Case study

Syndrome of Orthostatic Hypotension with Supine Hypertension: a therapeutic dilemma for cardiologists

Abstract:

Orthostatic hypotension (OH) and supine hypertension (SH) are two cardiovascular symptoms of autonomic failure that frequently coexist in the same patient.

Clinicians are faced with a dilemma because aggressive orthostatic intolerance treatment can exacerbate supine hypertension, and vice versa for supine hypertension management.

The objective of our article is to provide a better framework for the clinical evaluation, the right choice of therapeutic options and the improvement of the quality of life of patients with OH-SH syndrome. For these reasons, we report three observations, whose etiologies, clinical presentation, and treatment are different, namely diabetes, multiple system atrophy type C (MSA) and Parkinson's disease.

Key words: Orthostatic Hypotension, supine hypertension, cardiovascular symptoms

Introduction:

Orthostatic hypotension (OH) and supine hypertension (SH) are two cardiovascular symptoms of autonomic failure that frequently coexist in the same patient. This clinical feature was first identified about 80 years ago, but it is still mostly neglected.

Since it has been established that OH has a large morbidity burden and has been associated with higher mortality, and since SH increases the risk of hypertension-induced organ damage, clinicians from a wide range of specialties need to be aware about its diagnosis and therapy.

The therapeutic management of OH-SH syndrome represents a real dilemma, as treating one condition can aggravate the other. Thus, several studies offer solutions for the simultaneous management of them both.

In our paper, we aim to review the clinical data and therapeutic approaches that are effective for the OH-SH syndrome, doing so in the context of three clinical cases with various etiologies.

Case presentation :

We report three observations of patients who present this association:

The first patient is 68 years old man, followed for diabetes mellitus for 7 years. The patient presented to our autonomic nervous system exploration unit for symptoms that had been evolving for four months. This symptomatology is made up of attacks of diffuse paroxysmal abdominal pain concomitant with profuse sweating and nausea. Moreover, he reported deterioration in concentration with the notion of sleep disorders. The general examination was normal except a supine BP of 144/81 mmHg and 98/68 mmHg during the first minute of standing without modification in heart rate. It should be noted that digestive exploration (abdominal CT scan and endocopy), cardiac ultrasound, electrocardiogram and cerebral MRI did not reveal any abnormalities. The autonomic nervous system explorations revealed central and peripheral sympathetic hyperactivity, vagal hyperactivity, and orthostatic hypotension syndrome associated with supine hypertension. The ABPM (Ambulatory blood pressure monitoring) confirmed nocturnal systolo-diastolic hypertension with a non-dipper profile and orthostatic hypotension **(Figure 1)**. In addition to lifestyle measures including abundant rehydration (avoided before bedtime), compression stockings, a

normal sodium diet, and our patient was put on Phenobarbital 10 mg daily taken in the evening, with improvement, without worsening of the blood pressure figures in the supine position.

The second is a 58-year-old male patient, with no particular pathological history who present for 2 years: balance disorders, postural dizziness, fainting, urinary incontinence, and sleep disorders, while clinical examination showed high blood pressure in the supine position of 150/90 with BP after standing at 1 minute: 63/44 mmHg, a heart rate of 70 and a stato-kinetic cerebellar syndrome. Brain MRI showed an MSA type C. Cardiac ultrasound showed left ventricular hypertrophy with normal ejection fraction. The autonomic nervous system explorations revealed vagal deficiency, central (α and β) and peripheral (α and β) sympathetic deficiency. The ABPM find nocturnal hypertension, hypotension on awaking and others during the day **(Figure 2).** In addition to lifestyle measures including abundant rehydration (avoided before bedtime), compression stockings, a normal sodium diet, and our patient was put on Midodrine 2.5 mg twice a day, with improvement, without worsening of the blood pressure figures in the supine position.

The last patient is a 78-years-old man, followed for hypertension, Parkinson's disease (PD), and dementia for 9 years. He presents orthostatic dizziness, headache and neck pain, sleep disturbances, and abdominal bloating for 6 years. Clinical examination showed high pressure in the supine position of 164/98 mmHg, a full in BP after standing at 3 minutes: 110/80 mmHg, and a heart rate of 65. The autonomic nervous system explorations revealed vagal deficiency, central (α and β) and peripheral (α and β) sympathetic deficiency. The 24 hours ABPM finds nocturnal hypertension with orthostatic hypotension **(Figure 3).** In addition to lifestyle measures including abundant rehydration, compression stockings, a normal sodium diet, and our patient was put on Losartan 50 mg daily taken in the evening, with improvement, without worsening of the blood pressure figures in the supine position.

Discussion:

Supine hypertension (SH), one of the clinical forms of high blood pressure, is a less well-known condition that is caused by autonomous dysfunctions and develops alongside orthostatic hypotension (OH). These conditions are pathogenically and clinically correlated, therefore many authors have named this association the OH/SH syndrome(1,2).

On February 16, 2017, a round table discussion was held in Innsbruck with representatives from the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) to define clinical criteria for the diagnosis of SH in the setting of cardiovascular autonomic dysfunction(3).

Supine hypertension was defined in patients with proven OH, as systolic BP of ≥ 140 mmHg and/or diastolic BP of ≥ 90 mmHg, measured after at least 5 minutes of rest in the supine position(3). Three ranges of severity were defined:

- Mild SH: systolic BP values of 140–159 mmHg or diastolic BP values of 90–99 mmHg.
- Moderate SH: systolic BP values of 160–179 mmHg or diastolic BP values of 100–109 mmHg.
- Severe SH: systolic BP values of ≥ 180 mmHg or diastolic BP values of ≥ 110 mmHg.

The SH may be present also during sleep, i.e. nocturnal hypertension, with loss of the physiological nocturnal BP fall at night of ≥ 10% while supine and asleep (dipping). Two main pathological nocturnal BP profiles are distinguished:

- Reduced-dipping: characterized by a mean nocturnal BP reduction of < 10% with respect to mean daytime BP values.
- Non-dipping or rising: when the mean BP does not decrease or even increases during the night with respect to daytime(3–5).

The definition of orthostatic hypotension was updated in a consensus document that was supported by the American Autonomic Society, the European Federation of Autonomic Societies, the World Federation of Neurology's Autonomic Research Group, and the American Academy of Neurology's Autonomic Disorders section(6,7).

The gold standard test for OH is the measurement of blood pressure change from supine to standing (or head-up tilt [HUT]) after at least 5 minutes of rest. A sustained fall in systolic blood pressure of at least 20 mmHg or a diastolic blood pressure of at least 10 mmHg within 3 minutes of standing (or HUT) is now considered to be OH. However, a 30 mmHg decrease in systolic blood pressure or a 15-point fall in diastolic blood pressure may be a more appropriate criterion for patients with supine hypertension, as the magnitude of blood pressure fall is dependent on the baseline blood pressure. A severity grading system with five grades was suggested by the same consensus **(table 1)** (6,7).

On a physiopathological level, OH/SH syndrome may refer to a condition in which sympathetic outflow is inhibited due to a lack of norepinephrine release from postganglionic neurons, especially when standing. As the body is unable to generate a sufficient sympathetic response to support the upright position, OH would eventually manifest (2,8). These factors, along with deficient baroreflex function, increased blood volume, inappropriate natriuresis, and residual sympathetic output in the presence of hypersensitive postsynaptic adrenergic receptors, may lead to SH. In this approach, autonomic dysfunction is a significant risk factor to OH/SH syndrome (9).

"Long-term hypertension leads to desensitization of the baroreceptor reflex, which might also contribute to the pathogenesis of OH/SH syndrome" (2).

"Residual sympathetic tone acting on hypersensitive postsynaptic adrenergic receptors may also be a contributing factor in OH/SH. According to this mechanism, those with chronic hypertension may be more likely to acquire OH due to reduced baroreceptor and adrenergic receptor sensitivity, especially while standing up straight" (10,11).

"Patients with OH because of autonomic failure (primary or secondary) may at times develop supine hypertension, which could be a result of the medications used for the treatment of OH" (2).

From the perspective of epidemiology, the prevalence of SH varies with OH. With one-third of cases being ascribed to OH, the estimated overall prevalence of OH in people over the age of 65 exceeds 20% (12,13). According to prior studies, SH is present in 60–70% of patients with OH, depending on the underlying neurogenic disease (14,15). OH is increasing the risk of cardiovascular events and overall mortality(1,16–18). In their series comparing two groups with or without OH, Elzanaty et al demonstrated a similar likelihood of developing acute kidney injury, stroke and transient ischemic attack, and aortic dissection(19). Recent researches has shown a higher prevalence of organ damage caused by hypertension in individuals with SH, including microalbuminuria, increased carotid intima-media thickness, arterial stiffness measures, and left ventricular hypertrophy(20–23).

"The prevalence of HS has been reported in 34–46% of PD patients and 37% of MSA patients, taking into account the restrictions imposed on by inconsistent diagnostic criteria(24,25). Assuming an etiological relationship between OH and SH, the frequency rates of SH rise to 50% in parkinsonian patients with OH(24–26). In PD (48%) and MSA patients (up to 75%), loss of nocturnal BP dipping has frequently noted" (14,27,28,28).

"Although the epidemiology of SH in diabetes has not yet been studied, there is a strong correlation between the presence of OH and rising nocturnal BP profiles in both type 1 and type 2 diabetic patients" (27).

"The prevalence of SH in genetic and acquired amyloidosis, as well as in other kinds of autonomic neuropathies is unknown" (27).

"In terms of OH screening, there is no standardized or recommended procedure for patients that present with symptoms of orthostatic hypotension. Postural lightheadedness or dizziness, the sensation of blacking out, and falls with or without syncope are some of the current symptoms and indicators of OH. Less frequent signs and symptoms include platypnea, mental dulling, orthostatic cognitive impairment, generalized weakness, and neck pain or discomfort in the suboccipital and paracervical regions. As a result, the process of screening for OH begins with questions designed to identify the symptoms of OH. Next, blood pressures from supine to standing are then measured" (7,29–33).

The following five patient groups must undergo regular OH screenings(7):

1. Patients suspected of, or diagnosed with any neurodegenerative disorder associated with autonomic dysfunction, including Parkinson's Disease (PD), Multiple System Atrophy (MSA), Pure Autonomic Failure (PAF), or Dementia with Lewy Bodies (DLB);
2. Patients who have reported an unexplained fall or have had an episode of syncope;
3. Patients with peripheral neuropathies known to be associated with autonomic dysfunction (e.g., diabetes, amyloidosis, HIV);
4. Patients who are elderly (≥70 years of age) and frail or on multiple medications;
5. Patients with postural (orthostatic) dizziness or nonspecific symptoms that only occur when standing.

"For these five categories of patients, clinicians should ask about cardinal symptoms of OH, the time of day when it occurs (as symptoms of OH are most likely to occur in the morning and after meals), their frequency and severity, how long they can stand, and the effect of symptoms on their activities of daily living" (34–36). This condition should also be sought in patients who have had a history of COVID 19 infection, Eslami et al mentioned the presence of OH in 48.3% of cases in their series(37).

An electrocardiogram, routine biochemistry, complete blood count, vitamin B12, and serum protein electrophoresis should all be acquired as part of the paraclinical examination strategy. In patients with rapidly progressing unexplained autonomic failure, it is occasionally possible to measure specific autoantibodies, urine or plasma metanephrines, and catecholamines(11).

"The therapeutic management of OH associated with SH is a real dilemma, as treating one condition can aggravate the other. Additionally, patients may respond to treatment in very different ways, which makes results highly variable" (2,3,7).

"Physicians should discuss patient's intended outcomes and concentrate on symptom relief. This includes reducing symptomatic OH to improve quality of life and lower the risk of falls, as well as managing SH to decrease the risk of end organ damage in the future" (38).

"The treatment strategy requires a step-by-step approach with a careful assessment of the risk-benefit balance associated with antihypertensive therapy. It includes education and prevention, non-pharmacological and pharmacological treatment" (1).

"The non-pharmacological component holds a significant position. Patients should avoid autonomic stressors like excessive heat, strenuous exercise, and abrupt standing. Water is quite beneficial (the impact peaks at approximately 35 minutes and lasts for more than 60 minutes), but SH sufferers should avoid drinking it right before bedtime. The head-up tilt position (6-7 cm above the bed, 30 degrees) reduces the loss of sodium at night and may improve diurnal OH and cause a modest drop in SH. Postprandial hypotension is a common symptom of orthostatic hypertension in patients. Small and frequent low-carbohydrate meals are recommended in order to prevent severe postprandial hypotension" (1,7,9).

Any medication that might contribute to decreased orthostatic pressures should be eliminated or reduced as needed after a comprehensive medication evaluation. It's also crucial to treat underlying diseases that cause autonomic dysfunction, such as diabetes mellitus, as doing so might lessen the symptoms of neuropathy or slow its progression(1,7,38).

"Pharmacological treatment will be initiated in patients to whom blood pressure levels are not kept within adequate limits, despite compliance with the non-pharmacological strategy. Medication for OH must be introduced progressively and avoided at bed-time, while pharmacological treatment of SH must be based on drugs with short duration of action" (1,7,38)..

Among the medications for OH, pyridostigmine is occasionally helpful in preventing OH without exacerbating SH. Furthermore, short-acting pressor medications like Midodrine are preferred in patients with OH and supine hypertension. Starting with a single 2.5 mg dose, the course of treatment can then be increased up to 10 mg. For two to three hours at a time, these substances can raise blood pressure. If patients are going to stay seated or supine, pressor

agents shouldn't be administered. Due to the increased risk of developing supine hypertension, evening doses should be avoided (11,38,39).

"Droxidopa, a norepinephrine prodrug, is another drug that increases vascular tone. It is associated with the development of accelerated hypertension(7,38,40). A similar concern exists with the use of Fludrocortisone (0.05 to 0.4 mg daily), 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" (7,11,38).

Alpha-2 agonists like Clonidine, angiotensin receptor blockers, and combined alpha/beta blockers like Labetalol are frequently used to treat severe supine hypertension **(table 2)** (2,7,38).

"Besides aforementioned therapy, Erythropoietin (EPO), Octreotide, and immunomodulation therapy can be highly effective in appropriately selected patients(38). Successfully used therapies include intravenous immunoglobulins (IVIG), plasmapheresis, Prednisone, and Mycophenolate Mofetil" (41,42).

Conclusion:

The syndrome of OH-SH does, in fact, create a challenging situation for patients and their physicians. It is unrealistic to expect to achieve perfect blood pressure control; instead, treatment should focus on raising the patient's quality of life and lowering 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.

We still don't fully comprehend the OH-SH condition in many ways. Thus, additional research on the treatment of OH-SH syndrome should be conducted, in particular, to improve the algorithms for diagnosis and therapy and to give conclusive proof of the efficacy and safety of drugs that are currently used but still not approved.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

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FIGURES/TABLES:

Figure 1: Syndrome of orthostatic hypotension with supine hypertension in a patient with diabetes mellitus.

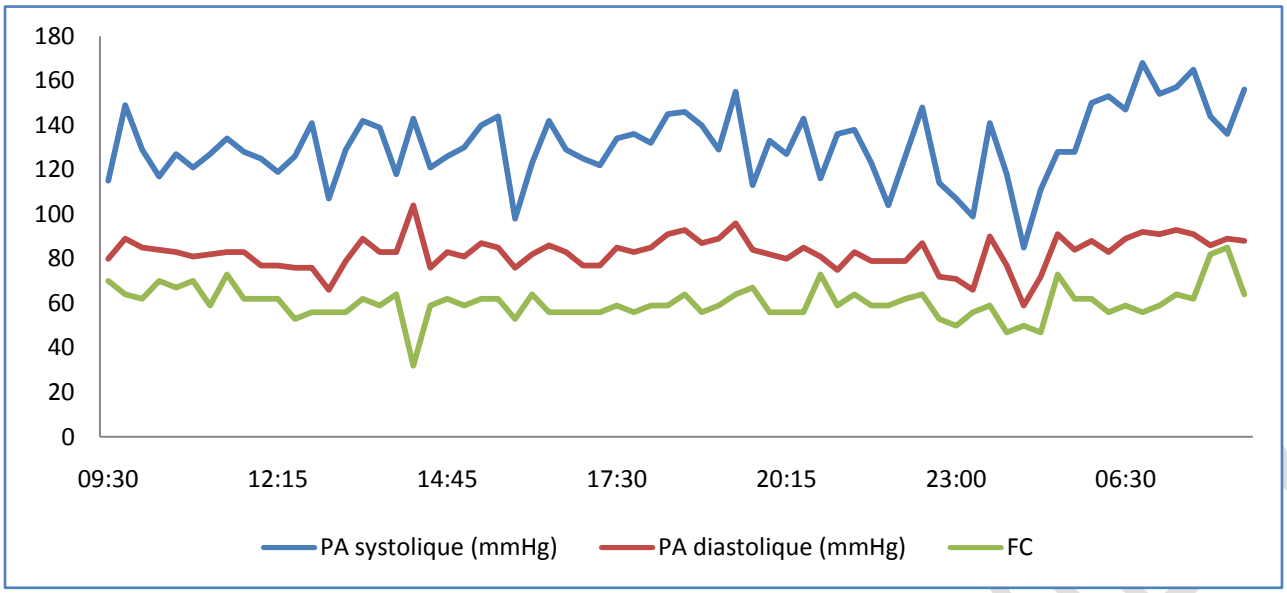

Figure 2: Syndrome of orthostatic hypotension with supine hypertension in a patient with type C multiple system atrophy (MSA).

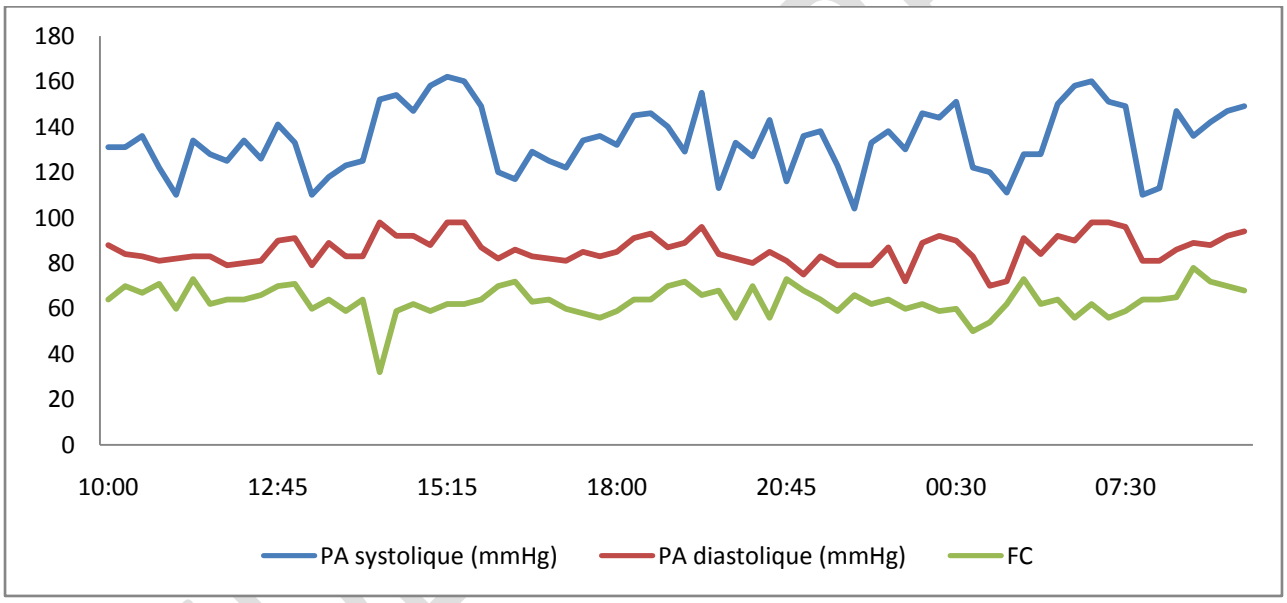

Figure 3: Syndrome of orthostatic hypotension with supine hypertension in a patient with hypertension and Parkinson's disease (PD).

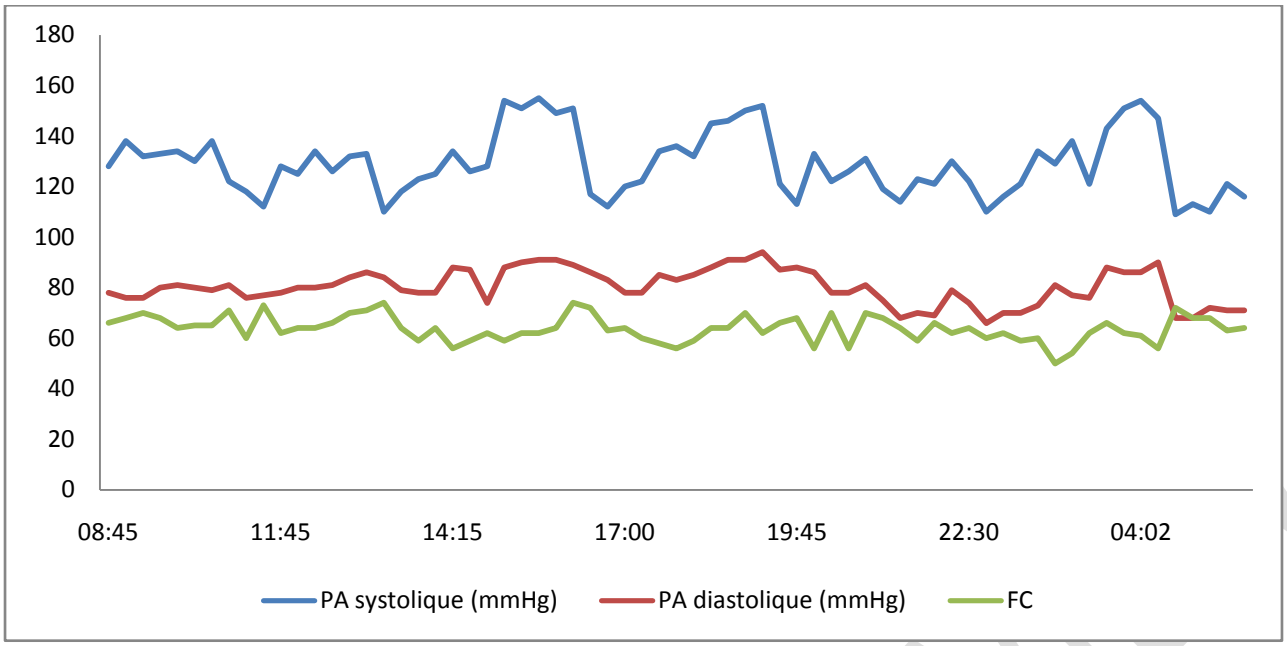

Table 1: Proposed grading scale for OH (7)**.**

Grade	Attributes
1	Infrequent symptoms/unrestricted standing time AND mild OH [20-30 mmHg drop in SBP during supine-to-standing test]
2	≥ 5 min standing time (but not unrestricted) AND [>30 mmHg drop in SBP OR moderate impact ADL]
3	< 5 min standing time AND [>30 mmHg drop in SBP OR severe impact on ADL]
4	<1 min standing time AND [>30 mmHg drop in SBP OR incapacitated]

- A patient with grade 3 or 4 OH should be treated by a healthcare provider with experience in managing OH
- **SBP** systolic blood pressure, **ADL** activities of daily living

Table 2 : Proposed treatments for supine hypertension related to OH (7).

Treatment options	Mechanism of action	Typical dose
Captopril	ACE inhibitor	25 mg qhs
Clonidine	Central α-2 agonist	0.2 mg with evening meal
Hydralazine	Peripheral smooth muscle relaxant	10–25 mg qhs
Losartan	Angiotensin II receptor antagonist	50 mg qhs
Nitroglycerine patch	Vasodilator	0.1 mg/h patch qhs (remove patch in AM)