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Teaching Course 13

How to manage a patient with autonomic dysfunction - Level 2

How to manage a patient with orthostatic hypotension

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Orthostatic Hypotension definition

OH is defined by consensus [1] as a drop in blood pressure (BP) of at least 20 mm Hg for systolic BP or 10 mm Hg for diastolic BP within 3 minutes of standing (or during a head up tilt test to at least 60°). The clinical features and pathophysiology of OH were reviewed in 2009 [2] and in 2011 [3] resulting in the publication of a new consensus. The authors recommend using a drop of at least 30 mm Hg in patients with hypertension (systolic blood pressure ≥ 160 mm Hg) to define OH. This consensus also identifies two other forms of OH: initial OH and delayed OH. Initial OH is defined as an exaggerated fall in blood pressure within the first few seconds of standing; this initial OH is considered excessive when the transient blood pressure decrease is over 40 mm Hg (systolic blood pressure) or 20 mm Hg (diastolic blood pressure) within 15-20 seconds of standing. This initial blood pressure fall is observed with continuous blood pressure monitoring, generally during active orthostatic tests and mainly in young subjects. It may be symptomatic when it occurs within a few seconds of standing but is not due to anatomic lesions [3].

The second form is delayed OH; some patients present OH that occurs beyond three minutes of standing (in general when orthostatic stress is prolonged more than 5 minutes) [2]. The clinical significance of delayed OH is less well known but may reveal an early or mild form of sympathetic adrenergic failure [4].
Orthostatic intolerance may also be observed in cases of excessive postural tachycardia (POTS for Postural Tachycardia Orthostatic Syndrome). In this heterogeneous, multifactor syndrome, the clinical signs of orthostatic intolerance are coupled with an excessive increase in heart rate (>30 bpm with an HR in upright position >120 bpm) but without any significant hypotension [5].

Pathophysiology of Orthostatic Hypotension

Under normal conditions, standing results in gravitational redistribution of about 500 ml of blood in the splanchnic circulation and in the lower limbs. As a consequence, venous return and cardiac filling pressure fall, resulting in temporarily decreased cardiac output and blood pressure. In response, the aortic and carotid baroreceptors which are sensitive to blood pressure variations send the information to centers localized in the brainstem; as a result the decrease in BP leads to cardiac parasympathetic inhibition and sympathetic activation with increased heart rate and above all peripheral vasoconstriction. Vasoconstriction in the lower members is also favored by the veino-arterial reflex. Neuro-hormonal mechanisms rapidly take over, triggering the renin-angiotensin system and secretion of noradrenaline (x 2 in upright position). An inadequate response from one of these mechanisms may be responsible for OH.

Diagnosis of Orthostatic Hypotension

Blood pressure measurement

The BP must be measured in both lying and standing positions. It is preferable to use an automatic measuring device than a manual one. The BP and heart rate (HR) are measured after the patient has been lying down for at least 5 min (or until BP values are stable), at a comfortable
temperature (20-24°C), with an empty bladder. Then the patient is asked to stand up and BP and HR are measured every minute for three to five minutes. The patient must be asked whether or not symptoms occur during the test. The test may be interrupted in case of pre-syncopal symptoms. If OH is suspected but the orthostatic test is negative, the test must be repeated at other times. In patients with suspected neurogenic OH, extending the orthostatic test up to 10 min is recommended in order to check for delayed OH ([6] [7]).

Under certain conditions, a passive test on a tilt-table (+60 à +80°) may be used to detect OH, either to sensitize the OH detection or in patients who have physical disorders [8].

HR variations must be monitored. A limited or no increase in HR associated with OH will indicate a neurogenic cause (Figure 1). A large increase in heart rate will be a sign of hypovolemia or anemia. These HR variations decrease significantly with age and should be interpreted accordingly.

![Figure 1](image.png)

**Figure 1**: Changes in BP and HR during a tilt test of 5 minutes on a patient showing neurogenic OH.
Figure from Low et al, 2013 [9]
In patients with autonomic failure characterized by neurogenic OH, OH is often associated with supine hypertension [10]. In this case it may be useful to carry out ambulatory blood pressure monitoring over 24h to detect associated post-prandial hypotension, excessive pressure variability, reduced or inverted circadian rhythm (non-dipping) or supine hypertension.

**Clinical signs**

OH may be asymptomatic or symptomatic. There is not always a correlation between the fall in BP and the symptoms severity. Characteristic signs include lightheadedness, visual blurring, dizziness and even loss of consciousness. These symptoms occur particularly when standing, rapidly after standing up or as a result of continued standing. Some symptoms are quite characteristic but less well known, such as a lower cervical and shoulder pain known as “Coat hanger ache” induced by reduced muscular flow. Some patients present non-specific complaints such as fatigue, weakness, buzzing in their ears, lack of concentration, orthostatic dyspnea, difficulty in walking and falls. The circumstances in which the symptoms occur must be carefully analysed in order to identify OH as a possible cause.

Questionnaires can also be used in particular during clinical trials to quantify these OH symptoms; specific OH questionnaires [11] or more general autonomic failure questionnaires could be used.

**Favoring factors**

Searching for favoring factors helps to identify OH. The symptoms may be favored by heat, physical deconditioning such as bed rest, or meals; OH is more common in the morning or after a meal. In patients with autonomic
failure, OH is often associated to postprandial hypotension which can be defined as a systolic fall of over 20 mm Hg occurring within 90 minutes following the meal. Elderly patients who are bed-ridden are particularly susceptible to OH when getting up.

**Orthostatic hypotension: a factor of morbidity-mortality**

Several studies have shown that OH is an independent factor of morbidity-mortality ([12]; [13, 14]). In a meta-analysis, Ricci et al [15] have reported a relative risk of mortality of 1.5[1.24, 1.81] in patients with OH, slightly higher in patients below 65 years (1.78 [1.25, 2.52]). OH may also cause falls.

**Main Causes of Orthostatic Hypotension**

The prevalence of OH increases significantly with age (Figure 2), in particular in institutionalised elderly individuals. [16].

![Figure 2: Prevalence of OH by age group](image)

From Wolters et al and Heart BrainConnection Collaborative Research Group - PLoS Med. 2016 Performed on 6,204 community-dwelling individuals participating in the Dutch population-based Rotterdam Study (Cardiovascular Health Study)
In these patients the prevalence also increases with the amount of medication. [17].

Indeed, drugs represent the first cause of OH. Some drugs may be responsible for OH such as anti-hypertensive treatment, particularly diuretics, vasodilators, some psychotropic drugs (antidepressants, neuroleptics), anti-Parkinsonian agents or alpha-blockers (prescribed for urinary disorders).

Other causes to be investigated include anemia, hypovolemia (dehydration, vomiting, diarrhea, adrenocortical insufficiency) or relative hypovolemia (severe venous insufficiency). OH may result from multiple factors (hypovolemia, associated neuropathy) in patients suffering from renal failure.

Neurogenic OH may be suspected when there are autonomic symptoms in other areas: digestive symptoms (constipation, alternating constipation and diarrhea ...), urinary symptoms, erectile dysfunction, sweating disorders, pupil disorders (photophobia, difficulty in accommodating), ptosis, vasomotor symptoms, hypo-or-hyperhidrosis, cold/heat intolerance...

OH is common among diabetic patients; prevalence varies from 8.2 to 43% according to the criteria used and the studied population [18]. A prevalence of 20% has been reported in the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study [19]. In diabetics, OH may be part of the autonomic neuropathy which is common in this population.
Neurogenic OH may also be suspected in case of associated neurological features, such as an extra-pyramidal syndrome or a peripheral neuropathy. The diagnosis can be oriented according to the patient’s complaints and associated neurological symptoms indicating a cerebral, spinal or peripheral pathology [20]. Neurogenic OH is common in some neurodegenerative disorders such as Parkinson’s disease where on average 30% of the patients are affected (Meta-analysis [21]) and up to 50% in some studies [22]. OH may be dramatic in rarer neurodegenerative disorders such as Multiple System Atrophy where autonomic failure is a key symptom, associated with a Parkinson or cerebellar syndrome [23], Lewy body dementia or pure autonomic failure (PAF) ([24], [25], [26]). PAF is a rare neurodegenerative disorder of the autonomic nervous system (sympathetic component) without motor symptoms; the disease duration may last up to 20 years. However, these patients must be followed up regularly to make sure no other neurological symptoms appear. In neurodegenerative disorders with autonomic failure, supine hypertension is observed in at least 50% of the patients with neurogenic OH (NOH) [24] - NOH severity is often correlated with supine hypertension severity ([7], [26]). There are numerous other possible causes of autonomic failure which may induce OH (metabolic, infectious, traumatic, paraneoplastic, genetic and toxic). The table 1 (adapted from a document published by a consensus of experts (French Society of Hypertension, French Society of Geriatrics and Gerontology and European Federation of Autonomic Societies) summarizes the main causes of OH [27].
**Secondary OH**

**Medications**
- Antihypertensive
- Psychotropics (neuroleptics, antidepressants)
- Vasodilators (nitrates, alpha-blockers, sildénafil...)
- Antiparkinsonian
- Anticholinergics
- Opiates, ..

**Hypovolemia**
- Dehydration
- Salt-free diet
- Denutrition
- Anemia
- Adrenal insufficiency
- Venous insufficiency (relative hypovolemia)

**Neurogenic OH**

**Neurodegenerative Diseases (mainly synucleinopathies)**
- Parkinson’s Disease
- Lewy Body Disease
- Multiple System Atrophy *
- Pure Autonomic Failure *

**Familial Dysautonomia **

**Dopamine beta-hydroxylase deficiency**

**Autoimmune Autonomic neuropathy**
- Autoimmune ganglionopathy
- Guillain-Barre syndrome

**Amyloidosis**

**Diabetes mellitus**

**Chronic Renal Failure**

**Other metabolic causes :**
- Vitamin B deficiency
- Alcoholism
- Porphyria
- Fabry disease

**Neoplasia :**
- Paraneoplastic
- Brain tumors (posterior fossa, medullary)
- Cervical radiotherapy

**Spinal cord injuries**
- Traumatic
- Multiple sclerosis
- Myelitis

**Other traumatic injuries :**
- Sympathectomy
- Cervical surgery

**Infections :**
- Botulism
- HIV
- Chagas disease, ...

**Toxic substances :**
- Heavy metals
- Medications (ex : vincristine , ..)
- Ciguatera
- ...

| Table 1: Main causes of Orthostatic Hypotension adapted from Pathak et al, Expert Consensus, 2014, [27]. *In these diseases, OH is a main symptom **These genetic diseases are very rare. |

In some cases it may be useful to get the opinion of a specialist, to search and quantify more precisely the autonomic failure through specific investigations of the autonomic nervous system (ANS) available in some centres. These tests are based on continuous monitoring of BP and HR and assess the response of the sympathetic, parasympathetic and baroreflex systems during physiological stimulations [9] Sweating may also be studied, to detect associated sympathetic sudoro-motor impairment [28].
Treatment of Orthostatic Hypotension

Identification of the mechanism of OH (disease, drug or other causes) is the first step in the treatment, followed by non-pharmacological measures. OH must be treated whilst it is symptomatic and/or severe. First of all, and when possible, treatments likely to induce OH should be stopped or limited. The factors favoring OH should be investigated and explained to the patient. Hot baths, large meals, especially meals high in carbohydrate and alcohol which are vasodilators, should be avoided [29]. The patient must also avoid changing positions too quickly.

Non-pharmacological measures

Non-pharmacological measures can be used to limit OH and its symptoms:

- Wearing force 2 to 3 compression tights or stockings (to be put on in the morning before getting up). Compression stockings which prevent blood from being stored under the waist are more efficient than stockings [25].

- Sufficient hydration, by drinking one to two large glasses of water before each meal to limit post-prandial hypotension, often associated with NOH. The increase in BP observed after drinking water is induced by a reflex mechanism [30].

- Eating meals more often, in small quantities and poor in rapidly absorbed carbohydrate, to limit post-prandial hypotension.

- Salty diet (to be adapted in case of edema/heart failure).

- Elevating the head and neck during the night (30° tilt) to activate the carotid and aortic baroreceptors and the renin-angiotensin-aldosterone system, in order to limit supine hypertension and reduce early morning hypotension.
Pharmacological measures

The drugs generally used and recommended to treat neurogenic OH are midodrine and fludrocortisone, either alone or together. Since 2014, Droxi-Dopa (L-Threo DOPS) can be used in US to treat NOH (FDA agreement); currently this drug does not have drug marketing approval for NOH in Europe. Other drugs such as dihydroergotamine and etilefrine have been prescribed for treating NOH but none of them proved to be effective for NOH. Some drugs listed hereafter are more rarely used and should be administered by a specialist.

- Midodrine is a prodrug which when hydrolysed becomes desmoglymidodrine, an α1 adrenoceptor agonist. This molecule has proved to be effective on NOH by increasing peripheral vascular resistance ([31]; [32]; [33]). This α1-adrenoceptor agonist (2.5 mg/tablet) can be administered up to maximum 30 mg/d, taken in three or four doses due to its short half-life (3-4 h). The last dose should be taken at least 4-5 h before sleeping to prevent supine hypertension.

Midodrine may favor the occurrence of urinary retention. Other side-effects are mainly piloerection (dose-dependent) and to a lesser degree irritability and insomnia. Midodrine is eliminated through the kidneys so renal function should also be monitored. Further studies are still needed to assess the benefit/risk ratio of midodrine in the long term in patients suffering from NOH.

- Fludrocortisone increases renal sodium re-absorption and expands plasma volume, thus leading to increased blood pressure. Effects last longer than those of midodrine, thus making it more difficult to avoid nocturnal supine hypertension. Fludrocortisone's efficacy remains
insufficiently documented. The dosage of around 50 to 150µg per day can be gradually incremented (up to a maximum of 300µg/day). Side-effects, resulting from its mineralocorticoid activity, are salt and water retention and hypokalemia. This drug may cause edema and may be contra-indicated with patients with heart failure.

- L-threo DOPS or Droxidopa, is a noradrenergic precursor, initially commercialised in Japan for Parkinson’s disease; it has been shown to improve NOH in clinical trials carried out against placebo, in patients suffering from neurodegenerative diseases (Parkinson’s Disease, Pure Autonomic Failure, Multiple System Atrophy) and familial amyloid neuro-pathy ([34]; [35]; [36]). This drug is also used in dopamine-beta-hydroxylase deficiency (very rare genetic disease). The drug received FDA approval for NOH treatment in US in February 2014 but is not routinely available in Europe. A clinical trial in MSA patients is still ongoing in France.

- Pyridostigmine is a cholinesterase inhibitor that may improve OH by facilitating ganglionic transmission; it has been shown to improve OH in comparison with placebo [37]. The same authors have suggested using it alone to treat moderate OH, starting with a dose of 30 mg 2 to 3 times a day (maximum dose 180 mg/d).

- Desmopressin, similar to vasopressin, reduces nocturnal polyuria and might improve morning OH ([38]; [39]). This treatment requires blood electrolyte monitoring.

- Erythropoietin which increases blood volume can also be used, when autonomic failure is associated with a reduced red cell mass.
Treatment of associated supine hypertension

Patients with autonomic failure are often experiencing both NOH and supine hypertension which may be severe. In these cases fludrocortisone should be limited and using evening short-acting antihypertensive agents may be proposed. However, long-term CV risks of supine hypertension in this population are not well known and the decision to treat or not the patient should be individualized [25].

Conclusion

OH is often under-estimated. Identification of OH mechanisms (disease, drug or other causes) is the first step in the management of these patients. Non-pharmacological measures are recommended first alone or associated with pharmacological treatment. An expert advice may be needed in some cases of NOH. There is no consensus regarding the treatment of associated supine hypertension.
Orthostatic Hypotension

Avoid and treat any potential factor which may favor OH ((hypovolemia, anemia, medications (in particular diuretics and alpha-blockers))

Non-pharmacological measures:
✓ Educate the patient: avoid precipitating factors such as rapid postural change, hot baths, alcohol, prolonged bed rest
✓ Increase water intake (up to 1.5 to 2 L) and add salt to the diet (6 à 10 g Na Cl/day - to be adapted in case of edema/cardiac failure) - Intake of two glasses of water before meals
✓ Compression tights or stockings
✓ Elevating the head of the bed of about 30’ during the sleep

Sufficient improvement

Maintain non-pharmacological measures

Maintain treatment (under regular medical and biological follow-up)

No or insufficient improvement - symptomatic OH

Pharmacological treatment: Midodrine (or DroxiDopa*)
or Fludrocortisone (si contra-indication)

Maintain treatment (under regular medical and biological follow-up)

Yes

Improvement

No

Midodrine (or DroxiDopa*)
+ Fludrocortisone (under medical and biological follow-up)

* available in US and Japan - no marketing approval in Europe. **Other medications could be used in some cases such as pyridostigmin or erythropoietin (see corresponding text)

Figure 3: Management of Orthostatic Hypotension
References


