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Cardiovascular autonomic failure in Parkinson's disease and Multiple System Atrophy: prognostic, diagnostic, epidemiological and therapeutic aspects

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- Fanciulli A, Strano S, Colosimo C, Caltagirone C, Spalletta G, Pontieri FE. The potential prognostic role of cardiovascular autonomic failure in α-synucleinopathies. Eur J Neurol, 2013; 20 (2): 231-23
- Fanciulli A, Wenning GK (book chapter) Chapter 1: Historical review. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014, pp. 1-9.
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The present dissertation has not been submitted, wholly or substantially, as an examination document to any other institution.

07th January 2015

Dr Alessandra Fanciulli

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List of abbreviations

24h-ABPM: 24 hours – ambulatory blood pressure monitoring

II_E: early phase II of the Valsalva maneuver

II_L: late phase II of the Valsalva maneuver

ANS: autonomic nervous system

BP: blood pressure (sysBP: systolic blood pressure; diaBP: diastolic blood pressure)

DLB: Dementia with Lewy bodies

HR: heart rate

OH: orthostatic hypotension

MSA-C: multiple system atrophy – cerebellar

MSA-P: multiple system atrophy – parkinsonian

PAF: pure autonomic failure

PD: Parkinson's disease

PDD: Parkinson's disease with dementia

SH: supine hypertension

WMH: white matter hyperintensities

1. Introduction

1.1. A two-players game

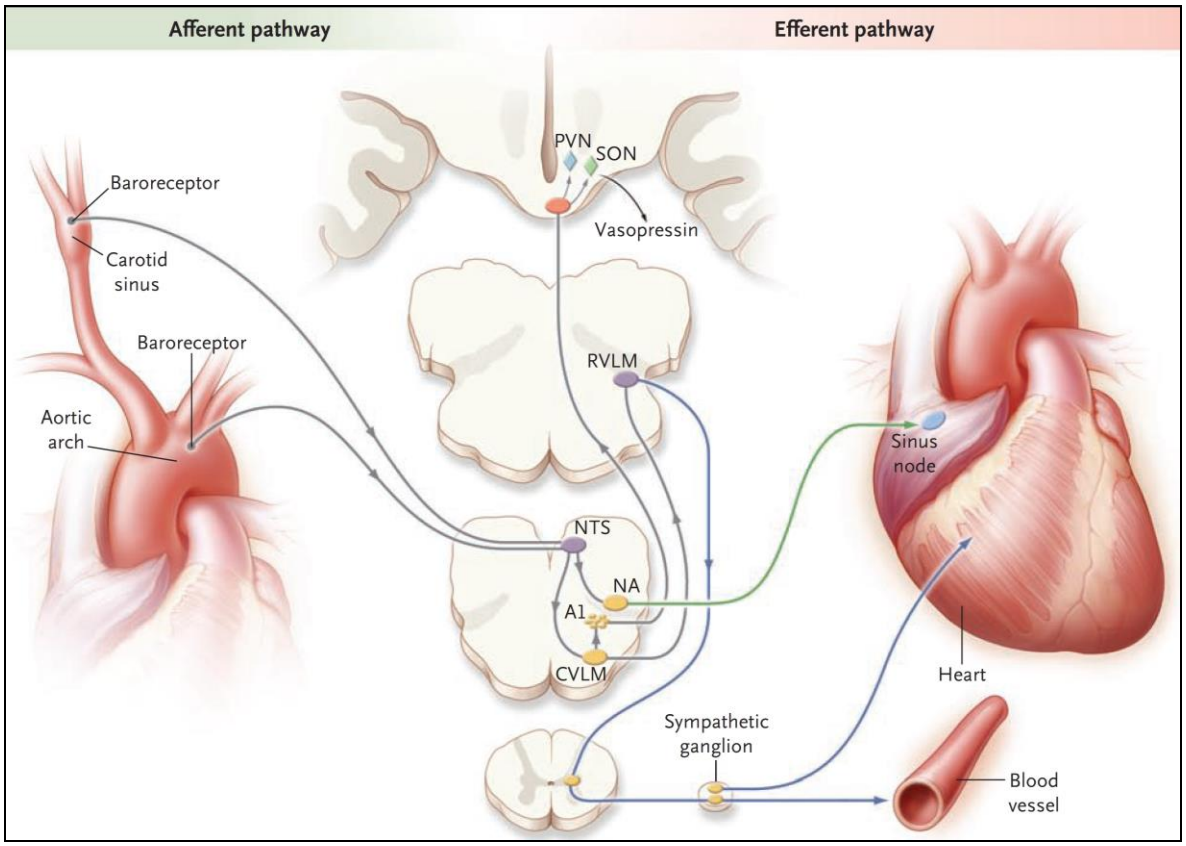
1.1.1. Player #1: the autonomic nervous system

The Autonomic Nervous System (ANS) mediates neuroendocrine, visceral and behavioural responses to environmental and inner challenges in order to ensure body homeostasis. The insular cortex, together with the medial prefrontal cortex and the extended amygdala, exerts high-order autonomic control on multiple parallel pathways of the ANS subcortical integrative network. This is constituted by the hypothalamus, periacqueductal grey matter, parabrachial pontine complex and ventro-lateral medullary nuclei (Benarroch, 1993). Main output of the central ANS runs through pre-ganglionic sympathetic and parasympathetic cholinergic neurons, the former located in the intermediolateral columns of the thoraco-lumbar spinal cord, the latter in the brainstem and sacral spinal myelomera. Parasympathetic cholinergic post-ganglionic fibers arise from ganglia which are generally located close or within the target organ. Activation of vagal parasympathetic fibers to the atrial sinus node induces bradycardia. Noradrenergic sympathetic post-ganglionic neurons originate from the paravertebral ganglia and mediate blood vessel constriction, positive inotropic and chronotropic cardiac effects among others (Goldstein, 2006).

Short-term regulation of blood pressure (BP) and heart rate (HR) is committed to the baroreflex arch, which modulates sympathetic and parasympathetic activation in order to ensure appropriate organ perfusion under postural and blood volume changes. If arterial BP falls, mechanical baroreceptors situated in the carotid sinus and aortic arch contemporarily inhibit vagal input to the sinus node and promote sympathetic outflow to

cardiac fibers and blood vessels. As the result, heart rate, heart inotropism and vascular peripheral resistances increase. If arterial BP rises, the opposite occurs: cardiovagal activation induces bradycardia, while inhibition of sympathetic fibers produces negative inotropic effects and blood vessel relaxation (Freeman, 2008).

Fig. 1.1 The baroreflex arch



PVN: paraventricular nucleus (hypothalamus); SON: sopraoptic nucleus, hypothalamus; RVLM: rostral ventrolateral medulla; CVLM: caudal ventrolateral medulla; NTS: nucleus of the tractus solitaries (vagus nerve); NA: nucleus ambiguous (vagus nerve). Reproduced from Freeman R (2008), NEJM; 358 (6): 615-624 with permission from the Massachusetts Medical Society.

Disorders of the ANS are classified as primary, if due to neurodegeneration, or secondary, if developing after brain injury, intoxication or metabolic diseases such as diabetes mellitus. The first report of degenerative autonomic failure dates back to 1925 when Bradbury and Egglestone described a case of orthostatic hypotension (OH) with

impotence and anhidrosis of idiopathic origin (Bradbury S, 1925). In the 60s of the past century Shy and Drager further reported the case of two men who developed multi-domain autonomic failure along with cerebellar, parkinsonian and pyramidal signs (Shy and Drager, 1960). Since then, autonomic failure has been recognized as major non-motor feature of multiple system atrophy (MSA), Parkinson's disease (PD) as well as other movement disorders (Wenning, 2013) with prominent diagnostic, therapeutic and prognostic implications.

1.1.2. Player #2: α-synucleinopathies

PD is an adult-onset neurodegenerative disease characterized by bradykinesia and a combination of rest tremor, rigidity and postural instability (Hughes *et al.*, 2001). Neuropathological hallmark of PD are the *Lewy bodies*, neuronal aggregates of misfolded α-synuclein developing in the central, peripheral as well as enteric nervous system (Braak *et al.*, 2003). Throughout disease course, PD patients additionally develop a wide spectrum of *non-motor* symptoms, including autonomic, behavioural and cognitive changes (Barone *et al.*, 2009), sometimes achieving a diagnosis of PD with dementia (PDD) in advanced stages.

MSA is an adult-onset, fatal neurodegenerative disease presenting with progressive autonomic failure, parkinsonian, cerebellar and pyramidal features in various combinations. It is classified as MSA-parkinsonian (MSA-P), if parkinsonism prevails, or MSA-cerebellar (MSA-C), if cerebellar features predominate. Proteinaceous oligodendroglial cytoplasmic inclusions (also known as *Papp-Lantos bodies*) are the hallmark of MSA. The main constituent of glial cytoplasmic inclusions is misfolded α-

synuclein, hence classifying MSA as an oligodendroglial α-synucleinopathy. As in PD, a considerable variety of non-motor symptoms may develop during MSA disease course and sometimes even precede development of motor symptoms (Jecmenica-Lukic *et al.*, 2012). Multi-domain autonomic failure, including urogenital, cardiovascular, gastrointestinal and thermoregulatory dysfunction invariably occurs in almost all patients (Fanciulli A, 2014) and significantly affects quality of life in MSA (Schrag *et al.*, 2006).

1.2. Focus on cardiovascular autonomic failure in PD and MSA

1.2.1. Clinical features and epidemiology

Cardiovascular autonomic failure is a common dysautonomic symptom in PD (Barone *et al.*, 2009) and a mandatory criterion for the diagnosis of MSA (Gilman *et al.*, 2008). The main feature of cardiovascular autonomic failure is orthostatic hypotension (OH) (Asahina *et al.*, 2012). OH is defined as a of systolic blood pressure (sysBP) fall ≥ 20 mmHg or diastolic (diaBP) ≥ 10 mmHg within 3 min of active standing or head-up tilt. In case of supine hypertension, a sysBP fall ≥ 30 mmHg is considered a more appropriate criterion for the diagnosis of OH. OH may manifest with recurrent syncope, light-headedness, weakness, nausea, fatigue, headache or shoulder-neck pain upon standing, but may also lack any symptomatology (Freeman *et al.*, 2011). Frequency rates of OH in PD range from 14-15% in drug-naïve and early-stage patients (Bonuccelli *et al.*, 2003, Barone *et al.*, 2009) to 52% in more advanced and older cases, on higher dopaminergic drug dosage and showing gait unbalance (Allcock *et al.*, 2006, Matinolli *et al.*, 2009, Velseboer *et al.*, 2011). Symptomatic OH occurs in 50% of MSA patients already in early disease stages (Sakakibara *et al.*, 2000), with peak cross-sectional prevalence of 75% and 81% in

European and American cohorts (Kollensperger *et al.*, 2010, Ha *et al.*, 2011). One cross-sectional study reported OH to be more frequent and severe in patients with MSA-C than with MSA-P (Wenning *et al.*, 2012).

Attending phenomena of OH are supine hypertension, nocturnal hypertension with reversal of physiological BP circadian rhythm, and postprandial hypotension. Supine hypertension is usually asymptomatic or only manifest with vague complaints. It has been reported in approximately 50% of MSA patients with overt OH (Shannon *et al.*, 1997, Biaggioni and Robertson, 2002), while no former study is available on the prevalence of supine hypertension in the setting of PD. Notably, no homogeneous cut-off values were used for the diagnosis of supine hypertension in the above mentioned papers (Schutzman *et al.*, 1994, Shannon *et al.*, 1997, Jordan *et al.*, 1999).

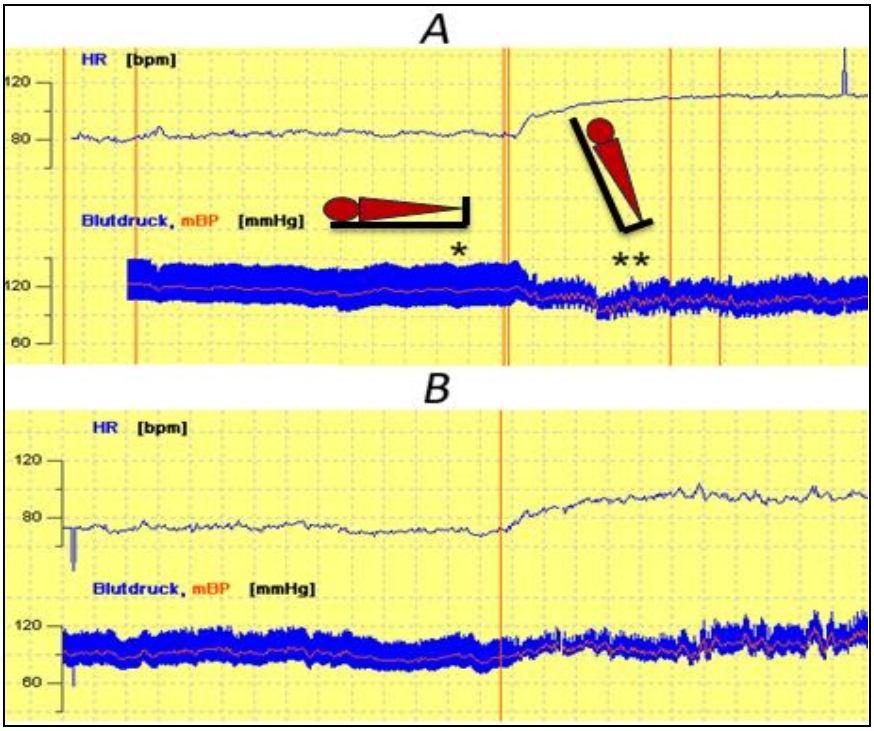
Specific cut-off values for the diagnosis of nocturnal hypertension in patients suffering from cardiovascular autonomic failure are also missing. Current consensus guidelines for the general population define two main pathological nocturnal BP profiles, named respectively as *non-dipping* and *reverse dipping* (Staessen *et al.*, 2001). A *non-dipping* profile is characterized by a nocturnal BP reduction lower than 10% with respect to daytime values, whereas a *reverse dipping* occurs if BP increases during night time (Staessen *et al.*, 2001). Loss of physiological nocturnal blood pressure fall has been reported in 48% of PD and 68% of MSA patients (Schmidt *et al.*, 2009). It may be even more frequent in patients with severe cardiovascular autonomic failure (Plaschke *et al.*, 1998), or in older and more advanced cases (Berganzo *et al.*, 2013), but, since almost asymptomatic, it is frequently underdiagnosed and undertreated.

1.2.2. Clinical investigation of cardiovascular autonomic function

Bedside screening of cardiovascular autonomic failure can be run by mean of a simple standing test (also known as *Schellong's test*): during this test, the patient is asked to lie for 5 to 10 minutes and then to stand up for 5 minutes. Oscillometric BP is recorded at the end of the supine phase and at 3 and 5 minutes after standing. If the test shows supine hypertension and/or OH (Freeman *et al.*, 2011), further investigation is recommended. Continuous heart rate (HR) and BP monitoring by means of non-invasive beat-to-beat BP recording and impedance cardiography (i.e. Task Force® Monitor or Finapres® devices) allows evaluation of cardiovascular autonomic function during provocative testing. Standard test procedures include passive head-up tilting at 60°, active standing, the Valsalva maneuver and the deep breathing test. Previous studies reported OH to occur more frequently during passive head-up tilt than active standing and often after the standard time cut-off of 3 minutes (Jamnadas-Khoda *et al.*, 2009). For this reason, both passive and active orthostatic challenges are routinely performed and examination time extended up to 10 minutes.

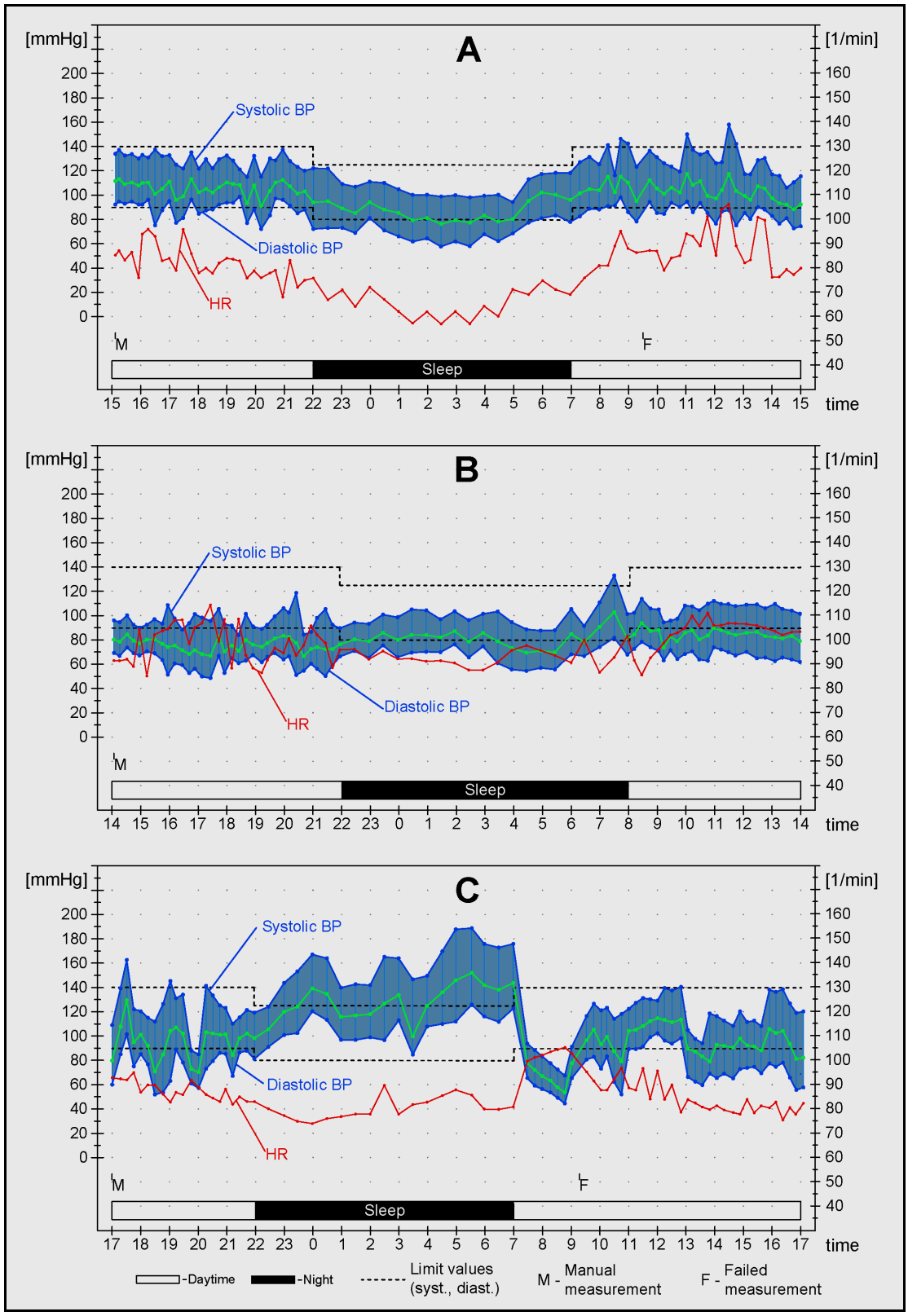
Finally, 24h ambulatory BP monitoring should be included in the initial evaluation of cardiovascular autonomic failure to detect supine and nocturnal hypertension attending OH, since latter phenomena are frequently asymptomatic or only manifest with unspecific symptomatology.

Fig. 1.2 Co-occurrence of supine hypertension (*) and OH (**) at head-up tilt test.



A. parkinsonian patients; B. Healthy control. Fanciulli et al., unpublished material

Fig. 1.3 Possible nocturnal BP profiles at 24h – ambulatory BP monitoring



A – *Dipping* (BP falls ≥10% with respect to daytime); B – *Non-dipping* (BP falls <10% with respect to daytime); C *Reverse-dipping* (BP increases with respect to daytime). Note the presence of post-prandial hypotension in profile C at 1:00 and 8:00 p.m. Reproduced from Fanciulli et al. (2014), Journal of Neurology; 261 (7): 1291-9 with permission from Springer Verlag GmbH.

1.2.3. Pathophysiology of cardiovascular autonomic failure in PD and MSA

The synergism between degeneration of sympathetic post-ganglionic fibers to the heart and blood vessels and baroreflex failure underlies the development of OH attending PD. Lewy bodies accumulating in distal axons of peripheral sympathetic neurons contribute to degeneration of sympathetic fibers first and subsequently drive retrograde neuronal death in the paravertebral ganglia (Orimo *et al.*, 2008). As the result, PD patients show low plasma noradrenaline levels while lying, which fail to rise appropriately under orthostatic challenge (Goldstein *et al.*, 2003)

Conversely, degeneration of autonomic preganglionic fibers represents the primary site of autonomic failure in MSA. Studies carried out by different research groups confirmed the significant relationship between degeneration of medullary intermediolateral columns and occurrence of cardiovascular autonomic failure in the disease (Papp and Lantos, 1994, Wenning *et al.*, 1997). Neurodegenerative changes have been also shown in the nucleus ambiguus of the vagus nerve and in catecholaminergic neurons of the ventrolateral medulla at post-mortem pathology of definite MSA cases, possibly explaining the more severe degree of autonomic failure observed in the disease (Benarroch, 2003, Benarroch *et al.*, 2006). In contrast to PD, MSA patients show normal or only minimally lowered plasma noradrenaline levels when supine, but almost missing increase of plasma noradrenaline concentration while standing (Goldstein *et al.*, 2003).

The pathophysiology of supine and nocturnal hypertension in the context of autonomic failure is unclear at present. Patients suffering from OH often develop peripheral edema due to insufficient residual hydrostatic venous pressure. During night time, a counter fluid shift from extracellular compartment into the vascular bed may occur, resulting in blood volume expansion and nocturnal hypertension (Plaschke *et al.*, 1998). An alternative

explanation is provided by the so-called *"vasoconstriction model".* According to this model, MSA patients suffering from OH may develop a denervation-dependant hypersensitivity of vascular α-adrenoceptors as an attempt to shelter themselves from excessive BP falls upon standing. In turn, the same hypersensitivity may produce exaggerated vasoconstrictor responses to tonic sympathetic stimulation while lying, which cannot be modulated due to impaired central autonomic pathways (Davies *et al.*, 1982). It is, however, unclear if this same explanatory model can justify the occurrence of supine hypertension in PD, since PD patients show lowered plasmatic noradrenaline levels in the upright as well supine position.

1.2.4. Orthostatic hypotension: principles of treatment

Orthostatic hypotension has been shown to significantly affect quality of life and activity of daily living in parkinsonian subjects (Colosimo et al, 2010). A multidimensional approach, with combined pharmacological and non-pharmacological measures is to be pursued in order to warrant best clinical management of dysautonomic symptoms in movement disorders (Mostile and Jankovic, 2009).

Non-pharmacological measures include avoiding OH-triggers such as rapid postural change, heavy meals, straining while coughing or passing stool, and exposure to hot temperature. If patients feel light-headed (dizzy), physical counter maneuvers like crossing legs, squatting or tensing muscles, may prevent syncope. Other non-pharmacological measures to ameliorate OH include increased water and salt intake, head-up tilt during sleep, compression stockings or abdominal binders (Freeman, 2008). If severe OH occurs, pharmacological measures are advisable to minimize the risk of

injurious falls. Drugs with hypotensive side-effects (e.g. anti-hypertensive medications, anti-anginal agents, α_1-adrenoreceptor antagonists for the treatment of prostatic hypertrophy) should be avoided or at least administered in the evening. Midodrine and droxidopa, sympathomimetic agents that increase arteriolar tone, are specifically licensed by the Food and Drug Administration for the symptomatic treatment of neurogenic orthostatic hypotension (Jankovic *et al.*, 1993, Low *et al.*, 1997, Wright *et al.*, 1998, Freeman *et al.*, 1999). Off-label administration of fludrocortisone can be helpful in addition to increase the intravascular volume (Chobanian *et al.*, 1979). Beneficial effects have also been reported for ephedrine, pseudoephedrine, piridostigmine, desmopressin and erythropoietin used off-label in orthostatic hypotension associated with autonomic failure (Fouad-Tarazi *et al.*, 1995, Perera *et al.*, 1995, Jordan *et al.*, 1998, Sakakibara *et al.*, 2003, Singer *et al.*, 2003).

Notably, most of the available evidences for the management of cardiovascular autonomic failure have been collected in cohorts with OH of different etiologies. Recently, an EBM-review endorsed from the International Parkinson Disease and Movement Disorder Society found that current evidence is not sufficient to conclude on safety and efficacy of currently available pharmacological options in the setting of PD and therefore classified their use as investigational (Seppi *et al.*, 2011). Due to limited literature availability, no similar EBM-review has been ever performed for the non-pharmacological management of OH either in PD or in MSA.

1.2.5. Prognostic impact of cardiovascular autonomic failure: evidence from the general population

Prospective epidemiological studies in the general population highlighted that OH represents a negative prognostic factor for mid-term and long-term survival in elderly people (Masaki *et al.*, 1998, Rose *et al.*, 2006). OH has been associated with an increased risk of major cardiovascular events (Rose *et al.*, 2000, Luukinen *et al.*, 2004, Rose *et al.*, 2006, Fagard and De Cort, 2010), future development of heart failure (Fedorowski *et al.*, 2010), hypertension and shifting to non-dipping or even reversal nocturnal BP profile (Rose *et al.*, 2002, Fagard and De Cort, 2010). OH and nocturnal hypertension have been also shown to predict major cerebrovascular events on a 5.5 to 7.9 year follow-up period (Eigenbrodt *et al.*, 2000, Iqbal and Stevenson, 2010) and to represent a major risk factors for brain subcortical white matter hyperintensities (WMH) in the elderly (de Leeuw *et al.*, 2002, Goldstein *et al.*, 2005, Murray *et al.*, 2005, Ma *et al.*, 2010).

It is still debated whether OH represents a risk factor for cognitive impairment in the general population. In the middle-aged to elderly independently living population, OH does not seem to correlate neither to predict future cognitive impairment at 2- to 6-year follow-up (Viramo *et al.*, 1999, Yap *et al.*, 2008, Rose *et al.*, 2010), whereas in older people attending memory clinics, OH has been associated with decreased verbal memory, reduced concentration ability, and a 2.19 hazard ratio of developing cognitive impairment over a 7-year follow-up time (Elmstahl and Rosen, 1997, Verghese *et al.*, 2003, Czajkowska *et al.*, 2010, Mehrabian *et al.*, 2010). Other studies showed a strong association between cognitive impairment and supine/nocturnal hypertension in the general population (Kuo *et al.*, 2004, Yano *et al.*, 2011), with WMH possibly representing the etiological link between these two phenomena (Matsubayashi *et al.*, 1997).

It is unclear at present which role does cardiovascular autonomic failure exert on survival, cardiovascular and cognitive outcome in the setting of α-synucleinopathies.

2. Research plan

The above described clinical scenario depicts several unmet needs concerning cardiovascular autonomic failure in the field of PD and MSA.

Up to date it is not clear whether features of cardiovascular autonomic failure like OH, supine and nocturnal hypertension have a negative prognostic impact in α-synucleinopathies like they do in the general population. Further, the occurrence of nocturnal hypertension remains largely underdiagnosed in the routine management of parkinsonian patients and the actual prevalence of supine hypertension in PD and MSA diagnosed according to the most recent international criteria hasn't been investigated yet. Finally, few randomized controlled trials have been run for the non-pharmacological management of OH in PD.

Given these premises, a 4-step research plan has been developed, the results of which will be discussed in the present dissertation. First, a systematic review of the literature has been run to evaluate the prognostic role of cardiovascular autonomic failure on survival, cardiovascular, cerebrovascular and cognitive outcome in α-synucleinopathies. In a second phase, a cross-sectional cohort has been enrolled to develop a screening algorithm to detect nocturnal hypertension in PD and MSA on the basis of standard tilt-test evaluations. In a third step, a large retrospective cohort of PD and MSA patients has been recruited thanks to the collaboration of the Innsbruck and Rome Parkinson equips with the aim of investigating the prevalence of supine hypertension in parkinsonian patients according to the American Heart Association consensus criteria (Chobanian *et al.*, 2003). Fourth, a randomized, placebo-controlled, cross-over trial, followed by a 4-weeks open-label phase has been performed to evaluate the efficacy of elastic abdominal

binders in reducing orthostatic blood pressure fall upon tilting and OH-related symptomatic burden in daily living in PD patients suffering from OH.

3. The prognostic role of cardiovascular autonomic failure in α-synucleinopathies

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Approval of the final version of the manuscript: AF, SS, CCol, CCalt, GS, FEP

Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

http://www.ncbi.nlm.nih.gov/pubmed/22834919

3.1. Background

In contrast with prior belief of protective effects from low BP values, recent studies highlighted the negative prognostic role of cardiovascular autonomic failure on cardiovascular and cerebrovascular outcomes, as well as mid-term and long-term mortality in the general population. Symptoms of cardiovascular autonomic failure including OH, supine and nocturnal hypertension may affect more than half of parkinsonian patients already from disease beginning. It is up to date unclear whether such symptoms have a similar negative impact in α-synucleinopathies.

3.2. Aim

Here we provide a systematic review of cardiovascular autonomic failure in α-synucleinopathies, focusing on its impact on survival, cardio-, cerebrovascular and cognitive outcome in PD and MSA.

3.3. Methods

A PubMed database search was performed using the keyword-based method indicated in Table 3.1. Studies with a retrospective, cross-sectional or prospective design as well as case reports assessing survival, cardiovascular, cerebrovascular and cognitive outcomes were analysed. Articles were restricted to the English language and spanned the period between January 1985 and April 2012. For the purposes of the present dissertation a

renewed PubMed search was run after the same criteria to include studies published until October 2014.

Table 3.1 Key-words based PubMed search

"Multiple system atrophy" OR "Parkinson's disease" OR "Parkinson's disease with dementia" OR "Dementia with Lewy bodies" OR "Pure autonomic failure"	AND	· "orthostatic hypotension" · "cardiovascular autonomic failure" · "cardiovascular dysautonomia" · "neurocardiovascular instability" · "supine hypertension" · "recumbent hypertension" · "nocturnal hypertension"

3.4. Results

The systematic search identified 25 studies, the main characteristics of which are summarized in Table 3.2.

In MSA, early development of autonomic failure, in particular of cardiovascular and urological type, predicted faster disease progression and shorter interval from onset to death (Watanabe *et al.*, 2002, Tada *et al.*, 2007, O'Sullivan *et al.*, 2008). In a mirror fashion, all case reports of MSA patients with prolonged survival were characterized by late-onset cardiovascular autonomic failure (Petrovic *et al.*, 2012, Calandra-Buonaura *et al.*, 2013). Contrasting evidence is available for PD. While OH did not represent an independent predictor of death in a cohort of newly diagnosed PD patients at 10-years

follow-up (Auyeung *et al.*, 2012), this was instead the case for PD patients with long disease duration (Cilia *et al.*, 2014) or superimposing dementia (Stubendorff *et al.*, 2012).

No study assessing the influence of autonomic failure on cardiovascular outcome in exclusively MSA or PD cohorts is available. An association between autonomic failure and left ventricular hypertrophy was found in mixed cohorts including PD and MSA patients (Vagaonescu *et al.*, 2000, Maule *et al.*, 2006, Maule *et al.*, 2012).

Epidemiological studies showed an increased prevalence of stroke and cerebrovascular mortality in PD, but due to their retrospective nature, a case-selection bias cannot be excluded (Gorell *et al.*, 1994). In PD, an association among OH, supine hypertension and cerebral subcortical ischemic damage was found in two studies (Oh *et al.*, 2013), but rebutted in a third one (Pilleri *et al.*, 2013). Notably, different methodologies were applied for the assessment of white matter hyperintensities (WMH) at MR scanning and duration of cardiovascular autonomic failure was not included as covariate in the statistical analysis of the above mentioned studies. Two studies from different research groups reported an association between severity of OH and supine hypertension and WMH burden in MSA (Lim *et al.*, 2009, Tha *et al.*, 2010).

A significant relationship between diverse cognitive deficits, OH and supine hypertension has been found in six out of seven cross-sectional studies in PD cohorts (Allcock *et al.*, 2006, Idiaquez *et al.*, 2007, Peralta *et al.*, 2007, Hohler *et al.*, 2012, Kim *et al.*, 2012, Pilleri *et al.*, 2013, Jones *et al.*, 2014). Finally, although overt dementia is an exclusion criterion for the diagnosis of MSA (Gilman *et al.*, 2008), minor degrees of cognitive impairment (especially in executive tasks) have been reported in this disease and significantly related

to the occurrence of cardiovascular autonomic failure (Deguchi *et al.*, 2001, Brown *et al.*, 2010).

Table 3.2 Prognostic impact of cardiovascular autonomic failure in PD and MSA: an overview per domain.

Author	*Sample size (n)*	*Study design*	*Outcome*
Survival			
(Cilia *et al.*, 2014)*	401 PD	Retrospective, cross-sectional, prospective	In patients with longer disease duration (>20 years) mortality is associated with male gender, older age, dysphagia, OH, postural instability, fractures and institutionalization
(Auyeung *et al.*, 2012)*	171 PD	Retrospective	OH is not an independent predictor of death at 10-years follow-up
(Stubendorff *et al.*, 2012)*	30 PDD/DLB	Prospective	Persistent OH is associated with shorter survival a 3-years follow up
(Calandra-Buonaura *et al.*, 2013)*	5 MSA	Prospective	Prolonged survival is associated with late onset of OH and urinary voiding symptoms
(Petrovic *et al.*, 2012)*	4 MSA	Retrospective	Late appearance of dysautonomia is a favorable prognostic factor in MSA-P.
(O'Sullivan *et al.*, 2008)	83 MSA	Retrospective	Early autonomic failure is associated with 6x increased risk of death
(Tada *et al.*, 2007)	49 MSA	Retrospective	Precocious autonomic failure (<2.5 years within disease onset) predicts higher disability, worse prognosis and sudden death
(Watanabe *et al.*, 2002)	230 MSA	Retrospective	Concomitant motor and autonomic involvement within 3 years of onset is associated with faster disease progression and worse prognosis
Cardiovascular outcome			
(Maule *et al.*, 2012)*	45 PD and 43 MSA with OH	Retrospective	51% prevalence of cardiovascular comorbidities (hypertension, angina, atrial fibrillation, heart failure)
(Vagaonescu *et al.*, 2000)	6 PAF, 8 MSA, 12 hypertensives, 14	Cross-sectional	Left-ventricular mass index in patients with autonomic failure is as high as in

Author	*Sample size (n)*	*Study design*	*Outcome*
	controls		hypertensives.
(Maule *et al.*, 2006)	25 patients with autonomic failure, 20 hypertensives	Cross-sectional	Left-ventricular hypertrophy positively correlates with high BP 24-h variability in autonomic failure.
Cerebrovascular outcome			
(Oh *et al.*, 2013)*	117 PD	Cross-sectional	Both supine hypertension and OH predict higher WMH burden
(Pilleri *et al.*, 2013)*	48 PD	Cross-sectional	No difference in subcortical ischemic load between PD patients with and without OH
(Kim *et al.*, 2012)*	87 PD	Cross-sectional	WMH burden correlated with orthostatic diastolic BP fall
(Gorell *et al.*, 1994)	8629 PD, 208933 controls	Retrospective	PD patients are more likely to die from cerebrovascular causes than the general population
(Tha *et al.*, 2010)	16 MSA, 16 controls	Cross-sectional	OH severity correlates with supra- and infratentorial white matter abnormalities in MSA.
(Lim *et al.*, 2009)	63 MSA, 63 controls	Cross-sectional	Supine hypertension is a major predictor of WMH severity in MSA.
Cognitive outcome			
(Jones *et al.*, 2014)*	341 PD	Cross-sectional	Hypertension, and to a lesser extent OH, are significantly associated with frontal executive dysfunction and impaired verbal memory
(Pilleri *et al.*, 2013)*	48 PD	Cross-sectional	OH is associated with worse cognitive performance (sustained attention, visuospatial, verbal memory) in PD
(Kim *et al.*, 2012)*	87 PD	Cross-sectional	Cognitive impairment is associated with the co-occurrence of supine hypertension and OH.
(Hohler *et al.*, 2012)*	44 PD	Cross-sectional	OH is associated with lower motor and cognitive performance
(Allcock *et al.*, 2006)	175 PD	Cross-sectional	PD patients with OH show significant impairment in sustained attention and visual episodic memory.

Author	*Sample size (n)*	*Study design*	*Outcome*
(Peralta *et al.*, 2007)	10 PD, 8 PDD	Cross-sectional	OH exacerbates attentional dysfunction in PDD patients.
(Idiaquez *et al.*, 2007)	40 PD, 30 controls	Cross-sectional	OH does not correlate with the severity of cognitive impairment in PD cases.
(Kitayama *et al.*, 2008)	95 PD	Cross-sectional	Cardiac ^{123}I-MIBG signal reduction is more severe in hallucinated and demented PD patients.
(Brown *et al.*, 2010)	372 MSA	Cross-sectional	In MSA, cardiovascular dysautonomia is predictive of cognitive impairment.
(Deguchi *et al.*, 2001)	9 MSA, 9 controls	Cross-sectional	Frontal lobe dysfunction positively correlates with systolic BP drop upon standing.

*: studies available after publication of the review in 2012. DLB: dementia with Lewy bodies; OH: orthostatic hypotension; MIBG: metaiodobenzylguanidine; PAF: pure autonomic failure; PDD: Parkinson's disease with dementia; WMH: white matter hyperintensities

3.5. Discussion

Current evidence underscores an association between cardiovascular autonomic failure and mortality in MSA and PD, especially in older and demented patients. Cardiovascular autonomic failure may indeed induce potentially life-threatening events like syncope and injurious falls. Alternatively, development of cardiovascular autonomic failure may reflect a more severe disruption of brainstem cardio-respiratory drive which may, in turn, increase the risk of sudden death in MSA.

Altered cerebral perfusion, vascular pressure stress, and related disruption of the blood-brain barrier may contribute to the subcortical ischemic damage and cognitive dysfunction frequently found in patients affected by cardiovascular autonomic failure, with duration and severity of BP disruption possibly playing a pivotal role. On the other

hand, OH and cognitive impairment may result from neurodegenerative changes affecting areas involved in both cognition and cardiovascular autonomic control like the anterior cingulate cortex (Poewe, 2007).

3.6. Conclusion

Current evidence supports the hypothesis that cardiovascular autonomic failure may play a negative prognostic role in PD and MSA and suggest that precocious screening and therapeutic management of cardiovascular autonomic failure may positively influence disease outcome and quality of life in α-synucleinopathies.

4. Detecting nocturnal hypertension in Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm

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Approval of the final version of the manuscript: AF, SS, JPN, GG, MR, LG, CCa, CCo, WP, GKW, FEP

Hereunder we report an excerpt of the study. Full-text of the related article can be found at:

http://link.springer.com/article/10.1007%2Fs00415-014-7339-2

4.1. Background

A pathological nocturnal blood pressure (BP) profile, either *non-dipping* or *reverse-dipping*, occurs in more than 50% of subjects diagnosed with multiple system atrophy (MSA) or Parkinson's disease (PD). This may play a negative prognostic role in α-synucleinopathies, but, being mostly asymptomatic, remains largely underdiagnosed.

4.2. Aim

In this *proof-of-concept* cross-sectional study, we aimed at developing a decision-support algorithm to predict pathological nocturnal BP profiles during a standard tilt-table examination in PD and MSA.

4.3. Methods

Sixteen MSA and sixteen PD patients underwent standard tilt-table examination and 24h-ambulatory BP monitoring (24h-ABPM). Clinical and tilt-test differences between patients with a normal (dipping) and a pathological (non-dipping or reverse-dipping) nocturnal BP profile at 24h-ABPM were assessed applying the Mann-Whitney U test for quantitative variables, and Pearson's X^2 test (or the Fisher's exact test, where appropriate) for categorical variables. Tilt-table parameters displaying the most significant difference between the normal and pathological nocturnal BP group were selected and a regression tree algorithm (CART) with 5-fold cross-validation methodology was developed to predict a pathological nocturnal BP profile in PD and MSA.

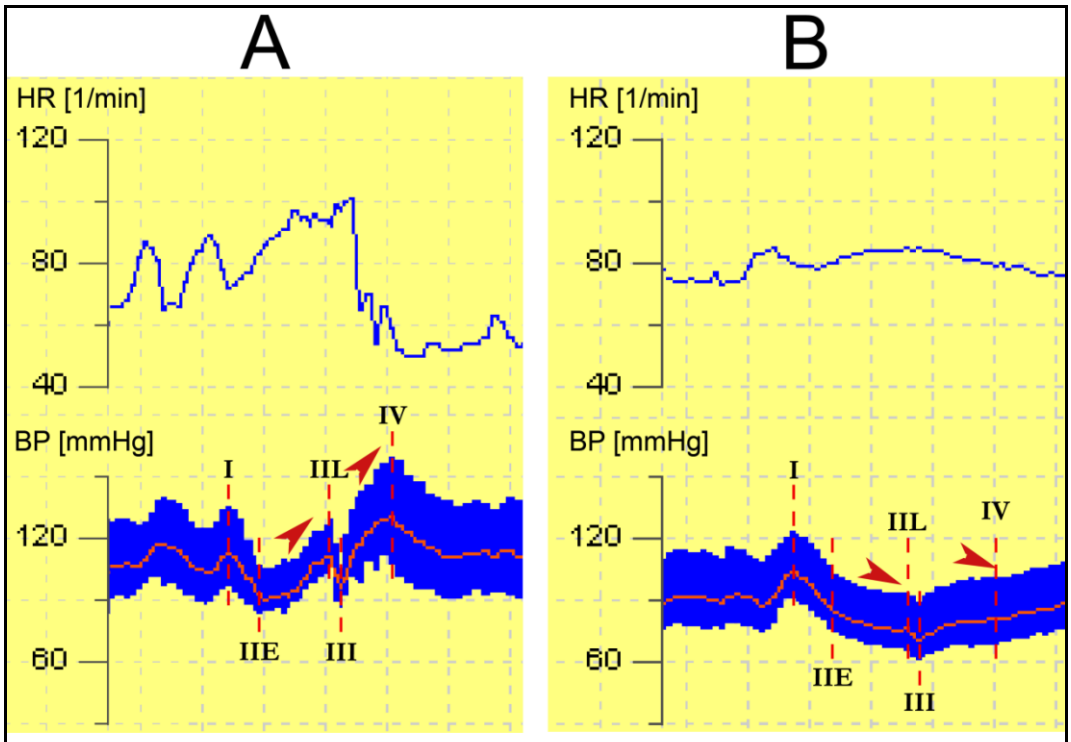
4.4. Results

75% of MSA (37, 5% non-dippers, 37, 5% reverse-dippers) and 31% of PD (25% non-dippers, 6% reverse-dippers) patients showed a pathological nocturnal BP profile. A significant association between MSA diagnosis and a pathological nocturnal BP profile was observed (p=0.032), but not between pathological nocturnal BP profiles and gender, age, disease stage/duration, L-dopa equivalent daily dosage or use of anti-hypotensive medications (seeTable 4.1). At tilt-test examination, pathological nocturnal BP profiles were associated with greater systolic/diastolic BP drop after 3 minutes of head-up tilting (p=0, 03), joint occurrence of orthostatic hypotension and supine hypertension (p=0, 03), and lack of the physiological BP overshoot in the late phase II (II_L, p=0, 002) and in the phase IV (p=0, 007) of the Valsalva maneuver (see Table 4.1). Combined Δ BP ≤ 0,5 mmHg in the II_L and ≤ -7 mmHg in the IV phase of Valsalva manoeuvre, correctly predicted a pathological nocturnal BP profile at 24h-ABPM with 87,5% sensitivity and 85,7% specificity (see Fig. 4.1 and Fig. 4.2).

Table 4.1 Clinical and tilt test associations of nocturnal BP profiles (normal vs. non-dipping & reverse-dipping) in PD and MSA

	Normal nocturnal BP profile	Pathological nocturnal BP profile	p
Clinical features			
N	15	17	-
Neurological diagnosis, MSA: PD (%)	4: 11 (27: 73)	12: 5 (71: 29)	***0.032***
Sex, female: male (%)	6: 9 (40: 60)	3: 14 (18: 82)	0,243
Age (yr)	65 (60; 69)	68 (60; 76)	0,737
Disease duration (yr)	4 (3; 5)	6 (3; 8)	0,082
Hoehn & Yahr Stage	2.5 (2; 3)	3 (2.5; 4)	0,058
L-dopa equivalent daily dose (mg)	505 (305; 680)	358 (270; 1015)	0,576
Anti-hypotensive medications, n (%)	0 (0)	3 (18)	0,229
Anti-hypertensive medications, n (%)	3 (20)	9 (53)	0,076
Tilt-test parameters			
Supine sys BP (mmHg)	124 (120; 131)	115 (99; 136)	0,551
Supine dia BP (mmHg)	79 (69; 84)	70 (63; 85)	0,551
Δ sys BP after 3 min tilting (mmHg)	4 (-16; +12)	-22 (-35; +10)	***0.03***
Δ dia BP after 3 min tilting (mmHg)	7 (-1; +9)	-7 (-22; +6)	***0.027***
SH, n (%)	3 (20)	5 (29)	0,691
OH, n (%)	1 (7)	11 (65)	***0.001***
OH only, n (%)	1 (7)	6 (35)	0,088
SH only, n (%)	3 (20)	0 (0)	0,092
SH+OH, n (%)	0 (0)	5 (29)	***0.046***
Δ BP Valsalva II_L (II_L-II_E), (mmHg)	1 (-6; +18)	-7 (-12; -2)	***0.002***
Δ BP Valsalva IV (IV-I), (mmHg)	-4 (-10; +7)	-11 (-16; -8)	***0.007***
Ewing's Score (sum of pathological Ewing's tests)	0 (0;1)	1 (0; 2)	0,089

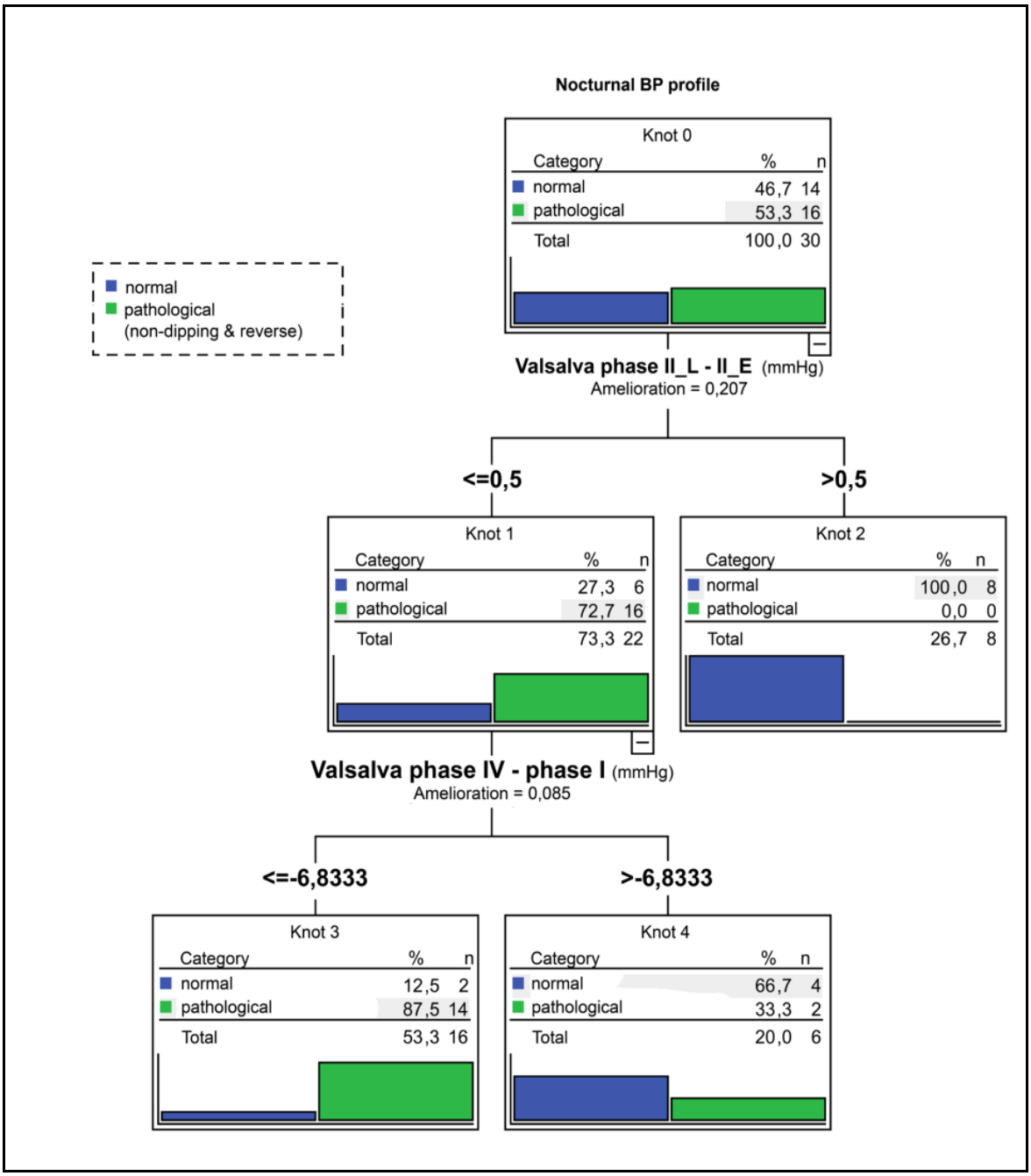
Fig. 4.1 Heart rate (HR) and BP behaviour during Valsalva maneuver, phase I to IV. A: normal finding, with BP overshoots in phase II_L and phase IV (arrows). B: pathological finding, with BP falls in phase II_L and phase IV



Physiological BP behavior during Valsalva Manouvre

	Phase	***BP behaviour***
I.	The patient begins to inflate. Intra-thoracic pressure raises and transiently increases cardiac stroke volume (mechanic effect)	Transient increase
II.	Early (II_E) Increased intra-thoracic pressure hinders venous return to the heart. Cardiac stroke volumes diminishes progressively	Decrease
II.	Late (II_L) BP fall activates brainstem baroreflex arch. Sympathetic outflow to the blood vessels increases and parasympathetic outflow to the heart decreases.	Overshoot with respect to phase II_E
III.	The patient stops inflating. BP falls briefly (mechanic effect, mirror image to phase I)	Transient decrease
IV.	Intra-thoracic pressure returns to negative values and enhances venous return to the heart. Cardiac stroke volumes increases, but the blood vessels are still constricted.	Overshoot with respect to phase I

Fig. 4.2 Two-step decision-support algorithm to predict a pathological nocturnal BP profile in PD and MSA. During the execution of the Valsalva maneuver, measure mean BP values achieved at the end of phase I, II_E, II_L and IV (see Fig. 4.1 for detailed description of Valsalva maneuver phases). If phase II_L BP - phase II_E BP is ≤ 0,5 mmHg (1st step) *and*, if phase IV BP - phase I BP is ≤-7 mmHg (2nd step), a pathological nocturnal BP profile can be predicted with 87,5% sensitivity and 85,7% specificity.



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4.5. Discussion

The strong association between OH, the lack of peripheral vasoconstriction during phase II_L and phase IV of Valsalva maneuver and pathological nocturnal BP profiles observed in the present study, suggests that cardiac and vascular noradrenergic denervation may play a key role in the development of circadian BP rhythm disruptions in PD and MSA. Notably, the presence or lack of BP overshoots in the phase II_L and phase IV of the Valsalva maneuver has good within-subject reliability (Lawrence *et al.*, 1992) and can be detected by naked-eye and in real-time during the execution of the Valsalva maneuver in standard tilt-table evaluations. Our results, therefore, suggest that, where this facility is available, tilt-table guided ABPM may increase the detection of pathological nocturnal BP profiles relevant for cerebrovascular and cognitive outcomes in parkinsonian disorders (Fanciulli *et al.*, 2013).

5. Supine hypertension in Parkinson's disease and multiple system atrophy

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Writing of the first draft: AF

Critical revision of the manuscript: GG, JPN, RG, SD, SS, CC, WP, FEP, GKW, *ongoing*

Approval of the final version of the manuscript: *in due course*

5.1. Introduction

As mentioned in the introduction, supine hypertension (SH) is an attending feature of cardiovascular autonomic failure in PD and MSA (Plaschke *et al.*, 1998, Fanciulli *et al.*, 2014). It is usually asymptomatic or only manifest with vague complaints, but recent evidence suggests that the occurrence of OH and SH may play a negative prognostic role on survival, cardio- and cerebrovascular outcome as well on cognition in PD and MSA (Lim *et al.*, 2009, Kim *et al.*, 2012, Fanciulli *et al.*, 2013, Oh *et al.*, 2013, Pilleri *et al.*, 2013, Jones *et al.*, 2014). SH has been reported in approximately 50% of MSA patients with overt OH (Shannon *et al.*, 1997, Biaggioni and Robertson, 2002), while no former study is available on the prevalence of SH in PD. Notably, no homogeneous cut-off values were used for the diagnosis of SH in the abovementioned papers. In the absence of consensus criteria, SH has been differently defined as systolic blood pressure (BP) ≥ 160 mmHg (Schutzman *et al.*, 1994), ≥ 90 mmHg diastolic (Shannon *et al.*, 1997) or ≥ 150 mmHg systolic/90 mmHg diastolic (Jordan *et al.*, 1999). More recently, the American Heart Association fixed the cut-off for the diagnosis of hypertension to ≥140 mmHg systolic or ≥90 mmHg diastolic and defined three severity degrees, namely *mild, moderate* and *severe* hypertension, with different prognostic and therapeutic implications (Chobanian *et al.*, 2003).

In the present study, conceived by the cooperation between the Medical University of Innsbruck and the Sapienza University of Rome, we aimed at investigating the prevalence of SH according to the American Heart Association criteria in a large retrospective cohort of PD and MSA patients. Furthermore, we compared the prevalence and severity of SH between Parkinson's disease with dementia (PDD) and gender-, age- and disease duration-matched non-demented PD patients and between MSA-P and gender-, age- and

disease duration-matched MSA-C patients. We finally assessed the clinical and tilt-test correlates of SH in PD and MSA.

5.2. Materials and methods

5.2.1. Study population

Parkinsonian patients who underwent a diagnostic tilt-test examination in the time frame between January 2008 and August 2013 in Innsbruck or between January and November 2011 in Rome were screened.

Inclusion criteria were: i – diagnosis of probable PD according to the UK Brain Bank criteria (Hughes *et al.*, 2001) OR; ii – diagnosis of probable PDD according to the International Parkinson Disease and Movement Disorder Society criteria (Emre *et al.*, 2007) OR; iii - diagnosis of probable MSA (parkinsonian or cerebellar variant) according to the 2nd Consensus conference on the diagnosis of MSA (Gilman *et al.*, 2008); iv – extensive clinical documentation with at least two follow-up visits with confirmed neurological diagnosis. Exclusion criteria were: i –other major neurologic or psychiatric diseases; ii – missing or incomplete clinical documentation; iii – low quality of tilt-test examination.

The study received approval by the local ethical committees and was performed according to the Declaration of Helsinki. Given the retrospective nature of the study, no written informed consent was due. Data were collected, archived and analysed anonymously following the current Austrian law for data protection.

5.2.2. Clinical demographic data set

For each enrolled patient, the following information was collected from clinical recordings contemporary to the tilt-test examination: i - age; ii – gender; iii – disease duration; iv –

Hoehn & Yahr stage; v – L-Dopa equivalent daily dosage calculated according to (Tomlinson *et al.*, 2010); vi – cardiovascular comorbidities and risk factors (e.g. coronary arteries disease, atrial fibrillation, heart failure, history of hypertension, diabetes mellitus); vii – use of anti-hypotensive medications; viii – use of anti-hypertensive medications.

5.2.3. Tilt-test data set

In the above mentioned time frames, the Innsbruck and Rome cardiovascular autonomic function laboratories applied the same tilt-test protocols. Standard basic tilt-test protocol consisted of: 10 minutes supine, 10 minutes 60° head-up tilt, 5 minutes supine, 5 minutes active standing. Heart rate and BP were continuously monitored by means of non-invasive beat-to-beat BP recording and impedance cardiography (Task Force® Monitor, CNSystems 2007). For the purposes of the present study, heart rate, systolic and diastolic BP values at 10^{th} minute supine, 3^{rd} and 10^{th} minutes tilt, 5^{th} minute supine, 3^{rd} and 5^{th} minutes standing were calculated by averaging 15 values of the continuous heart rate and BP recording at the above given time points.

According to the American Heart Association criteria, SH was diagnosed in case of systolic BP ≥140 mmHg or diastolic ≥90 mmHg at the end of any supine phase. Mild hypertension was defined as systolic BP values of 140-159 mmHg or 90-99 mmHg diastolic, moderate hypertension as 160-179 mmHg systolic or 100-109 mmHg diastolic and severe hypertension as ≥180 mmHg systolic or ≥110 mmHg diastolic (Chobanian *et al.*, 2003).

Following the 2011 consensus criteria, OH was defined as a systolic BP fall ≥ 20 mmHg or diastolic ≥10 mmHg within 3 minutes from tilting or standing in case of normal BP values in the supine position (Freeman *et al.*, 2011). In case of SH, a systolic BP fall ≥ 30 mmHg

within 3 minutes from tilting or standing was required for the diagnosis of OH (Freeman *et al.*, 2011).

5.2.4. Statistics

For descriptive purposes, qualitative variables were summarized by frequency and percentage. The Kolmogorow-Smirnow test was applied to proof the normal distribution of quantitative variables: latter were summarized by mean ± standard deviation if normally distributed, and by median (1^{st} quartile; 3^{rd} quartile) if not normally distributed. Qualitative variables were compared by means of the Pearson's X^2 test (or Fisher's exact test, where appropriate). Depending on the distribution of data, quantitative variables were compared using the Mann-Whitney U (for non-normally distributed data) or the T-test (for Gaussian distributed ones).

Subgroup comparisons were run first. PDD were paired 1:2 with gender-, age- and disease duration-matched PD patients without dementia, while MSA-P and MSA-C patients were compared without preliminary matching. Benjamini-Hochberg correction was applied to multiple tests and a post-hoc power analysis was performed to determine the probability of type 2 error in both subgroups' analysis.

In a second step, a comparison of clinical demographic features between the overall PD (including PDD patients) and MSA (both MSA-P and MSA-C patients) populations was run and the prevalence and severity of SH in the diseases calculated. The prevalence of SH in PD and MSA was subsequently compared by including those clinical demographic parameters showing a significant difference between the PD and MSA cohorts in a logistic regression model.

In a third step, clinical and tilt-test characteristics of PD patients with versus those without SH were investigated in a univariate fashion. Subsequently, multivariate logistic regression analysis and repeated measurements ANOVA were performed to respectively assess the clinical and tilt-test correlates of SH in PD. The same procedure was applied to investigate the clinical and tilt-test correlates of SH in the setting of MSA.

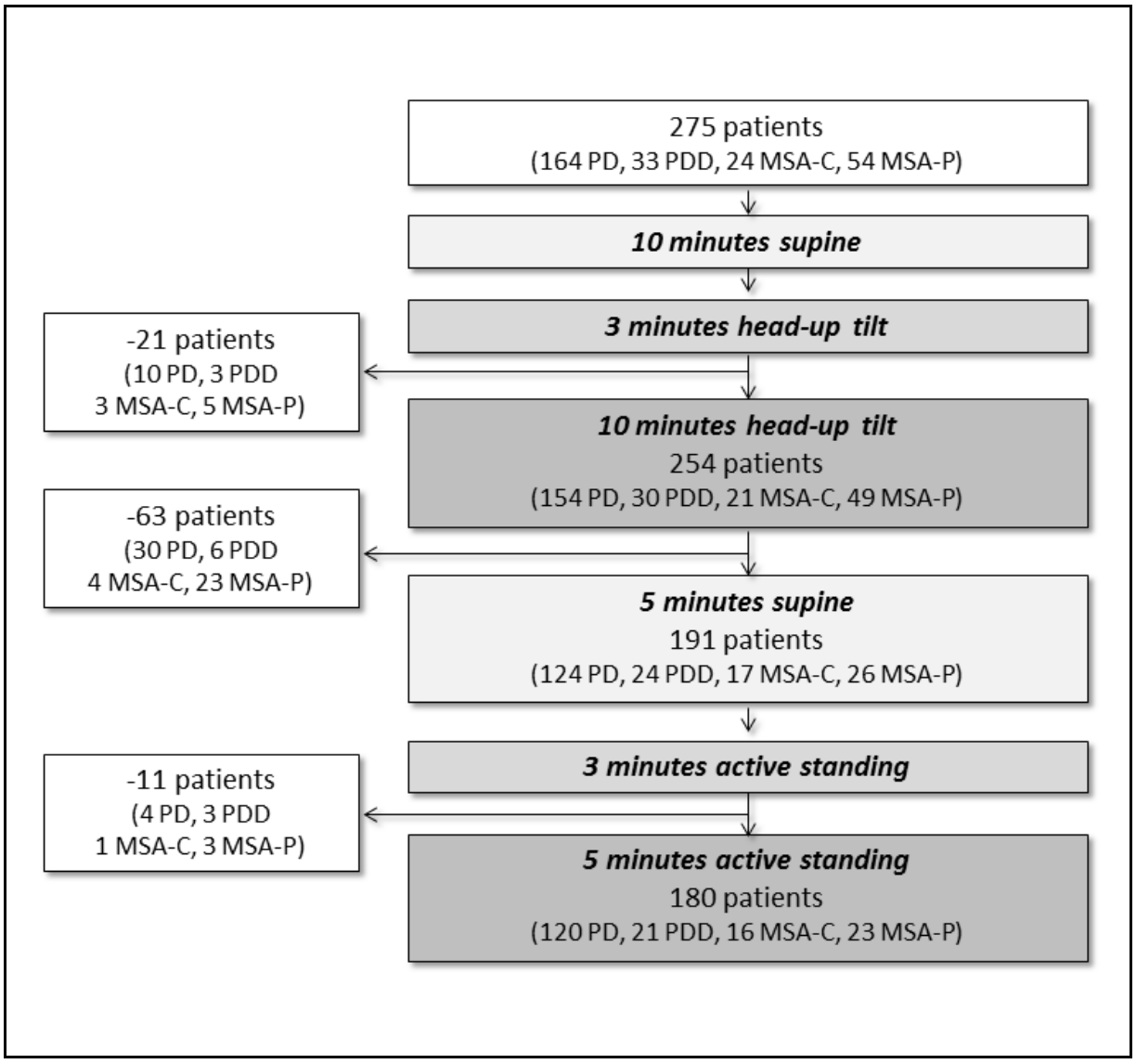
Statistical analysis was performed by means of SPSS®, version 20.0. P values < 0.05 were considered statistically significant.

5.3. Results

5.3.1. Study population

An overview of the study flow chart is provided in Fig. 5.1. At the end of the screening procedure, data from 275 patients were available for the primary outcome analysis (10 minutes in the supine position plus at least 3 minutes of 60° passive head-up tilt-test). In 254 patients the tilt-test was prolonged up to 10 minutes. 191 patients additionally underwent an active standing test: in 11 patients the test was discontinued after 3 minutes, while the remaining 180 patients completed it up to 5 minutes.

Fig. 5.1 Supine hypertension study flow chart



MSA-C: multiple system atrophy-cerebellar; MSA-P: multiple system atrophy-parkinsonian; PD: Parkinson's disease; PDD: Parkinson's disease with dementia

5.3.2. Parkinson's disease versus Parkinson's disease with dementia

Thirty-three patients with PDD [22 males, 11 females; median age 74 years (72; 79, 1st; 3rd quartile); median disease duration 5 years (3; 10)] were matched with 66 non-demented PD patients [44 males, 22 females; median age 74 years (71; 79); median disease duration (3; 9)]. Full clinical-demographic and tilt-test characteristics are reported in Table 5.1. There was no difference in the L-Dopa equivalent daily dosage, prevalence of

cardiovascular comorbidities or use of anti-hypertensive and anti-hypotensive medications between the two groups. Patients with PDD were in a significantly more advanced Hoehn & Yahr stage with respect to PD ones [3(2; 3) versus 2.5 (2; 3), p=0.04].

SH occurred in 27% of PDD patients and 44% of PD ones (p=0.108). Degree of SH was mild in 100% of PDD cases. In non-demented PD patients with SH, latter was mild in 76%, moderate in 21% and severe in 3% of cases, with no significant difference with respect to PDD (p=0.127). OH developed in 30% of PDD and 27% of PD patients at tilt-test examination (p=0.752). SH and OH co-occurred in respectively 9% and 14% of PDD and PD patients (p=0.383). No significant difference was observed in heart rate or BP behaviour upon tilting or standing between demented and non-demented patients.

At post-hoc power analysis, the sample size had a 0.36 power to detect a significant difference in the prevalence of SH between demented and non-demented patients with PD, with a type I error of 0.05 (two-sided).

Table 5.1 Clinical demographic and tilt-test characteristics in patients with Parkinson's disease with dementia versus gender, age and disease-duration matched Parkinson's disease patients without dementia. BP: blood pressure; HR: heart rate; OH: orthostatic hypotension; SH: supine hypertension.

	Parkinson's disease with dementia	Parkinson's disease	p
Clinical demographic			
n	33	66	-
Men, n (%)	22 (67)	44 (67)	1.000
Age (yr), median (Q1; Q3)	74 (72; 79)	74 (71; 79)	0.908
Disease duration (yr), median (Q1; Q3)	5 (3; 10)	4 (3; 9)	0.792
Hoehn & Yahr stage, median (Q1; Q3)	3 (2; 3)	2.5 (2; 3)	**0.04**
L-Dopa equivalent daily dose (mg), median (Q1; Q3)	400 (300; 1070)	463 (240; 1003)	0.988
Cardiovascular comorbidities, n (%)	17 (51)	33 (50)	0.887
Anti-hypertensive medications, n (%)	15 (46)	29 (44)	0.886
Anti-hypotensive medications, n (%)	4 (12)	4 (6)	0.251
Tilt-test			
OH, n (%)	10 (30)	18 (27)	0.752
SH, n (%)	9 (27)	29 (44)	0.108
SH severity_mild, n (%)	9 (100)	22 (76)	0.127
SH severity_moderate, n (%)	0 (0)	6 (21)	
Sh severity_severe, n (%)	0 (0)	1 (3)	
SH+OH, n (%)	3 (9)	9 (14)	0.383
Supine 10 min HR (n=33; 66), mean ± SD	70.6 ± 12.6	69.09 ± 11.5	0.568
Supine 10 min systolic BP (n=33; 66), mean ± SD	119.6 ± 15.8	123.6 ± 15.8	0.242
Supine 10 min diastolic BP (n=33; 66), mean ± SD	77.3 ± 11.3	81.4 ± 11.5	0.095
3 min head-up tilt HR (n=33; 66), mean ± SD	79.9 ± 15.0	76.9 ± 13.2	0.305
3 min head-up tilt systolic BP	114.5 ± 21.8	121.0 ± 19.7	0.143

	Parkinson's disease with dementia	Parkinson's disease	p
(n=33; 66), mean ± SD			
3 min head-up tilt diastolic BP (n=33; 66), mean ± SD	80.3 ± 12.1	84.4 ± 11.2	0.096
Δ HR 3 min head-up tilt (n=33; 66), mean ± SD	9.4 ± 8.8	7.8 ± 7.7	0.361
Δ systolic BP 3 min head-up tilt (n=33; 66), mean ± SD	-5.1 ± 15.0	-2.6 ± 17.1	0.480
Δ diastolic BP 3 min head-up tilt (n=33; 66), mean ± SD	3.1 ± 10.0	3.1 ± 11.2	0.995
Supine 5 min HR (n=24; 52), mean ± SD	73.2 ± 13.3	68.9 ± 13.8	0.214
Supine 5 min systolic BP (n=24; 52), mean ± SD	117.8 ± 13.0	121.9 ± 14.2	0.240
Supine 5 min diastolic BP (n=24; 52), mean ± SD	76.1 ± 9.6	82.1 ± 11.6	0.031
Standing 3 min HR (n=24; 52), mean ± SD	83.5 ± 12.4	80. 0 ± 14.4	0.314
Standing 3 min systolic BP (n=24; 52), mean ± SD	116.3 ± 24.4	127.4 ± 19.1	0.034
Standing 3 min diastolic BP (n=24; 52), mean ± SD	80.7 ± 18.3	90.4 ± 13.8	0.012
Δ HR 3 min standing (n=24; 52), mean ± SD	10.3 ± 7.3	11.1 ± 8.8	0.712
Δ systolic BP 3 min standing (n=24; 52), mean ± SD	-1.5 ± 24.3	5.5 ± 20.4	0.190
Δ diastolic BP 3 min standing (n=24; 52), mean ± SD	4.5 ± 17.6	8.3 ± 15.7	0.349

5.3.3. MSA-C versus MSA-P

The MSA cohort consisted of 24 patients with MSA-C [15 males, 9 females; mean age 62.8±8.2 years; median disease duration 3 years (2;4)] and 54 patients with MSA-P [35 males, 19 females; mean age 65±9.3 years; median disease duration 3 (2; 4)]. Full clinical-demographic and tilt-test characteristics are reported in

Table 5.2. MSA-C patients did not differ from MSA-P ones for any of the clinical demographic characteristic, except for L-Dopa equivalent daily dosage, which was higher in MSA-P patients [median dosage 600 (300; 1929) mg/day versus 0 (0; 300) mg/day, $p<0.001$).

At tilt-test examination, SH occurred in 50% of MSA-C and 32% of MSA-P patients ($p=0.118$). In MSA-P the prevalence of severe SH was significantly higher (41% versus 8% in MSA-C, $p=0.045$). OH was present in 33% of MSA-C and 50% of MSA-P patients ($p=0.172$). Seventeen per cent of MSA-C patients and 26% of MSA-P ones developed both SH and OH at tilt-table examination ($p=0.37$). Heart rate or BP behaviour did not differ either upon head-up tilt or standing between MSA-C and MSA-P patients.

At post-hoc power analysis, the sample size had a 0.34 power to detect a significant difference in the prevalence of SH between MSA-C versus MSA-P patients, with a type I error of 0.05 (two-sided).

Table 5.2 Clinical demographic and tilt-test characteristics in MSA-C versus MSA-P patients. BP: blood pressure; HR: heart rate; MSA-C: multiple system atrophy-cerebellar; MSA-P: multiple system atrophy-parkinsonism; OH: orthostatic hypotension; SH: supine hypertension

	MSA-C	MSA-P	p
Clinical demographic			
n	24	54	-
Men, n (%)	15 (63)	35 (65)	0.520
Age (yr), mean ± SD	62.8 ± 8.2	65 ± 9.3	0.302
Disease duration (yr), median (Q1; Q3)	3 (2; 4)	3 (2; 5)	0.539
Hoehn & Yahr stage, median (Q1; Q3)	4 (3; 5)	3 (2.5; 4)	0.252
L-Dopa equivalent daily dose (mg), median (Q1; Q3)	0 (0; 300)	600 (300; 1929)	**<0.001**
Cardiovascular comorbidities, n (%)	11 (46)	25 (46)	0.583
Anti-hypertensive medications, n (%)	10 (42)	15 (28)	0.225
Anti-hypotensive medications, n (%)	4 (17)	5 (9)	0.279
Tilt-test			
OH, n (%)	8 (33)	27 (50)	0.172
SH, n (%)	12 (50)	17 (32)	0.118
SH severity_mild, n (%)	9 (75)	7 (41)	**0.045**
SH severity_moderate, n (%)	2 (17)	3 (18)	
Sh severity_severe, n (%)	1 (8)	7 (41)	
SH+OH, n (%)	4 (17)	14 (26)	0.37
Supine 10 min HR (n=24; 54), mean ±SD	72.8 ± 11.1	73.2 ± 11.1	0.897
Supine 10 min systolic BP (n=24; 54), mean ±SD	127.8 ± 12.9	124.2 ± 22.2	0.463
Supine 10 min diastolic BP (n=24; 54), mean ±SD	85.2 ± 11.1	82.1 ± 18.8	0.458
3 min head-up tilt HR (n=24; 54), mean ±SD	80.3 ± 10.3	79.7 ± 12.5	0.852
3 min head-up tilt systolic BP (n=24; 54), mean ±SD	122.5 ± 22.6	113.2 ± 18.4	0.061
3 min head-up tilt diastolic BP (n=24; 54), mean ±SD	88.0 ± 15.3	78.7 ± 15.8	0.018
Δ HR 3 min head-up tilt	7.4 ± 5.7	6.5 ± 6.6	0.565

	MSA-C	MSA-P	p
(n=24; 54), mean ±SD			
Δ systolic BP 3 min head-up tilt (n=24; 54), mean ±SD	-5.4 ± 18.5	-11.0 ± 18.8	0.224
Δ diastolic BP 3 min head-up tilt (n=24; 54), mean ±SD	2.8 ± 12.9	-3.4 ± 14.5	0.074
Supine 5 min HR (n=17; 26), mean ±SD	70.9 ± 11.4	74.2 ± 11.0	0.355
Supine 5 min systolic BP (n=17; 26), mean ±SD	121.9 ± 23.5	124.7 ± 21.4	0.690
Supine 5 min diastolic BP (n=17; 26), mean ±SD	84.4 ± 16.8	82.6 ± 16.3	0.724
Standing 3 min HR (n=17; 26), mean ±SD	85.1 ± 10.5	81.8 ± 18.9	0.511
Standing 3 min systolic BP (n=17; 26), mean ±SD	122.4 ± 19.7	116.8 ± 23.5	0.423
Standing 3 min diastolic BP (n=17; 26), mean ±SD	87.5 ± 14.9	81.9 ± 17.3	0.278
Δ HR 3 min standing (n=17; 26), mean ±SD	14.2 ± 7.2	7.6 ± 20.7	0.214
Δ systolic BP 3 min standing (n=17; 26), mean ±SD	.4 ± 25.0	-9.1 ± 18.9	0.162
Δ diastolic BP 3 min standing (n=17; 26), mean ±SD	3.1 ± 15.9	-.7 ± 13.4	0.404

5.3.4. Prevalence of supine hypertension in PD and MSA

Since no substantial difference was observed either in the clinical demographic or in the tilt-test characteristics among the PD (demented versus non-demented) and MSA (MSA-P versus MSA-C) subgroups, data were pooled and a cohort of 197 patients with PD and 78 patients with MSA was available for the assessment of SH prevalence. Clinical demographic features of the overall PD and MSA cohorts are summarized in Table 5.3. Patients with PD (122 males, 75 females) had a median age of 71 years (65; 76, 1st; 3rd quartile), median disease duration of 5 years (3; 9) and median 2.5 (2; 3) Hoehn & Yahr stage. Median L-Dopa equivalent daily dosage was 510 mg/day (260; 1050). Cardiovascular comorbidities and risk factors were present in 40% of patients. Thirty-eight per cent of patients with PD took anti-hypertensive medications, 11% anti-hypotensive medications.

MSA patients (50 males, 28 females) had a median age of 65 years (57; 72), median disease duration of 3 years (2; 4) and median 3 (3; 4) Hoehn & Yahr stage. Median L-Dopa equivalent daily dosage was 505 mg/day (200; 1103). Forty-six per cent of MSA patients had cardiovascular comorbidities in the medical history, 32% took anti-hypertensive drugs, 12% anti-hypotensives.

As shown in Table 5.3, the PD and MSA cohort significantly differed for several clinical demographic characteristics, MSA patients being on average younger ($p<0.001$), with shorter disease duration ($p<0.001$), on lower daily dopaminergic dosage ($p=0.004$), but in a more advanced Hoehn & Yahr stage ($p<0.001$).

Table 5.3 Clinical demographic characteristics of the overall Parkinson's disease (including Parkinson's disease with dementia) and MSA (both parkinsonian and cerebellar variants) cohorts

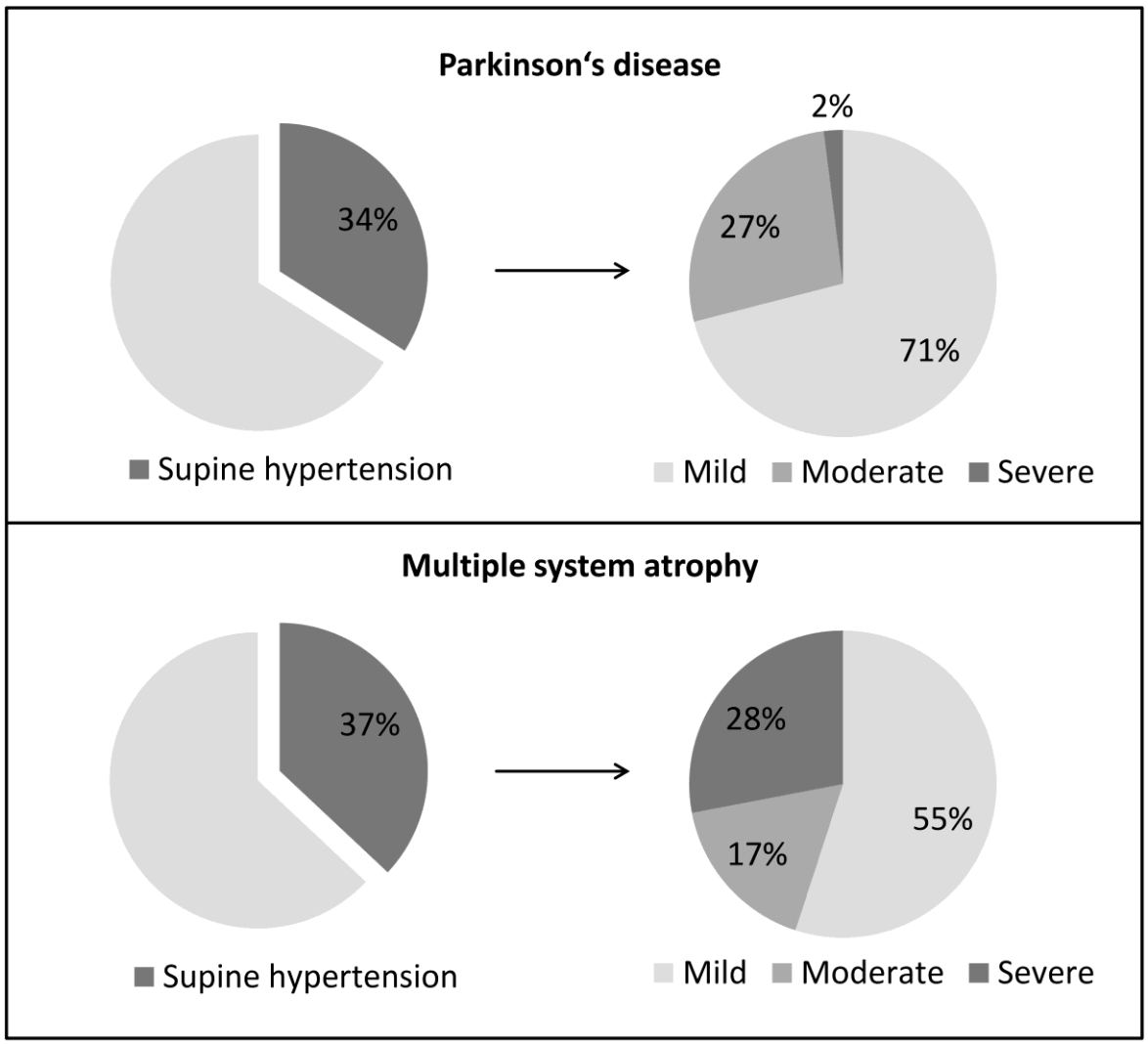
	PD	MSA	p
n	197	78	-
Men, n (%)	122 (62)	50 (64)	0.737
Age (yr), median (Q1; Q3)	71 (65; 76)	65 (57; 72)	**<0.001**
Disease duration (yr), median (Q1; Q3)	5 (3; 9)	3 (2; 4)	**<0.001**
Hoehn & Yahr stage, median (Q1; Q3)	2.5 (2 ;3)	3 (3 ;4)	**<0.001**
L-Dopa equivalent daily dose (mg), median (Q1; Q3)	510 (260; 1050)	505 (200; 1103)	**0.004**
Cardiovascular comorbidities, n (%)	78 (40)	36 (46)	0.32
Anti-hypertensive medications, n (%)	75 (38)	25 (32)	0.35
Anti-hypotensive medications, n (%)	11 (6)	9 (12)	0.087

Prevalence of SH in the overall PD cohort was 34% (n=47). SH was mild in 71% of cases, moderate in 27% and severe in 2% (see Fig. 5.2). OH developed in 24% (n=66) of PD patients at tilt-test examination. In 10% (n=20) of PD patients, SH and OH co-occurred.

In the MSA cohort, prevalence of SH was 37% (n=29). Degree of SH was mild in 55% of patients, moderate in 17% and severe in 28% (see Fig. 5.2). Forty-five per cent (n=35) of MSA patients had OH at tilt-test examination. Co-occurrence of SH and OH was observed in 23% (n=18) of patients. The prevalence of SH in MSA patients with OH was significantly higher than in MSA patients without OH (49% versus 26%, p=0.03). The prevalence of severe SH was also significantly higher in OH-positive MSA patients (44% versus 0% in OH-negative patients, p=0.031).

After adjusting for age, disease-duration, Hoehn & Yahr stage and L-Dopa equivalent daily dosage, no difference was observed in the prevalence of SH between the PD and MSA cohort (OR=1.301, 95% confidence intervals: 0.6-2.8, p=0.5).

Fig. 5.2 Prevalence and severity of supine hypertension in Parkinson's disease and multiple system atrophy



5.3.5. Clinical and tilt-test correlates of supine hypertension in Parkinson's disease

At univariate analysis, a significant association between SH and the presence of cardiovascular comorbidities ($p<0.001$) as well as use of anti-hypertensive medications ($p=0.03$) was observed in PD. Lower HR increase (+7.4±7.8 versus +9.8±6.9, $p=0.031$), a more pronounced systolic (-6.1±18.4 versus +2±15.6, $p=0.001$) and diastolic (-0.6±12.7 versus +7.3±11.6, $p<0.001$) BP fall after 3 minutes head-up tilt were observed in PD patients with SH with respect to those without (see Table 5.4).

Full results of logistic regression analysis are reported in Table 5.5. The presence of cardiovascular comorbidities in the medical history significantly predicted SH at tilt-table examination in patients with PD (OR= 4.06, 95% confidence intervals: 1.6-10.0, $p=0.002$). ANOVA for repeated measurements confirmed a significant association between SH and progressive systolic ($F=7.504$, $p=0.007$) and diastolic ($F=9.755$, $p=0.002$) BP fall upon tilting in the PD cohort. The same association was observed for the standing test ($F=7.157$, $p=0.008$ for systolic BP and $F=11.053$, $p=0.001$ for diastolic BP fall). Heart rate behaviour did not differ between patients with or without SH either upon head-up tilt ($F=0.735$, $p=0.392$) or standing ($F=1.283$, $p=0.259$), (see Fig. 5.3).

Table 5.4 Clinical demographic and tilt-test characteristics in Parkinson's disease patients with and without SH (univariate analysis). BP: blood pressure; HR: heart rate; OH: orthostatic hypotension; SH: supine hypertension.

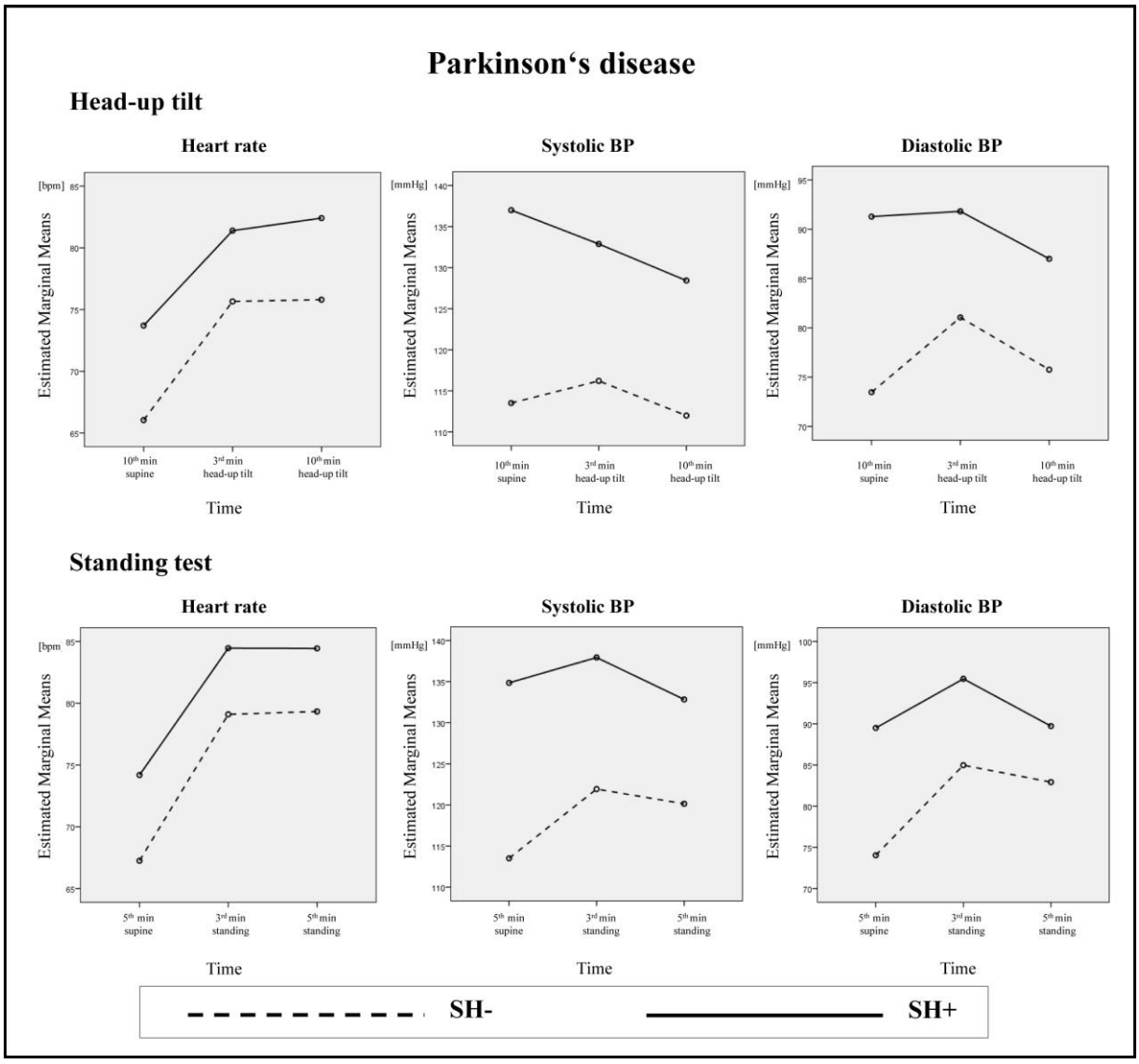
	SH -	SH +	p
Clinical-demographic			
n	131	66	-
Men, n (%)	78 (60)	44 (67)	0,331
Age (yr), median (Q1; Q3)	70 (65; 75)	71 (66; 77)	0,139
Disease duration (yr), median (Q1; Q3)	5 (3; 10)	5 (2; 9)	0,362
Hohen & Yahr stage, median (Q1; Q3)	2,5 (2; 3)	2 (2; 3)	0,413
L-Dopa equivalent daily dose (mg), median (Q1; Q3)	510 (300; 1060)	525 (100; 1055)	0,313
Cardiovascular comorbidities, n (%)	40 (31)	38 (58)	**<0,001**
Anti-hypertensive medications, n (%)	43 (33)	32 (49)	**0,03**
Anti-hypotensive medications, n (%)	6 (5)	5 (8)	0,387
Tilt test			
OH (%)	18 (27)	10 (30)	0,132
Supine 10 min HR (n=131; 66), mean ± SD	66,3 ± 11,0	73,5 ± 12,6	**<0,001**
Supine 10 min systolic BP (n=131; 66), mean ± SD	113,1 ± 12,5	136,9 ± 14,6	**<0,001**
Supine 10 min diastolic BP (n=131; 66), mean ± SD	73,2 ± 9,6	90,6 ± 8,9	**<0,001**
Δ 3 min head-up tilt HR (n=131; 66), mean ± SD	9,8 ± 6,9	7,4 ± 7,8	**0,031**
Δ 3 min head-up tilt systolic BP (n=131; 66), mean ± SD	2,0 ± 15,6	-6,1 ± 18,4	**0,001**
Δ 3 min head-up tilt diastolic BP (n=131; 66), mean ± SD	7,3 ± 11,6	-0,6 ± 12,7	**0,000**
Δ 10 min head-up tilt HR (n=123; 61), median (Q1; Q3)	11 (5; 16)	8 (4; 10)	0,736
Δ 10 min head-up tilt systolic BP (n=123; 61), mean ± SD	-1,7 ± 14,6	-8,2 ± 19,6	**0,023**
Δ 10 min head-up tilt diastolic BP (n=123; 61), mean ± SD	2,2 ± 12,2	-4,2 ± 15,0	**0,002**
Supine 5 min HR	66,9 ± 12,8	74,3 ± 13,7	**0,001**

	SH -	SH +	p
(n=97; 51), mean ± SD			
Supine 5 min systolic BP (n=97; 51), mean ± SD	113,7 ± 12,6	134,7 ± 15,1	**<0,001**
Supine 5 min diastolic BP (n=97; 51), mean ± SD	74,2 ± 8,5	89,8 ± 10,7	**<0,001**
Δ 3 min standing HR (n=97; 51), mean ± SD	9,8 ± 6,9	7,4 ± 7,8	**0,031**
Δ 3 min standing systolic BP (n=97; 51), mean ± SD	2,0 ± 15,6	-6,1 ± 18,4	**0,001**
Δ 3 min standing diastolic BP (n=97; 51), mean ± SD	7,3 ± 11,6	-0,6 ± 12,7	**<0,001**
Δ 5 min standing HR (n=91; 50), median (Q1; Q3)	13 (8; 18)	13 (5; 20)	0,218
Δ 5 min standing systolic BP (n=91; 50), mean ± SD	6,3 ± 17,4	-2,1 ± 19,2	**0,009**
Δ 5 min standing diastolic BP (n=91; 50), mean ± SD	8,7 ± 13,2	-0,1 ± 16,5	**0,001**

Table 5.5 Logistic regression analysis of clinical-demographic correlates of SH in Parkinson's disease and MSA. OH: orthostatic hypotension; OR: odds ratio

	p	OR	95% confidence interval
Parkinson's disease			
Sex	0.45	1.29	0.7-2.5
Age	0.81	1.00	1.0-1.0
Disease duration	0.16	1.05	1.0-1.1
Hoehn & Yahr stage	0.25	0.75	0.5-1.2
L-Dopa equivalent dose	0.37	0.95	0.9-1.1
Cardiovascular comorbidities	**0.002**	**4.06**	**1.6-10.0**
Antihypertensive medications	0.47	0.72	0.3-1.8
Antihypotensive medications	0.55	1.54	0.4-6.4
OH	0.17	1.72	0.8-3.7
MSA			
Sex	0.47	1.84	0.4-9.6
Age	0.62	1.02	0.9-1.1
Disease duration	0.62	1.10	0.8-1.6
Hoehn & Yahr stage	0.24	1.78	0.7-4.7
L-Dopa equivalent dose	**0.01**	**0.54**	**0.3-0.9**
Cardiovascular comorbidities	0.30	0.39	0.1-2.3
Antihypertensive medications	**0.04**	**7.67**	**1.1-53.1**
Antihypotensive medications	0.93	0.89	0.1-12.0
OH	**0.002**	**15.26**	**2.8-83.7**

Fig. 5.3 ANOVA for heart rate, systolic and diastolic BP changes upon head-up tilt and standing in Parkinson's disease patients with (SH+) and without SH (SH-). BP: blood pressure; SH: supine hypertension; bpm: beats per minute



5.3.6. Clinical and tilt-test correlates of supine hypertension in MSA

In patients with MSA, univariate analysis showed a significant association between SH, lower L-Dopa equivalent daily dosage (P=0.003) and presence of OH at tilt-table examination (p=0.02). In MSA patients with SH, mean systolic BP change after 3 minutes of head-up tilt was -15.0±23.6 versus -5.9±14.4 in MSA patients without SH (p=0.065). Mean diastolic BP change after 3 minutes of head-up tilt was -4.1±18.1 in MSA patients with SH and 0.0±11.2 in those without SH (p=0.275), (see Table 5.6).

The logistic-regression model confirmed a significant association between SH, lower L-Dopa equivalent daily dosage (0.54 OR, 95% confidence intervals: 0.3-0.9, p=0.01) and OH (15.26 OR, 95% confidence intervals: 2.8-83.7, p=0.002) in MSA patients. Additionally, a significant association between SH and use of anti-hypertensive medications was observed (7.67 OR, 95% confidence intervals: 1.1-53.1, p=0.04), (see Table 5.5).

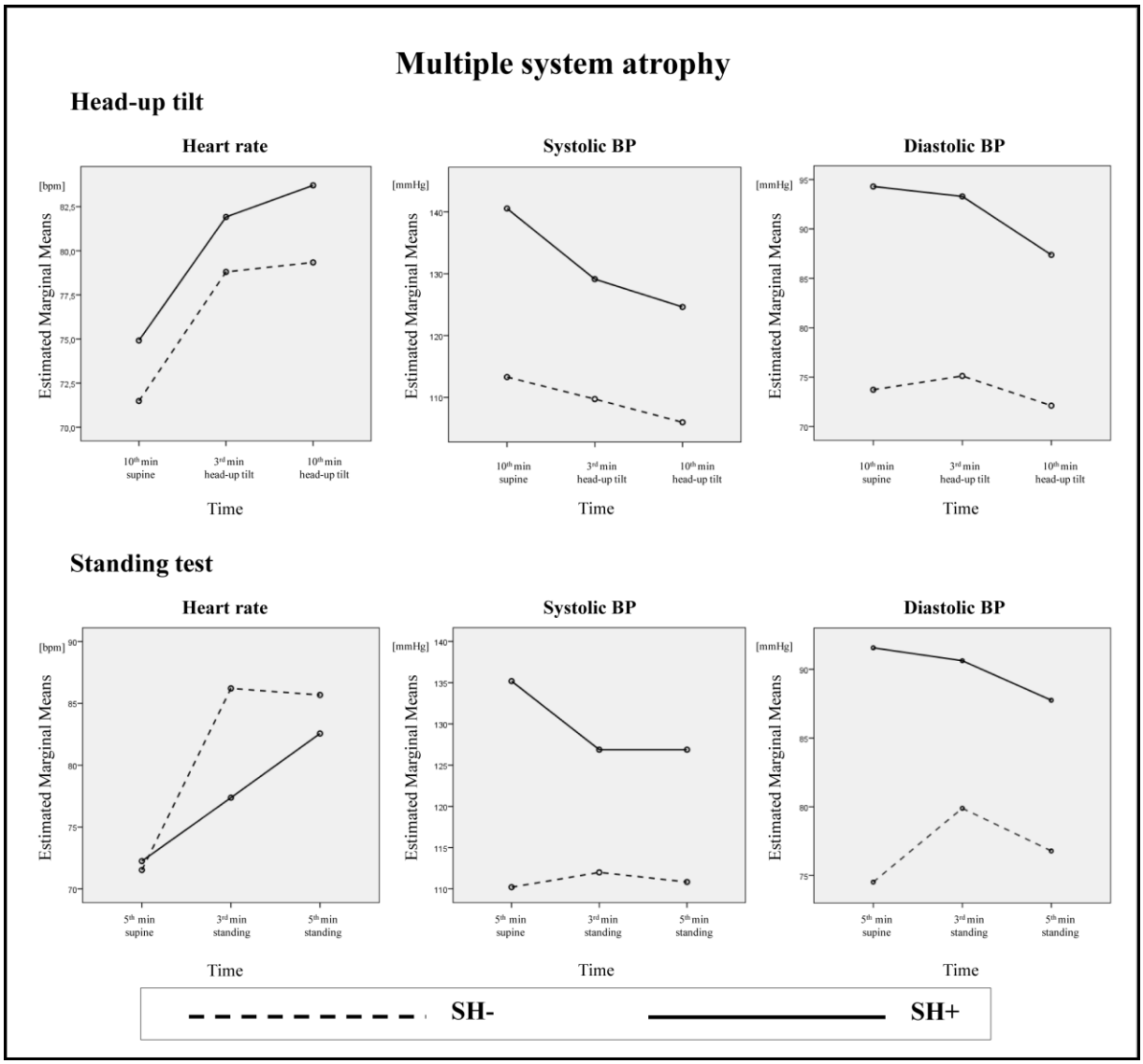
At ANOVA no difference in heart rate, systolic or diastolic BP behaviour was observed between MSA patients with and without SH, either upon head-up tilt (F=0.286, p=0.595 for HR; F=2.434, p=0.124 for systolic BP; F=2.123, p=0.150 for diastolic BP) or standing (F=1.942, p=0.173 for HR; F=1.451, p=0.237 for systolic BP; F=1.536, p=0.224 for diastolic BP), (see Fig. 5.4).

Table 5.6 Clinical demographic and tilt-test characteristics in MSA with and without SH (univariate analysis). BP: blood pressure; HR: heart rate; OH: orthostatic hypotension; SH: supine hypertension

	SH-	SH+	p
Clinical demographic			
n	49	29	-
Men, n (%)	32 (65)	18 (62)	0.773
MSA-P: MSA-C, n	37: 12	17:12	0.118
Age (yr), mean ± SD	64.9 ± 9.4	63.5 ± 8.3	0.506
Disease duration (yr), median (Q1; Q3)	3 (2; 6)	2 (2; 5)	0.363
Hohen & Yahr stage, median (Q1; Q3)	3 (2.5; 4)	4 (3; 5)	0.329
L-Dopa equivalent daily dose (mg), median (Q1; Q3)	550 (0; 1118)	0 (0; 400)	**0.003**
Cardiovascular comorbidities, n (%)	24 (49)	12 (41)	0.515
Anti-hypertensive medications, n (%)	15 (31)	10 (35)	0.723
Anti-hypotensive medications, n (%)	3 (6)	6 (21)	0.059
OH (%)	17 (35)	18 (62)	**0.02**
Tilt test			
Supine 10 min HR (n=49; 29), mean ± SD	72.2 ± 10.9	74.6 ± 11.2	0.354
Supine 10 min systolic BP (n=49; 29), mean ± SD	114.8 ± 12.1	143.2 ± 17.4	**<0.001**
Supine 10 min diastolic BP (n=49; 29), mean ± SD	75.0 ± 10.6	96.7 ± 16.7	**<0.001**
Δ 3 min head-up tilt HR (n=49; 29), mean ± SD	6.9 ± 6.7	6.6 ± 5.7	0.853
Δ 3 min head-up tilt systolic BP (n=49; 29), mean ± SD	-5.9 ± 14.4	-15.0 ± 23.6	0.065
Δ 3 min head-up tilt diastolic BP (n=49; 29), mean ± SD	0.0 ± 11.2	-4.1 ± 18.1	0.275
Δ 10 min head-up tilt HR (n=45; 25), median (Q1; Q3)	8.0 ± 6.4	8.6 ± 7.6	0.763
Δ 10 min head-up tilt systolic BP (n=45; 25), mean ± SD	-7.6 ± 21.7	-15.6 ± 18.6	0.122
Δ 10 min head-up tilt diastolic BP (n=45; 25), mean ± SD	-1.6 ± 12.7	-6.6 ± 15.3	0.145

	SH-	SH+	p
Supine 5 min HR (n=25; 18), mean ± SD	73.0 ± 9.9	72.7 ± 12.9	0.931
Supine 5 min systolic BP (n=25; 18), mean ± SD	112.6 ± 11.2	139.0 ± 24.3	**<0.001**
Supine 5 min diastolic BP (n=25; 18), mean ± SD	76.0 ± 9.6	93.5 ± 18.5	**<0.001**
Δ 3 min standing HR (n=25; 18), mean ± SD	14 (8; 21)	9 (4; 17)	0.082
Δ 3 min standing systolic BP (n=25; 18), mean ± SD	-1.1 ± 17.7	-11.3 ± 25.7	0.131
Δ 3 min standing diastolic BP (n=25; 18), mean ± SD	2.8 ± 12.1	-2.1 ± 17.0	0.279
Δ 5 min standing HR (n=23; 16), median (Q1; Q3)	13.5 ± 7.2	10.3 ± 9.5	0.238
Δ 5 min standing systolic BP (n=23; 16), mean ± SD	-1.3 ± 16.2	-8.3 ± 26.7	0.312
Δ 5 min standing diastolic BP (n=23; 16), mean ± SD	0.9 ± 11.8	-3.8 ± 17.3	0.321

Fig. 5.4 ANOVA for heart rate, systolic and diastolic BP changes upon head-up tilt and standing in MSA patients with (SH+) and without SH (SH-). BP: blood pressure; SH: supine hypertension; bpm: beats per minute



5.4. Discussion

To the best of our knowledge, this is the first study to investigate the prevalence of SH in PD and MSA according to the current consensus criteria for the diagnosis of hypertension (Chobanian *et al.*, 2003).

In the present retrospective cohort, the prevalence of SH in PD was 34%, in 71% of cases of mild degree. In MSA patients the prevalence of SH was 37%, of severe degree in 28% of cases. After adjusting for age, disease-duration, Hoehn & Yahr stage and L-Dopa equivalent daily dosage, the prevalence of SH did not differ between PD and MSA patients.

Due to different criteria for the diagnosis of hypertension and BP measurement methodologies, only partial comparisons can be made with previously published data in the general population. In the Malmö study, which was run on 33.346 Swedish individuals with a mean age of 45.6 ± 7.4 years, hypertension was defined either as systolic BP ≥ 140 mmHg, diastolic BP ≥ 90 mmHg at supine oscillometric BP measurement or use of anti-hypertensive medications and occurred in 40% of subjects (Fedorowski *et al.*, 2010). In the ARIC study, run on 12.433 black and white US natives, mean age in the 6th decade, hypertension at supine oscillometric BP measurement was reported in 30% of subjects without concomitant OH and 60% of patients with OH (Rose *et al.*, 2000). Although oscillometric versus continuous BP measurement may not be directly comparable, and although the definition of hypertension differed among the studies, rough comparison would conclude that parkinsonian patients do have a comparable or slightly lower prevalence of SH with respect to the general population. It is however unclear whether the prevalence of moderate and severe SH, especially in MSA patients, differs from the general population.

In contrast with previous findings from Kim et al. (Kim *et al.*, 2012), we did not observe any difference in the prevalence or severity of SH between PDD versus gender, age and disease duration matched PD patients without dementia. Severity of orthostatic BP fall, prevalence of OH or of combined OH and SH also did not differ between demented and non-demented PD patients. OH has been formerly associated with impaired attention, visuospatial and verbal memory in PD (Allcock *et al.*, 2006, Peralta *et al.*, 2007, Hohler *et al.*, 2012, Pilleri *et al.*, 2013). Hypertension has been also reported to exert an independent negative influence on executive function and delayed verbal memory in the setting of PD (Jones *et al.*, 2014). Neurocirculatory abnormalities like OH and SH may be therefore associated with frontal executive dysfunction rather than overt dementia in PD. However, the results of the present study cannot exclude that non-demented PD patients suffering from OH, SH or both might be at higher risk of developing cognitive impairment in the future. An eventual causative relationship should be addressed in prospectively designed studies.

In the present cohort, the prevalence of SH was 50% in MSA-C patients and 32% in MSA-P ones. OH occurred in 33% of MSA-C patients and 50% of MSA-P ones. Neither of these differences achieved statistical significance. Degree of orthostatic BP fall also did not differ between MSA-C and MSA-P patients. We were not therefore able to replicate previous findings reporting OH to be more frequent and more severe in MSA-C with respect to MSA-P patients (Wenning *et al.*, 2012). However, in the present study, MSA-P patients were on a significantly higher L-Dopa equivalent daily dosage with respect to MSA-C ones. Due to its renowned hypotensive effect, L-Dopa assumption might have on one hand lowered supine BP values, and on the other exacerbated orthostatic BP falls in

MSA-P patients, thus underestimating the prevalence of SH and overestimating that of OH in MSA-P.

The pathophysiology of SH in PD and MSA is not fully clear at present. It was previously proposed that SH develops as side effect of vasoactive agents used for the treatment of OH: this hypothesis has been discarded by the observation that SH develops also in a substantial proportion of patients who do not take anti-hypotensive medications. SH also likely represents a different nosological entity than essential hypertension, since parkinsonian patients with SH may have completely normal BP levels if measuring BP in the seated position.

In PD we found SH to be associated with history of cardiovascular comorbidities and more severe orthostatic systolic and diastolic BP falls. Orthostatic BP falls reflect a combination of cardiovascular noradrenergic degeneration and baroreflex failure in Parkinson's disease (Goldstein *et al.*, 2003). Although speculative, it is therefore conceivable that in PD patients with pre-existing essential hypertension or predisposed to it, minor degrees of cardiovascular autonomic failure unmask or worsen hypertension when lying due to impaired baroreflex buffering.

In MSA we found a strong association between SH and OH. This is in agreement with previous findings, reporting residual sympathetic stimulation to cause even severe supine hypertension in MSA due to autonomic failure-dependant hypersensitivity of noradrenergic receptors and lack of central autonomic modulation (Shannon *et al.*, 1997). SH further showed an inverse relationship with L-Dopa equivalent daily dosage, as well as an association with use of anti-hypertensive medications in MSA. The inverse relationship between SH and L-Dopa daily intake may be explained in different ways: it may reflect

cases with more severe cardiovascular autonomic failure, who do tolerate only low L-Dopa dosages; it may indicate more advanced cases in which a reduction of L-Dopa dosage followed lack of motor responsiveness or, yet, it may reflect L-Dopa vasodepressive properties, which are known to be augmented in patients with cardiovascular autonomic failure. The association between SH and use of anti-hypertensive drugs in MSA probably reflects suboptimal therapeutic approaches, since normotensive BP values can be only achieved at the expenses of worsening a frequently co-existing OH.

Our study has some limitations. First, due to its retrospective nature, we couldn't collect systematic information on additional risk factors for hypertension like positive familial history, renal failure, serum lipids or smoking habit, although this latter is fairly uncommon among parkinsonian patients (Vanacore *et al.*, 2000, Allam *et al.*, 2004). Second, the present study cohort consisted of patients who had undergone a tilt-test examination for diagnostic purposes. This might have introduced a selection bias towards more severe cases, with symptomatic OH or suspected of atypical Parkinsonism. Notwithstanding, OH prevalence was 24% in the present PD population, which is in agreement with a recent meta-analysis, reporting the estimated pooled prevalence of OH to be 30% in PD (Velseboer *et al.*, 2011). The prevalence of OH in the present MSA population (45%) was also consistent, if not lower, with previously reported data on large MSA cohorts (Gilman *et al.*, 2005, Kollensperger *et al.*, 2010). Third, we were not able to systematically document use of anti-hypotensive devices, like compression stockings or abdominal binders. However, according to the standard operating procedures of our cardiovascular autonomic function laboratories, patients who do wear such devices are invited to take them off during tilt test examinations. Eventual use of anti-hypotensive

devices should have therefore exerted only a minor influence on cardiovascular autonomic testing. Fourth, post-hoc analysis showed that both subgroups comparisons were underpowered to detect a significant difference in the prevalence of SH between PD patients with and without dementia or between MSA-C and MSA-P patients. Replication in larger cohorts is therefore needed to draw definitive conclusions as to these points.

Concluding, more than one third of patients with Parkinson's disease and MSA might suffer from SH in the context of cardiovascular autonomic failure. Due to its therapeutic and possibly prognostic implications, we suggest BP measurements in the supine and upright position to screen for SH and OH in the initial and follow-up diagnostic work-up of parkinsonian patients suspected of suffering from cardiovascular autonomic failure.

6. Elastic abdominal binders reduce orthostatic BP fall in Parkinson's disease: a randomized, placebo-controlled cross-over trial

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Data analysis: AF, GG, GKW, KS

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Critical revision of the manuscript: GG, BM, FS, WP, GKW, KS, *ongoing*

Approval of the final version of the draft: *in due course*

6.1. Introduction

OH affects up to 52% of patients with PD (Bonuccelli *et al.*, 2003, Allcock *et al.*, 2006, Barone *et al.*, 2009, Velseboer *et al.*, 2011) and may be accompanied by paradox supine hypertension in one third of cases. Treatment is mandatory in case of symptomatic OH in order to improve quality of life and prevent potentially life-threatening conditions like syncope and injurious falls. Pharmacological treatment relies either on vasopressor agents (e.g. direct/indirect α_1-adrenoreceptor agonists) or on drugs expanding intravascular volume (e.g. fludrocortisone, desmopressin) (Freeman, 2008), but exacerbation of supine hypertension is a common side effect. Non-pharmacological approaches are equally relevant for the clinical management of OH, either alone or in combination with drugs in more severe cases. The use of an elastic abdominal binder already proved effective in pediatric and adult patients with OH due to diabetes mellitus, pure autonomic failure, multiple system atrophy or of unknown etiology (Denq *et al.*, 1997, Tanaka *et al.*, 1997, Smit *et al.*, 2004, Podoleanu *et al.*, 2006).

Here we report the results of a single-centre, single-blinded, randomized, placebo-controlled, cross-over trial to evaluate the effects of an elastic abdominal binder in reducing orthostatic BP fall upon tilting in a population of PD patients with OH. A 4-weeks open-label trial followed to evaluate the effect of elastic abdominal binders on OH-related symptoms in daily living.

6.2. Patients and methods

6.2.1. Study population

Fifteen consecutive patients with probable PD according to the UK Brain Bank criteria (Hughes *et al.*, 2001) aged 40 to 90, with full legal competence and OH (Freeman *et al.*,

2011) were recruited from the Movement Disorder Unit of the Innsbruck Medical University between May 2013 and March 2014. Exclusion criteria were: other major neurologic, psychiatric or cardiac diseases, untreated diabetes mellitus with clinical features of peripheral neuropathy, varicose veins, known or suspected pregnancy, breast feeding, Hoehn & Yahr stage ≥ 4 or changes of the pharmacological therapy in the 6 weeks preceding enrolment.

The study received approval by the local ethical committee, was performed according to the declaration of Helsinki and was registered in ClinicalTrials.gov (Identifier: NCT01971008, ABOHP study). After giving written informed consent, each patient underwent thorough neurological and cardiological examinations. The following scales were administered at baseline: Unified PD Rating Scale (UPDRS), non-motor symptoms scale (NMSS), autonomic scale for outcomes in PD (SCOPA-AUT) and orthostatic hypotension questionnaire (OHQ).

6.2.2. Study design

An outline of the study flow chart is provided in Fig. 6.1. A single-blinded, randomized, placebo-controlled, cross-over design was adopted. For allocation of participants, a randomization sequence was generated on a computer-basis and kept in an agreed place, to which the recruiting investigator had no access. According to this sequence, patients were randomly assigned to first receive either an elastic abdominal binder (Abdo-Syncro 3-stripes abdominal binder, Syncro Med GmbH) or a placebo binder (Clima Care body warmer, Bort Medical GmbH).

On study day-1, all patients underwent a 1st baseline tilt-test examination. Afterwards they were asked to wear the assigned binder. 2 hours later, the 1st study tilt-test was

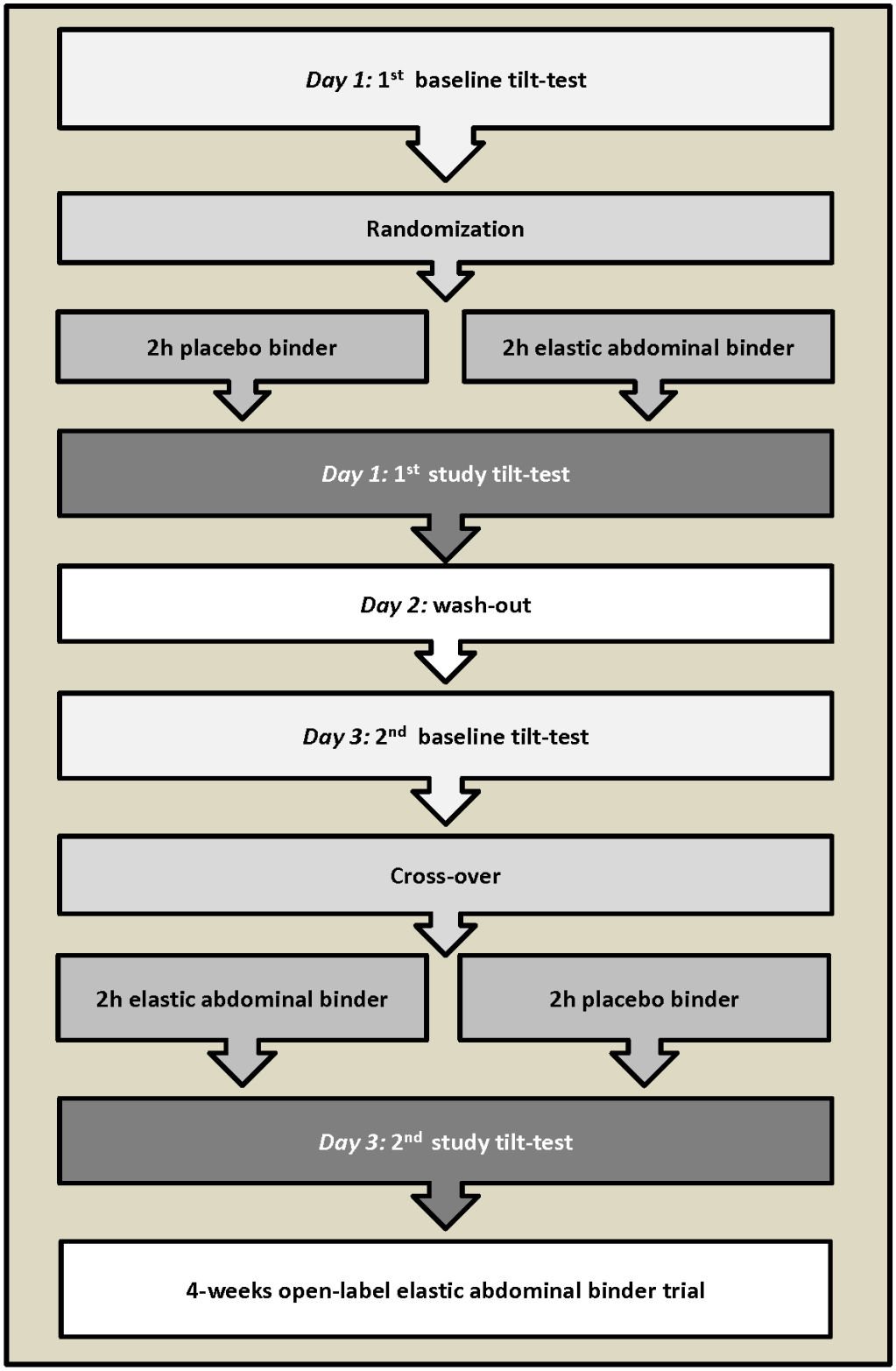
performed. The binder was subsequently taken off. On study day-2 a wash-out was operated. On study day-3, the patients underwent a 2nd baseline tilt-test, wore the other type of binder and 2 hours later had the 2nd study tilt-test. Participants were blinded to the type of binder during the cross-over phase. The investigator performing the tilt-test examination (AF) was not, since he had to check whether the binder exerted the appropriate pressure (20±2 mmHg for the elastic abdominal binder, 3±2 mmHg for the placebo binder) by placing a slightly inflated sphygmomanometer between the binder and the abdominal wall of the patient.

All the tilt-tests were performed between 9 a.m. and 12 p.m. under continuous non-invasive HR and BP monitoring (Task Force® Monitor, CNSystems 2007). On examination days, patients were invited not to drink any coffee, tea or taurine-containing beverages, but to take their medications regularly and to have their meals at least two hours before the scheduled tilt-test.

The following protocol was applied: 10 minutes supine, 10 minutes 60° head-up tilt, 5 minutes supine, 5 minutes active standing. Systolic, diastolic and mean BP values at 10th minute supine, 3rd and 10th minutes tilt, 5th minute supine, 3rd and 5th minutes standing were calculated in an automatized way by averaging 15 values of the continuous BP recording at the above given time points. If continuous BP recording failed, oscillometric BP records at the same time points were used for data analysis.

Once the cross-over phase was over, each patient was invited to wear the elastic abdominal binder every day during daytime. Four weeks later a phone interview took place, in which patient's compliance was assessed and the OHQ repeated.

Fig. 6.1 ABOHP study design



6.2.3. Study outcomes

Effect of the elastic abdominal binder versus placebo on mean BP change after 3 minutes of head-up tilt was defined as primary outcome. Secondary outcomes were:

- effect of the elastic abdominal binder versus placebo on systolic BP changes after 3 minutes of head-up tilt;
- effect of the elastic abdominal binder versus placebo on diastolic BP changes after 3 minutes of head-up tilt;
- effect of the elastic abdominal binder versus placebo on mean BP change after 3 minutes of standing test;
- effect of the elastic abdominal binder versus placebo on mean supine BP
- changes of the OHQ score after 4-weeks open-label regular use of the elastic abdominal binder with respect to baseline.

6.2.4. Statistics

Sample size of the present study was calculated according to previously published data on elastic abdominal binders (Smit *et al.*, 2004, Podoleanu *et al.*, 2006): 14 patients had to enter the 2-arms cross-over study with a 80% probability to detect a 10 mmHg treatment difference (SD 10 mmHg) at one-sided 0.05 significance level. The number of participants was rounded to 15 in order to counteract eventual drop-outs.

BP changes (hereinafter indicated as Δ) at 3rd minute of head-up tilt and at 3rd minute of standing test were calculated as follow:

- Δ 3rd minute tilt mean/systolic/diastolic BP = (3rd minute tilt mean/systolic/diastolic BP) - (10th minute supine mean/systolic/diastolic BP)

- Δ 3rd minute standing mean BP = (3rd minute standing mean BP) - (5th minute supine mean BP)

Effects of the elastic abdominal binder or placebo binder on supine BP or orthostatic BP changes were calculated with respect to the baseline examination of the same day in the following way:

- Δ 10th minute supine mean BP= (10th minute supine mean BP with abdominal binder/placebo)- (10th minute supine mean BP at respective baseline tilt-test)
- Δ 3rd minute tilt mean/systolic/diastolic BP = (Δ 3rd minute tilt mean/systolic/diastolic BP with abdominal binder/placebo) – (Δ 3rd minute tilt mean/systolic/diastolic BP at respective baseline tilt-test)
- Δ 3rd minute standing mean BP= (Δ 3rd minute standing mean BP with abdominal binder/placebo) - (Δ 3rd minute standing mean BP at respective baseline tilt-test)

Normal distribution of data was proofed with the Shapiro-Wilk test. Paired T-test was applied to evaluate vasopressor differences between the abdominal binder and the placebo binder at the above given time points. OHQ score changes after 4-weeks open-label follow-up were compared to baseline visit by means of the Wilcoxon signed-rank test.

Statistical analysis was performed using SPSS®, version 20.0. P values < 0.05 were considered statistically significant.

6.3. Results

Three patients dropped out from the study during the cross-over phase: two patients from the abdominal binder-placebo group (one because OH was not confirmed at 1st

baseline tilt-test on study day-1, one because receiving intravenous NSAIDs on study day-3 for low back pain) and one patient from the placebo-abdominal binder group because of syncope before 3 minutes during the 1st baseline tilt-test on study day-1 (missing baseline data for the primary outcome). Data from 12 patients (4 from the abdominal binder-placebo group, 8 from the placebo-abdominal binder group) were therefore available for the primary outcome analysis. Clinical and demographic characteristics of the study population are reported in Table 6.1.

The abdominal binder increased 3rd minute tilt mean BP by +7.7 mmHg [(+3.5; +11.9), 95% c.i] with respect to baseline examination. Compared to the placebo binder +10 mmHg [(+3.5; +16.5), p=0.006] mean BP increase at 3rd minute tilt was observed.

3rd minute head-up tilt systolic BP increased by +15.5 mmHg [(+5.9; +25.1), p=0.005] with the abdominal binder with respect to placebo and diastolic BP by +7.3 mmHg [(+1; +13.5), p=0.027]. The abdominal binder had no effect on supine mean BP values compared to placebo [+4.8 mmHg (-4.9; +14.5), p=0.3].

Two patients were further excluded from the analysis of Δ 3rd minute standing mean BP because of syncope within the 1st minute of baseline standing test. A trend towards increase of mean BP at 3rd minute standing was observed with the abdominal binder versus placebo [+13 mmHg (-0.3; +26.2), p=0.054].

During the open-label phase, the patients wore the abdominal binder an average of 5.6 (±0.6) days/week, 50-75% of daytime. Mean composite OHQ score at baseline was 5.2 (4.2-6.2, 95% c.i.), mean OH Symptom Assessment (OHSA) subscore was 4.9 (3.8-5.9, 95% c.i.) and mean OH Daily Activity Scale (OHDAS) was 5.6 (4.3-6.8, 95% c.i.). At 4-weeks follow-up a -2.5 points [(-3.4; -1.5) 95% c.i., p=0.003] reduction of the composite OHQ

score was observed. The OHSA subscore decreased by -2.1 points [(-3.0; -1.1), p=0.003] and the OHDAS by -3.4 [(-5.0; -1.7), p=0.007].

No side effect was observed during the cross-over phase. One patient with history of gastro-oesophageal reflux reported mild exacerbation of symptoms during the open-label follow-up.

Table 6.1 ABOHP study. Demographic and clinical characteristics of the study cohort. If not otherwise specified, values are reported as median (1st quartile; 3rd quartile). UPDRS: Unified Parkinson's Disease Rating Scale; NMSS: Non Motor Symptom Scale; SCOPA-AUT: Autonomic Scale for Outcomes in Parkinson's disease

***L-Dopa equivalent daily dosage calculated according to (Tomlinson *et al.*, 2010)**

****Compression stockings**

Characteristic	Value
n	12
Gender (M:F)	8: 4
Age (years)	69 (66; 75)
Disease duration (years)	6 (3; 12)
Hoehn & Yahr stage	2 (2; 2,5)
L-dopa equivalent dose* (mg/day)	555 (228; 1690)
Use of anti-hypertensives, n (%)	6 (50)
Use of anti-hypotensives, n (%)	2 (24)
Use of anti-hypotensive devices, n (%)**	2 (24)
UPDRS total score	54 (41; 66)
UPDRS - part I	12 (8; 18)
UPDRS - part I_item 12 (cardiovascular)	2,5 (1; 3)
UPDRS - part II	13 (9; 15)
UPDRS - part III	29 (19; 36)
NMSS total score	81 (50; 106)
NMSS cardiovascular subscore	8 (4; 8)
SCOPA-AUT total score	21 (14; 29)
SCOPA-AUT cardiovascular subscore	4 (2; 6)

6.4. Discussion

Our study confirms the previously reported (Tanaka *et al.*, 1997, Smit *et al.*, 2004, Podoleanu *et al.*, 2006) efficacy of elastic abdominal binders in reducing OH and extends its validity to PD (level I evidence). The binder had no influence on supine mean BP levels (level I evidence) and a clinically relevant (Kaufmann *et al.*, 2012) amelioration of OH symptoms was observed at open-label follow-up (level III evidence). The heterogeneity of the study population as to gender, age-range, disease-duration and severity suggests the results of the present study to be generalizable to both early and advanced disease stages of PD.

The mechanism of action of an elastic abdominal binder is entirely mechanical: it prevents orthostatic BP fall by reducing splanchnic venous pooling upon standing (Smit *et al.*, 2004). Its use for the management of OH may thus result profitable under several points of view: since not inducing pharmacological interactions, it may be preferable in patients with complex therapeutic schedules; not increasing supine BP, it may be preferred in case of overt supine hypertension and, being less cumbersome to wear than compression stockings, it may achieve higher compliance in advanced stages.

Some limits need to be addressed to our study. First, the investigator performing the tilt tests was not blinded, since such examinations need to be performed bare-chested for safety reasons. However, to minimize the risk of bias, outcome measures were collected in an automated way. Second, patients with varicose veins were excluded. Although previous studies reported no change of femoral vein diameter from a 40 mmHg pressure on the abdominal wall (Smit *et al.*, 2004), we cannot exclude that abdominal binders worsen leg venous insufficiency in the long-term. Third, we cannot either exclude that the exacerbation of gastro-oesophageal reflux reported from one patient during follow-up

was not related to the abdominal binder. Finally, the effect of the elastic abdominal binder on daily OH-related symptomatic burden was investigated in an open-label fashion only.

Concluding, our findings suggest that elastic abdominal binders may be a simple and complementary tool to alleviate OH in PD patients. Further randomized placebo-controlled trials to replicate the effect of elastic abdominal binders on OH symptomatic burden in daily living are warranted.

7. Conclusions and outlook

The studies here within presented showed that:

1. There's an association between cardiovascular autonomic failure and shorter survival as well as worse cardiovascular, cerebrovascular and cognitive outcome in PD and MSA. Association does not however imply causation. Prospectively designed studies are needed to assess whether cardiovascular autonomic failure actually exerts a negative prognostic role in α-synucleinopathies and, if yes, which is the single contribution of OH and supine/nocturnal hypertension in this context. This information will turn essential to assess the long-term benefit-risk ratio of treating OH versus supine/nocturnal hypertension in single patients.

2. According to the results of our proof-of-concept study, the naked-eye evaluation of BP behavior during phase II-L and phase IV of the Valsalva maneuver may represent a sensitive and specific screening test for nocturnal hypertension in PD and MSA during tilt-table examinations without additional costs. If replicated in larger cohorts, with concomitant 24h-ABPM and sleep monitoring, this two-step decision-support algorithm may represent a time-sparing approach to improve the detection of a modifiable cardiovascular risk factor by tilt-table guided 24h-ABPM in parkinsonian patients.

3. Against prior belief that parkinsonian patients have a lower risk of developing hypertension, we found that PD and MSA patients may suffer from supine hypertension to a similar extent as in the general population and that, especially in MSA, hypertension might be of severe degree in one third of cases. We did not find a higher prevalence of neurocirculatory abnormalities (either OH or supine

hypertension) in PD patients with dementia versus gender, age and disease duration matched PD patients without dementia. Since an association between cardiovascular autonomic failure and impairment of diverse executive functions has been already reported in the literature, this may imply that cardiovascular autonomic failure is associated with frontal executive dysfunction rather than with overt dementia in PD. Due to the cross-sectional nature of our observations, we cannot however exclude that PD patients without dementia but with cardiovascular autonomic failure might be at higher risk of developing dementia during the disease course. Prospectively designed studies are necessary to further clarify this issue. The results of our study also support the hypothesis that SH in MSA develops after hypersensitive adrenergic response to unrestrained tonic sympathetic stimulation, while in PD minor degrees of cardiovascular baroreflex failure likely unmask hypertension in the supine position in predisposed individuals. It is however unclear at present, whether additional factors contribute to the development of nocturnal hypertension. Further studies addressing the pathophysiology of supine and nocturnal hypertension and their relationship in in the setting of parkinsonian syndromes are needed to develop targeted pharmacological strategies.

4. Elastic abdominal binders represent a simple non-pharmacological approach to attenuate orthostatic BP fall, without increasing supine BP levels in PD patients suffering from OH (level I evidence). We also provide level III evidence that regular use of elastic abdominal binders may reduce OH-related symptomatic burden in daily living. Replication in randomized, placebo-controlled clinical is needed to proof this observation.

8. Related publications

8.1. Papers

1. Fanciulli A, Goebel G, Ndayisaba JP, Granata R, Dürr S, Strano S, Colosimo C, Poewe W, Pontieri FE, Wenning GK. *Supine hypertension in Parkinson's disease and Multiple System Atrophy.* In preparation.

2. Fanciulli A, Goebel G, Metzler B, Sprenger F, Poewe W, Wenning GK, Seppi K. *Elastic abdominal binders attenuate orthostatic hypotension in Parkinson's disease: a randomized controlled trial*. In preparation

3. Fanciulli A, Strano S, Ndayisaba JP, Goebel G, Gioffrè L, Rizzo M, Colosimo C, Caltagirone C, Poewe W, Wenning GK, Pontieri FE. *Detecting nocturnal hypertension in Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm.* J Neurol, 2014; 261(7):1291-9.

4. Fanciulli A, Strano S, Colosimo C, Caltagirone C, Spalletta G, Pontieri FE. *The potential prognostic role of cardiovascular autonomic failure in α-synucleinopathies*. Eur J Neurol, 2013; 20 (2): 231-235.

5. Fanciulli A, Assogna F, Caltagirone C, Spalletta G, Pontieri FE. *Rotigotine for non-motor symptoms of wearing-off in Parkinson's Disease with Dementia*. Aging Clin Exp Res, 2013; 25 (5): 601-603.

6. Berardelli A, Wenning GK, Antonini A, Berg D, Bloem BR, Bonifati V, Brooks D, Burn D, Colosimo C, Fanciulli A, Ferreira J, Gasser T, Grandas F, Kanovsky F, Kostic V, Kulisewsky J, Oertel W, Poewe W, Reese JP, Relja M, Ruzicka E, Shapira A, Schrag A, Seppi K, Taba P, Vidalhet M. *EFNS/MDS-ES Recommendations for the diagnosis of Parkinson's Disease*. Eur J Neurol, 2013; 20 (1): 16-34.

7. Pellicano C, Benincasa D, Fanciulli A, Latino P, Giovannelli M, Pontieri FE. *The impact of extended release dopamine agonists on prescribing patterns for therapy of early Parkinson's disease: an observational study*. Eur J Med Res, 2013; 18 (1): 60.

8.2. Book and book chapters

1. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014.

2. Fanciulli A, Wenning GK (book chapter) *Chapter 1: Historical review*. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014, pp. 1-9.

3. Fanciulli A, Wenning GK (book chapter) *Chapter 6: Clinical presentation*. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014, pp. 97-119.

4. Fanciulli A, Wenning GK (book chapter) *Chapter 7: Clinical diagnostic criteria*. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014, pp: 121-132.

5. Fanciulli A, Wenning GK (book chapter) *Chapter 8: Natural hystory*. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, 2014, pp. 133-142.

6. Fanciulli A, Wenning GK (book chapter) *Chapter 10: Treatment*. Multiple System Atrophy, edited by Gregor K. Wenning & Alessandra Fanciulli. Springer Verlag, pp. 169-194.

7. Wenning GK, Fanciulli A. (book chapter) *Dysautonomia in Movement Disorders.* Movement Disorders in Neurologic & Systemic Disease, edited by W.Poewe and J. Jankovic. Cambridge University Press, 2014; (V) 24: 363-382.

8.3. Non peer-reviewed publications

1. Fanciulli A, Wenning GK. *Screening nächtlicher Hypertonie bei M. Parkinson und MSA: ein Algorithmus* (Screening of nocturnal hypertension in Parkinson's disease and multiple system atrophy: an algorithm). Neurologisch, 2014; 2: 64.

2. Fanciulli A, Wenning GK. *Verzögerte orthostatische Hypotonie bei Morbus Parkinson* (Delayed orthostatic hypotension in Parkinson's disease). Neurologisch, 2013; 4: 38-39.

3. Fanciulli A, Wenning GK. *Diagnose und Behandlung der nächtlichen und liegenden Hypertonie bei Parkinson-Syndromen* (Diagnosis and therapy of nocturnal and supine hypertension in parkinsonian syndromes). Neurologisch, 2013; 2: 132-133.

4. Fanciulli A, Pontieri FE, Wenning GK. *Kardiovaskuläres Risiko und Mortalität bei Synukleinopathien* (Cardiovascular risk and mortality in α-synucleinopathies). Neurologisch, 2012; 4: 96-99.

5. Fanciulli A, Krismer F, Wenning GK. *Klinik, Diagnostik und Therapie autonomer Störungen bei Morbus Parkinson und anderen Parkinson Syndromen* (Diagnosis and therapy of autonomic failure in Parkinson's disease and other parkinsonian syndromes). P-Aktuell, 2012; 4: 1-20.

9. Scientific awards

1. 2013 LIMPE “Giovani e Ricerca” Research Award for the best presentation of the project “*Supine Hypertension in Parkinson’s disease and multiple system atrophy*”.
2. 2013 Research Award of the Austrian Parkinson Society for the project “*Detecting nocturnal hypertension in Parkinson's disease and multiple system atrophy: proposal of a decision-support algorithm*”
3. 2013 International Parkinson’s disease and Movement Disorders Society Travel Grant for the project “*Cardiovascular autonomic failure in Parkinson’s disease with dementia”*

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