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Review

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The difficult scenario of supine hypertension

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Abstract

Among the clinical forms of high blood pressure the supine hypertension (SH) is a lesser known condition, induced by autonomous dysfunctions evolving also with orthostatic hypotension (OH). It is defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg while in the supine position, despite normal seated and low upright blood pressures. It can be found in almost half of a patients with neurogenic orthostatic hypotension (nOH). The pathophysiology of SH is not fully understood, but until present it is considered a consequence of baroreflex dysfunction associated with residual sympathetic outflow, particularly in patients with central autonomic degeneration. It can be also induced or aggravated by the medication used for OH correction. SH has a high probability to be underdiagnosed, as long as standard blood pressure measurement is usually done in the seated position. The management of the SH/OH syndrome represents a real therapeutic challenge, because the treatment of one condition can lead to the aggravation of the other. Our goal is to drow the attention on SH and its mechanisms, to present the current diagnostic approach in patients at risk for this condition and to discuss the therapeutic solutions of this difficult clinical scenario, that includes increased blood pressure values in leaning position associated with orthostatic hypotension.

Keywords: hypertension; hypotension, orthostatic; autonomic nervous system disease; baroreflex, give

Abbreviations: 24h-ABPM - 24-hour ambulatory blood pressure monitoring; BP – blood pressure; DBP – diastolic blood pressure; HR – heart rate; nOH – neurogenic orthostatic hypotension**;** OH – orthostatic hypotension**;** SBP – systolic blood pressure**;** SH – supine hypertension;

Introduction

Supine hypertension (SH) is currently defined as systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg measured after at least 5 min of rest in the supine position [1]. We have to underline that theas features can be encounterd despite normal seated and low upright blood pressures[2]. SH is pathogenically and clinically correlated with neurogenic orthostatic hypotension (nOH), therefore many authors have named the association of these conditions the SH/nOH syndrome [3].

The appearence of high blood pressure (BP) while lining down was described in patients with

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autonomic failure almost 80 years ago, but since then this clinical feature was very much neglected [4].

The importance of SH was increasingly recognized in the last years and the interest of the scientific community for this subject is reflected in the position or consensus papers that have approached the SH in the context of nOH [5, 6, 7], culminanting with the recently published document on the definition of neurogenic supine hypertension in cardiovascular autonomic failure published by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) in 2018 [1].

The prevalence of SH varies with nOH. The estimated overall prevalence of OH in patients over age 65 reaches 20% [8] in one third of cases being attributed to nOH [9]. Previuos reports have indicated that 60 to 70% of patients with nOH are associated with SH, depanding on the underlying neurogenic disease [10,11]. OH is increasing the risk of cardiovascular events and overall mortality [12, 13, 14]. However, the availible data are not allowing us to depict the prognostic impact of SH independently of the associated nOH, but emergent studies have indicated a higher prevalence of hypertension-mediated organ damage in patients with SH, including left ventricular hypertrophy, arterial stiffness parameters, increased carotid intima-media thickness and microalbuminuria [15, 16, 17, 18]. In this paper we will present the mechanisms possibly implicated in the appearance of SH, the clinical features and the diagnostic work-up for SH, along with the therapeutic approach in this setting.

Aetiology and pathogenesis of supine hypertension

Standing position promotes the pooling of around 800 ml of blood to the lower extremities and other body compartments, which reduces venous return, cardiac output and blood pressure [19]. Normally, this should trigger a compensatory response, mediated by baroreceptors, consisting in augmentation of the sympathetic outflow and the inhibition of the parasympathetic release. Sympathetic activation is essential to increase peripheral vascular resistance and cardiac output in order to prevent the fall of blood pressure during orthostatic position [20]. In addition to this neurohumoral reactions are intervening hormonal factors as well, like the renin-angiotensin-aldosterone or vasopressin systems [21]. Consequently, the adaptation from the supine to the upright position relies on the anatomical and functional integrity of the baroreflex arch. During the transition from lining to orthostatic position, the activation of glossopharyngeal and vagal receptors integrated in the carotid sinus and aortic arch is decreasing, a situation that is perceived by the nucleus of the solitary tract in the dorsomedial medulla and passed on to the nucleus ambigus. This one is reducing the firing of parasympathetic input to the entire cardiovascular system. Therewith, the nucleus of the solitary tract is activating the caudal and rostral ventrolateral medulla, leading to activation of sympathetic ganglia (Figure 1) [22].

OH is defined as a sustained reduction of SBP of at least 20 mmHg or DBP of 10 mmHg within 3 minutes of standing or head-up tilt to at least 60° on a tilt table, with the specification that, in hypertensive patients, a decrease in SBP by 30 mmHg is more appropriate to define OH [5, 6, 7, 23].

The etiology of OH is presented in Table 1 and includes functional and structural conditions, the later being responsible for nOH [24, 25, 26]. Nevertheless, patients with chronic hypertension have often impaired baroreceptor and adrenoceptor function and they may be at risk for developing OH [27].

nOH is a form of orthostatic hypotension that can appear in patients with autonomic dysfunction of the sympathetic nervous system, resulting in an inability to assure a proper postural response of blood pressure and heart rate [7].

The definition of SH was already presented at the beginning of this article. There are few studies addressing the mechanisms of SH. Firstly, patients with neurogenic OH have similar blood volumes whether or not manifest SH, suggesting that the most likely explanation of SH relies on excessive vascular tonus and not on increased cardiac output [28]. Secondly, it has been shown that patients with multiple system atrophy and SH had a significant decrease in BP during infusion of the ganglionic blocker trimethaphan. This effect strongly suggests that the autonomic nervous system plays an important role

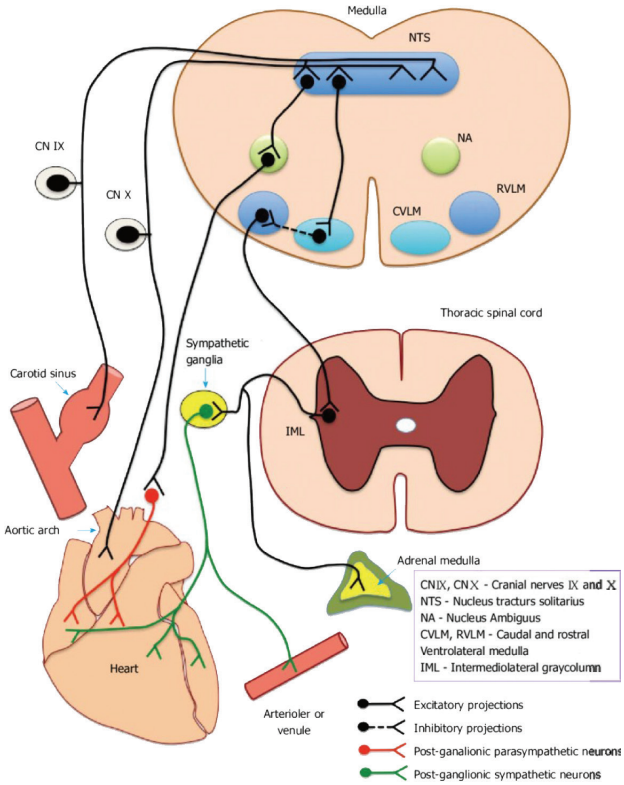

Figure 1. **Neuronal circuitry of the baroreflex arc**. Depicts the complete baroreflex arc - beginning from the baroreceptors (located in carotid sinus and aortic arch), afferents (IX and X cranial nerve) ascend to medullary centres and send efferents (sympathetic and parasympathetic) to end organs (heart and vasculature). CN IX and CN X: Cranial nerve IX and X; NTS: Nucleus tractus solitarius; NA: Nucleus ambiguous; CVLM: Caudal ventrolateral medulla; RVLM: Rostral ventrolateral medulla; IML: Intermediolateral gray column. Reproduced from: Kaur M, Chandran DS, Jaryal AK, Bhowmik D, Agarwal SK, et al – Baroreflex dysfunction in chronic kidney disease, World J Nephrol, 2016; 5: 53- 65.

in the elevation of blood pressure, but as long as SH evolves in some diseases characterized by central sympathetic system denervation it rises the hypothesis of a residual sympathetic outflow with hypersensitive postsynaptic adrenergic receptors [29]. Other pathological aspects resides in a vicious circle maintained, on one hand, by the recurrent episodes of OH - able to trigger the activation of renin-angiotensin-aldosterone system and the increase in SH [30] and, on the other hand, by the high BP values during the night that can induce pressure natriuresis and may result in relative daytime hypovolemia and OH [31]. Moreover, the medication administered for nOH can induce or exacerbate SH [7].

Table 1. etiological classification of orthostatic hypotension

Functional Causes	Hypovolemia Heart failure Severe venous stasis Drugs: vasodilators, diuretics, tricyclic antidepressants, chemotherapeutic agents
Neurogenic Structural Causes	
Primary causes	Alpha-synucleinopathies: Parkinson disease, Multiple System Atrophy, Pure Autonomic Failure, Dementia with Lewy bodies
Secondary causes	Diabetes mellitus, amyloidosis, severe renal failure

Clinical features and diagnostic work-up

SH has a high probability to be underdiagnosed, as long as standard blood pressure measurement is usually done in the seated position. Therefore, SH must be checked in all those at risk of having it, particularly in those with nOH.

Patients with SH/OH syndrome may be asymptomatic, but they usually have symptoms and signs of orthostatic intolerance, such as dizziness, lightheadedness, nausea, fatigue, visual blurring and, most severely, syncope. These are more severe and most frequently encountered under certain conditions, like heat exposure, fever, alcohol drinking, urination, post – exercise time. In contrast to vasovagal mechanisms, syncope due to nOH occurs without signs of autonomic activation such as diaphoresis, tachycardia, nausea or abdominal discomfort. As soon as they resume the supine position, patients with nOH usually recover quickly and may be unaware of the event [32].

The criteria for defining SH should only be applied to patients with proven nOH. Patients newly diagnosed with nOH must benefit from screening for SH, both conditions being evaluated during the same test.

A first step for diagnosing SH is office screening. Blood pressure will be measured as soon as the patient is in the supine position and after at least 5 minutes of rest in the same position. It can be

combined with a standing test, but if the patient can not mantain the standing position for several minutes, it is recommended to perform a tilt table examination.

BP in seated position may have large variations, from normal/elevated to low values, for this reason SH diagnosis should be considered independent of BP values in seated position.

If an elevated blood pressure in supine position is detected in a patient who is not known with autonomic cardiovascular dysfunction, screening for orthostatic hypotension is recommended. BP will also be measured in the seated position. If the systolic difference is greater than 10 mmHg, then a standing test will be performed. This is extremely useful to avoid misinterpretation of SH as essential hypertension.

Another step in nSH diagnosis is home BP recordings performed by the patients. The blood pressure will be measured for one week, three times a day (morning, after lunch , at bedtime) in supine, seated and standing position. This self-monitoring of BP will be performed at the time of diagnosis and then will be repeated after initiation of treatment, in order to evaluate its efficacy and possible side effects.

If office BP screening or home BP monitoring reveals the presence of SH, then the next step is performing an 24-hour ambulatory blood pressure monitoring (24h-ABPM).This is useful to document the presence of nocturnal hypertension and the absolute values of BP overnight.

It also highlights the severity of daytime or post-prandial orthostatic hypotension.

Patients will be advised to keep a diary on the day of monitoring, in order to record the events, the time they take the medication (especially anti-hypotensive or anti-hypertensive drugs), meals, physical activities, and the moments they get out of bed during the night. This is important because some daytime activities may cause significant drops in BP that will lower the BP's average and cause overestimation of nighttime BP rise. On the other hand, nocturnal standing or frequent bath visits during the night, can cause drop in BP values and underestimation of SH. For this reason, at the time of diagnosis and when initiating treatment, both, the mean of the nocturnal BP values and the absolute values should be taken into account.

There is currently no data on cut-off values for SH diagnosis. Due to this reason, for patients with cardiovascular autonomic dysfunction, the interpretation of 24-hour ambulatory blood pressure monitoring and the criteria for diagnosis the essential BP have been proposed to be used to define neurogenic supine hypertension.

Treatment

The therapeutic management of OH associated with SH is a challenge, as treating one condition can aggravate the other. In addition, patients may have very different responses to treatment and thus the results have a high variability. In the following section we are presenting the recommendations of the current guidelines [1, 7].

In patients with autonomic dysfunction, SH treatment requires a step-by-step approach with a careful assessment of the risk-benefit balance associated with antihypertensive therapy. Orthostatic hypotension treatment is primarily targeted for symptomatology, which may have important effects on quality of life, and SH treatment is intended to prevent hypertension-induced organ damage. Most patients with OH require treatment with pressure agents, but the concomitant presence of SH limits the use of these drugs. Unfortunately, there is no ideal drug currently availible to increase blood pressure in orthostatism without affecting blood pressure in the sitting or supine position, so any of the therapeutic agents used in OH may exacerbate SH.

As long as nOH and SH can aggravate each other, the clinicians must address them with caution: medication for nOH must be introduced progressively and avoided at bed-time, while pharmacological treatment of SH must be based on drugs with short duration of action.

The therapeutic management of SH includes education and prevention, non-pharmacological and pharmacological treatment. The aim of the treatment is to maintain blood pressure between certain limits that ensures the patient's safety and prevention of serious symptoms.

Patients with SH must avoid the supine posture during the day and for repose is recommended a head-up recling posture.

Table 2. Treatment of Neurogenic Supine Hypertension

Nonpharmacological Treatment	• Avoiding the supine position during daytime • Sleeping with the head of the bed raised 30- degrees • Avoiding the use of pressor agents before bedtime • Consider carbohydrates snacks before bedtime • Using a urinal/bedside commode to avoide hypotension and falls when the patients get up at night to urinate
Pharmacological Treatment	• Angiotensin receptor blockers • Combined alpha/beta blockers (labetalol) • Clonidine (0,1 mg at bedtime) • The short-acting nifedipine (30 mg at bedtime) • Nytroglicerin patch (at bedtime)

Drinking water is very useful (the effect is maximum at about 35 minutes and lasts more than 60 minutes), but it should be avoided before bedtime in patients with SH. Sleeping with the head- up tilt position (6-7 cm above the bed plan, 30- degrees) decreases the nightly loss of sodium and may lead to improvement of diurnal OH and to a moderate decrease in SH. Most patients with orthostatic hypertension also experience postprandial hypotension. Small and frequent low-carbohydrate meals are recommended in order to prevent severe postprandial hypotension [33].

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. In many situations, it is enough to reevaluate and eventually reduce the medication for the underlying conditions: antihypertensive drugs, diuretics, modification of antiparkinsonian regimen or the use of different antipsychotics.

Of the drugs for nOH, pyridostigmine is sometimes useful in the prevention of OH without aggravating SH. Moreover, in patients with OH and supine hypertension, short-acting pressor agents such as midodrine, are preferable. Treatment should begin with a single 2.5-mg dose, then it can be increased up to 10 mg. These agents will can rise BP for 2 to 3 hours at a time. Pressor agents should not be used if patients are going to remain seated or supine. Evening doses should be avoided because of increased risk of inducing supine hypertension [6].

Patients with severe SH (systolic blood pressure >180 mmHg or diastolic blood pressure >110 mmHg) may be treated in the evening with short-acting antihypertensive agents. In order to control severe SH, angiotensin receptor blockers and combined alpha / beta blockers (labetalol) and alpha-2 agonists may be used. Clonidine has prooved beneficial effects in multiple system atrophy and pure autonomic failure, in the last case probably because there is still some residual sympathetic tone [34].

The short-acting nifedipine (30 mg) and nitroglycerin patch (a dose of 0.05 to 0.2 mg/h) before sleeping significantly lowers BP in patients with autonomic dysfunction, with a maximal decrease in systolic BP during the following 4 hours after administration [35]. The nitroglycrerin patch must be applied at bedtime and removed before rising in the morning. In patients with autonomic dysfunction, due to baroreflex impairment, these anti-hypertensive drugs have an exaggerated depressor effect, compared to the healthy population. Therefore, whenever the anti-hypertensive medication is prescribed, the doses should be carefully titrated and patients should be advised of any side effects.

Conclusions

Supine hypertension has a high association with nOH, therefore it must be assessed in all patients with this condition. SH increases the risk of hypertension-induced organ damage which leads to

the conclusion that it might be useful to treat it. However, the BP threshold to start treatment or the target BP values under therapy are not well established. Therapeutic approach of patients with OH/SH represents a great challenge for clinicians as long as one condition can lead to the aggravation of the other. Thorough research and new studies are needed to clarify the pathophysiology of this syndrome, its long-term consequences and optimal treatment, depending on the underlying and associated pathologies.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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