Review

Clinostatic Hypertension and Orthostatic Hypotension

Address for correspondence:
Alfonso Lagi, MD
Emergency and Accident Department
Ospedale Santa Maria Nuova
P.zza di Santa Maria Nuova 1
50100 Florence, Italy
alfonso.lagi@asf.toscana.it
alfonso.lagi1@tin.it

Alfonso Lagi, MD and Simona Spini, MD, PhD
Emergency and Accident Department, Medicine Unit — Syncope and Autonomic Unit,
Ospedale S. Maria Nuova, Florence, Italy

ABSTRACT

Background: The association of clinostatic hypertension (CH) and orthostatic hypotension (OH) is described as the "Hyp-Hyp phenomenon," and it has been found in about 5.5% of hypertensive patients and in up to 50% of patients with OH. The importance of CH/OH in clinical practice is mainly due to the presence of troublesome symptoms, end-organ damage, and difficulties in its clinical management.
Hypothesis: The review focuses on the clinical problem of CH and review the international literature for the best management, including the diagnostic work-up and the taylored treatment for this kind of patients.
Methods: A systematic review of the literature was conducted through MEDLINE research to focus the main controversial issues about CH/OH. Included topics: (1) the diagnostic work-up, (2) the association with dysautonomic failure and syncope, and (3) the treatment options and prevention of end-organ damage.
Results: Current standard reference for OH diagnosis includes functional assessment of the cardiac vagal nervous system and the sympathetic adrenergic system. The association with dysautonomic failure and with syncope needs further investigation. Pharmacologic treatment of OH is aimed at controlling symptoms rather than restoring normotension. Midodrine is the only medication that has been put to multicenter placebo-controlled trial and subsequently approved by the U.S. Food and Drug Administration (FDA) for OH treatment. Short-acting oral antihypertensive agents at bedtime should be considered in patients with severe, sustained CH.
Conclusions: Data obtained from the literature review showed that clinical diagnosis of the Hyp-Hyp phenomenon is relatively simple, but it remains more difficult to establish the causal disease. In our opinion, it is advisable to define simple diagnostic standards for the selection of patients at risk of dysautonomic impairment so that a subsequent highly specific diagnostic work-up could be initiated.

Introduction

The term clinostatic hypertension (CH) generally includes a group of patients presenting an increase in arterial blood pressure (a systolic blood pressure [SBP] of more than 140 mm Hg and/or a diastolic blood pressure [DBP] of more than 90 mm Hg) when supine and a concurrent decrease of at least 20 mm Hg of SBP and/or at least 10 mm Hg of DBP upon standing so that we can define the diagnosis of orthostatic hypotension (OH).[1,2]

This association has been found to be quite common in medical practice. In fact, an incidence of about 5.5% was found among a population of hypertensive patients collected from the clinical work of five Italian hospitals.[3] The study also defined this association with the term "Hyp-Hyp phenomenon" and well described the features of patients suffering from it. The patients had an average age of 58 ± 16 years (range, 16–87) with a slight majority of males (the male/female [M/F] ratio was 1.4/1).

The existence of a clinostatic/orthostatic variability of arterial blood pressure in the hypertensive population had already been demonstrated in large population studies such as the National Health and Nutrition Examination Survey II (NHANES II)[4] and in appropriated studies such as the Systolic Hypertension in the Elderly Program (SHEP),[5] both of which showed an incidence of the disease that varied based on age and blood pressure values. A significant increase in the phenomenon was noticed after 45 years of age, with a peak incidence in patients older than 60 years of age.

Worldwide, CH is considered one feature of autonomic disorders. Autonomic neuropathy may be a primary disorder or may be linked to systemic illnesses. The first group of diseases includes multiple system atrophy (MSA), Parkinson disease (PD), and progressive autonomic failure (PAF). The second group includes autonomic disorders associated with diabetes mellitus or amyloidosis.

The association of CH and OH seems peculiar because of the coexistence of two apparently opposite clinical

All the authors have substantially contributed in the work conception and design, data acquisition, analysis, and interpretation; the authors certify that neither this manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere. The authors disclose all potential conflict of interest from publication of the manuscript. Final approval of the version to be published was obtained from the authors.

Clin. Cardiol. 33, 6, E10–E15 (2010)
Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722

Received: June 3, 2009
Accepted: November 16, 2009

features. The causes of such a disorder may be found in two possible mechanisms: (1) an impaired effectiveness of physiopathologic mechanisms inducing hypertension to preserve high blood pressure values when the patient is standing, or (2) an impaired control of blood pressure in normotensive patients when supine. It has been reported that CH may be caused by increased blood volume or impaired baroreflex buffering,[6,7] whereas OH may be explained through an impaired sympathetic tone, which, in turn, determines a reduction of systemic vascular resistances.[1,8] However, the presence of an increased blood volume or an increased cardiac output never has been demonstrated in these patients.[9,10] On the other hand, failure of the renin-angiotensin-aldosterone system (RAAS) and decreased levels of plasma catecholamines have been well established in dysautonomic patients.[10]

There is no agreement on the true incidence of the Hyp-Hyp phenomenon, as it does not represent a single disorder but has been noticed in many different diseases.[11] Moreover, it has not been established whether CH is associated in any case with dysautonomic failure. Data from the literature report CH incidence in about 26% of patients with PD and in 56% of patients with MSA.[2,11]

Finally, the relationship between the Hyp-Hyp phenomenon and syncope is not completely understood. The incidence of syncope in this population is not known, but the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) has shown that OH accounts for 10% of emergency department presentations for syncope.[12] Nevertheless, these data cannot be generalized, as the Hyp-Hyp population represents only a subgroup of patients with OH, even though the phenomenon may hold a certain importance within the syncope symptom.

If CH is associated with autonomic failure at times, it will therefore be possible that the Hyp-Hyp phenomenon is not restricted to autonomic disorders; in fact, these patients represent a heterogeneous population showing significant differences in the decrease of blood pressure, heart rate, and symptoms when standing and variable end-organ damage (left ventricular hypertrophy, vascular encephalopathy, syncope). If Hyp-Hyp patients seem to share only an association of symptoms (hypertension and hypotension), different hemodynamic and physiopathologic features can be expected.

A small number of very select patients showing different patterns of variance in peripheral vascular resistances when standing was examined.[13] Patients with low orthostatic vascular resistances were suffering from dysautonomic diseases (MSA, PD, PAF, diabetes), whereas those showing high vascular resistances could be affected by many different diseases or conditions, all of them sharing low blood volume as a pathologic mechanism (use of diuretics, pheochromocytoma, chronic renal failure, renal artery stenosis).

Methods

Diagnosis

The first step in the diagnosis is to establish orthostatic and clinostatic values of the blood pressure. Blood pressure has to be measured bilaterally first, in the supine position, and then for at least 3 minutes while the patient is standing. A suitable interval between the two determinations allows improved sensitivity of the test.[14] To obtain reliable results, the device must be correctly positioned over the arm.[15] CH is defined as indicated by the values that already have been reported in the literature,[16] whereas OH is defined as a variation of at least 20 mm Hg of SBP and of at least 10 mm HG of DBP.[17] Heart rate should be carefully monitored, as it has a relevant diagnostic significance: In fact, dysautonomic patients show a reduced heart rate increase responding to OH when compared with non-dysautonomic patients.[1]

The second step of the diagnostic work-up must consider that pharmacologic interactions, such as side effects of medications, represent the most common cause of OH. The medications usually associated with OH were antihypertensives, diuretics, tricyclic antidepressants, nitrates, α-blockers, and β-blockers.

The estimate of total peripheral vascular resistances is the third step. The formula to calculate arterial blood pressure (ABP = peripheral resistance × stroke volume) is used; although, practically, mean arterial blood pressure (DBP + 1/3 SBP/stroke volume) is considered. Stroke volume is evaluated through echocardiography and normalized for the body surface. Clinostatic and orthostatic estimate allows to obtain the two values. The change of the peripheral resistances (either the increase or the decrease) between clinostatism (supine) versus othostatism (upright) allows to distinguish between two different clinical and physiopathological conditions.

Results

The aim of the first clinical approach then is to indicate or to exclude the diagnosis of autonomic failure, keeping in mind that the Hyp-Hyp phenomenon is found more frequently in dysautonomic patients. Table 1 resumes the initial diagnostic work-up in the clinical check of the Hyp-Hyp phenomenon. The following work-up is designed to define cardiovascular effects of autonomic dysfunction. Noninvasive tests require specific devices and a dedicated laboratory; the evaluation of heart rate response to respiratory sinus arrhythmia during controlled breathing (6 deep breaths/minute) and the Valsalva maneuver (VM) are commonly employed, as they are relatively simple and reproducible tests. In the former test, the sinus arrhythmia ratio is calculated by dividing the longest R-R interval by the shortest R-R interval (usually normal ratio <1.2). The VM is carried out by having the subject blow against a pressure of 40 mm Hg for

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722

Table 1. Differential Diagnostic Features in Patients Presenting with the "Hyp-Hyp Phenomenon"

Diagnostic Features	Nondysautonomic Patient	Probable Dysautonomic Patient
Peripheral resistances (orthostatic vs clinostatic)	Increased	Normal/slightly increased
Heart rate variability (clinostatic vs orthostatic)	High variability	Low variability (<10–15 beats per minute)
Pharmacologic interference	Yes	No
Age	Young patients	Elderly patients (aged over 65 years)

Table 2. Primary Degenerative Disorders and Peripheral Autonomic Disorders Causing Autonomic Failure (Modified from Freeman[19])

Disorder	Autonomic Dysfunction	Associated Features	Other Clinical Features, Diagnostic Tests
MSA	Severe; develops early in clinical course; median survival 7–9 years	Parkinsonism[a] (80% of patients), cerebellar dysfunction (20% of patients)	Dysarthria, dystonias, dementia
PD	Often exacerbated by antiparkinsonism drugs	Parkinsonism[a]	REM sleep behavior disorder
DLB	Early autonomic dysfunction	Parkinsonism[a]	Dementia precedes or accompanies parkinsonism; visual hallucination; fluctuating alertness and cognitive impairment
PAF	Progressive autonomic dysfunction; better quality of life and prognosis than for patients with other primary autonomic degenerative disorders	None	None
Diabetes	Generalized polyneuropathy	Most common cause of autonomic dysfunction in Western countries	Fasting blood glucose and glucose-tolerance test
Primary amyloidosis	Generalized polyneuropathy, cardiomyopathy, and conduction abnormalities; organomegaly; nephrotic syndrome	Presents in the sixth to seventh decade of life; caused by production of amyloidogenic light-chain fragments in the perineuronal peripheral tissues	Fat aspirate or rectal or gingival biopsy specimen; immunoelectrophoresis of blood and urine
Familial dysautonomia	Insensitivity to pain and temperature stimuli but sparing visceral pain; absence of tears; hypoactive corneal and tendon reflexes	Autosomal recessive disorder seen primarily in Ashkenazi Jewish population	Genetic testing
Sjögren's syndrome	Sicca syndrome; orthostatic hypotension and visceral involvement	Autonomic manifestations may be present with normal serologic tests	Tests for anti-Ro/SSA and anti-La/SSB antibodies
Immune-mediated autonomic neuropathy	None	May respond to immunomodulating therapy	Nicotinic ganglionic acetylcholine receptor antibodies
Paraneoplastic autonomic neuropathy	Autonomic features may be first manifestation of a cancer	Most often associated with small-cell lung cancer	None

Abbreviations: DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PAF, progressive autonomic failure; PD, Parkinson disease.
[a] Symptoms of parkinsonism include resting tremor, bradykinesia, rigidity, and postural instability.

15 seconds; in autonomic failure, blood pressure continues to decrease during phase II and the normal overshoot is absent in phase IV. The Valsalva ratio is the ratio between the fastest heart rate during phase II and the slowest heart rate during phase IV (usually normal ratio <1.4). Details about the performing modalities of both tests are reported in specialized textbooks.[18] Noninvasive tests give precise information on autonomic dysfunction but cannot allow the final diagnosis of dysautonomic disease.

Table 2 lists primary and peripheral disorders associated with autonomic dysfunction.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722

Patients with autonomic diseases commonly suffer from postprandial hypotension due to blood pooling in the abdominal vascular network as well as in the lower limbs when standing. Symptoms generally arise within 30 minutes of meal ingestion and last 1 to 2 hours. The finding of postprandial hypotension determined by office measurement or by 24-hour outpatient monitoring is a good diagnostic indicator.

Finally, the measurement of circulating catecholamines (epinephrine and norepinephrine) allows the differential diagnosis between PAF and MSA patients.[1]

Treatment

The medical management of the Hyp-Hyp phenomenon is challenging for the physician and quite frustrating for the patient because of the coexistence of two opposite disorders, CH and OH, which each impair the beneficial effects of a pharmacologic treatment aimed to correct the other. Therefore, the therapeutic approach is designed to relieve symptoms rather than to resolve the root causes of the disorder.[19]

Controversy exists about how much harm will result from CH and whether it carries the same risks of essential hypertensions in terms of end-organ damage and its consequences. Data in the literature have demonstrated the association of CH and cardiac and cerebrovascular disease, even though the main prognostic determining factor in these patients remains the causal disease.[19,20] Patients with autonomic diseases have a worse prognosis than do nondysautonomic patients: Among them, those with MSA have a median survival of less than 10 years from the onset of symptoms.[21] Therefore, in these patients, the progression of the underlying disease, rather than autonomic failure, dominates the clinical picture and determines the medical treatment. On the other hand, patients with PAF are believed to have a normal estimated life span; therefore, hypertensive symptoms must be treated appropriately. It is not demonstrated that treatment of either OH or CH in these patients may change the prognosis, but the control of symptoms may improve quality of life.

Nonpharmacologic Treatment

Avoiding the supine position is a simple and effective treatment of CH during the daytime. The use of reclining chairs is recommended when resting, as it allows CH control and improves symptoms of OH, as well as reducing nocturnal activation of the RAAS and the subsequent natriuresis.[22] Table 3 lists nonpharmacologic treatment options to consider based on the patient's compliance and the severity of the disease.

Physical exercise should be always be recommended to avoid the impairment of baroreflex buffering; in patients with low compliance due to aging or severe hypotension, a head-up tilt or supine position is an alternative. For patients presenting with postprandial hypotension, a 2-hour postprandial rest may improve symptoms.

Table 3. Nonpharmacologic Interventions for the Treatment of Orthostatic Hypotension

Intervention	Comments
Perform gradual staged movements with postural change	Time should be allowed for autonomic adaptation
Avoid straining, coughing, and other maneuvers that increase intrathoracic pressure	These maneuvers decrease venous return to the heart and thereby reduce cardiac output
Avoid prolonged recumbency	Deconditioning exacerbates orthostatic hypotension
Perform isotonic exercise	The straining associated with isometric exercise decreases venous return to the heart
Perform physical counter-maneuvers, such as crossing legs, squatting, and tensing muscles	These reduce peripheral pooling and increase venous return to the heart
Discontinue or reduce hypotensive and antihypertensive medications	It may be necessary to accept some supine hypertension in order to maintain orthostatic tolerance
Wear custom-fitted elastic stockings and an abdominal binder	Reduces peripheral pooling in the lower limbs and splanchnic circulation
Minimize postprandial hypotension	Small meals, low in carbohydrates, are recommended. Alcohol should be avoided
Increase intake of fluid and salt	A daily dietary intake of up to 10 g of sodium per day and a fluid intake of 2.0–2.5 L per day is recommended
Drink water rapidly	Rapid ingestion of 0.5 L of water increases blood pressure within 5–15 minutes
Raise the head of the bed by 10° to 20°	Decreases supine hypertension and minimizes pressure diuresis

Pharmacologic Treatment

Pharmacologic control of CH should be limited to nighttime. Short-acting drugs are clearly recommended in these patients, as all antihypertensive drugs worsen OH. The range of possible drugs includes nitrates and vasodilators by transdermic route, to stop administration when the patient gets up and starts normal daily activities. Evening

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722

oral administration is suitable for vasodilators with a short half-life (nifedipine).

Vasodilators are not used in the treatment of essential hypertension because of their capacity to activate the baroreflex and the RAAS. This side effect is absent in dysautonomic patients[6,7]; thus, vasodilators represent a good choice in these patients. Low doses of a short-acting sartan drug may be tried to limit the pharmacological effect.[23]

Long-term treatment of OH includes blood volume expanders (fludrocortisone acetate), pressure agents, and other medications of uncertain and probably multiple pharmacological effects. Table 4 is a panel of the drugs that are commonly used to relieve symptoms of OH. The treatment of OH may be challenging, as all the available drugs have shown limited efficacy and dose-dependent side effects. Midodrine is considered the drug of choice, even though a full dosage and refracted administration are mandatory, as it is more effective than epinephrine. Ephedrine and pseudoephedrine are also used, although their β1 and β2–stimulating effect impairs the vasoconstricting effect.[24] An appropriated dose of fludrocortisone is indicated when fluids and sodium overload have failed, but lifelong treatment should be avoided. Other supplementary drugs may be an adjunct when all the other options have failed, but evidence of their efficacy is still lacking. Desmopressin may be recommended, as dysautonomic patients generally show low levels of vasopressin due to a degenerative process of the hypothalamic suprachiasmatic nucleus. Finally,

Table 4. Drugs Used in the Treatment of Orthostatic Hypotension (Modified from Freeman[19])

Drug	Mechanism of Action	Dosage	Adverse Effects	Comments
Volume-expanding agents				
9-α fluorohydrocortisone	Promotes renal sodium absorption; enhances sensitivity of blood vessels to circulating catecholamines	0.05–0.3 mg daily	Supine hypertension, edema, hypokalemia, hyperglycemia	Not available in Italy
Vasoconstrictor agents				
Midodrine	Direct α-1 adrenoreceptor agonist	2.5–10 mg, 2–4 times a day	Pilomotor reactions, pruritus, supine hypertension, bradycardia, urinary retention	Should not be taken in the 4-hour period before recumbency
Pseudoephedrine	Direct and indirect α-1 adrenoreceptor agonist	30–60 mg, 3 times a day	Supine hypertension, tachycardia, central sympathomimetic side effects, arrhythmias	Should not be taken in the 4-hour period before recumbency
Ephedrine	Direct and indirect α-1 adrenoreceptor agonist	25–50 mg, 3 times a day	Supine hypertension, tachycardia, central sympathomimetic side effects, arrhythmias	Should not be taken in the 4-hour period before recumbency
Supplementary agents				
Desmopressin	Acts on V2 receptors in collecting ducts, increasing free water reabsorption	Nasal spray, 4–40 mcg daily; oral formulation, 100–800 mcg daily	Water intoxication and hyponatremia	Fluid and electrolyte status should be monitored
Erythropoietin	Corrects the normocytic anemia of autonomic failure; supplements volume expansion and vasoconstriction	25–75 U/kg subcutaneously, 3 times a week, until normalization of hematocrit	Supine hypertension; polycythemia	Iron supplementation usually required
Pyridostigmine	Acetylcholinesterase inhibitor that enhances sympathetic neurotransmission	30–60 mg, 3 times a day	Excessive salivation, increased peristalsis, nausea, vomiting, muscular cramps	None

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722

the use of cyclo-oxygenase (COX) inhibitors, β-adrenergic agonists, clonidine, yohimbine, somatostatin, dihydroergotamine, and dopaminergic agonists occasionally has been reported.

Conclusion

Data obtained from review of the literature have shown that although the clinical diagnosis of the Hyp-Hyp phenomenon is relatively simple, it remains more difficult to establish the causal disease. In our opinion, it is advisable to determine simple diagnostic criteria for the selection of patients at risk of dysautonomic impairment so that a subsequent highly specific diagnostic work-up could be initiated.

References

1. Biaggioni I, Robertson, RM. Hypertension in orthostatic hypotension and autonomic dysfunction. *Cardiol Clin*. 2002; 20:291–301.
2. Goldstein DS, Pechnik S, Holmes C, et al. Association between supine hypertension and orthostatic hypotension in autonomic failure. *Hypertension*. 2003;42:136–142.
3. Lagi A, Rossi A, Comelli A, et al.; for FADOI Hypertension Group. Postural hypotension in hypertensive patients. *Blood Press*. 2003;12:340–344.
4. Ching GW, Beevers DG. Hypertension. *Postgrad Med J*. 1991; 67:230–246.
5. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension: final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA*. 1991;265:3255–3264.
6. Robertson D, Hollister AS, Biaggoni I, et al. The diagnosis and treatment of baroreflex failure. *N Engl J Med*. 1993;329:1449–1455.
7. Goldstein DS, Holmes C, Sharabi Y, et al. Plasma levels of catechols and metanephrines in neurogenic orthostatic hypotension. *Neurology*. 2003;60:1327–1332.
8. Goldstein DS, Holmes CS, Dendi R, et al. Orthostatic hypotension from sympathetic denervation in Parkinson's disease. *Neurology*. 2002;58:1247–1255.
9. Wilcox CS, Puritz R, Lightman SL, et al. Plasma volume regulation in patients with progressive autonomic failure during changes in salt intake and posture. *J Lab Clin Med*. 1984;104:331–339.
10. Shannon J, Jordan J, Costa F, et al. The hypertension of autonomic failure and its treatment. *Hypertension*. 1997;30:1062–1067.
11. Pathak A, Senard JM. Blood pressure disorders during Parkinson's disease: epidemiology, pathophysiology and management. *Expert Rev Neurother*. 2006;6:1173–1180.
12. Brignole M, Menozzi C, Bartoletti A, et al. A new management of syncope: prospective systematic guideline-based evaluation of patients referred urgently to general hospitals. *Eur Heart J*. 2006;27:76–82.
13. Lagi A, Cencetti S. Supine hypertension and orthostatic hypertension: is it causal or casual association? *Min Med*. 2008; 99:S66–S68.
14. Gibbons CH, Freeman R. Delayed orthostatic hypotension. *Neurology*. 2006;67:28–32.
15. Guss DA, Abdelnur D, Hemingway TJ. The impact of arm position on the measurement of orthostatic blood pressure. *J Emerg Med*. 2008;34:377–382.
16. The Italian Society of Hypertension. 2007 Guidelines for the Treatment of Hypertension [in Italian]. *Ipertensione e Prevenzione Cardiovascolare*. 2007;14:1–90.
17. The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure, and multiple system atrophy. *Neurology*. 1996;46: 1470–1475.
18. Bannister R, Mathias JC, eds. *Autonomic Failure: A Textbook of Clinical Disorders of Autonomic Nervous System*. 3rd ed. New York, NY: Oxford University Press USA; 1992.
19. Freeman R. Neurogenic orthostatic hypotension. *N Engl J Med*. 2008;358:615–624.
20. Vagaonescu TD, Saadia D, Tuhrim S, et al. Hypertensive cardiovascular damage in patients with primary autonomic failure. *Lancet*. 2000;355:725–726.
21. Silverberg R, Naparsteck Y, Lewis BS, et al. Angina pectoris with normal coronary arteries in Shy-Drager syndrome. *J Neurol Neurosurg Psychiatry*. 1979;42:910–913.
22. Bannister R, Ardill L, Fentem P. An assessment of various methods of treatment of idiopathic orthostatic hypotension. *Q J Med*. 1969;38:377–395.
23. Jordan J, Shannon JR, Biaggioni I, et al. Contrasting actions of pressor agents in severe autonomic failure. *Am J Med*. 1998;105: 116–124.
24. Fouad-Tarazi FM, Okabe M, Goren H. Alpha sympathomimetic treatment of autonomic insufficiency with orthostatic hypotension. *Am J Med*. 1995;99:604–610.

Published online in Wiley InterScience. (www.interscience.wiley.com)
DOI:10.1002/clc.20722