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Orthostatic Hypotension: Management of a Complex, but Common, Medical Problem

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Abstract

Orthostatic hypotension (OH), a common, often overlooked, disorder with many causes, is associated with debilitating symptoms, falls, syncope, cognitive impairment, and risk of death. Chronic OH, a cardinal sign of autonomic dysfunction, increases with advancing age and is commonly associated with neurodegenerative and autoimmune diseases, diabetes, hypertension, heart failure, and kidney failure. Management typically involves a multidisciplinary, patient-centered, approach to arrive at an appropriate underlying diagnosis that is causing OH, treating accompanying conditions, and providing individually tailored pharmacologic and non-pharmacologic treatment. We (i) propose a novel streamlined pathophysiological classification of OH; (ii) review the relationship between the cardiovascular disease continuum and OH; (iii) discuss OH-mediated end-organ damage; (iv) provide diagnostic and therapeutic algorithms to guide clinical decision making and patient care; (v) identify current gaps in knowledge and try to define future research directions. Using a case-based learning approach, specific clinical scenarios

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are presented highlighting various presentations of OH to provide a practical guide to evaluate and manage patients who have OH.

Keywords

orthostatic hypotension; cardiovascular autonomic dysfunction; case-based evaluation; pharmacology; non-pharmacological interventions; autonomic testing; Autonomic Nervous System; Electrophysiology

Introduction

Chronic orthostatic hypotension (OH) is a common, often underdiagnosed, disorder, defined by an excessive fall in blood pressure (BP) with standing. OH can be associated with postural lightheadedness, dizziness, fatigue, “coat hanger” pain, and, in extreme situations, syncope, falls, and injuries. OH is associated with increased risk of cardiovascular (CV) and total mortality[1–4]. Management requires recognition, focused diagnostic testing, treatment of comorbidities, removal of iatrogenic factors, and initiation of effective therapies[4]. OH can be disabling and difficult to treat, especially in elderly patients with concurrent supine hypertension[4,5].

In this state-of-the-art review, we (i) consider a novel, streamlined, pathophysiological classification of OH; (ii) review how cardiovascular disorders interact with and result in OH; (iii) discuss OH-associated end-organ damage; (iv) provide diagnostic and treatment algorithms to guide clinical decision making and patient care; (v) identify gaps in knowledge and define future research directions. Using a case-based approach, we present clinical scenarios that provide a practical guide for evaluation and management of OH.

Definition

Classical OH is present when a sustained reduction of systolic blood pressure (SBP) ≥20 mmHg or diastolic blood pressure (DBP) ≥10 mmHg within 3 minutes of active standing or on a head-up tilt test ≥60°[6–8]. Variants of OH include smaller, but symptomatic, reduction in SBP when the supine SBP is low (90-100 mm Hg) but drops well below this[1]. Moreover, in patients with supine hypertension, higher diagnostic thresholds, i.e. SBP/DBP decline ≥30/15 mmHg[6] may be more appropriate because the magnitude of the orthostatic BP fall depends upon baseline BP.

Epidemiology

The prevalence of OH in the general population is strongly correlated with age, ranging from <5% below age 50 to 20% above age 70[9,10]. Comorbidities associated with, or causal of, OH include neurodegenerative diseases (Parkinson’s disease, pure autonomic failure, multiple system atrophy and autonomic neuropathies) [2,11–14], hypertension[9,15,16], heart failure[17,18], diabetes[12,19–22], and renal failure[23,24]. Most patients in population-based and interventional studies where OH is diagnosed commonly during screening are asymptomatic or have minor symptoms, as seen, [25–27]. The magnitude of the systolic BP fall and the lowest upright

systolic BP may not correlate with symptoms [28]. Differences in symptoms may relate to cerebral autoregulatory function and rate and degree of BP drop as well as the nadir in BP.

As a neurodegenerative process is often associated with OH, other autonomic abnormalities may be present (e.g., constipation, sweating abnormalities, erectile dysfunction, urinary retention). Parkinson's disease (PD) or diabetes may be obvious and apparent, predating OH, but, also, only discovered subsequently. However, OH may be the first indicator of a progressive, otherwise undiagnosed, neurodegenerative process.[29].

Increasing evidence indicates that OH, asymptomatic or not, is associated with increased risk of death, incident coronary heart disease, heart failure, and stroke[30–32]. Notably, OH confers a higher relative risk in younger patients (<65 years) versus older patients[26,30]. OH is associated with risk for atrial fibrillation[33,34] and hypercoagulable states[35,36], both subsequently associated with elevated risk of cardioembolic stroke and unfavorable structural heart adaptations[37–40] It is an independent risk factor beyond associated concomitant and/or causal conditions (neurodegenerative diseases, diabetes or hypertension)[31]. (Figure 1)

Aside from increased CV risk, OH in patients with heart failure has a negative impact on symptoms and activity level and increases risk of falls, cognitive decline and mortality[41]. CV autonomic dysfunction in those with impaired orthostatic BP responses predicts or is associated with kidney failure[23,42], chronic obstructive pulmonary disease[42,43], falls, fragility fractures[14,44–46], and dementia[42,47,48]. (Figure 2)

In patients with neurogenic OH, the risk of all-cause mortality is much greater than in those patients with non-neurogenic OH. A small longitudinal study of patients with neurogenic OH reported a 44% mortality rate over an average of 30 months of follow up[49]. Similarly, a 10-year follow-up study of patients with predominantly neurogenic OH identified >60% 10-year mortality rates[29].

Pathophysiology

Circulatory homeostasis in humans relies on cardiovascular reflexes controlled tightly by the autonomic nervous system[50]. Upon standing, ~500-1000 ml of blood shifts from the central intravascular compartment to peripheral predominantly venous ("capacitance") vasculature (lower extremities and splanchnic bed) reducing venous return[1]. Under normal conditions, there is a slight increase in heart rate with associated venoconstriction and arteriolar constriction preserving systolic, but slightly increasing, diastolic BP[51], effective venous return and maintaining cardiac output. OH reflects failure of the homeostatic reflex autonomic response to postural change at many potential levels (baroreceptors, autonomic afferents, central processing, autonomic efferents, and peripheral sympathetic receptors) [1,2,13].(Figure 3)

With cardiovascular autonomic nervous system dysfunction, BP can decrease upon standing with resultant hypoperfusion of the upper body and brain[52,53]. Autonomic nervous system dysfunction may be present in patients with PD and other α -synucleinopathies, such as, dementia with Lewy bodies, multiple system atrophy and pure autonomic failure, in

which, accumulation of misfolded phosphorylated α-synuclein in neurons and glial cells may occur[54]. In PD, with predominant peripheral noradrenergic sympathetic denervation, baroreflex dysfunction, chronotropic incompetence, vascular tone dysregulation and altered inotropic efficiency may ensue.

Relationship of blood pressure to heart rate

The hemodynamic responses to changes in posture result in maintained stable SBP, accompanied by increased diastolic DBP of 10-15% (i.e., 5-10 mmHg in normotensive individuals), and increased pulse rate of 15-30 % (i.e., 5-15 beats per minute (bpm)[51]. By measuring change in heart rate (ΔHR) and change in supine (and/or seated) to standing SBP can differentiate neurogenic from non-neurogenic OH; neurogenic OH is associated with blunted compensatory HR increase (ΔHR <15 bpm)[2,4].

Conversely, individuals with non-neurogenic OH will typically demonstrate ΔHR ≥15 bpm within 3 minutes of standing. Monitoring postural ΔHR for diagnostic purposes requires consideration of possible confounders, such as, cardioactive medications or intrinsic cardiac rhythm disturbances (sick sinus syndrome, other bradyarrhythmias, or pacemaker-dependency) preventing compensatory HR increase during postural change[55].

Neurogenic OH can be diagnosed accurately by measuring the ratio of the HR increase and dividing it by the fall in SBP (ΔHR/ΔSBP) to provide a marker of cardiac baroreflex gain. A ΔHR/ΔSBP ratio <0.5 bpm/mmHg after 3 minutes standing indicates a diagnosis of neurogenic OH and discriminates neurogenic OH from non-neurogenic OH with significantly better sensitivity than ΔHR alone[56].

Clinical Presentation

Symptoms due to drop in SBP are only seen in a fraction of those with OH[28]. Whether the patient experiences symptoms is as much dependent on the rate of decrease as upon the absolute degree of change in cerebral perfusion pressure[53]. As cerebral autoregulation can compensate for wide swings in blood pressure and blood flow, major changes may be required for symptoms to occur. What has not been carefully evaluated is disruption in cerebral autoregulatory processes that may be present in those with OH. Further, symptoms may be due to pulmonary hypoperfusion, causing orthostatic dyspnea, myocardial ischemia causing orthostatic angina and musculature hypoperfusion distribution of the trapezius muscle causing “coat-hanger” pain.

Symptoms are more common and severe early after awakening; patients are most symptomatic at this time because of natriuresis and intravascular volume loss overnight - and are typically exacerbated by conditions predisposing to peripheral venous pooling and dehydration, such as, aging, heating, fever, alcohol drinking, urination, post-exercise, initiation/intensification of antihypertensive treatment, deconditioning and immobilization[57]. Despite this, most remain asymptomatic or have nonspecific symptoms, accounting for the high rate of unrecognized cases[58]. Clinical scores, such as the Orthostatic Hypotension Questionnaire[59] (Supplemental Table I), may help but no scoring approach has been generally accepted.

Based on existing definitions of OH, and our real-world experience with patients presenting with orthostatic intolerance, OH can be classified into 4 functional classes, according to the severity and frequency of symptoms [1]. This functional 4-stage classification is useful clinically to describe the extent of symptoms and when to start pharmacological treatment, but it has not yet been shown to relate to prognosis or magnitude of OH.

In functional class I, patients are asymptomatic but occasionally show symptoms of orthostatic intolerance, including, syncope, and unexplained falls. In functional class II, symptoms occur weekly or monthly, with overall mild to moderate limitations of daily living. Functional class III is characterized by more severe and frequent symptoms with marked limitation in daily living activities. In functional class IV, severe symptoms persist daily, leading to recurrent syncope and disability, if untreated. The pharmacological treatment is recommended in class III-IV, whereas non-pharmacological interventions should be applied earlier (please, see Treatment chapter, page, and Supplemental Figure I).

Classification of Orthostatic Hypotension

We propose a **novel** classification of OH intended to categorize multiple clinical conditions into three groups based on the predominant underlying pathophysiological mechanism. Accordingly, OH can be divided into *neurogenic*, *cardiogenic,* and *mixed forms*. Figure 4 details the etiologies included in each group.

Neurogenic OH

Neurogenic OH can be primarily due to central neurodegenerative disorders, such as, α-synucleinopathies (multiple system atrophy, PD or dementia with Lewy bodies) or secondary to peripheral autonomic neurodegeneration (e.g., pure autonomic failure, or peripheral neuropathies as might be seen in patients with diabetes). Neurogenic OH is characterized by a failure to release adequate peripheral norepinephrine leading to impaired systemic vascular tone.

Cardiogenic OH

Cardiogenic OH, featuring low cardiac output as the underlying predominant mechanism, is due to conditions affecting, preload (e.g., volume loss, impaired venous return, venous pooling, left ventricular stiffness, pulmonary hypertension), afterload (hypertension), contractility (e.g., left ventricular dysfunction, amyloid) and/or chronotropy.

Mixed OH

*M*ixed OH encompasses conditions characterized by low systemic vascular resistance and low cardiac output. These conditions share common pathways promoting changes affecting structural and functional components of the autonomic nervous system and the CV system, eventually compromising orthostatic hemodynamic homeostasis and triggering compensatory neuroendocrine mechanisms and possibly other biologic effectors.

Risk modifiers

Clinical factors and conditions modifying risk of onset/recurrence of OH, possibly enhancing the severity of symptoms, is listed in Figure 4.

OH can be further classified [60]:

- according to timing of occurrence during orthostatic stress, as *initial*, *classic*, *delayed or postprandial* OH;

- according to BP components, as *isolated systolic* OH, *isolated diastolic* OH, or *combined* OH;

- according to the clinical course;

- according to symptoms;

- according to the etiology.

OH Variants: initial, delayed, postprandial

Several variations in BP drop can cause symptoms of orthostatic intolerance deserving of specific notice, including *initial, and delayed OH and postprandial hypotension*[1,61–64].

Initial OH features an exaggerated abrupt decrease in BP (>40 mmHg SBP and/or >20 mmHg DBP) occurring within 15-30 seconds upon standing due to transient mismatch between cardiac output and systemic vascular resistance. It is associated exclusively with active standing, whereas drop in BP during passive tilting is significantly smaller or, in many cases, absent. *Initial* OH, the most common form of orthostatic intolerance in the young, can be observed in older patients, in particular, when treated with antihypertensive drugs[64], with dehydration and/or fluid or blood loss.

In *delayed* OH, BP drop occurs within 3-minutes of standing or upright tilt-testing[61]. Current evidence suggests that *delayed* OH is an early and milder phenotype of autonomic dysfunction preceding *classical* OH and presenting at younger age with less severe abnormalities of both autonomic and neuroendocrine control mechanisms[29,65].

Postprandial hypotension is a BP drop, with or without standing, after eating. Symptoms appear within 2 hours after food ingestion, particularly, with large and high-carbohydrate meals or alcohol intake. The pathogenesis appears related to gastric and/or esophageal distension, release of vasodilatory peptides and splanchnic blood pooling[66]. *Postprandial hypotension,* more frequently observed in elderly patients with neurologic comorbidities, can be asymptomatic[63].

Phenotypes of delayed OH and postprandial hypotension, however, include older individuals with unexplained syncope who have a negative initial evaluation including active standing test and ECG-monitoring. Usually, more advanced tests are required, such as, head-up tilt (HUT) with beat-to-beat BP monitoring and 24-hour ambulatory BP monitoring with detailed analysis of individual data, especially in the postprandial period.

OH with supine hypertension

Neurogenic OH is often associated with, and potentially causally related to, supine hypertension, sometimes presenting as “reverse dipping” (i.e., supine BP greater during sleep than when awake as is normally the circumstance). Supine hypertension can be associated with end-organ damage[49] and can worsen daytime OH by inducing pressure diuresis and volume loss during sleep. Mechanisms for this are manifold but possibly due to alterations in the renin-angiotensin-aldosterone system.

Evaluation

Evaluation of OH begins with a detailed patient history, symptom assessment, consideration of comorbidities, analysis of testing already performed and decision to pursue the correct diagnosis using OH-focused examinations, such as, CV autonomic assessment or 24-hour ambulatory blood pressure monitor. The evaluation of OH may be extensive and must include investigations into identifiable comorbidities that may exacerbate OH (Figure 5).

In complex cases, further evaluation and autonomic testing may be necessary. In patients presenting with severe symptoms of OH that are not responsive to treatment or with features suggesting major neurogenic component or disruption of autonomic cardiovascular control it may be appropriate to consider a panel of neurological and cardiovascular autonomic tests in consultation with appropriate experts (Supplemental Figure II).

Management

Management of OH includes non-pharmacological and pharmacological approaches. Non-pharmacological measures are the foundation of OH treatment and should be a mandatory component. As emphasized in Figure 5, addressing possible identifiable and treatable OH confounders, such as pharmacological drugs compromising CV compensatory reflexes (i.e. antihypertensive drugs such as beta-blockers and diuretics or antidepressants), should be the first priority.

Nonpharmacologic Interventions

Non-pharmacologic interventions are listed in an abbreviated Table 1 (Supplemental Table II with supporting evidence and contextual patient considerations available online). Targeted clinical outcomes are contextual – these will vary by patient etiology of OH, comorbidities, and respective goals of treatment. As noted by Arnold and Shibao[67], goals of management are not targeting arbitrary BP values. Rather, the goals of managing OH should be symptom reduction and working collaboratively with the patient to increase activity (e.g., safe ambulation, prevention of falls) and, ultimately, health-related quality-of-life.

Management of OH begins with nonpharmacologic interventions as part of a stepwise approach[67]. However, there are relatively few interventional studies for non-pharmacologic management of OH and many contain small sample sizes with bundled interventions. Further, there is lack of clarity for which, and how many, interventions are appropriate given the context (e.g., etiology of OH, age, goals for activities of daily living).

The majority of existing studies evaluated BP rather than symptoms, independence, syncope, falls, or health-related quality-of-life. The most important nonpharmacologic intervention – patient education – varies widely in content, assessment and availability of resources. Patient education handouts, then, should ideally contain central/generic messaging with individualized edits per patient (see: SAFE patient education sample; Supplemental Table III).

Patient understanding can be encouraged during diagnostic testing with continuous noninvasive BP monitoring. Patients and caregivers can discuss pre-syncopal symptoms and patients can be instructed on how to tense muscles or squat to counteract hypotension.[68] Physical counter-maneuvers are often helpful.[69,70] Further, ambulatory blood-pressure monitoring with patient activity diary can identify presence of postprandial hypotension as well as supine hypertension at night[5,71].

Avoidance of prolonged inactivity, large meals and alcoholic beverages is encouraged[72]. For capable patients (i.e., not on fluid restrictions for heart or kidney failure, without dysphagia), drinking 500 mL of water quickly before standing in the morning or to prevent OH during the day (e.g., before activity) is feasible and supported by evidence. [69,73]

Abdominal compression may offer better efficacy and feasibility than lower limb compression.[70] Compression stockings have low acceptability for daily use among older patients. Sleeping with the head of the bed elevated several inches has been recommended to avoid nocturia and supine hypertension[70]. However, head-of-bed elevation has not been shown to treat OH effectively and should be considered only in select patients with marked nighttime supine hypertension (“reverse dipping”). Head-of-bed elevated sleeping may increase ankle edema and may not be appropriate for all patients.

Insufficient evidence supports recommendations for knee-length compression stockings (only encompassing the calves) or for routine unsupervised increase in salt (Supplemental Table II). Exercise, tailored to etiology of OH, symptoms, and safety (i.e., reclining stationary bicycle, rowing, or swimming) may improve OH by activating skeletal muscle pump[74,75]. Cardiovascular training can increase plasma volume[76]. Nonpharmacologic management of OH should focus on feasible interventions that patients will use and should take into consideration age, ability, and etiology.

Pharmacological interventions

Pharmacologic interventions are listed in Table 2 (a complete table of proposed pharmacological approaches to OH - including supporting evidence - is available as Supplemental Table IV). Despite optimal non-pharmacological approaches to OH, debilitating symptoms can require pharmacological intervention as part of a stepwise approach.

Important caveats for include:

1. Improvement in symptoms and functionality as the goal, rather than correction of OH.

2. Consideration of underlying disease, comorbidities in lieu of beneficial and adverse effects of pharmacological intervention.
3. Avoidance of contradictory pharmacological interventions including concomitant use of fludrocortisone and spironolactone; minimize therapy exacerbating OH.
4. Need for drug combinations.
5. Lack of robust long-term data regarding drug therapy benefit.
6. Uncertainty of synergism between non-pharmacological and drug interventions.
7. Contradictory goals, such as, treatment of hypertension, with reverse dipping, and treatment of OH complicates management.
8. A hierarchical drug approach, i.e., “one-size-fits-all” has not been tested systematically.
9. Concerns about cost and adverse drug effects must be considered.

Despite lack of carefully controlled clinical trials, if nonpharmacological approaches are inadequate, the following approach is reasonable:

1. Carefully and systematically remove medications exacerbating OH used to treat underlying conditions, such as, hypertension, ischemia and heart failure. Consider 24-hour ABPM for more detailed evaluation of circadian BP profile and nighttime short-acting ARB to treat supine hypertension[72].
2. The only FDA approved drugs for OH include midodrine[77–79] and droxidopa (specifically for neurogenic OH)[80–82]. While midodrine can raise blood pressure, it is often not as well-tolerated as droxidopa and less likely to improve symptoms, perhaps, based on its mechanism of action (Figure 6). The adverse effect profile varies between the two with midodrine, working mostly peripherally on α-receptors, causing urinary retention and “goose bumps”, among other symptoms. Midodrine and droxidopa can cause headache; both can exacerbate supine hypertension.
3. Fludrocortisone, to increase intravascular volume and minimally enhance vasoconstriction, may improve neurogenic OH but controlled trials are not convincing; there is risk of hypokalemia and peripheral edema[83]. Fludrocortisone is contraindicated in heart and kidney failure. Fludrocortisone, in combination with midodrine or droxidopa, can be effective to manage neurogenic OH.
4. Pyridostigmine, an acetylcholinesterase inhibitor, affecting nicotinic receptors, and ganglionic neurotransmission, has been effective in small, controlled trials to treat OH, particularly, to increase diastolic BP without worsening in supine hypertension. It may be effective with concomitant use of atomoxetine [84–87]
5. Atomoxetine, blocking the norepinephrine transporter and increasing norepinephrine availability, may have beneficial effects but is only studied in small single center trials [88–90]. Some data, however, suggest atomoxetine may be superior to midodrine[89].

6. Yohimbine, recombinant erythropoietin, pseudoephedrine, desmopressin, octreotide, selective serotonin receptor inhibitors and other therapies have been tried without carefully controlled results[4,91,92] (Supplemental Table IV).

7. Regarding management of supine hypertension, the goal is to reduce SBP <160 mmHg. That level of BP is sufficient to reduce nocturnal pressure natriuresis and improve morning orthostasis; not all medications work equally efficaciously. Short-acting nifedipine, nitroglycerin patches applied at bedtime and removed with an alcohol swab one hour before rising, and shorter acting angiotensin receptor blockers (e.g. losartan) have the most utility. ACE-Inhibitors are less effective based on our experience and, mechanistically, this is supported by the observation that supine hypertension is a renin activity independent AT1 receptor mediated event[72].

8. In mixed OH, volume expanders and vasoconstrictors should be considered but, special regard to cardiac and renal failure is critical as volume expanders might be contraindicated. Optimization of cardiac function (revascularization, arrhythmia treatment, etc.) may substantially improve cardiac output, diminish orthostatic BP fall and alleviate symptoms. Daytime vasoconstrictor therapy and nighttime vasodilating drug administration should be considered.

9. Regarding management of patients with cardiac amyloidosis (±autonomic neuropathy), CHAD-STOP (Conduction and rhythm disorders prevention, High heart rate maintenance, Anticoagulation, Diuretic agents, and STOP ß-receptor and calcium-channel blockers, digoxin, RAAS inhibitors) measures should be considered[93]. Specific treatments, such as, transthyretin tetramer stabilizers (i.e. tafamidis, diflunisal) and transthyretin lowering treatments (i.e. patisiran, inotersen), may affect the natural history of OH, although dedicated studies are lacking[94].

10. To manage risk of OH secondary to polypharmacy, especially using drugs targeting orthostatic BP regulation (i.e. beta-blockers, tricyclic antidepressants, antipsychotics, alpha-blockers, SGLT-2 inhibitors)[95], alternative prescribing, shorter treatment, postural BP checks and heightened awareness by patient, family and clinicians (nurses, physical and occupational therapists, pharmacists) should be considered.

Pacing

Rate-adaptive pacemaker systems have not been carefully tested, are controversial and, in fact, may be completely ineffective to treat symptomatic OH. Short and intermediate effects of atrial pacing on symptoms and BP in severe, drug-refractory OH have been evaluated in two pilot studies yielding controversial results[96,97]. However, among elderly pacemaker patients with chronotropic incompetence transient pacing upon standing was observed to prevent OH[98].

In the CLEAR study, closed-loop stimulation enabled a more physiological response during performance of activities of daily living, with remarkable decrease in OH and an

increase in activities requiring lower energy expenditure in activities more sensitive to need for chronotropic response[99]. In symptomatic patients with marked bradycardia and suspected chronotropic incompetence (i.e., “sinus node dysfunction”) and neurogenic OH, rate-responsive (particularly, closed loop stimulation) pacing may offset the severity of OH as supported by recent randomized trials[100,101].

Recurrent syncope and unexplained injuries in paced patients are command prompt assessment. A likely etiology may be non-arrhythmic successfully identified by cardiovascular autonomic testing[102]. A common cause is OH (preferentially, in older subjects).

Clinical Cases

Representative cases illustrate the approach to complicated clinical issues.

Case #1

A 72-year-old man, referred for dizziness and recurrent transient loss of consciousness, had history of myocardial infarction, New York Heart Association (NYHA) functional class II heart failure and insulin-dependent type 2 diabetes complicated by chronic kidney disease, retinopathy and polyneuropathy. Transient loss of consciousness occurred during daily walks and activities when standing. The patient reported increasing daily symptoms in upright position, severely affecting his quality-of-life. During walks, he had to stop frequently due to sudden dizziness.

Evaluation—Evaluation included: 1. transthoracic echocardiography showing moderately impaired left ventricular global systolic function (ejection fraction 40%); 2. coronary angiography demonstrating non-obstructive coronary disease; 3. brain computed tomography documenting global cortical atrophy grade II along with minor white matter changes; 4. A 3-minute active standing test, revealing SBP decrease from 120 mmHg to 100 mmHg; 5. 24-hour ambulatory BP monitoring, revealing slightly elevated daytime and similar nighttime BPs indicating a non-dipping pattern. The Valsalva-maneuver was pathological with a blunted response (Supplemental Figure III). HUT showed SBP decrease of 60 mmHg associated with his typical symptoms (dizziness, nausea, headache) consistent with classic OH. The test was stopped after eight minutes of standing when the SBP reached 80 mmHg (Supplemental Figure IV).

Interpretation and diagnosis—This patient has *classical OH* (orthostatic symptoms and BP decrease during 3-minute active standing test) in the setting of several co-existing chronic conditions (heart failure, ischemic heart disease, cerebrovascular disease, diabetes, renal failure) consistent with *mixed OH* (cardiovascular and neuropathic) etiology, likely aggravated by β-blocker and nitroglycerin use. It is unknown whether the patient had asymptomatic OH before development of CV disease, or whether progression of CV disease led to the symptoms of OH.

Management—Management included avoidance of orthostatic intolerance triggers, non-pharmacological measures such as counterpressure maneuvers while standing, purposeful

hydration, keeping the head of the bed elevated, withdrawal/reduction of beta-blockers, and shift to nighttime heart failure medications. Night-time short-acting ACE/ARB inhibitors are a great choice for heart failure with reverse dipping hypertension in this circumstance.

As angiotensin II formation in autonomic failure is independent of plasma renal and activity, and perhaps angiotensin-converting enzyme, angiotensin II contributions to the hypertension and autonomic failure suggests that the use of AT_1 receptor blockers make the most sense[72]. If symptoms persist, further interventions include withdrawal of antihypertensive treatment and addition of BP elevating drugs during the daytime.

Case #2

Background—A 69-year-old man with hypertension, hyperlipidemia and renal insufficiency was referred for episodic dizziness, lightheadedness, “warmth in his head” and syncope. A 24-hour BP monitor showed mean BP of 155/81, daytime BP 159/84, nighttime BP 139/70, maximal value BP 211/151 and lowest BP 86/70.

Two years earlier, 24-hour ECG monitoring showed sinus rhythm, mean value 53 bpm (range: 41-83). Prior orthostatic vital signs showed sitting BP of 154/91 (pulse 44) to 129/94 (pulse 49) after 4 minutes and 144/86, (pulse 48) after 6 minutes of standing. The patient reported dizziness on rapid standing. Resting ECG showed sinus rhythm, rate 46 and a right bundle branch block.

Evaluation—An exercise ECG showed exercise capacity 104% (188 W) with maximal heart rate of 115 bpm (76% of normal value). The resting BP was 185/90 but under maximal workload was 220/- and 3 minutes after work, 215/65 mmHg. One minute after test termination, 45-seconds of supraventricular tachycardia was followed by a nodal rhythm with isolated monomorphic premature ventricular contractions. During an active standing test, systolic BP fell >50 mmHg within 15 seconds with symptom reproduction (Supplemental Figure V). Valsalva test was normal.

During carotid sinus massage, a short-lived nodal rhythm 37 bpm (right side), hypotension and presyncope were observed. During HUT, the supine BP was 160/88 mmHg. The patient demonstrated classical OH without syncope. During nitroglycerin provocation (starting at SBP 105 mmHg), no vasovagal reflex was present but pronounced hypotension led to reproduction of typical symptoms.

Interpretation and diagnosis—The patient had initial (immediate, transient) and classical OH, bradycardia and carotid sinus hypersensitivity. The patient had normal Valsalva response and no history of neurodegenerative disease, diabetes, cancer, or autoimmune disease, which spoke against the possibility of neurogenic OH. The most plausible etiology was cardiac related to chronotropic incompetence, and impaired venous return on standing, as demonstrated by progressive BP fall during tilt testing.

Management—Education, including safety measures, such as, walking with another person, avoidance of orthostatic intolerance triggers, non-pharmacological measures such water bolus drinking prior to walking and counterpressure maneuvers were recommended.

As symptoms persisted, a vasoconstrictor during daytime (midodrine) and pacemaker implantation were considered and applied. During one-year follow-up, the patient remained symptom free.

Case #3

Background—A 56-year-old woman was referred for episodes of dizziness, deconditioning, nausea, weight loss, migraine, chest pain, palpitations, headache and imminent loss-of-consciousness. She had history of mononucleosis, cholecystectomy, haemochromatosis, Hashimoto disease, and myalgic encephalitis/chronic fatigue syndrome.

Evaluation—HUT and cardiovascular autonomic testing demonstrated delayed OH followed by hypotension-evoked vasovagal reflex (Supplemental Figure VI) with good reproduction of spontaneous attacks. Valsalva test was normal (Supplemental Figure VII). The average BP was 150/90 mmHg.

Interpretation and diagnosis—The patient had delayed OH and vasovagal reflex susceptibility. There was a normal Valsalva response and no evidence of neurogenic OH. The most plausible etiology was cardiac related to impaired venous return, reduced cardiac output and hypotension. Chronotropic response was adequate. Delayed OH is often associated with neurodegenerative disease, may be an early manifestation of autonomic failure, and may convert to classical orthostatic hypotension. Long-term follow up of this and similar patients is warranted.

Management—Aside from counterpressure maneuvers, avoidance of triggers and non-pharmacological measures (increased fluid intake and compression stockings), stepwise pharmacological therapy may help.

Case #4

Background—A 55-year-old, otherwise healthy, male initially presented after collapsing briefly while standing following a large dinner. He had intermittent lightheadedness and blurred vision when walking, but symptoms abated with sitting, squatting or lying. He reported constipation, erectile dysfunction, and nocturia. Supine BP was 157/92 mmHg (heart rate 72 bpm). After standing 3 minutes, BP was 141/85 mmHg (heart rate 74 bpm). His gait was broad-based, with a reduced swing in the right arm; rapid alternating movements were reduced in the right hand.

Evaluation—During Valsalva, there was no BP overshoot after release of strain (i.e., phase IV), indicating impaired baroreflex-mediated sympathetic activation. During tilt testing (Supplemental Figure VIII), a slow decline in BP occurred with minimal increase in heart rate. Supine plasma norepinephrine (271 pg/mL) did not increase substantially during tilt testing consistent with *delayed neurogenic OH*. Considerations included: peripheral neuropathies (e.g., diabetes, amyloidosis) or neurodegenerative causes, such as synucleinopathies (Parkinson's disease, multiple system atrophy or dementia with Lewy bodies)[50,56].

Non-pharmacologic measures were unsuccessful. Instead, he developed progressive symptoms including dizziness/lightheadedness and dyspnea with walking or after climbing stairs. During active standing performed later, supine BP was 159/101 mmHg (heart rate 82 bpm), and after 3 minutes standing, BP was 84/37 mmHg (heart rate 98 bpm) with symptoms.

He noted “clumsiness”, falls, urinary urgency and frequency, and slurred speech. His wife noted he “acts out” and speaks during sleep. He developed dysarthric speech, ataxic gait (with reduced right arm swing), horizontal nystagmus on lateral gaze with broken-up smooth pursuit. Deep tendon reflexes were brisk and a right Babinski sign developed. He had no resting tremor. Finger-to-nose and heel-to-shin were inaccurate.

Brain MRI showed cerebellar and pontine atrophy with a “hot-cross bun” sign (Supplemental Figure IX). Polysomnography confirmed episodes of motor/behavioral activity as well as speaking/shouting during rapid eye movement (REM) sleep, consistent with REM behavior disorder.

Interpretation, diagnosis and management—Progressive neurogenic OH with features that include cerebellar (ataxia and dysarthria), parkinsonian (rigidity and bradykinesia), pyramidal (Babinski sign), and autonomic (neurogenic OH, urinary disorders) deficits fulfils criteria for multiple system atrophy.[103] Supporting this diagnosis was the MRI showing cerebellar and brainstem atrophy as manifest with a “hot cross bun” sign.

Multiple system atrophy is a rapidly progressive, fatal α-synucleinopathy. Approximately 50% require walking aids within 3 years after onset of motor symptoms, 60% require a wheelchair after 5 years, and the median time to death is 6-8 years.[104] In those patients presenting with severe OH, there is an urgency to maximize orthostatic tolerance early in the disease. However, this may increase the risk of supine hypertension with complications including renal failure, left ventricular hypertrophy, stroke.[49] A detailed neurological examination at initial evaluation in follow-up can identify patients at risk for this debilitating condition.[105]

CASE #5

Background—A 30-year-old mother passed out while caring for her sick child. After IV hydration in the emergency department, she was discharged. Subsequently, she had witnessed syncope and was admitted. Testing, including EKG, BP, Holter monitor, and echocardiogram, were normal. She noted progressive frequent postural lightheadedness with dyspnea and neck pain and developed constipation and urinary difficulties. Several more syncopal spells ensued, including an episode with head trauma. During re-evaluation at the emergency department, right-sided ptosis and bilateral pupil dilation with diminished pupillary reactivity was noted. Head CT and MRI were normal. Supine BP was 163/94 mmHg (pulse 60) but with standing, her BP decreased to 82/44 mmHg (pulse 60) with syncope. Intravenous fluids (3 liters), fludrocortisone 0.4 mg daily and midodrine 20 mg three times a day were without benefit.

Evaluation—Neurological examination showed bilateral ptosis, pupils not responsive to light, dry mouth, and dry eyes. CV autonomic testing showed reduced heart rate variability to paced breathing, sympathetic adrenergic failure with loss of BP recovery and overshoot on Valsalva maneuver and OH noted on tilt and stand with a drop in systolic BP of >60 mmHg (Supplemental Figure X). There were mild abnormalities noted on sudomotor function testing.

Interpretation and diagnosis—The symptoms and test results indicated involvement of parasympathetic and sympathetic divisions of the autonomic nervous system. Further work-up involved a malignancy evaluation including paraneoplastic autoantibody panel, CT of chest, abdomen and pelvis, and mammogram. The paraneoplastic panel identified an elevated titer of ganglionic acetylcholine receptor (AChR) antibodies (1900 pm/ml; normal values<5) consistent with autoimmune autonomic neuropathy (AAG). AAG shows unique clinical features including severe pan-autonomic failure with associated sicca syndrome (dry mouth and dry eyes). The clinical pearl, ptosis and pupillary responses, help support the clinical diagnosis, which is confirmed by measurement of AChR antibody titers.[106,107]

Management—Treatment included aggressive fluid regimen, salt, fludrocortisone (0.2 mg), droxidopa (600 mg three times a day) and polyethylene glycol (for constipation), but this was largely unsuccessful. The patient was started on a cycle of plasma exchange, prednisone, and mycophenolate mofetil.[108] She had modest benefit but more sustained improvement in BP with plasma exchange. With reduction in antibody titers, pharmacologic support for symptoms is reduced (Supplemental Figure XI).

Although symptomatic treatment may be helpful for initial management, long-term treatment requires immunomodulatory therapies to suppress autoantibody production, or removal of the underlying malignancy if found.[108] Other treatment options include intravenous immunoglobulins and rituximab.[109] Some reports have noted an associated of AChR autoantibodies and malignancy,[110] thus there is a need for vigilance in the monitoring of patients with AAG for the emergence of an underlying oncologic process.

Cardiovascular Autonomic Dysfunction In Post-Covid Syndrome—Recently, persistent cardiovascular autonomic dysfunction (CVAD) following acute coronavirus disease 2019 (COVID-19) has been observed[111–113]. Post-Acute COVID-19 Sequelae (PACS) or long COVID syndrome, typically presents as a spectrum of symptoms dominated by fatigue, exercise and orthostatic intolerance, exaggerated sinus tachycardia, chest pain, headache, sleep disturbances and dyspnea. According to the generally accepted definition[114], PACS stretches over a period exceeding 12 weeks after index infection, even if mild. Women aged 20-45 are most affected. Besides the two most prevalent forms of CVAD, postural orthostatic tachycardia syndrome and inappropriate sinus tachycardia[111,113], OH may occur as the main hemodynamic manifestation of PACS[113,115], particularly in patients over the age of 50. When long COVID syndrome is suspected, the patient should be evaluated by orthostatic vitals (both blood pressure and heart rate) or head-up tilt testing optimally with beat-to-beat hemodynamic monitoring. When in doubt, the tests should be repeated, and symptoms recorded as signs of CVAD may vary temporally depending on

disease progression, hydration status, medications and application of non-pharmacological measures.

Future Research—Gaps remain regarding pathophysiology and effective long-term management of OH. First, identifying a specific cause and the resulting pathophysiology may direct better pharmacological and non-pharmacological management approaches. Second, better understanding of pathological mechanisms underlying neurogenic, non-neurogenic and mixed forms of OH may contribute to more effective therapeutic strategies, especially for therapy-resistant individuals with comorbidities of heart failure, cardiac arrhythmia, or kidney failure. Further, long-term management based on pharmacological or non-pharmacological approaches for most patients remains challenging. Most therapies that improve OH increase the risk of supine hypertension with concerning consequences.

Similarly, well-powered, multi-site trials to evaluate non-pharmacologic interventions are needed to show benefit and find ways to avoid harm. These should include further evaluation of specific protocols for physical counter-pressure maneuvers, compression devices, oral fluid boluses, and combinations of various therapies. Integrative therapies, used successfully in other chronic patient populations, may deserve investigation for possible use in the OH population.

Robust trials with expanded pragmatic outcome measures may facilitate understanding for which interventions truly improve symptoms to the extent that patients experience less syncope, fewer falls, more independent activities, and ultimately better health-related quality-of-life and functionality.

Conclusions

OH is a common, yet, overlooked, condition often associated with, or due to, neurologic and cardiac diseases. We propose classifying OH into *neurogenic*, *cardiogenic* and *mixed forms* to guide a pragmatic approach to this potentially complex condition. Actual case studies presented here address critical evaluation and management strategies in patients with OH. Without doubt, management of OH optimally involves a multidisciplinary, patient-centered, often, individualized approach to arrive at an appropriate diagnosis, address underlying etiologies and accompanying conditions, and to provide tailored and potentially effective pharmacological and non-pharmacological treatment strategies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

BP	blood pressure

COVID-19	coronavirus disease 2019
CV	cardiovascular
CVAD	cardiovascular autonomic dysfunction
DBP	diastolic blood pressure
HR	heart rate
HUT	head-up tilt
NYHA	New York Heart Association
OH	orthostatic hypotension
PACS	Post-Acute COVID-19 Sequelae
PD	Parkinson disease
SBP	systolic blood pressure

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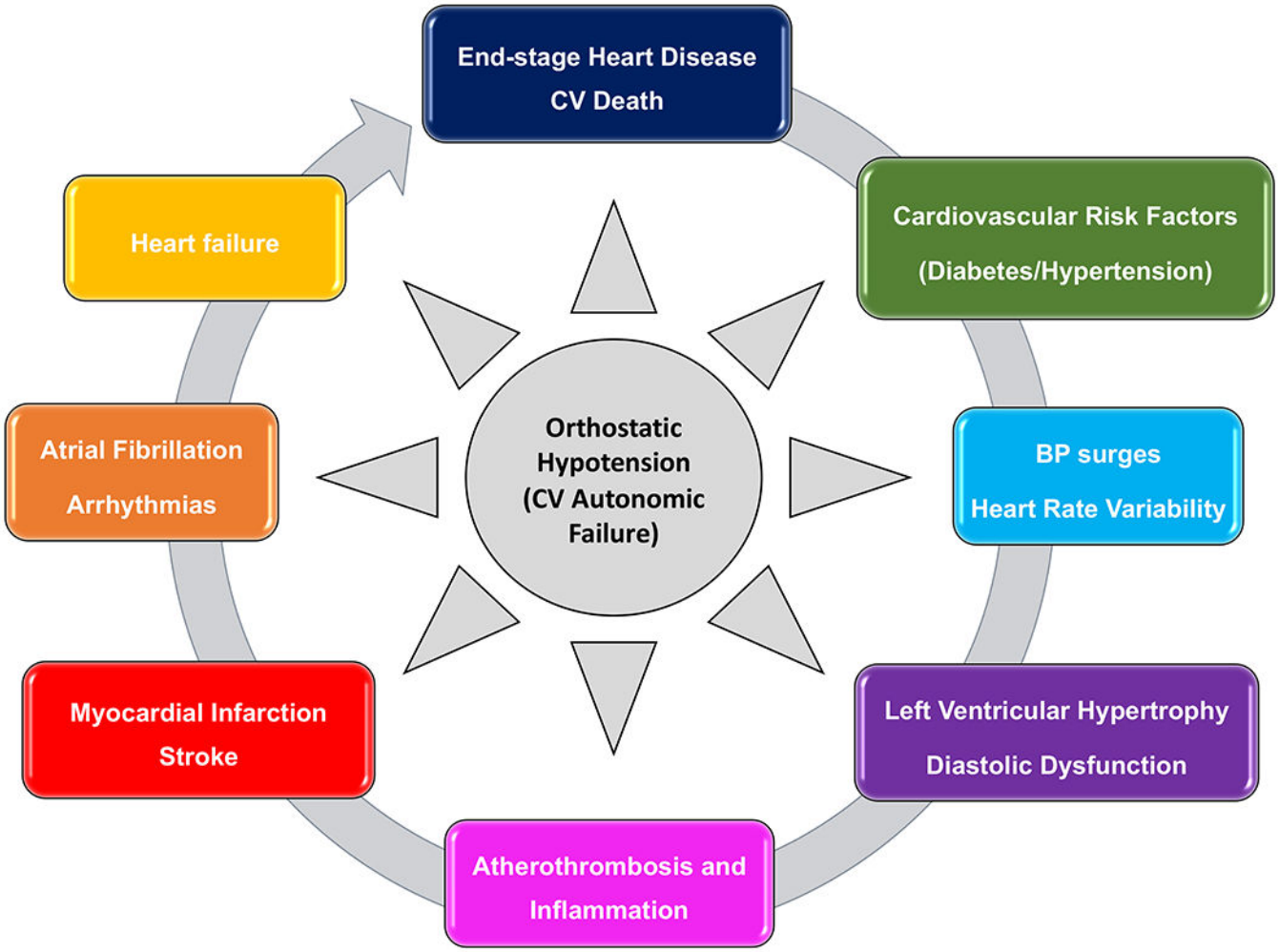

Figure 1.

Cardiovascular disease cascade and autonomic dysfunction. Orthostatic hypotension has been associated with different mechanisms involved in cardiovascular disease progression, from a strong relationship with traditional cardiovascular risk factors and subclinical changes on functional level to increased risk of cardiovascular death.

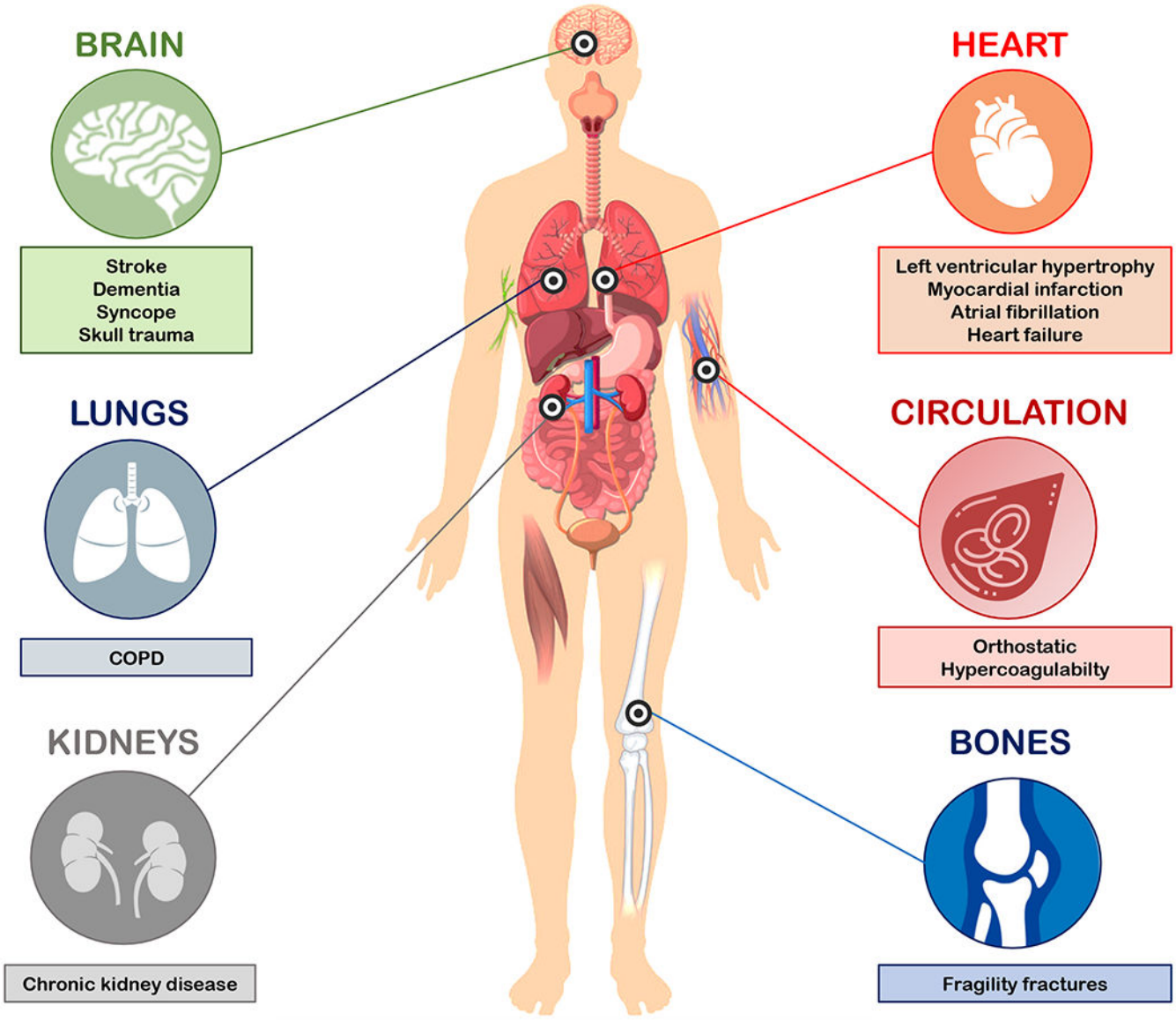

Figure 2.

Cardiac and extracardiac disorders associated with cardiovascular autonomic dysfunction as represented by orthostatic hypotension.

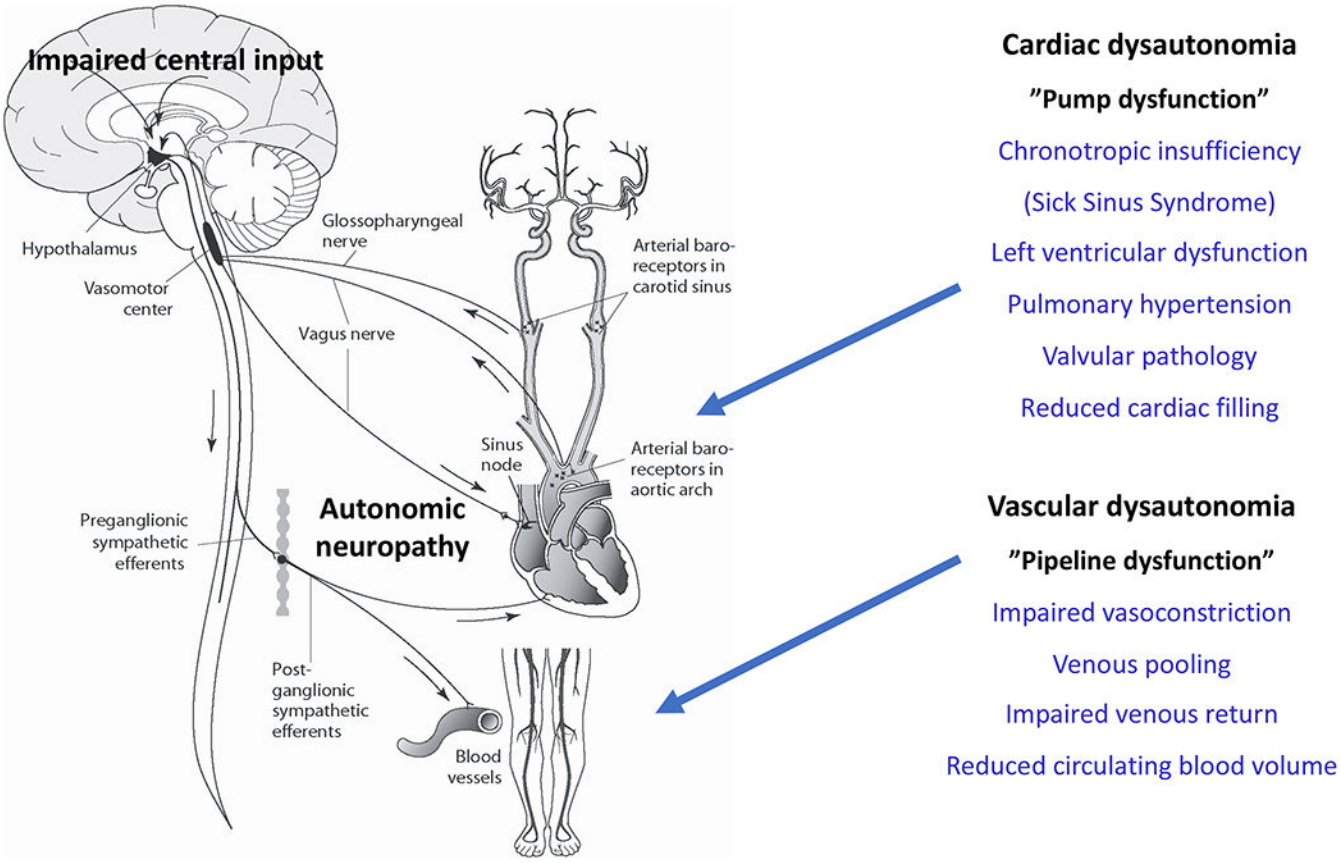

Figure 3.

Global blood pressure control and mechanisms of orthostatic hypotension. The etiology of orthostatic hypotension (OH) is heterogenous and spans neurodegenerative diseases (e.g., Parkinson's disease), diabetes, renal failure, inflammatory states, autoimmune diseases (e.g., Sjögren's disease), and cardiovascular conditions (e.g., essential hypertension and heart failure). Disorders that directly affect central and periphery autonomic neural input are traditionally termed "neurogenic OH". Two major types of cardiovascular autonomic dysfunction, i.e., cardiac and vascular dysfunction may overlap and interact.

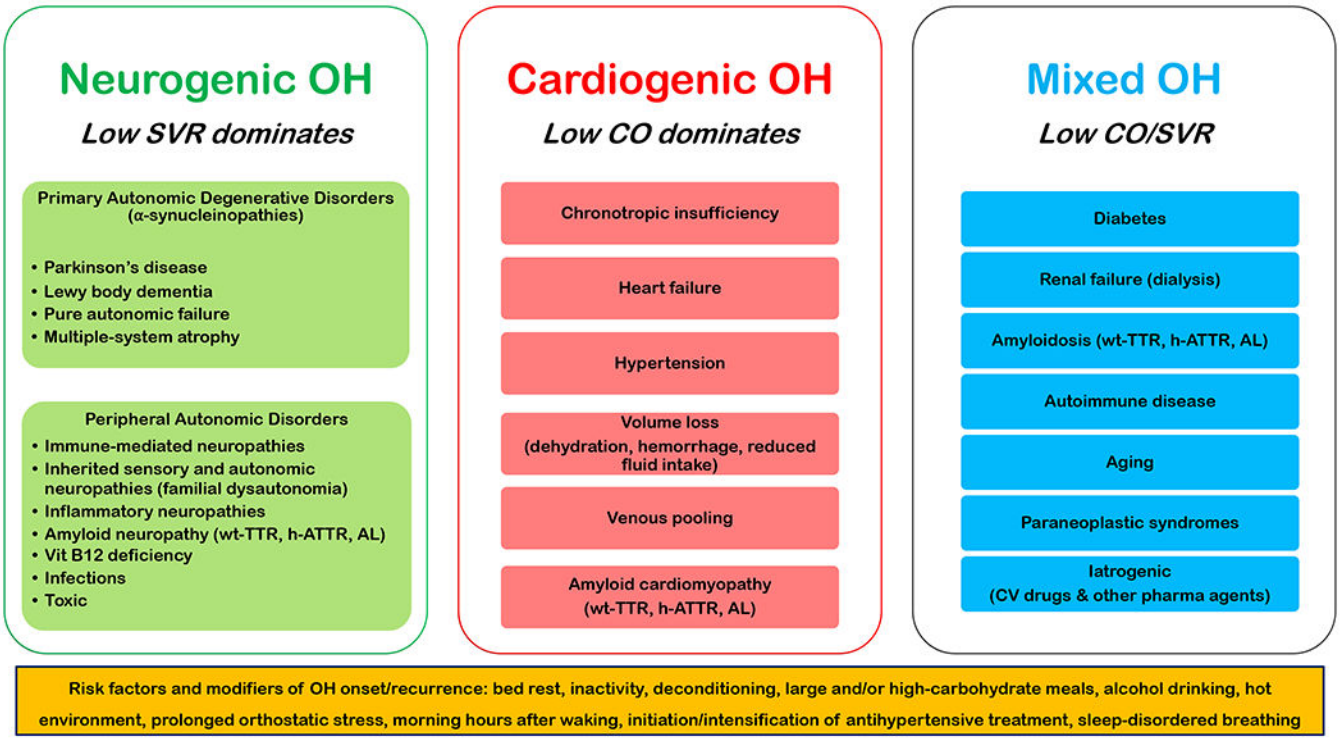

Figure 4.

Proposed classification of orthostatic hypotension based on interaction between autonomic nervous system and cardiovascular system. Mixed etiology affects both the autonomic nervous system and cardiovascular organs, the heart and the vessel.

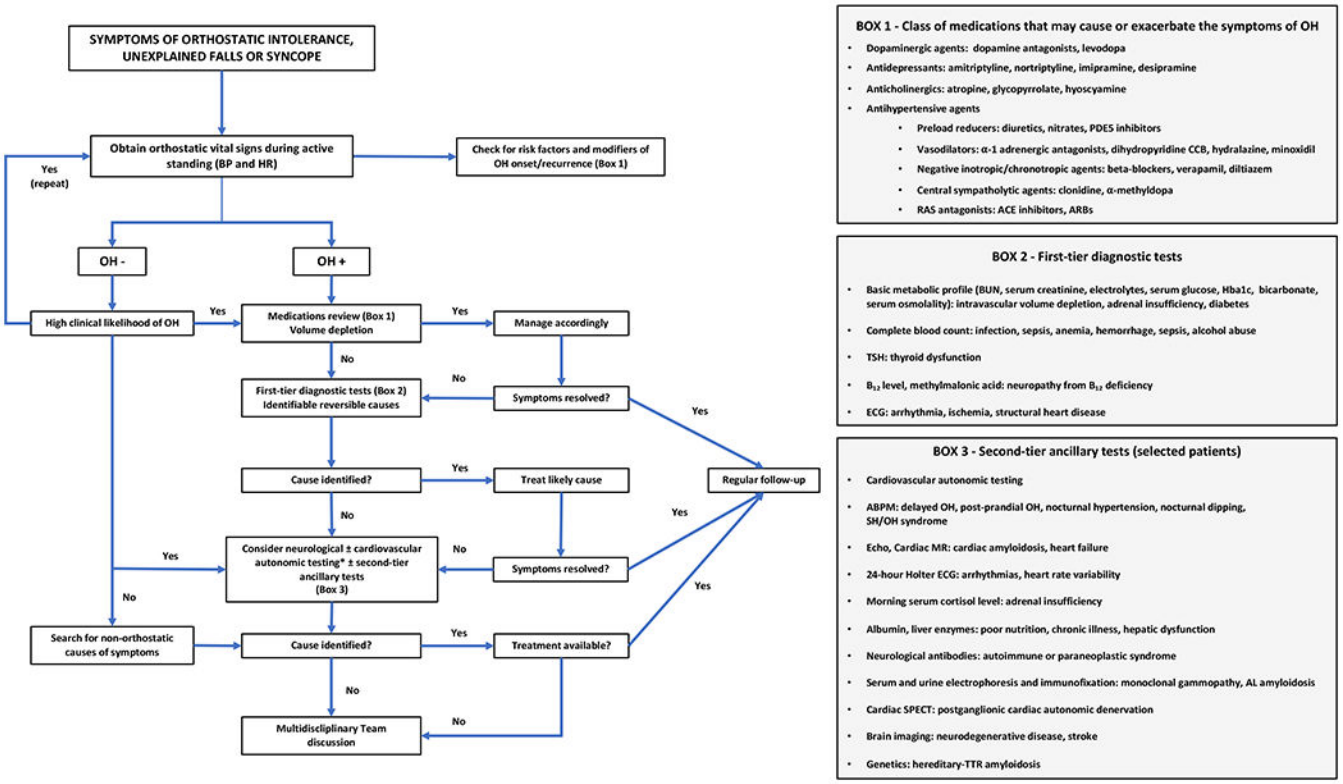

Figure 5.

Proposed orthostatic hypotension evaluation algorithm. Go to Supplemental Figure II for further details.

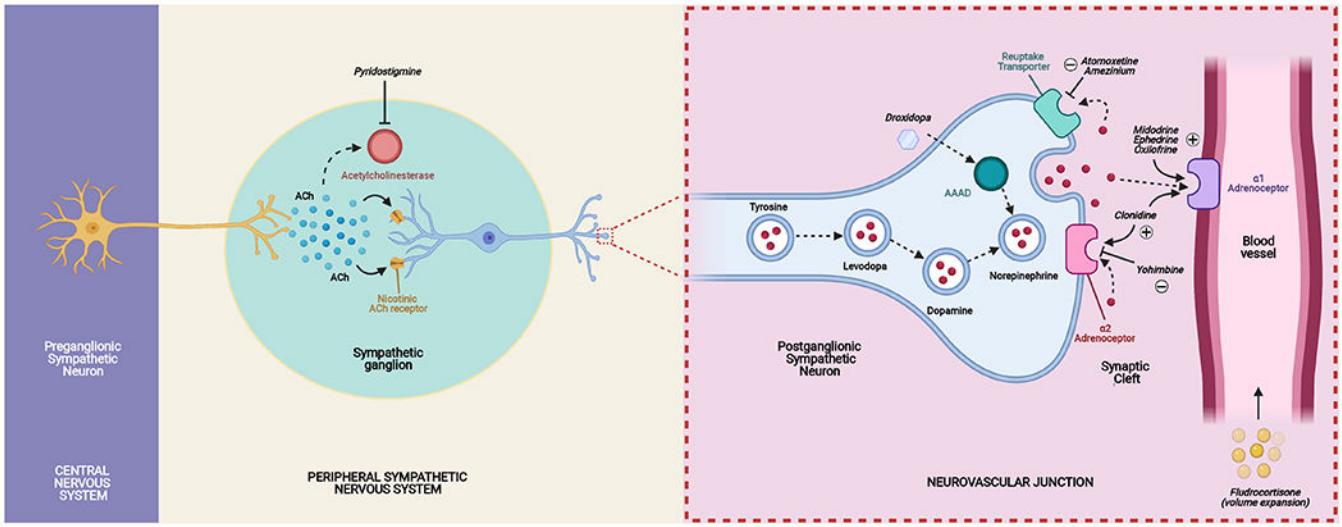

Figure 6.

Sites of action and mechanisms of therapeutic agents used for the treatment of neurogenic orthostatic hypotension. Modified from Palma et al.[54]

(Created with BioRender.com).

Table 1.

Non-pharmacologic interventions for OH

Intervention
Patient and family education for: • Reasons for symptoms • Safety measures to avoid OH-related falls • Recognition of pre-syncopal symptoms • Avoidance of triggers (i.e. heat exposure, over-exertion, alcohol, hot tubs, dehydration) • Caution with Valsalva-like maneuvers (avoiding strain with defecation, urination) • Patient diary to record physical activity and meals; further ambulatory blood-pressure monitoring *(with patient activity diary*) can help identify presence of postprandial hypotension as well as supine hypertension at night
Counterpressure maneuvers for preventing symptoms and/or emergency management of symptoms • crossing legs upon standing, • abdominal & leg muscle pumping/contractions, • and bending forward or squatting.
Activity & positioning • Avoid prolonged sitting or standing. If prolonged inactivity, do ankle pumps & cross/uncross legs • Avoid abrupt change from lying to standing (i.e., sit at the edge of the bed for a minute before standing) or sitting to standing • Rise gradually from sitting to standing (i.e., after being inactive or sitting on the toilet) • Sit after eating or exercise (i.e., for 20 minutes); record symptoms related to meals or exercise
Drinking fluids to ensure hydration • Additional oral water bolus (i.e., about 400-500 mL within 5 minutes) may help when symptomatic, before arising in the morning, before exercise or after eating (if not contraindicated due to co-morbidities) • Bolus drinking may not be appropriate for patients at risk for fluid overload (i.e., heart failure, end-stage kidney disease)
Compression garments if properly fit and patient is able to apply, remove, and tolerate • Abdominal binder may reduce symptoms for patients prior to an outing or event • Full leg compression stockings (e.g., ankle to hips compression stockings at 22-32 mmHg, not just calves or thighs)
Coping, support, and integrative therapies, such as, cognitive behavior strategies, support groups, and mindfulness stress reduction techniques, have been effective in similar populations and anecdotally recommended by clinicians
Due to limited evidence, negative studies, and/or potential side effects, avoid indiscriminate recommendation for:
Lower limb compression stockings
Sleeping with head of bed elevated
Increasing salt in diet

Note: For expanded table with references, please see Supplemental Table II.

Table 2.

Main drugs used for treatment of symptomatic patients with orthostatic hypotension

Drugs	Mechanism(s)	Adverse events
Droxidopa (100–600 mg tid) *	Norepinephrine precursor	Headache, nausea, supine hypertension
Midodrine (2.5–10 mg bid or tid) *	Direct alpha1-adrenoreceptor agonist	Goose bumps, paresthesia, pruritus, supine hypertension, urinary urgency
Fludrocortisone (0.05–0.3 mg qd)	Mineralocorticoid (volume expander), increases sodium reabsorption and enhances sensitivity of alpha-adrenoreceptors	Supine hypertension and hypokalemia
Pyridostigmine (30-60 mg bid or tid)	Acetylcholinesterase inhibitor	Gastrointestinal symptoms, urinary urgency
Atomoxetine (18 mg qd)	Norepinephrine reuptake inhibitor	Supine hypertension, urinary urgency
Octreotide (0.2–1.6 mg/kg qd, subcutaneous)	Somatostatin analog reducing postprandial splanchnic hyperemia induced by gastrointestinal vasodilatory peptides	Injection site discomfort, erythema, gastrointestinal disturbances, flushing, cholelithiasis, hyperglycemia, supine hypertension
Desmopressin (nasal spray, 5–40 mg qd; oral, 100–800 mg qd)	V1a (vascular smooth muscle) and V2 (distal convoluted tubule and collecting ducts of the kidney) receptor agonist. Vasopressin analogue (volume expander), increases water reabsorption and reduces nocturia	Limited data, safety issues unclear
Ephedrine/pseudoephedrine (25/30 - 50/60 mg 3 times per day)	Direct and indirect alpha1-adrenoreceptor agonist	Nausea, supine hypertension

* FDA approved.

Note: for expanded table with references and complete list of proposed pharmacological interventions for treatment of OH, please see Supplemental Table IV.