Head-up tilt sleeping in Parkinson disease and multiple system atrophy

Towards a better understanding and treatment of cardiovascular autonomic failure

Amber van der Stam

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Chapter 1

General introduction

Abbreviations

CO: Cardiac output
HR: Heart rate
HUTS: Head-up tilt sleeping
MAP: Mean arterial pressure
MSA: Multiple system atrophy
OH: Orthostatic hypotension
PD: Parkinson disease
SV: Stroke volume
TPR: Total peripheral resistance

Parkinson disease & atypical parkinsonism

Parkinson disease (PD, Box 1) was first described in 1817 [1,2], and is now the world's most rapidly growing neurodegenerative disorder [2,3]. While the cause of this disorder is still widely discussed, it appears to be resulting from a combination of exposure to environmental factors and an underlying genetic disposition. Our knowledge on the influence of, for example, pesticides on the risks of developing PD is rapidly developing [4]. Besides the relatively prevalent PD, there are several other rarer disorders with (at least initially) somewhat similar clinical phenotypes that are grouped under the term atypical parkinsonism. One important non-motor symptom of PD is autonomic failure, which is even more prominent in several forms of atypical parkinsonism (Lewy Body dementia and multiple system atrophy, MSA) [5,6]. Other forms of atypical parkinsonism, such as the tauopathies corticobasal degeneration and progressive supranuclear palsy, typically do not present with autonomic dysfunction [8]. In this thesis, I will focus my work on both PD and MSA (Box 2, Table 1.1).

Box 1: Parkinson Disease

Symptoms

The pathology of PD involves alpha-synuclein deposits across all parts of the nervous system, causing neurodegeneration which is most pronounced in the substantia nigra of the basal ganglia. It is primarily known as a movement disorder with asymmetric rigidity and bradykinesia as the main diagnostic criteria, and with in a proportion of affected individuals the characteristic tremor which gave it its original name: the Shaking Palsy [1]. In addition to the motor symptoms, many non-motor symptoms can occur, and these often have a severe impact on quality of life. These non-motor symptoms include (amongst others) pain, cognitive problems, sleep disturbances, and autonomic dysfunction [2,10].

Treatment and prognosis

There is currently no cure for PD, but there are treatments that can slow down progression. Clinical management is focused on alleviating symptoms. The time lived with the disease can vary significantly, and this depends in part on the dominant symptoms. Age at diagnosis is an important predictor for life expectancy; an earlier occurrence is associated with a larger reduction in life expectancy [9,12]. In general, the disease duration can span several decades, with the most common causes of death being pneumonia due to dysphagia and complications resulting from a fall [2,13,14].

Box 2: Multiple system atrophy

Pathology

PD, Lewy Body dementia and MSA classify as alpha-synucleinopathies. In PD the alpha-synuclein aggregates as Lewy bodies in the neurons themselves, but in MSA these deposits are primarily found in the oligodendrocytes [11]. The neurodegeneration is more widespread (noting that the distribution of the pathology depends in part on the subtype), which makes MSA a more heterogeneous disorder than PD. The alpha-synuclein deposits in MSA are also found in the central autonomic nervous system, resulting in more frequent and earlier occurrence of autonomic dysfunction [11].

Symptoms

In MSA, autonomic dysfunction is quite prevalent in the prodromal phase already. MSA and PD can actually be difficult to distinguish in the early stages of the disease, but for accurate counselling and optimal management (including prevention of specific complications) it is important to make the distinction on time. The core symptoms of MSA are urogenital or cardiovascular symptoms, parkinsonism defined as bradykinesia with either a tremor or rigidity, and/or cerebellar symptoms (ataxia, dysarthria, or oculomotor dysfunction). This provides a large variation in clinical phenotypes [15,16].

Table 1.1. Parkinson and multiple system atrophy: What is the difference?

	Parkinson disease	**Multiple system atrophy**
Prevalence	139 per 100 000 [3]	4 per 100 000 [7]
Life expectancy	7 years to several decades [2,9]	6-10 years [11]
Alpha-synuclein deposits	Lewy body inclusions [15]	Primarily in oligodendrocytes
Main symptom	Hypokinetic-rigid syndrome	Hypokinetic-rigid syndrome, combined with cerebellar ataxia, autonomic dysfunction, or both
Autonomic dysfunction	Common, but red flag when present early in the disease course. Postsynaptic origin and typically present only in later disease stages.	Prominent and early in the disease course. Presynaptic origin, and bladder function and blood pressure most affected.
Levodopa	Sustained and gratifying improvement; good tolerability	Limited (and short-lasting) to absent improvement; moderate to poor tolerability.

The autonomic nervous system

The anatomy of the autonomic nervous system

Besides all the obvious conscious choices we make throughout the day, there is also a part of the nervous system which is less noticeably present: the autonomic nervous system (Box 3). This autonomic nervous system is responsible for our body homeostasis, allowing for automated responses to changes that are either internal or come from our direct environment.

Box 3: The autonomic nervous system

The autonomic nervous system is subdivided into two parts, which, together, keep the balance: the sympathetic and parasympathetic nervous system. The parasympathetic nervous system promotes the bodily resting state, stimulating the gastrointestinal tract for example, while the sympathetic nervous system enables us to exercise and to respond to stress. It stimulates the sweat glands, amongst other things [17]. All vital organs are innervated by both arms of the autonomic nervous system, and the balance is maintained by simultaneous stimulation and inhibition.

The physiology of blood pressure

Blood pressure is one of the systems that is under autonomic control. The pressure within the system is directly modulated by changes in the cardiac output (CO) and the resistance produced by the vessels. The heart is responsible for the CO, which is the product of the heart rate (HR) and the stroke volume (SV): CO = HR * SV. The heart is innervated by both the sympathetic and parasympathetic branches[17]. The baroreceptors are critical links in this system. They are arterial stretch receptors with as the most prominent site the wall of the carotid sinus. The baroreceptors quickly respond to blood pressure changes and provide feedback via the brainstem. This then goes through both the sympathetic and parasympathetic nervous system, to the heart, blood vessels, and pituitary gland to respond to the change [18]. When the blood pressure increases, the arterial baroreflex is stretched and activated and via a negative feedback loop it then increases the activity of the parasympathetic nervous system, and inhibits the activity of the sympathetic nervous system. This feedback loop results in a net decrease in heart rate [18]. The opposite happens too: when the blood pressure decreases (for example due to the volume shift upon standing, Figure 1.1) the HR increases swiftly. The SV indicates the amount

of blood moved by each heartbeat. It is determined by the contractility of the heart, the preload and the afterload. This is heavily influenced by the HR, but also by the resistance of the system. The resistance is modulated by the contraction of the arterial blood vessels thereby changing the total peripheral resistance (TPR) of the system. Blood pressure itself is often expressed as mean arterial pressure (MAP), referring to the average pressure between the systole and the diastole. The following formula summarizes the influence of the different components on MAP:

$$MAP = SV * HR * TPR$$

This formula illustrates that all the factors are equally important, and that they are inherently connected, all affecting each other and the blood pressure.

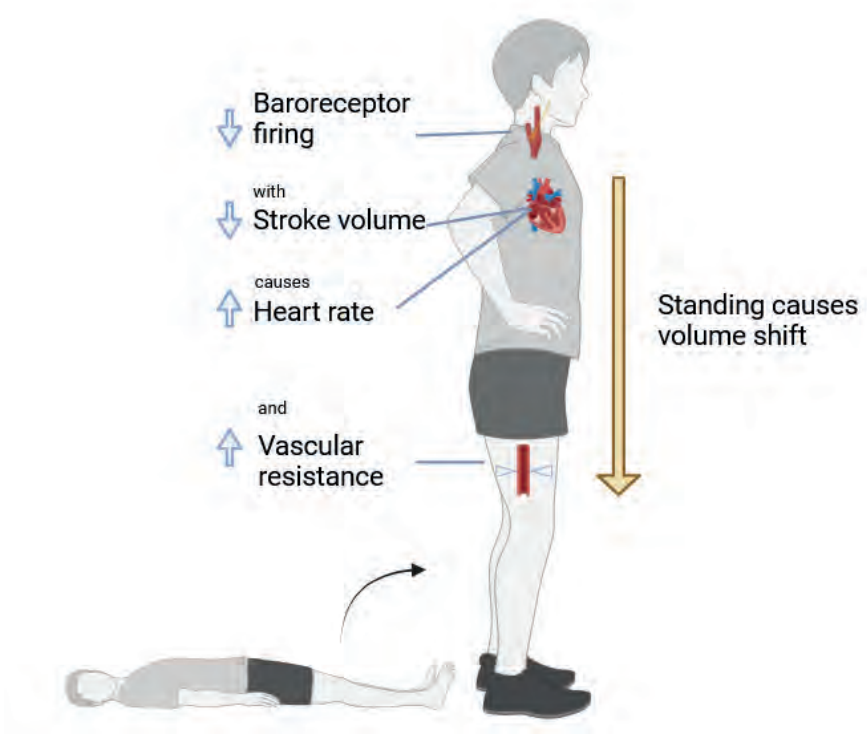

Figure 1.1. A schematic illustration of the response to standing in a healthy young individual. Upon standing, there is a volume shift towards the lower extremities, reducing the circulating volume. This reduces the blood pressure, which is measured by the baroreceptor, which in turn reduces its firing rate. Stroke volume is reduced due to a reduced preload, and the reduction in baroreceptor firing causes the heart rate to increase and vasculature to contract. Created in https://BioRender.com

In contrast to the heart, the vascular system is only innervated by sympathetic neurons [17]. When the baroreceptor is activated due to an increased blood pressure, the sympathetic nervous system is inhibited and the vascular resistance decreases. Upon reduced firing by the arterial baroreflex, the sympathetic response increases and the blood vessels contract, increasing the blood pressure through an increase in TPR. A secondary system by which the TPR is influenced is through hormones, for example vasopressin, of which the concentration is reduced upon activation of the baroreceptors, thereby also modulating vascular resistance [18]. Another hormone important for the regulation of blood pressure, specifically in the periphery, is norepinephrine. Norepinephrine is both a hormone, and the neurotransmitter used by sympathetic neurons. Norepinephrine causes vasoconstriction by directly binding to receptors on the smooth muscles. Levodopa is a medication often used by people with PD in combination with dopamine agonists, and to some extent also people with MSA. It is a precursor of norepinephrine and can influence blood pressure [19].

Autonomic failure

When dysfunction in the autonomic nervous system occurs, the ability to respond adequately to external situations is lost. This is called autonomic dysfunction, or autonomic failure. Autonomic failure is relatively rare, and is only present in a few neurological disorders, amongst which the alpha-synucleinopathies constitute the majority [20]. The origin of the autonomic failure lies in different anatomical locations for persons with different alpha-synucleinopathies. In Pure Autonomic Failure, the degeneration is purely in the periphery. In PD, the problem primarily lies with the peripheral neurons with sympathetic denervation occurring in several important organs. In MSA, the pre-ganglionic neurons degenerate, therefore the epicentre is located in the central nervous system [8]. Unlike in Pure Autonomic Failure, there can be mixed involvement in both PD and MSA [6,15,21]. One distinction that can be made between MSA and PD is that the concentration of norepinephrine in the blood plasma is reduced in those with peripheral autonomic denervation (including in those with PD), but remains relatively intact in people with central autonomic failure such as in MSA [21]. In people with PD, at least 30 to 40% of patients experience autonomic dysfunction, and the severity of the symptoms worsens as the disease progresses. On top of that, the presence of autonomic dysfunction itself is considered a risk factor for faster disease progression [22,23]. In MSA it is present in all patients, as it is one of the criteria for a clinically established diagnosis [16].

As the autonomic nervous system innervates many organs, a disbalance between parasympathetic and sympathetic innervation can produce a plethora of symptoms. Some examples of problems caused by failure of autonomic regulation

are urinary dysfunction with incontinence or urge problems, sexual dysfunction with for example erectile dysfunction in men, sweating disorders, dry eyes or mouth, obstipation (which is often one of the first occurring symptoms in PD) and not in the least cardiovascular symptoms [20,24]. In people with PD, an important component of autonomic failure encompasses predominantly sympathetic denervation of the heart, meaning the heart cannot increase its pumping rate as a response to a reduction in blood pressure, making a blunted heart rate response a common clinical phenomenon in this group. As described above, the source of the autonomic dysfunction lies more centrally in the nervous system for those with MSA. They often show a blunted heart rate response as well, but not as severely as those with PD since their typically have no or mild sympathetic denervation[25].

Cardiovascular autonomic dysfunction

Failure in cardiovascular autonomic control (Figure 1.2) can cause quickly changing blood pressures that are position dependent, resulting in limitations in mobility. The most common consequence of disturbed blood pressure control is orthostatic hypotension (OH). OH is defined as a systolic blood pressure reduction of more than 20 mmHg, or a diastolic reduction of more than 10 mmHg within three minutes of head up tilt or standing up from a supine position which can be measured in a clinical setting (Box 4) [26]. When standing up, even in healthy individuals, approximately 500ml of blood pools in the lower extremities. This reduces the circulating volume. In those with blood pressure regulation problems, this volume shift can not be compensated loss, therefore resulting in hypotension. OH is found in about 33% of all persons with PD, and up to 80% of persons with MSA. The real numbers are likely higher, because OH in PD can occur without symptoms [27] or with merely subtle signs that can only be noticed by bystanders, such as cognitive slowing or staring. These signs are easily mistaken as PD motor signs such as freezing [28]. For those who do experience symptoms, they can be relatively vague, such as ischemic pain in the shoulder region or fatigue. Regardless of the precise presentation, the consequences of OH can be severely incapacitating, such as dizziness, cognitive slowing, unexplained falls, and syncope [29]. Taken together, this often forces affected individuals to limit their mobility, which has many negative consequences in its own right.

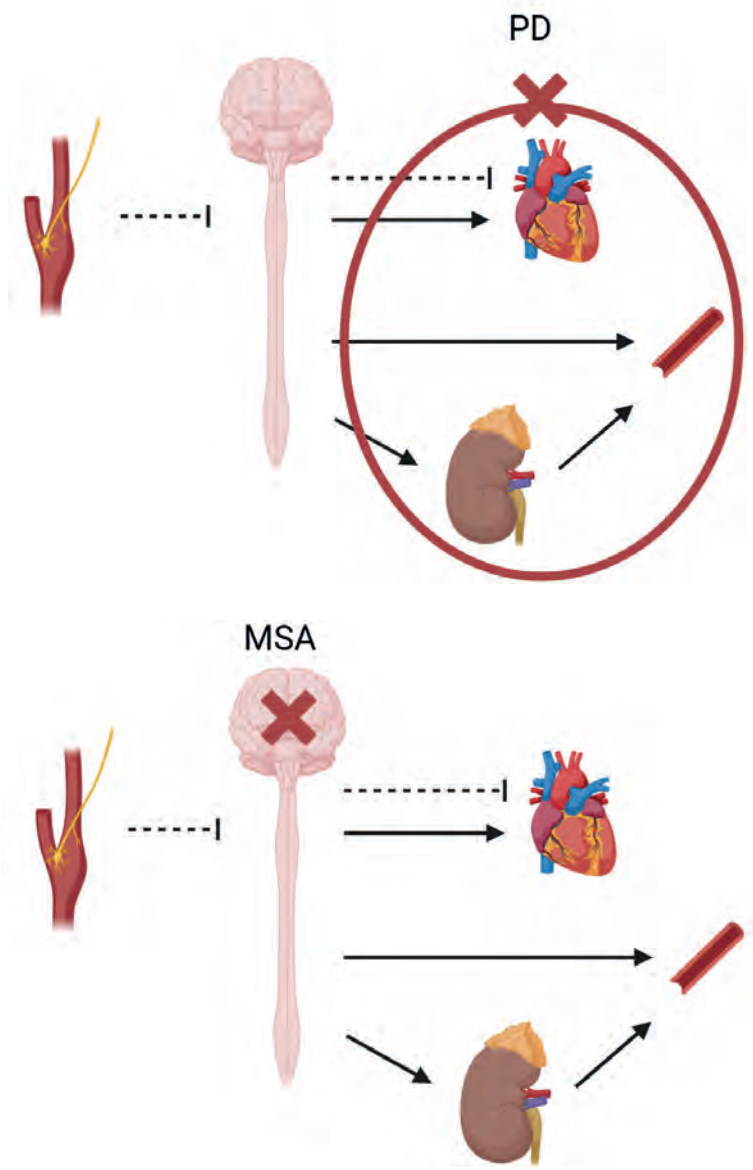

Figure 1.2. Cardiovascular autonomic dysfunction– simplified overview of what happens in two relatively common synucleinopathies causing autonomic failure in people with parkinsonism: Parkinson disease (PD) and multiple system atrophy (MSA). **A)** In PD the autonomic lesion is primarily postganglionic, causing peripheral denervation of effector organs. Most prominent is the predominantly sympathetic denervation of the heart, which can be visualized as an abnormal MIBG SPECT scan. **B)** In MSA the lesion is located centrally, thereby impacting baroreflex control. The MIBG SPECT scan will be normal in MSA. Created in https://BioRender.com.

OH often coincides with a reverse problem when lying down: supine hypertension. Supine hypertension is defined as a systolic blood pressure over 140 mmHg and/or diastolic blood pressure over 90 mmHg within 5 minutes of lying down [30]. Supine hypertension is seen in approximately half of all persons with PD & MSA presenting with OH [31,32]. It can persist during the night, causing a prolonged period with high blood pressure [32]. This can cause nocturia and thereby hypovolemia and increased symptoms of orthostatic intolerance [33,34], especially in the early morning [35].

Both OH and supine hypertension have been correlated to increased end-organ damage. OH independently has been correlated with cognitive impairment and white matter lesions in PD, cardiovascular issues and general mortality [36-40]. For hypertension the consequences are more widely known [31,40], with perhaps the most clear relation for supine hypertension during the night and cardiovascular events [41]. The fluctuations in blood pressure also increase the risk of cerebral, cardiac, and vascular issues [42].

In people with neurodegenerative disorders, OH and supine hypertension are explained primarily by baroreflex failure, but secondary factors such as medication and hypovolemia may play a role as well. In case of baroreflex failure, somewhere in either the central nervous system or in the peripheral nervous system innervating the heart and blood vessels there is a blockade not allowing this system to respond to the change in blood pressure [43]. The three factors HR, SV and TPR can then no longer compensate for each other. PD treatments such as dopaminergic medication (levodopa, dopamine agonists) may also worsen OH. Levodopa is an important factor in the production of norepinephrine and can disrupt the baroreflex. The proportion of levodopa that does not cross the blood-brain-barrier can cause a reduction in TPR, worsening orthostatic hypotension. Other concerns relate to cardiovascular drugs and even anti-inflammatory medication can cause an increase in blood pressure in those with autonomic dysfunction, and thereby worsen supine hypertension [44].

Box 4: Cardiovascular autonomic failure in the clinic

Diagnosis of cardiovascular autonomic failure is made with the help of several tests. It often starts with extensive history taking, followed by an active standing test using a blood pressure cuff. This may already be sufficient to identify OH and supine hypertension. If the bedside screening test is inconclusive and the clinical suspicion is high, a more detailed autonomic evaluation is needed. Additional autonomic function tests can help to demonstrate the presence and the classification of autonomic failure. This may encompass a tilt table test

that evaluates a passive orthostatic challenge [45], an active standing test with continuous blood pressure monitoring, 24-hour blood pressure monitoring, sympathetic and parasympathetic integrity through the Valsalva manoeuvre and parasympathetically mediated heart rate variability through deep breathing [6,20,46]. Additionally, measuring the catecholamine levels in a supine and upright position can help with distinguishing PD from MSA [21].

Treatment of blood pressure problems in PD and MSA

Treating OH is important, as it can prevent falls and fall-related injuries, and also lead to improvements in cognitive functioning and functional mobility in people with parkinsonism or PD [47]. In many cases the treatment of OH is prioritized over supine hypertension, due to the immediate incapacitating symptoms that can occur due to the first. Not taken into account here though, is the causal effect of supine hypertension on OH presumably through pressure natriuresis [34].

Treatment of cardiovascular autonomic dysfunction often proves to be a very complex hurdle that starts with deprescribing drugs that promote OH. The second step is lifestyle interventions. These non-pharmacological treatment options have as benefit that they can alleviate the symptoms of OH, without necessarily increasing the risk or severity of supine hypertension. Well known examples of this are increasing the fluid intake, adding more salt to the diet, avoiding big meals, and wearing compression abdominal belts [48]. The compression socks, however, show only limited improvement and are quite the hassle to put on, especially for those with limited mobility. One additional, promising but hitherto poorly studied, method for treating orthostatic intolerance is sleeping in the anti-Trendelenburg position (also referred to as head-up tilt sleeping (HUTS), Figure 1.3) [49,50]. This method sporadically has been studied in some small cohorts since the 1940's, and often in combination with supportive medication [51,52]. Currently, the optimal tilt angle and the optimal indications for using this method are therefore still unknown. In elderly persons with PD, HUTS is often disregarded as it is thought to disrupt sleep. The intervention is nevertheless attractive, as it has the potential to tackle both nocturnal supine hypertension and alleviate OH at the same time. The reason for this is that repeated nocturnal supine hypertension worsens OH because of damage to the kidneys, and by increasing pressure natriuresis which causes hypovolemia in the morning. This gives sleeping in the anti-Trendelenburg position a unique place in the therapeutic arsenal, as it is rare for interventions to treat both OH and supine hypertension. This is unlike the pharmacotherapeutic approaches such as treatment with the antihypertensive clonidine which still acts

Figure 1.3. A schematic depiction of full body head-up tilt sleeping, based on the study logo of the Heads-Up trial (chapter 4 and 5).

as a anti-pressor in the morning when the blood pressure should increase instead of decrease [53], or fludrocortisone and midodrine that are used to alleviate OH, but as a side effect can worsen supine hypertension. This makes medication only the third treatment option, as OH and supine hypertension are two opposite problems.

Both the hemodynamic responses to orthostatic problems and their treatment with head-up tilt sleeping are two areas that require more in dept research to further our understanding and increase efficacy of treatment. Understanding the underlying pathology and finding ways to treat these severely bothersome symptoms are therefore relevant for daily clinical practice. Taken together, the considerations above illustrate that the treatment of blood pressure problems in PD and MSA poses many challenges which require more knowledge on both the pathophysiology and clinical implications to optimize treatment and improve quality of life.

Aim and outline of this thesis

In this thesis I will:

1) Set apart the current evidence for the use of head up tilt sleeping (HUTS)

2) Study the effectiveness and tolerability of HUTS in Parkinson disease & multiple system atrophy

3) Evaluate the pathophysiology underlying supine hypertension in orthostatic hypotension

In *Chapter 2*, I will provide the current evidence on HUTS as a treatment option for symptoms of OH. In *Chapter 3* I discuss a patient seen in our outpatient clinic to illustrate the successful use of HUTS in a person with PD. In *Chapter 4* I discuss the design of the Heads-up trial and in *Chapter 5* its results. Finally, in *Chapter 6*, I review retrospective data from tilt table tests to attempt to determine the underlying pathophysiology of position-dependent failure in blood pressure regulation. In *Chapter 7* I bring all the previous chapters together to discuss how HUTS can be used in clinical practice, and dive into the possible working mechanism of HUTS in those with PD, MSA and cardiovascular autonomic failure.

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Part I

The context

Chapter 2

The impact of head-up tilt sleeping on orthostatic tolerance: a scoping review

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Simple Summary

Symptoms such as light-headedness and fainting upon standing can have a large negative impact on the quality of life, especially for people with orthostatic hypotension (blood pressure drop upon or during standing). One treatment option suggested in the clinic is head-up tilted sleeping (HUTS), where the full body is inclined. In this paper we reviewed the available evidence for the use of HUTS. We identified 10 studies focussing on HUTS as a treatment to improve orthostatic tolerance. Unfortunately, the overall evidence was weak, mainly because of the low number of included participants. We also noticed that the studied angles differed as well as the type of measurements to evaluate HUTS. Despite this, the anecdotal evidence suggested that HUTS therapy could slightly improve low standing blood pressure and its associated symptoms. The effects were more marked if higher angles were applied. These results provide some, although weak, evidence favouring HUTS, but the clinical relevance and the tolerability need to be studied further in larger-scale trials.

Abstract

To systematically summarize the evidence of head-up tilt sleeping (HUTS) on orthostatic tolerance, we conducted a systematic, predefined search in PubMed, OVID Embase, Cochrane, and Web of Science. We included studies assessing the effect of HUTS on orthostatic tolerance and other cardiovascular measures and rated the quality with the American Academy of Neurology risk of bias tool. We included 10 studies (n=185) in four groups: orthostatic hypotension (OH; 6 studies, n=103), vasovagal syncope (1 study, n=12), nocturnal angina pectoris (1 study, n=10) and healthy subjects (2 studies, n=58). HUTS duration varied (1 day - 4 months) with variable inclinations (5°-15°). In two of six OH studies HUTS significantly improved standing systolic blood pressure. Orthostatic tolerance was consistently enhanced in OH studies with higher angles (≥12°), in 2 out of 3 with smaller angles (5°) but also in one studying horizontal sleeping. In vasovagal syncope, HUTS significantly augmented resilience to extreme orthostatic stress. One study was rated class II risk of bias, one II/III and eight class IV. The evidence favouring HUTS to improve orthostatic tolerance is weak due to variable interventions, populations, small samples, and high risk of bias. Despite this, we found some physiological signs suggesting a beneficial effect.

Abbreviations
BP: Blood pressure
HUTS: Head-up tilt sleeping
OH: Orthostatic hypotension
RCT: Randomised controlled trial

Introduction

Orthostatic hypotension (OH) is an unusually large decrease in blood pressure (BP) upon standing and a very common physical sign, particularly among the elderly [1]. Causes can be neurogenic, e.g., synucleinopathies such as Parkinson disease, or non-neurogenic, e.g., drug-induced OH [2-4]. OH signifies the failure of compensational mechanisms (the fast baroreflex and the slower humoral activation) that are normally activated during sudden and prolonged orthostatic stress to maintain normotension against the effects of gravity while standing upright. OH has various clinical expressions, ranging from orthostatic intolerance (i.e., symptoms of presyncope while upright that are relieved when sitting or lying down) to unexplained falls and syncope [4,5]. As such, OH represents a significant clinical problem, as it is often associated with great disability and it may lead to debilitation and costly complications such as fall-related fractures or other injuries.

OH management primary consists of lifestyle advises such as standing with the legs crossed or increasing salt and water intake [4]. Pharmacological options are available for selected individuals, yet carry an important disadvantage as the BP increases, regardless of the body position. This is especially problematic in people with OH and an accompanying supine hypertension, which typically contributes to the long-term risk of adverse cardiovascular events in OH [6]. Sleeping in a head-up tilt position (HUTS) is a non-pharmacological intervention that not only alleviates symptomatic OH, but additionally does not worsen (and perhaps even improve) supine hypertension [7,8].

Although theoretically very attractive, the concept of HUTS is thus far merely based on several small-scale cohort studies and expert opinion [9]. Despite this lack of rigorous evidence, HUTS has been proposed as an effective and even first choice non-pharmacological treatment for OH for over three decades, for example in international guidelines [10-12]. It is, however, often not recommended by clinicians in daily practice because of a lack of evidence on its effectiveness, the presumed poor tolerability by patients, and lack of concrete advice on how to implement this intervention.

With this scoping review, we aimed to systematically identify and summarize all relevant literature on the effect of HUTS on cardiovascular function, to improve our understanding of the mechanisms of action underlying HUTS, and to identify knowledge gaps that may guide future research.

Methods

Search Strategy and Selection Criteria

We used the scoping review method to identify and summarize all relevant literature [13,14]. We followed the 2018 preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews while preparing the study protocol and study report [15]. We conducted a systematic search of PubMed, OVID Embase, Cochrane and Web of Science on January 12th 2023, using a combination of MeSH/EMTREE terms and key words (Supplementary Table 2.1).

We included (all criteria had to be met):

1) studies of people with or without autonomic dysfunction
2) studies of people aged ≥6 years
3) articles assessing the effect of full-body head-up tilt sleeping of any angle
4) articles with outcome measures related to cardiovascular control (e.g., orthostatic tolerance, BP, weight, oedema and nycturia)

We excluded:

1) studies simultaneously evaluating HUTS with another pharmacological treatments for OH, including salt loading
2) the following article types: case reports, narrative reviews, expert opinions, editorials, design studies and systematic reviews

We did not exclude studies based on publication language, but arranged for translation. If multiple articles were based on the same study data, we included the most complete report not to overrepresent the data. We included articles with any number of participants and of any quality or study design. We used Rayyan to screen the records (rayyan.ai/). We manually searched the bibliographies of all included studies for potentially relevant studies. We also checked the bibliography of all excluded systematic reviews.

Study Selection on Data Extraction

Two reviewers (S.S. and A.S.) independently screened all titles and abstracts identified by the initial search. Next, we obtained the full texts of any article deemed possibly relevant by either reviewer These full texts were then independently evaluated by two reviewers (R.D.T. with S.S. or A.S.) to decide whether the study was to be included. Disagreements were settled by consensus.

One reviewer (S.S.) extracted the data from each study using a form specifically designed for this review, including author(s), year of publication, study type, source population, sample characteristics (i.e., age, sex and cardiovascular medication), HUTS characteristics (e.g., angle(s), duration), OH definition, details of OH assessment (e.g., time of day, salt and fluid intake), and all cardiovascular outcome measures.

The relevant outcome measures to evaluate the impact of HUTS depend on the studied population. In people with OH a beneficial effect of HUTS would translate to an amelioration of orthostatic tolerance, a higher standing BP and lower orthostatic BP drop. In those with OH combined with supine hypertension we would also expect a lower supine BP. The aetiology of OH may also be relevant when evaluating HUTS as the mechanisms differ and disease courses may vary. Healthy people or cases with vasovagal syncope (i.e., a form of reflex syncope due to a specific set of emotional or orthostatic triggers) [5] have well-functioning compensatory mechanisms to maintain normotension in normal conditions. Therefore, little to no change on BP due to HUTS is expected. These subjects may, however, experience improved orthostatic tolerance for extreme orthostatic stress (i.e., longer time to syncope) or a reduction of the physiological BP perturbations in the first 30 seconds of active standing [4]. We therefore evaluated various BP parameters and selected the relevant ones depending on the study population.

Applied Methods

We selected a total of 16 study parameters for assessing the methodological quality of HUTS studies. Eight of these items were applicable to all studies i.e., reporting of duration, angle, tolerance and compliance of HUTS, quantitative evaluation of orthostatic symptoms, nocturia volume and overnight body weight change. Six parameters related to the circumstances of orthostatic BP measurements, i.e., sufficient duration of supine rest ≥5 min and standing time ≥3 min, report of similar time of day of measurements, hydration, and fasting state and before or after drug administration. Two of these were applicable to OH populations only, namely aetiology (neurogenic vs. non-neurogenic OH) and the presence of supine

hypertension (defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg after ≥5 min of supine rest) [16]. We counted the proportion of reported applicable parameters for each study.

Risk of Bias

We rated the risk of bias of each included article using the American Academy of Neurology (AAN) risk of bias class of evidence scheme for therapeutic studies, also known as the level of evidence [17]. In this scheme, studies rated Class I are judged to have a low risk of bias; Class II, a moderate risk of bias; Class III, a moderately high risk of bias; and Class IV, a very high risk of bias. Two reviewers (S.S. and A.S.) independently assessed the risk of bias of each study. Disagreements were settled by consensus.

Data Analysis

Descriptive statistics were used to present the results. To illustrate the effect size of HUTS on the orthostatic systolic BP values (supine, standing and BP change upon standing) in patients with OH, we calculated the mean, SE, and 95%-confidence intervals of the difference between the post- vs. pre-HUTS values and created a forest plot. We were unable to perform a formal meta-analysis due to the heterogeneous interventions (e.g., HUTS angle or duration), populations and outcomes.

Results

Selection of Sources

We identified 773 studies with our initial search (Figure 2.1). We excluded 739 studies after screening the titles and abstracts and assessed 29 reports for eligibility. Of these, we included six articles [18-23] and two meeting abstracts [24,25]. After reviewing the references of the included studies, we included two additional articles [26,27].

Study Protocols and Populations

Characteristics of the 10 included articles assessing the effect of HUTS on cardiovascular control are shown in Table 2.1. A total of 185 people underwent HUTS at different angles and with different durations. Study types were prospective cohort studies (n=6), case series (n=2), a cross-over trial (n=1) and a randomised controlled trial (n=1). Studied populations included OH (n=6; a total of 103 cases undergoing HUTS and 34 OH cases in a placebo group), vasovagal syncope (n=1; 12 cases), healthy people (n=2; 58 cases) and people with angina pectoris (n=1; 10 cases). Five out of six OH studies provided some clinical details to at least

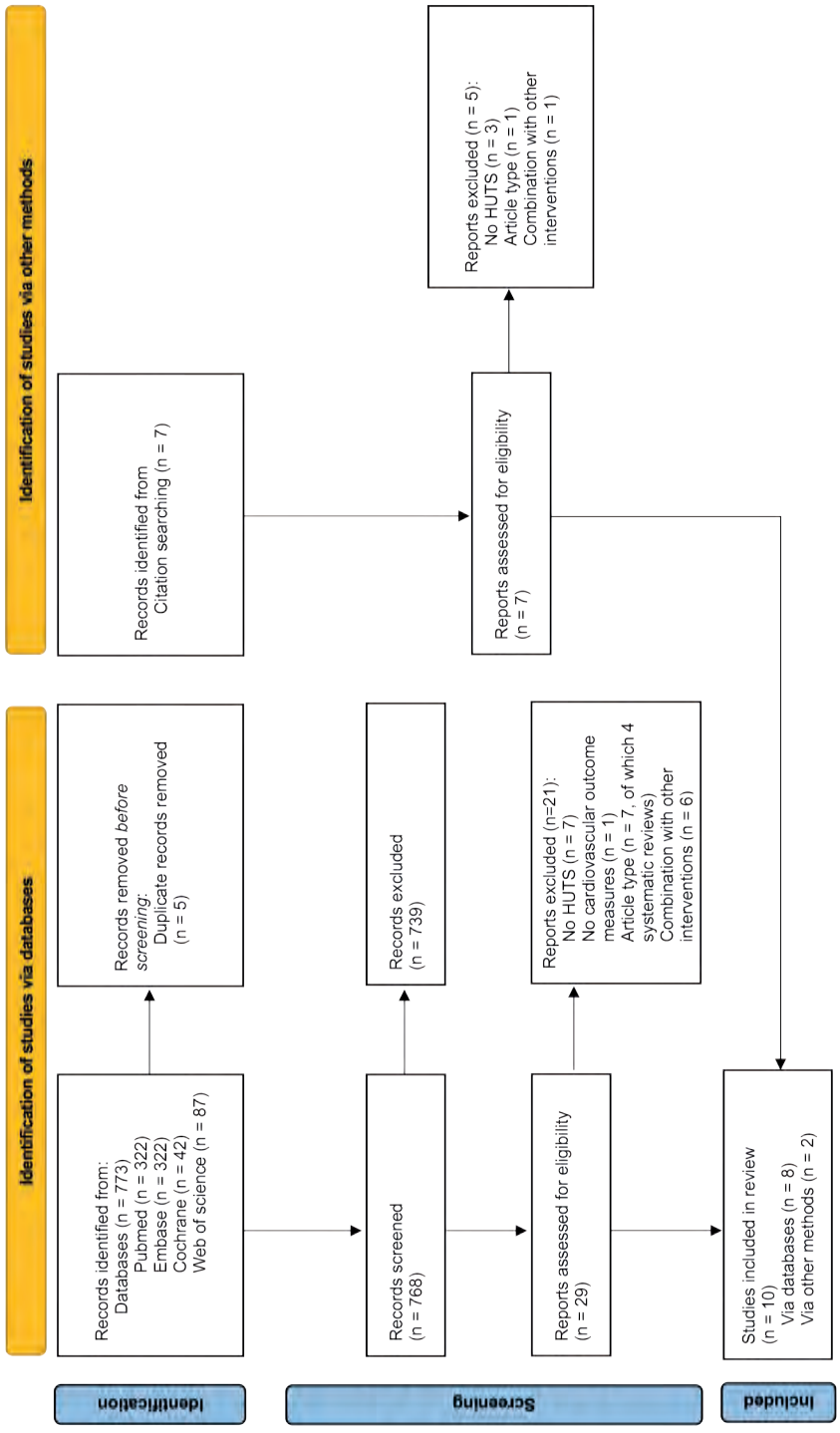

Figure 2.1. PRISMA Flow Diagram. HUTS = head-up tilt sleeping; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses [28].

Table 2.1. Characteristics of all included studies (n = 10) studying the impact of head-up tilt sleeping (HUTS) on the cardiovascular control. Sorted by population and angle.

First author and year	Study type	Population	Cases n	Age (y; mean (SD))	Femalen (%)	HUTS angle (°)
Fan et al. 2009	Prospective cohort	Elderly with symptomatic OH of all causes	9	76 (5)	5 (55)	5
Fan et al. 2011	Randomised controlled trial	Elderly with symptomatic OH of all causes	100 - HUTS 66 - contr. 34	(Median, IQR) 76 (71, 80) 76 (72, 83)	37 (56) 19 (56)	5
Prasertpan et al. 2022[a]	Prospective cohort	nOH in PD	18	69 (5.6)	11 (61)	6
Ten Harkel et al.1992	Prospective cohort	nOH	4[b]	23; 44; 59; 65	3 (50)	12
MacLean et al.1944	Case series	Non-nOH	2	35; 57	0 (0)	12
MacLean and Allen 1940	Case series	nOH and non-nOH	4	59; 30; 34; 47	2 (50)	13
Cooper and Hainsworth 2008	Prospective cohort	VVS and poor orthostatic tolerance	12	42 (5)	6 (50)	10
Fan et al. 2008	Prospective cohort	Healthy college students	29	22 (1.9)	16 (55)	13
Pham et al. 2019[a]	Cross-over	Healthy Peruvian highlanders	29	62.3 (8.9)	11 (38)	15
Mohr et al. 1982	Prospective cohort	Refractory nocturnal angina	10	56,4 (4,8)	2 (20)	10

[a] Meeting abstract.

[b] Six cases were studied; yet in only four cases HUTS was the sole intervention; in the other two HUTS was combined with fludrocortisone.

[c] We searched the articles for further details of OH assessment including time of day, prior to assuming sitting position, fasting state, salt intake, before/after drug administration, hydration state and exercise.

[d] As calculated using the American Academy of Neurology risk of bias tool [17].

HUTS duration	Collected data	Method orthostatic BP measurement	Details of OH assessment[c]	Risk of bias class[d]
1w	Orth. symptoms, orth. BP, ABPM, weight, lab	Active standing, beat-to-beat BP (Finapres). Supine 5m; stand 120s.	NR	IV
6w	Orth. symptoms, orth. BP, ABPM, weight, urine volume and Na, oedema	Active standing, beat-to-beat BP (Finapres). Supine 5m; stand 120s.	Both HUTS and non-HUTS group increased water intake to 2L a day.	II
1d	Orth. BP, ABPM	NR	Morning immediately after awaking.	IV
1w FU 8-70m	Orth. symptoms, orth. BP, weight, urine K/Na/Creatinine	Active standing, beat-to-beat BP (Finapres). Supine 20m; stand max 10m or until symptoms.	At 08.00 hours after an overnight fast. High salt intake of 150-200 mmol Na+/d and water intake of ≥2L started 1w before HUTS.	IV
4d FU 3-6m	Orth. symptoms, orth. BP, oedema, plasma volume, lab	Active standing. Supine before arising; stand various 1-25m.	Before arising in the morning after overnight fast. Intake of water was controlled (not specified).	IV
2-4d FU (n=3) 2-6m	Orth. symptoms, syncope, orth. BP, oedema, plasma volume, lab, sweating	Active standing. Supine duration NR; stand 1-60m or duration NR.	NR	IV
3-4m	Orth. symptoms, syncope, orth. BP, plasma volume	Orthostatic stress test: supine 20m; tilt 60° for 20m; lower body negative pressure until pre-syncope.	NR	IV
1w	Orth. symptoms, orth. BP, ABPM, oedema, weight, urine volume and Na, lab	Active standing, beat-to-beat BP (Finapres). Supine 5-10m; stand 2m.	Morning 9:00 - 11:00. Water intake of ≥2L started 1w before HUTS.	IV
1d	Sleep, respiratory variables, heart rate	NA	NA	II or III[f]
2d	Aortic pressure, central venous pressure, pulmonary artery pressure	NA	NA	IV

[f] Meeting abstract contains insufficient information to classify.

ABPM = ambulatory blood pressure measurement; BP = blood pressure; DM = diabetes mellitus; FU = follow-up; HUTS = head-up tilt sleeping; IHD = ischemic heart disease; NA = not applicable; NL = the Netherlands; NR = not reported; (n)OH = (neurogenic) orthostatic hypotension; OT = orthostatic tolerance; PAF = pure autonomic failure; PD = Parkinson disease; TTT = tilt-table test; UK = United Kingdom; USA = United States of America.

Table 2.2. Score of study parameters for assessing the methodological quality of HUTS studies for each of the included studies. NA = not applicable; (n)OH = (neurogenic) orthostatic hypotension; SH = supine hypertension. Red (🔴) indicates the parameter was absent, green (🟢) indicates the described parameter was available in the study.

	Fan et al. 2009	Fan et al. 2011	Prasertpan et al. 2022	Ten Harkel et al. 1992	McLean et al. 1944	McLean and Allen 1940
OH populations						
Report of OH aetiology	🟢	🔴	🟢	🟢	🟢	🟢
Presence of SH mentioned	🔴	🔴	🔴	🔴	🟢	🔴
Orthostatic BP protocol						
Supine rest ≥5m	🟢	🟢	🔴	🟢	🟢	🔴
Standing ≥3m	🔴	🔴	🔴	🟢	🔴	🔴
Constant time of day	🔴	🔴	🟢	🟢	🟢	🔴
Accounting for hydration state	🔴	🟢	🔴	🟢	🟢	🔴
Accounting for fasting state	🔴	🔴	🔴	🟢	🟢	🔴
Before/after drug administration	🔴	🔴	🔴	🔴	🔴	🔴
HUTS reporting						
HUTS duration	🟢	🟢	🟢	🟢	🟢	🟢
HUTS angle	🟢	🟢	🟢	🟢	🟢	🟢
HUTS tolerance	🟢	🔴	🔴	🟢	🟢	🟢
HUTS compliance	🔴	🟢	🔴	🔴	🔴	🔴
Quantitative symptom evaluation	🔴	🟢	🔴	🟢	🔴	🔴
Nocturia: urine volume	🔴	🔴	🔴	🔴	🔴	🔴
Overnight Δ body weight	🔴	🔴	🔴	🟢	🔴	🔴
Sleep quality	🔴	🔴	🔴	🔴	🔴	🔴
Total score (n)	5	7	4	11	9	4
Total score (%)	31	43	25	68	56	25

	Cooper and Hainsworth 2008	Fan et al. 2008	Pham et al. 2019	Mohr et al. 1982	Total score (n)	Total score (%)
	NA	NA	NA	NA	5	83
	NA	NA	NA	NA	1	17
	●	●	NA	NA	6	75
	●		NA	NA	2	25
	●	●	NA	NA	4	50
	●	●	NA	NA	4	50
	●	●	NA	NA	2	25
	●	●	NA	NA	0	0
	●	●	●	●	10	100
	●	●	●	●	10	100
	●	●	●	●	6	60
	●	●	●	●	1	10
	●	●	●	●	2	20
	●	●	●	●	2	20
	●	●	●	●	1	10
	●	●	●	●	1	10
	4	7	4	2		
	28	50	50	25		

partially differentiate between neurogenic and non-neurogenic OH. The authors of [24] specifically targeted a population with Parkinson disease and OH. The one RCT did not provide information on the aetiology [23].

Methodological Quality

Table 2.2 shows the score of study parameters for assessing the methodological quality of HUTS studies for each of the included studies. Six OH studies could score a maximum of 16 points, two non-OH studies measuring orthostatic BP could score a maximum of 14 points and two non-OH studies that did not perform orthostatic BP measurements could score a maximum of eight points. The median score of the 10 included studies is 37%, ranging from 25% to a maximum of 68%.

HUTS Implementation

Five of 10 studies applied HUTS at home [20,21,23-25], two in the hospital [18,22] and three started in the hospital and had a follow-up at home [19,26,27]. HUTS implementation varied among studies with variable tilting angles (median = 6° (5° to 15°)) as well various durations (median = 7 days (1 day to 6 months)) (Figure 2.2). There was one randomized controlled trial, which compared 5° HUTS (n=66) versus no HUTS (n=34) in a total of 100 people with symptomatic OH [23].

Several different HUTS application methods were used. Some used blocks or chairs underneath the head of the bed (n=3) [21,23,27], some used wedge matrasses (n=1) [25], or an adjustable hospital bed (n=1) [18], one study had HUTS implemented at home by an engineer (n=1) [20], and one used home built tools (n=1) [19]. Three studies did not specify the method [22,24,26].

Figure 2.2. Illustration of the different angles of HUTS applied in the included studies. The number of cases subjected to the specific angles are indicated.

A pillow underneath the matrass at the hight of the thighs is the most commonly deployed preventative method to keep patients from sliding down (n=3) [19,22,27]; two studies reported the use of a footboard with optional pillows to prevent foot pain (n=2) [19,22] and one study mentioned the use of a sleeping bag attached to the headboard of the bed (n=1) [19]. The remaining 7 studies did not mention the use of any precautions.

Orthostatic Hypotension Definition

Only two of the six studies of OH populations specified the definition of OH. Fan and colleagues (2009 and 2011) utilized the 1996 consensus statement of the American Autonomic Society and the American Academy of Neurology (i.e., systolic BP decrease of ≥20 mmHg, or a diastolic BP decrease of ≥10 mmHg, within 3 min after changing from a supine to standing position) [29]. This definition matches the 2011 consensus statement, which adds that supine rest before head-up tilt or standing up should be last at least 5 min and that in patients with supine hypertension, a decrease in systolic BP of ≥ 30 mmHg is required [30]. The two studies of Fan and colleagues did not report baseline supine BP values and therefore it is unknown whether any of the cases had supine hypertension. The other four studies did not define OH [19,24,26,27]. When studying the data of these four studies, however, it seems that three cases do comply with the abovementioned 1996 consensus statement. Only for one study, this is not completely certain as only the mean values are provided for supine BP as well as for the BP drop at baseline (orthostatic drop systolic BP 27±20 mmHg; diastolic BP 16±15 mmHg); (mean morning systolic BP 101±25 mmHg; diastolic BP 67±17 mmHg) [24].

Tolerance

Tolerance was reported in six of 10 studies. HUTS was tolerated well by all nine patients in one of the low angle studies (5°) [22]. The other five studies reporting on tolerance did not quantify this parameter. During HUTS of 12-13°, problems with tolerance were noted, with the most common complaints being sliding down [19,21] or stiff legs from leg oedema [21,26,27]. The study that used the steeper angle of 15° for one night noted that it was well tolerated in this healthy population, which was supported by an unchanged sleep time pre- vs. post-HUTS (380±14 min vs. 375±15 min) as scored automatically by a clinically validated home sleep test [25].

Compliance

Only one of five completely home based studies evaluated compliance, reporting a self-reported compliance of 77% (HUTS 5° for six weeks) [23]. Three studies did not

investigate compliance yet reported a long-term home-based follow-up of HUTS (n=9, 2-70 months) which may serve here as an indirect marker [19 26,27].

Main Findings

Orthostatic Blood Pressure

Eight studies conducted orthostatic BP measurements of OH (n=6), vasovagal syncope (n=1) and healthy populations (n=1). The methods used and details of the assessments are given in Table 2.1. We summarised the effect of HUTS on orthostatic systolic BP in the six OH studies (Figure 2.3). We could calculate mean difference pre- vs. post-HUTS and confidence intervals of standing systolic BP in five studies and systolic BP difference upon standing in four studies. Only few studies reported a significant difference following HUTS. Although all mean effect sizes were favouring of HUTS, in the RCT the mean increase in standing systolic BP following HUTS with a low HUTS angle (5°) did not significantly differ from horizontal sleeping [23].

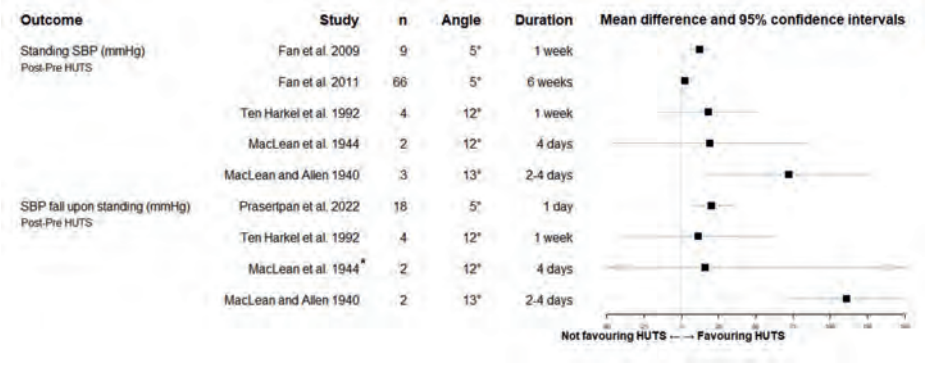

Figure 2.3. Forest plot showing mean differences and 95% confidence intervals of orthostatic systolic blood pressure (SBP) values (i.e., standing and change upon standing) between after and before head-up tilt sleeping intervention (HUTS) in studies with orthostatic hypotension (n=6; 102 cases). Favouring HUTS (towards the right) is a higher standing BP and smaller drop post-HUTS shown as the increase in the SBP change. Many of the included studies had a very limited sample size, resulting in unreliable estimations of the mean and confidence interval and a high likelihood of type II errors. In the case series we only calculated the mean difference if we had access to the data of at least two cases [26,27]. * Values corresponding to this study: 95% CI -130 to 162 mmHg. SBP = Systolic blood pressure; HUTS = Head up tilted sleeping.

In the vasovagal syncope population, the resilience to prolonged tilting with additional graded lower body negative pressure improved after three to four

months of HUTS at an angle of 10°. In 11/12 cases (92%) time to pre-syncope improved (mean increase of 7.8 ± 1.6 min; after) [20]. In the healthy population the mean Δ systolic BP drop after 10s of active standing reduced following HUTS without impacting the nadir systolic BP at two minutes [21].

Orthostatic Symptoms and Syncope

Orthostatic symptoms were reported in five of the OH studies. In three OH studies, all cases (total n=10) reported an amelioration of orthostatic symptoms (HUTS angles 12-13°) [19,26,27], one study reported improved symptoms in six of nine individuals (HUTS angle 5°) [22], and the last study (RCT) reported a significant improvement of symptoms of dizziness per week in the HUTS (5°) (n=66, p=0.0039) but this was also significant in the non-HUTS group (n=34, p=0.0013) and there was no difference between the groups (p=0.27) [23]. During long-term follow-up of 2-4 months, three out of four cases reported that no more syncope had occurred [26]. Two of these cases discontinued HUTS for a short period to investigate whether HUTS truly reduced the symptoms. In both cases, orthostatic intolerance returned supported by worsening of the orthostatic blood pressure and the return of symptoms within two days [26,27].

Among the 12 subjects with vasovagal syncope, 11 cases (92%) reported a reduction in presyncope following HUTS [20]. In the 29 healthy subjects, HUTS significantly lowered the incidence of light-headedness during an active standing test (from 93.1% to 41.4%) [21].

Other Blood Pressure Data

Three OH studies [22-24] and one study on healthy subjects [21] conducted 24h ABPM and found no significant change in mean overall, day or night time BP before and during HUTS (5-6°). None of these studies reported the presence of supine hypertension.

The study on nocturnal angina reported a significant decrease in central venous pressure and diastolic pulmonary artery pressure during whole body HUTS (10°) compared to the control night (only head-up) [18].

Other Variables

One of the mechanisms through which HUTS may ameliorate BP control is the increase in volume and a redistribution of body fluids. Three studies monitored plasma volume, all reporting an increase after HUTS (Table 2.3). One study showed that the blood volume increased after 3 to 4 months of HUTS, in six of eight cases with vasovagal syncope (average 3.18 l/kg to 3.40 l/kg). This increase correlated with the

prolonged time till syncope after tilt and lower body negative pressure application. The two cases with vasovagal syncope without increased plasma volume showed no or only a very limited increase in orthostatic tolerance [20]. Two OH studies measured the blood volume measured in two cases: both had a higher blood volume following HUTS (increase of 0.6 litres in one [27]; 6 cc/ kg in another [26]).

Five out of the 10 included studies monitored changes in body weight following HUTS (Table 2.3), one overnight weight loss and three urinary output. A total weight gain could indicate better fluid retention but can be explained by many other factors. The overnight weight is a more specific marker reflecting the amount of fluid lost over-night, with larger fluid depletion thought to increase the severity of OH in the morning. Overall, within the OH and healthy population, HUTS resulted in either an increase in weight [21,27] or did not influence weight [22,23]. One OH study using 12° HUTS showed that the average weight lost during the night did not change, even though total weight did increase [19]. In three studies the urine output (volume status and concentration) (Table 2.3) was evaluated; in all studies participants were required to have an intake of at least 2 litres of fluid during the day. Two of the studies focussing on an OH patient group split the urine collection into a day and night sample. One study found a non-significant increase in the day/ night ratio of sodium excretion, reflecting a lower excretion at night [19]. Urinary volume was only discussed in one other OH population where the night-time volume was significantly reduced by 145 mL after 6 days of HUTS [21]. The daytime volume did not change, and neither did night nor day-time sodium excretion [21]. None of the studies had nocturia as an outcome measure.

Water retention and the more upright position may lead to ankle oedema, and this was measured in four studies: three with OH and one with a healthy population (Table 2.3). One study measured ankle circumference both before and after HUTS in a healthy population and reported an increase in ankle circumference of 8 mm following 6 days of 12° HUTS [21]. The other studies encompassed two case studies where the individuals had slight pitting oedema after 3 and 4 days of HUTS [26,27]. A study in the OH population reported an increase in oedema to 41% in the HUTS group, compared to 19% in the non-HUTS group but did not specify the applied method [23]. Additionally, blood laboratory analysis were performed in four studies with varying outcome measures (Table 2.3).

Table 2.3. Other variables noted in the publications (n=8). * Indicates significant change.

Variable	First author and year	Population (n)	Method	Outcome
Plasma volume, pre and post HUTS	Cooper and Hainsworth 2008 MacLean et al. 1944 MacLean and Allen 1940	VVS (8) OH (1) OH (1)	Evans blue dye dilution method, 8 out of 12 cases Unknown method, in 1 case Congo red method, in 1 case	3.18 to 3.40 L/kg * 38.6 to 43.0 c.c./kg 45 to 51 c.c./kg
Body weight, pre and post HUTS	Ten Harkel et al. 1992 Fan et al. 2009 Fan et al. 2011 MacLean et al. 1944 Fan et al. 2008	OH (4) OH (9) OH (100) OH (1) Healthy (29)	Measured post-voiding at 22:00 and 8:00 Unknown method Unknown method, controls compared to HUTS group Day before and after 3 days of HUTS, in 1 case Measured post-voiding at 8:00	Morning weight:0.5 kg increase * Evening-morning difference: no change 70.0 to 70.7 kg No change 86.2 to 87.1 kg 66.1 to 66.5 kg *
Urine, Pre and post HUTS	Fan et al. 2008 Fan et al. 2011 Ten Harkel et al. 1992	Healthy (29) OH (100) OH (4)	Volume and sodium excretion 24-hour volume and sodium excretion Creatinine, sodium, and potassium as day/night ratio	Night-time volume: 622 to 477 mL * Day-time volume: 1510 to 1562 mL Sodium excretion: 373 to 382 mmol Volume and sodium excretion: No change Creatinine and Potassium, no change. Sodium: 0.63 to 0.81
Oedema	Fan et al., 2008 Fan et al., 2011 MacLean et al. 1944 MacLean and Allen 1940	Healthy (29) OH (100) OH (1) OH (1)	Measured calf and ankle circumference pre- and post-HUTS Unknown method Observation, 1 case Observation, 1 case	Ankle: 255 to 263 mm * Calf: 371 to 373 mm HUTS: 41%, controls: 19% * “slight pitting oedema” “slight oedema of the lower extremities”
Laboratory blood values Pre and Post HUTS	Fan et al. 2009 Fan et al. 2008 MacLean et al. 1944 MacLean and Allen 1940	OH (9) Healthy (29) OH (1) OH (4)	Haematocrit, plasma renin, electrolyte, aldosterone, creatinine Supine haematocrit, plasma renin, electrolytes, aldosterone, pro-ANP Haematocrit, chloride, protein Haematocrit, haemoglobin, and erythrocyte count	Creatinine: 101 to 95.6 mmol/L * All others: no change Haemoglobin 13.6 to 13.3 g/dL * All others: no change Haematocrit: 35.5% to 34.8% Chloride: 99.3 to 103.8 mEq/L Protein: 6.40 to 6.45 Gm/cL Haematocrit: 36% to 34% Haemoglobin: 8.5 to 8.1 Gm/cL Erythrocytes: 3.3 to 4.1 x10^6 per mL

Table 2.3. Continued

Variable	First author and year	Population (n)	Method	Outcome
Respiratory	Pham et al. 2019	Healthy (11)	Hypoxia burden during HUTS compared to flat sleeping	SpO_2: 83.6% to 85.5% * RDI: 21.5 to 17.8/hr *
Sleep	Pham et al. 2019	Healthy (11)	Total monitored sleep time, during HUTS compared to flat sleeping	Sleep time: 380 to 375 min

OH = Orthostatic hypotension; HUTS = Head up tilted sleeping; SpO2 = nocturnal oxyhaemoglobin saturation; RDI = respiratory disturbance index.

Discussion

This systematic scoping review of the impact of HUTS on orthostatic tolerance identified a small number of studies, collectively showing weak but consistent evidence of a potential positive effect of this non-pharmacological intervention. The 10 included studies were mostly cohort studies with small sample sizes, with a high risk is bias and included heterogenous study populations, a variable HUTS implementation (i.e., angles and duration) and a range of OH assessment methods. The overall methodological quality score, based on a total of 16 parameters including compliance and tolerance of HUTS, was very low.

Summary of Evidence

Our primary interest was the effect of HUTS on orthostatic blood pressure in populations with OH. Most studies failed to categorise the OH type. It is likely, however, that those with neurogenic OH will profit most from HUTS as OH in this population is severe and mostly coincides with supine hypertension. Although there appeared to be a fairly consistent trend towards BP effects favouring HUTS in the diverse OH populations, most results did not reach significance, possibly due to the small sample sizes. The impact of HUTS on OH was more pronounced for those OH cases subjected to higher vs. lower HUTS angles, but the number of studied cases with high HUTS angles was lower, thus causing wider confidence intervals. We observed that the protocol for measuring OH varied greatly among the studies, which may have also impacted the analysis of the efficacy of HUTS. Often only rather short periods of standing (<2 min) were applied to evaluate immediate OH, which may have hampered the identification of more long-term BP changes that are equally relevant in daily life. The circumstances of most OH measurements were not ideal as well. Most studies did not specify the time of day the orthostatic BP

measurements were done and whether the time was kept constant in both pre- and post-HUTS evaluation.

All persons with OH that were treated with high angles of HUTS and most persons treated with smaller HUTS angles reported less orthostatic symptoms. The placebo group of the one RCT, however, also reported significantly improved orthostatic symptoms, and this improvement did not differ from the HUTS group [23]. We speculate that, apart from the expectation effect, the natural course (over the 6 weeks treatment interval) may have explained the improvement as some forms of OH (particularly non-neurogenic OH) may be self-limiting. Another possible explanation for the improvement in the control group is the medical intervention itself: all people received information about the diagnosis and may have applied additional lifestyle measures. One practical recommendation for future studies is to predominantly include persons with longstanding OH that would therefore be unlikely to resolve spontaneously and the improvement that can be achieved here is the largest. At this moment there is only one RCT available, and due to the nature of the intervention control groups of a good quality will be difficult to create. A fully blinded control group is not achievable since, unlike in pharmacological interventions, a placebo cannot be given. Careful consideration must therefore be made on the precise composition of the control groups. Obviously, we must also consider the possibility that HUTS is not an effective treatment (and we are open to that option), but there are several arguments that would appear to argue against this.

Specifically, we found some physiological indications of a beneficial effect of HUTS. The improvement in orthostatic BP control among people with OH was more marked when comparing higher vs. lower HUTS angles, suggesting a dose-response effect that would be compatible with a genuine treatment effect (although the angle could understandably not be blinded). Also, although the angle studied was small, the HUTS group had more ankle oedema compared to the placebo group [23]. Ankle oedema indicates a redistribution of body fluids. It acts as a water jacket and was found to correlate with better orthostatic tolerance [31]. The incidence of oedema following HUTS thus a physiological sign that may contribute to improved BP control in OH although the inclination may have been too small to demonstrate efficacy [23]. Interestingly, we found some evidence that HUTS improves BP homeostasis in people with vasovagal syncope and healthy controls by increasing the resilience to extreme orthostatic stress [20,21]. Other physiological signs suggesting a beneficial effect of HUTS include the consistent trend towards increased volume and lower night-time urine [20,21,26,27]. HUTS has the unique

potential to lower supine BP in people with neurogenic OH and coexisting supine hypertension. From a physiological perspective, one would even expect a more marked effect on supine hypertension rather than on orthostatic hypotension. We could, however, not evaluate this effect here as none of the studies reported the presence of supine hypertension. We recommend that assessment of supine hypertension should be routinely included in future evaluations of HUTS.

Strengths and Weaknesses of the Review

This is the first review to systematically synthesise the evidence for the treatment of orthostatic intolerance with HUTS. Our review included all population types of all ages and a broad range of outcome measures that relate to cardiovascular function. A limitation of the review is that we could not pool the findings as the interventions (angle and duration) varied extremely across the studies. We did not include studies that simultaneously studied the effect of HUTS with another non-pharmacological or pharmacological intervention and therefore we had to exclude potentially relevant studies analysing the HUTS intervention.

Future Directions

Although HUTS is an attractive and simple intervention, with the unique ability to positively impact both orthostatic hypotension and supine hypertension, it has not been widely adopted in daily clinical practice because of the lack of well-controlled studies that could guide such a clinical implementation. Future research should provide robust data on the clinical efficacy of HUTS, particularly in those with longstanding neurogenic OH and co-existing supine hypertension. The optimal tilt angle should be determined, by studying the trade-off between tolerability and efficacy, which may vary among individuals. The minimal treatment duration that is needed to achieve a tangible clinical improvement also remains to be determined. Such future studies should be conducted in a home environment with BP evaluations, ideally complemented with standardised clinical evaluations of postural BP control. Outcomes should obviously be addressed towards blood pressure control (OH and supine hypertension), but should also focus on other more long-term consequences, such as falls and fall related injuries, or secondary vascular damage in the brain or elsewhere [4,32]. Long-term compliance also remains to be studied. Future studies are also needed to identify easy-to-access markers to predict a good clinical response and help to optimize clinical implementation.

Conclusion

The evidence of the impact of HUTS on orthostatic tolerance is weak due to heterogeneous populations, variable HUTS angles, variable cardiovascular and other outcome measures, small sample sizes and therefore high risk of bias. Despite these limitations, we found some physiological signs suggesting a beneficial effect HUTS with more marked changes at higher angles. Yet the trade-off between HUTS efficacy and tolerability is the major unknown. Future well-controlled studies are needed to provide robust data of the clinical efficacy, optimal tilt-angles, and tolerability.

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Supplementary material

Supplementary Table S2.1. Database search strategy consisting of part 1, terms to define sleeping in a head-up tilt position, and part 2, autonomic nervous system outcome measures.

Database	Search terms
Pubmed	Part 1("Sleep*"[Mesh] OR sleep*[Title/Abstract] OR night*[Title/Abstract] OR nocturnal[Title/Abstract]) AND (head up[Title/Abstract] OR head-up[Title/Abstract] OR tilt*[Title/Abstract] OR anti-trendelenburg[Title/Abstract] OR reverse trendelenburg[Title/Abstract] OR incline*[Title/Abstract] OR ((bed[Title/Abstract] OR head-of-bed[Title/Abstract]) AND (elevat*[Title/Abstract]))) Part 2("Hemodynamics"[Mesh] OR Hypotension"[Mesh] OR "Hypertension"[Mesh] OR "Edema"[Mesh] OR "Urinary Tract Physiological Phenomena"[Mesh] OR "Nocturia"[Mesh] OR "Water-Electrolyte Balance"[Mesh] OR "Water-Electrolyte Imbalance"[Mesh] OR "Syncope"[Mesh] OR autonom*[Title/Abstract] OR blood pressure[Title/Abstract] OR hypotensi*[Title/Abstract] OR hypertensi*[Title/Abstract] OR syncope[Title/Abstract] OR Hemodynamic*[Title/Abstract] OR Haemodynamic*[Title/Abstract] OR Cardiac Output[Title/Abstract] OR Stroke Volume[Title/Abstract] OR Edema[Title/Abstract] OR Oedema[Title/Abstract] OR Nycturia[Title/Abstract] OR Nocturia[Title/Abstract] OR Vascular resistance[Title/Abstract] OR Vasodilatation[Title/Abstract] OR Vasoconstriction[Title/Abstract])
Embase	Part 1((exp sleep/ OR (sleep* OR night* OR nocturnal).ti,ab,kf.) AND (head up OR head-up OR tilt* OR anti-trendelenburg OR reverse Trendelenburg OR incline* OR ((head-of-bed OR bed) AND elevat*)).ti,ab,kf.) Part 1(cardiovascular function/ or blood vessel function/ or cardiovascular effect/ or cardiovascular performance/ or cardiovascular reflex/ or cardiovascular response/ or circulation/ or heart function/ or hemodynamics/ or exp abnormal blood pressure/ or edema/ or peripheral edema/ or nocturia/ or exp faintness/ or exp electrolyte disturbance/ or urinary tract function/ or bladder function/ or diuresis/ or kidney function/ or urine acidification/ or urine flow rate/ or autonomic neuropathy/) OR (autonom* OR blood pressure OR hypotensi* OR hypertensi* OR syncope OR Hemodynamic* OR Haemodynamic* OR Cardiac Output OR Stroke Volume OR Edema OR Oedema OR Nycturia OR Nocturia OR Vascular resistance OR Vasodilatation OR Vasoconstriction).ti,ab,kf.)
Cochrane	Same as Pubmed
Web of science	Part 1((TS=sleep* OR TS=night* OR TS=nocturnal) AND ((TS="head up" OR TS=head-up OR TS=tilt* OR TS=anti-trendelenburg OR TS="reverse trendelenburg" OR TS=incline*) OR ((TS=bed OR TS=head-of-bed) AND TS=elevat*))) Part 2TS=Syncope OR TS=autonom* OR TS="blood pressure" OR TS=hypotensi* OR TS=hypertensi* OR TS=syncope OR TS=Hemodynamic* OR TS=Haemodynamic* OR TS="Cardiac Output" OR TS="Stroke Volume" OR TS=Edema OR TS=Oedema OR TS=Nycturia OR TS=Nocturia OR TS="Vascular resistance" OR TS=Vasodilatation OR TS=Vasoconstriction

Chapter 3

Head-up tilt sleeping to treat orthostatic intolerance in a patient with advanced Parkinson disease: a case report

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Abstract

Introduction: Orthostatic hypotension is common in people with Parkinson's disease due to autonomic dysfunction and medication use, and can have a significant negative impact on quality of life. Pharmacological treatment is often complicated due to complex blood pressure regulation problems. This case report presents a patient whose symptoms of orthostatic intolerance were successfully treated with the non-pharmacological method of Head-Up Tilt Sleeping (HUTS).

Case presentation: A 69-year-old man with Parkinson's disease and prominent autonomic failure received recommendation from the neurologist to use HUTS to battle orthostatic intolerance, of which complaints were worst in the early morning. The patient noted a marked improvement of the orthostatic intolerance after a period in which he slowly step-by-step inclined the bed to an angle just over 10°. When ceasing HUTS for a brief period, complaints of orthostatic intolerance immediately returned and the patient returned to tilted sleeping right away. After a follow-up of three months the patient did not report orthostatic intolerance during a standing test.

Conclusion: This case illuminates that, despite difficulties intrinsic to this method, whole-body head-up tilt sleeping can ameliorate orthostatic intolerance and improve the daily life of people with advanced movement disorders.

Abbreviations

PD: Parkinson disease
OH: Orthostatic hypotension
HUTS: Head-Up tilt sleeping

Introduction

Autonomic dysfunction is a common symptom of Parkinson's disease (PD), often presenting with problems in maintaining blood pressure homeostasis [1]. Blood pressure is closely regulated by the baroreflex, which coordinates vascular resistance and heart rate based on the pressure changes that it registers [2]. When the autonomic nervous system is affected by a neurogenerative process (e.g., in PD or a form of atypical parkinsonism such as multiple system atrophy), this can result in baroreflex failure. In PD peripheral denervation is an important factor for baroreflex failure, while in multiple system atrophy the problem lies at the pre-ganglionic level [3]. In both cases, the system can no longer respond to challenges such as the volume shift caused by standing up, resulting in orthostatic hypotension (OH) with debilitating symptoms of orthostatic intolerance. The prevalence of OH is about 1 in 3 for people with PD, and 4 in 5 for people with multiple system atrophy [1]. OH and other co-occurring blood pressure abnormalities (e.g., supine hypertension) have a direct negative influence on quality of life, largely due to a reduced mobility, and are also associated with long-term health risks such as cardiovascular events and dementia [4,5]. Pharmacological treatment is difficult because of the often complex blood pressure regulation problems and extensive medication regimens in PD (where dopaminergic medication may worsen OH). Moreover, caution is warranted because pharmacological treatment of OH can cause or worsen supine hypertension as a side effect. Non-pharmacological interventions are therefore an attractive alternative treatment approach, as these have limited to no side effects. Methods include increasing salt and water intake, physical counter manoeuvres and strength training [6,7]. One method that has been hypothesized to positively affect OH is sleeping with the head of the bed elevated: Head-Up Tilt Sleeping (HUTS). It is thought to alleviate orthostatic intolerance by reducing pressure natriuresis overnight, and by creating increased extracellular volume -and thereby pressure- in the legs preventing excessive venous pooling upon standing [8,9]. HUTS was first introduced over 80 years ago, and even though widely known, it is not often applied [10,11]. In this case report we present a patient whose symptoms of orthostatic intolerance were successfully treated with HUTS. The CARE Checklist has been completed for this case report and is included as online supplementary material.

Case Presentation

A 69-year-old man with a history of PD and depression was seen in December 2022 by a neurologist at the outpatient clinic of the Radboud University Medical Centre, Nijmegen, The Netherlands for a consultation concerning several non-motor symptoms related to PD and medication use. The first symptoms of PD occurred

20 years prior to the visit, and started with hyposmia. A diagnosis of PD was established 10 years ago based on the presence of bradykinesia, right-sided rigidity, and mild postural tremor in the right arm. The disease course was atypical, with cognitive problems already present at the time of diagnosis (short-term memory problems that affected daily life, difficulty concentrating and problems with planning and logical thinking). A differential diagnosis of multiple system atrophy was considered for several years due to the early prominent presence of autonomic dysfunction and a small perceived effect of levodopa use. Multiple system atrophy was considered but was deemed less likely than PD because of the small but nevertheless clearly present response to levodopa, the presence of hyposmia (which is not seen in MSA) and the slowly progressive course. Throughout the years autonomic dysfunction became more prominent. The complaints occurred primarily as urogenital dysfunction (urge with miction – but no incontinence – and impotence). Orthostatic intolerance appeared three years prior to the visit. At the moment of the latest visit, the patient reported feeling insecure due to orthostatic intolerance, in relation to which he reported consistent near-falls after getting out of bed in the morning. At this point a rapid eye movement sleep behaviour disorder had also been established based on the unambiguous presence of dream enactment behaviour. The Hoehn and Yahr stage was II, and autonomic dysfunction could be quantified with a Scale for Outcomes in Parkinson's Disease - Autonomic Dysfunction (SCOPA-AUT) [12] score of 37 out of 69. At this time, the patient was using four medications, including clomipramine (daily dose 50mg) and levodopa/benserazide (net daily dose 1673/184 mg) which could affect symptoms of cardiovascular autonomic dysfunction. The patient was then recommended to increase fluid and salt intake, which resulted in more nycturia and only slight improvement of orthostatic symptoms. Because of the nycturia and orthostatic complaints, which were the worst in the morning, the patient was also recommended to start HUTS, which he was able to implement two months later. This resulted in amelioration of the orthostatic intolerance, where the patient had less complaints of dizziness. Almost a year after starting HUTS he attempted to sleep horizontally for two nights to test the effects, and dizziness returned with several episodes of pre-syncope in the following days. The patient immediately returned to HUTS, and has slept in the tilted position every night since then.

The patient implemented HUTS at home by gradually increasing the height of the head of the bed over a period of two months in steps of approximately 10 cm, and currently sleeps at a 38 cm elevation (11° tilt; Fig. 3.1). At this height the patient reported improvements in the symptoms of orthostatic intolerance, which was not observed at the lower angles. The patient also noticed an improvement in breathing and coughing during the night which he had experienced prior to adopting a tilted

sleeping position. He never attempted further increasing the angle. No blood pressure measurements before HUTS and after the development of orthostasis are available to us. Three months after starting HUTS a standing test showed only a limited blood pressure drop with a supine blood pressure of 107/75 mmHg, and an orthostatic blood pressure of 97/64 mmHg after 3 minutes of standing, only just meeting the diastolic criterium for orthostatic hypotension [13].

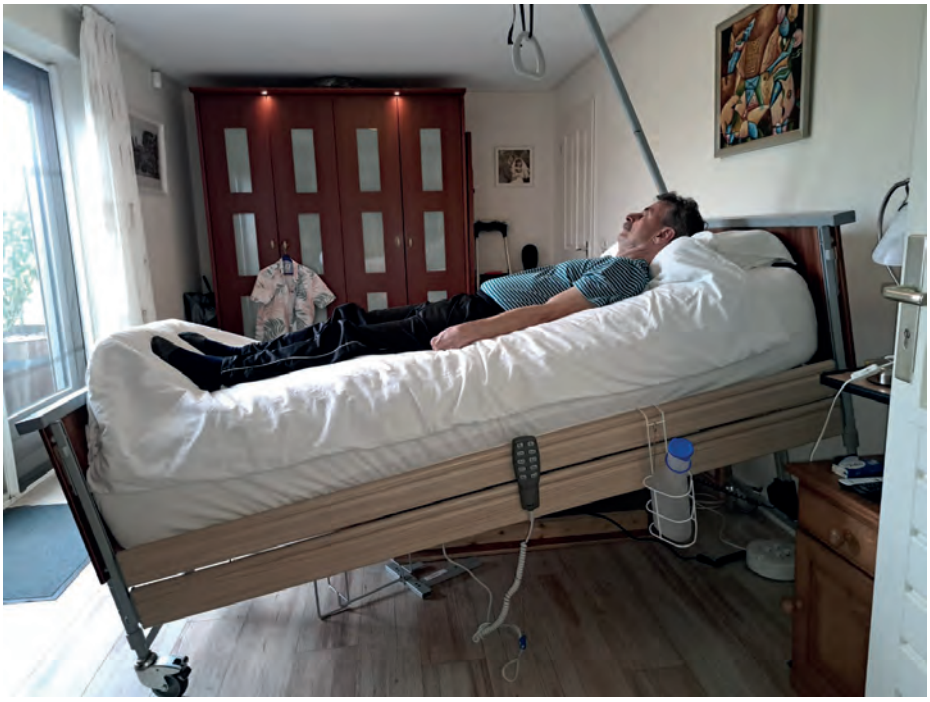

Figure 3.1. Application of the head-up tilt sleeping in the patient's home. The patient uses an automatic bed which can be moved up and down in the anti-Trendelenburg position freely. This eliminates the difficulty of getting in and out of a tilted bed. After lying down, the patient uses the remote control to raise the bed to the desired position. The head of the bed is elevated by just under 40 cm, at an angle slightly over 10° as measured with a degree gauge. The footboard of the bed provides a safety barrier to prevent him from sliding out of the bed at night. A pillow underneath the feet prevents discomfort, and is positioned in such a way as to avoid lifting the legs. This specific bed is also equipped with an overhead trapeze to help with turning during the night and with getting in and out of bed.

Discussion

Practical application of HUTS can be challenging. The method is still used only sporadically, presumably because healthcare professionals do not know which method and angle to recommend. Additionally, in the Netherlands – and we suspect in many other countries as well – a bed that allows the anti-Trendelenburg position with a concurrent footboard to prevent sliding is hard to come by through healthcare organisations. The patient described here is illustrative in this regard, as it took him several months to acquire this special bed. There is currently no evidence base on which to suggest a specific tilt angle that is likely to be most efficacious, so many individuals are left to a process of trial and error at home. This is again exemplified by the present case history, where the patient gradually increased the tilt angle until a sufficient reduction in complaints of the incapacitating morning orthostatic intolerance was experienced by him. Self-experimenting with such a gradual increase in angle seems helpful from a feasibility perspective, and to increase the likelihood that an effective and tolerable angle can be found for each individual patient, which can then be applied permanently. The individual differences between patients in specific symptoms, sleep comfort, severity of orthostatic intolerance and potential improvement following HUTS make it essential to weigh the pros and cons of HUTS for each individual, thus aiming to find the best personally tailored approaches to tilted sleeping. There is only limited evidence to support the efficacy of HUTS as a treatment of orthostatic intolerance [14] but the present patient reported definite improvement of orthostatic symptoms, especially in the morning where he experienced less dizziness upon standing suggesting there is indeed a continuing effect that is enabled during the night. The efficacy in this case is emphasized by worsening of the symptoms upon discontinuation of HUTS, which was also noted in previous case reports but has unfortunately not been documented in clinical studies to date [10].

The successful use of HUTS by this patient highlights the potential merits of this hitherto underutilised non-pharmacological treatment for OH, while also offering a good perspective on the practical challenges that come with introducing this treatment in a patient's own home situation. HUTS also had a beneficial effect on nocturnal breathing, which we explained via decreased gravitational pressure preventing obstruction of the upper airways [15]. We hope that these findings, albeit at the n=1 level, can serve as a motivation for dedicated further research studies, aiming to test different angles applied in an increasing order. Well designed randomized controlled trials could presumably give a better insight into what a minimally effective tilt angle is, and what a good starting position would be for

most patients. Such research can also look into compliance issues, since sleeping in a more vertical position is perceived as uncomfortable by some individuals. These new studies should also examine which patient profiles are particularly eligible for this type of intervention, and thereby gain better insight into the mechanism by which HUTS increases orthostatic tolerance. The specific patient group discussed here (persons with movement disorders) has not been represented in prior clinical trials that evaluated this intervention. Future work must include this population, so the results can offer guidance with respect to patient-specific advice on using HUTS. Such work is currently ongoing at our centre [16].

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Part II

The Heads-Up trial

Chapter 4

Study protocol for the Heads-Up trial: a phase II randomized controlled trial investigating head-up tilt sleeping to alleviate orthostatic intolerance in Parkinson disease and parkinsonism

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Abstract

Background: In persons with Parkinson Disease (PD) or certain forms of atypical parkinsonism, orthostatic hypotension is common and disabling, yet often underrecognized and undertreated. About half of affected individuals also exhibit supine hypertension. This common co-occurrence of both orthostatic hypotension and supine hypertension complicates pharmacological treatments as the treatment of the one can aggravate the other. Whole-body head-up tilt sleeping (HUTS) is the only known intervention that may improve both. Evidence on its effectiveness and tolerability is, however, lacking, and little is known about the implementability.

Methods*:* In this double-blind multicentre randomized controlled trial (phase II) we will test the efficacy and tolerability of HUTS at different angles in 50 people with PD or parkinsonism who have both symptomatic orthostatic hypotension and supine hypertension. All participants start with one week of horizontal sleeping and subsequently sleep at three different angles, each maintained for two weeks. The exact intervention will vary between the randomly allocated groups. Specifically, the intervention group will consecutively sleep at 6°, 12° and 18°, while the delayed treatment group starts with a placebo angle (1°), followed by 6° and 12°. We will evaluate tolerability using questionnaires and compliance to the study protocol. The primary endpoint is the change in average overnight blood pressure measured by a 24-hour ambulatory blood pressure recording. Secondary outcomes include orthostatic blood pressure, orthostatic tolerance, supine blood pressure, nocturia and various other motor and non-motor tests and questionnaires.

Discussion*:* We hypothesize that HUTS can simultaneously alleviate orthostatic hypotension and supine hypertension, and that higher angles of HUTS are more effective but less tolerable. The Heads-Up trial will help to clarify the effectiveness, tolerability, and feasibility of this intervention at home and can guide at-home implementation.

Abbreviations

ABPM: Ambulatory blood pressure measurement
BP: Blood pressure
HUTS: Head-up tilt sleeping
LUMC: Leiden University Medical Centre
MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale
MSA: Multiple system atrophy
PD: Parkinson disease

Radboudumc: Radboud University Medical Centre
RCT: Randomized controlled trial
TUG: Timed Up and Go

Background

Autonomic dysfunction is common, debilitating and often underrecognized in Parkinson Disease (PD) [1,2]. The risk of orthostatic hypotension increases with age and disease duration. Up to one third of all people with PD experience orthostatic hypotension at some point during their disease course [2]. Orthostatic hypotension is also common amongst certain types of parkinsonism, especially in multiple system atrophy (MSA) with prevalence of up to 80% [3,4]. In both PD and MSA, orthostatic hypotension is mostly neurogenic, but it may also be caused or aggravated by hypovolemia, dopaminergic drugs, or other blood pressure (BP) lowering medications [1]. Orthostatic hypotension can present with orthostatic intolerance (e.g., postural light headedness), but the symptoms may also be less recognizable such as fatigue, cognitive slowing or coat hanger pain while standing. It is important to recognize and treat orthostatic hypotension as it may lead to syncope and falls with resulting injuries [5,6]. The symptoms may also lead to a reduction in physical activity, which in turn aggravates other movement disorder symptoms such as balance and mobility problems [7], thereby increasing the risk of falling even further. Previous placebo-controlled randomised controlled trials (RCT) have shown that effective treatment of orthostatic hypotension increases physical activity [8], and improves functional mobility in people with orthostatic hypotension and PD or parkinsonism [9].

Up to half of all people with PD or MSA and orthostatic hypotension also exhibit supine hypertension [10]. Supine hypertension can be severe and last for several hours during nocturnal sleep, putting people at a higher risk for early morning hypertensive emergencies such as stroke and myocardial infarction [10-13]. Over time, the combination of the very high recumbent and very low upright BP may contribute to end-organ damage at the cerebral, cardiac and renal level [14,15]. Indeed, among people with PD the presence of white matter lesions was associated with both supine hypertension and orthostatic hypotension [16]. Supine hypertension is also known to foster pressure natriuresis overnight thus promoting orthostatic hypotension [1,13]. This may partially explain why orthostatic hypotension is often worse in the morning [17]. The common co-occurrence of orthostatic hypotension

and supine hypertension makes pharmacological treatment very complex, as treatment of one aggravates the other [13].

A non-pharmacological and non-invasive intervention that can improve both orthostatic hypotension and possibly also supine hypertension is head up tilt sleeping (HUTS). The concept of HUTS is based on clinical observations made over 80 years ago [18-20]. These observations showed symptomatic and objective improvement of orthostatic hypotension during daytime. However, thus far HUTS has only been investigated in small and largely observational cohort studies, and never in a population with movement disorders [21-24]. The optimal tilt angle of HUTS is currently unknown but based on the presumed gravitational effect a steeper head-up tilt sleeping position is likely to be most effective, but is also less tolerable due to more discomfort in the sleeping position. The studied angles showing improved orthostatic tolerance varied from 12° to 40° [18,19,21-23], yet these studies did not evaluate the impact on nocturnal supine hypertension. This could be attractive, however, because from a physiological perspective, one would expect a more marked effect on supine hypertension rather than on orthostatic hypotension. HUTS will likely alleviate supine BP due to direct gravitational effects while orthostatic BP improvement is mediated by changes in extracellular fluid compartments. Accordingly, a placebo controlled RCT applying low HUTS angles (5°) found no effect on orthostatic hypotension, but more frequent occurrence of ankle oedema in the intervention group. This suggests that even a modest angle has potential to reduce supine hypertension [25,26]. In clinical practice, HUTS is often not recommended, and when it is modest tilt angles are suggested with presumably at best also modest effects, as a guideline on practical implementation is still lacking [25,26].

We here describe the design of the Heads-Up study, in which we investigate the potential efficacy and tolerability of different angles of HUTS as a treatment for both supine hypertension and orthostatic hypotension in people with PD. We will evaluate the effect of different angles of HUTS on several BP outcomes, orthostatic intolerance, compliance, tolerability, nocturia, as well as motor- and non-motor PD symptoms. Finally, we will explore whether certain participant characteristics may predict the effectiveness of HUTS.

Methods

Study design

The Heads-Up trial is a double-blind, phase II RCT. Participants will be randomized in two groups: the treatment group and the delayed treatment group (Figure 4.1). It is a two-centre study performed at the Radboud University Medical Center (Radboudumc) and Leiden University Medical Center (LUMC), both located in The Netherlands. The total study duration for participants is seven weeks.

Population

We aim to include a diverse population of fifty adults diagnosed with PD or parkinsonism by a neurologist that have both supine hypertension (systolic BP of ≥140 mmHg, and/or diastolic BP of ≥90 mmHg, after 5 min of supine rest) [12] and orthostatic hypotension (systolic decrease of ≥ 30 mmHg [27] or diastolic decrease of ≥ 10 mmHg upon standing, i.e. the orthostatic hypotension criteria for those with co-existing supine hypertension) [27,28]. Participants must experience symptoms of orthostatic intolerance (e.g., dizziness, cognitive slowing or blurry vision while standing). Participants must be able to walk, with or without walking aid, must have a stable medication regime for both supine hypertension and orthostatic hypotension during participation, and are not allowed to simultaneously participate in other intervention trials. Finally, participants are only eligible if they can adhere to the study schedule themselves or with help of support at home.

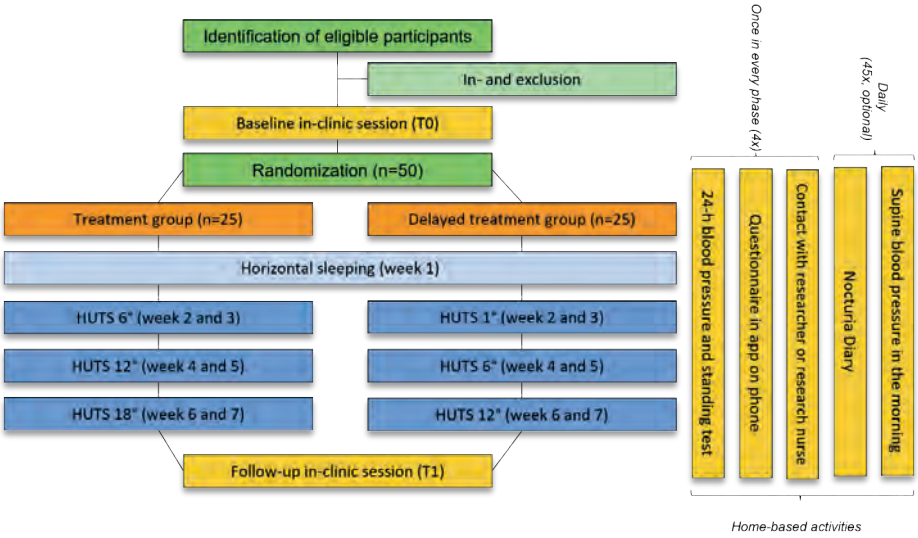

Figure 4.1. Overview of the trial. HUTS, Head-Up Tilt Sleeping;

Recruitment

We will recruit primarily at our outpatient clinics (Radboudumc & LUMC). In addition, other neurologists, Parkinson nurses, geriatricians and internists throughout the Netherlands will be invited to refer potentially eligible patients. We will also use open recruitment via social media and the media channels of the Dutch Parkinson Patient Association and ParkinsonNext (www.parkinsonnext.nl), a platform connecting people with PD and an interest in research with researchers (n>2000).

Procedure

Those who expressed their interest in participating are contacted by the research team to screen for eligibility and informed about the study protocol. If BP data is unavailable, we will discuss how these measurements can be obtained (self-measurements or with help from a researcher). All participants will receive elaborative explanation on the study procedures at the start of the first in-clinic session, and prior to participation they will sign an informed consent form. During the study duration of seven weeks there will be at least seven scheduled moments of contact. Participants will perform several activities and measurements:

- First, we will plan an in-clinic visit (either at the Radboudumc or LUMC). For consistency, this visit will always be scheduled in the early afternoon. Here, participants can ask additional questions and sign informed consent. The researchers will then gather baseline characteristics, perform their initial assessments with continuous BP measurements and several questionnaires. The assessments and questionnaires can be found in Table 4.1. Finally, the participant will be asked to install an app through which they can report their at-home measurements.
- After this session, the participants are randomized to one of the two groups. We will apply the randomization feature of the data management system Castor EDC with block sizes of two and four to allow the interim analysis. We will stratify based on gender. The researchers who perform the assessments and/or are involved in the analyses will remain blinded to the participant allocation during the study. Only the researchers who perform the randomization and deliver the materials at home will know which group the participants are allocated to. We will not inform the participants that we expect that the first angle in the delayed treatment group has no effect on BP regulation, making this a double-blind study.
- We will schedule an appointment to deliver all study materials within one week after the first session.
- Participants will perform daily at home measurements of supine BP and their weight. They will be asked to record their measurements in the app.

- We will schedule four video calls with the participants to discuss potential caveats and supervise the BP standing tests. Participants will also be asked to fill out several questionnaires in the app on this day and to disclose whether they slept in the prescribed angle. During this video check-in we will also guide the initiation of the 24-hour ABPM (Table 4.1).
- Participation ends with a follow-up in clinic session, also scheduled in the early afternoon for consistency, where the BP measurements and questionnaires from the first in clinic session are repeated and participants are asked about their experiences. When they want to proceed HUTS, they are offered to keep the materials and to do so under supervision of their primary care physician.

Intervention

All participants in this study are subject to a six-week intervention. They will be sleeping in a whole-body HUTS position at three different angles, for two weeks each. The treatment group will sleep at HUTS angles of 6°, 12° and 18°. The delayed treatment group will first sleep at the placebo angle of 1° which is considered the control, after which they also sleep at 6° and 12° HUTS (Figure 4.1). In both groups the intervention is preceded by a week of horizontal sleeping for baseline measurements.

The necessary materials will be delivered to the participants' homes. To facilitate implementation in the home situation we have developed a frame that can be used to tilt the mattress into all different angles (Figure 4.2A). For those who do not wish to use this frame, we offer wedge shaped mattresses with similar HUTS angles (Figure 4.2B). The effect of HUTS on sleep quality is not yet known, but higher angles of HUTS may cause discomfort. Slipping can be reduced by increasing the friction of bedcover fabric, placing a rolled-up towel under the hips or in several other ways. We will expand this list as participants figure out what works for them during the study. We offer to provide each participant with a sleeping partner the frame for both so that they can sleep next to each other in the same angle during the trial. For good application of the HUTS method in the participant's home, we will pay a home visit not only to deliver the materials, but also to offer support. For those who require or request extra help during the study we will provide this by offering a telephone or video call and, if necessary, by additional home visits.

Testing of materials

We organized several test sessions for patient researchers to test different HUTS methods and to provide feedback on the design and usability. From these preparatory sessions we learned that it is not feasible to apply the intuitive method

of blocks underneath the headboard of the participant's bed as this is very unstable at the higher angles. The final frame (Figure 4.2A) comes with a footboard to prevent participants from sliding down at the higher angles. This reduces the risk of falls from the bed during the night. We also supply handrails on the side of the bed for easier turning, as difficulties with turning is a common problem in people with PD. These handrails, together with the footboard, also form a safety barrier that prevents participants from sliding or falling out of bed and can help them get out of bed safely. For the safety of the participants, we decided to implement the highest two angles (12° and 18°) by placing the frame on the floor. We did realize that this may be problematic or even hinder participation for those who do not have the space at home for this additional frame on the floor, but we considered the alternative unsafe.

A

B

Figure 4.2. Image of the HUTS method for in the participant's home. In both situations a 12° angle is shown. A) The wedge-shaped mattress can be placed underneath the participant's mattress or used separately. B) The frame can easily be adapted to fit to all angles that are prescribed during the study.

Outcome measures

Primary outcomes

Efficacy

The primary outcome is the home-based overnight supine BP recorded four times with the 24-hour ambulatory blood pressure measurement (ABPM). This recording will be done during one of the last three days of every phase. The measurements during the baseline horizontal week will be used to calculate the change score to determine the effect of each angle on the BP. The BP device will measure the BP every half hour during the night, according to the guidelines for ABPM measurements [29]. Participants will self-report the actual time they spend lying down in bed.

Table 4.1. Overview of study procedures.

Activity	In-clinic 1	Wk1	Wk2-3	Wk4-5	Wk6-7	In-clinic 2
Informed consent	X					
Demographics	X					
Tilt-table and BP standing test	X					X
MDS-UPDRS	X					X
Questionnaires OHQ, PSQI, FES, selected questions from SCOPA, PDQ-39, HADS and MHC-SF	X					X
Timed Up and Go test	X					X
Average overnight and daytime BP with 24-h ABPM (4x)		X	X	X	X	
Supine BP (daily, 45x)		X	X	X	X	
Standing BP (guided, 4x)		X	X	X	X	
Questionnaire on phone app (4x) – OHQ – ICIQ-N – Number of falls – Nocturia – Subjective comfort of HUTS		X	X	X	X	
Nocturia measurements – Body weight (45x) – Nighttime urine production (4x)		X	X	X	X	
Interview on barriers and facilitators of HUTS						X
Protocol						
Instructions	X					
Sleeping horizontally		X				

Table 4.1. Overv

Activity	In-clinic 1	Wk1	Wk2-3	Wk4-5	Wk6-7	In-clinic 2
(Possible) Home visit to install angle		X	X	X	X	
HUTS angle 1			X			
HUTS angle 2				X		
HUTS angle 3					X	
Phone/video call with researcher		X	X	X	X	
Aftercare (personalized advice)						X

BP = blood pressure; HUTS = sleeping in head-up tilt; MDS-UPDRS = Movement Disorders Society Unified Parkinson Disease Rating Scale; OHQ = orthostatic hypotension questionnaire; PSQI: Pittsburgh sleep quality index; FES: Falls Efficacy Scale; SCOPA: SCales for Outcomes in PArkinson's disease; PDQ: Parkinson's disease questionnaire; HADS: Hospital anxiety and depression scale; MHC-SF: Mental Health Continuum Short Form; ICIQ-N: International Consultation on Incontinence Questionnaire Nocturia Module;

Tolerability

We will evaluate the tolerability of HUTS with four indicators: 1) compliance, as measured by the daily question if they slept in the right angle, presented as proportion of participants that were >80% of the study period compliant to the prescribed intervention; 2) the proportion of participants who did not tolerate the angle and returned to the previous angle; 3) the number of dropouts and if provided their reason for dropping out of the study, and; 4) reported barriers and motivators for using HUTS (evaluation during the final in-clinic session).

Secondary outcomes

The first secondary outcome is the daily supine morning BP. This is measured and reported by the participants themselves before taking a seated position in bed.

During the four video sessions data is gathered on orthostatic BP through supervised home-based standing tests and daytime BP measured by the 24-h ABPM, which records daytime BP three times per hour. Other ABPM parameters will be considered as well (e.g., BP variability and nocturnal dipping).

Besides BP, the symptoms of orthostatic intolerance are determined with the Orthostatic Hypotension Questionnaire (OHQ) [30] and the cardiovascular questions of the Scales for Outcomes in Parkinson's disease – Autonomic symptoms (SCOPA-AUT) [31]. Nocturia will be quantified during the ABPM measurement by collecting and reporting the total volume of urine produced during the night. On all other days, the overnight weight loss will be used to estimate the total volume lost. The International Consultation on Incontinence Questionnaire Nocturia Module (ICIQ-N) is used to determine the amount of bother experienced as a result of nocturia [32].

At both in-clinic sessions participants will be subjected to a phased tilt table test protocol including heart rate and beat-to-beat BP recordings (Finapres Medical Systems, Enschede, The Netherlands). We will tilt from a horizontal position to 15°, 30°, 45° and finally 60°. This will provide us with systematic measures of BP responses to different degrees of orthostatic positions. This, together with the standing test, will be used to investigate whether clinically relevant predictive values for the effectiveness of HUTS can be identified. Adverse events will be registered and grouped per treatment phase and group.

We selected several questionnaires which will be used to monitor the wellbeing of the participants in multiple areas:

- the Pittsburgh Sleep Quality Index (PSQI) [33] to investigate sleep quality, duration and parasomnias, the number of falls during participation, and the fear of falling as determined by the Falls Efficacy Scale (FES) [34].
- the Parkinson's Disease Questionnaire (PDQ-39) to evaluate mobility, activities, emotional wellbeing, stigma, social implications, cognitive impairment, and bodily discomfort [35].
- the Hospital Anxiety and Depression Scale (HADS) [36] and the Mental Health Continuum-Short Form (MHC-SF) [37] to monitor the emotional wellbeing of the participants.

Analysis

Interim analysis

The interim analysis will be used to provide information for a sample size calculation for a (phase III) follow-up study. No preliminary results with relation to the outcome of the study will be calculated. The average overnight BP from the first twelve participants will be used in this analysis. For these participants the change score comparing baseline (0°, week 1) and the 12° angle (week 5 or 7) will be determined, and only the average, standard deviation and confidence interval will be calculated. The researchers that are in contact with the participants will remain blinded to treatment groups, therefore this analysis will be performed by a non-blinded member of the research team. We will not use this analysis to terminate the study.

Final analysis

After completion of the study the data will be analysed according to the intention-to-treat principles. For the main analysis of the overnight BP measured with the

24-hour ABPM in each phase we will use the overnight BP measured in week 1 as baseline to determine the change score. The 1° angle will serve as placebo, and the rest of the HUTS angles are grouped together for overall effectiveness and the increasing angles separately for determining which angle is the most effective for reducing the overnight BP. To estimate the effect of the HUTS angle we will use a linear mixed model with as a dependent variable the change in overnight BP as measured during the 24-hour ABPM, with fixed effects for angle, group and visit and with a random effect for subject. As covariables the baseline BP value, age and disease duration will be used. The within group differences will also be analysed for all angles with a linear mixed effects model per group. Dependent variables in this calculation are the angle (fixed effect) and subject (random effect). The daytime variation will be calculated in the same way as described for the overnight BP.

The secondary outcome morning supine BP will be analysed by averaging the three consecutive morning measurements and comparing the 13 timepoints from each phase with the baseline for overall effect, and by comparing each of the three phases to investigate the difference in effect for angles taking into account the time-effect.

Additional explorative analyses based on the per-protocol principles will be performed, this includes the analysis on tolerability of HUTS, baseline characteristics collected at the in-clinic sessions, the results from the PSQI, falls, FES, PDQ-30, HADS and MHC-SF which all will be exploratively analysed. The tilt table test will be analysed to investigate the differences between responders and non-responders by looking at the severity of supine hypertension and orthostatic hypotension.

Sample size calculation

Since this is a phase II clinical trial, no formal sample size was calculated. We aim to study the effect of HUTS on clinical outcomes to power a future phase III RCT. We expect a large effect of the intervention on the main study parameters, meaning that 50 participants will be sufficient for this RCT [38].

Data monitoring

This study will be monitored by an independent monitor through several on-site visits. No serious adverse events are expected, therefore no study termination points are identified beforehand. We will not install a data safety monitoring board, and no auditing will occur. The trial will be coordinated and managed from the Radboudumc.

Discussion

We present the rationale and design of the Heads-Up trial, a double-blind phase II RCT to determine the potential benefit of different angles of HUTS as a treatment for both supine hypertension and orthostatic hypotension in people with PD and parkinsonism. Although the HUTS concept has been known for almost 80 years, many unknowns persist regarding the efficacy and feasibility. We therefore propose a home-based trial with a strong focus on the implementability.

Although HUTS is perceived as a simple method, there are several practical challenges which we tried to tackle in advance as much as possible. These can be found in the Methods section. The present study also focuses in part on investigating these challenges and hence the tolerability of the HUTS method. It may be difficult to acclimate to sleeping in a tilted position and all the adjustments that need to be made to implement it. The practical application is complex and highly individual, requiring a personalized approach. Measures will be taken to ensure that space or sleeping situations do not lead to an inclusion bias. To ensure this, we will provide each individual participant with all necessary support, including at least one home-visit for installation.

Apart from the practical challenges of the study, there are several important methodological issues. With the specific population studied here it may prove difficult to include a diverse group of participants (e.g., gender or with relation to socio-economic status), as men are more likely to be diagnosed with PD or parkinsonism, and underserved populations (such as those with a migration background) are often not reached. Among persons with PD, autonomic failure usually develops late in the course of the disease. This might impede recruitment due to frailty and abundant physical and cognitive symptoms. However, persons with parkinsonism, specifically those with MSA, often exhibit orthostatic hypotension at an earlier disease stage, sometimes even as the main presenting symptom. Although their disease progression may be faster, we expect that we will be able to recruit more mobile participants among these subgroups. To include underserved populations, we will recruit not only through neurologists in the outpatient clinics of university medical centres, but also in smaller or rural hospitals and clinics. We will also reach out to specialized nurses, physiotherapists, and people with PD themselves through open recruitment.

An additional methodological challenge due to the design of the study is the complexity of the statistical analyses. The order of the angles of the intervention

are not randomized, which was chosen due to the impact that the order may have on the perception of the different angles. By increasing the tilt angles step by step, the participants can slowly get used to tilted sleeping. We hope this improves the tolerability of the higher inclinations and reduces dropouts due to uncomfortable sleeping. If they still do not tolerate a new, higher angle, we will ask participants to return to the previous angle. From a physiological perspective one would expect that the impact HUTS will increase proportionally to the size of the angle. Randomizing the order of the angles would require wash-out periods to evaluate the independent effect of each angle but also longer intervention periods for steeper angles to reach a steady state of the effect. We therefore preferred the fixed and incremental order of HUTS inclination as a more practical design. The intention-to-treat analysis is likely to influence our results for the efficacy of the higher angles; we will therefore perform an additional per-protocol analysis.

Orthostatic hypotension often results from multiple contributing factors that can be neurogenic and non-neurogenic. Autonomic dysfunction, nocturnal hypertension, nocturia, hypovolemia, BP medication or dopaminergic medication may all contribute to orthostatic hypotension, but we cannot study each factor separately or their interaction with each other. We will try, however, to identify hemodynamic markers to predict HUTS efficacy. We will also monitor the impact of HUTS on nocturia, an often neglected and incapacitating symptom in PD or parkinsonism. Interestingly, nocturia seems more prominent in persons with supine hypertension and may contribute to orthostatic intolerance, but no concise evidence exists [17]. By monitoring nocturia and including those with supine hypertension and orthostatic hypotension, we hope to uncover the complex interplay between these factors.

Taken together, HUTS is an attractive intervention with the unique potential to positively impact supine hypertension and orthostatic hypotension simultaneously. Although the intervention seems simple and straightforward, the best way to implement in often frail people with movement disorders needs further study. If the current trial proves successful, a definitive phase III RCT will be designed, powered to study clinically relevant outcomes. The current study will help to determine which angles and target population this new trial should focus on. The current work will lay the foundation for practical guidelines for a structured and personalized application of HUTS.

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Chapter 5

The effect of head-up tilt sleeping on supine hypertension and orthostatic hypotension in Parkinson disease and multiple system atrophy (Heads-Up): a randomised, blinded, home-based phase 2 trial

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Abstract

Background: Orthostatic hypotension (OH) is a debilitating consequence of autonomic failure in Parkinson disease (PD) and multiple system atrophy (MSA). The co-existence with supine hypertension (SH) complicates pharmacological treatments. Head-up tilt sleeping (HUTS) is a simple intervention to alleviate both OH and SH, but its effectiveness and tolerability are understudied.

Methods: The Heads-Up trial is a phase 2, double-blinded, home-based, randomised controlled trial (completed, NCT05551377). Persons with PD or MSA and both SH and OH were assigned randomly to two HUTS schemes with gradually increasing angles: 1° (placebo), 6° and 12°; or 6°, 12° and 18°. Primary outcome was average nocturnal systolic blood pressure (SBP), recorded with ambulatory blood pressure measurements, once for each angle. Secondary outcomes included early morning supine SBP, nocturnal SBP dipping, average diurnal SBP, SBP fall upon standing, orthostatic hypotension symptom assessment scale (OHSA), and compliance. The effect of increasing the head of the bed (per cm elevation) was analysed with linear mixed models.

Findings: Twenty-two participants (18 PD) were included and randomised. Two participants withdrew before starting HUTS and were excluded from analysis. HUTS did not impact nocturnal SBP (estimate: -0.03 mmHg/cm, 95%CI [-0.2;0.1]). HUTS did improve other indicators of blood pressure control, including early morning supine SBP (estimate: -0.11 mmHg/cm, 95%CI [-0.21;-0.01]), nocturnal dipping profile (estimate: -0.12%/cm, 95%CI [-0.23;-0.005]), diurnal SBP (estimate: 0.15mmHg/cm, 95%CI [0.035;0.27]) and SBP fall upon standing (estimate: 0.4mmHg/cm, 95%CI [0.17;0.64]). These changes coincided with improved orthostatic tolerance (median OHSA before HUTS: 5 (IQR: 3-6), after HUTS: 4 (IQR: 2-5), p=0.0144). Adherence was 100% at 6°, 80% at 12°, and 60% at 18°.

Interpretation: HUTS did not reduce nocturnal SBP but improved other indicators of blood pressure control. Orthostatic tolerance also improved. Higher angles were more effective, but at the cost of lower tolerability.

Research in context

Evidence before this study

We conducted a literature search of all studies analysing the effect of head-up tilt sleeping (HUTS) on blood pressure (BP) in humans up to January 2025. We published a scoping review and performed an additional search in databases PubMed, Web of Science, and Cochrane for studies published between January 2023 and January 2025. We identified eight studies investigating the effect of HUTS as treatment to alleviate orthostatic intolerance. The populations that were studied varied, and only one focused on persons with Parkinson disease.

Three studies investigated HUTS at a 6° angle. Two studies reported amelioration of orthostatic hypotension, and one reported no effect. An unchanged nocturnal BP was reported in all three, but it could not be inferred whether the participants had supine or nocturnal hypertension. One study successfully applied HUTS at a 10° inclination, with an increase in plasma volume along with an improvement in orthostatic tolerance. Four publications tested HUTS at 12°, also showing consistent improvement. Based upon the predominantly positive reports for greater tilt angles, those up to 12° are presently recommended in guidelines. Thus far, HUTS was studied mostly in the short term and in a controlled setting. The optimal implementation for long-term, home-based treatment delivery remains unclear.

Added value of this study

The Heads-Up trial is a phase 2, home-based, double-blinded, randomised-controlled trial in people with Parkinson disease and multiple system atrophy with both orthostatic hypotension and comorbid supine hypertension. The study evaluates multiple sleeping angles within the same individual to determine the effectiveness, tolerability, and feasibility of this intervention.

Implications of all the available evidence

HUTS did not improve nocturnal systolic blood pressure (primary outcome). However, HUTS had a positive angle-dependent effect on other elements of BP regulation, reflected by a slight decrease in supine early morning BP and regaining of a nocturnal dipping pattern. Steeper angles were associated with a clear stepwise improvement of BP regulation, but at the cost of lower tolerability. A tilt angle of 12° HUTS offered the best compromise for at-home implementation. Individual variability was substantial, indicating a need to search for an optimal trade-off between tolerability and efficacy in individual patients.

Non-standard Abbreviations

ABPM: Ambulatory blood pressure measurement
BP: blood pressure
HUTS: head-up tilt sleeping
MSA: multiple system atrophy
OH: orthostatic hypotension
PD: Parkinson disease
SBP: systolic blood pressure
SH: supine hypertension

Introduction

Orthostatic intolerance due to orthostatic hypotension (OH) is a common, debilitating and often unrecognized non-motor symptom of Parkinson disease (PD) and several forms of atypical parkinsonism, such as multiple system atrophy (MSA) [1]. OH may present with overt symptoms such as light-headedness, blurred vision or syncope. Symptoms can also be more subtle, including cognitive slowing or fatigue, which challenges a timely recognition [2]. Approximately half of people with PD or MSA with OH have co-existent supine hypertension (SH), particularly when autonomic dysfunction is severe [3]. Early recognition and treatment of SH and OH is essential to preserve quality of life and reduce mortality [3-7]. However, pharmacological treatment is challenging when SH and OH co-exist. Severe OH is commonly treated with fludrocortisone, which increases blood pressure (BP) during both day- and nighttime, thus aggravating SH. The opposite occurs with pharmacological treatment of SH, which aggravates OH [1,2,8].

Non-pharmacological interventions that can be tailored to a person's body position offer an attractive alternative [2]. One example is full-body head-up tilted sleeping (HUTS), which could potentially ameliorate both SH and OH [4,8]. Specifically, HUTS is thought to reduce supine BP in persons with autonomic dysfunction, which in turn may reduce nocturnal volume loss through nocturia. This helps to preserve the fluid balance and thereby improves OH [8,9]. However, there is only limited evidence to support the effectiveness of this intervention [10,11]. Case reports and small studies studied tilt angles between 5 and 13°, with variable results on orthostatic BP depending on the angle and population studied [10,12-20]. Only one study focused on PD [20], and no study investigated the effect on SH. Problems with tolerability were reported for angles of 12° and higher [10,11].

We investigated the potential of different HUTS angles to reduce nocturnal BP and improve OH. We also studied the effect on nocturia. Furthermore, participant experiences with different angles of HUTS were explored to evaluate the balance between tolerability and efficacy.

Methods

Study design and participants

The Heads-Up trial is a two-centre, phase 2 randomized controlled trial. Recruitment started October 2022; the final participant completed the study in July 2024. The study duration was 7 weeks and consisted of a home-based intervention, including a placebo phase, with one in-clinic visit at the start (visit 1) and one at the end of the study (visit 2). We previously described the protocol and intervention in detail [21]. Participants were recruited from outpatient clinics throughout the Netherlands and through open recruitment via national on- and offline channels (e.g. Dutch Parkinson Society). All participants had a diagnosis of PD or MSA according to established international diagnostic criteria. Orthostatic intolerance had to be present, and SH and OH had to be confirmed by recent measurements. SH was defined as a systolic BP (SBP) ≥140 mmHg and/or a diastolic BP ≥90 mmHg after 5 minutes of supine rest in people with known neurogenic OH [6]. For OH we applied the cut-off values established for patients with co-existing SH: a reduction in SBP ≥30 mmHg and/or diastolic BP ≥15 mmHg, or a standing mean arterial pressure of ≤75mmHg within 3 minutes after rising from a supine position [7]. Participants had to be able to walk (with or without an aid), and had to remain on a stable medication regime during participation. The study protocol was approved by the institutional review boards of the Radboudumc and Leids Universitair Medisch Centrum, the Netherlands. Ethical approval was provided by the Medical Ethical committee Oost-Nederland, NL.80610.091.22 (registered at ClinicalTrials.gov NCT05551377). The study was executed according to the principles of the Declaration of Helsinki, and all participants signed informed consent prior to data collection.

Randomisation and masking

After visit 1, participants were assigned randomly to two groups (1:1), stratified by gender with block sizes 2 and 4: the immediate treatment group and the delayed treatment group. Both groups slept in a horizontal sleeping position for one week (baseline), followed by three phases of sleeping consecutively at the three increasing angles (each phase lasting two weeks). The delayed treatment group started at a placebo angle (1°), after which they continued to 6° and finally

12° HUTS. The immediate treatment group started at 6°, followed by 12° and 18°. Randomisation was done via Castor EDC by a coordinating senior researcher. Participants and other researchers were blinded for group allocation.

Procedure

Visit 1 marked the start of participation. At this time the following clinical data were obtained: sex, age, BMI, diagnosis, date of diagnosis, current medication, and current non-pharmacological treatment for OH. Additional information was collected for parkinsonian symptoms (Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [22] and Parkinson's Disease Questionnare-39), mobility (the Timed up and go test and Falls Efficacy Scale), symptoms of OH (Orthostatic Hypotension Questionnaire-Symptom Assessment (OHQ-OHSA) and cardiovascular questions of the Scale for Outcomes in Parkinson's Disease-Autonomic Dysfunction (SCOPA-AUT)), sleep (Pittsburgh Sleep Quality Index), and mental wellbeing (Hospital Anxiety and Depression Scale, and the Mental Health Continuum-Short Form). Directly after visit 1, participants were visited by a researcher who installed a wooden frame, enabling a systematic full-body head-up tilt of the mattress (Figure 5.1) [21]. The frame was developed through co-creation with patient-researchers. Participants were encouraged to reach out whenever questions or problems arose.

Figure 5.1. The method used for Head-tilt sleeping. The frame was a result of co-creation, and allowed systematic application of Head-up tilt sleeping in all participants. Previously published in Van der Stam et al., 2023,[21] with permission from the authors and the publisher.

Throughout the trial participants performed three supine BP measurements each morning, prior to getting out of bed. Subjects had been at least one hour supine prior to these measurements. Daily reports with supine BP measurements were exchanged via a web app. We averaged the three measurements from three available days closest to the end of each phase to determine the early morning supine SBP. During one of the last three days of each phase a secured video call with

a researcher was scheduled. Participants were asked about their experiences and adverse events, and were instructed how to start the next phase. Under guidance, participants self-performed an active standing test with a supine BP measurement after 5 minutes of rest, followed by three standing measurements after 1, 3 and 5 minutes. The call was always scheduled in the morning. ABPM (Mobil-O-Graph) was performed in each phase (baseline, 1° (placebo) 6°, 12° and 18° HUTS). The device was put on by the patient, supervised by the researcher during the video call. ABPM recordings included measurements every 20 minutes from the start, and every 30 minutes from 10 pm until 8 am. ABPM was supplemented with self-recorded bedtimes to separate diurnal and nocturnal BP values. All ABPMs with more than 70% successful measurements were considered adequate. Participants registered nocturnal urine volume (ml) during the ABPM by using a chamber pot.

Participants were asked to complete several questionnaires per study phase: the experienced burden of nocturia (International Consultation on Incontinence Questionnaire-Nocturia Module), three questions on sleep comfort related to HUTS (scoring ranged from 0 to 8, 8 indicating an improved comfort level compared to horizontal sleeping), and to keep a fall diary. We analysed tolerability according to three indicators:

1) Compliance, presented as proportion of patients that were compliant to HUTS for >80% (5.6 weeks) of the study period.
2) Proportion of patients who did not tolerate the angle and returned to the previous angle.
3) Reported comfort of HUTS from the questionnaire completed after the video call and discussed during visit 2.

Study participation was concluded with in-clinic visit 2, at which point the participants were debriefed, and the questionnaires from visit 1 were repeated.

Outcomes

The average nocturnal SBP taken from the 24-hour ABPM served as primary outcome measure. Secondary outcomes included nocturia (ml), nocturnal dipping (defined as the percentage reduction of the average nocturnal SBP compared to the diurnal SBP (formula: 100%-(nocturnal SBP/diurnal SBP)*100%)), average diurnal SBP, early morning supine SBP, the fall in SBP calculated at 3 and 5 minutes relative to the 5 minute supine SBP of the active standing test, the change in OHSA, SCOPA-AUT, Pittsburgh Sleep Quality Index, tolerability of HUTS according to the three indicators, International Consultation on Incontinence Questionnaire-Nocturia

Module, as well as change in MDS-UPDRS [22], Timed up and go test, Parkinson's Disease Questionnare-39, Hospital Anxiety and Depression Scale, Mental Health Continuum-Short Form, Falls Efficacy Scale, and falls diary.

Statistical analysis

We calculated the change scores compared to baseline for the nocturnal SBP derived from the ABPM measurements. The test angles 6°, 12° and 18° were grouped together and used as input for a one-sample t-test to verify an overall effect of HUTS. A separate one-sample t-test was performed for the placebo angle of 1°.

For the primary outcome a linear mixed model was used to study the angle-dependent effect of HUTS on nocturnal SBP. We modelled the inclination as cm elevation of the head end of the bed, according to the intention-to-treat principles. Elevation can be included in the linear mixed model as a continuous variable, because elevation in cm corresponds linearly to the impact of gravity on the participant's body. 1° HUTS was included as 3.5cm elevation, 6° HUTS as 21cm, 12° HUTS as 41.5cm and 18° HUTS as 62cm. The dependent variable of the model was nocturnal SBP from the 24-hour ABPM measurements. Fixed effects for elevation and randomisation group were included, and a random effect for subject. As covariables we included the centred age at baseline and disease duration.

Our original published plan included the time-dependent covariable 'visit'. However, due to the study design, this covariate was highly correlated with the fixed effect elevation. Therefore, we introduced a simplified model without the covariable 'visit'. We computed the Akaike Information Criterion (AIC) score for both models, and the simplified model scored better. We selected the simplified model for the analysis. In addition, the original plan included the baseline values of the dependent variable as covariable. In our simplified model, the baseline values were not added as covariable, but as observations.

Estimates (β), 95% confidence intervals (CI) and p-values calculated with Kenward-Roger's approximation are reported. We applied the same linear mixed model to analyse the effects of HUTS on nocturia, average diurnal SBP, nocturnal dipping, early morning supine SBP and SBP fall during the active standing test. We compared the composite scores of questionnaires of visit 1 and 2 with the Wilcoxon Signed Rank test. All data analyses were performed in RStudio (v1.1.463, rstatix and lmerTest packages) and SPSS (IBM SPSS Statistics 29).

Role of the funding source
The funding source had no part in design, collection, analysis, interpretation or reporting of the results.

Results

Twenty-two people were enrolled and randomised between January 2023 and April 2024 (Figure 5.2). Two participants (one per randomisation group) dropped out during the home-based baseline phase. One stopped due to a fear of falling out of the tilted bed. The other was unable to get in and out of bed without assistance when the wooden frame without inclination was applied; this person also felt limited wearing the ABPM device. Data were therefore collected from 20 participants. Demographics did not differ between the immediate and delayed treatment groups (Table 5.1).

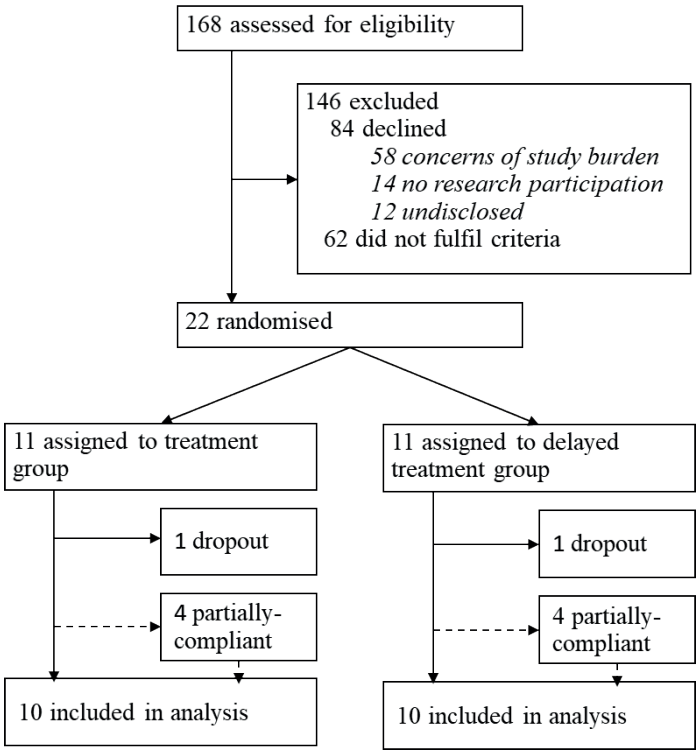

Figure 5.2. Inclusion flow diagram for the Heads-Up trial. Of the persons who declined it is unknown how many fulfilled the inclusion criteria. Both dropouts withdrew consent during the baseline phase, before starting the HUTS intervention. The eight persons who were partially compliant to the intervention went back to a lower angle in their final study phase but did complete the entire study protocol.

Table 5.1. Demographic characteristics and clinical measurements at baseline.

	Immediate treatment group (n = 10)	**Delayed treatment group (n = 10)**
Age in years (mean, SD)	67 (9.4)	71 (8.2)
Sex		
– Male	7 (70%)	7 (70%)
– Female	3 (30%)	3 (30%)
Diagnosis		
– PD	7 (70%)	8 (80%)
– MSA	2 (20%)	2 (20%)
– Undefined PD/MSA	1 (10%)	0
Hoehn and Yahr stage in ON-state		
– 1	1 (10%)	4 (40%)
– 2	6 (60%)	4 (40%)
– 3	3 (30%)	2 (20%)
Disease duration, months since diagnosis	35 (4-89)	41 (12-51)
MDS-UPDRS III score in ON-state at baseline (Median, IQR)	30 (26-35)	25.5 (20-41)
SBP fall during active standing test during baseline phase (mmHg) (median, IQR)*	-24.5 (-47; -8.3)	-62.5 (-62.5; -23.5)
Nocturnal hypertension (BP >120/>70 mmHg) (n)	10 (100%)	9 (90%)
Nocturnal urinary volume during baseline phase (ml) (median, IQR)	850 (613-1175)	900 (650-1125)
Body-mass index (mean, SD)	24.1 (2.7)	26.3 (3.5)
Patients on dopaminergic therapy	7 (70%)	9 (90%)
Levodopa equivalent daily dose (mg) (median, IQR)	550 (755)	1000 (1150)
Patients with advanced therapies	2 (20%)	0
Medication influencing blood pressure **	2 (20%)	4 (40%)
Non-pharmacological OH treatment		
– Increased water intake	7 (70%)	2 (20%)
– Increased salt intake	3 (30%)	4 (40%)
– Compression stockings	3 (30%)	1 (10%)
– Behavioural measures	6 (60%)	8 (80%)
Relevant comorbidities***		
– Atrial fibrillation	– 1 (10%)	– 2 (20%)****
– Endocrine disease	– 2 (20%)*****	– 0
– Sleep apnoea	– 1 (10%)	– 0

BP blood pressure; IQR interquartile range; MSA Multiple System Atrophy; MDS-UPDRS Movement Disorders Society Unified Parkinson's Disease Rating Scale; OH Orthostatic Hypotension; PD Parkinson's disease;

* The OH diagnosis was reproduced at least once in all but one participant during the home-based measurements.

**In the immediate treatment group one used furosemide, the other fludrocortisone and midodrine; all four in the delayed treatment group used fludrocortisone.

***A full overview of all self-reported comorbidities is provided in Supplementary Table S5.1.

****One of the two had a pacemaker.

*****One had diabetes mellitus, and one had diabetes mellitus and Addison's disease.

All measurements were complete except for the ABPM dataset. One ABPM recording of the last phase of one participant in the delayed treatment group (12°) was excluded due to a technical error. Two ABPM measurements did not meet our quality criterion. We excluded these recordings from the diurnal analysis and nocturnal dipping analysis, as the missed measurements were clustered during the day.

The placebo angle of 1° did not change nocturnal SBP (mean change= 1.3 mmHg (SD: 10), p=0.6897). When grouping all active tilt angles, HUTS did not have an overall effect on nocturnal SBP, as compared to the baseline phase (mean change= -3.2 mmHg (SD: 16), p=0.1745). We observed no significant angle-dependent change in nocturnal SBP (β: -0.03 mmHg/cm, CI [-0.2;0.1], p=0.7230, Figure 5.3a). Nocturia volume did not change following HUTS (β:0.23 ml/cm, CI [-4.3;5.3], p=0.892). The nocturnal dipping pattern increased in HUTS with higher angles (β: -0.12%/cm, CI [-0.23;-0.005], p=0.0428, Figure 5.3b). The average diurnal SBP increased in an angle-dependent manner (β: 0.15 mmHg/cm, CI [0.035;0.27], p=0.0173). With higher angles, there was a reduction in supine early-morning SBP measured just before getting out of bed (β: -0.11 mmHg/cm, CI [-0.21;-0.01], p=0.0286, Figure 5.4a). The SBP fall after 3 min of standing measured with the active standing test was smaller following HUTS in an angle-dependent manner (β:0.4 mmHg/cm, CI [0.17;0.64], p=0.0100, Figure 5.4b). Similar angle-dependent improvements were observed for the 5th minute of standing, (β:0.4 mmHg/cm, CI [0.17; 0.61], p=0.0015) and the largest BP fall within 5 minutes of standing (β: 0.4 mmHg/cm, CI [0.21; 0.64], p=0.0003).

Twelve participants reported orthostatic symptoms during the baseline test at home, and six reported symptoms during the final phase. Five participants could not complete the OHQ Daily Activities Scale because they had other mobility problems. We therefore restricted the analysis to the OHSA Symptom scale without missing values. HUTS significantly improved the results of the OHSA (visit 1: 5 (IQR 3-6), visit 2: 4(IQR 2-5); p=0.0144). We also found improvements on the SCOPA cardiovascular autonomic questions (SCOPA-AUT; visit 1: 3(IQR 2-5), visit 2: 2 (IQR 2-4); p=0.0050).

Twelve participants completed their participation according to the protocol. The other eight went back to a more shallow sleeping angle during the third phase: four in the delayed intervention group changed back from 12° to 6°, and three participants in the immediate treatment group changed back from 18° to 12°. The main reason was discomfort. One participant in the immediate treatment group experienced a non-injurious fall from the tilted bed in the final week due to concurrent REM sleep behaviour disorder, and returned to horizontal sleeping.

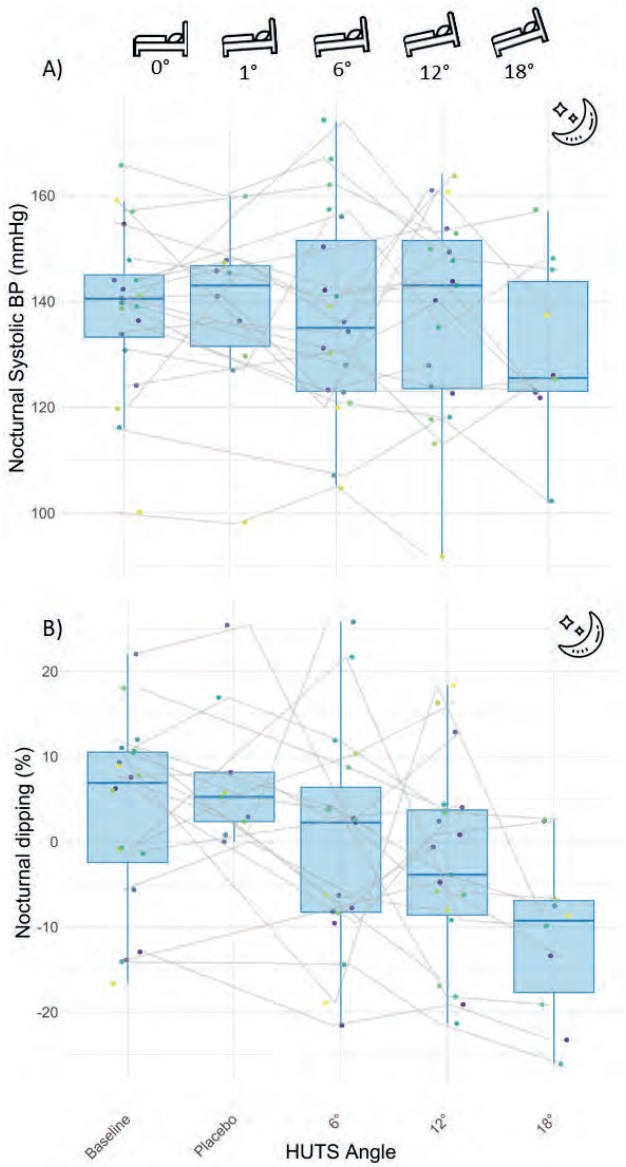

Figure 5.3. Nocturnal systolic blood pressure (BP) and dipping pattern over all five angles. All datapoints are the averages of all available ambulatory blood pressure measurements (ABPM's), performed once in each phase for all participants. Analysis was done with a linear mixed model, according to intention-to-treat principles. The models are adjusted for disease duration and age. Estimates are noted as change in BP (mmHg) per cm increase of the head of the bed. Baseline is horizontal sleeping, and placebo refers to 1° HUTS. A) the average nocturnal systolic BP as measured by the ABPM. (estimate: -0.03 mmHg/cm, 95% CI [-0.2;0.1], p=0.72) (baseline: n=20, placebo: n=10, 6°: n=20, 12°: n=19 and 18°: n=10) B) Nocturnal dipping pattern, calculated as the % reduction in nocturnal systolic BP, compared to the diurnal systolic BP (estimate: -0.12%/cm, 95% CI [-0.23;-0.005], p=0.04) (baseline: n=20, placebo: n=9, 6°: n=19, 12°: n=19 and 18°: n=10).

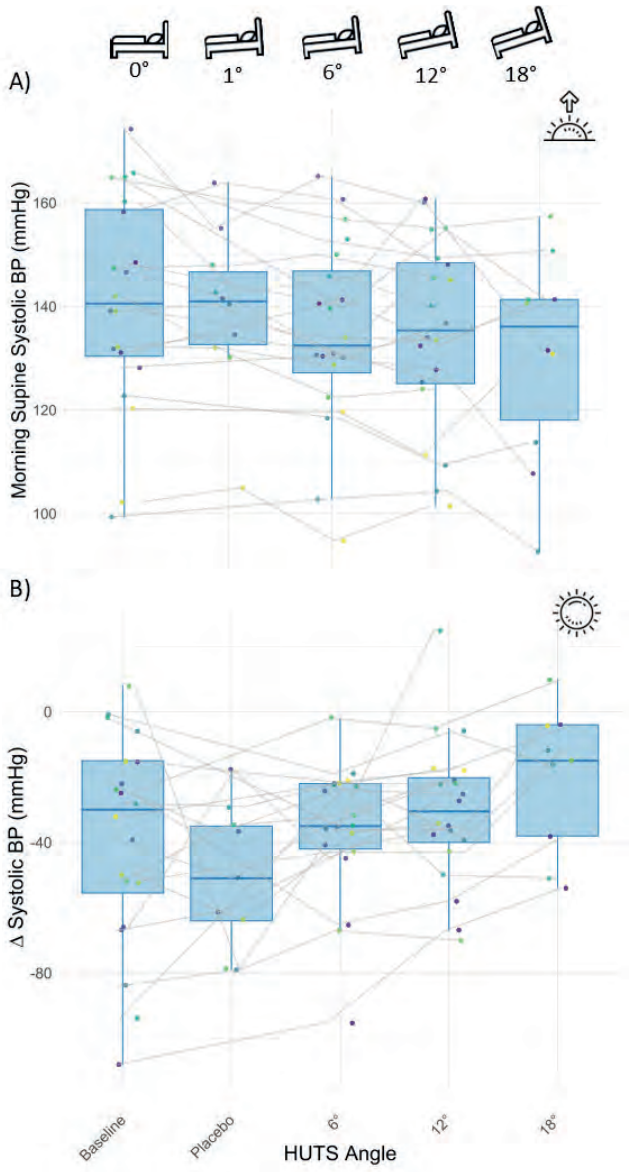

Figure 5.4. The supine blood pressure (BP) measurements in early morning and the active standing test during the morning. Baseline (0°) refers to the measurement in the week with horizontal sleeping, and placebo (1°) to the first two weeks of intervention for the delayed treatment group. Results were analysed with a linear mixed model, adjusted for disease duration and age. Estimates are noted in change in systolic BP (mmHg) per cm increase of the head of the bed. A) Early morning supine systolic BP, measured before getting out of bed. The average of the three last days in each phase is used, a total of nine supine BP measurements per datapoint of each participant. (Estimate: -0.11 mmHg/cm, 95% CI [-0.21;-0.01], p=0.03) (baseline: n=20, placebo: n=10, 6°: n=20, 12°: n=20 and 18°: n=10) B) The fall in systolic BP at 3 min during an active standing test. (Estimate:0.4 mmHg/cm, 95% CI [0.17;0.64], p=0.01; baseline: n=20, placebo: n=9, and 6°: n=19, 12°: n=20 and 18°: n=9).

Altogether, these results reflect an adherence to the protocol of over 5.6 out of 7 weeks (the criterion for compliance as defined in the study protocol) for 14 out of 20 participants, with a compliance of 100% for the 6° angle, 80% for the 12° angle and 60% for the 18° angle.

We found no change in sleep quality during the study (Pittsburgh Sleep Quality Index; p=0. 0.3708 Table S5.2), but the questions on comfort of HUTS indicated a clear decline in comfort with higher angles, starting with a median score of 5 for the placebo angle (IQR: 5-5) and 6° angle (IQR:4-5), which reduced to a score of 1 (IQR: 1-2) for the 18° angle (β =-0.07 point/cm, CI[-0.09;-0.06], p<0.0001). The main complaints were sliding down during the night for the 12° and 18° angles, disrupted sleep, and difficulties getting into bed. The main positive responses to HUTS were less complaints of orthostatic intolerance, participants perceived the 6° angle as comfortable, subjective improvement of nocturia at the higher angles, and habituation to tilted sleeping. Eleven out of 20 participants expressed an intention to continue with HUTS after the study period. No one reported a desire to continue sleeping at 18°, one person considered continuing sleeping at 12°, five people reported wanting to continue sleeping at a 6° angle, and the remaining five had not decided on how to continue.

No changes were found for nocturia frequency and nocturnal complaints experienced by participants, as reported by the ICIQ-Nocturia module. With stable medication usage, we found an improvement in the overall MDS-UPDRS score (visit 1: 56 (IQR 46.3-83.5), visit 2: 49 (IQR 41.5-71.5), p = 0.0114, Table S5.2). No changes were found for the Timed up and go test, Parkinson's Disease Questionnaire-39, Hospital Anxiety and Depression Scale or Mental Health Continuum-Short Form. There was a non-significant reduction in fear of falling, as measured by the Falls Efficacy Scale (Table S5.2). Fall incidents occurred eight times during the trial in six participants, four of whom fell at least once during the 6 months prior to inclusion. Two falls occurred during the baseline phase, three during the 1°, two during the 6° and one during the 12° HUTS phase. Participants indicated that a low BP might have caused three falls, but likely not for one fall. It was unclear for the remaining four falls.

Discussion

This study did not meet its primary endpoint: the overall average nocturnal SBP was not altered by any of the HUTS angles. We did observe positive effects of HUTS on several secondary outcomes, including an improved BP regulation in an

inclination-dependent manner (i.e. steeper angles offered greater improvements). The nocturnal dipping pattern and supine SBP just after awaking improved and HUTS resulted in a higher diurnal SBP and smaller SBP fall upon standing, with a reduction in OH complaints. All changes were inclination-dependent but higher angles were associated with tolerability issues.

This is formally a negative trial, since we found no improvement in the primary outcome, namely nocturnal SBP. The absent improvement in SH was in hindsight perhaps not entirely unexpected. Our choice for nocturnal SBP as primary outcome was based mainly on prior expert clinical consensus and guidelines [8], but was not supported by a strong body of published evidence. Indeed, our negative findings are consistent with the outcome of the few earlier studies that also used nocturnal SBP as outcome, and that neither found improvements. Specifically, this earlier work studied a 5° inclination in mixed OH populations and observed no change in nocturnal SBP [14,17]. The second reason why we did opt for nocturnal SBP as primary outcome was the anticipated impact on the participants' health. The Atherosclerosis Risk in Communities (ARIC) study reported a higher cardiovascular risk in those with SH, regardless of seated hypertension, compared to those with seated hypertension alone [5]. In patients with autonomic failure, SH is linked to an increased risk for target organ damage, cardiovascular events, and premature mortality [7]. It therefore remains important to strive for improvements in nocturnal SH using other therapies.

Despite the absence of effects on average nocturnal SBP, we were encouraged to see a positive effect of HUTS on other signs of blood pressure regulation, including two indirect measures of nocturnal blood pressure. First, HUTS was associated with a reduction in early morning supine SBP, which is a careful indication that HUTS did ameliorate some elements of the recumbent hypertension. However, this effect was weak (approximately 1 mmHg per 10cm elevation) and was insufficient to treat SH properly. Drug treatments, such as losartan, are more effective in reducing nocturnal supine BP, but carry the risk of aggravating OH during the night and morning [2,8]. Second, HUTS promoted nocturnal SBP dipping, which refers to the natural physiological BP reduction overnight. The observed improvement in this nocturnal dipping pattern is potentially relevant as absence of nocturnal dipping has been linked to poor survival and major cardiovascular events in patients with hypertension [23].

HUTS also resulted in improvements in several daytime outcomes, including both objective OH measurements and subjective complaints. Specifically, HUTS induced an inclination-dependent improvement of OH measurements. Our findings translate

into a reduced SBP fall by 8 mmHg for 6° HUTS, 17 mmHg for 12° and 25 mmHg for 18°. The observed effect size for the 6° inclination is comparable with the increase in SBP in a previous HUTS trial among 100 subjects with various, including iatrogenic, causes of mild OH [14]. Another non-pharmacological intervention, namely use of abdominal binders, improved the SBP fall by 10 mmHg in PD [24]. When we interpolate our data to reach a comparable 10mmHg improvement, this would equate to an angle of just over 7°. These BP changes were parallelled by subjective improvements, as documented using questionnaires which consistently indicated improved orthostatic tolerance following HUTS. These findings suggest that the relatively small BP changes were clinically relevant. We did not find a ceiling effect for the efficacy of HUTS: the higher the HUTS angle, the larger the beneficial effect on BP. Prior case studies suggested stronger BP effects with inclinations even higher than our maximal tilt angle,[15] but our findings indicate that tolerability limits acceptance. Our maximal (18°) and intermediate angle (12°) were more effective than the lower one (6°) but also created more discomfort. A previous study reported that with proper guidance, long-term implementation of a 12° inclination was feasible in all nine subjects with autonomic failure [16]. Our study corroborates this, as 80% of participants completed two weeks of sleeping at 12° HUTS. In contrast, only six participants completed sleeping at 18° for 2 weeks, but none of them considered continuing at this angle due to discomfort.

Although this is a negative trial, we feel that the observed positive effects on various secondary outcomes justify a phase 3 study, to confirm and extend the present findings. Such a study could also search for possible long-term health benefits. The observed daytime improvement following HUTS, albeit small, could help to promote cardiovascular health. In persons with autonomic failure, OH and SH have additive effects on poor vascular outcomes: repeated cerebral hypoperfusion due to OH may promote cerebrovascular damage, and so does the SH [2,5,7,25]. Prolonged follow-up of persons who faithfully adhere to HUTS is needed to see whether sustained improvements in OH, in the absence of reduced SH, is associated with a better prognosis.

Our study had a unique design, with a stepwise increase in sleeping angle, combined with a delayed treatment start in the control group. In contrast to a parallel groups design this does not allow for an exact 1-to-1 comparison of the different angles versus placebo. However, one advantage is that participants in the delayed start group could also be used to estimate the cumulative effect of HUTS angles. Moreover, increasing the angle step-by-step, and at home, is similar to the way this treatment would be implemented in clinical practice. Randomly assigning people to (potentially) large angles would presumably have hampered feasibility.

This study was not without shortcomings. We already mentioned why the primary outcome may not have been optimal. Sample size was another: we originally aimed to include 50 participants [21], but stopped recruitment when 20 participants were included due to recruitment difficulties, primarily because of the perceived study load. However, even this small sample was sufficient to demonstrate consistent, inclination-dependent effects across various cardiovascular outcomes (all secondary outcomes). Larger sample sizes are needed to detail the effect sizes with more precision, to further compare possible efficacy differences between tilt angles, and to allow for subgroup analyses. For example, the effect of HUTS may differ between those with peripherally or centrally located autonomic nervous system lesions [26]. We could not address this in our small population which predominantly included persons with PD with mainly peripheral autonomic failure [3]. Another drawback is that even though all participants had OH prior to participation, one participant did not exhibit OH during the trial. Our intention-to-treat analysis yielded positive results on secondary outcomes, even when including this participant and those who applied HUTS at a lower than desired angle.

The exact working mechanism of HUTS remains unclear. Our findings challenge the hypothesis that HUTS acts on BP control by reducing SH-induced nocturia [9,27]. We found that HUTS changed neither average nocturnal SBP nor nocturnal urine production. Sleeping at a 13° angle reduced nocturia by 145 ml in healthy subjects [18], but no change in nocturnal urine production was noted in a cohort with mild OH following 5° HUTS [14], which is in line with our findings. Neurogenic OH is characterized by inability to adapt vascular resistance to postural changes (under normal circumstances, this is raised during standing and lowered while supine) [26,28]. HUTS could alter baroreflex functioning by augmenting the sensitivity of the residual baroceptors. The heads-up position could cause a relatively lower BP at the level of the carotid body, hereby deactivating baroreceptors which, in turn, may trigger residual sympathetic vasoconstriction and compensatory neurohumoral changes, thus preventing nocturia [29]. Following the logic of gravity, the kidneys are located more caudally than the heart, resulting in a relatively higher BP there that could cancel out the neurohumoral effects on nocturia. Maintenance of daytime leg oedema due to the inclination during the night may be an alternative explanation. We did not investigate this, but HUTS was previously associated with increased ankle circumference and greater prevalence of oedema [12-14,18]. Leg oedema may act as a "water jacket" and increase vascular resistance in the lower extremities through a minor fluid shift from the intravascular to the interstitial space, thus preventing excessive venous pooling [19]. Such a fluid shift, even when minor, could explain the ameliorated orthostatic BP fall without impacting nocturia. However, we suspect

that leg oedema contributes only partially to the effects of HUTS because calf compression stockings offer only negligible improvement of BP control [30]. Another factor to consider is volume status, which may also determine the effect of HUTS. A case series of six people with OH suggested that HUTS is more effective when combined with low doses of fludrocortisone [16]. Further work therefore remains needed to better understand how HUTS works.

Finally, pending generation of further evidence, we can consider several pragmatic aspects related to a possible real-life implementation. We found considerable variations in the response to HUTS, which calls for a personalized approach. The efficacy of HUTS is evaluated easily; anecdotal evidence suggests that any improvements disappear rapidly following discontinuation of HUTS, with complaints returning within one or two days [12,13,16]. We recommend to implement HUTS using an automated, motorized bed that can mechanically move into the anti-Trendelenburg position. A stationary frame is also possible but seems more cumbersome for those with advanced movement disorders. Although greater HUTS angles produced stronger effects on BP homeostasis, we recommend to gradually increase the angle until a personal optimum is reached. We noted that tolerability may increase over time. Interestingly, all participants who did not tolerate the highest inclination completed the trial at their prior lower angle; this effect was seen in both treatment arms (i.e., those ending at 18° and those ending at 12° inclination). This suggests that tolerability is at least partially contextual, and related to titration scheme or prior expectations. Nurse specialists or physiotherapists can play an important role in optimising HUTS implementation. An animation video (https://radboudumc.bbvms.com/view/default/6197706.html) can help them explain how HUTS can be implemented. With proper guidance, higher angles up to 12° (42 cm) seem feasible and should be encouraged.

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Supplementary material

Supplementary Table S5.1. All self-reported co-morbidities at baseline.

	Immediate treatment group (n=10)	**Delayed treatment group (n=10)**
Average per person (median, IQR)	1 (0;1.25)	1 (0.75;2)
Neurology		
Migraine	1 (10%)	0 (0%)
Neuropathy	1 (10%)	0 (0%)
Past cerebrovascular disease	1 (10%)	1 (10%)
Cardiology		
Atrial fibrillation	1 (10%)	2 (20%)
Pacemaker	0 (0%)	1 (10%)
Coronary artery disease	2 (20%)	0 (0%)
Urology		
Recurrent urinary tract infections	0 (0%)	1 (10%)
Prostate cancer	1 (10%)	0 (0%)
Nephrology		
Solitary functioning kidney	0 (0%)	1 (10%)
Respiratory		
Asthma	0 (0%)	2 (20%)
COPD	1 (10%)	0 (0%)
Rheumatology		
Sarcoidosis	1 (10%)	1 (10%)
Endocrinology		
Diabetes Mellitus	2 (20%)	0 (0%)
Addison's disease	1 (10%)	0 (0%)
Prolactinoma	0 (0%)	1 (10%)
Hypothyroidism	1 (10%)	0 (0%)
Osteoporosis	1 (10%)	0 (0%)

Supplementary Table S5.2. Questionnaire outcome measures.
All questionnaires from the in-clinic sessions at the start of participation (visit 1) and at the end of participation (visit 2) are reported in median's and IQR's and analysed with the Wilcoxon Signed Rank test for paired samples. * Indicates a significant outcome for a two-sided test with threshold α = 0.05.

Questionnaire	visit 1	visit 2	p-value
OHAS	5.3 (2.9;6.5)	3.9 (2.2;5.1)	0.0144*
SCOPA-AUT (cardiovascular)	3 (2;5)	2 (2;4)	0.0050*
International Consultation on Incontinence Questionnaire-Nocturia Module†			
Urinary frequency diurnal	1 (1;1)	1 (0;1)	0.0060*
Urinary symptom burden diurnal	3 (1;5.75)	3 (0.25;7.75)	0.5450
Urinary frequency nocturnal	2 (1.25;3.75)	2.5 (1;3)	0.4374
Urinary symptom burden nocturnal	2 (1.25;7.75)	2 (1;7.75)	0.6244
Pittsburgh Sleep Quality Index	6 (4.75;8.0)	6 (4.75;9.0)	0.3708
MDS-UPDRS	56 (46.3;83.5)	49 (41.5;71.5)	0.0114*
Part I	16 (11.5;18.5)	15 (12;17)	0.1681
Part II	13 (7;17)	12 (6.5;17)	0.2191
Part III	28 (22;38.5)	25 (20;35.5)	0.0456*
Part IV	3 (0;6.5)	0 (0;6)	0.1196
Timed up and go	9.34s (7.18;10.88)	9.17s (7.42;10.32)	0.8696
Parkinson Disease Questionnare-39	36.5 (24.8;57)	38.5 (26.5;52)	0.9518
Hospital Anxiety and Depression Scale			
Fear	3.5 (2.75;6)	4.5 (1;7)	0.8489
Depression	4.5 (3;5.5)	5 (3;7.25)	0.9302
Mental Health Continuum-Short Form	40 (29.75;49.5)	40.5 (34;49)	0.8369
Falls Efficacy Scale	32 (22;6)	26 (21;33)	0.0579

SCOPA-AUT; Scale for Outcomes in Parkinson's Disease-Autonomic Dysfunction. OHSA; Orthostatic Hypotension Symptom Assessment scale. MDS-UPDRS; Movement disorders society-unified Parkinson's disease rating scale.

†The International Consultation on Incontinence Questionnaire-Nocturia Module data was collected in the baseline week and in phase 3, instead of at visit 1 and visit 2.

Part III

Haemodynamics

Chapter 6

Haemodynamic determinants of supine hypertension in patients with classical orthostatic hypotension

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Abstract

Objective: The relation between classical orthostatic hypotension (cOH) and supine hypertension (SH) is largely unknown. We investigated the relative contributions of heart rate (HR), stroke volume (SV) and total peripheral resistance (TPR) to supine and upright blood pressure (BP).

Methods: In this retrospective study, tilt tests were divided in four groups: 19 normotensive and 61 hypertensive controls, 50 cOH patients with SH (cOH/SH+) and 30 without (cOH/SH-). Hypertension was defined as supine systolic BP (SBP) ≥140mmHg. We used linear regression to relate cOH severity to supine SBP, and the logratio method to analyse relative contributions of HR, SV and TPR. P-values <0.003 were considered significant.

Results: High supine SBP was associated with high TPR in patients and controls. Orthostatic SBP decrease in cOH was larger in those with higher supine SBP. The main parameter explaining this effect was a high supine TPR that did not increase after tilt in cOH/SH+ compared to cOH/SH- (logratio difference, $p<0.002$). SV logratio decreased more in cOH/SH- than in cOH/SH+ ($p<0.003$), and HR logratio contributed similarly to orthostatic SBP in both cOH groups ($p=0.028$).

Conclusion: While high supine TPR explained SH, a failure to further increase upright TPR explained the orthostatic SBP fall in patients. Autonomic failure can explain the SBP fall but not directly the high supine TPR that causes SH. We assume that slow-acting humoral vasoconstrictors are triggered in the upright position and continue to act after tilting back, causing high TPR and SH.

Abbreviations

BP: Blood pressure
cOH: Classical orthostatic hypotension
DBP: Diastolic blood pressure
HR: Heart rate
MAP: Mean arterial pressure
nOH: Neurogenic orthostatic hypotension
OH: Orthostatic hypotension
SBP: Systolic blood pressure
SH: Supine hypertension
SV: Stroke volume
TPR: Total peripheral resistance
TTT: Tilt table test

Introduction

Orthostatic hypotension (OH) is common and associated with complaints in the upright position such as dizziness and syncope. Classical orthostatic hypotension (cOH) is defined as a drop in systolic blood pressure (SBP) of at least 20 mmHg or a diastolic blood pressure (DBP) drop of at least 10 mmHg within three minutes of standing or after tilt during a tilt table test (TTT) [1]. There are many possible causes of cOH, such as hypovolemia, medication use or heart failure, as well as disorders of autonomic nervous control that result in baroreflex failure [2,3]. When the latter regards efferent nerve fibres, the result is called neurogenic orthostatic hypotension (nOH), occurring for example in multiple system atrophy, Parkinson disease and pure autonomic failure [4].

A problem frequently associated with nOH is supine hypertension (SH). SH may occur in 50% of a nOH population [5,6]. Both cOH and SH impact quality of life and carry risks of damage to kidneys, heart and brain. cOH and SH are independently related to cardiovascular and non-cardiovascular mortality, making them important treatment targets [7-12].

The mechanisms of SH are unclear [6]. Some authors sought explanations for SH in neurohumoral effects, such as a reduction in plasma noradrenalin in those with peripheral neurodegeneration [13], or in residual sympathetic tone in central autonomic dysfunction like multiple system atrophy [6,14,15]. Various consensus statements described an association between SH and the severity of OH, defined here as the magnitude of the BP decrease after assuming the upright position [1,16]. The mechanism of this association is uncertain.

The three haemodynamic components of mean arterial pressure (MAP) are total peripheral resistance (TPR), stroke volume (SV) and heart rate (HR). We recently found that a failure of TPR to increase in the upright position was the main mechanism behind cOH [13,14,17].

Here, we compare haemodynamic parameters of SH in cOH patients to those causing hypertension in controls, determine whether the severity of cOH is related to SH, and explore the mechanism of this association. The logratio method allows a fully quantitative comparison of relative BP changes using HR, SV and TPR [18,19]. As the contributions of HR, SV and TPR in various causes of cOH are largely unknown, we studied cOH regardless of cause and did not a priori distinguish between nOH and non-nOH [17].

Methods

Population

The study was retrospective and based on the TTT database of Leiden University Medical Centre (LUMC, Leiden, The Netherlands). All patients were seen at the department of Neurology between January 2010 and July 2022 as part of regular care after being referred for syncope or suspected autonomic problems. In this period 3173 TTTs were performed (Figure 6.1). TTT records were first selected based on technical quality. To qualify as cOH, current definitions of cOH had to be met (i.e., a sustained SBP decrease of at least 20 mmHg or DBP decrease of at least 10 mmHg within three minutes of tilt). We included all cases of cOH, not confining data to any circumscribed group. The results may therefore represent various underlying conditions, although patients with known causes of neurogenic cOH formed the majority [17]. Patients were excluded if they had a pacemaker or additional TTT abnormalities. The control population comprised people who visited the outpatient clinic for dizziness but who exhibited no abnormalities during TTT, did not have autonomic dysfunction, and in whom complaints were likely due to a non-circulatory origin. Controls were groupwise matched for sex and age. Medication use and reason for the hospital visit were noted. We stress that in this patient group medication use did not affect the haemodynamic pattern of cOH [17]. Since the test was exclusively performed as part of regular care, medical-ethical approval was not needed according to Dutch law.

Tit table test protocol

The LUMC TTT protocol consisted of a rest period of 10 minutes followed by 70° head-up tilt for 20 minutes or until syncope or limiting complaints of pre-syncope occurred. Continuous BP measurements were gathered with the non-invasive volume clamp method using either the Finapres NOVA (Finapres Medical Systems, Enschede, The Netherlands) or the Nexfin (BMEye, Amsterdam, Netherlands). At least one electrocardiography lead and video-electroencephalography were part of the standard procedure [20,21].

Haemodynamic analysis

Video records were reviewed to extract the time of head-up tilt and other events with an accuracy of 1 second. Modelflow was used to derive beat-to-beat data of MAP, SBP, DBP, HR, SV and TPR. Modelflow is a physiological model that uses the shape of the continuously recorded SBP curve per heart beat to infer stroke volume; together with MAP and HR this allows calculation of TPR [19,22]. All six haemodynamic variables were resampled at 1 Hz using linear interpolation and interactively

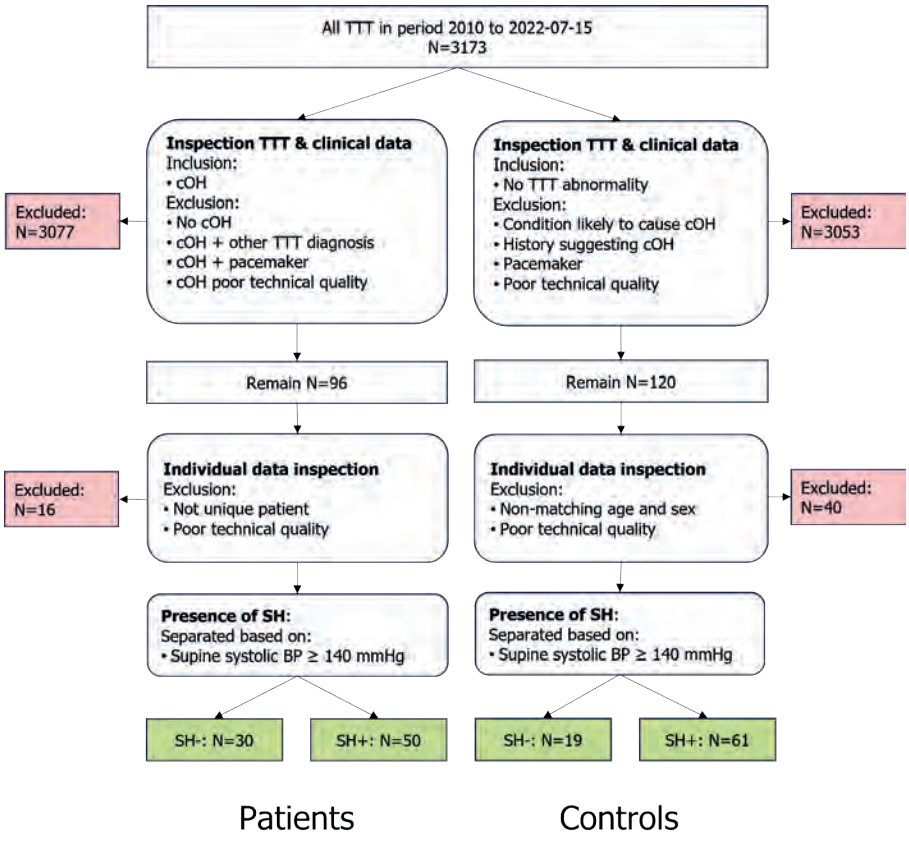

Figure 6.1. Flow diagram of participant selection.

Tilt table test recordings and reports were considered when selecting the patients and controls to include in the analysis.

BP, blood pressure; cOH, classical orthostatic hypotension; SH, supine hypertension; TTT, tilt table test.

cleaned of artifacts caused by extrasystolic beats, movement, or technical issues, using purpose-written software. Periods with artifacts were interpolated if they lasted less than 5 seconds and were flanked by stable data; if not, they were deleted.

Periods up to 6 minutes before tilt and up to 10 minutes after tilt were extracted. The beginning and end of this period could be shortened to avoid contamination with a different condition, e.g., active stand, another test, or a change in posture. To illustrate the temporal course of events, continuous haemodynamic data were plotted, but to simplify the quantitative analysis we reduced measurements to only the baseline and upright positions. As a measure of baseline supine values, we averaged measurements per person over 160 seconds, lasting from 180 seconds to

20 seconds before tilt for all variables (MAP, SBP, DBP, HR, SV and TPR). As a measure of the orthostatic condition we averaged data over 60 seconds, from 180 to 240 seconds after tilt (i.e., the fourth minute), corresponding with the convention to assess cOH 3 minutes after assuming the upright position.

Patient and control groups were each split into two groups, based on the consensus for SH in patients with nOH: a SBP of at least 140 mmHg or DBP of at least 90 mmHg, after at least five minutes rest in the supine position [16]. The groups were labelled SH+ and SH-, recognising that the term "SH" is strictly speaking not intended for use in controls without cOH.

Logratio analysis

First, we calculated the average of the supine baseline period for each person for MAP, HR, SV and TPR. The values for the entire time series were divided by this average value, resulting in time series of ratios with a value of 1 for the baseline period. The logarithm was then taken of all these values, resulting in time series of MAP_{LR}, HR_{LR}, SV_{LR} and TPR_{LR}. Note that MAP_{LR} is the sum of HR_{LR}, SV_{LR} and TPR_{LR} for each point in time. A negative logratio indicates a reduction compared to the baseline supine value, and a positive logratio indicates an increase [19,23]. For the statistical analysis the average of upright values were calculated per person over the fourth minute after tilt. All analyses were performed in Matlab version R2022a. For a post-hoc analysis of the relationship between the DBP and the reduction in SBP upon tilt, all patients were split into a low DBP group and a high DBP group according to the median of the supine DBP.

Statistics

We compared haemodynamic parameters of the fourth minute after tilt with supine values. As not all data were normally distributed, we used the two-tailed Mann-Whitney U-test throughout for consistency. To analyse the BP change in response to upright tilt we applied Pearson's linear regression, comparing the difference in SBP between the upright and supine position to the supine value. To correct for multiple testing the Bonferroni correction was applied for 18 comparisons (Table 6.2), resulting in a significance threshold of $p<0.003$. BP comparisons between SH+ and SH- groups were excluded from this correction, because these differed by definition. We reported a result as a trend when the p-value was $0.003<p<0.01$. For post-hoc analyses of interindividual variability in haemodynamic control Fisher's exact test was used, with a significance threshold of $p<0.05$.

Results

We selected 160 TTT records: 80 patients and 80 controls (Table 6.1). Fifty cOH patients (62.5%) and 61 controls (76.3%) met the systolic SH criterion and were categorised as SH+; the diastolic criterion for SH was met by 24 cOH patients (30%) and 25 controls (31.3%), all of whom already met the systolic criterion. Controls without SH were younger than controls with SH (p=0.035, Table 6.1). For patients with cOH, there was no difference in age between the two subgroups.

Table 6.1. Demographics of the population. Clinical profiles of all controls and patients with classical orthostatic hypotension (cOH) are displayed as well as the subgroups separated based on the presence or absence of supine hypertension (SH). *Two patients received a combination therapy of midodrine and fludrocortisone.

Demographics						
	Control total (n=80)	**Control SH- (n=19)**	**Control SH+ (n=61)**	**cOH total (n=80)**	**cOH SH- (n=30)**	**cOH SH+ (n=50)**
Age (years; median (range))	65 (50-87)	61 (50-75)	67 (50-87)	68 (43-90)	65.5 (43-79)	68.8 (50-90)
Female (%)	26 (33%)	4 (21%)	22 (36%)	24 (30%)	7 (23%)	17 (34%)
Duration cOH (months; median (range))	-	-	-	24 (1-288)	36.1 (3-120)	42.6 (1-288)
Diagnosis						
PAF	-	-	-	8	3	5
MSA	-	-	-	10	4	6
PD	-	-	-	27	10	17
Other nOH (likely)	-	-	-	13	4	9
Diabetes mellitus	-	-	-	3	0	3
Drug induced OH	-	-	-	4	1	3
Other non-nOH	-	-	-	15	8	7
Medication						
BP increasing drugs	**2**	**0**	**2**	**19***	**8**	**11***
BP lowering drugs	**42**	**6**	**36**	**50**	**20**	**30**

BP, blood pressure; cOH, classical orthostatic hypotension; PAF, pure autonomic failure; PD, Parkinson Disease; MSA, multiple system atrophy; nOH, neurogenic orthostatic hypotension; SH, supine hypertension.

Haemodynamic variables

SH+ groups for both controls and cOH patients had, by definition, higher supine MAP, SBP and DBP than SH- groups, which persisted after tilt (Figure 6.2, all $p<0.0001$ Table 6.2). The upright position caused a more pronounced MAP fall in the cOH/SH+ group than in the cOH/SH- group ($p=0.0003$, Figure 6.2). In the entire cOH group higher supine SBP was related to a larger SBP fall ($r=-0.470$, $p=2.4*10^{-8}$, Figure S6.1). The tilt-induced SBP response in controls did in contrast not depend on baseline SBP ($r=-0.012$, $p=0.863$, Figure S6.1). When the SBP change after tilt was expressed as a difference between supine and fourth minute SBP, the fall in the high DBP group was higher (53±30 mmHg) than in the low DBP group (33±15 mmHg, $p=0.0004$). However, the ratio of upright to supine SBP did not differ between those with high DBP (0.70±0.15 mmHg) and those with low DBP (0.75±0.10 mmHg, $p=0.09$).

We will discuss differences between SH+ and SH- groups within patients and controls, with regards to the three BP-determinants HR, SV and TPR.

Heart rate

HR did not differ between SH+ and SH- groups for patients or controls in either the baseline supine or the upright condition (Table 6.2, Figure 6.2).

Stroke volume

Supine SV did not differ between SH- and SH+ groups for cOH patients or controls (controls: $p=0.288$, cOH: $p=0.151$, Table 6.2). SV dropped immediately after tilt in all four groups. The fourth minute standing SV values did not differ between SH+ and SH- groups in controls ($p=0.498$) nor in cOH patients ($p=0.673$, Table 6.2).

Total peripheral resistance

Within the control group, we found a trend for higher supine TPR in the SH+ group than in the SH- group (control/SH- TPR=1.0, control/SH+ TPR=1.6, $p=0.0067$, Table 6.2). In patients, the SH+ group showed a higher TPR in the baseline supine position than the SH- group (cOH/SH- TPR = 1.0, cOH/SH+ TPR = 1.4, $p=1.5*10^{-5}$, Table 6.2).

TPR showed large differences between cOH patients and controls within the SH+ and SH- groups (Figure 6.2). When tilted to an upright position, TPR increased more and ended higher in the control/SH+ group than in the cOH/SH+ group, in whom TPR did not increase after head-up tilt (fourth minute: control/SH+ TPR=2.1, cOH/SH+ TPR=1.3, Figure 6.2). Due to the different response to tilt of this cOH/SH+ group, the TPR in the fourth minute of tilt did not differ for the cOH/SH- and cOH/SH+ groups (cOH/SH- TPR=1.1, cOH/SH+ TPR=1.3, $p=0.016$; Table 6.2).

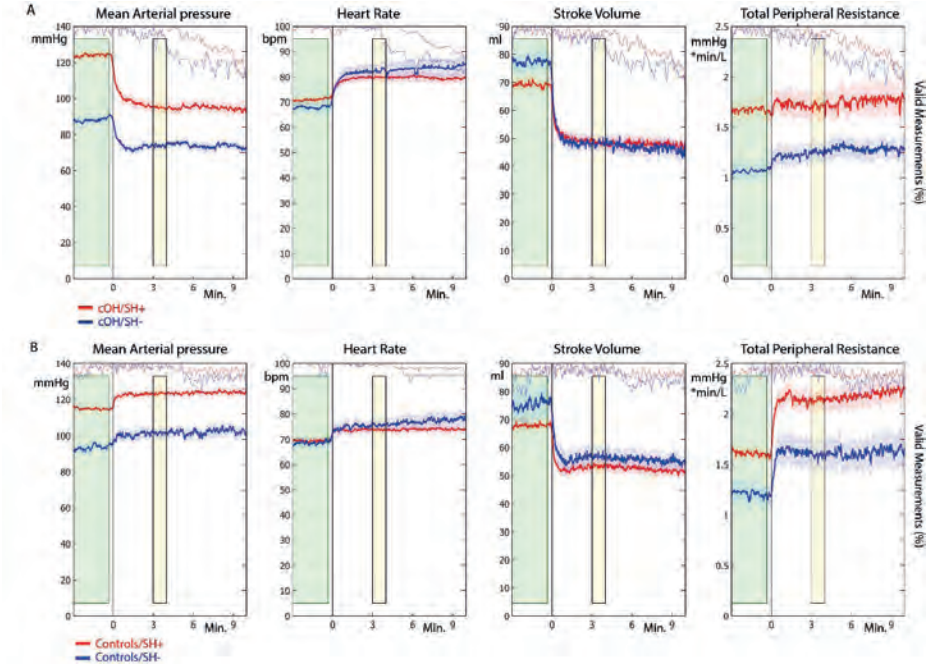

Figure 6.2. Haemodynamic changes over time.

For A) patients with classical orthostatic hypotension (cOH)(n=80) and B) controls (n=80), the mean arterial pressure (MAP), heart rate (HR), stroke volume (SV) and total peripheral resistance (TPR) are plotted as a group average with one standard error. Both cOH patients and controls were divided using a threshold of supine systolic BP of 140mmHg, resulting in a supine hypertension group (SH+, red) and a supine normotension group (SH-, blue). Thin pale-coloured lines indicate the percentage of measurements valid for each group at each point in time, with 100% at the top of the right-hand axis. The vertical line at 0 seconds indicates the moment the act of tilting up was completed. The green rectangle indicates the period used for the supine baseline, and the yellow rectangle highlights the fourth minute of the measurement used to quantify the upright position.

Table 6.2. Haemodynamic parameters. Comparisons of the three parameters and blood pressure during head-up tilt testing. The comparisons with a p-value smaller than 0.01 were classified as a trend, and due to Bonferroni correction those with a p-value below 0.003 classified as significant.

	Control SH- (n=19) Median (IQR)	**Control SH+ (n=61) Median (IQR)**	**P-value**	**cOH/SH- (n=30) Median (IQR)**	**cOH/SH+ (n=50) Median (IQR)**	**P-value**
Supine						
MAP (mmHg)	92.9 (82.8-101.1)	115.8 (107.3-122.9)	$8.1 * 10^{-9}$	89.5 (80.6 - 94.3)	121.6 (109.7 - 137.5)	$7.0 * 10^{-13}$
SBP (mmHg)	124.6 (114.4-130.3)	159.0 (148.3-171.1)	$5.9 * 10^{-11}$	125.6 (111.8-134.4)	169.8 (159.1-189.6)	$9.4 * 10^{-14}$
DBP (mmHg)	72.9 (65.3-80.0)	88.2 (80.7-93.6)	$3.4 * 10^{-6}$	66.5 (61.9-73.4)	86.7 (79.4-102.0)	$8.3 * 10^{-11}$
HR (bpm)	67.0 (61.7-76.0)	66.2 (62.4-78.8)	0.769	67.1 (61.9-73.4)	70.4 (64.4-76.2)	0.212
SV (ml)	67.8 (56.0-89.6)	63.9 (52.4-77.4)	0.288	75.7 (64.2-87.4)	73.1 (56.5-83.1)	0.151
TPR (mmHg * sec/ml)	1.0 (0.8-1.6)	1.6 (1.1-2.0)	0.0067	1.0 (0.8-1.2)	1.4 (1.2-2.0)	$1.5 * 10^{-5}$
Fourth minute 70° tilt						
MAP	98.2 (86.9-112.9)	124.6 (114.3-131.6)	$3.6 * 10^{-7}$	73.4 (67.7-79.6)	96.2 (82.4-104.8)	$1.4 * 10^{-6}$
SBP	123.0 (114.9-140.7)	163.5 (152.8-180.7)	$3.6 * 10^{-9}$	95.1 (84.2-103.1)	124.8 (103.5-141.9)	$2.0 * 10^{-7}$
DBP	81.2 (69.0-93.8)	95.9 (88.9-107.4)	$2.1 * 10^{-4}$	63.3 (54.7-67.4)	76.9 (64.0-90.4)	$2.2 * 10^{-5}$
HR	76.8 (70.1-82.8)	72.5 (64.9-82.9)	0.314	80.6 (72.5-88.8)	77.8 (71.9-87.0)	0.709
SV	51.7 (40.1-72.5)	47.7 (39.2-66.1)	0.498	47.2 (40.1-55.3)	52.2 (35.8-58.9)	0.673
TPR	1.4 (1.1-2.1)	2.1 (1.5-2.7)	0.012	1.1 (0.8-1.6)	1.3 (1.1-2.1)	0.016
Logratio fourth minute 70° tilt						
MAP_{LR}	0.032 (0.008-0.046)	0.027 (0.002-0.055)	0.643	-0.064 (-0.116 to -0.046)	-0.090 (-0.161 to -0.055)	0.047
HR_{LR}	0.046 (0.025-0.064)	0.021 (0.009-0.047)	0.018	0.058 (0.045 – 0.107)	0.045 (0.018 – 0.081)	0.028
SV_{LR}	-0.125 (-0.174 to -0.083)	-0.119 (-0.151 to -0.069)	0.325	-0.196 (-0.226 to -0.174)	-0.150 (-0.197 to -0.108)	$1.5 * 10^{-3}$
TPR_{LR}	0.110 (0.069-0.153)	0.105 (0.054-0.175)	0.709	0.055 (0.016 – 0.085)	-0.002 (-0.055 to 0.054)	0.0025

DBP, diastolic blood pressure; HR, heart rate; LR, logratio; MAP, mean arterial pressure; OH, orthostatic hypotension; NS, not significant; SH, supine hypertension; SV; stroke volume; TPR, total peripheral resistance.

Logratio analysis

Figure 6.3 shows cumulative logratio values of HR, SV and TPR and their relation to MAP. Within the control group, MAP_{LR}, HR_{LR}, SV_{LR} and TPR_{LR} did not differ between SH+ and SH-, showing that the *relative* contribution to standing MAP in controls did not depend on SH (Figure 6.3, Table 6.2).

Mean arterial pressure

In the cOH group, MAP_{LR} did not differ between the SH+ and SH- groups (cOH/SH-: MAP_{LR}=0.064 log units, cOH/SH+: MAP_{LR}=0.090 log units, p=0.047, Table 6.2, Figure 6.3). MAP_{LR} did not differ within the control group either (control/SH-: MAP_{LR}=0.032 log units, control/SH+: MAP_{LR}=0.027 log units, p=0.643, Table 6.2, Figure 6.3.

Heart rate

HR_{LR} was positive after tilt, indicating an increase and did not differ between the SH- and SH+ groups, neither within patients nor within controls (Table 6.2).

Stroke volume

SV_{LR} was negative, indicating a decrease; in cOH patients SV_{LR} showed a larger SV decrease in the SH+ than in the SH- group (p=0.00145, Table 6.2). In the control group, SV_{LR} did not differ between SH+ and SH- subgroups.

Total peripheral resistance

Within the control group, TPR_{LR} did not differ between SH+ and SH- (p=0.709, Table 6.2, Figure 6.3). For patients however, TPR_{LR} was positive in the cOH/SH- group and negative in the cOH/SH+ group. In other words, TPR decreased in the SH+ group but increased in the SH- group (p=0.0025, Table 6.2, Figure 6.3A).

Interindividual variability

Pronounced individual variation in contributions of the three haemodynamic variables to MAP was apparent in the fourth minute logratio values (Figure S6.2). Within the cOH group, the most severe OH occurred in patients with a negative TPR_{LR}, i.e., a decrease of TPR. This held for both SH+ and SH- patients. In the cOH/SH+ group 27 (54%) subjects had a decrease of TPR, coinciding with large reductions in MAP regardless of initial supine BP. Within the cOH/SH- group, only 6 (20%) cases had a decrease of TPR, also mainly regarding those with larger reductions of MAP_{LR}. The proportion of those with a reduction of TPR was larger in cOH/SH+ patients than in cOH/SH- patients (Fisher's exact test, p=0.0045).

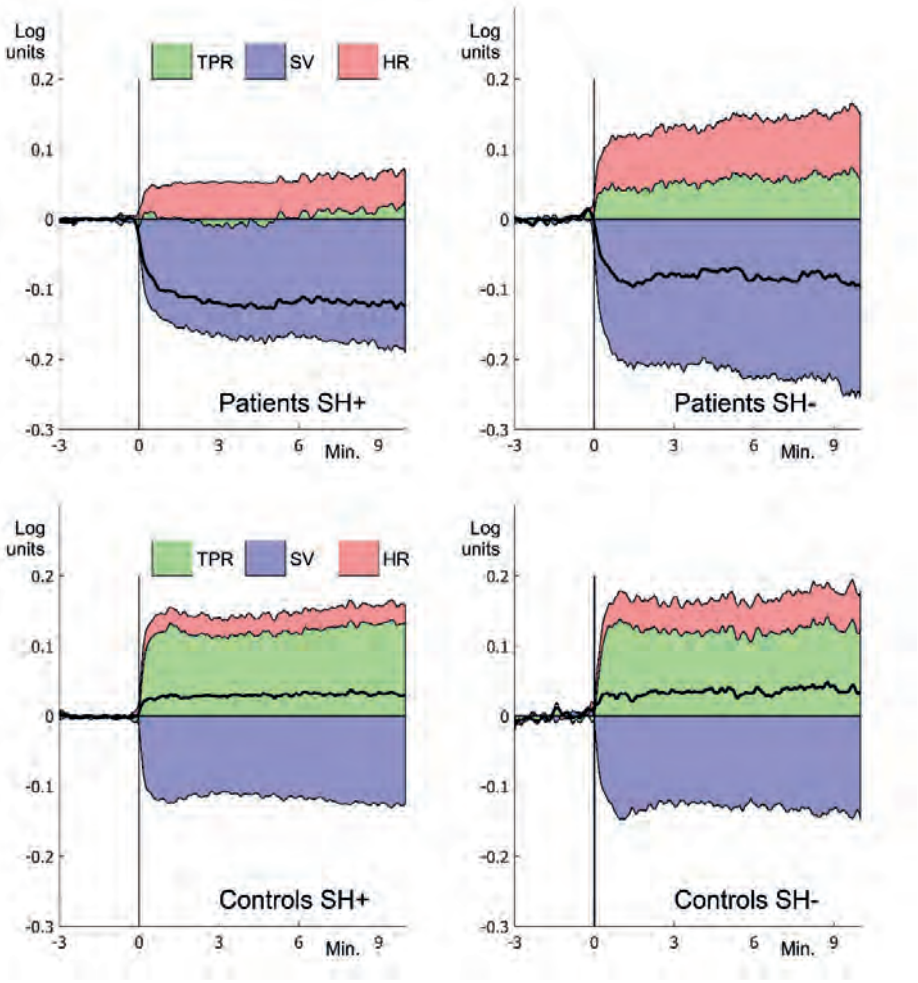

Figure 6.3. Logratio (LR) analysis of the head-up tilt.

Data are shown for patients and controls, both split into those with (SH+) and without (SH-) supine hypertension. The vertical line at T=0 minutes shows the moment of completion of head-up tilt. The respective influence of heart rate (HR; red), total peripheral resistance (TPR; green) and stroke volume (SV; purple) on mean arterial pressure (MAP; black line) are shown as cumulative areas. A positive LR value signifies a positive effect on the MAP, whilst a negative LR value signifies a negative effect of the parameter on the MAP. The cumulative values of all three parameters at each point in time result in the MAP.

Discussion

We confirmed that high TPR was the dominant mechanism explaining high supine BP; in our study this held both in those with and without cOH. Higher supine BP was accompanied by more severe cOH in cOH patients. We will show that this relation between severe SH and severe cOH is due to a seemingly paradoxical behaviour of TPR: while cOH patients with SH failed to increase TPR after tilt, they still displayed an excessively high TPR value in the supine position.

Supine hypertension

We confirmed earlier findings stating that higher supine BP was linked to higher TPR in patients with pure autonomic failure [14]. In our results this held true for cOH/SH+ patients and the hypertensive controls, with MAP and TPR at similar levels between those two groups. The main difference between cOH/SH+ and hypertensive controls was that TPR did not increase after tilt in cOH patients.

This failure to increase TPR further when needed is clearly visible in Figure 6.2A and is consistent with previous literature [13,24,25]. Consequently, the upright TPR was not high enough to compensate for gravitational demands, resulting in more severe cOH in SH+ than in cOH/SH-. The importance of TPR to these group differences is clearly apparent in the logratio analysis in the form of a small TPR_{LR} for the cOH/SH+ group. To our knowledge, this study is the first to examine individual variation in the interplay of the different haemodynamic variables.

Severity of orthostatic hypotension

We showed that supine BP, and thus SH, was related to the severity of cOH: higher supine BP correlated with a large BP reduction upon tilt. The close relation between DBP and SBP explains why results for DBP were very similar to those for SBP. Of interest, this held for absolute differences, but if the change of MAP after tilt was expressed as a ratio (e.g., logratio), the ratio did not differ between SH+ and SH- cOH patients (Table 6.2). The finding that more severe cOH was linked to higher supine BP complicates treatment decisions, as severe SH requires antihypertensive measures and cOH antihypotensive ones [26].

The mechanisms underlying SH may well differ between neurogenic causes. In multiple system atrophy patients, SH has been ascribed to residual sympathetic tone, which may not apply to other disorders [15,27]. In Parkinson disease, sympathetic denervation of vessels and the heart and concurrent hypersensitivity of cardiac beta-adrenoreceptors have been thoroughly documented, and hypothesized to be concurrent with para-

sympathetic dysfunction contributing to orthostatic hypotension [28,29]. Persons with OH and sympathetic denervation had higher BP than those with OH and intact sympathetic innervation, but no vascular resistance was reported [29].

We explored whether SH occurred more often in those with neurogenic causes of OH; for this purpose we first defined neurogenic OH as cOH with PD, MSA, PAF, unspecified nOH or DM. Supine SBP did not differ between those with nOH (157±30 mmHg) and without nOH (147±35mmHg, p=0.28). Proportions of SH+ and SH- did not differ either (chi square, p=0.31). We repeated the analysis counting only PD, MSA and PF as neurogenic OH; this did not alter the results.

Alternative mechanisms

The orthostatic BP fall in the cOH/SH+ group was clearly due to a failure of TPR to increase, which strongly suggests sympathetic damage in the sense of deficient vasoconstrictor ability. However, in these same patients, high supine BP was due to high TPR. This begs the question how patients unable to achieve sympathetic vasoconstriction in the upright position can have a high TPR in the supine position. In the cOH/SH- group the TPR increase was also blunted, but less than in the cOH/SH+ group (Table 6.2). Undoubtedly, the baroreflex does not function properly in neurogenic cOH [30], and most of our patients had causes of neurogenic cOH [17].

We first reason that a complete paralysis of the baroreflex should incapacitate the ability to achieve high TPR through sympathetic vasoconstriction, both supine as well as upright. Secondly, we posit that autonomic function is most important when quick changes are needed, such as immediately after standing up. If these assumptions are true, then the high supine TPR in those with cOH/SH+ is only compatible with autonomic failure if another, slow acting, factor causes high TPR in this situation. Examples of such slow effects may be the stated residual sympathetic tone or hypersensitivity to circulating neuro-humoral factors [6,31]. In addition, endocrine humoral responses may also play a role. The well-known BP overshoot after tilting back, regularly observed in those with autonomic failure [32], also suggests that slow-acting factors continue to maintain TPR and thus high BP after tilting back to the supine position.

Previous works have already hypothesized the influence of neurohumoral factors in this process [33-37]. We stress that TPR reflects vasoconstriction of any cause, not just vasoconstriction due to sympathetic nerve action. Circulating catecholamines have been studied most often, especially noradrenaline in Parkinson disease, in which sympathetic denervation reduces plasma noradrenalin levels and an

artificial increase in noradrenalin causes BP to rise rapidly [33]. Angiotensin II has been found to be elevated in cOH patients with SH [34], which could also explain high TPR. Vasopressin is primarily influenced by the baroreflex, but also via angiotensin II, and causes vasoconstriction. In more centrally caused baroreflex failure the release of vasopressin is reduced. This is most often observed in those with more severe hypotension, who often rely on a vasopressin response [35-37]. Accordingly, vasopressin is an important BP regulator in autonomic failure [38]. These neurohumoral factors may explain the seemingly paradoxical behaviour of TPR we found here, perhaps in combination with other factors such as residual sympathetic tone. In short, TPR may rely on the expression of actions that work at different speeds: autonomic failure may preferentially impair fast mechanisms and its failure therefore becomes most notable when fast action is needed, for example when standing up. In contrast, slow acting factors persist and cannot be countered quickly, explaining SH, at least in part.

Limitations

The results underline the well-known importance of TPR in BP regulation and fit well with a major autonomic contribution to all cases of cOH in the present paper [17]. As such, the data fit with the proposition that all cOH may be neurogenic in nature, with a variable contribution of non-neurogenic factors [39]. We did not measure neurohumoral factors to assess whether they help explain the behaviour of TPR.

The control group did not reflect perfectly healthy subjects but formed an age- and sex-matched population, including people using various types of medication. Medication can influence the determinants of BP but are unlikely to explain differences between groups as medication was used in both groups. More importantly, in an analysis of haemodynamic medication effects in the present study group we found that the results did not change after exclusion of those using BP medication [17]. While the resulting groups are not pathophysiologically pure, they do represent patients as seen in daily practice.

Finally, the study is based on Modelflow data, meaning SV and TPR are estimated, not measured directly. We stress that there is no technique to measure TPR directly, and Modelflow is best at estimating relative alterations of BP components, which we did in the present study [22]. Modelflow may be incorrect when BP changes extremely quickly as during vasovagal syncope, but the current study focused on measures in the fourth minute after tilt and is therefore not subject to these shortcomings [19]. Relative changes of TPR and cardiac output (the product of HR and SV) can be reliably derived using Modelflow [40].

Perspectives

A distinction between specific causes of cOH may yield interesting results when investigating the response of TPR and HR in different neurological and neurodegenerative disorders. Studies analysing differences and similarities are warranted to unveil the diverse underlying neurological and neurohumoral mechanisms. The large interindividual variability noticed here deserves further exploration; for instance, those with profound decreases of SV and those with profound TPR failure and SH may require different cOH treatments leading to personalised medicine.

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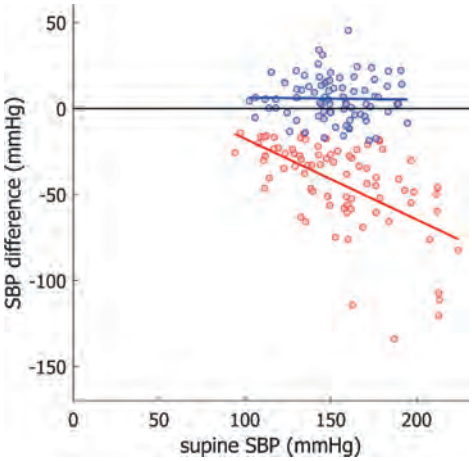
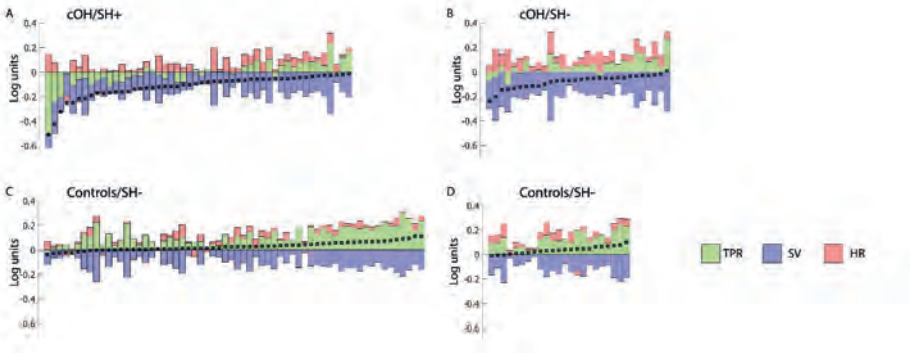
Supplementary material



Supplementary Figure S6.1. Change in systolic blood pressure (SBP) after head-up tilt.

The SBP difference is defined as the change of the supine SBP value to the fourth minute tilted value, meaning a negative SBP difference shows a reduction upon tilt. Blue dots and the blue line show control values (n = 80), and red dots and the red line show cOH data (n=80).



Supplementary Figure S6.2. Individual logratio analysis of the fourth minute after head-up tilt.

The respective contributions of heart rate (HR; red), stroke volume (SV; purple) and total peripheral resistance (TPR; green) to the upright mean arterial blood pressure are shown for individual cases. Cases were divided by patients and controls groups as well as by presence of supine hypertension (SH+) or its absence (SH-). Within each group subjects were sorted based on the relative change of MAP in the fourth minute after tilt, with the largest reduction in MAP shown on the left. A) classic orthostatic hypotension (cOH) and SH+ group, B) cOH/SH- group, C) control/SH+ group, D) control/SH- group. In general, the increase in supine MAP from left to right within each group is paralleled by an increase in TPR.

Part IV

Summary and discussion

Chapter 7

General discussion

Non-motor symptoms are common and debilitating for persons with Parkinson disease (PD) or a form of atypical parkinsonism. Fortunately, our understanding of the autonomic nervous system and its dysfunction is steadily increasing. With this thesis, I add to the existing knowledge on the mechanisms behind disrupted blood pressure homeostasis, which is often encountered in PD and atypical parkinsonism. I also provide proof of the positive effect of full-body head-up tilt sleeping (HUTS) on the commonly co-occurring supine hypertension (SH) and orthostatic hypotension (OH).

In people with PD or certain forms of atypical parkinsonism (such as multiple system atrophy, MSA), OH often occurs due to autonomic dysfunction and medication [1]. Non-pharmacological treatments are the cornerstone of treating blood pressure issues of all causes, but this is especially true in those with autonomic failure where polypharmacy may exacerbate the symptoms [2]. The method of HUTS has been known for over eight decades, but this intervention is still rarely applied in daily clinical practice, and even if so, often in low angles that are likely to be ineffective [3,4]. The results shown in this thesis expand our knowledge on non-pharmacological treatment of blood pressure issues beyond the daytime and into the night. This forms an important step towards a personalised and optimised application of HUTS in people with PD or atypical parkinsonism. In this chapter, I summarise the content of my thesis, put the findings in a broader context, discuss implications for clinical practice and outline what questions remain to be answered in future research.

Abbreviations

HUTS: Head-Up tilt sleeping
MAP: Mean arterial pressure
MSA: Multiple system atrophy
OH: Orthostatic hypotension
PD: Parkinson disease
SH: Supine hypertension
TPR: Total peripheral resistance

1. Summary

The current state of HUTS

In **chapter 2** I reviewed the existing evidence regarding the effect of HUTS on cardiovascular outcomes. There were a total of 10 studies investigating HUTS as a single treatment. Both the populations and the methods of these studies varied greatly. Studied populations included (neurogenic) OH, vasovagal syncope, nocturnal angina pectoris and healthy subjects. Only one study focused on a PD population, and one contained a subset of individuals with PD. Angles varied from 5 to 15°. In two of six studies with OH populations, HUTS significantly improved standing systolic blood pressure. There was a consistent gain in orthostatic tolerance in three OH studies with higher angles (12° or 15°) and in two out of three studies that evaluated lower angles (5/6°). One of these studies included a control OH group that slept horizontally and also had improved symptoms, indicating that the natural course can be favourable. In vasovagal syncope cases, HUTS significantly augmented resilience to extreme orthostatic stress as with a tilt table test and lower body negative pressure. The tolerability of HUTS was not well discussed in most studies. Nevertheless, we found some indications that 6° is tolerable and 12° feasible, but may give rise to complaints such as sliding downwards and oedema. Although the evidence is weak, studies do show a predominantly beneficial effect of HUTS on blood pressure and orthostatic tolerance. Currently, very little is known about the effect on nocturnal blood pressure, and on the usability among people with PD or atypical parkinsonism. I concluded that this promising underused non-pharmacological intervention needs to be studied more before it can be applied more widely in clinical settings.

The case report in **chapter 3** describes a person with advanced PD who successfully used HUTS to combat orthostatic intolerance, showing that with the right method, it can be tolerable in those affected by parkinsonism. HUTS was recommended by his neurologist due to prominent autonomic failure with disabling orthostatic intolerance, especially in the early morning. Upon the advice of the neurologist, the patient slowly increased the inclination of the bed until he noted a marked improvement in orthostatic intolerance. This occurred at an angle just over 10°. Notably, when ceasing HUTS for a brief period, the complaints of orthostatic intolerance returned immediately. After a follow-up of 3 months, the patient did not experience any symptoms during a standing test. This case clearly shows the potential effect of HUTS in PD and emphasises the importance to now develop evidence-based recommendations with regard to the optimal angle, and also to address implementation strategies.

The Heads-Up trial

To fill the gaps in knowledge that were uncovered in the previous section and to systematically assess the potential of HUTS as a treatment for both SH and OH, I conducted a randomised controlled trial. In **chapter 4** I describe the rationale and design of this trial. The aim was to provide proof of the effectiveness, tolerability, and feasibility of this intervention at home. We hypothesised that HUTS can simultaneously alleviate OH and SH. Within the Heads-Up trial we adopted a tailormade protocol, in which we tested three different angles of HUTS within the same person. I included people with PD or MSA who had both symptomatic OH and SH. All participants started with one week of horizontal sleeping for baseline measurements and then went on to sleep in three increasing angles, each for two weeks (6°, 12° and 18° for the intervention group and a placebo angle of 1°, followed by 6° and 12° for the delayed treatment group). The primary endpoint was the change in average nocturnal blood pressure, as measured by a 24-hour ambulatory blood pressure measurement in each phase. Secondary outcomes included other parameters of the ambulatory blood pressure measurement, early morning supine blood pressure measurement, the drop in blood pressure during an active standing test, orthostatic tolerance, nocturia and various other motor and non-motor tests and questionnaires. The experiences of participants were discussed after completion of the trial, and tolerability was evaluated using questionnaires and by reporting compliance to the study protocol. Data were analysed with a linear mixed model taking factors such as disease duration and age into account.

In **chapter 5**, I describe the results of the Heads-Up trial. A total of 20 participants completed all phases of the trial. Twelve of those were fully compliant to the prescribed inclinations, and eight people lowered the inclination in their last phase. Four people returned from 12° to 6°, three from 18° to 12° and one from 18° to horizontal sleeping. Amongst the 20 participants, we did not find a significant effect on the average nocturnal blood pressure as measured by the ABPM. Early morning supine blood pressure was reduced by 2 mm Hg for each increase in HUTS angle of 6°. I found an increase in the night-time dipping profile, and an increase in average daytime blood pressure of approximately 3 mmHg for each 6° increase in angle. In addition, the blood pressure drop upon standing improved with 8 mmHg for each 6° increase in angle. This coincided with a decrease in orthostatic intolerance as determined by the orthostatic hypotension symptom assessment and cardiovascular questions of the SCOPA-AUT. The nocturnal urine volume did not change over the course of the study. Altogether, this led us to conclude that HUTS improves blood pressure regulation. Steeper HUTS angles proved more effective to combat OH, with a higher blood pressure during the day and less

blood pressure reduction upon standing. We found indications for a trade-off with a clear angle-dependent improvement of blood pressure regulation, but also an angle-dependent reduction in tolerability. A practical way forward is to search for a different and highest feasible angle in every person.

Haemodynamics of supine hypertension

To better understand the physiology of the complex blood pressure issues as presented in the Heads-Up trial, **chapter 6** dives deeper into the haemodynamics underlying the co-existence of OH and SH. In a retrospective investigation, I compared beat-to-beat blood pressure data from tilt table tests of those with and without OH and divided each group in those with relative high and relative low supine blood pressure. With linear regression, we showed that the orthostatic systolic blood pressure fall in OH was larger in those with higher supine systolic blood pressure. The main parameter explaining this effect was a higher supine total peripheral resistance (TPR) that did not increase after tilt, and more so in people with OH and relative high supine blood pressure compared to those with OH without SH. With the logratio method we were able to analyse the relative contributions of HR, SV and TPR of which the sum results in the MAP. With this data transformation, we could see that the stroke volume logratio decreased more in OH patients without SH than those with SH, and heart rate logratio contributed similarly to orthostatic systolic blood pressure in both cOH groups. While high supine TPR explained SH, a failure to further increase this TPR when upright explained the orthostatic systolic blood pressure fall. I therefore concluded that the co-occurrence of OH and SH was due to seemingly contradictory behaviour of TPR. While TPR failed to increase after tilt, the TPR was excessively high in the supine position.

2. The working mechanism of HUTS

As can be read in chapter 5, HUTS had a positive effect on blood pressure regulation in a population of people with PD and MSA. The exact underlying mechanism behind this positive effect remains unknown.

Prior to the work in this thesis, the prevailing hypothesis for the working mechanism of HUTS was a reduction in nocturia. High supine blood pressure increases pressure diuresis, resulting in large amounts of fluid loss at night and a smaller circulating volume in the morning [5]. HUTS would lower supine blood pressure following the logic of gravity and hereby decrease nycturia which in turn would combat excessive overnight fluid loss that would promote OH. For this reason, I expected that HUTS

would work with nocturia as a mediator [6]. This was not supported by the findings as reported in **Chapter 5**.

This finding shifts our attention back to one of the oldest hypotheses: oedema is not just a common side effect of HUTS, but also one of its mechanisms of action. The theory is that the pressure caused by the increased gravitational stress put on the system by HUTS pushes the blood out of the blood vessels, into the interstitial space [7, 8]. Similar to the mechanism that can cause oedema due to the gravitational stress caused by standing [9]. The exuded interstitial fluid limits the extent to which the vessels can dilate, reducing pooling in the orthostatic position. This can be compared to the functioning of compression stockings. Compression stockings, however, have been shown to have a minimal effect on orthostatic blood pressure [10, 11]. Due to the difference in the way in which the force acts on the blood vessels -more internal than some degree of external force- the oedema could be more effective in reducing pooling than the compression stockings. Oedema was not systematically measured in the Heads-Up trial, but participants mentioned it more frequently towards the later phases. The relationship between oedema and improvement in blood pressure regulation should, however, be studied in future trials.

Another possible explanation could be residual baroreflex activation during the night, resulting in neurohumoral changes that continue to influence blood pressure regulation during the day. In **chapter 5** I uncovered that the average nocturnal systolic blood pressure did not change following HUTS. When sleeping in the HUTS position, however, the arterial baroreflexes are located more cranially than the heart, and therefore measure a slightly lower blood pressure [12]. This will in turn activate residual sympathetic-mediated vasoconstriction as well as neurohumoral activation to increase vascular volume. Following the logic of the gravity effect, the kidneys are consequently located more caudally than the heart, resulting in a slightly higher blood pressure potentially cancelling out the effects of the hypothesized altered circulating hormones on nocturia. The effect could be comparable to tilt training in vasovagal syncope, but little evidence is available on the precise mechanism. The scarce research into the effect of tilt training points to an increase in TPR, but it has also been stated that it is an increase in cardiac output, rather than the TPR that improves the orthostatic blood pressure [8,13]. The comparisons between a high supine blood pressure and the reduction upon standing in **chapter 6** favours the first explanation, as there TPR was identified as the culprit. This means an adaptation in TPR has the potential to cause the most prominent changes. The precise dynamics behind the mechanism must to be studied in future work.

Taken together, the current thesis describes the efficacy and tolerability of the different angles of HUTS. The working mechanism behind these findings could be the extravasation in the lower extremities, an increase in baroreflex sensitivity due to activation during the night, both, or a mechanism yet to be discovered.

3. The pieces of the supine hypertension puzzle

As I described in **chapter 1**, the pathophysiology underlying cardiovascular autonomic failure differs between PD, MSA and other disorders with baroreflex failure [14]. The group of patients described in **chapter 6** reflect a general OH population. We assume that slow-acting humoral vasoconstrictors are triggered in the upright position and continue to act after tilting back, causing high TPR and SH possibly uncoupled from or controlled by a more covert form of sympathetic control [15]. This slowly responsive system is supported by the overshoot that is often seen upon tilting back [16].

Autonomic failure can explain the blood pressure fall but not directly the high supine TPR that causes SH. There is still a piece of the puzzle missing. Blood pressure regulation is influenced by many neurotransmitters and compounds influencing the fluid balance. One of the best researched compounds is norepinephrine, for which the dynamics differ between the neurodegenerative alpha-synucleinopathies (for elaboration, see **chapter 1**). In case of autonomic failure one of the key mechanisms could be vasopressin, a hormone that is released upon baroreflex activation, and which increases both fluid retention and TPR. Research has shown that a blockade of vasopressin did not change supine blood pressure levels but greatly increased the blood pressure drop upon standing, which fits the pattern of HUTS [17]. The renin-angiotensin-aldosterone system is also known to be dysregulated in SH in autonomic failure [18]. The missing piece regards a factor that increases blood pressure when supine, but that fails to respond to orthostatic changes. One interesting revelation in **chapter 6** is that the relation between the blood pressure reduction and the supine blood pressure appears to be almost linear (**sup. fig. 6.1**). The current guidelines already take into account SH by having higher thresholds for determining OH [19]. However, it might be even better that for the diagnosis of OH a proportional calculation is implemented, giving more significance to the importance of '*how low you go*' [20]. The raise in blood pressure upon lying down could be considered either compensatory, or simply a consequence of a worsening pathology and an inflexible system. The results of **chapter 6** point towards the latter, with inflexibility sitting at the root of both SH and OH. The blood pressure

overshoot after prolonged passive orthostatic stress in autonomic failure that is not immediately washed out upon lying down supports this notion as well [16].

Regardless of its exact pathophysiology, SH is not harmless. A recent study showed that SH, independent of seated hypertension, is a risk factor for cardiovascular disease [21]. White matter lesions have also been observed in patients with OH and SH, with both the high supine blood pressure and the blood pressure fall and concurrent cerebral hypoperfusion during OH contributing to the presence of lesions [22-24].

There is a strong need to identify reliable biomarkers to timely detect SH, particularly in those in need of OH treatments. Yet, to do so we need to uncover the underlying neurological and endocrine mechanisms of SH.

4. HUTS in clinical practice

The first steps in OH include the screening for preventable causes such as hypovolemia, followed by a critical revision of the medication list [2]. After that, the non-pharmacological measures can take the stage. In clinical practice, a combination of measures that suites each individual will always have to be sought. With the Heads-Up trial (**chapter 4 & 5**), I gained valuable insights in the practical challenges that come with implementing HUTS in a home setting. I learned that there are several practical tricks that can help with sleeping in a head-up tilt position. The most common problem was sliding down, which can be stopped by placing a pillow underneath the hips and by using a footboard (both were also applied by the person depicted in the case report in **chapter 3**). Contrary to advise usually given to people with parkinsonism who sleep on smooth bedding to facilitate turning, here I would suggest opting for a rough surface to sleep on, either with rough bedding material, by placing a towel on the matrass cover, or by wearing pyjamas that provide friction to avoid sliding. In general, those sleeping on their back or belly slide down less easily, while side sleepers can easily end up in a crouched position at the lower end of the bed. Sleep quality and comfort remain important factors to keep in mind, as sleeping in HUTS might impact sleep in a negative way. A common effect of HUTS is lower leg oedema. This seems associated with its efficacy and can be anticipated as a side effect. Nevertheless, it is important to inform beforehand as this was experienced as unpleasant by some. In our study, none of the partners slept in HUTS together with the participants (even though they were offered to). This study was only just 6 weeks of separated sleeping, but for the long term this be a reason not to implement it permanently. An automated

bed can be costly, but might reduce this hurdle and provide a compromise. The importance of laying side-by-side prior to sleeping should not be underestimated. An adjustable bed that allows for a gradual increase of the angle seems essential for an optimal implementation of HUTS. The patient can increase the angle until a satisfactory effect is reached.

HUTS might be combined with other non-pharmacological interventions such as abdominal binders, which can raise the standing blood pressure, giving a full daytime cycle (day and night) of treatment. Besides in autonomic failure, HUTS can also be considered for those with hypotensive tendencies and vasovagal syncope. Possibly the HUTS effect may even be more pronounced as they have a functioning baroreflex.

Based on the results found here, I recommend to always try HUTS in disabling OH. Besides oedema there are no known negative side effects. It should be made clear that it is full-body tilt (not just the upper body), and safety should be prioritised. An automated bed that can return to a horizontal position before getting up minimises the fall-risk, and may help each person find the angle that works for them without compromising too much on sleep quality.

5. Shortcomings

The studied populations in this thesis are all, to some degree, mixed (**chapter 2**, **5 and 6**). I did not confirm the presence of neurogenic OH with for example a Valsalva test [25]. This is particularly relevant in **chapter 6** where I also studied OH cases without Parkinsonism. For the Heads-Up trial there are two elements inherent to the patient population that could potentially influence the results: participants used many different medications, but since medication regimes stayed stable during participation to the trial in **chapter 5**, this did likely not influence our findings regarding HUTS. Secondly, there are other causes for problems with movement in PD and MSA than OH, among others postural instability [26,27]. These symptoms can be hard to distinguish making it possible that the subjective measures do not always refer to OH. We therefore used questionnaires that are regularly used in the PD population, but this limitation cannot be removed completely. The study was also focused on a group-level response, and the total number of participants was too low to investigate subgroups. It would be interesting to see if there are specific characteristics that influence the effectiveness of HUTS at an individual level, and this is something for future research to uncover. Although the underlying working

mechanisms may vary between neurogenic OH and non-neurogenic OH, efficacy of HUTS has been suggested across the spectrum of OH causes.

6. Future outlook

In this thesis, I demonstrated an overall dose-dependent effect of HUTS on blood pressure regulation in people with both SH and OH and provided new insights regarding the mechanism of HUTS. More research is needed to predict for whom the intervention will be most effective, and if different angles should be recommended to people with for example severe vs mild autonomic dysfunction. To improve our understanding of the working mechanisms underlying HUTS, future studies should focus on oedema and hormonal levels prior to, during, and after discontinuation of HUTS. This will also help us understand the dynamics of SH. It is clear that on a haemodynamic level the TPR is the main disrupted factor, but understanding the cause of this high and unchanging TPR will help us advance blood pressure treatments in case of co-occurring OH and SH. In addition, systematic studies will have to be conducted to see if HUTS remains effective in the long term. Treatment of OH and SH will always require a personal approach, and in this regard HUTS is no exception. With proper guidance by a well-informed and trained healthcare professional, the highest angles that are manageable in terms of comfort should always be strived for.

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Chapter 8

Nederlandse samenvatting

De ziekte van Parkinson (ZvP) staat hoofdzakelijk bekend als een bewegingsstoornis, maar mensen met de ZvP ervaren daarnaast ook veel niet-motorische symptomen zoals pijn, cognitieve problemen, slaapstoornissen en disfunctie van het autonome zenuwstelsel. Het autonome zenuwstelsel is verantwoordelijk voor het behouden van homeostase in het hele lichaam. Het beïnvloedt bijna elk orgaansysteem en disregulatie kan een breed scala aan symptomen of problemen met zich meebrengen. Door de afbraak van neuronen in gebieden in het centrale zenuwstelsel die belangrijk zijn voor het autonome zenuwstelsel, staan niet-motorische symptomen zelfs op de voorgrond bij multiple systeem atrofie (MSA), een vorm van atypisch parkinsonisme. Bij de ZvP is er naast centrale degeneratie ook verlies van autonome neuronen in het perifere zenuwstelsel. Door deze neurodegeneratieve processen kan autonome disfunctie ontstaan. De bloedsomloop is een van de systemen die nauw gecontroleerd wordt door het autonome zenuwstelsel om voldoende perfusie van alle organen te waarborgen. Wanneer de homeostase in de bloedsomloop faalt, leidt dit tot houdingsafhankelijke variatie in de bloeddruk. Het meest bekende voorbeeld is orthostatische hypotensie (OH), waarbij de bloeddruk fors daalt direct na het opstaan, en ook na langere perioden van rechtop staan. Door deze bloeddrukdaling kunnen mensen met OH bijvoorbeeld duizelig worden en bij forse dalingen zelfs compleet wegraken en daardoor vallen. Soms leidt het ook tot subtielere klachten zoals problemen met het zicht of gehoor, vertraagd denken of pijn van de spieren in de nek en schouders door ischemie.

Bij de ZvP en MSA komt bij ongeveer de helft van de mensen met orthostatische hypotensie ook het tegenovergestelde probleem voor: liggende hypertensie. De precieze oorzaak van het gelijktijdig samen vóórkomen hiervan is nog niet bekend. Behandeling van OH en liggende hypertensie met medicatie is erg lastig omdat medicatie dat het ene aspect verbetert, het andere juist weer verergert. Voor OH is daarom niet-medicamenteuze behandeling, zoals het verhogen van de vocht- en zoutinname en fysieke bloeddrukverhogende manoeuvres, een belangrijk onderdeel van het behandelplan. Het slapen in de anti-Trendelenburgpositie (figuur 1) wordt ook aanbevolen. Dit houdt in dat het volledige bed schuin wordt gezet, met het hoofd omhoog (head-up tilt sleeping; HUTS). Deze methode is al lange tijd bekend, maar de effectiviteit is nog niet goed onderzocht. Het is ook niet bekend in welke kantelhoek HUTS het beste werkt. Er wordt gedacht dat HUTS tegelijkertijd de nachtelijke hypertensie en OH kan verbeteren. Dit zou uniek zijn omdat dit met medicatie niet mogelijk is. In dit proefschrift onderzoek ik het effect van HUTS in drie verschillende hoeken op zowel de liggende als de staande bloeddruk, en ga ik in op de hemodynamica van liggende hypertensie.

Figuur 1. Het slapen in HUTS (Head-Up Tilt Sleeping)
Afkomstig uit de animatievideo: https://radboudumc.bbvms.com/view/default/6197707.html.

1. Slapen met het hoofdeinde omhoog

In **hoofdstuk 2** analyseer ik de bestaande literatuur over HUTS, en het effect daarvan op het cardiovasculaire systeem. Sinds de jaren '40 zijn er in totaal 10 onderzoeken gepubliceerd waarbinnen de onderzochte populaties en de hoeken waarin het bed werd gezet erg varieerden. Het ging hierbij om mensen met (neurogene) OH, vasovagale syncope, nachtelijke angina pectoris en ook gezonde proefpersonen. Slechts één publicatie richtte zich alleen op mensen met de ZvP en één bevatte een subgroep van individuen met de ZvP. In twee van de drie onderzoeken die een kleinere hoek van 5° onderzochten was er een verbetering zichtbaar, en in het onderzoek met een grotere hoek (12° tot 15°) werd consistent een verbetering van de aan OH gerelateerde symptomen gevonden. In de groep mensen met vasovagale syncope verhoogde HUTS de tolerantie voor orthostatische stress aanzienlijk. De tolerantie voor schuin slapen werd niet systematisch geëvalueerd, maar er werd gesuggereerd dat het slapen in een hoek van 6° zonder problemen te verdragen is. Een hoek van 12° leek ook haalbaar te zijn in de bestudeerde artikelen, maar bracht wel ongemakken met zich mee zoals het naar beneden geleiden in het bed en oedeem. In **hoofdstuk 3** beschrijf ik de ziektegeschiedenis van een persoon met gevorderde ZvP en autonome disfunctie die HUTS succesvol gebruikte om orthostatische intolerantie te bestrijden. Deze persoon ervaarde HUTS als uitvoerbaar, en de effectieve hoek was goed te verdragen. Dit laat zien

dat HUTS ook toegepast kan worden bij mensen met een bewegingsstoornis. In deze specifieke ziektegeschiedenis werd HUTS door de neuroloog aanbevolen vanwege prominent autonoom falen met invaliderende orthostatische intolerantie, vooral in de vroege ochtend. Op basis van het advies van de neuroloog verhoogde de patiënt langzaam het hoofdeinde van het bed in stappen van ongeveer 10 cm, totdat hij een duidelijke verbetering van de orthostatische intolerantie opmerkte. Dit gebeurde bij een hoek van iets meer dan 10°. Opvallend was dat wanneer hij HUTS voor een korte periode stopte, de symptomen van orthostatische intolerantie onmiddellijk terugkwamen. Na een follow-up van 3 maanden had de patiënt geen symptomen meer tijdens een sta-test. Deze ziektegeschiedenis laat het potentiële effect van HUTS bij de ZvP zien en benadrukt het belang van goed onderbouwde aanbevelingen voor hoek- en implementatiestrategieën.

Hoewel het bewijs uit deze eerdere onderzoeken dus zwak is, suggereren ze wel een potentieel gunstig effect van HUTS op de bloeddruk **(hoofdstuk 2)**. Geen van deze onderzoeken hebben mensen met liggende hypertensie onderzocht, en daardoor is op dit moment maar weinig bekend over het effect van HUTS op de nachtelijke bloeddruk. Daarnaast is nog veel te leren over de bruikbaarheid van HUTS bij mensen met een vorm van atypisch parkinsonisme. Deze veelbelovende niet-farmacologische interventie moet nader worden onderzocht om tot goede richtlijnen te komen die in de dagelijkse praktijk kunnen worden toegepast.

2. Het Heads-Up onderzoek

Om de hierboven beschreven lacunes in kennis te verhelpen en HUTS systematisch te beoordelen, heb ik een gerandomiseerd placebogecontroleerd onderzoek met controlefase uitgevoerd. Hiermee heb ik het potentieel van HUTS als behandeling voor zowel liggende hypertensie als OH te onderzocht. In **hoofdstuk 4** beschrijf ik het ontwerp van dit "Heads-Up" onderzoek die als doel heeft om de effectiviteit, verdraagbaarheid en haalbaarheid van HUTS bij mensen met de ZvP en MSA thuis te onderzoeken. De hypothese was dat HUTS tegelijkertijd OH en liggende hypertensie kan verlichten, en dat hogere hoeken van HUTS effectiever zijn, maar tegelijkertijd minder goed te verdragen zijn. Het protocol van het Heads-Up onderzoek is uniek, omdat we elke deelnemer in drie verschillende hoeken hebben laten slapen. Deelnemers aan het onderzoek hadden een diagnose ZvP of MSA, en hadden allemaal zowel symptomatische OH als liggende hypertensie. Alle deelnemers begonnen met één week horizontaal slapen. Hierna werd iedere twee weken de kantelhoek van het bed stapsgewijs verhoogd. Deelnemers werden

verdeeld in twee groepen: de directe interventie groep sliep in de hoeken 6°, 12° en 18° terwijl de vertraagde interventiegroep in een placebohoek van 1°, gevolgd door 6° en 12°. De primaire uitkomst was de verandering in de liggende bloeddruk, gemeten als de gemiddelde nachtelijke bloeddruk (op basis van een 24-uurs ambulante bloeddrukmeting (ABPM) in elke fase van het onderzoek). Deze en andere secundaire uitkomstmaten werden geanalyseerd met een linear mixed model, waarbij rekening werd gehouden met de factoren ziekteduur en leeftijd.

In **hoofdstuk 5** beschrijf ik de resultaten van het Heads-Up onderzoek. In totaal hebben 20 mensen deelgenomen. We vonden geen significant effect op de primaire uitkomst: de gemiddelde door de ABPM gemeten nachtelijke bloeddruk. Als één van de secundaire uitkomsten hebben de deelnemers ook elke ochtend liggend in bed de bloeddruk gemeten. Deze verminderde met ongeveer 2 mmHg per 6° verhoging. Eén keer gedurende elke fase hebben de deelnemers ook hun nachtelijke urinevolume gemeten; dit veranderde niet in de loop van het onderzoek. Toen ik naar andere variabelen van de 24-uurs ABPM keek, vonden ik een verbetering in het nachtelijke dippingprofiel met 2,5% meer dipping per 6° toename van de HUTS hoek. Dit kwam door een toename van de bloeddruk overdag met ongeveer 3 mmHg per 6°. Bij een sta-test, die ook elke fase uitgevoerd werd, nam de bloeddrukdaling bij staan af (de OH) met 8 mmHg per 6°. De verdraagbaarheid van de verschillende hoeken werd geëvalueerd met behulp van vragenlijsten en regelmatige gesprekken met de deelnemers. Daarnaast werden de persoonlijke ervaringen besproken tijdens een afsluitende afspraak. Van de 20 deelnemers voltooiden twaalf de proef volgens het protocol. Slechts acht mensen (waarvan vier uit de interventie groep) gingen terug naar de hoek die zij hadden ondergaan in hun laatste fase vanwege problemen met slapen, o.a. door het naar beneden glijden in het bed. Alles bij elkaar concludeerde ik dat HUTS de algehele bloeddrukhomeostase in meerdere opzichten verbeterde, ook al veranderde de gemiddelde nachtelijke bloeddruk niet. De gunstige factoren bestonden uit de lagere liggende bloeddruk in de vroege ochtend, het betere nachtelijke dippingsprofiel en de afname van daling van de bloeddruk bij staan. Deze metingen werden ook ondersteund door een afname in de ervaren OH klachten.

In **hoofdstuk 7** beschrijf ik wat deze resultaten betekenen voor de toepassing van HUTS in de dagelijkse klinische praktijk. De hoeken die zorgen voor een verbetering in de bloeddruk homeostase zijn haalbaar, maar goede ondersteuning bij de praktische implementatie is belangrijk. Doordat hogere hoeken effectiever zijn, maar ook minder goed verdraagbaar is een goede inlichting over het gebruik cruciaal. Deze animatievideo kan helpen de methode in de praktijk toe te lichten

(https://radboudumc.bbvms.com/view/default/6197707.html). Het gebruik van een elektrisch bed dat over de gehele lengte schuin gezet kan worden lijkt de beste methode. Bij instap kan het bed dan horizontaal gezet worden. Dit zal zo het vergrote gevaar van vallen bij in en uit een gekanteld bed stappen wegnemen.

3. Liggende hypertensie

Om de fysiologie van de complexe bloeddrukproblemen beter te begrijpen, gaat **hoofdstuk 6** dieper in op de hemodynamica. In een retrospectief onderzoek naar kanteltesten heb ik de continue bloeddrukgegevens vergeleken tussen mensen met en zonder liggende hypertensie. Met lineaire regressie liet ik zien dat de orthostatische systolische bloeddrukdaling in klassieke OH groter was bij proefpersonen met een hogere systolische bloeddruk bij het liggen. De belangrijkste parameter die dit effect verklaarde, was een hogere totale perifere weerstand (TPR) bij liggen die niet toenam bij rechtop staan. Deze TPR was hoger bij de mensen met OH en liggende hypertensie dan bij degenen zonder liggende hypertensie. Ik heb de relatieve bijdrage van de hartslag, slagvolume en TPR aan de staande bloeddruk onderzocht met de logratiomethode. Met deze datatransformatie wordt duidelijk dat de slagvolumelogratio meer afnam bij mensen zonder SH dan bij mensen met SH, en dat de hartslaglogratio op vergelijkbare wijze bijdroeg aan de orthostatische systolische bloeddruk in beide OH-groepen. Daarbij komt dat de bloeddrukdaling vooral verklaard werd door een onveranderlijke TPR bij het kantelen. De conclusie is daarom dat het gelijktijdig voorkomen van OH en SH te wijten was aan een schijnbaar tegenstrijdig gedrag van TPR: terwijl de TPR in mensen met OH en liggende hypertensie te weinig omhoog ging bij een orthostatische uitdaging van het systeem, was de TPR bij het liggen in deze groep buitensporig hoog.

4. Met een blik op de toekomst

In **hoofdstuk 7**, beschrijf ik wat mogelijk de onderliggende werkingsmechanismen van HUTS kunnen zijn en hoe dit samenhangt met mijn bevindingen. Met het Heads-Up onderzoek heb ik laten zien dat de verbetering in de bloeddrukdaling bij het opstaan niet verklaard kan worden door een afname van de nycturie. De verminderde daling bij het opstaan kan bijvoorbeeld komen door het oedeem in de onderbenen, of door langzame neuro-humorale factoren die op gang komen gedurende de nacht, en die daardoor overdag de bloeddruk beïnvloeden. Er is nog veel te leren over de precieze oorzaak achter de verstoorde TPR regulatie bij

liggende hypertensie, en hoe dit mechanisme in verband staat met het succesvol toepassen van HUTS. In de toekomst zal uitgebreid onderzoek naar individuele karakteristieken een steeds beter beeld moeten geven van de eigenschappen verschillen in de effectiviteit van HUTS bepalen. Tot die tijd blijft HUTS een goede methode om de bloeddrukproblematiek aan te pakken. De behandeling heeft weinig bijwerkingen, en dus heeft HUTS een zeldzame eigenschap: baat het niet dan schaadt het (meestal) niet!

Appendices

Appendix A1. Research data management

This thesis followed the Dutch laws and ethical guidelines (**chapters 3**, **5 and 6**). Research Data Management was conducted according to the FAIR principles. Below it is specified how this was achieved.

Ethics and privacy

This thesis is based on the results of human studies, which were conducted in accordance with the principles of the Declaration of Helsinki. The Medical Ethical Committee of the East-Netherlands (METC Oost Nederland) has approved this study (**chapter 5**; 2022-13528). The board of directors of the Radboudumc and LUMC have also formally provided approval (Radboudumc; RvB22.51455) (LUMC; L23.003). The research in **chapter 6** is based upon data collected for another already published retrospective investigation. This thesis is funded by the Michael J. Fox Foundation for Parkinson's research (MJFF 020200).

The privacy of the participants in this thesis has been warranted by using pseudonymization. The code list was stored on a network drive separately from the research data, and was only accessible for members of the project who required access. The data in **chapter 6** were analysed in an anonymized way. Informed consent (**chapters 3 and 5**) was obtained on paper following the national procedures. The data for **chapter 6** was collected prior to the requirement for retrospective studies to obtain informed consent. The paper forms are archived in the central archive of the Radboudumc and LUMC for 15 years.

Data collection and storage

For **chapters 3**, **5 and 6** research data have been stored on the project drives in the respective executing institution. These data were accessible to all members involved in the project. The data in **chapter 3**, and part of the data of **chapter 5** were collected on paper or through medical devices. Additionally, data of **chapter 5** were collected with the use of Castor EDC. The physical documents are stored in a cabinet at the department, and will be archived separately from the identifiable forms. The retrospective data used in **chapter 6** are stored on a secured disk in the LUMC, and are only accessible by LUMC employees involved in the project.

Data sharing

All publications included in and following this thesis are published open access. The data of **chapter 3** will be archived in the Radboud Data Repository Data Acquisition Collection. It will be archived with closed access, since the data contain

identifiable information. The articles of **chapter 5 and 6** are still under review. The data of **chapter 5** will be made available through the KNAW DANS Life Sciences Data Station under restricted access, once these and future planned articles have been published. Anonymized data of **chapter 5** will also be shared with the MJFF, a statement on this has been included in the informed consent. The data of **chapter 6** will remain on the LUMC servers and is accessible upon reasonable request.

Where possible, the files will be stored as .csv or .pdf to ensure that data remains usable in the future. The data will be accompanied by read-me files, and made reproducible by providing a description of the experimental setup and scripts (r-studio, v1.1.463 and Matlab R2023B).

Appendix A2. Curriculum Vitae

Amber Hannelore van der Stam (1998, Eindhoven) completed her high school education, including a research project on circadian rhythms, in Best (2016). Later that same year, she moved to Nijmegen to start her studies in Biology at the Radboud University. Due to a long-standing interest in the brain, she quickly shifted her attention to the neurosciences during her bachelor's degree. Her studies were successfully completed in 2021 with a master's degree in Medical Biology, specializing in Neurobiology (cum laude). During her master's degree, she enjoyed an internship with the Donders Sleep and Memory Lab where she learned about lucid dreaming and the use of polysomnography. This was -despite the COVID pandemic- followed by an internship in Stockholm, Sweden with the Sleep, Health and Cognition group of the Karolinska Institute and Stockholm University psychology department. There she helped prepare for the 'Big Sleep Study' into sleep deprivation and set up her own trial on emotional metacognition. In January 2022, she started as a research employee within the Expertise Centre for Parkinson and Movement Disorders of the Radboudumc and the neurology department of the LUMC to execute the Heads-Up project. After assuring the project was well underway the opportunity was created to turn the project in to a PhD, resulting in the work included in this dissertation. Through the connection with the LUMC she was also able to further expand her clinical and research experience through the specialized syncope unit. Finally, she strengthened international collaboration on this and future projects with a 3-month research stay at the Dysautonomia Center of the Medical University of Innsbruck, Austria (2024). She currently works as a research fellow at University College London Hospitals, UCL Queen Square institute of Neurology in London, UK.

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Appendix A3. Portfolio

Courses

Year	Course
2022	Presentation course
2022	Basic course for regulations and organisation for clinical investigators (BROK)
2024	Scientific Integrity
2024	The Art of finishing up
2024	Design and illustration
2024	An introduction to statistical modelling
2024	MDS-ES Dysautonomia in movement disorders
2024	EFAS Exam on the Diagnosis and Management of ANS Disorders

Conferences & presentations

Year	Conference	Type	Title
2022	EFAS	Short presentation	Haemodynamic Determinants of Supine Hypertension in Orthostatic Hypotension
2023	NWB Symposium "consultation in movement disorders"	Pitch presentation	The Heads-Up trial
2023	EFAS	Short presentation	The impact of head-up tilt sleeping on orthostatic tolerance: a scoping review
2023	Parkinson café Delft	Oral presentation	Orthostatic hypotension in Parkinson
2023	Parkinson café Nijmegen	Oral presentation	Orthostatic hypotension in Parkinson
2024	EAN	Poster presentation	Haemodynamic determinants of supine hypertension in patients with classical orthostatic hypotension
2025	EFAS	Short presentation	The Heads-Up trial (EFAS audience award winner)

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Appendix A4. Dankwoord | Acknowledgements

Met veel trots heb ik dit proefschrift afgerond. Het traject was niet zonder obstakels en het was nooit gelukt zonder de hulp van mijn promotieteam, het Heads-Up consortium en alle andere onderzoekers, artsen, collega's, familie en vrienden.

Bas, door jouw inzichten, je aanstekelijke enthousiasme en met behulp van BasGPT hebben we mooi werk neergezet. Je passie voor alles wat op het centrum gedaan wordt is inspirerend en dat is te zien aan het werk wat door de groep verricht wordt in de kantoortuin en daarbuiten. Het expertisecentrum was een geweldige plek om met gelijkgestemde onderzoekers te werken.

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Nienke, je stond altijd klaar voor mij en je andere promovendi. Tijdens de onzekere periode van mijn aanstelling heb je geprobeerd alles zo vlot mogelijk op te lossen. Inmiddels ben je al even onderweg als associate professor, veel succes met je nieuwe uitdaging!

Sharon, we hebben elkaar iets minder gezien dan van tevoren gedacht, maar met een prachtige reden: je hebt tijdens mijn PhD traject een paar mooie kleine mensjes op de wereld hebt gezet. Toch heb ik veel van je kunnen leren. Bedankt voor de fijne samenwerkingen op de 6e verdieping en je luisterend oor tijdens onze koffiepauzes.

Gert, veel dank voor je expertise en wijsheden. Ik ben erg trots op het hoofdstuk over liggende hypertensie dat we samen neergezet hebben.

Alessandra, thank you for welcoming me in Innsbruck. Despite the hectic time with the MDS course you always still made time to teach me. I had many new experiences during your clinics.

Mijn paranimfen **Pauline** en **Colette**, heel erg bedankt voor al jullie hulp tijdens mijn PhD traject en bij het organiseren van de verdediging. Jullie steun heb ik erg gewaardeerd. De afleiding met lunchwandelingen, koffietjes en eten met Colette en sportuitjes met Pauline werkte (hopelijk wederzijds) erg goed om alle stres te

verlichten. In de toekomst zal ook mijn deur altijd voor jullie open staan, zoals die van jullie voor mij.

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And to my Innrain colleagues: **Bianca** -thank you for the fun ice-skating Sundays to take our minds of our PhD's. **Ilenia**, **Nicole**, **Karoline**, **Livia** and **Noelia**, thank you so much for all the support, aperitivos and hikes in Innsbruck. You made me feel right at home. Sending you a big hug and I hope to see you again soon!

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Appendix A5. Donders Graduate School

For a successful research Institute, it is vital to train the next generation of scientists. To achieve this goal, the Donders Institute for Brain, Cognition and Behaviour established the Donders Graduate School in 2009. The mission of the Donders Graduate School is to guide our graduates to become skilled academics who are equipped for a wide range of professions. To achieve this, we do our utmost to ensure that our PhD candidates receive support and supervision of the highest quality.

Since 2009, the Donders Graduate School has grown into a vibrant community of highly talented national and international PhD candidates, with over 500 PhD candidates enrolled. Their backgrounds cover a wide range of disciplines, from physics to psychology, medicine to psycholinguistics, and biology to artificial intelligence. Similarly, their interdisciplinary research covers genetic, molecular, and cellular processes at one end and computational, system-level neuroscience with cognitive and behavioural analysis at the other end. We ask all PhD candidates within the Donders Graduate School to publish their PhD thesis in de Donders Thesis Series. This series currently includes over 600 PhD theses from our PhD graduates and thereby provides a comprehensive overview of the diverse types of research performed at the Donders Institute. A complete overview of the Donders Thesis Series can be found on our website: https://www.ru.nl/donders/donders-series

The Donders Graduate School tracks the careers of our PhD graduates carefully. In general, the PhD graduates end up at high-quality positions in different sectors, for a complete overview see https://www.ru.nl/donders/destination-our-former-phd. A large proportion of our PhD alumni continue in academia (>50%). Most of them first work as a postdoc before growing into more senior research positions. They work at top institutes worldwide, such as University of Oxford, University of Cambridge, Stanford University, Princeton University, UCL London, MPI Leipzig, Karolinska Institute, UC Berkeley, EPFL Lausanne, and many others. In addition, a large group of PhD graduates continue in clinical positions, sometimes combining it with academic research. Clinical positions can be divided into medical doctors, for instance, in genetics, geriatrics, psychiatry, or neurology, and in psychologists, for instance as healthcare psychologist, clinical neuropsychologist, or clinical psychologist. Furthermore, there are PhD graduates who continue to work as researchers outside academia, for instance at non-profit or government organizations, or in pharmaceutical companies. There are also PhD graduates who work in education, such as teachers in high school, or as lecturers in higher

education. Others continue in a wide range of positions, such as policy advisors, project managers, consultants, data scientists, web- or software developers, business owners, regulatory affairs specialists, engineers, managers, or IT architects. As such, the career paths of Donders PhD graduates span a broad range of sectors and professions, but the common factor is that they almost all have become successful professionals.

For more information on the Donders Graduate School, as well as past and upcoming defences please visit: http://www.ru.nl/donders/graduate-school/phd/

Appendix A6. Dissertations of the Center of Expertise for Parkinson & Movement Disorders

Parkinson's disease

Jasper Visser. The basal ganglia and postural control. Radboud University Nijmegen, June 17th 2008.

Maaike Bakker. Supraspinal control of walking: lessons from motor imagery. Radboud University Nijmegen, May 27th 2009.

Wilson Farid Abdo. Parkinsonism: possible solutions to a diagnostic challenge. Radboud University Nijmegen, October 7th 2009.

Samyra Keus. Physiotherapy in Parkinson's disease. Towards evidence-based practice. Leiden University, April 29th 2010.

Lars Oude Nijhuis. Modulation of human balance reactions. Radboud University Nijmegen, November 29th 2010.

Maarten Nijkrake. Improving the quality of allied health care in Parkinson's disease through community-based networks: the ParkinsonNet health care concept. Radboud University Nijmegen, November 29th 2010.

Rick Helmich. Cerebral reorganization in Parkinson's disease. Radboud University Nijmegen, May 24th 2011.

Ilona Bruinsma. Amyloidogenic proteins in Alzheimer's and Parkinson's disease. Interaction with chaperones and inflammation. Radboud University Nijmegen, September21st 2011.

Charlotte Haaxma. New perspectives on preclinical and early stage Parkinson's disease. Radboud University Nijmegen, December 6th 2011.

Hanneke Kalf. Drooling and dysphagia in Parkinson's disease. Radboud University Nijmegen, December 22nd 2011.

Anke Snijders. Tackling freezing of gait in Parkinson's disease. Radboud University Nijmegen, June 4th 2012.

Bart van Nuenen. Cerebral reorganization in premotor parkinsonism. Radboud University Nijmegen, November 22nd 2012.

Wandana Nanhoe-Mahabier. Freezing of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, February 13th 2013.

Marlies van Nimwegen. Promotion of physical activity in Parkinson's disease, the challenge to change behavior. Radboud University Nijmegen, March 6th 2013.

Arlène Speelman. Promotion of physical activity in Parkinson's disease, feasibility and effectiveness. Radboud University Nijmegen, March 6th 2013.

Tjitske Boonstra. The contribution of each leg to bipedal balance control. University Twente, June 6th 2013.

Marjolein van der Marck. The Many faces of Parkinson's disease: towards a multifaceted approach? Radboud University Nijmegen, January 20th 2014.

Katrijn Smulders. Cognitive control of gait and balance in patients with chronic stroke and Parkinson's disease. Radboud University Nijmegen, May 21st 2014.

Marjolein Aerts. Improving diagnostic accuracy in parkinsonism. Radboud University Nijmegen, June 27th 2014.

Maartje Louter. Sleep in Parkinson's disease. A focus on nocturnal movements. Radboud University Nijmegen, February 13th 2015.

Frederick Anton Meijer. Clinical Application of Brain MRI in Parkinsonism: From Basic to Advanced Imaging, Radboud University Nijmegen, June 23th 2015.

Jorik Nonnekes. Balance and gait in neurodegenerative disease: what startle tells us about motor control, Radboud University Nijmegen, September 25th 2015.

Martijn van der Eijk. Patient-centered care in Parkinson's disease. Radboud University Nijmegen, December 1st 2015.

Ingrid Sturkenboom. Occupational therapy for people with Parkinson's disease: towards evidence-informed care. Radboud University Nijmegen, February 11th 2016.

Merel van Gilst. Sleep benefit in Parkinson's disease. Radboud University Nijmegen, April 13th 2016.

Arno Janssen. Transcranial magnetic stimulation - measuring and modeling in health and disease. Radboud University Nijmegen, June 2nd 2016.

Annette Plouvier. De ziekte van Parkinson, een gezamenlijke reis van huisarts en patiënt. Radboud University Nijmegen, juni 15th 2017.

Nico Weerkamp. Parkinson's disease in long-term-care facilities. Radboud University Nijmegen, September 1st 2017.

Digna de Kam. Postural instability in people with chronic stroke and Parkinson's disease: dynamic perspectives Radboud University Nijmegen, October 4th 2017.

Freek Nieuwhof. The complexity of walking: Cognitive control of gait in aging and Parkinson's disease Radboud University Nijmegen, October 27th 2017.

Koen Klemann. A molecular window into Parkinson's disease. Radboud University Nijmegen, November 3th 2017.

Jeroen Venhovens. Neurovestibular analysis and falls in Parkinson's disease and atypical parkinsonism. Radboud University Nijmegen, March 20st, 2018.

Claudia Barthel. Moving beyond: freezing of gait in Parkinson's disease. Radboud University Nijmegen, April 4th 2018.

Esther Bekkers. Freezing and postural control in Parkinson's disease. Defense at KU Leuven, May 15th 2018.

Erik te Woerd. Feeling the beat: The neurophysiology of cueing in Parkinson's disease. Radboud University Nijmegen, January 18th 2019.

Ana Silva de Lima. Quantifying Parkinson's disease: the use of technology for objective assessment of motor symptoms. Radboud University Nijmegen, March 26th 2019.

Monique Timmer. Neurocognitive mechanisms underlying depression in Parkinson's disease. Radboud University Nijmegen, April 16th, 2019.

Sabine Janssen. Virtual visual cues: vice or virtue? University of Twente, March 11th, 2020.

Anna Santaella Tortós-Sala. Tackling Parkinson's disease: a proteomic approach to biomarkers and regenerative therapy. Radboud University Nijmegen, October 22nd, 2020.

Nicolien van der Kolk. Towards a prescription for exercise for persons with Parkinson's disease. Radboud University Nijmegen, October 30th, 2020.

Michiel Dirks. Neural mechanisms of Parkinson's tremor. Radboud University Nijmegen, November 22nd, 2020.

Sjors van de Weijer. Digital technology-enabled home health care: Gamification in online cognitive therapies for Parkinson's disease. Maastricht University, September 1st 2021.

Taina Macherini Marques. Discriminating Parkinsonian Disorders. Radboud University Nijmegen, September 9th 2021.

Danny Hommel. Impairment and disability in late-stage parkinsonism. Radboud University Nijmegen, September 27th, 2021.

Floris Vlaanderen. Towards seamless and sustainable care for Parkinson's disease. Radboud University Nijmegen, October 27th, 2021.

Rui Araújo. The art of clinical neurology. Radboud University Nijmegen, March 7th, 2022.

Sara Riggare. Personal science in Parkinson's disease. Radboud University Nijmegen, March 25th, 2022.

Tamine Teixeira da Costa Capato. Clinical assessment and management of balance impairments in Parkinson's disease. Radboud University Nijmegen, June 29th, 2022.

Herma Lennaerts - Kats. Palliative care for people with Parkinson's disease and their family caregivers. Radboud University Nijmegen, July 6th, 2022.

Lieneke van den Heuvel. Towards personalized decision making in Parkinson's disease. Radboud University Nijmegen, August 24th, 2023.

Luc Evers. Stepping out of the clinic: towards objective, real-life monitoring of Parkinson's disease. Radboud University Nijmegen, June 19th, 2024.

Angelika Geerlings. Personalized care management in Parkinson's disease: One size does not fit all. Radboud University Nijmegen, October 7th, 2024.

Robin van den Bergh. Telemedicine and remote monitoring for people with Parkinson's disease. Radboud University Nijmegen, December 9th, 2024.

Frouke Nijhuis. Decision-making for advanced therapies in Parkinson's disease. It takes a shared choreography. Radboud University Nijmegen, January 23rd, 2025.

Sabine Schootemeijer. Promoting physical activity in Parkinson's disease. Towards scalable interventions. Radboud University Nijmegen, April 11th, 2025.

Amir Talebi. Leveraging Big Data to Improve Care for People with Parkinson's Disease. Radboud University Nijmegen, May 26th, 2025.

Thieme Stappe. Through the learning lens: On innovation towards integrated and person-centered Parkinson's care. Radboud University Nijmegen, August 28th, 2025.

Veerle van de Wetering-van Dongen. Respiratory issues screened and explored in Parkinson's disease. Radboud University Nijmegen, November 3rd, 2025.

Non-Parkinsonian disorders of movement

Sacha Vermeer. Clinical and genetic characterization of autosomal recessive cerebellarataxias. Radboud University Nijmegen, April 5th, 2012.

Susanne de Bot. Hereditary spastic paraplegias in the Netherlands. Radboud University Nijmegen, December 20th, 2013.

Catherine Delnooz. Unraveling primary focal dystonia. A treatment update and new pathophysiological insights. Radboud University Nijmegen, January 7th, 2014.

Ella Fonteyn. Falls, physiotherapy, and training in patients with degenerative ataxias. Radboud University Nijmegen, June 29th, 016.

Britt Hoffland. Investigating the role of the cerebellum in idiopathic focal dystonia. Radboud University Nijmegen, March 22nd, 2018.

Ilse Eidhof. Common biological denominators and mechanisms underlying ataxi alike motor dysfunction: from human to fly. Radboud University Nijmegen, April 2nd, 2020.

Bas van Lith. Balance and gait problems in people with hereditary spastic paraplegia. Radboud University Nijmegen, November 16th, 2020.

Nienke van Os. Ataxia telangiectasia – disease course and management. Radboud University Nijmegen, March 19th, 2021.

Kai Hui Yap. Trehalose in spinocerebellar ataxia type 3. UKM Medical Center, Kuala Lumpur (Malaysia), April 19th, 2023.

Lotte van de Venis. Mobility, stability, and adaptability – the challenges of walking for people with hereditary spastic paraplegia. Radboud University Nijmegen, June 7th, 2024.

Roderick Maas. Towards symptomatic and disease-modifying therapies in spinocerebellar ataxias. Radboud University Nijmegen, August 28th, 2024.

Stacha Reumers. Big problems arising from the little brain, novel insights on the Cerebellar Cognitive Affective Syndrome. Radboud University Nijmegen, May 26th, 2025.

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