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# Orthostatic hypotension: Role of autonomic nervous system exploration and its therapeutic implication: About a series of 25 cases

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**Abstract**
Orthostatic hypotension is a pathology frequently encountered in daily clinical practice. In addition to the morbidity associated with falls and syncope, it is a factor in cognitive decline, stroke, myocardial infarction, heart failure, and total mortality.
The autonomic nervous system plays a key role in the regulation of blood pressure during the transition to the standing position, by stimulation of the sympathetic nervous system and by vagal inhibition with the consequence of peripheral vasoconstriction, increased heart rate, and myocardial contractility.
The objective of our study is to evaluate the interest in exploring the autonomic nervous system, through the autonomic cardiovascular tests of Ewing, particularly the orthostatic test in the diagnostic confirmation, the etiological orientation, and the adoption of a therapeutic strategy adapted to the patient profile.
Orthostatic hypotension is frequent and serious, with significant economic and social consequences, however, this pathology is under-diagnosed explaining the interest in its systematic screening in people over 65 years, especially those with diabetes, Parkinson's disease, dehydration, and patients on antihypertensive treatment, through the orthostatic test, which must be supplemented in case of positive results by an exploration of the autonomic nervous system.

**Keywords:** Orthostatic hypotension, autonomic nervous system exploration, autonomic cardiovascular testing

## Introduction
Orthostatic hypotension (OH) is a decrease in systolic blood pressure of at least 20 mmHg and / or diastolic blood pressure of at least 10 mmHg occurring within 3 minutes of standing.
Although its prevalence is high in the elderly population, due to the aging of physiological functions, OH is mainly encountered during dysautonomias, primary or secondary diseases of the autonomic nervous system, characterized by baroreflex impairment [1].
The autonomic nervous system plays a central role in regulating blood pressure during the transition to an upright position, through stimulation of the sympathetic nervous system and vagal inhibition, resulting in peripheral vasoconstriction, increased heart rate, and myocardial contractility.
In addition to the morbidity associated with falls and syncope, OH is a factor in cognitive decline, cerebrovascular disease, and mortality, which explains the need for a better understanding and management of this pathology [2-3].
Our study aims to evaluate the role of autonomic nervous system exploration in the positive and etiological diagnosis of orthostatic hypotension, and its implication in therapeutic management, with a review of the literature.

## Patients and Methods
This is a retrospective study including 25 patients with symptoms suggestive of orthostatic hypotension who underwent exploration of the autonomic nervous system in the cardiology department of the university hospital IBN ROCHD in Casablanca.

After a thorough history-taking and a thorough clinical examination, the patients underwent an exploration of their autonomic nervous system, including symptoms of dysautonomia such as dizziness, discomfort on rising, intolerance to exertion, and repeated falls.

This test was performed on an empty stomach, after all treatment had been stopped for at least 48 hours, except patients with diabetes.

The patient is first placed in a quiet, supine position on an examination table. Blood pressure and heart rate are measured every 5 minutes for at least 30 minutes.

The autonomic cardiovascular tests, or EWING tests, are then carried out, in the following order: the Deep Breathing test, the Hand Grip test, the Hyperventilation test, the Mental Stress test, and the Orthostatism test, allowing us to explore the functioning of the nervous system with its two sympathetic and parasympathetic components. The various tests are performed with periods of rest in between, with parallel measurements of heart rate (HR) and blood pressure (BP).

The orthostatic test consists of measuring the variation in HR and BP following active rising after a period of rest in the supine position. It is the cornerstone for confirming the diagnosis of orthostatic hypotension and guiding the etiological investigation by distinguishing between two different entities: neurogenic OH with autonomic nervous system (ANS) involvement (concomitant rise in HR of less than 15 bpm) and non-neurogenic OH without ANS involvement (concomitant rise in HR of more than 15 bpm).

**Results**

The mean age was 67 years, with a female predominance and a sex ratio of 0.6. Symptomatology was dominated by discomfort on rising, exertional intolerance, vertigo, repeated falls, and visual disturbances: blurred vision, scotomas, dyschromatopsia, and syncope.

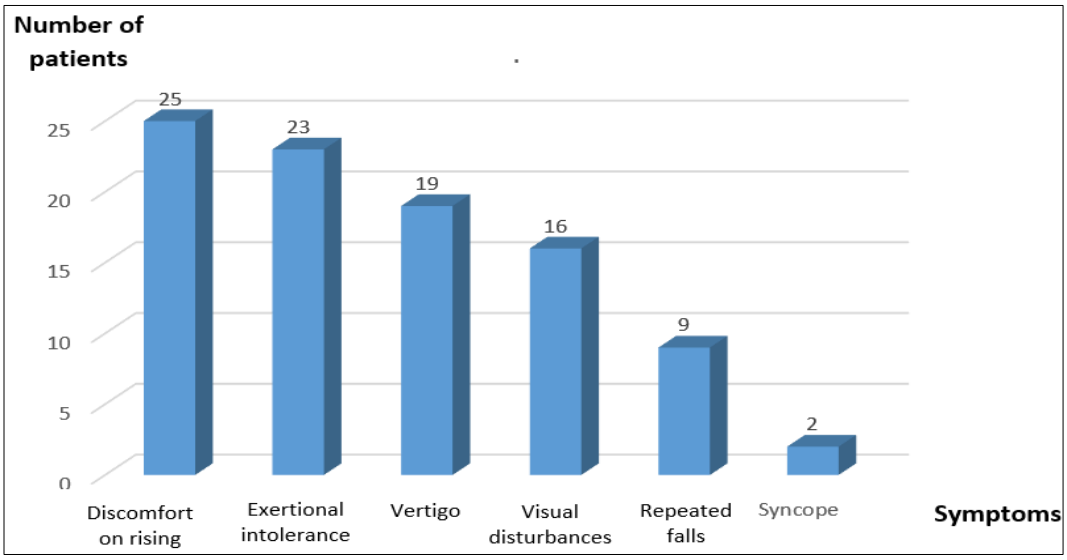


**Fig 1:** Functional symptoms reported by patients suggesting OH.

The concomitant analysis of HR and BP during the orthostatic test enabled etiological orientation, so a neurogenic cause was retained in 14 patients and a non-neurogenic cause was retained in 11 patients.

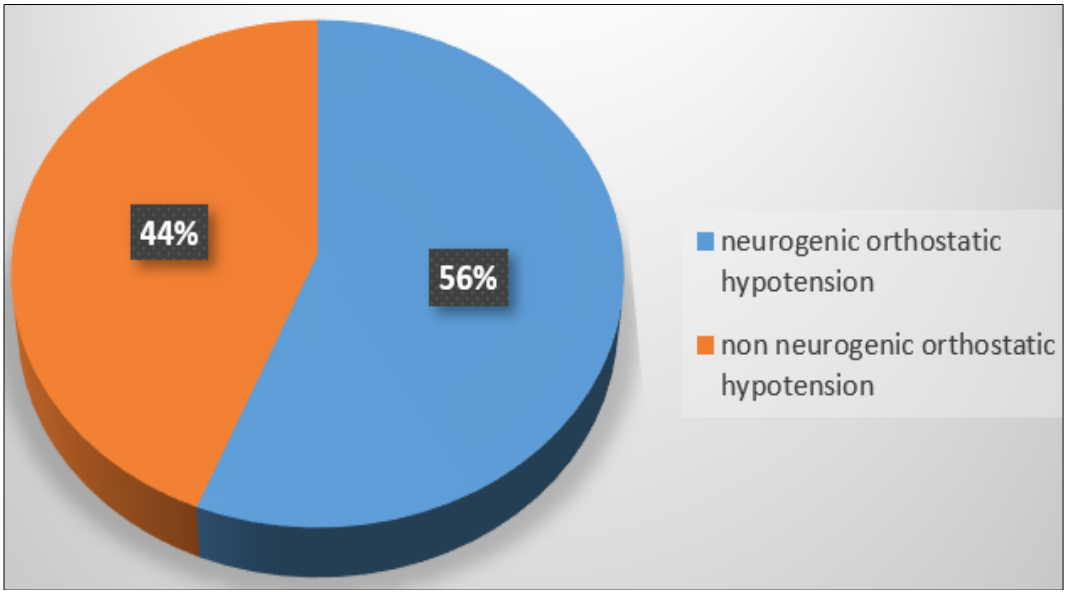


**Fig 2:** Distribution of orthostatic hypotension according to its neurogenic or non-neurogenic cause.

Neurogenic orthostatic hypotension was related to a drug cause in 5 patients, the drugs involved were: antihypertensive (diuretics, calcium inhibitors, nitrated derivatives) in 4 patients and antiparkinsonian treatment with Levodopa in one patient.
Dehydration and hypovolemia were responsible for non-neurogenic orthostatic hypotension in 6 patients.
A neurogenic cause involving the autonomic nervous system was considered in 14 patients.

Vagal hyperactivity and peripheral sympathetic deficiency were the main dysautonomias incriminated in the pathogenesis of neurogenic OH, so analysis of the autonomic profile found vagal hyperactivity in 7 patients, and alpha and beta peripheral sympathetic deficiency in 5 patients. In our series, the neurogenic causes of OH were related to diabetes in 6 patients, Parkinson's disease in 4 patients, pure autonomic insufficiency in 3 patients, and multisystem atrophy in one patient.

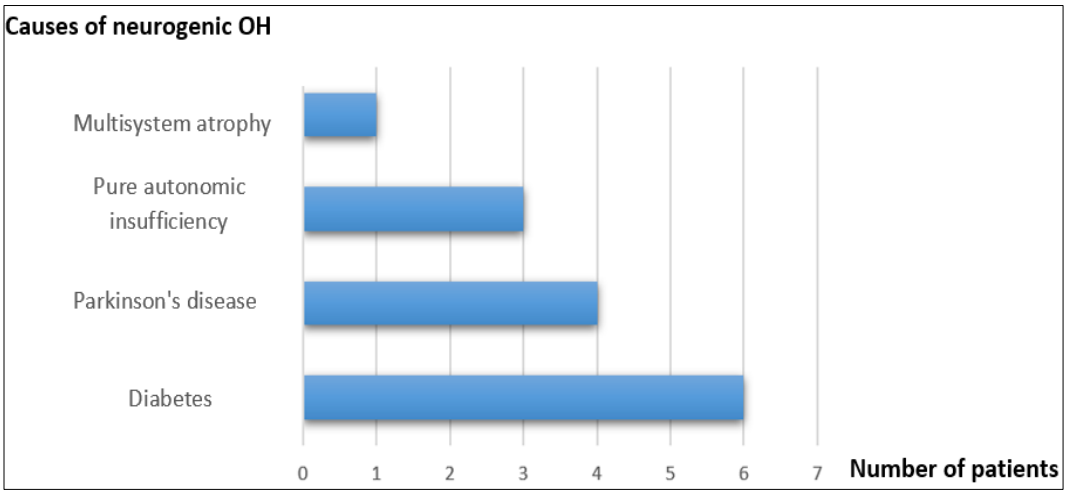


**Fig 3:** Causes of neurogenic orthostatic hypotension found.

All patients were treated with hygienic-dietary measures (salt-enriched diet; ample hydration; use of compression stockings for the lower limbs and abdomen, gradual transition from decubitus to orthostatism, raising the head of the bed by 5 to 10°). Medical treatment was initiated in all 5 patients, depending on the results of the investigation, mainly with Midodrine or Fludrocortisone.

## Discussion

Orthostatic hypotension is a common and underestimated condition. In the general population, its prevalence reaches 6.9%, and its incidence increases with age, so it affects 18.5% of subjects over 80 years [4].
Its prevalence is higher in more specific and very dysautonomic populations. It will concern a third of diabetic subjects [5], a third of Parkinsonian subjects [6], two-thirds of fragile elderly patients in institutions [8], and up to 100% of subjects with pure dysautonomic disease [8].
In our series, the average age was 67. Diabetes, Parkinson's disease, and pure autonomic insufficiency were the main causes of neurogenic OH.
Neurogenic orthostatic hypotension results from the impairment of the capacities of the autonomic nervous system (ANS) to compensate for the hemodynamic consequences of the transition to orthostatism. Thus the passage to the standing position causes an accumulation of blood in the peripheral venous compartment with consequently a fall of central blood volume, cardiac output, and blood pressure [9].
In physiological conditions, the autonomic nervous system allows an immediate adaptation of BP to the new hemodynamic conditions by the use of reflex arcs, whose starting point is at the level of carotid and aortic baroreceptors, thus stimulation of the sympathetic nervous system resulting in a release spurt of catecholamines responsible for an increase in heart rate, myocardial contractility and vasoconstriction of peripheral vessels, with parallel vagal inhibition leading to an increase in the heart rate [10].
These mechanisms explain that vagal hyperactivity and sympathetic deficiency represent the main autonomous disorders found in patients with orthostatic hypotension, consistent with the autonomic profile found in our series.
Exploration of the autonomic nervous system using cardiovascular reactivity tests, including the orthostatic test, enables us to make a positive diagnosis of orthostatic hypotension, and to provide an etiological orientation by distinguishing, through measurement of heart rate, between two main entities: neurogenic OH caused by damage to the autonomic nervous system, and non-neurogenic OH without damage to the autonomic nervous system.
Neurogenic orthostatic hypotension can be primary, directly linked to a failure of the autonomic nervous system, or secondary, linked to a disorder that influences this system.
Pure autonomic failure or Bradbury Eggleston syndrome is one of the causes of primary neurogenic OH, a neurodegenerative disease affecting the sympathetic component of the ANS without central nervous system involvement, causing OH often associated with erectile dysfunction and urinary and sudomotor disorders [11].
In our series, pure autonomic insufficiency was retained in 3 of our patients after confirming severe sympathetic involvement and excluding other causes of OH.
The second cause of primary neurogenic OH is Shy-Drager syndrome or multisystem atrophy. This is a form of primary dysautonomia associated with central nervous system involvement; OH represents a diagnostic criterion of the disease and is frequently associated with micturition disorders, sexual dysfunction, and heat intolerance with anhidrosis [12]. In our series, multisystemic atrophy was the cause of disabling OH in one of our patients.

Parkinson's disease also represents a cause of primary neurogenic OH, in which case OH is a cardinal sign of the disease, and may be associated with postprandial hypotension or supine hypertension, attesting to altered physiological circadian changes in blood pressure. Autonomic dysfunction in Parkinson's disease affects not only the cardiovascular system, but also the gastrointestinal, vesico-sphincter, genito-sexual, and thermoregulatory systems. This autonomic dysfunction must be investigated and treated, as it may be aggravated by antiparkinsonian treatment, with a greater impact on quality of life than motor signs [13]. In our study, Parkinson's disease was the second most common cause of neurogenic OH, found in 4 patients.

As for secondary neurogenic HO, the cause can be neurological, such as Guillain-Barré syndrome, stroke, tabès, syringomyelia, spinal cord injuries, surgical sympathectomy which interrupts sympathetic reflex arc and alter normal adrenergic reaction to orthostatism, causing orthostatic hypotension. Peripheral neuropathies such as vitamin B deficiency, exposure to heavy metals, amyloidosis, and certain chemotherapeutic agents may also be involved [14-15].

Diabetes is one of the most common causes of secondary neurogenic OH. In diabetics cardiac autonomic neuropathy is the main dysautonomia, it is primarily related to a parasympathetic deficit responsible for permanent tachycardia with loss of adaptation of the HR to effort, sympathetic involvement is later and corresponds to a more severe stage of the disease. Sympathetic deficiency often induces orthostatic hypotension which can be extremely disabling [16]. The development of OH in patients with diabetes suggests a much poorer prognosis [17]. In our series, diabetes was the leading cause of neurogenic OH, seen in 6 patients, as part of cardiac autonomic neuropathy.

Secondary hypertension may also be associated with neurogenic OH secondary to disruption of blood pressure homeostatic mechanisms. This is the case in most patients with pheochromocytoma and primary hyperaldosteronism [18].

Alongside neurogenic OH, non-neurogenic OH with intact ANS is a frequently encountered situation, especially in the elderly population, and is most often related to profound hypovolemia or drug-induced hypovolemia.

Hypovolemia is the most frequent cause of orthostatic hypotension. Hemorrhages, severe vomiting, prolonged diarrhea, hypersudation, osmotic diuresis in unbalanced diabetes mellitus, and intense fluid restriction can cause hypovolaemia, dehydration, and orthostatic hypotension if hydroelectrolytic losses are not adequately compensated [19-20]. In our study, hypovolemia was retained as the cause of OH in 6 patients, given the clinical signs of dehydration and the evocative context, after eliminating the other causes of OH.

Non-neurogenic OH is frequently caused by drugs, such as excessive-dose antihypertensives (Diuretics, central antihypertensives, nitrate derivatives, clonidine, methyldopa), antiparkinsonian agents (Levodopa), neuroleptics (Clozapine, risperidone), tricyclic antidepressants, vasodilators (α-blockers), phosphodiesterase-5 inhibitors (Sildenafil, tadalafil), anticholinergics (Including herbs, belladonna) and certain cancer chemotherapies [9]. In our study, a drug origin was retained in 5 patients related to antihypertensives and antiparkinsonians.

Hygienic-dietary measures are the cornerstone of OH treatment and should be introduced as soon as OH is detected and sustained throughout its management [21].

Its measures consist of a sufficient fluid intake of 1.5 to 3 L per day taking into account the concomitant clinical conditions, an increase in sodium intake by adding 2.3 to 4.6 g of NaCl per day to the normal diet with a joint nutritional assessment, the taking of several small meals low in carbohydrates, the taking of caffeinated drinks and the limitation of alcohol intake [22].

Physical interventions play a crucial role in hygienic and dietary measures, they consist of an elastic restraint of the lower limbs and the abdomen, a gradual transition from decubitus to the orthostatism, an elevation of the head of the bed from 5 to 10°, avoidance of prolonged, immobile standing positions, with the achievement of isometric contractions of the limbs to increase venous return [23].

Treatment of OH depends on the cause, in the case of drug-induced OH, adjustment or discontinuation of drugs predisposing to OH is the initial intervention of choice [24].

Overtreatment of hypertension is a common cause of OH, hence the value of re-evaluating treatment targets, fragmenting doses, and modifying their schedules to reduce OH at peak drug effect [25].

Dehydration and hypovolemia are frequent and reversible causes of OH, particularly in the elderly, hence the importance of ensuring adequate fluid intake and compensating for hydroelectrolytic losses.

In practice, pharmacological treatment is indicated in patients with neurogenic OH, particularly those with neurodegenerative disease (Multisystem atrophy, Parkinson's disease, pure autonomic failure) [26].

For patients with non-neurogenic OH, pharmacological treatment is considered when therapeutic adjustment of the drugs incriminated in OH and non-pharmacological measures are not sufficient to improve symptomatology, or cannot be applied.

Midodrine is the treatment of choice for OH, it is an adrenergic alpha-1 agonist that increases BP by direct peripheral vasoconstriction of arterioles and increased venous return. It is started at a dose of 2.5 mg per day, to be increased to 10 mg if necessary, up to three times a day, avoiding evening intake given the risk of supine hypertension [27].

Next to the midodrine, fludcortisone occupies an important place in the OH therapeutic arsenal. It is a synthetic mineralocorticoid that acts by increasing intravascular volume through marked renal sodium retention. It can be administered in doses of 0.1 to 0.3 mg/day and should be avoided in cases of uncontrolled hypertension or heart failure [24].

For refractory cases, other therapies are available, notably Atomoxetine, Domperidone, Octreotide, and Pyridostigmine, with the need to analyze the benefit-risk balance of each molecule to adopt the therapeutic strategy most adapted to the patient profile [9].

## Conclusion

Orthostatic hypotension is a pathology frequently encountered in clinical practice. It is associated with significant cardiovascular morbidity and mortality, related to an increased risk of stroke, myocardial infarction, heart failure, and total mortality.

The autonomic nervous system plays a key role in the regulation of blood pressure during the transition to the standing position, so the exploration of this system thanks to the autonomic cardiovascular tests of EWING makes it possible to confirm the diagnosis of OH, to guide the etiological investigation and to adopt a therapy adapted to the profile of each patient.

Finally, the high cardiovascular risk associated with OH explains the interest in its screening in people over 65 years [27], especially those with diabetes, Parkinson's disease, dehydration, malnutrition, and patients on antihypertensive treatment, through a rigorous methodology of orthostatic testing.

**Abbreviations**

ANS: Autonomic nervous system
BP: Blood pressure
BPM: Beat per minute
HR: Heart rate
OH: Orthostatic hypotension

**Conflict of Interest**

Not available

**Financial Support**

Not available

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