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Pharmacotherapy of autonomic failure

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Abstract

The clinical picture of autonomic failure is characterized by severe and disabling orthostatic hypotension. These disorders can develop as a result of damage of central neural pathways or peripheral autonomic nerves, caused either by a primary autonomic neurodegenerative disorder or secondary to systemic illness. Treatment should be focused on decreasing presyncopal symptoms instead of achieving blood pressure goals. Non-pharmacologic strategies such as physical counter-maneuvers, dietary changes (i.e. high salt diet, rapid water drinking or compression garments) are the first line therapy. Affected patients should be screened for co-morbid conditions such as post-prandial hypotension and supine hypertension that can worsen orthostatic hypotension if not treated. If symptoms are not controlled with these conservative measures the next step is to start pharmacological agents; these interventions should be aimed at increasing intravascular volume either by promoting water and salt retention (fludrocortisone) or by increasing red blood cell mass when anemia is present (recombinant erythropoietin). When pressor agents are needed, direct pressor agents (midodrine) or agents that potentiate sympathetic activity (atomoxetine, yohimbine, pyridostigmine) can be used. It is preferable to use short-acting pressor agents that can be taken on as needed basis in preparation for upright activities.

Keywords

Autonomic failure; Treatment; Multiple system atrophy; Pure autonomic failure; Autonomic agents; Pharmacology

1. Introduction

The autonomic nervous system regulates the function of multiple organ systems. Impairment of the autonomic nervous system, therefore, results in a myriad of symptoms, but the clinical picture of autonomic failure is often dominated by disabling orthostatic hypotension. Severely affected patients are able to stand only for a few seconds because of dramatic blood pressure falls produced by impaired cardiovascular adaption to upright posture.

Virtually any disease that affects peripheral nerve function can produce autonomic failure, as is often the case with diabetes mellitus or amyloidosis. In this review, we will focus in a group of neurodegenerative disorders that primarily affect the autonomic nervous system. Distinct clinical forms are characterized either by impairment of central autonomic cardiovascular pathways with intact peripheral postganglionic noradrenergic fibers (multiple system atrophy, MSA), or loss of peripheral noradrenergic fibers with intact central autonomic pathways (pure autonomic failure, PAF, and Parkinson's disease, PD).

Understanding the pathophysiology of autonomic failure has led to the recognition that pharmacological agents can produce different responses in patients with central compared to those with peripheral autonomic failure, and this should be considered in the treatment of these disorders. We will first review the pathophysiology of autonomic failure and the co-morbidities associated with this condition, and will use this as a background to discuss their pharmacotherapy.

2. Pathophysiology of autonomic failure

Patients with autonomic failure share a similar clinical presentation; they are unable to tolerate upright posture because of severe orthostatic hypotension. However, it is important to distinguish the different syndromes associated with autonomic failure because they differ in their disease pathophysiology, response to pharmacological treatment, and prognosis. The etiology of autonomic failure varies significantly; this condition can arise from a primary neurodegenerative disease or can be secondary to systemic conditions that affect peripheral nerves (i.e. diabetes mellitus, amyloidosis, paraneoplastic syndromes, B12 deficiency). Moreover, autonomic failure can result from an immune-mediated process (i.e. autoimmune autonomic ganglionopathy), and rarely from a genetic enzymatic defect (i.e. dopamine beta-hydroxylase deficiency).

All the primary neurodegenerative forms of autonomic failure are associated with cellular lesions involving protein precipitates that are rich in alpha-synuclein. Therefore, they are grouped as alpha-synucleinopathies. Considering this common pathogenesis, it is not surprising that there is a clinical overlap among these conditions. The molecular mechanisms that cause these precipitates are not known, but the different clinical presentations that characterize these disorders can be explained by the site of the lesion (Table 1).

There are two main forms of primary autonomic failure depending on the level of the autonomic lesion. In MSA, protein precipitates are found in glial cells (glial cytoplasmic inclusions, GCI), and are present either in basal ganglia, resulting in a clinical phenotype where parkinsonian features predominate (MSA-P), or in cerebellar structures with a clinical predominance of truncal ataxia (MSA-C).

In PAF, protein deposits occur in neurons and form a characteristic pattern known as Lewy bodies (Kaufmann et al., 2001). This distribution is widespread and includes pre and postsynaptic neurons in the spinal cord, autonomic ganglia and peripheral noradrenergic fibers. Paradoxically, these Lewy bodies are indistinguishable from those seen in classic Parkinson's disease, and yet PAF patients do not have a movement disorder. Even though overt autonomic failure is seen in only a small percentage of patients with PD, it is now clear that autonomic failure of varying degree is part of the clinical picture of this disorder. When present, the autonomic disorder is analogous to that of PAF, with loss of peripheral efferent noradrenergic fibers. Another condition associated with autonomic failure is dementia with Lewy bodies, with prominent features of mental confusion and hallucinations.

The difference in the level of the lesions explains distinct pathophysiological findings between these groups of patients. In MSA, the lesion resides within the central nervous system and involves the neural connections responsible for baroreflex modulation of sympathetic tone (Fig. 1). On the other hand, the neurons that tonically discharge sympathetic activity appear to be intact in MSA. Accordingly, MSA patients have normal or only slightly reduced supine plasma norepinephrine concentrations (Goldstein et al., 1989) and intact noradrenergic innervations to the heart (Goldstein et al., 1997). In patients with PAF and PD with autonomic failure, the neural damage involves more distal structures (Fig. 1). Central pathways involved in baroreflex responses are intact, but sympathetic tracts in

the intermediolateral column of the spinal cord and postganglionic noradrenergic fibers are lost. This state of affairs is evidenced by the very low plasma levels of norepinephrine levels found in these patients (Goldstein et al., 1989) and the lack of 6-[¹⁸F] fluorodopamine uptake in the heart (Goldstein et al., 1997).

In autoimmune autonomic neuropathy the clinical presentation is often acute or subacute, and this condition was formally known as acute pandysautonomia. Currently, it is recognized that in many cases this disorder can be mediated by autoantibodies against the nicotinic (N_N) receptor responsible for neurotransmission at the level of the autonomic ganglia, which can be detected in plasma. In addition to disabling orthostatic hypotension, these patients tend to have prominent gastrointestinal symptoms. A cause–effect relationship between this antibody and autonomic failure was supported by the notion that autonomic function could be restored by antibody removal through plasmapheresis (Schroeder et al., 2005) or intravenous immunoglobulin treatment (Iodice et al., 2009). There are cases with clinical characteristics of an autoimmune neuropathy but in whom the nicotinic receptor antibody is negative. They may respond to plasmapheresis as well but the associated antibody has not been discovered.

A sub-acute or rapidly progressive course of autonomic failure should alert the clinician about a possible paraneoplastic syndrome. The clinical picture may be otherwise indistinguishable from other forms of autonomic failure, but it is important to have this possibility in mind because it can be the first sign of a malignancy, and has obvious implications for treatment. The most common conditions associated with autonomic impairment are small cell lung cancer, monoclonal gammopathies (including light chain disease) and amyloidosis.

In rare cases, autonomic failure results from a genetic disorder associated with absence of the dopamine-beta-hydroxylase enzyme (Biaggioni et al., 1987). These patients are not able to convert dopamine to norepinephrine. The physiologic findings encompasses sympathetic noradrenergic failure and adrenomedullary failure, but intact vagal and sympathetic cholinergic function; the biochemical features include minimal or undetectable plasma norepinephrine and epinephrine levels, and a five-to tenfold elevation of plasma dopamine.

In general, any systemic illness that causes peripheral neuropathy can cause autonomic neuropathy. Arguably the most common cause of autonomic neuropathy is diabetes mellitus. Factors that can influence the development of diabetes autonomic neuropathy (DAN) are the patient's age and long standing history of diabetes mellitus. The classical presentation of DAN is the patient who has inadequate glycemic control and has other complications associated with diabetes, particularly polyneuropathy, nephropathy and retinopathy (Tsfaye et al., 2010). Sub-clinical autonomic impairment is likely to be more common in diabetes than currently recognized (Low et al., 2004).

3. Clinical features associated with autonomic failure

Orthostatic hypotension is the hallmark of autonomic failure, and is defined as a fall in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 min of standing or head-up tilt to at least 60 degree angle (Freeman et al., 2011). Patients usually request medical advice because of pre-syncope symptoms such as lightheadedness or dizziness beginning within a few seconds upon standing. These patients lose their ability to engage sympathetic activity because of impaired autonomic reflexes, and cannot prevent the normal venous pooling in the lower limbs imposed by gravitational forces in the upright posture. This is translated into a decrease in blood pressure on standing. As expected, symptoms resolve when the patient lies down to prevent frank syncope. The exact prevalence of orthostatic hypotension is unknown. However, it is estimated that each

year orthostatic hypotension causes the hospitalization of approximately 80,000 adults aged 75 years and older in the US (Shibao et al., 2007b). Over the last two decades, evidence from cross-sectional and longitudinal epidemiological studies has identified OH as an independent risk factor for cardiovascular morbidity and all-cause mortality (Shibao & Biaggioni, 2010). In prospective cohort studies the presence of OH at baseline increased the risk of subsequent adverse outcomes, including stroke, coronary heart disease and all-cause mortality (Rose et al., 2000; Fedorowski et al., 2010).

3.1. Postprandial hypotension

Postprandial hypotension (PPH) also complicates the clinical picture of autonomic failure. This condition is defined as a fall in systolic blood pressure of more than 20 mm Hg occurring within 2 h after a meal (Lipsitz et al., 1983; Mathias, 1991). The average decrease in systolic blood pressure in patients with severe autonomic failure is around 50 mm Hg. The drop in blood pressure usually starts within the first 15 min after the meal is finished and has a nadir between 30 and 60 min. This hypotensive effect lasts for up to 2 h and this period can be so debilitating that pre-syncope symptoms can be present even while seated, and patients are unable to do any physical activity for fear of fainting.

Post-prandial hypotension can be associated with a variety of symptoms that range from feelings of lightheadedness, nausea, blurred vision and weakness to somnolence or syncope. This condition is particularly worrisome in patients with existing carotid stenosis or coronary artery disease, in whom large blood pressure reductions after a meal could precipitate episode of transient ischemic attack or post-prandial angina.

The etiology of PPH is likely multifactorial. In normal subjects, food ingestion promotes biochemical and hormonal changes that result in blood pooling within the splanchnic circulation. In order to maintain blood pressure within a normal range, a variety of hemodynamic changes are necessary, including an increase in heart rate, stroke volume and cardiac output, that are mediated by the sympathetic nervous system. Failure of these compensatory mechanisms explains the greater prevalence of this condition in subjects with autonomic impairment.

It is noteworthy that food composition is an important factor contributing to the severity of postprandial hypotension. Postprandial reductions in blood pressure are greater after meals rich in carbohydrates rather than fat or protein, which suggest a role of hormones involved in glucose metabolism in the pathogenesis of PPH. Notably, drugs that blunt the release of gastrointestinal peptides with vasoactive properties, e.g., octreotide, or that antagonize the actions of other vasodilators like adenosine, e.g., caffeine, attenuate PPH and are integral components of the treatment strategy for this condition (Onrot et al., 1985; Hoeldtke et al., 1998; Luciano et al., 2010).

3.2. Supine hypertension

Paradoxically, many patients with autonomic failure also suffer from hypertension while recumbent. Studies in patients with primary forms of autonomic failure (i.e. MSA and PAF) have shown that supine hypertension, conservatively defined as systolic blood pressure $\geq$ 150 mm Hg or diastolic blood pressure $\geq$ 90 mm Hg is present in about half of patients with autonomic failure. In many cases, systolic blood pressure could be as high as 200 mm Hg (Shannon et al., 1997; Garland, 2009). In contrast to essential hypertension, there are no longitudinal studies examining the clinical significance of supine hypertension. Nonetheless, cross-sectional studies have shown that autonomic failure patients with supine hypertension develop end-organ damage such as left ventricular hypertrophy and renal impairment (Vagaonescu et al., 2000; Maule et al., 2006; Garland, 2009). Furthermore, there are clinical

reports of acute events such as stroke, cerebral hemorrhage, papilledema and heart failure, following hypertensive crisis in this population (Bannister & Mathias, 1992; Sandroni et al., 2001). Furthermore, sustained nighttime hypertension is associated with increased pressure natriuresis, which leads to volume depletion and worsening orthostatic hypotension in the morning (ten Harkel et al., 1992). There is a positive association between the severity of supine hypertension and that of orthostatic hypotension (Goldstein et al., 2003), but unlike the latter, supine hypertension can remain undetected for prolonged periods, because it is asymptomatic and blood pressure is commonly measured only in the seated position. In most cases, supine hypertension is sustained throughout the night, but in others it may drop to normal values also known as “dipping” phenomenon (Okamoto et al., 2009). This has important clinical implications for the treatment of this condition. Clinicians should avoid the use of anti-hypertensive in patients who dip at night because of increase risk of syncope, particularly in those who suffer from excessive nocturia. Thus, twenty-four-hour ambulatory blood pressure monitoring or overnight blood pressure monitoring may be useful in the assessment of this condition (Ejaz et al., 2007).

The mechanisms underlying supine hypertension in primary autonomic failure differ according to the level of the autonomic lesion. In patients with central autonomic failure (i.e. MSA), residual sympathetic tone contributes to supine hypertension, possibly acting on hypersensitive adrenoreceptors and unrestrained by the lack of baroreflex modulation (Shannon et al., 2000). In contrast, the cause of hypertension in peripheral autonomic failure (i.e. PAF) remains unknown. These patients have increased systemic vascular resistance (Kronenberg et al., 1990) despite having very low plasma norepinephrine and renin activity (Shannon et al., 2000). The driving force for this increased vascular tone is not known, but it is unlikely that sympathetic mechanisms play an important role. In some patients, however, supine hypertension may represent a worsening of pre-existing essential hypertension, or may be a side effect of the treatment for orthostatic hypotension (e.g. pressor agents or fludrocortisone).

4. Treatment of autonomic failure

4.1. Management of orthostatic hypotension. A stepwise approach

Orthostatic hypotension is a substantial problem in patients with autonomic failure and the cause of morbidity secondary to syncope and falls. Treatment of orthostatic hypotension should not be focused on achieving blood pressure goals. Instead, the treatment should be directed toward ameliorating symptoms, improving patient’s functional status, and reducing the risk of falls and syncope. We have divided all available treatment strategies as non-pharmacological and pharmacological; a stepwise approach for the treatment of orthostatic hypotension is presented in Table 2.

4.1.1. Non-pharmacological interventions—The first step for the management of orthostatic hypotension is to discontinue any medication that has the potential to cause or exacerbate orthostatic hypotension. Among common offenders are alpha-blockers used to treat symptoms of prostate hyperplasia, diuretics and tricyclic antidepressants.

The primary mechanism by which orthostatic hypotension ensues is the inability to counteract the gravitational blood pooling that normally occurs in the lower abdomen and lower extremities. Therefore, the second step is to educate patients about the use of simple physical countermeasures aimed at reducing venous pooling. Such maneuvers include moving from the supine to standing position in gradual stages, particularly in the mornings when symptoms are at their peak, avoid standing motionless, crossing one leg in front of the other while standing, squatting, and tensing the leg muscles. These maneuvers have shown to help maintain blood pressure and can be applied instantaneously. In addition, devices can

also be used to reduce venous pooling. Among them are custom-fitted compression stockings that apply graded pressure to the lower body. It is very important that they cover the lower abdomen because most of the pooling occurs in the splanchnic circulation (Diedrich & Biaggioni, 2004). Although these support garments can be very helpful, they require a motivated patient because they are difficult to put on, and uncomfortable to wear. An alternative are abdominal binders that are based on the same principle but are easier to use.

The third step is to increase central volume. Patients should be advised to increase salt and water consumption; up to 6–10 g of sodium and 2–3 L of water a day. In patients with supine hypertension, particularly non-dippers, the persistent elevation in blood pressure causes pressure natriuresis and volume depletion. In these cases, raising the head of the bed 6 to 9 in. or eating a high carbohydrate snack before bedtime may help reduce their nighttime hypertension.

4.1.2. Pharmacological interventions—In most autonomic failure patients these non-pharmacologic measures are insufficient to control pre-syncopal symptoms. In these cases, we suggest to start pharmacological therapy with the goal of maintaining upright blood pressure above the threshold that overcomes cerebral blood flow auto-regulation. Therefore, the fourth step in the management of orthostatic hypotension is the use of pharmacological agents that increase intravascular volume; this can be achieved by adding fludrocortisone, a synthetic mineralocorticoid. Fludrocortisone increases renal sodium re-absorption and expands plasma volume. Treatment is initiated with 0.1 mg a day and then increased up to 0.3 mg/day. The effect on plasma volume is only transient; its long-term benefit may be related to potentiation of the pressor effects of norepinephrine and angiotensin II (Hickler et al., 1959; van Lieshout et al., 2000). Only two descriptive case series assessed the effects of fludrocortisone for the treatment of OH, one in patients with diabetes mellitus (Campbell et al., 1976) and one in patients with Parkinson's disease on Levodopa (Hoehn, 1975). Assessment of the efficacy of this medication was based on reporting of pre-syncopal symptoms and improvements in postural hypotension as measured by supine and standing blood pressure during treatment. These studies suggested that fludrocortisone was effective in the treatment of OH based on the improvement of these parameters (Hoehn, 1975). Of note only in one study the patients served as their own controls (Campbell et al., 1976). Despite the limited information on the effectiveness of fludrocortisone, this drug has been used for the treatment of OH for the past 40 years (Frick, 1966). Fludrocortisone can induce or worsen supine hypertension, raising concerns about its long-term safety particularly in patients with history of congestive heart failure. In such cases it may be worth verifying its effectiveness by stopping it to determine if symptoms of orthostatic hypotension worsen and deciding if the symptomatic relief it provides is worth the potential deleterious effects of supine hypertension. In patients with severe supine hypertension, it may be preferable to try treatment with short acting pressor agents before fludrocortisone.

There are two additional therapeutical approaches aimed at improving blood volume that are usually reserved for refractory patients. Patients that suffer from severe autonomic failure have a high incidence of anemia, which is in part due to impaired erythropoiesis associated with their sympathetic failure. The severity of the anemia is usually mild and may be dismissed as unlikely to contribute to the patient's symptoms. Nonetheless, these patients are very sensitive to volume changes and reversing anemia has the theoretic advantage of selectively increasing intravascular volume, and through this mechanism improving venous return and blood pressure. *Recombinant erythropoietin*, even when used at modest doses (epoetin alpha 25–50 units/kg body weight, subcutaneously, three times a week) can reverse the anemia of autonomic failure and even though there is limited number of published reports, it has been shown to improve upright blood pressure and ameliorate symptoms

(Biaggioni et al., 1994). Long-term studies that evaluate the safety and efficacy of this medication for the treatment of orthostatic hypotension are not available. The cost and route of administration often limits its use.

An alternative approach to improve blood volume in these patients is the use of the vasopressin analog *DDAVP* (2–4 µg given intramuscularly at bedtime) to prevent nocturia and early morning worsening of orthostatic hypotension (Mathias et al., 1986). DDAVP is devoid of the pressor effects of vasopressin, and can be used, therefore, in patients with supine hypertension. It should be used with caution because of the risk of inducing symptomatic hyponatremia.

The final step in the treatment of orthostatic hypotension is the use of pressor agents. It is preferable to use short-acting drugs that can be added to the previous regimen to increase blood pressure for 2 to 3 h at a time. They should be given on a PRN-basis, only to allow periods during the day when patients can be active. We recommend that they be taken 30 to 45 min before activity. They should not be prescribed at fixed intervals with no consideration of the patient's activity because of the risk of inducing or worsening supine hypertension. The direct acting α -1 agonist *midodrine* is the only FDA approved medication for the treatment of orthostatic hypotension. The efficacy of midodrine in increasing blood pressure has been evaluated in double-blind placebo controlled trials (Kaufmann et al., 1988; Wright et al., 1998). There was a significant linear relationship between midodrine dosage and mean systolic blood pressure in a dose–response study. Furthermore, midodrine improved standing systolic blood pressure and symptoms (dizziness/lightheadedness, weakness/fatigue, syncope, low energy level, impaired ability to stand) compared with placebo (Jankovich et al., 1993; Low et al., 1997; Wright et al., 1998). The effect of midodrine on standing blood pressure and ability to stand up has been superior compared with ephedrine (Fouad-Tarazi et al., 1995), but no comparison exists with fludrocortisone. The FDA approved Midodrine in 1996 under accelerated approval for orphan diseases, on the basis of studies demonstrating an improvement in blood pressure. This approval required subsequent studies verifying actual clinical symptomatic benefit to patients. It is not certain if the drug will be removed from the market unless such studies are forthcoming.

An alternative to the use of direct vasoconstrictors, one can harness pharmacologically any residual sympathetic activity the patient may have, with the goal of producing a pressor effect. Even small increases in plasma norepinephrine induced by these agents may lead to exaggerated rises in blood pressure because of autonomic denervation-induced-up-regulation of adrenoreceptors and inability to buffer hemodynamic changes due to lack of baroreflex capacity. Among these strategies, the α -2 antagonist *yohimbine*, is particularly effective in improving orthostatic tolerance in autonomic failure. This agent increases norepinephrine release from sympathetic nerves by augmenting central sympathetic outflow and by interfering with inhibitory modulation of pre-synaptic α -2 adrenoreceptors. In an open label study, oral administration of 5.4 mg of yohimbine increased blood pressure by 50 mm Hg with a peak effect at 75 min. This pressor effect was comparable to midodrine and phenylpropanolamine (Jordan et al., 1998). More recently, in a single-blind, placebo-controlled, crossover study, the same dose of yohimbine increased standing diastolic blood pressure by 11 mm Hg and reduced pre-syncope symptoms, particularly lightheadedness in 31 patients with autonomic failure (Shibao et al., 2010). Yohimbine is well tolerated in autonomic failure patients. It should be noted that all of the published trials were done in acute settings; the long-term efficacy of yohimbine is unknown. Even though yohimbine was widely marketed for the treatment of erectile dysfunction in the US, currently this medication is available only through compounding pharmacy or it can be found also as part of herbal supplements. Alternatively, one can use ephedra alkaloids such as *pseudoephedrine*, a sympathomimetic amine (Jordan et al., 2004).

Pharmacological inhibition of the norepinephrine transporter (NET) is another example of an approach that can take advantage of the patient's own residual sympathetic tone. NET inhibition will increase synaptic norepinephrine that is tonically released, which should result in an increase in blood pressure. Indeed, in a proof-of-concept study we found that the norepinephrine transporter blocker, *atomoxetine*, is an effective pressor agent in autonomic failure patients, and acutely improves orthostatic tolerance even in pediatric doses (18 mg). This pressor effect is maximized in patients with intact peripheral sympathetic fibers (MSA with central autonomic failure impairment) who can achieve an average increase in blood pressure of about 50 mm Hg. Patients with PAF and PD are less likely to experience a pressor response given their peripheral autonomic denervation (Shibao et al., 2007c). This divergent effect could be useful as a diagnostic tool to determine the level of the lesion within the autonomic nervous system in patients presenting with orthostatic hypotension and therefore, identify early forms of MSA prior to the development of motor deficits.

Another strategy to achieve fast increases in blood pressure consists on the rapid ingestions of *tap water* (16 oz, in 3–4 min). This can be used as a rescue measure when autonomic failure patients are symptomatic due to excessive hypotension on standing. The blood pressure effect is observed in the first 5 min and peaks around 30 min after ingestion; this is thought to be a sympathetic-mediated effect because the blood pressure elevation is eliminated during autonomic withdrawal with trimethaphan, a ganglionic blocker. Water therapy has rapidly assumed an important role in our treatment armamentarium and is certainly one of the most cost-effective therapies (Jordan et al., 1999a).

The magnitude of responses to these agents varies significantly between patients, maybe because of differences in residual sympathetic activity. We recommend testing individual responses by measuring seated and standing blood pressure before and 1 h after drug administration. All of these drugs will increase supine blood pressure, but the effect may be less pronounced with *pyridostigmine*, a cholinesterase inhibitor that facilitates cholinergic neurotransmission at the level of autonomic ganglia and, therefore, may increase blood pressure preferentially on standing, when residual sympathetic tone is increased. In an initial open label study of 15 patients with neurogenic orthostatic hypotension due to a variety of diseases (PAF, MSA, PD and others), 60 mg of pyridostigmine by mouth produced only a nonsignificant increase in supine blood pressure but significantly increased orthostatic blood pressure and reduced the fall in blood pressure during head-up tilt. The improvement in orthostatic blood pressure was associated with a significant improvement in symptoms (Singer et al., 2003). A subsequent double-blind, randomized 4-way crossover study in 58 patients with neurogenic orthostatic hypotension confirmed that 60 mg pyridostigmine prevented the orthostatic fall in blood pressure without worsening supine hypertension. The pressor effect of pyridostigmine, however, was rather modest; 2 h after drug administration, upright systolic blood pressure was only 4 mm Hg higher in the pyridostigmine group compared with the placebo group. Pyridostigmine appears to be less efficacious in patients with severe forms of autonomic failure (Shibao et al., 2010).

Current treatment with short-acting pressor agents is far from satisfactory. Most of these agents increase peripheral vascular resistance, and it is questionable that this is the most effective way of increasing cerebral perfusion. Arguably, drugs that induce venoconstriction and improve venous return may be more effective. There are only a few agents currently available with these characteristics. *Ergotamine alone or in combination with caffeine* is effective in increasing blood pressure and improving symptoms, but oral bioavailability is variable, and there is concern about its long-term use particularly in patients with coronary artery disease (Biaggioni et al., 1990; Dewey et al., 1998). *Octreotide* is also very effective, even when other agents fail, in part because of its ability to constrict the splanchnic circulation, where most of the orthostatic blood pooling occurs (Diedrich & Biaggioni,

2004). Its use is limited by the need for parenteral administration, and by worsening of gastrointestinal symptoms in patients who have these symptoms at baseline. The effect of octreotide on orthostatic tolerance as measured by standing time 1 h after the administration was comparable to midodrine and their combined use seems to potentiate this effect (Hoeldtke et al., 1998).

4.1.3. Emergent therapies for autonomic failure—Understanding the pathophysiology of autonomic failure has led to the discovery of new therapeutic pathways to treat this condition. For example, the discovery of DBH deficiency has led to the use of droxidopa (L-dihydroxyphenylserine) which is the first successful pharmacological approach to circumvent an autonomic enzyme defect. Droxidopa has a structure similar to norepinephrine but with a carboxyl group, it can be administered orally and is converted to norepinephrine through the enzyme dopa-decarboxylase which is found centrally and in the periphery. Robertson and collaborators have shown that after oral administration, droxidopa is taken up by post-ganglionic sympathetic neurons, decarboxylated to norepinephrine and can be successfully used to treat patients with DBH deficiency (Biaggioni & Robertson, 1987). Since then, this medication has been tested in other autonomic disorders such as MSA, PAF, autonomic failure associated with amyloidosis and even autoimmune autonomic failure (Kaufmann et al., 2003; Kaufmann, 2008). The optimal dose varied between 200 mg and 2000 mg, patients should require careful titration given different degrees of adrenergic denervation. The pressor effect is observed after 1 h and lasts for 6 h. Droxidopa is currently under evaluation for approval through the FDA as an orphan drug for the treatment of orthostatic hypotension.

4.2. Treatment of associated co-morbidities

4.2.1. Should we treat postprandial hypotension in patients with autonomic failure?—Postprandial hypotension is an important clinical condition in patients with autonomic failure that often complicates the treatment of orthostatic hypotension. This condition if left untreated produces an additive hypotensive effect when associated with orthostatic hypotension and increases the risk of syncope and falls. In some mild cases, non-pharmacologic strategies may be beneficial; advising patients to reduce the meal size and increase their frequency of meals, i.e., eat 6 small meals instead of 3 large ones, can help ameliorate pre-syncope symptoms.

Other non-pharmacological measures include decreasing the consumption of carbohydrates, although this can be difficult to adhere to because carbohydrates are contained in 60% of the normal Western diet; and rapid water drinking (16 oz, 3–4 min) with meal ingestion, which can attenuate the post-prandial decrease in blood pressure (Deguchi et al., 2007). Pharmacological interventions are recommended when patients fail non-pharmacological therapy or when they have other co-morbid conditions such as transient ischemic attack or post-prandial angina that puts them at risk for complications. Three different pharmacological approaches have been studied for the treatment of PPH; one approach has been to increase the baseline sympathetic nervous system prior to meal ingestion with droxidopa (Freeman et al., 1996). Another has been to block the release of gastrointestinal and pancreatic hormones with octreotide. A third approach has been to antagonize the effect of vasodilators such as adenosine with caffeine (Onrot et al., 1985). Although, these drugs seem to ameliorate PPH, their use is limited by their mode of administration and side effects. In the case of caffeine, studies have yielded controversial results (Lipsitz et al., 1994).

Recent studies have shown that acarbose, a medication commonly used to treat hyperglycemia in type 2 diabetes mellitus, could have an important therapeutic role for the treatment of PPH. Case reports have shown that this medication improves PPH in patients

with type 1 (Maule et al., 2004) and 2 diabetes mellitus (Sasaki et al., 2001) and patients with autonomic failure. A randomized, double-blind crossover study has shown that 100 mg acarbose, 20 min before a meal, attenuates the postprandial fall in blood pressure in patients with pure autonomic failure (Shibao et al., 2007a). Similar results were found with 50 mg of acarbose in elderly Chinese (Jian & Zhou, 2008). The mechanism underlying this effect appears to be associated with decreases in glucose absorption and the release of vasodilatory gut peptides. Long-term effect of this therapy has not been evaluated.

4.2.2. Should be treat supine hypertension in patients with autonomic failure?

—The traditional goal of treating essential hypertension is to prevent end-organ damage and reduce cardiovascular events (i.e. stroke, nephropathy, and cardiac disease). In autonomic failure, the long-term benefit of antihypertensive treatment is less clear. There are no longitudinal or efficacy studies that show an association between supine hypertension and end-organ damage, or whether antihypertensive treatment prevents it. Moreover, the long-term benefit of antihypertensive therapy would depend on the underlying condition. MSA patients have a median survival of less than 10 years from the onset of symptoms (Silverberg et al., 1979), and their clinical course is mainly conditioned by the neurologic degeneration. On the other hand, PAF patients have better prognosis, with a normal life expectancy. Prevention of hypertensive complications might be more important in these patients. Nonetheless, most patients with supine hypertension may benefit from antihypertensive therapy on the short-term, either by 1) reducing nocturnal volume depletion, which would improve orthostatic tolerance in the morning; or by 2) allowing a more liberal use of pressor agents during daytime. Several treatment strategies have been shown to be effective in reducing BP during the night, however none of them have shown to meet all of these goals. Treatment of supine hypertension is not without risks; pharmacological treatment could potentially aggravate orthostatic hypotension during the night, increasing the risk of falls in patients. Furthermore, nighttime BP spontaneously decreases (“dipping”) to normal levels in some primary autonomic failure patients with supine hypertension (Okamoto et al., 2009). Antihypertensive treatment, therefore, should be only directed to patients who would benefit the most, and it should be based on a comprehensive clinical evaluation that should include an overnight or 24 h BP monitoring.

4.2.2.1. Non-pharmacological interventions: Conservative approaches can be very effective in the management of supine hypertension (Low & Singer, 2008). All patients should receive education on the judicious use of interventions aimed to increase BP (Table 3), and should be instructed to self-monitor BP daily, particularly after starting a new therapy. During daytime, supine hypertension is best treated by simply avoiding the supine position. Patients should be instructed to rest in a reclining chair if tired, and avoid the use of pressor agents, water boluses or other non-pharmacologic measures used in the treatment of orthostatic hypotension while supine, close to bedtime, or when sitting BP is elevated. During the night, sleeping with the head of the bed elevated 6 to 9 in. reduces BP and nocturnal natriuresis; this improves orthostatic hypotension in the morning (ten Harkel et al., 1992). Other non-pharmacological measures are presented in Table 3.

4.2.2.2. Pharmacological interventions: In many cases, however, the approach outlined above is not sufficient to control supine hypertension, and pharmacological interventions are necessary (Table 3). The cut-off BP level to start antihypertensive therapy has not been determined. The decision to treat should be made on a patient-by-patient basis. In most cases, antihypertensive medication is used only during bedtime, when supine hypertension is sustained, and uncontrolled by non-pharmacological measures. Currently, no antihypertensive drug has been approved specifically for this condition. Commonly used antihypertensives are usually selected based on their BP-lowering effect shown in acute,

small trials. The hypotensive effect of the ideal agent should be long enough to control BP during the night and prevent natriuresis, but short enough to wane by the following morning. Patients with primary autonomic failure have a good depressor response to *transdermal nitroglycerin*. A dose of 0.05 to 0.2 mg/h applied at bedtime and removed before rising in the morning (~6 AM) has shown to reduce BP in both MSA and PAF patients, with a maximal decrease in systolic BP of 36 ± 10 mm Hg 4 h after the nitroglycerin patch was applied (Jordan et al., 1999b). *Short-acting nifedipine* (30 mg) given at bedtime has also shown to be effective in decreasing BP during the night. A maximal decrease in systolic BP of 37 ± 9 mm Hg was achieved 4 h after nifedipine was given (Jordan et al., 1999b). However, upright blood pressure in the morning tended to be lower with nifedipine (77 ± 3 mm Hg) compared to placebo (91 ± 12 mm Hg), and more patients (3/10) were not able to stand up because of severe orthostatic symptoms (versus 1 patient with placebo). Other vasodilators such as *hydralazine* 50 mg and *minoxidil* 2.5 mg were less effective antihypertensives in autonomic failure patients, with an average reduction in BP of 13 ± 7 mm Hg and 22 ± 8 mm Hg, respectively (Jordan et al., 1999b). Unfortunately, none of these medications reduced pressure natriuresis and nocturia, and nifedipine even increased the nocturnal sodium loss, which would explain the trend toward worse morning orthostatic tolerance with this medication (Jordan et al., 1999b). *Clonidine* (0.1 mg), a selective α_2 -adrenergic agonist, has also been effective in lowering BP in MSA and PAF patients (Shibao et al., 2006). The maximum decrease in systolic BP was 26 ± 6 mm Hg 6 h after drug administration. Unlike the other antihypertensive medications, clonidine reduced nocturnal pressure natriuresis. Orthostatic tolerance in the morning, however, did not improve, possibly because of residual hypotensive effects of clonidine carried over into the morning. A recent study has shown that treatment with the phosphodiesterase inhibitor *sildenafil* 25 mg significantly decreased nighttime hypertension, with a maximal decrease in systolic blood pressure of 52 ± 18 mm Hg after 6 h of drug administration (Gamboa et al., 2008). Given the baroreflex impairment in autonomic failure patients, these anti-hypertensive drugs have an exaggerated depressor response as compared to that in healthy subjects. Thus, doses need to be carefully titrated in each patient, and whenever antihypertensive drugs are prescribed, patients should be warned about the potential risk of falls if they get up at night to urinate.

5. Lessons learned from autonomic failure

Autonomic failure is a relatively rare disorder; patients who suffered from this condition provide a unique learning opportunity to understand the role of the autonomic nervous system to blood pressure regulation. When this system fails, disabling orthostatic hypotension is the predominant clinical presentation; however patients also develop other disorders of blood pressure regulation such as postprandial hypotension and supine hypertension that sometimes are overlooked. Treatment of these conditions is important to achieve adequate control of pre-syncope symptoms and prevent long-term complications. Non-pharmacological interventions should be the first line of therapy. However, when these approaches are not sufficient, pharmacological interventions are necessary, though it is important to understand the pathophysiology of these disorders to determine adequate treatment for these patients.

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Abbreviations

DAN	diabetes autonomic neuropathy
GCI	glial cytoplasmatic inclusion
MSA	multiple system atrophy
OH	orthostatic hypotension
PAF	pure autonomic failure
PD	Parkinson's disease
PPH	post-prandial hypotension

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Fig. 1.
Simplified scheme of the level of the autonomic lesion in patients with MSA, PD and PAF.

Table 1

Clinical and pathologic spectrum of alpha-synucleinopathies.

	DLB	PD	PAF	MSA
Autonomic failure	+/-	+/-	+++	+++
Movement disorder	+/-	++	-	++
Neuronal Lewy bodies	++	++	++	-
Glial cytoplasmic inclusions	-	-	-	+

DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PAF, pure autonomic failure; PD, Parkinson's disease.

Table 2**Approach to treat orthostatic hypotension.**

Non-pharmacologic interventions
Eliminate any offending agents (alpha-blockers, diuretics)
Increase fluid and salt intake
Avoid getting up quickly or standing motionless
Use of abdominal binder or compressive waist-high stockings
Raise head of the bed by 6–9 in. during nighttime
Avoid prolonged standing during hot weather
Leg crossing while standing (cocktail party posture)
16 oz of tap water (drink as a bolus)
Pharmacological interventions
Increase intravascular volume
Fludrocortisone 0.1–0.3 mg qday
Recombinant erythropoietin 25–50 units/kg body wt (if Hgb less than 12 gr/dl)
Vasopressin analog, DDAVP 2–4 µg/day at bedtime
Adrenergic agonists and sympathomimetics
Midodrine 5–10 mg
Yohimbine 5.4 mg
Pyridostigmine 60 mg
Pseudoephedrine 30 mg
Atomoxetine 18 mg
Other pressor agents
Ergotamine/cafeine 1 mg/100 mg
Octreotide 12.5µg–25 µg subcutaneously
Emergent therapy
Droxidopa (L-DOPS, experimental)

Table 3**Approach to treat supine hypertension.**

Non-pharmacologic interventions
Instruct patients to self-monitor BP
Instruct patients about over-the-counter medications with pressor effects
Avoid the use of abdominal binder or elastic waist high stockings when supine
Avoid fluid intake at bedtime
Avoid pressor agents before bedtime (~6 PM)
Rest in reclining chair with feet on floor during the day
Raise head of the bed by 6–9 in. during nighttime
Allow snack or judicious alcohol consumption before bedtime
Pharmacological interventions (single dose given at bedtime)
Transdermal nitroglycerin 0.05–0.2 mg/h, removed in the morning
Hydralazine 50 mg po
Short-acting nifedipine 30 mg po
Clonidine 0.1 mg po, early in the evening
Sildenafil 25 mg po
Minoxidil 2.5 mg po