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REVIEW ARTICLE

Arterial hypertension, a tricky side of Parkinson's disease: physiopathology and therapeutic features

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Abstract The role of arterial hypertension (HT) as risk factor for Parkinson's disease (PD) is still debated. Case–control and retrospective studies do not support an association between HT and PD and the risk of PD seems to be lower in hypertensive than in normotensive subjects. In addition, the use of calcium-channel blockers (CCBs) and angiotensin-converting enzyme inhibitors seems to have a protective effect on the risk of developing PD. In clinical practice, a crucial finding in subjects with PD is the high supine systolic blood pressure (SBP) coupled with orthostatic hypotension (OH). It is not clear whether this SBP load could be a risk factor for target organ damage as this load can be largely due to the drugs used to treat OH (i.e., fludrocortisone acetate, midodrine) or PD itself (i.e., monoamine oxidase inhibitors, dopamine D2-receptor antagonists). This blood pressure (BP) load is largely independent of medications as the 40 % of subjects with PD have a non-dipping pattern of BP during 24 h ambulatory monitoring (24-h ABPM). In PD, nocturnal HT is usually asymptomatic and 24-h ABPM should be used to track both supine HT and OH. Treatment of HT in PD is difficult because the reduction of supine BP could worsen OH. To avoid this, short-acting dihydropyridine CCBs, clonidine or nitrates are recommended, assuming between meals, in late afternoon or in the evening in avoiding an aggravation in the post-prandial hypotension characteristic of PD.

Keywords Blood pressure monitoring · Calcium-channel blockers · Hypertension · Orthostatic hypotension · Parkinson disease

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Introduction

Although arterial hypertension (HT) is an established risk factor for cardiovascular (CV) and cerebrovascular disease [1], its role in Parkinson's disease (PD) is still not yet defined. This is probably due to the higher burden of orthostatic hypotension (OH) observed in subjects with PD rather than HT by itself [2]. Therefore, there are relatively few studies in literature investigating the pathophysiological role of HT in PD, yielding conflicting results [3–10]. Differently to the classic OH (or pure baroreflex failure), subjects with PD have high supine systolic blood pressure (SBP) levels [11, 12]. Little is known whether or not this SBP load could be a risk factor for target organ damage (TOD), as supine HT in PD patients is largely considered due to the drugs used to treat OH (i.e., fludrocortisone acetate, midodrine) [13, 14], or PD itself (i.e.,

monoamine oxidase inhibitors, dopamine D2-receptor antagonists) [15, 16]. In addition, treatment of HT in PD is difficult because reducing supine SBP could worsen OH [17].

This review aims to address the following issues: (1) Does HT represent a risk factor for PD? (2) Are the antihypertensive drugs able to influence the risk of developing PD? (3) Can we understand the mechanism(s) whereby HT occurs in PD and is associated with OH? (4) How do the anti-Parkinson drugs influence blood pressure (BP) and OH? (5) What is the antihypertensive treatment recommended in PD?

Blood pressure pattern in PD

BP modifications are frequently observed in PD [3]. OH is a frequent finding in the clinical picture of subjects with PD, but paradoxically about 50 % of them suffer from HT, which induces pressure natriuresis and in turn worsening of OH [17]. Both OH and supine HT are usually asymptomatic [18]. An abnormal BP profile with reversal of circadian pattern, modification in average daytime, postprandial hypotension, nocturnal HT, and non-compensatory heart rate variability [19, 20] are frequently found through the 24 h ambulatory blood pressure monitoring (ABPM). In addition, 61.5 % subjects with PD had high daytime BP, in the pre-hypertensive stage, and 23 % were ascribed to stage-1 of HT [20]. The 24-h ABPM is widely used in the diagnosis, evaluation, and treatment of HT [21], and different studies showed that TOD due to HT was more strongly correlated with ABPM than with clinic BP measurements [20, 22]. In clinical practice, the 24-h ABPM provides the BP regulation trend over time,that is much more reliable compared to clinical BP measurements. In particular, the 24-h ABPM is important to record sudden BP increases during the night and nocturnal HT, which are both associated with increased cerebrovascular risk [23]. Schmidt et al. [24] found that 40 % of subjects with PD had a loss of the nocturnal BP dipping. In the presence of loss of nocturnal BP fall, well known as non-dipping status, the 24-h ABPM is recommended as an easy tool to evaluate the BP pattern of subjects with PD as well as to monitor the effectiveness of antihypertensive treatment during night and/or of the antihypotensive therapy during the day.

However, it has been recently demonstrated that in subjects with uncomplicated HT, nocturnal HT is a more frequent pattern than non-dipping and it is associated with TOD, independently of dipping/non-dipping status [25]. This fact suggests that antihypertensive treatment aimed at restoring a blunted nocturnal BP fall may be insufficient to prevent cerebrovascular and cardiovascular complications unless night-time BP values are fully normalized.

Mechanisms inducing HT and OH in PD

It has been suggested that supine HT (mainly systolic HT) observed in subjects with PD is correlated with the widespread use of α-sympathomimetic and mineralocorticoid agents used to treat OH [14]. On the other hand, some antiparkinson agents (see below) are also able to increase BP [15, 16, 26], but supine HT has been reported even in untreated subjects [11, 27]. Therefore, HT in PD occurs through different mechanisms.

Clinical and preclinical studies of primary chronic autonomic failure have consistently noted increased BP levels or vasoconstrictor responses to exogenously given adrenergic-receptor agonists in PD with OH [28–30]. In clinical practice, primary chronic autonomic failure is classified into three forms: pure autonomic failure (PAF), multiple-system atrophy (MSA), and autonomic failure in the setting of PD [31]. All three forms typically have OH and an impaired baroreflex-cardiovagal function (gain). The latter is normally calculated from the relation between the interval between heart beats (interbeat interval) and systolic BP values after intravenous injection of a vasoconstrictor or vasodilator agent [32]. The extent of increase in the interbeat interval, for a given increase in systolic BP, provides a measure of baroreflex-cardiovagal gain [33]. A particular pattern of beat-to-beat BP responses to the Valsalva manoeuvre indicates deficient sympathetic cardiovascular stimulation in response to decreased cardiac filling [34]. In subjects with PD and OH (PD–OH), BP decreases progressively in phase II and fails to overshoot the baseline pressure in phase IV, which are signs of sympathetic neurocirculatory or baroreflex-sympathoneural failure. PD–OH also features baroreflex-cardiovagal failure, manifested by constant interbeat interval despite arterial hypotension. In addition, patients with PD and OH have impaired baroreflex-cardiovagal function and loss of sympathetic innervation diffusely in the left ventricular myocardium [34]. By contrast, patients with MSA, which is clinically difficult to distinguish from PD, have intact cardiac sympathetic innervations.

As suggested by Goldstein et al. [12], all the forms of chronic primary autonomic failure having OH had supine HT, unlike subject groups with MSA, PAF or PD lacking OH, indicating an overall association between OH and supine HT in these diseases.

When OH dominates the clinical picture of PD, a sympathetic neurocirculatory failure during the supine rest is observed. The latter is characterized by a postganglionic sympathetic noradrenergic lesion with a marked loss of sympathetic nerves throughout the left ventricular myocardium [35], low plasma norepinephrine (NE) levels and a low mean baroreflex-cardiovagal gain during the Valsalva manoeuvre [12]. On the contrary, subjects with PD and

without OH had a higher residual sympathetic activity to the vessel that largely contributes to determine supine HT [36]. These findings were confirmed during spectrum analysis of RR interval and systolic BP variability evaluation [37], suggesting that the abnormalities in the hemodynamic and in the indices of autonomic function were mainly observed in PD subjects with OH, whereas PD subjects without OH are comparable to healthy subjects.

Hypertension and risk of PD

In the PRIAMO (PaRkinson dIseAse non-Motor symptoms) study, a cross-sectional longitudinal prospective research performed in Italy [38], HT was the most frequently reported concomitant, non-neurological disorder accounting for the 41.5 % of the subjects enrolled. Moreover, in this study, the role of HT in PD has not been fully elucidated.

In a case–control study performed in Japan, HT was significantly associated with a decreased risk of PD [9]. On the contrary, in a different case–control study conducted in Australia, a significant inverse relationship between hypertension and PD was found [4]. In the Nurses' Health Study, a self-reported history of physician-diagnosed HT was not related to the risk of PD [8]. A case–control study in Italy found that high systolic BP and high blood glucose were independently related to a reduced risk of PD, whereas no association between serum total cholesterol and PD was observed [39]. In a large prospective cohort study of 13,979 residents of Leisure World Laguna Hills in California, the assumption of antihypertensive drugs was significantly inversely related to the risk of PD [3]. Other studies found no association between hypertension and PD [6–9]. In particular, this was confirmed in a large prospective study performed in 8,006 men taking part in the Honolulu Heart Program, according to whom HT and other cardiovascular risk factors were found not related to the risk of PD [40].

All these discrepancies can be explained by differences in the study population and/or study design. In the study of Miyake et al. [9], the inverse association between PD and HT might be ascribed to a decreased sympathetic activity, although in this survey HT was defined according to the use of antihypertensive medications prior to the onset of PD. As an alternative, McCann et al. [4] suggested that HT had an advantageous effect of persistent elevation of brain perfusion resulting in lower incidence of PD. In the Nurses' Health Study and the Health Professionals Follow-up Study, the average values for supine SBP among individuals with PD before the diagnosis were similar to those found among individuals without PD, although a small but significant decline in supine SBP among those with PD was observed after the diagnosis [8]. This finding might be due to autonomic dysfunction in PD patients [34]. A recent population-based, prospective study performed in Finland provided evidence that only women with high-normal BP and HT were associated with a >60 % increased risk of PD, especially when BP was left untreated or poorly controlled [10]. This study may have had important limitations as some vascular Parkinsonism cases were classified as PD because of lack of neuroimaging and postmortem data. Furthermore, diagnosis of PD was more likely to occur in HTs than normotensives as the former were followed more closely in the healthcare services as compared to the latter.

On the whole, the relationship between PD and HT remains elusive as the different studies performed showed conflicting results: time to time, a direct association [10], an inverse association [3–5] or no association at all [6–9, 40].

Antihypertensive drugs and risk of PD

PD is a neurodegenerative illness in which the selective dopaminergic cell death involves different mechanisms such as the oxidative stress [41], mitochondrial impairment [42] and a neuroinflammatory model [43]. Therefore, the search for neuroprotective agents able to play a definite role in reducing these mechanisms is ongoing. With regard to the antihypertensive drugs, studies in animal models with dihydropyridine calcium-channel blockers (CCBs) and angiotensin converting enzyme inhibitors (ACE-I) showed promising results such as a significant reduction of experimentally induced dopaminergic cell impairment [44, 45] and an increase in striatal dopamine content [46].

A study performed in Denmark [47] showed that subjects treated with dihydropyridine-CCB2 (excludes amlodipine) 2 years before the diagnosis of PD had a 27 % risk reduction to develop PD, and the risk was not related to the CCBs amount and duration.

In old age, the dopaminergic neurons seem increasingly rely on L-type calcium channels for their activation and so were more vulnerable to neurologic damage [48]. If these calcium channels are blocked, neurons make use of the less harmful mechanisms and cell damage may be decreased. A cross-sectional study reported a lower prevalence to CCBs in patients with prevalent PD and with HT, as compared to another group of HTs without PD [49]. However, CCBs were also related to potentially harmful effects with regard to PD; flunarizine and cinnarizine, which have dopaminergic receptor blocking properties [50] and non- dihydropyridine CCBs as diltiazem have been reported to damage dopaminergic cells in vitro [51]. However, in a population-based case–control study, the prior use of CCBs was found to have no effect on the subsequent risk of developing PD [52].

As for CCBs, the role of ACE-I in PD provided conflicting results. A small double blind placebo-controlled crossover study showed that perindopril facilitated dopaminergic release, improving motor functions in subjects with moderately severe PD [53]. On the contrary, oral sublingual captopril 25 mg administration for high BP levels during the "off" state of PD increased the severity and duration of akinesia [54].

There are experimental evidences suggesting that angiotensin II facilitates nigrostriatal dopaminergic release by acting on angiotensin type-1 receptor [55, 56]. Therefore, antihypertensive treatment with angiotensin II receptor antagonists (ARBs) potentially could block these receptors and inhibit dopaminergic release. On the contrary, ACE-I may facilitate dopaminergic release [53]. In this respect, a case of PD worsened during treatment with losartan has been described [57]. Little is known about the potential effects of diuretics or β-blockers in PD [58].

However, in a retrospective case–control analysis using data from the UK-based General Practice Research Database, in 3,637 subjects aged over 40 years the long-term use of CCBs was associated with a significantly reduced risk of PD diagnosis particularly in women, while no association was found for ACE-I, ARBs, and β-blockers [59].

Anti-Parkinson drugs and their influence on HT and OH

As mentioned above, some drugs used in PD treatment are able to raise BP levels. The orally administered monoamine oxidase inhibitors (MAOIs) are well recognized as effective antidepressant agents but are rarely used for the risk of hypertensive crisis following the ingestion of foods high in tyramine, namely "cheese reaction" [15]. However, compared to oral administration, a transdermal formulation of selegiline (STS), a selective monoamine oxidase B inhibitor used for the adjunctive treatment of PD at low doses, showed no evidence of a tyramine pressor effect on systolic BP levels or evidence of hypertensive crisis during the STS treatment [60]. These data were confirmed in the PRESTO study, where in PD subjects with an unrestricted diet, rasagiline did not induce postprandial HT or variations on supine and standing BP values as compared to placebo [61]. The peripheral dopamine D2-receptor antagonist domperidone, increased BP and heart rate without inducing nocturnal HT in apomorphine-treated patients with PD [16]. Catechol-*O*-methyltransferase (COMT) is an enzyme that inactivates catecholamines which play an important role in BP regulation. COMT inhibitors are used in PD treatment, and among this class of drugs entacapone and tolcapone are the most prescribed, and particularly the former is recommended as first choice. It was observed that dopamine, NE, adrenaline and total catecholamines levels significantly increased during treatment with tolcapone [62]. In this study, 24-h ABPM did not reveal cardiovascular side effects in patients treated for less than one year. However, to assess the true impact on BP of entacapone and tolcapone a longer follow-up would be necessary.

Antihypertensive treatment in PD and management of OH

The hypertension specialist encounters a dilemma treating supine HT because of the risk of worsening OH [63]. Nevertheless, antihypertensive treatment is mandatory in PD, as it was shown that the prevalence of cardiac TOD (left ventricular hypertrophy) is similar to that observed in subjects with essential hypertension [64]. However, no clear recommendations are available in current ESH/ESC guidelines for the treatment of HT in PD.

In PD the antihypertensive treatment for supine HT can be divided into non-pharmacological and pharmacological.

As regards non-pharmacologic treatment, daytime supine HT is easily prevented by simply avoiding the supine position [65]. However, this simple and obvious recommendation is often overlooked. If patients need to rest, they should be instructed to sit in a reclining chair with the feet on the floor. To avoid the night-time supine HT, raising the head of the bed is recommended: this measure reduces BP and nocturnal natriuresis and improves OH in the morning. The use of pressor agents and water boluses should be avoided close to bedtime. Other non-pharmacological measures are shown in Table 1.

Short-acting antihypertensive therapy may be useful in controlling nocturnal supine HT. Drugs that have been used are clonidine [66] and topical or oral nitrates [67]. Peripheral vasodilators as non-dihydropyridine CCBs and diuretics should be avoided for the risk to worsen OH. On the other hand, ACE-I, ARBs, and β-adrenoceptor antagonists with intrinsic sympathomimetic activity are less likely to worsen OH. Different studies showed improvement in the postural baroreflex by long-term β-blocker treatment, but not with ACE-I, CCBs, diuretics, and ARBs. In this respect, β-blockers, especially those with intrinsic sympathomimetic activity such as pindolol may, therefore, be the most appropriate antihypertensive agents as they protect particularly the elderly from OH [68]. When OH is associated with supine HT, the former can be worsened by the night-time pressure natriuresis induced by the latter. Several pharmacological agents effectively reduce night-time HT, but none of them prevent pressure natriuresis. As hypertension of autonomic failure can be driven by residual sympathetic tone, it has been found that clonidine in

Table 1 Stepwise approach to treat supine hypertension

Non-pharmacological treatment
Education and avoidance
Instruct the patients about over-the-counter medication with pressor effects
Avoid fluid intake at bedtime
Avoid using elastic stocking when supine
Avoid the use of pressor agents before bedtime
Avoid the use of pressor agents before bedtime
Raise the head of the bed up 6–9 in
Rest on a semirecumbent chair with feet on floor during the day
Allow minimal alcohol consumption before bedtime
Pharmacological treatment
Clonidine (0.1 mg), early in the evening
Nitrates, transdermal nitroglycerin (0.1–0.2 mg/h, removed in the morning)
Short-acting calcium blocker, like nifedipine (30 mg)

subjects with autonomic failure is effective in reducing BP and nocturnal natriuresis [64]. Early diagnosis and treatment of asymptomatic HT probably improve CV mortality of the subjects with PD [24]. In clinical practice, however, the treatment of OH in PD always foregoes the antihypertensive therapy and can be immediately rewarding by alleviating symptoms of cerebral hypoperfusion.

OH is commonly defined as the reduction of systolic BP of at least 20 mmHg or diastolic BP of at least 10 mmHg within 3 min of standing [69]. An alternative diagnostic method to evaluate OH in standing position is the demonstration of a similar drop in BP within 3 min, using a tilt table in the head-up position, at an angle of at least 60°. However, a reduction in systolic BP of 30 mmHg may be a more appropriate criterion for OH because the magnitude of the orthostatic BP fall is dependent on the baseline BP levels.

Drug treatment for OH must always be used together with aggressive lifestyle changes. Pharmacologic treatment of OH is largely based on case series rather than prospective clinical trials. Frequently more than one drug is needed to alleviate symptoms; however, as mentioned above, all drug treatments may exacerbate supine HT.

The initial treatment of OH in PD consists on the increase of the plasma volume, and subjects with PD should ingest about 10 g of sodium daily and increase the fluid intake to overcome the autonomic failure. In this regard, it has been reported that the drinking of water 480 mL minimally increased BP in healthy subjects but determined a significant increase of BP in subjects with autonomic disorders. The effect is rapid in onset and goes on for 60–90 min, but the subjects should be recommended to go up slowly from supine position and remain sitting for several minutes. Muscle pumping in the calves before standing may be useful. The use of custom-fitted elastic stockings may also be useful. Abdominal compression has been proven to be highly effective in increasing BP and reducing OH symptoms. It is prudent for patients to avoid situations that may exacerbate fluid loss or cause vascular dilation. In this respect, it is important to avoid hot showers and hot environments, large meals, and alcohol. It is also recommended to sleep in a semi-sitting position with the head of the bed elevated to minimize supine HT. These lifestyle changes substantially ameliorate symptoms of OH, especially in the early stage. However, most subjects require pharmacologic therapy (Table 2). Before starting pharmacological therapy, the recognition and removal of drugs which can cause OH is necessary: the most common involved drugs are diuretics, sympathetic blockers, antianginal, and antidepressants drugs.

It has been suggested a stepwise pharmacologic treatment using fludrocortisone acetate commencing with a 0.1 mg daily dose (anyhow not exceeding 0.4 mg daily) followed by a sympathomimetic pressor agent, such as midodrine, for patients who remain symptomatic or who develop intolerance to fludrocortisone. Because of the short half-life, midodrine treatment should be adapted to the patients' symptoms [14]. A typical midodrine dose ranges from 2.5 to 10 mg taken two to three times per day. Midodrine and other vasoconstrictors should be avoided in subjects with acute coronary artery disease and congestive heart failure. Other mixed α-adrenoreceptor agonists such as ephedrine, pseudoephedrine, and phenylpropanolamine are less used. On the other hand, intravenous NE has been used successfully in subjects with severe refractory OH with syncope and minimal ambulation [70].

Occasionally, a third-line therapy is required to ameliorate OH symptoms, including vasopressin receptor agonists, somatostatin analogues, dihydroergotamine, clonidine and β-blockers, selective serotonin reuptake inhibitors, serotonin NE reuptake inhibitor, dopamine antagonists, pyridostigmine and less frequently MAOIs.

Conclusion

HT is common and in most cases asymptomatic in PD patients. It is associated with additional increase in cardiac damage and requires an appropriate antihypertensive treatment to reduce the risk of cardiovascular events. Treatment of HT in PD is difficult because of the risk of simultaneous worsening of OH. Several lifestyle changes are firstly recommended. When antihypertensive therapy is needed, the administration of short-acting drugs is recommended, to be taken between meals to avoid the typical

Table 2 Management of orthostatic hypotension

Non-pharmacological treatment
Arise slowly, in stages, from supine to seated to standing
Dorsiflexion of the feet, handgrip isometric or mental exercise before standing
Raise the head of the bed by 10–20°
Leg-crossing and squatting may help those with autonomic failure
Small meals and coffee only in the early morning
Pharmacological treatment
Mineralocorticoids: fludrocortisone acetate with a high salt diet is the treatment of choice
Adrenergic agonists: midodrine and norepinephrine; yohimbine, ephedrine, phenylpropanolamine, pseudoephedrine, phenylephrine, methylphenidate, dextroamphetamine (less used)
Supplementary agents: non-steroidal anti-inflammatory drugs, caffeine, and erythropoietin (if anemia)
Third-line and experimental drugs: clonidine, vasopressin receptor agonists (desmopressin and lysine vasopressin) somatostatin analogues (octreotide), dihydroergotamine, β-blockers (especially those with intrinsic sympathomimetic activity such as pindolol), selective serotonin reuptake inhibitors (fluoxetine), serotonin norepinephrine reuptake inhibitor (venlafaxine), dopamine antagonists (metoclopramide, domperidone), pyridostigmine, Monoamine oxidase inhibitors (with tyramine can produce severe hypertension

post-prandial hypotension of PD. The suggested drugs, such as dihydropyridine CCBs, clonidine, β-blockers or nitrates, should be taken in the late afternoon or evening before sleeping. As supine night-time HT is not easy to detect using occasional BP measurement, a 24-h ABPM is recommended which is also useful to assess the effects of therapy.

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