43. Figueroa, J. J., Basford, J. R., & Low, P. A. Preventing and treating orthostatic hypotension: As easy as A, B, C. *Cleveland Clinic Journal of Medicine*, 2010;77(5), 298-306. doi: 10.3949/ccjm.77a.09118
44. Fouad-Tarazi, F. M., Okabe, M., & Goren, H. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. *The American Journal of Medicine* 1995;99(6), 604-610. doi:10.1016/S0002-9343(99)80246-0
45. Hoeldtke, R. D., Davis, K. M., Joseph, J., Gonzales, R., Panidis, I. P., & Friedman, A. C. Hemodynamic effects of octreotide in patients with autonomic neuropathy. *Circulation*, 1991;84(1), 168-176. doi:10.1161/01.cir.84.1.168
46. Hoeldtke, R. D., Horvath, G. G., Bryner, K. D., & Hobbs, G. R. Treatment of Orthostatic Hypotension with Midodrine and Octreotide. *The Journal of Clinical Endocrinology, & Metabolism*, 1998;83(2), 339-343. doi:10.1210/jcem.83.2.4534
47. Hoeldtke, R. D., & Streeten, D. Treatment of Orthostatic Hypotension with Erythropoietin. *New England Journal of Medicine*, 1993;329(9), 611-615. doi:10.1056/nejm199308263290904
48. Kaufmann, H., Norcliffe-Kaufmann, L., & Palma, J. Droxidopa in neurogenic orthostatic hypotension. *Expert Review of Cardiovascular Therapy*, 2015;13(8), 875-891. doi:10.1586/14779072.2015.1057504
49. Mathias, C. J., Fosbraey, P., Costa, D. F., Thornley, A., & Bannister, R. The effect of desmopressin on nocturnal polyuria, overnight weight loss, and morning postural hypotension in patients with autonomic failure. *Bmj*, 1986;293(6543), 353-354. doi:10.1136/bmj.293.6543.353
50. Maule, S., Papotti, G., Naso, D., Magnino, C., Testa, E., & Veglio, F. Orthostatic Hypotension: Evaluation and Treatment. *Cardiovascular & Hematological Disorders-Drug Targets*, 2007;7(1), 63-70. doi:10.2174/187152907780059029
51. McDonald, C., Newton, J. L., & Burn, D. J. Orthostatic hypotension and cognitive impairment in Parkinson's disease: Causation or association? *Movement Disorders*, 2016;31(7), 937-946. doi:10.1002/mds.26632
52. Metzler, M., Duerr, S., Granata, R., Krismer, F., Robertson, D., & Wenning, G. K. Neurogenic orthostatic hypotension: Pathophysiology, evaluation, and management. *Journal of Neurology*, 2012;260(9), 2212-2219. doi:10.1007/s00415-012-6736-7
53. Omara, G., & Lyons, D. Postprandial hypotension. *Clinics in Geriatric Medicine*, 2002;18(2), 307-321. doi:10.1016/s0749-0690(02)00012-5
54. Verwaerde, P., Tran, M., & Montastruc, J. Effects of yohimbine, an α 2-adrenoceptor antagonist, on experimental neurogenic orthostatic hypotension. *Fundamental & Clinical Pharmacology*, 1997;11(6), 567-575. doi:10.1111/j.1472-8206.1997.tb00862.x
55. Lanier JB1, Mote MB, Clay EC. Evaluation and management of orthostatic hypotension. *American Family Physician*, 2011;84(5):527-536.
56. Wells R, Spurrier AJ, Linz D, et al. Postural tachycardia syndrome: Current perspectives. *Vasc Health Risk Manag* 2017;14:1-11.
57. Arnold AC, Ng J, Raj SR. Postural tachycardia syndrome – diagnosis, physiology, and prognosis. *Auton Neurosci* 2018;Feb 28. Doi: 10.1016/j.autneu.2018.02.005 (Epub ahead of print).
58. Raj V, Opie M, Arnold AC. Cognitive and psychological issues in postural tachycardia syndrome. *Auton Neurosci* 2018;Mar 27 doi: 10.1016/j.autneu.2018.03.004.
59. Garland EM, Celedonio JE, Raj SR. Postural tachycardia syndrome: Beyond orthostatic intolerance. *Curr Neurol Neurosci Rep* 2015;15:60. Doi: 10.1007/s11910-015-0583-8.
60. Novak P. Orthostatic cerebral hypoperfusion syndrome. *Front Aging Neurosci* 2016;8:22. Doi: 10.3389/fnagi.2016.00022. eCollection.
61. Metwalley KA, Hamed SAA, Farghaly HS. Cardiac autonomic function in children with type 1 diabetes. *Eur J Pediatr* 2018;Mar 2. Doi: 10.1007/s00431-018-3122-1 [Epub ahead of print].
62. Kanjwal K, Karabin B, Kanjwal Y, Grubb BP. Autonomic dysfunction presenting as postural orthostatic tachycardia syndrome in patients with multiple sclerosis. *Int J Med Sci* 2010;7:62-67.
63. Ruzieh M, Grubb BP. Orthostatic intolerance and postural tachycardia syndrome: New insights into pathophysiology and treatment. *Herzschrittmacherther Elektrophysiol* 2018; Apr 25. Doi: 10.1007/s00399018-0563-1 [Epub ahead of print].
64. Edwards BJ, Perry HM 3rd, Kaiser FE, et al. Relationship of age and calcitonin gene-related peptide to postprandial hypotension. *Mech Ageing Dev* 1996;87:61-73.
65. Seyer-Hansen K. Postprandial hypotension. *Br Med J* 1977;12:1262.
66. Trahair LG, Horowitz M, Jones KL. Postprandial hypotension: A systematic review. *J A Med Dir Assoc* 2014;15:394-409.
67. Jansen, R. W., & Lipsitz, L. A. Postprandial Hypotension: Epidemiology, Pathophysiology, and Clinical Management. *Annals of Internal Medicine*, 1995;122(4), 286. doi:10.7326/0003-4819-122-4-199502150-00009
68. Zou, X., Cao, J., & Li, J. Prevalence of and risk factors for postprandial hypotension in older Chinese men. *Journal of Geriatric Cardiology*, 2015;12(6), 600-604. doi:10.11909/j.issn.1671-5411.2015.06.003
69. Pavelić, A., Skorić, M. K., Crnošija, L., & Habek, M. Postprandial hypotension in neurological disorders: Systematic review and meta-analysis. *Clinical Autonomic Research*, 2017;27(4), 263-271. doi:10.1007/s10286-017-0440-8
70. Teramoto, S., Akishita, M., Fukuchi, Y., Toba, K., & Ouchi, Y. Assessment of Autonomic Nervous Function in Elderly Subjects with or without Postprandial Hypotension. *Hypertension Research*, 1997;20(4), 257-261. doi:10.1291/hypres.20.257
71. Aronow, W. S., & Ahn, C. Association of Postprandial Hypotension with incidence of falls, syncope, coronary events, stroke, and total mortality at 29-month follow-up in 499 older nursing home residents. *Journal of the American Geriatrics Society*, 1997;45(9), 1051-1053. doi:10.1111/j.1532-5415.1997.tb05965.x
72. Barochiner J, Alfie J, Aparicio LS, et al. Postprandial hypotension detected through home blood pressure monitoring: A frequent phenomenon in elderly hypertensive patients. *Hypertension Research*, 2013;37(5), 438-443. doi:10.1038/hr.2013.144
73. Idiaquez, J., Rios, L., & Sandoval, E. Postprandial hypotension in Alzheimers disease. *Clinical Autonomic Research*, 1997;7(3), 119-120. doi:10.1007/bf02308837
74. Tabara, Y., Okada, Y., Uetani, E., Nagai, T., Igase, M., Kido, T., Miki, T. Postprandial hypotension as a risk marker for asymptomatic lacunar infarction. *Journal of Hypertension*, 2014;32(5), 1084-1090. doi:10.1097/hjh.0000000000000150
75. Trahair, L. G., Horowitz, M., & Jones, K. L. Postprandial Hypotension: A Systematic Review. *Journal of the American Medical Directors Association*, 2014;2014;15(6), 394-409. doi:10.1016/j.jamda.2014.01.011
76. Van Orshoven, N. P., Jansen, P. A., Oudejans, I., Schoon, Y., & Oey, P. L. Postprandial Hypotension in Clinical Geriatric Patients and Healthy Elderly: Prevalence Related to Patient Selection and Diagnostic Criteria. *Journal of Aging Research*, 2010, 1-7. doi:10.4061/2010/243752
77. Luciano, G. L., Brennan, M. J., & Rothberg, M. B. Postprandial Hypotension. *The American Journal of Medicine*, 2010;123(3). doi:10.1016/j.amjmed.2009.06.026
78. Morley, J. E. The Aging Gut: Physiology. *Clinics in Geriatric Medicine*, 2007;23(4), 757-767. doi:10.1016/j.cger.2007.06.002
79. Puisieux, F., Bulckaen, H., Fauchais, A. L., Drumez, S., Salomez-Granier, F., & Dewailly, P. Ambulatory Blood Pressure Monitoring and Postprandial Hypotension in Elderly Persons With Falls or Syncope. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 2000;55(9). doi:10.1093/gerona/55.9.m53
80. Maurer, M. S. Upright Posture and Postprandial Hypotension in Elderly Persons. *Annals of Internal Medicine*, 2000;133(7), 533. doi:10.7326/0003-4819-133-7-200010030-00012
81. Shannon, J. R., Diedrich, A., Biaggioni, I., Tank, J., Robertson, R. M., Robertson, D., & Jordan, J. Water drinking as a treatment for orthostatic syndromes. *The American Journal of Medicine*, 2002;112(5), 355-360. doi:10.1016/s0002-9343(02)01025-2
82. Morley, J. E. Gait, Falls, and Dementia. *Journal of the American Medical Directors Association*, 2016;17(6), 467-470. doi:10.1016/j.jamda.2016.03.024
83. Lange-Maia BS, Newman AB, Jakicic JM, et al. Relationship between sensorimotor peripheral nerve function and indicators of cardiovascular autonomic function in older adults from the Health, Aging and Body Composition Study. *Exp Gerontol* 2017;96:38-45.
84. Agarwal G, Singh SK. Arrhythmias in Type 2 diabetes mellitus. *Indian J Endocrinol Metab* 2017;21:715-718.
85. Vinik AI, Erbas T Diabetic autonomic neuropathy. *Handb Clin Neurol* 2013;117:279-294.
86. Morley JE, Asvat MS, Klein L, Lowenthal MN. Autonomic neuropathy in Black diabetic patients. *S Am Med J* 1977;52:115-116.
87. Allan LM, Ballard CG, Allen J, Murray A, Davidson AW, McKeith IG, Kenny RA. Autonomic dysfunction in dementia. *J Neurol Neurosurg Psychiatry* 2007;78:671-677.
88. Taralov ZZ, Terziyski KV, Kostianev SS. Heart rate variability as a method for assessment of the autonomic nervous system and the adaptations to different physiological and pathological conditions. *Folia Med (Plovdiv)* 2015;57:173-180.

89. da Silva VP, Ramalho Oliveira BR, Tavares Mello RG, et al. Heart rate variability indexes in dementia: A systematic review with a quantitative analysis. *Curr Alzheimer Res* 2018;15:80-88.
90. Sciaraffia E, Chen J, Hocini M, et al. Use of event recorders and loop recorders in clinical practice: Results of the European Heart Rhythm Association survey. *Europace* 2014;16:1384-1386.
91. Kapoor, W. N. Syncope. *New England Journal of Medicine*, 2000;343(25), 1856-1862. doi:10.1056/nejm200012213432507
92. Morley, J. E. White Matter Lesions (Leukoaraiosis): A Major Cause of Falls. *Journal of the American Medical Directors Association*, 2015;16(6), 441-443. doi:10.1016/j.jamda.2015.03.023
93. Fox, M. C., Lakdawala, N., Miller, A. L., & Loscalzo, J. A Patient with Syncope. *New England Journal of Medicine*, 2013;369(10), 966-972. doi:10.1056/nejmcps1300093
94. Makowiec, D., Graff, B., & Struzik, Z. R. Multistructure index characterization of heart rate and systolic blood pressure reveals precursory signs of syncope. *Scientific Reports*, 2017;7(1). doi:10.1038/s41598-017-00354-x
95. Shen, W., & Sheldon, R. S. Assessment and Treatment of Syncope. *JAMA Cardiology*, 2017;2(8), 920. doi:10.1001/jamacardio.2017.1784
96. Shen, W., Sheldon, R. S., Benditt, D. G., Cohen, M. I., Forman, D. E., Goldberger, Z. D., Yancy, C. W. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*, 2017;136(5). doi:10.1161/cir.0000000000000499
97. Palmisano, P., Accogli, M., Zaccaria, M., Luzzi, G., Nacci, F., Anaclerio, M., & Favale, S. Predictive factors for pacemaker implantation in patients receiving an implantable loop recorder for syncope remained unexplained after an extensive cardiac and neurological workup. *International Journal of Cardiology*, 2013;168(4), 3450-3457. doi:10.1016/j.ijcard.2013.04.179