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REVIEW ARTICLE

Syndrome of Supine Hypertension with Orthostatic Hypotension: Pathophysiology and Clinical Approach

Aamir Ahmed[1], Mohammed Ruzieh[2,*], Shaffi Kanjwal[3] and Khalil Kanjwal[4]

[1]*Department of Internal Medicine, Rush University, Chicago, IL 60612, USA;* [2]*Penn State Heart and Vascular Institute. Hershey, PA 17033, USA;* [3]*St Mary's of Michigan, USA;* [4]*McLaren Greater Lansing Hospital, Lansing, MI 48910, USA*

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Abstract: This article is intended to provide guidance and clinical considerations for physicians managing patients suffering from supine hypertension with orthostatic hypotension, referred to as "SH-OH". We review the normal physiologic response to orthostasis, focusing on the appropriate changes to autonomic output in this state. Autonomic failure is discussed with a generalized overview of the disease and examination of specific syndromes that help shed light on the pathophysiology of SH-OH. The goal of this review is to provide a better framework for clinical evaluation of these patients, review treatment options, and ultimately work toward achieving a better quality of life for patients afflicted with this disease.

Keywords: Orthostatic hypotension, supine hypertension, autonomic failure, dysautonomia, blood pressure, orthostatic posture.

1. INTRODUCTION

Orthostatic hypotension (OH) is a potentially debilitating condition that is more prevalent in the elderly. The development of this condition is related to dysfunction of the autonomic nervous system, which is essential for the physiologic response to orthostatic posture. Though age-related degeneration of sympathetic output is responsible for many cases of orthostatic hypotension, this condition is also quite prominent in diseases of the autonomic nervous system such as multiple system atrophy, pure autonomic failure, Parkinson's disease, and diabetes mellitus [1]. In addition to orthostatic hypotension, pathologic autonomic dysfunction can also be associated with the development of concurrent supine hypertension (SH) [2]. This paradoxical effect speaks of the complexity of the pathogenesis of autonomic disease and greatly complicates the management of these patients. Clinicians are faced with a dilemma, as aggressive treatment of orthostatic intolerance can worsen supine hypertension and attempts to control supine hypertension can worsen orthostatic intolerance.

2. EPIDEMIOLOGY

The prevalence of orthostatic hypotension is relatively uncommon in otherwise healthy elderly individuals [3]. In hypertensive patients, the prevalence of orthostatic hypotension ranges between 5% and 12% depending on the population studied [4, 5]. Many of these patients were asymptomatic. In these studies, orthostatic hypotension was associated with advancing age and cardiovascular diseases [4, 6].

3. PHYSIOLOGY OF ORTHOSTATIC POSTURE

Response to a cardiovascular insult or any factor that alters hemodynamic status is profoundly complex and multifaceted. The cardiovascular system itself is composed of several physiologic parameters which reflect the overall cardiac function. Cardiac output is measured as the product of stroke volume and heart rate, but these factors themselves are determined by intricate and complicated interactions. Stroke volume is affected by factors affecting both the end-systolic volume (*i.e.* preload, afterload, myocardial contractility, heart rate) and end-diastolic volume (*i.e.* filling pressures, filling time, ventricular compliance). Heart rate is subject to intrinsic regulation stemming from characteristics of pacemaker cells such as threshold potential and slope of depolarization, as well as extrinsic regulation from humoral stimulation and autonomic innervation. Aside from these intrinsic cardiovascular pathways and systems, the cardiovascular system as a whole is largely dependent on input from other body systems, including the autonomic nervous system, the endocrine system, the urinary system, and the respiratory system, among several others [1, 2].

The physiology of standing presents the human cardiovascular system with a challenge, as the effect of gravity propels blood away from the organs of the upper body, including the brain and heart, to the veins of the lower extremities. In a uniform system with 5 liters of blood, moving from a horizontal to vertical position theoretically causes a signifi-

*Address correspondence to this author at the Penn State Heart and Vascular Institute. Hershey, PA 17033, USA; E-mail: Moh.ruzieh@gmail.com

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cant drop in right atrial pressure and pooling of nearly 2 liters in the lower extremities. However, the actual amount of this pooling is closer to 0.5 liters in healthy adults [1]. This is due to several factors. Firstly, blood is not uniformly distributed throughout the body. Normally, two-thirds of the total blood volume is found in the systemic venous system. When a patient is supine, most of this blood can be found in the thoracic veins. Upon standing, cardiac output is initially greater than the venous return to the heart, and this excess of blood makes up majority of the blood that pools in the legs. The presence of muscle pump systems also enhances venous return. Muscles of the legs and abdomen are coupled with valves in the venous system that project blood upward during contraction.

Perhaps, the most important contributor to the body's adjustment to the orthostatic position is the effect of the autonomic nervous system. The initial decrease in venous return to the right atrium eventually leads to a decrease in left ventricular stroke volume. This results in a nearly 20% drop in cardiac output, which leads to a decrease in arterial pressure [1]. The drop in arterial pressure triggers high-pressure baroreceptors in the carotid sinus and aortic arch, innervated by glossopharyngeal and vagal afferents, respectively. These receptors then send signals of decreased pressure to the nucleus tractus solitarii (NTS) located bilaterally in the dorsal medulla. The NTS communicates with the vasomotor area of the ventrolateral medulla, which facilitates an increase in sympathetic output, leading to an increase in vascular tone, heart rate, and contractility in order to re-establish arterial pressures. This also increases venous tone and venous return to the right atrium. Simultaneously, the NTS decreases output from the cardioinhibitory area (composed of the nucleus ambiguus and the dorsal motor nucleus of the vagus) to decrease parasympathetic output. The magnitude of this autonomic response to standing is highly variable and depends on several systemic and hemodynamic factors. Any defect in this pathway can result in significant clinical consequences, including cerebral hypoperfusion and syncope [1].

3.1. Autonomic Failure

The syndrome of supine hypertension with orthostatic hypotension (SH-OH) is associated with conditions causing autonomic failure [1, 7]. Therefore, it is necessary to understand the physiology and clinical manifestations of autonomic dysfunction in order to better understand the pathogenesis of SH-OH.

The autonomic nervous system allows the body to ascertain information from the periphery, to process this information, and to evoke an appropriate physiologic response to adjust to its specific needs at that moment. It can be thought of as three separate processes: 1) the transfer of information regarding the physiologic state of the body from the peripheral nervous system to the central nervous system via afferent inputs, 2) the processing of this input in the central nervous system, and 3) the physiologic response of the body evoked through efferent neurons traveling back to the peripheral nervous system. This efferent response is either sympathetic or parasympathetic, depending on the specific needs of the body. Dysfunction of the autonomic nervous system, or dysautonomia, can be a result of damage to any of these three limbs. Disorders of the brain that can cause dysautonomia include Parkinson's disease, multisystem atrophy (MSA), as well as tumors and other lesions. Dysautonomia can also be associated with spinal cord pathologies, such as traumatic injury, auto-antibodies against adrenergic and cholinergic receptors, tetanus, or multiple sclerosis. Peripheral neuropathies resulting from diseases such as diabetes mellitus, amyloidosis, or Guillain-Barré syndrome can also lead to autonomic dysfunction [8, 9].

Regardless of the etiology of autonomic failure, the clinical presentation tends to be similar in that the OH tends to be the most prominent and disabling symptom due to impairment of the baroreflex and excessive pooling of blood in the lower extremities [8, 10]. Certain studies have shown that up to half of the patients suffering from OH as a result of autonomic dysfunction also have SH [8, 11, 12]. SH can have serious consequences and greatly complicate management of patients, as it has been associated with left ventricular hypertrophy, organ damage, and increased mortality [11, 13, 14]. SH can also worsen symptoms of OH, likely secondary to increased nocturnal natriuresis stemming from increased pressures, which leads to excessive volume depletion and worsening of cerebral hypoperfusion upon standing [7, 8, 15].

Though there are many potential secondary causes of autonomic dysfunction, dysautonomia with impaired blood pressure regulation is more typical of primary autonomic dysfunction [7]. Primary autonomic disorders include MSA and pure autonomic failure [1, 7, 8]. It is important to be familiar with the pathophysiology and clinical picture of these conditions in order to better understand the development of SH-OH.

3.2. Primary Autonomic Failure

A thorough understanding of primary autonomic failure can shed light on the pathophysiology of SH-OH and thus help to direct management of these patients. Primary autonomic failure can be divided into two categories based on the location of the lesions causing autonomic dysfunction. Patients may experience primary autonomic failure due to either central or peripheral lesions.

MSA is an example of central primary autonomic failure. This disease can be further divided into two subcategories: 1) MSA-P, which is a form of MSA associated with parkinsonism and lesions to glial cells of the nigrostriatal system in the form of alpha-synuclein protein inclusions, and 2) MSA-C, which presents with more cerebellar symptoms such as truncal ataxia due to protein inclusions in cerebellar regions. Both MSA-P and MSA-C may be associated with some degree of autonomic dysfunction [10, 16]. MSA-P is the most common form of MSA; the parkinsonism of this disease is differentiated from that of Parkinson's disease in that the tremor of MSA-P is usually less pronounced and unresponsive to treatment with levodopa [1]. In addition, although Parkinson's disease is associated with autonomic failure, MSA tends to have more severe and widespread dysautonomia.

The differentiation between MSA and Parkinson's disease can be further elucidated based on the pathophysiologic nature of the autonomic dysfunction. One measure of this is the degree of postganglionic noradrenergic innervation to the heart. This can be determined by measuring the uptake of fluorodopamine by peripheral sympathetic fibers via positron emission tomography. Uptake of fluorodopamine shows a significant decrease in autonomic dysfunction of Parkinson's disease suggesting a peripheral mechanism, but this uptake is preserved in MSA [10, 17, 18]. This finding further supports the idea that MSA is associated with central autonomic dysfunction. In addition, plasma levels of norepinephrine are normal in MSA [10, 17].

MSA can be contrasted with a condition known as Pure Autonomic Failure (PAF), which is thought to be a peripheral autonomic neuropathy. PAF has been associated with neuronal lesions in the form of Lewy bodies invading postganglionic sympathetic fibers and peripheral noradrenergic neurons [10, 19, 20]. Patients with PAF have also been shown to have low levels of plasma norepinephrine, as well as decreased noradrenergic innervation to the heart [17, 18]. These findings support the idea that PAF is caused by peripheral autonomic dysfunction. Although, PAF may produce severe autonomic symptoms such as orthostatic hypotension and bladder dysfunction, it generally does not reduce lifespan.

As discussed earlier, autonomic failure can have many different etiologies, though the clinical picture tends to be somewhat consistent between different diseases. In both MSA and PAF, patients are afflicted with disabling orthostatic intolerance even though the pathophysiology of these disorders differs greatly [10, 21]. However, it is useful to be aware of these differing mechanisms when attempting to understand the development of SH in the setting of autonomic dysfunction.

3.3. Development of Supine Hypertension in Autonomic Dysfunction

The presence of SH in a patient with orthostatic intolerance secondary to autonomic dysfunction greatly complicates the management of that patient. Additionally, the etiology of this SH can be difficult to ascertain. In fact, the physiology behind the development of SH in patients with autonomic failure differs between diseases, but there appears to be an association between the severity of SH and the degree of OH [22].

Patients with a primary autonomic failure syndrome (*e.g.* multiple system atrophy, pure autonomic failure, Parkinson's disease) who have orthostatic intolerance have been found to have significantly higher mean arterial pressure than patients who suffer from these same diseases without OH [22]. For instance, a study by Goldstein *et al.* [22] demonstrated that patients with Parkinson's disease and OH had higher supine mean arterial pressure than patients with Parkinson's disease without OH. The same trend was true for patients with MSA with OH compared to patients with MSA without OH. These trends suggest a common etiology for these seemingly paradoxical fluctuations in blood pressure, though the mechanism of this remains uncertain.

MSA is considered a disorder of central regulation of autonomic output. It is postulated that the etiology of SH in MSA is due to residual sympathetic tone in peripheral nerve fibers. In addition, the postsynaptic adrenergic receptors with which these fibers communicate are thought to become hypersensitive in the setting of this type of autonomic failure [10, 23].

A study by Shannon *et al.* [23] supports this assertion. Their study explored the effect of trimethaphan in patients with MSA. Trimethaphan is a ganglion-blocking agent, which is a competitive inhibitor of acetylcholine, preventing stimulation of postsynaptic receptors. Administration of trimethaphan to MSA patients was found to significantly decrease supine blood pressures by decreasing cardiac output and peripheral vascular resistance.

Shannon *et al.* [23] further explored the idea that SH in MSA is due to residual sympathetic tone with the use of yohimbine, a pre-synaptic alpha 2-adrenergic blocking agent. Yohimbine increases sympathetic drive from the central nervous system and increases the release of norepinephrine in the periphery. They also found that yohimbine significantly increased supine blood pressure in patients with MSA. Moreover, MSA patients who had a higher supine blood pressure at baseline experienced a greater response to yohimbine than those patients who had lower supine pressures. Another study by Shibao *et al.* [24] found that the use of atomoxetine, a norepinephrine reuptake inhibitor, caused a significant increase in blood pressure in patients with MSA. These findings further support the theory that SH in central autonomic disorders such as MSA is due to residual sympathetic tone in peripheral nerve fibers.

The cause of SH in pure autonomic failure is less clear. For instance, the response of patients with PAF to ganglion blockade with trimethaphan was less pronounced and required higher doses to decrease supine blood pressure [23]. In addition, the response to yohimbine was also significantly lower in PAF patients than in MSA patients [23]. These findings suggest an alternative mechanism of SH in PAF patients. The decreased response of PAF patients to ganglion blockade with trimethaphan is likely due to the fact that this disease is a form of peripheral dysautonomia, manifesting as a decreased number of postganglionic sympathetic neurons [25]. These patients may thus have increased sensitivity to norepinephrine on the postsynaptic membrane, which can be a contributing factor to SH [1, 22]. Regardless, the lack of response to ganglion blockade in PAF indicates that there are other mechanisms of hypertension in these patients that do not rely on the sympathetic nervous system. These patients have increased vascular resistance but low levels of norepinephrine in plasma [22, 26, 27].

Understanding the complex pathophysiology of SH-OH in primary autonomic dysfunction is the first step to promoting future research aimed at developing a definitive treatment of this disorder. However, it is important to remember that autonomic dysfunction can have many causes and is usually not due to a primary disorder such as MSA or pure autonomic failure. Disorders such as these can be helpful as they provide a framework for understanding the complexity of this disease. In the next section, we review current meth-

ods and techniques for evaluation and treatment of autonomic dysfunction with SH-OH.

4. CLINICAL EVALUATION

The clinical evaluation of a patient with autonomic failure begins with a detailed history and thorough physical examination (Fig. **1**). As mentioned earlier, OH tends to be the most prominent symptom of autonomic dysfunction [8, 10]. However, orthostatic intolerance can be caused by a multitude of reversible causes. For this reason, it is important to conduct a thorough review of all the medications a patient is currently taking. Medications that can affect orthostatic blood pressure and autonomic responses consist of antihypertensive drugs including beta-blockers and calcium channel-blockers, diuretics, tricyclic antidepressants, dopamine agonists, narcotics, and ethanol, among others [1].

Patients who have underlying autonomic dysfunction have a lower threshold for orthostatic intolerance, and this adverse reaction to these types of medications may be an initial indicator of underlying dysautonomia. Though most

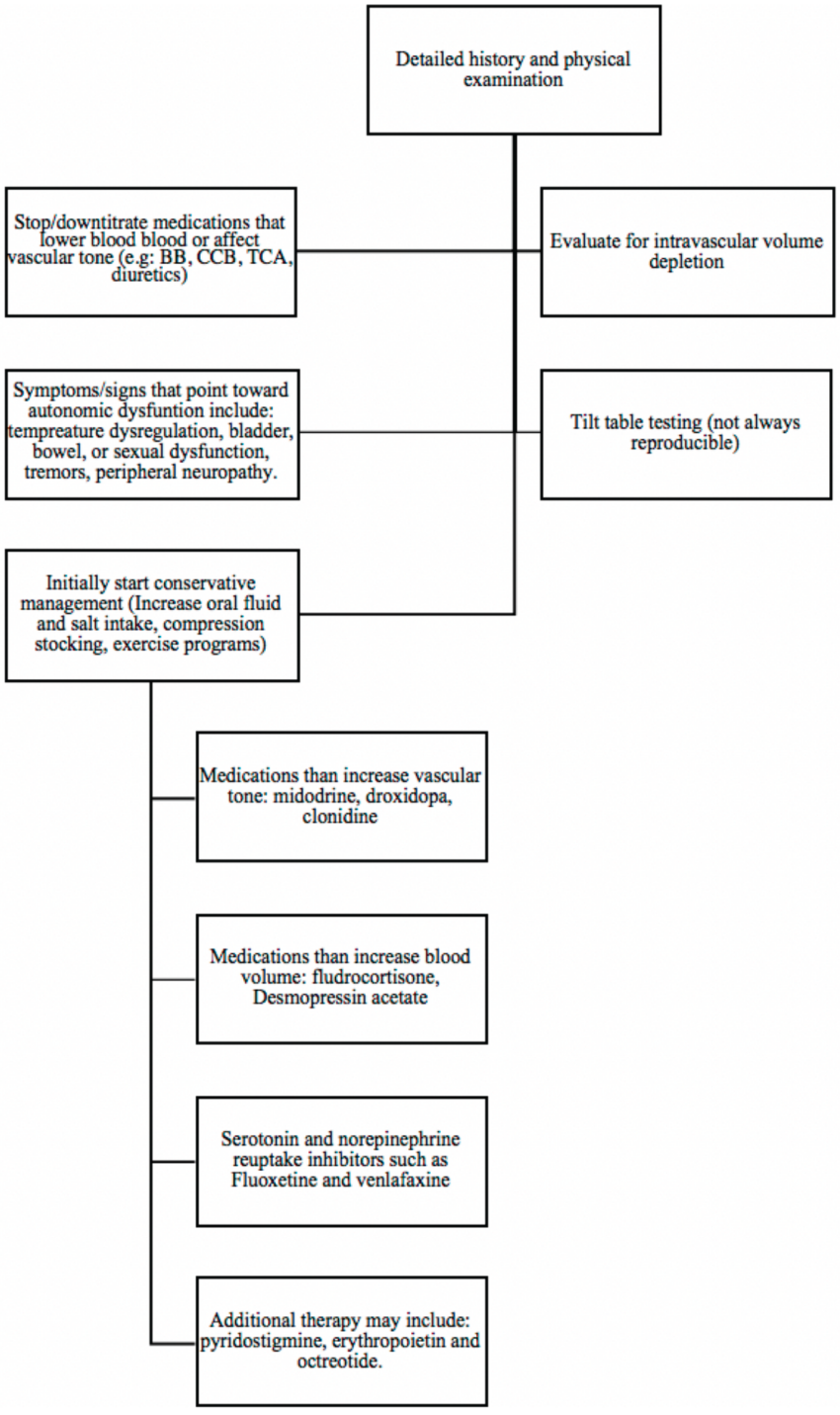

Fig. (1). Management approach to patients with supine hypertension and orthostatic hypotension.

causes of OH are non-neurologic (cardiac pump failure, medication-induced, reduced intravascular volume), it is important to keep neurogenic causes under consideration until they have been ruled out. Further evaluation of dysautonomia should focus on the relation of symptoms with autonomic stressors. These stressors include factors that increase pooling of blood in the splanchnic vasculature, such as large meals or increased temperatures and exercise leading to systemic and muscular vasodilation. Temperature dysregulation may present in the setting of anhidrosis or hyperhidrosis. Bladder, bowel, and sexual dysfunction can also be seen and further point toward the diagnosis of autonomic dysfunction [1, 8].

Assessment of patients with orthostatic intolerance in the setting of suspected dysautonomia should include a detailed neurologic examination consisting of cranial nerve testing, evaluation of motor tone and observation of any parkinsonian tremor, as well as deep tendon reflexes and a full sensory exam. Any abnormal findings would point to autonomic dysfunction in the setting of underlying disorders such as Parkinson's disease or diabetes mellitus. Measurement of supine and orthostatic blood pressures at the bedside is also a crucial element of the workup. Measuring heart rate and blood pressure changes during physical maneuvers such as the Valsalva maneuver and tilt table testing are also useful in determining if the autonomic response is appropriate, though these tests are not always reproducible.

5. TREATMENT OPTIONS AND MANAGEMENT OF SH-OH

Education is the first step in the management of patients with autonomic dysfunction, especially when concurrent SH is present. Physicians should discuss desired patient goals and focus on relief of symptoms. This includes minimizing symptomatic OH to improve quality of life and decrease risk of falls, as well as controlling SH to avoid future risk of end organ damage [8].

Patients should avoid autonomic stressors like excessive heat, strenuous exercise, abrupt standing, and large meals. As discussed earlier, a comprehensive review of medications should be done, and any medication that could contribute to decreased orthostatic pressures (*e.g*. antihypertensives, diuretics, dopamine agonists, *etc*.) should be removed or tapered down as indicated. Other initial measures to treat OH include implementing a high salt diet, increasing fluid intake, and using compression stockings. Physical maneuvers such as sitting on the side of the bed for several minutes before standing and sleeping with the head of the bed elevated or in a reclining chair can be helpful to some patients. Treating underlying conditions that contribute to autonomic dysfunction (*e.g*. diabetes mellitus) is also important as this can alleviate or slow the progression of neuropathy. Finally, engaging in exercise programs is strongly recommended. Although exercise does not reverse the underlying etiology, it leads to an increase in blood volume and left ventricular mass leading to more stable hemodynamics. Since many patients do not tolerate exercises that require upright posture, performing exercises that do not require upright posture, such as recumbent biking, is usually better tolerated.

Although conservative measures can be effective in some patients, many people remain symptomatic and often require pharmacological treatment. It is important to keep in mind that medications directed to treat OH often exacerbates SH and vice versa. Midodrine, through its alpha-1 agonist activity increases vascular tone reducing OH [28]. Due to its rapid pharmacokinetics, the medication needs to be taken three or four times a day. Avoiding a bedtime dose is important in this population to prevent SH. Another medication that increases vascular tone is Droxidopa, a norepinephrine prodrug. It is associated with the development of accelerated hypertension [29]. A similar concern exists with the use of fludrocortisone, a mineralocorticoid that acts on the kidney to promote sodium reabsorption and increase intravascular volume. Alternately, Desmopressin acetate (DDVAP) increases blood volume by causing water but not sodium retention and is less likely to cause significant SH. The central alpha-2 agonist, clonidine, is helpful as well. Interestingly, the blood lowering effect of clonidine seen in normal individuals, which is caused by lowered sympathetic flow, is not observed in patients with autonomic failure. The reason for this is low sympathetic activity in patients with autonomic failure allowing the peripheral effects of clonidine to predominate. Serotonin and norepinephrine reuptake inhibitors such as Fluoxetine and venlafaxine can be used. These medications will improve orthostatic intolerance without causing SH.

Treating the hypertension component is often more challenging, and in general higher goals of blood pressure might be accepted. Patients should be instructed to avoid medications that may exacerbate SH, including over-the-counter decongestants and nonsteroidal anti-inflammatory drugs (NSAIDS). The peripheral acetylcholinesterase inhibitor pyridostimine has been shown to improve orthostatic hypotension without worsening SH [30]. This drug acts by increasing ganglionic transmission, which is maximal in the standing position and minimal when supine [30]. Pyridostigmine can be combined with a central alpha-2 agonist like clonidine as well as non-selective blockers such as carvedilol or labetalol. This regimen can be employed to prevent excessive swings in pressure and decrease hypertension when supine without drastically altering orthostatic pressures.

In cases of refractory hypotension, despite aforementioned therapy, we have successfully used erythropoietin (EPO) and octreotide. EPO is specially associated with hypertension.

Finally, immunomodulation therapy can be highly effective in appropriately selected patients where autoimmunity is thought to be the primary cause of autonomic failure. Successfully used therapies include intravenous immunoglobulins (IVIG), plasmapheresis, prednisone and mycophenolate mofetil [31, 32].

CONCLUSION

In conclusion, the syndrome of SH-OH indeed presents a challenging scenario for patients and their physicians. Achieving perfect control of blood pressure is not a realistic goal, and treatment should be aimed primarily at improving the patient's quality of life and decreasing their risk of injury

and organ damage. Moreover, the etiology and severity of autonomic dysfunction vary greatly between patients, so each case is unique and treatment must be individualized. The complex pathophysiology of SH-OH opens the door to research opportunities further exploring the development of SH in autonomic dysfunction. It is our hope that this review can provide physicians and researchers with an overview of this complex disorder, ultimately leading to advances in treatment options so that clinicians are able to provide patients afflicted with SH-OH with the best possible therapy to improve their quality of life and minimize mortality.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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