Orthostatic Hypotension and Supine Hypertension in the Patient with Autonomic Failure

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About the Author

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Summary

Orthostatic hypotension and supine hypertension are two cardiovascular symptoms of autonomic failure that can coexist in the same patient. Treatment of these conditions is difficult and needs to be tailored according to the objectives that should be set through a discussion with the patient.

Résumé

L'hypotension orthostatique et l'hypertension en position couchée sont des symptômes cardiovasculaires d'une défaillance du système nerveux autonome qui peuvent coexister chez le même patient. Leur traitement est complexe et doit être choisi en fonction d'objectifs établis en discussion avec ce dernier.

Upright posture forces about 500 mL of blood to be moved downward toward the lower limbs and abdominal capacitance vessels. Without regulatory mechanisms, the decrease in venous return results in a decrease in cardiac output and a symptomatic decrease in blood pressure (BP). The sympathetic system can be activated within seconds to counteract effects of gravity on cardiovascular homeostasis. In certain pathological states, the autonomic nervous system does not function appropriately and cannot adjust for exogenous influences on blood pressure. Accordingly upright posture will cause orthostatic hypotension (OH). Severe OH can cause many symptoms such as dizziness, fatigue, and syncope and it can be very debilitating. Because autonomic failure causes dysfunction of BP homeostasis, its impact on BP will not be limited to orthostatic hypotension. Supine hypertension is in fact present in most patients with autonomic failure and OH.¹ OH is defined as a 20 mm Hg systolic or 10 mm Hg diastolic sustained decrease in BP when a patient goes from the supine to the upright posture. Supine hypertension is more difficult to define but relates to high BP in the supine position when BP is

normal when seated or standing. There are no clear accepted definitions for supine hypertension but a 150 mm Hg systolic and 90 mm Hg diastolic BP thresholds when supine have been suggested.²

Autonomic failure with blood pressure disorders can be associated with many diseases but is mostly associated with primary neurodegenerative diseases namely Parkinson's disease, multisystem atrophy and pure autonomic failure (Table 1). Whatever the cause, the impacts of autonomic failure on cardiovascular homeostasis are largely similar.

The prevalence of OH with or without supine hypertension due to autonomic failure is largely unknown. This prevalence can greatly vary with the definition of OH that may include or exclude patients that are non or slightly symptomatic. There are almost 100,000 patients with Parkinson's disease in Canada³ and 30% of these patients have significant OH.⁴ Almost 30% of all elderly patients have OH⁵ but it is not clear how frequently this OH is clinically significant. One study suggests that more than half of patients with severe OH also present with supine hypertension.¹

Table 1. Etiologies for Autonomic Failure

Neurodegenerative diseases	
	Parkinson's disease
	Multiple system atrophy
	Pure autonomic failure
Metabolic, toxic	
	Diabetes
	B ₁₂ deficiency
	Uremic neuropathy
	Drug induced neuropathy
	Alcohol induced neuropathy
Auto immune	
	Acute pandysautonomia
	Lupus erythematosus
	Celiac disease
	Sjögren's syndrome
	Guillain-Barré syndrome
Infectious causes	
	Lyme disease
	HIV infection
	Neurosyphilis
Inherited autonomic neuropathies	
	Familial dysautonomia
	Familial amyloid polyneuropathy
	Hereditary sensitive autonomic neuropathy
	Fabry disease
	Acute intermittent porphyria variegated porphyria
Other	
	Spinal cord injuries
	Amyloidosis
	Paraneoplastic autonomic neuropathy
	Holmes Adie syndrome

Clinical Importance of Orthostatic Hypotension and Supine Hypertension

OH has obvious consequences on functioning in the upright position. Patient complaints will range from slight dizziness when standing upright for long periods of time to syncope with small orthostatic challenges. OH has also been identified as a marker of frailty and associated with an increase in mortality.^{6,7} There is lack of knowledge on the importance of supine hypertension in autonomic failure whether it is associated with OH or not. It has not been determined that supine hypertension in the patient with autonomic failure is associated with cardiovascular events or mortality but supine hypertension has been linked to left ventricular hypertrophy⁸ and loss of kidney function.⁹ There is no known threshold over which there is an impact on target organs. Because of this paucity of data, it appears appropriate to extrapolate from other populations such as essential hypertensive subjects. In these

patients, the non-dipper phenotype defined as the absence of an appropriate decrease in BP at night has been associated with cardiovascular morbidity.¹⁰ It has been clearly shown that ambulatory BP monitoring is better than clinic BP measurements at identifying patients with high cardiovascular risk.^{11,12} Night time, day time and 24 hour blood pressure thresholds have been identified but it is not known if they can be applied to patients with autonomic failure. Ambulatory BP monitoring's strength comes from averaging unbiased BP measurement over many hours. This as in essential hypertensives remains true in patients with supine hypertension due to autonomic failure.

Diagnostic Workup

The clinical evaluation of patients with OH should start with a thorough questionnaire oriented at the clinical manifestations of autonomic failure and OH and their impact on daily living. Cardiovascular symptoms should also be assessed. During the physical exam, BP and heart rate should be assessed supine and after standing 1, 2, and 3 minutes. The physical signs of hypertension target organ damage and of secondary hypertension should be looked for. Routine biochemistry, complete blood count, vitamin B₁₂, serum protein electrophoresis and an electrocardiogram should be obtained (Table 2). Rarely, urine or plasma metanephrines and catecholamines can be measured. They may help diagnose a pheochromocytoma that can induce high BP with OH or help identify neurodegenerative disorders with autonomic failure that are associated with very low catecholamine levels. Rarely, specific auto antibodies for autonomic failure (mainly ganglionic acetylcholine receptor auto antibodies) can be measured in patients with rapidly evolving unexplained autonomic failure. Ambulatory BP monitoring should be obtained in all autonomic failure patients with OH unless contra indicated. It offers unique insight on night-time BP and invaluable information on BP averages. The tilt table test is usually not necessary since OH can be easily demonstrated during the physical exam but it is useful when OH is suspected but cannot be demonstrated at the bedside and when it is necessary to safely measure orthostatic tolerance. This test aims to measure BP supine and during a 20 to 30 minutes stand using a dedicated table and BP and electrocardiographic monitors. Other tests can be used to measure the autonomic nervous system function. The deep breathing test and the Valsalva test measure the difference in heart rate with breathing or raised intrathoracic pressure. The cold pressor test measures the increase in BP with a painful stimulus. These tests are not done frequently because they add little to the management of blood pressure.

Table 2. Routine Tests for Orthostatic Hypotension and Supine Hypertension Due to Autonomic Failure

Complete blood count
Serum creatinine and electrolytes
Vitamin B ₁₂
Protein electrophoresis
Electrocardiogram
Ambulatory blood pressure monitoring

Table 3. Pharmacological Treatments for Orthostatic Hypotension

Drug	Dose Ranges and Usual Frequency	Level of Evidence
Midodrine	2.5 to 10 mg three time a day	++
Fludrocortisone	0.05 to 0.4 mg daily	±
Domperidone	5 to 10 mg three times a day	±
Salt tablets	2 to 6 grams daily	0
Octreotide	25 to 100 µg sc before meals	±
Erythropoietin	50 U/Kg three times a week	±
Pyridostigmine	30 to 60 mg twice a day	±
Yohimbine	2.7 to 5.4 mg three times a day	±
Acarbose	25 to 100 mg three times a day	±

++: Moderate level of clinical evidence, ±: very low level of clinical evidence, 0: no formal clinical evidence

Treatment

Treatment of OH and supine hypertension begins with a clear definition of the therapeutic objectives. These objectives should be prioritized with the patient as it is not always possible to successfully reach every goal. OH objectives are symptom-based and have a strong quality of life component. Supine hypertension objectives are BP-based and rely heavily on ambulatory BP monitoring and self-measurements. The treatments for OH and supine hypertension will frequently evolve over time. Neurodegenerative diseases are frequently progressive, incidental co morbidities or their treatment can have an impact on BP and OH symptoms, and exogenous factors such as outdoor temperature and diet changes can induce important changes in BP homeostasis. Chronopharmacology and pharmacodynamic properties of drugs will have a strong influence on the pharmacological solutions considered by the physician.

The level of evidence underlying the use of drugs for OH and supine hypertension is low and physician expertise is of importance in the treatment of these disorders.

OH and supine hypertension are two manifestations of the same disease and their treatments can interact but the differences in therapeutic objectives and in therapeutic modalities warrant separate discussions.

Treatment of Orthostatic Hypotension

Treatment of OH starts with non-pharmacological modalities (Table 3). Patients should abstain from activities during which orthostatic symptoms would put them at risk. They should also be careful with ambient heat, heavy meals and alcohol that can all have an exaggerated antihypertensive effect in autonomic failure patients. Patients should stay well hydrated and always keep a bottle of water at hand as 500 mL can increase BP within a few minutes.¹³ Salt intake should be encouraged unless supine hypertension is problematic. Caffeine can be used at meals to decrease the post prandial BP drop. Two cups of brewed coffee

will contain a total of about 200 mg of caffeine and could increase systolic BP by more than 20 mm Hg.^{14,15} Compressive stockings that ideally go up to the waist can be of great help¹⁶ if they are tolerated. Head-of-bed elevation can theoretically increase morning blood volume and decrease orthostatic BP symptoms but a recent study has shown this treatment to be ineffective.¹⁷

Pharmacological treatments for OH mainly rely on midodrine and fludrocortisone. Midodrine is a prodrug quickly metabolized into desglymidodrine by the liver. It is a peripheral alpha-1 receptor agonist that increases arterial resistance and venous return over a period of 3–4 hours. Randomized trials have demonstrated its hypertensive properties and clinical beneficial effects^{18–21} at dosages ranging from 2.5 mg to 10 mg given up to three times a day. Its adverse effects are mainly scalp pruritus, urinary retention, and supine hypertension. Midodrine's short biological half-life helps in tailoring the pharmacological treatment to the patient's needs. Fludrocortisone is a mineralocorticoid agonist with an 18 hour long biological half-life. It has been shown to increase BP by causing salt and water retention²² but there is no clinical trial that demonstrates its clinical benefits. It is nonetheless a well-known drug that it frequently used for treatment of OH at doses ranging from 0.1 to 0.4 mg daily. Adverse effects are oedema, decompensated heart failure, supine hypertension, and hypokalemia. About a third of elderly patients will not tolerate this drug.²³

The following treatments have been shown to have hypertensive properties but the evidence for their clinical benefits in OH is scant. Sodium tablets will increase water retention and BP but an increase in sodium intake can also be addressed through diet. Domperidone is a dopamine receptor antagonist that does not cross the blood-brain barrier. It has been shown to block to the hypotensive influences of levodopa in Parkinson's patients.²⁴ Recent warning about its

Table 4. Pharmacological Treatments for Supine Hypertension

Drug	Dose ranges and usual frequency	Level of evidence
Transdermal nitroglycerine	0.05 to 0.4 mg/hr night-time	+
Diltiazem	30 to 120 mg at bedtime	+
Clonidine	0.1 mg at bedtime	+

+ : Low level of clinical evidence

proarrhythmic influences limits its use though.²⁵ Anti-inflammatory drugs can be used to increase BP by water and salt retention²⁶ but have inherent adverse effects that can be troublesome. Erythropoietin has been shown to increase BP by increasing blood volume and can be used in patients with low hematocrits.²⁷ Octreotide, a somatostatin analogue^{28–30} and acarbose, an alpha glucosidase inhibitor³¹ can reduce post prandial drop in BP by decreasing the release of digestive vasoactive peptides. Pyridostigmine³² and yohimbine²⁶ can both increase sympathetic flow. Yohimbine may be more effective³³ but the influence of both of the drugs on BP are still unclear.³⁴ Ergotamine can increase BP³⁵ but has potential ischemic adverse effects.

Treatment of Supine Hypertension

Nonpharmacologic treatment of supine hypertension is limited (Table 4). A reduced salt diet is theoretically pertinent but will be limited by its impact on OH. Head-of-bed elevation appears to be an elegant way of reducing supine BP but a recent study surprisingly did not confirm the antihypertensive properties of this treatment.¹⁷ Pharmacological treatments of supine hypertension need to be limited to the night-time period. Any antihypertensive treatment may increase OH and great care must be taken to decrease risks of falls. The first choice treatment is transdermal nitroglycerin. This drug has been shown to have strong antihypertensive properties in patients with autonomic failure. Small doses ranging from 0.025 to 0.2 mg/hr have been shown to have significant antihypertensive properties.^{1,2} It should be applied at bedtime and removed 1 to 2 hours before getting up in the morning. Calcium channel blockers have also been shown to be effective.² Regular formulations should be selected to minimize residual morning influences. Diltiazem may be the most appropriate calcium channel blocker for this indication. Clonidine is another option that has been shown to decrease night-time BP in autonomic failure patients.³⁶

Conclusion

OH and supine hypertension are two cardiovascular symptoms of autonomic failure that can coexist in the same patient. Treatment of these conditions is difficult and needs to be

tailored according to the objectives that should be set through a discussion with the patient. Non pharmacologic modalities and regular re-evaluation of all drugs with an impact on blood pressure should always precede introduction of BP modifying drugs. Pharmacologic treatment of OH and supine hypertension can coexist even if the objectives are different by nature. Regular re-evaluation of these treatments through time is essential to optimize patient benefits. Much clinical research is needed to better understand how available OH treatments improve quality of life and how supine hypertension treatments decrease target organ damage.

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