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SLEEPING WITH THE HEAD UP OF THE BED

TILTED UP:

PHYSIOLOGY & THERAPY

Chie Wei Fan MB, BCh, BAO, MRCPI, DME

A thesis submitted in fulfilment of the requirements for the degree of Doctor of Medicine

UNIVERSITY OF DUBLIN,

TRINITY COLLEGE.

APRIL 2008
To Whom It May Concern:

The following errors have occurred during the printing of the thesis. The errors are found in the legends from figures 9.3 to 9.16 on pages 164, 165, 170-181. The correct legends should be as below: The bold lines were suppose to represent “at 6 weeks” while the thin line represent “at baseline” as shown below.

_______ at baseline
at 6 weeks

The errors have occurred on the following figures:

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Yours truly,

Dr Chie Wei Fan, MD, MRCPI
DECLARATION

I declare that the work contained in this thesis is entirely my own, except where credit is given in the acknowledgement section.

All participants in the studies gave full and informed consent. The investigations and interventions were permitted by approval of the research ethics committee of AMNCH/St. James’s Hospital.

This thesis has not been submitted as an exercise for a degree at this or any other university. It is entirely my own work except where noted in acknowledgements.

I agree that the Library of the University of Dublin may lend or copy this thesis upon request.

Signed

Chie Wei Fan

Date

20/11/08
Orthostatic hypotension (OH) is common and affects people with increasing age and co-morbidity. It is associated with increased vascular risk, falls and dementia. While pharmacological and non-pharmacological treatments exist they are either poorly tolerated or poorly studied. One of the non-pharmacological therapies is sleeping with the head of the bed elevated (SHU). This treatment option has been described since the 1940's. However, the scientific evidence for SHU, up to now, has been case reports in middle aged people (i.e. younger than 65 years) and SHU has been prescribed in conjunction with anti-hypotensive medications and extra salt intake so that direct benefits are unclear. It is also unclear to what extent it is used in people aged 65 and over, the group with the greatest prevalence of OH. Furthermore, there is a lack of clarity in the expert guidelines to what height the head of the bed should be tilted even though this factor is likely to be important for physiological effect. Where specific heights are given, for instance 18 inches, this height is unlikely to be tolerated by older people.

It is timely, therefore, to conduct research on the use of SHU in clinical practice, the physiological responses to SHU in young, and older people with OH, at different heights of elevation and for varying durations.

The aims of this work were:

1. To determine the extent of use of SHU in current clinical practice for treatment of OH and the angles at which SHU was prescribed
2. To investigate the physiological effects of SHU at 18 inches for one week in young, well-hydrated healthy people
3. To investigate the physiological effects of SHU at 6 inches for one week in hospital patients with OH
4. To investigate the effects of SHU at 6 inches for 6 weeks in community-living patients who have OH using an open labelled randomised controlled trial

Methods

The first study was a cross-sectional postal survey of clinicians who attended an international syncope conference. The respondents to the survey included geriatricians, cardiologists and neurologists. The second, third and fourth studies comprised of repeated measures of haemodynamic variables (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, heart rate, Modelflow-derived left ventricular stroke volume, cardiac output, total peripheral resistance) during active stands in the morning before and after SHU of various angles and durations depending on the studies. 24-hour ambulatory blood pressure monitor were also applied at baseline and the last day of SHU. In studies 2 and 4, 24-hour urinary volume and sodium excretions collections were performed, while blood samples were drawn in the supine position for full blood count, urea and electrolyte, aldosterone, plasma renin activity and pro-anti-natriuretic peptide (1-98) for studies 2 and 3. Calf and ankle circumferences were measured in the second study while the presence of ankle oedema was noted in study 4. All participants in study 4 were asked to drink at least 2 litres of water a day. They were interviewed about the symptoms of dizziness, compliance and tolerability with SHU and water drinking. Paired t-test were used to compare non-haemodynamic variables. Haemodynamic variables were
analysed separately for recumbent and standing phases using a series of analysis of variance models with factors representing condition (before or after SHU), time point, subject and interventions (in study 4). Categorical variables were analysed using Chi-square tests. In addition to the absolute values, we also analysed the relative percentage change of the Modelflow parameters as defined as (post-pre values)/pre values*100%.

Results

SHU ranked 5th in the treatment armamentarium for OH, was prescribed by half of the clinicians surveyed, and routinely by a quarter. A majority of the prescribers used tilt angles between 3 to 5 degrees, which were much lower than what was reported in the literature as effective. Following SHU, both young and old participants had evidence of shift of extracellular fluid to the lower extremities and/or intravascular fluid accumulation as shown by a significant reduction in haemoglobin and creatinine, and presence of ankle oedema and weight gain. There were also attenuations in stroke volume decline during standing after SHU even though the effect on blood pressure was not as pronounced. Relative percentage changes in stroke volume reflected similar trends. SHU, at 18 inches in young people and 6 inches in the older patients with OH, exerted similar haemodynamic effects and symptomatic improvement. The physiological changes were most pronounced at one week in the hospitalised patients but were no different from controls.

Discussion

These findings suggest that SHU has definite physiological effects (in both young controls and older patients) and that 6 inches of elevation is capable of producing these effects. The acute effect of SHU at 6 inches in hospitalised patients who were medically unwell is striking and suggests that the therapy may have a use in that context. However it appears to have no additional effects on blood pressure and orthostatic symptoms at 6 weeks in older out-patients than existing non-pharmacological measures. Its use in this context should therefore be discouraged. Given that existing case reports focus mainly on benefit for patients with autonomic dysfunction further research in that cohort may be worthwhile. Future studies should include a control group who do not undergo SHU.
ACKNOWLEDGEMENTS

I would like to thank Dr Conal J Cunningham, my supervisor, for his time, attention, personal supervision and assistance data analysis for the last 5 years from its inception to completion of this thesis. I would like to thank Professor Davis Coakley for his advice on the thesis proposal and the Medicine for the Elderly department (MedEL) in St James’s Hospital for their support and providing a nurturing environment within Mercer Institute for research on Ageing (MIRA) where research in older people are actively promoted. I would also like to thank all the staff in the Falls and Blackout clinic, in particular Ms Nessa Fallon, Ms Lisa Byrne and Ms Dymphna Hade in their assistance with blood sampling, active stands and 24-hour ABPM measurements. I want to thank Dr Cathal Walsh for advice on statistics, Declan Gasparro, Gerry Cox, Dr Michael Healy, Dr Vivion Crowley in the biochemistry department for their assistance in analysis of blood samples and advice on the results. I am inspired by the enthusiasm and organisational skills of Ms Elizabeth O’Sullivan for her assistance in conducting the study in young controls, I now use webtext to remind participants of the research protocol. I am grateful to the 31 young and 109 older participants who agreed to take part in the studies for altruism.

I would also like to thank Mr Ken Martin, my neighbour who is a skilled carpenter, for the custom-made 6 inch blocks and proof-reading my thesis. I also want to thank Ms Heather Bailey for casting an eye over my grammar. I want to acknowledge my circle of support outside work, in the Chinese Gospel Church of Dublin, who have baby-sat and collected my daughter from the crèche at the last minute notice when I was delayed due to research meetings, in particular, Ms Jenny Ng who is fondly known as Jenny ‘Ma’ to us. I also want to thank my mother-in-law, Ling, for ‘mothering’ me at the initial phase of the project.

I want to thank my daughter Calista, who has missed out ‘loads’ of playtime because Mama was on the computer again !!! Finally, I want to thank my husband Sam for his belief in me, his steady encouragement and support to take on and then complete this ‘mammoth’ task, without whom I would not have the courage to embark on the MD.
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LIST OF ABBREVIATIONS

Δ HRmax ≥12  Initial heart rate rise on standing greater or equal to 12 bpm compared with baseline
Δ HRmax<12  Initial heart rate rise on standing less than 12 bpm compared with baseline
ACE   Angiotensin converting enzyme
ADH antidiuretic hormone
AF Autonomic failure
AII angiotensin II
ANN American association of neurology consensus definition for orthostatic hypotension
ANP atrial natriuretic peptide
ANP brain natriuretic peptide
ATG angiotensinogen
BHS British Hypertension Society
BMI Body mass index
BP Blood pressure
bpm beats per minute
CCF Congestive cardiac failure
CNP C-type natriuretic peptide
CO Cardiac output
DBP Diastolic blood pressure
DM Diabetes Mellitus
IIBΣΔ mean drop from I0 to nadir SBP
ECF extracellular fluid
ED Emergency department
GFR glomerular filtration rate
GP General practitioner
Hb haemoglobin
Hct haematocrit
HCU height correction unit
HR Heart rate
I0 10-second interval immediately before standing
I1 and I2 the first two 10-second intervals
IHD Ischaemic heart disease
JG juxtaglomerular
L-DOPS L-threo-dihydroxyphenylserine
MAP Mean arterial pressure
min Minutes
ml millilitres
MMSE Mini mental test score
MSA Multisystem atrophy
MSNA muscle sympathetic nerve activity
NICBP non-invasive continuous beat-to-beat BP monitoring
NOH Neurogenic orthostatic hypotension
OH Orthostatic hypotension
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>OH-D1</td>
<td>Diastolic BP fall of 10mmHg at 1 min</td>
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<tr>
<td>OH-S3</td>
<td>Fall in systolic blood pressure of greater than 20mmHg at 3 minutes</td>
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<tr>
<td>OI</td>
<td>Orthostatic intolerance</td>
</tr>
<tr>
<td>PAF</td>
<td>Progressive autonomic failure</td>
</tr>
<tr>
<td>PCM</td>
<td>Physical counter-manoeuvres</td>
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<td>PD</td>
<td>Parkinson Disease</td>
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<tr>
<td>POTS</td>
<td>Postural orthostatic tachycardia syndrome</td>
</tr>
<tr>
<td>PRA</td>
<td>Plasma levels of renin activity</td>
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<tr>
<td>RAAS</td>
<td>Renin-angiotensin-aldosterone system</td>
</tr>
<tr>
<td>rCO</td>
<td>Relative percentage change in cardiac output</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>rSV</td>
<td>Relative percentage change in stroke volume</td>
</tr>
<tr>
<td>RTF</td>
<td>Return-to-flow</td>
</tr>
<tr>
<td>rTPR</td>
<td>Relative percentage change in total peripheral resistance</td>
</tr>
<tr>
<td>s</td>
<td>Seconds</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
</tr>
<tr>
<td>SDOH</td>
<td>Systolicdrop of 20 or greater and diastolic drop in blood pressure of 10 mmHg or greater</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SH</td>
<td>Supine hypertension</td>
</tr>
<tr>
<td>SHEP</td>
<td>Systolic Hypertension in the Elderly Programme</td>
</tr>
<tr>
<td>SHU</td>
<td>Sleeping head up</td>
</tr>
<tr>
<td>SOH</td>
<td>Systolic blood pressure fall of 20mmHg or greater</td>
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<tr>
<td>SV</td>
<td>Left ventricular stroke volume</td>
</tr>
<tr>
<td>SyOH</td>
<td>Any drop in systolic blood pressure with symptoms</td>
</tr>
<tr>
<td>TPR</td>
<td>Total peripheral resistance</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
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<tr>
<td>US</td>
<td>United States of America</td>
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</tbody>
</table>
Chapter 1.1 Definition of orthostatic hypotension

Orthostatic hypotension (OH) is defined in a number of ways. The definition of orthostatic hypotension was arrived at during a consensus meeting in 1995 by the American Autonomic Society and the American Academy of Neurology Consensus Committee (1996) where they defined OH as a systolic blood pressure (SBP) decrease of at least 20 mm Hg or a diastolic blood pressure decrease of at least 10 mm Hg within three minutes of standing or upright tilt of at least 60 degrees. This definition was accepted by Lipsitz (Lipsitz 1989) and Mathias (Mathias 1995). The diagnosis of OH is irrespective of the lowest SBP reached on standing or presence or absence of symptoms. It is conceivable that persons with hypertension may have greater tendency to postural drop consistent with OH and yet may not be symptomatic (Applegate, Davis et al. 1991; Beckett, Connor et al. 1999).

The Mayo Clinic General Clinical Research Centre (Rochester, Minnesota), on the other hand, used a stricter criterium of a systolic BP reduction of 30 mm Hg or higher or mean BP reduction of 20 mm Hg or higher that occurs within 3 minutes of standing up in their study. (Singer, Sandroni et al. 2006)
Chapter 1.2 Detection of orthostatic hypotension

Apart from selecting the instrument of measurement, the detection of OH is dependent on how it is measured and the timing of the measurement. Confounding variables are: food ingestion, time of day, state of hydration, ambient temperature, recent recumbency, postural deconditioning, hypertension, medications, gender and age (1996).

As with any procedure, lying and standing blood pressure should be carried out in a standardised fashion.

- Time of day when BP is measured
- Timing of measurement from supine to standing
- Instrument of measurement

An observational study (Vloet, Smits et al. 2002) evaluated nurses knowledge on BP measurement to diagnose OH. There were significant deviations from standard protocol in the following areas: Standing BP was measured 0 min to 30 min after standing, 46% had wrong cuff placement, and in 28% the arm was not at heart level. Nurse education of correct procedure improved knowledge of measurement of lying and standing BP from 11% to 69% (Vilches and Hyatt 2003).

Time of day when BP is measured

BP responses to orthostasis are variable amongst older persons, depending what time the measurements are taken (Ward and Kenny 1996; Ooi, Barrett et al. 1997; Belmin, Abderrhamane et al. 2000). Although OH was detected in more than half of the subjects (51.5%) of nursing home residents (Ooi, Barrett et al. 1997), only 20% of them were persistent. Another study also found that OH was detected in two-thirds of older persons with established OH if measurements were carried out in the afternoon (Ward and Kenny 1996). Therefore, it is recommended that postural BP measurement be carried out in the morning.

BP should also be measured at least an hour after food to avoid post-prandial hypotension.

BP can fall abnormally an hour following antihypertensive medications and therefore the timing of BP measurement after medications should be noted (Lipsitz 1989).

The detection rate of OH depends on methodology and instrument used.
Procedure for measuring supine and standing blood pressure

Various BP measurement protocols have been described. The most common measurement of supine and standing BP is as follows (Wieling and Karemaker 2002)(Mader 1989). BP is taken when the person is lying supine for at least 5 to 10 minutes. Then the person is instructed to move from supine to standing in about 3s, if necessary with assistance. BP measurements can be recorded continuously with various devices: a beat-to-beat phasic BP device (Finometer), an oscillometric device, or a sphygmomanometer. The measurements are taken when supine and immediately after standing upright, at 1 and at 3 minutes. The Cardiovascular Health Study Research group (Rutan, Hermanson et al. 1992) measured BP at supine and at 3 minutes standing. Using a sphygmomanometer, Mader (Mader 1989) found most of the BP decline had occurred by 1min and Atkins (Atkins, Hanusa et al. 1991) by 2 minutes of standing. Other investigators found the nadir SBP occurred as early as 30s (de Biase, Amorosi et al. 1988; Macrae and Bulpitt 1989) and that the BP will usually have returned to the supine value by 2 minutes (Macrae and Bulpitt 1989).

A proper size BP cuff is required to carry out a bedside measurement (Carlson 1999). For the auscultatory method, the BP is measured with the cuff arm positioned with the brachial artery held at the level of the heart. If postural BP is measured from sit to stand (as distinct from supine to stand), this has to be stated clearly. The postural drop in BP will be much reduced as some of the transthoracic blood shift will have occurred.

The estimated prevalence of OH depends on the methods of measuring BP. The arm position is important: in one study when the arm was supported at heart level, a SBP drop of 20mmHg or greater occurred in 18.2% of subjects but when the arm was not supported, SBP drop of 20mmHg occurred in only 6% (Mariotti, Alli et al. 1987). It is also important to let the subject rest for 5 minutes before the supine reading is taken. Mader (Mader 1989) found the first supine reading was higher than subsequent readings. Therefore the largest drop of BP was found when the first supine measurement was taken as the baseline reading.

Instruments for measurement

The list of instruments and how it measures BP will be discussed in Chapter 3. In patients attending a syncope clinic, Caine (Caine, Alsop et al. 1998) reported that sphygmomanometer and oscillometric devices had a sensitivity of only 25% and 32% respectively when compared with digital photoplethysmography.
When using Finapres devices to measure postural BP, the nadir of the BP reached is illustrated as below. If there are a lot of fluctuations in Finapres trace, Wieling et al (Wieling and Karemaker 2002) suggested taking an average BP at 10s intervals to reduce artefactual readings.

Fig. 1.2.1 Systolic and diastolic blood pressure response to standing

In patients where there is a failure of recovery of blood pressure, it has been suggested that the reading at 20s is taken as the nadir (Wieling and Karemaker 2002) as shown in the figure 1.2.2.
Fig.1.2.2 Systolic and diastolic blood pressure and heart rate response to standing in a patient with autonomic failure

Active stand trace of patients with autonomic failure with no blood pressure recovery

BP nadir at 20s
Chapter 1.3 Prevalence of orthostatic hypotension

BP falls when we assume postural change: either from supine to sitting, supine to standing, or sitting to standing. The American Autonomic Society and the American Academy of Neurology consensus statement defines OH as a fall in systolic blood pressure of at least 20mmHg and/or diastolic blood pressure of at least 10mmHg within 3 minutes of assuming an upright position from supine position, or during tilt (1996). Other experts in the field have minor variations in the definitions (see Chapter 1.1 for definition of OH). Persons who have 'Orthostatic intolerance' also complain of dizziness. Blood pressure patterns are (i) no decline, (ii) modest decline, or (iii) increase in BP when assuming an upright posture (Ali, Daamen et al. 2000). Some of the studies use orthostatic intolerance (OI) and orthostatic hypotension (OH) interchangeably.

OH or OI occur frequently, and different prevalence rates have been reported amongst different population groups. Different rates have also been reported in similar populations, for instance community living older persons, depending on the procedure and equipment used for BP measurement. The objective of this chapter is to report the prevalence of OH in various settings and population groups.

The reported prevalence of orthostatic hypotension is divided into the following categories:

According to measuring protocol

According to various patients groups

• Young
• Middle age
• Older people
  o community-living
  o institutional care
  o acute wards
  o rehabilitation wards
• Special patient groups
  o emergency department
  o Parkinsons Disease / Multi-system Atrophy
  o diabetes mellitus
Table 1.3.2 is a summary for the prevalence of OH, measuring instruments and setting in which blood pressures were taken.

According to measuring protocol
Postural BP can be affected by various confounding factors including the time of day when the measurements are taken (Ward and Kenny 1996), the timing of meals (Puisieux, Boumbar et al. 1999; Maurer, Karmally et al. 2000; Le Couteur, Fisher et al. 2003), the timing of medications and the measuring instruments (Caine, Alsop et al. 1998). Therefore when analysing papers reporting on the prevalence, we need to account for these factors.

Time of day when blood pressure is measured
If orthostatic BP is measured in the afternoon, Ward and Kenny (Ward and Kenny 1996) reported that one-third of patients with established OH will not have a drop in BP consistent with OH. Also if BP is measured within 90 minutes after a meal, the fall in BP may be confounded by post-prandial hypotension (Puisieux, Boumbar et al. 1999; Maurer, Karmally et al. 2000). Anti-hypertensive medications can also cause a fall in BP and should be accounted for when reporting postural BP.

Instruments used for measurement
The measuring instruments also affect the detection rate of OH. Currently the instruments available for measuring postural blood pressure include aneroid sphymomanometer, semi-automated oscillometer, tonometer, and continuous beat-to-beat digital plethysmography. Caine et al (Caine, Alsop et al. 1998) reported differing detection rates depending on the type of instruments used. The sensitivity of measuring instruments may affect the detection rates.

When interpreting the prevalence of OH we also take cogniscence of the measuring procedure in the study (see chapter 1.2)

Physiological orthostatic intolerance
2004) also reported a high prevalence of OH in young women (1 in 500 people). These patients may present with symptoms such as dizziness, visual changes, head and neck discomfort, poor concentration, fatigue, palpitations, tremulousness, anxiety, and, in some cases, syncope. In some cases persons with increased heart rate associated with upright posture are classified as having postural tachycardia syndrome (POTS).

Winker et al (Winker, Barth et al. 2003) found 4% of 138 young men (mean age 21.6 years) in military service had OH on tilt table testing while 14 (10%) of the young men had POTS.

Symptoms

Although OH is common, in a majority of cases the fall in BP is asymptomatic and incidental. In one study one in three of the over 75-year olds had OH, though only 2.6% had symptoms (Tilvis, Hakala et al. 1996). A USA study (Ensrud, Nevitt et al. 1992) amongst osteoporotic women also found more patients with postural dizziness compared with demonstrable OH (19% vs. 14%). Another large population based study (Rutan, Hermanson et al. 1992) reported more asymptomatic OH than those with symptoms (16.2% vs. 2.0%).

Community living older people

In a community study by Johnson et al (Johnson, Smith et al. 1965) in 1965, 17% of normal older people had OH, while MacLennan and Hall (MacLennan, Hall et al. 1980) in a later Scottish series (1980) reported a prevalence rate of 22% in community-living older people. The reasons for the differences were unclear. Most studies till then did not clarify the presence or absence of co-existing diseases. Another community study found that 13.7% of older subjects who had diseases or culprit medications (i.e. known to cause OH), compared with 10.7% in the absence of these risk factors (Mader, Josephson et al. 1987) suggesting a slight modifying effect of co-morbidity.

The prevalence of OH increases with age (Shin, Abbott et al. 2004; Rutan, Hermanson et al. 1992; Masaki, Schatz et al. 1998) (see table 1.3.1) Amongst middle age men and women in Korea, Shin et al (Shin, Abbott et al. 2004) found OH to be 6.4% in 40-44 year olds and 23.1% in 65 to 69 year olds. The Cardiovascular Heart Study and the Honolulu Heart Programme (Masaki, Schatz et al. 1998) also reported increases in prevalence with ageing.
Table 1.3.1 Prevalence of Orthostatic Hypotension by age

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>40-44</th>
<th>65-69</th>
<th>70-74</th>
<th>75-79</th>
<th>80-84</th>
<th>85+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shin (Shin, Abbott et al. 2004)</td>
<td>6.4%</td>
<td>23.1%</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rutan (Rutan, Hermanson et al. 1992)</td>
<td>14.8%</td>
<td>19.2%</td>
<td>20.1%</td>
<td>20.2%</td>
<td>26.0%</td>
<td></td>
</tr>
<tr>
<td>Masaki (Masaki, Schatz et al. 1998)</td>
<td>-</td>
<td>-</td>
<td>5.1%</td>
<td>6.3%</td>
<td>9.2%</td>
<td>10.9%</td>
</tr>
</tbody>
</table>

Overall prevalence in Masaki study was 6.9%.

In other Finnish studies, Raiha (Raiha, Luutonen et al. 1995) found a rate of 28.0% of older people (age 65 years and over) to have OH, while Luukinen et al (Luukinen, Koski et al. 1999) reported 22% of community-living older persons aged 70 years and over had OH within 1 minute of standing (Luukinen, Koski et al. 1999). Furthermore, one in three in the study population of the Helsinki Ageing Study (Tilvis, Hakala et al. 1996), people age 75 years and over, had drops in BP consistent with OH.

In a Taiwan study, Wu et al (Wu, Wu et al. 1996) found that 16.3% of 728 community living Chinese experienced OH. People with OH were older, had higher BMI, higher seated BP, higher plasma creatinine and increased HbA1C.

In Turkey, Atli et al (Atli and Keven 2006) reported OH rates of 14.7% in a group of 61 healthy elderly subjects. These nine subjects had higher left ventricular mass and lower fasting plasma insulin levels compared to the 52 without OH. This finding in relation to diabetes/insulin sensitivity would appear to be in contradiction to Wu (Wu, Wu et al. 1996) but the much smaller sample size may suggest chance.
Primary care setting

There were several prevalence studies of OH in the primary care setting. In a Spanish general practitioners setting, Vara Gonzalez (Vara Gonzalez, Domínguez Rollan et al. 2001) reported an OH prevalence of 14.6% amongst elderly with hypertension. A review article by Hale and Chambliss (Hale and Chambliss 1999) reported rates between 13 to 30%. An Italian study (Alli, Avanzini et al. 1992) was conducted in 444 general practice (GP) settings of 3858 men and women aged over 65 years. They visited their GPs twice, 7 days apart and underwent supine and upright BP measurement. The investigators defined OH in the following categories: SOH, Systolic fall in BP of 20mmHg or greater; SDOH, systolic drop of 20 or greater and diastolic drop in BP of 10 mmHg or greater; SyOH, any drop in systolic BP with symptoms. The investigators found reducing rates between the first and second visits: SOH 13.8% and 12.6%, SDOH 5.3% and 4.8%, and SyOH 14.1% and 11.8%. All criteria for OH were met in less than 2% of the older patients at each visit, and OH was reproduced on both occasions in only 36.3% of cases for SOH, in 25.7% for SDOH and 43.9% for SyOH. The paper suggests that a systolic fall in BP is more common than a fall in both systolic and diastolic BP. It is also interesting to note that many subjects had symptoms despite small drops in systolic BP. It could be postulated that the instruments of measurement might not have been sufficiently sensitive to detect the fall in BP. On the other hand changes in cerebral autoregulation might account for the symptoms rather than peripheral fall in BP.

Geriatric outpatients

Robertson (Robertson, DesJardin et al. 1998) reported a drop of 20mmHg in SBP or greater in 13% of those attending a geriatric out-patient clinic with 4% having a drop of 10mmHg in diastolic BP on standing when the BP measurement was performed using a sphygmomanometer. Patients who were hypertensive when recumbent were more like to have drops in BP (16% prevalence).

Older patients in hospital or institutions

Kapoor (Kapoor, Sunstad et al. 1986) reported that 14% of elderly patients with syncope had OH. OH was also associated with persons who had difficulty walking (OR 1.23), frequent falls (1.52), a history of myocardial infraction (1.24), or transient ischaemic attacks (1.68).

In 2002, a study by Weiss (Weiss, Grossman et al. 2002) revealed an OH prevalence rates of 33.1% - 67.9% of patients (mean age 81.2 years) in an acute geriatric ward in Israel. He also
reported seasonal variation in OH prevalence in another study (Weiss, Beloosesky et al. 2006). Although the overall OH prevalence was 34.8% in summer and winter, persistent OH, which was defined as OH confirmed on at least two occasions during the day, was more prevalent in summer than winter (37.9% vs. 27.1%). The risk of developing OH was 64% higher in summer in older inpatients. Possible explanations could be dehydration or vasodilation due to the hot environment. OH was cited as one of the reasons for admission into hospital.

In a Dutch series, Rhebergen (Rhebergen and Scholzel-Dorenbos 2002) found that 24% of medical patients over the age of 70 years had OH. He also found that 34% had post-prandial hypotension.

Another inpatient study also found high prevalence of OH in patients in a French geriatric short stay ward (48%) (Puisieux, Boumbar et al. 1999). Half of the patients in nursing homes were found to have a fall in BP consistent with OH (Ooi, Barrett et al. 1997). OH was reproducible in 13.3% of the residents at varying times of the day (before and after breakfast, before and after lunch). It occurred most frequently before breakfast and after lunch. Residents with a previous fall and OH were also 2.6 times more likely to fall if they had reproducible OH on repeated measurements (Ooi, Hossain et al. 2000).

Gorelik (Gorelik, Fishlev et al. 2005) reported significant levels of OH (64.5%) in older patients who were in-patients, especially in those with a history of renal dysfunction and heart failure. Chambers et al (Chambers 2005) reported OH of 27% amongst palliative care patients.

Patients with Co-morbidity

There are certain conditions in which OH is more prevalent. For instance, in a series of 60 patients by Bonuccelli et al (Bonuccelli, Lucetti et al. 2003), the investigators found 14% of Parkinson patients and 60% of patients with multi-system atrophy had OH. The detection of OH was made using manometric measurements. Allcock et al (Allcock, Ullyart et al. 2004) reported higher rates (47%) using semi-automated oscillometric measurements at 1 and 2 minutes standing. There were compelling data showing that the presence of OH (albeit asymptomatic) preceded Parkinson disease in 60% of cases (Goldstein 2006). OH following acute stroke is also common. More than half of the patients undergoing acute stroke rehabilitation in Singapore had OH (Kong and Chuo 2003). Other patient groups where OH is
prevalent are: osteoporosis (Ensrud, Nevitt et al. 1992) (14%), patients with cardio-inhibitory carotid sinus syndrome (Mulcahy, Jackson et al. 2003) (50%), patients attending syncope clinic (McIntosh, Lawson et al. 1993) (33%), and in elderly patients undergoing hemodialysis (Roberts, Kenny et al. 2003) (in particular 70% post dialysis vs. 35% pre-dialysis). Half of the dialysis patients described syncopal/ presyncopal symptoms, 72% of them had dizziness, and 29% had fallen in the past year.

Patients with congestive heart failure (CCF) were more likely to develop OH when compared with those without CCF (Potocka-Plazak and Plazak 2001) (83.3% vs. 53.3%). Almost three quarters of patients with spinal cord injuries undergoing rehabilitations had OH (Illman, Stiller et al. 2000).

Prevalence in the emergency department
Patients attending emergency departments are also vulnerable to OH. Sarasin (Sarasin, Louis-Simonet et al. 2002) reported prevalence rate of 25% amongst patients who attended emergency departments with syncope. The aetiology of OH described included drug induced OH (37%), hypovolemia (21%), post-prandial hypotension (12%) and the causes were unknown in 29% of patients. Atkins (Atkins, Hanusa et al. 1991), similarly, reported one third of the patients attending ED with syncope had OH.

Medication induced OH
Medications are widely implicated in causing OH. Culprit medications include psychiatric medications and anti-hypertensives medications. In a group of schizophrenic patients on medications, Silver (Silver, Kogan et al. 1990) found that 77% of them had OH at 1 minute and 16.8% at 3 minutes. A study by Fotherby et al (Fotherby, Robinson et al. 1994) showed that a third of the elderly treated with anti-hypertensive medication had OH. More than half of the participants in the studies who had symptomatic OH required medication withdrawal. In another hypertension trial, the Systolic Hypertension in the Elderly Programme (SHEP), Applegate (Applegate, Davis et al. 1991) reported OH to affect 17.3% of the participants. The authors reported an overall OH rate of 17.3%, 10.4% at 1 minute, 12.0% at 3 minutes. In 5.3% of the participants, OH was persistent at 1 and 3 minutes.
Seated orthostatic hypotension

In hospitalised patients who were acutely unwell, and were on anti-hypertensive medications, Cohen (Cohen, Gorelik et al. 2003) reported that more than half of the older inpatients could become hypotensive with a SBP fall greater than 20 mmHg on sitting up after 12 hours bed rest. The fall in BP was associated with dizziness, palpitations and sweating, and could last up to five minutes.

In summary, orthostatic hypotension or orthostatic intolerance can affect people at any age. It appears to be more prevalent in adolescence, women, older persons and those who are acutely unwell or have chronic diseases. The prevalence can be as high as 50% in those who are frail and have co-morbidity. The majority of patients with OH are asymptomatic. Specialised equipment improves the detection of this common condition.
<table>
<thead>
<tr>
<th>Population studied &amp; Setting</th>
<th>Author, Year</th>
<th>Definition of OH</th>
<th>Timing of measurement</th>
<th>Equipment used</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger people</td>
<td></td>
<td></td>
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<tr>
<td>Young women in USA</td>
<td>Ali 2000 (Ali, Daamen et al. 2000)</td>
<td>500,000 people in US</td>
<td></td>
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<tr>
<td>Young person</td>
<td>Lu 2004 (Lu, Tseng et al. 2004)</td>
<td>1:500</td>
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</tr>
<tr>
<td>138 young men in military service in Austria, mean age 21.6 years</td>
<td>Winker 2003 (Winker, Barth et al. 2003)</td>
<td>4% OH &amp; 10% POTS on tilt table</td>
<td>30 minute standing</td>
<td></td>
<td></td>
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<tr>
<td>Middle age people</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Middle aged men and women in Korea (Korean Health and Genome study), 8908, aged 40-69 years</td>
<td>Shin 2004 (Shin, Abbott et al. 2004)</td>
<td>AAN</td>
<td>Supine for 5 minutes then stand at 0 and 2 minutes</td>
<td>0 &amp; 2 minutes, 12.3% and 2.9%, Age 40-44 years 6.4%, 65 to 69 years 23.1%</td>
<td>OH increase with age</td>
<td></td>
</tr>
<tr>
<td>Older people living in community</td>
<td></td>
<td></td>
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<tr>
<td>Normal older people in community</td>
<td>Johnson 1965 (Johnson, Smith et al. 1965)</td>
<td></td>
<td></td>
<td></td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Scottish older people in community</td>
<td>MacLennan 1980 (MacLennan, Hall et al. 1980)</td>
<td></td>
<td></td>
<td></td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Study Description</td>
<td>Year</td>
<td>Measurements</td>
<td>Findings</td>
<td></td>
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<td>--------------------------------------------------------------------------------</td>
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<tr>
<td>Healthy elderly living in community in US attending senior citizen health screening programme, 300</td>
<td>1987</td>
<td>AAN Supine and 1 minute standing</td>
<td>13.7% in those with OH risk factors vs. 10.7% with no risk factors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese American men (Honolulu Heart Programme), age (71-93), 3522</td>
<td>1998</td>
<td>AAN Supine &amp; 3 minutes standing</td>
<td>6.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5201 Older people US (Cardiovascular Health Study), age, n</td>
<td>1992</td>
<td>AAN Supine and 3 minutes</td>
<td>18.2% (16.2% no symptoms, 2.0% had symptoms with fall in BP)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>480 Finish people aged over 65 years in community, age, n</td>
<td>1995</td>
<td>Supine and 3 minutes stand</td>
<td>28.0%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>833 Finish study, 70 years and over, living in community, age, 833</td>
<td>1999</td>
<td>AAN Supine 1 and 3 minute standing</td>
<td>30% OH, 22% at 1 minute, 19% at 3 minutes, diastolic OH 1 &amp;3 min, 6% each.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>569 Helsinki Ageing Study, age 75 and over (75, 80 and 85 cohort),</td>
<td>1996</td>
<td>AAN</td>
<td>SOH 30.3%, SDOH 7.5%, SyOH 2.6%.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>728 Community living Chinese in Taiwan,</td>
<td>1996</td>
<td>Supine 5 minutes, 1 minute upright</td>
<td>16.3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>61 Healthy elderly subjects</td>
<td>2006</td>
<td>AAN</td>
<td>14.7% had OH</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Older people in primary care settings –with disease

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Author(s)</th>
<th>Type of Measurement</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>295 Elderly hypertensive patients in Spanish primary care settings</td>
<td>Vara Gonzalez 2001 (Vara Gonzalez, Dominguez Rollan et al. 2001)</td>
<td>AAN Supine, and the 1 and 5 minutes stand</td>
<td>14.6% overall, 1 &amp; 5 min SOH 5.8% at both</td>
</tr>
<tr>
<td>Review article on primary care patients</td>
<td>Hale 1999 (Hale and Chambliss 1999)</td>
<td>Review article</td>
<td>13-30%</td>
</tr>
<tr>
<td>3858 Elderly Italian attending GP practice, Italian study (SPAA), age 65 and over</td>
<td>Alli 1992 (Alli, Avanzini et al. 1992)</td>
<td>Lying &amp; standing BP on two visits 7 days apart</td>
<td>Systolic OH 13.8% at first and 12.6% second visit.</td>
</tr>
<tr>
<td><strong>Geriatric outpatients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elderly patients attending general medicine outpatients</td>
<td>Robertson 1998 (Robertson, DesJardin et al. 1998)</td>
<td></td>
<td>13% SBP fall, 4% DBP fall.</td>
</tr>
<tr>
<td><strong>Acute geriatric ward</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>502 Acute geriatric ward in Israel, mean age 81.6 years</td>
<td>Weiss 2002 (Weiss, Grossman et al. 2002)</td>
<td>AAN 30 minutes after food</td>
<td>67.9% overall, 34.8% OH at least twice, 33.1% only once</td>
</tr>
<tr>
<td>50 Dutch patients 70 and over, admitted to medical ward prevalence of study in OH &amp; PPH mean age 78.8</td>
<td>Rhebergen 2002 (Rhebergen and Scholzel-</td>
<td>AAN Supine and 3 minute stand, sitting before and 30 min after</td>
<td>24% OH, 34% also had post-prandial hypotension</td>
</tr>
<tr>
<td>Other patient groups</td>
<td>Elderly patients with syncope (review articles)</td>
<td>Kapoor 1986 (Kapoor, Sunstad et al. 1986)</td>
<td>14% with OH</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>60 new PD patients followed for 7 years (15% excluded because they develop MSA or PSP) n= 51, age matched controls</td>
<td>Bonuccelli 2003 (Bonuccelli, Lucetti et al. 2003)</td>
<td>AAN</td>
<td>OH in 14% of PD patients, 60% MSA</td>
</tr>
<tr>
<td>Study Description</td>
<td>Authors/Year</td>
<td>Methodology</td>
<td>BP Drop Criteria/Duration</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>------------------------------------------------------------------------------</td>
<td>--------------------------------------------</td>
</tr>
<tr>
<td>89 Parkinsons patient in the community</td>
<td>Allcock 2004 (Allcock, Ulliyart et al. 2004)</td>
<td>Automated sphygmomanometer</td>
<td>10 minute supine, stand 1 and 2 minutes</td>
</tr>
<tr>
<td>71 Acute Stroke patient undergoing rehabilitation, mean age 58.4 years</td>
<td>Kong 2003 (Kong and Chuo 2003)</td>
<td>Supine 10 minutes than tilted to 90 degrees, reading at 5 minutes or when symptoms present</td>
<td>SBP drop of 20mmHg or more or SBP less than 100 mmHg</td>
</tr>
<tr>
<td>9704 Osteoporotic women over an dover (Osteoporotic Fracture research group)</td>
<td>Ensrud 1992 (Ensrud, Nevitt et al. 1992)</td>
<td>1 minute standing, postural dizziness</td>
<td>SBP fall of 20mmHg or greater</td>
</tr>
<tr>
<td>47 Haemodialysis patients aged 70 and over</td>
<td>Roberts 2003 (Roberts, Kenny et al. 2003)</td>
<td>AAN</td>
<td>10 minutes supine, stand 3 minutes</td>
</tr>
<tr>
<td>160 patients with Carotid Sinus Syndrome, 72 years</td>
<td>Mulcahy 2003 (Mulcahy, Jackson et al. 2003)</td>
<td>AAN</td>
<td>10 minutes supine, stand 3 minutes</td>
</tr>
<tr>
<td>65 Patients attending syncope clinic, mean age 78</td>
<td>McIntosh 1993 (McIntosh, Da Costa et al. 1993)</td>
<td>AAN</td>
<td>Systolic BP fall of 20mmHg</td>
</tr>
<tr>
<td>36 Elderly Polish women with and without congestive heart failure,</td>
<td>Potocka-Plazak 2001 (Potocka-</td>
<td>Tilt test 60 degree for 10 minutes, fasting morning</td>
<td>unknown</td>
</tr>
<tr>
<td>Study</td>
<td>Methodology</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Age, mean age 82.215 controls 82.5 years</td>
<td>Plazak and Plazak 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14 Spinal cord injury patients undergoing rehabilitation</td>
<td>Illman 2000 (Illman, Stiller et al. 2000)</td>
<td>AAN</td>
<td>10 minutes supine than 1 min interval till 10 minutes upright</td>
</tr>
<tr>
<td>223 Patients attending ED with syncope</td>
<td>Atkins 1991 (Atkins, Hanusa et al. 1991)</td>
<td>SBP falls 20mmHg or greater</td>
<td>BP measurements at 0,1,2,3,5,10 minutes after standing or until symptoms</td>
</tr>
<tr>
<td>650 Swiss ED patients presenting with syncope, 62 year for OH, VVS 54</td>
<td>Sarasin 2002 (Sarasin, Louis-Simonet et al. 2002)</td>
<td>Divide into no drop in BP, (Group A) SBP fall between 20-10mmHg but SBP less than 90 mmHg with or without symptoms, (Group B) SBP fall by 20mmHg</td>
<td>BP measurements after 5 minutes supine at 0,1,2,3,5,10 minutes after standing or until symptoms</td>
</tr>
<tr>
<td>Study Description</td>
<td>Method</td>
<td>Findings</td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-------------------------------</td>
<td></td>
</tr>
<tr>
<td>196 Schizophrenic patients on long term medications, age, n</td>
<td>Silver 1990 (Silver, Kogan et al. 1990)</td>
<td>Unclear BP at 1 and 3 minutes instrument used unclear 77% at 1 minute and 16.8% at 3 minutes</td>
<td></td>
</tr>
<tr>
<td>86 Hypertensive patients attending outpatients, mean age 76</td>
<td>Fotherby 1994 (Fotherby, Robinson et al. 1994)</td>
<td>SBP fall 20 or greater BP at supine and 3 minutes A third (get proper numbers)</td>
<td></td>
</tr>
<tr>
<td>4736 Systolic Hypertension in the Elderly Programme (SHEP) cohort</td>
<td>Applegate 1991</td>
<td>SBP fall 20 or more Seated and standing at BP at 1 and 3 minutes 17.3% overall, 10.4% at 1 minute, 12.0% at 3 minutes, 5.3% persistent OH.</td>
<td></td>
</tr>
<tr>
<td>98 older inpatients mean age 76.7 years</td>
<td>Cohen 2003 (Cohen, Gorelik et al. 2003)</td>
<td>AAN BP measured supine and then seated 54% had OH, 80.6% had symptoms</td>
<td></td>
</tr>
</tbody>
</table>
Chapter 1.4 Clinical presentations and aetiology of orthostatic hypotension

Clinical presentation
The most familiar symptom of OH is dizziness or light-headedness during postural change from supine to upright or sitting to upright (Mathias and Kimber 1999). There is also a case series of seated postural hypotension affecting more than half (54%) of frail older in-patients (mean age 76 years) after sitting up for 5 minutes (Cohen, Gorelik et al. 2003). The presence of cardiac acceleration (tachycardia) associated with hypotension was more pronounced compared with those without seated hypotension.

The symptoms of OH are due to hypoperfusion of end-organs (Mathias and Kimber 1999). Some of the OH symptoms can be non-specific, such as backache, fatigue, poor concentration and dyspnoea (Gibbons and Freeman 2005). However the cardinal feature of OH symptoms is that they improve with lying down.

Cerebral hypoperfusion can present with a spectrum from dizziness, to grey out to blackout. Some patients complained of poor concentration and muzziness in the head. Some would yawn with OH, either from poor perfusion of reticular activating system in the brain stem or fatigue associated with it.

Muscle hypoperfusion may present itself as coat-hanger pain (suboccipital and paracervical neck and shoulder pain) or low back pain (Bleasdale-Barr and Mathias 1998). It is conceivable that unsteadiness in an older person may not be solely due to cerebral hypo-perfusion but muscle hypoperfusion.

Renal hypoperfusion presenting itself as oliguria during the day is also common on questioning. The patients tend to complain of nocturia as blood pressure becomes higher at night. Other symptoms of OH are summarised in table 1.4.1.
Table 1.4.1 Table summarising the symptoms as a result of end-organ hypoperfusion

<table>
<thead>
<tr>
<th>End-Organ hypoperfusion</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral</td>
<td>Dizziness, visual disturbance, grey or blackout, scotoma, tunnel vision, loss of consciousness, impaired cognition, yawning</td>
</tr>
<tr>
<td>Muscle</td>
<td>Suboccipital, paracervical pain, low back or buttock pain</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Angina pectoris</td>
</tr>
<tr>
<td>Renal</td>
<td>Oliguria during the day</td>
</tr>
<tr>
<td>Non-specific</td>
<td>Weakness, fatigue, lethargy, falls, dyspnoea</td>
</tr>
</tbody>
</table>

Adapted from (Mathias 1995; Bleasdale-Barr and Mathias 1998; Heitterachi, Lord et al. 2002; Gibbons and Freeman 2005)

Aetiology of OH

The main causes of OH can be divided into

- neurogenic (autonomic-failure)
- non-neurogenic
- medication-induced

During postural change, if there is an absence of cardiac acceleration (greater than 10 beats per minute) despite hypotension, autonomic failure is suspected (Lipsitz 1989). Initial maximum heart rate response (cardio-acceleration) decreases with age. Normal response in adolescence (15-19 years) is expected to be at least 19 bpm, while in older people (65 –74 years) the rise is lower to 12 bpm over baseline. (Wieling and Karemaker 2002) The symptoms of OH are shown in table 1.4.2.

Table 1.4.3 showed the causes of OH according to the mechanism. One unusual cause of OH was a bleed into a benign intra-abdominal tumour (renal angiomyolipoma) resulting in post-haemorrhage anemia (Bragg and Kumar 2005).
Table 1.4.2 Ranking of symptoms in a group of patients with autonomic failure (progressive autonomic failure (PAF) and multi-system atrophy (MSA))

<table>
<thead>
<tr>
<th>Symptom</th>
<th>PAF</th>
<th>MSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weakness, lethargy, fatigue</td>
<td>91%</td>
<td>85%</td>
</tr>
<tr>
<td>Syncope</td>
<td>91%</td>
<td>45%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>84%</td>
<td>83%</td>
</tr>
<tr>
<td>Coat hanger pain</td>
<td>81%</td>
<td>53%</td>
</tr>
<tr>
<td>Visual disturbances</td>
<td>75%</td>
<td>53%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>44%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Adapted from Mathias 1999 (Mathias, Mallipeddi et al. 1999)
<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autonomic failure</strong></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>Acute or subacute dysautonomia</td>
</tr>
<tr>
<td></td>
<td>Pandysautonomia ± neurological deficit</td>
</tr>
<tr>
<td>Chronic (pure</td>
<td>Multisystem atrophy (Shy-Drager), Parkinson associated autonomic failuret</td>
</tr>
<tr>
<td>autonomic failure)</td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Congenital</td>
</tr>
<tr>
<td></td>
<td>Nerve growth factor deficiency</td>
</tr>
<tr>
<td>Hereditary</td>
<td>Familial amyloid neuropathy, porphyria, familial dysautonomia, dopamine beta-hydroxylase deficiency</td>
</tr>
<tr>
<td>Metabolic disease</td>
<td>Diabetes mellitus, chronic renal failure, chronic liver disease, alcohol-induced, vitamin B12 deficiency</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Guillain-Barre Syndrome, transverse myelitis</td>
</tr>
<tr>
<td>Infection</td>
<td>Bacteria (tetanus), Virus (human immunodeficiency virus)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Brain tumour (3rd ventricle or posterior fossa)</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Adenocarcinoma of lung, pancreas, Eaton-Lambert syndrome</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>Rheumatoid arthritis, systemic lupus erythromatosis</td>
</tr>
<tr>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Regional sympathectomy (splanchnic denervation)</td>
</tr>
<tr>
<td>Trauma</td>
<td>Spinal cord transection, spinal injury*</td>
</tr>
<tr>
<td>Others</td>
<td>Syringomyelia, syringobulbia, systemic amyloidosis</td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Central nervous</td>
<td>Reserpine, Barbiturate, Methyldopa, clonidine</td>
</tr>
<tr>
<td>system</td>
<td></td>
</tr>
<tr>
<td>Peripheral nervous</td>
<td>Imipramine, α-adrenergic blocker, propanolol</td>
</tr>
<tr>
<td>system</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td>Levo-dopa, phenothiazine</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Alcohol, vincristine, tricyclic antidepressant</td>
</tr>
<tr>
<td>neuropathy</td>
<td></td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>Nitrates, hydralazine, Angiotensin converting enzyme inhibitor, angiotensin-II blocker, potassium and calcium chAAANel blocker, sildenafil citrate, betahistine, dipyridamole</td>
</tr>
<tr>
<td>Aetiology</td>
<td>Condition</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------</td>
</tr>
<tr>
<td>Other causes (non-neurogenic)</td>
<td></td>
</tr>
<tr>
<td>Cardiac Pump failure</td>
<td>Aortic stenosis, myocarditis, constrictive myopathy, atrial myxoma</td>
</tr>
<tr>
<td>Decrease intravascular volume</td>
<td>Dehydration, adrenal insufficiency, diarrhoea, haemorrhage, vomiting, hemodialysis, diabetes insipidus, diuretics</td>
</tr>
<tr>
<td>Venous pooling</td>
<td>Alcohol, fever, sepsis, hot environment, post-prandial hypotension, prolonged standing or sitting, vigorous muscular activity (exercise), extensive varicose veins</td>
</tr>
</tbody>
</table>

Adapted from Mathias (Mathias and Kimber 1999) and Grubb (Grubb, Kosinski et al. 2003)

* Claydon (Claydon, Steeves et al. 2006)
† Goldstein (Goldstein, Eldadah et al. 2005)
Chapter 1.5 Sequelae or complications of orthostatic hypotension

The majority of subjects who fulfill the criteria for OH are asymptomatic (Rutan, Hermanson et al. 1992), and in them it is an incidental finding. In some cases however, its presence signifies significant underlying co-morbidity and pathology. A recent report showed that over 80,000 hospitalisations were related to OH, and overall in-hospital mortality of 0.9% (Shibao, Grijalva et al. 2007). This review aims to clarify the complications associated with OH.

Sequelae

In the mild end of the symptom spectrum, OH causes transient dizziness on postural change which impacts on quality of life. These symptoms are uncomfortable, but most sufferers adapt to it by avoiding sudden movement. However, OH can result in syncope (Kapoor, Sunstad et al. 1986; Brignole, Alboni et al. 2004) and falls (Graafmans, Ooms et al. 1996) (Ooi, Hossain et al. 2000). OH has also been linked with strokes (Eigenbrodt, Rose et al. 2000), white matter hyperintensity (Ballard, O'Brien et al. 2000; Allcock, Kenny et al. 2006), myocardial infarction (Luukinen, Koski et al. 2004), vascular death (Raiha, Luutonen et al. 1995; Luukinen, Koski et al. 1999) and cognitive decline (Allcock, Kenny et al. 2006). Furthermore, it is associated with an increase in all-cause mortality (Masaki, Schatz et al. 1998). Whether OH is cause of these conditions or merely a marker of disease and frailty is an important question the remains to be answered.

<table>
<thead>
<tr>
<th>OH is associated with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality – all-cause, vascular, coronary</td>
</tr>
<tr>
<td>Coronary heart disease, myocardial infarction, stroke</td>
</tr>
<tr>
<td>Arterial stiffness, supine hypertension</td>
</tr>
<tr>
<td>Cognitive decline, dementia</td>
</tr>
<tr>
<td>Recurrent falls</td>
</tr>
</tbody>
</table>
Association

Mortality

All-cause mortality

The Honolulu heart programme was a cohort study of 3522 Japanese-American ambulatory elderly men aged between 71-93 years. Masaki and colleagues (Masaki, Schatz et al. 1998) found an overall prevalence of OH of 6.9% and the prevalence increased with age. The presence of OH was a significant independent predictor of 4-year mortality from all causes, after adjusting for age, smoking, diabetes mellitus, weight, physical activity, hypertension, coronary heart disease, stroke, and cancer. (RR 1.64, 95% CI 1.19 to 2.26).

OH also predicts mortality in middle-aged people. Rose et al (Rose, Eigenbrodt et al. 2006) examined data from the Atherosclerosis Risk in Community Study (1987-1989) and found that a 13-year all-cause mortality was higher in those with OH (13.7%) compared with those without OH (4.2%). After adjusting for ethnicity, gender and age, the hazard ratio for OH for all-cause mortality was 2.4.

Coronary mortality

Upon further analysis, Schatz (Schatz 2002) found that the presence of OH increased the risk of coronary heart disease and coronary mortality by 2.0 and 2.9 fold respectively.

Vascular mortality

In 1995, Raiha (Raiha, Luutonen et al. 1995) found that 28% of older people (65 year) demonstrated a fall in systolic blood pressure of greater than 20mmHg at 3 minutes (OH-S3) but was not associated with an increase in 10-year vascular mortality. Diastolic BP fall of 10mmHg at 1 min (OH-D1), on the other hand, conferred a 2.7 fold increase in vascular mortality. Multivariate analysis showed that the increased mortality from OH was probably linked with other cardiovascular disease.

Luukinen (Luukinen, Koski et al. 1999) in a cohort study found OH-S3 and OH-D1 to affect 19% and 6% respectively. Hazard ratio for vascular death for OH-S3 was 1.69 and OH-D1 was 2.2. Furthermore, the presence of OH in older diabetics increased vascular death by 3.69 times (Luukinen and Airaksinen 2005).
A later study from an Israeli geriatric ward, however, demonstrated no difference in vascular death (Weiss, Beloosesky et al. 2006). The length of follow-up was shorter than the other studies (3.4 years).

**Cardiovascular disease**

**Myocardial infarction & Stroke**

The presence of OH places the subjects at greater cardiovascular risk as well. Orthostatic diastolic hypotension at one minute standing (OH-D1) was also associated with 2-fold increase in risk of MI (Luukinen, Koski et al. 2004). After nearly 8 years follow-up, the ARIC cohort who had OH according to consensus was found to be twice as likely to have ischaemic stroke compared with those without OH (Eigenbrodt, Rose et al. 2000; Burton, Ballard et al. 2003)

**Supine hypertension**

This is a recognised association with orthostatic hypotension. Supine hypertension is more prevalent in those with autonomic failure. This condition can be compounded by antihypotensive treatment for OH, such as florinef or midodrine. One series found that 56% of patients with OH had supine diastolic hypertension (Shannon, Jordan et al. 1997). The treatment option for supine hypertension is described in Chapter 4.4.

Using the 24 hour ambulatory blood pressure monitor, Lagi et al (Lagi, Rossi et al. 2003) found that 5.5% of his study population (615) had supine hypertension and postural hypotension. The subjects tend to be older (mean age 58 years) and had a higher incidence of left ventricular hypertrophy.

**Arterial stiffness**

Arterial stiffness is also a marker of cardiovascular disease. In the Rotterdam study of 3362 subjects aged 55 and over, Mattace-Raso and colleagues used carotid-femoral pulse wave velocity to measure arterial stiffness (Mattace-Raso, van der Cammen et al. 2006). In subjects with higher stiffness, the authors reported a larger drop with no increase in HR suggesting reduced baroreflex sensitivity in older subjects. Sengstock (Sengstock, Vaitkevicius et al. 2005), on the other hand, did not find arterial stiffness amongst older subjects with OH.

Boddaert et al (Boddaert, Tamim et al. 2004) conducted a cross-sectional study of a convenience sample of older men and women who were admitted to French hospital with falls. Of the 57 patients, 18 of them had OH according to AAN criteria when measured by
oscillometric devices at 1, 2, and 3 minutes standing. Pulse wave velocity was 16% higher than those without OH (p<0.02). Higher arterial stiffness was found amongst fallers who had OH.

The following could be the possible mechanism:
Orthostatic challenge causes reduction in cardiac pre-load, which results in fall in arterial pressure. Baroreceptors and mechanoreceptors in the vasculature respond by reducing parasympathetic drive and stimulating the sympathetic nervous system. Alpha-adrenergic stimulation results in vasoconstriction while β-adrenergic activation results in an increase in heart rate and contractility. Arterial stiffness may impair vasoconstriction as well as detection of fall in blood pressure. The response of the autonomic system may also be affected.

**Dementia**

Amongst patients with Parkinson disease, Allcock (Allcock, Kenny et al. 2006) reported that PD patients with OH had impaired sustained attention and visual episodic memory, as compared to PD patients without OH. Ballard and Kenny (Ballard, O'Brien et al. 2000) reported that neurovascular instability (NVI), which is manifested by episodic fall in blood pressure (OH being one of the causes), leads to white matter hyperintensity. This is a marker of silent cerebral infarcts. NVI is more common amongst those with cognitive impairment (Kenny, Shaw et al. 2004) (Ballard, Shaw et al. 1998). Matsubayashi (Matsubayashi, Okumiya et al. 1997) also reported a decline in cognitive function and correlation with brain lesion on MRI in the presence of OH. These subjects were asymptomatic of their BP changes.

In an interesting observation of regional cerebral blood flow Passant (Passant, Warkentin et al. 1997) reported that during head up tilt, despite marked blood pressure drops, few of the 35 patients with organic dementia complained of symptoms of OH. All patients demonstrated decreased blood flow to the frontal lobes.

The lack of dizzy symptoms highlights the need to treat OH upon diagnosis, regardless of burden of symptoms. These patients may present with falls or syncope without ever complaining of dizziness. Possible explanations could be the reduced blood flow, lack of ability to describe symptoms, or genuine unawareness of hypotension. Further research designed to study hypotension unawareness is needed. Treatment of OH should not be based
solely on symptoms but on the overall impact of hypotension. Furthermore, failure to treat the OH could lead to further silent infarcts and hence further cognitive decline. Conversely, one study failed to demonstrate cognitive decline with OH (Viramo, Luukinen et al. 1999). A possible explanation might be the lack of sensitivity of the instrument used (MMSE).

Falls
Most risk factor profiles for falls would include OH. It is suggested that treatment for OH would reduce falls (Society, Society et al. 2001). Contrary to popular belief, the evidence for OH as a single risk factor for falls is sparse. OH exacerbates falls in recurrent fallers (Rutan, Hermanson et al. 1992; Graafmans, Ooms et al. 1996; Ooi, Hossain et al. 2000), but there are other studies that did not find OH as a risk factor for falls (Campbell, Borrie et al. 1989; Chan, Pang et al. 1997; Koski, Luukinen et al. 1998; Kario, Tobin et al. 2001). Ooi et al. reported an increase in falls risk of 2.6 times only in residents who had previous recurrent falls and reproducible OH. Heitterachi (Heitterachi, Lord et al. 2002) reported that those with unstable SBP (i.e. fall in blood pressure) during tilt test were 1.7 times as likely to fall. In community studies Rutan (Rutan, Hermanson et al. 1992) and Graafmans (Graafmans, Ooms et al. 1996) found reported falls risk of 2.0 and 1.52 respectively if OH were present. OH treatment has also become one of the established components in multifactorial intervention trials in falls prevention (McMurdo, Millar et al. 2000). Two of the trials (Davison, Bond et al. 2005) were beneficial in reducing falls while one was not (McMurdo, Millar et al. 2000). OH alone does not cause falls. There needs to be other co-existing factors to precipitate falls.

In summary, OH is associated with frailty, cardiovascular risk and increased mortality. There is increasing evidence that repeated orthostatic hypotension is associated with white matter disease and cognitive impairment. In recurrent fallers, OH seems to be a risk factor for falls, but currently no study has demonstrated falls reduction by treating OH alone.
Chapter 2.1: Physiological response to standing

Quadruped animals are able to maintain effective cerebral perfusion as their heart and brain are at the same level. In order to maintain cerebral perfusion while standing, the neuronal and humoral systems work in synchrony to prevent gravity-induced hypotension through a series of rapid reflex adjustments. When this neuro-regulatory system fails, orthostatic hypotension or syncope ensues. Standing upright is therefore a physiological stress, and an intact autonomic function system is required to maintain cerebral perfusion when we move from supine to standing position without loss of consciousness.

Normal response

In a healthy person, the initial compensatory response is cardio-acceleration by 5 to 12 bpm (Lipsitz 1989), followed by sympathetic vasoconstriction in the resistance and capacitance vessels in the splanchnic, musculo (cutaneous) and renal vascular beds to prevent a decline in mean arterial pressure. The rate of cardio-acceleration declines with age from 19 bpm in the 20’s to 11 bpm in the 80’s (Wieling and Karemaker 2002). At the outset, the compensatory mechanism is neurally-mediated, followed by humoral response at a latter stage.

The response occurs in three phases (Wieling and Karemaker 2002):

- initial heart rate and blood pressure response (within the first 30s)
- early stabilization (after 1 to 2 minutes standing)
- prolonged standing (at least 5 minutes upright)
Heart rate response

When a healthy person stands up from supine position, there is an abrupt increase in heart rate to a peak at 3 s (primary peak), followed by a secondary peak at 12 s, and then a decline to a bradycardia at 20s, after which the heart rate gradually rises again. See figure 2.1.1.

Fig 2.1.1 Blood pressure and heart rate response moving from supine to upright position

![Graph showing heart rate response](image)

Primary heart rate peak is due to a vagal-mediated exercise reflex that is activated under voluntary muscle contractions. The secondary heart rate rise is modulated through further vagal inhibition and sympathetic outflow to the sinus node, linked with decreased baroreceptors firing during hypotension. The bradycardia at 20s coincides with recovery of blood pressure and once again is mediated by vagal tone. An indicator of an intact baroreceptor reflex is the maximum heart rate reached in the first 15 s of standing. The magnitude of heart rate rise is dependent on age and also preceding supine rest. The heart rate rise decreases with age and there is a greater rise in heart rate if the subject has been lying supine for 20 minutes compared with 5-10 minutes. Reference values (supine rest of 5-10min) provided by Wieling and Karemaker (Wieling and Karemaker 2002) showed the decline in heart rate response from 19bpm in the late teens (15-19 years) to 12 bpm in older adults aged 65 to 74 years. Heart rate rise after the first minute is predominantly dependent on sympathetic activity.
Blood pressure response

In a normal person, about 30% of circulatory blood is in the thorax. Upon standing up from the supine position, gravity causes about 400 to 800 ml of blood to be transferred rapidly (within a few seconds) from the thoracic to the abdomen and upper thighs region. This represents about a third of the thoracic blood volume (Sjostrand 1952). The bulk of the venous pooling occurs within 10s and total transfer is complete within 3 to 5 minutes. This abrupt fall in central blood volume causes a rapid decline in venous return to the heart, which in turn reduces the end-diastolic filling of the right ventricles. A fall in venous return results in a 40% fall in left ventricular stroke volume or a 20% fall in cardiac output, which results in arterial blood pressure drop in orthostatic hypotension (Stead, Warren et al. 1945; Wang, Marshall et al. 1960). Using beat-to-beat blood pressure recordings (Portapres), Omboni (Omboni, Smit et al. 2001) showed that OH in autonomic failure patients was due to falls in stroke volume and cardiac output.

There are different mechanisms involved in active standing and passive head up tilt, even though both procedures can result in OH. While the drop in blood pressure in the first 3 minutes in tilt is predominantly due to gravity-associated venous pooling, the BP drop in active standing is exaggerated by a relative vasodilation where blood is diverted to the large muscle mass in the legs (initial orthostatic hypotension) (Sprangers, Wesseling et al. 1991; Wieling, Krediet et al. 2007). When a person stands up from supine position, the muscles in both the legs and the abdomen contract, producing a compression of resistance and capacitance vessels. This in turn causes a transient rise in right atrial pressure and cardiac output, which activates the low-pressure receptors of the heart. The increase in neural traffic to the brain from these events causes a decrease in the peripheral resistance as much as 40%. This may allow a fall in mean arterial pressure by as much as 20 mmHg that may last for up to 6-8 seconds (Grubb, Kosinski et al. 2003). Lower body muscle tension during standing, which increases venous return, is effective in attenuating the drop in blood pressure (Krediet, van Lieshout et al. 2006).

In most cases during active stand the nadir blood pressure will have occurred within the first 10-15 s followed by an overshoot of blood pressure (blood pressure recovery) within 30 s. See Figure 2.1.2.
There is an increase in diastolic blood pressure by 10 mmHg in the early phase stabilisation. There is no change in systolic blood pressure, and increase of 10 beats per minute in heart rate. In autonomic failure, however, there is no recovery or overshoot of blood pressure. See figure 1.2.2. During a prolonged stand, there should only be minor fluctuations to blood pressure in healthy adults. A persistent fall in systolic blood pressure of 20 mmHg or diastolic blood pressure of 10 mmHg after 1 minute of standing is considered abnormal.
Neuronal and Humoral responses involved during standing

Neuronal response

The neuronal response is facilitated by the mechanoreceptors in the aortic arch and carotid sinuses (baroreceptors).

There are two separate pressure receptors in the systematic vasculature.

1. The low pressure receptors in the heart and lungs (mechanoreceptors)
2. The high pressure centres in the arch of aorta and carotid sinuses (baroreceptors)

The mechanoreceptors in the heart and lungs only respond when blood pressure becomes abnormally low. They are less vigorous than the baroreceptors in the carotid sinus which detect minor changes in blood pressure.

Carotid Sinus Body

The carotid sinus consists of a group of baroreceptors and nerve endings situated in an enlarged area of the internal carotid artery just after the origin from the common carotid artery. The actual mechanoreceptors are embedded in the adventitia of the arterial wall. The afferent signals generated by the local stretch on the arterial wall are transmitted through the sensory fibres of the carotid sinus nerve that travels with the glossopharyngeal nerve. The afferent pathways also terminate in the nucleus tractus solitarii of the medulla, located near the dorsal and ambiguous nuclei.

On standing, the fall in cardiac output sets off a sequence of events starting in the baroreceptors in the carotid sinus.

- When arterial pressure falls, the stretch on the baroreceptors is reduced, which causes a decrease in the firing rates to the vasomotor centre.
- This change in the firing rate to the vasomotor centres affects both vagal centre (nucleus ambiguous and the dorsal vagal nucleus) and sympathetic nucleus.
- Any decrease in firing signal to the vagal centre will reduce vagal tone and increase heart rate.
- Any decrease in the firing signal to the sympathetic nucleus causes sympathetic activation leads to the systemic resistance and splanchnic capacitance vessels constriction.
• There is also a local axon reflex (the venoarteriolar axon reflex) that reduces blood flow to the skin, muscles, and adipose tissue.

• This whole process accounts for a 50% increase in limb vascular resistance during standing.

**Fig 2.1.3** Cardiovascular responses moving from a lying to a standing position

\[ \downarrow \text{Cardiac Output} \rightarrow \downarrow \text{Baroreceptor stretch} \rightarrow \downarrow \text{medullary input} \]

\[ \uparrow \text{Vasoconstriction} \leftarrow \uparrow \text{sympathetic outflow} \rightarrow \downarrow \text{Vagal tone} \]

- Systemic resistance vessels
- Splanchnic Capacitance vessels

\[ \downarrow \text{Tachycardia} \]

(5 to 12 bpm)

\[ \uparrow \text{limb vascular resistance by 50\%} \]
Humoral response

Apart from vagal inhibition, the vasomotor centre in the midbrain stimulates sympathetic ganglia to release noradrenaline from the nerve endings. Noradrenaline has a positive chronotropic and inotropic effect on the heart, and also causes venous and arteriolar vasoconstriction (Dey and Kenny 1998).

The degree of neuro-humoral response is dependent on the volume status of the person. Dehydration produces greater activation of the humoral system. The renin-angiotension-aldosterone and vasopressin systems are responsible for maintaining blood pressure over a longer period. See chapter 2.2

Sequestration on prolonged stand

On prolonged standing, additional sequestration of venous blood occurs due to a slow continuous relaxation of the dependent capacity vessels. About 80% of the blood is pooled in the abdomen, pelvic regions and upper thighs (Denq, Opfer-Gehrking et al. 1997; Smit, Halliwill et al. 1999).

The interplay between hydrostatic and oncotic pressure in the dependent region results in plasma loss to the interstitial space. The degree of fluid shift depends on the length of time a person stands. The rate of plasma loss to interstitial space declines over time and reaches equilibrium after 10 to 20 minutes (Lundvall, Bjerkhoel et al. 1996). The plasma loss is reflected by the increase in hematocrit (8.6%) on prolonged standing during head up tilt (Lagi, Rossi et al. 2003). In healthy people, plasma volume can fall by as much as 6 to 25% after prolonged standing (Jacob, Raj et al. 2005). Jacob et al (Lundvall, Bjerkhoel et al. 1996) reported that plasma volume decreases by about 10% (500ml) after 5 minutes standing and 15-20% (750ml) after 10 minutes.

Frank oedema during prolonged standing does not occur because of arterial vasoconstriction, colloid osmotic hydrostatic counter-forces in plasma and interstitium, and by increased lymph drainage.

The skeletal muscle pump in the lower limbs also prevents venous sequestration by propelling blood back to the heart through muscular contractions. Persons with leg muscle
atrophy, which may develop in protracted bed-rest, frailty, or low gravity (astronauts), are more vulnerable to hypotension during prolonged standing.

**Failure to compensate**

The neuro-humoral system can fail to compensate in a number of situations.

Failure of compensation can occur in

- dehydration
- autonomic failure
- medications that affect heart rate or causes vasodilatation
- significant varicose veins that promote sequestration of blood in the lower limb
- poor cardiac function
- muscle atrophy

Ageing influences all phases of the compensatory mechanism. The heart rate response to standing in the elderly is blunted (Imholz, Dambrink et al. 1990) (Wieling, Veerman et al. 1992). In spite of which, a healthy, well-hydrated, normotensive, older person can maintain adequate blood pressure on standing (Imholz, Dambrink et al. 1990).

On the other hand, elderly subjects with hypertension or cardiovascular diseases receiving vasoactive drugs may have impaired vasoconstriction or cardioacceleration during standing. This group of patients is vulnerable to orthostatic hypotension.

When compared to young people, the elderly also show an increased variability of blood pressure and decreased variability of heart rate (Kenny, Atkins et al. 1987) (Drayer, Weber et al. 1982). Normally blood pressure is the lowest at night and early morning. It gradually rises to the maximum level at midday. The normal circadian variation is reversed in patients with orthostatic hypotension, with lower pressures in the morning and higher BP at night (MAAN, Altman et al. 1983). This account for the worsening of symptoms in the patients with orthostatic after a night sleep.

In summary, standing up while maintaining cerebral perfusion requires a functioning neuro-humoral system. A series of complex rapid reflexes, in response to changes in blood pressure,
occurs when we move from supine to standing position. Failure to compensate for gravitational venous pooling results in OH.
Chapter 2.2 Circulating catecholamines for maintaining blood pressure

2.2.1 Renin-Angiotension-Aldosterone system & Atrial Natriuretic peptide

2.2.2 Effect of prolonged standing on circulating catecholamines

2.2.1 Renin-angiotensin-aldosterone system & Atrial natriuretic peptide

The renin-angiotensin-aldosterone system (RAAS) is a hormonal cascade system responsible for maintaining blood volume and arterial pressure. Total body water content and blood pressure is also linked with sodium homeostasis.

Hormonal cascade

Sodium homeostasis and blood pressure is mainly controlled by renin. The kidney, is the primary site for renin release, is activated in the following conditions,

- sympathetic stimulation (acting via beta-adrenoceptors)
- renal artery hypotension
- decreased sodium delivery to the distal tubules

Figure 2.2.1 Renin-angiotensin-aldosterone pathway

<table>
<thead>
<tr>
<th>Renin (Enzyme from J.G apparatus)</th>
<th>Angiotensinogen (liver)</th>
<th>Converting enzymes (pulmonary capillaries)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angiotensinogen I</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td></td>
<td>(10 amino acids)</td>
<td>(8 amino acids)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aldosterone</td>
</tr>
</tbody>
</table>
Angiotensinogen

The first compound of the hormonal cascade is angiotensinogen (ATG), a 453-amino acid molecule. It is mainly produced by the liver, although other minor sites are also involved in its production. Circulating levels are raised by plasma corticosteroids, estrogen, thyroid hormone and angiotensin II levels.

Angiotensin I

ATG undergoes proteolytic cleavage by renin to form the decapeptide angiotensin I, an inactive compound. Angiotensin converting enzyme (ACE), an endothelial surface enzyme found mainly in the lung, cleaves off two amino acids from Angiotensin I to form angiotensin II (AII), a biologically active peptide.

Angiotensin II

AII has several very important mechanisms to increase blood pressure. AII
- constricts resistance vessels (via AII receptors) hence increasing systemic vascular resistance and arterial pressure
- acts upon the adrenal cortex to release aldosterone, which in turn causes the kidneys to increase sodium and fluid retention
- stimulates the release of vasopressin (antidiuretic hormone, ADH) from the posterior pituitary, which promotes renal fluid retention
- stimulates thirst centres within the brain
- facilitates norepinephrine release from sympathetic nerve endings and inhibits norepinephrine re-uptake by nerve endings, thereby enhancing sympathetic adrenergic function
- stimulates cardiac hypertrophy and vascular hypertrophy
Figure 2.2.2 Hormonal responses to prolonged standing

* Sympathetic stimulation
* Hypotension
* ↓ Sodium delivery to kidneys

KIDNEY

Angiotensinogen

Renin

AI

Adrenal Cortex

Pituitary

ADH

Aldosterone

Cardiac & Vascular hypertrophy

Systemic Vasoconstriction

Thirst

Renal sodium & Fluid retention

Increase Blood volume
The molecular structure of the circulating hormones, the control of their release, and the mechanism by which they mediate their effects are described below:

**Renin**

Human renal renin is a single-chained glycosylated-carboxy-peptidase that belongs to the aspartyl proteinases family (Slater and Strout 1981). It has a molecular weight of about 41,000 Dalton. The gene is located on chromosome 1. The initial transcriptional product is preprorenin. The transcriptional rate is stimulated directly by cyclic AMP but inhibited by AII. A low sodium diet stimulates transcription.

**Regulation of renin release**

Regulation of renin synthesis takes place at the level of mRNA. Renin is synthesised and stored, and released by cells located in the afferent arteriole (juxtaglomerular apparatus). The intra-cellular messengers responsible for renin release are calcium and the cyclic nucleotides, C-AMP and cGMP. The JG cells are highly sensitive to changes in the extracellular osmolality (Skott, Briggs et al. 1990). The exposure of JG cells to hypoosmolity results in greater renin secretions. Renin levels are higher in the upright position compared to supine in healthy controls. The stimulation of the sympathetic system that innervates the renal blood vessels and tubular structures (including the JG apparatus) causes vasoconstriction, reduced GFR, increased proximal tubular fluid reabsorption, and enhanced renin secretion (DiBona and Kopp 1997).
Factors that stimulate and inhibit renin secretions are summarised in the following table. Local and circulating hormones, particularly AII, nitric oxide, and prostaglandins, also affect renin secretion.

<table>
<thead>
<tr>
<th>Factors associated with increase renin release</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>Angiotensin receptor blocker</td>
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<tr>
<td></td>
<td>High dose diuretic therapy</td>
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<tr>
<td></td>
<td>beta-adrenergic agonist</td>
</tr>
<tr>
<td></td>
<td>norepinephrine</td>
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<tr>
<td></td>
<td>Oral contraceptive pill</td>
</tr>
<tr>
<td>Hypo-osmolality</td>
<td></td>
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<tr>
<td>Renal baroreceptors sensing renal perfusion pressure &lt;90mmHg</td>
<td></td>
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<tr>
<td>Activation of sympathetic system</td>
<td></td>
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<tr>
<td>Low urinary sodium at macula densa</td>
<td></td>
</tr>
<tr>
<td>Upright posture</td>
<td></td>
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<tr>
<td>Salt restriction</td>
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</tbody>
</table>

**Factors that inhibit renin release**

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Dopa</td>
</tr>
<tr>
<td>Reserpine</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
</tr>
<tr>
<td>High urinary chloride load at macula densa (Vander and Miller 1964)</td>
</tr>
</tbody>
</table>

**Aldosterone**

Aldosterone, a mineral corticoid, is formed in the cells of the zona glomerulosa of the adrenal gland by converting corticosterone to aldosterone. Aldosterone release is regulated by circulating levels of ACTH, potassium, and AII. AII is the main stimulus for its release. High plasma potassium also stimulates aldosterone secretion, whereas atrial natriuretic peptide (ANP) has an inhibitory effect.

Aldosterone acts primarily on the cells of the distal nephrons, where it stimulates the reabsorption of NaCl and secretion of potassium. The retention of sodium causes water
Retention which restores the ECF. This removes the stimulus for additional renin secretion. Aldosterone circulates in fairly low concentrations and, as all steroids, binds to specific intracellular receptors inside target cells.

**Effect of age on renin and aldosterone levels**

With increasing age, the basal renin level, whether estimated by the plasma renin level or renin activity, decreases by 30 to 50% despite normal levels of renin substrate. Under the same conditions such as dehydration or diuresis, the renin levels in older persons can be as low as a third or half of younger subjects. Nakamaru (Nakamaru, Ogihara et al. 1981) also reported a decrease in supine active renin level with ageing. In older subjects, the renin rise associated with frusemide and upright posture is less with younger subjects. The lower renin levels in elderly persons consequently result in lower AII and plasma aldosterone levels. Aldosterone deficiency in the elderly is usually a function of the co-existing renin deficiency, and is not secondary to intrinsic adrenal changes.

The impact of age-related decreases in renin and aldosterone levels contributes to the development of various fluid and electrolyte abnormalities in older persons. For example, elderly persons on salt-restricted diets have a decreased ability to conserve sodium. Decreased AII production can also seriously impair tubular concentrating ability. These conditions render the older persons more susceptible to volume depletion and hence OH. Hypernatremic dehydration is particularly common when water loss is greater than sodium loss. This is exacerbated by the loss of thirst, which is characteristic in the elderly, in response to increased serum osmolality or volume contraction. Hypernatremia in the elderly is associated with significant mortality (Kugler and Hustead 2000). Age-related decreases in renin and aldosterone also contribute to increased risk of hyperkalemia in various clinical settings.

**Atrial Natriuretic Peptide**

The natriuretic peptide hormone family consists of three members, namely atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). They are involved in the regulation of blood pressure and fluid homeostasis. ANP and BNP are cardiac hormones which cause natriuresis, diuresis, and vasorelaxation, whilst inhibiting the renin-angiotensin system, endothelin and vasopressin secretions (Leskinen, Vuolteenaho et al. 1997).
ANP is a 28-amino acid peptide hormone, which is synthesized as prohormone, stored as secretory granules in atrial myocytes, and released into circulation. The predominant signal for ANP release is atrial wall stretch or atrial distension due to volume expansion (Ruskoaho, Lang et al. 1987). Hypoxia is also a potent stimulus to ANP release. Atrial stretch, increased heart rate, sympathetic stimulus, and metabolic factors may mediate this effect. Endothelin-1, a potent vasoconstrictor of smooth muscle, induces ANP secretion directly from the heart. Therefore, elevated levels of ANP are found during increased circulatory volume.

ANP is involved in long-term regulation of sodium and water balance, blood volume, and arterial pressure. ANP decreases aldosterone release, increases glomerular filtration rate, and produces natriuresis and diuresis. The half-life of ANP is 2 to 5 minutes. The hormone is eliminated enzymatically or through its receptor. The ANPc receptor internalizes ANP and delivers it to lysosomes for degradation, while the receptor itself is recycled.

ANP was first identified by de Bold (de Bold, Borenstein et al. 1981) from granule-enriched atrial extracts. This substance caused natriuresis and vasodilatation. It was sequenced later in 1984 (Kangawa and Matsuo 1984). BNP and CNP were found later. The gene of ANP is located on chromosome 1. Pro-ANP is a 126-amino acid pro hormone. On release, the prohormone is split into equimolar amounts of highly biologically active proANP (99-126), also known as α-ANP, and the N-terminal part of proANP (1-98). α-ANP binds to specific receptors and therefore is rapidly cleared from the circulation.

Pro-ANP is a useful surrogate marker for ANP secretory patterns. No receptors for ProANP (1-98) are known at present, and therefore this peptide circulates longer in the system. This leads to significantly higher concentrations in the blood as compared to α-ANP. Thus, circulating proANP (1-98) is less sensitive to the pulsatile secretion of ANP, and may better reflect chronic levels of ANP secretion than the rapidly fluctuating levels of α-ANP. Pro-ANP is excreted via the kidneys.
The effects of ANP are as follows:

- Systemic vascular smooth muscle relaxation
- Decreases blood pressure and total peripheral resistance
- Enhances urinary sodium and water excretion and inhibits NaCl reabsorption.
- Inhibits ADH secretion and its action on renal tracts
- Inhibits renin and aldosterone secretion
2.2.2 Effect of prolonged standing on circulating catecholamines

The activation of the renin-angiotensin-aldosterone system (RAAS) occurs gradually during standing. Jacob et al (Jacob, Ertl et al. 1998), in an elegant study, reported the effect of prolonged standing on circulating catecholamines and kidney excretion of sodium in 10 healthy volunteers (age 22-46 years).

The investigators made the following observations

- Plasma volume fell by 13% over 14 minutes and later smaller drops occurring at 45 minutes.
- The effective circulating volume was reduced by 375 ±35ml over 30 minutes.
- Circulating plasma catecholamines showed a three-fold rise between supine and standing values.
  - Norepinephrine level rose from 195 to 590 pg/ml
  - epinephrine from 23 to 69 pg/ml
  - plasma renin activity from 0.7 to 2.0 ng/ml/h
  - aldosterone from 10 to 32
- There was no change in plasma osmolality during the 30 minutes standing.
- Renal excretory patterns were affected by prolonged stand.
  - After 30 minutes of standing, renal sodium excretion fell by 40%, and after 60 minutes by 63%.
  - The authors suggested that the effect is most likely to be mediated by an increase in circulating aldosterone.
- Urinary osmolality also increased 1.3 fold (584 to 743 mosmol/kgH2O) after 1 hour standing.
- The mechanism is most likely due to rising arginine vasopressin (ADH, as there was a three-fold rise in the plasma level between supine and 60 minute standing values, as the body attempts to conserve water.

In conclusion, the RAAS is responsible for maintenance of blood volume, arterial pressure, and fluid balance. A functioning RAAS is essential for maintaining blood pressure during prolonged standing.
Chapter 3: Techniques of measuring postural blood pressure

3.1 Mercury sphygmomanometer & aneroid manometers
3.2 Semi automated oscillometric devices
3.3 Non-invasive beat-to-beat continuous blood pressure monitoring
   3.3(i) Radial tonometry
   3.3(ii) Digital photoplethysmography (Finapres, Portapres, Finometer™)
   (a) Historical – volume clamp method of Penaz
   (b) Pressure-diameter relationship & Wesseling criteria for Physiocal
   (c) Development of Finometer™ from Finapres
   (d) Modelflow
   (e) Settings in which Finometer™ has been used
   (f) Beatscope software

Introduction

Blood pressure (BP) can be measured either by intra-arterial cannulation or non-invasive methods.

Non-invasive methods of assessment include the following:

- Auscultatory method using Korotkoff sounds
- Oscillometric (vessel wall vibration) devices or
- Plethysmography

Table 3.1 Instruments available for measuring blood pressure

<table>
<thead>
<tr>
<th>Auscultatory measurement</th>
<th>Oscillometric measurement</th>
<th>Continuous beat-to-beat blood pressure measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Mercury sphygmomanometer</td>
<td>* Semi-automated</td>
<td>* Tonometry</td>
</tr>
<tr>
<td>* Aneroid manometer</td>
<td>* 24 hour ambulatory blood pressure monitoring</td>
<td>* Plethysmography – Finometer™</td>
</tr>
</tbody>
</table>
DEVICES

3.1 Mercury sphygmomanometer & aneroid manometers

The gold standard, against which all other blood pressure (BP) devices are measured, is still the mercury sphygmomanometer. The British Hypertension Society recommends the mercury sphygmomanometer for validation of other BP devices.

Mechanism of action

The mercury sphygmomanometer & aneroid manometer make use of Korotkoff sounds to measure BP. In 1905, Dr Nicolai Korotkoff introduced a method of determining blood pressure by placing a stethoscope over the brachial artery, inflating a cuff around the upper arm, and listening for different sounds. The sounds heard during gradual deflation of the cuff may be classified into five phases. The first and fifth phases of the Korotkoff sounds determine the systolic and diastolic BP. Due to environmental concerns, mercury sphygmomanometers have been replaced by aneroid devices. Aneroid manometers rely on bellows and levers systems to gauge pressure levels. They lose their accuracy over time and require frequent calibrations with mercury sphygmomanometer. Hybrid devices replace mercury column with an electronic gauge and BP is measured manually by auscultation.

3.2 Semi-automated oscillometric devices

Increasingly, automated devices are being used in clinics and hospitals for BP measurement. This device eliminates operators' subjective judgement on when they hear the Korotkoff sounds. The advantage of the oscillometric device is that it allows ambulatory measurement outside the clinical settings. Furthermore, ambulatory BP monitors ascertain the pattern of BP over a longer period and therefore suitable for recording 24-hour tracings of BP whilst patients are at home.

Mechanism of action

The oscillometric device relies on the vibrations in the arterial wall caused by turbulent blood flow between systolic and diastolic BP. The vibration is transduced into electrical signals to produce a digital readout (Berger 2001). The cuff is inflated to reach a BP that occludes the brachial artery (above systolic blood pressure). No blood flows through the artery at this time. As the cuff is deflated gradually (usually by 4 mmHg at a time) below systolic BP, the blood flow sets up a vibration within the arterial wall. The vibration stops when the pressure...
falls below diastolic BP. This method of assessing BP, although slower than mercury sphygmomanometer, is less operator dependent.

Inaccuracies may occur in the presence of cardiac arrhythmia, excessive arm movement or when the arm muscle is tensed up. Stiff, incompressible blood vessels also impede arterial wall vibrations, which may give higher readings (pseudohypertension).

Validated device

According to international guidelines, only validated devices should be used for measurement. The British Hypertension Society has published a list of validated devices and these are found on the following website. Only devices that achieved B grade for both systolic and diastolic measurements for the revised BHS protocol or pass the accepted criteria of the International Protocol are listed below.

Automatic Digital Blood Pressure Devices for Clinical Use and also suitable for Home/Self Assessment

http://www.bhsoc.org/bp_monitors/automatic.htm

For aneroid approved device

http://www.bhsoc.org/bp_monitors/automatic_clinic_aneroid.htm

Ambulatory Blood Pressure Measuring Devices Oscillometric Monitors

http://www.bhsoc.org/bp_monitors/ambulatory.htm

Guidelines for proper measurement of blood pressure

Procedures for obtaining accurate blood pressure, using mercury blood pressure monitors or electronic blood pressure monitors, are clearly outlined in the British Hypertension Society website as follows: http://www.bhsoc.org/how_to_measure_blood_pressure.htm
3.3 Non invasive beat-to-beat continuous blood pressure monitoring

In a situation where rapid variation in BP is anticipated, beat-to-beat BP monitoring is preferred to conventional BP instruments. Beat-to-beat devices are useful in settings such as hemodialysis, cardiac surgeries, cardiac re-synchronisation, cardiovascular physiology research and in the syncope laboratory. They are also a useful research tool for baroreceptor sensitivity and autonomic function studies.

Traditionally, beat-to-beat BP measurement is obtained by inserting an intra-arterial cannula into the radial, femoral, dorsalis pedis or brachial artery. The blood pressure is monitored beat-by-beat and a waveform (a graph of pressure against time) is obtained. However, invasive arterial monitoring requires close monitoring, and potentially the cannula can become dislodged resulting in significant haemorrhage. The development of non-invasive beat-to-beat blood pressure monitoring allows us to track changes in BP with each recorded heartbeat without invasive monitoring.

There are two monitors available for non-invasive continuous beat-to-beat BP monitoring (NICBP)

1. radial artery tonometry and
2. Finger arterial pressure monitoring.

3.3(i) Radial tonometry

The Colin CBM-7000 is currently the only arterial tonometer available in this market. The tonometer is used for patient monitoring in critical care, and cardiovascular assessment during tilting, sleep or exercise. It is also used in research into aortic stiffness and pulse wave velocity.

Mechanism of action

The principles of tonometry are based on partially compressing and partial flattening (applanation) of the superficial artery against the underlying structures, preferably bone (Weiss, Spahn et al. 1996). The flattened surface of the arterial segment "balances" the pressure-induced circumferential stress on the arterial wall and the forces exerted by the arterial pressure become perpendicular to the wall tension. The on-going intra-arterial forces,
sensed by a pressure transducer attached firmly on the skin surface above the artery, are
translated into arterial pressure waveforms.

A radial tonometer, however, does not have a height correction function. The arm should be
held at the heart level during measurement in order to ensure correct measurements. A splint
is required to keep the wrist extended so that the applanation is satisfactory. Ideally when the
readings are taken, patients should stay in one position rather than be moving around. Weiss
et al (Weiss, Spahn et al. 1996) found tonometry to be moderately accurate but it should not
replace invasive monitoring in high-risk patients during major surgical procedures. It
provided a useful trend indicator to blood pressure.

Finger Arterial Pressure

3.3(ii) Digital photoplethysmography (Finapres, Portapres, Finometer™)

The other method of obtaining non-invasive continuous beat-to-beat BP measurement is by
using finger arterial waveforms. This technology has been available since the 1980’s (Boehmer
1987)(Bogert and van Lieshout 2005) and the earliest prototype device was the “Finapres”.
Subsequent refinements have aimed to improve the accuracy and reliability of the BP
measurements. The latter versions of Finapres are Portapres and Finometer™. Imholz
(Omboni, Parati et al. 1998) reviewed the 15 years’ experience of finger arterial pressure
monitoring and followed the development of the technology behind non-invasive finger
arterial pressure monitoring of BP.

Principles of measurement

Finger arterial pressure measurement employs the principle of volume-clamp technique and
Physiological criteria of Wesseling to ensure that the measurements are reliable.

(a) Historical

Volume-clamp method of Penaz

The volume-clamp method is used in the Finapres, Portapres and Finometer™ devices. It
was originally described by a Czech physiologist, Jan Penaz (Penaz 1954), to measure BP in
the finger. The finger is clamped with a wrap-around cuff which keeps the diameter of the finger artery constant, even though arterial pressure changes during each heartbeat.

(b) Pressure-Diameter relationship & Wesseling criteria for Physiocal

Pressure-Diameter relationship
Arterial compliance is dependent on transmural pressure (pressure on the vessel wall), i.e. the pressure difference between the pressure inside the artery and the pressure of the surrounding tissue (Langewouters, Zwart et al. 1986).

If arterial pressure is greater than the cuff pressure, the arterial wall becomes stiff. Alternatively, if the finger cuff pressure is higher than the arterial pressure, the vessel collapses. Therefore, the optimum pressure within the artery is between systole and diastole. We often observed that, after a few minutes of clamping, the finger at which the arterial waveform is derived becomes engorged and cyanosed.

At near zero transmural pressure (when the pressure inside the artery equals the pressure in the finger cuff) the changes in the arterial diameter will be at the largest (Lawrence 1978). Any oscillation in the arterial wall will be maximum in this state. The artery is in the 'unloaded' state. The fast pressure servo controller system in the frontend keeps the finger artery in the unloaded state during the study.

Fig 3.3.1 Pressure gradient to ‘unload’ an artery
Unloaded artery

Finger Cuff
Blood pressure is measured with a special finger cuff in the Finapres, Portapres & Finometer system consists of
- A built-in infrared LED photodiode
- An air bladder lining the inside of the cuff.
The LED photo-diode detects changes in the arterial diameter during systole and diastole by sensing the amount of light absorbed. During systole, the vessel diameter is wider. More light is absorbed, while less light is absorbed in diastole. The air bladder is also mounted within the finger cuff. This counteracts the pressure changes via a fast pressure servo-controller. The finger cuff is applied in the middle phalanx of the finger as per manufacturer instructions.

**Wesseling criteria for Physiocal (physiological calibration)**

A Dutch Physicist, K.H. Wesseling (Wesseling 1996), used an algorithm to track the diameter to define and maintain the correct diameter at which the finger artery is clamped. The periodic interruptions during calibration is referred to as Physiocal. During Physiocal, varying levels of air pressure is set within the finger cuff. The amplitude and shape of the resultant plethysmograph determines the volume-clamp diameter.

(c) Development of Finometer™ from Finapres

Finapres, Portapres and Finometer™ use the principle of digital plethysmography.

**Finapres (Finger arterial pressure)**

The output from Finapres is finger arterial pressure and the mean finger BP is lower than mean intra-arterial brachial pressure. As the arterial waveform travels from the aorta to the finger, there are pulse wave distortions, pressure gradient and slower flow in smaller vessels. Systolic and diastolic BP readings from the finger were found to be on average 3.2mmHg and 8.4mmHg lower than brachial pressure (Bos, van Goudoever et al. 1996). The fall off (decay) in BP also increase with age (Nichols, O'Rourke et al. 1997). Pulse wave amplification is highest in the young (Mahmud and Feely 2003). Due to the combined effects of pulse wave amplification and pressure decay, SBP is elevated in the young but equal or lower than brachial pressure in older subjects (Bogert and van Lieshout 2005)(Idema, van den Meiracker et al. 1989; Bos, Imholz et al. 1992)(Rongen, Bos et al. 1995). Finger systolic arterial pressure tracks changes correctly during orthostasis (Rongen, Bos et al. 1995).

**Portapres**

Portapres is considered sufficiently adequate to study blood pressure changes. This fulfils the criteria set by AAMI during orthostatic and cardiovascular maneuvers such as Valsalva (Omboni, Parati et al. 1998).
The Finometer™ is the latest device using finger arterial waveform to configure beat-to-beat blood pressure. See page 222 for the various components of the Finometer™. It has a built in bias and precision for tracking against intrabrachial artery pressure so that the measurement approaches the accuracy of an intra-arterial reading. It fulfils the AAMI criteria for BP measurement. There are additional features available in the Finometer™ which makes the BP measurements more reliable. Apart from continuous monitoring of finger arterial pressure waveform with the volume-clamp method of Penaz (Penaz 1992) and the Physiocal criteria of Wesseling (Wesseling 1996) as in Finapres, there are additional features outlined below.

- Reconstruction of brachial artery pressure waveform and level from finger pressure via generalised waveform inverse modelling (Gizdulich, Imholz et al. 1996; Gizdulich, Prentza et al. 1997).
- A height correction unit
- Brachial arterial pressure reconstruction
- Automated individual Riva-Rocci arm cuff return-to-flow (RTF) pressure level calibration (Bos, van Goudoever et al. 1996).
- Stroke volume and cardiac output monitoring with Modelflow modelling method (Wesseling, Jansen et al. 1993)

Finger arterial pressure is converted into brachial pressure by

- Wave distortion correction
- Brachial arterial pressure reconstruction
  - Height correction Unit and
  - Level calibration by RTF method

Wave distortion correction

Gizdulich (Gizdulich, Imholz et al. 1996) formulated waveform distortion correction, which is also known as waveform filtering, and level corrections. He (Bos, van Goudoever et al. 1996) used a multiple regression model to correct for the difference between brachial and finger arterial pressure (Gizdulich, Prentza et al. 1997). The result of the re-modelling makes the intra-brachial arterial reading and non-invasive finger blood pressure readings virtually identical.
Brachial arterial pressure reconstruction

Hydrostatic pressure influences the reading obtained from the finger cuff. A 1.3 cm difference in height causes a 1mmHg difference in pressure. The height correction unit (HCU) allows the subject to move the arm freely during measurements. Without the HCU, the cuffed finger has to remain at heart level to ensure accuracy.

To reconstruct the brachial pressure from finger arterial pressure, the Finometer™ applies
- A generalised waveform filter to remove pulse shape differences
- A generalised Level correction equation to correct level differences (by HCU) and
- Return to flow (RTF) systolic measurement on the ipsilateral upper arm for individual calibration (Bos, van Goudoever et al. 1996).

After the above adjustments the reading from the Finometer™ is the reconstructed brachial arterial pressure (reBAP). The accuracy of the finger BP after reconstruction is within the AAMI (AAMI, 1993) requirements of ±5±8 mmHg against intra-brachial pressure (Bos, van Goudoever et al. 1996).

There is no current published data according to the BHS protocol comparing Finometer™ readings and Riva-Rocci/ Korotkoff upper arm auscultatory pressure levels.

(d) Modelflow

Modelflow (Wesseling, Jansen et al. 1993; Harms, Wesseling et al. 1999; Jansen, Schreuder et al. 2001) is a mathematical model by which aortic flow curve is computed from an arterial pressure pulsation. The parameters derived include left ventricular stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR). Modelflow provides close tracking of changes in SV and CO. Entry of patient gender, age, height and weight are required for best precision.

(e) the settings in which the Finometer™ has been used

The absolute values of the cardiovascular parameters, such as SV, CO and TPR from Modelflow computation, need calibration before they can be taken as absolute values.
Harms & Wesseling (Harms, Wesseling et al. 1999) performed continuous stroke volume monitoring by modelling flow from non-invasive measurement of arterial pressure in 10 young controls under orthostatic stress. They used the Modelflow to compute the aortic flow from arterial pressure (Jansen, Schreuder et al. 2001) by an invasive (intra-brachial arterial pressure) and non-invasive (finger arterial pressure) determination of arterial pressure. For comparison, a computer-controlled series of four thermodilution estimates (thermodilution-determined stroke volume TDSV) were averaged in various positions including supine, standing, head down tilt and head up tilt. The investigators reported that Modelflow-calculated aortic flow from finger arterial pressures were closer to thermodilution values than when derived from brachial arterial pressure.

Jansen (Jansen, Schreuder et al. 2001) reported during major surgery that a once-off calibration was required initially to ensure that Modelflow-derived stroke volume matched with thermodilution values. After the calibration, Modelflow was accurate in tracking the changes in cardiac parameters during surgery. Modelflow derived can also be used to monitor cardiac output in septic shock after single calibration (Jellema, Wesseling et al. 1999). Similarly, Tam et al (Tam, Azabji Kenfack et al. 2004) reported that it was necessary to incorporate a correction factor to Modelflow-derived cardiac output when he compared it to cardiac output derived from acetylene uptake open circuit re-breathing. Again, after calibration, Modelflow accurately tracked changes that occurred at rest and during exercise.

More recently, Finometer has been used to optimise cardiac synchronisation (Whinnett, Davies et al. 2006) and during haemodialysis (Roberts, Kenny et al. 2003).

(f) Beatscope software

The Beatscope software programme enables the usage of waveform filtering and level correction methods to obtain brachial pressure waveforms and compute derived variables. With the Modelflow cardiac output method (Wesseling, Jansen et al. 1993; Harms, Wesseling et al. 1999; Jansen, Schreuder et al. 2001), the following data may be computed for every heart beat.

- The instant of upstroke
• systolic, diastolic and mean BP
• heart rate
• inter-beat interval
• SV
• CO
• ventricular ejection time
• TPR
• aortic characteristic impedance
• aortic compliance

In conclusion, finger arterial pressure is a non-invasive method of monitoring BP. It is useful in tracking changes in BP at rest, during exercise and orthostatic stress. It had been used previously in the settings of critically ill patients and during open-heart surgery.

The BP measurement was validated against brachial intraarterial pressure and radial arterial pressure. Due to waveform distortion, a filter is required to reconstruct finger to brachial waveform. Non-invasive finger arterial pressure measurement underestimates BP in the elderly, but overestimates BP in the young. By hydrostatic adjustment and RTF calibration, the measurement fulfils the American Advance Medical Instrument (AAMI) criteria for standard of performance.

The Finometer™ utilises the Modelflow technique which uses three-element model of aortic input impedance to calculate SV, CO and TPR.

Three recent studies have shown that without calibration, the measurements of CO by computation and thermodilution differ significantly. When the SV measurements performed by finger arterial pressure Modelflow were compared with rebreathing (C2H2) technique, the measurements also differed significantly. However, with calibration (by thermodilution or rebreathing method), the subsequent readings correlated better with the values obtained by invasive measurement.

Conclusions
There are different instruments available for measuring BP and the circumstances will determine which one is the best. The rate of detection of OH is dependent on the sensitivity
and speed at which BP is measured. Beat-to-beat BP recording allows us to investigate the
hemodynamic responses from lying to standing and better understand the mechanisms
when OH occurs.
Chapter 4 Treatment of Orthostatic Hypotension

The treatment of orthostatic hypotension (OH) principally acts through increasing circulating plasma volume, peripheral resistance or venous return. The means of treatment can be divided into pharmacological and non-pharmacological therapies. This chapter outlines these therapies in some detail.
Chapter 4.1 Water

Giving a glass of water to someone when they feel faint has a definite scientific foundation. Studies from Germany (Jordan 2002; Schroeder, Bush et al. 2002), UK (Mathias and Young 2004; Claydon, Schroeder et al. 2006) and USA (Shannon, Diedrich et al. 2002; Lu, Diedrich et al. 2003; Raj, Biaggioni et al. 2006) support these findings. Drinking water has been found to be effective in reducing dizzy spells (Shannon, Diedrich et al. 2002) and syncope (Lu, Diedrich et al. 2003). Persons with a tendency to faint were made less symptomatic by drinking a large volume of water (Jordan 2002; Claydon, Schroeder et al. 2006). Drinking about 500ml before blood donation has reduced the incidence of venesection-induced vasovagal syncope in blood donors (Newman, Tommolino et al. 2007). Patients with autonomic failure (AF) have reported decreased severity of orthostatic symptoms after drinking water (Jordan, Shannon et al. 2000). In fact, drinking 1.5 to 2L of water a day is part of the non-pharmacological treatment in patients with symptomatic OH.

This section seeks to review the literature surrounding the effect of water drinking and the mechanism by which it exerts its effect on patients with autonomic failure (AF) and in healthy controls.

One of the earliest reports of using water to increase BP was in an Australian journal. Frewin (Frewin and Bartholomeusz 1983) described how a patient with OH had an ingenious treatment by drinking 900ml of sea-water daily. However, his treatment was terminated by troublesome diarrhoea from hyperchloraemia.

Pressor effect of water

In 1999, Jens Jordan (Jordan, Shannon et al. 1999), one of the earlier investigators on the effect of water on BP, found that drinking a pint of water raised BP acutely. He called this phenomenon the pressor effect of water. Water drinking had a profound effect on BP especially in patients with AF. He showed that by drinking about half a litre of non-sparkling mineral water, 19 patients with AF, who suffered from severe OH, had substantial rises in BP (seated BP rose by 11 mmHg 35 minutes post water) (Jordan, Shannon et al. 1999). This effect was equivalent to smoking two unfiltered cigarettes (Cryer, Haymond et al. 1976; Benowitz 1986) or ingesting 250 mg (2 cups of strong coffee) caffeine (Robertson, Frolich et al. 1978). In a later study (Jordan, Shannon et al. 2000), Jordan also found that systolic BP had risen by as much as 37 mmHg in patients with AF after drinking 480 ml of water.
The pressor effect was thought to be related to the volume of water rather than the mineral content within the fluid itself as BP also rose in patients with AF when they drank 500ml of distilled water (Cariga and Mathias 2001). Furthermore, Cariga et al (Cariga and Mathias 2001) reported a rise of seated BP in 14 subjects with pure AF of 18/9mmHg (Systolic BP went from 115 to 133 mmHg, Diastolic BP 64 to 73 mmHg). This effect was evident within minutes of drinking water, peaked at 10 to 35 minutes, and lasted for 50 minutes.

On the other hand, adding salt to the water blunted the pressor response from 37mmHg to 18mmHg at 30 minutes post ingestion (Raj, Biaggioni et al. 2006). The attenuation was not as marked at 60 minutes (17mmHg vs. 10 mmHg). Fluid with a lower osmolality may be absorbed faster, and thereby exert its effect better than fluids with higher osmolality. This finding was further supported by Lipp et al (Lipp, Tank et al. 2005) when a water infusion via a nasogastric tube elicited a higher response in BP than isotonic saline.

BP seemed to increase only in the middle-aged participants (mean age 57 years) and patients with AF. After drinking the same volume of water, the older subjects had a greater rise in BP (11mmHg) compared with in younger controls whose mean age was 25 years (0mmHg) (Jordan, Shannon et al. 2000).

**Settings in which water is useful**

**Table 4.1.1 Conditions in which water has been prescribed as treatment**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Orthostatic hypotension</td>
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<tr>
<td>Post-prandial hypotension</td>
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<tr>
<td>Postural related syncope</td>
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<tr>
<td>Exercise-induced syncope</td>
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<tr>
<td>Postural orthostatic tachycardia syndrome</td>
</tr>
<tr>
<td>Post space flights hypotension</td>
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<tr>
<td>Orthostatic hypotension in Tetraplegia</td>
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<tr>
<td>Before blood donation</td>
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</tbody>
</table>
Orthostatic hypotension

Patients with OH are advised to increase their water intake (Mathias and Young 2004). The rationale of this is to increase intravascular volume and attenuate stroke volume fall due to gravity.

Post prandial hypotension

Water is also useful in preventing post-prandial hypotension as it negates a fall in BP following a meal (Shannon, Diedrich et al. 2002). Imai (Imai, Muratani et al. 1998) reported that there was no fall in BP after food ingestion when older subjects (age 70) drank 400ml of water with their meals. Drinking half a litre of water, at room temperature, was effective within 5 minutes in increasing standing BP. Even 120ml was effective in some patients (Jordan, Shannon et al. 2000).

Postural related and Exercise induced syncope

By drinking 500ml of water, patients with postural related syncope delayed the onset of presyncope symptoms during tilt and lower body negative pressure by 5 minutes (20 to 25 min) (Claydon, Schroeder et al. 2006). The investigators reported higher BP, smaller SV reduction and greater TPR during the tilts. Therefore drinking water is a practical option for treatment of postural related syncope. Drinking water before exercise also prevented exercise-induced syncope as it reduced post-exercise BP reduction that occurred because of post-exercise vasodilatation (Thijs, Reijntjes et al. 2003).

Postural Orthostatic Tachycardia Syndrome

Water has also been reported to be an effective monotherapy in some patients with postural orthostatic tachycardia syndrome (POTS) (Shannon, Diedrich et al. 2002). Although there was no difference in standing BP, the standing HR was significantly lower (123 bpm to 108 bpm) at 3 minute stand. The effect of drinking 500ml of water is as efficacious as taking midodrine (by 5 bpm), an alpha-agonist, or an infusion of 1-2 litres of normal saline (by 18 bpm) in HR attenuation (Jacob, Shannon et al. 1997).

Space-flight hypotension

After short-term space flights, astronauts are advised to drink water and take salt to reduce post spaceflight hypotension (Watenpaugh 2001).
Orthostatic hypotension in Tetraplegia

Drinking 500ml of tap water elicited a rise in BP from 123/65 mmHg to 138/73 mmHg and a corresponding fall in HR from 64 to 60 bpm after drinking water in 13 patients with tetraplegia (Tank, Schroeder et al. 2003). This effect was observed within 5 minutes of drinking water and peaked at 40 minutes.

Improving orthostatic tolerance in young healthy controls

Water also has an effect on young healthy controls. Schroeder (Schroeder, Bush et al. 2002) and Lu (Lu, Diedrich et al. 2003) established that water improved orthostatic tolerance in young healthy controls. In a cross-over study, Schroeder, gave the young healthy subjects (n=13) either 50 or 500ml of water and subjected them to 60 degrees head up tilt and incremental lower body negative pressures. After drinking 500ml of water, the time to pre­syncope in these subjects increased by 5 minutes (from 31 to 36 minutes), which supported the findings of the study by Claydon et al (Claydon, Schroeder et al. 2006). The effect of drinking 500ml of water was present within 15 minutes. Although cerebral blood flow velocity was similar in supine position, there was a greater fall when subjects drank only 50 ml (19% vs. 12%), as was SV decline (-45% vs. -38%). There were also increases in supine BP correlating to increases in TPR. Drinking water also blunted HR rise during tilt.

Another larger study (22 normal healthy adults)(Lu, Diedrich et al. 2003) found that drinking half a litre of water prevented the episodes of pre-syncope (from 8 to 1) during tilt. The attenuation of HR was observed which supported another study in young controls (Schroeder, Bush et al. 2002) and the average time to pre-syncope increased by 26%. After 45 minutes of tilt, participants who did not drink water had a more pronounced increase in haematocrit compared with participants who drank 500ml of water before tilt (16.7% vs. 13.8%). The authors concluded that water enhanced tolerance during upright posture and acted as a prophylaxis against vasovagal faints. They suggested drinking water prior to events that were likely to trigger faints such as blood donation and prolonged standing.

Patients with AF need to be aware of a potential dramatic effect of water, as in some cases, the patients can increase their BP by as much as 100mmHg after water drinking (Jordan, Shannon et al. 2000). Water induced BP rise could also be exacerbated by concomitant use of ephedra alkaloids (Jordan, Shannon et al. 2004). When Phenylpropanolamine and Pseudoephedrine
are taken with 450 ml of water, systolic BP increased by as much as 88 mmHg. The sudden increase in BP could potentially result in hemorrhagic strokes.
Mechanism of action of water on BP

There are several different theories regarding how water causes a rise in BP.

Table 4.1.2. The proposed mechanism of action of water

<table>
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<th>Mechanism</th>
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<tr>
<td>Sympathetic activation</td>
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<tr>
<td>Gastric distension</td>
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<tr>
<td>Oropharyngeal stimulation</td>
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<tr>
<td>Volume repletion</td>
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<tr>
<td>Hypo-osmolar effect on gastro-intestinal circulation</td>
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</table>

**Sympathetic activation**

A few investigators believe that water effects are mediated through sympathetic system activation. Water drinking increased plasma norepinephrine levels in elderly controls (Jordan, Shannon et al. 2000) and muscle sympathetic nerve activity (MSNA) in young healthy subjects (Scott, Greenwood et al. 2001). Scott (Scott, Greenwood et al. 2001) found that water drinking caused an increase in s-MSNA and MSNA which peaked 30 minutes after ingestion. Calf vascular resistance and plasma noradrenaline levels also increased. In these young healthy controls, however, there was no increase in peripheral BP. In line with the theory of sympathetic activation, JoAANides (JoAANides, Moore et al. 1999) reported a sharp rise in radial artery resistance in young volunteers after drinking 11ml/kg of water. This was possibly mediated by neural vasoconstriction of the smooth muscles of the resistance vessels.

**Gastric distension**

Patients with residual efferent sympathetic function have a greater pressor response than those with little or no residual autonomic function (Jordan, Shannon et al. 2000). There was little BP rise in patients with absent autonomic function. Sympathetic activation was thought to be triggered by visceral stretch. In dogs, gastric infusion of distilled water elicited a two-fold greater pressor response compared to infusion of the same volume of normal saline or balloon gastric distension. Rossi (Rossi, Andriesse et al. 1998) showed that MSNA and BP rose when he distended the stomach of 8 healthy volunteers. There was a greater increase in sweat production (a sympathetic response) after nasogastric infusion of hypo-osmolar solutions compared to isotonic solution. Nevertheless, it is difficult to explain how such small volumes
(240ml) can elicit a pressor response. The pressor response, therefore, is not entirely due to mechanical distension of the stomach, but a combination of mechanical and osmotic stimuli.

A study by Raj (Raj, Biaggioni et al. 2006) found that drinking water, instead of salt water, increased sympathetic activation which was accompanied by a rise in norepinephrine level (from 1.55 nmol/L to 2.20 nmol/L).

**Oropharyngeal Stimulation**

Another theory proposed by Japanese investigators suggested that BP rise was due to oropharyngeal stimulation. Endo (Endo, Yamauchi et al. 2002) compared *drinking* water to direct *infusion* of 500ml of water into the stomach via nasogastric tubes of normal controls over 2 minutes. There was a transient rise in mean arterial pressure (MAP) of 12 mmHg and an increase HR of 19 beats/min after *drinking* water. A curious observation from this study showed that there was an abrupt decrease in MSNA when water was drunk instead of infused into the stomach, although some investigators believed that water caused sympathetic activation. In this study, gastric infusion had little effect on MAP, HR or MSNA. He concluded that the rapid rise in BP might be caused through stimulation of the oropharyngeal region or swallowing-induced factors.

**Volume repletion**

Patients with autonomic failure (AF) are susceptible to fluid depletion from pressure diuresis and are exquisitely sensitive to small changes in intravascular volume. Volume depletion can lower blood pressure rapidly (Mathias 2000), while infusion of saline can raise blood pressure sharply. This sensitivity is compounded by the patients' inability to retain salt and water effectively due to lack of sympathetic nerve activity on solute and water absorption by the renal tubules. Mathias et al (Mathias, Fosbraey et al. 1986) proposed that water intake repleted the volume loss caused by pressure diuresis and hence resulted in BP rise. Another study which supported this theory (Young and Mathias 2004) reported BP rise after instillation of 480ml of water in a group of pure autonomic failure (PAF) patients. Water was administered via a percutaneous endoscopic gastrostomy (PEG) tube. Seated SBP, in that study, rose by 36.5 mmHg and DBP by 24.3 mmHg after water instillation. The effect was observed between 5 and 8 min after water. While HR, CO, and SV remained unchanged, TPR increased after water. They concluded that *instilling* water directly into the stomach in a patient with PAF resulted in the same haemodynamic responses to *drinking* water in other
studies. Thus, oropharyngeal factors and swallowing were not essential in causing the pressor effect in patients with AF.

Cariga (Cariga and Mathias 2001) suggested that other investigators (Jordan, Shannon et al. 2000) failed to detect a difference in hematocrit because the volume repletion occurred in the central vasculature, while blood sampling was drawn from peripheral veins. However, the theory of volume repletion failed to explain why there was a rise in sympathetic activity shown by increases in TPR and radial artery resistance with water.

**Hypo-osmolar effect on gastro-intestinal circulation**

The most recent study by Lipp et al (Lipp, Tank et al. 2005) seemed to refute all the above mechanisms. In this elegant experiment, Lipp instilled 500ml of water or saline through nasogastric tubes in patients with multi-system atrophy. The investigators found that water raised finger arterial pressure by 8mmHg while normal saline had no effect. Therefore, the pressor effect was not due to gastric distension or fluid replenishment but appeared to be from hypo-osmolarity of water.

Although the majority of the water studies require the subjects to drink about half a litre of water within 5 minutes, Shannon (Shannon, Diedrich et al. 2002) reported that smaller volumes could still elicit an effect albeit smaller rises. PAF patients’ responses were much faster than MSA patients (5 min vs. 13 min) (Young and Mathias 2004). There were also no differences in response with differing water temperatures (9 degrees vs. 24 degrees) (Jordan, Shannon et al. 2000).

An interesting observation by Boschmann et al (Boschmann, Steiniger et al. 2003) found that drinking 500ml of cold-water increase the metabolism rate by 30%.

**Conclusion**

Water is inexpensive, readily available and has a rapid onset of action. However it does have a few drawbacks. Firstly there is currently no published evidence that water is effective for treatment of orthostatic hypotension in persons older than 57 years. It is useful in post-prandial hypotension in older persons (70 years). Secondly, the short duration of action of water (90 minutes) necessitates the patients to drink a large volume regularly to maintain blood pressure effect (Shannon, Diedrich et al. 2002) (Jordan, Shannon et al. 1999) (Jordan, Shannon et al. 2002).
Shannon et al. (2000) and Cariga and Mathias (2001). Therefore, it is only useful in subjects with predictable trigger events, such as vasovagal faints from blood donation, pre-exercise, postural related syncope or in hot weather. Most of the work carried out involved using more than 450 ml of water taken within 5 minutes. However, those who are frail may not be able to manage such a large volume at a time. Drinking such a large volume would also result in frequent toileting. Shannon et al. (Shannon, Diedrich et al. 2002) however did demonstrate a dose-response curve of blood pressure rise to the volume of water taken in autonomic failure patients. Perhaps smaller volumes more frequently may work (250 ml every half an hour). Drinking water alone, may not therefore be a feasible option for treatment for OH in the elderly. Other means of chronic volume expansion should also be considered.
Chapter 4.1.2 Sleeping in Head Up tilt position: A Treatment option for Orthostatic Hypotension

Sleeping with the head of the bed elevated or sleeping head up (SHU) is an established treatment modality for OH (Mathias and Kimber 1998; Bradley and Davis 2003; Brignole, Alboni et al. 2004). The European Society of Cardiology guidelines (Brignole, Alboni et al. 2004) recommend raising the head of the bed on blocks to permit gravitational exposure during sleep, resulting in chronic intra-vascular volume expansion. Mathias and Bannister (Mathias and Bannister 2002) recommend SHU as first line treatment for OH in patients with autonomic failure (AF).

Our literature review suggests that SHU at 12 degrees or greater confers some benefit in patients with OH. However, the studies were small with sample sizes of 8 subjects or less with varying ages (23 to 66 years) and the majority of the patients had AF (see table 1). A number of the studies used a combination of SHU, fludrocortisone, and increased water and salt intake, so identifying the exact contribution from SHU is often not possible. The improvement in orthostatic blood pressure with SHU from the studies is shown in table 1.

Patients with OH tended to be most symptomatic in the morning with symptoms improving during the day, and worsening after sleeping horizontal overnight. This observation was made by two American physicians, MacLean and Allen (MacLean and Allen 1940) in 1940. Four of their patients with OH were advised to sleep in a semi-inclined or 'head-up' position. The 'head-up' position is accomplished by placing the posts of the head of a bed on two ordinary kitchen chairs (i.e. about 18-inch in height). Patients can sleep comfortably in this position, although some may need a hard pillow under the mattress at the level of the thighs to prevent slipping. The tilt corresponds to 13 degrees in a standard 75-inch length bed. The patients were also instructed not to lie horizontally at any time. After SHU for three days, there was a marked improvement in patients' orthostatic symptoms. While previously they were dizzy or had syncope within 1 minute of standing up they were able to remain upright for greater than one hour. MacLean and Allen used this treatment for patients with spontaneous OH, sympathectomy for essential hypertension, orthostatic tachycardia and in a patient with anaemia.
Corcoran (Corcoran, Browning et al. 1943) later described how SHU was beneficial in a 40-year old woman who has OH after prolonged bed-rest from pneumonia. Her symptoms improved after SHU at 40 degrees.

Bannister (Bannister, Ardill et al. 1969) in 1969 also asked his patients to sleep head up by sleeping seated. After three days the patient’s body weight increased by 2.6kg from fluid retention as evident by lower limb oedema. He found no increase in blood-volume. There was also a reversal in the diurnal urinary excretion in that more urine was passed during the day than night when patient slept seated where previously the patients had greater urinary output at night. The symptomatic improvement disappeared after sleeping horizontal for one night.

More recently, Ten Harkel and colleagues (Ten Harkel, Van Lieshout et al. 1992) used SHU as part of the treatment for OH in 6 patients with autonomic failure. SHU was used in conjunction with extra salt (150-200mmol sodium) and water intake (2 liters a day). SHU alone improved the mean drop in systolic/diastolic BP by 11/5 mmHg (64/42 to 53/37mmHg). When combined with fludrocortisone, the BP improvement was greater by 42/21 mmHg (63/40 to 21/19 mmHg). The investigators reported that SHU allowed the patient to be symptom free for at least 14 months. The patients, on average, gained 0.5kg (range –0.3/+1.7) after SHU alone and with fludrocortisone the weight gain was 1.6kg. The investigators also found increase in sodium excretion during the day in all but one patient during SHU. Day sodium excretion was greater with fludrocortisone.

Van Lieshout (van Lieshout, ten Harkel et al. 2000) also reported a smaller drop in upright BP at 1 minute standing after three weeks treatment with SHU and fludrocortisone. By using beat-to-beat finger arterial waveform, the investigators reported that the fall in SV and CO on standing was smaller after SHU. The subjects also gained an average of 1.3 kg (range, 0.5-2.4kg) without any change in haematocrit. The rise in BP of 14mmHg from fludrocortisone and SHU were comparable to effects of midodrine (14 to 23mmHg) (Hoeldtke, Horvath et al. 1998) and erythropoeitin (19mmHg) (Hoeldtke and Streten 1993).

Another case report by Kardos (Kardos, Avramov et al. 1996) showed that following 15-degree SHU, in addition to salt and fludrocortisone, a 66-year old patient with recurrent
syncope (three times daily) became symptom-free. The patient's symptoms returned after sleeping horizontal for two weeks.

Some patients with OH have co-existing supine hypertension (Ten Harkel, Van Lieshout et al. 1992; Omboni, Smit et al. 2001). SHU might help to lower co-existing supine hypertension (Freeman) (Oldenburg, Kribben et al. 2002) in AF patients. A 20-25 cm elevation of the head of the bed lowers cerebral arterial pressure by about 15 mmHg due to hydrostatic effects (Oldenburg, Kribben et al. 2002).

**Mechanism of action**

The effect of SHU was thought to act through activation of the renin-angiotensin system by relative renal hypoperfusion (Mathias and Kimber 1999). Elevation leads to sodium and water conservation thereby increasing intra-vascular volume. It also increases extracellular fluid with evidence of ankle oedema (Bannister, Ardill et al. 1969) (Ten Harkel, Van Lieshout et al. 1992). SHU decreases sodium and water excretion during the night and this is associated with improvement in orthostatic tolerance in patients with autonomic failure (Mathias and Bannister 2002). In fact, patients become asymptomatic when slight oedema occurs in the lower limbs (MacLean and Allen 1940). The increase in extra-cellular fluid volume in the lower extremities may play a crucial role in this intervention. MacLean suggested that the increased tissue pressure prevented venous pooling in the lower limb when the patient stood.

**Angle of the head up tilt**

There are a variety of recommendations for the angle of head of tilt (table 2). The American neurologists recommended tilts between 10 to 30 degrees. Freeman (Freeman 2003) and Bradley (Bradley and Davis 2003) suggested 10 to 20 degrees whereas Engstrom(Engstrom and Aminoff 1997) also suggested SHU at 30-degree. Oldenburg (Oldenburg, Kribben et al. 2002) advises 15 to 30 degrees head up to treat co-existing supine hypertension. Grubb (Grubb, Kosinski et al. 2003) in a review in 2003 suggested sleeping at 45 degrees tilt in hospital beds or alternatively 4 to 6 inches with the back post of bed elevated. The European counterpart, on the other hand, advised lower angles of 10 to 15 degrees tilts. The 2004 European society Guidelines for syncope management recommended raising the head of the bed on blocks to permit gravitational exposure or tilts of >10 degrees. Ten Harkel et al (Ten Harkel, Van Lieshout et al. 1992), Van Lieshout (van Lieshout, ten Harkel et al. 2000) and Omboni (Omboni, Smit et al. 2001) all used 12 degrees as per MacLean protocol (MacLean
and Allen 1940). Wieling (Wieling, Van Lieshout et al. 2002) recommended an elevation of 20–30 cm at the head-end of the bed. Mathias and Kimber (Mathias and Kimber 1998) suggested raising the bed head by blocks or a polystyrene wedge beneath the mattress. Patients were advised to use home-built devices to achieve the required tilts (Ten Harkel, Van Lieshout et al. 1992). In one case, this was made portable by a sleeping bag and was used during camping.

An elevation of 12 degrees head up tilt corresponds to 15 inches in a normal length bed. MacLean’s original elevation was 18 inches head up. Some patients (Ten Harkel, Van Lieshout et al. 1992) reported sliding to the end of the bed when they slept head up. Wieling (Wieling, Van Lieshout et al. 2002) suggested a hard pillow under the mattress at the level of the thighs to prevent sliding. A footboard is also helpful to prevent falling off the end of the bed. Some patients also complained of pain at the soles of the feet from pushing against the footboard (Ten Harkel, Van Lieshout et al. 1992). Others attached a sleeping bag to the frame of the bed to keep head up. The patients in Ten Harkel (Ten Harkel, Van Lieshout et al. 1992) and Omboni (Omboni, Smit et al. 2001) studies continued with this prescribed treatment because of symptomatic improvement, and tolerated the discomfort even after 14 months (Ten Harkel, Van Lieshout et al. 1992). Some patients with PAF with incapacitating OH had been maintained satisfactorily for years on this form of treatment alone (Mathias and Bannister 2002).

The studies to date include subjects aged 68 years and younger and there are no published data on the tolerability and safety of SHU 18 inches in older subjects. Elevation of 4 inches and 6 inches corresponds with 3° and 5°. These elevations may be more tolerable to elderly patients. Experience from our own clinic data suggested that 6 inches elevation was safe and well-tolerated in older patients (Fan, Coakley et al. 2005). It remains to be seen if these lower angles are effective in treating OH.

In conclusion, SHU is a well-recognized treatment. SHU is thought to mediate through neurohumoral pathways by causing salt and fluid retention. There is a lack of clarity of the angles recommended in the literature. Higher elevations, though effective, may not be tolerated in older subjects. Further research should be carried out to investigate if 6 inches is efficacious in treating OH.
Proposed mechanism of action of sleeping head up

Blood pressure and sodium homeostasis are closely linked. Pechere-Bertschi (Pechere-Bertschi, Nussberger et al. 1998) found that patients with OH without AF had significantly greater glomerular filtration rate (GFR) at night when compared with healthy controls. These findings suggested a decreased sodium reabsorption from the proximal tubules. On a high sodium diet, the symptoms of OH and circadian variation became blunted. Patients with AF also have complex defects of renal sodium conservation that can result in excessive nocturnal polyuria. Sodium wasting at night had been postulated to cause OH (Davidson, Smith et al. 1976).

SHU is effective within three days of sleeping head up (SHU) (MacLean and Allen 1940). These physicians from 1940's hypothesized that sleeping on the tilted bed maintained the postural adaptation which the patient gained during the day. They thought that it was related to alterations of activity of the autonomic nervous system which affected the musculature of the venous vessel walls or the tone of the striated muscles. There was a definite increase in the extracellular fluid in the lower limb which, possibly represented an increase in circulating blood volume.

Corcoran et al (Corcoran, Browning et al. 1943) later found that the effect of SHU on arterial pressure, pulse rate and renal haemodynamics was similar to infusion of angiotonin, a vasoconstrictor substance similar to angiotensin which was commercially available in 1940's with the trade name of Hypertensin). Before SHU, the patient was tilted to 40 and 60 degrees from a horizontal position. The intense renal ischaemia and hypotension were noted as blood pressure fell from 124/85 to 66/53 mmHg. The patient was pre-syncopal. This corresponded to a fall in inulin clearance of 53.5 ml/min to 6.35 ml/min. After intravenous injection of angiotonin, there was a great increase in arterial blood pressure with an associated increase in renal blood flow. After treatment with two months of SHU, the authors observed changes in BP similar to the effect of angiotonin injection. Instead of a fall in BP from 124/72 mmHg to 75/60 mmHg after 1 minute at 60 degrees tilt, BP recovered to 124/83 mmHg after 3 minutes with SHU and angiotonin infusion. Corcoran et al suggested that the similarity between the effect of angiotonin and SHU in response to tilting implied that there was a vascular adaptation to the erect posture related to the renin-angiotensin system activation.
SHU is believed to act through a reduction in overnight recumbency-induced diuresis and natriuresis (Mathias and Kimber 1999; Freeman; Oldenburg, Kribben et al. 2002; Ergstrom and Aminoff 1997; Mathias and Bannister 2002; Wieling, Van Lieshout et al. 2002; Grubb, Kosinski et al. 2003; Brignole, Alboni et al. 2004). In 1969, Bannister (Bannister and Mathias 1992) reported the observation of SHU resulting in reduced nocturnal urinary water and sodium loss. In a normal subject, blood volume falls by 150-200 ml overnight. This can be as high as 500ml in patients with ganglion-blocking drugs (which simulate autonomic failure) (Cranston and Brown 1963). In the study by Bannister, one subject had an overall increase in weight of 2.6 kg over a few days. He presumed the weight gain was due to fluid retention in the extracellular space as he found no blood-volume increases. He suggested that the patient’s first attempts at standing each morning resulted in the release of angiotensin which resulted in a progressive improvement in orthostatic tolerance through the day.

By repeated exposure to low BP when upright, Mathias and Bannister (Mathias and Bannister 2002) suggested that the renin-angiotensin system became activated by renal hypoperfusion. Low renal artery pressure leads to renin release, which in turn leads to angiotensin II formation, and aldosterone release. The ultimate result is an increase in total body fluid. SHU could also be used in combination with extra water and salt intake (Mathias and Kimber 1999).

In fact, Van Lieshout (van Lieshout, ten Harkel et al. 2000) tested this hypothesis in 4 patients with PAF. He measured HR, packed cell volume, plasma levels of renin activity (PRA), aldosterone level, and atrial natriuretic peptide (ANP) level before and after 3 weeks of SHU, 150mmol/L of salt and 2 litres of water daily. Supine PRA decreased (<1.2ng angiotensin II generation/L/min) with SHU, salt and water. In combination with fludrocortisone, PRA fell while ANP levels increased in the supine and upright samples. Aldosterone levels remained unchanged. The explanations for the increase in supine plasma ANP levels and decrease in PRA were consistent with intra-vascular volume expansion. These changes were only detectable in patients with residual autonomic function.

The release of renin is thought to be due to (i) a decrease in distending pressure in the afferent arterioles, referred to as renal baroreflex, (ii) a decrease in the amount of sodium reaching the adjacent macula densa tubular cells, and (iii) an increase in the efferent sympathetic renal nerve activity to beta-adrenoceptors on the juxtaglomerular cells. SHU in combination with
fludrocortisone, salt and water, appears to reduce renin release in both the supine and upright position. It is unclear if SHU alone will result in these neuro-humoral changes.

Finally, MacLean suggested that the lower limb oedema from SHU acted as a ‘water jacket’, thereby preventing venous pooling. In fact, the development of ankle oedema coincided with improvement in dizzy symptoms (MacLean and Allen 1940) (van Lieshout, ten Harkel et al. 2000). Van Lieshout reported a decrease in compliance of the legs after SHU which supported the collection of extracellular fluid to the peri-vascular space rather than to the intravascular space. Staying upright or leg down sleeping could be a partial conservation of this “water jacket”.

In conclusion, SHU is thought to work through a humoral response by reducing nocturnal diuresis and natriuresis. Activation of the renin-angiotensin-aldosterone system results in both fluid retention and peri-vascular fluid retention reducing venous pooling. In combination, these two mechanisms result in improved orthostatic tolerance.
<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Year</th>
<th>Patient Number</th>
<th>Age range (years)</th>
<th>Patient type</th>
<th>SHU Intervention</th>
<th>Δ BP (mmHg) *</th>
</tr>
</thead>
</table>
| MacLean (MacLean and Allen 1940) | 1940 | 4 | 30-59 | 1 patient with AF \(\diamond\) 3 with NOH\(\diamond\) | 12 degrees for 3 days | +120/+70 (1 patient)  
102/+64 (1 patient) |
| Corcoran (Corcoran, Browning et al. 1943) | 1943 | 1 | 40 | 1 patient post prolonged bed rest | 40 degrees for 2 months | +49/+34 |
| Bannister (Bannister, Ardill et al. 1969) | 1969 | 4 | 45-65 | 3 with AF 1 with NOH | 90 degrees for 4 nights  
Patients slept seated in chairs and prescribed fludrocortisone as well | +40/+17 |
| Ten Harkel (Ten Harkel, Van Lieshout et al. 1992) | 1992 | 6 | 23-65 | 5 with AF 1 with NOH | 12 degrees alone  
12 degrees and fludrocortisone for one week | +11/+5  
+42/+21 |
| Kardos (Kardos, Avramov et al. 1996) | 1996 | 1 | 66 | Not specified | 15 degrees for 2 weeks | Not available |
| Van Lieshout (van Lieshout, ten Harkel et al. 2000) | 2000 | 8 | 23-65 | 8 with AF | 12 degrees and fludrocortisone for 3 weeks | +29/+10 |
AF means autonomic failure

NOH means neurogenic orthostatic hypotension or non autonomic failure orthostatic hypotension

* ΔBP denotes the change in mmHg in supine and upright systolic/diastolic blood pressure post SHU compared to pre SHU.

Supine Systolic BP (SSBP), Upright Systolic BP (USBP), Supine diastolic BP (SDBP), Upright diastolic BP (UDBP).

ΔBP = (SSBP_{post} - USBP_{post}) - (SSBP_{pre} - USBP_{pre}) / (SDBP_{post} - UDBP_{post}) - (SDBP_{pre} - UDBP_{pre})
Table 4.1.2.2. Recommended angles by different authors

<table>
<thead>
<tr>
<th>Author</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman (Freeman 2003)</td>
<td>10-20</td>
</tr>
<tr>
<td>Bradley (Bradley and Davis 2003)</td>
<td>10-20</td>
</tr>
<tr>
<td>Engstrom (Engstrom and Aminoff 1997)</td>
<td>30</td>
</tr>
<tr>
<td>Oldenburg (Oldenburg, Kribben et al. 2002)</td>
<td>15-30</td>
</tr>
<tr>
<td>Grubb (Grubb, Kosinski et al. 2003)</td>
<td>45</td>
</tr>
<tr>
<td>European society of cardiology (Brignole, Alboni et al. 2004)</td>
<td>&gt;10</td>
</tr>
<tr>
<td>MacLean &amp; Allen</td>
<td>13</td>
</tr>
<tr>
<td>Ten Harkel (Ten Harkel, Van Lieshout et al. 1992)</td>
<td>12</td>
</tr>
<tr>
<td>Van Lieshout (van Lieshout, ten Harkel et al. 2000)</td>
<td>12</td>
</tr>
<tr>
<td>Omboni (Omboni, Smit et al. 2001)</td>
<td>12</td>
</tr>
<tr>
<td>Woulter Wieling (Wieling, Van Lieshout et al. 2002)</td>
<td>6-10</td>
</tr>
<tr>
<td>Mathias and Kimber (Mathias and Kimber 1998)</td>
<td>Polystyrene wedge</td>
</tr>
</tbody>
</table>
Chapter 4.1.3 Salt

Sodium plays an integral part in maintaining intra and extra-vascular volume. Daily intake of sodium affects blood pressure. An animal study (Denton, Weisinger et al. 1995) in chimpanzee showed that BP rose with increased salt intake and reverted to normal when salt increase stopped. Increased intake of salt appears to affect only some hypertensive patients and not others. These groups of patients are called the sodium-sensitive group and the latter sodium-resistant group (Alderman 2000; Sullivan 1991).

In 1982, the collaborators of the INTERSALT project (Elliott, Stamler et al. 1996) set out to study 52 populations in 32 countries. The cohort included 10,074 men and women aged 20 to 59 years. There was a significant positive correlation between urinary sodium excretion and systolic BP. The investigators found that a 100mmol difference (for example 170 and 70 mmol/d) of urinary sodium excretion was associated with a difference of systolic BP of 5 to 7 mmHg and a diastolic difference of 4-6 mmHg. The difference was greater in older subjects.

Sodium intake varies widely from person to person. The kidney is the main organ responsible for sodium equilibrium in filtration, re-absorption and excretion. A normal adult usually excretes about 1-2 litres of urine and 150-250 mmol of sodium a day. The work to reabsorb sodium is energy demanding and requires oxygen and ATP and the oxygen demand of the kidneys is a quarter of the total CO. Water is re-absorbed with sodium both actively and by passive diffusion.

Aldosterone and atrial natriuretic peptide (ANP) are the main hormones responsible for sodium reabsorption in the distal segments. Low perfusion pressure in the afferent arteriole triggers the JG apparatus to release renin. Anything that increases renin will ultimately increase aldosterone and leads to sodium absorption. Increased serum sodium, on the other hand, inhibits renin secretion. Pressure natriuresis, from increased extracellular fluid (ECF), and natriuretic peptides maintain sodium homeostasis.

Koeppen and Stanton’s (Berne, Levy et al. 2003) textbook of physiology described an experiment to looking at the effect of sodium loading and depletion on ECF volume and renal excretion of sodium. The renin-angiotensin-aldosterone mechanism kept the plasma osmolality constant throughout the salt challenge.
Fig 4.1.3.1 The role of sodium in regulating extracellular.

**Regulation of ECF Volume**

ECF volume is regulated by the interactions of the renin-angiotensin-aldosterone system, ANP, BP and Na⁺ intake.

The graph above is split into 5 day intervals. During the first 5 days, Na⁺ intake is a baseline of 150 mmol/d, as are all the other factors that regulate ECF volume. For the next 5 days, Na⁺ intake is increased to 300 mmol/d, but the urinary Na⁺ excretion does not respond immediately. The lag time results in ECF expansion which stimulates ANP release and inhibits the RAS system. After a certain time, urine Na⁺ output is matched to 300 mmol/d, and the person reestablishes Na⁺ balance. This response is what prevents us from expanding to the size of whales. After day 10, Na⁺ intake returns to baseline, as do all the factors that regulate ECF volume. Note that during baseline Na⁺ intake, there is a transition period before all values return to normal. From day 15 to 20, Na⁺ intake is reduced to 60 mmol/d. Again, urinary Na⁺ excretion does not respond immediately. During this lag time, the person will continue to excrete Na⁺ and water, resulting in a reduced ECF volume. Na⁺ excretion gradually transitions to 60 mmol/d to match intake as the RAS is stimulated and ANP is reduced. Finally, when we return to baseline Na⁺ intake, we observe a transition period before all values return to normal again. Throughout all of the above processes, in a normal individual, blood pressure (MAP), plasma Na⁺, and K⁺ remain constant.

Permission from Koeppen and Stanton (Berne, Levy et al. 2003)

The graph above shows normal auto-regulation when the body is challenged with salt loading. Animal studies in sodium-depleted conscious dogs (Krieger, Liard et al. 1990) showed that chronic high-salt intake resulted in net retention of water and sodium with no change in MAP, HR or blood volume and the fluid retention occurred in the extra vascular space.

However, salt-sensitive individuals respond by increasing BP when salt intake is increased (Weinberger, Luft et al. 1982). Ethnicity also influenced the salt-associated MAP increase. When salt intake exceeded 800mEq/d in black subjects and 1200mEq/d in white subjects, MAP rose. Furthermore, there was significant PRA, aldosterone, and noradrenaline levels...
suppression during salt loading. Excessive sodium intake in subjects with borderline hypertension also produced abnormal increases in forearm vascular resistance, neurogenic vasoconstriction and arterial pressure (Mark, Lawton et al. 1975).

When 24-hour blood pressure monitors were applied to salt sensitive subjects, high salt intake resulted in a blunted nocturnal decline in BP with disturbance of normal circadian rhythm (Hou, Liu et al. 2000).

Therefore, high salt intake is best avoided in those with hypertension. In patients with OH, we can use increased salt and water intake to therapeutic effect. A case report by Frewin (Frewin and Bartholomeusz 1983) showed how an Australian man who drank sea-water as a treatment for OH. Another case report described a 14-year old Japanese boy with instantaneous OH, in whom alpha-agonist failed to control his symptoms (Shichiri, Tanaka et al. 2002). However within 2 days of taking a high salt diet (extra 5-6 g sodium daily), his symptoms improved greatly and this was associated with increased plasma volume. He gained 1.6kg in weight.

El-Sayed (El-Sayed and Hainsworth 1996) carried out an elegant double blind placebo controlled trial in 20 patients, and an open labelled study in 11 patients in which he studied the effect of giving 120mmol/d of sodium chloride on orthostatic tolerance in these subjects. Patients who showed an improvement in orthostatic tolerance were those whose salt excretion prior to the study were less than 170mmol/d. It was interesting to note that patients who improved in the placebo group also showed an increase in urinary salt excretion suggesting an increase in salt intake. Salt loading increased plasma volume by 300ml. The effect of salt was evident after 3 days (Mtinangi and Hainsworth 1998). This is consistent with the study by Koeppen and Stanton (Berne, Levy et al. 2003) of the salt loading and depletion study in normal subjects.

Cooper & Hainsworth (Cooper and Hainsworth 2002) studied the effect of dietary salt on orthostatic tolerance in patients with recurrent syncope. The investigators examined orthostatic tolerance using head up tilt and lower body suction. Patients with low salt excretions and poor orthostatic tolerance were given daily salt supplements of 1.5mmol/kg and reassessed after three months. At baseline, patients with sodium excretion of <170mmol/day had significantly lower orthostatic tolerance than those with higher excretion.
Salt loading was shown to increase MAP by 1.8 mmHg without any significant change in supine systolic BP. More than two-thirds of the patients who were given salt supplementation had increases in orthostatic tolerance by 2 minutes or more during tilt testing. None of the patients who were given salt supplementation (about 100mmol/d) in this study developed hypertension.

In a later study, Claydon (Claydon and Hainsworth 2004) found that 100mmol/day of salt improved orthostatic tolerance in 10 of 11 subjects with recurrent syncope. There was also no change in supine BP. For patients who responded to salt supplementation, there were also increases in the forearm vascular resistance.

Extra fluid and liberal salt intake have now become part of the standard management in patients with OH (Engstrom and Aminoff 1997) (Bradley and Davis 2003) (Mathias and Kimber 1999) (Oldenburg, Kribben et al. 2002). However, patients with hypertension and OH will need close monitoring while on extra salt intake (Sclater and Alagiakrishnan 2004). Water and salt tablets (Waters, Platts et al. 2005) are also used to prevent post spaceflight OH.

Salt supplementation is a useful therapy in patients with OH and low urinary sodium excretion. It can be used in conjunction with other therapies such as water and antihypotensive medications. However, salt-sensitive subjects may be at risk of developing hypertension when extra salt are taken. We recommend 24-hour ambulatory BP monitoring for subjects taking extra salt to avoid excessive blood pressure rise.
Chapter 4.1.4 Other non-pharmacological management of orthostatic hypotension

The first line treatment of OH in general is non-pharmacological therapy. It works principally through three mechanisms: increasing circulating volume, peripheral resistance and venous return.

At the outset, simple lifestyle changes may be sufficient. Patient education centers on recognizing trigger situations that exacerbate OH. Symptomatic OH patients should:

1. **Avoid sudden head-up postural changes** such as standing up from prolonged sitting (for example rushing to get up to answer the telephone or doorbell) or getting out of the bed quickly. Before getting out of the bed we advise physical movements such as tensing and relaxing lower limb to activate the muscle pump action thereby reducing venous pooling. The patient is then advised to sit by the side of bed for a few minutes before standing up slowly.

2. **Avoid prolonged motionless stand or sit.** If the patient is required to sit or stand for a prolonged period, we suggest regular crossing and uncrossing of the legs to prevent venous pooling (Krediet, van Dijk et al. 2002).

3. **Avoid early morning activities.** Patients with OH tend to be worse in the morning due to overnight recumbency fluid and salt loss (Mathias, Fosbraey et al. 1986). They are advised to leave most of their activities to the afternoon. A glass of water on rising may lessen dizzy symptoms by replacing overnight loss (Mathias 2000).

4. **Avoid upright activities after meals.** Patients with OH may have post-prandial hypotension up to three hours after meals. Supine blood pressure may be as low as 80/50 mmHg and the hypotension is mediated through the release of insulin and vaso-active peptides into the circulatory systems. The patients are advised on the effects of food on BP, and they may consider having smaller meals to decrease large carbohydrate load which in turn may exacerbates post-prandial hypotension (Maurer, Karmally et al. 2000; O'Donovan, Feinle et al. 2002; Smith, Psaty et al. 2003). Drinking water with the meal (Shannon, Diedrich et al. 2002) and taking caffeine (Rakic, Beilin et al. 1996) can also reduce post-prandial hypotension and OH.

5. **Avoid straining at micturition, defecation or lifting heavy weights.** Straining mimics a Valsalva manoeuvre resulting in a substantial reduction in BP. These patients may be prescribed laxatives or stool softener to reduce constipation. We
would advocate surgery in patients with prostatism to reduce the use of sphincter-relaxing medication such as alpha-antagonists which exacerbate OH (Wilt, Howe et al. 2002).

6. **A hot environment worsens OH.** One of the clinical features of AF is the inability to sweat (Sandroni, Ahlsgkog et al. 1991). Their core temperature can rise and they become over-heated. Patients with intact autonomic system can become dehydrated through sweating in a hot environment. Heat, which causes cutaneous vasodilatation, can exacerbate OH. We encourage increase intake of salt and water during the hot weather and also to stay cool. In addition, vulnerable patients should be warned about deterioration in symptoms after long hot showers and baths.

7. **Beware of the effects of alcohol.** Alcohol impairs vasoconstriction and thereby exacerbates OH (Narkiewicz, Cooly et al. 2000). Alcohol not only causes mesenteric vasodilatation, which lowers BP, it also suppresses anti-diuretic hormone secretions resulting in diuresis (Lamdin, Kleeman et al. 1956). We advise patients to refrain from excessive alcohol intake, and advise them to drink water with alcohol.

8. **Effect of exercise.** Exercise-induced hypotension is common in patients with AF (Puvi-Rajasingham, Smith et al. 1998). BP can drop with mild exertion such as walking up stairs or during prolonged walking. The hypotension is thought to be from diversion of blood to the large muscle groups without compensatory vasoconstriction or tachycardia. Patients without autonomic failure also can have exercise-induced hypotension from vasodilatation of cutaneous and muscular vessels. Salt and water loss from sweating should be replaced with isotonic fluid. Patients with OH can participate safely in exercises such as swimming or rowing do not cause venous pooling in the lower limb. The hydrostatic pressure from the water also counteracts venous pooling while the patients are standing in the pool.

**Other specific therapies**

**Abdominal binders and compression hosiery**

Application of graduated pressure from support garments to the abdomen and lower limbs reduces venous pooling and improves ventricular filling. Devices that are used thus far include anti-gravity suits (Bannister, Ardill et al. 1969), leg tourniquet (Stead and Ebert 1941; Bannister, Ardill et al. 1969), inflatable abdominal band (Smit, Wieling et al. 2004; Tanaka,
Yamaguchi et al. (1997) and compression hosiery (Henry, Rowe et al. 1999). Some of these devices work in theory but are not practical for daily purposes.

Denq et al (Denq, Opfer-Gehrking et al. 1997) reported that compression of specific compartments of the body, for instance lower abdomen, thighs and calves, raised standing BP by 26 mmHg. In particular, compression of the abdomen significantly reduces fall in orthostatic BP. Several studies have shown that compressions of abdomen between 20 to 40mmHg are effective (Tanaka, Yamaguchi et al. 1997; Smit, Wieling et al. 2004; Podoleanu, Maggi et al. 2006). Tanaka (Tanaka, Yamaguchi et al. 1997) found that by inflating an abdominal band to 20 mmHg, there was an attenuation of the fall in BP during standing in his subjects (6 boys and 3 girls, mean age of 13.8 years) at one minute from 17 mmHg to 5 mmHg. The band also reduced orthostatic symptoms. Furthermore, Smit (Smit, Wieling et al. 2004), during a head up tilt of 60 degrees, showed that there was a mean increase of 14% in SV when the abdominal band was increased to 40mmHg in his patients with neurogenic OH. Abdominal binders have also been used to reduce post-dialysis hypotension (Yamamoto, Sasaki et al. 2006).

There are several drawbacks with abdominal binders. Firstly, there are no abdominal bands made specifically for treatment of OH. Patients adapted back support corsets as therapeutic bands. Secondly it is also not possible to apply the bands to the right pressure of 40mmHg single-handedly. Another person is required to pull the bands from behind to ensure sufficient tightness. There are also no indicators within the band itself on whether the compression pressure is sufficient. Patients only require the high pressure intermittently during the day when their orthostatic tolerance is low or when they are standing. With those limitations in mind, when designing a new abdominal binder one should consider the following points: easy to put on, intermittent pressure when required and is specifically designed for OH.

Lower limb compression hosiery is another device that reduces venous pooling. Henry et al (Henry, Rowe et al. 1999) found that the BP drop during standing was significantly reduced when patients wore thigh length compression stockings. Leg bandaging is another way to treat seated OH (Gorelik, Fishlev et al. 2004). A more recent study by Italian investigators (Podoleanu, Maggi et al. 2006) reported that a compression bandage of the lower limb to pressure of 40 to 60mmHg followed by abdominal bandages of 20 to 30mmHg increased
standing BP in older persons (mean age of 71 years) during tilt table tests. The older persons also reported fewer orthostatic symptoms during the month where they wore the lower limb compression hosiery.

However, compression hosiery is only a temporary measure and patients can become more vulnerable when they are not wearing the garments (Bannister and Mathias 1992). There was also a case where a patient with OH developed acute pulmonary edema 45 minutes following high waist compression stockings (including leg compressions) (McCardell, Berge et al. 1999).

**Physical counter-manoeuvres**

Physical counter-manoeuvres (PCM), in particular leg-crossing and lower body muscle tensing, have become established as an effective treatment for OH and posture related syncope Krediet, van Dijk et al. 2002; Krediet and Wieling 2003; Krediet, Jardine et al. 2004; Krediet, van Lieshout et al. 2006; Krediet, Van Lieshout et al. 2006; Krediet, Go-Schon et al. 2007). There are specific PCM that are helpful in promoting venous returns and reducing venous pooling in the abdomen and lower limbs. Krediet and Van Lieshout (Krediet and Wieling 2003) demonstrated BP rise from these physical measures. They showed that peripheral resistance also increases with these measures.

Patients with AF often complained of debilitating dizziness in the upright position. The treatment goal is to maintain cerebral perfusion when standing so these symptoms do not occur. There are a few self-determined PCM that allow OH patient to stand longer (Wieling, van Lieshout et al. 1993). The manoeuvres work by increasing peripheral resistance and PCM increases BP by 10-15mmHg. PCM may be used in conjunction with adequate salt intake, fludrocortisone and sleeping in a 12° head-up tilted position (van Lieshout, ten Harkel et al. 1991). Some patients found standing with leg crossed very effective in preventing dizziness or syncope (van Lieshout, ten Harkel et al. 1992). Other positions include squatting and stooping, legs-crossing, squatting, thigh contractions and toe extension all seem to be effective in preventing OH (Bouvette, McPhee et al. 1996). These postures increase BP by increasing vascular resistance and venous return.

Ghrist and Brown (Ghrist and Brown 1928) in 1928 described how lowering the head into a stooped position and crossing the legs improved orthostatic tolerance. The benefit of squatting, bending forward and placing one foot on a chair were reported to be useful in
other studies (Jeffers, Montgomery et al. 1941; Nylin and Levander 1948; BickelmAAN, Lippschutz et al. 1961). BickelmAAN, in a case report, described a businessman whose work required him to stand talking to customers. He averted syncope by tensing the muscle of his arms and legs or bending forwards as if to tie his shoe laces (BickelmAAN, Lippschutz et al. 1961). Biaggioni (Biaggioni, Goldstein et al. 1990) showed that a complex manoeuvre of ‘crossing his legs at 30° angle and leaned his torso 30° forward, placing his right hand on his right thigh for support’ also helped in preventing BP drop while standing. Patients can maintain blood pressure if they leg-cross while sitting (Takishita, Touma et al. 1991).

In another case report, Wieling (Wieling, van Lieshout et al. 1993) described how a patient who had dysautonomia after Hodgkin’s disease was able to use PCM to alleviate orthostatic symptoms. Before adopting the PCM, she had incapacitating postural symptoms that limited her to lying down. However, she noticed that she was able to move around by adopting a series of manoeuvres.

She seemed to be less dizzy when she squatted. Her orthostatic tolerance also improved markedly when she stood with her head bent while contracting her abdominal muscles. By applying these techniques, she was able to walk short distances in a stooped position. The lady also climbed stairs by hopping backwards up the stairs while maintaining a knee bent posture. During exercise (such as riding a bike), the patient relieved exercise induced hypotension by drawing her knees to the frame of the bicycle or bending forwards over the handle bar.

Leg crossing, leg muscle pumping and tensing (Ten Harkel, van Lieshout et al. 1994), shifting weight from leg to leg, and putting one foot on a chair also bring relief of dizzy symptoms. A more recent report from Krediet and collaborators (Krediet, van Lieshout et al. 2006; Krediet, Go-Schon et al. 2007) showed that leg crossing, muscle tensing, squatting and crash position increases CO by 25%. Leg crossing also conferred orthostatic tolerance during LBNP tilt in healthy controls (time to pre-syncope increased from 26 min to 34 min, p<0.001) (Krediet, van Lieshout et al. 2006) Perhaps hypotension akathisia where patients with OH fidget when seated is an unconscious effect to reduce venous pooling (Cheshire 2000).
PCM work through increasing venous return and/or increasing peripheral resistance

**Squatting.** During squatting, blood is squeezed from the veins of the legs and the splanchnic vascular bed (abdominal compression). This increases cardiac filling pressure and CO. The temporary shortcutting of circulation to the legs increases systemic vascular resistance mechanically (Sharpey-Schafer 1956; O'Donnell and Mc 1962; Lewis, Lewis et al. 1980). Van Lieshout (van Lieshout, ten Harkel et al. 1992) reported that squatting increased BP more in patients with OH compared to healthy controls (44mmHg vs. 8mmHg).

**Sitting in the knee-chest position.** Pooling of blood in the buttocks and legs occur after prolonged sitting in healthy subjects. The end result is a decline in venous return which potentially can cause BP to fall (Shvartz, Gaume et al. 1983). Additional splanchnic pooling, due to defective vasoconstrictor mechanism, is one of the explanations why patients with OH are intolerant of prolonged sitting. Pulling the legs up to the chest intermittently during bicycle exercise is effective in maintaining BP. The knee to chest maneuver is similar to squatting.

**Abdominal compressions** translocate blood from splanchnic venous pool towards chest and therefore increase thoracic blood volume, cardiac filling pressures, and stroke volume. Bending forward at the waist also reduces the hydrostatic height between the heart and brain.

**Leg crossing** increases SV by compressing the venous vessels in the legs and/or abdomen which then causes an increase in central blood volume. This maneuver is also useful for patients with postural tachycardia. Van Lieshout (van Lieshout, ten Harkel et al. 1992) found that leg crossing enabled patients with hypo-adrenergic OH to stand 10 more minutes than before. There was an increase in mean BP of 13mmHg in patients.

**Muscle tensing during standing.** The effect of muscle tensing on middle cerebral blood flow, as measured by trans-cranial Doppler, increased central blood pressure by 1.4mmHg. However, the effect was short-lived. Within 2 minutes after leg tensing, the effect disappeared. Therefore, the subjects would need to repeat this action regularly. An aged-old practice in Italy was squeezing a wooden egg to prevent fainting. Brignole (Brignole, Croci et al. 2002) found that by isometric arm contraction, patients with vasovagal syncope were able...
to increase blood pressure from 92 mmHg to 105 mmHg during head up tilt. The contraction was used in 95 of 97 episodes and was successful in 99% of time in averting syncope.

A similar study (Krediet, van Dijk et al. 2002), carried out in 21 patients with recurrent syncope, found that muscle tensing and leg crossing for at least 30 seconds at the onset of presyncope during tilt-table testing, increased systolic BP by 41 mmHg (65 mmHg to 106 mmHg) and diastolic BP by 22 mmHg (43 mmHg to 65 mmHg). During the manoeuvre, the prodromal symptoms disappeared and none of the subjects lost consciousness. Thirteen of the 20 patients used these manoeuvres in their daily lives. By tensing the lower limb muscles, as much as 1.5 litres of blood volume that was shunted to the skeletal muscles preceding vasovagal syncope can be restored to the circulation (Engel and Romano 1947).

PCM is helpful in younger patients with OH and syncope. Older patients may be able to perform manoeuvres such as leg crossing, lower limb muscle tensing and isometric contraction of arm muscles. However, more complicated PCM which require balance such as squatting, leg muscle pumping (tip-toeing), abdominal contractions and bending forwards may be difficult to perform in the elderly population who have gait imbalance. PCM may be used in the right setting as a non-pharmacological measure of managing OH.

If physical counter-manoeuvres fail, one could consider carrying a portable fishing chair and sit on it to relieve orthostatic symptoms. Sitting on the fishing chair would cause a sufficient rise in BP to alleviate OH symptoms (Smit, Hardjowijono et al. 1997).

Electric stimulation of lower limb in tetraplegic patients (Chao and Cheing 2005) or deep brain stimulation (Green, Wang et al. 2006) for treatment of movement disorder seemed to attenuate BP fall as well.
Chapter 4.2 Pharmacological treatment of orthostatic hypotension

Introduction

Anti-hypotensive medication has a role in the management of OH where non-pharmacological methods have not been effective or patients are unable to tolerate non-pharmacological treatments.

The mechanism by which anti-hypotensive medications act:

- Plasma volume expansion & reducing salt loss
- Anti-diuretic effects
- Vasoconstriction directly or indirectly on resistance and capacitance vessels
- Preventing vasodilatation
- Preventing post-prandial hypotension
- Increasing cardiac output
- Increasing red cell mass

The list of medications and their mode of action are outlined in table 4.2.1

The aims of pharmacological treatment are the same as non-pharmacological treatments, which are to increase circulating volume, peripheral resistance and venous return. Pathak (Pathak, Raoul et al. 2005) sought to profile the side effects of anti-hypotensive treatments in a group of 121 patients with OH. He reported that the majority (66.7%) of the patients (mean age 67 years) were on a single agent and the most common single agent used was midodrine (49.4%). The most common combination therapy in Pathak’s study was midodrine and fludrocortisone.

The medications commonly used are fludrocortisone, midodrine and desmopressin (DDAVP). Newer medications include erythropoietin, octreotide, L-threodihydroxyphenylserine (L-DOPS) and pyridostigmine.
Fludrocortisone

Fludrocortisone (9-alpha fluhydro-cortisone) is often the initial drug of choice for OH. It causes volume expansion, reduces natriuresis and sensitizes \( \alpha \)-adrenoceptors to noradrenaline. Patients usually start with a dose of 0.1mg to 0.2mg daily. Fludrocortisone is often used effectively in combination with SHU (Ten Harkel, Van Lieshout et al. 1992; van Lieshout, ten Harkel et al. 2000). The drug however is poorly tolerated, especially in older patients. Hussain (Hussain, McIntosh et al. 1996) reported that one-third of the older patients discontinued treatment after an average period of 5 months. Reasons for discontinuation included hypertension, cardiac failure, depression and oedema. Regular electrolyte monitoring is required as hypokalaemia can occurred in about a quarter of patients. This can often be managed by potassium supplementation.

Midodrine

Midodrine acts directly on resistance vessels by causing sympathomimetic vasoconstriction. Midodrine is effective for treatment of moderate to severe OH (Jankovic, Gilden et al. 1993), dialysis related hypotension (Prakash, Garg et al. 2004), postural orthostatic tachycardia syndrome (Hoeldtke, Bryner et al. 2006), vasodepressor carotid sinus syndrome (Moore, Watts et al. 2005) and post-spaceflights hypotension (Platts, Ziegler et al. 2006). It increases standing BP by 21.8 mmHg and improve symptoms of OH (Low, Gilden et al. 1997). Treatment dose starts at 2.5 mg three times a day to a maximum dose of 30 mg/day. Adverse effects include pilomotor reaction, gastrointestinal symptoms, cardiovascular and central nervous systems toxicities. Side effects are mostly mild and can be reduced by lowering dosage. However, there have been reported serious side effects such as supine hypertension (Chaimberg and Travis 2002), cerebral haemorrhage from supine hypertension (Sandroni, Benarroch et al. 2001), intestinal occlusion (Pathak, Raoul et al. 2005) and altered taste (Young and Mathias 2004). Only 7% of patients discontinued midodrine due to supine hypertension. As with all sympathomimetics, the first dose should be taken before getting out of bed in the morning, and the last dose should be taken early in the evening to avoid worsening of supine hypertension at night (Shannon, Jordan et al. 1997).
DDAVP and desmopressin

DDAVP has potent anti-diuretic and mild pressor effects. Intransal doses of 5 to 40 microgram at bedtime are useful as this reduces recumbency-associated diuresis. DDAVP can be combined with fludrocortisone with synergistic effect. The other agent is desmopressin (2-4 micrograms given intramuscularly at 8 pm), which also reduces nocturnal polyuria and diminishes overnight weight loss. However, the side effects include raised supine BP and fluid retention (Kooner, Frankel et al. 1988). Desmopressin may be a useful alternative to, or may supplement, other forms of treatment in some patients with AF (Mathias, Fosbraey et al. 1986).

Pyridostigmine

A promising new drug reported by Singer et al in 2003 (Singer, Opfer-Gehrking et al. 2003) improved OH without adverse supine hypertension. This agent acts through inhibiting acetylcholinesterase. The standing systolic BP rose from 110 mmHg to 124 mmHg after 60mg of pyridostigmine. Most patients showed good tolerance for this medication (Sandroni, Opfer-Gehrking et al. 2005). Another study found improvement in standing diastolic blood pressure when 60mg of pyridostigmine was used alone or in combination with midodrine 2.5mg or 5mg (Singer, Sandroni et al. 2006). There was a decrease in fall in standing BP by 6.8mmHg when pyridostigmine-midodrine (5.0mg) was used when compared with a placebo (27.2mmHg vs. 34.0mmHg). Similar improvement was found when pyridostigmine was used alone compared with a placebo. A case report from Japan found that pyridostigmine (180 mg/day orally) has an additional effect of improving underactive detrusor bladder function beyond the treatment of OH. Side effects of pyridostigmine include abdominal cramps, sweating and diarrhoea.

L-threo-dihydroxyphenylserine (L-DOPS)

Another neuro-transmitter enhancing agent is L-DOPS. It acts by increasing norepinephrine in the synaptic cleft. L-DOPS is a pro-drug converts to norepinephrine outside the central nervous system. After administration of the drug, MAP of subjects rose by 40mmHg in the supine and standing positions (KaufmAAN, Saadia et al. 2003). Gibbons (Gibbons, Vemino et al. 2005) reported that L-DOPS was effective where treatments with midodrine, fludrocortisone, erythropoietin, vasopressin, salt, and fluid loading had failed in a patient with autoimmune autonomic neuropathy.
Erythropoietin

Erythropoietin is particularly efficacious when OH occurs concurrently with renal failure-induced anemia (Hadjadj, Torremocha et al. 2001; Winkler, Landau et al. 2001). Supplementation with recombinant erythropoietin and iron reversed the anemia and improved OH (Hoeldtke and Streiten 1993). Patients with amyloidosis or diabetic autonomic neuropathy may also benefit from this treatment (Winkler, Landau et al. 2001; Kawakami, Abe et al. 2003).

Octreotide

Octreotide, a somatostatin analogue, is reported to prevent post-prandial hypotension and OH in patients with autonomic neuropathy (Hoeldtke, Boden et al. 1986). Midodrine accentuates the effect of octreotide when taken in combination for treatment of post-prandial hypotension and OH (Hoeldtke, Horvath et al. 1998). Octreotide inhibits the release of vasodilating gastrointestinal peptides, thereby preventing post-prandial hypotension. After subcutaneous injection of octreotide, the splanchnic vascular resistance and mean BP increased even after food ingestion (Hoeldtke, Davis et al. 1991). The use of octreotide is limited by cost and significant side effects such as abdominal cramps and nausea.

Other drugs

Other drugs for treatment of OH include clonidine, metoclopramide, indomethacin, selective serotonin-reuptake inhibitors such as fluoxetine (Montastruc, Pelat et al. 1998), paroxetine (Di Girolamo, Di Iorio et al. 1999) and sertraline (Grubb, Samoil et al. 1994) used in OH from Parkinson’s Disease and neurally-mediated syncope, Vitamin B12 (Moore, Ryan et al. 2004) and β adreno-blockers. In severe cases of refractory OH where AF patients are immobile, ambulatory norepinephrine infusion therapy can be used to respotore mobility by increasing upright BP (Oldenburg, Erbel et al. 1999; Oldenburg, Mitchell et al. 2001). Table 4.2.1 shows the list of medications and their mode of action.

Side effects

Drug treatment for OH is often associated with difficulties. Accurate localization of the lesion causing OH is essential. Inaccuracy in diagnosis not only leads to failure of treatment but is also marked with unpredictable drug response due to ‘denervation supersensitivity phenomenon’. Medications can lead to supine hypertension and water retention. The side effects of these agents limit their use. Pathak (Pathak, Raoul et al. 2005) reported that
incidence of adverse drug events occurred in 1.6 per patient and 17% of which were considered serious. There were also unexpected side-effects observed in 11% of his population (in particular with heptaminol). Monitoring for electrolyte imbalance, supine hypertension, gastrointestinal upsets, congestive heart failure and specific adverse effects is essential when using these medications.

Table 4.2.1 Lists of medications and the mode of action

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Site of action</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma expansion &amp; reducing salt loss</td>
<td>Site of action</td>
<td>Fludrocortisone</td>
</tr>
<tr>
<td>Antidiuretic</td>
<td></td>
<td>Vasopressin-2-receptor agonist: Desmopressin</td>
</tr>
<tr>
<td>Vasoconstriction (Sympathetic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Direct effect</td>
<td>on arteries</td>
<td>Midodrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenylephrine</td>
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<tr>
<td></td>
<td></td>
<td>noradrenaline</td>
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<td></td>
<td></td>
<td>Clonidine</td>
</tr>
<tr>
<td></td>
<td>on veins</td>
<td>dihydroergotamine</td>
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<tr>
<td>Indirect effect</td>
<td></td>
<td>Ephedrine</td>
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<tr>
<td></td>
<td></td>
<td>Tyramine with MAOI</td>
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<tr>
<td></td>
<td></td>
<td>Yohimbine</td>
</tr>
<tr>
<td>Pro-drug</td>
<td></td>
<td>L-threo-dihydroxyphenylserine</td>
</tr>
<tr>
<td>Vasoconstriction (non-sympathetic)</td>
<td></td>
<td>Vasopressin-1 agonist: terlipressin</td>
</tr>
<tr>
<td>Preventing vasodilatation</td>
<td>Prostaglandin</td>
<td>Indomethacin</td>
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<tr>
<td></td>
<td>synthetase inhibitors</td>
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<tr>
<td></td>
<td></td>
<td>Flurbiprofen</td>
</tr>
<tr>
<td></td>
<td>Dopamine receptor</td>
<td>Metoclopramide</td>
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<tr>
<td></td>
<td>blockade</td>
<td>Domperidone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beta2-adrenoreceptor blockade</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Propanolol</td>
</tr>
<tr>
<td>Preventing post-prandial</td>
<td>Adenosine receptor</td>
<td>Caffeine</td>
</tr>
<tr>
<td>hypotension</td>
<td>blockade</td>
<td></td>
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<tr>
<td>-------------</td>
<td>----------</td>
<td></td>
</tr>
<tr>
<td>Peptide release</td>
<td>Somatostatin analogue: octreotide</td>
<td></td>
</tr>
<tr>
<td>inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers with</td>
<td>Pindolol</td>
<td></td>
</tr>
</tbody>
</table>

**Increasing cardiac output**

| intrinsic sympathetic activity | xamoterol |
| Dopamine agonist | Ibopamine |

**Increasing red cell mass**

| Recombinant erythropoietin | |

**Cholinesterase inhibition**

| Pyridostigmine bromide | |

**Increasing systemic vascular resistance** (Moore, Ryan et al. 2004)

| Vitamin B12 | |

Adapted from Mathias 1999 (Mathias and Kimber 1999)
Chapter 4.3 Treatment of supine hypertension

Supine hypertension (SH) often coexists with OH and poses a challenge in the management of OH. It may occur in patients with AF due to a number of reasons: impaired baroreceptor control, supersensitivity of denervated blood vessels to even small amounts of neurotransmitters or supersensitivity to pressor drugs, and fluid shift from periphery to central compartment when changing posture (Shannon, Jordan et al. 1997; Mathias and Bannister 2002). SH is not entirely explained by increased blood volume or RAAS, as there is no difference detected between AF patients with or without SH.

The rationale for treatment of supine hypertension is two-fold.
- to reduce end-organ-damage from sustained hypertension
- to reduce pressure-diuresis and associated dehydration in the morning.

In a case series of 117 patients with AF, Shannon (Shannon, Jordan et al. 1997) found that 56% had supine hypertension (diastolic ≥ 90mmHg). Other studies, using 24 hour ambulatory BP monitoring reported a prevalence of 5.5% in a group of hypertensive patients (Lagi, Rossi et al. 2003) and 84% amongst patients with AF (Ejaz, Haley et al. 2004).

Table 4.3.1. Systolic blood pressure response to meal and medication challenge in patients with autonomic failure (Shannon, Jordan et al. 1997)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>BP decrease mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(mmHg)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Seated BP 44 (2)</td>
</tr>
<tr>
<td>High carbohydrate breakfast</td>
<td>414 calories (51.7 carbohydrate)</td>
<td></td>
</tr>
<tr>
<td>Hydralazine</td>
<td>50mg</td>
<td>Supine BP 13 (7)</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>2.5mg</td>
<td>Supine BP 22 (7)</td>
</tr>
<tr>
<td>Nitroglycerin patch</td>
<td>0.023mg/h to 0.1mg/h</td>
<td>Supine BP 36 (7)</td>
</tr>
<tr>
<td>Sleeping with head of bed</td>
<td>6 to 10 inches</td>
<td>Unknown</td>
</tr>
<tr>
<td>elevated</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nocturnal transdermal nitroglycerin, a useful short-acting agent, caused an average decrease of 36mmHg in SBP (Shannon, Jordan et al. 1997). The BP lowering effect was significant within 4 hours and was sustained when the patch was on. However, patients should be
warned that nitroglycerin exacerbates OH if they get up at night. Sleeping head up (SHU) therefore potentially provides an attractive therapeutic option as it does not exacerbate OH but may treat SH (Bannister, Ardill et al. 1969). The degree by which blood pressure is lowered by SHU remains to be seen however.
Chapter 5 General Aims

Study 1: To determine the use of Sleeping Head Up in the treatment of Orthostatic Hypotension in clinical practice

Study 2: To determine the physiological response and tolerability of Sleeping Head Up at 18 inches (13 degrees) for one week on young healthy volunteers

Study 3: To determine the effects and tolerability of Sleeping Head Up at 6 inches (5 degrees) for one week on elderly inpatients with Orthostatic Hypotension – an observational study

Study 4: To determine the effectiveness and tolerability of Sleeping Head Up at 6 inches (5 degrees) for 6 weeks on elderly outpatients with Orthostatic Hypotension – a randomised controlled trial
Chapter 6: The use of sleeping with the head of the bed tilted up for treatment of orthostatic hypotension in clinical practice

Introduction

Sleeping with the head of the bed elevated (SHU) or nocturnal head-up tilt is established as part of the treatment modality for OH (Mathias and Kimber 1998; Bradley and Davis 2003; Brignole, Alboni et al. 2004). The European Society of Cardiology guidelines (Brignole, Alboni et al. 2004) recommend raising the head of the bed on blocks to permit gravitational exposure during sleep resulting in chronic intra-vascular volume expansion. In fact, Mathias and Bannister (Mathias and Bannister 2002) recommend SHU as first line treatment for OH in patients with autonomic failure.

The aim of our study was to determine the extent to which SHU is used in current clinical practice for the treatment of OH amongst experts and how it is prescribed.

Methods

Design
We carried out a postal survey of medical practitioners who attended an international symposium on syncope in Newcastle-upon-Tyne, United Kingdom that took place in November 2003.

Sample
We identified 220 medical practitioners from the delegate attendance list of 238 attendees. We excluded 18 non-clinical delegates who were representatives of pharmaceutical or medical equipment companies. The breakdown of specialities of medical practitioners is as follows: 128 (58%) geriatric medicine, 33 (15%) general medicine, 26 (12%) cardiology, 15 (7%) physiology, 11 (5%) neurology and 7 (3%) not determinable. Personalised cover letters, structured questionnaires and return envelopes were sent to the clinical delegates in February 2004. A follow-up letter and questionnaire was posted to non-respondents two months following the first mail-out date. We completed the survey on 31st August 2004. See figure 6.1 for the flow diagram of respondents.
**Survey Instrument**

The structured questionnaire ascertained the country and positions in the departments of the respondents. The rest of the questionnaire was divided into four sections. They were asked (i) if they routinely prescribed SHU, (ii) whether SHU was used before medications, (iii) the angle and the height of elevation of the head of the bed and (iv) their reasons for not using SHU. Other modalities of treatment for OH were also obtained. Where the respondents gave specific heights of elevation instead of angles, we calculated the corresponding angle of the tilt of the bed based on the standard 75-inch bed. Figure 6. 2 illustrates the formula for calculating the angle of tilt to the elevation of the head of bed. An example of the questionnaire is shown on page 108.

**Data Analysis**

All responses were analysed using Excel spreadsheet. Chi-squared test was used to compare different categories.

**Ethical Approval**

Ethical approval was not sought for this study.
Results

Characteristics of respondents
There were 149 respondents from 121 hospitals. This represented an overall 67% response rate. Of the responders, 135 (91%) were from the United Kingdom, 13 (9%) were from the rest of Europe and one reply came from Australia. One hundred and five (70%) of the respondents were consultants or heads of departments, 34 (23%) were registrars or associate specialists, 3 were clinical nurse specialists. Seven doctors did not specify their positions. The specialties represented by the respondents were as follows: geriatric medicine 96 (64%), general medicine 29 (20%), cardiology 12 (8%), physiology 7 (5%) and neurology 5 (3%).

Prescription pattern
Ninety (60%) of the respondents prescribed SHU; 40 (27%) routinely and 50 (33%) occasionally. Fifty-nine (40%) respondents never prescribed SHU. Thirty-eight respondents (25%) used SHU before prescribing medications. Geriatricians were no different in their prescription compared to other specialties whether as part of OH treatment (geriatricians (G) vs non-geriatricians (non-G) 57/96 vs. 33/53, Chi²= 0.1191, df=1, p=0.729,) or using before medications (G vs. non-G, 25/96 vs. 13/53, Chi²=0.411, df=1, p=0.839).

Angles used
Of the respondents, 66 gave specific heights or angles they used. Of these, 44 (67%) used angles < 12 degrees. Twenty-four (36%) prescribed angles between 3 to 5 degrees (see table 6.1). The median (IQR) angle of elevation was 6.5 (16) degrees. Twenty-four respondents did not specify angles or heights. They suggested raising the head of the bed using pillows, telephone books, bricks, blocks or heights as “high as the patient could tolerate”.

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Fig 6.2. Positioning of the bed for sleeping head up and calculations of the angle of tilt by elevating the head of the bed

**How to position your bed for sleeping head up**

![Diagram showing how to position the bed for sleeping head up](image)

**Calculation of bed angle**

A normal bed - length = 6 feet 3 inches (75 inches)

For instance,

\[
\sin \theta = \frac{1}{h}, \quad h = \frac{1}{\sin \theta}, \quad \theta = \sin^{-1} \left( \frac{h}{l} \right)
\]

<table>
<thead>
<tr>
<th>Angles $\theta$</th>
<th>Elevation height (inches)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.06</td>
<td>4.0</td>
</tr>
<tr>
<td>5.0</td>
<td>6.0</td>
</tr>
<tr>
<td>12</td>
<td>15.59</td>
</tr>
<tr>
<td>6.12</td>
<td>8.0</td>
</tr>
<tr>
<td>12</td>
<td>15.59</td>
</tr>
<tr>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>30</td>
<td>37.5</td>
</tr>
<tr>
<td>45.0</td>
<td>53.03</td>
</tr>
</tbody>
</table>
Table 6.1. The angle of tilt of the bed (based on a standard 75-inch bed), the corresponding height of elevation in inches and the number of medical practitioners prescribing it

<table>
<thead>
<tr>
<th>Angles (θ) in degrees</th>
<th>Corresponding heights in Inches</th>
<th>Number of practitioner prescribing this angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3</td>
<td>&lt; 4</td>
<td>6</td>
</tr>
<tr>
<td>3.5</td>
<td>4-6</td>
<td>24</td>
</tr>
<tr>
<td>5.5-10</td>
<td>8-13</td>
<td>14</td>
</tr>
<tr>
<td>12-25</td>
<td>16-32</td>
<td>11</td>
</tr>
<tr>
<td>30-45</td>
<td>38-53</td>
<td>11</td>
</tr>
</tbody>
</table>

Reasons for non-prescription
In total 68 (46%) respondents gave reasons for not prescribing SHU. The main reasons for not using were lack of belief in its effectiveness 37 (54%), patient inconvenience 18 (26%), patient intolerance 16 (24%) and 16 (24%) felt that more effective treatments were available.

Other Treatment modalities for OH
The treatment modalities used by the medical practitioner is summarised in table 6.2. Fludrocortisone was the most commonly prescribed treatment followed by increased fluid intake, physical counter manoeuvres, and salt-loading. Other modalities used were midodrine, exercise-training, compression hosiery, desmopressin, caffeine tablets, ephedrine and non-steroidal anti-inflammatory medications.
Table 6.2. Modalities for Treatment of OH from survey

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of response</th>
<th>Percentage of total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludrocortisone</td>
<td>134</td>
<td>89.9</td>
</tr>
<tr>
<td>Drinking 1.5 to 2.0 litres of water</td>
<td>105</td>
<td>70.5</td>
</tr>
<tr>
<td>Physical Counter manoeuvres</td>
<td>99</td>
<td>66.4</td>
</tr>
<tr>
<td>Salt loading</td>
<td>87</td>
<td>58.4</td>
</tr>
<tr>
<td>Sleeping head up</td>
<td>79</td>
<td>53.0</td>
</tr>
<tr>
<td>Midodrine</td>
<td>74</td>
<td>49.7</td>
</tr>
<tr>
<td>Exercise training</td>
<td>41</td>
<td>27.5</td>
</tr>
<tr>
<td>Compression hosiery</td>
<td>32</td>
<td>21.4</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>10</td>
<td>6.7</td>
</tr>
</tbody>
</table>

Others include caffeine tablets, ephedrine and non-steroidal anti-inflammatory drugs

Discussion

Our survey showed that SHU was regularly used by a significant proportion of syncope experts for the treatment of OH and that geriatricians were the largest specialty involved in this treatment.

The most common angles used were between 3 to 5 degrees (corresponding to 4-6 inch elevation). Only a third of those who used SHU were recommending angles for which evidence exists (i.e. ≥12 degrees). It is noteworthy however that a significant proportion of respondents were unconvinced about its efficacy or tolerability.

SHU is postulated to work through the renin-angiotensin system (RAAS) by reducing overnight natriuresis and diuresis (Bannister, Sever et al. 1977) as patients with OH can lose up to 1 kg in weight over-night (Mathias, Fosbraey et al. 1986) while recumbent. A reduction in renal arterial pressure by SHU is thought to activate the RAAS, which results in sodium and water retention (Mathias and Bannister 2002). Given the physiological basis for its perceived mechanism of action, the angle of tilt may be quite important for efficacy.

Although the original studies demonstrated efficacy at angles of at least 12 degrees, our literature review found a variety of recommendations for SHU angles. The European Society of Cardiology (Brignole, Alboni et al. 2004) recommends 10 to 20 degrees while American
physicians, such as Bradley (Bradley and Davis 2003) and Engstrom (Engstrom and Aminoff 1997), suggest angles of $5^\circ$ to $20^\circ$ and greater than $30^\circ$ respectively. Other proponents (Mathias and Kimber 1998) recommend raising the bed head by blocks, or tilting the mattress with polystyrene wedges rather than the bed, but did not specify an angle.

Some limitations to this study must be acknowledged. We did not ascertain the age range of the patients seen by respondents, although almost two-thirds were geriatricians suggesting that a significant proportion of patients treated were elderly. Users of this therapy may have been more likely to respond which may have lead to an overestimation of its use. However, a response rate of 67% is good for a study of this type and the specialty breakdown of respondents is similar to the overall sample.

The evidence for the effectiveness of SHU is sparse and there is currently no literature to support SHU at less than 12 degrees, or indeed in older people at all. At 12 degrees, some patients have complained of sliding down to the end of the bed (Ten Harkel, Van Lieshout et al. 1992). Others developed peripheral oedema. Therefore, there must be some concern about compliance when advising older persons to sleep at this degree of elevation.

The surveyed showed that the majority of practitioner would use medications rather than non-pharmacological means to manage orthostatic hypotension. The medication of choice was fludrocortisone instead of midodrine. This finding is consistent with the fact that the majority of the medical practitioners surveyed practised in the United Kingdom. Midodrine is prescribed only by consultants and on a named basis. Hence there is relative limited usage in those surveyed.

Conclusions
In conclusion, the conflicting recommendation of SHU angles in the literature is reflected in the lack of clarity in clinical practice. SHU is not an uncommon treatment, being used by more than half of the medical practitioners surveyed. The majority of respondents used smaller angles, for which there is no literature support. Further studies are required to determine if the more commonly prescribed lesser angles are effective and safe in older patients. The mechanisms of action of SHU and its effectiveness, in those with and without AF, need to be further investigated. Comparison with existing treatments would also be worthwhile.
Questionnaire on Clinical Practice: Sleeping in the Head Up Position

Position in department
Head of department Consultant Clinical Fellow/Registrar
Nurse specialist Others Specify _____________________

1. Do you routinely advise patient with Orthostatic Hypotension to sleep with the Head of the bed raised?
   Yes No Sometimes
   Would you routinely use this before starting patients on medications?
   Yes No Sometimes

2. If yes, how high do you ask patient to raise the head of the bed?
   Degree _____________________ Height raised _____________________
   Exact height not specified (few inches)___________________

3. If no, why not?
   Patient Inconvenience Not tolerated by patients
   Not convinced it is effective More effective treatment available

   Others

4. Please tick the following measures you are advising for treatment of Orthostatic Hypotension (you may choose as many as you like)

   Drink 1.5 to 2 litres of non-caffeinated fluids
   Salt loading
   Physical counter-manoeuvres
   Exercise training
   Sleep Head Up
   Fludrocortisone
   Midodrine
   Desmopressin
   Others

   Please specify

Comments:
Chapter 7: The physiological response and tolerability of sleeping head up at 18 inches for one week in young healthy volunteers

Introduction
Although SHU has been included in several guidelines (Mathias and Bannister 2002; Oldenburg, Kribben et al. 2002; Bradley and Davis 2003; Brignole, Alboni et al. 2004) as one of the non-pharmacological treatments for OH, a substantial proportion of syncope experts remain unconvinced about the evidence for SHU’s effectiveness and tolerability and it is used routinely by a minority only (Fan, Coakley et al. 2006). A few reports have demonstrated that sleeping with the head of the bed tilted upwards (SHU) greater than 12 degrees is associated with an increased orthostatic tolerance the next morning. Early observations were predominantly case reports (MacLean and Allen 1940) (Corcoran, Browning et al. 1943). Although recent studies have tended to support these observations (Ten Harkel, Van Lieshout et al. 1992; van Lieshout, ten Harkel et al. 2000), sample sizes were very small (less than 10 subjects) and in most cases interventions such as water and salt loading and/or medications were also being used. It is still not clear whether sleeping head up has any additive benefits to existing treatments.

The aim of our study was to investigate the acute physiological effects of SHU on a large group of healthy young volunteers

Methods

Subjects
We recruited 29 healthy subjects (13 men) with a mean (standard deviation) age of 22 (1.9) years. Subjects were all college students, non-smokers, free from chronic medical conditions and did not use recreational drugs. While healthy subjects obviously may not respond in a similar fashion to patients with OH, their use did allow us to study the intervention in much more detail than heretofore and allowed us to look for any broad physiological effects. Our rationale was that if SHU could be shown to have general physiological effects then the rationale for conducting further research in more frail patients would be stronger. All subjects signed an informed consent document approved by the St James’s Hospital Research Ethics Committee.
Protocol

The study protocol is outlined in figure 7.1. All subjects were required to drink at least 2 litres of water a day for one week prior to starting SHU. While sleeping "head up" they were required to drink at least 2 litres of water from 0700-2100hr and exactly 500ml at 2100hr and no more till 0700hr. Subject were required to sleep head up 18 inches from days 3 to 9 which corresponds to 12 degrees of elevation for a standard 75 inch bed. The bed arrangements of SHU were as described by MacLean (MacLean and Allen 1940).

The head of the bed was tilted up 18 inches higher than the foot of the bed using two sturdy 18-inch chairs. During this period subjects were required to sleep on the tilted bed during any nap-time and at night (2300 to 0700hr). The subjects were reminded to keep hydrated and sleep head up each night by text messages.

Haemodynamic parameters

Haemodynamic variables were recorded during an “active stand”. After a total of 5-10 min of preceding supine rest, subjects were instructed to move from supine to standing in about 3 seconds, if necessary with assistance, and stand for at least 2 minutes without support. The subjects underwent active stands on four occasions between 0900 to 1100 hrs (see figure 7.1); on two consecutive days before SHU (i.e. days 2 and 3) and 2 consecutive days after SHU (i.e. days 9 and 10).

A non-invasive continuous beat-to-beat device was used for haemodynamic measurements (“Finometer” TNO, Amsterdam) recording the systolic blood pressure (SBP) and heart rate (HR). Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were derived from Modelflow® calculations (Wesseling, Jansen et al. 1993).

Non-haemodynamic parameters

The subjects were questioned regarding postural dizziness at the end of each stand. 24-hour urine was collected as 2 samples: a ‘day sample’ comprised of urine passed between 0700 hr to 2300hr excluding the first urine sample on rising and a ‘night sample’ from 2300 hr till 0700 hr the following day including the first sample on rising. Urine sodium and volume were recorded. All subjects were weighed fasting, without shoes, in the same set of clothes and post-micturition at 0800 hr.
The calf and ankle circumferences were recorded to the nearest mm in the supine position at designated points of the right lower limb, i.e. calf circumference at 100mm below the lower border of patella, ankle circumference at 100 mm above the lower border of medial malleolus using a measuring tape accurate 1mm. All blood samples were taken between 0900 and 1100 hrs. After lying supine for one hour, blood was drawn for hematocrit (Walters and Garrity 2003), plasma electrolytes (Roche/Hitachi Modular System, ISE Unit), plasma renin activity (PRA) (Renin MAIA, Adaltis, Italy, intra-assay coefficient of variation (C.V.) 5.1 %, inter-assay C.V 5.1%), aldosterone (Aldosterone MAIA, Adaltis, Italy, intra-assay coefficient of variation (C.V.) 5.4%, inter-assay C.V 6.4%) and pro-atrial natriuretic peptide (pro-ANP 1-98) (Biomedica Gruppe, Vienna, Austria, intra-assay coefficient of variation (C.V.) 6% , inter-assay C.V 7%). Only supine levels were taken. Blood samples were taken and analysed as per manufacturer’s instructions. The 24-hr ambulatory blood pressure monitoring was measured using A&D TM-2430 (Palatini, Frigo et al. 1998). Mean day (0700 to 2300 hrs) and night (2300 to 0700 hrs) SBP were calculated for each subject.

The primary outcome measures were the nadir Systolic Blood Pressure (SBP) during the “active stand” and the mean drop in SBP (ΔSBP), comparing the 10-second interval (I₀) immediately before standing to the first two 10-second intervals (I₁ and I₂) immediately after standing. The secondary outcome measures were symptoms of postural dizziness, haemodynamic variables during the active stand (i.e. HR, SV, CO and TPR) and weight, day and night urinary volumes, urinary sodium, right calf and ankle circumferences, supine plasma renin activity (PRA), aldosterone, pro-atrial natriuretic peptide (Pro-ANP 1-98), serum haemoglobin and electrolytes and mean night and day SBP before and after SHU.

Statistical analysis
Haemodynamic parameters recorded during four “active stands” (i.e. two before and two after SHU) were averaged to produce “before” and “after” variables.

All cardiovascular parameters were exported in 1-second bins. Data were then averaged in 10-second bins so as to reduce error due to random beat-to-beat blood pressure variation. We decided to analyse data from the first 20 seconds as the time when nadir SBP was likely to occur. Nadir SBP, ΔSBP (defined as the mean drop from I₀ to nadir SBP), peak HR, SBP and HR at I₁ and I₂ during standing were calculated. Percentage change from I₀ to peak/ nadir, and percentage from I₀ to I₁ and I₂ during standing were also calculated for SV, CO and TPR.
All data was analysed for normal distribution and were evaluated using paired t-tests or Wilcoxon signed rank tests as appropriate. Analysis of variance was performed on supine and standing haemodynamic parameters. Postural symptoms were said to be present before SHU if either the active stand on day 2 or 3 was associated with symptoms and were said to be present after SHU if either active stand on day 9 or 10 was symptomatic. McNemar’s test was used to test for significant change in symptoms.

Measurement parameters and power calculations were based on pilot studies of healthy young individuals carried out by our group. A sample of 28 subjects would have a power of 80% and an alpha of 5% to detect a significant difference in nadir SBP of 9 mmHg and a reduction in drop in SBP of 4 mmHg with p<0.05.

Datadesk statistical software was used (version 8 Ithaca, NY) for data analysis. All statistical tests were two-sided.

Results

Haemodynamic variable are shown in table 1. Although there was no change in the nadir SBP on standing, the mean drop in SBP (ΔSBP) was significantly lower after one week of SHU. There was a significant increase in CO at I: (8.6%) and a reduction in TPR at I: (12.1%) and I: (9.1%). See table 7.1. Analysis of variance showed a reduction in supine and standing heart rate, an increase in standing stroke volume and decrease in total peripheral resistance. See table 7.2. In non-haemodynamic parameters, there were significant increases in median weight (0.4kg) and ankle circumference (8mm). The night urinary volume fell by 145ml from SHU, despite similar 24-hour urinary volume and sodium excretion. There was also a 0.3g/dL reduction in hemoglobin but no difference was found in PRA, aldosterone and pro-ANP. The non-haemodynamic effects of SHU are shown in table 7.3. There was no difference in mean day or night blood pressure. The graphs illustrating the hemodynamic parameters during the active stand are shown in figures 7.2 to 7.6. Figures 7.7 to 7.9 illustrate the relative percentage of stroke volume, cardiac output and total peripheral resistance from baseline and one-week post SHU at 18 inches.

In addition, the participants were significantly less dizzy during active stands after one week of SHU (27 [93.1%] subjects symptomatic on day 2 or 3 vs. 12 [41.4%] subjects symptomatic on days 9 or 10, χ² =13.1, p=0.001). Many of the subjects tolerated SHU for the week but all
complained of sliding down to the bottom of the bed and needed to push themselves up the bed during the night. They also complained of heavier or stiffer legs due to ankle oedema.

Discussion
This study represents the largest series examining the effect of SHU at 18 inches to date, albeit in normal subjects. In these healthy subjects we confirmed the antidiuretic effect of SHU, as described by Bannister and Mathias for subjects with autonomic failure (Mathias and Bannister 2002). Symptoms of orthostatic dizziness were considerably reduced, as was the ASBP. There was an increase in SV and a reduction in TPR (a surrogate marker of vasoconstriction) during active stands after SHU in keeping with an increase in intravascular volume.

Previous reports since the 1940’s have demonstrated that SHU greater than 12 degrees is associated with an increased orthostatic tolerance the next morning (MacLean and Allen 1940). The improvement in symptoms is thought to be due to a reduction in overnight diuresis and natriuresis (Bannister, Ardill et al. 1969; Wilcox, Aminoff et al. 1974), which can cause weight loss of up to 1 kg patients with autonomic failure (Mathias, Fosbraey et al. 1986).

Although subjects in our study were young healthy volunteers and had relatively constant salt and water intake (as demonstrated by the unchanged 24 hour urinary sodium and volume) urinary volume at night was reduced by almost 150 ml and the subjects gained an average weight of 400g from both extravascular (i.e. ankle oedema) and intravascular (i.e. drop in haemoglobin and change in haemodynamic variables) fluid retention in a healthy group. These support and expand the findings of Bannister who demonstrated a reversal of day and night urinary sodium and water excretion in patients with autonomic failure using SHU (Bannister, Ardill et al. 1969).

The concept of renin-angiotensin-aldosterone system (RAAS) activation by SHU was first considered by Corcoran in 1943 when he demonstrated that an infusion of angiotonin had the same effect on arterial pressure, pulse rate and renal hemodynamics as SHU (Corcoran, Browning et al. 1943). Van Lieshout later reported reduced supine and upright PRA and increased ANP levels in both supine and upright positions in 4 patients with autonomic failure. The aldosterone levels were unchanged (van Lieshout, ten Harkel et al. 2000). He suggested that supine plasma ANP increases and PRA decreases after SHU were physiological responses to expansion of the intra-vascular volume. We were unable to
confirm these findings in this study. However, measurement of renin, aldosterone and pro-
ANP were not our primary outcome and, as we studied healthy subjects only, we may have
been underpowered to investigate these variables. Furthermore the anti-diuretic effect seen
was not associated with an anti-natriuretic effect (i.e. change in sodium excretion) and
possible mediating effects of other hormones, such as anti-diuretic hormone, should be
considered.

Mathias and Bannister (Mathias and Bannister 2002) proposed that recurrent exposure to
lower blood pressure while sleeping upright in OH patients would activate the RAAS due to
renal hypoperfusion. We did not show any effect on nocturnal blood pressure after a week of
SHU however suggesting that SHU does not cause nocturnal hypotension in healthy subjects
though we cannot exclude the possibility of transient effects on BP occurring before this time.

An alternate theory of SHU is that it reduces venous pooling in the lower limb in the same
way as compression hosiery (‘water jacket theory’) where the increase in fluid retention in the
legs acts as a perivascular “water jacket” limiting the vascular volume available for
orthostatic venous pooling (MacLean and Allen 1940; Henry, Rowe et al. 1999). An associated
decrease in leg compliance has been found after SHU (van Lieshout, ten Harkel et al. 2000).
Our finding of an increase in ankle, though not calf circumference, would go some way to
support this theory though the increase was modest. Further work is required to see if
increases of this magnitude would be associated with haemodynamic effects.

Although relatively well tolerated, many of the subjects complained of sliding to the bottom
of the bed and stiff legs from leg oedema. This degree of elevation (12 degrees) is unlikely to
be tolerated by older patients though work carried out by our group suggests that
prescription of lesser degrees of elevation (commonly 5 degrees or 6 inches) for older patients
with OH is commonly used in Ireland and the United Kingdom (Fan, Coakley et al. 2006).

Our study has several limitations. Healthy subjects may have a different response to SHU
than patients with OH. However, the observed effects were similar to that reported for such
patients, suggesting broad physiological anti-diuretic effects for this intervention (Bannister,
Ardill et al. 1969). We looked at the effects, during the first week only, and it is unknown
whether the observed changes are maintained after a week. The uncontrolled design means
that changes cannot unequivocally be attributed to the effects of SHU and the possibility that
some of the observed changes were due to “acclimatisation” to repeated testing cannot be excluded. For example, some of the observed difference in SBP after SHU occurred in the ten seconds before standing and may reflect an anticipatory response with repeated testing. However the reduction in ΔSBP is less easily explained by this mechanism and could also represent an effect of SHU via the observed increase in intra-vascular volume. A reduction in orthostatic symptoms over time may be due to the effects of training, but the observation that little or no reduction in orthostatic symptoms was seen between the first and second active stands, and that the greatest reduction in symptoms was seen between the second and third stands (i.e. just after sleeping head up) would tend to support an effect of SHU. Also, we did not record menstrual cycle histories for the female subjects and therefore we cannot exclude the possibility that some of the observed fluid retention was mediated through this mechanism. However, as the interval between measures was only 7 days we do not feel it likely that results were appreciably affected. While extra care was taken to encourage compliance, we did not directly observe whether subjects used SHU at all times. Poor compliance would tend to obscure any effects of SHU however and make the observed significant differences less likely.

Our study has several strengths. The large sample size and adherence to a strict fluid intake over 2 weeks (as reflected by unchanged 24 hour urine output throughout the study) by a group of motivated and unpaid college students is noteworthy. The scarcity of research into this treatment, in the 70 years since it was first described, testifies to the difficulty in carrying out such research. The fact that subjects were pre-hydrated for a week and continued to drink extra fluids while sleeping head up means that the effects of SHU were demonstrated to be in addition to any effects of hydration. The fact that subjects were healthy suggests that SHU is associated with broad physiological effects, rather than being restricted to subjects with autonomic failure as the early literature suggested (MacLean and Allen 1940; Bannister, Ardill et al. 1969; Mathias and Kimber 1998).

In conclusion, sleeping head up for one week was associated with a nocturnal anti-diuretic effect in healthy controls, with fluid retention of about 400 ml, alterations in haemodynamic variables and a reduction in orthostatic symptoms. Further research should examine the effects of lesser degrees of elevation that might be better tolerated, effects in clinical populations (with OH and / or autonomic failure) and longer-term effects.
Fig. 7.1. Study protocol over 10 days

<table>
<thead>
<tr>
<th>Day-7 to 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4-7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-hydration</td>
<td>24 hour Urine collection</td>
<td>Weight AS</td>
<td>Calf &amp; Ankle circumference Blood sampling AS</td>
<td>24 hour Urine collection</td>
<td>Weight AS</td>
<td>Calf &amp; Ankle circumference Blood sampling AS</td>
<td></td>
</tr>
</tbody>
</table>

↑

Recruitment

Hydration

AS = “Active stand”

Sleeping head up
Table 7.1. Change in haemodynamic parameters after SHU for 1 week

<table>
<thead>
<tr>
<th></th>
<th>Pre SHU</th>
<th>Post SHU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nadir SBP (mmHg)</strong></td>
<td>77.6 (14.5)</td>
<td>78 (13.9)</td>
<td>0.92</td>
</tr>
<tr>
<td><strong>Mean drop in SBP (mmHg) baseline to 10 seconds after standing</strong></td>
<td>-22.3 (10.1)</td>
<td>-16.2 (12.3)</td>
<td>0.016*</td>
</tr>
<tr>
<td><strong>Mean drop in SBP (mmHg) baseline to 20 seconds after standing</strong></td>
<td>-21.8 (11.3)</td>
<td>-19.1 (14.4)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Peak HR (bpm)</strong></td>
<td>101.8 (2.1)</td>
<td>100.8 (2.0)</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Average change HR baseline to I (bpm)</strong></td>
<td>14.1 (6.6)</td>
<td>15.2 (6.5)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Average change HR baseline to II (bpm)</strong></td>
<td>19.7 (8.7)</td>
<td>21.2 (7.2)</td>
<td>0.35</td>
</tr>
<tr>
<td>% change in SV from baseline to nadir</td>
<td>-35.0 (12.7)</td>
<td>-31.8 (15.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>% change in SV from baseline to I</td>
<td>-10.9 (10.0)</td>
<td>-9.0 (13.0)</td>
<td>0.41</td>
</tr>
<tr>
<td>% change in SV from baseline to II</td>
<td>-22.3 (10.4)</td>
<td>-17.8 (15.1)</td>
<td>0.10</td>
</tr>
<tr>
<td>% change in CO from baseline to peak</td>
<td>28.1 (21.2)</td>
<td>33.2 (25.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>% change in CO from baseline to I</td>
<td>7.58 (13.0)</td>
<td>10.5 (21.6)</td>
<td>0.44</td>
</tr>
<tr>
<td>% change in CO from baseline to II</td>
<td>-0.5 (17.1)</td>
<td>8.1 (21.6)</td>
<td>0.032*</td>
</tr>
<tr>
<td><strong>% change in TPR from baseline to peak</strong></td>
<td>17.1 (-0.6,70.2)</td>
<td>10.1 (1.0,28.5)</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>% change in TPR from baseline to I</strong></td>
<td>-1.2 (-12.2, 7.3)</td>
<td>-13.3 (-22.2, 6.1)</td>
<td>0.0015*</td>
</tr>
<tr>
<td><strong>% change in TPR from baseline to II</strong></td>
<td>-12.8 (-22.5, -4.1)</td>
<td>-21.8 (-29.8, 15.2)</td>
<td>0.0067*</td>
</tr>
</tbody>
</table>
Table 7.2. Analysis of variance of absolute and relative changes in haemodynamic variables at baseline and 1 week of SHU at 18 inches.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Supine</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-pre Mean (SE)</td>
<td>F (df)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>4.08 (0.49)</td>
<td>69.58 (1, 347)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>-0.96 (0.46)</td>
<td>4.45 (1, 347)</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>0.12 (0.79)</td>
<td>0.024 (1, 347)</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>119 (64)</td>
<td>3.47 (1, 347)</td>
</tr>
<tr>
<td>TPR (dynes/s/cm5)</td>
<td>0.0045 (0.023)</td>
<td>0.036 (1, 347)</td>
</tr>
<tr>
<td>Relative percentage change from baseline = ( \frac{\text{post-pre}}{\text{pre}} \times 100% )</td>
<td>Percentage change Mean (SE)</td>
<td>F (df)</td>
</tr>
<tr>
<td>rSV (%)</td>
<td>2.30 (1.06)</td>
<td>4.69 (1, 347)</td>
</tr>
<tr>
<td>rCO (%)</td>
<td>0.64 (1.24)</td>
<td>0.27 (1, 347)</td>
</tr>
<tr>
<td>rTPR (%)</td>
<td>4.49 (1.91)</td>
<td>5.54 (1, 347)</td>
</tr>
</tbody>
</table>
### Table 7.3. Change in non-haemodynamic parameters after SHU for 1 week

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre SHU Mean (s.d.)</th>
<th>Post SHU Mean (s.d.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night urine volume (ml)</td>
<td>622 (359)</td>
<td>477 (236.)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Day urine volume (ml)</td>
<td>1510 (768)</td>
<td>1562 (630)</td>
<td>0.68</td>
</tr>
<tr>
<td>24 hour urine volume (ml)</td>
<td>2133 (973)</td>
<td>2039 (734)</td>
<td>0.56</td>
</tr>
<tr>
<td>Night urinary sodium excretion (mmol)</td>
<td>373.3 (23.3)</td>
<td>382 (25.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Day urinary sodium excretion (mmol)</td>
<td>84.3 (42.5)</td>
<td>102.1 (40.9)</td>
<td>0.085</td>
</tr>
<tr>
<td>24 hour urinary sodium excretion (mmol)</td>
<td>121.6 (54.4)</td>
<td>140.3 (47)</td>
<td>0.098</td>
</tr>
<tr>
<td>Night urinary potassium excretion (mmol)</td>
<td>14.3 (9.4)</td>
<td>13.4 (8.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Day urinary potassium excretion (mmol)</td>
<td>44.6 (18.9)</td>
<td>46.3 (17.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>24 hour urinary potassium excretion (mmol)</td>
<td>58.9 (22.9)</td>
<td>59.8 (22.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Glomerular Filtration Rate (ml/min)</td>
<td>107.7 (24.3)</td>
<td>109.7 (24.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Day SBP (mmHg)</td>
<td>124.4 (12.1)</td>
<td>124.1 (11.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Night SBP (mmHg)</td>
<td>105.3 (8.9)</td>
<td>104.8 (11.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Calf circumference (mm)</td>
<td>371 (39)</td>
<td>373 (38)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Ankle circumference (mm)</td>
<td>255 (22)</td>
<td>263 (26)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>13.6 (1.4)</td>
<td>13.3 (1.5)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pro-ANP (1-98)(fmol/ml)</td>
<td>6583 (4920)</td>
<td>6107 (4141)</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>Median (IQR)</strong></td>
<td><strong>Median (IQR)</strong></td>
<td><strong>P value</strong></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.1 (60.5, 79.8)</td>
<td>66.5 (60.5, 79.8)</td>
<td>0.0048*</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>1.3 (0.77, 1.65)</td>
<td>1.0 (0.87, 2.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>430 (327, 628)</td>
<td>414 (342, 550)</td>
<td>0.84</td>
</tr>
</tbody>
</table>
Fig 7.2. Graph showing systolic blood pressure response following one week of SHU at 18 inches

Systolic Blood Pressure before and after SHU at 18 inches
Fig 7.3. Graph showing heart rate response following one week of SHU at 18 inches

Heart Rate before and after SHU for one week at 18 inches

-100 -50 0 50 100 150
Time (s)

-100 -50 0 50 100 150
Time (s)
Fig 7.4. Graph showing stroke volume response following one week of SHU at 18 inches
Fig 7.5. Graph showing cardiac output response following one week of SHU at 18 inches.
Fig 7.6. Graph showing total peripheral resistance response following one week of SHU at 18 inches.
Fig 7.7. Graph showing relative percentage change of stroke volume from baseline and 1 week post SHU at 18 inches.
Fig 7.8 Graph showing relative percentage change of cardiac output from baseline and 1 week post SHU at 18 inches
Fig 7.9 Graph showing relative percentage change of total peripheral resistance from baseline and 1 week post SHU at 18 inches.

Young controls % change TPR from baseline

Time (s)
Chapter 8: The haemodynamic effects of sleeping head up at 6 inches for one week in older hospital in-patients with orthostatic hypotension

Orthostatic hypotension (OH) is defined as a fall in systolic blood pressure (≥ 20mmHg) or diastolic blood pressure (≥ 10mmHg) within 3 minutes of free standing from a supine position (1996). OH is a common condition affecting one in five adults age 65 and over in the community (Rutan, Hermanson et al. 1992) (Applegate, Davis et al. 1991). The prevalence is higher amongst patients in hospital (Illman, Stiller et al. 2000; Weiss, Grossman et al. 2002) and those attending a syncope clinic (McIntosh, Da Costa et al. 1993). OH can be a transient phenomenon following prolonged-recumbency due to acute illness (Kong and Chuo 2003) or become chronic in patients with Parkinson disease (Allcock, Ullyart et al. 2004) and autonomic failure (Bonuccelli, Lucetti et al. 2003).

The treatment principally acts through increasing extracellular volume, peripheral resistance or venous return. Pharmacological treatments are associated with side effects. Patients treated with drugs such as fludrocortisone (Hussain, McIntosh et al. 1996) and midodrine (Sandroni, Benarroch et al. 2001; Chaimberg and Travis 2002) may experience side effects such as supine hypertension, cardiac failure, depression, oedema and hypokalaemia, which warrant discontinuation of medications (Pathak, Raoul et al. 2005). Non-pharmacological treatment includes compression hosiery (Henry, Rowe et al. 1999; Podoleanu, Maggi et al. 2006), abdominal binders (Smit, Wieling et al. 2004), water-drinking (Mathias 2000; Cariga and Mathias 2001; Shannon, Diedrich et al. 2002), increasing salt intake (Shichiri, Tanaka et al. 2002; Claydon and Hainsworth 2004), physical counter-manoeuvres (van Lieshout, ten Harkel et al. 1992; Krediet, van Dijk et al. 2002) and sleeping with the head of the bed elevated (Brignole, Alboni et al. 2004).

There have been a few reports showing that sleeping with the head of the bed tilted upwards (SHU) greater than 12 degrees (18 inch elevation) is associated with an increased orthostatic tolerance the next morning in middle-aged patients with autonomic failure. The improvement in symptoms is postulated to be due to a reduction in over night diuresis and natriuresis as a result of a reduction in venous return due to sleeping with the heart higher than the legs (Bannister, Ardill et al. 1969) or fluid shifts with an increase in extra-cellular fluid (Omboni, Smit et al. 2001; Wieling, Van Lieshout et al. 2002). Early observations were predominantly case reports (MacLean and Allen 1940) (Corcoran, Browning et al. 1943) and were conducted in subjects age 66 and under (age range 23-66years) with autonomic failure.
Recent studies have tended to support these observations (Ten Harkel, Van Lieshout et al. 1992) (van Lieshout, ten Harkel et al. 2000) although sample sizes were very small (less than 10 subjects) and in most cases interventions such as water and salt loading and/or medications were also being used. It is still not clear whether sleeping head up has any additive benefits to existing treatments.

While steeper angles are likely to have a greater physiological effect this has to be balanced by an angle that the patient can tolerate. There is ambiguity in the literature regarding the angle of SHU (Fan, Coakley et al. 2006), its use in patients with OH without autonomic dysfunction and in patients aged over 65 years. A recent survey (Fan, Coakley et al. 2006) amongst clinicians attending an international syncope conference found that most clinicians who used SHU therapy prescribed much smaller angles (median 6.5 degrees) than those recommended by standard guidelines (Brignole, Alboni et al. 2004) (Oldenburg, Kribben et al. 2002) (Bradley and Davis 2003). The majority of respondents were physicians for older people suggesting that older patients are frequently given this treatment.

The aim of our study was to determine the initial (within 1 week) physiological and clinical effects of SHU at 5 degrees of elevation in hospital in-patients who were symptomatic with OH.

**Methods**

Nine consecutive patients with persistent symptomatic OH of at least 2 weeks duration were recruited from the geriatric wards of a major teaching hospital. All patients were undergoing in-patient rehabilitation after an acute illness and all were referred to the authors’ OH service because of the development of severe symptomatic OH that limited their rehabilitation progress. Details of subjects are shown in table 8.1 and median length of stay at the time of referral was 47 days and a mean systolic BP (SBP) drop on standing of 68 (27.8) mmHg and the nadir SBP of 94 (19.2) mmHg. The inclusion criteria were: no acute illness within preceding week, no change in medications in the previous 7 days prior to start of study, symptoms of dizziness on postural change for the past week, drop in systolic BP of at least 20mmHg and/or diastolic BP of at least 10mmHg within 3 minutes of free standing from a supine position (AAN (1996) definition of OH), able to stand with or without help. Subjects were excluded if they were on patients on diuretics, NSAID for 4 weeks before enrolment, unable to stand even with help, medically unstable such that the likelihood of medications
change deemed to be likely during the study period, unable to describe symptoms of dizziness due to severe cognitive impairment (MMSE <18/30).

The head of the bed was elevated 6 inches from the horizontal for one week (at night and at nap-time). A pillow was placed under the buttocks to minimise slipping to the bottom of the bed and each bed had a footplate at the end. A call button was given to each patient and he/she were supervised in getting in and out of the SHU bed during the study period. The subjects underwent measurements over two 24-hour periods on days 1 (i.e. before starting SHU) and 8 (i.e. after 7 days of SHU).

On the first day of each time point, blood was drawn for hematocrit (Sysmex XE-2100 automated haematology analyser (Sysmex Corp. Kobe, Japan) (Walters and Garrity 2003)), supine plasma renin activity (PRA) (Renin MAIA, Adaltis, Italy), serum electrolytes (Roche/Hitachi Modular System) and aldosterone (Aldosterone MAIA, Adaltis, Italy) before they were out of bed. They wore an ambulatory blood pressure monitor (AND, TM-2430 (Palatini, Frigo et al. 1998)) for 24 hours. Daytime was defined as 0700 hr to 2300 hr. On the second day the patients underwent phasic beat-to-beat blood pressure recording (Finometer \textsuperscript{TM}, volume-clamped method) (Bogert and van Lieshout 2005) during 5-minute supine rest and 2-minutes of standing (Mathias and Bannister 2002). All active stands were conducted between 0900 to 1100hrs and patients were weighed just before conducting active stands. All subjects stood up or were helped to standing from supine position within 5 seconds. Basic characteristics, weights before and after SHU, systolic blood pressure (SBP), heart rate (HR), Modeflow parameters (Bogert and van Lieshout 2005) of stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were recorded during supine rest and standing. After SHU, the patients were asked if they felt better and also how tolerable SHU at 6 inches was. The study was approved by the local hospital research ethics committee.

Data analysis

The Finometer recordings (SBP, HR, SV, CO and TPR) were exported in 1-second bin from 60s before to 120s after standing and then averaged at 10-second intervals to reduce beat-to-beat variability in the haemodynamic parameters. Modeflow is a model-based method and algorithm used to compute the aortic flow waveform from an arterial blood pressure pulsation by simulating a nonlinear, self-adaptive (three-element Windkessel) model of the aortic input impedance and is modelled in accordance with the subject's gender, age height
and weight (Voogel and van Montfrans 1997; Bogert and van Lieshout 2005). Since there was no change in the factors for calculating aortic input impedance in the patients in the week of SHU, we compared the absolute change of before and after derived values (Harms, Wesseling et al. 1999). We also ensured as much as possible the placement of the finger cuff was applied in the same manner on the two occasions of active stand to minimise difference in finger waveform. We also carried out the analysis of the Modelflow parameters in relative as well as absolute values. The values of rSV, rCO and rTPR were derived from (post-pre values)/pre values*100%.

Nadir SBP was defined as the lowest point of SBP over two minutes of free standing.

All results were expressed as mean (standard deviation) and mean (SE) unless stated otherwise.

**Statistical analysis**

The sample size was calculated with alpha of 0.05 and power of 80%. In order to show a change in nadir MAP of 20 mmHg or greater, we need a total sample size of 9.

Paired t-tests were used to compare non haemodynamic variables before and after SHU. Haemodynamic variables were analysed separately for recumbent (-60 to 0 seconds) and standing phases (0 to 120 seconds). Haemodynamic variables were investigated in a series of analysis of variance models with factors representing condition (before or after SHU), time point (there were six ten second time points [i.e. -60 to -10] for the recumbent phase and 12 time points for the standing phase [i.e. 0 to 110]) and subject. Individual effects on SBP were compared by looking at the lowest SBP within 120 seconds of standing (nadir BP) in each case. Statistical significance was set at p<0.05. Datadesk statistical software was used (version 8 Ithaca, NY).
Results

Nine patients (5 women) with a mean (s.d.) age of 76 (5) years underwent SHU. The summary of the description of the participants is shown in table 8.1.

Recumbent phase

There were significant changes in most haemodynamic variables after one week of SHU (see table 8.2). SBP and TPR were significantly lower, SV and CO were greater and heart rate was unchanged. Using percentage relative change from baseline values, rSV and rCO increased but rTPR remain unchanged.

Standing phase

There were significant changes in all haemodynamic variables after one week of SHU (see table 2). SBP, SV and CO were significantly higher and HR and TPR were lower. Similarly rSV and rCO showed a significant increase but there were no differences in rTPR after one week of SHU.

See figures 8.1 to 8.10 for a graphical plot of the haemodynamic variables including relative change of SV, CO and TPR. Subjects were a mean of 0.7kg heavier though due to the small sample size this was not significant. Mean serum creatinine was reduced by 5.4mmol/L. There were no differences in haemoglobin, haematocrit, urea or 24 hours ambulatory blood pressure (overall, day or night means). See table 8.3.

All patients tolerated sleeping head up. Six of the nine patients reported improvement in symptoms. Seven of the nine patients showed an increase in nadir SBP after treatment and five of the nine patients demonstrated both symptomatic and haemodynamic improvement and these five became independently mobile after one-week SHU whereas previously they were unable to walk due to OH.
Discussion

This study represents the first observational study of sleeping head up in older patients. The angle used is also much lower than that previously investigated and in line with the angle commonly prescribed in practice for older people (Fan, Coakley et al. 2006). The main findings are consistent with significant haemodynamic changes and better orthostatic tolerance after sleeping head up at 6 inches for one week.

In the recumbent phase there were significant increases in SV and CO. Similarly there were pronounced increases in standing SBP, SV and CO and reductions in standing HR. These are all in keeping with an increase in intravascular volume (Frey, Lathers et al. 1994; Routledge, Chowdhary et al. 2002), which is further supported by the drop in serum creatinine and mean weight gain (albeit the latter was not significant). Interestingly, the effects on standing DBP and MAP were much less pronounced than SBP though the reasons for this are unclear. The results for the Modelflow derived variables were similar for SV and CO whether absolute or relative changes were used. Relative changes for TPR were not significant however suggesting that absolute changes are not accurate for this variable even when testing the same individuals over time.

Two thirds of the patients reported improvement in orthostatic symptoms and there was an associated dramatic improvement in mobility after one week of SHU in 5 patients.

Although SHU at 18 inches (12 degrees) has been shown to be effective in patients with syncope due to orthostatic hypotension, previous research has focused on younger patients with autonomic failure (the oldest of whom was 66 years) (MacLean and Allen 1940; Corcoran, Browning et al. 1943; Bannister, Ardill et al. 1969; Ten Harkel, Van Lieshout et al. 1992; Kardos, Avramov et al. 1996; van Lieshout, ten Harkel et al. 2000) and improvement was usually seen with 3 days (MacLean and Allen 1940; Bannister, Ardill et al. 1969). Many of these younger subjects complained of sliding to the bottom of the bed and also stiff legs from leg oedema. This degree of elevation is unlikely to be tolerated by older frailer patients and prescription of smaller degrees of elevation (commonly 5 degrees or 6 inches) is commonly used in the clinical settings amongst geriatricians in Ireland and the United Kingdom (Fan, Coakley et al. 2006).
SHU at 6 inches presents a reasonable therapeutic option for frail older persons with OH with the important caveat that it is shown to be effective and safe. While our study does not do this it does establish that this degree of elevation for 7 days was associated with beneficial changes in both symptoms and haemodynamic variables in older in-patients and was tolerated within that setting.

Current pharmacological treatments for OH are poorly tolerated (Hussain, McIntosh et al. 1996; Sandroni, Benarroch et al. 2001) and non-pharmacological treatments are only beginning to be tested (Henry, Rowe et al. 1999; Podoleanu, Maggi et al. 2006). One reassuring observation is that SHU did not result in higher resting blood pressure, which can be a potential side effects of other anti-hypotension therapy.

Our study has several limitations. The uncontrolled design means that changes cannot be unequivocally be attributed to the effects of SHU and the possibility that some of the observed changes were due to other factors must be considered but the fact that patients had been in hospital for a median of 47 days before trying SHU and a majority improved dramatically with a week of treatment suggests a causative association. We did not use a formal questionnaire for symptom improvement though the study would not have been powered for subtle changes. We did not control for fluid intake in these subjects but dehydration was clinically addressed in these patients before commencement of study as part of their treatment. We did not measure salt intake over the period of observation. The study was not powered to investigate changes in non-haemodynamic variables so it is difficult to comment on mechanisms of action.

Although we have looked at the acute haemodynamic changes of SHU in one week, we do not know if the effects are sustained. We also do not know if patients adhere to SHU after they are discharged from hospital. Nevertheless our patients slept head up for the remainder of their hospital stay afterwards. Therefore, a randomised controlled study of SHU at 6 inches is required to examine the longer-term efficacy and compliance outside the hospital settings to address the above limitations.

In conclusion, sleeping head up for one week at 6 inches was well tolerated by older in-patients with OH, associated with improved orthostatic tolerance, and with haemodynamic changes in keeping with increased intravascular volume. SHU at 6 inches has a role in the
acute treatment of OH for patients in hospital but its longer-term effects and in the out-
patient setting require further study.
Fig 8.1. Systolic Blood pressure during active standing before and after one week of sleeping head up at 6 inches.
Fig 5.2. Diastolic blood pressure during active standing before and after one week of sleeping head up at 6 inches.
Fig 8.3. Mean arterial pressure during active standing before and after one week of sleeping head up at 6 inches.

Mean Arterial response of inpatients after one week of SHU at 6 inches
Fig 8.4. Heart Rate during active standing before and after one week of sleeping head up at 6 inches.

Heart rate response of inpatient before and after one week of SHU at 6 inches

Time
Fig 8.5. Left ventricular stroke volume (Modelflow parameter) during active standing before and after one week of sleeping head up at 6 inches.

Stroke volume response of inpatient before and after one week SHU at 6 inches
Fig 8.6. Cardiac Output (Modelflow parameter) during active standing before and after one week of sleeping head up at 6 inches.
Fig 8.7. Total Peripheral Resistance (Modelflow parameter) during active standing before and after one week of sleeping head up at 6 inches.
Fig 8.8. Relative percentage change in stroke volume after one week of SHU at 6 inches
Fig 8.9. Relative percentage change in cardiac output after one week of SHU at 6 inches
Fig 8.10. Relative percentage change in total peripheral resistance after one week of SHU at 6 inches
<table>
<thead>
<tr>
<th>Age/Sex</th>
<th>Past Medical History</th>
<th>BMI (kg/m²)</th>
<th>ΔSBP (mmHg)</th>
<th>Nadir SBP (mmHg)</th>
<th>Treatment for OH before SHU</th>
<th>Delay* (days)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>72F</td>
<td>OH, PD, recurrent falls, Type 2 DM</td>
<td>23.6</td>
<td>88.7</td>
<td>82.3</td>
<td>Compression hosiery, stop β-blocker</td>
<td>47</td>
<td>No longer dizzy on standing after SHU</td>
</tr>
<tr>
<td>80M</td>
<td>Type 2 DM, nephrotic syndrome (4.4g/24 hr urinary protein) and polyuria, recurrent</td>
<td>20.0</td>
<td>80.3</td>
<td>115.9</td>
<td>Stop all antihypertensive medications.</td>
<td>22</td>
<td>Nocturnal polyuria resolved, syncopal events stopped after SHU</td>
</tr>
<tr>
<td></td>
<td>syncope for 1 year due to OH, Autonomic Dysfunction</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80M</td>
<td>PD, OH, Supine hypertension, falls and syncope, Autonomic Dysfunction</td>
<td>22.9</td>
<td>114.3</td>
<td>96.3</td>
<td>Compression hosiery, florinef, midodrine</td>
<td>39</td>
<td>Not much improvement</td>
</tr>
<tr>
<td>80F</td>
<td>OH for 3 years, pulmonary fibrosis, DM</td>
<td>26.7</td>
<td>62.8</td>
<td>104.6</td>
<td>Compression hosiery, hydration</td>
<td>153</td>
<td>No further dizziness after SHU</td>
</tr>
<tr>
<td>66F</td>
<td>OH and spinal stenosis</td>
<td>29.0</td>
<td>37.2</td>
<td>64.7</td>
<td>hydration</td>
<td>50</td>
<td>No difference in symptoms</td>
</tr>
<tr>
<td>79M</td>
<td>PD, IHD, OH, left knee osteoarthritis</td>
<td>29.3</td>
<td>53.1</td>
<td>105.8</td>
<td>Hydration, compression hosiery</td>
<td>85</td>
<td>Immobile before with dizziness, was able to walk 6 m without help afterwards</td>
</tr>
<tr>
<td>78M</td>
<td>Long standing OH, sepsis, IHD</td>
<td>28.7</td>
<td>81.5</td>
<td>73.7</td>
<td>Hydration, compression hosiery</td>
<td>173</td>
<td>Unable to stand for 30s due to dizziness, after SHU able to walk for 6 m without weakness</td>
</tr>
<tr>
<td>76F</td>
<td>Osteoporosis, fell, dizziness, OH</td>
<td>22.1</td>
<td>22.6</td>
<td>121.1</td>
<td>Hydration</td>
<td>22</td>
<td>Slight improvement of dizziness after</td>
</tr>
<tr>
<td>85F</td>
<td>Fell, OH, colles fracture</td>
<td>22.3</td>
<td>72.9</td>
<td>84.4</td>
<td>Hydration, compression hosiery</td>
<td>25</td>
<td>Steady on feet, less dizzy after</td>
</tr>
</tbody>
</table>

* Delay denotes time between admission to hospital and commencement on SHU6
Abbreviation used in table: OH=Orthostatic hypotension, PD=Parkinsons Disease, DM=Diabetes Mellitus, IHD=Ischaemic heart disease, ΔSBP=Mean supine systolic blood pressure – nadir systolic blood pressure

Mean SBP nadir 94 (19.2)mmHg, ΔSBP pre 68 (27.8) mmHg

Autonomic dysfunction if increase in HR from supine to standing is less than 12 bpm(Lipsitz 1989)
Table 8.2. Analysis of variance of haemodynamic responses of SBP, HR, SV, CO and TPR during the resting and standing phase.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Supine</th>
<th>Standing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Post-Pre Mean (SE)</td>
<td>F (df)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-11.82 (3.63)</td>
<td>10.6 (1, 107)</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>-9.04 (1.95)</td>
<td>21.46 (1, 107)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>-10.08 (2.71)</td>
<td>13.87 (1, 107)</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>-1.6 (1.44)</td>
<td>1.23 (1, 107)</td>
</tr>
<tr>
<td>Modelflow SV (ml)</td>
<td>12.01 (2.28)</td>
<td>27.8 (1, 107)</td>
</tr>
<tr>
<td>Modelflow CO (l/min)</td>
<td>1.06 (0.21)</td>
<td>26.9 (1, 107)</td>
</tr>
<tr>
<td>Modelflow TPR (dynes/s/cm²)</td>
<td>-0.367 (0.12)</td>
<td>9.82 (1, 107)</td>
</tr>
<tr>
<td>Relative change (post-pre)/pre*100%</td>
<td>% Change from baseline Mean (SE)</td>
<td>F (df)</td>
</tr>
<tr>
<td>Modelflow rSV (%)</td>
<td>26.81 (4.49)</td>
<td>35.70 (1, 107)</td>
</tr>
<tr>
<td>Modelflow rCO (%)</td>
<td>26.77 (4.83)</td>
<td>30.70 (1, 107)</td>
</tr>
<tr>
<td>Modelflow rTPR (%)</td>
<td>-3.48 (7.74)</td>
<td>0.20 (1, 107)</td>
</tr>
</tbody>
</table>
Table 8.3. Non-haemodynamic parameters

<table>
<thead>
<tr>
<th>Variables</th>
<th>Pre mean (s.d.)</th>
<th>Post mean (s.d.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>70.0 (11.4)</td>
<td>70.7 (12.1)</td>
<td>0.65</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.5 (1.6)</td>
<td>11.5 (1.8)</td>
<td>0.89</td>
</tr>
<tr>
<td>Hct</td>
<td>0.357 (0.05)</td>
<td>0.361 (0.06)</td>
<td>0.51</td>
</tr>
<tr>
<td>Urea (mmol/l)</td>
<td>6.6 (1.7)</td>
<td>5.9 (1.5)</td>
<td>0.20</td>
</tr>
<tr>
<td>Creatinine (mmol/l)</td>
<td>101.0 (26.7)</td>
<td>95.6 (22.2)</td>
<td>≤ 0.0001</td>
</tr>
<tr>
<td>24 hour mean SBP</td>
<td>146 (16.0)</td>
<td>149 (19.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>24 hour mean DBP</td>
<td>80 (7.9)</td>
<td>83 (8.8)</td>
<td>0.21</td>
</tr>
<tr>
<td>Day mean SBP</td>
<td>149 (19.0)</td>
<td>150 (25.5)</td>
<td>0.90</td>
</tr>
<tr>
<td>Day mean DBP</td>
<td>82 (8.6)</td>
<td>84 (12.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>Night mean SBP</td>
<td>145 (19.6)</td>
<td>154 (22.6)</td>
<td>0.16</td>
</tr>
<tr>
<td>Night mean DBP</td>
<td>78 (11.5)</td>
<td>81 (9.5)</td>
<td>0.32</td>
</tr>
<tr>
<td>PRA</td>
<td>0.2 (0.8)</td>
<td>0.2 (0.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>220.7 (221.3)</td>
<td>250.9 (345.2)</td>
<td>0.46</td>
</tr>
</tbody>
</table>
Chapter 9: The effect of sleeping with the head of the bed elevated six inches on elderly patients with orthostatic hypotension: an open randomised controlled trial.

Introduction
Orthostatic hypotension (OH) is defined as a fall in systolic (≥20mmHg) and/ or diastolic (≥10mmHg) blood pressure on assuming an upright position from supine position (1996). Its prevalence is up to 22% in community dwelling elderly (MacLennan, Hall et al. 1980) and it is associated with significant morbidity (Ooi, Hossain et al. 2000) and mortality (Masaki, Schatz et al. 1998). Treatment of OH is problematic as existing treatments such as salt replacement and medications may lead to hyperension and tend to be poorly tolerated in the elderly (Hussain, McIntosh et al. 1996). Drinking extra fluids may be effective in younger patients (Jordan, Shannon et al. 2000) but its use in older patients is less clear.

A few researchers have found that sleeping with the head of the bed elevated (SHU) greater than 12 degrees is associated with an increased orthostatic tolerance. The mechanism is thought to be activation of the renin-angiotensin pathway (Mathias and Bannister 2002) with improvement in symptoms due to plasma expansion from a reduction in overnight naturesis (Bannister, Ardill et al. 1969). Sample sizes were very small (less than 10 subjects) and in most cases interventions such as water and salt bading and/ or medications were also being used so it is still not clear whether sleeping head up has any additive benefit to existing treatments. However, SHU at 13 degrees (18 inches) was associated with patients slipping off or down to the end of beds and is unlikely to be tolerated by older patients. In practice, many clinicians advocate sleeping with the head of the bed elevated at 6 inches (5 degrees). In a previous study sleeping head up at 6 inches at one week in older in-patients with OH was associated with significant haemodynamic changes consistent with an increase in intravascular volume (Chapter 7). However the sample size was small (n=9), the period of follow-up short and the intervention uncontrolled so both the efficacy and generalisability of this treatment remain uncertain.

The aim of the study was to determine the physiological effect of sleeping head up 6 inches on orthostatic tolerance for six weeks in a large group of patients age 60 and over who had chronic orthostatic hypotension in an open randomised controlled trial.

Methods
One hundred consecutive patients, aged 60 and over, who attended the falls and blackout clinic from 8/2/2005 to 24/1/2007 with symptomatic OH according to consensus criteria (1996) were recruited to the study. Participants were excluded if the duration of their symptoms was less than 1 month, if they were in a hospital ward, had chronic renal failure (calculated GFR (Cockcroft and Gault 1976) of < 30ml/min ) or congestive cardiac failure (NYHA class 3 or greater (1964)) or significant urinary incontinence such that 24-hour urine measurement would be unreliable. These patients had received medication optimisation, i.e reduction or discontinuation of medications which lowered blood pressure (such as diuretics, nitrates, or anti-hypertensives) for at least a month before enrolment into the study. Patients were advised to remain on the same medications during the 6-week study period. The subjects were randomised into SHU or control at a ratio of 2 to 1 using minimisation (for factors age, gender and baseline nadir MAP) with weighted randomisation. The ratio of 2 to 1 was decided based on our previous clinical experience of 50% compliance with SHU (Fan, Coakley et al. 2005) so as to maximise study of its tolerability.
Protocol

All participants were asked to increase their water intake to at least 2 litres a day for the duration of the study. In addition subjects randomised into the SHU group were given two 6 inch customised blocks to be placed under the head of the bed as shown in fig 9.1. They were advised to sleep in the bed for naps and at night. As far as possible the participants were advised to remain on the same medications. However any changes in medications were noted.

The patients were assessed at two time points; immediately before (Day 1-2) and after (Day 42-43) sleeping head up. During each time point, the participants wore ambulatory blood pressure monitors (ABPM) for 24 hours, performed a 24-hour urine sample for volume and urinary sodium, completed a structured questionnaire and underwent an active stand between 0900 and 1100 hr. The hemodynamic parameters during the active stand were measured using phasic beat-to-beat blood pressure recording (Finometer™, volume-clamped method) (Bogert and van Lieshout 2005) during 5-minute supine rest and 2-minute of standing (Mathias and Bannister 2002). All participants stood up or were helped to standing from supine position within 5 seconds. Participants were classified as SHU compliant if they self-reported compliance and their beds were raised with blocks at the end of the 6-week study period during a home visit by the researcher. Participants were classified as water compliant if they reported drinking 2 litres or more of water per day. At the second visit, the patients were asked if their symptoms had improved and the SHU group were questioned about its tolerability. The study was approved by hospital research ethics committee.

Data analysis

The Finometer recordings (SBP, HR, SV, CO and TPR) were exported in 1-second bin from 60s before to 120s after standing and then averaged at 10-second intervals to reduce beat-to-beat variability in the haemodynamic parameters. Modelflow is a model-based method and algorithm used to compute the aortic flow waveform from an arterial blood pressure pulsation by simulating a nonlinear, self-adaptive (three-element Windkessel) model of the aortic input impedance and is modelled in accordance with the subject’s gender, age, height and weight (Voogel and van Montfrans 1997; Bogert and van Lieshout 2005). Since there was no change in the factors for calculating aortic input impedance in the patients in the week of SHU, we compared the absolute change of before and after derived values (Harms, Wesseling et al. 1999). We also ensured as much as possible the placement of the finger cuff was applied in the same manner on the two occasions of active stand to minimise difference in finger waveform. We also carried out the analysis of the Modelflow parameters in relative as well as absolute values. The values of rSV, rCO and rTPR were derived from (post-pre values)/pre values*100%.

Nadir SBP was defined as the lowest point of SBP over two minutes of free standing.

Statistical Analysis

In order to establish a clinically meaningful difference we carried out a pilot study on elderly patients referred to our clinic with and without OH. Based on this pilot study (carried out on 81 elderly individuals) we found the mean (standard deviation) difference in nadir MAP between patients with OH and controls was 18.8 (22.0) mmHg.

The sample size was calculated with alpha of 0.05 and power of 80% in order to show a change in MAP of 15 mmHg or greater we need a total sample size of 66 (33 per group). In order to allow for patient drop out of up to 50% in the intervention group (based on our experience in the clinic) we
aimed to recruit twice as many cases as controls. Total sample size therefore was set at 99 (66 cases and 33 controls).

Design was by minimisation (for factors age, gender and baseline nadir MAP) with weighted randomization. Analysis was on an intention to treat basis with last observation carried forward. As initial analysis of MAP in the time domain did not show any particular time latency period (including time of nadir BP) being more affected by SHU it was decided to analyse the entire 180 second period so as to maximize power. As supine and standing periods were considered physiologically distinct it was decided to analyse them separately.

Analysis was conducted by a repeated measures analysis of variance with MAP as the dependent variable. Subject, condition (visit 1 or 2), intervention group (SHU or control), time point during the active stand (-60 to -10 seconds for supine period and 0 to 120 seconds for standing period) and the condition x intervention interaction terms were the independent variables. Other hemodynamic parameters (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), Modeflow parameters (Bogert and van Lieshout 2005) of stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR)) were also studied as the dependent variable in models otherwise identical to above. Symptoms, self-reported compliance with water drinking and sleeping head up were also recorded.

Planned post-hoc analyses were performed in two subgroups in order to investigate any modifying effects on SHU by hydration status or autonomic failure. Autonomic failure was defined as failure to increase heart rate during both active stands by 12 bpm in the first 15s (ΔHR max<12 bpm and ΔHRmax ≥12) as per Wieling et al (Wieling and Karemaker 2002). Hydration status was categorised by 24-hr urinary volume out put ≥ or < 1.5L at visit 2. The groups were sub-divided according to these criteria and the analyses repeated in an identical manner to the full sample.

All results were expressed as mean (standard deviation) and mean (SE) unless stated otherwise. Datadesk statistical software was used (version 8 Ithaca, NY). Paired t-test, Wilcoxon Signed rank test and ANOVA were used to compare continuous results while Chi-squared test was used to compare categorical results before and after SHU. Statistical significance was set at p<0.05.

Statistical advice was supplied by Dr. Cathal Walsh of the Department of Statistics Trinity College Dublin.
Results

Ninety-two participants completed the 6-week study. The flow diagram of the patient allocation in the randomised controlled trial is shown in figure 9.2. The basic characteristics of the SHU and controls were similar in sex, age, initial nadir MAP, symptom of dizziness per week and dizziness during initial active stands (see table 1)

Haemodynamic parameters

There were significant increases in blood pressure in both groups over time (see table 9.2 and figures 9.3 and 9.4). There were no differences in ΔSBP, ΔDBP between SHU and controls (see table 3). There was a greater increase in supine and standing heart rate over time for the SHU group compared to controls of 2.7 bpm and 2.1 bpm respectively. The SHU group also had greater increases over time in supine cardiac output (by 367 ml/min, p=0.012) and standing stroke volume (3.73 ml, p=0.016) compared with controls. See table 9.3. Figures 9.5 to 9.16 show the plots of haemodynamic responses at baseline and 6 weeks between SHU and controls. Figures 9.17 to 9.19 show the relative percentage change in SV, CO and TPR of SHU and controls.

Planned sub-group analyses

Table 9.4 Table showing the participants in SHU and controls hydration status (24 urinary output less than or greater or equal to 1.5 litres).

<table>
<thead>
<tr>
<th></th>
<th>SHU</th>
<th>Controls</th>
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<tbody>
<tr>
<td>Urinary output &lt;1.5L/day</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>Urinary output &gt;1.5L/day</td>
<td>21</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>29</td>
</tr>
</tbody>
</table>

Post hoc analyses of haemodynamic parameters showed that there were no statistical differences between SHU and controls in participants who were dehydrated (Urinary output <1.5L/day). However in participants who were well hydrated (Urinary output ≥1.5L/day) standing SBP and MAP were higher in controls than SHU by 7.46 mmHg and 5.19 mmHg respectively. In participants who were well hydrated, the SHU group had a more pronounced increase in supine and standing HR (Δsupine HR: 3.78 bpm, p= 0.0001, Δstanding HR: 1.84 bpm, p=0.035,) and SV (Δsupine SV: 11.16ml, p=0.0004, Δ standing SV: 6.17ml, p=0.0052). Compared with controls, SHU also showed higher supine CO (733ml/min, p=0.0007) and lower standing TPR (0.143dynes/s/cm5, p=0.0011). See tables 9.6 and 9.6a

Table 9.5 Table showing the participants in SHU and controls with age appropriate initial heart rate response to orthostasis of less than or greater than or equal to 12 bpm (ΔHR max < or >12bpm)

<table>
<thead>
<tr>
<th></th>
<th>SHU</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHRmax &lt;12</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>ΔHRmax ≥12</td>
<td>44</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>66</td>
<td>34</td>
</tr>
</tbody>
</table>

There were no statistical differences in SBP, DBP and MAP between participants with or without appropriate heart rate rise during active stand. In participants with autonomic dysfunction there were
greater increases in supine HR (6.59 bpm, F ratio (d.f.) =33.81 (1,347), p <0.0001), SV (5.09 ml, F ratio (d.f.)=7.60 (1,347) p=0.0062 ) and CO (796 ml/min, Fratio (d.f.)=7.50 (1,347), p=0.0065) with SHU than controls. In intact autonomic function group, supine and standing HR were higher in SHU than controls (supine by 0.7 bpm, p=0.022; standing by 2.2 bpm, p=0.0017). The increase in standing SV and fall in standing TPR were more pronounced in SHU than controls (SV: 4.8 ml, F ratio, (df) =5.99 (1,1703)p=0.015, CO: 350 ml/min F ratio (df) =6.77 (1,1703), p=0.0093, TPR: 0.165 dynes/cm^5, F ratio (df)= 7.22(1,1703), p=0.0073). See tables 9.6 and 9.6b.

**Dizziness and Oedema**

Both SHU and controls reported overall improvement and had fewer episodes of dizziness per week after interventions. Similar proportion of both groups (SHU vs. Controls - 69% vs. 58%, p=0.35) reported overall improvement in symptoms. SHU group had significantly more oedema than controls (41% vs 19%, p=0.038) although there was no difference in weight (see tables 9.7 and 9.7a). SHU group were 2.89 times more likely to experience oedema than controls (OR=2.89, 95% CI 1.03 to 8.08). However, the symptom improvement was more marked in the SHU group as there were fewer participants in the SHU groups complaining of 2 or more episodes of dizziness per week (30% vs. 52%, p=0.038). See Tables 9.8

**24-hour ambulatory blood pressure**

Ninety-one participants had a 24hr ABPM measurement performed before interventions, 21 (23%) of them had overall higher night-time than mean day time blood pressures. There was no difference in blood pressure trends after 6 weeks interventions in SHU or controls. See table 9.9.

**Compliance with Sleeping Head up and drinking water**

**Sleeping head up**

Of the 61 who completed the study in the SHU group, the compliance rate was 77% (47/61). Twelve did not sleep head up. See table 10 for side effects of SHU.

**Compliance for water**

The self reported compliance and urine analysis revealed interesting results. Forty-five (49%) of participants reported compliance with drinking 2 litres of water a day. Twenty four-hour urine collection gave an indication of how much the person had been drinking on the last day of the study provided that all the urine was placed into the container and the participants had no excessive fluid loss or acute renal impairment. If water compliance was defined as 24-hr urinary output at 6 weeks of 1.5L or greater, participants in the SHU group were more water compliant than controls (64% vs. 41%, p=0.047). There was moderate agreement between self-reported water compliance and 24-hr urinary volume at 6 weeks greater or equal to 1.5L (κ=0.48, C.I. 0.29, 0.67) (Table 9.10). Table 9.11 illustrates the difference in urinary output in participants who reported water compliance and non-compliance. The mean 24-hr urinary output at 6 weeks was higher in SHU than controls (1914 ml vs. 1431 ml, p=0.013). See table 9.12. Of the 47 participants who reported non-compliance with water drinking, the most common reasons cited were dislike of water drinking, urinary frequency from water drinking and feeling bloated when drinking water. Many could only manage 750 ml to 1 litre a day. One participant had to stop drinking water 2 litres of water because her frequency stopped her from walking her dog. Table 9.13 summarised the reported side effects of drinking water.
Urine volume

Of the 92 participants who completed the study, 82 (89%) of the participants had urine samples before and after the 6-week intervention period. There was no significant increase in urinary output between baseline and at 6 week for either group (table 9.12). Forty (49.4%) had at least 1.5 L/day of urinary output at visit 1 and 47 (58%) had at least 1.5L/day of urinary output at 6 weeks. However there was no statistical difference in the proportions, p=0.27. Self reported water compliance was only in moderate agreement with urinary output ≥ 1.5L/day (κ= 0.485 (C.I. 0.294, 0.675). Table 9.11 showed the urinary volume of participants who self-report they were and were not compliant with water drinking and shows a significant greater urinary output in those who reported compliance.

Drop outs

SHU
One lady was too frail to attend and to sleep head up, another lady developed unstable angina for reasons considered unrelated to the intervention. The reason for dropping out was not clear in one man and one woman. One woman developed inferior myocardial infarction before intervention.

Control
One man was unable to attend. Another man had a chest infection and was hospitalised. One man developed haematuria (subsequently diagnosed with bladder cancer) and did not attend further.
Discussion
This is the first randomised controlled trial to test the effectiveness of sleeping with the head of the bed elevated at 6 inches as a treatment for orthostatic hypotension in subjects aged 60 years and over. The result of the study showed that SHU at 6 inches (SHU6) had no clinical benefit on blood pressure or symptoms in the treatment of OH compared with controls.

A majority of both groups reported improvement in symptoms and in blood pressure parameters at the second active stand. As drinking extra water was part of the intervention in both limbs of the RCT, we might postulate that the overall improvement in symptoms was attributable to an effect of increased water intake. However, the mean increase in urinary volume between baseline and 6 weeks in SHU and controls was non-significant at 87ml and 112 ml respectively suggesting that significant increases in water intake were unlikely. The symptomatic improvement may have been due to better use of physical counter manoeuvres (all clinic patients are advised about these at their first visit) or due to a placebo response therefore.

The failure of a group of older individuals to significantly increase their water intake during a monitored clinical trial suggests that water drinking as a primary treatment is unlikely to be a widely tolerated or effective treatment for most older patients with OH despite promising evidence of its effectiveness in younger subjects (Jordan, Shannon et al. 2000; Schroeder, Bush et al. 2002; Shannon, Diedrich et al. 2002; Claydon, Schroeder et al. 2006). It is noteworthy that compliance with water was less than with SHU. There was only moderate agreement between stated compliance with water intake and urine output suggesting that the latter should be used in future research studies though direct questioning may be sufficient for clinical practice.

The improvement in orthostatic tolerance during the repeat active stand may also have been due to physical counter manoeuvres, a placebo effect or to the effects of repeated testing (i.e. subjects who have previously being exposed to an active stand may have less significant haemodynamic changes on repeated testing). Given the apparent change in measured blood pressure haemodynamics over time (for whatever reason) it is important that future trials of interventions in OH should be controlled.

An interesting finding in this study was that subjects in the SHU group had significantly higher supine and standing heart rates after 6 weeks of therapy. The reasons for these heart rate responses to SHU are unclear but suggest activation of the sympathetic nervous system.

Even though SHU6 had no blood pressure effects, there were significant effects on other haemodynamic parameters such as stroke volume and cardiac output. SHU6 attenuated the fall in stroke volume and cardiac output with standing especially in well-hydrated patients. The stroke volume and cardiac output attenuation effect was more pronounced in the supine phase in autonomic dysfunction patients and the standing phase of the autonomic intact patients. The clinical significance of these findings is unclear but may be worthy of further study.

From our study, SHU6 was a relatively safe though uncomfortable intervention. The main side effects were leg oedema and sliding down the bed. SHU6 were almost 3 times more likely to develop leg oedema compared with controls.

There were a number of limitations to this trial. We tested SHU in individuals aged 60 years and over and can’t comment of the effectiveness of this intervention in younger individuals. We tested SHU at 6 inches and cannot exclude the possibility of an effect at greater degrees of elevation. However we
have previously shown that SHU6 has physiological effects on water retention and blood pressure (Chapter 8). Furthermore SHU at greater degrees of elevation are unlikely to be tolerated by older people (Fan, Coakley et al. 2006) (chapter 6). We did not ascertain the exact aetiology of patient OH by formal autonomic function testing though our sub-group analysis did not suggest any greater effect in those with probable autonomic failure. We also did not measure haemoglobin, haematocrit and plasma creatinine to detect an intravascular haemodilution effect of SHU or investigate humoral mechanisms of action by measuring plasma aldosterone, renin and ADH levels. However the main purpose of the trial was to investigate the clinical effectiveness of SHU so mechanisms of action were less relevant. The study was not blinded though the use of an intervention in both groups would have tended to reduce any differential placebo effects.

The study has several strengths also. It is the first study looking at the effectiveness of SHU in older patients. Sample size was determined by power calculation and using pilot studies from a similar clinical population and almost all patients completed the study. By using a stratified randomisation process the control group was very similar to the intervention group at baseline and compliance with interventions was observed directly and objectively. The use of existing accepted treatments (water and medication modification) was optimised prior to study entry. By analysing measurements over the entire 60 seconds before and 120 seconds after standing we were able to explore any effects more fully than if we had concentrated on specific time points.

In conclusion, in patients with OH sleeping head up at 6 inches for 6 weeks was not associated with improvement in blood pressure or symptoms in older patients with OH attending a blackout clinic. Sleeping head up at 6 inches is therefore not at present recommended for older patients with orthostatic hypotension.
Fig 9.1. Diagram to show patients how to raise the bed
Fig 9.2. The Flow Diagram of subjects from RCT

Randomisation

Eligible patients
n=100

Sleeping head up
n=66

SHU
n=61

Drop out
n=5

Yes
n=47

No
n=14

Controls
n=34

Controls
n=31

Drop out
n=3

Not applicable

SHU compliant

Controls
n=31
Table 9.1. The basic characteristics of the participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHU</th>
<th>Control</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>31</td>
<td>0.26</td>
<td>0.610</td>
</tr>
<tr>
<td>Female (%)</td>
<td>34 (56%)</td>
<td>19 (61%)</td>
<td>0.26</td>
<td>0.610</td>
</tr>
<tr>
<td>Age (yrs) Median (IQR)</td>
<td>75 (71,79)</td>
<td>76 (71,84)</td>
<td>0.263</td>
<td></td>
</tr>
<tr>
<td>Lag time to follow-up (days)</td>
<td>44 (43,51)</td>
<td>48 (44,53.5)</td>
<td>0.1342</td>
<td></td>
</tr>
<tr>
<td>Nadir MAP mmHg</td>
<td>66.1(14.5)</td>
<td>69.0(18.4)</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Symptom of dizziness per week median (IQR)</td>
<td>7(1,7)</td>
<td>7(2,7)</td>
<td>0.7311</td>
<td></td>
</tr>
<tr>
<td>Dizziness during Active Stand</td>
<td>55 (90%)</td>
<td>30 (96%)</td>
<td>1.23</td>
<td>0.258</td>
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</table>
Table 9.2. Changes in Mean Arterial Blood Pressure, Systolic Blood pressure and Diastolic Blood Pressure over time

<table>
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<th>SHU</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Post-Pre</td>
<td>F Ratio (d.f.)</td>
</tr>
<tr>
<td>Mean Arterial Pressure (MAP)</td>
<td>Mean (SE)</td>
<td></td>
</tr>
<tr>
<td>ΔSupine MAP mmHg</td>
<td>0.94 (0.56)</td>
<td>2.76 (1,791)</td>
</tr>
<tr>
<td>ΔStanding MAP mmHg</td>
<td>2.07 (0.57)</td>
<td>13.45 (1,1583)</td>
</tr>
<tr>
<td>Systolic Blood Pressure (SBP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSupine SBP mmHg</td>
<td>-1.45 (0.82)</td>
<td>3.09 (1,791)</td>
</tr>
<tr>
<td>ΔStanding SBP mmHg</td>
<td>1.98 (0.80)</td>
<td>6.11 (1,1583)</td>
</tr>
<tr>
<td>Diastolic Blood Pressure (DBP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔSupine DBP mmHg</td>
<td>2.42 (0.51)</td>
<td>22.77 (1,791)</td>
</tr>
<tr>
<td>ΔStanding DBP mmHg</td>
<td>2.62 (0.46)</td>
<td>31.6 (1,1583)</td>
</tr>
</tbody>
</table>
Fig 9.3. Graph showing changes in mean arterial pressure at baseline and at 6 weeks of patients in the control group.
Figure 9.4. Graph showing changes in mean arterial pressure at baseline and at 6 weeks of patients who SHU at 6 inches.
Table 9.3. Analysis of variance of haemodynamic parameters during active stands

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th>Standing</th>
<th></th>
<th></th>
<th>Standing</th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>SHU mean(SE)</td>
<td>Controls mean(SE)</td>
<td>F-ratio (d,f)</td>
<td>p</td>
<td>SHU mean(SE)</td>
<td>Controls mean(SE)</td>
<td>F-ratio (d,f)</td>
</tr>
<tr>
<td>SHU Percentage change (post-pre)/pre*100%</td>
<td>SHU Percentage change Mean (SE)</td>
<td>Controls Percentage change Mean (SE)</td>
<td>F-ratio (d,f)</td>
<td>p</td>
<td>SHU Percentage change Mean (SE)</td>
<td>Controls Percentage change Mean (SE)</td>
<td>F-ratio (d,f)</td>
</tr>
<tr>
<td>rSV (%)</td>
<td>-0.77 (1.95)</td>
<td>5.56 (2.72)</td>
<td>3.59 (1,1199)</td>
<td>0.059</td>
<td>5.46 (1.93)</td>
<td>19.22 (2.70)</td>
<td>17.18 (1, 2399)</td>
</tr>
<tr>
<td>rCO (%)</td>
<td>6.48 (2.26)</td>
<td>0.52 (3.14)</td>
<td>2.37 (1,1199)</td>
<td>0.12</td>
<td>11.72 (2.14)</td>
<td>16.07 (2.99)</td>
<td>1.40 (1, 2399)</td>
</tr>
<tr>
<td>rTPR (%)</td>
<td>17.93 (2.10)</td>
<td>25.29 (2.93)</td>
<td>4.15 (1,1199)</td>
<td>&lt;0.0001*</td>
<td>20.26 (2.50)</td>
<td>25.20 (3.50)</td>
<td>1.17 (1, 2399)</td>
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* 0.01< p <0.05, ** 0.001< p <0.01, *** 0.0001< p <0.001, **** p <0.0001
Table 9.6. Modifying effects on SHU by hydration status or autonomic failure

<table>
<thead>
<tr>
<th></th>
<th>Supine</th>
<th></th>
<th>Standing</th>
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<th></th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Interactions with urinary output</td>
<td>Interactions with HR increase</td>
<td>Interactions with urinary output</td>
<td>Interactions with HR increase</td>
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<tr>
<td>Overall effect</td>
<td>&lt;1.5 L/day</td>
<td>&gt; 1.5L/day</td>
<td>ΔHR\text{max} &lt;12</td>
<td>ΔHR\text{max} ≥12</td>
<td>Overall effect</td>
<td>&lt;1.5 L/day</td>
</tr>
<tr>
<td>SBP</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>DBP</td>
<td>N</td>
<td>N</td>
<td>N (0.05)</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>MAP</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>HR</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y (0.05)</td>
</tr>
<tr>
<td>SV</td>
<td>N</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
</tr>
<tr>
<td>CO</td>
<td>Y</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>TPR</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>N</td>
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Table 9.6a. Post hoc analysis showing differences at 6 weeks and baseline with and without adequate hydration.

<table>
<thead>
<tr>
<th>Supine</th>
<th>Urinary output &lt;1.5L/day</th>
<th>Post-Pre Differences</th>
<th>F-ratio (d,f)</th>
<th>p</th>
<th>Urinary output ≥1.5L/day</th>
<th>Post-Pre Differences</th>
<th>F-ratio (d,f)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SHU</td>
<td>Controls</td>
<td></td>
<td></td>
<td>SHU</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>-1.62 (1.81)</td>
<td>-1.06 (2.00)</td>
<td>0.04 (1,457)</td>
<td>0.84</td>
<td>-1.44 (1.10)</td>
<td>1.69 (1.97)</td>
<td>1.92 (1,597)</td>
<td>0.17</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>1.56 (1.26)</td>
<td>1.13 (1.39)</td>
<td>0.05 (1,457)</td>
<td>0.82</td>
<td>3.03 (0.60) ^d</td>
<td>4.27 (1.07) ^c</td>
<td>1.03 (1,597)</td>
<td>0.31</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.15 (1.39)</td>
<td>0.16 (1.54)</td>
<td>0.000001 (1,457)</td>
<td>1.0</td>
<td>1.39 (0.67)</td>
<td>2.94 (1.21)</td>
<td>1.27 (1,597)</td>
<td>0.26</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>1.47 (0.73)</td>
<td>-0.33 (0.81)</td>
<td>2.72 (1,457)</td>
<td>0.10</td>
<td>1.22 (0.46)</td>
<td>-2.56 (0.82) ^a</td>
<td>15.98 (1,597)</td>
<td>0.0001*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>-1.74 (2.68)</td>
<td>-1.08 (2.96)</td>
<td>0.028 (1,457)</td>
<td>0.87</td>
<td>-3.99 (1.52)</td>
<td>-15.15 (2.72) d</td>
<td>12.80 (1,597)</td>
<td>0.0004*</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>22 (177)</td>
<td>-158 (196)</td>
<td>0.47 (1,457)</td>
<td>0.50</td>
<td>-201 (104)</td>
<td>-934 (187) d</td>
<td>11.73 (1,597)</td>
<td>0.0007*</td>
</tr>
<tr>
<td>TPR dynes/s/cm5</td>
<td>0.295 (0.069) ^c</td>
<td>0.244 (0.077) ^b</td>
<td>0.24 (1,457)</td>
<td>0.62</td>
<td>0.158 (0.0542)</td>
<td>0.0214 (0.067)</td>
<td>3.20 (1,597)</td>
<td>0.07</td>
</tr>
<tr>
<td>Standing</td>
<td>SHU</td>
<td>Controls</td>
<td></td>
<td></td>
<td>SHU</td>
<td>Controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>1.19 (1.52)</td>
<td>-3.17 (1.68)</td>
<td>3.71 (1,911)</td>
<td>0.05</td>
<td>2.75 (1.09)</td>
<td>10.21 (1.95) ^d</td>
<td>11.18 (1,1199)</td>
<td>0.0009*</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>0.69 (0.88)</td>
<td>-0.19 (0.97)</td>
<td>0.44 (1,911)</td>
<td>0.51</td>
<td>4.08 (0.58) ^d</td>
<td>5.88 (1.04) ^d</td>
<td>2.29 (1,1199)</td>
<td>0.13</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>0.47 (1.04)</td>
<td>-0.72 (1.16)</td>
<td>0.58 (1,911)</td>
<td>0.45</td>
<td>3.28 (0.74) ^d</td>
<td>8.47 (1.32) ^d</td>
<td>11.72 (1,1199)</td>
<td>0.0006*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>0.39 (0.75)</td>
<td>-1.76 (0.83)</td>
<td>3.70 (1,911)</td>
<td>0.05</td>
<td>1.27 (0.43) ^a</td>
<td>-0.57 (0.76)</td>
<td>4.45 (1,1199)</td>
<td>0.035*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>2.02 (1.88)</td>
<td>0.14 (2.10)</td>
<td>0.45 (1,911)</td>
<td>0.50</td>
<td>-1.18 (1.08) ^a</td>
<td>-7.35 (1.92) ^c</td>
<td>7.83 (1,1199)</td>
<td>0.0052*</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>263 (132)</td>
<td>-2 (147)</td>
<td>1.81 (1,911)</td>
<td>0.18</td>
<td>47 (80)</td>
<td>-193 (143)</td>
<td>0.79 (1,1199)</td>
<td>0.37</td>
</tr>
<tr>
<td>TPR dynes/s/cm5</td>
<td>0.136 (0.078)</td>
<td>0.262 (0.02) ^b</td>
<td>1.30 (1,911)</td>
<td>0.25</td>
<td>0.0616 (0.040)</td>
<td>0.205 (0.071) ^a</td>
<td>10.68 (1,1199)</td>
<td>0.0011*</td>
</tr>
</tbody>
</table>

- 0.01 < p < 0.05, ^ 0.001 < p < 0.01, c 0.0001 < p < 0.001, d p < 0.0001
Table 9.6b. Heart rate response ΔHRmax<12 or ΔHRmax ≥12

<table>
<thead>
<tr>
<th></th>
<th>ΔHRmax&lt;12</th>
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<th>ΔHRmax ≥12</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>SHU</td>
<td>Controls</td>
<td>Post-Pre Differences</td>
<td>F-ratio (d,f)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SHU</td>
<td>1.87 (1.38)</td>
<td>2.21 (2.44)</td>
<td>0.02 (1,347)</td>
<td>0.90</td>
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<tr>
<td>DBP (mmHg)</td>
<td>2.67 (0.84) b</td>
<td>6.06 (1.23) c</td>
<td>3.92 (1,347)</td>
<td>0.049</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>2.48 (0.95)</td>
<td>5.58 (1.68) b</td>
<td>2.59 (1,347)</td>
<td>0.11</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>1.31 (0.55)</td>
<td>-5.28 (0.98) d</td>
<td>33.81 (1,347)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>-4.30 (1.60)</td>
<td>-9.39 (2.83) b</td>
<td>7.60 (1,347)</td>
<td>0.0062*</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>14 (143)</td>
<td>-782 (253) a</td>
<td>7.50 (1,347)</td>
<td>0.0065*</td>
</tr>
<tr>
<td>TPR dynes/s/cm5</td>
<td>0.279 (0.053) d</td>
<td>0.370 (0.094) b</td>
<td>0.71 (1,347)</td>
<td>0.40</td>
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<tr>
<td>SHU</td>
<td>3.67 (1.54)</td>
<td>3.93 (2.74)</td>
<td>0.01 (1,695)</td>
<td>0.93</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>2.23 (0.80) a</td>
<td>0.06 (1.42)</td>
<td>1.74 (1,695)</td>
<td>0.19</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>2.74 (1.06)</td>
<td>3.07 (1.84)</td>
<td>0.02 (1,695)</td>
<td>0.88</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>0.004 (0.652)</td>
<td>-2.65 (1.16)</td>
<td>4.00 (1,695)</td>
<td>0.05</td>
</tr>
<tr>
<td>SV (ml)</td>
<td>3.74 (1.10) b</td>
<td>7.79 (1.95) c</td>
<td>3.27 (1,695)</td>
<td>0.07</td>
</tr>
<tr>
<td>CO (ml/min)</td>
<td>259 (100)</td>
<td>776 (177) d</td>
<td>6.50 (1,695)</td>
<td>0.011*</td>
</tr>
<tr>
<td>TPR dynes/s/cm5</td>
<td>0.163 (0.078)</td>
<td>-0.328 (0.139)</td>
<td>9.42 (1,695)</td>
<td>0.0022*</td>
</tr>
</tbody>
</table>

*a 0.01 < p < 0.05, b 0.001 < p < 0.01, c 0.0001 < p < 0.001, d p < 0.0001
Fig 9.5 Graph showing changes in systolic blood pressure at baseline and at 6 weeks of patients who SHU at 6 inches.
Fig 9.6 Graph showing changes in diastolic blood pressure at baseline and at 6 weeks of patients who SHU at 6 inches.
Fig 9.7 Graph showing changes in heart rate at baseline and at 6 weeks of patients who SHU at 6 inches.

![Graph showing changes in heart rate at baseline and at 6 weeks of patients who SHU at 6 inches](image)

- At baseline
- At 6 weeks
Fig 9.8 Graph showing changes in stroke volume at baseline and at 6 weeks of patients who SHU at 6 inches
Fig 9.9 Graph showing changes in cardiac output at baseline and at 6 weeks of patients who SHU at 6 inches
Fig 9.10 Graph showing changes in total peripheral resistance at baseline and at 6 weeks of patients who SHU at 6 inches
Fig 9.11 Graph showing changes in systolic blood pressure at baseline and at 6 weeks of patients in the control group.
Fig 9.12. Graph showing changes in diastolic blood pressure at baseline and at 6 weeks of patients in the control group.
Fig 9.13. Graph showing changes in heart rate at baseline and at 6 weeks of patients in the control group.

HR control by 10 s bin

At baseline
At 6 weeks
Fig 9.14. Graph showing changes in stroke volume at baseline and at 6 weeks of patients in the control group.
Fig 9.15. Graph showing changes in cardiac output at baseline and at 6 weeks of patients in the control group.

**CO control by 10 s bin**

At baseline

At 6 weeks
Fig 9.16. Graph showing changes in total peripheral resistance at baseline and at 6 weeks of patients in the control group.

Graph titled "TPR control by 10 s bin" with data points showing fluctuations in total peripheral resistance. The x-axis represents time in seconds from -60 to 140, and the y-axis represents dynes/s/cm² with values ranging from 0 to 3.

Legend:
- Solid line: At baseline
- Dotted line: At 6 weeks
Fig 9.17. Graph showing the relative percentage of stroke volume from baseline to 6 weeks between SHU and controls
Fig 9.18. Graph showing the relative percentage of cardiac output from baseline to 6 weeks between SHU and controls.
Fig 9.19. Graph showing the relative percentage of stroke volume from baseline to 6 weeks between SHU and controls.
Table 9.7. Weight and presence of ankle oedema before and after 6 weeks of interventions

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHU</th>
<th>Control</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall improvement (yes)</td>
<td>42 (69%)</td>
<td>18 (58%)</td>
<td>0.86</td>
<td>0.352</td>
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<tr>
<td>Weight (kg)</td>
<td></td>
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</tr>
<tr>
<td>Pre</td>
<td>68(11.8)</td>
<td>68(16.3)</td>
<td>0.996</td>
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</tr>
<tr>
<td>Post</td>
<td>67(12.6)</td>
<td>69(15.1)</td>
<td>0.6593</td>
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</tr>
<tr>
<td>Pre vs. post, p values</td>
<td>0.2937</td>
<td>0.5066</td>
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</tr>
<tr>
<td>Oedema present</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>11</td>
<td>5</td>
<td>0.05</td>
<td>0.82</td>
</tr>
<tr>
<td>Post</td>
<td>25</td>
<td>6</td>
<td>4.30</td>
<td>0.038*</td>
</tr>
<tr>
<td>Pre vs. post, Chi-square</td>
<td>7.72</td>
<td>0.111</td>
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<tr>
<td>P values</td>
<td>0.0054*</td>
<td>0.74</td>
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Table 9.7a Number of participants in SHU and controls developing ankle oedema

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<tr>
<th>Study Group</th>
<th>Oedema Yes</th>
<th>Oedema No</th>
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<tbody>
<tr>
<td>SHU</td>
<td>Yes=25</td>
<td>No=36</td>
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<tr>
<td>Controls</td>
<td>Yes=6</td>
<td>No=25</td>
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</table>
Table 9.8. The symptoms of dizziness during active stand and in the study period of SHU and controls.

<table>
<thead>
<tr>
<th>Variables</th>
<th>SHU</th>
<th>Control</th>
<th>Chi-square</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms during Active Stand (yes)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>55</td>
<td>30</td>
<td>χ²=1.23</td>
<td>0.258</td>
</tr>
<tr>
<td>Post</td>
<td>37</td>
<td>19</td>
<td>χ²=0.003</td>
<td>0.953</td>
</tr>
<tr>
<td>Pre vs. post, Chi square</td>
<td>14.32</td>
<td>11.77</td>
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<td></td>
</tr>
<tr>
<td>p values</td>
<td>0.00015*</td>
<td>0.0006*</td>
<td></td>
<td></td>
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<tr>
<td>Symptoms of dizziness per week median (IQR)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>7(1.7)</td>
<td>7(2.7)</td>
<td>Z=0.34</td>
<td>0.7311</td>
</tr>
<tr>
<td>Post</td>
<td>0.17(0.2)</td>
<td>2(0.7)</td>
<td>Z=2.23</td>
<td>0.026*</td>
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<tr>
<td></td>
<td>Z=5.54,</td>
<td>Z=2.89,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0001*</td>
<td>p=0.0038</td>
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<tr>
<td>2 or more dizzy episodes per week</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>41/61</td>
<td>24/31</td>
<td>χ²=1.03</td>
<td>0.31</td>
</tr>
<tr>
<td>Post</td>
<td>18/61</td>
<td>16/31</td>
<td>χ²=4.31</td>
<td>0.038</td>
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<tr>
<td></td>
<td>McNemar χ²</td>
<td>McNemar χ²</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>=13.83, p=0.0004</td>
<td>=4.08, p=0.087</td>
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</tr>
<tr>
<td>3 or more dizzy episodes per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>37/61</td>
<td>22/31</td>
<td>χ²=0.95</td>
<td>0.33</td>
</tr>
<tr>
<td>post</td>
<td>13/61</td>
<td>12/31</td>
<td>χ²=3.14</td>
<td>0.076</td>
</tr>
<tr>
<td></td>
<td>McNemar χ²</td>
<td>McNemar χ²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>=15.56, p=0.0002</td>
<td>=5.79, p=0.032</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 or more dizzy episodes per week</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>35/61</td>
<td>21/31</td>
<td>χ²=0.93</td>
<td>0.34</td>
</tr>
<tr>
<td>post</td>
<td>13/61</td>
<td>11/31</td>
<td>χ²=2.14</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>McNemar χ²</td>
<td>McNemar χ²</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>=12.97, p=0.0006</td>
<td>=5.06, p=0.049</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 9.9 24-hour blood pressure measurements before and after intervention

<table>
<thead>
<tr>
<th>24 hour ABPM results</th>
<th>SHU</th>
<th>Controls</th>
<th>P value for SBP</th>
<th>P Value for DBP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number in group</td>
<td>61</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>51 (83%)</td>
<td>24 (77%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day (Awake) Mean Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>144(15)/81(8)</td>
<td>145(16)/83(7)</td>
<td>0.77</td>
<td>0.29</td>
</tr>
<tr>
<td>Post</td>
<td>143(15)/82(13)</td>
<td>146(12)/81(6)</td>
<td>0.29</td>
<td>0.96</td>
</tr>
<tr>
<td>Night (Sleep) Mean Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>132(19)/72(10)</td>
<td>137(24)/74(10)</td>
<td>0.42</td>
<td>0.48</td>
</tr>
<tr>
<td>Post</td>
<td>130(20)/73(16)</td>
<td>134(23)/73(10)</td>
<td>0.95</td>
<td>0.49</td>
</tr>
<tr>
<td>Overall mean Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>141(14)/79(8)</td>
<td>143(17)/81(6)</td>
<td>0.55</td>
<td>0.20</td>
</tr>
<tr>
<td>Post</td>
<td>140(16)/79(8)</td>
<td>142(13)/79(6)</td>
<td>0.49</td>
<td>0.94</td>
</tr>
<tr>
<td>Post - Pre mean blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day</td>
<td>-1.3(16)/0.8(12)</td>
<td>-1(12)/-1.3(6)</td>
<td>0.47</td>
<td>0.46</td>
</tr>
<tr>
<td>Night</td>
<td>-1.7(20)/-0.6(8)</td>
<td>-2.7(19)/1.4(14)</td>
<td>0.82</td>
<td>0.52</td>
</tr>
<tr>
<td>Overall</td>
<td>-1.3(15)/0.1(8)</td>
<td>-1.3(10)/-2.1(6)</td>
<td>0.90</td>
<td>0.19</td>
</tr>
</tbody>
</table>
Table 9.10. The agreement between self reported compliance and urinary output

<table>
<thead>
<tr>
<th>6 week urine ≥ 1.5L</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>No</td>
<td>9</td>
<td>27</td>
</tr>
</tbody>
</table>

$k= 0.485$ (C.I. 0.294, 0.675)

Table 9.11. 24 hour Urinary output before, after and post-pre 6-week intervention.

<table>
<thead>
<tr>
<th></th>
<th>Self reported compliance</th>
<th>Self reported non-compliance</th>
<th>p values</th>
<th>t statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>43</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>1946 (785)</td>
<td>1393 (740)</td>
<td>0.0015</td>
<td>-3.28</td>
</tr>
<tr>
<td>post</td>
<td>2189 (0.911)</td>
<td>1252 (639)</td>
<td>&lt;0.0001</td>
<td>-5.43</td>
</tr>
<tr>
<td>Post-pre</td>
<td>+243 (813)</td>
<td>-141 (830)</td>
<td>0.037</td>
<td>-2.11</td>
</tr>
<tr>
<td>Post &gt; pre</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>42</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary Volume (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre</td>
<td>1458 (777)</td>
<td>1918 (785)</td>
<td>0.0092</td>
<td>-2.67</td>
</tr>
<tr>
<td>Post</td>
<td>2138 (933)</td>
<td>1328 (702)</td>
<td>&lt;0.0001</td>
<td>4.45</td>
</tr>
<tr>
<td>Post - pre</td>
<td>+679 (431)</td>
<td>-590 (505)</td>
<td>&lt;0.0001</td>
<td>10.54</td>
</tr>
</tbody>
</table>

Table 9.12. 24-hour urinary output in SHU group and controls

<table>
<thead>
<tr>
<th></th>
<th>SHU</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>53</td>
<td>29</td>
</tr>
<tr>
<td>Pre Median (IQR) L</td>
<td>1.827 (1.074, 2.366)</td>
<td>1.274 (0.877, 1.773)</td>
</tr>
<tr>
<td>Post Median (IQR) L</td>
<td>1.914 (1.081, 2.535)</td>
<td>1.386 (1.004, 1.810)</td>
</tr>
<tr>
<td>$z= 0.49, p =0.62$</td>
<td></td>
<td>$z= 0.23, p = 0.82$</td>
</tr>
</tbody>
</table>
Table 9.13. The side effect reported from sleeping head up
Total number randomised to SHU completed 61

<table>
<thead>
<tr>
<th>Side effects of sleeping head up</th>
<th>Numbers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oedema developed*</td>
<td>18 (29.5%)</td>
</tr>
<tr>
<td>Slid down the bed</td>
<td>15 (24.5%)</td>
</tr>
<tr>
<td>Difficulty sleeping in the bed</td>
<td>10 (16.4%)</td>
</tr>
<tr>
<td>Spouse complaining of sleeping arrangements</td>
<td>6 (9.8%)</td>
</tr>
<tr>
<td>Painful back/buttocks/legs</td>
<td>3 (4.9%)</td>
</tr>
<tr>
<td>Headaches</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Bed slipped off blocks when moving the bed</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Stopped because of very heavy legs which impeded mobility</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Oedema causing worsening leg ulcers</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>One fell between bed and wall</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

* compared with only 2 in controls where oedema developed following intervention
Chapter 10 General discussion

Clinical effects of sleeping with the head of the bed elevated

Problems of safety and tolerance with existing treatments for OH means that the search for better treatments continue. Patients with OH tend to have worse symptoms in the morning. The aim of SHU is to counteract the deleterious effect of recumbency associated pressure natriuresis and diuresis (Mathias 2000). There are significant physiological effects reported in a limited literature regarding SHU supporting an increase in total extracellular fluid (interstitial or intravascular). Firstly Bannister et al (Bannister, Ardill et al. 1969) observed a reversal of day and night urinary excretion where subjects SHU reduced night-time urinary output. Secondly, there was an associated increase in weight (up to 1 to 2.6kg) and ankle oedema. MacLean et al (MacLean and Allen 1940) correlated the improvement in orthostatic symptoms with development of ankle oedema. Ten Harkel (Ten Harkel, Van Lieshout et al. 1992) also reported long-term tolerability and efficacy of this treatment for up to 14 months in one of his patients. SHU was used as a monotherapy or in conjunction with low dose fludrocortisone (150 to 200mcg). All of their patients were advised to drink at least 2 litres of water daily and take at least 150mmol of sodium a day. In general the patients investigated in these studies had severe autonomic failure and were aged under 65 years.

In addition to reducing pressure natriuresis and diuresis, SHU has been postulated to expose the juxtaglomerular apparatus to renal hypoperfusion thereby promoting renin secretion which results in fluid retention. Corcoran (Corcoran, Browning et al. 1943) reported that the effect on blood pressure in a patient with neurogenic OH of SHU was akin to the infusion of angiotonin. Another proposed mechanism was that the oedema in the lower limb might act as a physiological “compression hosiery” (water jacket) preventing venous pooling in the lower limb (MacLean and Allen 1940). The patients reported improvement of dizziness when leg oedema occurred.

The theme of the current research was to determine the extent of use of SHU as a therapy for OH in older subjects in current clinical practice and to investigate its physiological effects in a range of subjects (young and old, healthy and with OH) and at a range of elevations.

Our questionnaire survey (Chapter 6) found that SHU was a clinically relevant intervention for treatment of OH in current practice amongst clinicians who attended an international syncope
conference (Fan, Coakley et al. 2006). It was not a first line treatment, SHU ranked 5th in the treatment scheme amongst those surveyed. Approximately half of respondents would prescribe SHU at some stage in their clinical practice though only a quarter would use it routinely. As a majority of the respondents were geriatricians we can infer that it is used frequently in older patients. The survey also revealed that most of the prescribers of SHU used angles less than 12 degrees (the minimum angle studied in the literature) and half of them recommended SHU at 3 to 5 degrees which is equivalent to 4 to 6 inches in height. The commonest reason for non-use of SHU given by the clinicians we surveyed was a lack of confidence of the evidence available to support its use, and secondly they cited patient intolerance and discomfort with this practice. Therefore there was a clear need to conduct further research to determine if SHU had any physiological effect and in particular in older subjects and at degrees of elevation more commonly used in clinical practice.

With those reservations in mind, we set out to see if SHU had any physiological effects first of all in young healthy subjects (mean age of 22 years) and then in older symptomatic OH patients in hospital (mean age 76 years). The first experiment (Chapter 7) was conducted using the original bed design of MacLean's case reports (MacLean and Allen 1940) by asking young volunteers to sleep head up at 18 inches for one week. The study showed that even in well-hydrated healthy subjects with intact autonomic function, there were haemodynamic changes consistent with an increase in intravascular volume status such as increased SBP, SV and reduced heart rate and TPR. In addition, there was a significant increase in weight, and ankle circumference (indicating oedema) and a fall in haemoglobin. There was an increase in day/night urinary volume ratio during the week of sleeping head up similar to Bannister's observations. The healthy subjects also reported less dizziness during active stand one week after SHU. Interestingly nighttime BP was not affected by SHU suggesting that renal hypoperfusion was unlikely to be a mechanism of action for the haemodynamic changes observed with SHU. This study therefore confirmed the existing literature but extended it to healthy subjects with intact autonomic function.

The next experiment (Chapter 8) was performed in older patients with OH. Since we had confirmed that SHU at 18 inches indeed had a fluid retention effect, we designed an in-patient study to examine its effect on patients with OH. We chose the more commonly used height of 6 inches as this had not been tested before. This study was conducted on nine in-patients with OH. The patients slept in a hospital bed which was tilted 5 degrees (equivalent of 6 inches head up) for one week. Again significant changes in BP and other haemodynamic variables were observed in keeping with an
increase in intravascular volume and symptoms were improved in a majority. This study was important in demonstrating clinically relevant physiological changes in older subjects at an elevation of only 6 inches.

The final experiment (Chapter 9) was an open-labelled randomised control trial conducted on older out-patients (mean age 75 years old) with OH to look at the effects of SHU at 6 inches over 6 weeks. A secondary aim was to assess compliance and tolerability. In order to assess any additive effects to existing therapies all patients were encouraged to remain well hydrated before and during the trial and were advised about lifestyle and physical counter-manoeuvre measures at the outset in keeping with best clinical practice. The use of a control group was important as it allowed the effects of SHU to be studied independently of temporal effects for the first time. Interestingly both groups improved in terms of symptoms and BP after 6 weeks but to an equal extent. SHU therefore had no clinical benefit above and beyond existing measures though it was associated with some other haemodynamic effects, the significance of which is unclear. Sub-group analysis did not suggest any significant BP changes according to autonomic function or hydration. This clearly is not concurrent with the existing literature on SHU but it must be noted that we were studying its effects at a lower angle and in a different population than heretofore.
Physiological effects of sleeping with the head of the bed elevated

SHU, whether at 18 inches in young subjects or 6 inches in older inpatients, had definite physiological effects which were obvious by one week which is consistent with other studies in the literature (MacLean and Allen 1940; Bannister, Ardill et al. 1969; Ten Harkel, Van Lieshout et al. 1992). Both young and old participants showed results consistent with increased fluid volume. SHU at 18 inches in young participants caused a significant weight gain of 400g (in keeping with fluid retention), a fall in haemoglobin of 0.3dg/L from haemodilution (in keeping with an increase in intra-vascular fluid volume) and an ankle circumferences increase of 8mm (in keeping with extra-vascular fluid retention). SHU at 6 inches in older participants also was associated with a weight gain of 700g and a drop in serum creatinine of 5.4mmol/L was also consistent with an increase in intra-vascular fluid. Noteworthy effects on haemodynamic parameters were also observed. While there was a marginal increase in SBP of 3.4 mmHg in well-hydrated younger participants, SBP in older inpatients rose by 12 mmHg during standing. There were also pronounced increases in standing SV in young and old by 3.0 ml and 14.6 ml respectively. Standing CO increased by 1343 ml/min in older inpatients but was not significant in younger participants. Furthermore, five of the in-patients who were previously immobile due to debilitating OH were now able to walk independently. It is noteworthy that the physiological responses to OH were more pronounced in the older patients than in the younger controls even though the degree of elevation was much less. What can be deduced from these studies is that SHU does therefore have clinically significant physiological effects in in-patients aged 65 years and over and that an elevation of 6 inches is capable of producing these effects.

On the other hand, the haemodynamic response was more complex when SHU at 6 inches was applied for a longer period in older patients in an out-patient setting. The randomised controlled trial comparing SHU at 6 inches and water-drinking with water-drinking alone showed that sleeping head up was no better than controls with regards to our primary outcome measure (MAP) or other blood pressure parameters. There was also no significant weight gain in either group. Furthermore the fact that ankle oedema developed in 40% of the SHU group despite no overall increase in weight (in fact there was a non significant drop in weight of 0.7 kg) suggests a possible reduction in intra-vascular volume with fluid being shifted into the extra-vascular space. This suggests that the increases in intravascular fluid volume seen by 1 week with SHU are gone by 6 weeks, which may go some way to explain the negative clinical findings on BP.
Although SHU did not have a clinical advantage at 6 weeks over drinking water, SHU had more pronounced haemodynamic effects on secondary measures such as standing SV and CO especially in the participants with intact autonomic function and in those who were well hydrated. While the young participants and inpatient studies showed SV and CO increases in the standing phase of active stands, the RCT found significant results of attenuating the fall in standing SV and CO. While HR fell in the one-week studies (2.0 bpm in young and 3.6 bpm in the older inpatients), we reported persistent increases in supine and standing HR in the SHU groups by as much as 1.2 bpm higher than controls. The reasons for these observations are unclear though could be explained by the initial increase in intra-vascular volume at 1 week being gradually lost over time and eventually leading to a reduction in intra-vascular volume by 6 weeks. This theory would explain the changes in weight and oedema mentioned in the last paragraph also.

Whether this is the case or not it does suggest that the physiological effects of SHU alter over time with effects after one week not necessarily being representative of effects at 6 weeks. This has important implications for future research of non pharmacological interventions especially which are often studied over a short period of time given that clinical effects need to be present over months at least if they are to be worthwhile.

Several authors have indicated that Modelflow derived parameters are not accurate without calibrations (Imholz, Settels et al. 1990; Jansen, Wesseling et al. 1990; Harms, Wesseling et al. 1999; Tam, Azabji Kenfack et al. 2004). We performed our analysis based on relative changes of SV, CO and TPR from baseline values according to the following formula (post-pre)/pre*100%. There were largely consistent findings with minor variations. For instance, in the young controls, SHU resulted in significant increases in SV (in absolute and relative terms) but CO increases were found only in standing CO in relative changes. In the inpatient study, there were pronounced increases in absolute and relative SV and CO but not in TPR. Although the changes in absolute and relative values of SV in the RCT were consistent, there were more complicated for CO and TPR. We would advocate using relative change as a measure of haemodynamic changes.
Symptomatic effects of sleeping with the head of the bed elevated

Both the SHU and control groups reported overall symptomatic improvement and complained of fewer episodes of dizziness (the latter was slightly more prominent in the SHU group). The improvement in the participants could not be attributed to water-drinking alone as neither group significantly increased their urine output. While some of the effects may be attributable to better use of physical counter manoeuvres it is likely that other factors were also important including a placebo effect and a possible "learning" effect from being exposed to repeated testing. The smaller number of dizzy spells seen in the SHU group was most probably a placebo effect given the absence of differential effects in blood pressure. While double blinding will remove placebo effects it isn't always possible to blind patients to non-pharmacological treatments and obviously not to something like SHU. While it would be possible to blind the rater it is debateable to what extent this would be useful when the main outcome variables are haemodynamic data that is being collected automatically by a machine using continuous beat to beat measurement (as distinct from intermittently and manually which might well be altered by observer expectation) and given the extra resource implications we decided not to do so in this study. One clear point that emerges from this work is that further studies of the effects of SHU (or other interventions) in OH should have a control group.
Safety and tolerability of SHU

SHU was shown to be a relatively (though not completely) safe intervention at 18 inches in young people and 6 inches in older patients. All the inpatients tolerated sleeping head up at 6 inches though there were drop-outs over the longer period in the RCT (47 of 66 subjects [77%] were compliant at 6 weeks). The two main side effects from SHU were leg oedema and a tendency to slide down the bed while sleeping. Due to fluid accumulation in the lower limbs, some young participants found that their legs were heavier and 41% of the older participants had leg oedema when they slept head up. Two of the older participants stopped treatment due to worsening mobility and leg ulcers from oedema. One participant fell between the tilted bed and the wall. Falling from bed would be a concern in prescribing a treatment such as this to frail older individuals. One faller out of 66 (1.5% [95% CI 1.4-4.4%], number needed to harm 66) over 6 weeks might be acceptable in an efficacious treatment but is clearly not when the treatment is ineffective.
Effects of hydration

While designing the experiments, we looked at the other common treatment for OH, which was hydration. Following diagnosis of OH, most clinicians will advise their patients to maximise their water intake to at least 2 litres of water a day. When we advised all our older participants in the RCT to drink at least 2 litres of water a day, half of the participants reported adherence with this advice. The urinary volume analysis showed 55% of the participants had a urinary output greater than 1.5 litres which meant that they were drinking at least 2 litres a day. We found moderate agreement (kappa 0.48) between self-reported water compliance and greater than 1.5 L urinary output suggesting that self-reporting may be sufficient for clinical work in this area but that more objective measures are required for research.

Urinary output at baseline and at 6 weeks were similar in both groups suggesting that even in a group of highly motivated older people who were willing to take part in research, it is difficult to further increase water intake. Many of the participants complained of troublesome urinary frequency which impacted adversely on their lives from drinking extra water. Many of the participants complained of a bloating discomfort after drinking water. Participants with higher oral intake as reflected by a higher urinary volume at study end were already drinking these amounts before coming to our clinic/ starting the study. Such patients may already have increased their water intake to the maximal tolerated amount before attending the clinic or it may have proved impossible for them to increase it all. Regardless of the explanation it would appear that despite encouraging physiological data (Jordan, Shannon et al. 2000; Schroeder, Bush et al. 2002; Shannon, Diedrich et al. 2002; Claydon, Schroeder et al. 2006) our results suggest that drinking extra water may not be a feasible option for most older patients with OH who present to specialist clinics for further treatment.
Limitations

There are a number of limitations to these studies that must be acknowledged. First of all we did not perform formal autonomic function tests to ascertain the presence of autonomic dysfunction causing OH. While we used age appropriate initial HR rise during active stands as a marker for intact autonomic function (Wieling and Karemaker 2002), it is possible that this may be less sensitive. A second limitation was that the sample sizes for hormone analysis were too small to investigate changes in the young and old participants. Furthermore, we only measured supine blood sample. We, therefore, were not able to ascertain the exact humoral mechanisms by which SHU exerted its physiological effects. Further research to determine humoral mechanisms of action would require much larger sample sizes for renin and aldosterone assays. Based on our results sample sizes of 300 to 700 individuals would be required to more fully investigate the minor changes we found suggesting that supine testing of these hormones is not practicable. Standing measures of renin and aldosterone as well as other blood assays such as atrial natriuretic peptide, brain natriuretic peptide, anti-diuretic hormone, noradrenaline and angiotensin levels could be considered in future research and may be more sensitive.
Chapter 11: General Conclusion

SHU is used not infrequently in older people as a treatment for OH by syncope practitioners.

Most prescribe elevation that is less than those suggested by the literature with 6 inches being the commonest height.

SHU at 6 inches (SHU6) has clinically significant physiological effects at one week but these seem to be less apparent at six weeks.

SHU6 is no more clinically effective at 6 weeks than existing practice of encouraging water intake and advising about physical counter manoeuvres.

SHU6 appears to be relatively safe though uncomfortable.

There is small risk of falling out of bed (1-4%).

SHU6 is not recommended for as a routine treatment for older outpatients (65yrs+) with OH attending a specialist clinic.

SHU6 may have a role in quickly improving orthostatic tolerance as an initial inpatient treatment of OH.

More research may identify patient sub-populations that would benefit from SHU and in particular subjects with significant autonomic failure (defined by formal autonomic function testing) may be worthy of further study.
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Failure: A textbook of Clinical disorders of the autonomic nervous systems. R.

Failure: A textbook of Clinical disorders of the autonomic nervous systems. R.


Appendices

Appendix:

Finometer

Frontend

Finger cuff

Height correction unit
Ambulatory blood pressure monitor

Monitor

18-inch chair used to elevate the head of the bed
6-inch blocks for the head of the bed
Non-pharmacological management of orthostatic hypotension in the elderly patient

Dr Chie Wei Fan and Conal J Cunningham
St James's Hospital, Dublin, Ireland

Orthostatic hypotension (OH) is defined as a systolic blood pressure (SBP) drop of at least 20 mmHg, or a diastolic blood pressure drop of at least 10 mmHg within three minutes of standing from a supine position. It can be symptomatic or asymptomatic and is a common condition that can affect up to one in three older people living in the community. The prevalence is higher amongst those with Parkinson's disease and, unsurprisingly, amongst those attending a syncope clinic. The aetiology and pathophysiology of OH have been comprehensively discussed in a previous article in this journal.

OH can accompany acute illness or present more chronically in individuals who are not obviously unwell. The management of OH in the acute setting is to treat the underlying cause and rarely presents a significant management problem. The management of chronic symptomatic OH is more problematic however.

Medication review
Initially, offending medications should be stopped or tailored to the patient's symptoms. Alsop and Mac Mahon reported that 19% of patients had an improvement in OH symptoms as a result of medication cessation. However, for those with chronic OH in whom medication withdrawal is not an option, the alternative is to consider pharmacological or non-pharmacological means of management. The goal of treatment should be to improve the patient's quality of life rather than to achieve a specific blood-pressure target.

Treatment of OH works through two mechanisms, either by increasing plasma volume or increasing peripheral resistance.

Anti-hypotensive medications are associated with side-effects which can limit their utility.

Commonly-used drugs such as fludrocortisone and midodrine have side-effects of hypertension, cardiac failure, depression, oedema and hypokalaemia. French investigators found a rate of 1.6 adverse reactions per patient (17% of them serious) with antihypotensive medication (especially the cardiac stimulant, heptaminol).

Another avenue open to the physician is the non-pharmacological route (see Table 1). Education of patients to recognize symptoms and avoid situations that exacerbate the condition is essential.

Lifestyle modification
Patients are advised to sit down quickly at the onset of symptoms and, if possible, to keep their head at the same level as the heart by bending forward (putting their head between their knees) or lying down. OH tends to be worst in the morning and patients are advised to carry out most activities in the afternoon. They should also avoid quick postural changes. Hot environments exacerbate cutaneous vasodilation and increase fluid loss through sweating. Patients with OH are advised to avoid hot environments (hot rooms, hot baths or showers) and need to be more vigilant about symptoms during the summer. Petrofsy et al. reported that diabetic patients who develop OH during head-up tilt-testing have greater falls in blood pressure in a hot environment of 42 degrees celsius that at 22 degrees. During the heat wave of 2004 in France, Pathak found higher morbidity amongst those with OH.

Post-prandial hypotension, defined as a fall in systolic blood pressure of greater than 20 mmHg up to 90 minutes following a meal, is a common condition. It can co-exist with OH and is related to the rate of glucose entering the small intestine. OH patients with concomitant post-prandial hypotension should avoid eating large carbohydrate meals and should drink extra water with their meal.
Table 1. Non-pharmacological treatment of orthostatic hypotension

- Lifestyle modification
- Water drinking
- Extra salt intake
- Sleeping with the head of the bed elevated
- Compression hosiery and abdominal binders
- Physical counter-maneuvres
- Portable folding chair
- Tilt-training and resistance-training

Alcohol causes diuresis by suppressing antidiuretic hormone release and it also prevents vasoconstriction, thereby exacerbating OH. Alcohol should therefore be used in moderation by patients with OH.

Water-drinking

The advice to drink 1.5 to 2 L of extra water a day is part of the non-pharmacological measures in patients with symptomatic orthostatic hypotension. In addition to re-hydration, water-drinking has an acute pressor effect.

One of the earliest reports of the documented pressor effect of water was by Jens Jordan. In 1999, he reported that when patients with severe autonomic failure drank 480 ml of tap water quickly, there was a substantial rise in blood pressure of up to 35 mmHg. This effect is equivalent to smoking two unfiltered cigarettes or ingesting 250 mg caffeine (2 cups of strong coffee). In a later study, he found that systolic blood pressure had risen by as much as 37 mmHg in those with autonomic failure half an hour after drinking water. In some patients the rise was as much as 100 mmHg. Water-drinking has also been shown to be effective in attenuating post-prandial fall in blood pressure. Its effectiveness is seen within five minutes.

Water-drinking is also effective in patients with tetraplegia. Water raised blood pressure within five minutes of drinking and reached a peak at 40 minutes. The response was more marked in the older subjects than in the young. Jordan found a rise (11 mmHg) in BP after water-drinking in older subjects (age 57 years), and no effect in younger controls (age 2.5 years), suggesting an attenuation of its pressor effect in younger persons. Tank's observation of a corresponding fall in heart rate (64 to 60 bpm) after water ingestion is consistent with the results of other investigators. Interestingly, the temperature of the water does not seem to affect blood pressure rise.

Mechanism of action

There are several theories as to how water-drinking exerts a pressor effect. One consistent finding amongst those with normal or residual autonomic nervous function is that water-drinking causes sympathetic system activation. Jordan found that, when older controls (mean age 57 years) drank 480 ml of water, there was an increase in plasma norepinephrine levels. Increased muscle sympathetic nerve activity (MSNA) was also noted by Scott in young healthy subjects after drinking water. Another investigator also noted a sharp increase in radial artery resistance in young volunteers after drinking 11 ml/kg of water. Jordan found that patients with residual efferent sympathetic function have a greater pressor response than those patients with little or no residual autonomic function. There is little blood pressure rise in those with absent autonomic function.

The exact mechanism by which water-drinking causes a rise in sympathetic activity is unclear. Oropharyngeal activation, gastric dilatation, osmosensitive afferent structures in the gastrointestinal tract and rehydration of subtle volume depletion have all been implicated. Water, being inexpensive and readily available, would appear to be an ideal potential treatment for OH but evidence on its tolerability and acceptability to older people requires further work.

Salt

Sodium plays an integral part in maintaining intra- and extra-vascular volume and therefore daily intake of sodium has an effect on blood pressure. An animal study in chimpanzees showed that blood pressure rose with increased salt intake and reverted to normal when the increase was stopped.

Salt has received bad publicity from its casual link with hypertension. In 1982, the collaborators of the INTERSALT project set out to study populations in 32 countries. Amongst 10,074 subjects, there was a significant positive correlation between urinary sodium excretion and systolic blood pressure. A 100 mmol difference (for
example 170 and 70 mmol/day) of urinary sodium excretion was associated with a difference of systolic blood pressure of 5 to 7 mmHg and a diastolic difference of 4–6 mmHg. The difference was greater in those who were older.

Sodium intake varies widely. A person usually excretes only about 1–2 litres of urine and 150–250 mmol of sodium a day. Aldosterone and atrial natriuretic peptide (ANP) are the main hormones that are responsible for sodium reabsorption in the distal segments of the nephron. Low perfusion pressure in the afferent arteriole triggers the juxtaglomerular apparatus to release rennin, which in turn leads to an increase in aldosterone and thereby causes sodium absorption and retention. Excessive sodium intake in subjects with borderline hypertension also produced abnormal increases in forearm vascular resistance, neurogenic vasoconstriction and arterial pressure. When a 24-hour blood-pressure monitor was applied to salt-sensitive subjects, high salt intake resulted in a blunted nocturnal dip in blood pressure. The normal circadian rhythm to blood pressure was disturbed. For these reasons high salt intake is best avoided in those with co-existing supine hypertension.

However, in patients with isolated OH, increased salt and water intake has been used with therapeutic effect. A case report described how salt was useful in a 14-year-old Japanese boy with OH in whom alpha-agonists had failed to control symptoms. Within two days of taking a high salt diet (i.e. an extra 5–6 g sodium daily), his symptoms improved greatly, and this was associated with increased plasma volume. He gained 1.6 kg in weight.

El-Sayed and Hainsworth carried out an elegant double-blind, placebo-controlled trial in 20 patients, and an open study in 11 patients, of the effect of giving 120 mmol/day of sodium chloride. Patients who showed an improvement in orthostatic tolerance were those whose salt excretion prior to the study was less than 170 mmol/day. Salt-loading increased plasma volume by 300 ml. The effect of salt was evident after three days.

Cooper and Hainsworth studied the effect of dietary salt on orthostatic tolerance in patients with recurrent syncope. The investigators examined orthostatic tolerance using head-up tilt and lower-body suction. Those with low salt excretions and poor orthostatic tolerance were given daily salt supplements of 1.5 mmol/kg and reassessed after three months. At baseline, those with sodium excretion of <170 mmol/day had significantly lower orthostatic tolerance than those with higher excretion. Salt loading was shown to increase mean arterial pressure by 1.8 mmHg without any significant change in supine systolic blood pressure. More than two-thirds of the patients given salt supplementation had increases in orthostatic tolerance by two minutes or more. None of the patients who were given salt supplementation (about 100 mmol/day) in this study developed blood pressure in the hypertensive range.

Claydon in a later study found that 100 mmol/day of salt supplementation improved orthostatic tolerance in 10 of the 11 subjects who had recurrent syncope. There was no change in supine blood pressure. For those who responded to salt supplementation, the forearm vascular resistance also increased.

Increased fluid and liberal salt intake has now become part of the standard advice for patients with orthostatic hypotension. However, we need to caution against its use in those who are hypertensive. It is our practice to perform 24-hour ambulatory blood-pressure monitoring initially to identify an excessive blood-pressure rise in those to whom we advocate extra salt intake.

Sleeping with the head of the bed elevated

Sleeping with the head of the bed elevated (SHU) is widely recommended in the literature for treatment of orthostatic hypotension. (see Figure 1) The European Society of Cardiology recommends it as treatment for OH as several researchers have reported that sleeping with the head of the bed elevated greater than 12 degrees (18 inches head-up) is associated with an increased orthostatic tolerance in patients the following day.

This practice was first described in 1940 by two physicians from the Mayo Clinic, MacLean and Allen. They instructed four of their patients with orthostatic hypotension not to sleep or lie on a flat bed but to lie in a semi-inclined or head-up position. The term ‘head-up’ was used to describe a position accomplished by placing the posts of the head of a bed on ordinary kitchen chairs or on chairs of similar height, that is about 18 inches. This tilt of the bed corresponded to 13 degrees in a standard 75-inch length bed. The
How to position your bed for sleeping head-up

Figure 1 Schematic diagram showing how the head of the bed is elevated by blocks

patients were also instructed to rest in chairs or the SHU bed during the day. There was a marked improvement in patients' orthostatic symptoms. The improvement was evident within three days. The improvement disappeared after sleeping horizontally for a night.

Since then physicians have tried a variety of angles to some effect. In 1943, Corcoran used SHU at 40 degrees in a woman who had OH following severe pneumonia, whilst Bannister et al. in 1969 advised their patients to sleep seated in chairs (i.e. 90 degrees elevation).

Most researchers used SHU in combination with increased water and salt intake as well as fludrocortisone. In 1992, Ten Harkel and colleagues used SHU (at 12 degrees of elevation) as part of the treatment for OH in six patients with autonomic failure. These patients were also maintained on a high salt diet (150-200 mmol sodium) and were asked to drink at least two litres of water a day. SHU alone reduced the mean drop in systolic/diastolic BP by 11/5 mmHg. When combined with fludrocortisone, the improvement was more significant (i.e. by 42/21 mmHg). The patients gained an average of 0.5 kg after SHU alone and, when combined with fludrocortisone, the weight gain was 1.6 kg. Some patients with incapacitating OH until the introduction of head-up tilt, have been maintained satisfactorily for years solely on this form of treatment.

Kardos used SHU effectively in a 66-year old man who had three syncopal episodes a day prior to treatment. The patient became symptom-free after SHU at 15 degrees in combination with salt and fludrocortisone. His symptoms deteriorated when he returned to sleeping in a horizontal position after two weeks despite salt and fludrocortisone.

Van Lieshout et al. reported smaller reductions in upright BP at one-minute standing after three-weeks treatment with SHU and fludrocortisone in eight patients with autonomic failure. They also found that the decline in stroke volume and cardiac output were less after treatment. There was a rise in BP of 14 mmHg as a result of the combination of low-dose fludrocortisone and nocturnal head-up tilting. The treatment was associated with weight gain as a result of fluid retention.

SHU is believed to work through increasing circulating plasma volume by reducing overnight diuresis. It has been suggested that SHU operates through activation of the renin-angiotensin system due to lowered renal artery pressure. This leads to sodium and water conservation thereby increasing intra-vascular volume. It also increases extracellular fluid deposition with evidence of
ankle oedema.\textsuperscript{49,50} It has been suggested that the increased extra-cellular fluid volume in the lower extremities may play a role by increasing tissue pressure and preventing venous pooling in the lower limb when the patient stands up.\textsuperscript{47}

**Compression hosiery, abdominal binders and others**

Application of graduated pressure from a support garment to the lower limbs reduces venous pooling and improves ventricular filling. However, this effect is temporary and quickly wears off when the garment is removed.\textsuperscript{53} Deng et al.\textsuperscript{34} evaluated the efficacy of compression of various compartments of the body (for instance calves, thighs, lower abdomen, and all compartments combined) using a modified anti-gravity suit. This experiment was carried out in patients with autonomic failure. Orthostatic systolic blood pressure rose by 26.3 mmHg with full compression of various components. The single compression most effective in reducing blood pressure fall was at the level of the lower abdomen. Tanaka\textsuperscript{55} and Smit\textsuperscript{56} reported the benefits of using inflatable abdominal bands or abdominal binders to reduce the capacitance beds. The more commonly-used compression hosiery was evaluated by Henry et al.\textsuperscript{57} who found that the drop in blood pressure was significantly reduced when thigh-length compression stockings were worn. Anti-gravity suits and leg tourniquets,\textsuperscript{49,58} though effective in theory, are not practical for daily purposes.

**Physical counter-manoeuvres**

Patients with OH often complain of debilitating dizziness in the upright position. The treatment goal is to maintain cerebral perfusion when standing, so that symptoms do not occur. Physical counter-manoeuvres (PCM) that increase peripheral resistance and venous return allow patients to stand longer without symptoms.\textsuperscript{59} These manoeuvres increase the blood pressure by up to 10–15 mmHg and may be used in conjunction with other therapies for OH.\textsuperscript{60}

Lowering the head into a stooped position and crossing the legs has been described since 1928.\textsuperscript{61,62-64} Leg-crossing, leg-muscle pumping and tensing, shifting weight from leg to leg and putting one foot on a chair can also bring relief of symptoms.\textsuperscript{65} Some patients find standing with legs crossed is very effective in preventing symptoms, while others are helped by squatting and stooping.\textsuperscript{66} Thigh contractions and toe extension have been shown to be effective as well.\textsuperscript{67}

In a case report, Bickelmann\textsuperscript{68} described a businessman whose work required him to stand talking to customers. He averted syncope by tensing the muscle of his arms and legs or bending forwards as if to tie his shoelaces. An Italian physician, Biaggioni,\textsuperscript{69} described a complex manoeuvre of 'leg-crossing at a 30° angle, leaning the torso 30° forward and placing his right hand on his right thigh for support'. Takishita\textsuperscript{70} reported that patients could maintain blood pressure if they leg-crossed while sitting.

Wieling\textsuperscript{79} described how a patient who had dysautonomia after Hodgkin’s disease was able to use PCM to alleviate orthostatic symptoms. Before adopting PCM, the patient had such incapacitating postural symptoms that she was confined to the supine position. However, she noticed that she was able to move around by adopting a series of manoeuvres. Squatting seemed to help dizzy symptoms that came on shortly after standing. Orthostatic tolerance also improved markedly when she stood with the head bent with contracted abdominal muscles. By applying these PCM, she was able to walk short distances in a stooped position. She climbed stairs by hopping backwards up the stairs, while maintaining a knee-bent posture. During exercise (such as riding a bike), the patient relieved exercise-induced hypotension by drawing her knees to the frame of the bicycle or bending forwards over the handlebar.

Patients can be trained to perform these manoeuvres effectively by biofeedback. Leg-crossing has been found to be more effective than neck flexion or abdominal contractions.\textsuperscript{57} Certain manoeuvres such as thigh contractions and leg-crossing improved with practice. These physical manoeuvres seem to be helpful in younger patients with OH. Their utility in older patients is less clear. Leg-crossing during prolonged standing and sitting, and isometric contraction of arm muscles would probably be tolerated by elderly patients. However, squatting, leg-muscle pumping (tip-toeing), abdominal contractions and bending forwards may be less acceptable to older patients with gait imbalance. Nevertheless, PCM can be used very effectively in the right setting as a non-pharmacological measure of managing orthostatic hypotension.
Portable fishing chair

If physical counter-manoeuvres fail, one can carry a portable ‘fishing’ chair and sit on it to relieve orthostatic symptoms. Smit et al. found the fishing chair to be more effective than the Derby chair. Sitting on a chair has been shown to cause a sufficient rise in blood pressure to alleviate OH symptoms.

Tilt-training and resistance-training

Tilt-training or an orthostatic self-training programme is mainly used in those with neurocardiogenic syncope. The orthostatic self-training programme includes standing against a wall without moving, twice a day every day for a planned duration of up to 30 minutes each time. The studies to date had been done in patients with vasovagal syncope and effectiveness in OH is therefore unclear.

Zion et al. prescribed an eight-week home-based resistance-training programme for elderly patients with OH. Even though there were significant increases in dynamic strength, no significant effect was seen upon blood pressure.

Summary

In conclusion, there are many non-pharmacological therapies for OH with good scientific plausibility and a respectable evidence base for effectiveness. Most are inexpensive and free of significant side-effects. On the other hand, they require time and motivation on behalf of both patient and physician and this has limited their use to date. Care with both individualization of treatment and patient selection is required. Most evidence so far has been in younger patients, but there is no reason why most would not be equally effective in older patients, who are frequently more compliant of therapies in any case. More research is required in order to establish the most appropriate and acceptable methods for older patients and more time-effective ways for busy clinicians to impart training (e.g. information leaflets and videos versus group or individualized instruction). In the interim, we recommend that non-pharmacological therapies be considered in all patients with symptomatic orthostatic hypotension before medication is instituted, and as an adjunct for patients who are not adequately controlled using medication.

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Postal questionnaire survey: the use of sleeping with the head of the bed tilted upright for treatment of orthostatic hypotension in clinical practice

SIR—Orthostatic hypotension (OH) is common and affects one in five community-living older persons [1]. The incidence is higher amongst older in-patients [2] and those attending a syncope clinic [3].

The treatment of OH is through increasing peripheral vascular resistance and/or intravascular volume. Existing treatments such as increased water intake, salt replacement [4] and medications may lead to hypertension, and older people tend to tolerate these interventions poorly [5]. Drinking 2–2.5 l of fluids daily may be effective in younger patients [6, 7] but may be undesirable in older patients who can be prone to urinary incontinence.

Sleeping with the head of the bed elevated (SHU) is established as part of the treatment modality for OH [6, 8, 9]. The European Society of Cardiology guidelines [9] recommend raising the head of the bed on blocks to permit gravitational exposure during sleep, which results in chronic intravascular volume expansion. Mathias and Bannister [10] recommend SHU as first-line treatment for OH in patients with autonomic failure (AF).

Our literature review suggests that SHU at 12° or greater confers some benefit in patients with OH. However, the studies were small with sample sizes of eight subjects or less with varying ages (23–66 years), and the majority of the patients had AF (Table 1). A number of those studies used a combination of SHU, fludrocortisone, and increased water and salt intake, so identifying the exact contribution from SHU is often not possible. The improvement in orthostatic blood pressure (BP) with SHU from the studies is summarised in Table 1.

SHU was first described by two American physicians, MacLean and Allen [11], in 1940. They observed that patients with OH were most symptomatic early in the morning after lying horizontal overnight but that they improved during the day. They therefore advised their patients to place the head-end of the bedposts on two 18-inch height chairs. This was equivalent to an angle of 13° in a standard 75-inch bed. This resulted in improvements in both BP and symptoms. In 1943, Corcoran et al. [12], also American, showed how SHU was beneficial to a 40-year-old woman after she slept at 40° tilt for 2 months. In 1969, Banister et al. [13] reported that three out of four of his patients improved after sleeping in chairs and taking fludrocortisone. This improvement disappeared when the patients slept horizontal for one night.

More recently, Ten Harkel et al. [14] and van LIESHOUT et al. [15] described studies using SHU at 12° in combination with fludrocortisone, intake of fluid of at least 2 l and >150 mmol sodium per day. They found improvement in both BP and orthostatic tolerance. Finally, Kardos described how SHU at 15° rendered a 66-year-old man symptom-free when salt-enriched diet and fludrocortisone had been insufficient to prevent recurrent syncope.

The aim of our study was to determine the extent to which SHU is used in current clinical practice among experts for the treatment of OH and how it is prescribed.

Methods

We carried out a postal survey of medical practitioners who attended an international symposium on syncope in Newcastle, upon Tyne, UK, which took place in November 2003. A total of 238 delegates attended the conference, of which 18 non-clinical delegates were excluded. We sent out 220 questionnaires at the first mailing in February 2004. The breakdown of specialty of delegates was as follows: 128 (58%) were in geriatric medicine, 33 (15%) general medicine, 26 (12%) cardiology, 15 (7%) physiology, 11 (5%) neurology and 7 (3%) not determinable. The second mailing was carried out 2 months later to non-respondents. We completed the survey on 31 August 2004.

The structured questionnaire ascertained the respondents' country and positions in their departments. The rest of the questionnaire was divided into four sections. They were asked (i) if they routinely prescribed SHU, (ii) whether SHU was used before medications, (iii) about the angles and the heights of elevation of the head of the bed and (iv) their reasons for not using SHU. The other modalities of treatment for OH they used were also obtained. Where the respondents gave specific heights of elevation instead of angles, we calculated the corresponding angle of the tilt of bed based on the standard 75-inch bed.

Results

There were 149 respondents from 121 hospitals, who represented an overall 67% response rate. Of the respondents, 135 (91%) were from the United Kingdom. Consultants or heads of departments accounted for 135 (70%) of the replies, registrars or associate specialists 34 (23%) and clinical nurse specialists 3; seven doctors did not specify their positions. The specialties in which the respondents practised are as follows: geriatric medicine 96 (64%), general medicine 29 (20%), cardiology 12 (8%), physiology 7 (5%) and neurology 5 (3%).

Of the respondents, 90 (60%) prescribed SHU—40 (27%) routinely and 50 (33%) occasionally. Fifty-nine (40%) respondents never prescribed SHU. Thirty-eight respondents (25%) used SHU before prescribing medications. Geriatricians were no different in their prescription compared with other specialties whether in using it as part of OH treatment (geriatricians (G) versus non-geriatricians (non-G),...
Table 1. Blood pressure (BP) improvement from sleeping in a ‘head-up’ position: a review of the literature

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient number</th>
<th>Patient type</th>
<th>SHU intervention</th>
<th>ΔBP (mm Hg)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>MacLean and Allen [11]</td>
<td>4</td>
<td>One patient with AF</td>
<td>12° for 3 days</td>
<td>+120/+70</td>
</tr>
<tr>
<td>Corcoran et al. [12]</td>
<td>1</td>
<td>Three patients with NOH</td>
<td>+102/+64</td>
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</tr>
<tr>
<td>Bannister et al. [13]</td>
<td>4</td>
<td>One patient post prolonged bed rest</td>
<td>40° for 2 months</td>
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<tr>
<td>Ten Harkel et al. [14]</td>
<td>6</td>
<td>Three patients with AF</td>
<td>90° for four nights</td>
<td>+40/+17</td>
</tr>
<tr>
<td>Karlos et al. [19]</td>
<td>1</td>
<td>One patient with NOH</td>
<td>12° alone</td>
<td>+11/+5</td>
</tr>
<tr>
<td>van Lieshout et al. [15]</td>
<td>8</td>
<td>Eight patients with AF</td>
<td>12° and fludrocortisone for 1 week</td>
<td>+42/+21</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15° for 2 weeks</td>
<td>Not available</td>
</tr>
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AF, autonomic failure; NOH, neurogenic orthostatic hypotension or non-autonomic failure orthostatic hypotension; SDBP, supine diastolic BP; SHU, sleeping with the head of the bed elevated; SSBP, supine systolic BP; UDBP, upright diastolic BP; USBP, upright systolic BP.

57/96 versus 33/53, chi-square = 0.0191, df = 1, P = 0.729

Table 2. The angle of tilt of the bed (based on a standard 75-inch bed), the corresponding height of elevation in inches and the number of medical practitioners prescribing it

<table>
<thead>
<tr>
<th>Angles in degrees</th>
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<td>&lt;3</td>
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<tr>
<td>30-45</td>
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<td>11</td>
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ΔBP = (SSBP_post - USBP_post) - (SSBP_pre - USBP_pre)/[(SDBP_post - UDBP_post) - (SDBP_pre - UDBP_pre)].

*BP denotes the change in mm Hg in supine and upright systolic/diastolic BP post-SHU compared with pre-SHU.

Discussion

Our survey showed that SHU was regularly used by a significant proportion of syncope experts for the treatment of OH and that geriatricians were the largest specialty involved in this treatment.

The most common angles used were between 3 and 5° (corresponding to 4- to 6-inch elevation). Only a third of those who used SHU were recommending angles for which evidence exists (i.e. >12°). It is noteworthy, however, that a significant proportion of respondents were unconvinced about its efficacy or tolerability.

SHU is postulated to work through the renin-angiotensin system (RAS) by reducing overnight natriuresis and diuresis [16], as patients with OH can lose up to 1 kg in weight overnight [17] while recumbent. A reduction in renal arterial pressure by SHU is thought to activate the RAS, which results in sodium and water retention [10]. Given the physiological basis for its perceived mechanism of action, the angle of tilt may be important for efficacy.

Although the original studies demonstrated efficacy at angles of at least 12°, our literature review found a variety of recommendations for SHU angles. The European Society of Cardiology [9] recommends 10-20°, while American physicians such as Bradley and Davis [8] and Engstrom and Aminoff [18] suggest angles of 5-20° and >30°, respectively. Other proponents [6] recommend raising the bed head by blocks or tilting the mattress, rather than the bed, with poly-styrene wedges but did not specify an angle.

Some limitations to this study must be acknowledged. We did not ascertain the age range of the patients handled by the respondents although almost two-thirds were geriatricians, suggesting that a significant proportion of patients treated were elderly. Users of this therapy may have been more likely to respond, which may have led to an overestimation of its use. However, a response rate of 46% is good for a study of this type, and the specialty breakdown of respondents was similar to the overall sample.
The evidence for the effectiveness of SHU is sparse, and there is currently no literature to support SHU at <12° or indeed in older people at all. At 12°, some patients have complained of sliding down to the end of the bed [14] and some have developed peripheral oedema, so there must be some concern about compliance when advising older persons to sleep at this degree of elevation. In conclusion, the conflicting recommendation of SHU angles in the literature is reflected in the lack of clarity in clinical practice. SHU is not an uncommon treatment, being used by more than half of the medical practitioners surveyed. The majority of respondents used smaller angles for which there is no literature support. Further studies are required to determine whether the more commonly prescribed lesser angles are effective and safe in older patients. The mechanisms of action of SHU and its effectiveness in those with and without AF need to be further investigated. Comparison with existing treatments would also be worthwhile.

Further research is required to determine if angles <12° are effective and safe in older patients.

**Key points**

- More than half of the medical practitioners surveyed used sleeping head-up as a treatment for OH.
- Two-thirds of respondents recommended angles (<12°) for which there is no literature support.

**Conflicts of interest**

None.

**References**


doi:10.1093/ageing/af073
Research letter

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<td>3-5</td>
<td>4-6</td>
<td>24</td>
</tr>
<tr>
<td>5.5-10</td>
<td>8-13</td>
<td>14</td>
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<tr>
<td>12-25</td>
<td>16-32</td>
<td>11</td>
</tr>
<tr>
<td>30-45</td>
<td>38-53</td>
<td>11</td>
</tr>
</tbody>
</table>

AF, autonomic failure; NOH, neurogenic orthostatic hypotension or non-autonomic failure orthostatic hypotension; SDBP, supine diastolic BP; SHU, sleeping with the head of the bed elevated; SSBP, supine systolic BP; UDBP, upright diastolic BP; USBP, upright systolic BP.

ΔBP = [(SSBP post - USBP post) - (SSBP pre - USBP pre)] / [(SSBP post - UDBP post) - (SSBP pre - UDBP pre)].

*BP denotes the change in mm Hg in supine and upright systolic/diastolic BP post-SHU compared with pre-SHU.

Discussion

Our survey showed that SHU was regularly used by a significant proportion of syncope experts for the treatment of OH and that geriatricians were the largest specialty involved in this treatment.

The most common angles used were between 3 and 5° (corresponding to 4- to 6-inch elevation). Only a third of those who used SHU were recommending angles for which evidence exists (i.e. ≥12°). It is noteworthy, however, that a significant proportion of respondents were unconvinced about its efficacy or tolerability.

SHU is postulated to work through the renin-angiotensin-aldosterone system (RAS) by reducing overnight natriuresis and diuresis [16], as patients with OH can lose up to 1 kg in weight overnight [17] while recumbent. A reduction in renal arterial pressure by SHU is thought to activate the RAS, which results in sodium and water retention [10]. Given the physiological basis for its perceived mechanism of action, the angle of tilt may be important for efficacy.

Although the original studies demonstrated efficacy at angles of at least 12°, our literature review found a variety of recommendations for SHU angles. The European Society of Cardiology [9] recommends 10–20°, while American physicians such as Bradley and Davis [8] and Engstrom and Aminoff [18] suggest angles of 5–20° and >30°, respectively. Other proponents [6] recommend raising the bed head by blocks or tilting the mattress, rather than the bed, with poly-styrene wedges but did not specify an angle.

Some limitations to this study must be acknowledged. We did not ascertain the age range of the patients handled by the respondents although almost two-thirds were geriatricians, suggesting that a significant proportion of patients treated were elderly. Users of this therapy may have been more likely to respond, which may have led to an overestimation of its use. However, a response rate of 67% is good for a study of this type, and the specialty breakdown of respondents was similar to the overall sample.
The evidence for the effectiveness of SHU is sparse, and there is currently no literature to support SHU at <12° or indeed in older people at all. At 12°, some patients have complained of sliding down to the end of the bed and angles in the literature is reflected in the lack of clarity in required to determine whether the more commonly prescribed lesser angles are effective and safe in older patients. The mechanisms of action of SHU and its effectiveness in those with and without AF need to be further investigated. Comparison with existing treatments would also be worthwhile.

Further research is required to determine if angles <12° are effective and safe in older patients.

Key points
- More than half of the medical practitioners surveyed used sleeping head-up as a treatment for OH.
- Two-thirds of respondents recommended angles (<12°) for which there is no literature support.

Conflicts of interest
None.

References

Research letter

doi:10.1093/ageing/afl073
# Appendix

**Questionnaire on clinical practice: sleeping in the head-up position**

<table>
<thead>
<tr>
<th>Position in department</th>
<th>Head of department</th>
<th>Consultant</th>
<th>Clinical fellow/registrar</th>
<th>Nurse specialist</th>
<th>Others</th>
<th>Specify</th>
</tr>
</thead>
</table>

1. Do you routinely advise patients with orthostatic hypotension to sleep with the head of the bed raised?
   - Yes [ ]
   - No [ ]
   - Sometimes [ ]

Would you routinely use this before starting patients on medications?
   - Yes [ ]
   - No [ ]
   - Sometimes [ ]

2. If yes, how high do you ask patients to raise the head of the bed?
   - Degree [ ]
   - Height raised [ ]

3. If no, why not?
   - Patient inconvenience [ ]
   - Not convinced it is effective [ ]
   - Others [ ]

4. Please tick the following measures you are advising for treatment of orthostatic hypotension (you may choose as many as you like).
   - Drink 1.5–2l of non-caffeinated fluids [ ]
   - Salt loading [ ]
   - Physical counter-maneuvers [ ]
   - Exercise training [ ]
   - Sleep head-up [ ]
   - Fludrocortisone [ ]
   - Midodrine [ ]
   - Desmopressin [ ]
   - Others (please specify) [ ]

**Comments**

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Page 4 of 4
Physiological effects of sleeping with the head of the bed elevated 18 in. in young healthy volunteers

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Received: 12 July 2007 / Accepted: 25 September 2008 / Published online: 25 October 2008
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Abstract

Background Sleeping with the head of bed tilted upwards (SHU) is recommended as a treatment of orthostatic hypotension though the supporting evidence is weak.

Aim To investigate the physiological effects of SHU amongst a group of young healthy volunteers.

Methods Twenty-nine volunteers, mean age 22 years, underwent 1-week of SHU at 18-in. elevation. Before and after hemodynamic and non-haemodynamic parameters were recorded.

Results After SHU, there were reductions in the systolic blood pressure drop on standing, upright total peripheral resistance, haemoglobin, nocturnal urinary volume, orthostatic dizziness and increases in weight, standing cardiac output and ankle circumference. There were no differences in heart rate, stroke volume, renin, aldosterone, pro-atrial natriuretic peptide or 24-h blood pressure.

Conclusions In these healthy subjects, SHU for 1 week had a nocturnal antidiuretic effect with both intra- and extra-vascular accumulation of fluid and was associated with reduced postural drop in SBP and improved orthostatic tolerance.

Keywords Sleep · Blood pressure · Physiology

Introduction

Orthostatic hypotension (OH) is defined as a fall of 20 mmHg in systolic blood pressure (SBP) or a 10 mmHg drop in diastolic blood pressure in response to standing from a supine position [1]. The treatment of OH principally acts through increasing circulating plasma volume, peripheral resistance or venous return. Pharmacological treatments such as fludrocortisone [2] and midodrine [3, 4] are associated with significant side effects that necessitate discontinuation of treatment [5]. On the other hand, conservative management, which includes water-drinking [6–8], increasing salt intake [9, 10], physical counter-manoeuvres [11] and sleeping with the head of the bed elevated (SHU) may be better tolerated.

Although SHU has been included in several guidelines [12–15] as one of the non-pharmacological treatments for OH, a substantial proportion of syncope experts remain unconvinced about the evidence for SHU’s effectiveness and tolerability and it is used routinely by a minority only [16]. A few reports have demonstrated that sleeping with the head of the bed tilted upwards (SHU) greater than 12 degrees is associated with an increased orthostatic tolerance the next morning. Early observations were predominantly case reports [17, 18]. Although recent studies have tended to support these observations [19, 20], sample sizes were very small (less than 10 subjects) and in most cases, interventions such as water and salt loading and/or medications were also being used. It is still not clear whether sleeping head up has any additive benefits to existing treatments.
The aim of our study was to investigate the acute physiological effects of SHU on a large group of healthy young volunteers.

**Methods**

We recruited 29 healthy subjects (13 men) with a mean (standard deviation) age of 22 (1.9) years. Subjects were all college students, non-smokers, free from chronic medical conditions and did not use recreational drugs. While healthy subjects obviously may not respond in a similar fashion to patients with OH, their use did allow us to study the intervention in much more detail than heretofore and allowed us to look for any broad physiological effects. Our rationale was that, if SHU could be shown to have general physiological effects, then the rationale for conducting further research in more frail patients would be stronger. All subjects signed an informed consent document approved by the St James's Hospital Research Ethics Committee.

**Protocol**

The study protocol is outlined in Fig. 1. All subjects were required to drink at least 2 l of water a day from 1 week prior to starting SHU. While sleeping "head up" they were required to drink at least 2 l of water from 0700 to 2100 h and exactly 500 ml at 2100 h and no more till 0700 h. Subject were required to sleep head up 18 in. from days 3 to 9, which corresponds to 12 degrees of elevation for a standard 75 in. bed. The bed arrangements of SHU were as described by MacLean [17].

The head of the bed was tilted up 18 in. higher than the foot of the bed using two sturdy 18-in. chairs. During this period, subjects were required to sleep on the tilted bed during any nap-time and at night (2300 to 0700 h). The subjects were reminded to keep hydrated and sleep head up each night by text messages.

**Haemodynamic parameters**

Haemodynamic variables were recorded during an “active stand”. After a total of 5–10 min of preceding supine rest, subjects were instructed to move from supine to standing in about 3 s, if necessary with assistance, and stand for at least 2 min without support [21]. The subjects underwent active stands on four occasions between 0900 and 1100 hrs (see Fig. 1); two occasions before SHU (i.e. days 2 and 3) and on two occasions after SHU (i.e. days 9 and 10).

A non-invasive continuous beat-to-beat device was used for haemodynamic measurements (“Finometer” TNO, Amsterdam) recording the SBP and heart rate (HR). Stroke volume (SV), cardiac output (CO) and total peripheral resistance (TPR) were derived from Modelflow® calculations [22].

**Non-haemodynamic parameters**

The subjects were questioned regarding postural dizziness at the end of each stand.

At 24 h urine was collected as 2 samples: a ‘day sample’ comprised of urine passed between 0700 and 2300 h excluding the first urine sample on rising and a ‘night sample’ was from 2300 till 0700 h the following day including the first sample on rising. Urine sodium and volume were recorded. All subjects were weighed fasting, without shoes, in the same set of clothes and post-micturition at 0800 h.

The calf and ankle circumferences were recorded to the nearest mm in the supine position at designated points of the right lower limb, i.e. calf circumference at 100 mm below the lower border of patella, ankle circumference at 100 mm above the lower border of medial malleolus using a measuring tape accurate 1 mm. All blood samples were taken between 0900 and 1100 h. After lying supine for 1 h, blood was drawn for haematocrit [23], plasma electrolytes (Roche/Hitachi Modular System, ISE Unit), plasma renin activity (PRA) (Renin MAIA, Adaltis, Italy, intra-assay coefficient of variation (C.V.) 5.1%, inter-assay C.V 5.1%), aldosterone (Aldosterone MAIA, Adaltis, Italy, intra-assay coefficient of variation (C.V.) 5.4%, inter-assay C.V 6.4%) and pro-atrial natriuretic peptide (pro-ANP 1–98)(Biomedica Gruppe, Vienna, Austria, intra-assay coefficient of variation (C.V.) 6%, inter-assay C.V. 7%). Only supine levels were taken. Blood samples were taken and analysed as per manufacturer’s
instructions. The 24-h ambulatory blood pressure monitoring was measured using A&D TM-2430 [24]. Mean sleep and awake SBP were calculated for each subject.

The primary outcome measures were the nadir SBP during the "active stand" and the mean drop in SBP (ΔSBP) comparing the 10-s interval (I0) immediately before standing to the first two 10-s intervals (I1 and I2) immediately after standing. The secondary outcome measures were the change in symptoms of postural dizziness, the haemodynamic variables during the active stand (i.e. HR, SV, CO and TPR) and 1 week interval change in weight, day and night urinary volumes, urinary sodium, right calf and ankle circumferences, supine plasma renin activity (PRA), aldosterone, pro-atrial natriuretic peptide (Pro-ANP 1–98), serum haemoglobin and electrolytes and mean sleep and awake SBP.

Statistical analysis

Haemodynamic parameters recorded during four "active stands" (i.e. two before and two after SHU) were averaged to produce "before" and "after" variables.

All cardiovascular parameters were exported in 1-s bins. Data were then averaged in 10-s bins so as to reduce error due to random beat-to-beat blood pressure variation. We decided to analyse data from the first 20 s as the time when nadir SBP was likely to occur. Nadir SBP, ΔSBP (defined as the mean drop from I0 to nadir SBP), peak HR, SBP and HR at I1 and I2 during standing were calculated. Percentage change from I0 to peak/nadir, from I0 to I1 and I2 during standing were also calculated for SV, CO and TPR.

Results

Haemodynamic variable are shown in Table 1. Although there was no change in the nadir SBP on standing, the mean drop in SBP (ΔSBP) was significantly lower after 1 week of SHU. There was a significant increase in CO at I2 (8.6%) and a reduction in TPR at I1 (12.1%) and I2 (9.1%). There were no differences in HR and SV. In non-haemodynamic parameters, there were significant increases in median weight (0.4 kg) and ankle circumference (8 mm). The night urinary volume fell by 145 ml from SHU despite similar 24-h urinary volume and sodium excretion. There was also a 0.3 g/dL reduction in

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Change in haemodynamic parameters after SHU for 1 week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre SHU</td>
</tr>
<tr>
<td>Nadir SBP (mmHg)</td>
<td>77.6 (14.5)</td>
</tr>
<tr>
<td>Mean drop in SBP (mmHg) baseline to 10 s after standing</td>
<td>-22.3 (10.1)</td>
</tr>
<tr>
<td>Mean drop in SBP (mmHg) baseline to 20 s after standing</td>
<td>-21.8 (11.3)</td>
</tr>
<tr>
<td>Peak HR (bpm)</td>
<td>101.8 (2.1)</td>
</tr>
<tr>
<td>Average change HR baseline to I1 (bpm)</td>
<td>14.1 (6.6)</td>
</tr>
<tr>
<td>Average change HR baseline to I2 (bpm)</td>
<td>19.7 (8.7)</td>
</tr>
<tr>
<td>Change in SV from baseline to nadir (%)</td>
<td>-35.0 (12.7)</td>
</tr>
<tr>
<td>Change in SV from baseline to I1 (%)</td>
<td>-10.9 (10.0)</td>
</tr>
<tr>
<td>Change in SV from baseline to I2 (%)</td>
<td>-22.3 (10.4)</td>
</tr>
<tr>
<td>Change in CO from baseline to peak (%)</td>
<td>28.1 (21.2)</td>
</tr>
<tr>
<td>Change in CO from baseline to I1 (%)</td>
<td>7.58 (13.0)</td>
</tr>
<tr>
<td>Change in CO from baseline to I2 (%)</td>
<td>-0.5 (17.1)</td>
</tr>
<tr>
<td>Change in TPR from baseline to peak (%)</td>
<td>17.1 (−0.6, 70.2)</td>
</tr>
<tr>
<td>Change in TPR from baseline to I1 (%)</td>
<td>-1.2 (−12.2, 7.3)</td>
</tr>
<tr>
<td>Change in TPR from baseline to I2 (%)</td>
<td>-12.8 (−22.5, −4.1)</td>
</tr>
</tbody>
</table>

All data were analysed for normal distribution and were evaluated using paired t tests or Wilcoxon signed rank tests as appropriate. Postural symptoms were said to be present before SHU if either the active stand on day 2 or 3 was associated with symptoms and were said to be present after SHU, if either active stand on day 9 or 10 was symptomatic. McNemar's test was used to test for significant change in symptoms.

Measurement parameters and power calculations were based on pilot studies of healthy young individuals carried out by our group. A sample of 28 subjects would have a power of 80% and an alpha of 5% to detect a significant difference in nadir SBP of 9 mmHg and a reduction in drop in SBP of 4 mmHg with $P < 0.05$.

Datadesk statistical software was used (version 8 Ithaca, NY) for data analysis. All statistical tests were two-sided.
haemoglobin but no difference was found in PRA, aldosterone and pro-ANP. The graph illustrating the hemodynamic parameters during the active stand is shown in Fig. 2. The non-haemodynamic effects of SHU are shown in Table 2.

In addition, the participants were significantly less dizzy during active stands after 1 week of SHU [27 (93.1%) subjects symptomatic on day 2 or 3 versus 12 (41.4%) subjects symptomatic on days 9 or 10, $\chi^2 = 13.1, P = 0.001$]. Many of the subjects tolerated SHU for the
Table 2 Change in non-haemodynamic parameters after SHU for 1 week

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pre SHU Mean (SD)</th>
<th>Post SHU Mean (SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Night urine volume (ml)</td>
<td>622 (359)</td>
<td>477 (236.)</td>
<td>0.025*</td>
</tr>
<tr>
<td>Day urine volume (ml)</td>
<td>1,510 (768)</td>
<td>1,562 (630)</td>
<td>0.68</td>
</tr>
<tr>
<td>24 h urine volume (ml)</td>
<td>2,133 (973)</td>
<td>2,039 (734)</td>
<td>0.56</td>
</tr>
<tr>
<td>Night urinary sodium excretion (mmol)</td>
<td>373.3 (23.3)</td>
<td>382 (25.1)</td>
<td>0.86</td>
</tr>
<tr>
<td>Day urinary sodium excretion (mmol)</td>
<td>84.3 (42.5)</td>
<td>102.1 (40.9)</td>
<td>0.085</td>
</tr>
<tr>
<td>24 h urinary sodium excretion (mmol)</td>
<td>121.6 (54.4)</td>
<td>140.3 (47)</td>
<td>0.098</td>
</tr>
<tr>
<td>Night urinary potassium excretion (mmol)</td>
<td>14.3 (9.4)</td>
<td>13.4 (8.8)</td>
<td>0.61</td>
</tr>
<tr>
<td>Day urinary potassium excretion (mmol)</td>
<td>44.6 (18.9)</td>
<td>46.3 (17.9)</td>
<td>0.57</td>
</tr>
<tr>
<td>24 h urinary potassium excretion (mmol)</td>
<td>58.9 (22.9)</td>
<td>59.8 (22.9)</td>
<td>0.82</td>
</tr>
<tr>
<td>Glomerular filtration rate (ml/min)</td>
<td>107.7 (24.3)</td>
<td>109.7 (24.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Day SBP (mmHg)</td>
<td>124.4 (12.1)</td>
<td>124.1 (11.3)</td>
<td>0.83</td>
</tr>
<tr>
<td>Night SBP (mmHg)</td>
<td>105.3 (8.9)</td>
<td>104.8 (11.3)</td>
<td>0.74</td>
</tr>
<tr>
<td>Calf circumference (mm)</td>
<td>371 (39)</td>
<td>373 (38)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Ankle circumference (mm)</td>
<td>255 (22)</td>
<td>263 (26)</td>
<td>0.07</td>
</tr>
<tr>
<td>Haemoglobin (g/dL)</td>
<td>13.6 (1.4)</td>
<td>13.3 (1.5)</td>
<td>0.006*</td>
</tr>
<tr>
<td>Pro-ANP (1–98)(fmol/ml)</td>
<td>6,583 (4,920)</td>
<td>6,107 (4,141)</td>
<td>0.47</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.1 (60.5, 79.8)</td>
<td>66.5 (60.5, 79.8)</td>
<td>0.0048*</td>
</tr>
<tr>
<td>PRA (ng/ml/h)</td>
<td>1.3 (0.77, 1.65)</td>
<td>1.0 (0.87, 2.0)</td>
<td>0.95</td>
</tr>
<tr>
<td>Aldosterone (pg/ml)</td>
<td>430 (327, 628)</td>
<td>414 (342, 550)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

week but all complained of sliding down to the bottom of the bed and needed to push themselves up the bed during the night. They also complained of heavier or stiffer legs due to ankle oedema.

Discussion

This study represents the largest series examining the effect of SHU at 18 in. to date albeit in normal subjects. In these healthy subjects, we confirmed the antidiuretic effect of SHU as described by Bannister and Mathias for subjects with autonomic failure [15]. Symptoms of orthostatic dizziness were considerably reduced, as was the ΔSBP. There was an increase in CO and a reduction in TPR (a surrogate marker of vasoconstriction) during active stands after SHU in keeping with an increase in intravascular volume. Previous reports since 1940’s have demonstrated that SHU greater than 12 degrees is associated with an increased orthostatic tolerance the next morning [17]. The improvement in symptoms is thought to be due to a reduction in over night diuresis and natriuresis [25, 26], which can cause weight loss of up to 1 kg patients with autonomic failure [27].

Although subjects in our study were young healthy volunteers and had relatively constant salt and water intake (as demonstrated by the unchanged 24 h urinary sodium and volume), they reduced their urinary volume at night by almost 150 ml and gained an average weight of 400 g from both extravascular (i.e. ankle oedema) and intravascular (i.e. drop in haemoglobin and change in haemodynamic variables) fluid retention. These support and expand (to a healthy group) the findings of Bannister, who demonstrated a reversal of day and night urinary sodium and water excretion in patients with autonomic failure using SHU [28].

The concept of renin–angiotensin–aldosterone system (RAAS) activation by SHU was first considered by Corcoran in 1943, when he demonstrated that an infusion of angiotonin had the same effect on arterial pressure, pulse rate and renal hemodynamics as SHU [18]. Van Lieshout later reported reduced supine and upright PRA and increased ANP levels in both supine and upright positions in four patients with autonomic failure. The aldosterone levels were unchanged [20]. He suggested that supine plasma ANP increase and PRA decrease after SHU was a physiological response to expansion of the intra-vascular volume. We were unable to confirm these findings in this study. Measurement of renin, aldosterone and pro-ANP, however, were not our primary outcome and, as we studied healthy subjects only, we may have been underpowered to investigate these variables. Furthermore, the anti-diuretic effect seen was not associated with an anti-natriuretic effect (i.e. change in sodium excretion) and possible...
mediating effects of other hormones such as anti-diuretic hormone should be considered.

Mathias and Bannister [15] proposed that recurrent exposure to lower blood pressure while sleeping upright in OH patients would activate the RAAS due to renal hypoperfusion. We did not show any effect on nocturnal blood pressure after a week of SHU; however, suggesting that SHU does not cause nocturnal hypotension in healthy subjects though we cannot exclude the possibility of transient effects on BP occurring before this time.

An alternate theory of SHU is that it reduces venous pooling in the lower limb in the same way as a compression hosiery (‘water jacket theory’) where the increase in fluid retention in the legs acts as a perivascular “water jacket” in the legs limiting the vascular volume available for orthostatic venous pooling [17, 29]. An associated decrease in leg compliance has been found after SHU [20]. Our finding of an increase in ankle, though not calf circumference, would go some way to support this theory though the increase was modest and further work is required to see if increases of this magnitude would be associated with haemodynamic effects.

Although relatively well tolerated, many of the subjects complained of sliding to the bottom of the bed and stiff legs from leg oedema and this degree of elevation (12 degrees) is unlikely to be tolerated by older patients, though work carried out by our group suggests that prescription of lesser degrees of elevation (commonly 5 degrees or 6 in.) for older patients with OH is commonly used in Ireland and the UK [16].

Our study has several limitations. As previously mentioned we looked at healthy subjects who may have a different response to this intervention than the patients with OH who may be prescribed it. However, the observed effects were similar to that reported for such patients suggesting broad physiological anti-diuretic effects for this intervention [25]. We looked at the effects during the first week only and whether the observed changes are maintained after a week is unknown. The uncontrolled design means that changes cannot be unequivocally be attributed to the effects of SHU and the possibility that some of the observed changes were due to “acclimatisation” to repeated testing cannot be excluded. For example, some of the observed difference in SBP are after SHU occurred in the 10 s before standing and may reflect an anticipatory response with repeated testing. However, the reduction in ΔSBP is less easily explained by this mechanism and could also represent an effect of SHU via the observed increase in intra-vascular volume. A reduction in orthostatic symptoms over time may be due to the effects of training but the observation that little or no reduction in orthostatic symptoms was seen between the first and second active stands and that the greatest reduction in symptoms was seen between the second and third stands (i.e. just after sleeping head up) would tend to support an effect of SHU. In addition, we did not record menstrual cycle histories for the female subjects and therefore, cannot exclude the possibility that some of the observed fluid retention was mediated through this mechanism but as the interval between measures was only 7 days, we do not feel it likely that results were appreciably affected. While extra care was taken to encourage compliance, we did not directly observe whether subjects used SHU at all times. Poor compliance would tend to obscure any effects of SHU, however, and make the observed significant differences less likely.

Our study has several strengths also. The large sample size and adherence to a strict fluid intake over 2 weeks (as reflected by unchanged 24 h urine output throughout the study) by a group of motivated and unpaid college students is noteworthy. The scarcity of research into this treatment in the 70 years since it was first described testifies to the difficulty in carrying out such research. The fact that subjects were pre-hydrated for a week and continued to drink extra fluids while sleeping head up means that effects of SHU were demonstrated to be in addition to any effects of hydration. The fact that subjects were healthy suggests that SHU is associated with broad physiological effects rather than being restricted to subjects with autonomic failure as the early literature suggested [17, 25, 30].

In conclusion, sleeping head up for one week was associated with a nocturnal anti-diuretic effect in healthy controls, with fluid retention of about 400 ml, alterations in haemodynamic variables and a reduction in orthostatic symptoms. Further research should examine the effects of lesser degrees of elevation that might be better tolerated, effects in clinical populations (with OH and/or autonomic failure) and longer-term effects.

References