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Management Approaches to Hypertension in Autonomic Failure

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Abstract

Purpose of Review—Supine hypertension is a common finding in autonomic failure that can worsen orthostatic hypotension and predispose to end-organ damage. This review focuses on non-pharmacologic and pharmacologic approaches to manage hypertension in these patients, in the face of disabling orthostatic hypotension.

Recent Findings—The hypertension of autonomic failure can be driven by sympathetic dependent or independent mechanisms, depending on the site of autonomic lesions. Management of supine hypertension should include simple non-pharmacologic approaches including avoiding the supine position during the daytime and head-up tilt at night. Most patients, however, require pharmacologic treatment. Several antihypertensive therapies lower night-time pressure in autonomic failure, but none improve nocturnal volume depletion or morning orthostatic tolerance. Regardless, treatment may still be beneficial in some patients but must be determined on an individual basis, considering disease type and overnight monitoring. Further, doses must be carefully titrated as these patients are hypersensitive to depressor agents due to loss of baroreceptor reflexes.

Summary—Autonomic failure provides a unique opportunity to study blood pressure regulation independent of autonomic influences. Understanding mechanisms driving supine hypertension will have important implications for the treatment of autonomic failure and will improve our knowledge of cardiovascular regulation in other populations, including essential hypertension and elderly hypertensives with comorbid orthostatic hypotension.

Keywords

hypertension; autonomic nervous system; pure autonomic failure; multiple system atrophy; blood pressure

Introduction

Autonomic failure patients are a clear example of how crucial the autonomic nervous system is in the regulation of blood pressure. The clinical hallmark of autonomic failure is disabling orthostatic hypotension; however, at least half of these patients also have supine hypertension which can be severe and associated with end-organ damage. This review will focus on management approaches of supine hypertension in patients with primary forms of autonomic failure who also suffer from orthostatic hypotension. These are relatively rare

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medical conditions, but lessons learned can be applied to the common situation of the elderly patient who develops orthostatic hypotension.

Clinical Presentation and Pathophysiology of Primary Autonomic Failure

Primary autonomic failure is a neurodegenerative condition associated with cellular lesions involving protein inclusions rich in α-synuclein. The two main types of autonomic failure are classified depending on whether autonomic lesions are of central (multiple systems atrophy, MSA) versus peripheral (pure autonomic failure, PAF) origin. In MSA patients, protein inclusions are present in the cytoplasm of glial cells in the striato-nigral system to produce parkinsonian features (MSA-P) or in olivopontocerebellar structures resulting in cerebellar signs of truncal ataxia (MSA-C). In both cases there is often involvement of brainstem regions that participate in autonomic cardiovascular modulation (Shy-Drager syndrome).[1;2] MSA patients have normal plasma norepinephrine levels and noradrenergic innervation of the heart, indicating that peripheral sympathetic fibers are intact and provide a tonic sympathetic discharge that cannot be modulated because of impaired central autonomic pathways.[3;4] In contrast, PAF is associated with protein precipitates that form Lewy bodies in spinal cord neurons, autonomic ganglia and peripheral noradrenergic fibers.[5;6] Histologically, the neural involvement with Lewy bodies is identical to classical Parkinson's disease,[7] but PAF patients do not exhibit movement disorders. On the other hand, patients with Parkinson's disease or with dementia of Lewy body disease often have autonomic abnormalities with orthostatic hypotension, and all three conditions are likely part of a spectrum of disease.[8;9] PAF patients have very low plasma norepinephrine levels and loss of noradrenergic innervation to the heart, indicating peripheral sympathetic denervation.[3;4] Despite these pathophysiologic differences, the clinical picture of both MSA and PAF is dominated by disabling orthostatic hypotension due to inadequate vasoconstriction and excessive venous pooling.[10] The loss of the baroreceptor reflex function in autonomic failure also exacerbates the inability to control for blood pressure changes resulting in exaggerated responses to pressor and depressor stimuli that would produce little effect in healthy subjects.[11;12]

Paradoxical Supine Hypertension in Autonomic Failure

In addition to profound orthostatic hypotension, at least half of autonomic failure patients have high blood pressure while lying down. The supine hypertension can be severe with levels greater than 200 mmHg.[11;13] This phenomenon often goes undetected as blood pressure is usually measured only in the seated position when it is likely to be normal. The severity of supine hypertension is positively associated with the magnitude of orthostatic hypotension.[14] Supine hypertension may result from treatment with long acting pressor agents including the mineralocorticoid fludrocortisone, but is also seen in untreated patients. It is unclear whether these patients develop *de novo* hypertension, or if they had pre-existing essential hypertension that is unmasked or worsened by loss of baroreflex buffering. The presence of hypertension in autonomic failure has numerous deleterious consequences. It can limit the use of pressor agents for the treatment of orthostatic hypotension; it increases nocturnal pressure natriuresis inducing volume depletion and worsening of morning orthostatic hypotension; and is associated with end-organ damage. Longitudinal studies are not available, butcross-sectional studies show an increased prevalence of left ventricular hypertrophy and renal impairment in autonomic failure patients with supine hypertension.[15–17*]

The pathophysiology of hypertension in autonomic failure varies depending on the disease type. As mentioned previously, patients with MSA have residual sympathetic tone that is ineffectual in preventing orthostatic hypotension because it cannot be modulated to increase

in response to gravitational stress. On the other hand, this residual sympathetic tone contributes to hypertension in MSA because blood pressure is entirely normalized by the ganglion blocker trimethaphan.[18*] While it seems paradoxical that sympathetic activity could contribute to hypertension in autonomic failure, this phenomenon is likely explained by the residual sympathetic activity acting on hypersensitive adrenoreceptors and unrestrained due to ineffective baroreflexes. MSA patients also have enhanced pressor responses to yohimbine, an α_2-adrenoreceptor antagonist which increases norepinephrine release,[18*] and to the norepinephrine reuptake blocker atomoxetine,[19*] further suggesting that the residual sympathetic tone can be engaged to elevate blood pressure.

In contrast, sympathetic-independent mechanisms are more important in PAF because their hypertension is less responsive to ganglionic blockade.[18*] The supine hypertension in PAF is not explained by changes in intravascular volume or cardiac output as previous studies show no differences in patients with or without supine hypertension.[11;20] The hypertension in PAF appears to be driven by increased vascular resistance [21] but the factors responsible for this vasoconstriction are not known. PAF patients have very low levels of plasma norepinephrine and plasma renin activity, but plasma aldosterone levels are normal,[22] which could independently contribute to elevations in blood pressure [23]. Nitric oxide is another metabolic factor that tonically lowers blood pressure in humans [24] and nitric oxide deficiency has been proposed to contribute to the development of essential hypertension [25]. It is not clear, however, if nitric oxide deficiency contributes to hypertension in the absence of autonomic function [26] and nitric oxide function is increased rather that impaired in autonomic failure patients with supine hypertension [27**].

Management Approaches for the Supine Hypertension of Autonomic Failure

During the daytime, the most effective means to prevent hypertension is to avoid the supine position. This seemingly obvious recommendation is often overlooked. Patients can sit in a reclining chair with feet on the floor if rest is needed. It is especially important to avoid the supine position while using methods to treat orthostatic hypotension such as abdominal binders, compression stockings and pressor agents. The use of pressor agents is a common cause of supine hypertension, particularly in hospitalized patients who are given medications at fixed intervals while they are confined to bed to prevent falls. This mismanagement leads to aggravation of supine hypertension, pressure diuresis with volume loss and worsening of orthostatic hypotension, creating a vicious cycle that can render patients disabled. Instead, pressor agents should be given as needed, approximately 30 to 45 minutes before upright activities, to allow patients to be active for 2 to 4 hours at a time. It should be remembered that the goal of pressor agents is to reduce orthostatic symptoms and improve quality of life, not to treat the underlying disease. As such, it is often sufficient to use pressor agents only in the morning and early afternoon when symptoms are worse, and patients should be instructed not to lie down for at least 3 to 4 hours after each dose. Fludrocortisone is frequently required to treat patients with severe orthostatic hypotension, but this comes at the expense of worsening of supine hypertension. In less severe patients it may be worth determining if short acting pressor agents are sufficient to improve orthostatic symptoms. Also, autonomic failure patients should be instructed to avoid over-the-counter medications that increase blood pressure such as nasal decongestants or eye drops containing sympathomimetics, and non-steroidal anti-inflammatory agents like indomethacin and ibuprofen.[28]

If these recommendations are followed, most patients do not require treatment of hypertension during the day. In our practice, we do not even monitor supine blood pressures during the day, and guide our daytime treatment using seated blood pressure measurements.

A few patients are hypertensive while seated, and this greatly complicates their management. While there are no controlled studies that would guide treatment of patients with seated hypertension, calcium channel blockers and arterial vasodilators like hydralazine can be tried.

In most patients, supine hypertension only needs to be treated during the night. Automated 24-hour ambulatory blood pressure monitoring is useful in guiding treatment in these patients.[29] A significant proportion of patients may have supine hypertension at bedtime, but their blood pressure may dip during the night to normal values, and pharmacological treatment may not be justified.[30**] Such patients may only require ingestion of a snack prior to bedtime to induce postprandial hypotension and transiently lower pressure.[12] Another conservative approach to manage supine hypertension is to raise the head of the bed by 6 to 9 inches during the night. It has been shown that head-up tilt reduces nighttime pressure natriuresis and improves morning orthostatic tolerance in autonomic failure.[31] This approach should be instituted in all patients, but is not sufficient in patients with severe hypertension, which would necessitate impractical levels of tilt. In most patients, therefore, the addition of pharmacologic agents is required.

There are currently no medications approved for the treatment of hypertension in autonomic failure and thus the appropriate choice of medication is often based on small clinical trials in which the primary outcome is short-term efficacy to lower night-time blood pressure. The ideal pharmacologic agent to treat hypertension in autonomic failure should effectively lower blood pressure during the night, but with a duration of action short enough so that it would not worsen orthostatic hypotension in the morning. On the contrary, it would improve morning orthostatic tolerance by reducing nocturnal pressure natriuresis. Unfortunately, no medication studied so far has met all of these criteria. Transdermal nitroglycerin patches (0.01 mg per hour) applied at bedtime and removed in the morning, effectively lower systolic blood pressure on average by 36±10 mmHg.[32] In contrast, oral administration of other vasodilators including hydralazine (50 mg) and minoxidil (2.5 mg) are less potent, but could still be useful in a given patient.[32] The differences in these treatments may be due to the ability of the nitric oxide donor nitroglycerin to dilate both arteries and veins, whereas other vasodilators act predominantly on arterial vessels. It should be noted that vasodilators would not be first line antihypertensive treatment if the goal is to prevent end-organ damage because they evoke reflexive increases in sympathetic and renin activity. However, this limitation does not apply to autonomic failure patients due to their loss of baroreflex mechanisms.

Consistent with previous studies showing increased nitric oxide function, night-time oral administration of 25 mg sildenafil, a phosphodiesterase-5 inhibitor that potentiates nitric oxide, effectively lowers systolic blood pressure on average by 52±18 mmHg.[27**] The short-acting calcium channel blocker nifedipine (30 mg) also reduces systolic blood pressure by 37±9 mmHg, but induces natriuresis and may lower standing morning blood pressure.[32] In MSA patients, where supine hypertension can be driven by residual sympathetic tone, 0.1 mg of the central sympatholytic clonidine lowers pressure by 26±6 mmHg.[33] Clonidine reduces nocturnal pressure natriuresis but does not improve morning orthostatic tolerance, likely due to residual effects of the medication. Finally, although autonomic failure is associated with very low plasma renin activity, aldosterone levels are preserved.[22] The effectiveness of drugs targeting the renin-angiotensin aldosterone system is currently under investigation in autonomic failure. In summary, even though the ideal anti-hypertensive agent has not been identified, findings from acute trials suggest that several medications can effectively lower night-time blood pressure in these patients.

Considerations for the Treatment of Supine Hypertension

The finding of hypertensive end organ damage in autonomic failure patients with supine hypertension has provided a rationale for pharmacologic treatment of this condition. We should recognize, however, that the long-term benefits of this treatment on either end organ damage or overall prognosis has not been proven, and outcome trials would be impossible to perform. When deciding how aggressive we should be in the treatment of supine hypertension, the patient's prognosis should also be considered. Patients with PAF have a better prognosis and a near normal life expectancy, and thus may benefit more from prevention of hypertensive complications. In contrast, patients with MSA have a median survival of approximately 8 years after diagnosis and the clinical picture in later stages is dominated by neurodegenerative symptoms, rather than by orthostatic hypotension or supine hypertension.[1;2;34] We should also consider that pharmacologic treatment of hypertension has the potential to aggravate orthostatic hypotension during the night and increase the risk of falling. This is particularly relevant because nocturia is a virtually universal complaint in these patients. Worsening of orthostatic symptoms during the night should be monitored and patients instructed to use a bedside commode. Despite these limitations, treatment of supine hypertension plays an important role in the management of these patients.

These concepts are also relevant to the elderly patient with essential hypertension who develops orthostatic hypotension because of age-related impairment of autonomic function. In these patients antihypertensive medications are often stopped for fear of worsening orthostatic hypotension, but this is a misguided approach. The incidence of orthostatic hypotension is greater in elderly with uncontrolled hypertension than in those with controlled hypertension.[35;36] Further, withholding antihypertensive treatment in order to improve orthostatic hypotension often worsens it by promoting pressure diuresis. Thus, it is important that both conditions be treated simultaneously.

Conclusions

Although primary autonomic disorders are relatively rare, these patients provide an opportunity to study blood pressure regulation in the setting of profound loss of sympathetic and baroreceptor reflex function. Orthostatic hypotension dominates the clinical picture of autonomic failure and as a result is the focus of most treatment efforts in these patients. However, increasing evidence suggests that the supine hypertension of autonomic failure may also be associated with deleterious consequences and may indirectly worsen morning orthostatic tolerance. While conservative non-pharmacologic approaches are ideal in these patients, they are often not sufficient to correct the hypertension. Several small clinical studies have provided data that commonly used antihypertensives can effectively lower nocturnal blood pressure in these patients, but none have been able to improve pressure natriuresis or orthostatic tolerance. Since autonomic failure patients have exaggerated depressor responses to pharmacologic agents, due to loss of baroreflex buffering, it is necessary to titrate doses to each individual. The need for treatment of supine hypertension should also be determined on an individual basis, taking into account several factors and incorporating overnight blood pressure monitoring rather than single day-time measurements. Finally, MSA and PAF patients provide unique human models of sympathetic dependent and independent hypertension, respectively. Since sympathetic activation has long been implicated as a primary determinant of essential hypertension, it is of interest that autonomic failure patients can develop high blood pressure in the absence of sympathetic or renin influences. Understanding the mechanisms driving this paradoxic supine hypertension will have important implications for the treatment of autonomic failure and will improve our knowledge of cardiovascular control in the setting of essential hypertension.

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Key Points

- About half of primary autonomic failure patients with disabling orthostatic hypotension suffer from supine hypertension, which can be severe, associated with end-organ damage, and can worsen orthostatic hypotension by inducing pressure natriuresis.
- A common cause of worsening of supine hypertension is patients receiving pressor agents for the treatment of orthostatic hypotension while remaining supine; this provides no clinical benefit and, through pressure diuresis, further aggravates orthostatic hypotension.
- Fludrocortisone also worsens supine hypertension but is often needed to treat orthostatic hypotension; in less severe patients short acting pressor agents should be tried first.
- During the day, avoiding the supine posture is all that is needed; at night patients should sleep with the head of the bed elevated by 6 to 9 inches.
- Ambulatory 24-hour monitoring can guide night-time treatment as many patients will spontaneously normalize their blood pressure (dipping). Those with sustained nocturnal hypertension can be treated with nitroglycerin patch applied at bedtime and removed in the morning, sildenafil or short acting nifedipine.