# Do abnormalities in dynamic cerebral auto-regulation underlie the pathophysiological processes behind syncope in older people?

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## Abstract

**Do abnormalities in dynamic cerebral auto-regulation underlie the pathophysiological processes behind syncope in older people?**

**Introduction**: The aim of this thesis was to investigate whether abnormalities in dynamic cerebral auto-regulation (dCA) explain the symptoms associated with orthostatic (OH) and post-prandial hypotension (PPH).

**Methods**: Based on clinical symptoms and signs for the OH study: 4 Groups: Asymptomatic No OH (control), Symptomatic No OH, Asymptomatic OH, and Symptomatic OH. PPH study: double-blind placebo controlled cross-over study of glucose (50g) drink. 2 Groups: No PPH (control) and PPH. Baseline and head-up-tilt (HUT, for OH maximum 30 minutes study or to symptoms; PPH study maximum 60 minutes per visit). All had Transcranial Doppler ultrasound, beat-to-beat BP, ECG and $CO_2$ monitoring. Baseline autonomic function, arterial stiffness, cardiac baroreceptor sensitivity (BRS) were calculated and dynamic cerebral auto-regulation (as the auto-regulatory index ARI) assessed before and during tilt.

**Results**: OH: n=85, mean age 73.9±7.1 years; PPH: n= 40, mean age 73.4±7.3 years Baseline: No significant differences were found between groups for cardiac BRS, arterial stiffness, cerebral blood flow velocity (CBFV) or dCA in either study. HUT both studies: falls in BP, $CO_2$ and CBFV, increases in HR, and fall in ARI amongst symptomatic subjects prior to the end of HUT (maximum duration or symptom onset) compared to pre-HUT values. PPH study: fall in ARI with HUT irrespective of whether glucose or placebo phase.

**Conclusions**: The development of symptoms during tilt in both studies was related to a fall in CBFV and impaired cerebral auto-regulation. Abnormalities in cerebral auto-regulation may explain the symptoms of OH and PPH although these changes can only be detected during head-up-tilt.

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## *List of Abbreviations*

| | |
|---|---|
| ABP | Arterial Blood Pressure |
| ACEi | Angiotensin Converting Enzyme Inhibitor |
| AIIRB | Angiotension II Receptor Blocker |
| AIx | Augmentation Index |
| ARI | Auto-regulatory Index |
| BP | Blood Pressure |
| BRS | Baroreceptor Sensitivity (cardiac) |
| CA | Cerebral Auto-regulation |
| CASS | Composite Autonomic Symptom Score |
| CBF | Cerebral Blood Flow |
| CBFV | Cerebral Blood Flow Velocity |
| CO | Cardiac Output |
| $CO_2$ | Carbon Dioxide |
| CrCP | Critical Closing Pressure |
| CVR | Cerebral Vascular Resistance |
| $CVR_i$ | Cerebral Vascular Resistance Index |
| DBP | Diastolic Blood Pressure |
| dCA | Dynamic Cerebral Auto-regulation |
| HUT | Head-Up Tilt |
| HR | Heart Rate |
| MRI | Magnetic Resonance Imaging |
| NA | Noradrenaline |
| OH | Orthostatic Hypotension |
| PI | Pulsatility Index |
| PPH | Post-prandial Hypotension |
| PWV | Pulse Wave Velocity |
| SBP | Systolic Blood Pressure |

sCA Static Cerebral Auto-regulation

SNSA Sympathetic Nervous System Activation

TCD Transcranial Doppler Ultrasound

$tCO_2$ Transcutaneous Carbon Dioxide

TPR Total Peripheral Resistance

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# 1 Introduction

Syncope can be defined as a "*transient loss of consciousness due to transient global cerebral hypoperfusion characterised by rapid onset, short duration, and spontaneous complete recovery*"(Moya et al., 2009). Although some may be familiar with the following: "*The only difference between syncope and sudden death is that in one you wake up*." (Engel, 1978)

Syncope has many causes, and some, but not all, are associated with reduced survival as illustrated by Figure 1 (Soteriades et al., 2002). Orthostatic hypotension (OH) and post-prandial hypotension (PPH) are common causes of syncope in older populations, and are associated with significant morbidity (Vaitkevicius et al., 1991) and in the case of orthostatic hypotension can increase mortality (Fedorowski et al., 2010, Rose et al., 2006). However some people can experience symptoms of OH or PPH without necessarily having a fall in systemic BP levels whilst others can have a systemic BP drop but no symptoms (Moya et al., 2009, Mader et al., 1987). The pathophysiological reasons for why some experience symptoms and others do not is unclear and less well researched despite its potential importance, as this knowledge may assist in the future development of new therapeutic pathways.

This thesis aims to explore firstly, whether abnormalities in dynamic cerebral auto-regulation explain the symptoms of post-prandial and orthostatic hypotension, and secondly to systematically review the effects of pharmacological treatment for OH and PPH which may potentially highlight the underlying pathophysiological mechanisms for symptom production.

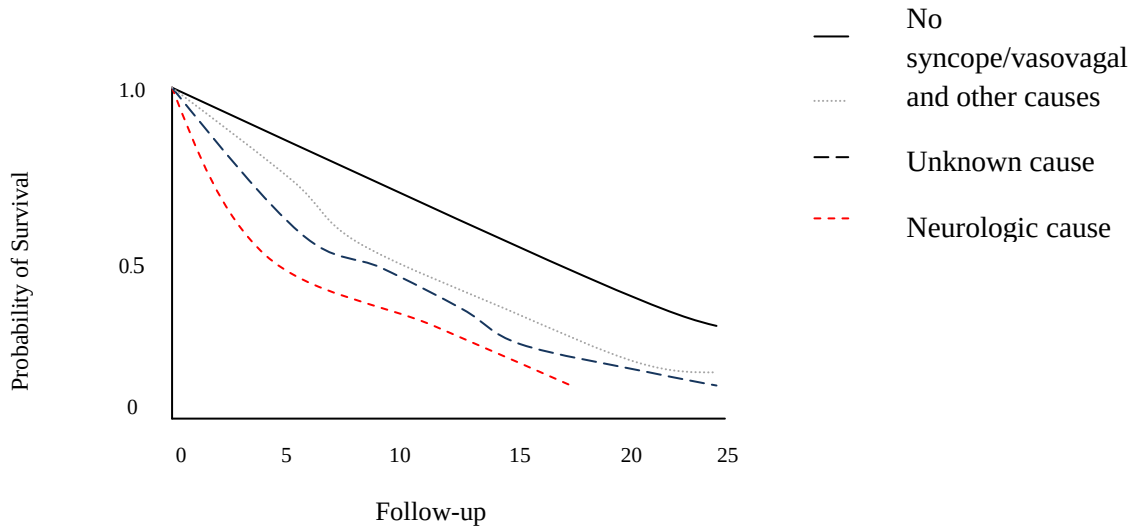


**Figure 1 Reduced probability of survival with syncope of differing aetiology over a 25 year period (Adapted from Figure 2 in Soteriades et al, 2002)[The Kaplan Meier survival curves demonstrate that those with cardiac syncope have a lower survival than those without syncope]**

# 2 Background

## 2.1 Orthostatic Hypotension and Post-Prandial Hypotension in the context of Syncope

Syncope can be classified according to three primary categories related to causation: 1) those which are neurally-mediated, 2) those due to orthostatic hypotension, and 3) those with a cardiac basis for syncope (Moya et al., 2009). Neurally-mediated syncope relates to conditions where there is an inappropriate vasodilatation and/or bradycardia, resulting in a fall in systemic blood pressure (BP) and presumably a resulting decrease in cerebral blood flow (CBF) in response to a trigger or carotid sinus hypersensitivity. It is considered to be, 1) vasodepressor where there is a fall in BP as a result in a reduction in the vasoconstrictor tone, 2) cardio-inhibitory where bradycardia or asystole is more prominent and 3) mixed if both vasodepressor and cardio-inhibitory signs are present. Neurally-mediated (or reflex) syncope includes vasovagal syncope which can be due to both emotional stress e.g. pain or orthostatic stress, as well as that directly related to a specific situation e.g. coughing, post-prandial hypotension, post-voiding of urine (i.e. post-micturition syncope). Orthostatic hypotension (OH) has a complex underlying pathophysiology and can be related to primary autonomic failure, and secondary autonomic failure, as shown in Table 1. However the complex nature of OH means there are many other causes including drugs e.g. diuretics, and volume depletion e.g. due to diarrhoea. The current classification recommended by the European Society of Cardiology is shown in Table 1 (Moya et al., 2009).

| | | | | |
|---|---|---|---|---|
| **Neurally-mediated (reflex) syncope** | Vasovagal | | Emotional e.g. fear, pain | |
| | | | Orthostatic | |
| | Situational | | Cough, sneeze | |
| | | | Gastrointestinal stimulation e.g. swallow, defaecation, visceral pain | |
| | | | Micturition (post-voiding) | |
| | | | Post-exercise | |
| | | | Post-prandial | |
| | | | Others e.g. laughter, playing brass instruments, weightlifting | |
| | Carotid sinus syncope | | | |
| | Atypical | | | |
| **Orthostatic hypotension** | Primary autonomic failure | | Pure autonomic failure | |
| | | | Multiple system atrophy | |
| | | | Parkinson's disease with autonomic failure | |
| | | | Lewy body dementia | |
| | Secondary autonomic failure | | Diabetes mellitus | |
| | | | Amyloidosis | |
| | | | Uraemia | |
| | | | Spinal cord injury | |
| | Drug-induced | | Alcohol | |
| | | | Vasodilators | |
| | | | Diuretics | |
| | | | Phenothiazines | |
| | | | Anti-depressants | |
| | Volume depletion e.g. haemorrhage, diarrhoea, vomiting | | | |
| **Cardiac syncope** | Primary arrhythmia | Bradycardia | Sinus node dysfunction | |
| | | | Atrioventricular conduction system disease | |
| | | | Implanted device malfunction | |
| | | Tachycardia | Supraventricular | |
| | | | Ventricular | Idiopathic |
| | | | | Secondary to structural heart disease |
| | | | | Channelopathies |
| | | Drug induced bradycardia or tachyarrhythmia | | |
| | Structural disease | Cardiac | Valvular disease | |
| | | | Acute myocardial infarction or ischaemia | |
| | | | Hypertrophic cardiomyopathy | |
| | | | Cardiac mass e.g. atrial myxoma | |
| | | | Pericardial disease or tamponade | |
| | | | Congenital anomalies of coronary arteries | |
| | | | Prosthetic valve disease | |
| | | Others | Pulmonary embolus | |
| | | | Acute aortic dissection | |
| | | | Pulmonary hypertension | |

**Table 1 The Classification of Syncope by the European Society of Cardiology (2009)(Moya et al., 2009)**

Figure 1 in the previous section illustrates the reduced survival associated with some causes of syncope. In particular a cardiac cause of syncope confers a large reduction in survival, with a survival probability of 0.4 at 10 years compared to 0.8 for no syncope or vasovagal and other causes (Soteriades et al., 2002). From the Framingham study cohort (n=7814, mean age 51.1 ±14.4 years), the incidence of a the first report of syncope (n=822, n=727 in outcome analysis, mean age 65.8 years) has been estimated at 6.2 per 1000 person-years, with 36.6% of cases having an unknown cause, 21.2% vasovagal, 9.5% cardiac and 9.4% orthostatic (Soteriades et al., 2002). Thus it can be seen that the classification of syncope can have a significant impact on an individual person's life expectancy.

## 2.2 Orthostatic Hypotension (OH)

### 2.2.1 Definition

The many types of OH, as described by the European Society of Cardiology (ESC), reflect the complex nature of orthostatic hypotension with its multi-factorial underlying pathophysiological origins (Moya et al., 2009). On the one hand it defines OH as "*an abnormal decrease in systolic BP upon standing*", the magnitude of BP fall dependent on the sub-type of OH. However the associated signs and symptoms are described simply as "*orthostatic intolerance*".

Some individuals lack symptoms despite a postural fall in systemic BP (usually measured in the brachial artery) defined as "Classical OH" by the European Society of Cardiology. This is simply described as a systolic blood pressure (SBP) reduction of ≥20mmHg and/or a diastolic blood pressure (DBP) reduction of ≥10mmHg within a

period of 3 minutes of standing from a supine position, symptoms are not considered as a necessary component in this definition. However the ESC definition of "Initial OH" requires a fall in SBP of ≥40mmHg accompanied by transient symptoms lasting less than 30 seconds. The entity of "Delayed OH" is characterised by the progressive fall in SBP alone, after standing for several minutes and may include the presence or absence of symptoms (Moya et al., 2009). There has been the suggestion that because OH is likely to represent a wide range of underlying causes, it could be classified using modelflow measures of total peripheral resistance (TPR) and cardiac output (CO) to produce physiological types (Deegan et al., 2007). Where there is a large drop in TPR then it would be calssified as "arteriolar", where the drop was mostly in terms of CO, then it could be classed as "venular", and if both TPR and CO were involved, it would be classed as "mixed"(Deegan et al., 2007).

However, the complexity of orthostatic hypotension is further burdened by whether the falls in SBP and DBP should include changes associated in beat-to-beat measurments of BP, which is often done in research, and can therefore provide a higher estimate of the prevalence of OH within a population than cuff measurements(van der Velde et al., 2007, Cooke et al., 2013). The consensus statement published during the period of this thesis also takes into account the use of beat-to-beat monitoring, by considering initial OH to be that which occurs within 15 seconds of standing, or passive tilting, and is the result of conflicting CO and TPR (Freeman et al., 2011). The 2011 consensus also recgonises delayed OH in both active standing and passive tilting, as that which occurs after 3 minutes (Freeman et al., 2011).

More recently, there has been a suggestion for dividing OH into morphological types depending on the slope of SBP and DBP decay, and their proportionate recovery from baseline i.e. “small drop, overshoot”, “medium drop, slow recovery” and “large drop, nonrecovery (Cooke et al., 2013). Of course, there is the ongoing debate, as to how long should a fall in BP last when using beat-to-beat monitoring be considered as significant, although it has been suggested that less than 30 seconds would not be enough to cause symptoms (Romero-Ortuno et al., 2010).

### 2.2.2 Epidemiology

The multiple underlying aetiologies of OH has resulted it in being a common condition in community, hospital or care home environments. As might be expected the prevalence of OH varies between studies, depending on many factors, in particular the age and population type that are included. It should be noted that there is some variation in the definition of OH and older studies may not always include a fall in DBP in the study definition. The actual incidence of OH is unknown, although the incidence of first reports of orthostatic syncope is 0.58 per 1000 person-years (Soteriades et al., 2002) it has been suggested that for initial OH it is around 3.6% where it is the primary diagnosis of transient loss of consciousness (Wieling et al., 2007). Although some studies have defined OH as a postural fall in SBP of ≥30mmHg (Low et al., 1995), most studies generally refer to a fall in SBP of ≥20mmHg (Applegate et al., 1991a, Hiitola et al., 2009). Thus amongst hospital patients and the general population over the age of 65 years, the reported prevalence rates vary between 6.4% (excluding those who had any risk factors for OH) and 65% (Vloet et al., 2005, Soteriades et al., 2002, Poon and Braun, 2005, Applegate et al., 1991a, Mader et al., 1987, Caird et al., 1973, Räihä et al., 1995, Luukinen et al., 1999, de la Iglesia B. et al.,

2013, Rutan et al., 1992, Weiss et al., 2002, Kamaruzzaman et al., 2010, Valbusa et al., 2012). However it should be noted that Cooke et al (2013), compared beat-to-beat BP changes during HUT with sit to stand BP, with a reported prevalence of 58.6% versus 17.3% in community dwelling adults over the age of 65 years. Furthermore it has been suggested that subtypes of OH will need to be considered in addition to the overall prevalence, with arteriolar OH accounting for 47%, 33% venular, and 9% mixed (Cooke et al., 2013). Data collected from community Norfolk patients attending a Transient Ischemic Attack (TIA) clinic, where 43.8% were classed as non-TIA, OH was found to have a prevalence of 22.3% (de la Iglesia B. et al., 2013). It has been shown that even after excluding those with primary autonomic dysfunction and Parkinson's disease the prevalence can remain high at 55% in the population studied (Poon and Braun, 2005).

Furthermore studies have shown that not all those with a postural fall in BP associated with OH are symptomatic. Even amongst those over the age of 75 years, only 33% reported symptoms associated with the BP fall, and this included those with a history of falls (Poon and Braun, 2005). The prevalence of OH has been observed to increase as the number of potentially causative medications increased from zero (prevalence of 35%) to three or more (65%) (Poon and Braun, 2005). One study found that a fall in SBP of at least 20mmHg after 1 minute of standing was present in only 10.7% of independently living older poeople (mean age of 69.8 years, range 56-93 years), and in the population studied only 21.9% of those with a fall in BP had symptoms on standing (Mader et al., 1987). Furthermore 18.3% had symptoms on standing, but did not have a significant fall in systemic BP (Mader et al., 1987). There was no significant difference in the frequency of postural symptoms on standing between those with or without a

fall in BP, but a higher proportion of those with a postural fall, compared to those with no postural fall, had hypertension (31.3% vs. 14.6%, p=0.016) (Mader et al., 1987). Elsewhere it has been shown that applying diagnostic BP criteria of OH without necessarily including postural symptoms for OH amongst unselected community dwelling older people the prevalence of OH is higher than the previous study (Mader et al., 1987), at 28% (Räihä et al., 1995), and 34% in those over the age of 75 years (Hiitola et al., 2009). Of course it is recognised that the prevalence will vary with the differing criteria applied for the diagnosis of OH over the years (Frith et al., 2014). Table 2 summarises selected studies on the prevalence of OH in older adults.

| **Study (Author, Year, Country)** | **Study Population** | | | | **Prevalence of OH (% of study population)** |
|---|---|---|---|---|---|
| | *N* | *Age (years) (Mean ± SD unless otherwise specified)* | *Sex M:F (%)* | *Population Group* | |
| Applegate et al, 1991, USA | 4736 | ≥60 (72.1 ±6.6; n=817 OH) | 40.3:59.7 | Systolic hypertension | 17.3 |
| Caird et al, 1972, UK | 494 | 45.7% ≥75 | 36.2:63.8 | Home dwelling ≥ 65 years of age | 24.0 |
| Hiitola et al, 2009, Finland | 653 | 81 (range 75-99) | 30:70 | Home dwelling ≥75 years of age | 34.0 |
| Kamaruzzaman et al, 2010, UK | 3775 | Range 60 to 80 (69.4 ±5.5, n=1059 OH) | 0:100 | Community dwelling older women | 28.0 |
| Luukinen et al, 1999, Finland | 792 | 76 ±4.9 | 38:62 | Community dwelling older people | 30.0 |
| Mader et al, 1987, USA | 300 | 69.8 (range 56 to 93) | 33:77 | Community dwelling older people ≥55 years of age | 10.7 (overall) 13.7 (OH risk factors*) 6.4 (no OH risk factors) |
| Ooi et al, 2000, USA | 844 | 73.8% ≥80 | 19.7:80.3 | Nursing home residents ≥60 years of age | 50.0 |
| Poon et al, 2005, USA | 342 | 82 ±4.7 | 96:4 | Veterans attending geriatric clinic | 55.0 (overall) 35.0 (no causative medication) |
| Räihä et al, 1995, Finland | 329 | ≥65 | 53:47 | Community dwelling older people ≥65 years of age | 28.3 |
| Rutan et al, 1992, USA | 4931 | ≥65 | 43.5:56.5 | Community dwelling older people ≥65 years of age | 16.2 |
| Valbusa et al, 2011, France and Italy | 994 | 88±5 | 33:77 | Older people in nursing homes | 18.0 |
| Vloet et al, 2005, Netherlands | 85 | 80± 7 | 51.7:48.3 | Geriatric Ward in-patients | 52.0 |
| Weiss et al, 2002, Israel | 502 | 81.6 ±7.0 | 48:52 | Geriatric in-patients | 67.9 |

**Table 2 The prevalence of orthostatic hypotension in various populations of older adults (* OH risk factors include e.g. diabetes mellitus, hypertension, medication)**

In terms of predictors of OH, Mader et al (1987) found a significant difference between those with and without a postural BP fall in terms of the proportion having at least one risk factor for OH (75% versus 56.3%, p = 0.04), this could include various medications e.g. anti-hypertensives, as well as active medical conditions e.g. cardiac disease, clinical findings of e.g. varicose veins and laboratory findings e.g. low haematorcrit (Mader et al., 1987). Another study (Ensrud et al., 1992) found that whilst Parkinsonism was strongly associated with a postural fall in BP as well as postural dizziness, the relationship with diuretics was weaker for both postural BP and postural symptom. Both systolic and diastolic hypertension was found to be associated with postural hypotension (Ensrud et al., 1992).

### 2.2.3 Morbidity and Mortality

Orthostatic hypotension is not a benign condition, being frequently associated with recurrent falls and their complications e.g. fracture. (Graafmans et al., 1996). In addition OH is associated with a significant increased mortality (Fedorowski et al., 2010). This increasing mortality over time associated with cardiac syncope is much greater than other causes and is illustrated in Table 1. For example even amongst community dwellers with OH there is an increased risk of vascular death (Caird et al., 1973, Räihä et al., 1995) and in a population of the Atherosclerosis Risk in Communities (ARIC) Study involving nearly 12,000 middle-aged adults, OH has been shown to be predictive of ischaemic stroke even after adjustment for stroke factors (HR: 2.0, 95% CI 1.2 to 3.2) (Eigenbrodt et al., 2000). However OH is also associated with an increased risk of all-cause mortality (HR 2.4, 95% CI 2.1 to 2.8), even after adjusting for the presence of cardiovascular disease (HR 2.0, 95% CI 1.6 to 2.7) in around 13,000 middle age participants (mean age 57 years) of the ARIC cohort over a

13 year period (Rose et al., 2006). On the one hand the presence of a postural BP fall in those with hypertension increases the risk of cerebrovascular disease in older adults (Kario et al., 2002). Conversely an increase in cerebrovascular disease is also seen in older adults with hypertension who have an increase in SBP of ≥20mmHg on head-up tilt. Thus there is a U-shaped relation between postural BP change and cerebrovascular disease, whereby a fall or rise in BP is associated with cerebrovascular disease (Kario et al., 2002). In both of these instances the presence of cerebrovascular disease may be related to alterations in not only systemic BP, but also changes in cerebral auto-regulation (CA). For example an abnormal localised cerebral vasoconstriction would result in reduced perfusion of brain tissue and hence an infarct.

### 2.2.4 Clinical Presentation

There are a variety of symptoms associated with orthostatic intolerance (which does not necessarily relate to a corresponding postural drop in BP) and OH (diagnosed by the postural drop in BP), which include dizziness, general loss of strength, the sense of instability, nausea and a tendency to fall (Vloet et al., 2005). However as stated previously not all older people with OH are symptomatic; only between 23-59% of older adults with OH have symptoms associated with a fall in systemic BP (Soteriades et al., 2002, Ensrud et al., 1992, Graafmans et al., 1996). Furthermore it has been demonstrated that there are some who have postural dizziness but no postural fall in systemic SBP levels (18.9% of those with no postural fall in BP) (Ensrud et al., 1992). It should also be noted that a history of falls has been shown to be more closely associated with the symptom of dizziness rather than the postural reduction in BP per se (Soteriades et al., 2002, Ensrud et al., 1992, Graafmans et al., 1996). The most common symptoms of orthostatic hypotension amongst those with autonomic

dysfunction (i.e. pure autonomic failure, multisystem atrophy, autonomic neuropathy, diabetic autonomic neuropathy) and a postural BP fall reported by older subjects are "*light-headedness*" or "*dizziness*" in 88% of cases, "*weakness*" or "*tiredness*" in 72%, with reduced cognition in terms of thinking or concentrating as common as "*blurred vision*" in 47%. Other symptoms include "*tremulousness*" (38%), "*vertigo*" (37%), "*pallor*" (31%), "*anxiety*" (29%), "*tachycardia*" or "*palpitations*" (26%), "*clammy feeling*" (19%) and "*nausea*" (18%) (Low et al., 1995). However there is evidence that OH is not simply explained by autonomic dysfunction (Lagro et al., 2013).

Low et al (1995) used the composite autonomic symptom score (CASS) (Low, 1993) and a composite symptom score based on the frequency of orthostatic intolerance (0 = never, 1 = uncommon, 2 = at least once a week, 3 = more often than not, 4 = consistently present), standing time to develop orthostatic symptoms (0 = never, 1 = more than 5 minutes, 2 = within 2 to 5 minutes, 4 = less than 1 minute) and frequency of syncope (0 = never, 2 = less than once per month, 4 = at least once per week). It was found that by analysing the regression between the CASS and the composite symptom score, the best correlation was amongst those with symptomatic OH ($y = 3.612 + 0.331x$, where y = symptom score, x= CASS, $p = 0.00513$, $r = 0.3009$) or all groups combined, but not with asymptomatic OH or those with a negative head-up tilt (HUT) but with a history of symptoms of OH (Low et al., 1995). The variation in types of symptoms may be related to the underlying aetiology of OH (Low et al., 1995), but whether an individual with a postural drop in BP has symptoms may potentially reflect control of cerebral blood flow rather than maintenance of systemic BP levels through cardiovascular autonomic function (Lagro et al., 2013).

## 2.3 Post-prandial Hypotension (PPH)

### 2.3.1 Definition

Post-prandial hypotension (PPH) has be defined as a reduction in the SBP of ≥20mmHg within 2 hours of the start of a meal or when SBP falls to ≤90mmHg within this period where the pre-prandial SBP was ≥100mmHg (Jansen and Lipsitz, 1995). Like OH it may not always be associated with symptoms (Jansen and Lipsitz, 1995), conversely symptoms are not always accompanied by a low BP (Vloet et al., 2003).

### 2.3.2 Epidemiology

Post-prandial falls in BP are common in older community dwelling adults. However the incidence of PPH is unknown, although the incidence of first reports of other causes of syncope is 0.47 per 1000 person-years (Soteriades et al., 2002); and the prevalence rates of PPH has been reported to be up to 36% of those residing in care homes (Vaitkevicius et al., 1991, Aronow and Ahn, 1994) and as high as 67% in the older hospital population (Vloet et al., 2005). However although post-prandial falls in BP is prevalent amongst community dwelling healthy older people, the actual fall in SBP is smaller, with SBP changes of -11±9mmHg by 60 minutes after a meal compared to 1±7mmHg in similar conditions without a meal (Lipsitz and Fullerton, 1986, Heseltine et al., 1991a). Amongst those in care home facilities it was found that 24% of residents (mean age 80±9 years) had a SBP fall of over 20mmHg after a meal (Aronow and Ahn, 1994). The fall in post-prandial SBP amongst those in long-term care is larger in those with a history of syncope in the previous 6 months (24±5mmHg) compared to those without such a history (14±5mmHg) (Aronow and Ahn, 1994). Thus amongst those without a history of syncope, it is similar to healthy older people

living within the community. Table 3 summarises the prevalence rates of PPH amongst various groups of older people.

| **Study (Author, Year, Country)** | **Study Population** | | | | **Prevalence of PPH (% of study population)** |
|---|---|---|---|---|---|
| | *N* | *Age (years) (Mean ± SD unless otherwise specified)* | *Sex Ratio M:F (%)* | *Population Group* | |
| Aronow et al, 1994, USA | 499 | 80 ±9 | 29:71 | Long-term health care residents | 24.0 |
| Maurer et al, 2000, USA | 50 | 78 (range 61 to 96) | 32:68 | Older persons from community and inpatients | 22.0 |
| Vaitkevicius et al, 1991, USA | 113 | 78 ±9 | 27:73 | Nursing home residents | 36.0 |
| Vloet et al, 2005, Netherlands | 85 | 80 ±7 | 51.7:48.3 | Geriatric Ward in-patients | 67.0 |

**Table 3 The prevalence of post-prandial hypotension in populations of older adults**

### 2.3.3 Morbidity & Mortality

PPH has been found to be present in half of those with unexplained syncope (Jansen and Lipsitz, 1995) and is associated with acute vascular events such as stroke and angina (Vaitkevicius et al., 1991, Kohara et al., 1999). It has been suggested that amongst older patients with hypertension, the extent of the post-prandial SBP pressure fall (categorised as SBP fall <5mmHg, 5-9mmHg, ≥10mmHg) correlates with magnetic resonance imaging (MRI) evidence of cerebrovascular damage in terms of the number of lacunar infarcts present and degree of advanced leukoaraiosis. Those shown to have a larger SBP fall post-meal had more damage despite the fact that there were no significant differences in mean daytime or night-time BP levels (Kohara et al., 1999). It has been suggested that the more severe cerebrovascular changes are likely to be a reflection of the relative change between pre and post-prandial BP, and not merely the post-prandial BP (Kohara et al., 1999).

### 2.3.4 Clinical Presentation

PPH has been shown to be independent of a history of syncope (Lipsitz et al., 1983) and can be asymptomatic (Heseltine et al., 1991a) in around a third of cases (Vloet et al., 2005). Older people within institutionalised care (mean age 87.8 years, SEM±1.0 years), regardless of whether they have a history of syncope or not, can have large asymptomatic post-prandial falls in SBP (mean 15mmHg, SEM±2mmHg; and mean 11mmHg, SEM±4mmHg) within 35 minutes after the start of a meal (Lipsitz et al., 1983). Maximal falls in SBP can reach a mean of 25mmHg, SEM±5mmHg amongst those with a history of syncope, and 24±9mmHg in those without a history ($p<0.03$) (Lipsitz et al., 1983). Symptomatic post-prandial hypotension can result in a poor quality of life, often presenting with dizziness, falls, visual disturbances, nausea, yawning and tiredness (Vloet et al., 2005, Jansen and Lipsitz, 1995, Vloet et al., 2003).

The fall in SBP after standardised meal ingestion amongst care home residents (n=113, mean age 78±9 years) has been shown to be greater than the response to head-up tilt (HUT) alone, with symptoms present in 22% after a meal versus 12% with HUT alone (Maurer et al., 2000). Furthermore the time to symptoms occurred sooner after meal ingestion than HUT alone (Maurer et al., 2000). However it should be noted that although there was a high prevalence of hypertension (44%), and half were on BP lowering medication (Maurer et al., 2000), there was no sub-group analysis to determine whether a history of hypertension or anti-hypertensive medications (in terms of drug class and the number of drugs used) influenced whether or not participants had symptomatic falls in post-prandial BP. Furthermore it has been suggested that PPH, like OH in older adults is not fully explained by abnormalities in cardiovascular autonomic function (Lagro et al., 2013).

In older patients it has been shown that there is variation in the post-prandial BP response depending on the time of day, with falls decreasing over the course of the day with the greatest fall in SBP at breakfast. The fall in SBP with the evening meal was significantly smaller than that at breakfast ($p<0.0001$) and at lunch ($p<0.0004$), with only 57% of patients having PPH (defined as a decrease in SBP $\geq$20mmHg) after the evening meal (Vloet et al., 2003). However this greater fall in BP after breakfast may simply be related to the prolonged supine position assumed for sleeping or perhaps reflects the composition of the meal as it is known that a high simple carbohydrate meals result in a greater fall in SBP than a complex carbohydrate meal (Heseltine et al., 1991a). The varying effects of meal composition and the type and volume of drinks ingested on BP, and is discussed further in Section 2.10.

## 2.4 The relationship between the pathophysiology of OH, PPH and symptoms

### 2.4.1 The case of OH

The relationship between OH, hypertension and antihypertensive drugs is complex but may provide insight into the relationship between OH, cerebral auto-regulation (CA), arterial BP (ABP), arterial stiffness and symptoms. There are many associations with OH including drugs especially some anti-psychotic agents and anti-hypertensives, and diseases such as diabetes (Mader et al., 1987). The possible causal relationship between anti-hypertensive medication and orthostatic hypotension is supported by the fact that withdrawal of anti-hypertensive medication has been shown to reduce the prevalence of OH (Fotherby and Potter, 1994). However normalising supine BP levels

with treatment also reduces OH (Räihä et al., 1995). Those with postural hypotension were more likely to have supine hypertension defined as SBP >160mmHg or DBP >90mmHg (31.3% vs. 14.6%, p=0.016) (Mader et al., 1987). In addition regardless of whether participants had or had no postural hypotension, similar proportions had postural symptoms on examination (21.9% vs. 18.3%, p>0.05) (Mader et al., 1987). This would support the possibility that symptoms may be related to the ability of a person's CA to maintain cerebral blood flow.

Although OH amongst those with autonomic failure is associated with supine hypertension (Goldstein et al., 2003), the variable association of OH with isolated supine hypertension is shown in the placebo phase of the Syst-Eur trial. Only 21% of the 2716 included in the study showed at least one episode of a fall in SBP of at least 20mmHg with only 2.5% showing this on three occasions. For a DBP fall of at least 10mmHg, 9.7% has at least one occurrence and 0.4% had three occurrences. The supine SBP was 175±13mmHg and DBP was 86±6mmHg (Vanhanen et al., 1996). Other studies also show that supine SBP, DBP and mean BP are significantly higher amongst those with a SBP fall of at least 20mmHg (Räihä et al., 1995). Even in studies where the prevalence of OH was reported to be lower (Mader et al., 1987) supine SBP and DBP was significantly higher. In addition, recent evidence suggests cardiac autonomic function is similar in older adults with and without OH (Lagro et al., 2013).

However on the other hand the prevalence of OH is significantly lower amongst those where hypertension was treated (13% vs. untreated 23%, p<0.001), and pulse pressure was higher amongst those with OH (Valbusa et al., 2012). Thus although baroreceptor sensitivity (BRS) declines with hypertension (Parati et al., 1988), treating hypertension

with antihypertensive agents improves BRS (Berdeaux and Giudicelli, 1987). Thus a difficult paradox remains to be solved for the older hypertensive patient. Where does the role of anti-hypertensive agents fit in with OH (whether symptomatic or asymptomatic) and perhaps CA?

### 2.4.2 The case of PPH

For post-prandial hypotension the most significant reduction in BP in those over 65 years of age occurs within 90 minutes of ingestion of a high in simple carbohydrate substrate e.g. glucose, and is independent of the presence or absence of systemic hypertension (Visvanathan et al., 2005, Jansen et al., 1987, Potter JF, 1989) even after medication withdrawal (Lipsitz et al., 1983). Caffeine (an adenosine antagonist) when given after meals can reduce post-prandial symptoms and BP reduction (Heseltine et al., 1991c, Heseltine et al., 1991b) and thus suggesting adenosine may have an underlying pathophysiological role by inducing splanchnic vasodilatation resulting in the reduction in BP. Other studies have shown that the cardiac baroreflex in older people is impaired as HR does not increase enough to compensate for a lowering of BP after meals (Lipsitz et al., 1983) which may contribute further to post-prandial falls in BP. However recent evidence does suggest that there is little difference in cardiac autonomic dysfunction in older adults with PPH compared to those without (Lagro et al., 2013).

Research has shown that the post-meal reduction in BP relates to glucose levels (Jansen et al., 1987) rather than the direct insulin effect of impairing baroreceptor sensitivity (BRS). This impairment is thought to be due to the lack of a compensatory increase in HR after meals (Lipsitz et al., 1983). Furthermore peripheral

vasoconstriction appears to be absent in the presence of hypotension after a meal in older participants with a history of syncope compared to older adult controls (Jansen et al., 1995). Therefore it may be that PPH reflects the failure to maintain systemic vascular resistance in order to compensate for blood diverted into the splanchnic circulation (Jansen and Lipsitz, 1995). This has been supported by the fact that BP is maintained in the same way in both healthy younger and older adults; by increasing HR and forearm vascular resistance associated with an increased plasma norepinephrine. In contrast those with autonomic dysfunction due to a variety of causes, the lack of adequately maintained vascular resistance observed suggests this may be the pathophysiological basis for PPH (Lipsitz et al., 1993).

## 2.5 The physiological processes

There are several physiological parameters important to the understanding of the relationship between systemic arterial blood pressure (ABP) and cerebral blood flow (CBF) control by cerebral auto-regulation (CA) in OH and PPH. This includes the normal response to active standing and how this differs from head-up-tilt in the laboratory environment, as well as the differences in the physiological response between younger and older adults; and the normal physiology associated with the ingestion of meals in terms of the effect on arterial blood pressure, as previously discussed. Central to these ideas is the haemostatic control of arterial blood pressure in response to posture and digestion, and the changes in ability of baroreceptors (essentially sensors of a feedback loop) to provide an adequate feedback mechanism in the presence of increasing arterial stiffness with age. This is described in detail in the following section. Key to understanding CA is its primary purpose to maintain adequate cerebral blood flow (CBF) for perfusion of brain tissue despite normal

physiological fluctuations in arterial blood pressure during routine day to day activities. The question remains as to why some people with systemic falls in BP to standing or after meals have symptoms whilst others do not. Furthermore some people have no systemic BP changes following standing or post-meal but may have symptoms suggestive of PPH. Are there differences in CA to account for this? Are there differences in arterial stiffness?

## 2.6 Cerebral auto-regulation

### 2.6.1 Physiology

Cerebral blood flow (CBF) is controlled via several different mechanisms including those reliant on metabolic, myogenic and neurogenic processes. Normally CBF is maintained at approximately 50ml/100g $min^{-1}$ where $P_aCO_2$ (arterial partial pressure of carbon dioxide) remains constant. However $P_aCO_2$ will vary regionally and thus there is increased CBF to regions of the brain that are metabolically active (Lassen, 1974). In terms of chemical control a high $P_aCO_2$ results in cerebral vasodilatation, and low levels cause vasoconstriction causing relative hypoxia. $P_aCO_2$ is further influenced by the pH of the cerebrospinal fluid (CSF) around arterioles and the bicarbonate levels in the CSF. Unlike $P_aCO_2$, $P_aO_2$ (arterial partial pressure of oxygen) only has a major effect on CBF if significantly low and is at the level at which lactic acidosis of brain tissue occurs (approximately less than 50mmHg). The neurogenic control of CBF is in part due to the innervation of the pial arteries which run across the surface of the brain. The smooth muscle within the arteries will result in vasoconstriction and vasodilatation according to whether the stimulus is norepinephrine or acetylcholine respectively (Lassen, 1974). The brain can tolerate a small reduction in CBF before symptoms develop, but when CBF drops by more than 30% of normal levels, the $O_2$

requirements can no longer be met by increasing its extraction from the blood. At this point symptoms such dizziness, light-headedness etc. will appear (Paulson et al., 1990).

Cerebral auto-regulation (CA) refers to the intrinsic mechanisms by which CBF is maintained despite variations in cerebral perfusion pressure i.e. the pressure difference between the venous and arterial systems of the brain (Lassen, 1974, Blaha et al., 2007). Static CA relates to the changes in CBF over a longer period of time which occurs as a result with gradual changes in systemic BP. This is likely due to smooth muscle response in the arteriolar wall and can be affected for example by the partial pressure of carbon dioxide in arterial blood (Lassen, 1974, Blaha et al., 2007) as well as nitric oxide (Dawson et al., 2009). On the other hand dynamic CA (dCA) relates to the rapid changes of CBF that occur in response to quick (occurring over a few seconds) changes in arterial BP within the range of static CA (van Beek et al., 2008).

The rapid changes in CBF, which can be within seconds, can be non-invasively assessed with Transcranial Doppler ultrasound (TCD) using the cerebral blood flow velocities (CBFV) e.g. of the middle cerebral artery, as a surrogate marker of CBF. (Aaslid et al., 1982 , Aaslid et al., 1989) Using TCD to record cerebral blood flow velocity (CBFV) of the MCA allows exploration of its relationship with real-time systemic BP and $CO_2$ changes. Although this allows CA to be assessed using CBFV as a surrogate marker for CBF it does assume that the arterial diameter is constant, this has been shown to be the case (Newell et al., 1994, Berlowitz et al., 2011, Wilkinson et al., 2000). The use of static CA is limited by the fact that in the semi-steady state measures of CBFV and the associated cerebrovascular resistance is the outcome of the

stable BP level. In addition as static CA is reflected by average long-term changes in BP, its use is limited by the need for sustained changes in BP induced by pharmacologically active agents. As dynamic CA reflects the changes in CBFV in response to rapid changes in BP it can provide information on beat-to-beat changes in BP (van Beek et al., 2008). However CBF will only be maintained across a particular range of perfusion pressures, and this range will vary according to $P_aCO_2$ (Lassen, 1974). However recent MRI (magnetic resonance imaging) study showed that in conscious participants, the diameter of the MCA is constant across a range of $P_{ET}CO_2$ (end-tidal partial pressure of carbon dioxide) (Serrador et al., 2000). Thus under stable conditions CA is able to maintain constant CBF between a MAP of around 60mmHg to 150mmHg as shown by Figure 2 (Paulson et al., 1990) and CA is rarely absent, but can be found to be impaired. The underlying mechanisms of static and dynamic CA differ, as it has been shown that by inducing a response from either component by chemically invoking a sustained increase in BP or by reducing BP with lower body negative pressure respectively, the resultant response would be vasoconstriction and vasodilatation respectively. However as both of methods of measuring CA have the same result, i.e. maintain CBF, then it is likely that the processes causing vasoconstriction would differ from those resulting in vasodilatation (Tiecks et al., 1995).

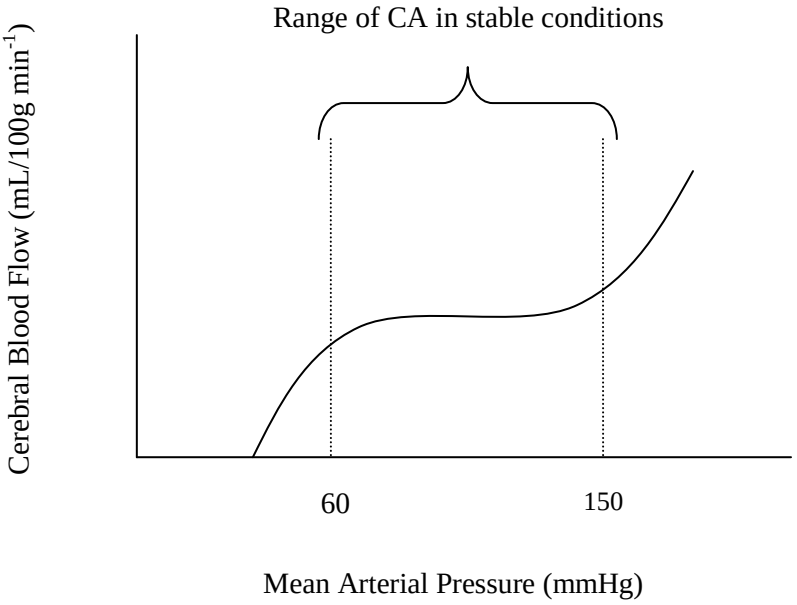


**Figure 2 Cerebral Auto-regulation Curve under stable conditions**

Cerebral perfusion fails when the cerebral perfusion pressure falls to less than approximately 40mmHg, which triggers an increase in SNSA response resulting in an increase in systemic ABP (Lassen, 1974). Studies using $^{133}Xe$ and correlating blood flow and symptoms of hypoxia have shown that the critical level of CBF, or that at which ischaemia occurs, is approximately 18-20ml/100 $min^{-1}$ (Lassen, 1974). Furthermore it has been shown that CA is impaired if associated with cerebral ischaemia (Symon et al., 1973). A recent study in healthy female volunteers, looking at the relationship between cardiac output and dCA, not only showed that these were independent but has also shown that there is a significant difference in the auto-regulatory index (ARI) dependent on whether the participant is supine or seated (Deegan et al., 2010). The ARI is a constant based on a mathematical model which allows us to compare how well an individual's CA compares to normal, and is discussed below.

To assess dynamic CA a stimulus a rapid step change in ABP (of ≥15mmHg) is necessary in order to allow the response in ABP and CBFV to be simultaneously analysed, this can be done using several methods e.g. thigh-cuff deflation, head-up-tilt (HUT). The time it takes for CBFV to recover and attain its original level will vary according to the state of CA.

A classical mathematically derived model of assessing cerebral auto-regulation, defined as an auto-regulatory index (ARI), was developed by Asalid and is measured on a scale from 0 to 9 (as shown in Figure 16) to indicate whether cerebral auto-regulation is perfect (score 9) or markedly impaired (score 0). It uses the CBFV and ABP after thigh-cuff release to attain a change in CVR per second relative to changes in ABP. The ARI relies on computer modelling based on the actual recorded ABP from the moment of thigh-cuff release over 30 seconds, from which a theoretical or hypothetical CBFV response based on no cerebral auto-regulation would be created. Within this model of zero CA a linear relationship between ABP and CBFV is assumed with falls CBFV following a similar percentage fall in ABP. A further nine models of other possible CBFV responses are made with an increase in the ability of CA being assumed. Thus an actual CBFV response can be matched against these models in order to determine best fitting model and thus the ARI value (Tiecks et al., 1995). Thus from Figure 3 it can be seen that normal cerebral auto-regulation will have an ARI of around 5.

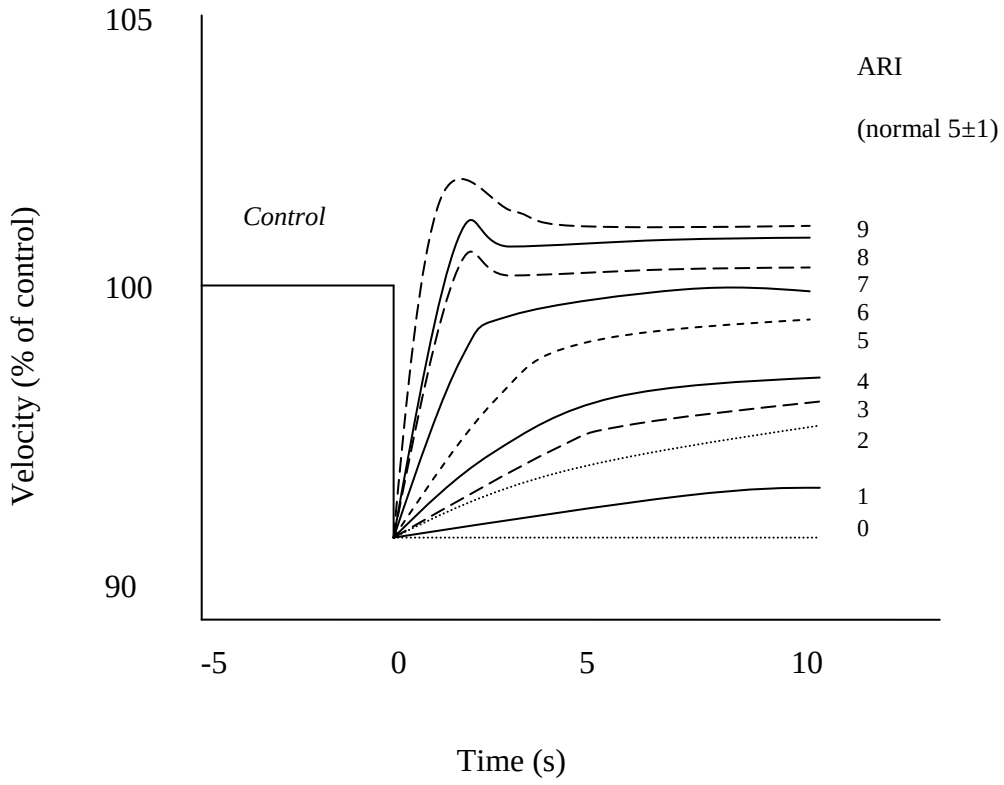


**Figure 3 The Auto-regulatory Index (ARI), adapted from Tiecks et al. (2005)**

Other methods to assess CA include using spontaneous fluctuations in BP and CBFV (Panerai et al., 1998) and considering the frequency domain (versus the time domain of the previous method) transfer function analysis whereby the power spectra of the oscillations in BP and CBFV are assessed in terms of gain, phase and coherence, i.e. spectral analysis (Panerai, 2009, van Beek et al., 2008). These methods shall be discussed further in the Methodology section.

In addition it has also been suggested that there is a sex difference in terms of the effectiveness of CA, with females being better able to maintain CBFV with changes in posture during assessment of sit-to-stand, as well as showing better $CO_2$ reactivity and

higher ARI (Deegan et al., 2011b). It should also be noted that there is little difference in the regional cerebral vascular response to hypercapnia and hypocapnia between healthy young and older men using positron emission tomography (PET), although a reduction in the total vascular response was noted amongst older men to indicate sclerotic changes in both the cerebral and medullary arteries (Ito et al., 2002). ARI is further discussed in the Methodology Chapter.

## 2.7 The physiological response to standing

### 2.7.1 Systemic BP and standing

Blood pressure (BP) is maintained via a negative feedback mechanism and is summarised in Figure 4 and 5. Activation of these components is dependent on whether it relates to short or long-term control, and include high and low pressure baroreceptors (which include cardiac stretch receptors and the great vessel pressure receptors) and chemoreceptors (which detect pH, $CO_2$ levels, endothelin peptides, nitrous oxide and other factors) strategically located along the vasculature (Kohan et al., 2011). Thus when the body assumes an upright posture from a physiologically stable supine position, the resultant peripheral venous pooling causes a fall in arterial BP (ABP). This is due to a decrease in the filling pressure within the heart and the subsequent fall in stroke volume. This triggers the feedback loop as shown in Figure 4. This triggers signals (mechanical and chemical) via the afferent limb of the reflex arc from the arterial baroreceptors found in the carotid sinus and aortic arch, as well as the cardiac mechanoreceptors, to the brainstem via the autonomic nervous system (Borst et al., 1982) The arterial (high pressure) baroreceptors (discussed later) are predominantly found in the carotid sinus at the bifurcation of the internal and external carotid artery and the aortic arch, but can also be found within the common carotid

artery (around the thyroid artery). These mechanoreceptors detect arterial wall stretch in response to intravascular pressure. Afferent signals are conveyed via both myelinated and unmyelinated fibres of the sinus nerve (conveying rapid changes in BP via the glossopharyngeal nerve) from the carotid sinus and via the vagus nerve (conveying more sustained changes in BP) from the aortic arch, to the nucleus tractus solitarius (NTS) in the medulla.

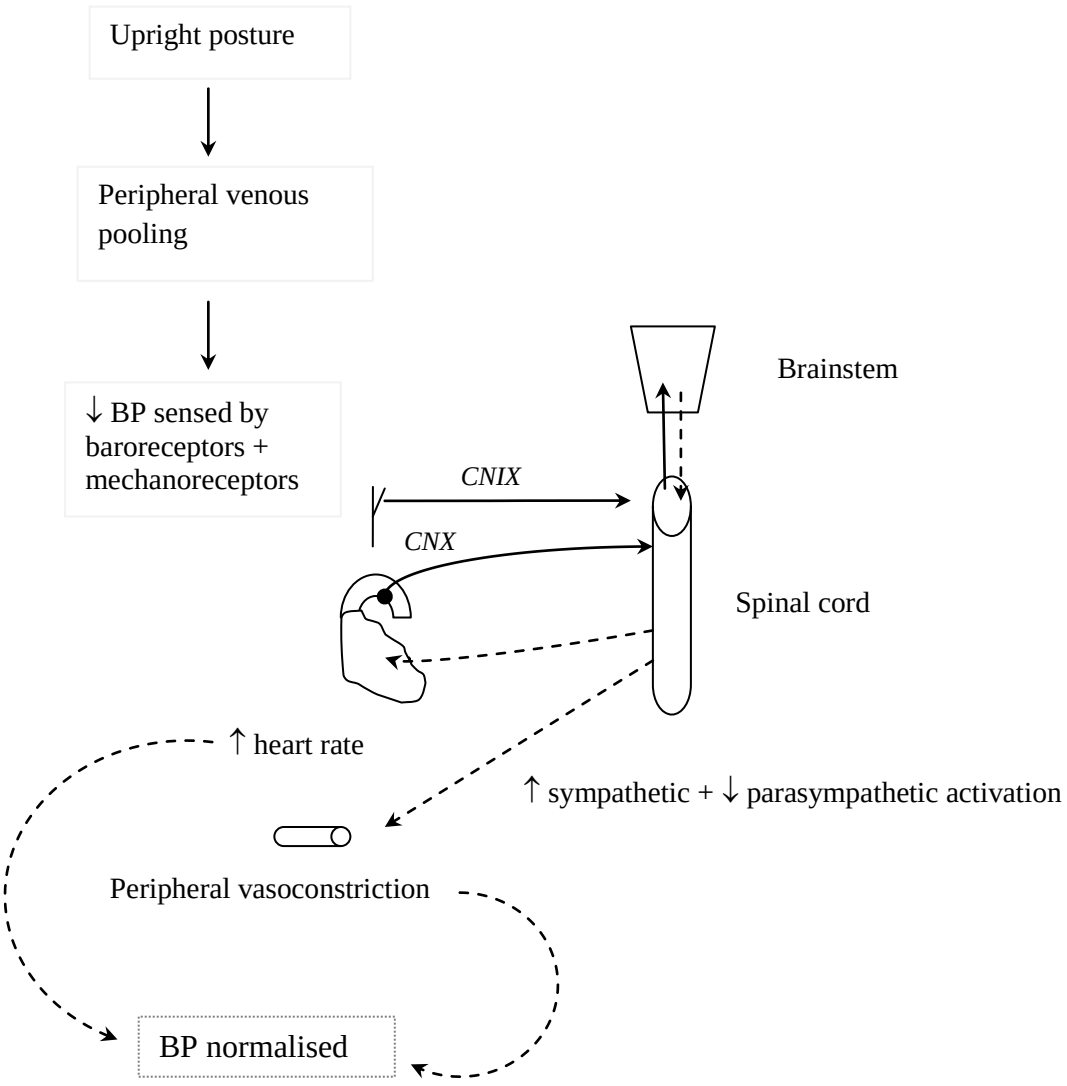


**Figure 4 Normal control of BP**

The brainstem component of the feedback mechanism is illustrated in Figure 5. From the NTS there are pathways leading to the origins of the efferent parasympathetic component of vagus nerve in the nucleus ambigus (NA) and dorsal vagal motonucleus (DVM) within the medulla; but also another which connects to the anterior hypothalamus before synapsing with the NA and DVM. The sympathetic efferent component of the baroreflex is relayed via the intermediolateral column of the spinal cord from the rostral ventrolateral medulla (RVLM), which in turn receives information from the NTS via the caudal ventrolateral medulla (Kirkman and Sawdon, 2010, Ackermann, 2004). This results in signals via the efferent limb to adjust for the fall in ABP by increasing the sympathetic drive and reducing the parasympathetic response in order to increase the heart rate transiently for around 10 seconds (Borst et al., 1982). With this there is also peripheral vasoconstriction to help increase the cardiac filling pressure and therefore together with the increase in heart rate assists in maintaining the ABP (Borst et al., 1984). Thus it can be seen that an abnormality of either the afferent or efferent limb of the BP control arc can result in failure of a compensatory BP rise, and therefore BP remains low.

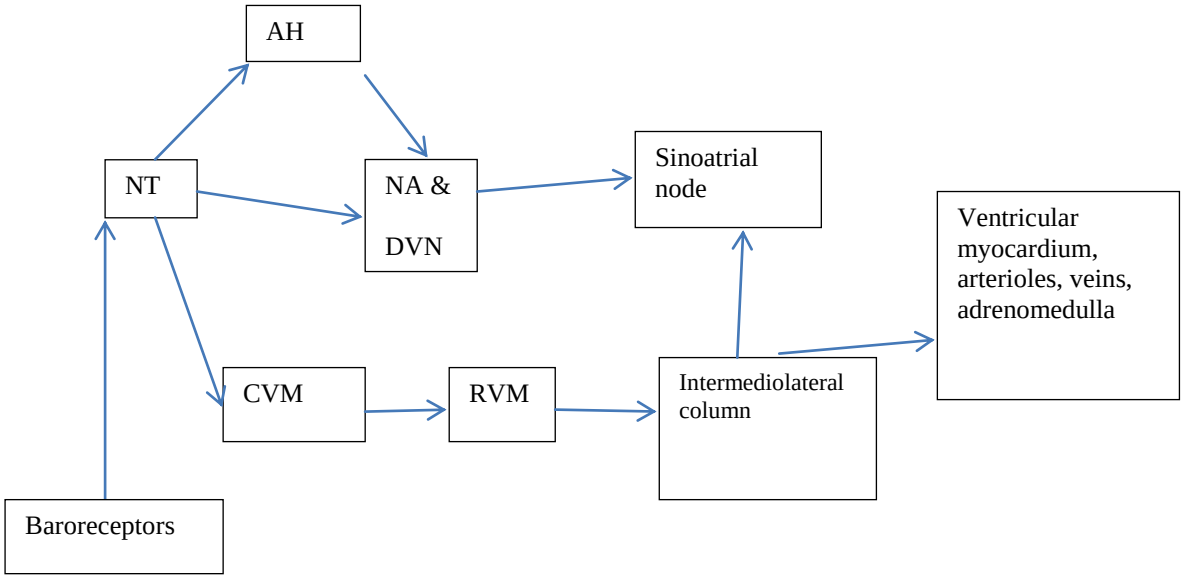


**Figure 5 Brainstem control of BP [Key: AH=anterior hypothalamus, CVM=caudal ventrolateral medulla, DVN=dorsal vagal motonucleus, NA=nucleus ambigus, NTS=nucleus tractus solitarius, RVM=rostral ventrolateral medulla]**

## 2.8 The baroreceptor reflex arc

Arterial baroreceptors are stretch receptors innervated by 9th and 10th cranial nerves and are important in the control of BP (See Figure 4 and 6). Those found in the carotid artery and aorta are arterial or high-pressure baroreceptors, whilst those found in cardiopulmonary areas are low pressure baroreceptors. The reflex arc is a negative feedback loop which is initiated when baroreceptors are triggered to a point less or greater than the stable set point of baroreceptor firing or discharge. This is illustrated in Figure 6, adapted from (Berdeaux and Giudicelli, 1987).

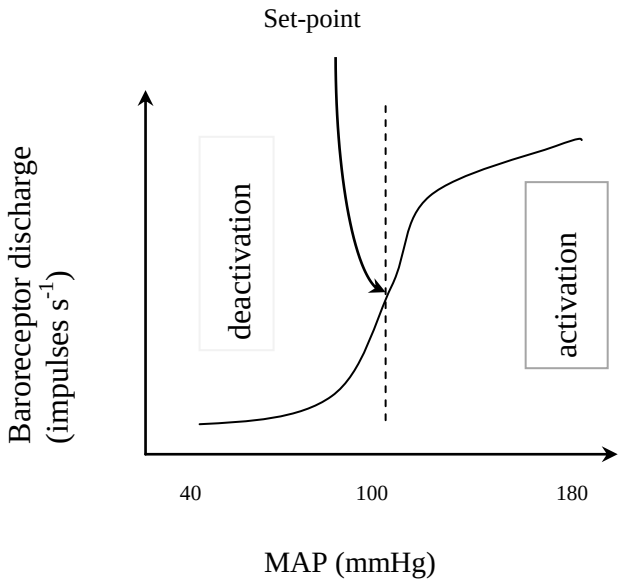


**Figure 6 Baroreceptor discharge and mean arterial pressure (MAP)** ***(adapted from Berdeaux and Giudicelli, 1987)***

Thus it can be seen from Figure 6 that there will be an associated reduction in afferent signals from the baroreceptors as a result of a fall in BP. This in turn via the reflex arc will result in an efferent response consisting of an increase in sympathetic and decrease in the parasympathetic activity resulting in a compensatory increase in BP to within normal levels (Monahan, 2007). Therefore the less sensitive these baroreceptors are,

the less able they are to provide a correct discharge or firing rate in response to the BP level, and the less able they are to control BP.

### 2.8.1 About baroreceptor sensitivity

Baroreceptor mechanisms which help maintain systemic BP levels at a set level in response to acute haemodynamic challenges, via the baroreceptor reflex arc, and require an intact autonomic nervous system (Monahan, 2007). Cardiac baroreceptor sensitivity (BRS) can be measured non-invasively (Dawson et al., 1997) by assessing the change in the duration of the inter-beat interval (R to R interval in milliseconds on the ECG) in relation to an acute change in systemic SBP (units of msec/mmHg) (Bothová et al., 2010). There are various mathematical methods of calculating cardiac BRS (Davos et al., 2002) using either spontaneous variations in BP (Eveson et al., 2005) or by inducing BP changes by a particular stimulus, e.g. Valsalva (Palmero et al., 1981) or pharmacologically e.g. phenylephrine infusions (Robbe et al., 1987), to induce BP changes. An example of normal BRS where a stimulus causes an increase in the change SBP and R-R interval is demonstrated in Figure 7 with the corresponding ideal regression line showing good correlation in Figure 8. One example of an abnormal BRS is shown in Figure 9 where there is little change in the R-R interval after a stimulus induces an increase in SBP, and the associated regression line is shown in Figure 10.

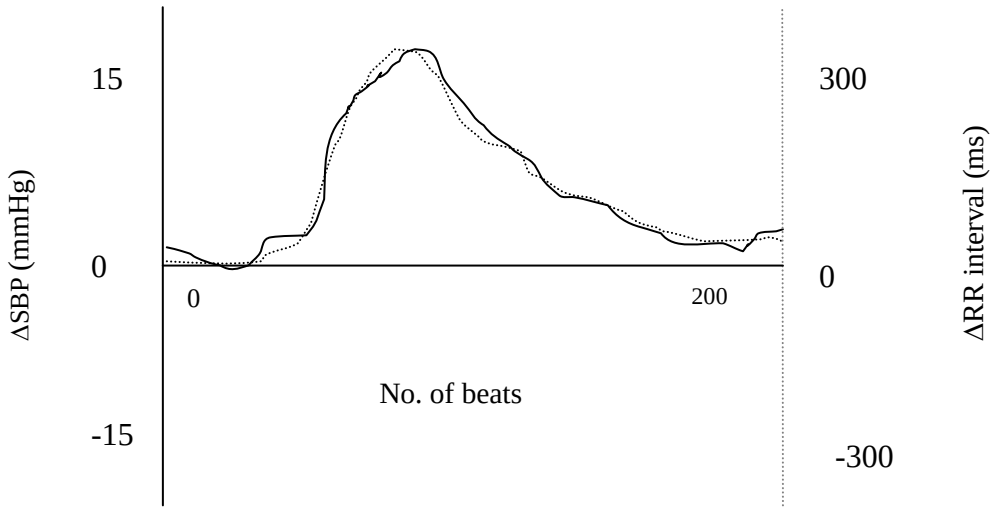


**Figure 7 Normal BRS. ΔSBP (solid line) and corresponding ΔRR interval (dotted line) for consecutive beats.**

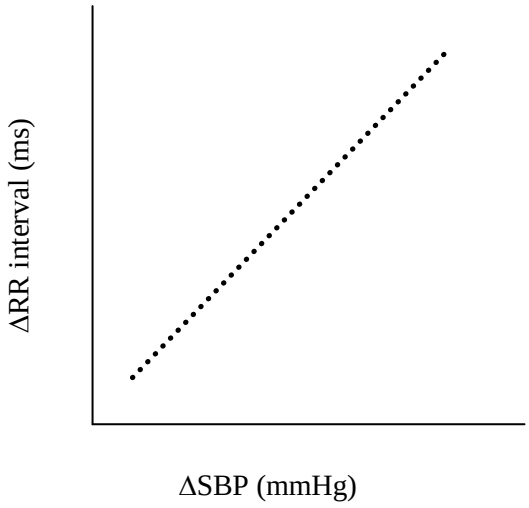


**Figure 8 Normal BRS. Correlation of regression line between ΔSBP and ΔRR interval.**

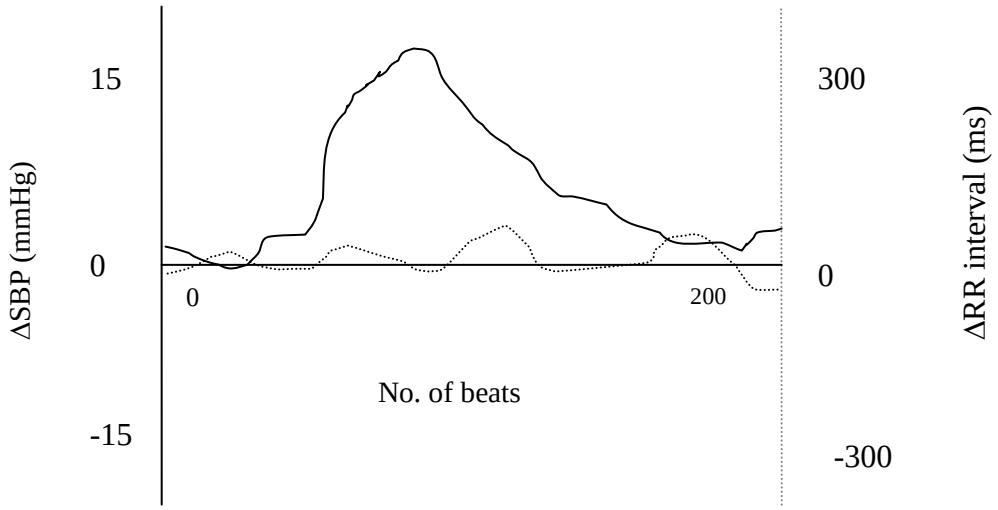


**Figure 9 Abnormal BRS. ΔSBP (solid line) and corresponding ΔRR interval (dotted line) for consecutive beats.**

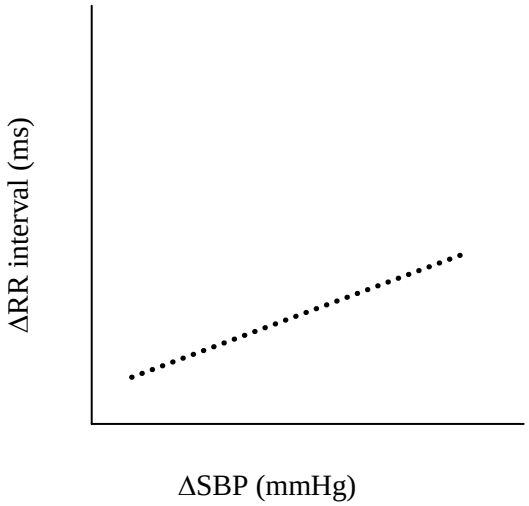


**Figure 10 Abnormal BRS. Correlation of regression line between ΔSBP and ΔRR interval.**

## 2.9 Active versus passive upright posture

### 2.9.1 Younger adults

There are important physiological differences between the haemodynamic responses to active and passive attainment of the upright posture. It has been shown that in healthy young adults (mean age  30 years, range 24-41 years) there are differences between active standing and passive head-up-tilt in the first 30 seconds,  active standing producing a greater reduction in SBP and DBP (Borst et al., 1984, Tanaka et al., 1996), albeit transient, and a higher elevation in heart rate (Tanaka et al., 1996, Borst et al., 1982) probably as a result of a greater fall in total peripheral resistance (TPR) without a compensatory increase in cardiac output (Sprangers et al., 1991) with active standing (Tanaka et al., 1996).

Another difference associated with active standing is that there appears to be an increase in intra-abdominal pressure, absent with passive tilt. With no significant changes between passive and active standing after this initial period (<1 minute) of assuming the upright posture, it has been concluded that the greater fall in ABP with active standing is due to reduced TPR, as a result of vasodilation, which is not fully compensated for by cardiopulmonary baroreflex activation. The shift of blood flow from the splanchnic circulation as a result of increased intra-abdominal pressure is also thought to contribute in the distension of the right atrium and activation of the cardiopulmonary baroreflex (Tanaka et al., 1996). Of note later in the upright position (1-7 minutes), HR, SBP and DBP are higher in active standing than passive tilt, likely because of sustained muscular contraction in active standing providing ongoing positive chronotropic action (Tanaka et al., 1996). The differences in haemodynamic

parameters between active and passive upright posture in younger and older healthy adults are summarised in Table 4.

| Posture | Age Group | Haemodynamic parameter | Initial response (0-10secs) | Intermediate response (10-30secs) | Later (after 30 secs) |
|---|---|---|---|---|---|
| **Active Upright** | **Young adult** | **HR** | ↑↑ | ↑ | = |
| | | **BP** | ↓↓ | ↑ | = |
| | | **TPR** | ↓↓ | ↓ | = |
| | **Older adult** | **HR** | ↑ | = | = |
| | | **BP** | ↓↓ | ↑ | = |
| | | **TPR** | ↓ | = | = |
| **Passive Upright** | **Young adult** | **HR** | ↑ | = | = |
| | | **BP** | ↓ | ↑ | = |
| | | **TPR** | ↓ | ↑ | = |
| | **Older adult** | **HR** | = | = | = |
| | | **BP** | ↓ | ↑ | = |
| | | **TPR** | ↑ | ↑ | ↑ |

**Table 4 Summary of haemodynamic changes in younger and older adults during active and passive upright posture (Key: ↑ small increase, ↑↑ larger increase, ↓ small decrease, ↓↓ larger decrease, = equilibrium reached, ↑/↓ blunted response)**

### 2.9.2 Older adults

Differences in the haemodynamic responses between active standing and passive head-up-tilt to assume an upright posture have also been observed in older adults above the age of 70 years. Like their younger counterparts there is a transient BP fall in the first 10 seconds to posture change followed by an increase around 20 seconds after standing with an accompanying transient increase in heart rate. However these features were not observed during head-up tilt in reasonably healthy older adults who were not on any medication that may negatively affect postural BP control or with systemic disease (with the exception of anti-hypertensive medications). The response of SBP to

standing also depended on whether participants were in the upper or lower quartile of supine BP, with a higher but not significant fall associated in those who were in the upper quartile of supine BP (Imholz et al., 1990). Thus increasing systemic BP levels appear to influence an effect on the BP response to tilt in older persons.

It has been suggested that when a subject actively stands from a supine or sitting position, this only alters the diastolic component of BP (DBP) with no significant change in HR or SBP responses (Ten Harkel et al., 1990). However, earlier work using invasive electrophysiological studies in adults with a mean age of 50 years (range 18-72 years) confirms that with HUT there is an increase in HR, with significant increases in both systemic blood norepinephrine and epinephrine levels, and a lower increase in dopamine indicating an increase in sympathetic nervous system activation (SNSA) (Hermiller et al., 1984). Although there are some differences between the BP response to assuming active and passive upright posture, for practical reasons and for standardisation of assessment of the physiological response, HUT is commonly used in the research setting, as well as to aid assessment of syncope in the clinical setting.

### 2.9.3 The Haemodynamic response to tilt

Healthy older adults physiologically respond differently to passive HUT compared to younger adults. A tilt angle of >60º is usually used, although it has been suggested that the changes associated with passive tilt can be seen from as little as 20º (Hainsworth and Al-Shamma, 1988). In young adults the main adaptations to a fall in BP with 60º HUT are an increase in HR and reduction in end-systolic volume to maintain cardiac output and the mean arterial pressure (Shannon et al., 1991). To maintain mean arterial

pressure, the main response in older adults is an increase in peripheral vascular resistance (PVR) with a reduced ability to decrease the end-systolic volume (Shannon et al., 1991) as marked by a blunted HR response with sit to stand and with supine to 60º upright tilt with increasing age (Goldstein and Shapiro, 1990, Hainsworth and Al-Shamma, 1988), and a reduced cardiac output with 60◦ HUT (Hainsworth and Al-Shamma, 1988). More recently it has been found that although there is an increase in the systemic vascular resistance with age, this is not significant once confounders (e.g. waist and hip circumference, cholesterol, haematocrit etc.) were adjusted for (Tahvanainen et al., 2007). However the increased PWV associated with increasing age remained significant ($p<0.05$) (Tahvanainen et al., 2007). Thus the differences in how BP is maintained with HUT, and the increasing PWV with age, probably accounts in part, the rising prevalence of OH and PPH with age.

### 2.9.4 Cerebral blood flow and postural change

A change in posture from the supine to the upright position requires cerebral blood flow to adapt to maintain adequate cerebral perfusion; this is known as cerebral auto-regulation (CA) and shall be discussed in detail later.

CBF can be assessed at the macrovascular level with transcranial Doppler ultrasound (TCD) which measures cerebral blood flow velocity (CBFV) and also at the microvascular level. By using diffuse correlation and near-infrared spectroscopy to measure blood flow directly at the microvascular level, no significant changes to the relative cerebral blood flow in the frontal lobe cortex can be seen when moving from supine to standing in healthy older adults (Edlow et al., 2010). However there were significant declines in the relative cerebral blood flow across all age groups on

standing (Edlow et al., 2010). The initial fall in BP on assuming the upright posture in the first 15 seconds or so can be associated with transient symptoms of light-headedness, dizziness and nausea. However this and its associated transient reduction in cerebral hypoperfusion as evidenced by a fall in the middle cerebral artery (MCA) velocities, detected by TCD ultrasound, is not related to pre-syncope or orthostatic tolerance in young healthy volunteers (mean age 25±5 years) (Thomas et al., 2009). Nevertheless, the transient reductions in cerebral blood flow velocities do occur with the assumption of the upright posture, and the fact that these can sometimes cause symptoms of orthostatic intolerance, may be a clue to potential underlying changes associated with OH and PPH.

## 2.10 The physiological response to eating

The normal physiological response to meal consumption includes diversion of blood to the splanchnic circulation (Sidery et al., 1993) resulting in a reduction in the systemic vascular resistance and thus the maintenance of blood pressure requires this to be counteracted by haemodynamic and humoral responses (Jansen and Lipsitz, 1995, Fagan et al., 1986). Amongst adults (without OH) a small post-prandial decline in supine mean ABP of 2-5mmHg is present and does not significantly differ in groups of young, middle-aged or older adults (over the age of 60 years) (Oberman et al., 2000). Furthermore healthy older people have been shown to consistently have some asymptomatic reduction in BP after meals (Lipsitz and Fullerton, 1986).

Forearm vascular resistance, as a surrogate marker of systemic vascular resistance, falls in all age groups to a similar degree, despite the higher baseline level in middle-

aged and older adults (Oberman et al., 2000). Neurohumoral responses can be evaluated by determining changes in plasma levels of vasoactive peptides such as norepinephrine, renin, endothelin and aldosterone (Oberman et al., 2000). Accompanying this is a small increase in heart rate as a result of increased sympathetic nervous system activation (SNSA) as reflected by the increase in plasma norepinephrine levels which is present in all ages (albeit greater with age) (Oberman et al., 2000). Plasma renin activity (also an indicator of SNSA) and renin peptides increase within 30 minutes post-ingestion, and subsequently declines in all groups. Endothelin, a vasoconstrictor, shows an age related plasma endothelin response, in older adults as 30 minutes after a meal the levels fall, whereas this does not occur in adults less than 40 years of age. Furthermore the decline in endothelin in older adults continues even at an hour after the meal, whereas it increased in younger adults and is associated with no significant change in middle-aged adults (Oberman et al., 2000).

Adenosine is a vasodilator in the splanchnic circulation (Granger et al., 1978) and thus in part explains why caffeine as an adenosine receptor blocker (as well as associated sympathetic stimulation and renin-angiotensin system) can increase systemic post-prandial BP in seated older adults.(Heseltine et al., 1991c) A rise in plasma insulin (which may also stimulate SNSA and thus noradrenaline (NA)) accompanies the rise in plasma glucose after a carbohydrate or mixed meal or oral glucose ingestion, with a much flatter response to oral fructose (Jansen et al., 1987, Potter JF, 1989). Carbohydrate and lipid dense meals both have been shown to significantly reduce the total peripheral index in older adults with hypertension compared to a pure protein-rich meal within a one hour period (Ferreira-Filho et al., 2009).

Meal composition can affect post-prandial changes in BP, for example there is little BP change following a fructose, compared to a similar energy content, glucose drink, this may result from a flatter insulin response to fructose (Jansen et al., 1987). It has also been shown that there is a greater fall in supine and erect SBP occurs following a high simple, compared to high complex, carbohydrate load (Heseltine et al., 1991a). Furthermore no significant BP fall is associated with a high fat meal in either the supine or erect positions, compared to the post-prandial fall in supine SBP and DBP associated with the high protein and high carbohydrate meals (Potter JF, 1989). There was no significant post-prandial fall in the upright position for the high protein, high carbohydrate or mixed meal, and additionally no post-prandial fall was associated with the mixed meal in the supine position (Potter JF, 1989). The actual volume load in addition to meal composition can also affect post-prandial BP with larger drink volumes of 600ml compared to 200ml being shown to attenuate the fall in BP associated with glucose (Jones et al., 2005). Drinking water prior to consumption of a meal has been shown to have a pressor response which attenuates the post-prandial fall in BP associated in patients with multiple system atrophy (MSA) (Deguchi et al., 2007). It has also been suggested that the extent of a post-prandial fall in SBP can vary, with smaller falls associated with evening meals compared to breakfast or lunch-time; which were also associated shorter duration of symptoms, and lower frequency and severity (Vloet et al., 2003).

## 2.11 Changes in Cardiac BRS with age and disease

Cardiac BRS relates to the physiological responses to the acute BP changes was found to decline during the third and fourth decades, with no evidence of age-related

reduction beyond this in those with a normal BP (Dawson et al., 1999), with similar results being reported in other studies (Tank et al., 2000). Others have shown a linear decline in BRS with increasing age, and a lower BRS in women throughout the age range studied (Laitinen et al., 1998) or a large reduction in BRS in those over the age of 58 years (Barantke et al., 2008). Studies have shown that cardiac BRS in older patients with a history of falls is impaired and may be involved in the underlying mechanism of the fall (Boddaert et al., 2004). Increasing age and BP levels have been found to be associated with impaired cardiac BRS and therefore there may be a common abnormality of cardiovascular homeostasis in hypertension and orthostatic hypotension (James and Potter, 1999, Carey et al., 2003, Moreira et al., 1992, James et al., 1996, Takeshita et al., 1975). Furthermore even amongst those with orthostatic intolerance without OH (i.e. those with symptoms and an increase in HR>30bpm within 10 minutes of standing), BRS can be abnormal (Farquhar et al., 2000). Similarly those with impaired reflex vasoconstriction without the BP fall, i.e. those with the loss of the late phase 2 of the Valsalva, as well as those with OH or borderline OH have been shown to have reductions in BRS (Schrezenmaier et al., 2007). Even amongst healthy older adults it has been shown that there is reduced heart rate variability related to a decline in baroreceptor function on standing compared to younger adults who had a larger increase in HR on standing for a similar change in BP (Simpson and Wicks, 1988). Thus it can be seen that changes in BRS may have a potential role in the pathophysiology of OH and PPH.

## 2.12 Pulse Wave Velocity, Augmentation Index and Arterial Stiffness

### 2.12.1 Arterial stiffness and disease

Amongst those with hypertension arterial stiffness is associated with cardiovascular disease and aortic stiffness is an independent predictor of primary coronary events (Boutouyrie et al., 2002), all cause and cardiovascular mortality (Laurent et al., 2001) and fatal stroke (Laurent et al., 2003). The characteristic shape of the arterial pulse wave varies according to the site it is detected due to the associated morphology of the arterial tree, and also changes with age. The contours of the radial pulse, with increasing age in adulthood, shows a progression of a broadening systolic peaks in early systole. In the carotid artery the wave shows another peak towards late systole and indicates the SBP. As age increases beyond the third decade the two peaks merge, with the second one remaining dominant. The femoral pulse also shows a progressive increase in the systolic component with an accompanying disappearance of the diastolic component with advancing age (Kelly et al., 1989).

Pulse wave velocity (PWV) reflects arterial stiffness which in turn influences BRS, and thus a high PWV indicates stiff arteries and impaired BRS (Eveson et al., 2005). Augmentation Index (AIx) has been suggested as a surrogate marker of arterial stiffness showing significant correlation with PWV in rabbits (Obara et al., 2009) and humans (Yasmin and Brown, 1999). However other studies failed to find AIx correlating with PWV in healthy adult humans (Gurovich et al., 2009). Together with PWV, AIx is a useful indicator of arterial stiffness, separate from brachial BP measurement alone (Wilkinson et al., 1998a). Increases in PWV have been associated with higher postural falls in BP, and a higher mean PWV has been found in those with

OH. However it should be noted that the difference between mean PWV between these two groups was small (around 0.5ms$^{-1}$) and associated with a wide confidence interval for the OH group (Mattace-Raso et al., 2006). A relationship between arterial stiffness and OH would be suggested by the fact that a higher pulse pressure is associated with OH. It has been recently shown in a study of 994 adults (over the age of 80 years, mean age 88 ±5 years) that those with OH have a higher augmentation index (31.1±SD14.0%) compared to those without (27.2±SD13.6%; $p<0.01$) (Valbusa et al., 2012). Although the less direct method of assessing arterial stiffness was shown to be higher the more direct carotid-femoral pulse wave velocity was not significantly different (Valbusa et al., 2012). Thus it can be seen that arterial stiffness may potentially have a role to play in the underlying pathophysiology of OH and PPH.

## 2.13 Cerebral auto-regulation and ageing

It has been shown that ageing per se does not alter dynamic CA (dCA), unlike other important haemostatic regulatory mechanisms such as cardiac baroreceptor function (Carey et al., 2000). Furthermore previous work has been shown that the static and dynamic cerebral ARI are not affected by hypertension in middle aged or older people within the range studied (systolic 137-206mmHg, diastolic 71-121mmHg) (Eames et al., 2003). Profound falls in cerebral blood flow velocities occur with small reductions in systemic BP in patients with auto-regulatory failure (Novak et al., 1998). Of note, in a small study of five subjects, mean age of 41 years, it was suggested that CA dysfunction causing loss of consciousness can occur without the presence of systemic hypotension (Grubb et al., 1998). Paradoxical changes in CBFV and cerebrovascular resistance during provoked hypotension in patients with recurrent unexplained and neurally mediated syncope also suggest abnormal CA.(Grubb et al., 1991a, Schondorf

et al., 1997, Folino, 2006) Similarly this has been found in a small TCD study of PPH in institutionalised patients (Krajewski et al., 1993).

## 2.14 Dynamic cerebral auto-regulation and arterial baroreceptor sensitivity

Whilst it is recognised that the baroreflex arc helps maintain systemic BP levels within a specific range and that cerebral auto-regulation maintains cerebral blood flow, the relationship between CA and BRS is unclear. However it has been shown that in young healthy adults that there may be a compensatory mechanism liking BP and cerebral blood flow control as those with attenuated dynamic CA had a higher BRS (Tzeng et al., 2010). Dynamic CA was measured using both the rate of regulation (RoR) and auto-regulatory index from the thigh-cuff release method as well as the transfer function of spontaneous oscillations in BP and mean CBFV. Inverse relationships between RoR and ARI were found with BRS, whilst a positive relationship was found between transfer function gain and BRS (Tzeng et al., 2010).

## 2.15 Cerebral auto-regulation and symptoms in subjects with OH and PPH

The causes of symptoms associated with a change in posture from supine/sitting to standing have been debated (Mader et al., 1987, Low et al., 1995, van Osch et al., 2005, Khandelwal et al., 2011). It has been suggested that symptoms were simply related to cerebral hypoperfusion but others have not shown a definite relationship between postural BP changes and associated symptoms. A magnetic resonance imaging cerebral perfusion study in symptomatic OH patients has raised the possibility

of a link between the high cerebral blood volume (possibly as a result of vasodilatation), increases in the mean transit time of blood flow and a trend towards a decrease in CBF in the supine position and the severity of postural falls in BP (van Osch et al., 2005). However other work has shown no difference in supine cerebral blood flow velocities (CBFV, the surrogate of CBF) between healthy controls and those with OH (individuals for which HUT resulted in a fall in SBP ≥30mmHg, DBP ≥10mmHg or MBP ≥15mmHg) despite the higher resting supine HR and BP (Novak et al., 1998). It has been suggested that those with OH can be grouped according to three differing auto-regulatory responses based on the relationship between CBFV and BP; however this was not correlated with symptoms. The groups include: 1) impaired auto-regulation and a flat CBFV-BP curve, 2) intact auto-regulation with an expanded auto-regulatory range and 3) failed auto-regulation with a steep CBFV-BP regression curve (Novak et al., 1998). Furthermore a study comparing fifteen patients with OH and fifteen matched control participants (mean age 41.8 ±12.9 years and 42.0 ±11.8 years respectively) found a significant reduction in CBF amongst those with OH during HUT. Furthermore there amongst those with OH, the seven symptomatic patients had a significantly greater percentage fall in CBF compared to the eight asymptomatic patients (median 38.8, IQR 25.7 to 41.7 versus median 18.7, IQR 9.95 to 23.09) (Khandelwal et al., 2011). This suggests that those with OH with HUT have falls in CBF and have evidence in CA, and that those with symptoms have a greater fall in CBF which may account for symptoms.

Another surrogate marker of CA is the pulsatility index (PI) is defined as the difference between the end diastolic and the peak systolic amplitude of cerebral blood flow velocity divided by the mean cerebral blood flow velocity i.e. PI= (Peak systolic

amplitude CBFV – End diastolic amplitude CBFV)/mean CBFV. A reduced PI is found in those with autonomic nervous system dysfunction (pure autonomic failure and multiple system atrophy) compared to healthy controls when using lower body negative pressure induced by thigh cuff inflation as a depressor stimulus in the supine position (Lagi et al., 1994). However others have shown that CA is preserved in autonomic failure when a modest 45° head-up-tilt is used as a reactive vasodilatation occurs which lowers CBFV and vascular resistance to maintain CBF (Brooks et al., 1989). This modest HUT is less than the majority of other studies who use a tilt of at least 60°. Thus there is conflicting evidence as to how CA and autonomic dysfunction, and potentially OH in older people may be linked. Whether it is due to the differing methodology of the studies (lower body negative pressure versus HUT), or perhaps a variable pathophysiological mechanism needs to be considered.

A small study in institutionalised older people with mean age 84.9 years (SD±7.9years) showed that after a mixed meal, the fall in SBP, DBP and mean arterial pressure within 55 minutes, was not associated with significant changes in the maximum or mean cerebral blood flow velocity. However there was an increase in the PI during this period suggesting an increase in arteriolar resistance. In the control group where no meal was given, there were no changes in BP, CBFV or PI. Participants were in the sitting position throughout. Post-prandial hypotension participants had a fall in SBP of mean 32mmHg (SD±15mmHg), whilst the remainder had a fall in SBP of 3mmHg (SD±10mmHg) (Krajewski et al., 1993). Thus this suggests that if PI as a surrogate of the adequacy of CA, then perhaps symptoms in PPH, may also be related to CA, rather than systemic falls in BP.

At the time of writing the research protocol for this PhD thesis in late 2009 there had been no studies published assessing any potential differences in dCA for those patients with and without orthostatic symptoms in relation to actual postural BP changes. Although it has been shown that cerebral vasoconstriction even in young healthy adults occurs with graded orthostatic stress using lower body negative pressure, and that this may potentially worsen any reduction in CBF associated with systemic hypotension (Levine et al., 1994). Furthermore another study found that those with symptomatic OH have a higher CBF in the supine position compared to controls (van Osch et al., 2005). However since late 2009, a study of 30 participants (in two groups, symptomatic vs. asymptomatic, with similar falls in BP) showed that those with symptoms showed a significant fall in cerebral blood flow on 70º HUT within a five minute period ($p=0.003$) compared to baseline whereas the asymptomatic participants did not ( baseline: symptomatic group 33.46ml/100ml tissue/min, range 20.38-38.57 ml/100ml tissue/min vs asymptomatic group 31.30 ml/100ml tissue/min range 24.64-32.16 ml/100ml tissue/min; 5 minutes HUT: symptomatic group 25.40 ml/100ml tissue/min range 21.0-30.76 ml/100ml tissue/min vs asymptomatic group 27.84 ml/100ml tissue/min, 21.59-32.31 ml/100ml tissue/min) (Khandelwal et al., 2011). Furthermore the study also suggested that the decrease in cerebral conductance (cerebral flow divided by SBP) amongst those with symptoms implied a loss in auto-regulation of CBF, whereas those who were asymptomatic had auto-regulation of CBF as there was an increase in cerebral conductance over the 5 minutes of HUT (Khandelwal et al., 2011). These differences would suggest that there are differences in dCA between those with symptoms and those asymptomatic of OH, and those without OH who have symptoms suggestive of OH and those who do not.

## 2.16 Summary of the issues

There are several questions arising from the above discussion. Given that both OH and PPH are relatively common, what drug treatments are there available, and what ones may be best. Furthermore what remains unclear is why only some patients are symptomatic with a drop in BP with posture change or after ingesting a simple carbohydrate meal, and yet why others have no systemic BP changes but have symptoms suggestive of OH or PPH. Symptomatic individuals may have underlying abnormalities in cerebral auto-regulation (CA) and perhaps alterations in autonomic function as evidenced by impairment of spontaneous cardiac baroreflex sensitivity (BRS) and associated arterial stiffness (Eveson et al., 2005). We do not know if the higher prevalence of OH in the older population is a direct reflection of these abnormalities, which may in part be related to increasing arterial stiffness per se, or additionally due to some other mechanisms affecting CA. Furthermore as some patients have OH with other types of syncope (McIntosh et al., 1993), there may be a common mechanism for these conditions involving changes in arterial stiffness and CA.

Thus the aims of this thesis are:

- To assess the drug treatment of OH with a systematic review
- To assess the drug treatment of PPH with a systematic review
- Orthostatic Hypotension Study - To investigate if there are abnormalities in dynamic cerebral auto-regulation, BRS and arterial stiffness in relation to the symptoms of orthostatic hypotension in patients with and without a postural BP fall

- Post-prandial Hypotension Study - To investigate if there are abnormalities in cerebral auto-regulation, BRS and arterial stiffness in participants with and without a history of symptoms suggestive of post-prandial hypotension.

The hypothesis is:

Abnormalities in dynamic cerebral auto-regulation explain why some patients have postural symptoms independent of changes in arterial blood pressure in both orthostatic hypotension and post-prandial hypotension.

# 3 A systematic review of the pharmacological management of orthostatic hypotension

*This Chapter has been published elsewhere:*

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## 3.1 Introduction

OH is a common condition in older adults (Poon and Braun, 2005, Mader et al., 1987), varies in the presence (Lahrmann et al., 2006, Davis et al., 1987) or absence of symptoms, and is associated with morbidity and mortality (Davis et al., 1987, Rose et al., 2006). The varying controversies around the definition of OH in terms of timing, duration and size of BP changes and its multiple causations have been described in the previous Chapter (Moya et al., 2009), (Lahrmann et al., 2006, Deegan et al., 2007, Freeman et al., 2011, Romero-Ortuno et al., 2010).

Various drug treatments have been tried in the management of OH, although only two are recommended in the recent ESC guidelines (Moya et al., 2009), i.e. fludrocortisone (Campbell et al., 1975, Decaux, 1979) and midodrine (Jankovic et al., 1993, Hoeldtke et al., 2006, Kaufmann et al., 2002). Other agents that have been tried include pyridostigmine (Singer et al., 2006) , dihydroergotamine (Bellamy and Hunyor, 1984, Bevegard et al., 1976, Fouad et al., 1981), D,L-3,4-threo-DOPS (Birkmayer et al.,

1983), octreotide (Bordet et al., 1995), yohimbine (Shibao et al., 2010), domperidone (Montastruc et al., 1985), Korodin (Belz et al., 2002) along with increasing dietary sodium intake (Claydon and Hainsworth, 2004) and non-pharmacological methods, e.g. abdominal compression or lower limb bandaging, sleeping head up, drinking water, as well as strength training. However, the quality of evidence of benefit from these studies has been limited by the fact that many are methodologically flawed, lacking randomisation, blinding, a control group and were of short duration. The magnitude of the effects of these therapeutic agents in a randomised controlled trial setting has not been examined systematically using meta-analysis techniques. Thus, the objective of this report was a systematic review of blinded randomised controlled studies involving the pharmacological management of OH using a 'single dose' and 'repeated doses'.

## 3.2 Methods

### 3.2.1 Study selection

#### *3.2.1.1 Eligibility and selection criteria*

All single- or double-blind, randomised controlled trials, which compared the efficacy of a drug treatment with placebo or another drug in the treatment of OH in humans over the age of 18 years, were eligible to be considered. This included 'single dose' use of a drug (i.e. single-dose studies, or where the effect of a drug on blood pressure was measured for up to 24 hours after dosing) and studies where treatment involved 'repeated doses' and where blood pressure (BP) measurements were made over at least 48 hours. We used the original study authors' definition of OH because of the considerable variability in the criteria between studies. The causes of OH in the studies selected included pure autonomic failure, multiple system atrophy, Parkinson's disease, diabetes mellitus and idiopathic OH. To be eligible, the studies needed to report changes in supine or sitting and standing [or head-up-tilt (HUT)] systolic (SBP) and diastolic blood pressure (DBP) and/or mean arterial pressure (MAP). The study characteristics of eligible longer term studies and short-term studies are shown in Table 5 and 8, respectively.

#### *3.2.1.2 Information sources*

OVID SP MEDLINE (1950-Week 7, 2011), OVID SP EMBASE (1980-Week 7, 2011), CINAHL (Week 7, 2011) were systematically searched on the 28th of February 2011. Hand-searching of the bibliography of the full-text articles and cross-referencing with de-duplicated screened articles was also carried out (Figure 11).

#### *3.2.1.3 Search*

Searches were limited to ‘English language’ and ‘humans’. The following individual terms were used: ‘orthostatic hypotension.mp. or exp Hypotension, Orthostatic/’, ‘postural hypotension.mp. or exp Hypotension, Orthostatic/’, ‘fludrocortisone.mp. or exp Fludrocortisone/’, ‘exp disease management/or exp medication therapy management/’, ‘exp therapeutics/or exp clinical protocols/or exp drug therapy/ or patient care/or exp placebos/’, ‘drug treat- ment.mp.’, ‘drug management.mp.’, ‘droxidopa.mp. or exp threo 3, 4 dihydroxyphenylserine/’, ‘korodin.mp. or exp camphor/’, ‘domperidone.mp. or exp Domperidone/’, ‘ergotamine.mp. or exp Ergotamine/ ’, ‘octreotide.mp. or exp Octreotide’, ‘salt.mp. or exp sodium chloride/’, ‘midodrine.mp. or exp Midodrine/’, ‘Pyridostigmine.mp. or exp Pyridostigmine Bromide/’, ‘propranolol.mp. or exp Propranolol/’. The first two were individually combined with each of the subsequent terms. All results were imported by ACLO into Endnote X4, de-duplicated, and those relevant to OH were screened for any relevant articles for its pharmacological treatment. This included papers on the use of erythropoietin amongst others. These full-text articles were then independently assessed by three authors (ACLO, JFP and PKM).

### 3.2.2 Data extraction and synthesis

#### *3.2.2.1 Data collection*

Data from the studies in Table 5 and Table 8 were extracted by one observer (ACLO) on a specially designed form and the data were then independently checked by two blinded observers (JFP and PKM). Authors were contacted, where possible, when essential data were not available from the published papers.

#### *3.2.2.2 Data items*

Information on study participant characteristics (age, sex, and diagnosis), trial inclusion/exclusion criteria and drug intervention including dose and duration of treatment was extracted. The outcome measures of the responses in SBP and DBP and/or MAP including baseline and on treatment for all arms of the study were recorded where available.

#### *3.2.2.3 Risk of bias in individual studies*

Eligible trials were reviewed regarding adequacy of randomisation, concealment of allocation, blinding and loss to follow up, as well as transparency of reporting based on current recommendations (Higgins and Green, 2008).

#### *3.2.2.4 Synthesis of results*

Eligible trials were categorised into 'repeated doses' treatment where pharmacological agent(s) had been administered for over 24 hours and included more than one dose, and the resulting effects on standing or HUT SBP and DBP were examined. For 'single dose' treatment trials, we considered those where a single dose of an agent had been given and the subsequent effects on blood pressure assessed. Because of the variability in the parameters the papers presented, a meta-analysis was not considered suitable. Data are presented as mean ±SD unless otherwise stated.

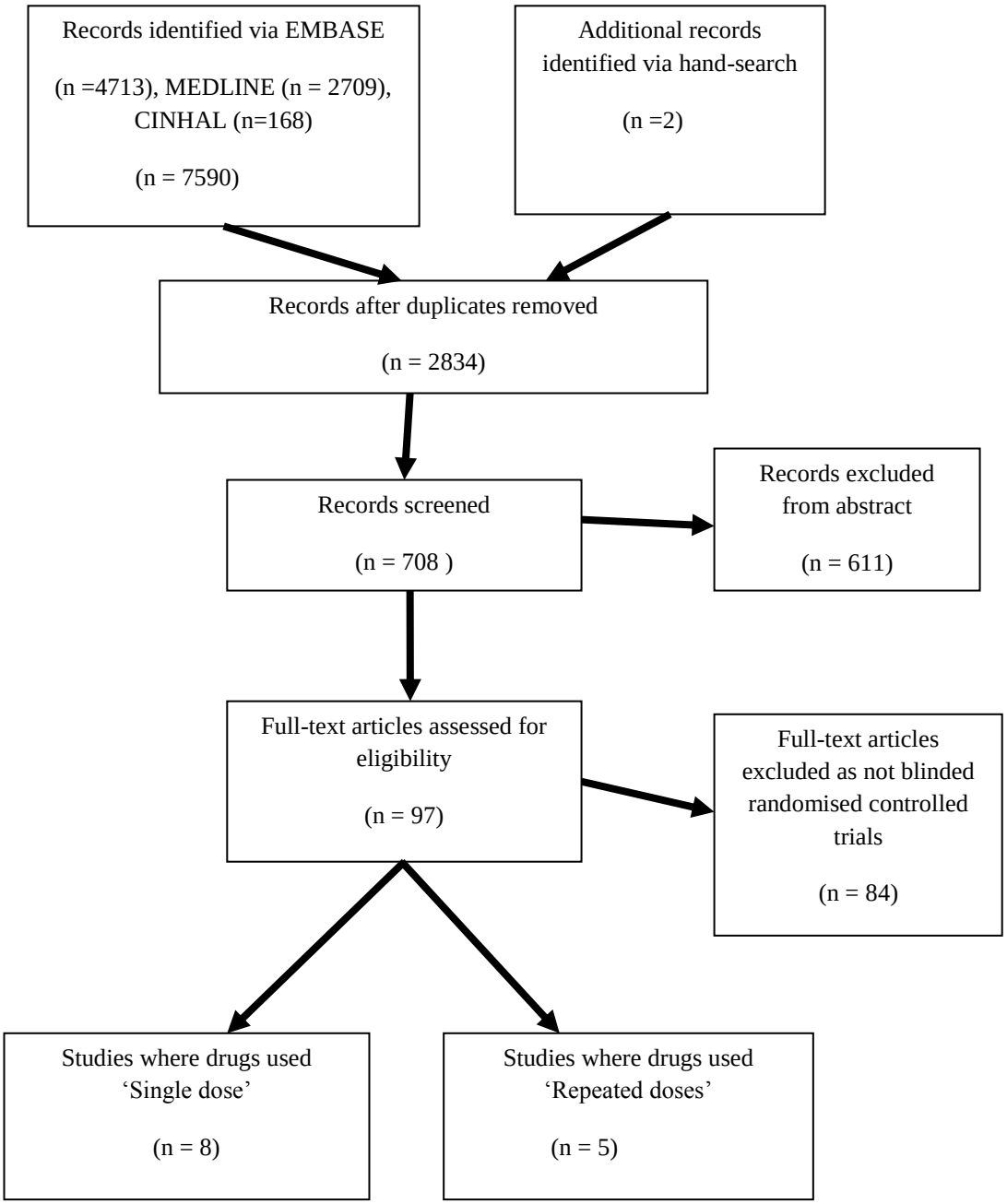


**Figure 11 Flow diagram of Orthostatic Hypotension Treatment Systematic Review**

| Study | Design | Characteristics | Inclusion | Exclusion | Groups | Outcome measures |
|---|---|---|---|---|---|---|
| ***Fludrocortisone*** | | | | | | |
| **Campbell et al 1975 (UK)** | Randomised double-blind placebo controlled cross-over trial | Sex: 6M<br>Data for 5<br>Age 52.2 (11.4 ) years | Diabetes<br>symptomatic OH ≥30mmmHg SBP reduction<br>Autonomic neuropathy confirmed | Ischaemic heart disease or cardiac failure | 3 week control period before and between<br>Fludrocortisone 0.1mg bd, 3 weeks<br>Versus<br>Placebo, 3 weeks | SBP, DBP and HR after 10 minutes 70* HUT (mean of minute interval measurements) |
| **Kaufmann et al 1988 (USA)** | Randomised double blind placebo controlled crossover trial | Sex: 1M, 6F<br>Data for 7<br>Age: 59.1 (7.6) years | OH due to autonomic failure (1-15 years duration)<br>Severe OH not defined | Peripheral neuropathy based on nerve conduction studies +clinical examination | 2 days washout between drugs<br>0.1mg fludrocortisone + placebo, 1 week<br>versus<br>0.1mg fludrocortisone + midodrine (0.5mg per kg), 1 week | Upright MAP±SE (after 2 minutes stand)<br><br>MAP=DBP+1/3(SBP-DBP) |
| **Schoffer et al 2007 (Canada)** | Randomised, double-blind cross-over trial (Phase 2) | Sex: 13M, 4F<br>13 in drug part of trial<br>Age: 69 (11)years | Idiopathic P, duration 6.0(4.5) years<br>Sustained response to PD medication, stable during study, symptomatic orthostasis<br>Postural drop SBP+/or DBP at baseline | Acute Coronary Syndrome, unable to consent, other cause for autonomic failure, SBP>200 or DBP >100 | 1/52 washout between drugs<br>0.1mg fludrocortisone od (placebo bd), 3 weeks<br>versus<br>Domperidone 10mg tds, 3 weeks | Reduction in SBP and DBP at 3min, 5min after 80*HUT, mean(SD) |
| ***Midodrine*** | | | | | | |
| **Jankovic et al 1993 (USA)** | Randomised double-blind placebo controlled parallel group trial | Sex: 53M, 44F<br>Data for 75 only<br><br>Mean age: 61 (range 22-86) years | OH due to idiopathic OH, DM, PD (0.5-10 years duration)<br>Moderate-severe OH with Autonomic failure + history syncope/near syncope<br>+SBP reduction ≥15mmHg (Supine to stand) or ≥ 2 OH symptoms | Supine hypertension >180/110<br>Renal/hepatic impairment<br>Phaeochromocytoma<br>Severe cardiac abnormalities | 1/52 single blind placebo run in<br><br>Placebo (18) 4 weeks<br>versus<br>Midodrine (total of 57) 2.5mg (17); 5mg (19); 10mg (21) tds 4 weeks | SBP, DBP and HR supine + stand (mean±SE) |
| **Fouad-Tarazi et al 1995 (USA)** | Randomised double-blind placebo controlled cross-over trial | Sex: 4M, 4F<br>Data for 8<br>Age: 60.4 (13.5) years | OH due to idiopathic OH, MSA, duration 5.9 (4.6)years<br><br>OH BP not defined<br><br>Unable to tolerate other treatment | Supine hypertension >180/110<br>Symptomatic coronary disease, Acute/chronic renal failure, Thyrotoxicosis | 2/7 single blind placebo run in<br><br>Placebo 4 days<br>versus<br>Midodrine titrate 3-5 days, maintenance 3-5 days (mean | SBP, DBP and HR supine + stand, mean(SD) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | Significant Liver disease, Phaechromocytoma, Dementia<br>MAOI | 8.4mg tds)<br>versus<br>Ephedrine titrate 3-5 days, maintenance 3-5 days (mean 22.3mg tds) | |
| **Low et al 1997 (USA)** | Randomised double-blind placebo controlled parallel group trial | Sex: 81M, 81F<br>Data for 162 (171 randomised)<br>Age: 60 (1.7) years (midodrine); 59(1.7) years (placebo) | OH due to idiopathic OH, PD, DM<br>>15mmHg orthostatic reduction with symptoms<br>Concomitant fludrocortisone + compression garments allowed 45/89 in placebo group, 33/82 in midodrine group – no significant difference | Pregnant or lactating<br>Supine hypertension >180/110 | 1/52 single blind placebo run in<br><br>Midodrine (40M, 39F) 10mg tds, 3 weeks<br>versus<br>Placebo (41M, 42F), 3 weeks | SBP and DBP mean change (no SD) |
| ***Other*** | | | | | | |
| **Cleophas et al 1986 (Netherlands)** | Randomised double-blind , placebo controlled cross-over trial (Trial 2) | Sex: unknown<br>N=10<br>Mean age: 55.1 (range 28-79) years | Diabetes type 1 >10 years, symptoms of dizziness/collapses/near collapse<br>Other symptoms of autonomic neuropathy<br>Fall of MAP of ≥10mmHg at clinic | Exclusion unclear | 1 wk single blind placebo run in<br><br>Pindolol 5mg tds, 1 week<br>Versus<br>Placebo, 1 week | SBP supine + stand (mean±SE) |
| **Kroll et al 2005 (Germany)** | Randomised double blind placebo controlled parallel groups trial | Sex: 22M, 16F<br>Data for 38<br>Age: 65.6(6.3) (Korodin); 71.8(8.6) (placebo) | OH on 2 visits, ≥50yrs<br>Orthostatic dysregulation = reduction SBP ≥20mmg OR reduction DBP ≥10mmHg within 3 minutes in upright position | Severe hypotension, cardiovascular disease e.g.myocardial infarction ≤ 3months, arrhythmia, angina, acute autoimmune disease, clinically significant pulmonary, hepatic, gastrointestinal, neurological or haematological disease or cancer | Korodin 25 drops tds (1 drop=1mg D-camphor+38.62mg cratageus berry extract) (13M, 8F) 1 week<br>versus<br>Placebo (9M, 8F) 1 week | MAP supine + stand at 3 minutes |

**Table 5 Summary of study characteristics of 'Repeated doses' drug treatment (≥24 hours) DM = diabetes mellitus, F = female, M = male, MSA = multi-system atrophy, OH = orthostatic hypotension, PAF = pure autonomic failure, PD = Parkinsons disease; Mean (SD) unless stated**

| Study | Adequate sequence generation | Allocation concealment | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---|---|---|---|---|---|
| **Campbell et al 1975 (UK)** | Randomisation method unclear | Unclear if recruiter aware<br>Double blinded with placebo identical to active medication | One patient left study, data not available | Yes, report data intended | Patient selected from clinic – potential to introduce selection bias; confounding BP medication unclear |
| **Kaufmann et al 1988 (USA)** | Randomisation method unclear | Unclear allocation concealment for double blinding | No missing data | Unclear, methods state supine and stand/sitting BP, but results also discuss changes in BP. | Drug provided by pharmaceutical company, any other financial involvement unclear. |
| **Schoffer et al 2007 (Canada)** | Computer generated randomisation of random number by staff not otherwise involved in study | Other staff used to maintain double blinding of investigators but was aware of group participant allocated to. Assumed that staff member did not have contact with participants | Patient withdrawal within the first week<br>13 of 17 patients data used for drug phase | Yes, adverse events mentioned | Recruitment from 2 clinics, potential selection bias<br>High dropout rate |
| **Jankovic et al 1993 (USA)** | Randomisation method unclear | Unclear concealment<br>Medication dispensed in double blind fashion | Some missing BP data (12 out of 97 patients excluded)<br>Missing questionnaire responses (63 out of 97 used) | Yes, report primary outcomes, comment on one protocol violation | Unclear, 18 centres recruited unknown if one recruited more than others. Observer bias potential. Drug company distributed medication, but did they also provide other financial help? |
| **Fouad-Tarazi et al 1995 (USA)** | Double-blind, block design, crossover, randomisation and sequence generation method unclear | Unclear method, Double blind mentioned | Missing data ephedrine phase (1 patient out of 8, 47 out of 48 cells analysed) | Yes, titration and maintenance phase outcomes | Some sitting and some standing BP |
| **Low et al 1997 (USA)** | Multicentre double-blind randomised parallel group study – each centre received double-digit number | Study monitor off site ensured centres unaware of allocation<br>Patient received coded containers with medication | 15% missing data due to drop out/adverse events | Yes, report primary outcomes. | Authors report that majority of participants came from 3 centres. Possible selection bias. Drug company financial grant |

| | | | | | |
|---|---|---|---|---|---|
| | and pre-randomised codes, unclear method of randomisation | | | | |
| **Cleophas et al 1986 (Netherlands)** | Block randomisation method unclear | Unclear allocation concealment, but double blinded with placebo group same number of daily tablets | No missing data | Unclear (DBP not reported) | Unclear, no financial statement |
| **Kroll et al 2005 (Germany)** | Computer randomisation with variable block length | Placebo same colour, medication bottled. Pre-numbered based on randomisation. Masking of group throughout. Good concealment of allocation allowing double blinding | 39 randomised, 1 unknown treatment group thus not evaluated | Yes | Rehabilitation unit clinic and two doctor's practices, potential confounders |



**Table 6 Assessment of risk of bias of 'Repeated doses' treatment for OH**

## 3.3 Results

### 3.3.1 Systematic review of 'Repeated doses' drug interventions

Eight repeated doses studies (Campbell et al., 1975, Jankovic et al., 1993, Kaufmann et al., 1988, Schoffer et al., 2007, Fouad-Tarazi et al., 1995, Low et al., 1997, Cleophas et al., 1986, Kroll et al., 2005) fulfilled selection criteria for inclusion in the systematic review, their characteristics and risk of bias are shown in Table 5 and Table 6, respectively, with the full compilation of results being available online (Supplementary Table 1, *http://onlinelibrary.wiley.com/doi/10.1111/ijcp.12122/suppinfo*). The risk of bias was considered moderate, due to the lack of clarity over methods of randomisation and concealment of allocation. There was considerable variability between these eight studies in terms of what comparable data parameters and respective standard deviations were presented making it difficult to carry out a meta-analysis. Table 7 shows a summary of drug effectiveness.

#### *3.3.1.1 Midodrine studies*

In a 6- to 10-day duration cross-over trial of eight subjects with idiopathic OH or multi-system atrophy (mean duration of 5.9 SD ± 4.6 years) who were unresponsive to fludrocortisone, support stockings or a high salt diet (Table 5). Fouad-Tarzi et al. (1995) compared the effects of midodrine and ephedrine with placebo on the BP changes from baseline. They found that a mean titrated dose of midodrine of 8.4 mg tds over 3–5 days, with a maintenance dose given for a further 3–5 days significantly increased standing SBP from a baseline mean of 89 (± 8) mmHg to 106 (± 11) mmHg ($p < 0.05$). Standing SBP on midodrine was significantly higher compared with placebo (106 ± 11 vs. 87 ±13 mmHg, $p < 0.001$)) or a mean 22.3 mg tds dose of ephedrine (90 ± 13 mmHg, $p < 0.001$). There was similar significant improvement in

the standing DBP values after treatment with midodrine (69 ±9 mmHg, $p < 0.001$) compared with placebo (61 ± 9 mmHg) and ephedrine (63 ± 9 mmHg). They concluded that midodrine improved standing BP and symptoms.

Jankovic et al. (1993) randomised 75 subjects with OH (mean postural fall SBP 44 ± 27 mmHg) attributable to autonomic failure of varying aetiologies, in a parallel group trial to 4 weeks using stepped doses of midodrine 2.5 mg, 5 mg and 10 mg tds or placebo. The 10 mg tds dose increased standing SBP (by 22 ± 4 mmHg) from a baseline value of 94 ± 7 mmHg, $p < 0.001$; however, this was accompanied by a significant increase in the supine SBP (13 mmHg, no SD reported, $p < 0.05$) to a mean of 174 ±7 mmHg. A subgroup analysis of patients whose mean postural BP fall was > 15 mmHg pre-treatment, demonstrated that midodrine 10 mg tds improved the standing SBP by 31% ($p < 0.01$) and standing DBP by 15 mmHg (no SD given, $p < 0.05$) from a pre-midodrine level of 62 ± 3 mmHg. The authors suggested that midodrine was effective for moderate-to-severe OH associated with autonomic failure. The randomised, double-blind controlled trial by Low et al. (1997) reported the mean change in supine and standing BP for systolic and diastolic components with midodrine and placebo, but no accompanying standard deviation, giving only the percentage change. They used a parallel group design to administer 3 weeks of placebo or midodrine 10 mg tds after a 1-week placebo run-in period. One hundred and sixty-two subjects with OH resulting from Brad- bury-Eggleston syndrome, Shy-Drager syndrome, Parkinson's disease and diabetes mellitus were studied after 15 days of midodrine 10 mg tds or placebo, which resulted in a significant standing SBP increase compared with placebo (22.4 mmHg, $p < 0.01$). This was independent of the concomitant use of fludrocortisone, compression garments or both, in the midodrine

and placebo groups. Thirty three of 82 subjects randomised to midodrine took fludrocortisone and 18 compression hosiery compared with 45 of 89 in the placebo group who also received fludrocortisone and 17 used compression stockings with no significant difference between the groups. Midodrine significantly improved the standing SBP as well as the global evaluation as assessed by both investigator and study subject.

#### *3.3.1.2 Fludrocortisone studies*

Fludrocortisone 0.1 mg bd given in a 3-week cross- over study of five diabetic patients with symptomatic OH (7) resulted in a significantly higher mean tilted SBP (154 ± 29 mmHg) compared with after placebo (110 ± 16 mmHg, $p < 0.005$). There was also a significant reduction ($p < 0.001$) in the postural BP fall (supine SBP 180 ± 26 mmHg, tilted SBP 154 ± 29 mmHg) on fludrocortisone, compared with placebo (supine SBP 149 ± 21 mmHg, tilt SBP 110 ± 16 mmHg). The overall conclusion drawn was that fludrocortisone was an effective treatment for patients with diabetes and symptomatic postural hypotension. Schoffer et al. (2007) found no significant reduction in maximal drop in BP at 3 minutes of standing, with domperidone 10 mg tds and fludrocortisone 0.1 mg od compared with baseline. However, the drop in SBP at 3 minutes was similar with fludrocortisone (mean 21 ± 24 mmHg), and domperidone (18 ± 23 mmHg) and was not significantly different from the baseline fall of 35 ± 23 mmHg. For DBP, the corresponding mean differences were 8 ± 13 mmHg and 7 ± 15 mmHg, respectively, compared with baseline 7 ± 7 mmHg. Although the investigators of the study concluded that the symptoms and postural BP fall improved with both domperidone and fludrocortisone, the study was omitted as it only reported BP change on tilt rather than the actual BP values and no SDs were given. A cross-over study in seven

participants, with OH resulting from autonomic dysfunction, by Kaufmann et al. (1988) demonstrated a variable response in MAP in individual patients with midodrine alone, fludrocortisone alone and the combination of both. In three participants, there was a significant improvement in MAP between baseline and midodrine, but lower in another participant. MAP was significantly lower with fludrocortisone in two participants, with a significant increase in only one participant. In Supplementary Table 1 (*http://onlinelibrary.wiley.com/doi/10.1111/ijcp.12122/suppinfo)* we have calculated the change in MAP to give some comparison with other studies.

Other drug interventions Cleophas et al. (1986) reported that pindolol 5 mg tds in 11 participants with diabetes reduced the postural SBP fall, there being no significant difference between supine and standing BP after active treatment. Kroll et al. (2005) report that the median reduction in MAP was less with Korodin (11.4 mmHg) compared with placebo (14.0 mmHg). The box and whisker plots clearly in the publication illustrate both a deterioration and improvement in MAP for both single dose and with 1 week of application.

The following table summarises the repeated doses treatment of OH Table 7.

| Study | Drug | Improve postural BP | Improve symptoms |
|---|---|---|---|
| **Campbell et al 1975 (UK)** | Fludrocortisone | Yes | Yes |
| **Kaufmann et al 1988 (USA)** | Midodrine | Some | Some |
| | Fludrocortisone | Some | Some |
| **Schoffer et al 2007 (Canada)** | Fludrocortisone | Yes | Yes |
| | Domperidone | Yes | Yes |
| **Jankovic et al 1993 (USA)** | Midodrine | Yes | Yes |
| **Fouad-Tarazi et al 1995 (USA)** | Ephedrine | No | No |
| | Midodrine | Yes | Yes |
| **Low et al 1997 (USA)** | Midodrine | Yes | Yes |
| **Cleophas et al 1986 (Netherlands)** | Pindolol | Yes | Yes |
| **Kroll et al 2005 (Germany)** | Korodin | Yes | Yes |

**Table 7 Overall study conclusions for 'Repeated doses' treatment**

### 3.3.2 Systematic review of 'Single dose' drug intervention

Five studies (Bordet et al., 1995, Wright et al., 1998, Kaufmann et al., 2003, Freeman et al., 1999, Singer et al., 2006) were eligible for inclusion in the systematic review. The study characteristics and risk of bias within these studies are shown in Table 8 and 9, respectively, with a full compilation of results being available online as Supplementary Table 2 (*http://onlinelibrary.wiley.com/doi/10.1111/ijcp.12122/suppinfo*).

Table 10 shows a summary of drug effectiveness. Risk of bias was considered moderate due to unclear randomisation methods and allocation concealment.

| Study | Design | Characteristics | Inclusion | Exclusion | Groups | Outcome measures |
|---|---|---|---|---|---|---|
| **Wright et al 1998 (USA)** | Randomised double-blind placebo controlled cross-over trial | Sex:11M, 14F<br>Data for 24<br>Age: 62 (38-78) years | Orthostatic hypotension with SBP reduction from supine to stand of ≥15mmHg and symptoms | Pregnancy, lactating, supine hypertension ≥180/110, sympathomimetics/ vasoactive drugs, significant systemic, cardiac, renal or gastrointestinal disease | Single dose<br>Placebo vs 2.5mg midodrine vs 10mg midodrine vs 20mg midodrine<br>Breakfast 2 hours before | Standing SBP after 1 to 6 hours (mean, SE) measured after 1 minute standing (and up to 15 minutes) |
| **Bordet et al 1995 (France)** | Randomised double blind placebo controlled cross-over trial | Sex: 3m, 6F<br>Data for all<br>Age: 71 (6.8) years | MSA<br>OH if SBP decreased by >30mmHg or DBP by 20mmHg within 5 minutes of standing symptomatic | Diabetes, amyloidosis | Single dose<br>Placebo vs octreotide 100µg subcutaneous injection<br>Breakfast 3 hours before | SBP, DBP, MBP<br>Supine and minimal levels on 60◦ HUT |
| **Kaufmann et al 2003 (USA)** | Randomised double blind placebo controlled cross-over trial | Sex: 15M, 4F<br>Data for all<br>Age: 64 (2)[a] years | MSA, PAF<br>Symptomatic orthostatic hypotension, decrease of systolic/diastolic BP >20/10mmHg on standing (no time period specified) | Hypertension >180/110mmHg, significant coronary artery, cerebrovascular, peripheral vascular disease or cardiac arrhythmias | Single dose<br>L-DOPS (200-2000mg) vs placebo capsules<br>On fludrocortisone<br>Breakfast 1 hour before | Supine MAP, MAP 3 minutes after standing, up to 12 hours from baseline |
| **Freeman et al 1999 (USA)** | Randomised double blind placebo controlled cross-over trial | Sex: 7M, 3F<br>Data for all<br>Age: 60 (18.1)[a] years | Age 20-70 years with symptomatic neurogenic orthostatic hypotension<br>SBP decrease ≥20mmHg or DBP ≥10mmHg within 3 minutes of standing | Other causes of OH, systemic illness affecting autonomic function, significant coronary artery, cerebrovascular or peripheral vascular disease or malignant cardiac arrhythmias, where relevant not on birth control, medications affecting vasomotor function that could not be discontinued (except fludrocortisone) | Single dose<br>DL-DOPS vs placebo<br>Breakfast 1 hour before | Supine, 60◦HUT<br>SBP, DBP up to 8 hours |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Singer et al 2006 (USA)** | Randomised double blind placebo controlled cross-over trial | Sex: 30M, 28F<br>Data for all (BP)<br>Age: 59(11) years | MSA, PAF, autoimmune autonomic neuropathy, diabetic autonomic neuropathy, unspecified neurogenic OH<br>Reduction in SBP of ≥30mmHg or mean BP reduction of ≥20mmHg within 3 minutes of standing | Unclear | Single dose<br>Pyridostigmine 60mg vs<br>Pyridostigmine 60mg and midodrine 2.5mg vs<br>pyridostigmine 60mg and midodrine 5mg | Supine, standing<br>SBP, DBP 1 minute after standing and HR, up to 6 hours |

**Table 8 Summary of study characteristics of 'Single dose' drug treatment** ***([a] standard error reported)***

| Study | Adequate sequence generation | Allocation concealment | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---|---|---|---|---|---|
| **Wright et al 1998 (USA)** | Unclear if computer generated. Randomisation method – Latin square design | Unclear as it appears participants were substituted for one taking in the same sequence, yet states double blinded | Incomplete data mentioned for 2 participants | Unclear, but appears to report primary end points, and in addition mentions adverse reaction. | Patients who dropped out were replaced by patient taking medication in the same sequence Unclear regarding financial bias, but authors state that by using product, they are not endorsing |
| **Bordet et al 1995 (France)** | Randomisation method unclear | Double blinded but unclear method of allocation concealment | Not mentioned if any incomplete data | Unclear as aim was to investigate standing BP, yet report HUT BP changes | Unclear financial involvement of pharmaceutical company beyond supplying drug |
| **Kaufmann et al 2003 (USA)** | Randomisation by pharmacist at each location, and not centrally. Unclear method or if computer generated. | Only pharmacist aware of allocation, otherwise double blinded | Incomplete data as participants not always able to stand for period required. Mention intention to treat, but unclear as to data for those who could not stand. | Yes, adverse events reported | Yes, pharmaceutical company only supplied drug and did not provide financial support, design study, and not involved in collection, analysis of data, or writing up or report. |
| **Freeman et al 1999 (USA)** | Randomised by pharmacist at centre, unclear method and if computer used | Pharmacist aware of allocation, but other staff double blinded | Incomplete data not mentioned | Actual SBP and DBP reported | Unclear of pharmaceutical financial involvement |
| **Singer et al 2006 (USA)** | Randomised by statistician involved in study, unclear if computer generated | Other than statistician, other study personnel blinded. Concern about statistician analysing data though. | At least 1 measurement missing for 12 patients | Yes, report data specified. No comment about adverse events. | Assuming statistician analysed anonymised data, given method of allocation |

**Table 9 Assessment of risk of bias for single-dose double blind randomised controlled trial**

#### *3.3.2.1 DL-DOPS*

In a single-dose cross-over study, Freeman et al. (1999) showed that in 10 subjects with mixed cause autonomic failure and OH, DL-DOPS significantly reduced the postural BP fall to tilt compared with placebo 4 to 7 hours post dose, the greatest reduction in postural BP fall being at 5 hours, mean 125.3 (SEM ± 12.5) mmHg vs. placebo 97.4 (SEM ± 8.9) mmHg, $p < 0.05$. Similar results for DBP on tilt were also seen with an improvement between 2 and 7 hours, but the greatest improvement occurred at 5 hours with a mean 68 (SEM ± 4) mmHg compared with placebo mean 57 (SEM ± 4.0) mmHg, $p < 0.05$. Kaufmann et al. (2003) demonstrated that L-DOPS improved mean standing BP from 60 (SE ± 4) mmHg to 100 (SE ± 6) mmHg with a peak effect at 3.5 hours, with a mean dose of 1137 (SE ± 131) mg in 19 patients with severe neurogenic OH in a cross- over study. Participants were able to stand for 3 minutes in 94% of occurrences after active treatment, compared with 84% with placebo ($p < 0.001$).

#### *3.3.2.2 Pyridostigmine and midodrine*

Singer et al. (2006) evaluated the effects of pyridostigmine 60 mg for up to 6 hours post administration and showed a significant increase in standing DBP, while the combination of pyridostigmine 60 mg plus midodrine 5 mg not only significantly improved the primary end-point of standing DBP fall compared with placebo alone ($p = 0.002$) but also to pyridostigmine alone ($p = 0.03$). As the primary end-point was fall in standing DBP, the study differed from the majority of studies, which reported changes in SBP or MAP, and thus was not comparable to other short-term studies.

#### *3.3.2.3 Octreotide*

A single injection of octreotide (a synthetic analogue of somatostatin) 100 µg subcutaneously in nine patients (Bordet et al., 1995) with OH resulting from MSA delayed the time to maximal BP fall during HUT to 43 (SEM ± 5.7) minutes compared with placebo 28.5 (SEM ± 6) minutes and increased supine BP [octreotide 175 (SEM ± 9) mmHg, placebo 150(SEM ± 8) mmHg, p = 0.02]. The minimal SBP and DBP on tilt were not significantly different between groups were octreotide 94 (SEM ± 10) mmHg and 45 (SEM ± 5.3) mmHg, placebo 81 (SEM ± 5) mmHg and 37 (SEM ± 3) mmHg and for the control arm 81 (SEM ± 6) mmHg and 40 (SEM ± 3.7) mmHg. A further study using a single dose of midodrine 10 mg improved standing SBP at 1 hour 121.9 (SEM ± 8.2) mmHg, and for up to 4 hours with 20 mg (mean 123 (SEM ± 9.2) mmHg compared with baseline values of 87.6 (SEM ± 5.2) mmHg and 95.6 (SEM ± 6.1) mmHg (Wright et al., 1998).

| Study | Drug | Improve postural BP | Improve symptoms |
|---|---|---|---|
| **Wright et al 1998 (USA)** | Midodrine | Yes | Yes |
| **Bordet et al 1995 (France)** | Octreotide | Some | No information |
| **Kaufmann et al 2003 (USA)** | L-DOPS | Yes | Yes |
| **Freeman et al 1999 (USA)** | DL-DOPS | Yes | No |
| **Singer et al 2006 (USA)** | Pyridostigmine | Yes | Yes |
| | Pyridostigmine + midodrine | Yes | Yes |

**Table 10 Overall study conclusions for 'Single dose' treatment**

### 3.3.3 Bias

The trials used in this systematic review on the whole had been unclear with regards to random sequence generation and concealment of group allocation. Although many mention randomisation by e.g. statistician, pharmacist, it was unclear if the method

used was using a computer or a toss of a coin. The majority commented on any missing results, e.g. because of dropout of participants, but it remained sometimes unclear if there was a degree of selective reporting. In several instances, it was also unclear if other sources of bias were introduced, whether if one recruitment centre was more heavily involved, if there were financial involvement of pharmaceutical companies beyond supplying the drug. In one instance (Wright et al., 1998), it appeared that if a participant dropped out, another may have been substituted with the same drug allocation sequence, raising issues of allocation concealment, and deviation from the study protocol. Of course this may simply be unclear reporting. Overall there is a moderate risk of bias.

## 3.4 Discussion

Although postural hypotension is a common problem in elderly people with significant morbidity and mortality, there appears to be little high-quality data as to the best pharmacological management. We report a systematic review of the results from 13 blinded heterogeneous RCTs, which examined the effects of drug treatment for OH. Of the 708 reports screened, 97 full-text articles were examined, but only 13 fitted our entry criteria, eight involving ‘repeated doses’ treatment and five ‘single dose’ studies. There was a general paucity of good quality trials with comparable data parameters, which precluded a good quality meta-analysis. There was a considerable difference in effect on postural BP fall not only between trials (despite using the same pharmacological agent at the same dosages) whether short- or long-term effects were studied, but perhaps more predictably between agents. In general, these trials did show treatment increased standing or HUT SBP levels, but there was limited evidence of a greater clinical benefit of any specific therapeutic regime.

Current guidelines recognise the limited availability of prospective randomised controlled trials. The European Federation of Neurological Societies 2006 guidelines recommend fludrocortisone as first-line treatment and then midodrine, on its own or combined with fludrocortisone, after non-pharmacological measures have been tried including education and physical measures. They also recommend DOPS (dihydroxyphenylserine) and octreotide for the treatment of OH (Lahrmann et al., 2006), which are also included in the recommendations in the European Handbook of Neurological Management in 2011 (Lahrmann et al., 2010). The ESC 2009 guidelines similarly recommend non-pharmacological measures in the treatment of OH, including adequate hydration and salt intake, as first-line management followed by midodrine and fludrocortisone along with pyridostigmine (Moya et al., 2009). Other drugs such as octreotide were also proposed where hypotension may be as a result of post-prandial haemodynamic changes or erythropoietin where anaemia was the underlying cause (Moya et al., 2009). Potential confounding factors that may have had a significant influence on the effects of the different pharmacological treatments on orthostatic BP change, as well as in symptoms, will have been the variation in the aetiology of the OH and the differing mechanisms of actions of the various agents. For example, fludrocortisone (9-alpha fludrohydrocortisone acetate) acts not only by increasing plasma volume by its sodium retaining effects as a synthetic mineralocorticoid thus increasing cardiac output but also by potentially increasing sensitivity to sympathetic nerve stimulation resulting in an increase peripheral vascular resistance; this latter effect being independent of norepinephrine release from the sympathetic nerve endings in response to HUT (Hickler et al., 1959). Midodrine is a pro-drug and its active agent desglymidodrine is an alpha-1-adrenoceptor agonist, which also increases mean

systemic arterial pressure by raising peripheral vascular resistance (Figueroa et al., 2010).

Future trials should take into account the likely aetiology of OH to select the agent with the most appropriate pharmacological profile. This could be aided by classifying OH according to changes in total peripheral resistance and cardiac output to determine whether OH is resulting from arteriolar, venous or mixed dysfunction (Deegan et al., 2007). Whether any improvement in the systemic orthostatic BP fall with treatment is associated with symptomatic improvement is less well known. We considered carrying out a detailed systematic review, but only some of the RCTs attempted to examine the effect of pharmacological intervention on symptoms (Shibao et al., 2010); however, there was no consistency between these studies in terms of methodology (e.g. questionnaire used). Midodrine has been reported to significantly reduce the incidence of a patient's inability to stand (Fouad-Tarazi et al., 1995), and improve the global postural symptom score (Wright et al., 1998), with good concurrence between patient and investigator scores (Figueroa et al., 2010). In the case of fludrocortisone therapy, it has also been reported to result in subjective improvement although the studies were too small to draw firm conclusions (Campbell et al., 1975).

Many clinical reviews highlight the benefit of drug therapy (Freeman, 2003) for OH, as well as the many non-pharmacological options (Figueroa et al., 2010). ESC guidelines of 2009 based the recommendation of the use of midodrine in the treatment of OH on three studies (Jankovic et al., 1993, Wright et al., 1998, Low et al., 1997), which because of differences in parameters given made it difficult to meta-analyse. However, this systematic review, which included small and large studies of varying

duration, highlighted that although there is evidence of some beneficial effect of treatment in reducing the postural BP fall, the benefits in terms of symptom relief were unclear especially as duration of therapy and underlying aetiology of OH differed considerably between studies.

The data on the benefits of 'repeated doses' of pharmacological treatment of OH are limited both in terms of the effects on postural BP changes as well as symptom relief and should be weighed against potential side effects and adverse effects including cardiac failure, systolic hypertension and stroke (Hussain et al., 1996, Pathak et al., 2005). There are limitations to this review. There was significant variability in the definition of OH between the studies, with some groups including participants with only symptoms (in recognition that the actual fall in systemic BP may be limited), whilst others requiring in fall in postural BP greater than the current ESC guidelines on Syncope (Moya et al., 2009) or the Consensus Statement (Freeman et al., 2011). This highlights the suspicion that it may not be the fall in systemic BP that causes symptoms, but the failure to maintain cerebral blood flow as a result of impaired auto-regulation resulting in a fall in cerebral perfusion to the drop in systemic BP that is the underlying problem. Thus, treatments that are used solely to increase systemic BP levels may be inappropriate for some patients. There was a large variability in end-point parameters in studies involving the drug treatment of OH, making a meta-analysis comparing differing drugs and their effectiveness in treating the postural fall in BP impossible.

This systematic review included reports that were published in the English language only. The studies included were carried out in Western Europe and North American

and the results should be interpreted with caution as they may not be generalizable across other ethnic groups. Furthermore, the studies included young and older adults where the pathophysiology mechanisms may differ, with arterial stiffness and baroreceptor function affecting blood pressure with increasing age (Mattace-Raso et al., 2006, Protogerou et al., 2008). In addition, the heterogeneity of the participants in the studies is high, with varying underlying causes of OH being included even within the same study. There is always a possibility of publication bias with only positive effects being emphasised in clinical trials to date. Disappointingly, there was a lack of reporting of the amount of change in postural BP levels and standard deviations (i.e. the difference a drug exerted on the actual change from supine or sitting to standing or tilt blood pressure). Most studies did not report the magnitude of effect of drugs on in terms of the improvement or reduction (if any) in postural BP drop and more importantly none made any detailed comment on patients symptoms or quality of life factors. We suggest that future trials should study the improvement in symptoms and QOL measures rather than concentrate just on changes in BP measurements. Using the ESC definition of OH in future studies as well as publishing standard deviations for changes in postural BP will allow comparison across studies. Of the few studies that did comment on the improvement in symptoms of OH with therapy, only Schoffer et al. (2007) used COMPASS-OD (questions relating specifically to OH and part of the Mayo clinic autonomic Symptom Profile), which is correlated with part of the Composite Autonomic Scoring Scale (CASS) (Low, 1993) in their outcome assessment.

The strength of this review is that we used strict selection criteria based on quality of methodology as well as reporting and three authors independently reviewed trials to

select those eligible. In the absence of firm clinical evidence of the effect of pharmacological intervention for this common condition with its associated higher morbidity and mortality, non- pharmacological management may remain as an important first step towards the management of this condition although the evidence of their effectiveness is equally lacking.

At present there is only one open randomised trial of non-pharmacological management of OH in older patients to date, which concluded no benefit of a 6-inch head-of-bed elevation on BP or symptoms to other non-pharmacological management (Fan et al., 2011). A recent systematic review of non-pharmacological management of OH identified 23 studies covering eight differing interventions, concluded that although physical counter manoeuvres, eating smaller and frequent meals, compression of legs and/or the abdomen, as well as functional electrical stimulation with spinal cord injuries could be beneficial, further studies would be needed(Mills et al., 2015). It is recognised that others have published systematic reviews on pharmacological and non-pharmacological management of OH. One study only included midodrine, and included a total of nine open and blinded studies for meta-analysis, of which four were blinded (Parsaik et al., 2013) and included in this systematic review. Like this systematic review, the meta-analysis suggests midodrine can improve OH symptoms, but the meta-analysis suggests that only standing SBP is improved, the postural change was not greatly reduced(Parsaik et al., 2013). Another systematic review which included drug treatment, also noted issues of heterogeneity in studies, and included studies published in German (Logan and Witham, 2012). They also agree with Parsaik et al (2013) regarding the limited benefit of midodrine but suggest that there is limited evidence generally that drugs improve OH with many studies including a risk of bias.

They also agree with this systematic review that further research needs to be done including pharmacological and non-pharmacological methods, to include investigation of symptoms as well as postural BP changes.

A useful comparison for future trials could include pharmacological and non-pharmacological measures. Participants with OH could be randomised to a drug where a crossover of non-pharmacological measures is unsuccessful in terms of symptomatic relief and quality of life rather than BP improvement alone.

## 3.5 Conclusions

There is limited evidence as to the benefits of pharmacological agents for treatment of OH, with only midodrine and fludrocortisone potentially being of use. Well-designed double-blind, randomised controlled trials comparing different drug options (and dosages) in the treatment of OH and symptom relief need to be conducted. Ideally, this should be done in combination with non-pharmaceutical interventions.

# 4 Pharmacological Treatment of Post-prandial Reductions in Blood Pressure: A Systematic Review

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## 4.1 Introduction

The definition of PPH and the degree to which BP may change after eating can vary and its epidemiology has been discussed in Chapter 1 of this thesis. In essence it is common in older adults (Vaitkevicius et al., 1991, Aronow and Ahn, 1994), (Vloet et al., 2005), and may or may not be symptomatic (Vloet et al., 2003, Vloet et al., 2005, Jansen and Lipsitz, 1995) and may have an associated morbidity (Vaitkevicius et al., 1991). Post-prandial hypotension (PPH) can be defined as a reduction in systolic blood pressure (SBP) of 20 mmHg or more within 2 hours of the start of a meal or if SBP falls to 90 mmHg or less within this period if pre-prandial SBP was 100 mmHg or greater (Jansen and Lipsitz, 1995).It is unclear as to how best to pharmacologically treat post-prandial falls in BP and its associated symptoms where conservative measures such eating smaller meals fails. The evidence for treating PPH has not been systematically reviewed, and it is unclear as to which drug, if any is of clinical benefit in terms of BP or symptoms.

It is known that the post-prandial reductions in BP is independent of the presence or absence of systemic hypertension (Visvanathan et al., 2005, Jansen et al., 1987, Potter JF, 1989) even when anti-hypertensive medication is withdrawn (Lipsitz et al., 1983). This post-prandial reduction in BP reflects the failure of the normal homeostatic mechanisms to maintain BP levels in the face of a reduction in systemic vascular resistance due to splanchnic and peripheral vasodilation not being compensated for by an increase in cardiac output (Jansen and Lipsitz, 1995, Heseltine et al., 1991b). Evidence suggests that caffeine (an adenosine antagonist that blocks splanchnic methylxanthine sensitive adenosine receptors) when given after meals can reduce post-prandial symptoms and reductions in BP, (Heseltine et al., 1991b, Heseltine et al., 1991c, Sawynok, 1995) indicating that adenosine may have an underlying pathophysiological role in inducing this splanchnic vasodilatation.

In addition to some lifestyle measures several other agents have also been tried in the treatment of PPH by addressing possible underlying pathophysiological mechanisms (Jansen and Lipsitz, 1995). For example, acarbose reduces complex carbohydrate breakdown, delaying gut glucose absorption (Shibao et al., 2007, Gentilcore et al., 2011). Whereas 3,4- DL-threo-dihydroxyphenylserine (DL-DOPS), is a norepinephrine precursor that converts to norepinephrine in the peripheral and central nervous system to replace levels of norepinephrine in autonomic failure (Freeman et al., 1996). Guar gum reduces post-prandial reductions in BP by delaying gastric emptying and glucose absorption in the small intestine (Jones et al., 2001). Other agents such as octreotide (which inhibits the vasodilation of the splanchnic vasculature by inhibiting vasoactive peptides) given before a meal have been also been shown to

have some benefit in preventing PPH in older adults with hypertension (Jansen et al., 1989), as has midodrine (an $\alpha_1$-adrenergic agonist) administered concomitantly with denopamine (a selective $\beta_1$-adrenergic agonist) (Hirayama et al., 1993). Although there is some evidence of these agents being useful in this setting, the magnitude of the effects of these therapeutic agents in a randomised controlled trial setting has not been examined systematically.

Herein is reported a systematic review of randomised controlled trials involving the pharmacological management of PPH and post-prandial reductions in BP.

## 4.2 Methods

### 4.2.1 Eligibility Criteria

Studies that specifically investigated the effect of the drug intervention on post-prandial change in BP were selected. They had to be controlled randomised studies that reported supine or erect BP and included administration of a standardised meal or glucose (oral or intraduodenal). Because of the nature of some treatments, open and blinded studies were included. Individuals being assessed by medical staff for potential symptoms related to PPH or under medical care for any reason and healthy volunteers were included in the analysis if they were aged 18 and older, as long as the aim of the study was to assess the effects of treatment on post-prandial BP changes.

### 4.2.2 Information Sources

MEDLINE (1950–), EMBASE (1980–), and CINAHL (1937–) were searched on July 16, 2013, limited to studies in English and involving human subjects, followed by

hand-searching of the bibliographies of the full-text articles to identify potentially relevant studies.

### 4.2.3 Search Terms

Search terms included “postprandial hypotension.mp.” or “hypotension.mp.” or “Hypotension/or hypotension, orthostatic/” and “eating/or meals.mp.” or “food/or prandial.mp. or postprandial period/.” Individual drugs were searched, including “octreotide.mp. or octreotide/,” “caffeine.mp. or caffeine/,” “NSAIDS.mp. or anti-inflammatory agents, non-steroidal/,” “indomethacin.mp. or indomethacin/,” “fludrocortisone.mp. or fludrocortisone/,” “midodrine.mp. or midodrine/,” “acarbose.mp. or acarbose/,” “somatostatin.mp. or somatostatin/,” in addition to more generic terms, including “drug treatment.mp. or adult/,” “drug therapy.mp. or drug therapy/,” “autonomic nervous system diseases/co, et, pp, th [complications, etiology, physiopathology, therapy]”.

### 4.2.4 Data Collection

Articles were initially assessed for suitability using the Critical Appraisal Skills Programme approach for randomised controlled trials (accessed September 7, 2012, *http://www.casp-uk.net/find-appraise-act/*), and are shown in the Table 11. Data parameters were originally extracted (ACLO) using a standardised form used previously to assess article suitability for meta-analysis. The form was developed specifically for the review after piloting with three randomly selected articles in the first instance to ensure that all relevant data were captured. Articles were independently reviewed (ACLO, JFP) and discrepancies resolved (PKM).

### 4.2.5 Data Items

Information was extracted on study participant characteristics (age, sex, diagnosis), trial inclusion and exclusion criteria, and drug intervention, including dose and duration of treatment. The outcome measures of SBP and diastolic BP (DBP) or mean arterial pressure (MAP) at baseline and with treatment for all arms of the study had to be available as individual components of BP, MAP, or a change in these parameters. Results are given as mean mmHg ±standard deviation unless otherwise stated.

### 4.2.6 Risk of Bias in Individual Studies

Risk of bias for included studies was assessed, including adequacy of sequence generation (presence of random component and method), allocation concealment (pre-assignment), whether missing data were accounted for, and whether there was evidence of within-study selective reporting or other bias (Higgins and Green, 2008). Other bias, particularly for cross-over studies may include observer bias, as participants may attend on differing days or the introduction of confounders which may significantly affect outcome parameters.

### 4.2.7 Summary Measures

Because of the inconsistencies in outcome measurements and reporting, it was not possible to synthesise summary statistics using a formal meta-analytical approach.

## 4.3 Results

Fourteen randomised studies were included in the final selection for systematic review (Figure 12). The characteristics of the studies (including population and meal type) are shown in Table 11. Overall, the studies were of reasonable quality; the risks of bias in these studies are shown in Table 12.

The timing of the intervention depended on the nature of the agent being studied; in the majority of studies, drug treatment was given before or with the meal or glucose load, and in the remainder, it was given immediately after the meal or glucose load. BP in all but two studies (Heseltine et al., 1991b, Heseltine et al., 1991c) was not explicitly measured more than once at each time point. The majority of studies used an automated oscillometric BP monitor, others used an ultrasonic BP monitor(Lenders et al., 1988) or a random zero sphygmomanometer (Heseltine et al., 1991b, Heseltine et al., 1991c). Only two studies (Shibao et al., 2007, Lipsitz et al., 1994) were conducted in participants with a formal diagnosis of PPH using the defined criteria (Jansen and Lipsitz, 1995). The trials reported the haemodynamic responses but not the symptomatic relief of PPH. Shorter-term studies investigated the effects of a single dose of treatment within a 24-hour period. In repeated dose studies the intervention was continued for longer than 24 hours.

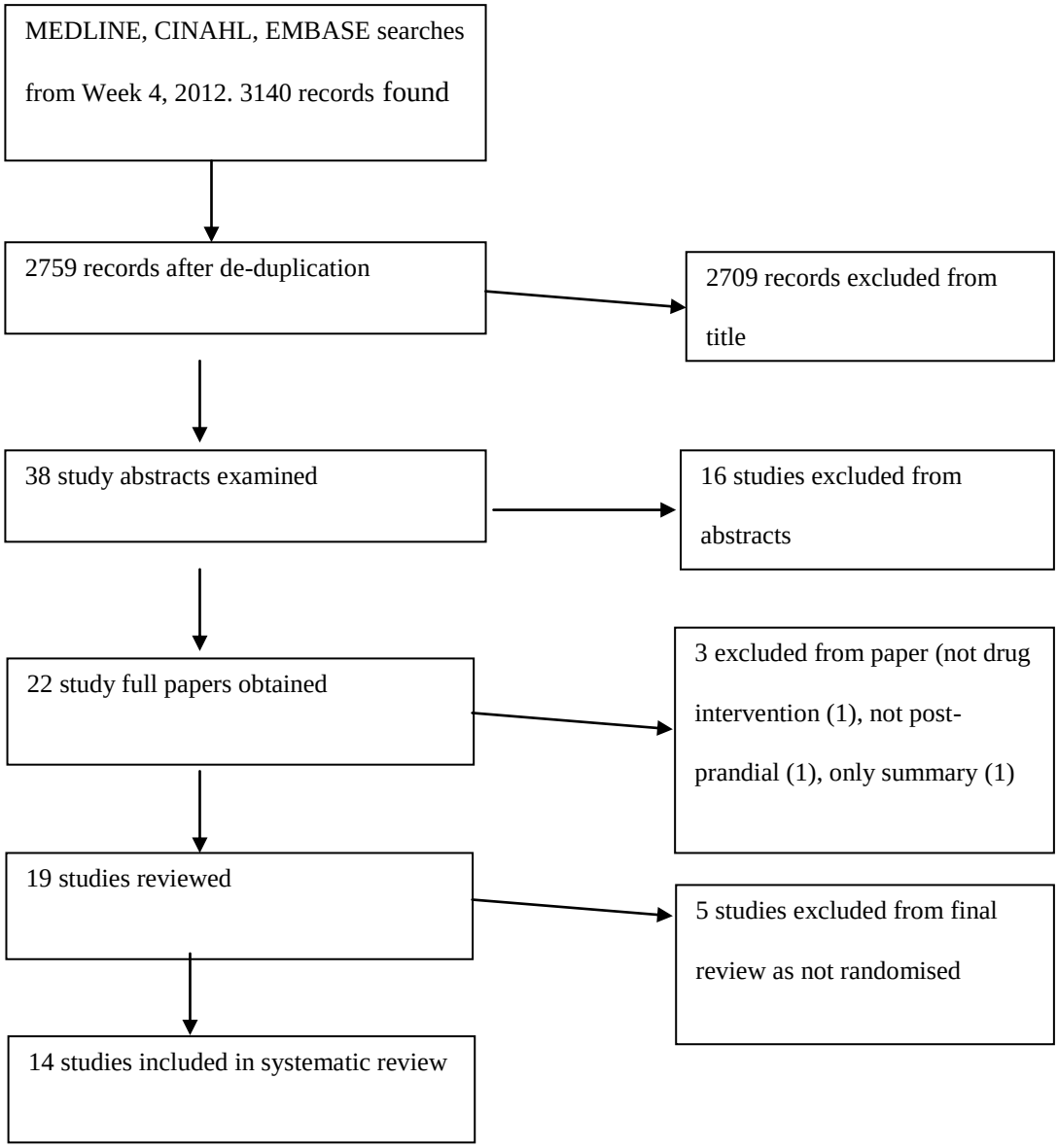



**Figure 12 Flow diagram of post-prandial BP reductions systematic review of drug treatment**

| Study Author (Year) | Drug/ Intervention | Meal/Glucose | Study Population | Known PPH | PPH defined in study | Age (years) | Number | Gender | Groups |
|---|---|---|---|---|---|---|---|---|---|
| **Onrot et al. (1985)** | Caffeine 250mg capsule | standard mixed meal (kcal not given) | Autonomic failure (primary – 11, secondary -1) | No | N/A | 63.6 (SD ± 5.9) | 12 | 6M:6F | Meal(12)/ Caffeine(12)/ Meal & Caffeine (6) |
| **Lenders et al. (1988)** | Caffeine 250mg capsule | standard mixed meal (405kcal) | Healthy | No | N/A | 75.4 (SD ± 6.6) | 15 | 8M:7F | Placebo(15)/Caffeine (15) |
| **Heseltine et al. (1991)** | Caffeine 200mg coffee | standard mixed meal (585kcal) | Healthy | No | N/A | 67.4 (range 64-72) | 7 | 2M:5F | Placebo(7)/ Caffeine(7) |
| **Heseltine et al. (1991)** | Caffeine 100mg coffee | glucose drink (400kcal) | Post-acute admission (CVD, IHD, CCF, PVD, DM, COPD, PD) | No | N/A | 84 (SD ± 5) | 20 | 10M:10F | Decaffeinated (20)/ Caffeine(20) |
| **Lipsitz et al. (1994)** | Caffeine 250mg capsule | liquid meal (1674kJ) | Pure autonomic failure, Shy-Drager, PD, unknown | Yes | ≥20mmHg fall supine/seated SBP ≤60mins of meal | 79 (SD ± 9) | 9 | 2M:7F | Placebo (9)/ Caffeine (9) |
| **Rakic et al. (1996)** | Caffeine 60mg 5 times/day as tea/ coffee | high carbohydrate meal (unspecified) | Normotensive (62)/treated HTN (46)/untreated HTN (63) | No | N/A | 75.2 (SD ± 0.7) | 171 | 41M:127F | Decaffeinated/ Caffeine |
| **Shibao et al. (2007)** | Acarbose 100mg | standard mixed meal (414kcal) | Pure autonomic failure (12), PD (1) [secondary cause excluded] | Yes | ≥20mmHg fall in SBP ≤120mins | 65 (SD ± 2.64) | 13 | 5M:8F | Placebo (13)/ Acarbose (13) |
| **Gentilcore et al. (2011)** | Acarbose 100mg | Intraduodenal sucrose (6kcal/min) | Healthy | No | N/A | Median 70 (range 66-77) | 8 | 4M:4F | No acarbose/Acarbose |
| **Freeman et al. (1996)** | DL-DOPS 1000mg | standard mixed meal (400kcal) | All Orthostatic hypotension | No | N/A | 54 (SD ± 13) | 11 | 7M:4F | Placebo (11)/ DL-DOPS (11) |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | (undefined by BP); mix of MSA, PD, PAF | | | | | | |
| **Jones et al. (2001)** | Guar gum 9g | 50g glucose drink | Healthy | No | 30 min sustained fall SBP ≥20mmHg | median 70 (range 67-78) | 10 | 5M:5F | Guar gum/ No guar gum |
| **Russo et al. (2003)** | Guar gum 9g | 50g glucose drink | Type 2 DM | No | 30 min sustained fall SBP ≥20mmHg | median 61 (range 57-69) | 11 | 8M:3F | Guar gum/ No guar gum |
| **O'Donovan et al. (2005)** | Guar gum 4g | Intraduodenal glucose (3kcal/min) | Healthy | No | N/A | 70.3 (SD ± 3.4) | 8 | 4M:4F | Guar gum/ No guar gum |
| **Jansen et al. (1988)** | Octreotide 50µg SC | 75g glucose drink | Normotensive, HTN | No | No | 74 (SD ± 4) | 20 | unknown | Placebo/ octreotide |
| **Jansen et al. (1989)** | Octreotide 50µg SC | 75g glucose drink | Normotensive, HTN | No | No | 74 (SD ± 4) | 20 | 7M:13F | Placebo/ octreotide |
| **Alam et al. (1995)** | Octreotide 1µg/kg SC bd (8am,6pm) | Meal (unspecified) | Symptomatic OH (fall ≥30mmHg SBP); PAF, Shy-Drager. [Secondary causes excluded] | No | No | range 44-73 | 18 | 11M:7F | Octreotide/ No octreotide |

**Table 11 Study characteristics post-prandial falls in BP treatment systematic review (***Key: DM=diabetes mellitus; HTN=hypertension; OH=orthostatic hypotension; PAF=pure autonomic failure; MSA=multi-system atrophy; PD=Parkinson disease; CVD=cerebrovascular disease; PVD=peripheral vascular disease; IHD=ischemic heart disease; CCF=congestive cardiac failure; COPD=chronic obstructive pulmonary disease***)**

| Study (Author, Year) | Adequate sequence generation | Allocation concealment | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---|---|---|---|---|---|
| Onrot et al. (1985) | Unclear method. Study days randomised, consecutive patients used. | Not blinded allocation not concealed, controlled. | No missing data | Yes, expected data reported | One patient had a pacemaker, potential confounder in small study. |
| Lenders et al. (1988) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | Yes, expected data reported. | No obvious other bias. |
| Heseltine et al. (1991) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | Plasma caffeine level not available for 5 participants | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Heseltine et al. (1991) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Lipsitz et al. (1994) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | Not all participants able to stand | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Rakic et al. (1996) | Unclear method, simply stated randomised, cross-over | Not blinded allocation not concealed, controlled. | No missing data | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Shibao et al. (2007) | Hospital pharmacy randomised participants for cross-over | Hospital pharmacy kept the blind codes to maintain allocation concealment for single & double blind components, controlled | No missing data | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Gentilcore et al. (2011) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states | No missing data | Yes expected data reported. No adverse event | No obvious other bias. |

| | | | | | |
|---|---|---|---|---|---|
| | | double blind, controlled | | reported | |
| Freeman et al. (1996) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | Yes expected data reported. No adverse event reported | No obvious other bias. |
| Jones et al. (2001) | Unclear method, simply stated randomised, cross-over | Not blinded allocation not concealed, controlled. | No missing data | Yes, expected data reported Adverse event reported | No obvious other bias. |
| Russo et al. (2003) | Unclear method, simply stated randomised, cross-over | Not blinded allocation not concealed, controlled. | No missing data | Yes, expected data reported . No adverse event reported. | Type 2 diabetes possible underlying delay in gastric emptying and thus confounding results |
| O'Donovan et al. (2005) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | Yes, expected data reported No adverse event reported | No obvious other bias. |
| Jansen et al. (1988) | Randomised Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | MAP rather than SBP, DBP. No adverse event reported | Publication bias by duplication and with differing parameters. |
| Jansen et al. (1989) | Unclear method, simply stated randomised, cross-over | Unclear how concealment of allocation kept, although states double blind, controlled | No missing data | Yes, expected data reported. No adverse event reported | Publication bias by duplication |
| Alam et al. (1995) | Unclear method, simply stated randomised, cross-over | Not blinded allocation not concealed, controlled. | No missing data | Yes, expected data reported. No adverse event reported | No obvious other bias. |



**Table 12 Systematic review of treatment Post-prandial reductions in BP - Risk of bias**

### 4.3.1 Single dose Studies

#### *4.3.1.1 Caffeine*

There were six randomised controlled studies (Heseltine et al., 1991b, Heseltine et al., 1991c, Lenders et al., 1988, Lipsitz et al., 1994, Onrot et al., 1985, Rakic et al., 1996) involving caffeine administered in various doses and forms: as tea or coffee or as pure caffeine in capsule form (e.g., 60 mg five times a day, 250 mg capsule single intervention); four of these studies were double-blind. (Heseltine et al., 1991b, Heseltine et al., 1991c, Lenders et al., 1988, Lipsitz et al., 1994) Only one study enrolled participants with confirmed PPH (defined as a reduction in supine or seated SBP of at least 20 mmHg within 60 minutes of the meal), with symptoms of weakness or dizziness (Lipsitz et al., 1994). Most participants in these trials were regular caffeine consumers, and no adverse effects were reported with caffeine consumption. One study (Onrot et al., 1985) of six participants with primary or secondary autonomic failure who were regular caffeine consumers but who had no history of PPH demonstrated that a single 250 mg dose of caffeine before a standardised meal (Table 11) resulted in a significantly smaller post-prandial reduction in SBP and DBP by 60 minutes ($p < 0.05$) than without caffeine. As seen previously, there was no significant difference in HR changes between the placebo and caffeine phases. Because no participants had a history of PPH, symptomatic differences with treatment were not recorded. A study of 15 healthy participants who regularly consumed caffeine showed no difference in change in MAP from baseline between subjects who had a single 250 mg dose of caffeine 1 hour before a standardised meal and those who received placebo. HR was also unchanged from baseline in the placebo and caffeine phases (Lenders et al., 1988).

Another study showed that caffeine (200 mg coffee) reduced the post-prandial fall in standing and supine SBP less than placebo in seven healthy older adults who were regular caffeine consumers (Heseltine et al., 1991b). Participants in these two studies were healthy volunteers with no symptoms of PPH (Heseltine et al., 1991b, Lenders et al., 1988). In 20 regular caffeine drinking older adults with various comorbidities, four of whom had symptoms suggestive of orthostatic or PPH, 100 mg of caffeine (given as coffee) resulted in a significantly smaller overall sitting post-prandial reduction in SBP than with placebo (decaffeinated coffee) (Heseltine et al., 1991c). No significant post-prandial difference was noted in DBP or standing SBP between placebo and caffeine. Three participants were noted to have a reduction in SBP consistent with PPH. Caffeine, but not placebo, alleviated symptoms of PPH in two participants (Heseltine et al., 1991c). Another study showed that caffeine (250 mg) did not attenuate the decline in SBP, DBP, or MAP associated with ingestion of a meal in nine participants with autonomic failure who experienced symptomatic PPH (Lipsitz et al., 1994). Although this study included individuals with symptomatic PPH, there was no reporting of the effect of caffeine on symptoms.

#### *4.3.1.2 Acarbose*

In 13 participants with autonomic failure and PPH randomised to acarbose (100 mg capsule) or placebo given 20 minutes before a mixed meal, acarbose reduced the post-prandial reduction in supine SBP and DBP, with no effect on HR and no adverse effects reported (Shibao et al., 2007). There was no specific reporting on the effects of treatment on symptoms. In another study, eight healthy older participants, randomised in a double-blind order to receive 100 mg of acarbose with an intraduodenal sucrose infusion (6 kcal/ min) or sucrose alone on 2 separate days, showed a similar

attenuation in SBP and DBP, although a rise in HR accompanied this ($p<0.05$) (Gentilcore et al., 2011).

#### *4.3.1.3 DL-DOPS*

The effect of DL-DOPS (1,000 mg) given 3 hours before a meal on post-prandial BP was assessed in a cross-over study in 11 participants with autonomic failure(Freeman et al., 1996). The greatest BP reduction occurred 30 minutes after the mixed meal, and reductions in SBP ($p =0 .01$) and DBP ($p < 0.01$) were significantly greater after placebo than with DL-DOPS. There were no significant differences in HR between placebo or DL-DOPS and no effect on symptoms reported.

#### *4.3.1.4 Guar Gum*

Three studies compared the effect of guar gum with that of placebo or control on post-prandial BP in older adults after a 50 g glucose drink or intra-duodenal glucose (Jones et al., 2001, Russo et al., 2003, Jones et al., 1998). A randomised cross-over trial in 10 healthy adults demonstrated that 9 g of guar gum resulted in a significantly smaller reduction in SBP ($p = 0.02$), DBP ($p < 0.05$) and MAP ($p = 0.05$) 30 minutes post-prandially than control, with no HR changes (Jones et al., 2001). A randomised crossover study of 11 participants with type 2 diabetes mellitus showed that 9 g of guar gum resulted in a significantly ($p <0.05$) smaller post-prandial reduction in BP in response to a 50-g oral glucose load (Russo et al., 2003). The use of an intra-duodenal, rather than oral, glucose load allows observation of changes in BP independent of any effects of the intervention on gastric emptying, because the rate of gastric emptying influences the reduction in post-prandial BP (Jones et al., 1998). A significantly smaller reduction in SBP, but not DBP, was demonstrated with 4 g of guar gum after a

50g intra-duodenal glucose infusion in eight healthy adults than with a glucose-only infusion (O'Donovan et al., 2005).

#### *4.3.1.5 Octreotide*

Three articles reporting the effect of subcutaneous octreotide on post-prandial BP did not include symptomatic PPH, and symptoms of PPH were not considered (Jansen et al., 1989, Jansen et al., 1988, Alam et al., 1995) although the data presented in two of these articles may have been from the same participant group (Jansen et al., 1988, Jansen et al., 1989). These studies (Jansen et al., 1988, Jansen et al., 1989) included 10 hypertensive and 10 normotensive adults who received a single dose of subcutaneous octreotide (50µg) or placebo (saline) in a double- blind randomised fashion together with a 75g glucose drink. Both the normotensive and hypertensive groups showed significant reductions in MAP at 30 and 60 minutes with placebo but showed no significant reduction after octreotide (Jansen et al., 1988). A significant difference between placebo and octreotide was shown for SBP ($p = 0.008$), DBP ($p < 0.001$), and MAP ($p < 0.001$) in the hypertensive group and for DBP ($p = 0.005$) and MAP ($p = 0.007$) in the normotensive group (Jansen et al., 1989). Another study demonstrated in 10 participants with autonomic failure and symptomatic orthostatic hypotension that octreotide (1 µg/kg of body weight) resulted in a smaller reduction in post-prandial BP from 10 to 120 minutes than no treatment (SBP, $p < 0.01$; DBP, $p < 0.05$). There were no significant differences in HR, and no adverse effects were reported (Alam et al., 1995).

### 4.3.2 Repeated doses Studies

#### *4.3.2.1 Caffeine*

In a study of 171 participants (98% regular caffeine drinkers) that included people without hypertension and those with treated or untreated hypertension randomised to a 2-week period of regular caffeine consumption (60 mg five times daily) or no caffeine, baseline reductions in post-prandial supine SBP were greater in those with untreated and treated hypertension than in those without hypertension, with similar changes seen in standing SBP (Rakic et al., 1996). Coffee resulted in a significantly smaller post-prandial reduction in supine and standing SBP in regular coffee drinkers without hypertension and in tea drinkers with treated hypertension. The effects on HR were not reported. Those with untreated hypertension who had no caffeine for 2 weeks also had a significantly smaller reduction in post-prandial supine SBP. The effect of treatment on symptoms was not reported. In a study of the longer-term effects of caffeine (Onrot et al., 1985), five participants were administered caffeine as a 250 mg capsule daily for 7 days. Participants were then randomised to receive placebo or caffeine as a single dose. Despite longer-term caffeine, post-prandial BP remained higher after caffeine ($p < 0.05$) than with placebo after a standardised meal (Onrot et al., 1985).

### 4.3.3 Results Summary

Table 13 shows a summary of the various drug effects on post-prandial reduction in BP, although the majority of studies were conducted in participants who did not have a diagnosis of PPH with a proven minimal reduction in post- prandial BP or who had symptoms suggestive of PPH (Jansen and Lipsitz, 1995). However bias from sequence generation and allocation concealment needs to be considered moderate.

| Study (Author, Year) | Participant Group | Drug | Approximate Mean Change in BP Compared to Baseline (mmHg) * | Original Author Conclusion | Our View |
|---|---|---|---|---|---|
| **Onrot et al. (1985)** | Autonomic Failure | Caffeine (250mg capsule) | SBP: -3<br>DBP: -6 | Beneficial | Although only carried out in a small group, it is certainly worth considering |
| | | Control | SBP: -23<br>DBP: -14 | | |
| **Lenders et al. (1988)** | Healthy participants | Caffeine (250mg capsule) | MAP: 0% (maximal increase of 12.5%) | Beneficial | |
| | | Control | MAP: -6.1% | | |
| **Heseltine et al. (JAGS, 1991)** | Healthy participants | Caffeine (200mg coffee) | SBP: 12 | Beneficial | Improves post-prandial BP in healthy older adults |
| | | Control | SBP: -17 | | |
| **Heseltine et al. (PMJ, 1991)** | Multiple comorbidities (4 of 20 had symptoms suggestive of PPH or OH) | Caffeine (100mg coffee) | Sitting SBP: 2 | Beneficial for sitting SBP (but not erect) | Appears to reduce the fall in BP despite co-morbidities |
| | | Control | Sitting SBP: -8 | | |
| **Lipsitz et al. (1994)** | Autonomic Failure | Caffeine | MAP: -31 | Not beneficial for PPH | |
| | | Control | MAP: -19 | | |
| **Rakic et al. (1996)** | Normotensive/Hypertension/Untreated Hypertension | Caffeine | Standing SBP: -8 (UHTN), -9 (HTN), -3 (NTN) | Beneficial | |
| | | Control | Standing SBP: -10 (UHTN), -12 (HTN), -8 (NTN) | | |
| **Shibao et al. (2007)** | Autonomic failure | Acarbose | SBP: -17 | Beneficial for PPH | |
| | | Control | SBP: -40 | | |
| **Gentilcore et al. (2011)** | Healthy | Acarbose | SBP: -1<br>DBP: -3 | Beneficial | |
| | | Control | SBP: -8<br>DBP: -9 | | |
| **Freeman et al. (1996)** | Autonomic failure | DL-DOPS | MBP: -13 | Beneficial | |
| | | Control | MBP: -30 | | |

| | | | | | |
|---|---|---|---|---|---|
| **Jones et al. (2001)** | Healthy | Guar gum | SBP: -4<br>DBP: -6<br>MBP: -4 | Beneficial | The magnitude of change is small. |
| | | Control | SBP: -7<br>DBP: -7<br>MBP: -8 | | |
| **Russo et al. (2003)** | Type 2 diabetes mellitus | Guar gum | SBP: -2.5<br>DBP: -2.9<br>MAP: -6.8 | Beneficial | Perhaps some improvement for SBP |
| | | Control | SBP: -4.9<br>DBP: -5.5<br>MAP: -10.2 | | |
| **O'Donovan et al. (2005)** | Healthy | Guar gum | SBP: -2.5<br>DBP: -4 | Beneficial | Improves SBP |
| | | Control | SBP: -11<br>DBP: -5 | | |
| **Jansen et al. (1988)** | Hypertension and Normotensive | Octreotide | MAP: 0 (NTN), -2 (HTN) | Beneficial | Appears to be the case for those with hypertension |
| | | Control | MAP: -7 (NTN), -14 (HTN) | | |
| **Jansen et al. (1989)** | Hypertension and Normtensive | Octreotide | SBP: 1 (NTN), -1 (HTN)<br>DBP: 0 (NTN), 0 (HTN) | Beneficial | Appears to be the case for those with hypertension |
| | | Control | SBP: -5 (NTN), -12 (HTN)<br>DBP: -9 (NTN), -15 (HTN) | | |
| **Alam et al. (1995)** | Autonomic failure | Octreotide | SBP: 0<br>DBP: -2 | Beneficial | Little difference between sitting and post-prandial BP noted. |
| | | Control | SBP: -3<br>DBP: -5 | | |

**Table 13 Overall Study Conclusion for Alleviating Post-Prandial Falls in BP or PPH** *(Key: * Note that many values are estimated from graphs depicted by original authors. UHTN= Untreated Hypertension, HTN = Hypertension, NTN = Normotensive)*

## 4.4 Discussion

Despite PPH being associated with significant morbidity and mortality in older people, evidence of the benefits of pharmacological intervention in reducing these BP reductions is limited. The studies included in this systematic review had great heterogeneity in terms of intervention drug type, dose, and frequency and time of intervention relative to type and size of energy load. Another important influencing factor on effect is the heterogeneity in the population studied (e.g., healthy adults vs those with hypertension and diabetes mellitus, those with autonomic dysfunction), with only one study specifically investigating the effect on those with symptomatic PPH. Thus caution is needed in the interpretation and use of any therapeutic interventions based on the findings of this systematic review, especially in older adults with symptomatic PPH.

This systematic review confirms that certain drug interventions may attenuate post-prandial reductions in BP, whether given as a once only intervention or as a regular intervention over a period of time. The time and size of the effects of intervention on BP are summarised in Table 13, but the majority of studies did not specifically include participants with symptoms of PPH or who had a confirmed diagnosis of PPH (Jansen and Lipsitz, 1995). Some studies tried to overcome this by including those with a history of orthostatic hypotension (OH), but the underlying pathophysiology of OH and PPH probably differs, although both conditions can exist in the same patient. It is therefore difficult to state conclusively which drug is the best for PPH, particularly because adverse effects need to be considered, such as supine hypertension with DL-DOPs (Freeman et al., 1996).

Post-prandial hypotension reflects the failure to maintain systemic BP levels that fall as a result of a decrease in systemic resistance, with blood being diverted into the splanchnic circulation (Jansen and Lipsitz, 1995). Thus, potential methods of decreasing PPH might focus on delaying the rate of food absorption from the gut or reducing local splanchnic bed vasodilation, although the drugs used to attenuate post-prandial reductions in BP in this review have many differing mechanisms of action, and the effects are likely to be variable, even more so between population groups. There is some supportive evidence that caffeine, an adenosine blocker, has a positive effect on ameliorating post-prandial reductions in BP in infrequent and regular users, although only one small study specifically examined individuals with symptomatic PPH (Lipsitz et al., 1994). When used in individuals with autonomic failure, caffeine resulted in a smaller reduction in post-prandial in the group mean SBP (Onrot et al., 1985). Caffeine increased MAP when given an hour before a meal, although the time elapsed between treatment administration and likely maximum post-prandial BP reduction may have negated its maximal potential effect on reducing PPH (Lenders et al., 1988). The lack of effect on erect SBP (Heseltine et al., 1991c) may have been due to the smaller dose of caffeine administered. Given that caffeine is readily available in the form of tea and coffee, its use in PPH could simply be part of a lifestyle change, although it would appear that a pre-prandial dose of at least 200 mg is needed.

DL-DOPS, by increasing noradrenaline (Freeman et al., 1996), and acarbose, by delaying gut glucose absorption (Shibao et al., 2007, Gentilcore et al., 2011), were shown to attenuate the post-prandial reduction in BP, and acarbose was shown to attenuate PPH in those with severe autonomic failure (Shibao et al., 2007). One study of acarbose (Jian and Zhou, 2008) in individuals with PPH did not randomise the order in which participants underwent the control study or took acarbose (50 mg) and was therefore excluded from this systematic review, although it found a statistically significantly smaller post-meal reduction in SBP (at 60 minutes: 17.8 ± 11.7 to -4.2 ± 13.1 mmHg, $p< 0.001$), DBP (-7.6 ± 8.5 to -3.9 ± 6.9 mmHg, $p < 0.05$) and MAP (-10.3 ± 8.4 to -3.3 ± 8.1 mmHg, $p < 0.05$). Guar gum, presumably by delaying absorption, also attenuated post- prandial BP declines, although in some instances, the BP changes were small (<5 mmHg) and of doubtful clinical significance. Octreotide subcutaneously attenuates the post-prandial reduction in BP in those with orthostatic hypotension and hypertension, as well as those who are classified as normotensive.

The variability of timing of drug administration relative to the energy load (a glucose drink, liquid meal, or standardised mixed meal), as well as which BP parameters were recorded, made it difficult to compare studies and include in a meta-analysis. Although some reported all BP parameters and HR changes, others reported only MAP values and some only the maximal post-prandial BP changes. For a "positive" treatment effect, the majority of studies used the lack of a statistically significant reduction in BP from baseline with the drug intervention, rather than a change that might be clinically significant. Furthermore, the majority of studies (except two (Heseltine et al., 1991b, Heseltine et al., 1991c)) did not explicitly measure BP more than once at each time point, although single

measurements were made using validated methods. Also of importance and not reported in the studies is the effect of treatment on symptoms in those with symptomatic PPH.

The limitations of this systematic review include the fact that only studies reported in English were included and that there were only a few studies available for each intervention. Furthermore, only studies that were randomised and controlled in some way were included, although it was not required that they be blinded because this was difficult for the original investigators with some of the interventions. This may be a potential source of bias from included studies. The heterogeneity of study design and parameters assessed within the studies included in this systematic review prohibited meta-analysis. Overall, the pharmacological agents included have been shown to have some effect on the attenuation of post-prandial reductions in BP, although only two studies (Shibao et al., 2007, Lipsitz et al., 1994) examined the effect of a drug intervention (caffeine and acarbose) on PPH; caffeine was found to be ineffective. Thus, future studies should be directed at comparing the effect of these drug interventions on PPH with lifestyle changes, including regular caffeine consumption in the form of tea or coffee. Consideration should be given to other methods of reducing post-prandial reductions in BP such as altering meal composition in terms of energy load and carbohydrate type, paying particular attention to their influence on PPH symptoms.

The effects of PPH and its treatment on the blood supply to important organs other than the gut (e.g., cerebral blood flow control), which may account for some of the symptoms, also justifies further research. The variable nature of the BP parameters measured in the current studies and the heterogeneity of the populations studied make it difficult to project the results of this systematic review accurately to older adults with symptomatic PPH. The

studies reviewed suggest that caffeine may be helpful in attenuating post-prandial reductions in BP but may not be useful in those with PPH. The evidence also suggests that acarbose may similarly be of some benefit in individuals with PPH. For the clinician managing older adults with symptomatic PPH, the most pragmatic approach appears to advise that individuals avoid large simple-carbohydrate meals, consume small frequent meals instead, and avoid alcohol (and other vasodilators) with meals. In some individuals, having regular caffeinated beverages after meals may be of benefit in terms of reduction in PPH symptoms.

## 4.5 Conclusion

This systematic review highlights the limited data on the pharmacological treatment of PPH in terms of attenuating post-prandial reductions in BP and symptom improvement. Future studies should investigate the effectiveness of drug treatment and lifestyle changes in symptomatic PPH. In the meantime, the best pragmatic advice would be to avoid large simple-carbohydrate meals, alcohol, and vasodilators; in some cases, caffeine may also reduce symptoms of PPH.

# 5 Methodology

## 5.1 Introduction

The limited understanding of the physiological changes underlying orthostatic and post-prandial hypotension (2.1 and 2.3) and the limits of current management has been outlined in previous sections, with systematic reviews of their drug treatments in previous chapters (Chapters 3 and 4). Furthermore the possibility that abnormalities in cerebral auto-regulation are associated with these conditions along with important changes in other physiological parameters with age e.g. the decline in BRS and increase arterial stiffness with age, suggests that a better understanding of the underlying pathophysiology is required in order to treat these conditions more effectively in future.

The justification for the methodology used in this thesis will be outlined in this chapter with particular reference to the role of TCD and dCA, $CO_2$, continuous BP and BRS measurement, as well as assessment of arterial stiffness. Details of the study methods used for the Orthostatic Hypotension Study and the Post-prandial Hypotension Study are outlined in Chapters 6, and specific Methods for OH in Chapter 7 and for PPH in Chapter 13.

## 5.2 Assessing autonomic function

The autonomic nervous system consists of two components, the sympathetic and parasympathetic systems which can be assessed non-invasively using the classical methods originally described by Ewing and Clarke (Ewing and Clarke, 1982). Spontaneous heart rate variability (Bellavere et al., 1992) and cardiac baroreceptor sensitivity (BRS) (Frattola et al., 1997) are considered more sensitive than the classical Ewing and Clarke selection of tests, although some do not consider it necessarily better at detecting cardiac autonomic neuropathy in older adults with Type 2 diabetes mellitus (Tank et al., 2001). Regardless of which methods are used, impaired autonomic function is associated with increased mortality in those with diabetes mellitus, hypertension or cardiovascular disease(Gerritsen, 2001). Furthermore, the classical selection of tests are relatively straightforward for the clinician to carry out, and remains a useful assessment of autonomic function in clinical research (Allan, 2007).

The parasympathetic system can be examined using the heart rate response to the Valsalva manoeuvre, variation during deep breathing and the immediate response to standing. Similarly the sympathetic system can be assessed using the BP response to sustained handgrip or to standing from supine (Ewing and Clarke, 1982). From these five different observations a widely used scoring system allows a score out of 10 to be calculated and is shown in more detail in Section 6.7 (Ewing and Clarke, 1982, Ewing, 1985). Normal function scores zero, borderline function scores one point and abnormal function scores two points. However as heart rate variation normally declines with

ageing, age per se must be taken into account when assessing if a test is abnormal or not (O'Brien et al., 1986, Piha, 1991). Of course on the other hand it is unclear whether these factors in part or as a whole may be contributory to the increasing prevalence of syncope with age (Soteriades et al., 2002) or if there are other important mechanisms that may also have an important role. However for this thesis as it has been suggested that postural falls of SBP≥20mmHg are found in even apparently "healthy" older people (O'Brien et al., 1986) and thus those without symptoms, the original Ewing and Clarke (1982) parameters for what may be considered "normal", "borderline" or "abnormal" were used. For this thesis both the classical Ewing and Clarke (1982) assessment was carried out alongside spontaneous cardiac BRS.

## 5.3 Assessing Arterial Stiffness

As discussed previously in Chapter 2, not only is there evidence that an impaired cardiac BRS is associated with OH (Schrezenmaier et al., 2007), but also increased arterial stiffness is associated with impaired BRS (Eveson et al., 2005). Increasing arterial stiffness is furthermore associated with an increased risk of OH in older adults (Mattace-Raso et al., 2006), including those with a history of falls (Boddaert et al., 2004). Both pulse wave velocity (PWV) and the augmentation index (AIx) provide information on arterial stiffness, however there are some differences and these have been outlined in Chapter 2.

There are various methods to measure PWV and AIx including applanation tonometry (SphygmoCor, AtCor Medical Pvt. Limited, Sydney, Australia) which uses the upstroke during systole to detect the pressure wave and an oscillometric technique

(Vicorder™, Skidmore Medical Limited, Bristol, UK) which uses the time point of maximal pressure (van Leeuwen-Segarceanu et al., 2010). As previously discussed in Chapter 1, the wave morphology varies with location and changes with age (Kelly et al., 1989). The Vicorder™ has been shown to give a reliable estimate of central SBP when compared to invasive measurements of MAP, and therefore provides a useful non-invasive tool for research (Pucci et al., 2013). This is particularly important in that it has been shown that the carotid artery waveform was more likely than the peripheral brachial BP waveform to show the decline of the wave reflection used in assessing AIx (Tabara et al., 2005).

PWV (measured in metres per second) is derived by determining the time it takes for a pulse wave to travel between two sites, usually the carotid and femoral artery (Wilkinson et al., 1998a), and thus arterial stiffness as determined by PWV is intrinsically related to the blood vessel (Laurent et al., 2006). AIx (shown in Figure 13) is calculated as the difference between the first and second peak of the pulse upstroke ($\Delta P$) as a proportion of the pulse pressure (PP) and is thus reported as a percentage (Wilkinson et al., 1998a). Thus a high PWV directly represents increased arterial stiffness, whilst the AIx using pulse wave reflections is an indirect surrogate measure and index of stiffness (Laurent et al., 2006). Furthermore although AIx is more readily affected by HR and BP (Yasmin and Brown, 1999), it can be adjusted for by HR itself (Wilkinson et al., 2000), and aortic stiffness itself does not vary by any acute changes in HR (Wilkinson et al., 2002). Due to the differences between PWV and AIx and arterial stiffness, both PWV and AIx measurements from the previously validated Vicorder™ shall be used in this study (Pucci et al., 2010).

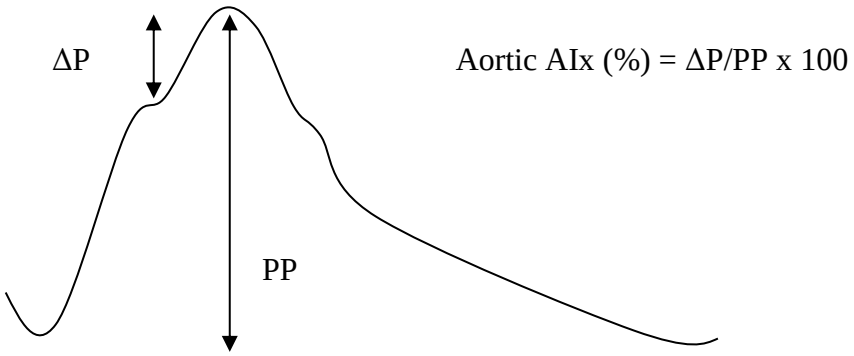



**Figure 13 Augmentation Index (AIx) calculation (adapted from Wilkinson et al., 1998a)**

As HR varies between subjects, and decreases by 3.9% for each increase in HR of 10bpm (Wilkinson et al., 2000), this shall be adjusted for, and reported at 75bpm (AIx (@75)). This correction is given by:

$$\text{AIx (@75)} = [(\text{mean HR-75}) \times 0.0039 \times \text{mean AIx}] + \text{mean AIx},$$

because 3.9/ (100%x10bpm) =0.0039 takes into account both percentage change and per 10bpm change.

## 5.4 Measuring Blood Pressure

Several non-invasive methods have been developed as alternatives to invasive intra-arterial blood pressure to determine beat to beat systemic blood pressure. The Finapres™ (and the Portapres™) are examples of the Penáz or Wesseling method using a volume-clamp technique which works by maintaining the size of the artery constant by changing the pressure of the finger cuff and detects changes in the artery size with an infrared plethysmograph. The BP value is automatically computed using

an algorithm based on the volume-clamp set-point, being set at zero transmural pressure when the cuff pressure is equal to the arterial blood pressure (Langewouters et al., 1998). A summary of both the positive and negative aspects of using the Finapres is given here.

The beat-to-beat BP data acquired using Finapres permits the assessment of BP variability by using a technique known as power spectral analysis. The BP signal recorded consists of several sinusoidal signals each with two components: amplitude and phase (in radians), as shown in Figure 14. Each sinusoidal signal will consist of an integer multiple of the frequency of the original signal. By breaking down the original BP signal which is in the time-domain into its various frequency components, a frequency spectrum is created, which is in the frequency-domain (Figure 14). A power spectrum can be created by taking the amplitude of these sinusoids and squaring it to represent the power of the sinusoid (Panerai et al., 1999). Spectral analysis has been used to show that for some frequency bands (i.e. a specific range of frequencies) there is some variation between intra-arterial measurements and Finapres recordings, which may be explained by peripheral resistance of arterial blood vessels (Pinna et al., 1996). However other work suggests that the differences between Finapres measures of BP and intra-arterial measures of aortic BP are consistent, and good enough for use in estimation of cardiac BRS (Smith et al., 2008). Although low-frequency oscillations of SBP could be overestimated by Finapres, it is thought that overall both the frequency and time domain components of BP and pulse interval are reasonably accurate as compared to intra-arterial BP measurements (Omboni et al., 1993).

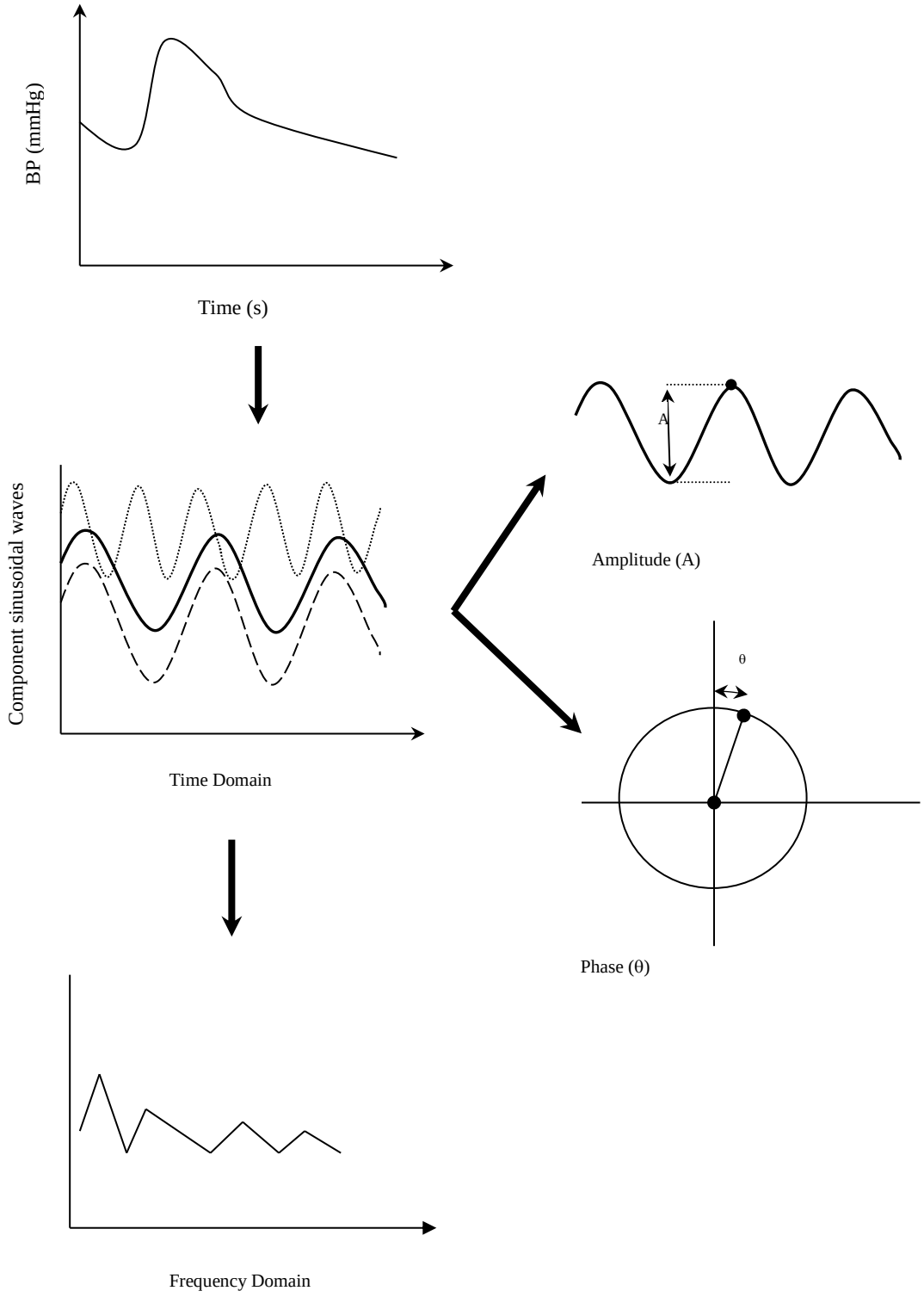



**Figure 14 Time and Frequency Domain of a BP signal**

Although the Finapres can accurately estimate the mean artery pressure and the diastolic pressure when compared to intra-arterial measurements, it is less able to do so for the systolic pressure (Van Orshoven et al., 2010). In a study on estimating cerebral critical closing pressure the difference between Finapres and aortic ABP, data from 27 individuals was shown to be not significant in SBP 4.3±18.0 (p=0.22) and mean ABP -2.5±8.4 mmHg (p=0.14) but significant for DBP 3.2±7.0 mmHg (p=0.027) (Panerai et al., 2006). It has also been shown that compared to intra-arterial brachial pressure measurements the effects of peripheral vasoconstriction with phenylephrine and vasodilation with nitroprusside can be underestimated and overestimated respectively (Applegate et al., 1991b). Extrapolating from this, hypothetically changes in $PaCO_2$, which in turn may affect peripheral vasoconstriction and vasodilation, could result in significant changes in BP being undetected. Using the brachial and radial arteries from 175 patients across 5 publications it was calculated that the proportion of Finapres measurements expected to be ±5, ±10 and ±15mmHg of the intra-arterial pressure was 48.2%, 72.9% and 90.4% (Silke and McAuley, 1998). Furthermore the average bias for the SBP was 2.2±12.4mmHg in 449 participants across 20 publications used in the meta-analysis (Silke and McAuley, 1998). Problems with incremental bias has also been noted where measurements are continued for a 3 to 4 hour period (Ristuccia et al., 1997). In addition, very short recordings can also add in errors due to the presence of positive and negative transient drifts which last approximately 20 seconds (Lagro et al., 2013). These drifts can alter the size of the relative difference between Finapres and intra-arterial measurements, resulting to distortions if the period being measured coincides with a drift. Therefore BP should be averaged over at least 30 seconds to reduce the effect of these drifts in relation to intra-arterial measurements. However despite these shortcomings Finapres measurements of BP still provides useful

information, in a non-invasive and arguably more participant acceptable manner, on the relative beat-to-beat changes in BP, particularly in terms of the actual magnitude of responses (Imholz et al., 1998) to HUT and its use in estimating spontaneous cardiac BRS (Smith et al., 2008).

For both the OH and the PPH study in dCA, the reproducibility BP recordings over a long period is important, not only for a single session, but for the two week period required in the case of the PPH study where participants attend for two sessions. It has been shown that the changes to HUT in Finapres recorded beat-to-beat SBP, DBP and MAP values along with surface ECG to record HR, is highly reproducible over a 12 month period in healthy men aged 65 to 75 years (Gabbett and Gass, 2005, Omboni et al., 1993). Of course whether the reliability of orthostatic responses seen in "healthy" older men is applicable to all groups of "healthy" older persons is not clear. However it has been shown that stable haemodynamic baseline values can be achieved with the Finapres within 5 to 12 minutes of supine rest in older adults (Mehagnoul-Schipper et al., 2000). This is important as this study is looking at relative changes in BP during the course of a particular session. Although there is some evidence that Finapres can overestimate the SBP during HUT (mean 7.2± SE 1.6mmHg) compared to intra-brachial arterial readings (Van Orshoven et al., 2010) the Finapres remains a useful non-invasive method of determining beat-to-beat changes in BP and was therefore used in this study.

## 5.5 Measuring carbon dioxide

How the partial pressure of arterial $CO_2$ can influence CA has been previously discussed in Chapter 1. Studies have shown the importance of monitoring $CO_2$ when assessing CA because of the potential influence a fall in $PCO_2$ has on CBF. It has been shown that $PCO_2$ levels fall when changing from supine to an upright position due to an increase in tidal volume (Gisolf et al., 2003) as well as alterations in lung ventilation and perfusion due to gravity (Cencetti et al., 1997, Gisolf et al., 2003). However it has since been shown that although this decrease in $PCO_2$ is maintained, it only has a transient effect on CBFV within the MCA (Immink et al., 2009). Methods to estimate arterial $PCO_2$ in the research setting ideally has to be balanced by accuracy and participant comfort. Although an invasive arterial blood sample may provide more accurate measurements, this is often not appropriate for the research setting due to patient acceptability, and risks associated with invasive measurement. It has been shown that capillary sampling is not significantly different from arterial measurements (Dar et al., 1995, Pitkin et al., 1994). Furthermore it has been shown that the use of a transcutaneous monitor (TINA, Radiometer, Copenhagen) for the measurement of $PCO_2$ closely agreed with that given by capillary earlobe samples (Dawson et al., 1998). Thus for this thesis a transcutaneous monitor to record the relative change in $PCO_2$ during HUT was used because it balanced the need to monitor $PCO_2$ with patient comfort and compliance with an already demanding procedure.

## 5.6 Measuring spontaneous cardiac BRS

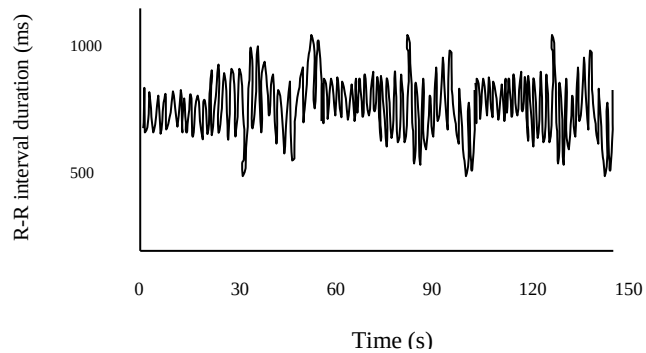
As previously described in Chapter 1 cardiac BRS relates to the change in the duration of the inter-beat heart rate interval (R to R interval on the ECG) caused by the change in 1mmHg of BP (msec/mmHg) such that an increase in BP will result in a slowing of heart rate (Bothová et al., 2010). Cardiac BRS begins to decrease with normal ageing around the age of 30 years but does not significantly change after the 4$^{th}$ decade (Dawson et al., 1999). It is more closely associated with BP and is reduced in older people with hypertension compared to adults with a normal BP (Shimada et al., 1986, McGarry et al., 1983, Dawson et al., 1999). For example, with the Valsalva manoeuvre, cardiac BRS amongst adults over the age of 60 years (mean 70 ±1 years) with normal BP has been reported as 4.8±0.8 ms/mmHg significantly higher (p=0.02) than those with hypertension (2.2±0.5 ms/mmHg) (Dawson et al., 1999). More specifically cardiac BRS has been found to be reduced in both combined systolic and diastolic hypertension as well as isolated systolic hypertension (James et al., 1996). Furthermore it has been suggested that the postural fall in BP during head up tilt in older people with hypertension may be due to the reduced cardiac BRS associated with hypertension (James and Potter, 1999).

Various methods have been used to calculate BRS (Davos et al., 2002) but the spontaneous variations in BP shall be used here (Eveson et al., 2005). The use of spontaneous changes in BP and HR to estimate continuous BRS (Oosting et al., 1997) have advantages over provoking changes in HR and BP using drugs, such as phenylephrine and sodium nitroprusside, or physical manoeuvres e.g. Valsalva (James and Potter, 1999). Firstly, vasoactive drugs could potentially affect the baroreflex itself

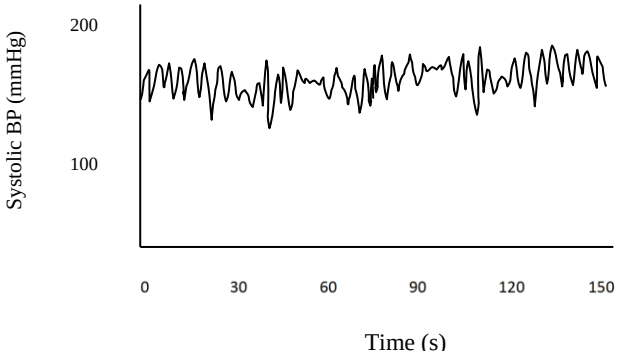
by acting on e.g. receptors (Oosting et al., 1997). It has also been reported that the BRS values from using the Valsalva method were lower than those acquired from spontaneous BP and HR (Dawson et al., 1997). Furthermore, anything inducing time limited changes (drug or mechanical) may in itself introduce error in BP monitoring with the Finapres, as it has been shown that transient drifts can last for around 20 seconds. Thus the beat-to-beat BP data obtained using Finapres in this study was used with the simultaneous surface ECG record of R-R intervals to calculate the spontaneous BRS.

BRS can be estimated using sequence analysis (time domain) or power spectral analysis (Robbe et al., 1987), however it has been shown that spectral analysis of BRS correlates best (Smith et al., 2008), albeit its reproducibility has been considered as moderate (Hojgaard et al., 2005). Assessing BRS using power spectral analysis is based on the idea that each spontaneous oscillation in BP occurs at the same frequency in R-R interval as a result of the baroreflex. It has been shown that using fast Fourier transforms (FFT) of BP and ECG recordings to assess cardiac BRS correlates with other methods involving pharmacological agents (James and Potter, 1999). FFT derived cardiac BRS declines rapidly in the third and fourth decades, and in one study of healthy adults with a mean age of 53 years (range 22-82 years) the mean cardiac BRS was 13.7±8.3ms/mmHg (Dawson et al., 1999). Figure 15 illustrates the original BP signal and the R-R interval in the time and frequency domain, and the resultant power density spectrum for these and their coherence. By dividing the spectrum into frequency bands, where variations in the low frequency band (<0.07Hz) are thought to relate to vasomotor tone (body temperature, task adaptation), medium frequency (0.07-0.14Hz) variations thought to be from BP regulation, and the high frequency band

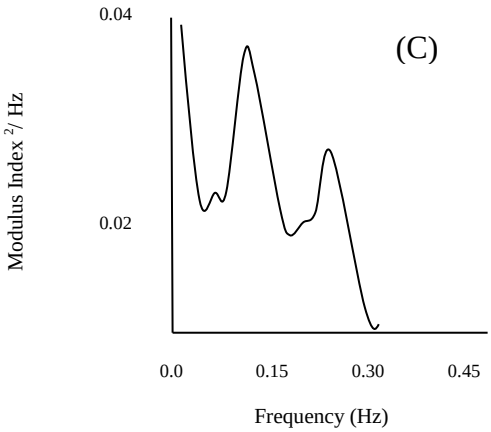
(0.15-0.40Hz) thought to be parasympathetic, and mostly respiratory (Robbe et al., 1987). The relationship between BP and R-R interval can be demonstrated by assessing the coherence for each frequency, where 1.0 indicates perfect coherence between these variables. The gain or modulus is the ration between the change in the time duration of the R-R interval and the BP (ms/mmHg) for each frequency. However the latter requires that the coherence cannot be low, as it makes it unreliable (Robbe et al., 1987). Out of interest there are other methods to look at BRS which negates the need for preselecting specific frequencies, the impulse response function. Simply put, this function is the output as a result of an impulse as the input (a spike of data) and can be obtained by using the inverse FFT of the transfer function between SBP and pulse interval (Dawson et al., 1997). Thus by making comparisons with a model corresponding to a particular BRS (in ms/mmHg) we can compare patient groups.


R-R interval duration (ms)
1000
500
0
30
60
90
120
150
Time (s)

(A)


Systolic BP (mmHg)
200
100
0
30
60
90
120
150
Time (s)

(B)


Modulus Index ²/ Hz
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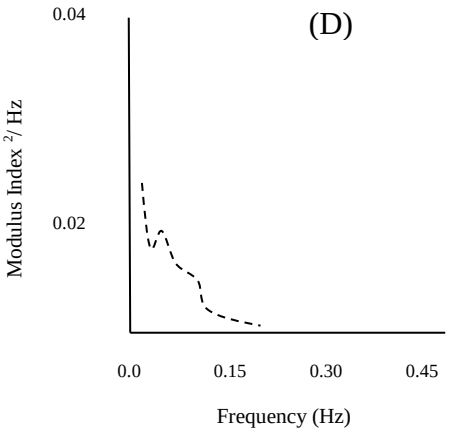
0.02
0.0
0.15
0.30
0.45
Frequency (Hz)

(C)


Modulus Index ²/ Hz
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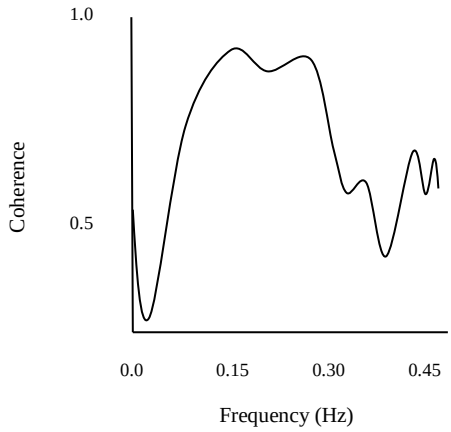
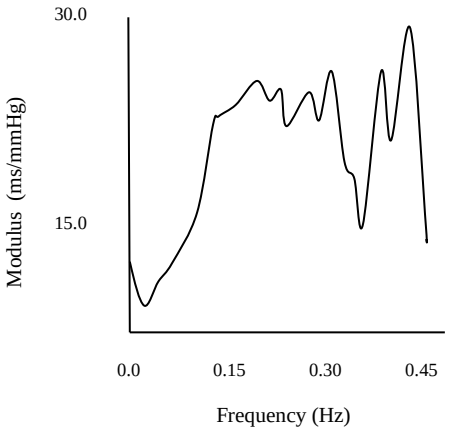
0.02
0.0
0.15
0.30
0.45
Frequency (Hz)

(D)




(E)




(F)

**Figure 15 SBP (A) and R-R interval (B) with Time, Power Density Spectrum of SBP (C) and R-R interval (D), Coherence between SBP and R-R interval (E), Modulus or Gain (F)**

Power spectral analysis of spontaneous changes in BP and the pulse interval in the low frequency bands 0.05-0.15Hz ) or the combined low and high band (0.15-0.35Hz), termed the α value, was assessed using a custom written computer algorithm by Prof R Panerai (University of Leicester) to assess the number of oscillatory components, as well as the frequency and the amplitude of the oscillatory parameters, in addition to the phase and coherence (Dawson et al., 1999). BRS is the square root of the ratio of the pulse interval (R-R interval) power to the BP power in the low frequency band where coherence is ≥0.4 (Smith et al., 2008). For this analysis original signals would be low pass filtered with an eighth-order Butterworth filter with a cut-off frequency of 20Hz. Linear interpolation allowed removal of any ectopic beats. Data sequences were rejected if there were more than a few ectopics (>3) present. Fast Fourier transform (FFT) using 512 samples with beat-to-beat changes interpolated using a third-order polynormial and then resampled with a 0.5 second interval. Power spectra was averaged (over three readings) and smoothed (using a 13 point triangular window). Thus the baraoreflex sensitivity index (alpha) can be calculated from the mean of the square roots of the ratios of the spectral powers of SBP and pulse interval using FFT (Dawson et al., 1999).

As mentioned earlier in this subsection, another aspect of BRS which can be compared when data are transformed into the frequency domain is the differences in phase at the various frequency bands as well as coherence. It has been found that although the low frequency band (0.05-0.15Hz) phase did not significantly differ between younger and older adults, there were differences in the high frequency band (0.15-0.35Hz) the older adults showed a positive phase (+0.0014±0.14 radians) compared to the younger group (-0.011±0.14 radians, $p<0.001$) (Dawson et al., 1999). Coherence relates to the

frequency domain and is similar to a squared correlation coefficient in the time domain. It is a measure of a linear association between spectral powers of two different variables (Omboni et al., 1993). However because coherence in the high frequency bands was low in both age groups (<0.5), it was unclear as whether on this occasion the phase difference was due to something else such as signal noise, age-related changes associated with BP control external to baroreceptors or another central system impacting on control e.g. cerebral vasomotor regulation. (Dawson et al., 1999)

## 5.7 Estimating cerebral auto-regulation

### 5.7.1 Transcranial Doppler Ultrasound

Transcranial Doppler Ultrasound (TCD) of the cerebral arteries, most frequently the MCA is a useful non-invasive method of determining the CBFV, a surrogate measure of CBF. It has been suggested that differences in CA may account for why some people with falls in BP are asymptomatic whilst others are not (Wollner et al., 1979). Static (sCA) and dynamic (dCA) cerebral auto-regulation can now be easily and reliably measured using non-invasive transcranial doppler (TCD) ultrasound techniques which insonate the cerebral arteries (usually the middle cerebral arteries) to record changes cerebral blood flow velocities (CBFV) that occur over a few seconds along with beat to beat changes in BP (Bishop et al., 1986, Aaslid et al., 1982 ). It has the advantage of not only being non-invasive but relatively straightforward to perform with excellent temporal resolution highlighting the advantage over other potential techniques such as positron emission tomography (PET) as well as not involving the injection of radioactive material (Chen et al., 2008). Magnetic resonance perfusion imaging although has better temporal resolution than PET (Chen et al., 2008), is still

considered more expensive than TCD and does not have the necessary time resolution needed for the assessment of dynamic cerebral auto-regulation. A blocked or tortuous MCA or an inadequate temporal bone window may prevent the adequate recording of the MCA therefore restricting the assessment of CA (Lorenz et al., 2009). Although hypercapnia is known to increase CBF by causing vasodilatation (Valdueza et al., 1999), small changes in $CO_2$ do not significantly affect the diameter of the MCA (ter Minassian et al., 1998) and as previously noted in Chapter 2, there is little difference in the regional cerebral vascular response to hypercapnia and hypocapnia (Ito et al., 2002).

As briefly discussed in Chapter 2 CBFV has been validated as a good surrogate for CBF and provides a simple method of reflecting changes in CBF without having to directly assess the changes in diameter of the MCA (Newell et al., 1994, Aaslid et al., 1991). It has also been shown that there is good correlation between sCA and dCA in adults (Tiecks et al., 1995). The use of static CA is limited by its relationship with CBFV and BP, as in the semi-steady state measures of CBFV and the associated cerebrovascular resistance (CVR) is the outcome or product of a stable BP level, and is given by CVR=ABP/CBFV (Tiecks et al., 1995). In addition as static CA is reflected by average long-term changes in BP, its use is limited by the need for sustained changes in BP induced by pharmacologically active agents. Dynamic CA reflects the changes in CBFV in response to rapid changes in BP (over a few seconds such that would occur during standing) hence the need for measurement of beat-to-beat changes in BP (van Beek et al., 2008). Thus for the rapid changes in BP provoked by head-up-tilt in this study, dCA was assessed.

As was noted in previous discussions, there are several methods which researchers have used to change systemic BP, in order to assess CA. Although there are other methods which can be used to invoke systemic falls in BP e.g. lower body negative pressure (Panerai et al., 2001) which may limit movement artefact, it was felt that HUT would provide a physiological response more closely representative of HUT in the clinical setting, and also provide some control over the period of postural change which active standing would not.

Sonograms displaying the CBFV over time from Transcranial Doppler Ultrasound (TCD) consist of the maximum velocity envelope extracted using a fast Fourier transform algorithm on the raw Doppler shift signal to provide a power spectrum at each frequency. The Doppler shift signal consists of several frequencies representative of the velocities of its scattered components as the original ultrasound signal usually from a 2MHz piezoelectric transducer is reflected from the surface of red blood cells within blood vessels. A piezoelectric transducer converts electrical energy into sound or acoustic energy (Nichols et al., 2011b, Panerai, 2009). The middle cerebral artery is insonated usually via the transtemporal window starting at a depth of around 50mm, and its identity is confirmed by the fact it is positive on the sonogram with flow towards the transducer and it is also traceable in terms of depth (Katz and Alexandrov, 2003, Gillard et al., 1986).

### 5.7.2 Static CA

Although static CA (sCA) will not be used in this thesis, it may aid the understanding of dynamic CA (dCA). Static CA can be estimated using linear system analysis with the change in BP accounting for the associated cerebral blood flow ($CBF$). In order to understand the principles behind dCA, an idea of how sCA is determined is useful. The resistance between the BP as the input of the system and the CBFV as the output of the systemic can be shown as the cerebrovascular resistance ($CVR$) using Ohm's law taking into account brain weight. Thus:

$$CVR = \frac{BP_{mean}}{CBF_{mean}}$$

However as TCD and the use of CBFV as a surrogate of CBF does not take brain mass into account an index of CVR is used ($CVR_i$) to give:

$$CVR_i = \frac{BP_{mean}}{CBFV_{mean}}$$

(van Beek et al., 2008)

Another estimate of CVR is Gosling's pulsatility index (PI) (Gosling et al., 1971) which is the difference between the systolic and diastolic components of CBFV over the mean CBFV. This gives:

$$PI = \frac{CBFV_{sys} - CBFV_{dias}}{CBFV_{mean}}$$

Thus CVRi and PI can be described as inversely correlated to CBFV, such that a decrease in CBFV is associated with an increase in PI. However this only holds true in

stable conditions and thus useful for assessing static CA as it has been found that a reduction in CVRi is associated with an increase in PI (Schondorf et al., 1997).

TCD has been shown to be a valid method of measuring static CA according to the Fick principle and assuming a constant cerebral metabolism of oxygen (Larsen et al., 1994). The Fick principle states that the blood flow within a certain period of time is equal to the amount of a substance entering the flow within that time frame divided by the difference between the concentration upon entering and upon leaving. Therefore,

$$\text{Cardiac Output (L/min)} = \frac{\text{O}_2 \text{ consumption (mL/min)}}{\text{P}_\text{a}\text{O}_2\text{(mL/min)} - \text{P}_\text{v}\text{O}_2\text{(mL/min)}}$$

(Nichols et al., 2011a)

Static cerebral auto-regulation can be determined by infusing pressor or depressor agents (e.g. phenylephrine or GTN) to provoke an increase/decrease in the mean arterial BP (ABP) whilst simultaneously recording the ABP and corresponding CBFV over a period of time ($t_2$-$t_1$). Thus the estimated cerebrovascular resistance ($CVR_e$) percentage change associated with the relative change in BP and CBFV over time is used to calculate the static cerebral auto-regulation as a percentage proportion of the full CA potential (Tiecks et al., 1995).

This can be summarised as:

$$\text{CVR}_\text{e} = \frac{\text{ABP}}{\text{CBFV}}$$

$$\% \, \Delta \mathrm{CVR} = \frac{(\mathrm{CVR}_2 - \mathrm{CVR}_1)}{\mathrm{CVR}_1}$$

$$\% \, \Delta \mathrm{ABP} = \frac{(\mathrm{ABP}_2 - \mathrm{ABP}_1)}{\mathrm{ABP}_1}$$

Thus static CA is:

$$Static\ CA = \frac{\%\Delta CVR}{\%\Delta ABP} \times 100\%$$

This would infer that if no static CA occurred then a fall in ABP would be associated with no change in the CVR and thus a reduction in the CBFV. Whereas if a perfect static CA of 100% were present then the CVR would compensate for a reduction in ABP (Tiecks et al., 1995).

Although CVR and PI may be useful to assess sCA in stable physiological situations, they are not ideal for dynamic changes in BP such as during HUT, as CVR relies on the direct relationship of a stable BP against CBFV and PI relies on CBFV stability. The dCA, gives more information regarding the efficiency of CA over a short time period, important in situations such as supine to standing, and the brief periods encountered with symptom onset in such situations (Tiecks et al., 1995).

### 5.7.3 Dynamic CA

Using TCD to record cerebral blood flow velocity (CBFV) of the MCA, as a surrogate of CBF (Newell et al., 1994, Berlowitz et al., 2011, Wilkinson et al., 2000) allows exploration of its relationship with real-time systemic BP and $CO_2$ changes. . As

previously noted in previous sections of Chapter 2 (2.6, 2.13, 2.14 and 2.15) and the preceding section on sCA, dCA relates to rapid changes in CA over a few seconds which can be assessed using several different methods though time and frequency domains are the most frequently used, and are described below.

#### *5.7.3.1 Rate of recovery in the Time Domain*

The time it takes for the CBFV to return to baseline values following a BP change (both pressor and depressor) as stimulus can indicate the efficiency of dynamic CA. An increasing time delay would indicate poor dCA. Thus for normalised changes in CVRi with a BP decrease, assuming a CBFV is representative CBF in a particular state:

$$Rate\ of\ recovery = \frac{\Delta CVR_i/\Delta T}{\Delta BP}$$

Where $\Delta CVR_i/\Delta T$ relates to the rate at which cerebrovascular resistance changes over a defined period of time ($\Delta T$).

(Aaslid et al., 1989)

#### *5.7.3.2 Auto-regulatory Index (ARI) in the Time Domain*

To assess dynamic CA either spontaneous BP transients or an applied stimulus can be used to induce a rapid step reduction in ABP (of ≥15mmHg e.g. such as thigh-cuff release) or step increase (e.g. cold pressor test or phenylephrine infusion) in order to allow the response of the ABP and CBFV to be simultaneously analysed over a period of time, usually less than 1 minute. The time it takes for CBFV to recover and attain its original level will vary according to the state of dCA. The mathematically derived

model of cerebral auto-regulation as an index (ARI) is one recognised method in which dCA can be measured and can be from 0 (no auto-regulatory function) to 9 (perfect auto-regulatory response) as shown in Figure 16. It uses the CBFV and ABP responses after a sudden BP change (e.g. thigh-cuff release or HUT) to attain a change in CVR per second relative to ABP.

The ARI relies on computer modelling based on the actual recorded CBFV response to ABP change from the start of the stimulus e.g. the moment of thigh-cuff release over 30 seconds, from which a theoretical or hypothetical CBFV response based on no cerebral auto-regulation would be created. Within this model of zero CA a linear relationship between ABP and CBFV is assumed with falls CBFV following a similar percentage fall in ABP. A further nine models of other possible CBFV responses are made with an increase in the ability of CA being assumed. Thus an actual CBFV response can be matched against these models in order to determine best fitting model and thus the ARI value (Tiecks et al., 1995). Thus from Figure 16 it can be seen that normal cerebral auto-regulation will have an ARI of around 5.

Mathematical models exploiting the spontaneous CBFV-BP relationship such as auto-regressive moving averages (ARMA) allows estimation of spontaneous fluctuations in ARI during HUT or ARMA-ARI (Panerai et al., 2008).

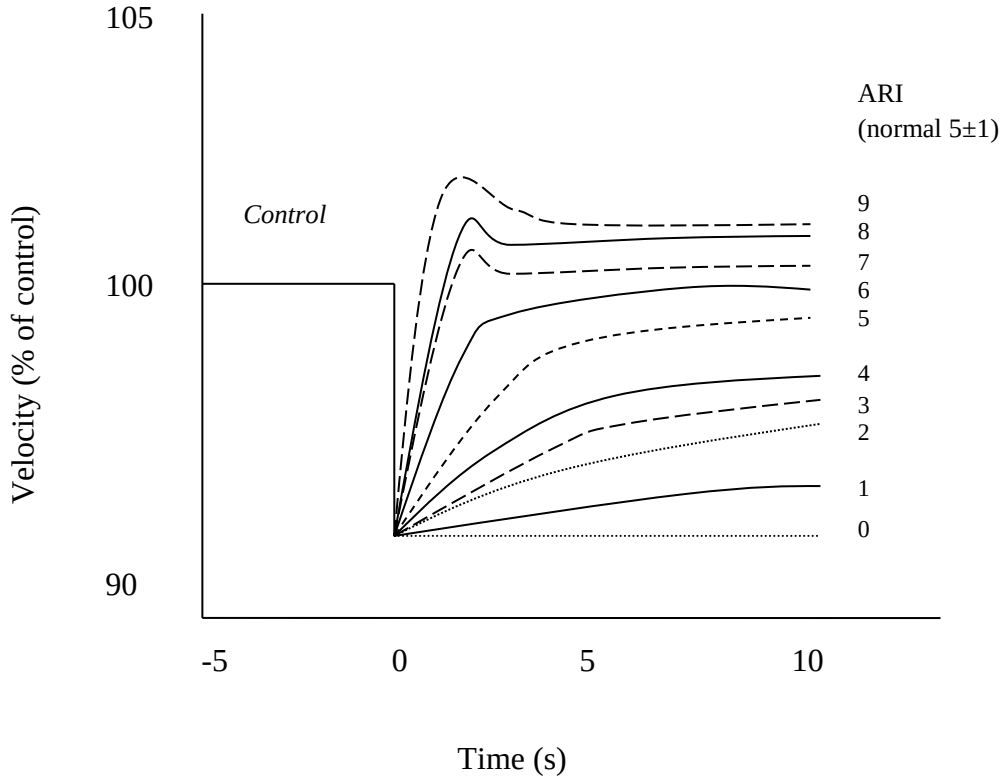



**Figure 16 Auto-regulatory indices, Tiecks et al. (2005)**

#### *5.7.3.3 Critical Closing Pressure and Resistance-Area Product from instantaneous CBFV-BP relationship*

The critical closing pressure (CrCP) is defined as the point at which for a given level of systemic BP CBF ceases (Panerai, 2003) and is estimated from instantaneous ABP-CBFV changes (Panerai et al., 2011). There are several methods to assess this, most common of which is using a linear model where $v(n)$ is the CBFV signal for the cardiac cycle with $N$ number of samples, and $p(n)$ is the associated BP measurement.

$$v(n) = a.p(n) + b$$

$$n = 1,2, \dots \dots . N$$

Therefore RAP and CrCP is estimated for each cardiac cycle using

$$RAP = \frac{1}{a}$$

$$CrCP = -\frac{b}{a}$$

Or where the mean CBFV ($Vm$)and mean BP ($BPm$) is used where:

$$Vm = (BPm - CrCP)/RAP$$

Then:

$$CrCP = BPm - RAP.Vm$$

(Panerai et al., 2011)

However it has been recently shown that using the first harmonic (H1), MAP or DBP when used in the calculation of the constant $a$, were the best suited for both dynamic CA assessment, providing similar estimates of CrCP and RAP using non-invasive Finapres for BP measurement as with intra-aortic values, and therefore is used in this thesis (Panerai et al., 2011, Panerai et al., 2006).

Thus for the H1 method, H1 is fitted to $v(n)$ and $p(n)$ with corresponding amplitudes for $V_1$ the CBFV and $P_1$ the BP. Therefore using the slope $a$,

$$a = \frac{V_1}{P_1}$$

Or if using (2Pm), calculating, with the mean $(V_m)$and diastolic values $(V_d)$of CBFV and those of BP, $(P_m)$ $(P_d)$

$$a = \frac{V_m - V_d}{P_m - P_d}$$

Therefore substituting $a$ into

$$RAP = \frac{1}{a}$$

$$CrCP = -\frac{b}{a}$$

Although RAP and CrCP are not presented in this thesis, they are useful indicators of dCA.

#### *5.7.3.4 Power spectral analysis of CBFV and BP and Fast Fourier Transform*

A signal can be separated into its component sine waves, with each sine wave having a different frequency, where the frequency is the time for one complete wave cycle to complete (F=1/T). Data collected in the time-domain can be converted to the frequency-domain to further explore the relationship between BP and CBFV using a fast Fourier transform (FFT) method for transfer function analysis (Panerai et al., 2005). A graphical representation of transfer function analysis is shown below (Figure 17).

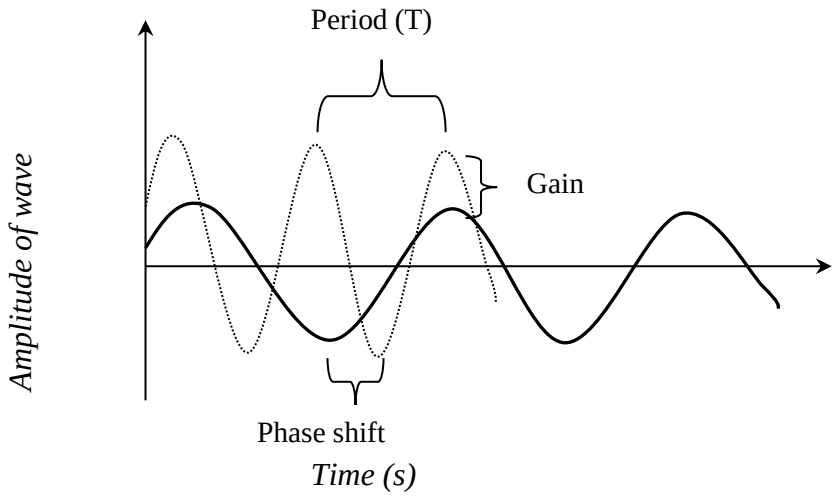



**Figure 17 Principles of Transfer Function Analysis. [The diagram shows two sinuoidal waveforms and within the period (T), the phase shift illustrates a delay between solid wave and dotted wave, and an alteration in gain]**

Transfer function $[H(f)]$ is the ratio between the smoothed cross-spectra $[G_{PV}(f)]$ to the autospectra of ABP $[G_{PP}(f)]$ represented as:

$$H(f) = \frac{G_{PV}(f)}{G_{PP}(f)}$$

(Panerai et al., 2005)

**Phase and Gain frequency response**

The gain is the change in amplitude between the input and output signal of the transfer function and the phase indicates the time delay between the BP (input) and resultant CBFV (output) (van Beek et al., 2008). The magnitude of the gain therefore reflects whether adequate CA has taken place to buffer the oscillations of BP. The number of degrees (or radians) of phase shift is used and so zero degrees i.e. no difference between response in BP and CBFV indicates no auto-regulation. So for example if there was a phase shift of 90º or π/2 with a period of 10 seconds (0.1 Hz), then there is a time gap of 2.5 seconds between BP and CBFV. Similarly if the phase shift was π, where the period was 10 seconds, then time delay would be 5 seconds. The amplitude and phase response are obtained using the real and imaginary components of $H(f)$ to give:

Amplitude $|H(f) = [H_R\,(f)^2 + H_1\,(f)^2]^{1/2}$

Phase $\varphi(f) = \tan^{-1}\left[\frac{H_1\,(f)}{H_R\,(f)}\right]$

(Panerai et al., 2005)

However a phenomenon known as aliasing is a limitation which can affect the results. Simply put, in order to reduce this, the sampling rate has to be twice the frequency of the original function. Inadequately sampled data will result in the incorrect reconstruction resulting in aliasing. However this needs to be balanced with the time it takes to compute the sampled signal. This is also known as “wrapping” because

software when calculating the transfer function use the angle between –π and +π radians, which leads to phase shifts of 2π radians. Thus mathematically, a phase delay of –π/3 is the same as -7π/3 and so on (2007, Nichols et al., 2011b).

**Coherence Function**

The coherence function (similar to that of Figure 15 (E)) indicates the proportion of variation in CBFV explained by BP variation in a linear relationship, such that coherence of 1.0 indicates that changes in CBFV are directly proportional to those of BP. A coherence of zero indicates a non-linear relationship which could be caused by blood flow velocity (auto-regulation) or background noise depending on the frequency at which the coherence occurs on the spectrum. Therefore the squared coherence function is the fraction of the output power linearly determined by the input power and is estimated using:

$$\gamma^2(f) = \frac{|G_{PV}(f)|^2}{G_{VV}(f)G_{PP}(f)}$$

(Panerai et al., 2005)

**Impulse and Step Response**

The impulse response function can be defined as the temporal response of CBFV to a change in ABP, whilst the step response is the impulse response function used to predict the CBFV response to ABP, and can be graded in a similar fashion to Tiecks et al (1995) model for ARI (Panerai et al., 1998).

To visualise the impulse and step response an inverse FFT is used to change it from the frequency domain to the time domain. The CBFV step response is calculated from the integration of $h_{PV}(n)$, (i.e. the inverse FFT of the impulse response) for positive values of time (Panerai et al., 2005).

### 5.7.4 Limitations of TCD

Perhaps one significant limitation which needs to be considered is the effect of the quality of BP and TCD signals on the evaluation of CA. Transfer function analysis can become unreliable at differing frequencies depending on the duration of the missing data. For example if there is 5 second loss of data even every 50 seconds, transfer function estimates of CA become unreliable at 0.07 to 0.5Hz; whereas if there is a 2 second loss then only bands above 0.15Hz is affected (Deegan et al., 2011a).

Of course TCD and thus the measure of CBFV has problems which may affect the evaluation of CA such as the fluctuations at different frequencies. Firstly, the obvious oscillations in CBFV are that related to the BP pulse waves; and secondly the slower oscillations in CBFV including respiratory R-waves at 9-20 cycles per minute (cpm or 0.15 – 0.33Hz), M-waves at 3-9 cpm (0.33 – 0.11 Hz) and low frequency waves at 1 cpm (1 Hz). It has been shown that the oscillation amplitudes for CBFV can be greater than the BP oscillations despite any falls in CBF being due to CA (Diehl et al., 1998). It has thus been suggested that spectral analysis of these waves may be an alternative method for determining CA as the oscillations in BP, HR and CBFV are present in supine and HUT (Diehl et al., 1998).

# 6 General Methods

There were two components to this thesis. The Orthostatic Hypotension Study and the Post-prandial Hypotension Study, with Methods particular to these in Chapter 7 and Chapter 13 respectively. Both shared similar general methods in terms of physiological measurements and are described here.

## 6.1 Recruitment

Recruitment commenced in December 2010 following approval by the Norfolk Research Ethics Committee and the Norfolk & Norwich University Hospital Research & Development.

Potential participants were identified by medical staff from all Medicine for the Elderly out-patient clinics and General Practice (GP) Surgery records as being possibly suitable for the study, based on inclusion and exclusion criteria outlined below. These clinics included Syncope Clinic, Falls Clinic, General Clinic and TIA Clinic. For example, of the 43.8% non-TIA patients attending a TIA out-patient clinic at NNUH, OH was present in 22.3% (de la Iglesia B. et al., 2013). Similarly participant information leaflets were distributed via GP Surgeries by seeking the assistance of the NIHR Norfolk Primary Care Research Network who contacted surgeries that would be interested in assisting with recruitment through patient identification via their practice database. Once potential participants aged over 60 years were identified (which included search terms such as “orthostatic/postural hypotension), and exclusion criteria checked they were given pre-stamped envelopes containing a Participant Information

Sheet to send out with a GP surgery cover letter. Furthermore posters were displayed in the waiting areas of GP Surgeries who had agreed to assist with recruitment, and a local newspaper advertisement (Eastern Daily Press) was placed asking for volunteers with and without symptoms. Potential participants were asked to contact Dr Alice Ong by telephone if interested and a call back allowed verbal screening to confirm eligibility. This allowed further discussion of the study, and what it involved, giving potential participants the opportunity to ask questions. A follow-up telephone call was made at least 24 hours later, to obtain verbal consent to attend the hospital for participation in the study.

## 6.2 Sample size

As the main outcome in this study is to investigate differences in cerebral auto-regulation, a sample size calculation was based on detecting a difference between groups of an ARI (auto-regulatory index) of at least 1.5 with 80% power with $\alpha$=0.05. This would similar to the difference seen between stroke patients and controls in previous research, (Brodie et al., 2009) where the sample size for each group is based on $45/\Delta ARI^2$. Therefore to detect an ARI of 1.5, 20 participants was required for each group. OH was classed as being present, with either a SBP or a DBP fall at 1 or 3 minutes (Moya et al., 2009); and symptoms were classed as present if the score was 2 or more on the Orthostatic Grading Score or OGS (Schrezenmaier et al., 2005).

## 6.3 Inclusion criteria

(FOR BOTH STUDIES)

| |
|---|
| ≥ 60 years of age |
| World Health Organisation (WHO) performance status of 0 to 2 (i.e. ambulatory) |
| With or without known postural hypotension (OH Study) or post-prandial hypotension (PPH Study) |
| With or without symptoms suggestive of postural hypotension (OH Study) or post-prandial hypotension (PPH Study) |

## 6.4 Exclusion criteria

(FOR BOTH STUDIES)

| |
|---|
| Intra-current acute illness (e.g. pneumonia, myocardial infarction, major surgery) in the preceding 4 weeks |
| Atrial fibrillation |
| Transient ischaemic attack or completed stroke in preceding 3 months (unless normal carotid dopplers) |
| Carotid stenosis |
| Raynaud's disease |
| Terminal cancer with a life expectancy <6 months |
| Anaemia where Hb ≤ 9g/dL |
| Known autonomic disturbance from any cause e.g. diabetes, Parkinson's disease |
| On drugs known to affect autonomic function |

## 6.5 Consent

Written and informed consent was obtained from all participants, and participants were made aware that they were free to withdraw at any time.

## 6.6 Ethics

Full ethical approval was been obtained for this study (Norfolk Research Ethics Committee) [REC No. 10/H0310/46].

Approval was sought from the local Research & Development Office at the Norfolk & Norwich University Hospital. [R&D No. 2010MFE12S (142-10-10)]

This study has also been registered. ISRCTN92525381 - Do abnormalities in the control of brain blood flow account for dizziness on standing or after meals in older people? http://www.controlled-trials.com/ISRCTN92525381/

## 6.7 Measurements

### 6.7.1 Clinical Data

Participants attended in the morning of the study day with an empty bladder having had no caffeine since the evening of the previous day, but were permitted a light breakfast. Participant age, sex, medical history including history of falls and frequency of falls and drug history were recorded. In order to represent real world older patients as closely as possible participants were not asked to stop their regular medication. It was recognised by the Ethics Committee that those on anti-hypertensives would potentially be at increased risk of stroke if discontinued. However those on medication known to affect autonomic function such as β-blockers were excluded from the study (Section 6.4). Furthermore it was desirable to have a "real world" study. Their height, weight, BMI, baseline sitting BP and HR (using a validated monitor OMRON 705IT) and postural change in BP were measured (supine BP lying for 5 minutes) and standing BP at 1 and 3 minutes (after both feet touch the floor were recorded) using a

BP cuff of the appropriate size to detect initial OH. OH defined as a fall in SBP of at least 20mmHg and/or a fall in DBP of at least 10mmHg at 1 or 3 minutes of standing (Moya et al., 2009). The presence or absence of orthostatic symptoms and the effect on daily life was assessed using the Orthostatic Grading Scale (Schrezenmaier et al., 2005), with those scoring ≥2 being classed as "symptomatic". A full clinical history and examination was carried with particular attention paid to undiagnosed exclusion criteria e.g. those with previously undetected atrial fibrillation, to exclude carotid bruit which may indicate carotid stenosis, and to exclude conditions such as benign positional vertigo which may cause symptoms of dizziness.

### 6.7.2 Autonomic Function Tests

All participants underwent standard autonomic function tests to assess sympathetic and parasympathetic function using the methods of (Ewing and Clarke, 1982) the *Taskforce® Monitor* system (Figure 18, Figure 19, Figure 20) was used to record R to R intervals, heart rate and beat to beat BP responses. The beat-to-beat BP reading from the finger (Figure 20) is intermittently validated against the brachial BP.

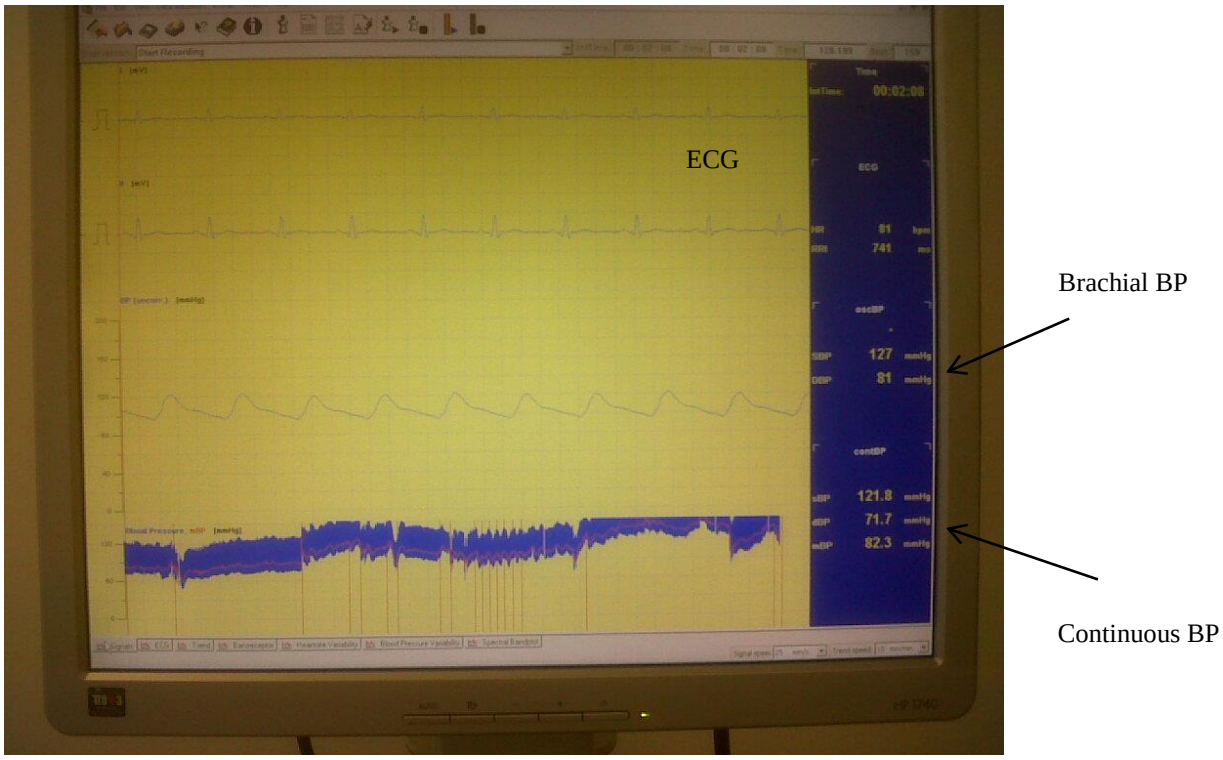



**Figure 18 Taskforce Monitor Screen showing ECG, beat-to-beat BP and oscillometric BP**

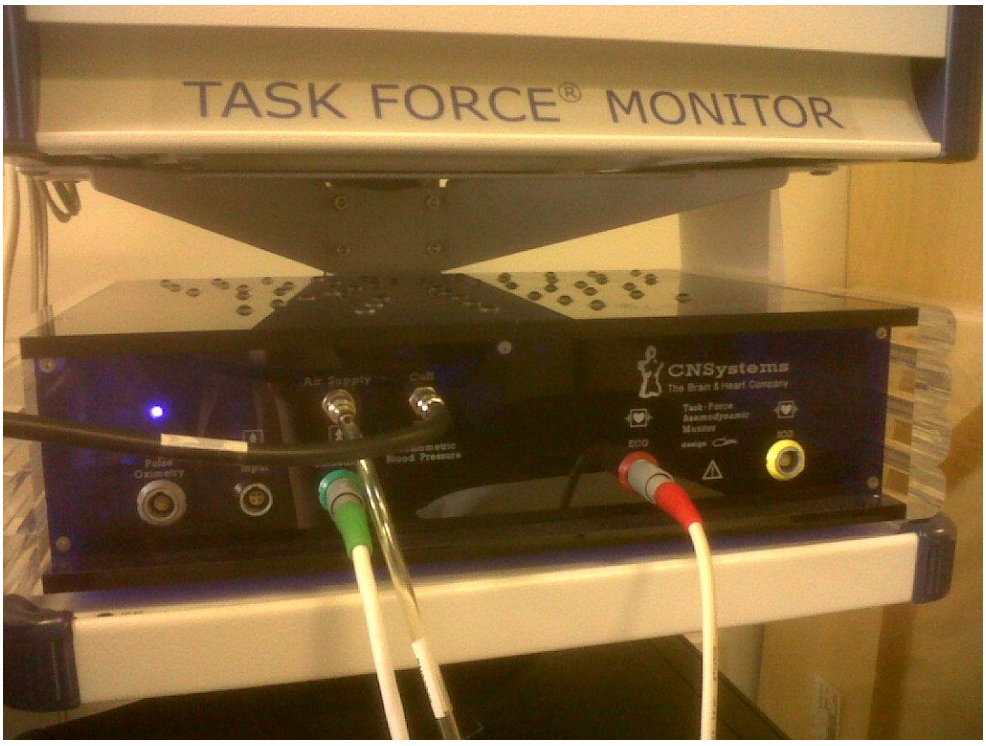



**Figure 19 Taskforce connections**

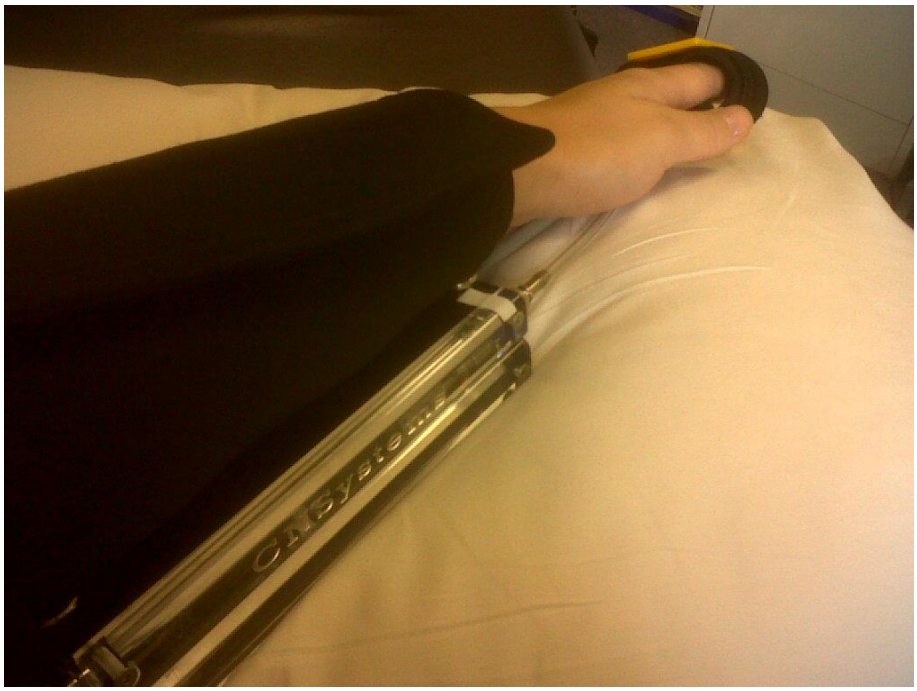


**Figure 20 Taskforce beat-to-beat BP measurements**

Parameters used to obtain the final autonomic function score (out of 10) (Ewing and Clarke, 1982) were:

1) Heart rate response to Valsalva in the sitting position reflects parasympathetic function. The Valsalva manoeuvre was carried out by asking the participant to seal their lips around the Leur lock end of a clean plastic 20ml syringe and to then blow out the plunger. The mean ratio of the longest R-R interval after Valsalva to the shortest R-R interval during Valsalva shall be used to score as follows.

| *Ratio of R-R interval* | *Outcome* | *Score* |
|---|---|---|
| ≥1.21 | Normal | 0 |
| 1.11 to 1.20 | Borderline | 1 |
| ≤1.10 | Abnormal | 2 |

2) Heart rate variation during six deep breaths assesses parasympathetic function. Deep breathing is carried out at a rate of 6 breaths a minute whilst sitting and

timed using the display on the TFM with Dr Alice Ong, counting inspiration and expiration. The mean difference between the maximum and minimum heart rate (which can be calculated from the RR interval) is used to give a score as follows.

| *Heart rate variation (bpm)* | *Outcome* | *Score* |
|---|---|---|
| ≥15 | Normal | 0 |
| 11 to 14 | Borderline | 1 |
| ≤10 | Abnormal | 2 |

3) BP response to sustained handgrip whilst sitting assesses sympathetic function. Participants were asked to handgrip in their "strongest" hand a partly inflated soft covered fabric BP cuff bladder and then to maintain 30% of their maximal handgrip strength for up to 5 minutes, and ideally for at least 3 minutes.(Figure, *Greenlight 300*). BP is measured at 1 minute intervals and the difference between the highest diastolic BP achieved and the mean of three DBP values before handgrip is calculated to give a score.

| *Diastolic BP change (mmHg)* | *Outcome* | *Score* |
|---|---|---|
| ≥16 | Normal | 0 |
| 11 to 15 | Borderline | 1 |
| ≤10 | Abnormal | 2 |

**Figure 21 Handgrip using Greenlight 300 blood pressure cuff**

4) Immediate HR response to standing from supine assesses parasympathetic function. The ratio of the longest R-R interval at or around the 30$^{th}$ heart beat after the participant starts to stand, to the shortest R-R interval at or around the 15$^{th}$ beat is calculated to allow scoring as follows.

| *Ratio 30$^{th}$ beat R-R interval :15$^{th}$ beat R-R interval* | *Outcome* | *Score* |
|---|---|---|
| ≥1.04 | Normal | 0 |
| 1.01 to 1.03 | Borderline | 1 |
| ≤1.00 | Abnormal | 2 |

5) BP response to standing from supine reflects the sympathetic function. The postural fall in BP is calculated as the difference in the systolic BP from supine to stand at 3 minutes to give scores as follows.

| *Postural SBP fall (mmHg)* | *Outcome* | *Score* |
|---|---|---|
| ≤10 | Normal | 0 |
| 11 to 29 | Borderline | 1 |
| ≥30 | Abnormal | 2 |

By giving each participant a score for each component a maximal score of 10 for autonomic dysfunction can be allocated (Ewing, 1985).

### 6.7.3 Laboratory Data

The most recent electrolytes, blood glucose and haemoglobin values from the last 3 months were checked for participant eligibility.

### 6.7.4 Transcranial Doppler Measurements Generic Procedure

Participants attended for TCD having only had a light meal and no caffeine on the day of attending the study, and were asked to wear comfortable loose fitting clothing. Recordings were carried out in a quiet research laboratory with temperature controlled to 20-22°C. Patients lay on a padded couch with a footplate to allow the participant to be passively placed into the head up tilt position, and a single pillow was provided for head support. The participant went from a supine to the 70° HUT position within a 5 second period. Whilst supine the arms were rested by their side, and when in the upright position during tilt, a table was secured to the tilt-table to allow arms to rest at the level of the heart, and the participant was secured to the table using straps across their body and legs.

Simultaneous recording at baseline of: 1) transcutaneous $CO_2$ partial pressure using a transcutaneous gas monitor (Figure 22, *TINA*, Radiometer, Copenhagen)(Dawson et al., 1998) or the end-tidal $CO_2$ level using an infrared capnograph (Capnogard, Novametrix, USA), 2) continuous non-invasive beat-to-beat BP measurements with a plethysmograph using a Finapres device (Figure 23 and Figure 24, Ohmeda, Colorado, USA)(Panerai et al., 2003, Omboni et al., 1993) on the middle finger of the non-dominant hand with Physiocal being switched on at the start of a ten minute segment, 3) bilateral middle cerebral artery velocity using TCD as identified according to velocity, depth and waveform (DWL Compumedics, Germany and QL Software version 2.5) Figure 26, and 4) three lead surface ECG monitoring (Cardiac Monitor 304, Graseby Medical, England, Figure 25). The middle cerebral artery (MCA) velocity analogue signals (Figure 26) and other analogue signals were digitally converted at 200 Hz for off-line analysis. All physiological signals were recorded into a data acquisition system (Figure 27, Physidas software, Professor Ronney Panerai, Medical Physics, University of Leicester).

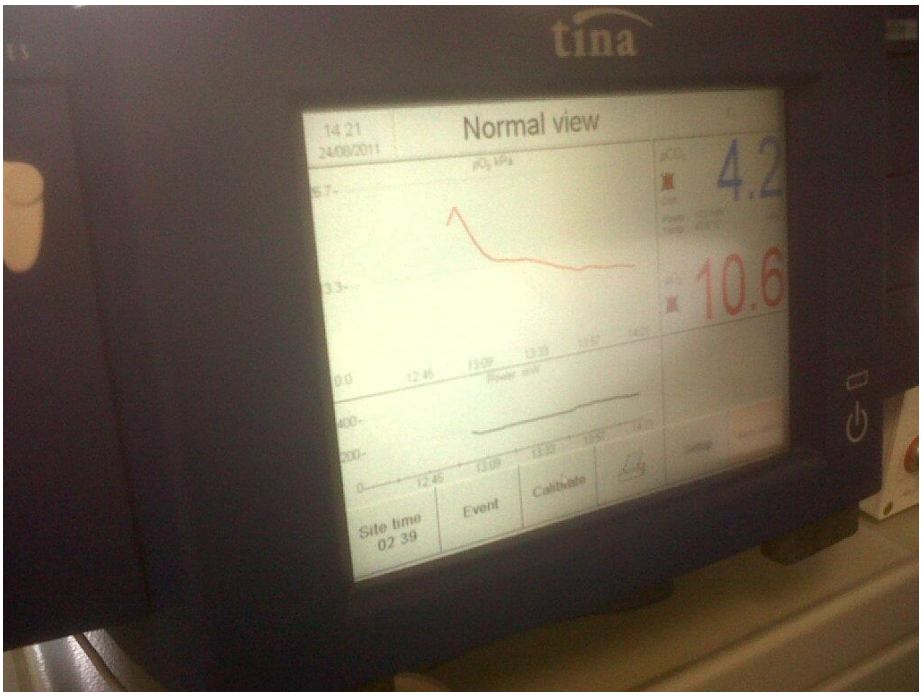



**Figure 22 Transcutaneous carbon dioxide sensor (TINA)**

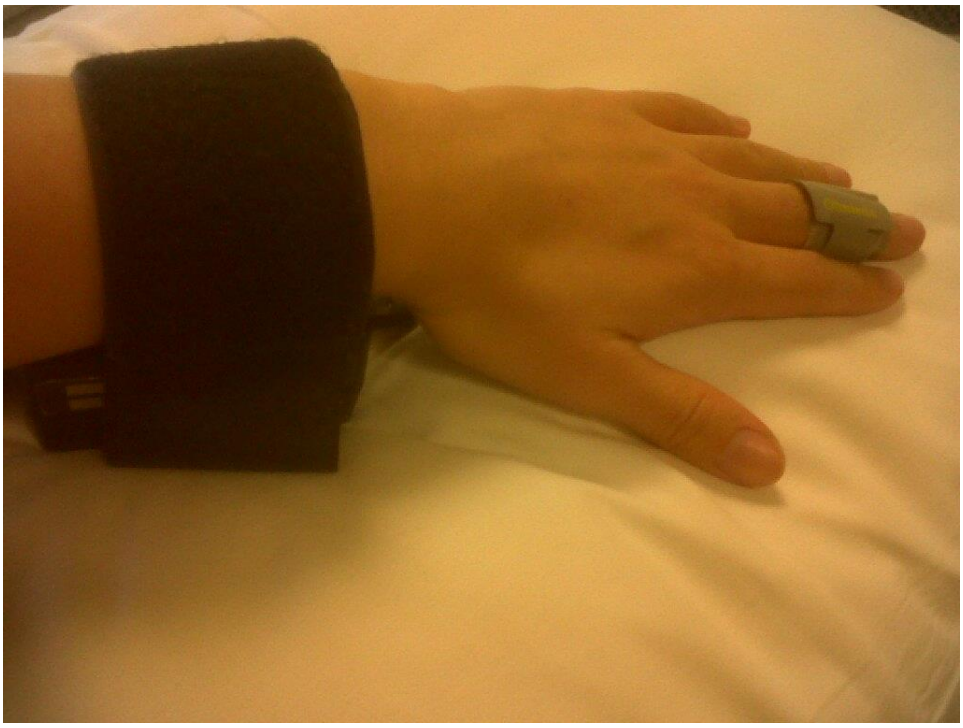


**Figure 23 Finapres BP finger cuff**

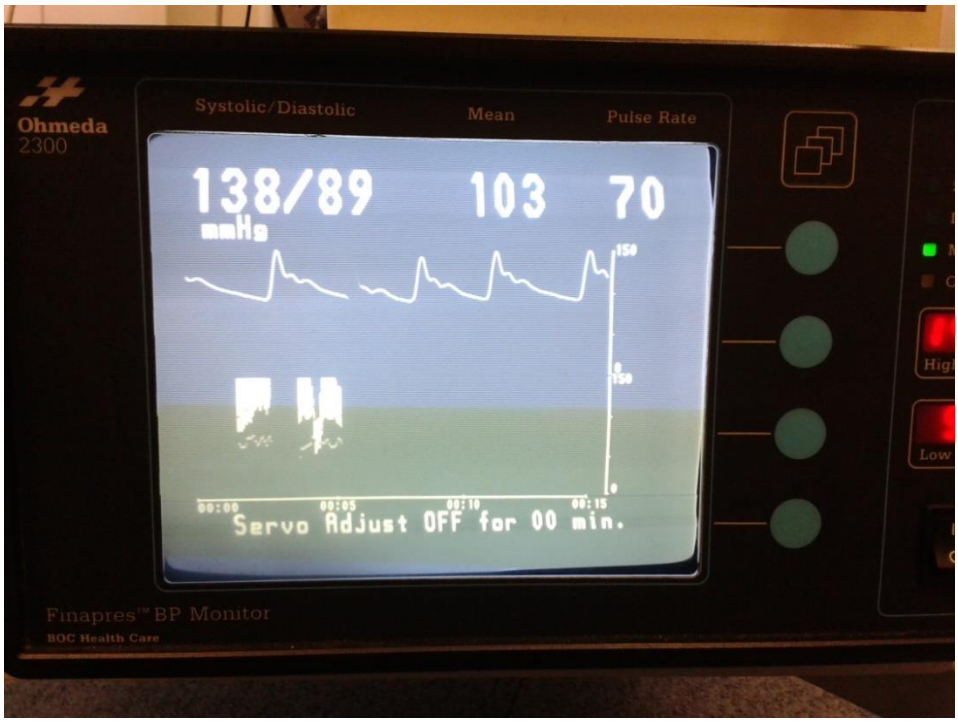



**Figure 24 Finapres BP monitor**

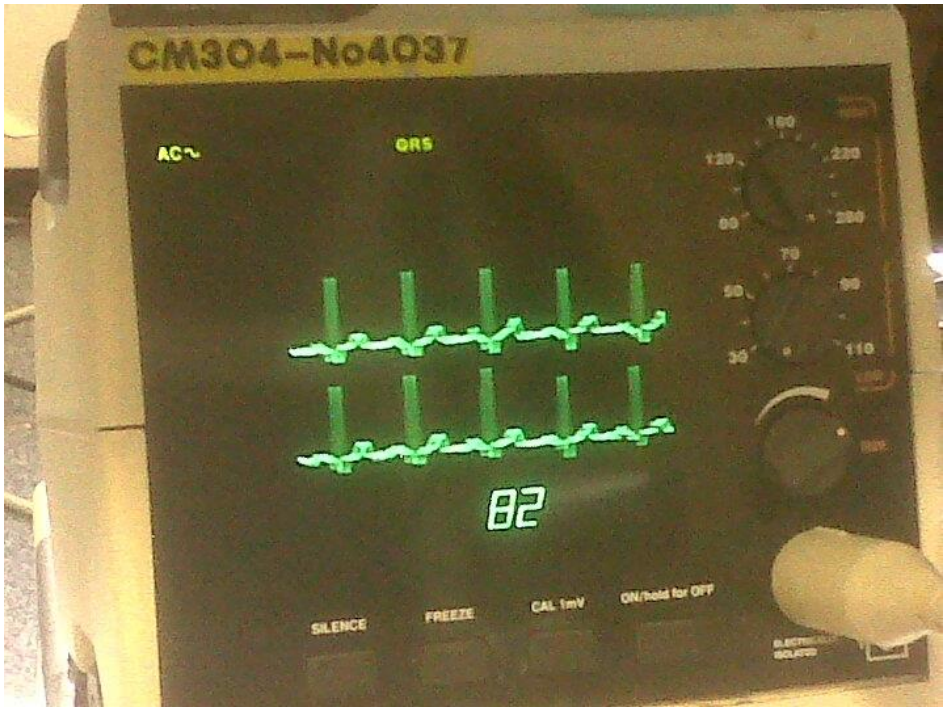



**Figure 25 ECG signal**

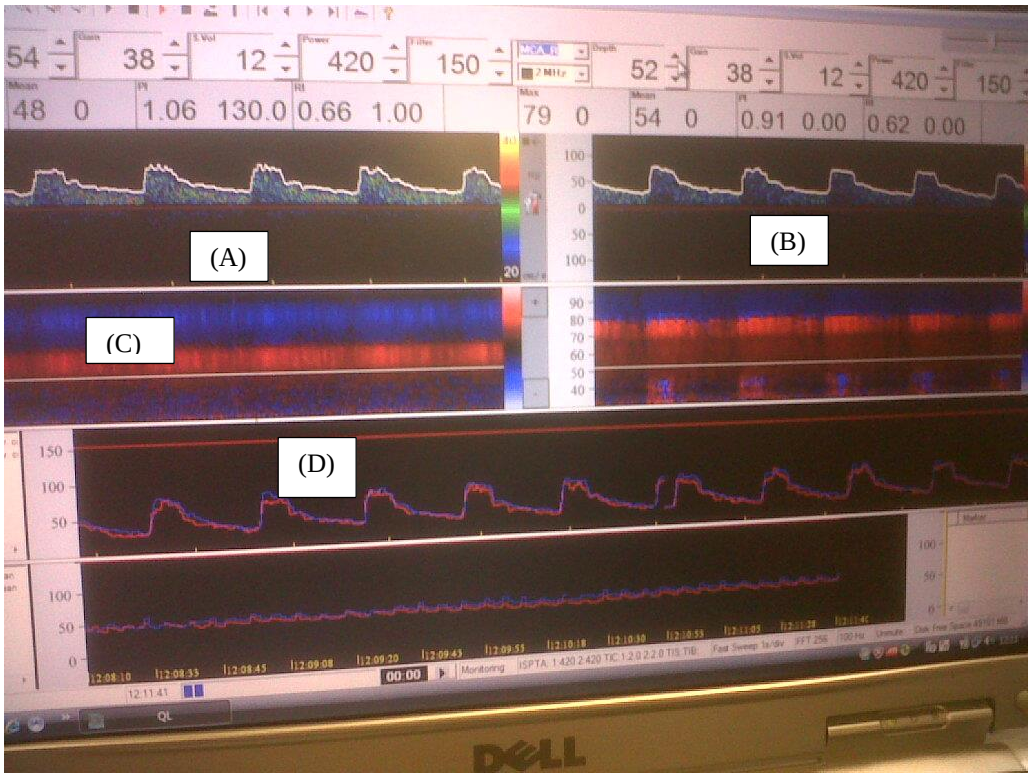



**Figure 26 Doppler signal showing CBFV from Left MCA (A) and Right MCA (B). Doppler signal (C) towards probe (red) and signal away from probe (blue). Left and right CBFV superimposed on each other in real time recording (D).**

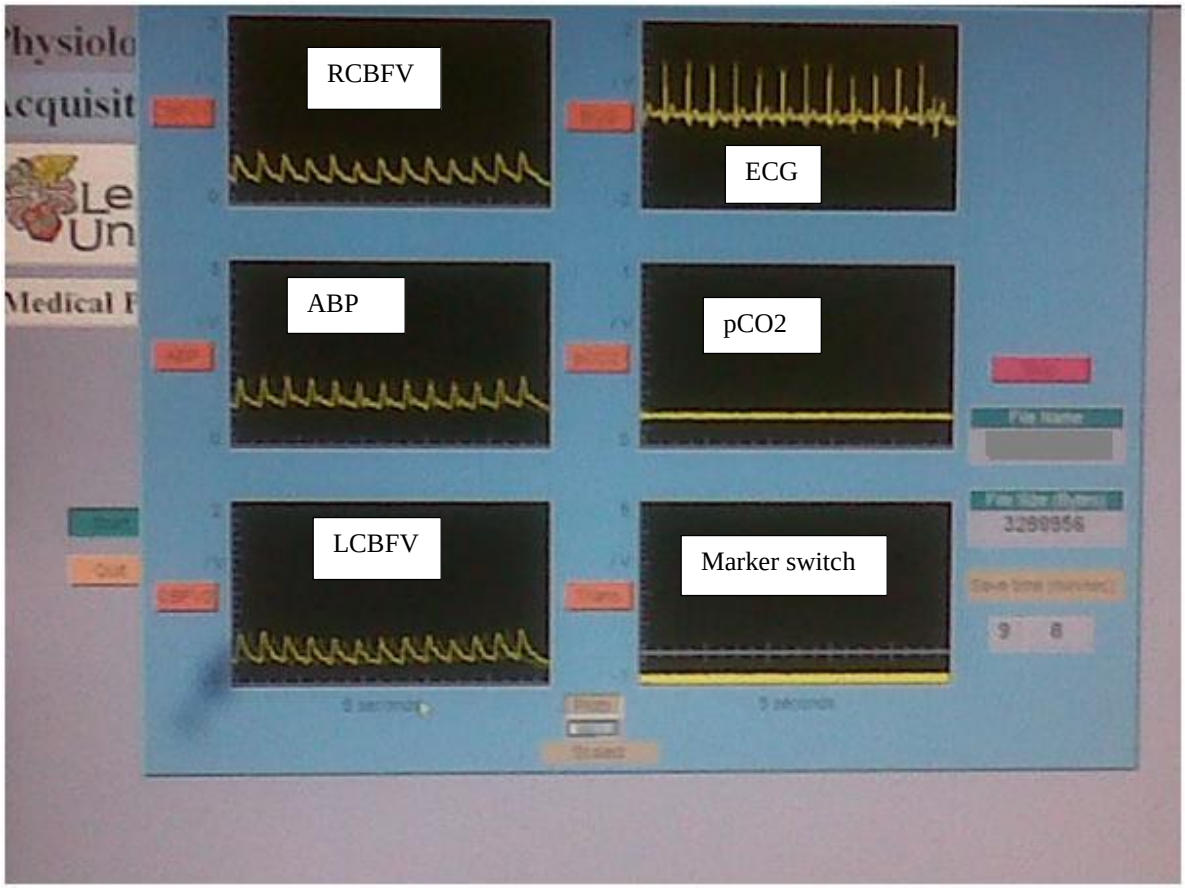



**Figure 27 Physidas screen**

Cerebral blood flow velocities in the left and right middle cerebral arteries (Figure 26) were simultaneously obtained by insonation using the standard trans-temporal window in an area superior to the zygomatic arch (Aaslid et al., 1982 ). A 2 MHz Transcranial Doppler probe (DWL, Germany) was fitted securely with a custom silicon head-band to allow continuous readings to be taken (Figure 28). Participants were asked to remain as still as possible to prevent the introduction of artefact as a result of either head movement or probe movement. Once transcutaneous $CO_2$ and beat-to-beat BP stabilised and after approximately 30 minutes, recordings began when there was less than 10% variation in all values.

At the beginning and the end of each 10 minute segment recording in the supine position at baseline and in the HUT position for each of the maximum of three (for Orthostatic Hypotension) and six (for the Post-prandial Hypotension)10 minute segment recordings a calibration for BP was carried out by using the Finapres device to provide a voltage calibration. Thirty minutes of 70º HUT was selected for OH, as this seemed to be a reasonable amount of time to reflect initial OH, and to provoke symptoms in the older adult (Moya et al., 2009, Carey et al., 2003). Indeed it has been proposed that most positive tests occur within 15 minutes (Pitzalis et al., 2002) and other researchers have also used 30 minutes (Grubb et al., 1991b). Although some research has suggested longer periods of HUT of 45 minutes, this was at a lower incline of 60º HUT (Fitzpatrick et al., 1991). Sixty minutes was selected for PPH as this also appeared to be a reasonable time period to allow glucose absorption, and BP changes to occur in the HUT position (Krajewski et al., 1993). Prior to this the Finapres internal calibration of BP or physiocal was switched on to validate the BP. The physical is the baseline pressure servo adjust system for the Finapres, and was

disabled during the recordings to prevent zero data output periods. CBFV was recorded in the supine and 70° HUT positions, recording the systolic, diastolic and the mean CBFV for each MCA to allow calculation of the auto-regulatory indices for each side off-line. The mean ARI of both hemispheres is the ARI for that one individual as it has been previously shown that the auto-regulatory response does not depend on which hemisphere is being assessed (Dawson et al., 2000). Auto-regulatory indices were taken before tilt at baseline, at 1 and 3 minutes after tilt, the last 3 and 1 minute of the tilt before the participant is returned to supine, and at 1 and 3 minutes after return to supine using a standard protocol for our laboratory (James and Potter, 1999).

### 6.7.5 Baroreflex sensitivity

Continuous baroreflex sensitivity (BRS) whilst supine was derived using Finapres BP and corresponding ECG data using spectral analysis as previously discussed earlier in this Chapter(Dawson et al., 1997, Youde et al., 2002). In summary this involves changing the R-R interval and BP data into the frequency-domain from the time-domain to give the power spectrum from which the gain or modulus, phase and coherence between the R-R interval and BP can be considered.

### 6.7.6 Pulse Wave Velocity and Augmentation Index

As previously discussed pulse wave velocity and augmentation index are two different measures of arterial stiffness but can be measured using the same data (Vicorder, Skidmore Medical Limited, UK) and were measured in the supine position after 10 minutes of rest (Wilkinson et al., 1998b, Asmar et al., 1995). The neck cuff (Figure 29) was positioned over the carotid artery with the participant at 30° to the horizontal

plane, and a thigh cuff (Figure 30) was placed over the proximal part of the right leg (to obtain the femoral artery waveform), with both attaching to the Vicorder Unit (Figure 31). The distance between the carotid cuff and the centre of the thigh cuffs were measured. Three recordings of reasonable quality (when HR showed less than 10% variation) was taken to calculate the mean PWV and AIx for each participant (Figure 32).

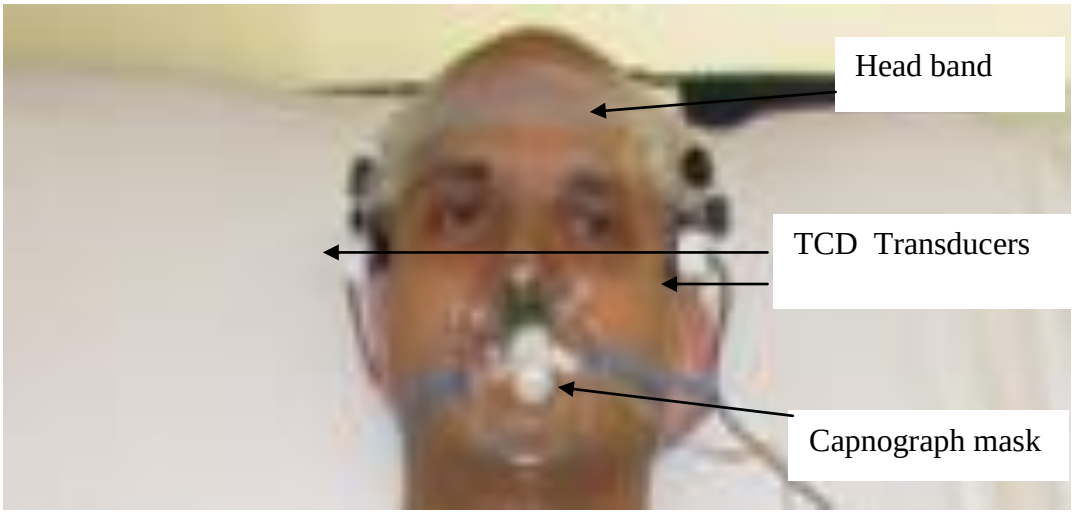



**Figure 28 Headband holding transducers (as demonstrated by a colleague)**

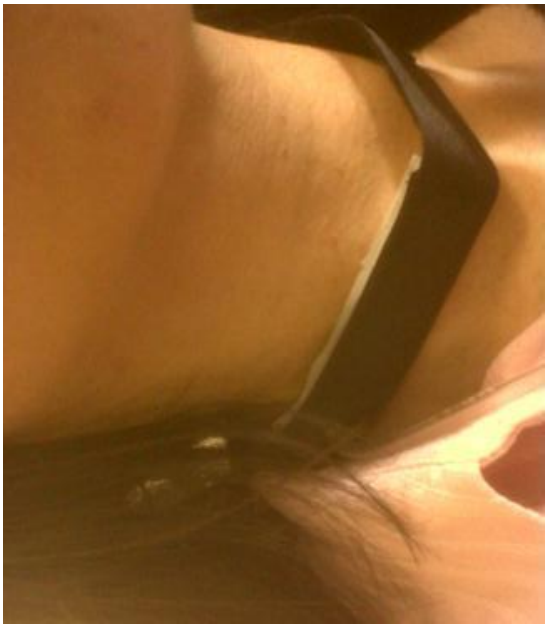


**Figure 29 Neck cuff of Vicorder**

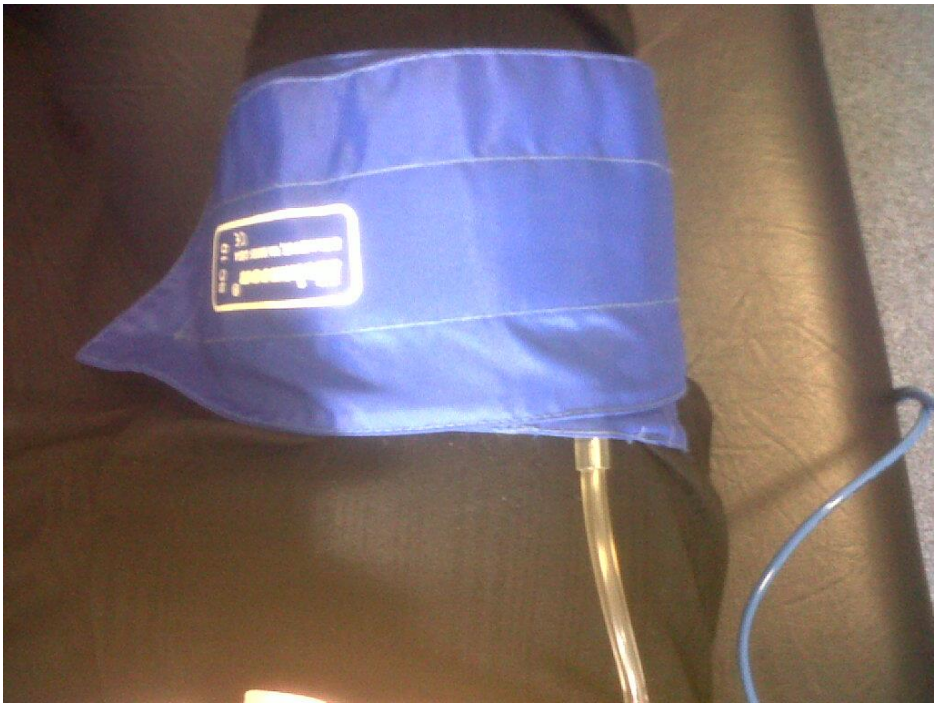


**Figure 30 Thigh cuff of Vicorder**


**Figure 31 Vicorder Unit**

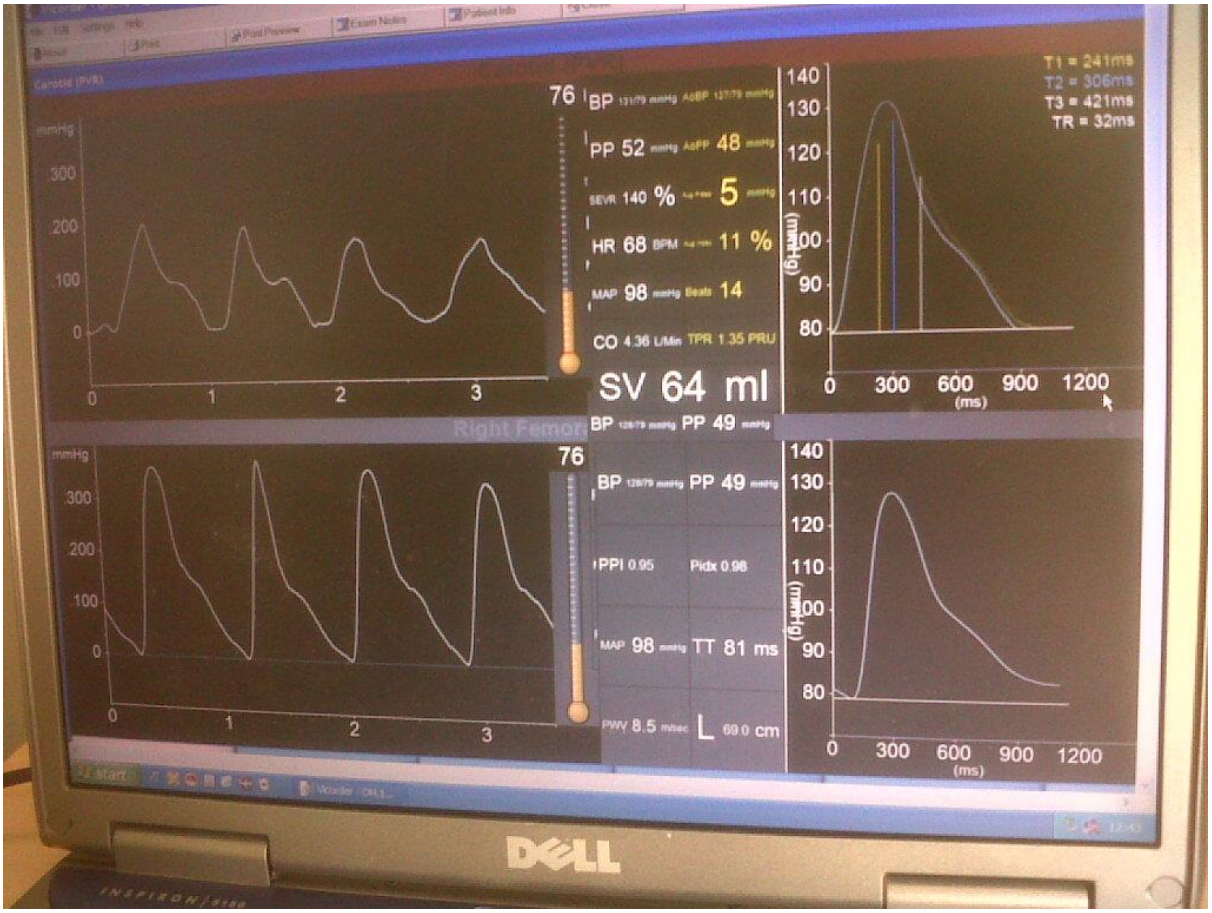



**Figure 32 Vicorder screen showing adequate tracings for carotid and femoral pulses**

### 6.7.7 Data analysis

In summary, data files were cleaned in terms of removing artefact data spikes (e.g. when patient inadvertently moved their arm causing a spike in ECG etc.) whilst blinded to the subject group. Data files were kept separately from the master file linking data file names with the actual participant during this process. Once files were cleaned, parameter data were extracted and BRS and CA information were analysed using special software (Professor Ronney Panerai, Medical Physics, University of Leicester), this data and baseline data were analysed using SPSS software package (v 21). The digital signal processing software (RP) will be discussed in later sections.

#### *6.7.7.1 Baseline continuous data*

The baseline characteristics of the four groups were statistically analysed for any significant differences this included the mean ±SD of continuous variables: age, body mass index (weight in kg/height in $m^2$), baseline SBP, DBP, HR, capillary blood glucose, orthostatic grading score (Schrezenmaier et al., 2005), autonomic function score, mean augmentation index, mean augmentation index (@75bpm), change in SBP, DBP and HR at 1 minute and 3 minutes. BRS in the very low frequency band, low frequency band and the high frequency band were also compared.

#### *6.7.7.2 Baseline categorical data*

Categorical data were also examined for differences between the four groups using a Pearson Chi-square or Fisher's exact test where appropriate, and included: sex, smoking status, history of blackouts/syncope, hypertension, diabetes mellitus, use of diuretics as a group (and sub-groups of loop and thiazide), use of ACEi or AIIRB (and as sub-groups of ACEi and AIIRB), calcium channel blocker, alpha blocker, tricyclic antidepressant, any BP lowering drugs, and the presence of symptoms on HUT.

#### *6.7.7.3 Assessment of Cerebral Auto-regulation*

After digital signal processing as described below a comparison between the four groups of the baseline ARI (Tiecks et al., 1995) in the supine position was made. This included direct fitting of Tiecks model, and reporting the mean coherence, mean gain, mean phase, mean phase unwrapped in the low, middle and high frequency bands, and the percentage step response recovery. In order to permit continuous estimates of dynamic CA this was followed by auto-regressive moving averages or ARMA modelling of ABP-CBFV followed by least-squares fitting of Tiecks model to give ARMA-ARI (Panerai et al., 2008).

Continuous ARI was calculated by using data 1 minute before HUT (data were linearly interpolated backwards if this was not the case) and for 2 minutes after. The point of HUT was digitally marked where a switch creates a positive voltage gain on a recording channel. Similarly, when participants had orthostatic symptoms, or when the maximal time of HUT had been reached, this was digitally marked, to allow analysis of data 1 minute before returning to supine and for 2 minutes after. Mean (±SD)

CBFV, MAP, HR, $tCO_2$ and ARI are calculated. The t-tests of the coherent averages were dependent on the f-test statistic, were dependent upon whether unequal (f, $p<0.05$) or equal (f, $p>0.05$) variances were assumed. The mean (SD) maximal change for each group in SBP, DBP at 1 and 3minutes from HUT as well as at onset of symptoms was also assessed.

The PWV and ARI for each group were statistically analysed to assess whether there was an association between arterial stiffness and ARI.

#### *6.7.7.4 Digital Signal Processing*

A fast Fourier transform method was used to convert the Doppler signals into maximum frequency velocity envelopes and to achieve temporal resolution a window of 6.25ms. Data from the Finapres, TINA™ and ECG output was converted to 200Hz and stored. The BP trace was calibrated, visually inspected and any artefact data spikes were mathematically removed using linear interpolation by using special software (RP) after being imported into an MS-DOS system. From the ECG tracing the cardiac cycle was marked to determine the R to R interval and any ectopics manually marked and removed by linear interpolation. Where the peak of the R wave did not have significant amplitude which meant the software incapable of detecting the R waves, these had to be individually manually marked and saved. Alternatively where there were too many incidences in a single recording of this occurring, the process was repeated by using BP data instead. For each cardiac cycle an estimate of the mean MCA velocity, mean arterial BP, systolic and diastolic BP using spline interpolation for the supine and head-up-tilt positions (Dawson et al., 2000). CBFV signals were subjected to a median

filter, and all signals had a low-pass Butterworth filter with a cut-off frequency of 20Hz applied. Dynamic cerebral auto-regulation was analysed using time domain analysis (Tiecks et al., 1995), ARI from velocity step response and transfer function analysis of coherence, phase and gain (Smith et al., 2008) .

# 7 Methods - Orthostatic Hypotension Study

## 7.1 Aims

- To investigate if differences in dynamic cerebral auto-regulation, BRS and arterial stiffness are related to the symptoms of orthostatic hypotension in patients with and without a postural BP fall.
- The hypothesis was that abnormalities in dynamic cerebral auto-regulation explain why some patients have postural symptoms independent of changes in arterial blood pressure in orthostatic hypotension i.e. orthostatic symptoms are more closely related to abnormalities in dCA then to postural changes in systemic BP levels.

## 7.2 Methods

### 7.2.1 Recruitment

Details of participant recruitment is given in the General Methods section. Using BP and symptom criteria four groups were generated. Symptomatic OH (i.e. those with symptoms e.g. dizziness, nausea, diaphoresis, diplopia (Carey et al., 2001) but with an OGS≥2 (Schrezenmaier et al., 2005)) and measurable postural drop in BP), Asymptomatic OH (i.e. those without symptoms and measurable postural drop in BP), Symptomatic No OH (i.e. those with symptoms but no significant postural drop in BP), and Asymptomatic No OH (i.e. normal control).

### 7.2.2 Study Groups

Based on the sample size calculation explained in the General Methods section, 20 participants in each of four groups were distributed based on the following:

a) OH with symptoms i.e. Symptomatic OH

b) OH without symptoms i.e. Asymptomatic OH

c) No OH and postural symptoms i.e. Symptomatic No OH

d) No OH and no symptoms (control) i.e. Asymptomatic No OH

### 7.2.3 Data collection

Baseline categorical and continuous data was collected as described in the General Methods Chapter including BRS, PWV and AIx.

As described previously, with TCD and its associated recordings of $tCO_2$, BP and HR, the participant was initially placed in the supine position with a 10 minute baseline recording, then the 70º HUT position for up to 30 minutes or until symptoms were provoked whichever was sooner, and then returned to the supine position. Recordings were continued until stable. Whether a participant had symptoms during the procedure, and the time at which it occurred were noted and electronically marked on the recording. The 30 minutes duration of HUT allowed for some consideration of later falls in BP as per the current ESC guidelines (Moya et al., 2009).

### 7.2.4 Data analysis

Baseline categorical data and continuous data, as well as TCD data for baseline, pre-HUT, initial HUT ("UP") and just before the end of HUT ("DOWN") for the Symptomatic No OH, Asymptomatic OH and Symptomatic OH groups were compared to the control group (Asymptomatic No OH).

# 8 Results – Orthostatic Hypotension Study - Baseline

## 8.1 Baseline data

A total of 103 participants (51 female, 52 male, mean age 73.92±7.11 years) were successfully recruited for screening between the 15th of February 2011 and the 22nd of July 2013. The final number of participants with at least a unilateral baseline TCD signal was 85, and were separated into the four groups based on whether there was a significant postural drop in BP (using the recognized definition i.e. a fall in SBP ≥20mmHg and/or fall in DBP≥10mmHg at 1 and/or 3 minutes of standing using clinic measurements) and the *Orthostatic Grading Scale* score (i.e. a score of ≥2 indicates symptoms) (Schrezenmaier et al., 2005). Although the original plan was to recruit 80 participants, it was difficult to predict how many of those recruited would have an adequate TCD signal. Thus as Figure 33 demonstrates, the numbers in each group were: the symptomatic OH group n=23, symptomatic no OH group n=18, asymptomatic OH group n=20 and the asymptomatic no OH group n=24 which was taken as the "control or normal" subjects. The 30 minutes duration of HUT allowed for some consideration of later falls in BP as per the current ESC guidelines (Moya et al., 2009).

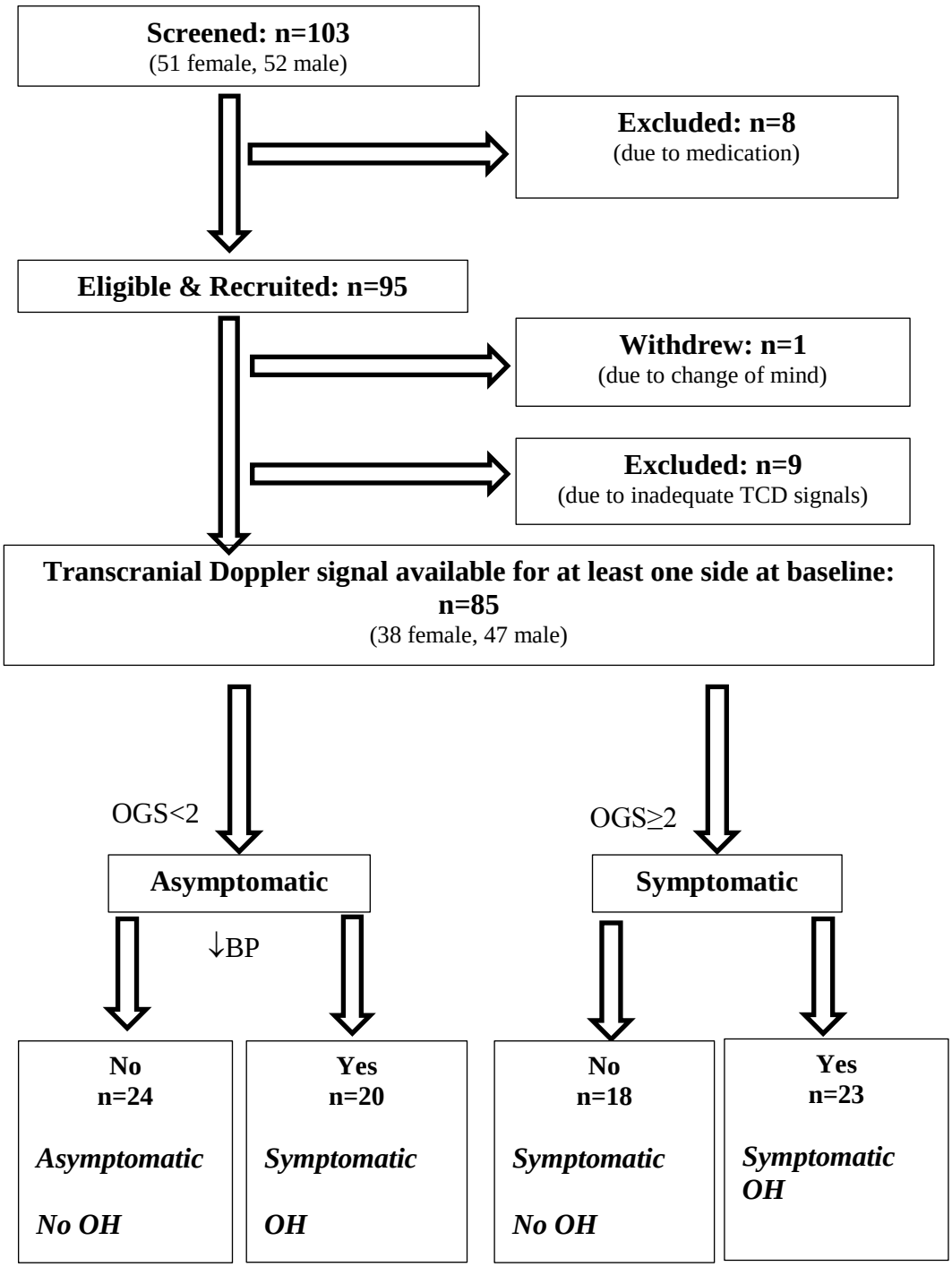



**Figure 33 Flowchart for the Orthostatic Hypotension Study**

## 8.2 Population summary

A summary of the OH study participants basic characteristics are presented in Table 14. Data for the variables were assessed for normality, and either one-way ANOVA or the Kruskal Wallis test was used, followed with Student's t-Tests (with Levenes test for equality of variances) or Mann-Whitney U test to compare against the Asymptomatic No OH group (which acted as the control group). As participants were grouped according to symptoms and changes in BP from the supine to standing position, there were the expected statistical differences between groups for OGS and postural changes in BP. Of note, the symptomatic OH group were significantly older than the asymptomatic No OH group which was taken as the control group (p=0.019). Furthermore the autonomic function score (out of 10) compared to the asymptomatic No OH (2.21±1.50), was significantly higher in the symptomatic OH group (4.78±1.86, p<0.001). However this was not significantly different to the asymptomatic OH group (3.00±2.00, p=0.226) nor the symptomatic No OH group (2.94±1.92, p=0.271).

In the asymptomatic No OH group (n=24), there were no postural falls in SBP (≥20mmHg) or DBP (≥10mmHg) at 1 minute or 3 minutes. In the symptomatic No OH group (n=18) there was no significant postural change in DBP and only one fall in SBP at 1 minute, but no falls in DBP or SBP at 3 minutes. In the asymptomatic OH group (n=20), there were postural reductions for DBP in eleven cases and SBP in ten cases at 1 minute, four in SBP and ten in DBP at 3 minutes. In the symptomatic OH group (n=23) there were fifteen postural reductions in DBP and fourteen for SBP at 1 minute,

with seventeen cases of reduction in DBP and SBP at 3 minutes. There were no significant changes in HR at 1 and 3 minutes across the groups, as shown in Table 14.

Categorical data are presented in Table 15. The only characteristic that was statistically significant (p=<0.05) between the groups was in the use of an ACEI or ARB as anti-hypertensive agents (p=0.043), being highest in the symptomatic No OH group (38.9%) compared to the others (asymptomatic OH group (25%), asymptomatic No OH (8.3%) and symptomatic No OH (8.7%). This may be a potential a confounder. Overall there was no difference in the prevalence of hypertension between the groups or in diabetes.

## 8.3 Baroreceptor Sensitivity

There were no significant differences between the 4 groups in cardiac baroreceptor sensitivity calculated in the low frequency spectrum band (0.05-0.15Hz) as shown in Table 16. All values were within expected normal ranges for age and BP levels.

## 8.4 Arterial Stiffness

There was no significant difference in Pulse Wave Velocity, as a measure of arterial stiffness or in Augmentation Index corrected for pulse rate (AIx and AIx @75 respectively) between groups (Table 17). However the mean AIx and the mean AIx corrected for HR@75bpm (p=0.032) were higher in the Symptomatic No OH group than the Control group (p=0.03).

| Participant Characteristic | Asymptomatic No OH (24) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (20) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Age (years)** | 71.6 | *5.9* | 72.1 | *8.2* | *0.828** | 74.0 | *7.4* | *0.243** | 76.0 | *6.6* | *0.019** | *0.181** |
| **BMI (kg/m$^2$)** | 27.6 | *3.3* | 28.3 | *3.9* | *0.588** | 29.3 | *4.7* | *0.189** | 26.5 | *4.4* | *0.333** | *0.085** |
| **Baseline SBP (mmHg)** *-supine* | 136.6 | *13.4* | 150.4 | *23.3* | *0.017* | 141.6 | *16.1* | *0.283* | 152.3 | *24.2* | *0.032* | *0.053* |
| **Baseline DBP (mmHg)** *-supine* | 86.2 | *11.3* | 80.4 | *14.8* | *0.333* | 82.9 | *11.5* | *0.262* | 83.9 | *11.5* | *0.782* | *0.674* |
| **Baseline HR (bpm)** *-supine* | 76.8 | *10.6* | 72.4 | *10.4* | *0.347* | 74.9 | *9.1* | *0.981* | 76.5 | *10.9* | *0.701* | *0.802* |
| **Capillary Blood Glucose (mmol/l)** | 6.7 | *2.4* | 7.0 | *2.3* | *0.611* | 7.4 | *2.9* | *0.066* | 7.1 | *3.1* | *0.991* | *0.304* |
| **Orthostatic Grading Scale** | 1.0 | *0.8* | 4.6 | *2.0* | *<0.001* | 1.0 | *0.9* | *0.871* | 6.0 | *2.7* | *<0.001* | *<0.001* |
| **Autonomic Function Score** | 2.2 | *1.5* | 2.9 | *1.9* | *0.271* | 3.0 | *2.0* | *0.226* | 4.8 | *1.9* | *<0.001* | *<0.001* |
| **Change in SBP at 1 minute of standing (mmHg)** | 7.5 | *13.3* | 0.9 | *15.2* | *0.127* | -16.5 | *13.8* | *<0.001* | -26.5 | *26.5* | *<0.001* | *<0.001* |
| **Change in DBP at 1 minute of standing (mmHg)** | 11.1 | *13.0* | 7.9 | *13.1* | *0.394* | -11.5 | *9.5* | *<0.001* | -14.0 | *19.3* | *<0.001* | *<0.001* |
| **Change in HR at 1 minute of standing (bpm)** | 8.3 | *11.7* | 19.0 | *16.9* | *0.034* | 11.3 | *8.3* | *0.423* | 14.6 | *11.1* | *0.103* | *0.097* |
| **Change in SBP at 3 minutes of standing (mmHg)** | 3.7 | *12.6* | 4.3 | *13.3* | *0.859* | -12.1 | *19.4* | *0.002* | -23.1 | *20.2* | *<0.001* | *<0.001* |
| **Change in DBP at 3 minutes of standing (mmHg)** | 5.0 | *8.3* | 10.3 | *15.3* | *0.353* | -10.3 | *12.8* | *<0.001* | -16.0 | *13.7* | *<0.001* | *<0.001* |
| **Change in HR at 3 minutes (bpm)** | 6.8 | *10.0* | 10.7 | *9.9* | *0.445* | 7.4 | *8.1* | *0.741* | 7.2 | *18.5* | *0.856* | *0.803* |

**Table 14 Baseline Characteristics of OH participants (Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| Participant Characteristic | | Asymptomatic No OH (24) | | Symptomatic No OH (18) | | Asymptomatic OH (20) | | Symptomatic OH (23) | | Difference between groups | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *No. participants* | *%* | *No. participants* | *%* | *No. participants* | *%* | *No. participants* | *%* | *Test statistic* | *p-value* |
| **Sex** | *Female* | 13 | *54.2* | 9 | 50 | 8 | *40* | 8 | *34.8* | 2.168 | *0.549** |
| | *Male* | 11 | *45.8* | 9 | 50 | 12 | *60* | 15 | *65.2* | | |
| **Smoker** | *Yes* | 1 | *4.2* | 2 | 11.1 | 0 | *0* | 0 | *0* | 4.648 | *0.574#* |
| | *No* | 19 | *79.2* | 12 | 66.7 | 17 | *85* | 17 | *73.9* | | |
| | *Ex* | 4 | *16.7* | 4 | 22.2 | 3 | *15* | 6 | *26.1* | | |
| **Blackout** | *Yes* | 7 | *29.2* | 9 | 50 | 8 | *40* | 9 | *39.1* | 5.467 | *0.428#* |
| | *Pre-syncope* | 0 | *0* | 1 | 5.6 | 0 | *0* | 2 | *8.7* | | |
| | *No* | 17 | *70.8* | 8 | 44.4 | 12 | *60* | 12 | *52.2* | | |
| **Hypertension** | | 6 | *25* | 8 | 9 | 50 | 8 | *40* | *21.7* | 4.814 | *0.192** |
| **Diabetes Mellitus** | | 1 | *4.2* | 3 | 1 | 5.6 | 3 | *15* | *13* | 2.137 | *0.546#* |
| **Diuretics** | | 3 | *12.5* | 2 | 5 | 27.8 | 2 | *10* | *13* | 2.054 | *0.583#* |
| *Furosemide* | | *0* | *0* | *0* | 1 | 5.6 | *0* | *0* | *13.0* | *4.346* | *0.107#* |
| *Thiazide* | | *2* | *8.3* | *2* | 5 | 27.8 | *2* | *10* | *4.3* | *4.951* | *0.159#* |
| **ACEI or ARB** | | 2 | *8.3* | 5 | 7 | 38.9 | 5 | *25* | *8.7* | 7.832 | *0.043#* |
| *ACEI* | | *1* | *8.3* | *5* | 4 | 22.2 | *5* | *25* | *8.7* | *5.307* | *0.146#* |
| *ARB* | | *1* | *4.2* | *0* | 3 | 16.7 | *0* | *0* | *0* | *5.320* | *0.041#* |
| **Alpha Blocker** | | 1 | *4.2* | 4 | 1 | 5.6 | 4 | *20.0* | *8.7* | 3.135 | *0.375#* |
| **Tricyclic Antidepressant** | | 1 | *4.2* | 1 | 0 | 0 | 1 | *5* | *4.3* | 1.252 | *1.000#* |
| **Any BP lowering drugs** | | 7 | *29.2* | 11 | 9 | 50 | 11 | *55* | *26.1* | 5.663 | *0.130** |
| **Symptoms on HUT** | | 5 | *20.8* | 9 | 4 | 22.2 | 9 | *45* | *43.5* | 5.002 | *0.174** |

**Table 15 Categorical characteristics of OH study participants (Key: *Pearson Chi-Square, # Fisher's Exact Test)**

| | **Asymptomatic No OH (24)** | | **Symptomatic No OH (18)** | | **T-test** (p-value) | **Asymptomatic OH (20)** | | **T-test** (p-value) | **Symptomatic OH (23)** | | **T-test** (p-value) | **ANOVA** (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean BRS (ms/mmHg)** | ***SD*** | **Mean BRS (ms/mmHg)** | ***SD*** | | **Mean BRS (ms/mmHg)** | ***SD*** | | **Mean BRS (ms/mmHg)** | ***SD*** | | |
| **Low Frequency Band** (0.05-0.15Hz) | 8.6 | *5.2* | 8.1 | *6.7* | 0.268 | 10.5 | *5.5* | 0.262 | 7.7 | *5.6* | 0.337 | 0.559 |

**Table 16 Baseline Cardiac BRS – OH study (T-test to compare each group with the Control, i.e. Asymptomatic No OH; ANOVA to examine for variances across groups)**



| **Participant Characteristic** | **Asymptomatic No OH (24)** | | **Symptomatic No OH (18)** | | **T-test** (p-value) | **Asymptomatic OH (20)** | | **T-test** (p-value) | **Symptomatic OH (23)** | | **T-test** (p-value) | **ANOVA** (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Mean Augmentation Index (%)** | 9.6 | *16.0* | 20.2 | *19.9* | *0.029* | 10.7 | *12.5* | *0.509* | 7.8 | *15.3* | *0.695* | *0.085* |
| **Mean HR with Augmentation Index (bpm)** | 78.8 | *15.8* | 74.1 | *8.1* | *0.056* | 83.9 | *15.5* | *0.579* | 81.4 | *14.0* | *0.555* | *0.253* |
| **Mean Augmentation Index (%, @75bpm)** | 9.7 | *16.3* | 20.0 | *19.3* | *0.032* | 10.8 | *12.5* | *0.528* | 8.1 | *15.5* | *0.720* | *0.099* |
| **Mean Pulse Wave Velocity (ms-1)** | 10.1 | *2.5* | 9.7 | *3.1* | *0.530* | 9.8 | *2.4* | *0.406* | 9.2 | *2.2* | *0.205* | *0.682* |

**Table 17 Arterial Stiffness – OH study (T-test to compare each group with the Control, i.e. Asymptomatic No OH; ANOVA to examine for variances across groups)**

## 8.5 Baseline Supine Cerebral Haemodynamic Measurements

### 8.5.1 Supine Measurements

Baseline TCD measurements were taken in the supine position after 10 minutes rest and when haemodynamic values varied by <10%, and are shown in Table 18. Left and Right CBF velocities of the respective MCA's were similar across the groups ($p>0.05$). In the Symptomatic No OH group (Table 18), the mean CBFV on the right side was significantly lower compared to Controls, ($p=0.036$), and corresponded to a lower diastolic CBFV ($p=0.002$).

Comparing Left and Right mean CBFVs, values were similar between groups but there were statistical differences between sides in the symptomatic OH group (n=22), with the left mean CBFV being higher (Wilcoxon signed ranks, $p=0.01$), but not the other groups (asymptomatic no OH (n=16), $p=0.98$; asymptomatic OH (n=19), $p=0.18$; symptomatic no OH (n=17), $p=0.79$). As there were some differences between left and right hemispheres, data was reported for left and right sides separately in addition to the mean of both sides (where data are missing for left or right, then it is that side the recording was performed on that is used).

### 8.5.2 Estimates of supine Dynamic Cerebral Auto-regulation (Tiecks model)

Baseline measurements did not show any significant differences between groups in terms of dCA taken as the ARI and its associated parameters, data are presented for the mean of both MCAs (Table 19). For the right and left MCAs individually, please see

Appendix Table 37and Table 38 respectively. From Table 19, it can be seen that the mean ARI of the combined right and left MCAs were similar across groups.

In addition to the data presented in the tables, the Wilcoxon Signed Rank Test for related samples, did not show any significant differences between values for the left and right MCA in the Asymptomatic OH, Asymptomatic No OH or the Symptomatic No OH groups ($p>0.05$). Furthermore there was no significant difference between the left and right MCAs in the groups for coherence or phase in the low frequency band ($p>0.05$). This is despite the slight differences in diastolic CBFV, demonstrating that dCA is a complex relationship between BP and CBF.

### 8.5.3 Baseline ARI and ARMA ARI estimates of Dynamic Cerebral Auto-regulation

To further assess if differences in baseline dynamic cerebral auto-regulation (dCA) in the 4 groups existed, data were also analysed using two different methodologies Tiecks model (Tiecks et al., 1995) and by auto-regressive moving average (ARMA) (Panerai et al., 2008) using spontaneous fluctuations in BP and CBFV for both left and right MCA, and the mean of both MCAs (Table 20). Results for all methods showed no significant between group differences in dCA during supine rest. This is consistent with the fact that those with symptoms are asymptomatic in the supine position and therefore not a surprising finding.

| | **Asymptomatic No OH** *(n=23, Right MCA only=5, Left only=2)* | | **Symptomatic No OH** *(n=18, Right only =1)* | | **Mann Whitney U Test or T-Test*** *(p-value)* | **Asymptomatic OH** *(n=20, Right MCA only=1)* | | **Mann Whitney U Test or T-Test*** *(p-value)* | **Symptomatic OH** *(n=23, Right only=1)* | | **Mann Whitney U Test or T-Test*** *(p-value)* | **Kruskal Wallis Test or ANOVA*** *(p-values)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV[1] Right (cm/s)** | 44.5 | *11.0* | 38.3 | *8.0* | *0.834* | 47.1 | *12.6* | *0.284* | 46.1 | *14.1* | *0.036* | 0.047 |
| **CBFV[1] Left (cm/s)** | 44.3 | *12.2* | 43.9 | *10.2* | *0.875* | 42.5 | *13.9* | *0.942* | 47.4 | *16.5* | *0.991* | 0.990 |
| **Mean CBFV[2] (cm/s)** | 41.6 | *8.2* | 44.0 | *9.8* | *0.875* | 46.7 | *13.4* | *0.827* | 44.6 | *12.1* | *0.267* | 0.693 |
| **Systolic CBFV Right (cm/s)** | 62.8 | *18.9* | 58.5 | *13.8* | *0.431* | 69.8 | *19.3* | *0.181* | 69.0 | *20.4* | *0.258* | 0.160 |
| **Systolic CBFV Left (cm/s)** | 63.5 | *17.0* | 66.5 | *15.9* | *0.386* | 65.4 | *18.0* | *0.527* | 70.5 | *23.2* | *0.531* | 0.923 |
| **Mean systolic CBFV (cm/s)** | 62.2 | *13.1* | 63.5 | *14.3* | *0.495* | 69.7 | *18.9* | *0.342* | 67.5 | *18.0* | *0.668* | 0.470 |
| **Diastolic CBFV Right (cm/s)** | 28.2 | *8.8* | 24.0 | *4.3* | *0.753* | 30.5 | *7.8* | *0.626* | 29.9 | *9.2* | *0.002* | 0.009 |
| **Diastolic CBFV Left (cm/s)** | 30.1 | *8.7* | 27.6 | *5.8* | *0.854* | 27.1 | *10.6* | *0.559* | 31.1 | *11.6* | *0.386* | 0.797 |
| **Mean diastolic CBFV (cm/s)** | 25.4 | *4.6* | 29.7 | *6.9* | *0.765** | 30.4 | *9.2* | *0.581** | 28.7 | *8.0* | *0.055** | 0.161* |
| **SBP (mmHg)** | 129.2 | *26.0* | 141.1 | *22.4* | *0.252** | 137.6 | *19.8* | *0.854** | 141.0 | *26.1* | *0.780** | 0.534* |
| **DBP (mmHg)** | 73.8 | *15.8* | 74.9 | *13.5* | *0.078* | 71.4 | *10.0* | *0.592* | 67.0 | *12.3* | *0.717* | 0.205 |
| **MAP (mmHg)** | 91.0 | *13.8* | 97.1 | *14.8* | *0.581* | 93.8 | *13.0* | *0.697* | 90.8 | *16.2* | *0.267* | 0.425 |
| **Heart Rate (bpm)** | 63.7 | *8.8* | 67.2 | *11.8* | *0.546* | 65.3 | *10.0* | *0.355* | 61.6 | *9.3* | *0.199* | 0.319 |
| **tCO2 (mmHg)** | 96.4 | *63.7* | 98.9 | *67.5* | *0.331* | 135.7 | *20.4* | *0.103* | 118.2 | *59.0* | *0.767* | 0.330 |

**Table 18 Baseline Transcranial Doppler Measurements in OH participants (Key: CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| *Mean of Right and Left sides* | **Asymptomatic No OH (24)** | | **Symptomatic No OH (18)** | | **Mann Whitney U Test** *(p-value)* | **Asymptomatic OH (20)** | | **Mann Whitney U Test** *(p-value)* | **Symptomatic OH (23)** | | **Mann Whitney U Test** *(p-value)* | **Kuskall Wallis Test** *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **ARI** | 4.5 | *1.0* | 4.8 | *1.5* | 0.467 | 4.7 | *1.3* | 0.646 | 4.8 | *1.6* | 0.571 | 0.887 |
| **Coherence Low Frequency** (<0.07Hz) | 0.41 | *0.14* | 0.41 | *0.13* | 0.931 | 0.38 | *0.16* | 0.606 | 0.36 | *0.15* | 0.285 | 0.702 |
| **Gain Low Frequency** (<0.07Hz) | 0.41 | *0.18* | 0.43 | *0.17* | 0.908 | 0.42 | *0.18* | 0.989 | 0.31 | *0.08* | 0.051 | 0.089 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.44 | *0.26* | 0.64 | *0.32* | 0.009 | 0.46 | *0.32* | 0.770 | 0.56 | *0.37* | 0.285 | 0.107 |
| **Step Response Recovery (%)** | 66.5 | *20.0* | 74.0 | *33.8* | 0.416 | 67.9 | *17.7* | 0.606 | 67.1 | *24.3* | 0.772 | 0.920 |



**Table 19 Baseline ARI (Tiecks model) Mean of Right and Left Middle Cerebral Artery (Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| | Asymptomatic No OH (24) | | Symptomatic No OH (18) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (20) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test (p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **ARI Right** | 5.0 | *3.0* | 6.0 | *2.6* | 0.198 | 5.2 | *2.9* | 0.751 | 6.2 | *2.6* | 0.173 | 0.441 |
| **ARI Left** | 5.0 | *2.7* | 5.6 | *2.5* | 0.588 | 4.3 | *3.6* | 0.478 | 5.7 | *3.0* | 0.371 | 0.519 |
| **Mean ARI (Left and Right)** | 5.0 | *2.4* | 5.9 | *2.1* | 0.248 | 4.8 | *2.5* | 0.733 | 5.9 | *2.2* | 0.125 | 0.309 |
| **ARMA ARI Right** | 5.3 | *2.0* | 4.9 | *1.8* | 0.189 | 4.5 | *2.1* | 0.137 | 4.9 | *2.5* | 0.928 | 0.411 |
| **ARMA ARI Left** | 4.6 | *2.4* | 5.0 | *2.2* | 0.874 | 4.5 | *1.9* | 0.718 | 4.9 | *2.3* | 0.687 | 0.839 |
| **Mean ARMA ARI** | 5.0 | *1.9* | 4.9 | *1.7* | 0.694 | 4.5 | *1.7* | 0.318 | 4.9 | *2.0* | 0.910 | 0.741 |

**Table 20 Baseline ARMA estimates of ARI**

## 8.6 Orthostatic Hypotension Study – Summary of Baseline Data Results

In terms of the main outcomes for the study, cardiac BRS was similar in all groups (Table 16). The mean AIx (p=0.029) and the mean AIx corrected for HR@75bpm (p=0.032) were higher in the symptomatic No OH group than the control group (Table 17). However the PWV was similar across all groups (Table 17). There were no significant differences between groups in supine dCA for either Tiecks model or ARMA methodology (Table 20).

However it should be noted that the symptomatic OH group was significantly older than the control group, and had a significantly higher baseline supine SBP, as did the symptomatic No OH group, compared to the Controls (Table 14). More participants in the symptomatic No OH group and the asymptomatic OH group were on ACEi or AIIRBs than the control group (Table 15). The baseline right MCA diastolic CBFV (Table 18) was statistically significantly lower in the Symptomatic No OH group compared to the control group (Asymptomatic No OH), although the combined mean of the right and left CBFV was not different across the groups.

# 9 Orthostatic Hypotension Study – Discussion of Baseline Data

At baseline, cardiac BRS, PWV and dCA were similar across the groups with other small differences noted.

Participants over the age of 60 years were recruited to the study, and included healthy volunteers as well as participants using hospital or GP services in the community. Therefore it was not surprising that older participants were found in the Symptomatic OH group compared to the Asymptomatic No OH (control) group. The association of hypertension with OH (Applegate et al., 1991a, Mader et al., 1987), makes it unsurprising that the Symptomatic OH group had a higher supine baseline SBP than the control group. However it was found that the Asymptomatic OH group had a similar baseline SBP to the control group. Therefore there may be a suggestion that a higher supine SBP is associated with the symptoms of OH, regardless of whether there is a postural drop in systemic BP (Poon and Braun, 2005). Of course, it should be remembered that not everyone with postural falls in BP have symptoms (Mader et al., 1987).

As the Orthostatic Grading Scale and postural changes in BP were used to classify participants into their respective groups, it is interesting to note that the autonomic function score was significantly lower in the Symptomatic OH group, suggesting a degree of autonomic cardiovascular dysfunction in this group as might be expected.

However cardiac BRS values were similar in all 4 groups suggesting parasympathetic cardiac control, one part of the autonomic nervous system, was not impaired and perhaps not responsible for the postural BP fall of production of postural symptoms. The presence of some differences in those taking ACEi and AIIRBs (greater in the Asymptomatic OH and Symptomatic No OH groups) may of course be a confounding factor. For the clinician this is perhaps a useful vignette. It is well documented that both age and increasing BP are associated with impaired cardiac BRS, and thus could common to both hypertension and OH (James and Potter, 1999, Takeshita et al., 1975, Moreira et al., 1992). Abnormal cardiac BRS has also been found in those with orthostatic intolerance without OH (i.e. symptoms and increase in HR>30bpm within 10 minutes of standing) (Farquhar et al., 2000). Thus it would not be unreasonable to expect the older group of Symptomatic OH to have impaired cardiac BRS, however like the other two groups they had a similar cardiac BRS to the control.

With a higher baseline supine SBP, perhaps as an indicator of arterial stiffness, it might be expected to find a higher augmentation index and/or PWV in the Symptomatic No OH and the Symptomatic OH groups. However although the Symptomatic No OH group had a significantly higher mean AIx than the control, this was not true for the Symptomatic OH group. It may be that the sample size was not large enough, or perhaps other factors than arterial stiffness accounts for the reason why Symptomatic No OH differs to "normal", but the Symptomatic OH does not differ from the "normal" in terms of arterial stiffness. The proportion of those with hypertension was similar in all groups. It also follows on from this that drug treatment for hypertension may also have a positive effect on arterial stiffness (Boutouyrie et al., 2011). However whilst other studies have suggested that higher PWV values (Mattace-Raso et al., 2006) or AIx

(Valbusa et al., 2012) may be found amongst those with OH, the latter study did not find a significantly higher PWV amongst those with OH (Valbusa et al., 2012). The differences in whether or not PWV or AIx may be higher (or not) in those with OH, may be partly attributable to the fact that AIx whilst using pulse wave reflections is an indirect surrogate measure. Of course PWV itself has its own fallacies, and relies on accurate estimation of the distance between two points. However the PWV values found in this study are not dissimilar to other studies for this age group (Mattace-Raso et al., 2006, Valbusa et al., 2012, 2010).

It may be that the lack of the expected increase in arterial stiffness associated with a higher supine SBP can also be reflected by the higher supine combined mean of systolic and diastolic CBFV (right MCA) found in the Symptomatic OH group compared to the control. This was also associated with a significantly higher right diastolic CBFV in this group compared to the control group. Furthermore in the supine position, there was a difference in CBFV between right and left MCAs only in the Symptomatic OH group, being higher in the left MCA. The clinical significance of this is difference is unclear and although a history of stroke was amongst the exclusion criteria for the study, given the age group of the participants. It is possible that these differences in CBFV may be related to asymptomatic cerebrovascular arterial disease leading to a degree of stenosis (though this might have been expected to increase rather than decrease CBFV unless a critical stenosis was present) of either the internal carotid artery or its intracranial arterial branches (no visualisation of the cerebral arterial system was undertaken prior to the study).

In the supine position at baseline, the ARI values (Tiecks and ARMA-ARI) were similar in all groups, suggesting that despite the differences in supine SBP and CBFV between the Symptomatic OH group and the control group, in the supine position at least, the cerebral auto-regulation system is able to maintain adequate control associated with the absence of any postural symptoms. Other work which supports this has shown that neither static nor dynamic ARI are affected by hypertension or age (Eames et al., 2003).

# 10 Orthostatic Hypotension Study – Effects of Head-Up-Tilt

## 10.1 Cerebral Blood Flow Velocities and Blood Pressure

The effects of HUT on the four groups were assessed in two ways: 1) by comparing actual mean values, and 2) by examining the changes from baseline between groups.

As previously described in the General Methods, the effects of HUT can be divided into the "UP" and "DOWN" periods, where "UP" relates to the beginning of HUT, and "DOWN" relates to the end of HUT. The "UP" component includes the pre-HUT phase, the initial few minutes of HUT and "DOWN" component includes the end of HUT signalled by the end of 30 minutes where participants were asymptomatic, or a shorter time period where participants became symptomatic.

### 10.1.1 Group Measurements

The duration of HUT for each group was: Asymptomatic No OH 27.4±4.6 minutes, Symptomatic No OH 25.2±8.7 minutes, Asymptomatic OH 22.1±9.2 minutes, Symptomatic OH 24.4±8.6minutes. There was no statistical difference between the latter three groups compared to the Asymptomatic No OH group in tilt duration ($p>0.05$). The number of participants in each group who had HUT terminated early due to symptoms were five of 24 in the Asymptomatic No OH, four of 18 in the

Asymptomatic OH, nine of 20 in the Symptomatic No OH and ten of 23 in the Symptomatic OH groups respectively (Chi Square, p=0.17).

TCD data of high quality suitable for analysis were not obtained in all subjects for sub-group analysis, resulting in different numbers in each group from baseline numbers.

The values for CBFV, BP and HR prior to HUT were obtained at 1 minute and 3 minutes following HUT, and for the minute prior to the end of HUT (as determined by the onset of symptoms, or the end of the 30 minutes of HUT which ever occurred sooner) are shown in the Appendix Table 39, Table 40, Table 41, and Table 42, respectively. Friedman's Two Way analysis of variance across all time points for each variable was significant in all groups ($p<0.001$).

### 10.1.2 Blood Pressure and Heart Rate with HUT

There were no significant differences across the groups or in any group compared to the control group, in BP and HR prior to HUT, at 1 minute or 3 minutes of HUT, or prior to end of HUT (see Appendix Table 39, Table 40, Table 41 and Table 42). The effect of HUT on SBP, DBP, MAP and HR can be seen in Figure 34, Figure 35, Figure 36 and Figure 37 respectively.

With HUT, a brief fall in BP associated with a small rise in HR is expected. In OH, one would expect a significant fall of ≥20mmHg in SBP and/or ≥10mmHg in DBP. When this fall in BP occurs will depend on the classification of OH.

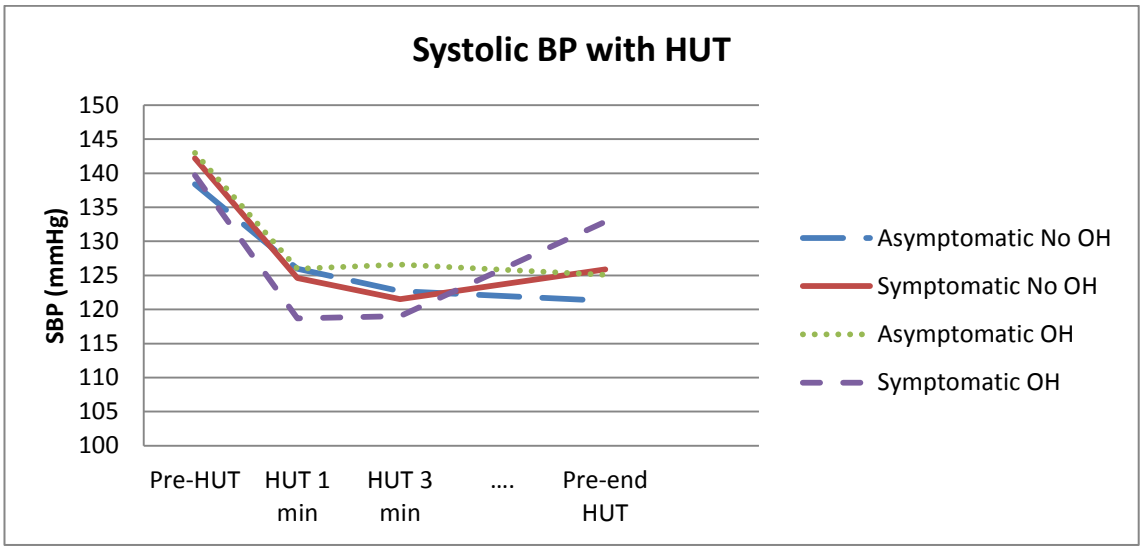



**Figure 34 The effect of HUT on SBP** ***(…. = varying time scale)***

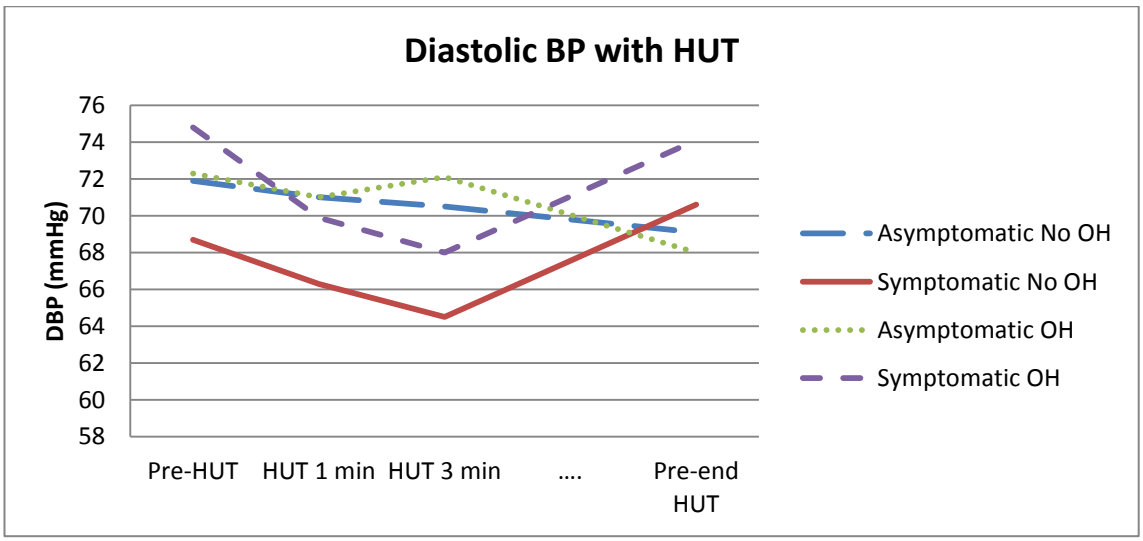



**Figure 35 The effect of HUT on DBP** ***(…. = varying time scale)***

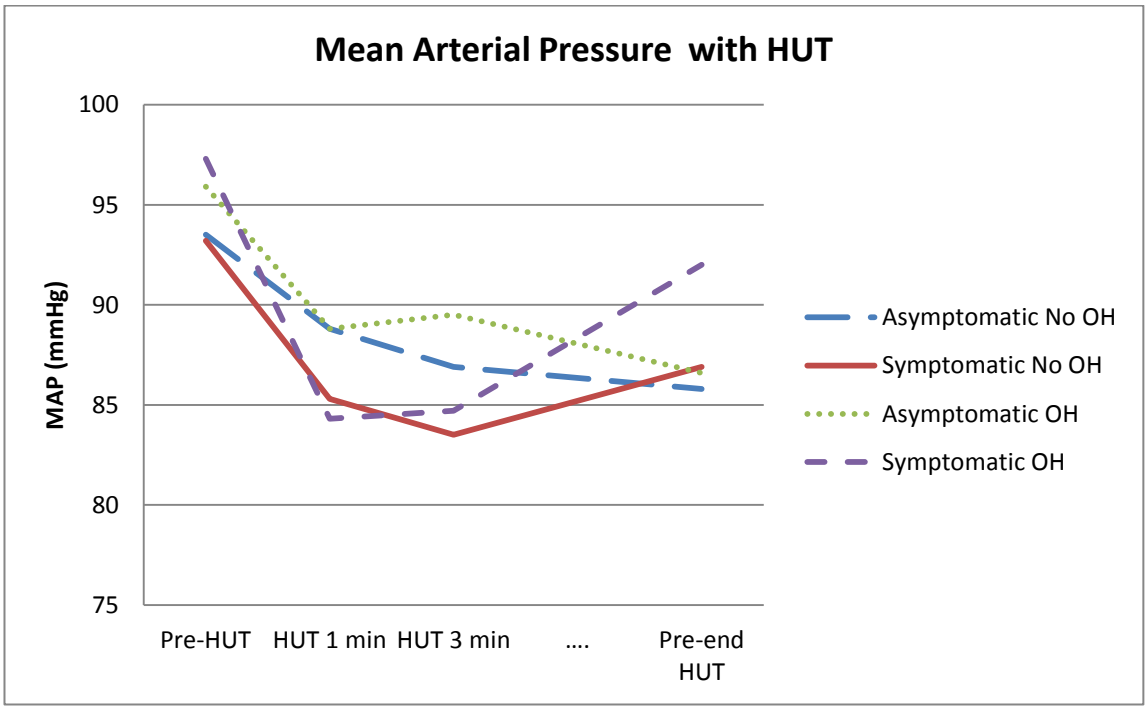



**Figure 36 The effect of MAP with HUT** ***(…. = varying time scale)***

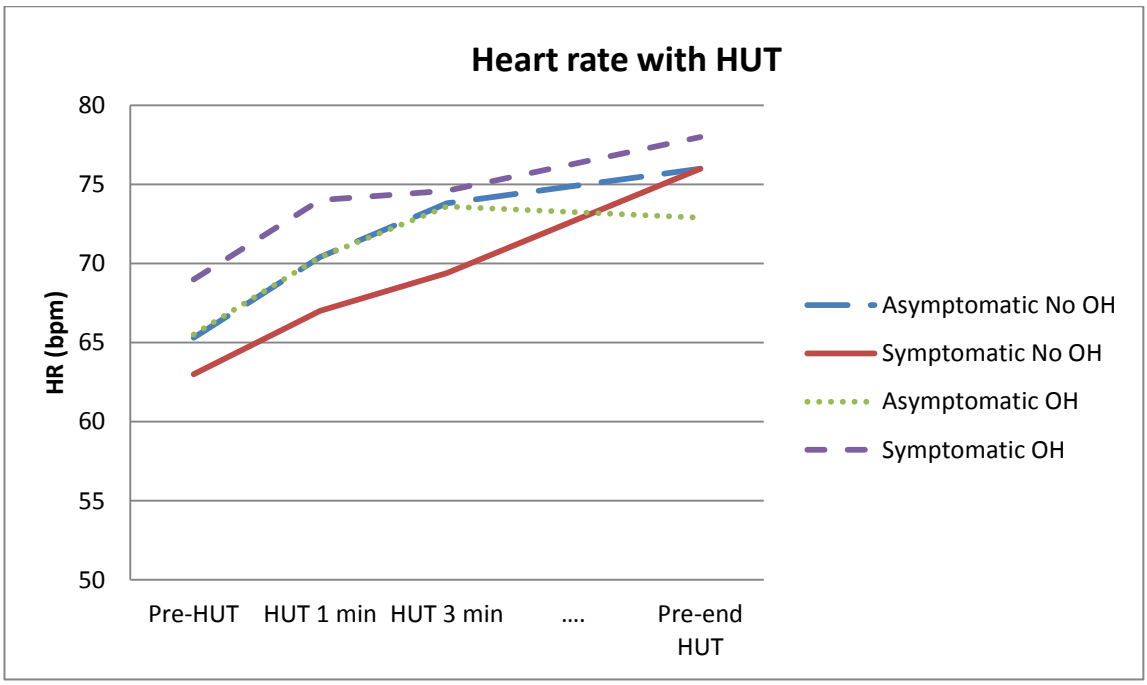



**Figure 37 The effect of HUT on HR** ***(…. = varying time scale)***

### 10.1.3 Cerebral Haemodynamic measurements with HUT

The effect of HUT on the mean CBFV (the average of left and right side of the mean of systolic and diastolic CBFV) and $tCO_2$ is illustrated in Figure 38 and Figure 39. CBFV and other parameters during HUT, at 1 minute or 3 minutes of HUT, or prior to end of HUT are shown (see Appendix Table 39, Table 40, Table 41 and Table 42).

Prior to tilt (see Appendix Table 39) the symptomatic OH group had a significantly lower right MCA CBFV (mean of systolic and diastolic CBFV) and right diastolic CBFV compared to the control group (37.4±6.4 cm/s vs. 45.3±12.1cm/s, p=0.038 and 23.0±3.8 cm/s vs. 29.8±7.9cm/s, p=0.001 respectively). One would not necessarily expect differences in CBFV between hemispheres to account for symptoms. The differences may be related to the diameter of the MCA. The mean diastolic CBFV was significantly lower (p=0.007) compared to the control group, 24.5±4.6cm/s vs.

29.9±7.1cm/s. $TCO_2$ was similar across the groups pre-HUT which is not necessarily unexpected.

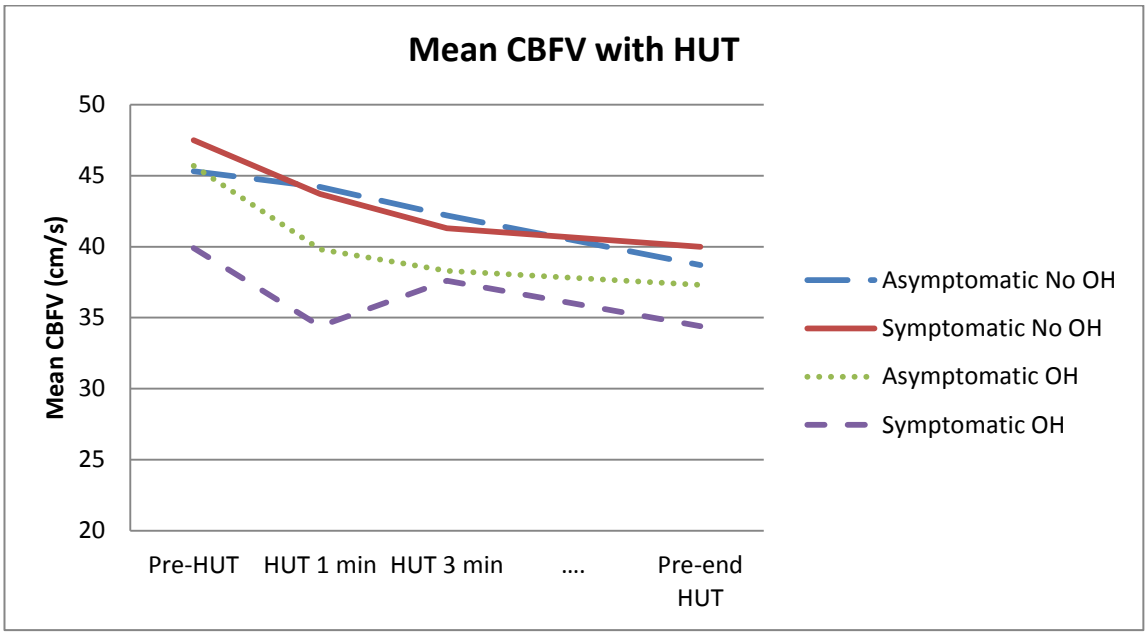



**Figure 38 The effect of HUT on mean CBFV**

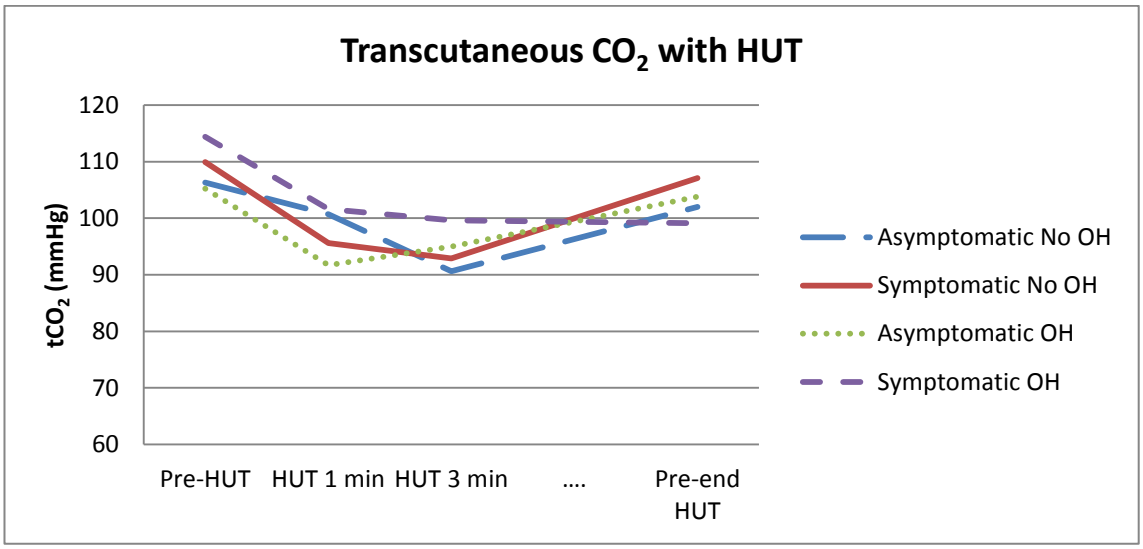



**Figure 39 The effect of HUT on $tCO_2$**

At 1 minute during HUT (see Appendix Table 40), the mean CBFV that is the average of the left and right sides (mean of systolic and diastolic CBFV) and also the mean of the left and right diastolic CBFV were significantly lower in the symptomatic OH group compared to the control ($p=0.006$ and $p<0.0001$ respectively). This may suggest a delay in dCA preventing the maintenance of CBFV to the supine levels. The fall in tCO2 in all groups during the first minute of HUT is consistent with a compensatory hyperventilation to promote relative vasoconstriction to improve blood flow.

At 3 minutes of HUT (Appendix Table 41), the mean of both left and right diastolic CBFV remained significantly different between groups, being lower in the symptomatic OH group compared to the control ($p=0.019$).

By the end of HUT, there were no differences in mean CBFV between groups but the mean (of left and right) diastolic CBFV ($p=0.004$) remained significantly lower in the symptomatic OH group (20.2±6.2cm/s) compared to the control group (25.9±8.3cm/s) (Appendix Table 42). It is unclear how this may fit in with the concept of symptoms and No OH, but may be relevant to symptomatic vs. asymptomatic OH. The changes in $tCO_2$ remained similar in all groups during HUT.

### 10.1.4 Group Changes during HUT

The differences between groups in the changes between measurements compared to pre-HUT were compared at 1 minute and 3 minutes following HUT and prior to the end of HUT, and are shown in Appendix Table 43, Table 44 and Table 45 respectively. They are further illustrates in Figure 40, Figure 41, Figure 42. The relationship between the various parameters are further illustrated by groups in Figure 46, Figure 47, Figure 48 and Figure 49.

#### *10.1.4.1 Changes in Blood Pressure and Heart Rate*

The Asymptomatic OH group demonstrated a statistically significant decrease in HR compared to the control group (-3.2±-4.4bpm vs. 2.6±-4.8bpm, p=0.001) after 1 minute of HUT (Appendix Table 43). There were no other significant changes noted at 1 minute. At 3 minutes of HUT (Appendix Table 44) there was a significant increase in SBP in the Asymptomatic OH group ($p<0.001$) but not the Symptomatic OH group which like the control group showed a fall in SBP. However by the end of HUT (Table 45), there was a significant fall in SBP (p=0.011) and MAP (p=0.018) in the Symptomatic OH group compared to the control group, which one would expect given the baseline classification on active standing. Graphs of the mean group changes in SBP, DBP and HR are shown in Figure 40, Figure 41 and Figure 42 respectively.

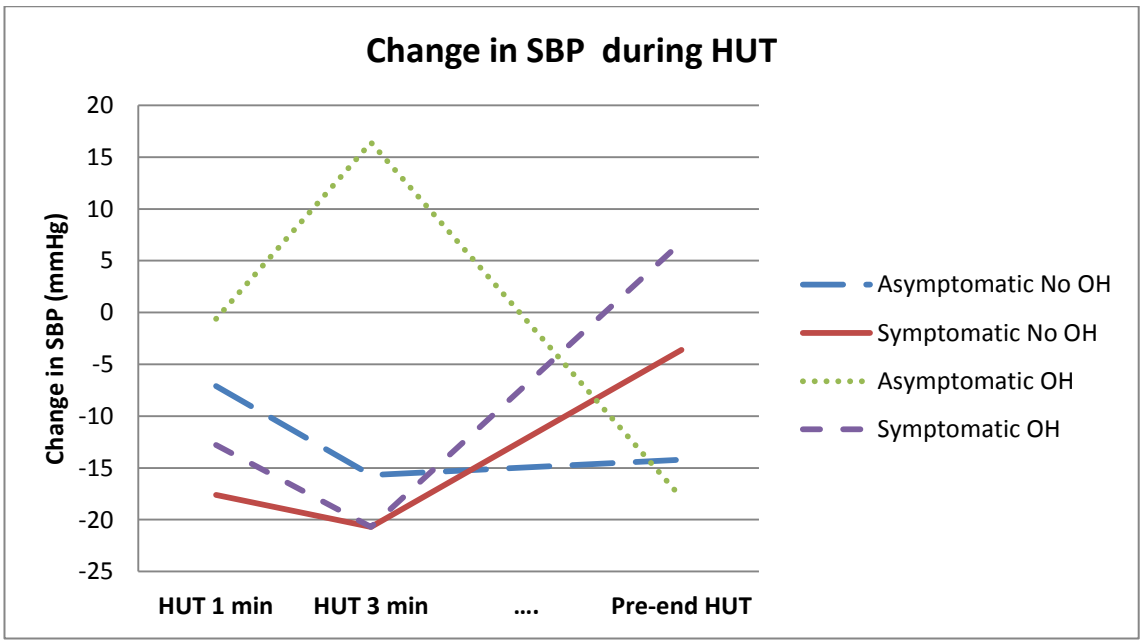



**Figure 40 The mean group change in SBP during HUT**

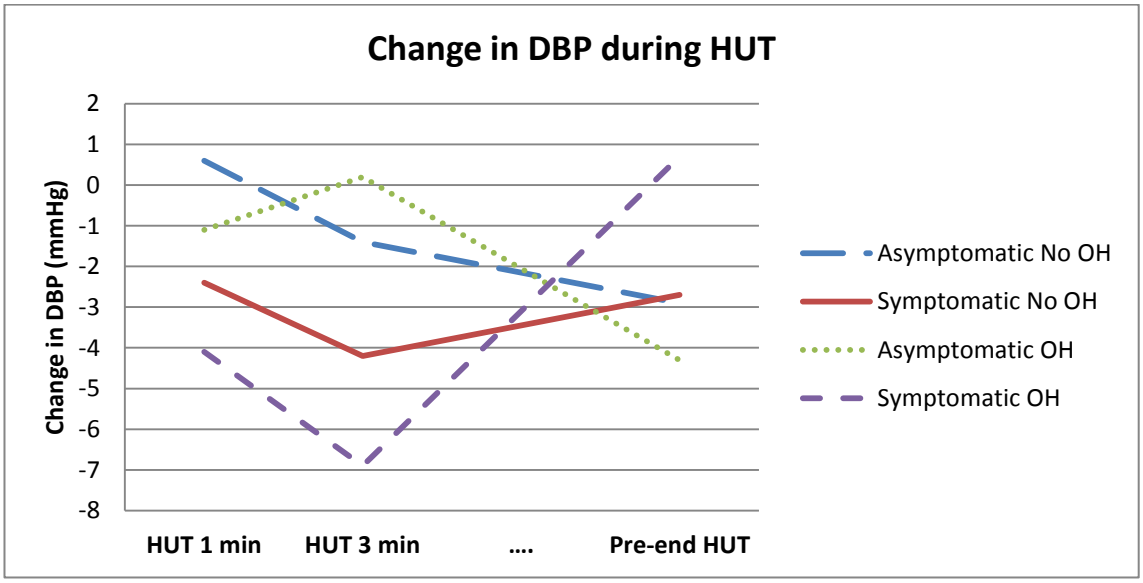



**Figure 41 The mean group change in DBP during HUT** ***(The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT)***

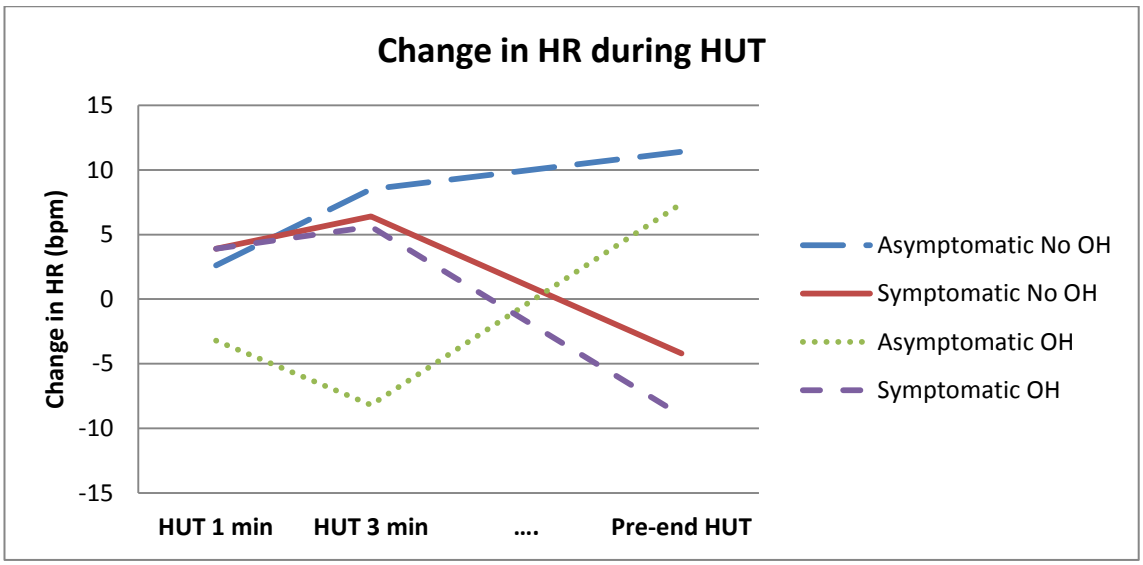



**Figure 42 The mean group change in HR during HUT** ***(The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT)***

### *10.1.4.2 Changes in Cerebral and Haemodynamic values during Tilt*

The mean change CBFV (combining left and right CBFV values) are shown in Figure 43, and the mean change in $tCO_2$ is illustrated in Figure 50. These figures illustrate an increase in the mean CBFV in the symptomatic group with a greater fall in $tCO_2$ than the two asymptomatic groups. This is associated with a return to baseline BP towards the end of HUT. This picture suggests CBFV improves with a fall in $tCO_2$. The asymptomatic groups had a persistent decline in BP at the end of HUT, associated with a persisting decline in mean CBFV and a return to baseline of $tCO_2$. Furthermore for the symptomatic groups, the CBFV seemed to mirror changes in BP, which may suggest by its direct relationship to each other, that dCA is dysfunctional. CBFV and other values are found in Appendix Table 43, Table 44 and Table 45. Change in systolic and diastolic CBFV are shown in Figure 44and Figure 45.

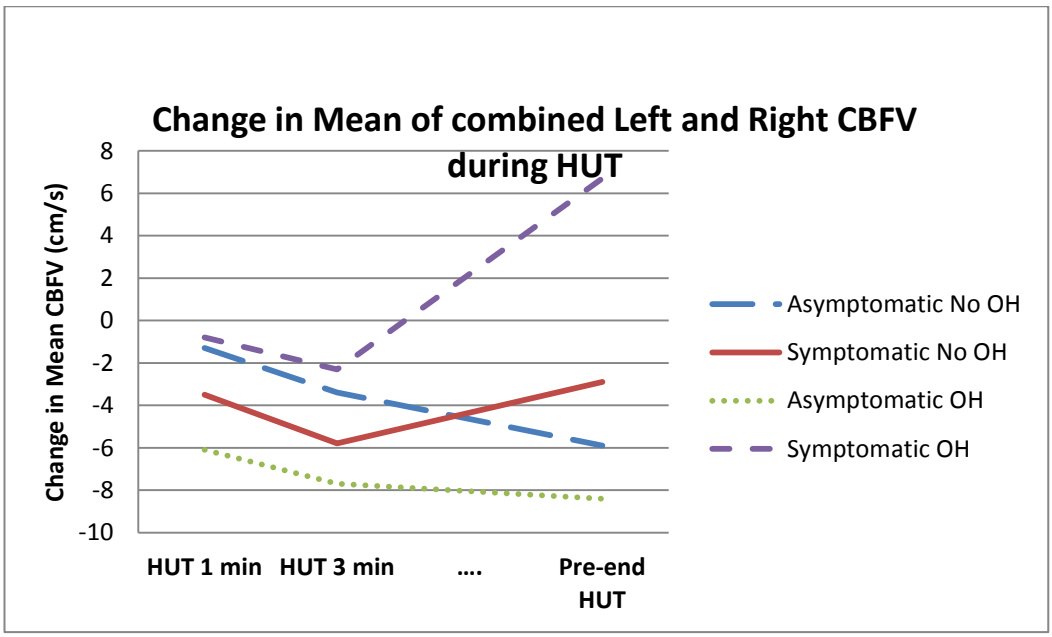



**Figure 43 The mean group change in CBFV (combined mean of left and right CBFV) during HUT** ***(The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT)***

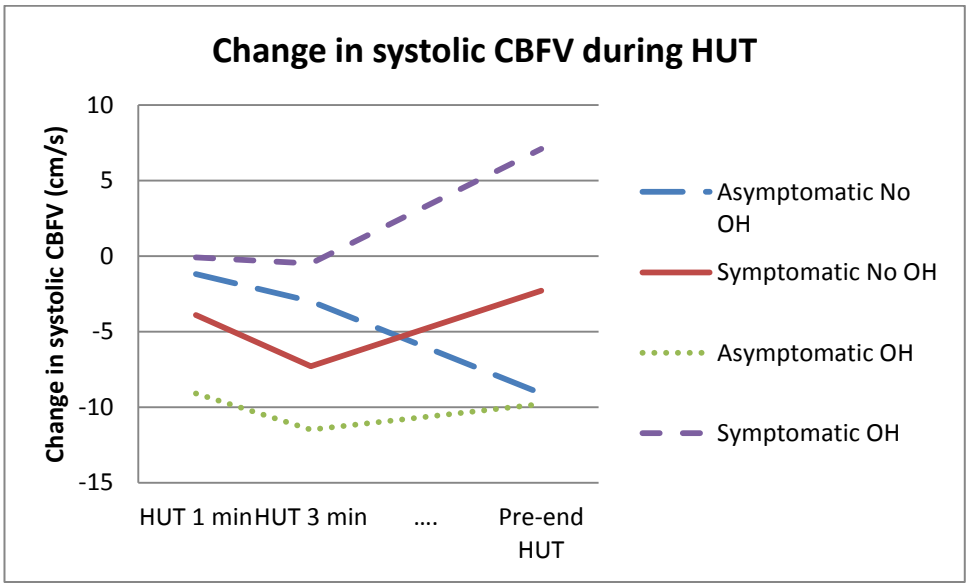



**Figure 44 The mean group change in systolic CBFV (combined mean of left and right CBFV) during HUT (*The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT*)**

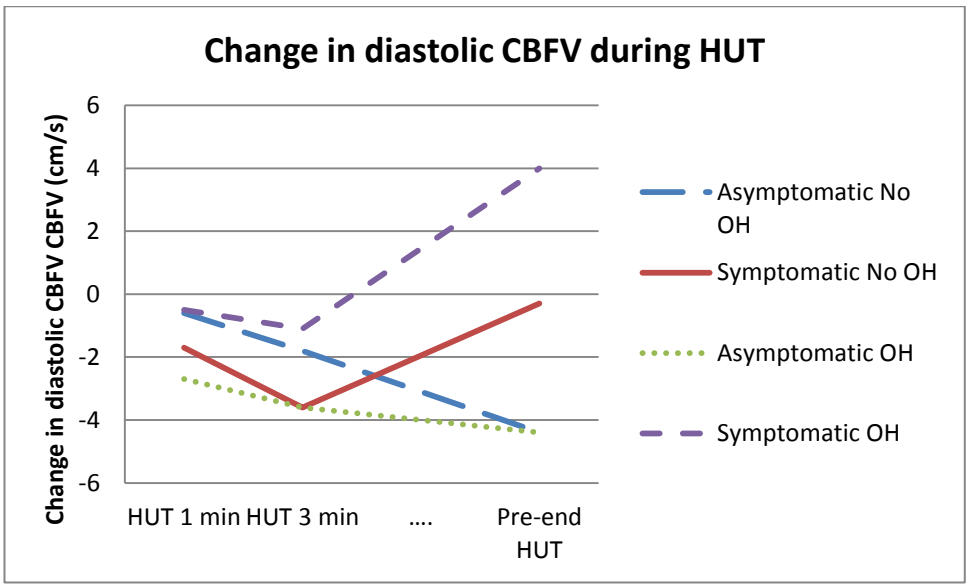



**Figure 45 The mean group change in diastolic CBFV (combined mean of left and right CBFV) during HUT** ***(The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT)***

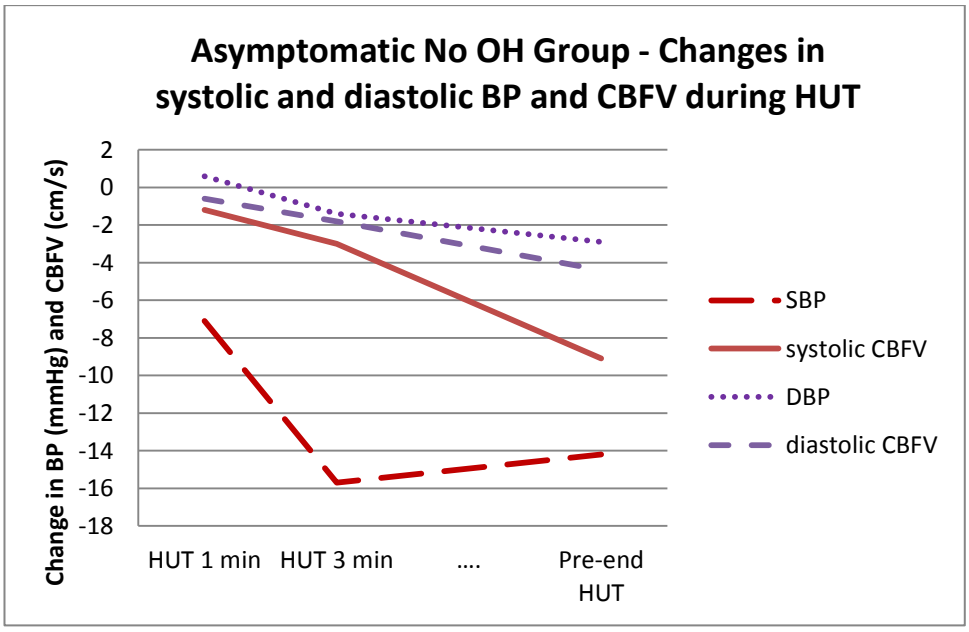



**Figure 46 Changes in BP and CBFV during HUT - Asymptomatic No OH (control) group**

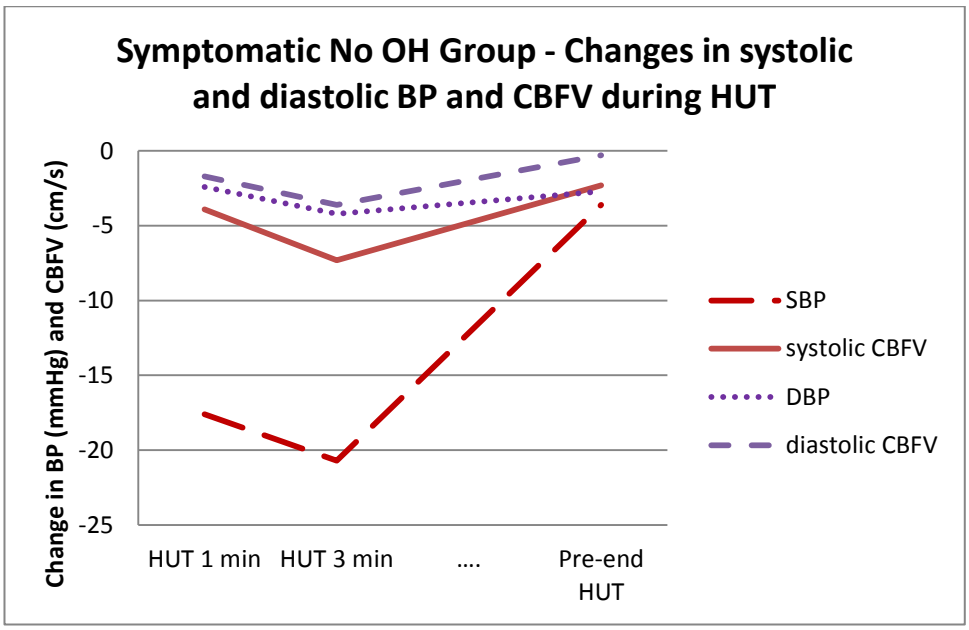



**Figure 47 Changes in BP and CBFV during HUT - Symptomatic No OH group**

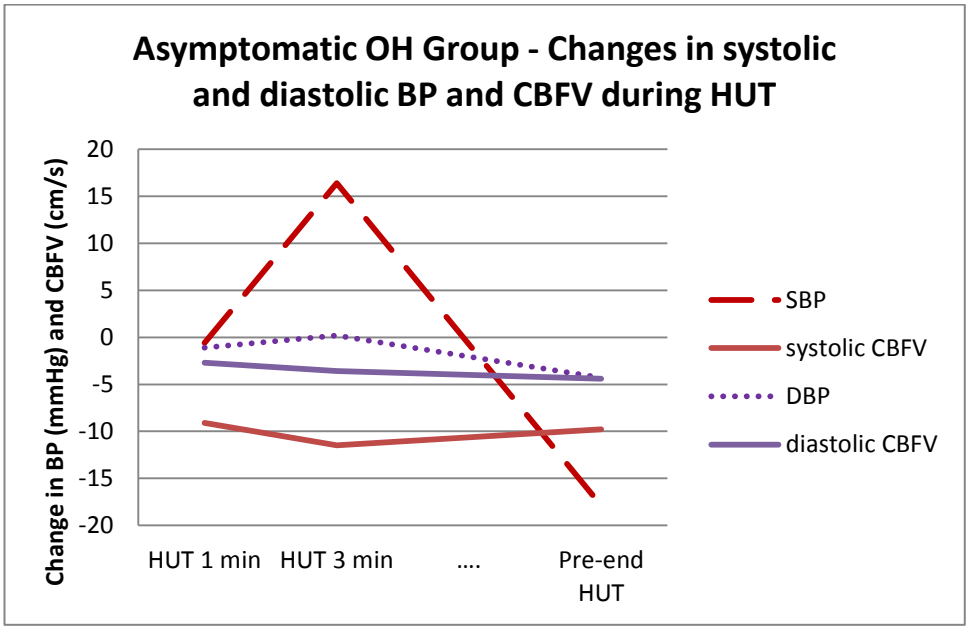



**Figure 48 Changes in BP and CBFV during HUT - Asymptomatic OH group**

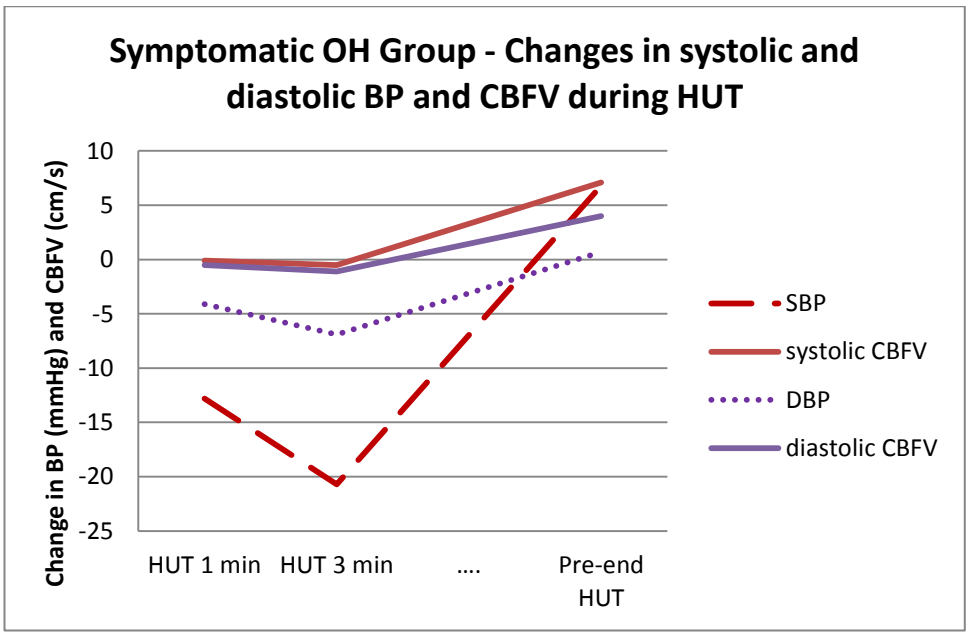



**Figure 49 Changes in BP and CBFV during HUT - Symptomatic OH group**

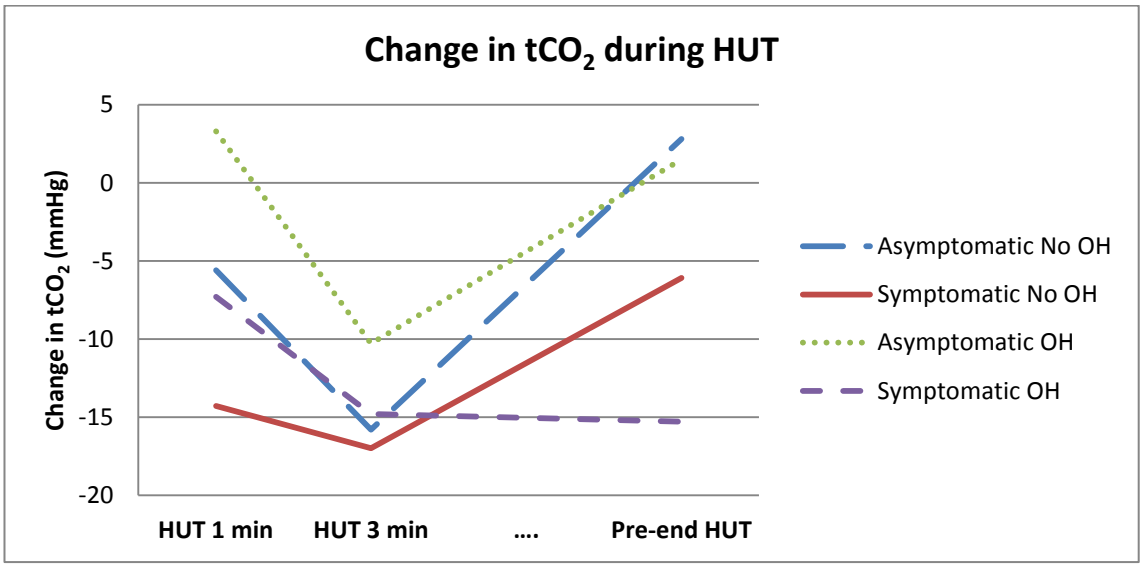



**Figure 50 The mean group change in $tCO_2$ during HUT** ***(The change from pre-HUT to HUT at 1 and 3 minutes, and in the minute prior to the end of HUT)***

At 1 minute of HUT the reduction in mean values of the left and right MCAs combined CBFV (Appendix Table 43), was greater in the Asymptomatic OH group compared to the control ($p=0.008$). No other statistical differences between the groups were demonstrated ($p>0.05$). The significance of this is unclear.

With respect to change at 3 minutes (Appendix Table 44) there were statistically significant differences ($p<0.05$) between the groups in the changes in mean CBFV, systolic and diastolic CBFV and in transcutaneous $CO_2$. The smallest mean reduction seen in these parameters occurred in the Asymptomatic No OH group, who showed significant reductions at 1 minute, which may indicate recovery via a more responsive dCA system. Only the mean systolic CBFV showed a statistically significantly difference at 3 minutes compared to pre-HUT ($p<0.05$), with the greatest increase being seen in the Symptomatic OH group. The Asymptomatic OH group had the greatest reduction in mean CBFV, and in particular the systolic component ($p<0.05$). It is unclear why this could be the case.

There were significant differences ($p<0.05$) in the change between pre-HUT and prior to the end of HUT between groups in the mean MCA CBFVs and their systolic and diastolic components (Appendix Table 45). The largest increase in the CBFV was seen in the Symptomatic OH group, and was statistically greater than the control group ($p<0.05$). This was despite the greatest fall in SBP being seen in this group, and the fact that the fall in $tCO_2$ was similar.

### 10.1.5 Time varying estimates of ARI

Only optimal quality data files were used to assess ARI in the 1 minute prior to HUT, the first minute after HUT, and between the second and third minute of HUT. Each participant's data were divided into 100 samples for each 1 minute period. Thus a SD is also give for these 100 samples, as well as the group SD. It should be noted that not all participants had the required quality of data for the HUT or the end of HUT (where the patients is returned to the supine position). As there were differences between left and right MCA CBFVs, the ARI has been reported separately. The "UP" components include the pre-HUT values, and at 1 and 2 minutes of HUT. The "DOWN" components refer to the minute prior to the end of HUT, when symptoms occur or the end of the 30 minutes of HUT, and 1 minute and 2 minutes in the supine position, after the end of HUT.

Graphs of the time varying ARI for the "UP" and "DOWN" components illustrate the mean ARI of the combined left and right MCAs for each group (Figure 51) and for the right and left MCA separately (Figure 52 and Figure 53). The parameters extracted using this method are shown in Appendix Table 46 to Table 63 for combined right and left MCA, right MCA and left MCA. Note that the pre-HUT values use time varying estimates, and are not the same as the baseline values. The symptomatic OH group ARI is quick to adjust back to normal upon return to the supine position from the pre-end HUT state.

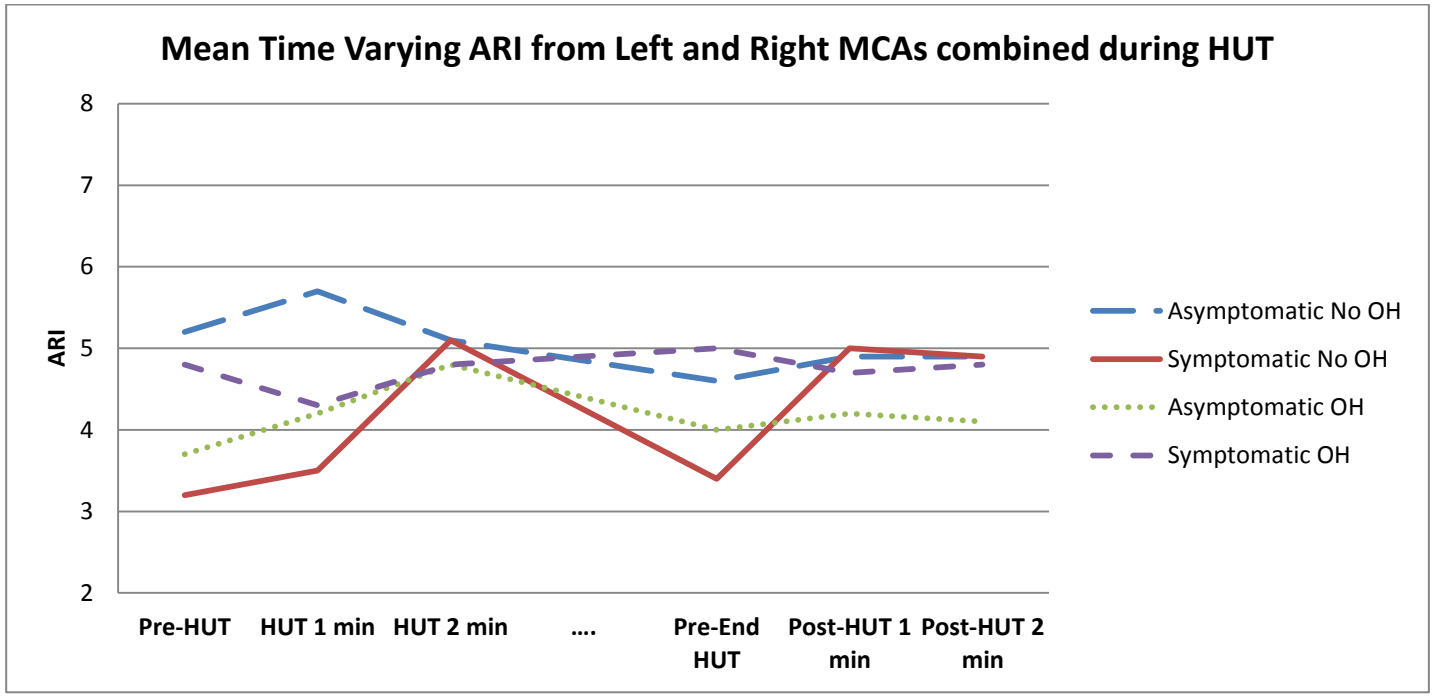



**Figure 51 Time varying estimate of the mean ARI (combined left and right) during HUT** ***(Data calculated from time-varying estimates, Pre-HUT value is not always equal to the baseline value)***

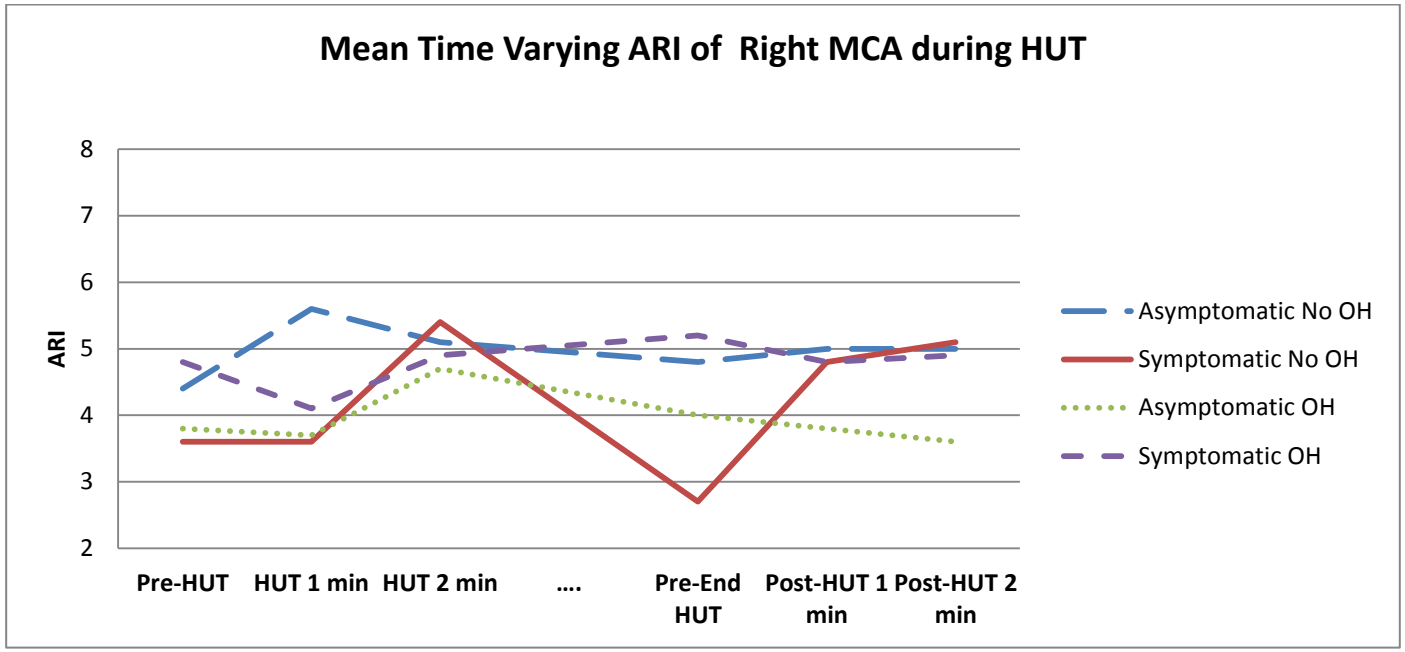



**Figure 52 Time varying ARI of Right MCA during HUT (Data calculated from time-varying estimates, Pre-HUT value is not always equal to the baseline value)**

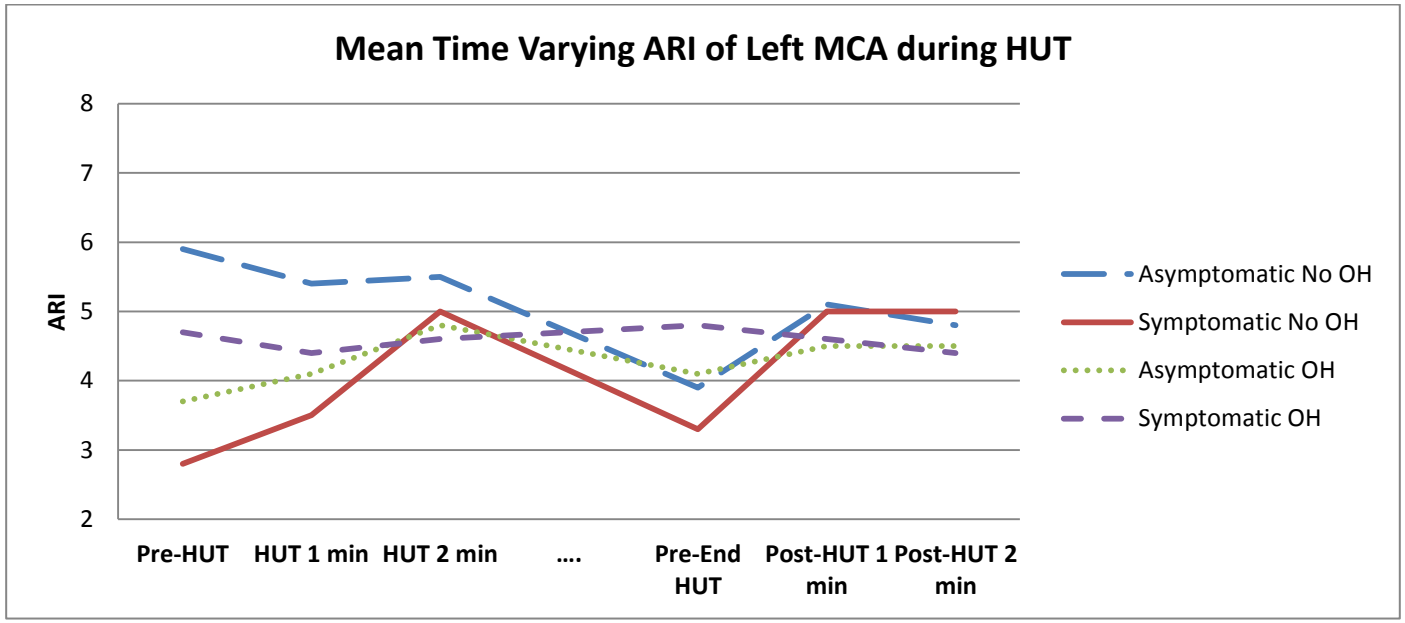



**Figure 53 Time varying ARI of Left MCA during HUT (Data calculated from time-varying estimates, Pre-HUT value is not always equal to the baseline value)**

#### *10.1.5.1 The "UP" component: Pre-HUT*

There were significant differences in the ARI and CBFV between groups taking the mean of both of right and left MCAs in the pre and post-tilt period (Appendix Table 46). The data for the right MCA (Appendix Table 47), and the left MCA (Appendix Table 48) are also presented for completeness though the mean of left and right values (Appendix Table 46) will be used for analysis. The lowest mean ARI was seen in the Symptomatic OH group compared to the highest in the control group (Table 47, $p<0.001$).

#### *10.1.5.2 The "UP" component: HUT 1 minute*

Mean values for ARI and CBFV values differed between groups (Appendix Table 49), the right (Appendix Table 50) and left MCAs (Appendix Table 51) in the first minute of HUT. The highest mean ARI was found in the control group which was significantly higher than for all other groups ($p<0.001$). This suggests that in the control group, dCA responds rapidly to the change in BP associated with HUT.

#### *10.1.5.3 The "UP" component: HUT 2 minutes*

The mean ARI for both MCAs combined at 2 minutes of HUT is given in Appendix Table 52 and for right (Table 53) and left (Table 54) MCA separately and shows that the lowest ARI was seen in both Asymptomatic and Symptomatic OH (versus Control group, $p<0.001$) suggesting that these two groups are similar at this time point. However the ARI was similar in the Control and Symptomatic No OH group ($p=0.233$).

#### *10.1.5.4 The "DOWN" component: Prior to end of HUT*

This data is from the minute before the end of HUT when either participants were symptomatic. Values for ARI and CBFV for the mean of both MCAs (Appendix Table 55), right (Appendix Table 56) and left (Appendix Table 57) MCAs were significantly different between the groups. The mean CBFV was lowest in the symptomatic OH group compared to the control ($p<0.001$), but this group had a higher MAP and ARI compared to the control group ($p<0.001$). This suggests that despite BP being compensated for during HUT, there is evidence dCA is dysfunctional with the lowering of the mean CBFV in this symptomatic OH group. The lowest ARI was in the symptomatic No OH group was significantly lower than the control group ($p<0.001$). This would suggest that symptoms is associated with poor dCA, consistent with the original hypothesis.

#### *10.1.5.5 The "DOWN" component: Post-HUT 1 minute*

This data reflects responses in the first minute of recovery from HUT in the supine position. The ARI and CBFV values varied between the groups, for the combined right and left values (Appendix Table 58), the right MCA (Appendix Table 59) and the left MCA (Appendix Table 60) individually. The mean ARI of both sides was lower in the asymptomatic and symptomatic OH groups, but the mean ARI was lowest in the asymptomatic OH group. It is unclear why this may be the case, but may be related to the readjustment to the supine.

#### *10.1.5.6 The "DOWN" component: Post-HUT 2 minutes*

Similar to the results for Post-HUT at 1 minute there were significant differences at 2 minutes Post-HUT in ARI and CBFV between the groups, including the mean of both MCAs (Appendix Table 61), the right MCA (Appendix Table 62), and the left MCA (Appendix Table 63). Mean CBFV was similar in the control and Symptomatic OH group, but lower in the Asymptomatic OH and higher in the Symptomatic No OH group. Once again it is unclear why this may have occurred but it is likely related to dCA making adjustments in cerebral blood flow.

### 10.1.6 The changes in Time varying estimates of ARI

As there appeared to be differences in the majority of parameters at various time points compared to the control group, the changes in the mean of the various parameters combined right and left MCAs compared to pre-HUT, were analysed. Firstly, within each group the changes were compared with pre-HUT to HUT at 1 minute, at 3 minutes, and prior to end-HUT when participants were either symptomatic, or had come to the maximum 30 minutes of HUT. The percentage changes for MAP, HR, CBFV, ARI and $tCO_2$ are shown in Figure 54, Figure 55, Figure 56, Figure 57 and Figure 58. The actual mean changes at 1 minute HUT, 2 minutes HUT and prior to end of HUT are shown in Appendix Table 64, Table 65 and Table 66 respectively with the percentage changes in Appendix Table 67, Table 68 and Table 69.

#### *10.1.6.1 Changes in Blood Pressure and Heart Rate during HUT*

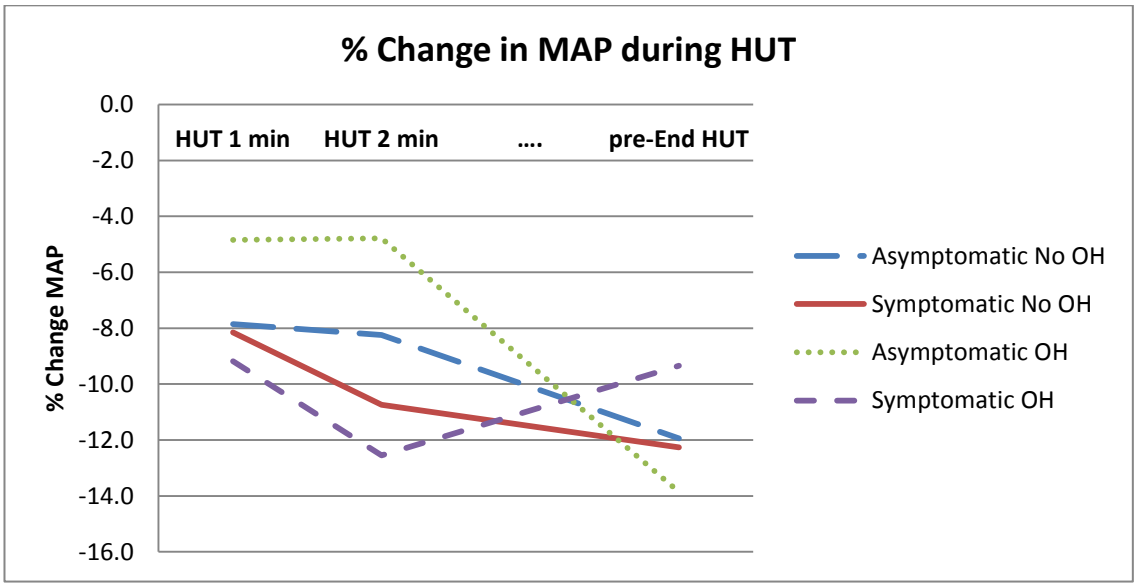



**Figure 54 Percentage change in MAP from pre-HUT during HUT**

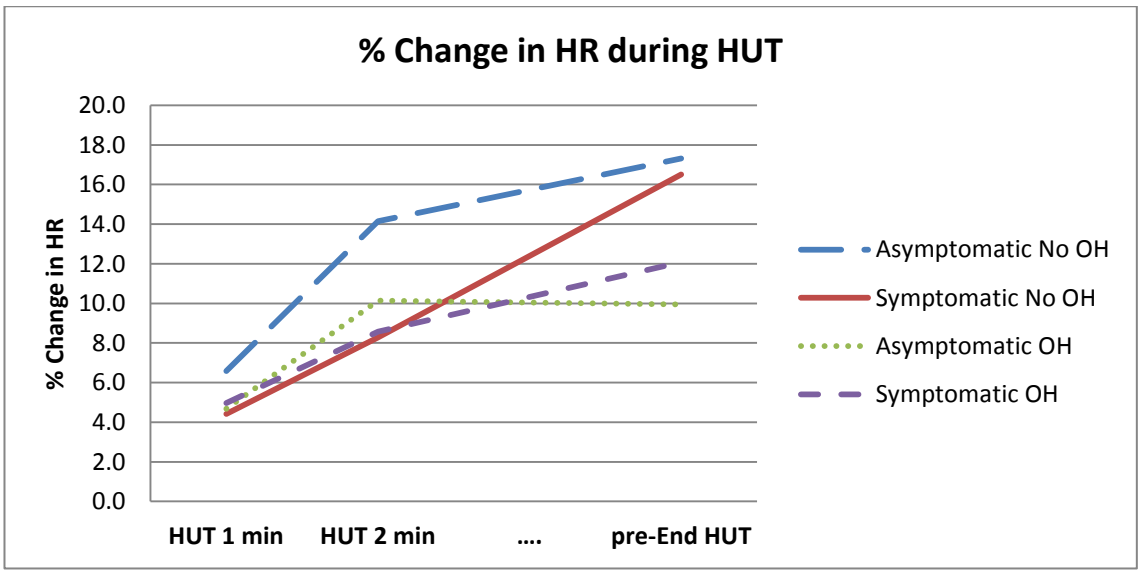



**Figure 55 Percentage change in HR from pre-HUT during HUT**

All groups showed falls in MAP during 1 and 2 minutes of HUT (Figure 54) compared to their pre-HUT values. The greatest reduction in MAP at 2 minutes of HUT were in the Symptomatic OH and Symptomatic No OH (12.6% and 10.7%). However by the end of HUT, the greatest reduction in MAP was in the Symptomatic OH group (9.3%) as one would expect based on the original classification.

There were increases in HR across all groups by the end of HUT (Figure 55), with the greatest in the control (17.3%) and the Symptomatic No OH groups (16.5%) and the least in the Asymptomatic OH (9.9%) and Symptomatic OH groups (12.1%). However all increases in HR were statistically significantly less than the control group ($p<0.001$).

### *10.1.6.2 Changes in dynamic ARI*

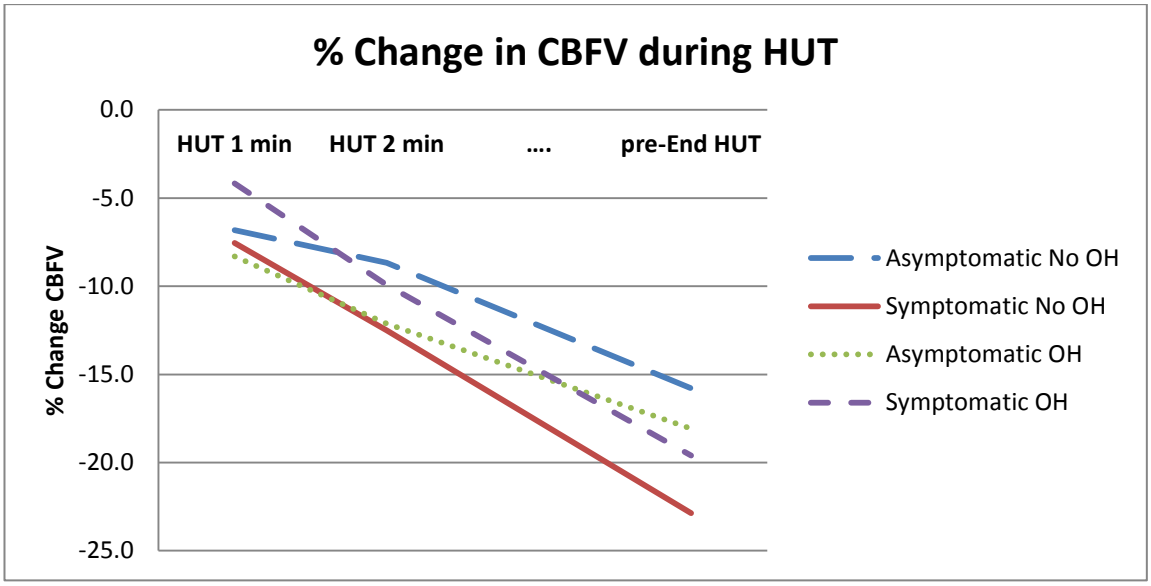



**Figure 56 Percentage change in CBFV from pre-HUT during HUT**

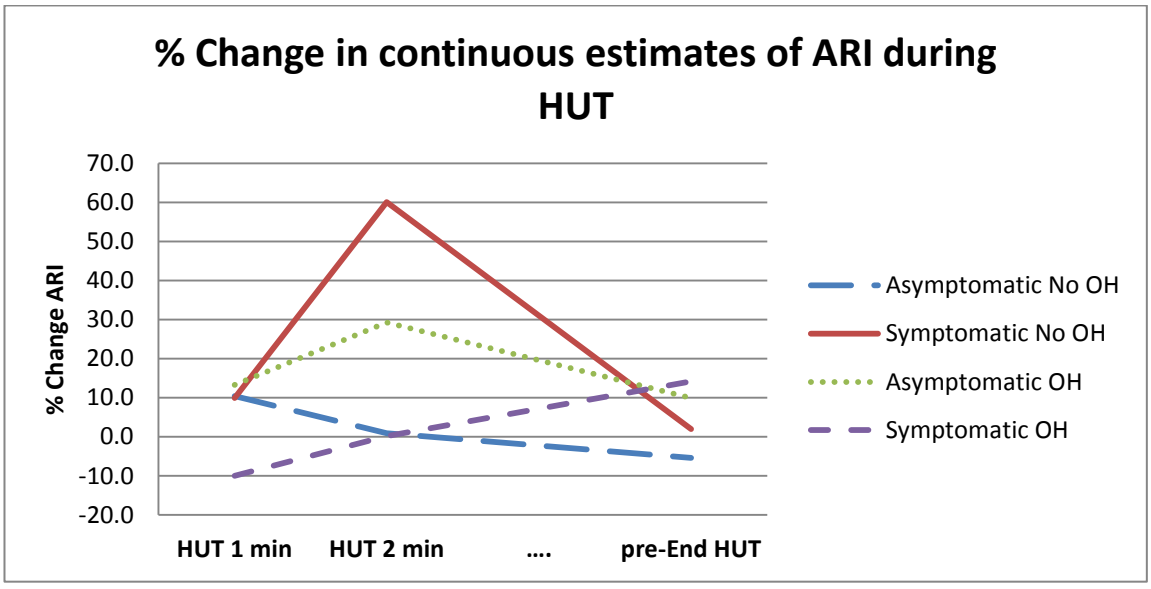



**Figure 57 Percentage change in ARI from pre-HUT during HUT**

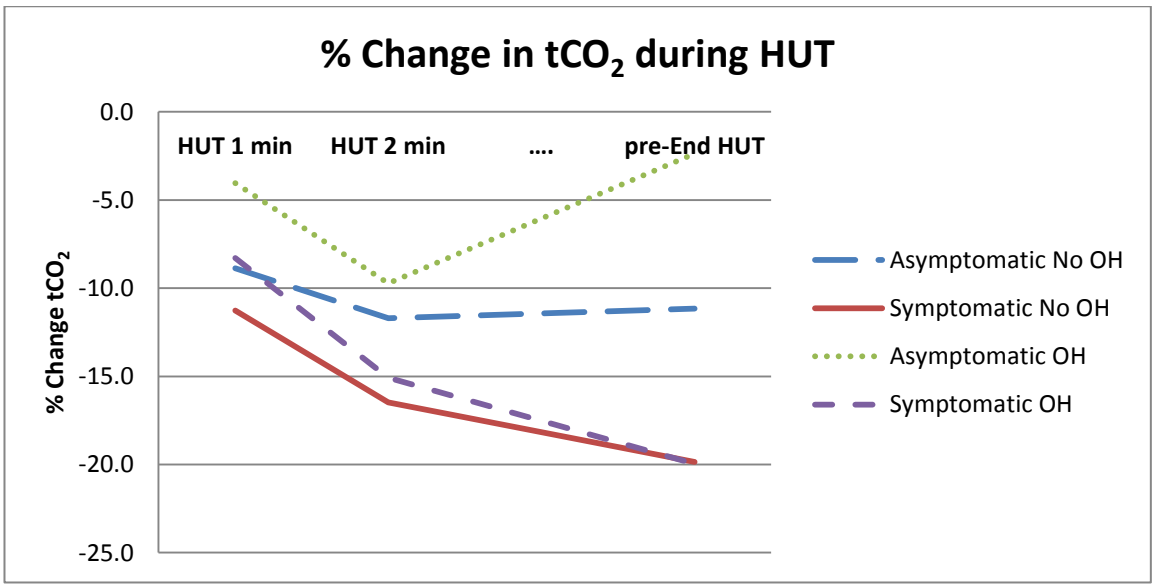



**Figure 58 Percentage change in $tCO_2$ from pre-HUT during HUT**

All groups showed increases in the mean CBFV compared to pre-HUT (Figure 56), and by the end of HUT (Table 66) the control group showed the smallest decrease of 15.8%, with larger falls of 22.9%, 18.1% and 19.6% in the Symptomatic No OH, Asymptomatic OH and Symptomatic OH groups ($p<0.001$, $p=0.001$, $p<0.001$). Of course what may be statistically significant differences, may not necessarily translate to a clinically significant difference between the three groups and the control.

The change in mean ARI was not significantly different in the Asymptomatic OH group (reduction of 13.3%) compared to the control (reduction of 9.9%). Thus suggesting that adequate dCA does not produce postural symptoms. However there is a significant reduction in mean ARI in the first minute of HUT (Appendix Table 68) in the Symptomatic OH group of 10.0% (Figure 57) versus the control group which showed a an increase of 10.4%, $p<0.001$. At 2 minutes (Appendix Table 68), the pattern reverses for the mean ARI, with the Symptomatic OH group being similar to the control,

showing very small mean increases of 0.2% and 1.0% respectively (p=0.89). The Symptomatic No OH and Asymptomatic OH groups showing large percentage increases in ARI (60.1% and 29.3%) significantly different from the control group (p<0.001). It may be that the intact dCA in the asymptomatic OH group prevents symptoms which might otherwise occur with a postural change. In the minute at the end of HUT (Appendix Table 69), the Symptomatic OH group shows a smaller 14.2% rise in the mean ARI, significantly different from the increase of 5.4% in the control group (p<0.001). Whilst the control group have a normal dCA system, the lack of an increase in the ARI in the symptomatic OH is likely to indicate failure for the dCA to compensate for systemic BP changes and thus result in symptoms during HUT. There were significant differences in the changes from pre-HUT in the Symptomatic No OH group (+2.0%, p<0.001) and the Asymptomatic OH groups (+9.9%, p<0.001) compared to the control. However at the pre-end of tilt all 4 groups had similar changes in ARI values despite the initial differences in response following tilt, there being little change from baseline.

The Symptomatic No OH (19.9%) and Symptomatic OH (20%) groups showed similar reductions in $tCO_2$ (Figure 58) prior to the end of HUT, significantly (<0.001) greater than the fall seen in the control group (11.2%). The Asymptomatic OH group significantly differed from the control (p<0.001), with only a 2.4% reduction from pre-HUT values. These differences between the symptomatic No OH and OH versus the asymptomatic OH and control may suggest that changes in CO2 are central to the mechanism by which symptoms are produced.

## 10.2 Sub-Group Analysis of Original Groups with HUT

### 10.2.1 Comparing symptomatic versus asymptomatic HUT within original groups

As it was difficult to predict those who were likely to have a positive HUT based on active supine to standing BP and thus group classification, it was decided that it would be useful to carry out post-hoc analysis comparing those who were classed as symptomatic against those who were asymptomatic during HUT. Thus in the first instance the participants of the original four groups were divided into those with and those without symptoms during HUT. In order that time varying averaging could be used, only good quality data files were used. In these eight groups, Wilcoxon signed ranks test demonstrated significant changes ($p<0.001$) across all variables (including left and right MCA individually and combined). Pre-HUT values are given for each group (Appendix Table 70, Table 72,Table 74,Table 76).

The changes between the one minute prior to HUT and pre-End HUT (in the one minute prior to end of HUT) are shown in Figures (Figure 59, Figure 60, Figure 61, Figure 62, Figure 63) and Tables (Appendix Table 71, Table 73, Table 75, Table 77). The change in mean of the combined CBFV and ARI, are the mean of right and left MCA values. However numbers were very small in some instances, hence a second post-hoc analysis was carried out.

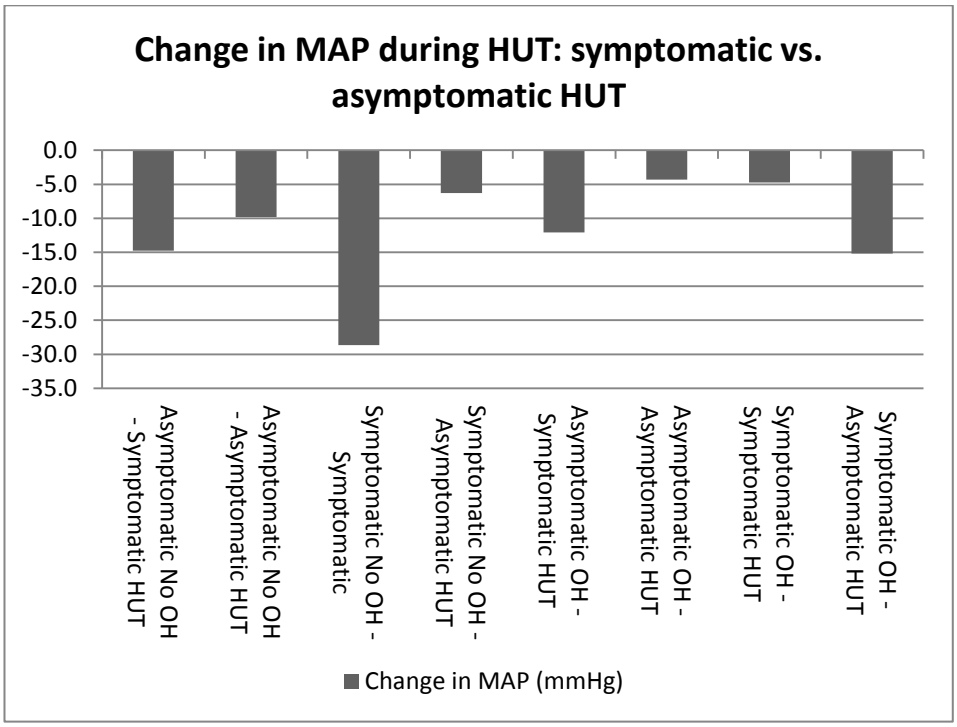



**Figure 59The mean change in MAP during HUT, a comparison of symptomatic and asymptomatic HUT of original groups**

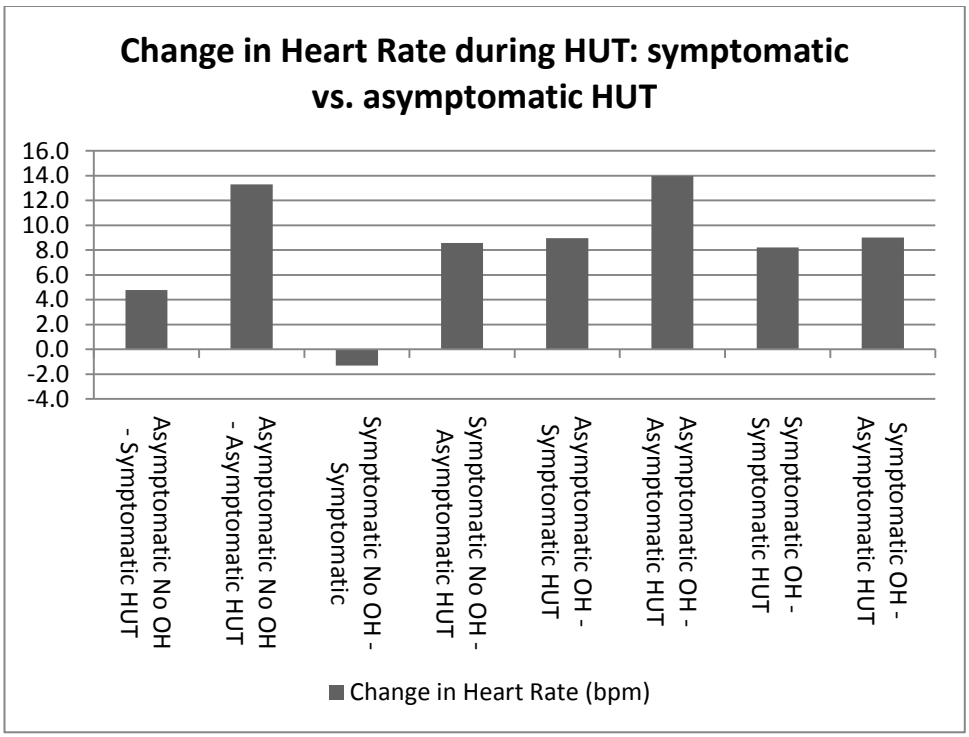



**Figure 60 The mean change in heart rate during HUT, a comparison of symptomatic and asymptomatic HUT of original groups**

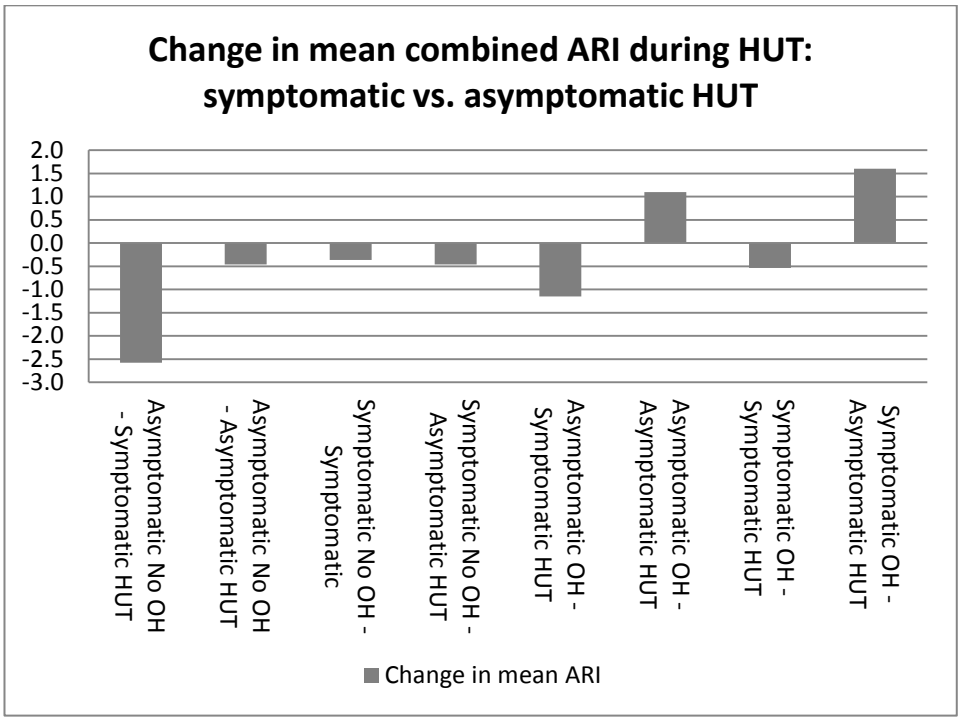



**Figure 61 The change in the mean ARI during HUT, a comparison of symptomatic and asymptomatic HUT of original groups**

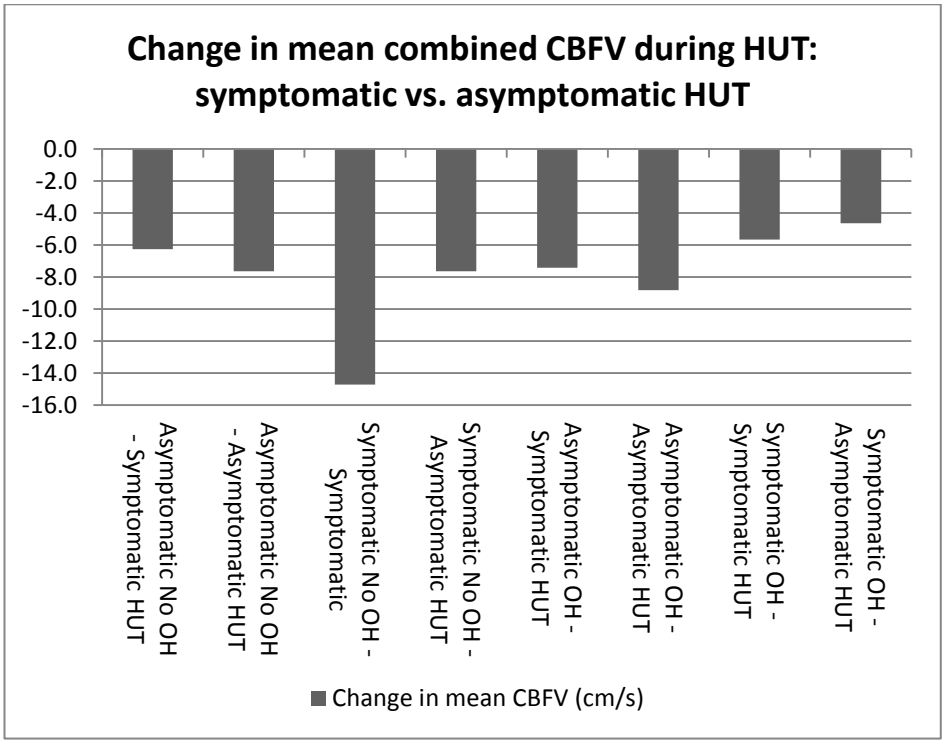



**Figure 62 The change in mean of the combined right and left CBFV during HUT, a comparison of symptomatic and asymptomatic HUT of original groups**

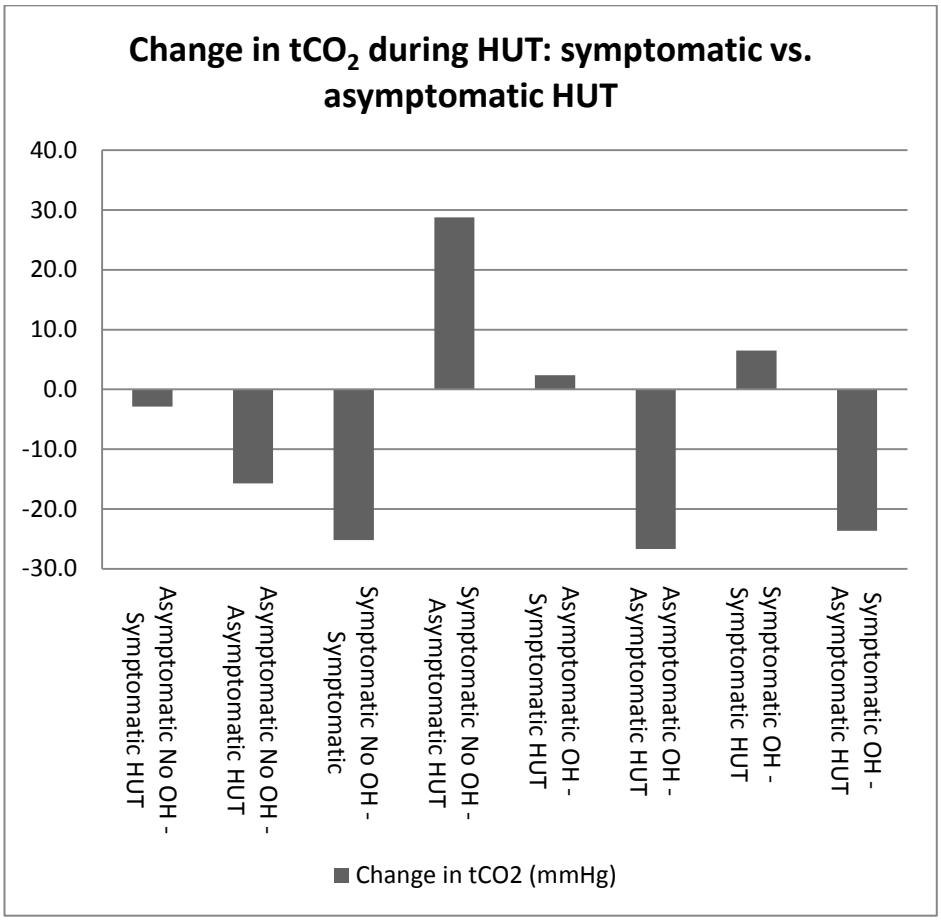



**Figure 63 The mean change in transcutaneous $CO_2$ during HUT, a comparison of symptomatic and asymptomatic HUT of original groups**

There were significant statistical differences within each group, between who were symptomatic on HUT and those who were not symptomatic on HUT, across all parameters including the mean combined ARI. In general there appears to be a fall in ARI associated with those who were symptomatic in most of the groups (except for the asymptomatic No OH i.e. control group). However the data from the sub-analysis needs to be interpreted with caution, as the data considers only 3 participants in some instances. Therefore the second post-hoc analysis was carried out as outlined in the next section.

### 10.2.2 Comparing symptomatic versus asymptomatic HUT – All groups combined

This second post-hoc analysis was carried out in order to determine if there were differences in dCA between those who were symptomatic during HUT, vs. those who were asymptomatic, regardless of their original classification. Pre-HUT values are given (Table 21). Given the differences within groups regarding differences in the change in ARI, all participants across the four groups were divided into those who were symptomatic on HUT and those who were asymptomatic (Table 22). Once again the mean combined values of right and left MCA values were used for ARI and CBFV. The figures illustrate the mean changes (Figure 64, Figure 65, Figure 66, Figure 67, Figure 68).

| | **All original groups combined** | | | | **T-test** *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=23)*** | | ***Asymptomatic HUT (n=46)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Mean combined CBFV (cm/s)** | 48.2 | *7.9* | 42.9 | *2.8* | <0.001 |
| SD time sample | 2.3 | *7.0* | 10.3 | *3.3* | <0.001 |
| **MAP (mmHg)** | 93.8 | *4.8* | 93.3 | *3.6* | <0.001 |
| SD time sample | 11.5 | *5.5* | 13.1 | *4.3* | <0.001 |
| **$tCO_2$ (mmHg)** | 107.2 | *15.9* | 110.8 | *20.2* | <0.001 |
| SD time sample | 56.1 | *3.7* | 54.1 | *8.0* | <0.001 |
| **Mean combined ARI** | 3.4 | *0.9* | 4.1 | *0.8* | <0.001 |
| SD time sample | 2.2 | *0.5* | 2.7 | *0.3* | <0.001 |
| **Heart Rate (bpm)** | 68.4 | *2.5* | 67.1 | *3.7* | <0.001 |
| SD time sample | 9.9 | *3.5* | 11.8 | *2.8* | <0.001 |

**Table 21 Pre-HUT values of symptomatic versus asymptomatic during HUT with all four groups combined**

| | All original groups combined | | | | T-test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=23)*** | | ***Asymptomatic HUT (n=46)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in mean combined CBFV (cm/s)** | -8.5 | *4.3* | -7.3 | *1.8* | <0.001 |
| Change in SD time sample | -2.7 | *5.7* | -0.9 | *3.1* | <0.001 |
| **Change in mean MAP (mmHg)** | -15.1 | *10.0* | -8.9 | *4.8* | <0.001 |
| Change in SD time sample | 9.2 | *14.2* | 2.9 | *3.9* | <0.001 |
| **Change in mean $tCO_2$ (mmHg)** | -4.8 | *13.9* | -9.3 | *22.5* | <0.001 |
| Change in SD time sample | -14.5 | *18.9* | -5.0 | *8.0* | <0.001 |
| **Change in mean combined ARI** | -1.2 | *1.1* | 0.7 | *0.9* | <0.001 |
| Change in SD time sample | -0.8 | *0.4* | 0.1 | *0.4* | <0.001 |
| **Change in mean Heart Rate (bpm)** | 5.2 | *5.6* | 11.2 | *3.1* | <0.001 |
| Change in SD time sample | 2.3 | *7.0* | 3.5 | *3.7* | <0.001 |

**Table 22 Comparison of changes between pre-HUT and pre-End HUT of those who were symptomatic versus asymptomatic during HUT with all four groups combined**

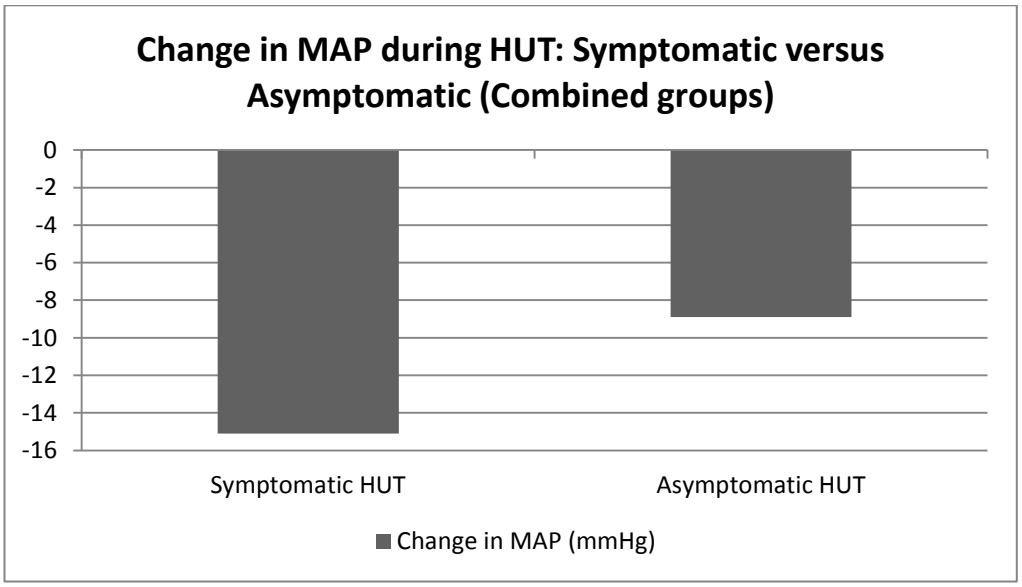



**Figure 64 The change in mean MAP during HUT, a comparison of symptomatic and asymptomatic HUT of original groups combined**

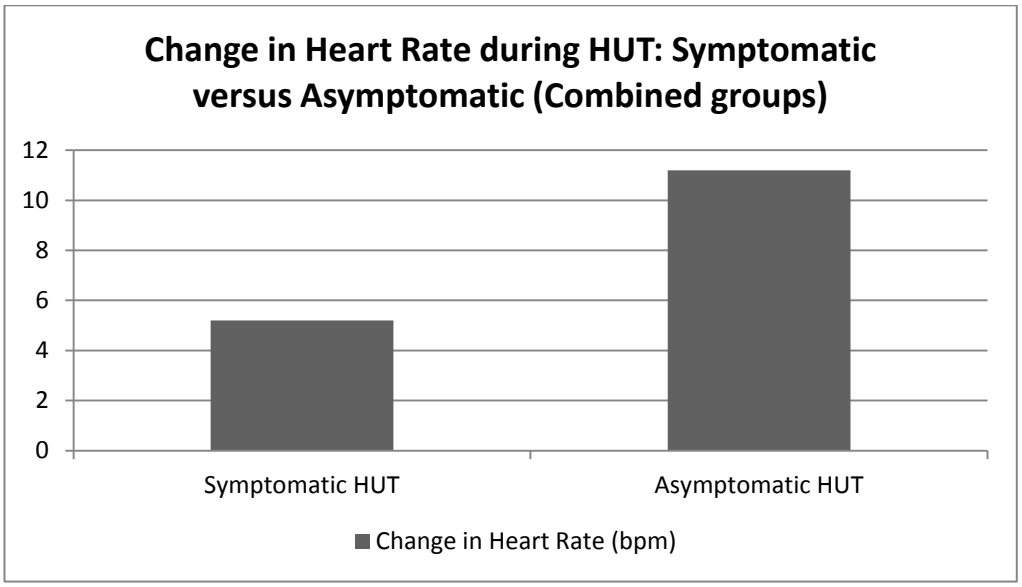



**Figure 65 The change in mean HR during HUT, a comparison of symptomatic and asymptomatic HUT of original groups combined**

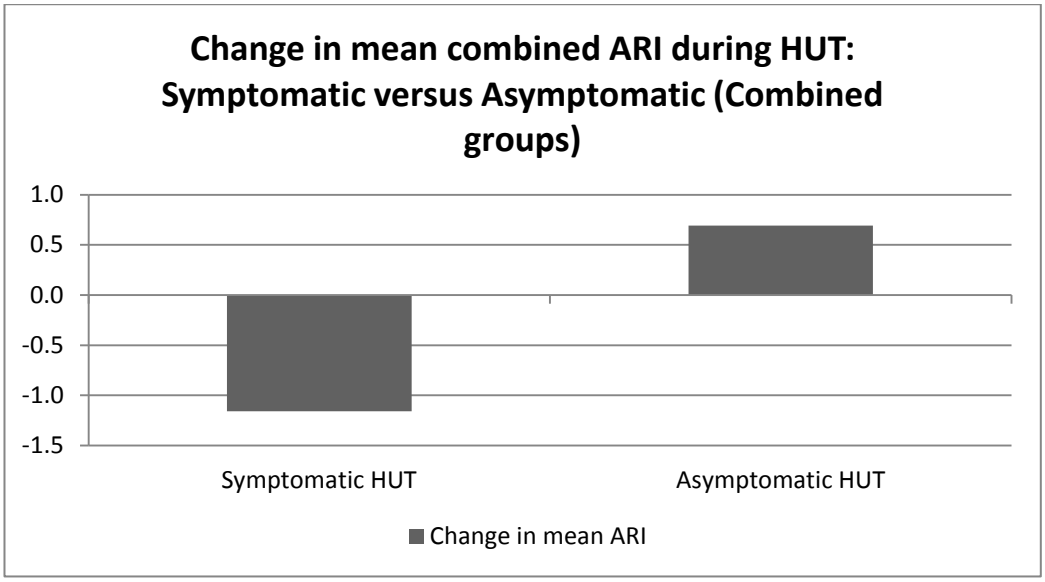



**Figure 66 The change in the mean combined ARI during HUT, a comparison of symptomatic and asymptomatic HUT of original groups combined**

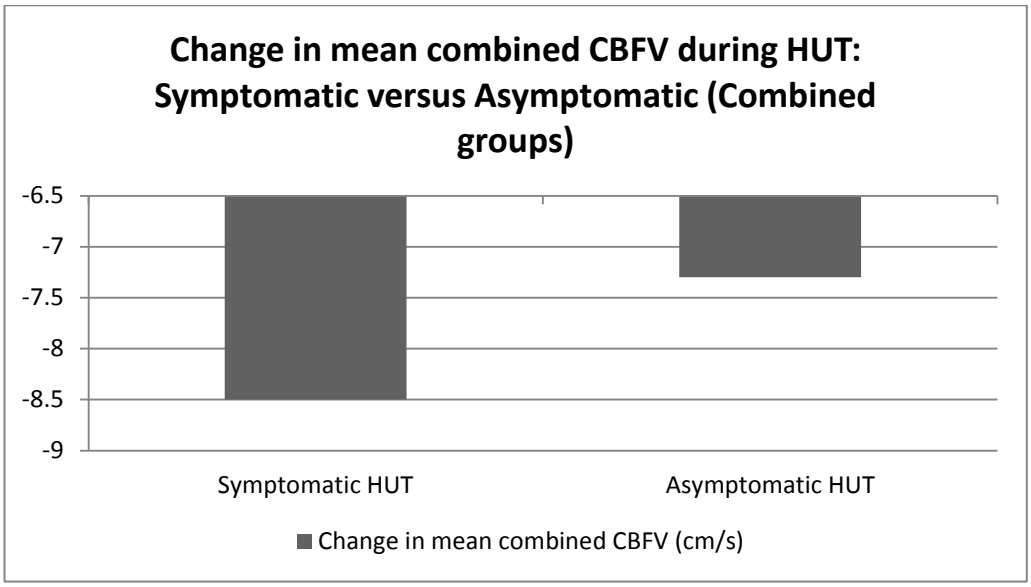



**Figure 67 The change in the mean combined CBFV during HUT, a comparison of symptomatic and asymptomatic HUT of original groups combined**

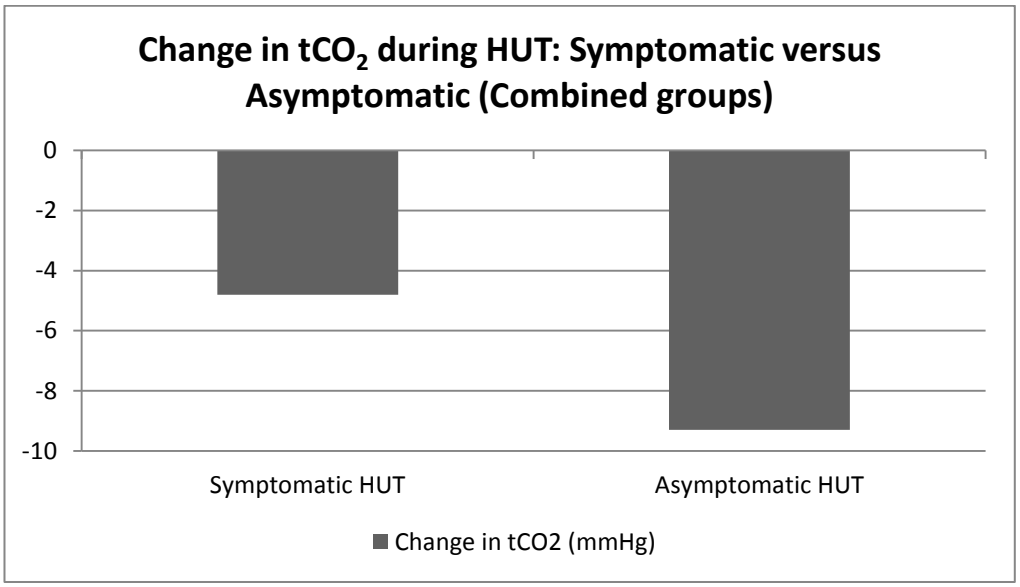



**Figure 68 The change in mean $tCO_2$ during HUT, a comparison of symptomatic and asymptomatic HUT of original groups combined**

By combining all those who had symptoms during HUT and comparing them against those who remained asymptomatic during HUT, it can be seen that there were significant differences in ARI with the symptomatic group showing a fall in the mean combined ARI from pre-HUT unlike the asymptomatic group who showed a small increase. The asymptomatic group showed a statistically significant greater increase in the mean HR and a smaller fall in the group mean MAP and combined mean CBFV, as well as a greater fall in $tCO_2$. This would indicate that the asymptomatic group had adequate dCA, likely mediated by a fall in $tCO_2$ to prevent a sustained fall in CBFV. The difference in CBFV is a small figure, but a greater proportion of the pre-HUT values.

## 10.3 Orthostatic Hypotension Study – Effects of HUT Results Summary

The most interesting data can be found in the post-hoc analysis of those who were symptomatic versus those who were asymptomatic by combining the original four groups, suggest that there is a fall in ARI associated with symptoms with HUT. On further sub-group analysis comparing those with symptoms versus those who remained asymptomatic on HUT, there was evidence of a statistical difference in ARI, with a fall in ARI in the symptomatic group, and an increase in the asymptomatic group. $TCO_2$ fell the greatest in the asymptomatic group, with an increase in CBFV suggesting that this the fall in $CO_2$ improves dCA to increase CBF.

The main pattern demonstrated during HUT was the small but progressive decline in the continuous ARI measurements in the Asymptomatic OH group (Figure 57) although just prior to the end of tilt the changes in all 4 groups were very similar. The other groups in this study although demonstrated initial increases in ARI compared the pre-HUT state, although these increases in ARI progressively got smaller over time. This is despite the fact that all groups showed a decrease in CBFV over the duration of the HUT (Figure 43).

The greatest increase in HR was seen in the Asymptomatic No OH group, and occurred by 1 minute of HUT to continue to the end of HUT. The Symptomatic No

OH group also showed a substantial increase in HR, but this was after 2 minutes of HUT and persisted to the end of HUT. MAP appeared to fall amongst all four groups. The Symptomatic OH showed the greatest proportionate fall compared to pre-HUT early on, however by the end of HUT the MAP came up significantly. This differed from the Asymptomatic OH group who showed a minimal fall in MAP within the first couple of minutes of HUT, but showed the greatest fall by the end of HUT. The fall in MAP was associated with a reduction in $tCO_2$. All groups showed fall in BP and CBFV over the course of HUT, however the symptomatic OH group showed an increase in CBFV at the end of HUT despite a fall in BP.

# 11 Orthostatic Hypotension Study – Discussion of Effects of HUT

The primary aim of the OH study was to determine if there were differences in dCA between those who did or did not have symptoms, whether they had systemic changes in BP. HUT was used in this study in order to reduce data artefact from movement, and to provide consistency in the duration attaining the changes in posture. Despite the classification of participants at baseline being based on postural changes in BP during active standing and symptoms, there were no significant differences in duration of HUT of the three groups compared to the control group. However it should be noted that tilt tests are not always consistently positive (Moya et al., 2009). Thus the post-hoc analysis combining all of those who were asymptomatic (n=46) during HUT and comparing them to those who were symptomatic (n=23) during HUT provided interesting results. Firstly, the ARI fell in the symptomatic group, whereas the asymptomatic group showed good dCA. Furthermore the asymptomatic group showed evidence of a fall in $tCO_2$ perhaps as a result of hyperventilation leading to vasoconstriction, with an increase in CBFV noted with this (Aaslid et al., 1989).

The significant difference between the Symptomatic OH group and the control group in terms of right, left and the mean of both MCAs in the first minute of assuming a passive upright posture, was not associated with a difference in MAP compared to the control group as one might expect. The higher proportionate increase in HR early on with the Asymptomatic No OH (control) group, may partly explain why the participants within the control group did not have symptoms reported using the Orthostatic Grading Scale (OGS), whereas the Symptomatic No OH group did not

have such a rapid increase in HR on HUT making them more likely to report postural symptoms with the OGS. Although it has been well established that older adults do have a blunted HR response to HUT (Goldstein and Shapiro, 1990, Hainsworth and Al-Shamma, 1988), this study does suggest that those who are symptomatic despite not having a postural drop in BP, do have some evidence of failure of the autonomic response. Another fact to note, is that systemic vascular resistance increases with age (Tahvanainen et al., 2007), and this may account for why the older participants in the Symptomatic OH group, did not have a significantly different beat-to-beat MAP to the control group at baseline.

At the end of HUT, the only persisting difference is in the diastolic CBFV, being lower in both the Symptomatic No OH and Symptomatic OH groups compared to the control. However whilst other studies have shown no difference in CBFV compared to those with OH in the supine position (Novak et al., 1998), a small study in younger patients with OH (mean age 41.8±12.9 years) showed a significant fall in cerebral blood flow with HUT, of which CBFV is a surrogate, compared to controls (Khandelwal et al., 2011). Although an interesting phenomenon similar to what was found here, it should be noted that the sample population is smaller and is different to the participants who took part in this study. However it should be noted that an initial transient fall in CBFV is found in young healthy volunteers and is not related to postural symptoms (Thomas et al., 2009). Amongst those with of orthostatic pre-syncope (mean age 57 SEM 4 years) there is evidence of a fall in CBFV before MAP (Dan et al., 2002). It has been shown that diastolic CBFV is lower in those with OH and autonomic dysfunction early in the period of lower body negative pressure (a method which causes provokes falls in BP)(Lagi et al., 1994) and this reduction in

diastolic CBFV is also found with HUT vasovagal syncope (Grubb et al., 1991a). Although both symptomatic groups (No OH and OH) showed lower CBFV compared to the control, these two groups differed from each other as a lower ARI value compared to control was found in the Symptomatic No OH group, and a higher ARI value (vs. control) was found in the Symptomatic OH group. Thus this might suggest that not only does a lower CBFV account for postural symptoms in those with or without an associated fall in BP, but that those who have symptoms without a postural fall in BP, may also have an abnormal dynamic CA accounting for these symptoms. Furthermore the symptomatic OH group showed a relative increase in CBFV at the end of HUT despite the associated fall in BP. Other groups did not differ from the control at baseline, 1 or 3 minutes of HUT in terms of CBFV, BP or HR. The lack of changes between groups may be due to the reliance of classifying participants into groups based on the postural changes in BP on active standing, rather than the passive change with HUT.

The symptomatic No OH and the symptomatic OH groups showed greater reductions in CBFV by the end of HUT compared to pre-HUT than the other two groups. This was associated with greater reductions in ARI also. Sub-group analysis suggests that symptoms is associated with a greater fall in ARI. The HR shows a statistically significant increase compared to the fall in HR seen in the control group. The fall in CBFV seen at 2 minutes of HUT resolves in the Asymptomatic OH group, but becomes evident at the end of HUT in the symptomatic OH group. Thus this study confirms that in older people with OH like their younger counterparts with OH (although perhaps the latter a different cohort), there is evidence of a reduction in cerebral blood flow during HUT (Khandelwal et al., 2011). Despite CBFV being lower

in older adults, ARI values in older adults are similar when measured at rest (Carey et al., 2003). Once again there is a significant increase in HR at the end compared to pre-HUT, albeit proportionately less than the control group. The early termination of any significant change in CBFV in the Asymptomatic OH group, may be why the participants differed from the Symptomatic OH group, with the signs of a falling CBFV developing after the first 2 minutes of HUT. This perhaps correlates with the ESC classification of OH in terms of time course (Moya et al., 2009). $CO_2$ levels can affect cerebral auto-regulation, with lower levels allowing cerebral blood flow to be restored more quickly after a fall in BP (Aaslid et al., 1989). It is likely that the sudden reduction in transcutaneous $CO_2$ seen across the four groups, in part reflects this physiological change, in order to attempt to maintain CBFV as markedly seen in the initial period of HUT.

By using continuous estimates of the mean ARI (left and right MCA) in the minute pre-HUT, there was evidence that all groups differed from the control by being higher at the end of HUT. This persisted at 1 minute of HUT, but by 2 minutes of HUT, the symptomatic No OH group showed no difference in ARI compared to the control. The remaining two groups (Asymptomatic and Symptomatic OH) showed persisting differences to the control group. However it may be that the unclear changes in ARI during passive HUT may be related to the classification of participants at baseline being dependent on active standing.

The changes in continuous estimates of ARI showed that at the end of HUT, the Symptomatic No OH, Asymptomatic OH and Symptomatic OH groups were different

to the control (Asymptomatic No OH) in that they all showed a reduction in the ARI. It may suggest that there are some differences in dCA in these groups compared to the control group but whether one hemisphere is affected more than another at differing time points is variable. Of course one needs to consider the underlying differences between these three groups, which makes it difficult to draw definite conclusions.

# 12 Closing Remarks on the Orthostatic Hypotension Study

## 12.1 Orthostatic Hypotension Study Results Summary

Abnormal dCA is present in those who are symptomatic during HUT. Participants within the four groups had similar characteristics at baseline in terms of BRS, PWV and autonomic function. There appears to be differences in the left and right MCA, despite all subjects being right-handed with a left hemisphere dominance. In general the symptomatic OH group had a lower CBFV throughout. However this group did show an increase in CBFV despite a greater fall in SBP during HUT. Compared to the asymptomatic No OH groups, the other groups appear to show a time delay in response to HUT, with the small increase in ARI only taking place at 2 minutes of HUT, instead of at 1 minute. At the end of HUT, there is an decrease in the continuous ARI across all groups, although for the Symptomatic OH and Symptomatic No OH group, there appears to be a greater relative change in ARI values. Post-hoc analysis of combined data suggests that there is a greater reduction in ARI associated with those who are symptomatic during HUT.

## 12.2 Discussion of the Orthostatic Hypotension Study

The goal of this study was to bring new information within the field of OH and cerebral auto-regulation by investigating if there were abnormalities in dCA, cardiac BRS or arterial stiffness which would account for whether a person has symptoms or not whether they have postural falls in BP or not. Although data during HUT between the four groups were unclear at times, by combining all those who were symptomatic during HUT and comparing them to those who were asymptomatic during HUT regardless of the original grouping showed interesting results, which have not been shown elsewhere before with such a large group. Post-hoc analysis demonstrated that those who were symptomatic during HUT had a significant decline in their ARI during HUT. Those who were asymptomatic showed a significantly greater fall in $tCO_2$ with a statistically smaller decline in CBFV, which the latter is likely to be physiologically insignificant.

Those in the Symptomatic OH Group had lower CBFV during HUT and this may account for symptoms themselves (Novak et al., 1998). The patterns of ARI change are similar in the Asymptomatic OH and the Symptomatic OH group suggesting that perhaps they may be one single group. The control group (Asymptomatic No OH) showed a small steady decline in ARI during the course of the HUT. The Symptomatic OH group on the other hand, shows a mirror image pattern to the control group, with the initial fall in ARI, steadily increasing with time. This suggests that there may be two groups to OH as a condition. Research in a smaller study (n=21, age 61.8±2.4 years) suggests the possibility of three OH groups. Those who have impaired auto-regulation with a flat flow-BP curve, those with intact auto-regulation and expansion

of the systemic BP range which auto-regulation can function, and lastly a group with failure of auto-regulation associated with a steep flow-BP curve (Novak et al., 1998). Whilst this study in older people confirms falls in CBFV during HUT with symptomatic OH which occurs later in the time course of HUT, it has additionally shown that those with asymptomatic OH has an earlier fall in CBFV which then improves. Furthermore this study has revealed changes in dCA during HUT in those with symptomatic OH, asymptomatic OH and those with symptoms of OH but in the absence of postural falls in BP. This suggests that despite maintained CBFV and the lack of a postural drop in BP in the latter group, the presence of symptoms is perhaps due to an impairment of dCA. Once again this may tie into the theory by Novak et al. (1998). Subgroup analysis shows a significant reduction in ARI with HUT amongst those with symptoms, and an increase in ARI in those without symptoms. The difference between the two groups is 1.9, and greater than the 1.5 which was hoped to be detected in this study. However there is evidence of a greater fall in CBFV and MAP in those with symptoms. Of course although statistically significant, whether the difference in the mean fall in CBFV of 1 cm/s and a fall in MAP of 6mmHg is physiologically significant to each individual is unclear. And in the context of a larger difference in mean combined ARI, these differences in CBFV and MAP are arguably small. Recent preliminary work elsewhere also suggest a reduction in CA as a cause for symptoms in older people (Sanders et al., 2014).

In this study cardiac BRS values were similar in all 4 groups suggesting parasympathetic cardiac control, one part of the autonomic nervous system, was not impaired and perhaps not responsible for the postural BP fall of production of postural symptoms. However it is well known that both age and increasing BP are associated

with impaired cardiac BRS, and common to both hypertension and OH (James and Potter, 1999, Takeshita et al., 1975, Moreira et al., 1992). Furthermore abnormal cardiac BRS has also been found in those with orthostatic intolerance without OH (i.e. symptoms and increase in HR>30bpm within 10 minutes of standing) (Farquhar et al., 2000). Thus this study brings contradicting information to current research. However it is noted that the age and use of ACEi/AIIRBs were slightly different and does raise the possibility of Type 2 statistical error. The fact that there were no differences between groups in cardiac BRS, may reflect the long term benefits of drug treatment with ACEi and AIIRBs.

Whilst other studies have suggested that a higher PWV (Mattace-Raso et al., 2006) or AIx (Valbusa et al., 2012) may be found amongst those with OH, little difference in arterial stiffness between the groups was found in this study. However it may be that anti-hypertensive treatment accounts for this, as it has been shown that treatment reduces arterial stiffness (Boutouyrie et al., 2011). Thus in this thesis, the slightly differing numbers of participants taking ACEi and AIIRBs may have been a potential confounder in the original four groups.

## 12.3 Strengths and Limitations

The strengths of this study include: 1) it is one of the few studies in dCA of this size to include older participants (>60 years) with and without OH and with consideration of the presence or absence of symptoms, 2) the broad inclusion criteria and limited exclusion criteria allowing the results of this study to be transferred to a wider patient population in Western society. However it is offset by weaknesses including: 1) use of

passive HUT which likely differs from active standing both in the research and clinical settings, 2) the duration of HUT meant deterioration of TCD US signals due to contact gel drying out which could have a negative effect on data quality in addition to inadequate bone windows (Lorenz et al., 2009) and 3) the reliance of participant compliance at all times during the study to ensure consistent and adequate measures of CBFV, BP and HR. For the latter part of study looking at time-varying measures, this required very high quality data files which were sometimes difficult to obtain during the physical manoeuvre of HUT and variation in bone windows particularly in this older population.

## 12.4 Future work in the Orthostatic Hypotension Study

Although participants were originally grouped by methods which would be available to the clinician, not all participants remained true to their group during HUT. This in part may be due to the difference in active standing versus passive HUT. In future, it may be better to allocate participants according to the result of the HUT, as it is difficult to predict the response to HUT.

## 12.5 Conclusion of the Orthostatic Hypotension Study

This study adds new information in the first of a large study in this area. There appears to be differences in dynamic cerebral auto-regulation in the non-normal older population with early falls in ARI values in the Symptomatic OH group which may account for the symptoms of OH, without the associated postural falls in BP. Sub-group analysis reveal that those who have symptoms on HUT have evidence of a reduction in ARI.

# 13 Methods - Post-Prandial Hypotension Study

As previously indicated, much of the technical methods used during this section are the same as for the Orthostatic Hypotension study, and can be found in the General Methods Chapter.

## 13.1 Aims

- To investigate if a) cerebral auto-regulation is impaired in patients with post-prandial hypotension, and b) if it is impaired to investigate if this relates to symptoms, and c) investigate any changes in BRS or arterial stiffness
- The hypothesis was that abnormalities in dynamic cerebral auto-regulation explain why some patients have postural symptoms independent of changes in arterial blood pressure in post-prandial hypotension.

## 13.2 Methods

### 13.2.1 Participants

Participants were recruited as previously described (Section 6.1) with the exception of the exclusion of those with known diabetes mellitus. Those who had a history of light-headedness, pre-syncope or syncope or other symptoms suggestive of a fall in BP within a 2 hour period of a meal on a consistently regular (daily) basis, which differed from postural symptoms were placed in the PPH group. Participants recruited to study 2 who were found to have unfasted capillary blood glucose (>7.0) suggestive of diabetes mellitus were informed on the day, and asked to see their GP. A letter was

sent to their GP surgery informing them of this and participants were offered the option to participate in the OH instead.

Based on the sample-size estimate for ARI like for the OH study, for the PPH study it was estimated that there would need to be 20 participants in each group: 1) those with possible PPH based on clinical history, and 2) 20 controls, those without a history suggestive of PPH.

### 13.2.2 Randomisation

Participants were allocated to Lucozade™ (containing 50g glucose) and orange flavoured sparkling water (placebo) in a double blind, cross-over method using computer block randomisation (using blocks of 4) carried out by a colleague not involved in the study, such that participants received each on a different day within a 2 week period.

### 13.2.3 Data collection

As for the OH study, both categorical and continuous data were collected, including measures of arterial stiffness, BRS and autonomic function. As noted in the General Methods section sixty minutes was selected for PPH as this appeared to be a reasonable time period to allow glucose absorption, and BP changes to occur in the HUT position (Krajewski et al., 1993). It was also likely to be reasonably well tolerated in older adults.

After a 10 minute period in the supine position where measurements did not fluctuate by more than 10%, a 10 minute recording of baseline data was collected. After baseline recordings were taken in the supine position, participants were asked to drink either 275ml of Lucozade™ energy orange flavour (equating to 50g of glucose) or 40ml of sugar-free orange flavour diluting juice with 235ml of carbonate water within a 3 minute period. This was followed by HUT. In addition to the standard recordings as for the OH study previously outlined (Chapter 6), the capillary blood glucose was monitored using a finger prick blood test at baseline, and at 30 and 60 minutes of HUT. It has been previously shown that these responses to HUT in healthy elderly subjects are reproducible up to 6 weeks apart (Youde et al., 2003).

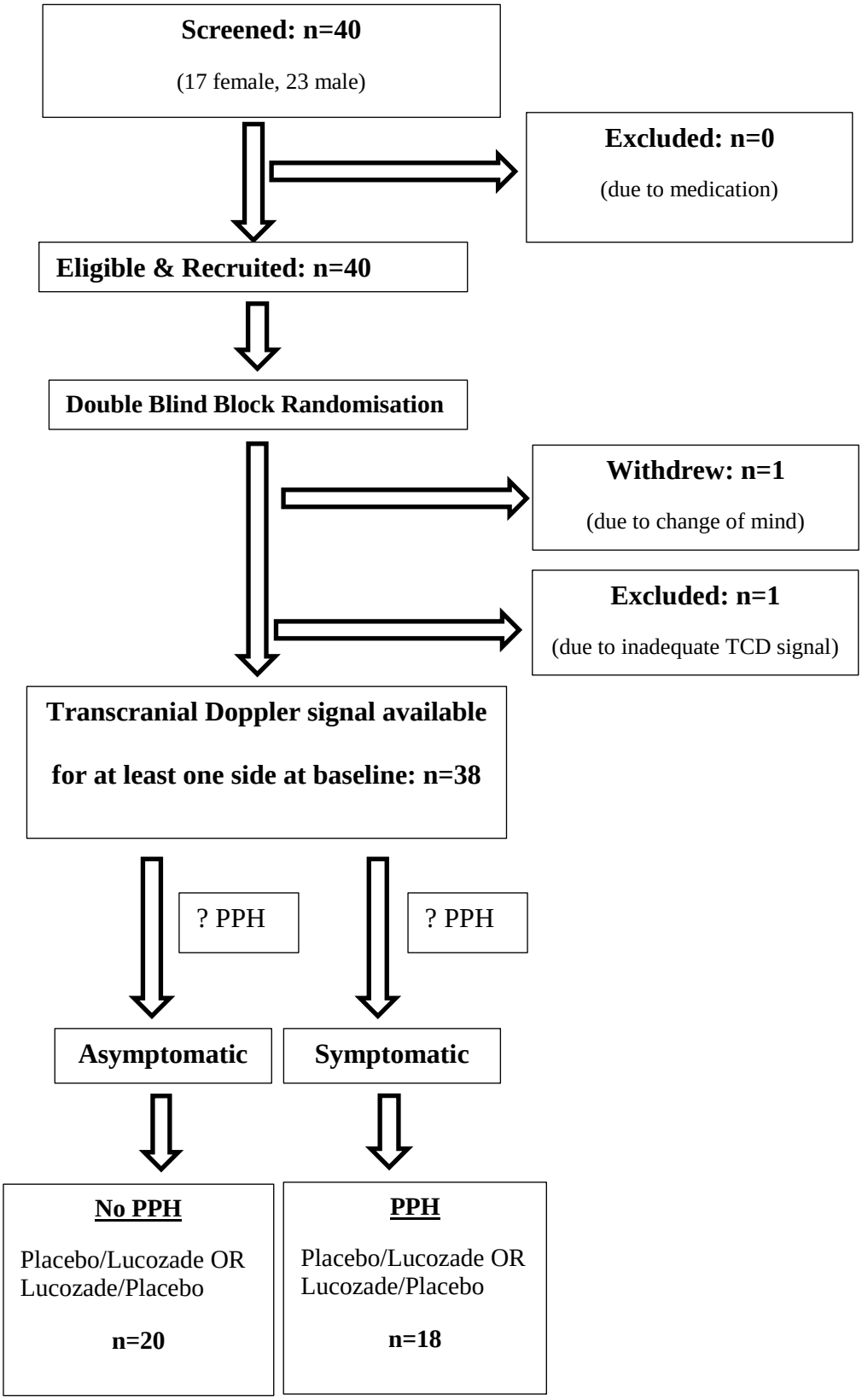
### 13.2.4 Data Analysis

Baseline continuous and categorical data were analysed in a similar fashion to the OH study, except that as it was a cross-over study, statistical analysis allowed for non-independent samples. In addition to that described for the Orthostatic Hypotension study participants (Section 6.7.7) with possible post-prandial hypotension and controls had cerebral auto-regulatory indices compared in terms of both the glucose and placebo arms. As for the OH study, baseline and HUT data were analysed. The latter was considered as “UP” and “DOWN” components representing HUT and the end of HUT respectively.

# 14 Results - Post-Prandial Hypotension Study - Baseline

## 14.1 Post-Prandial Hypotension Study Recruitment

There were a total of 40 participants (17 female, 23 male, mean age 73.45 ±7.28 years) who were successfully recruited for screening between the 15th of February 2011 and the 22nd of July 2013. The final number of participants with at least a unilateral baseline TCD signal was 38. Participants were recruited into a symptomatic and asymptomatic group based on whether there was a history suggestive of PPH. They were subsequently block randomised in a double blind fashion to receive placebo (with sugar free orange squash and carbonated water, 280ml) or Lucozade © (equivalent to 50g glucose, 280ml) prior to HUT on two different occasions within a 2 week period. Thus participants could either receive placebo on visit 1 and glucose on visit 2, or glucose on visit 1 and placebo on visit 2 as per Section 13.2.


Screened: n=40
(17 female, 23 male)
Excluded: n=0
(due to medication)
Eligible & Recruited: n=40
Double Blind Block Randomisation
Withdrew: n=1
(due to change of mind)
Excluded: n=1
(due to inadequate TCD signal)
Transcranial Doppler signal available
for at least one side at baseline: n=38
? PPH
? PPH
Asymptomatic
Symptomatic
No PPH
Placebo/Lucozade OR
Lucozade/Placebo
n=20
PPH
Placebo/Lucozade OR
Lucozade/Placebo
n=18

## 14.2 Baseline data for the PPH Study

### 14.2.1 Population summary

A summary of the PPH study participants basic characteristics are presented in Table 23. Both groups had similar age and supine BP levels but as expected a difference in the Orthostatic Grading Scale, as participants were divided into symptomatic and asymptomatic groups based on a history of symptoms suggestive of post-prandial falls in BP.

Categorical data are presented in Table 24 and again no significant difference between the two groups was found, in particular the Autonomic Function Score.

### 14.2.2 Cardiac Baroreceptor Sensitivity

This was assessed in the supine position over a period of 10 minutes, following a 10 minute resting period in the supine position. There was no significant difference in cardiac BRS, between the No PPH and PPH groups, or within these groups by visit (placebo vs. glucose phase, Wilcoxon Signed Ranks Test for related samples). See Table 25 for the Low Frequency Band.

### 14.2.3 Arterial Stiffness

Similarly arterial stiffness was assessed in the supine position, after a 10 minute supine resting period. PWV was similar between the symptomatic group and the asymptomatic group (Table 26), as was AIx and AIx @75 values.

| Participant Characteristic | No PPH (20) | | PPH (20) | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | |
| **Age (years)** | 74.0 | *7.4* | 74.3 | *7.7* | 0.620 |
| **BMI (kg/m2)** | 29.3 | *4.7* | 27.6 | *3.5* | 0.820 |
| **Baseline SBP (mmHg)** | 147.0 | *19.5* | 145.2 | *15.7* | 0.904 |
| **Baseline DBP (mmHg)** | 83.6 | *10.7* | 88.0 | *9.6* | 0.277 |
| **Baseline HR (bpm)** | 71.5 | *5.7* | 76.6 | *12.4* | 0.265 |
| **Baseline Capillary Glucose (mmol/l) *** | 6.1 | *1.3* | 6.1 | *1.2* | 0.874 |
| **Orthostatic Grading Scale** | 1.7 | *1.2* | 5.4 | *2.5* | <0.001 |
| **Autonomic Function Score** | 3.1 | *2.0* | 3.7 | *2.3* | 0.496 |
| **Change in SBP at 1 minute of standing (mmHg)** | -6.7 | *17.9* | -14.0 | *22.6* | 0.640 |
| **Change in DBP at 1 minute of standing (mmHg)** | -1.2 | *14.7* | -5.1 | *13.9* | 0.758 |
| **Change in HR at 1 minute of standing (bpm)** | 11.0 | *5.7* | 13.2 | *7.2* | 0.396 |
| **Change in SBP at 3 minutes of standing (mmHg)** | -1.5 | *12.5* | -6.8 | *19.3* | 0.620 |
| **Change in DBP at 3 minutes of standing (mmHg)** | -1.2 | *14.7* | -5.1 | *13.9* | 0.758 |
| **Change in HR at 3 minutes (bpm)** | 8.3 | *7.1* | 9.7 | *9.3* | 0.784 |

**Table 23: Baseline Characteristics of PPH participants (Key: * placebo arm given here)**

| | | No PPH (20) | | PPH (20) | | Difference between groups | |
|---|---|---|---|---|---|---|---|
| | | *No. participants* | *%* | *No. participants* | *%* | *Test statistic* | *p-value* |
| **Sex** | *Female* | 7 | 35.0 | 10 | 50.0 | 0.921* | 0.523 |
| | *Male* | 13 | 65.0 | 10 | 50.0 | | |
| **Smoker** | *Yes* | 1 | 5.0 | 0 | 0.0 | 1.032# | 0.597 |
| | *No* | 15 | 75.0 | 16 | 80.0 | | |
| | *Ex* | 4 | 20.0 | 4 | 20.0 | | |
| **Blackout** | *Yes* | 9 | 45.0 | 9 | 45.0 | 8.25* | 0.012 |
| | *Pre-syncope* | 0 | 0.0 | 6 | 30.0 | | |
| | *No* | 11 | 55.0 | 5 | 25.0 | | |
| **Hypertension** | | 7 | 35.0 | 4 | 20.0 | 1.129* | 0.480 |
| **Diuretics** | | 4 | 20.0 | 3 | 15.0 | 0.173* | 1.00 |
| *Furosemide* | | *2* | *10.0* | *0* | *0.0* | 2.105* | 0.487 |
| *Thiazide* | | *2* | *10.0* | *2* | *10.0* | 0.000* | 1.000 |
| *Spironolactone* | | *0* | *0.0* | *1* | *5.0* | 1.026* | 1.000 |
| **ACEi or AIIRB** | | 5 | 25.0 | 2 | 10.0 | 1.558* | 0.407 |
| *ACEi* | | 3 | 15.0 | 2 | 10.0 | 0.229* | 1.000 |
| *AIIRB* | | 2 | 10.0 | 0 | 0.0 | 2.105* | 0.487 |
| **Alpha Blocker** | | 3 | 15.0 | 3 | 15.0 | 0.000* | 1.000 |
| **Tricyclic Antidepressant** | | 1 | 5.0 | 0 | 0.0 | 1.026* | 1.000 |

**Table 24 Categorical characteristics of PPH study participants (Key: *Pearson Chi-Square, # Fisher's Exact Test)**

| | Group | No PPH (20) | | Wilcoxon Signed Rank Test (p-value) | PPH (20) | | Wilcoxon Signed Rank Test (p-value) | Mann-Whitney U Test (p-value) |
|---|---|---|---|---|---|---|---|---|
| | | Mean BRS (ms/mmHg) | *SD (ms/mmHg)* | | Mean BRS (ms/mmHg) | *SD (ms/mmHg)* | | |
| **Low Frequency Band** (0.05-0.15Hz) | *Placebo* | 7.0 | *6.0* | 0.167 | 6.8 | *6.7* | 0.535 | 0.519 |
| | *Lucozade* | 5.1 | *2.8* | | 5.5 | *6.4* | | 0.369 |

**Table 25 Baseline BRS of PPH participants (p-values for both independent No PPH vs PPH groups and related samples within groups Placebo vs Glucose days)**

| Participant Characteristic | No PPH (20) | | PPH (20) | | Mann-Whitney U Test (p-value) |
|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | |
| **Mean Augmentation Index (%)** | 10.3 | *16.9* | 10.7 | *12.7* | 0.678 |
| **Mean HR with Augmentation Index (bpm)** | 75.7 | *14.2* | 77.4 | *12.3* | 0.620 |
| **Mean Augmentation Index (%, @75bpm)** | 10.1 | *16.6* | 10.8 | *12.9* | 0.640 |
| **Mean Pulse Wave Velocity ($ms^{-1}$)** | 10.0 | *2.2* | 9.6 | *2.6* | 0.369 |

**Table 26 Arterial Stiffness of PPH participants**

## 14.3 Baseline Supine Cerebral Haemodynamic values of PPH study participants

As for the OH study, after a 10 minute period in the supine position where measurements did not fluctuate by more than 10%, a 10 minute recording of data was collected.

### 14.3.1 Cerebral Haemodynamic Supine Measurements

Data are reported for the left and right MCA individually (Table 27), and as a mean of both sides (where data are missing for left or right, then the available side is used). There were no significant differences between placebo or glucose, or between the No PPH and the PPH group at baseline in the supine position. In the supine position where participants are asymptomatic, it was not expected to find any differences between or within the two groups regardless of phase.

### 14.3.2 Estimates of supine ARI (Tiecks model)

No significant differences between groups in terms of ARI values were found (or anticipated) when calculated for the mean of both right and left MCA (Table 28) or the right (Appendix Table 78) and left (Appendix Table 79) MCA individually.

### 14.3.3 ARI and ARMA ARI estimates

ARI (calculated using Tiecks model and by the ARMA method) for both left and right MCAs, and the mean of both MCAs (Table 29) were similar for the PPH and no PPH groups at baseline and between visits.

| Participant Characteristic | No PPH – placebo (n=20) | | No PPH – glucose (n=20) | | Wilcoxon Signed Rank Test (p-values) | PPH – placebo (n=18) | | PPH – glucose (n=18) | | Wilcoxon Signed Rank Test (p-values) | Mann-Whitney U Test (p-values) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | | Mean | *SD* | Mean | *SD* | | Placebo | Glucose |
| **CBFV Right (cm/s)** | 44.4 | *9.5* | 46.3 | *6.7* | 0.852 | 44.9 | *9.5* | 44.3 | *8.4* | 0.501 | 0.912 | 0.422 |
| **CBFV Left (cm/s)** | 47.6 | *7.2* | 45.7 | *9.5* | 0.313 | 42.8 | *9.9* | 45.9 | *10.8* | 0.278 | 0.189 | 0.863 |
| **Mean CBFV (cm/s)** | 46.0 | *7.3* | 46.0 | *7.6* | 0.737 | 43.8 | *8.7* | 45.1 | *8.7* | 0.163 | 0.369 | 0.789 |
| **Systolic CBFV Right (cm/s)** | 66.3 | *14.6* | 64.7 | *17.0* | 0.709 | 67.1 | *14.7* | 67.1 | *14.7* | 1.000 | 0.765 | 0.741 |
| **Systolic CBFV Left (cm/s)** | 71.2 | *11.8* | 67.6 | *12.9* | 0.232 | 63.3 | *14.9* | 63.3 | *14.9* | 0.352 | 0.178 | 0.863 |
| **Mean systolic CBFV (cm/s)** | 68.8 | *11.8* | 66.1 | *10.7* | 0.654 | 65.2 | *13.2* | 66.4 | *13.2* | 0.438 | 0.648 | 0.863 |
| **Diastolic CBFV Right (cm/s)** | 29.1 | *6.3* | 28.4 | *8.1* | 0.823 | 29.0 | *6.9* | 29.0 | *6.9* | 0.535 | 0.718 | 0.714 |
| **Diastolic CBFV Left (cm/s)** | 31.0 | *4.7* | 30.3 | *6.8* | 0.411 | 28.1 | *7.3* | 28.1 | *7.3* | 0.255 | 0.095 | 0.648 |
| **Mean diastolic CBFV (cm/s)** | 30.1 | *4.8* | 29.4 | *5.7* | 0.601 | 28.6 | *6.5* | 29.7 | *6.1* | 0.148 | 0.158 | 0.789 |
| **SBP (mmHg)** | 129.6 | *16.6* | 129.9 | *17.8* | 0.970 | 132.8 | *21.8* | 136.1 | *22.8* | 0.234 | 0.604 | 0.386 |
| **DBP (mmHg)** | 70.3 | *11.4* | 68.5 | *11.2* | 0.455 | 72.3 | *12.7* | 76.1 | *11.8* | 0.196 | 0.539 | 0.058 |
| **MAP (mmHg)** | 89.7 | *12.0* | 88.7 | *11.2* | 0.737 | 94.1 | *14.4* | 97.9 | *14.9* | 0.352 | 0.386 | 0.072 |
| **Heart Rate (bpm)** | 63.0 | *6.4* | 61.6 | *6.1* | 0.179 | 63.0 | *4.7* | 63.4 | *4.9* | 1.000 | 1.00 | 0.336 |
| **$tCO_2$ (mmHg)** | 100.8 | *52.5* | 96.0 | *56.5* | 0.765 | 114.4 | *47.6* | 108.0 | *56.3* | 0.796 | 0.479 | 0.582 |

**Table 27 Baseline Transcranial Doppler Measurements in PPH participants** ***(Measurements based on a 10 minute baseline recording, Mean CBFV =combined right and left CBFV)***

| | No PPH - placebo | | No PPH - glucose | | Wilcoxon Signed Ranks (p-value) | PPH - placebo | | PPH - glucose | | Wilcoxon Signed Ranks (p-value) | Mann Whitney U (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | | Mean | *SD* | Mean | *SD* | | **Placebo** | **Glucose** |
| **Mean ARI** | 4.89 | *1.36* | 4.84 | *1.49* | 0.199 | 5.10 | *1.48* | 5.23 | *1.24* | 0.605 | 0.621 | 0.523 |
| **Coherence Low Frequency** (<0.07Hz) | 0.42 | *0.14* | 0.34 | *0.11* | 0.076 | 0.32 | *0.15* | 0.30 | *0.13* | 0.717 | 0.042 | 0.243 |
| **Gain Low Frequency** (<0.07Hz) | 0.45 | *0.10* | 0.38 | *0.08* | 0.064 | 0.36 | *0.17* | 0.32 | *0.13* | 0.569 | 0.039 | 0.161 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.57 | *0.49* | 0.57 | *0.30* | 0.267 | 0.61 | *0.51* | 0.55 | *0.24* | 0.278 | 0.670 | 0.857 |
| **Step Response Recovery (%)** | 72.2 | *14.8* | 71.4 | *26.6* | 0.231 | 88.3 | *29.8* | 82.7 | *31.7* | 0.379 | 0.117 | 0.385 |

**Table 28 Baseline ARI (Tiecks model) Mean of Right and Left Middle Cerebral Artery, *Mean ARI =combined right and left ARI***

| | **No PPH – placebo (n=12)** | | **No PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-values) | **PPH – placebo (n=12)** | | **PPH – glucose (n=14)** | | **Wilcoxon Signed Ranks Test** (p-values) | **Mann-Whitney U Test** (p-values) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **ARI Right** | 5.93 | 2.00 | 6.16 | *2.27* | *0.735* | 5.09 | *2.86* | 4.12 | *3.32* | 0.433 | 0.592 | 0.067 |
| **ARI Left** | 5.27 | 2.39 | 4.65 | *3.28* | *0.735* | 4.96 | *3.76* | 4.75 | *3.46* | 0.851 | 1.000 | 0.231 |
| **Mean ARI (Left and Right)** | 5.60 | 2.01 | 5.40 | *1.56* | *0.866* | 5.03 | *2.15* | 4.43 | *2.17* | 0.826 | 0.340 | 0.060 |
| **ARMA ARI Right** | 6.91 | 2.61 | 5.15 | *3.69* | *0.735* | 3.97 | *4.16* | 3.97 | *3.64* | 0.784 | 0.120 | 0.899 |
| **ARMA ARI Left** | 6.35 | 3.08 | 4.33 | *3.59* | *0.866* | 3.81 | *3.71* | 3.67 | *3.51* | 0.724 | 0.083 | 0.560 |
| **Mean ARMA ARI** | 5.21 | 2.66 | 4.74 | *2.64* | *0.368* | 3.89 | *3.36* | 3.82 | *2.21* | 0.814 | 0.432 | 0.742 |

**Table 29 ARMA estimates of ARI *Mean ARI =combined right and left ARI***

## 14.4 Post-Prandial Hypotension Study – Summary of Baseline Data Results

There were no statistical differences between the No PPH and the PPH group, in terms of baseline characteristics for continuous or categorical data, except for the expected presence or absence of symptoms (Orthostatic Grading Score and history of PPH), upon which participants were divided into the No PPH versus the PPH groups. Furthermore, there were no differences between these two main groups in terms of cardiac BRS in the low frequency band, arterial stiffness and CBFV. ARI, using either method for assessment (Tiecks and ARMA-ARI), in the supine position was no different on either visit 1 or 2 for both the No PPH and PPH group. The only exception to this was a difference between groups in the placebo arm, where there was a statistically significant difference in the ARI at baseline was in respect of the mean of the right and left MCA in the low frequency band gain. The significance of this is unclear.

# 15 Post-Prandial Hypotension Study – Discussion of Baseline Data

The lack of differences between groups at baseline (Van Orshoven et al., 2010, Vloet et al., 2005) and in the supine position is not surprising, given that the condition by definition requires the consumption of glucose or an alternative test meal to cause a significant reduction in BP. In general no differences in groups would be expected at baseline, prior to ingestion of either a glucose drink or a placebo drink (Jones et al., 2005). Furthermore it was not surprising that there were no significant differences between the No PPH and the PPH group with respect to postural falls in BP, as only 38% of older people have been reported to have both PPH and OH (Vloet et al., 2005).

The AIx was actually lower than anticipated, as elsewhere values of 28±9% and 34±9% for men and women aged 60-69 years (McEniery et al., 2005, Salvi et al., 2010), whereas here it was 10.3±16.9% and 10.7±12.7% for the No PPH and the PPH groups respectively. As HR may affect AIx, this was corrected for HR in this study (Wilkinson et al., 2000, Yasmin and Brown, 1999). PWV in this study was similar to that reported elsewhere for a similar age group, with the expectation of PWV being over 8 m/s in those over 60 years of age (McEniery et al., 2005). Elsewhere PWV of 12.3±4.0 m/s have been reported amongst those age>80 years (Salvi et al., 2010). This may suggest that AIx is perhaps less reliable as a marker of arterial stiffness in older people than PWV.

Values for cardiac BRS in the supine position, using spontaneous fluctuations in HR and BP for spectral analysis, were similar to that reported by Dawson et al (1999) using similar methodology (Dawson et al., 1999) and for aged matched healthy volunteers (Youde et al., 2002). Furthermore it has been recognised that autonomic dysfunction alone is not always related to whether older adults have PPH or not (Lagro et al., 2013).

However given the association of PPH with cerebrovascular damage as indicated by leukoaraiosis, in patients with hypertension (Kohara et al., 1999), one could expect differences in CBFV between the No PPH and the PPH groups. Furthermore there is evidence that CBFV measured in the supine position is lower in older adults (49±13 cm/s) compared to younger adults (61±14 cm/s) with no differences in supine ARI (Carey et al., 2003). The results presented in this study for the baseline data for the 2 showing no significant differences in CBFV or ARI in the supine position are in keeping with other studies in older adults (Carey et al., 2003).

# 16 Post-Prandial Hypotension Study – Effects of HUT

## 16.1 Duration of HUT

Head up Tilt (HUT) at $70^0$ was potentially performed for 60 minutes in each group for each phase but terminated early with the onset of symptoms. There were no significant differences in the duration of HUT in the No PPH group between placebo or glucose arms, being 55.4 ±11.2 minutes and 56.8 ±9.6 minutes respectively (Wilcoxon signed ranks test, p=0.484). Similarly there were no significant differences in tilt duration for the PPH group following placebo 33.6 ±23.6 minutes or glucose 37.5 ±22.9 minutes (Wilcoxon signed ranks test, p=0.975). However the duration of tilt was significantly shorter for the PPH group than for those with no PPH for both placebo and glucose phases (Mann-Whitney U Test p=0.002 and p=0.018 respectively).

For the No PPH group, six and three were terminated early due to symptoms in the placebo and glucose phase respectively. For the PPH group the number of early termination of HUT was fourteen and nine for the placebo and glucose arm respectively (Pearson Chi Square p=0.001). Of those who had a SBP fall ≥20mmHg by the end of HUT, there were 7 in the placebo arm and 4 in the glucose arm of the No PPH group; 2 in the placebo and 9 in the glucose arm of the PPH group (Pearson Chi Square p=0.265).

## 16.2 Capillary blood glucose

Capillary blood glucose during HUT is shown (Table 30) with changes from baseline (Table 31).

There were no differences between or within groups for baseline capillary glucose. An increase compared to baseline glucose was seen in the glucose arm of both groups. As expected there were significant increases in capillary glucose at 30 and 60 minutes post-ingestion of glucose compared to baseline ($p<0.001$) in both groups, but again there was no difference in the increases between groups. Capillary blood glucose during HUT is also shown graphically (Figure 69).

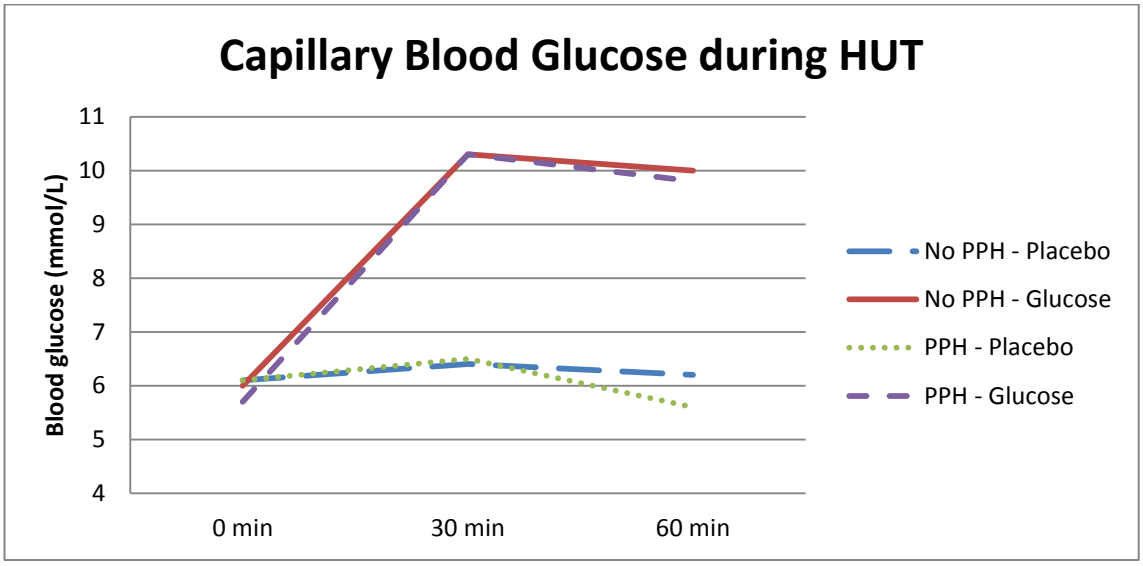



**Figure 69 Capillary blood glucose during HUT**

| **Time (minutes)** | **No PPH – Placebo Blood glucose (mmol/l)** | | **No PPH – Glucose Blood glucose (mmol/l)** | | **Wilcoxon Signed Ranks Test** *(p-value)* | **PPH – Placebo Blood glucose (mmol/l)** | | **PPH – Glucose Blood glucose (mmol/l)** | | **Wilcoxon Signed Ranks Test** *(p-value)* | **Mann-Whitney U test** *(p-value)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | | Mean | SD | Mean | SD | | Placebo | Glucose |
| 0 | 6.1 | *1.3* | 6.0 | *0.8* | 0.686 | 6.1 | *1.2* | 5.7 | *1.0* | 0.201 | 0.874 | 0.189 |
| 30 | 6.4 | *1.5* | 10.3 | *1.4* | <0.001 | 6.5 | *2.8* | 10.3 | *2.3* | <0.001 | 0.426 | 0.814 |
| 60 | 6.2 | *1.3* | 10.0 | *2.2* | <0.001 | 5.6 | *0.5* | 9.8 | *3.2* | 0.003 | 0.099 | 0.528 |

**Table 30 Capillary blood glucose during HUT**



| **Time (minutes)** | **No PPH – Placebo Blood glucose (mmol/l)** | | **No PPH – Glucose Blood glucose (mmol/l)** | | **Wilcoxon Signed Ranks Test** *(p-value)* | **PPH – Placebo Blood glucose (mmol/l)** | | **PPH – Glucose Blood glucose (mmol/l)** | | **Wilcoxon Signed Ranks Test** *(p-value)* | **Mann-Whitney U test** *(p-value)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean Change | SD | Mean Change | SD | | Mean Change | SD | Mean Change | SD | | Placebo | Glucose |
| 30 | -0.2 | 1.7 | 4.4 | 1.6 | <0.001 | -0.4 | 1.9 | 4.6 | 2.2 | <0.001 | 0.942 | <0.001 |
| 60 | -0.1 | 1.4 | 4.1 | 2.4 | <0.001 | 0.3 | 0.7 | 4.4 | 3.1 | <0.001 | 0.454 | <0.001 |

**Table 31 Changes in Capillary blood glucose during HUT**

## 16.3 Cerebral Blood Flow Velocity and Blood Pressure changes

CBFV, BP and HR prior to HUT, at 1 minute and 3 minutes of HUT, and prior to the end of HUT are shown in Appendix Table 80, Table 81, Table 82 and Table 83 respectively. At the top of each table, the number of participants included for each variable is given as not all participants had an adequate quality data at all time-points.

### 16.3.1 Blood Pressure and Heart Rate with HUT

The effect of HUT, with placebo or glucose in both the No PPH and the PPH groups, on SBP (Figure 70), DBP (Figure 71), MAP (Figure 72) and HR (Figure 73) are shown. There were no significant differences in SBP, DBP or MAP at any of the time points between the No PPH and PPH groups (Appendix Table 80, Table 81, Table 82 and Table 83). It should be noted from Appendix Table 80, that the heart rate in the No PPH group was statistically higher in the placebo arm (Wilcoxon Signed Ranks Test $p=0.025$). Furthermore, the SBP was significantly higher in the PPH group during the placebo phase (Mann Whitney U Test, $p=0.034$, Appendix Table 80). Friedman's two way analysis of variance for related samples demonstrated that there were significant changes in SBP, DBP and HR from pre-HUT in all groups ($p<0.01$). In general one would expect a greater fall in BP with glucose in the PPH group compared to placebo, and compared to the No PPH group.

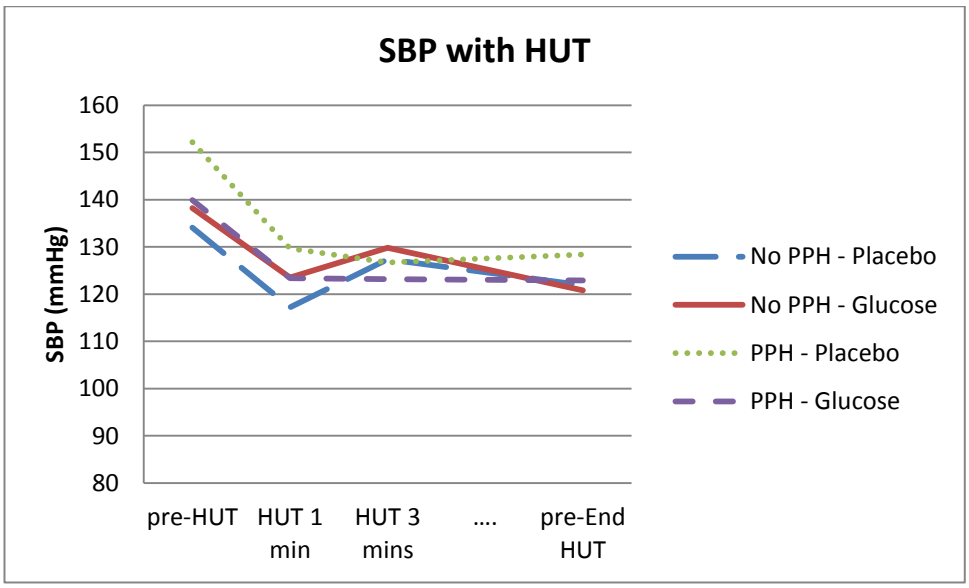



**Figure 70 The effect of HUT on SBP** ***(… = varying time scale)***

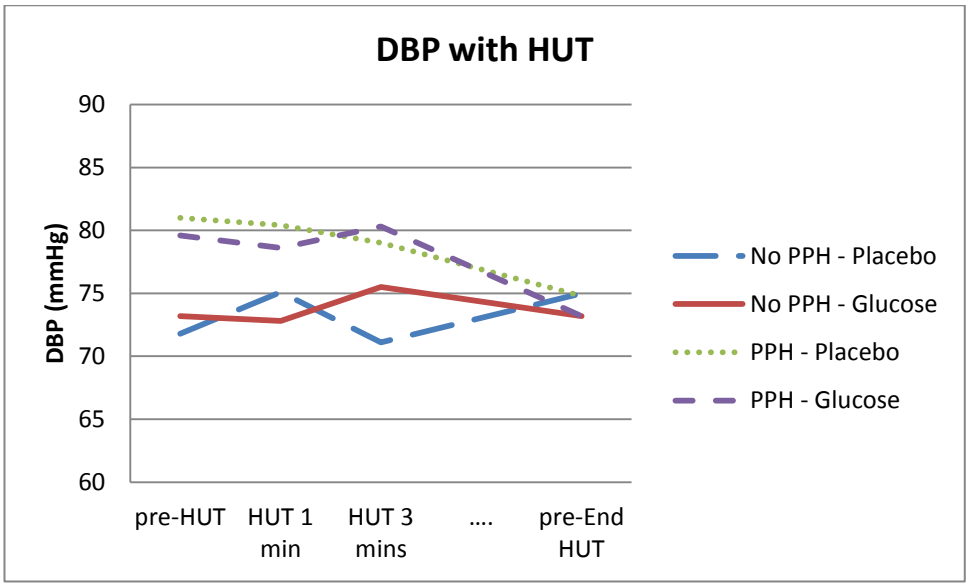



**Figure 71 The effect of HUT on DBP** ***(… = varying time scale)***

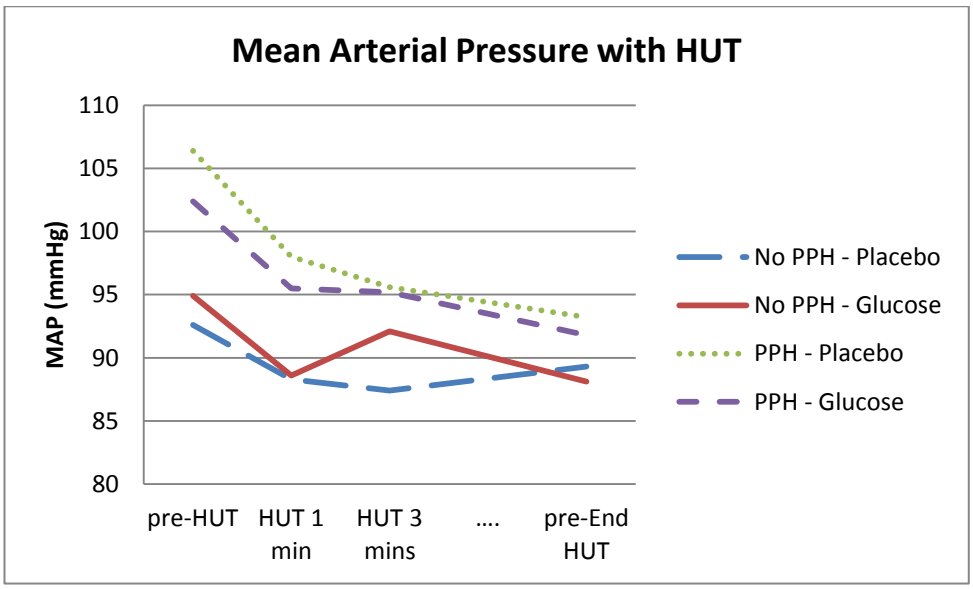



**Figure 72 The effect of HUT on MAP** ***(… = varying time scale)***

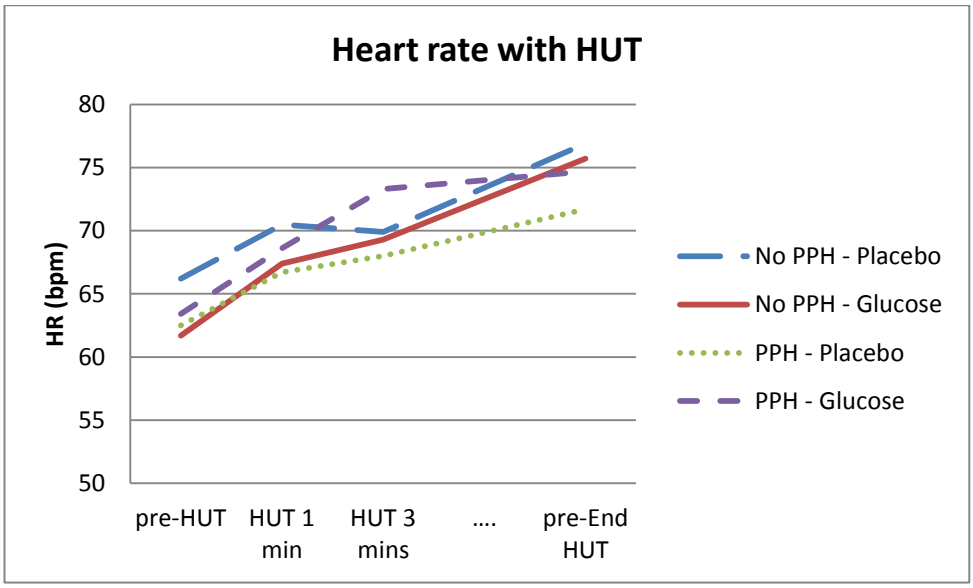



**Figure 73 The effect of HUT on HR** ***(… = varying time scale)***

### 16.3.2 Cerebral Haemodynamic responses to HUT

The effect of HUT on CBFV and $tCO_2$ are shown below (see Figure 74 and Figure 75).

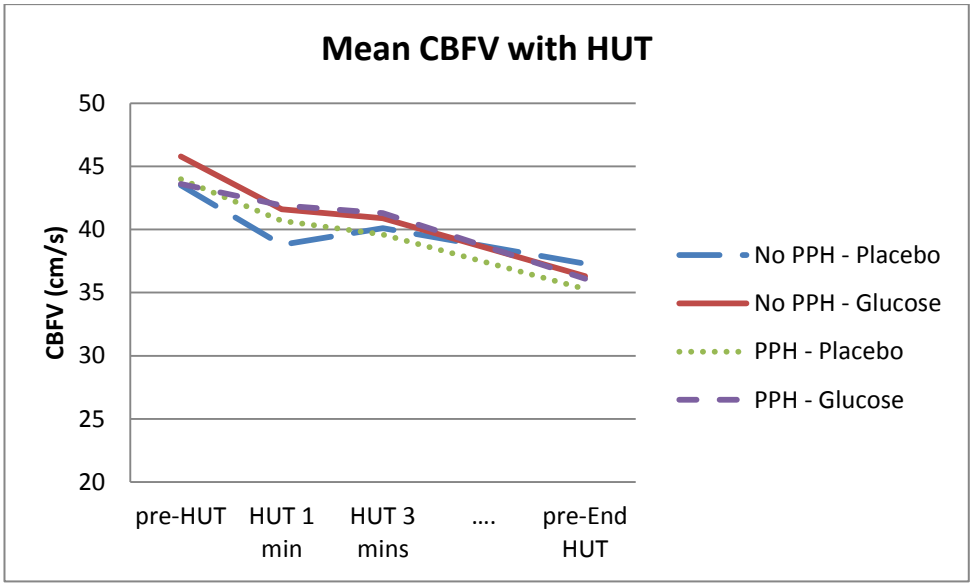



**Figure 74 The effect of HUT on the mean of left and right (combined) CBFV** ***(… = varying time scale)***

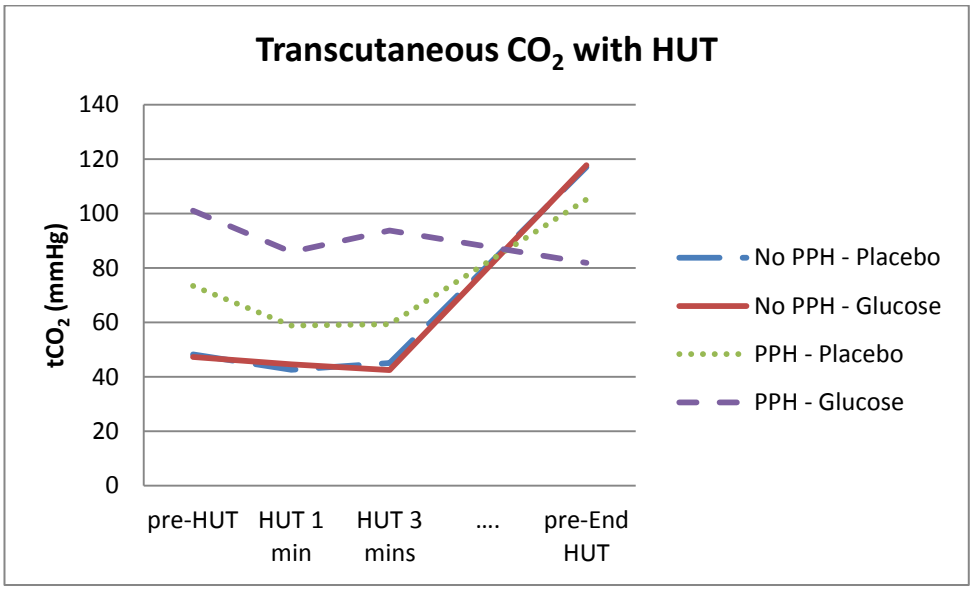



**Figure 75 The effect of HUT on $tCO_2$** ***(… = varying time scale)***

In the glucose phase, the right systolic CBFV was higher in the No PPH group (Mann Whitney U Test, p=0.030). It is unclear as to why this may the case. There were few significant differences between hemispheres at either 1 or 3 minutes of HUT, nor towards the end of HUT (Appendix Table 81, Table 82 and Table 83 respectively).

Towards the end of HUT the $tCO_2$ was statistically higher in the No PPH group of the glucose arm than the PPH group (Mann Whitney U, p=0.043), why this was the case is unclear but may be related to glucose metabolism.

## 16.4 Group Changes during HUT

In this section the differences between measurements in the minute prior to HUT were compared to those at 1 and 3 minutes of HUT and the 1 minute prior to the end of HUT, and are shown in Appendix Table 84, Table 85 and Table 86 respectively. These changes are also illustrated in the Figures below.

### 16.4.1 Changes in Blood Pressure and Heart Rate

There was a marked fall in SBP at 3 minutes of HUT in the PPH group during the placebo arm (Mann Whitney U test, p=0.027). However at the end of HUT there were no statistical differences between groups or phases. For the change in HR at 3 minutes of HUT (Table 85) there was a statistically significant increase in the HR in the glucose arm of the No PPH group (Wilcoxon Signed Ranks test, p=0.028). However there was no statistical difference in the change in HR the placebo and glucose phase for the two groups, nor between the two groups. Graphs of the change in SBP (Figure 76), DBP (Figure 77) and HR (Figure 78) during HUT are shown below. The changes over time were significantly different within each phase of each group ($p<0.01$). Although the graphs illustrate the expected greatest decline in SBP is in the glucose arms of the PPH group, with the second greatest decline by the end of HUT being found in the glucose arm of the No PPH group. This was not statistically significant. This was associated with a similar pattern with DBP, but again not statistically significant. These patterns in BP may be partly explained by the smaller increase in HR at the end of HUT with the PPH glucose arm, albeit not shown to be significant.

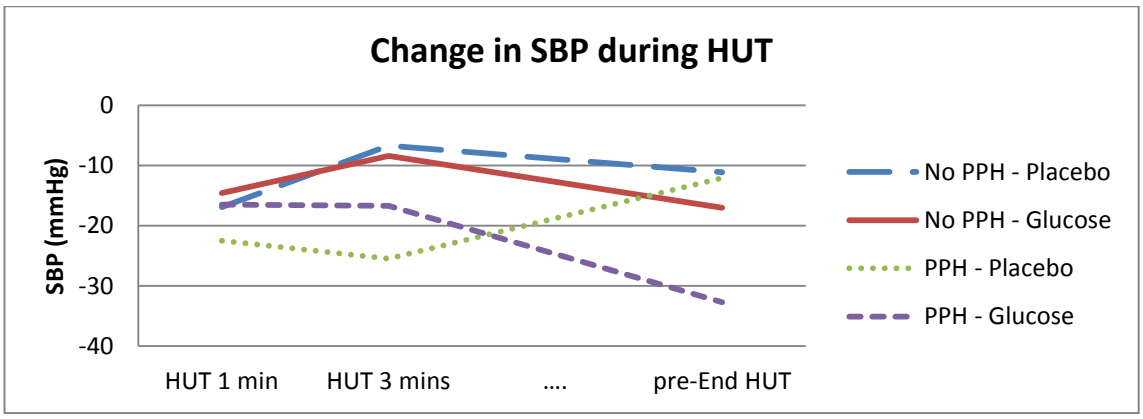



**Figure 76 The mean group change in SBP during HUT*(… = varying time scale)***

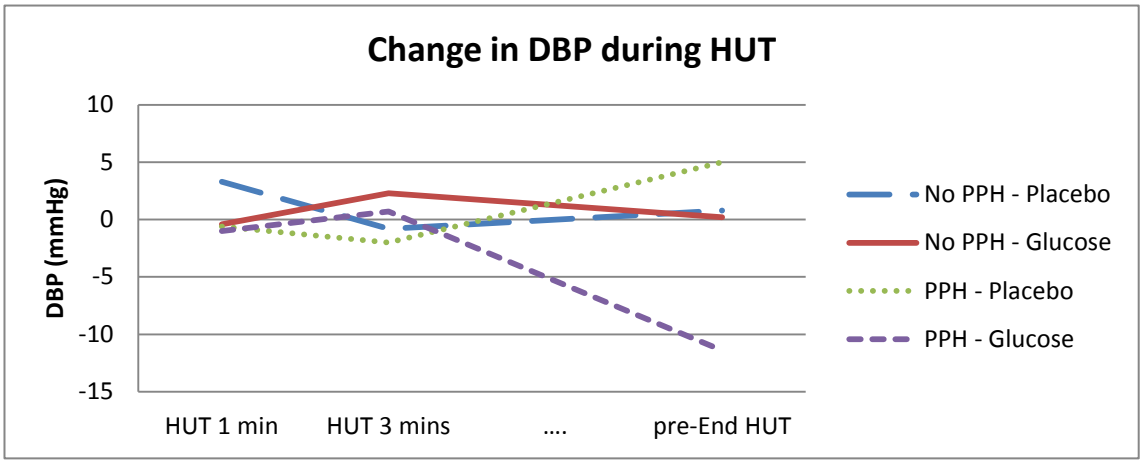



**Figure 77 The mean group change in DBP during HUT *(… = varying time scale)***

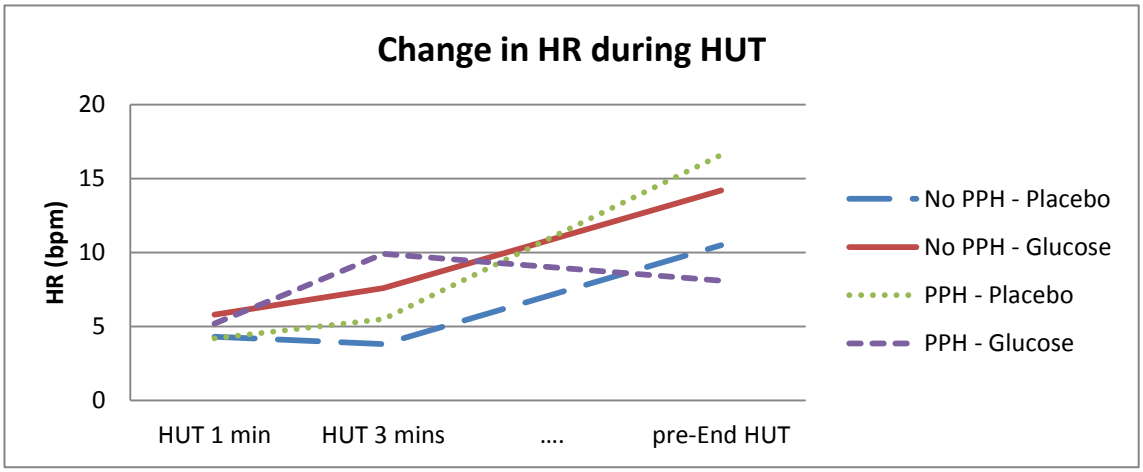



**Figure 78 The mean group change in HR during HUT*(… = varying time scale)***

### 16.4.2 Changes in Cerebral Haemodynamic values

The mean change of the combined left and right MCA is shown in Figure 79. The change in the mean systolic CBFV at 1 minute of HUT compared to pre-HUT, was greater in the No PPH group, with a statistically significant greater fall seen (Mann Whitney U, p=0.023) (Appendix Table 84). Furthermore at 3 minutes of HUT(Appendix Table 85) in the glucose arm, the fall in the right systolic CBFV was greater in the No PPH group (Mann Whitney U p=0.018).

In the No PPH group when comparing measurements at the end of HUT compared to before HUT (Appendix Table 86) CBFV on the right showed a greater reduction in the glucose arm (Wilcoxon Signed Rank test, p=0.020). This was also significant for the right MCA systolic and diastolic CBFV components individually (Wilcoxon Signed Ranks p=0.011 and p=0.015 respectively). $TCO_2$ (Figure 80) showed greater increases in the No PPH group at the end of HUT in the placebo arm (Mann Whitney U, p=0.018) as well as the glucose arm where $tCO_2$ was falling at the end of HUT (Mann Whitney U, p=0.002). In the PPH group, a relative fall in $tCO_2$ was seen during the glucose phase, compared a slight increase in the placebo arm, albeit this increase was smaller than the No PPH placebo or glucose phase for end of HUT (Table 86). This may suggest a metabolic effect of glucose on $tCO_2$, and thus CA.

Hypothetically one would perhaps expect a greater fall in CBFV in the PPH group with glucose compared to the No PPH group, and similarly one may expect no difference between groups with placebo.

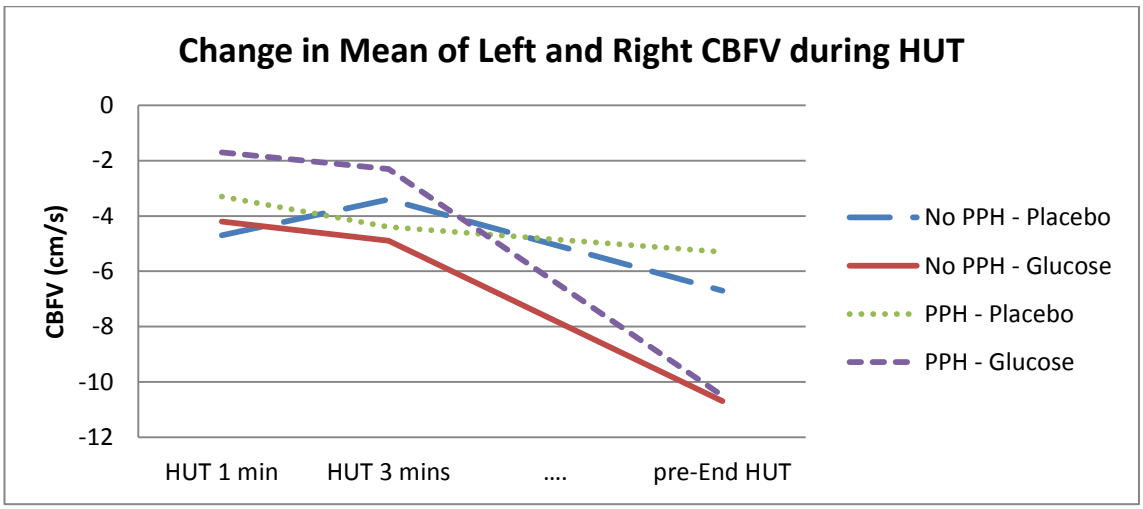



**Figure 79 The mean group change in CBFV (combined mean of left and right CBFV) during HUT *(… = varying time scale)***

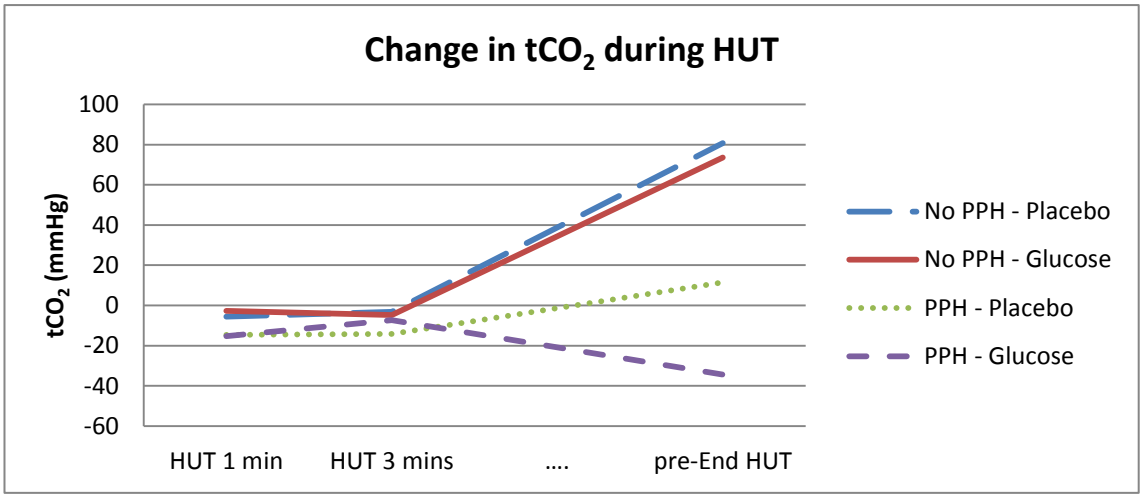



**Figure 80 The mean group change in $tCO_2$ during HUT *(… = varying time scale)***

## 16.5 Time varying estimates of ARI

This section uses a mathematical method of calculating time varying estimates of data. As such actual values of ARI may differ from the previous sections because only optimal very high quality data files were used to assess ARI in the 1 minute prior to HUT, the first minute after HUT, and between the second and third minute of HUT. The number of participants used are shown at the top of each table. Each participant's data were divided into 100 samples for each 1 minute period. Thus a SD is also give for these 100 samples, as well as the group SD. It should be noted that not all participants had the required quality of data for the HUT or the end of HUT (where the patients is returned to the supine position). As there were significant differences between left and right MCA CBFVs, the ARI and other variables have been reported separately. The HUT component as previously discussed in the General Methods section, can be split into the "UP" and "DOWN" components. Graphs of the time varying ARI can be found between the two "UP" and "DOWN" sections and include the mean of right and left MCA (Figure 81), right MCA (Figure 82), and left MCA (Figure 83).

### 16.5.1 The "UP" component: Pre-HUT

The mean ARI of both sides i.e. combined value (Appendix Table 87) did not show significant differences within the groups, but did for between groups in the glucose arm, being lower in the PPH group. This difference is interesting as participants are in the supine position. There were significant differences in the ARI and CBFV between the No PPH and PPH groups, as well as within the groups (placebo vs. glucose) in the right MCA (Appendix Table 88), left MCA (Appendix Table 89) in the minute preceding HUT.

### 16.5.2 The "UP" component: HUT 1 minute

The mean of both the right and left MCA (i.e. combined values) showed a significant difference within and between groups (Appendix Table 90) in the first minute of HUT. A higher ARI in the No PPH group for placebo, with a lower ARI for glucose, but for the PPH group the reverse was true. A statistically significant higher combined CBFV in both groups was associated with glucose. This was also true for the differences in the ARI and CBFV between and within the groups in the right MCA (Appendix Table 91), left MCA (Appendix Table 92). The only exception to this was that the PPH group did not show a significant difference in the right MCA ARI with placebo and glucose. However at this stage glucose will have yet to be absorbed, and thus any differences cannot be attributed to post-prandial falls.

### 16.5.3 The "UP" component: HUT 2 minutes

At 2 minutes of HUT (Appendix Table 93), the combined right and left MCA ARI, the No PPH group did not show a difference between the placebo and glucose arm. However in the PPH group with glucose ARI values were higher and a significantly higher ARI was found in the PPH group for both placebo and glucose. There were significant differences in the ARI and CBFV between groups in the right MCA (Appendix Table 94) and the left MCA (Appendix Table 95). It is likely that any differences are attributable to postural changes rather than glucose.

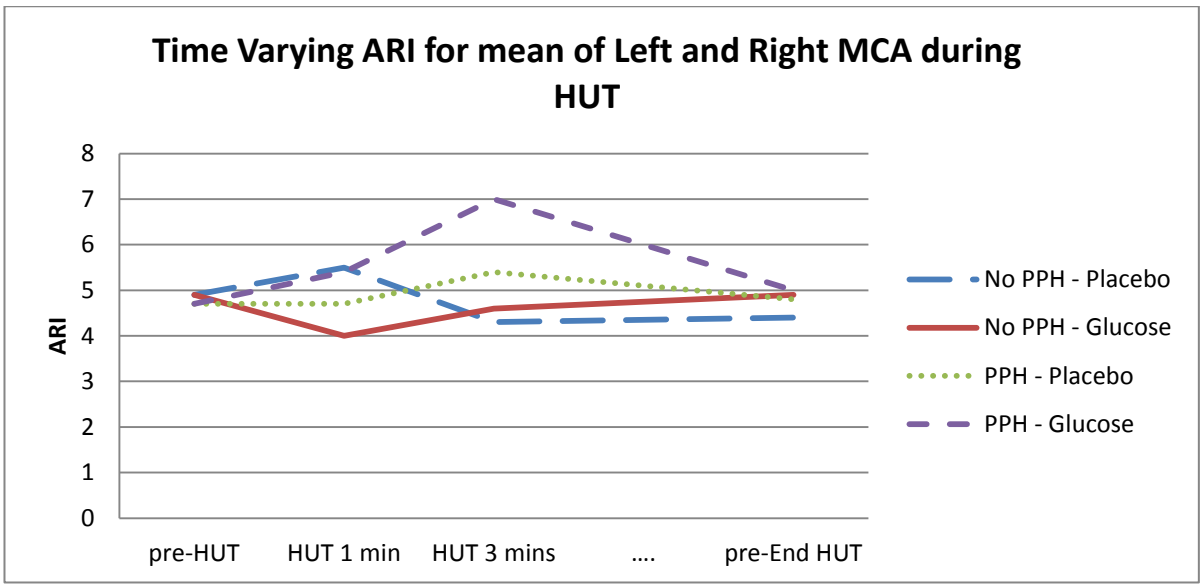



**Figure 81 Mean of Right and Left MCA Time Varying ARI** ***(… = varying time scale)***

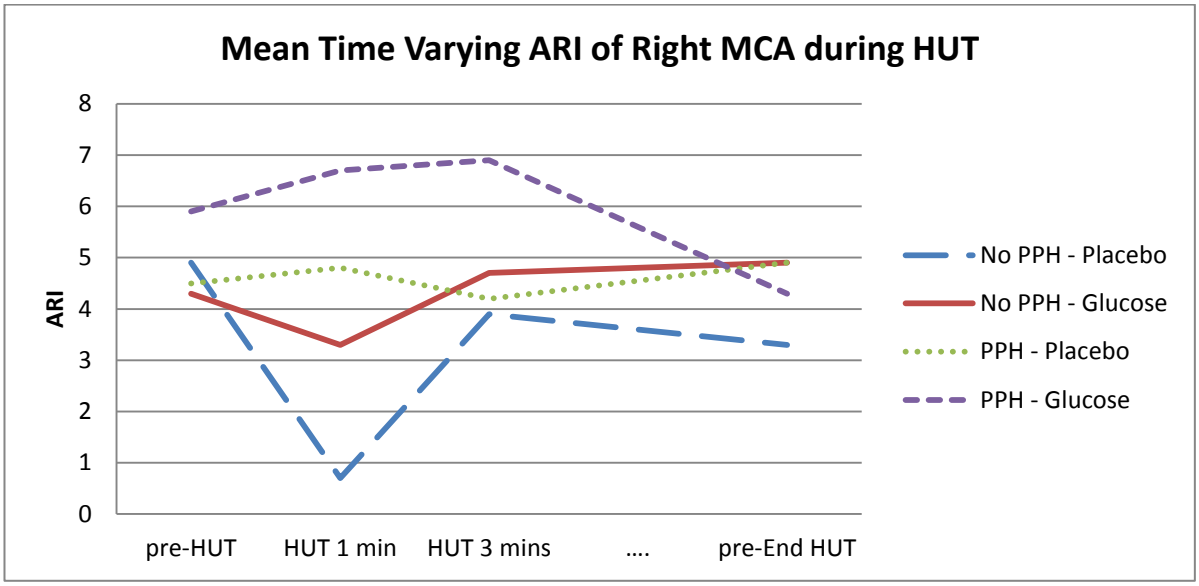



**Figure 82 Right MCA Time varying ARI** ***(… = varying time scale)***

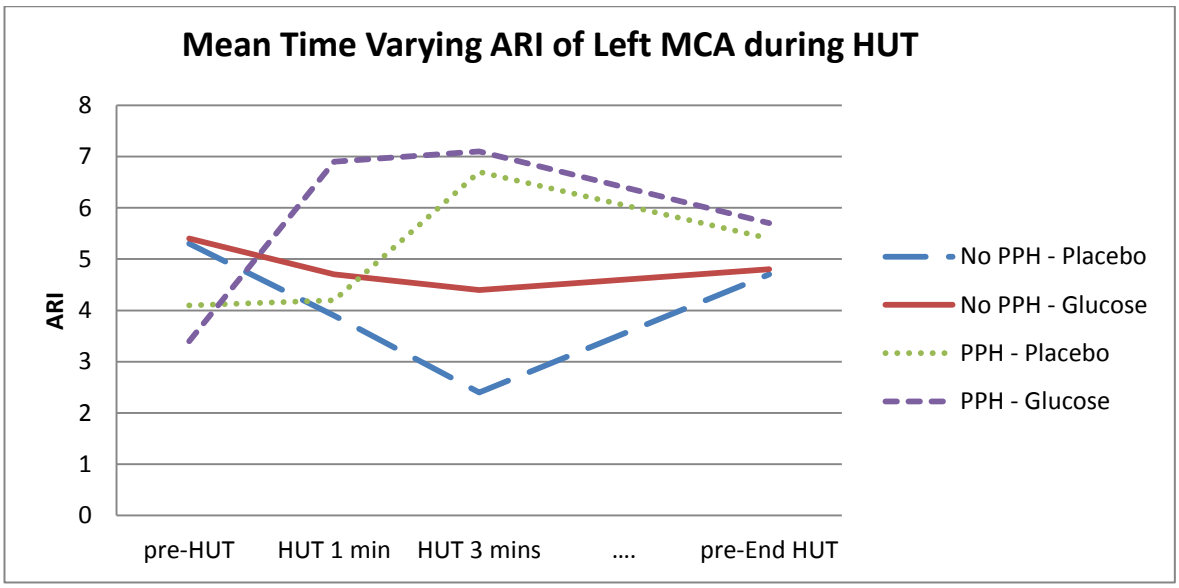



**Figure 83 Left MCA Time varying ARI** ***(… = varying time scale)***

### 16.5.4 The "DOWN" component: Prior to end of HUT

There were significant differences in ARI and CBFV between the groups in the minute prior to the end of HUT, for the mean of the combined right and left MCA (Appendix Table 96) as well as the individual right MCA (Appendix Table 97) and left MCA (Appendix Table 98). This time period is perhaps the most interesting when considering post-prandial falls, as the PPH glucose arm shows the greatest decline in ARI from the 3 minute of HUT mark and along with No PPH glucose shows a decline in CBFV.

### 16.5.5 The "DOWN" component: Post-HUT 1 minute

Even in the one minute after the end of HUT, there persisted a significant difference in ARI and CBFV between the groups (Appendix Table 99), and individually the right MCA (Appendix Table 100) and the left MCA (Appendix Table 101).

### 16.5.6 The "DOWN" component: Post-HUT 2 minutes

Looking at 2 minutes after the end of HUT, the combined mean of right and left MCA values (Appendix Table 102) for ARI and CBFV remained significantly different between the groups, as well as in the individual cases of the right MCA (Appendix Table 103) and the left MCA (Appendix Table 104).

### 16.5.7 Group Changes during HUT

#### *16.5.7.1 Blood pressure and Heart Rate*

The actual changes at 1 minute, 2 minutes and at the end of HUT compared to pre-HUT are shown (see Appendix Table 105, Table 106, Table 107). The % changes are shown in tables (Appendix Table 108, Table 109, Table 110) and are illustrated in graphs (Figure 84, Figure 85).

MAP at 1 minute HUT, showed a significant change within the No PPH and the PPH group (placebo vs glucose) as well as between these groups for placebo, but not for glucose (Appendix Table 105). With glucose (vs placebo), the HR showed a statistically significant small fall in both groups (Appendix Table 105). In general by the end of HUT, all groups showed no change or an increase in MAP, surprisingly the greatest increase was in the PPH group.

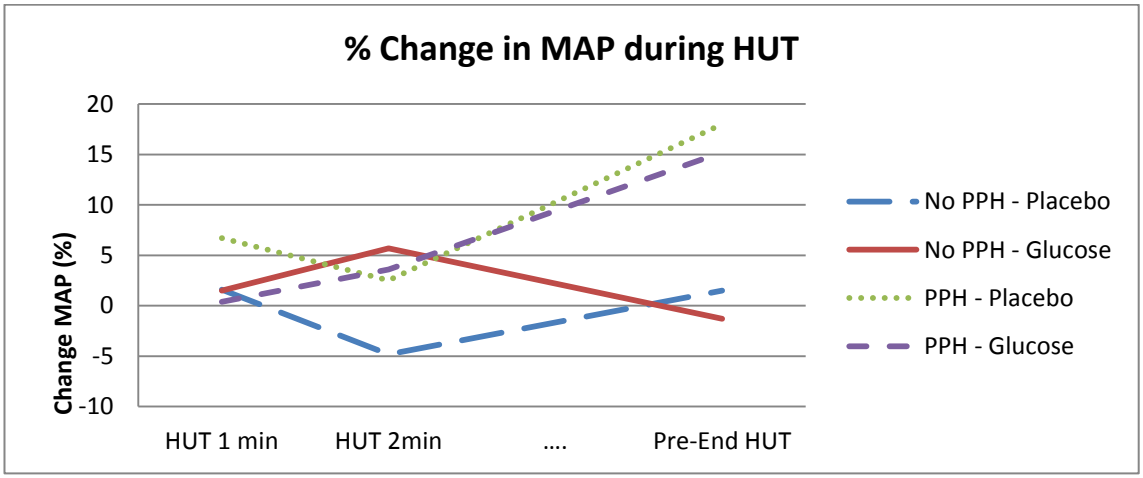



**Figure 84 The percentage change in MAP from pre-HUT during HUT** ***(… = varying time scale)***

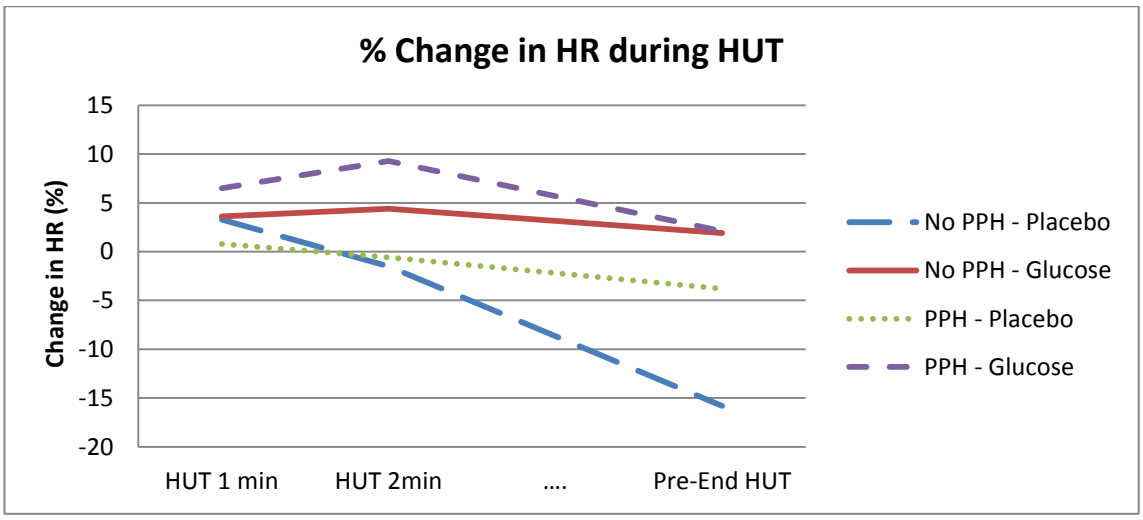



**Figure 85 The percentage change in HR from pre-HUT during HUT** ***(… = varying time scale)***

### *16.5.7.2 Dynamic Cerebral Auto-regulation*

The actual changes at 1 minute, 2 minutes and at the end of HUT compared to pre-HUT are shown (see Appendix Table 105, Table 106, Table 107). The % changes are shown in tables (Appendix Table 108, Table 109, Table 110) including graphs of CBFV (Figure 86) and ARI (Figure 87).

There were no significant differences in the change of ARI with placebo between the No PPH and the PPH group at 1 minute of HUT. However there was a significant difference when glucose was given, with a small positive change in ARI being seen in the PPH group by the end of HUT (Figure 87). The increase in ARI in the PPH group may reflect attempts at maintaining CBFV with glucose ingestion. However the fall in ARI in the No PPH group may suggest a failure of dCA due to posture, regardless of whether in the glucose or placebo phase. It is likely that the general fall in CBFV over the period of HUT is more to do with posture, although the glucose arms of both groups show a greater decline, which may be metabolically related.

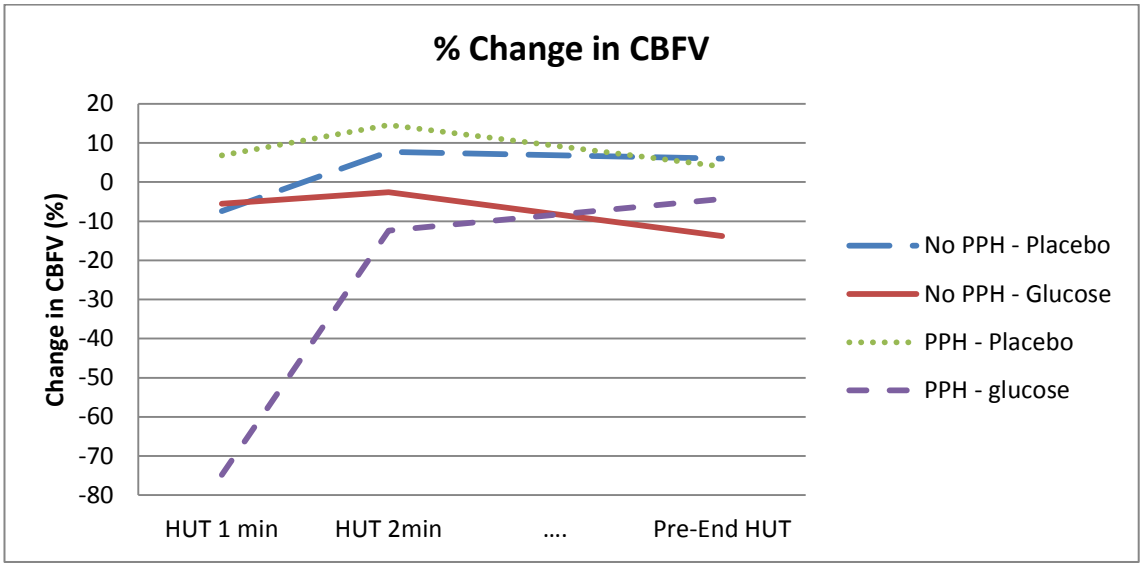



**Figure 86 The percentage change in CBFV from pre-HUT during HUT *(… = varying time scale)***

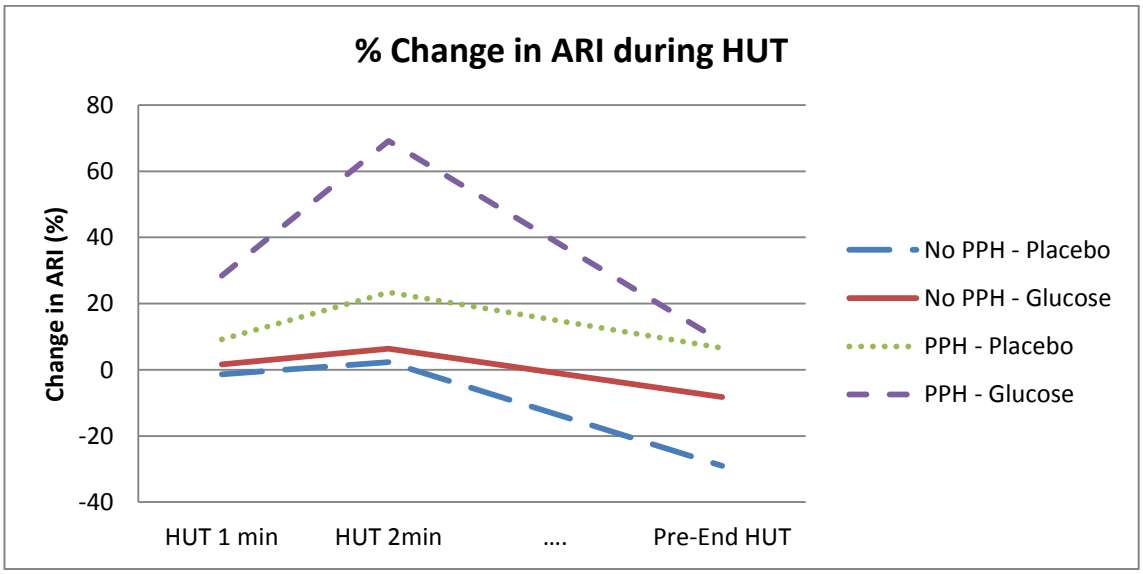



**Figure 87 The percentage change in ARI from pre-HUT during HUT *(… = varying time scale)***

## 16.6 Sub-group analysis

This section was limited by the quality of data files required for time varying analysis. Like for OH, it was difficult to determine from the original groupings, whether participants were likely to have a significant fall in BP with glucose, and thus post-hoc analysis was carried out dividing the participants into those who did have a post-prandial fall in BP and those who did not, firstly based on their original symptomatic (i.e. likely PPH) and asymptomatic groups (i.e. No PPH); and secondly with all participants combined based on actual HUT irrespective of original groups or phase (i.e. both glucose and placebo combined).

### 16.6.1 Post-prandial fall in BP

The participants who had evidence of a significant fall in SBP during HUT were divided into four. Each individual participant was only represented once. Therefore placebo asymptomatic BP decrease (n=5), placebo symptomatic BP decrease (n=6), glucose asymptomatic BP decrease (n=10), glucose symptomatic BP decrease (n=2).

Analysing the change from pre-HUT (Table 32) to end-HUT, those who received placebo were compared asymptomatic vs symptomatic, and similarly for glucose; and furthermore those who were asymptomatic or symptomatic, were compared placebo versus glucose. A further analysis compared those with symptoms and those who remained symptomatic regardless of whether placebo or glucose (Table 33). Figure 88 and Figure 89 illustrate the changes.

| | Placebo Asymptomatic (n=5) | | Placebo Symptomatic (n=6) | | Placebo (Mann-Whitney, p-value) | Glucose Asymptomatic (n=10) | | Glucose Symptomatic (n=2) | | Glucose (Mann-Whitney, p-value) | Asymptomatic (Wilcoxon Signed Ranks, p-value) | Symptomatic (Wilcoxon Signed Ranks, p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | | |
| **Combined CBFV (cm/s)** | 36.4 | *1.5* | 38.0 | *1.8* | <0.001 | 32.7 | *8.8* | 34.1 | *1.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 11.6 | *0.5* | 6.2 | *1.3* | <0.001 | 5.6 | *1.1* | 5.6 | *0.6* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 75.3 | *4.1* | 106.0 | *2.4* | <0.001 | 84.4 | *6.4* | 92.2 | *3.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 10.5 | *1.8* | 9.4 | *2.3* | <0.001 | 5.0 | *0.8* | 26.8 | *4.5* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 39.4 | *3.0* | 57.8 | *2.0* | <0.001 | 123.6 | *8.6* | 56.4 | *6.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 51.5 | *3.9* | 45.1 | *1.8* | <0.001 | 47.8 | *1.5* | 52.7 | *6.1* | <0.001 | <0.001 | <0.001 |
| **Combined ARI** | 5.2 | *0.3* | 4.7 | *0.8* | <0.001 | 3.2 | *1.7* | 5.6 | *0.35* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.0 | *0.3* | 2.5 | *0.5* | <0.001 | 0.5 | *0.1* | 1.0 | *0.4* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 67.9 | *3.1* | 69.5 | *1.1* | <0.001 | 68.4 | *1.7* | 72.4 | *3.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 11.4 | *2.7* | 9.8 | *1.4* | <0.001 | 6.9 | *1.2* | 5.1 | *3.9* | <0.001 | <0.001 | <0.001 |

**Table 32 Fall in BP, pre-HUT parameters asymptomatic versus symptomatic with placebo and glucose**

| | Placebo Asymptomatic (n=5) | | Placebo Symptomatic (n=6) | | Placebo (Mann-Whitney, p-value) | Glucose Asymptomatic (n=10) | | Glucose Symptomatic (n=2) | | Glucose (Mann-Whitney, p-value) | Asymptomatic (Wilcoxon Signed Ranks, p-value) | Symptomatic (Wilcoxon Signed Ranks, p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | | |
| **Change in combined CBFV (cm/s)** | -9.9 | *2.1* | -9.8 | *2.8* | <0.001 | 2.6 | *10.1* | 2.6 | *2.2* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 3.5 | *1.0* | 3.6 | *1.5* | <0.001 | 8.6 | *2.5* | -2.8 | *0.6* | <0.001 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | 6.6 | *7.4* | -15.6 | *3.5* | <0.001 | 5.8 | *7.0* | -2.0 | *4.2* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 2.6 | *3.9* | 14.3 | *2.0* | <0.001 | 15.5 | *2.7* | -21.2 | *4.5* | <0.001 | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 79.0 | *8.5* | 30.7 | *3.8* | <0.001 | 7.8 | *7.6* | 80.0 | *6.8* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -29.0 | *5.7* | -15.4 | *2.9* | <0.001 | 20.1 | *2.7* | -51.3 | *6.1* | <0.001 | <0.001 | <0.001 |
| **Change in combined ARI** | -0.1 | *1.0* | -1.0 | *0.8* | <0.001 | 1.5 | *2.6* | -1.8 | *1.1* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 0.7 | *0.3* | -0.2 | *0.6* | <0.001 | 2.7 | *0.5* | -0.1 | *0.6* | <0.001 | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 2.3 | *6.8* | -12.7 | *2.8* | <0.001 | -1.2 | *4.4* | -1.4 | *4.0* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -1.1 | *4.1* | 23.1 | *2.5* | <0.001 | 9.3 | *4.1* | -3.7 | *3.8* | <0.001 | <0.001 | <0.001 |

**Table 33 Fall in BP, comparing changes in parameters asymptomatic versus symptomatic with placebo and glucose**

There is evidence that ARI decreases significantly ($p<0.001$) in those who are symptomatic compared to those who are asymptomatic whether they have consumed placebo (mean -1.0 vs. -0.1) or glucose (mean -1.8 vs. 2.7) associated with a fall in SBP ≥20mmHg. It is likely that those who had a fall in BP with placebo had orthostatic hypotension.

### 16.6.2 No post-prandial fall in BP

Those who did not have evidence of a significant fall in SBP during HUT were similarly divided. Thus placebo asymptomatic no significant BP decrease (n=11), placebo symptomatic no BP decrease (n=3), glucose asymptomatic no BP decrease (n=10), glucose symptomatic no BP decrease (n=6). As for those with a fall in BP, analysing the change from pre-HUT (Table 34) to end-HUT was carried out in a similar fashion. Those who received placebo were compared asymptomatic vs symptomatic, and similarly for glucose; and furthermore those who were asymptomatic or symptomatic, were compared placebo versus glucose. In addition further analysis compared those with symptoms and those who remained asymptomatic regardless of whether placebo or glucose (Table 35). Figure 88 and Figure 89 illustrate the relative changes as mean values of combined ARI and combined CBFV.

| | Placebo Asymptomatic (n=5) | | Placebo Symptomatic (n=6) | | Placebo (Mann-Whitney, p-value) | Glucose Asymptomatic (n=10) | | Glucose Symptomatic (n=2) | | Glucose (Mann-Whitney, p-value) | Asymptomatic (Wilcoxon Signed Ranks, p-value) | Symptomatic (Wilcoxon Signed Ranks, p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | | |
| **Combined CBFV (cm/s)** | 36.6 | *1.5* | 41.4 | *2.3* | <0.001 | 37.4 | *1.8* | 39.4 | *2.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 12.8 | *0.9* | 10.2 | *2.1* | <0.001 | 5.5 | *1.3* | 6.7 | *1.7* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 90.2 | *2.6* | 90.8 | *3.5* | <0.001 | 95.4 | *1.9* | 100.1 | *3.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 15.8 | *1.6* | 18.2 | *4.4* | <0.001 | 15.0 | *1.6* | 15.5 | *5.3* | <0.001 | 0.006 | <0.001 |
| **$tCO_2$ (mmHg)** | 36.2 | *1.6* | 71.4 | *4.1* | <0.001 | 54.5 | *1.6* | 104.5 | *2.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 51.4 | *2.4* | 48.6 | *3.4* | <0.001 | 48.8 | *1.2* | 53.8 | *1.8* | <0.001 | <0.001 | <0.001 |
| **Combined ARI** | 4.5 | *0.3* | 5.6 | *1.0* | <0.001 | 5.7 | *0.3* | 4.5 | *0.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 3.1 | *0.2* | 2.6 | *0.7* | <0.001 | 2.0 | *0.5* | 2.1 | *0.4* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 66.3 | *2.1* | 66.8 | *2.3* | <0.001 | 75.8 | *2.2* | 64.6 | *1.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 8.4 | *3.2* | 2.9 | *1.9* | <0.001 | 20.0 | *2.0* | 4.7 | *1.7* | <0.001 | <0.001 | <0.001 |

**Table 34 No fall in BP, pre-HUT parameters asymptomatic versus symptomatic with placebo and glucose**

| | Placebo Asymptomatic (n=11) | | Placebo Symptomatic (n=3) | | Placebo (Mann-Whitney, p-value) | Glucose Asymptomatic (n=10) | | Glucose Symptomatic (n=6) | | Glucose (Mann-Whitney, p-value) | Asymptomatic (Wilcoxon Signed Ranks, p-value) | Symptomatic (Wilcoxon Signed Ranks, p-value) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | | |
| **Change in combined CBFV (cm/s)** | 3.4 | *1.9* | -0.1 | *3.5* | <0.001 | 4.1 | *1.8* | -5.4 | *3.8* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -2.8 | *2.1* | -2.2 | *3.2* | <0.001 | 0.9 | *1.4* | 0.0 | *3.8* | <0.001 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | 9.5 | *2.8* | 13.0 | *4.7* | <0.001 | 1.6 | *2.6* | -1.8 | *4.4* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -5.7 | *2.4* | -15.7 | *4.7* | <0.001 | -9.9 | *2.2* | -5.6 | *5.1* | <0.001 | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 114.6 | *4.0* | -2.8 | *4.7* | <0.001 | 96.7 | *3.1* | -30.4 | *4.6* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -36.9 | *4.2* | 16.6 | *3.9* | <0.001 | -43.0 | *2.3* | -3.1 | *3.5* | <0.001 | <0.001 | <0.001 |
| **Change in combined ARI** | -0.3 | *0.6* | -1.4 | *1.4* | <0.001 | 0.7 | *0.8* | 0.9 | *0.5* | 0.016 | <0.001 | <0.001 |
| Change in SD time sample | -0.6 | *0.3* | -0.2 | *1.2* | <0.001 | -0.7 | *0.8* | 0.7 | *0.8* | <0.001 | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | -3.1 | *3.3* | 0.3 | *3.2* | <0.001 | -13.8 | *2.4* | 9.0 | *3.5* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -5.2 | *3.3* | 2.4 | *2.2* | <0.001 | -16.1 | *3.1* | 2.8 | *4.2* | <0.001 | <0.001 | <0.001 |

**Table 35 No fall in BP, comparing the changes in parameters asymptomatic versus symptomatic with placebo and glucose**

### 16.6.3 BP fall versus No BP fall comparison

Comparing those with and without falls in SBP ≥20mmHg amongst those who were Asymptomatic with placebo showed that pre-HUT were significantly different ($p<0.001$) for all parameters, except the combined right and left CBFV ($p=0.97$). The changes in parameters were different between these two groups except for ARI ($p=0.08$) with similar falls in ARI (-0.3 vs. -0.1). With glucose, the pre-HUT parameters were different for those with and without falls in BP ($p<0.001$). However there was no significant difference in ARI increase (0.7 vs. 1.5, $p=0.62$) for the asymptomatic glucose group regardless of whether they had a fall in SBP or not. Although MAP, HR, CBFV, $tCO_2$ changes differed ($p<0.001$).

Amongst those who were symptomatic with placebo, there were differences in pre-HUT parameters between those with and without falls in SBP ($p<0.001$). The changes were also different ($p<0.001$), except for reduction in ARI, which were similar for those with and without a fall in BP (-1.0 vs -1.4, $p=0.07$). With glucose, in those who were symptomatic, the baseline parameters and changes with HUT differed between those with and without falls in BP during HUT ($p<0.001$). ARI was also different between those with or without a BP fall (-1.8 vs. 0.9, $p<0.001$). Figure 88 and Figure 89 illustrate the changes in ARI and CBFV.

### 16.6.4 Symptomatic versus Asymptomatic combined groups

As the previous post-hoc analysis suggested possible trends, and the numbers were small, further analysis was carried out. Thus in order to determine the influence of dCA on symptoms, participants were divided into those who did or not have symptoms regardless of whether they received placebo or glucose and regardless of whether they demonstrated a significant fall in BP (Table 36). There was evidence of a fall in ARI amongst those who were symptomatic regardless of whether placebo or glucose was consumed, or whether there was a fall in BP ($p<0.001$). How this compares to the previous sub-group analysis is shown in Figure 88 and Figure 89 (ARI and CBFV respectively).

| | **Asymptomatic (n=37)** | | **Symptomatic (n=15)** | | **Mann-Whitney, p-value** |
|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in combined CBFV (cm/s)** | 0.1 | *7.8* | -3.2 | *5.7* | <0.001 |
| Change in SD time sample | 2.5 | *4.6* | -0.3 | *3.6* | <0.001 |
| **Change in MAP (mmHg)** | 5.9 | *6.1* | -1.6 | *11.0* | <0.001 |
| Change in SD time sample | 0.6 | *10.1* | -7.1 | *14.2* | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 74.5 | *41.1* | 19.4 | *41.5* | <0.001 |
| Change in SD time sample | -22.2 | *25.3* | -13.3 | *25.2* | <0.001 |
| **Change in combined ARI** | 0.4 | *1.6* | -0.9 | *1.4* | <0.001 |
| Change in SD time sample | 0.5 | *1.4* | 0.0 | *0.9* | <0.001 |
| **Change in Heart Rate (bpm)** | -4.0 | *7.5* | -1.2 | *8.4* | <0.001 |
| Change in SD time sample | -3.3 | *9.8* | 6.1 | *10.7* | <0.001 |

**Table 36 Asymptomatic versus Symptomatic - groups combined**

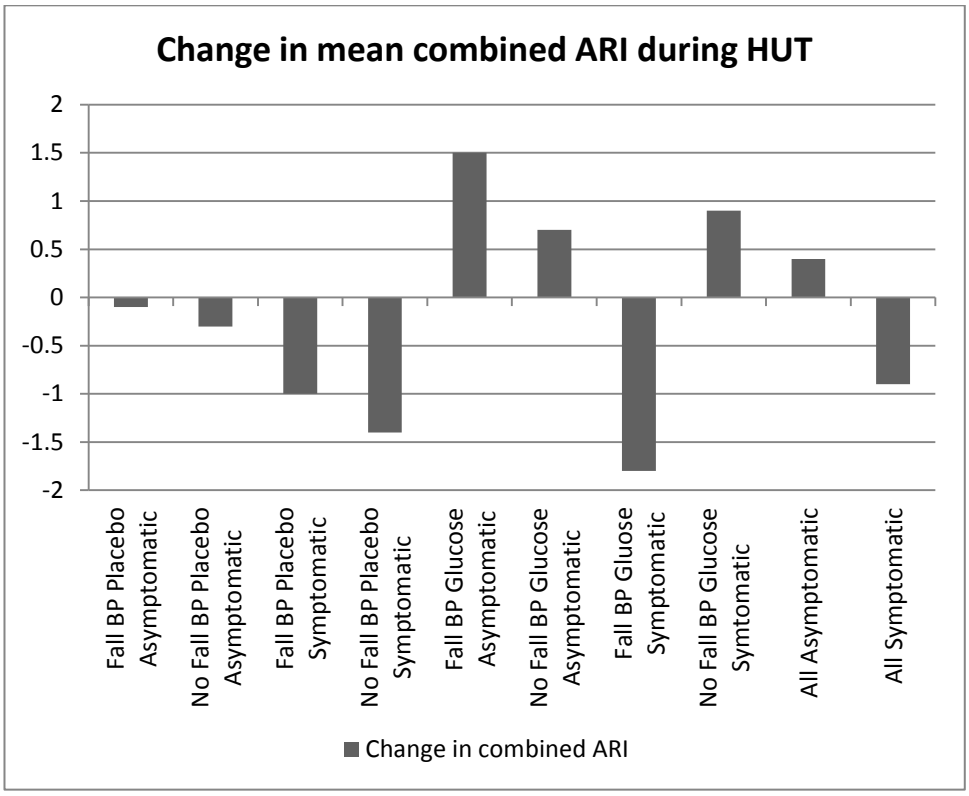



**Figure 88 The mean changes in ARI - post-hoc analysis**

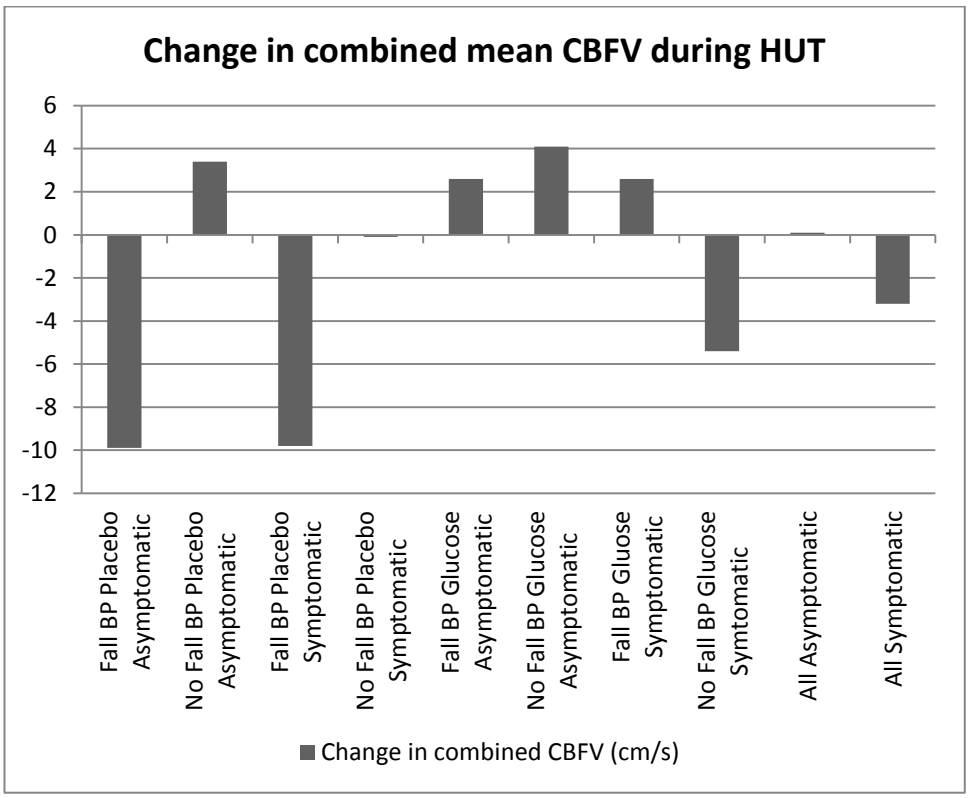



**Figure 89The mean changes in CBFV - post-hoc analysis**

## 16.7 Post-Prandial Hypotension Study – Effects of HUT Results Summary

There were no baseline differences in any of the haemodynamic (PWV, BRS) or cerebrovascular parameters (including dCA) between the PPH and non-PPH groups. After the glucose challenge the changes in capillary blood glucose levels peaked at 30 minutes with a small fall by 60 minutes with little change after placebo but no significant differences between the PPH and non-PPH groups. SBP, MAP and CBFV declined over the course of HUT, the mean fall with glucose ingestion being particularly marked in the PPH group although this did not reach formal statistical difference compared to the non-PPH group probably resulting from the large SD for the SBP changes when compared to the pre-HUT period. Associated with glucose ingestion was an increase in HR noted in both groups whether earlier or later on during HUT. Levels of $tCO_2$ remained similar in both groups in either phase in the initial post-tilt period but rose in the Non-PPH group prior to the end of tilt. In the PPH group, $tCO_2$ values remained similar throughout the two phases.

During the course of HUT there was a fall in the mean combined CBFV across all groups (Figure 79). Continuous estimates of ARI showed that whilst there was no difference in the mean values for the combined ARI for pre-HUT between groups, differences were evident between the groups for the changes after the glucose or placebo drinks from 1 minute post-tilt, with the PPH group showing significantly greater increases in ARI after both phases, with no change being seen in the non-PPH group. At 2 minutes post-tilt PPH group, again showed a significantly greater proportional increase following glucose and placebo in combined ARI but there was

no different between the placebo and glucose phase for the No PPH group. However by the end of tilt there was no difference in ARI between phases for the PPH group, but a fall in ARI was significant in the No PPH group.

Further sub-group analysis demonstrated that those who had symptoms whether or not they had a fall in BP during HUT, for either the placebo or glucose phase, had a greater reduction in ARI compared to those who were asymptomatic.

## 16.8 Post-Prandial Hypotension Study – Discussion of Effects of HUT

It was anticipated that those in the PPH group would have a significant fall in BP with glucose, but not with placebo; with the No PPH group, not having a significant fall in BP with either placebo or glucose. As it was thought that symptoms with or without falls in BP was more to do with dCA, it was hypothesised that those with symptoms without a large fall in BP would have impaired dCA. Although this study showed evidence of a fall in CBFV during HUT across all groups, it also showed evidence of a decline in dCA (i.e. ARI) in those who were symptomatic, regardless of what happened to their blood pressure. Changes in $CO_2$, BP and HR although sometimes statistically different between groups, clinically they were relatively small. The changes in CBFV within each group over the duration of HUT was statistically significant, but again, this appeared separate to the changes in dCA.

There is an associated fall in CBFV, during HUT, but the differing behaviour of each cerebral hemisphere may be due to undiagnosed significant stenosis of the cerebral arteries. A reduction in CBFV during HUT has been found amongst those with orthostatic intolerance suggesting prolonged cerebral vasoconstriction but in the post-prandial this does not appear to be related to changes in systemic BP levels or $CO_2$ levels (Lin et al., 2011). Even in young adults with initial orthostatic hypotension it has been found that there is a reduction in MCA CBFV from baseline when using HUT with lower body negative pressure which was also present with pre-syncope (Thomas et al., 2009). During HUT (without glucose ingestion) in a normal subject, it would be expected that ARI remained the same throughout (Carey et al., 2003). Although there were falls in CBFV and BP during HUT, it was the symptomatic not the asymptomatic

participants who showed a greater reduction in ARI. This was more evident with sub-group and further data analysis.

# 17 Summary of Results: Post-Prandial Hypotension Study

Post-hoc analysis demonstrated abnormalities in dCA amongst those who were symptomatic during HUT despite no evidence of differences between the two groups (PPH vs. No PPH) at baseline.

The No PPH and the PPH groups were similar in terms of age, BMI, DBP, DBP, HR, autonomic function score, postural BP changes or capillary blood glucose at baseline. They were also similar in terms of categorical data such as sex, smoking status, drugs and a history of hypertension. They did differ in terms of orthostatic grading scale score and the presence of pre-syncope, where the PPH group had a higher orthostatic grading score and more participants with a history of pre-syncope. This difference was likely due to the participant classification and group allocation.

Furthermore there was no difference at baseline within or between groups for both phases (placebo and glucose) in terms of cardiac BRS and measures of arterial stiffness (PWV and AIx). In the supine position there were no differences between the placebo and glucose phase, nor between the No PPH and the PPH groups, for the mean of combined right and left MCA: Tiecks model of ARI and ARMA-ARI models, CBFV, and these components for right and left MCAs individually. MAP as well as SBP and DBP, HR, $tCO_2$ were also no different in the supine position at baseline.

Furthermore as the continuous estimates of dCA (which had to be used in this study as other methods of dCA estimation e.g. Tiecks method call for a stable recording

situations which while suitable for baseline recordings is not appropriate in a dynamic situation such as during post-prandial tilt) relies on the need for exceptionally high quality data recordings, this resulted in the recordings from some subjects being rejected. It may be therefore that a Type 2 statistical error may have been present as there were insufficient numbers of participants available with such data especially given the natural variability of such measurements.

Using continuous estimates, ARI at the end of HUT, when participants were symptomatic or at the end of the maximal 60 minute period, were higher in the glucose arm in both the No PPH and the PPH group. This was due to a greater fall in the ARI in the No PPH placebo arm. However sub-group analysis showed evidence of a significant reduction in ARI amongst those with symptoms irrespective of whether glucose was consumed or not, or in terms of BP changes.

# 18 Summary of Discussion: Post-Prandial Hypotension Study

It was hypothesised that those who had symptoms of PPH would have abnormalities in dCA. This study is the first of its kind and suggests that those who have symptoms may have abnormalities in dCA, irrespective of BP changes. The finding of no differences between phases or groups in baseline BP has been found by others (Van Orshoven et al., 2010, Vloet et al., 2005, Jones et al., 2005) Only 38% of older people have been reported to have both PPH and OH (Vloet et al., 2005) and therefore it was not surprising that there were no differences between the two groups in terms of postural changes in BP. PPH amongst those with hypertension has been associated with cerebrovascular damage (Kohara et al., 1999), one could expect baseline differences in CBFV between the No PPH and the PPH groups. However in the population used in this thesis, there were no significant differences in supine BP between the two groups, which may account for the absence of a difference in CBFV supine position. Other research suggests that although there are differences in supine CBFV, there are no differences in ARI in healthy older adults compared to younger adults (Carey et al., 2003). AIx in this study was lower than other studies (McEniery et al., 2005, Salvi et al., 2010), although PWV was similar. BRS was similar to other studies (Dawson et al., 1999).

The absence of a statistically significant difference between groups in terms of changes in BP during HUT which one would expect (Krajewski et al., 1993) was perhaps a result of participants being classified based on a clinically history suggestive of PPH. It is likely that participant classification impacted the measures of ARI and other parameters. During HUT (without glucose ingestion) in a normal subject, it would be

expected that ARI remained the same throughout (Carey et al., 2003). Where there is systemically higher BP, it has been shown that this may be associated with lower cerebral blood flow, and thus one could expect this to indicate perhaps failure of cerebral auto-regulation (Waldstein et al., 2010). Similarly, postural changes in BP can induce falls in CBFV, and if significantly so, can indicate poor CA(Zhang et al., 1998). Age itself does not affect dynamic CA, despite a decrease in cardiac BRS being associated with ageing(Carey et al., 2000).

## 18.1 Strengths and Limitations

This is the largest study in older adults investigating the changes in dynamic CA in PPH. It has proven that older adults are willing to participate in studies which could be perceived as uncomfortable due to the duration of HUT. Although a reasonable number of participants were successfully recruited, one did withdraw due to inconvenience; another could not tolerate HUT due to symptoms and did not wish to partake further. Transcranial Doppler US signal was a limiting factor. Although reasonable quality signals were obtained in the supine position, this was not always the case during HUT, particularly at the beginning and oat the end of HUT. This resulted in a loss of data, at the critical points which were key to this study.

Classification of subjects into those with post-prandial hypotension and those without was based solely on clinical history as there is no universally agreed classification. However the general consensus is that there should be a fall in BP within a 2 hour period of meal consumption. This can inevitably lead to miss-classification of subjects and a separate analysis of those who had and those who did not have a symptomatic

BP fall after the glucose phase and not after placebo is possibly statistically underpowered in this regard. Similarly the time to the maximum fall in BP after drink ingestion varied considerably so it is perhaps not surprising that there was considerable variation in BP and dCA responses within and between groups. The glucose load used in this study (a 50g glucose drink) has been shown by others (Jones et al., 2005) to result in a peak glucose level at around 39.0±4.0 minutes (Berry et al., 2003) with an associated fall in SBP of around 10 mmHg at around 30 minutes post-ingestion hence this this dose and duration of HUT used in this study. A solid mixed meal has been shown to take as long as 67.5± 10.3 minutes to reach peak blood glucose level, with a smaller reduction in BP (Berry et al., 2003). In one small study of older people with PPH (liquid meal with 40% carbohydrate), it was shown that a statistically significant steady fall in BP occurred between 30 and 55 minutes after a meal (Krajewski et al., 1993).

## 18.2 Future work

In hindsight, perhaps it would have been better to ask participants to attend another session whereby they were screened for PPH with a glucose load, as originally considered. However this would have involved participants attending for three separate visits. At the time of planning the study, it was anticipated that recruitment for multiple or prolonged visits would increase the difficulty in recruitment. On this basis a screening for PPH using physiological measurements and a glucose load was not carried out. However several studies looking at the drug treatment of post-prandial falls in BP also did not do so either (Russo et al., 2003, O'Donovan et al., 2005, Jones et al., 2005, Gentilcore et al., 2011). However this would certainly be considered in future, where time scales for recruitment to the study was less limited. There were

participants who withdrew after one visit, as they felt it inconvenient and it was a challenge recruiting participants who were willing to attend for two visits. There were some participants who had already taken part in the OH study, who if they had not already taken part in the OH study, perhaps would have been willing to make three visits for this study.

Further analysis was based on the tilt result to assess the changes in dynamic CA, BP and HR however care must be taken in the interpretation of such post-hoc analyses. Given that only four in the glucose arm of the No PPH group and nine in the glucose phase of the PPH group had a SBP fall ≥20mmHg, any potential analysis is limited. However there was evidence that those who became symptomatic have a fall in dynamic cerebral auto-regulation which might explain their symptoms. It may be that future studies will need to have adequate screening to carefully randomise participants to No PPH and PPH groups, based on actual HUT with a glucose load prior to placebo versus glucose randomisation. Another method if time permitted would be to leave recruitment as an open and ongoing process until adequate numbers were met for each group. This would of course result in unbalanced groups, but if time permitted, then it would be one way of dealing with this problem.

## 18.3 Conclusion

In conclusion, this novel study adds new information in the area of PPH and dCA, by demonstrating no baseline haemodynamic or cerebrovascular differences between those with and without symptoms linked to post-prandial hypotension. Following glucose or placebo ingestion there was no significant fall in BP during either phase but

large individual differences in responses with glucose during HUT were found. Dynamic cerebral auto-regulation differed between placebo and glucose phases for the No PPH and the PPH groups with a higher ARI associated with glucose. Post-hoc analysis demonstrated a fall in ARI amongst any participant with symptoms.

# 19 Thesis Discussion

Individuals with orthostatic hypotension and post-prandial hypotension, both common conditions in older people, have an increased risk of cardiovascular events, falls and death. However not all those who have a fall in systemic BP levels are symptomatic (Mader et al., 1987), similarly there are those people who have symptoms of postural hypotension or post-prandial hypotension but no associated fall in BP can be detected. To date there are few effective treatments for these conditions all of which are directed at raising systemic BP levels but if the main cause of symptoms is related to abnormalities in brain blood flow control, not changes in systemic BP levels, this may be the wrong therapeutic approach. The main objectives of this thesis were therefore 1) to review the current treatments for these conditions to assess which therapies were effective in reducing symptoms and therefore giving an insight into potential underlying pathophysiological mechanisms and 2) most importantly to investigate whether abnormalities in brain blood flow control as reflected by differences in dynamic cerebral auto-regulation are present in those who are symptomatic with these conditions compared to those who are asymptomatic whether or not they have an actual fall in systemic BP.

It was hypothesised that an underlying difference in dCA may account for why some people have the symptoms associated with OH, but yet do not have the postural fall in BP expected. A difference in dCA might also account for why some who have a postural fall in BP fail to note any symptoms. Similarly for the Post-Prandial Hypotension study it was hypothesised that there are differences in dCA for those with a history of PPH compared to those without PPH, and that perhaps glucose can also

affect dCA. Other parameters which were investigated included cardiac BRS and arterial stiffness. Both of these studies were targeted at the older population and includes participants over the age of 60 years of age representative of the Caucasian population in Western society where the ageing population is of particular concern.

By understanding the physiological basis for symptomatic orthostatic hypotension and post-prandial hypotension it was anticipated that better ways of managing these conditions can be developed in the future. It has been shown in the two systematic reviews (Chapter 3 and 4) that drug treatment options at the present time are limited for both conditions, and the primary emphasis has been on improvements in postural BP rather than symptoms. Of the thirteen randomised controlled trials on OH, only three considered symptoms in addition to BP changes, two related to midodrine (Fouad-Tarazi et al., 1995, Low et al., 1997) and one related to fludrocortisone (Campbell et al., 1975). However the method of reporting differed between each study. The systematic review carried out on the treatment of OH concluded that both fludrocortisone and midodrine may be helpful in improving postural BP. Of the fourteen studies included in the systematic review on post-prandial reductions in BP, only one study commented on improvements in symptoms as well as BP, and this was with caffeine ingestion (Heseltine et al., 1991c). Furthermore, the majority of studies included did not include many with PPH, and thus did not meet the criteria of a fall ≥20mmHg within 2 hours of a start of a meal or if SBP falls to ≤90 mmHg within this period if pre-prandial SBP was ≥100 mmHg (Jansen and Lipsitz, 1995). The body of evidence from the systematic reviews was that there were very limited data as to the best treatments for these two conditions, all of which concentrated on raising systemic

BP levels without assessing the underlying mechanisms or effects on the patient's symptoms.

The second phase of this thesis focussed on the study of dynamic cerebral auto-regulation in those with and without symptoms related to postural and post-prandial hypotension as it was proposed that abnormalities in auto-regulation accounted for the symptoms related to these conditions. The first study concentrated on the mechanisms underlying the symptoms related to orthostatic hypotension, where participants were classified by whether they had evidence of a postural fall in BP in the clinic setting based on the ESC criteria for OH (≥20mmHg fall in SBP and/or a fall ≥10mmHg in DBP) (Moya et al., 2009), and had evidence of postural symptoms as recorded by the orthostatic grading scale (Schrezenmaier et al., 2005). However one of the main limitations with this method of classification is that not all participants who had a postural fall in BP on active standing would go on to have a fall on passive HUT and it is well recognized that the reproducibility of a postural BP fall with and without symptoms on standing or HUT is poor (Cooke et al., 2009). For the second study on PPH, participants were divided into two groups based on a history of symptoms of cerebral hypo-perfusion within a 2 hour period of a meal, though this classification can be inaccurate for several reasons including the accuracy of participant reporting symptoms.

The two studies in this thesis both had a sample size calculated to be big enough to detect a difference in an index of dynamic cerebral auto-regulation (dCA) i.e. ARI of clinical significance (a problem with previous studies, which were too small to detect

such a difference). All analyses were conducted blinded to the classification of the subject status (ie symptomatic or asymptomatic).

Baseline measures of cardiac baroreceptor sensitivity were similar in all groups of the OH study. This would suggest that parasympathetic cardiac control, one part of the autonomic nervous system, was not impaired and perhaps not responsible for the production of postural symptoms despite the baroreceptor being integral in control of systemic BP variation especially to posture. However both age and increasing BP are associated with impaired cardiac BRS, and other studies demonstrate that impaired BRS are common to both hypertension and OH (James and Potter, 1999, Takeshita et al., 1975, Moreira et al., 1992). In contradiction to this thesis abnormal cardiac BRS has been found in those with orthostatic intolerance without OH (i.e. symptoms and increase in HR>30bpm within 10 minutes of standing) (Farquhar et al., 2000). Cardiac BRS values were however similar to other studies using a similar aged population and methodology (Dawson et al., 1999). Arterial stiffness, as reflected by pulse wave velocity and augmentation index, was similar in all groups of the OH study. However other studies have shown an association between higher PWV (Mattace-Raso et al., 2006) or AIx (Valbusa et al., 2012) and OH in terms of BP changes alone. It is unlikely that concomitant anti-hypertensive treatment accounts for this difference between studies but cannot be discounted as some, but not all, anti-hypertensive drug groups do reduce arterial stiffness (Boutouyrie et al., 2011). The OH study groups did not show any differences in supine CBFV between groups whether or not there was a postural BP fall and if this produced symptoms. It should be remembered that although CBFV is a useful surrogate marker of CBF, it does assume that there is no significant change in arterial diameter. Cerebral auto-regulation, as measured by ARI values

(Tiecks model and ARMA-ARI), was similar amongst all OH and PPH study groups in the supine position. This is consistent with other studies which demonstrated that neither static nor dynamic ARI are affected by hypertension or age (Eames et al., 2003). Furthermore although other research suggests that differences in supine CBFV may exist, there are no differences in ARI in healthy older adults compared to younger adults (Carey et al., 2003).

For the OH study, those in the Symptomatic OH Group had lower CBFV values during HUT which became more marked with the development of symptoms, the latter probably resulting from reduced cerebral perfusion as suggested by others (Novak et al., 1998). Postural changes in systemic BP levels should not normally result in a fall in brain perfusion if cerebral auto-regulation is intact within the normal physiological BP changes seen with standing, but falls in CBFV are evident if there is impaired CA (Zhang et al., 1998). However ARI changes were similar in the Asymptomatic OH and the Symptomatic OH group suggesting that perhaps they may be one single group. The control group (Asymptomatic No OH) showed a small steady decline in ARI during the course of the HUT. The Symptomatic OH group on the other hand, shows a similar pattern to the control group, with the initial fall in ARI, steadily increasing with time. This suggests that there may be two groups to OH as a condition. Research in a smaller study (n=21, age 61.8±2.4 years) suggests the possibility of three OH groups. Those who have impaired auto-regulation with a flat flow-BP curve, those with intact auto-regulation and expansion of the systemic BP range which auto-regulation can function, and lastly a group with failure of auto-regulation associated with a steep flow-BP curve (Novak et al., 1998). Whilst this study in older people confirms falls in CBFV during HUT with symptomatic OH which occurs later in the time course of HUT, it has

additionally shown that those with asymptomatic OH have an earlier fall in CBFV which then improves towards pre-HUT values. This may be related to $CO_2$ changes during HUT, with a theoretical reduction in $CO_2$ causing relative vasoconstriction and increases in $CO_2$ resulting in relative vasodilatation. Furthermore this study has revealed changes in dCA during HUT in those with symptomatic OH, asymptomatic OH and those with symptoms of OH but in the absence of postural falls in BP. This suggests that despite maintained CBFV and the lack of a postural drop in BP in the latter group, the presence of symptoms is perhaps due to an impairment of dCA. Once again this may tie into the theory by Novak et al. (1998).

Subgroup analysis of the OH study data showed a significant reduction in ARI with HUT amongst those with symptoms, and a relative increase in ARI in those without symptoms. The mean difference in ARI value between those with and without symptoms during HUT was substantial at 1.9 (a greater difference than is seen between controls and stroke patients for example (Eames et al., 2002)). However there was an associated greater fall in CBFV and MAP in those with symptomatic HUT, but although statistically significant, the difference in the mean fall in CBFV of 1 cm/s was small and a fall in MAP of 6mmHg may not be physiologically significant. In the context of a larger proportionate difference in mean combined ARI, these differences in CBFV and MAP are arguably small. The fall in CBFV and MAP was also seen in all groups in the PPH study, and perhaps suggesting that some participants may have both OH and PPH (Vloet et al., 2005). Preliminary work done by another group suggest a reduction in CA is also responsible for symptoms in orthostatic intolerance in older people (Sanders et al., 2014).

With the PPH study, during HUT (without glucose ingestion) in a normal subject, it would be expected that ARI remained the same throughout (Carey et al., 2003). Although there were falls in CBFV and BP during HUT whether participants consumed placebo or glucose in either group, it was the symptomatic not the asymptomatic participants who showed a greater reduction in ARI. To date there are no known published studies investigating the association between symptoms, glucose ingestion and dCA.

Post-hoc analysis of the PPH study data showed evidence that those who became symptomatic did have a fall in dynamic cerebral auto-regulation which might explain their symptoms. Although care must be taken in the interpretation of such post-hoc analyses, both the OH and the PPH study do provide evidence that symptoms during HUT may be due impairment in dynamic CA. This finding which is new and important as it may have important therapeutic implications in that new therapies for these conditions should potentially concentrate on treatments that may stop the fall in cerebral auto-regulation to prevent the onset of symptoms.

## 19.1 Strengths of the studies

The strengths of both the OH and the PPH studies included in this thesis are twofold. Firstly both studies are one of the few studies in dCA of this size to include older participants (>60 years) with consideration to the cause of symptoms. The relatively large participant numbers included compared to many studies published to date adds to the power to detect the differences in dCA. Secondly the broad inclusion criteria and limited exclusion criteria permit the results of this study to be considered applicable to

the general patient population that present to their physician with these common but under-researched conditions.

## 19.2 Limitations of the studies

However there are weaknesses including: 1) use of passive HUT which likely differs from active standing both in the research and clinical settings, 2) the duration of HUT meant deterioration of TCD US signals due to contact gel drying out which could have a negative effect on data quality in addition to inadequate bone windows (Lorenz et al., 2009) and 3) the reliance of participant compliance at all times during the study to ensure consistent and adequate measures of CBFV, BP and HR. For the latter part of study looking at time-varying measures, this required very high quality data files which were sometimes difficult to obtain during the physical manoeuvre of HUT and variation in bone windows particularly in this older population. Classification of participants for the PPH study was not optimal. In hindsight it would have been better to ask participants to attend another session whereby they were screened for PPH with a glucose load, as originally considered. However this would have involved participants attending for three separate visits. However it was already a challenge recruiting older participants who were willing to attend for two visits. It may be that future studies will need to have adequate screening to carefully randomise participants to No PPH and PPH groups, based on actual HUT with a glucose load prior to placebo versus glucose randomisation. Another method if time permitted, would be to leave recruitment as an open and ongoing process until adequate numbers were met for each group. This would of course result in unbalanced groups, but if time permitted, then it would be one way of dealing with this problem. The underlying mechanism for the fall in ARI amongst those with symptoms, in this thesis was not investigated. However it

may be that local changes in $CO_2$, can account for this. High arterial $CO_2$ results in vasodilation of the cerebral vessels, increasing cerebral blood flow (Lassen, 1974). Thus if CA is abnormal relative vasoconstriction may occur as a result in a fall in $CO_2$ which then reduces cerebral blood flow resulting in symptoms. Furthermore the technical difficulties in acquiring accurate measurements using transcranial Doppler ultrasound does pose a problem as regards to the quality of data recorded and may potentially affect results unless care is taken, with only acceptance of good quality signals for the basis of analysis. Furthermore other factors such as the use of anti-hypertensives in research participants may mask any underlying differences in characteristics between groups.

## 19.3 Thesis Conclusion

In conclusion for the OH study, the abnormalities in dynamic cerebral auto-regulation were found during HUT, but not in the supine position, in those who were symptomatic, regardless of postural changes BP. The PPH study also suggested that symptoms were associated with impairment in dCA. However other important haemodynamic parameters including cardiac BRS and arterial stiffness were similar in those with/without symptoms and no orthostatic hypotension, and in those with/without symptoms and orthostatic hypotension; as well as similar in those with/without a history of symptoms of post-prandial hypotension.

# 20 Future Work

Future research should try and objectively assess whether current treatment options for both orthostatic and post-prandial hypotension should concentrate not only on reducing the fall in systemic blood pressure levels which may precipitate symptom onset but also on measures that reduce the fall in cerebral auto-regulation which may prevent symptom onset. It would be useful to determine whether the reduction in ARI and associated symptoms demonstrated in this can be reversed in the context of improvements in systemic BP. It may be that fludrocortisone and midodrine do more than just may small improvements in postural BP, perhaps they reverse the fall in the ARI seen with HUT in this thesis. Furthermore, perhaps the small effect in systemic BP seen in previous studies with caffeine is only half the story. Caffeine is known to improve concentration, and maybe it can improve dCA and prevent the fall in ARI amongst symptomatic individuals.

# 21 Appendix

Herein contains various tables for the OH and PPH study, referred to as “Appendix Table” within the main text.

| *Right side* | **Asymptomatic No OH (24)** | | **Symptomatic No OH (18)** | | **Mann Whitney U Test** *(p-value)* | **Asymptomatic OH (20)** | | **Mann Whitney U Test** *(p-value)* | **Symptomatic OH (23)** | | **Mann Whitney U Test** *(p-value)* | **Kuskall Wallis Test** *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **ARI** | 4.4 | *1.2* | 4.7 | *1.6* | 0.581 | 4.7 | *1.4* | 0.568 | 4.6 | *1.5* | 0.624 | 0.924 |
| **Coherence Low Frequency** (<0.07Hz) | 0.41 | *0.16* | 0.41 | *0.14* | 1.000 | 0.41 | *0.18* | 0.922 | 0.36 | *0.15* | 0.191 | 0.583 |
| **Gain Low Frequency** (<0.07Hz) | 0.42 | *0.24* | 0.43 | *0.17* | 0.728 | 0.43 | *0.20* | 0.686 | 0.30 | *0.09* | 0.040 | 0.049 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.43 | *0.37* | 0.65 | *0.32* | 0.750 | 0.49 | *0.30* | 0.856 | 0.53 | *0.37* | 0.678 | 0.228 |
| **Step Response Recovery (%)** | 65.5 | *25.9* | 77.8 | *50.3* | 0.542 | 64.8 | *14.9* | 0.587 | 67.5 | *24.5* | 0.489 | 0.859 |



**Table 37 Baseline ARI (Tiecks model) Right Middle Cerebral Artery (Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| *Left side* | **Asymptomatic No OH (24)** | | **Symptomatic No OH (18)** | | **Mann Whitney U Test** *(p-value)* | **Asymptomatic OH (20)** | | **Mann Whitney U Test** *(p-value)* | **Symptomatic OH (23)** | | **Mann Whitney U Test** *(p-value)* | **Kuskall Wallis Test** *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **ARI** | 4.5 | *1.3* | 4.9 | *1.4* | 0.399 | 4.6 | *1.3* | 0.989 | 4.9 | *1.7* | 0.443 | 0.792 |
| **Coherence Low Frequency** (<0.07Hz) | 0.41 | *0.16* | 0.40 | *0.13* | 0.816 | 0.36 | *0.17* | 0.308 | 0.37 | *0.17* | 0.385 | 0.680 |
| **Gain Low Frequency** (<0.07Hz) | 0.41 | *0.26* | 0.43 | *0.18* | 0.581 | 0.40 | *0.20* | 0.989 | 0.33 | *0.09* | 0.513 | 0.501 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.44 | *0.36* | 0.62 | *0.37* | 0.064 | 0.43 | *0.43* | 0.900 | 0.58 | *0.43* | 0.204 | 0.221 |
| **Step Response Recovery (%)** | 67.6 | *24.0* | 70.1 | *23.2* | 0.706 | 71.0 | *23.8* | 0.587 | 66.8 | *27.0* | 0.753 | 0.952 |



**Table 38 Baseline ARI (Tiecks model) Left Middle Cerebral Artery (Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| | Asymptomatic No OH (21) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV[1] Right (cm/s)** | 45.4 | *13.4* | 47.4 | *14.9* | 0.686 | 48.2 | *11.5* | 0.361 | 37.4 | *6.4* | 0.038 | 0.014 |
| **CBFV[1] Left (cm/s)** | 45.2 | *13.7* | 47.6 | *14.3* | 0.666 | 43.2 | *14.0* | 0.936 | 42.3 | *11.0* | 0.518 | 0.665 |
| **Mean CBFV[2] (cm/s)** | 45.3 | *12.1* | 47.5 | *14.0* | 0.989 | 45.7 | *10.4* | 0.915 | 39.9 | *7.3* | 0.130 | 0.201 |
| **Systolic CBFV Right (cm/s)** | 65.9 | *19.9* | 70.5 | *21.4* | 0.443 | 71.5 | *17.8* | 0.169 | 57.8 | *11.4* | 0.209 | 0.062 |
| **Systolic CBFV Left (cm/s)** | 64.9 | *22.3* | 70.7 | *20.2* | 0.335 | 67.1 | *18.2* | 0.469 | 65.2 | *16.4* | 0.769 | 0.694 |
| **Mean Systolic CBFV (cm/s)** | 65.4 | *19.1* | 70.6 | *19.7* | 0.349 | 69.3 | *15.1* | 0.187 | 61.5 | *12.4* | 0.488 | 0.174 |
| **Diastolic CBFV Right (cm/s)** | 29.8 | *7.9* | 30.7 | *10.2* | 0.945 | 30.4 | *6.8* | 0.573 | 23.0 | *3.8* | 0.001 | 0.001 |
| **Diastolic CBFV Left (cm/s)** | 30.1 | *8.3* | 31.4 | *10.5* | 1.000 | 27.1 | *10.6* | 0.537 | 26.1 | *8.3* | 0.124 | 0.426 |
| **Mean Diastolic CBFV (cm/s)** | 29.9 | *7.1* | 31.0 | *10.1* | 0.922 | 28.8 | *7.0* | 0.649 | 24.5 | *4.6* | 0.007 | 0.034 |
| **SBP (mmHg)** | 138.4 | *22.4* | 142.2 | *29.4* | 0.686 | 143.0 | *17.5* | 0.130 | 139.7 | *23.8* | 0.664 | 0.739 |
| **DBP (mmHg)** | 71.9 | *12.4* | 68.7 | *13.1* | 0.335 | 72.3 | *8.2* | 1.000 | 74.8 | *12.5* | 0.613 | 0.473 |
| **MAP (mmHg)** | 93.5 | *14.3* | 93.2 | *18.4* | 0.950* | 95.9 | *10.0* | 0.549* | 97.3 | *15.4* | 0.399* | 0.771* |
| **Heart Rate (bpm)** | 65.3 | *10.7* | 63.0 | *10.2* | 0.410 | 65.5 | *10.7* | 0.503 | 69.0 | *12.0* | 0.124 | 0.290 |
| **$tCO_2$ (mmHg)** | 106.3 | *62.3* | 109.9 | *67.0* | 0.989 | 105.2 | *65.5* | 0.728 | 114.4 | *56.5* | 0.630 | 0.958 |

**Table 39 Group Measurements pre-HUT CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| | Asymptomatic No OH (21) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV[1] Right (cm/s)** | 44.3 | *14.2* | 42.6 | *16.5* | 0.606 | 41.9 | *11.4* | 0.810 | 35.4 | *7.2* | 0.028 | 0.107 |
| **CBFV[1] Left (cm/s)** | 44.0 | *12.1* | 44.7 | *17.6* | 0.606 | 36.0 | *15.6* | 0.145 | 33.4 | *13.2* | 0.012 | 0.069 |
| **Mean CBFV[2] (cm/s)** | 44.2 | *12.0* | 43.7 | *16.4* | 0.494 | 39.8 | *10.0* | 0.247 | 34.4 | *8.2* | 0.006 | 0.043 |
| **Systolic CBFV Right (cm/s)** | 65.1 | *21.7* | 65.1 | *23.3* | 0.878 | 62.7 | *16.4* | 0.851 | 57.5 | *12.1* | 0.341 | 0.675 |
| **Systolic CBFV Left (cm/s)** | 64.0 | *21.5* | 66.6 | *24.0* | 1.000 | 57.0 | *21.1* | 0.436 | 53.9 | *18.2* | 0.124 | 0.352 |
| **Mean Systolic CBFV (cm/s)** | 64.6 | *20.1* | 65.9 | *22.4* | 0.878 | 60.8 | *15.1* | 0.830 | 55.7 | *12.2* | 0.118 | 0.394 |
| **Diastolic CBFV Right (cm/s)** | 29.4 | *9.1* | 28.3 | *12.5* | 0.686 | 27.5 | *8.6* | 0.537 | 21.6 | *5.8* | <0.0001 | 0.007 |
| **Diastolic CBFV Left (cm/s)** | 29.4 | *7.6* | 30.4 | *13.0* | 0.749 | 23.3 | *11.7* | 0.105 | 20.5 | *10.2* | 0.003 | 0.018 |
| **Mean Diastolic CBFV (cm/s)** | 29.4 | *7.3* | 29.4 | *12.1* | 0.530 | 26.0 | *7.5* | 0.178 | 21.0 | *6.1* | <0.0001 | 0.004 |
| **SBP (mmHg)** | 131.2 | *29.3* | 124.6 | *26.0* | 0.394 | 126.0 | *25.7* | 0.936 | 118.7 | *35.8* | 0.226 | 0.604 |
| **DBP (mmHg)** | 72.4 | *17.7* | 66.3 | *15.7* | 0.192 | 71.0 | *13.5* | 0.810 | 69.9 | *15.5* | 0.296 | 0.475 |
| **MAP (mmHg)** | 91.1 | *20.6* | 85.3 | *17.1* | 0.644* | 88.8 | *16.7* | 0.695* | 84.3 | *22.5* | 0.303* | 0.654* |
| **Heart Rate (bpm)** | 68.0 | *10.3* | 67.0 | *11.5* | 0.770 | 70.4 | *8.8* | 0.124 | 74.0 | *12.9* | 0.065 | 0.173 |
| **$tCO_2$ (mmHg)** | 100.7 | *61.0* | 95.6 | *57.5* | 0.394 | 91.7 | *59.7* | 0.611 | 101.6 | *56.4* | 0.953 | 0.883 |

**Table 40 Groups Measurements at 1 minute of HUT CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| | Asymptomatic No OH (21) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV[1] Right (cm/s)** | 43.7 | *13.5* | 41.4 | *13.4* | 0.379 | 40.2 | *10.4* | 0.486 | 36.9 | *8.2* | 0.055 | 0.318 |
| **CBFV[1] Left (cm/s)** | 40.7 | *12.3* | 41.1 | *14.4* | 0.835 | 36.4 | *11.2* | 0.361 | 38.3 | *9.1* | 0.597 | 0.829 |
| **Mean CBFV[2] (cm/s)** | 42.2 | *11.3* | 41.3 | *12.3* | 0.606 | 38.3 | *8.1* | 0.376 | 37.6 | *7.9* | 0.209 | 0.618 |
| **Systolic CBFV Right (cm/s)** | 63.8 | *21.1* | 62.7 | *19.9* | 0.770 | 60.0 | *16.0* | 0.789 | 59.7 | *15.5* | 0.630 | 0.967 |
| **Systolic CBFV Left (cm/s)** | 62.0 | *19.2* | 61.7 | *18.8* | 0.967 | 57.3 | *15.5* | 0.649 | 62.5 | *12.4* | 0.630 | 0.678 |
| **Mean Systolic CBFV (cm/s)** | 62.9 | *18.1* | 62.2 | *16.5* | 0.791 | 58.7 | *14.0* | 0.592 | 61.1 | *11.7* | 0.681 | 0.865 |
| **Diastolic CBFV Right (cm/s)** | 29.7 | *8.3* | 27.3 | *9.2* | 0.223 | 26.9 | *6.8* | 0.258 | 23.3 | *6.0* | 0.005 | 0.033 |
| **Diastolic CBFV Left (cm/s)** | 26.8 | *11.1* | 27.4 | *11.0* | 0.394 | 23.7 | *8.9* | 0.226 | 23.4 | *9.1* | 0.142 | 0.466 |
| **Mean Diastolic CBFV (cm/s)** | 28.3 | *8.1* | 27.4 | *8.9* | 0.379 | 25.3 | *5.4* | 0.130 | 23.4 | *6.8* | 0.019 | 0.103 |
| **SBP (mmHg)** | 122.7 | *19.5* | 121.5 | *30.2* | 0.891* | 126.6 | *28.1* | 0.733* | 119.0 | *36.5* | 0.680* | 0.872* |
| **DBP (mmHg)** | 70.5 | *11.4* | 64.5 | *17.4* | 0.204* | 72.1 | *17.7* | 0.606* | 68.0 | *17.8* | 0.580* | 0.506* |
| **MAP (mmHg)** | 86.9 | *12.3* | 83.5 | *19.9* | 0.519* | 89.5 | *19.3* | 0.601* | 84.7 | *21.9* | 0.698* | 0.765* |
| **Heart Rate (bpm)** | 73.8 | *10.8* | 69.4 | *12.3* | 0.244* | 73.6 | *9.1* | 0.953* | 74.6 | *12.3* | 0.823* | 0.490* |
| **$tCO_2$ (mmHg)** | 90.6 | *57.0* | 92.9 | *56.8* | 0.878 | 95.0 | *60.9* | 0.936 | 99.6 | *56.7* | 0.787 | 0.980 |

**Table 41 Groups Measurements at 3 minutes of HUT CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| | Asymptomatic No OH (22) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV[1] Right (cm/s)** | 39.1 | *12.5* | 41.5 | *11.3* | 0.530* | 38.7 | *9.2* | 0.920* | 36.5 | *10.1* | 0.452* | 0.546* |
| **CBFV[1] Left (cm/s)** | 38.3 | *13.2* | 38.6 | *9.9* | 0.943* | 35.9 | *11.7* | 0.548* | 33.9 | *7.6* | 0.183* | 0.452* |
| **Mean CBFV[2] (cm/s)** | 38.7 | *11.6* | 40.0 | *8.9* | 0.677 | 37.3 | *7.5* | 0.794 | 34.4 | *7.3* | 0.229 | 0.321 |
| **Systolic CBFV Right (cm/s)** | 58.3 | *21.1* | 64.1 | *16.9* | 0.155 | 60.4 | *14.2* | 0.333 | 55.1 | *20.5* | 0.856 | 0.371 |
| **Systolic CBFV Left (cm/s)** | 52.8 | *25.4* | 58.9 | *15.0* | 0.312 | 58.7 | *16.4* | 0.347 | 52.4 | *18.0* | 0.910 | 0.511 |
| **Mean Systolic CBFV (cm/s)** | 57.1 | *20.6* | 61.5 | *12.8* | 0.209 | 59.6 | *12.2* | 0.320 | 53.8 | *15.5* | 0.633 | 0.250 |
| **Diastolic CBFV Right (cm/s)** | 26.4 | *8.3* | 27.9 | *7.2* | 0.677 | 25.6 | *6.0* | 0.497 | 21.2 | *8.5* | 0.013 | 0.033 |
| **Diastolic CBFV Left (cm/s)** | 23.8 | *11.9* | 26.3 | *7.0* | 0.861 | 23.2 | *9.1* | 0.433 | 19.1 | *10.8* | 0.093 | 0.189 |
| **Mean Diastolic CBFV (cm/s)** | 25.9 | *8.3* | 27.1 | *6.0* | 0.798 | 24.4 | *5.3* | 0.333 | 20.2 | *6.2* | 0.004 | 0.003 |
| **SBP (mmHg)** | 121.3 | *24.3* | 125.9 | *27.0* | 0.567* | 125.1 | *31.2* | 0.662* | 132.9 | *33.3* | 0.188* | 0.602* |
| **DBP (mmHg)** | 69.1 | *14.5* | 70.6 | *14.0* | 0.749* | 68.0 | *18.1* | 0.836* | 74.1 | *17.4* | 0.298* | 0.621* |
| **MAP (mmHg)** | 85.8 | *16.0* | 86.9 | *17.0* | 0.839* | 86.6 | *22.0* | 0.896* | 92.0 | *20.8* | 0.268* | 0.689* |
| **Heart Rate (bpm)** | 76.0 | *13.1* | 76.0 | *13.8* | 0.994* | 72.9 | *9.7* | 0.397* | 78.0 | *14.1* | 0.627* | 0.649* |
| **$tCO_2$ (mmHg)** | 102.0 | *52.0* | 107.1 | *51.8* | 0.545 | 103.8 | *53.2* | 0.875 | 99.1 | *63.5* | 0.964 | 0.985 |

**Table 42 Group Measurements prior to End HUT (CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across groups)**

| | Asymptomatic No OH (21) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change CBFV[1] Right (cm/s)** | -1.1 | -4.4 | -4.8 | -6.3 | 0.038* | 1.6 | -5.8 | 0.095* | -4.2 | -9.3 | 0.168* | 0.015* |
| **Change CBFV[1] Left (cm/s)** | -1.1 | -4.1 | -3.0 | -7.8 | 0.294 | 1.3 | -4.6 | 0.124 | -3.2 | -9.6 | 0.488 | 0.145 |
| **Change Mean CBFV[2] (cm/s)** | -1.3 | -3.2 | -3.5 | -6.2 | 0.195* | -6.1 | -7.0 | 0.008* | -0.8 | -8.3 | 0.789* | 0.050* |
| **Change Systolic CBFV Right (cm/s)** | -0.8 | -6.3 | -5.4 | -8.1 | 0.078 | 2.7 | -8.1 | 0.226 | -4.9 | -10.9 | 0.148 | 0.028 |
| **Change Systolic CBFV Left (cm/s)** | -0.9 | -5.3 | -4.0 | -10.3 | 0.294 | -0.4 | -12.0 | 0.537 | -1.9 | -16.4 | 0.418 | 0.425 |
| **Change Mean Systolic CBFV (cm/s)** | -1.2 | -4.2 | -3.9 | -7.8 | 0.204* | -9.1 | -10.4 | 0.003* | -0.1 | -12.3 | 0.682* | 0.014* |
| **Change Diastolic CBFV Right (cm/s)** | -0.4 | -3.8 | -2.3 | -6.1 | 0.349 | 0.6 | -4.8 | 0.503 | -2.2 | -8.2 | 0.318 | 0.386 |
| **Change Diastolic CBFV Left (cm/s)** | -0.7 | -3.7 | -1.0 | -6.3 | 0.686 | -0.4 | -7.3 | 0.520 | -0.2 | -11 | 0.787 | 0.803 |
| **Change Mean Diastolic CBFV (cm/s)** | -0.6 | -2.9 | -1.7 | -5.2 | 0.450* | -2.7 | -4.9 | 0.108* | -0.5 | -6.2 | 0.899* | 0.455* |
| **Change SBP (mmHg)** | -7.1 | -15.8 | -17.6 | -26.4 | 0.151* | -0.6 | -21.2 | 0.272* | -12.8 | -30.2 | 0.435* | 0.164* |
| **Change DBP (mmHg)** | 0.6 | -13.4 | -2.4 | -14.1 | 0.646 | -1.1 | -15.8 | 0.688 | -4.1 | -19 | 0.404 | 0.629 |
| **Change MAP (mmHg)** | -2.4 | -14 | -7.9 | -16.7 | 0.266* | -0.7 | -15.5 | 0.730* | -7.2 | -20.1 | 0.364* | 0.462* |
| **Change Heart Rate (bpm)** | 2.6 | -4.8 | 3.9 | -7.8 | 0.626 | -3.2 | -4.4 | 0.001 | 3.9 | -10.4 | 0.916 | 0.004 |
| **Change $tCO_2$ (mmHg)** | -5.6 | -14.6 | -14.3 | -23.1 | 0.183 | -3.3 | -13.1 | 0.915 | -7.3 | -25.6 | 0.751 | 0.537 |

**Table 43 Differences between pre-HUT and 1 minute HUT (Negative values indicate a fall from baseline, CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| | Asymptomatic No OH (22) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change CBFV[1] Right (cm/s)** | -1.7 | -5.9 | -6 | -10.9 | 0.053 | 7.9 | -8.7 | <0.001 | -0.5 | -8.5 | 0.916 | <0.001 |
| **Change CBFV[1] Left (cm/s)** | -4.4 | -7.4 | -6.5 | -10.7 | 0.460 | 6.7 | -7.8 | <0.001 | -4 | -9.4 | 0.991 | <0.001 |
| **Change Mean CBFV[2] (cm/s)** | -3.4 | -5.1 | -5.8 | -9.3 | 0.311* | -7.7 | -7.2 | 0.034* | -2.3 | -7.5 | 0.593* | <0.001 |
| **Change Systolic CBFV Right (cm/s)** | -2.1 | -8 | -7.8 | -15.4 | 0.094 | 11.5 | -12.9 | <0.001 | 1.9 | -15 | 0.630 | <0.001 |
| **Change Systolic CBFV Left (cm/s)** | -3 | -12 | -8.9 | -14 | 0.223 | 7.3 | -16.3 | <0.001 | -2.7 | -10.9 | 0.991 | <0.001 |
| **Change Mean Systolic CBFV (cm/s)** | -3 | -7.2 | -7.3 | -12.4 | 0.181* | -11.5 | -11.1 | 0.006* | -0.5 | -10.1 | 0.362* | 0.015 |
| **Change Diastolic CBFV Right (cm/s)** | 0 | -4.2 | -3.4 | -7.3 | 0.043 | 3.5 | -5 | 0.057 | 0.3 | -5.8 | 0.391 | 0.004 |
| **Change Diastolic CBFV Left (cm/s)** | -3.3 | -8.6 | -4 | -8.8 | 0.477 | 1.8 | -8.2 | 0.047 | -2.6 | -9.9 | 0.565 | 0.015 |
| **Change Mean Diastolic CBFV (cm/s)** | -1.8 | -5 | -3.6 | -6.9 | 0.371* | -3.6 | -4.2 | 0.233* | -1.1 | -6.5 | 0.702* | 0.315 |
| **Change SBP (mmHg)** | -15.7 | -19.6 | -20.7 | -25.4 | 0.493* | 16.4 | -24.4 | <0.001* | -20.7 | -25.8 | 0.477* | <0.001 |
| **Change DBP (mmHg)** | -1.4 | -10.7 | -4.2 | -11 | 0.426 | 0.2 | -17.6 | 0.270 | -6.9 | -12.1 | 0.254 | 0.174 |
| **Change MAP (mmHg)** | -6.7 | -12 | -9.7 | -14.9 | 0.443 | 6.4 | -17.7 | 0.003 | -12.6 | -15.5 | 0.296 | 0.001 |
| **Change Heart Rate (bpm)** | 8.5 | -6.5 | 6.4 | -9.7 | 0.282 | -8.2 | -6.6 | <0.001 | 5.6 | -5.7 | 0.148 | <0.001 |
| **Change $tCO_2$ (mmHg)** | -15.8 | -26.1 | -17 | -18.8 | 0.606 | 10.3 | -18.3 | 0.002 | -14.8 | -18.3 | 0.787 | 0.001 |

**Table 44 Differences between pre-HUT and 3 minutes HUT (Negative values indicate a fall from baseline, CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| | Asymptomatic No OH (22) | | Symptomatic No OH (18) | | Mann Whitney U Test or T-Test* *(p-value)* | Asymptomatic OH (19) | | Mann Whitney U Test or T-Test* *(p-value)* | Symptomatic OH (23) | | Mann Whitney U Test or T-Test* *(p-value)* | Kruskal-Wallis Test or ANOVA* *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change CBFV[1] Right (cm/s)** | -5.7 | -8.2 | -4.2 | -12.5 | 0.659* | -9.5 | -9.5 | 0.181* | 1.9 | *-9.5* | 0.006* | 0.001 |
| **Change CBFV[1] Left (cm/s)** | -6.2 | -11.3 | -1.6 | -17.6 | 0.330* | -7.2 | -10.0 | 0.754* | 11.6 | *-11.9* | <0.001* | <0.001 |
| **Change Mean CBFV[2] (cm/s)** | -5.9 | -8.9 | -2.9 | -11.9 | 0.368* | -8.4 | -6.0 | 0.325* | 6.7 | *-7.8* | <0.001* | <0.001 |
| **Change Systolic CBFV Right (cm/s)** | -6.8 | -10.2 | -5.5 | -15.3 | 0.563 | -11.1 | -13.1 | 0.250 | 1.5 | *-15.3* | 0.008 | 0.010 |
| **Change Systolic CBFV Left (cm/s)** | -11.4 | -17.3 | 1.0 | -22.6 | 0.075 | -8.4 | -16.1 | 0.937 | 12.7 | *-21.4* | <0.001 | <0.001 |
| **Change Mean Systolic CBFV (cm/s)** | -9.1 | -10.8 | -2.3 | -11.8 | 0.064* | -9.8 | -8.5 | 0.835* | 7.1 | *-15.3* | <0.001* | <0.001 |
| **Change Diastolic CBFV Right (cm/s)** | -2.9 | -6.6 | -1.9 | -8.9 | 0.737 | -4.8 | -5.8 | 0.129 | 1.1 | *-7.1* | 0.097 | 0.032 |
| **Change Diastolic CBFV Left (cm/s)** | -5.9 | -11.9 | 1.2 | -15.8 | 0.427 | -4 | -6.6 | 0.676 | 6.9 | *-9.4* | <0.001 | <0.001 |
| **Change Mean Diastolic CBFV (cm/s)** | -4.4 | -7.7 | -0.3 | -9.9 | 0.153* | -4.4 | -4.5 | 0.995* | 4 | *-5.5* | <0.001* | <0.001 |
| **Change SBP (mmHg)** | -14.2 | -24.3 | -3.6 | -34.3 | 0.263* | -17.9 | -29.5 | 0.656* | 6.8 | *-28.6* | 0.011* | 0.027 |
| **Change DBP (mmHg)** | -2.9 | -12.8 | -2.7 | -14.9 | 0.959* | -4.3 | -14.5 | 0.748* | 0.7 | *-13.6* | 0.369* | 0.711 |
| **Change MAP (mmHg)** | -6.8 | -16.2 | -3.6 | -18.2 | 0.555* | -9.3 | -16.8 | 0.634* | 5.3 | *-16.7* | 0.018* | 0.040 |
| **Change Heart Rate (bpm)** | 11.4 | -6.9 | -4.2 | -13.2 | <0.001* | 7.4 | -9.2 | 0.117* | -9 | *-8.3* | <0.001* | <0.001 |
| **Change $tCO_2$ (mmHg)** | -2.8 | -65.9 | 6.1 | -77.1 | 0.476 | -1.5 | -52.1 | 0.601 | 15.3 | *-38.2* | 0.084 | 0.184 |

**Table 45 Differences between pre-HUT and prior to end of HUT (Negative values indicate a fall from baseline, CBFV[1]=mean of systolic and diastolic CBFV for that side, Mean CBFV[2]=mean of both sides calculated by substitution if only one MCA available; Mann Whitney U or T-test to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test or ANOVA to examine for variances across groups)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 45.4 | *0.6* | 47.6 | *0.5* | <0.001 | 46.0 | *0.5* | <0.001 | 39.3 | *0.4* | <0.001 | <0.001 |
| SD time sample | 13.7 | *1.5* | 15.3 | *0.9* | <0.001 | 12.5 | *0.4* | <0.001 | 7.1 | *0.7* | <0.001 | <0.001 |
| **MAP (mmHg)** | 92.2 | *0.7* | 95.5 | *0.8* | <0.001 | 95.0 | *0.9* | <0.001 | 97.5 | *0.7* | <0.001 | <0.001 |
| SD time sample | 11.2 | *0.6* | 19.7 | *0.9* | <0.001 | 11.9 | *0.9* | <0.001 | 15.8 | *0.8* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 115.1 | *0.8* | 123.1 | *1.5* | <0.001 | 98.3 | *0.9* | <0.001 | 120.1 | *1.1* | <0.001 | <0.001 |
| SD time sample | 52.4 | *0.8* | 55.9 | *0.6* | <0.001 | 66.6 | *0.8* | <0.001 | 55.1 | *0.7* | <0.001 | <0.001 |
| **ARI** | 5.2 | *0.2* | 3.2 | *0.1* | <0.001 | 3.7 | *0.1* | <0.001 | 4.8 | *0.3* | <0.001 | <0.001 |
| SD time sample | 2.6 | *0.2* | 2.8 | *0.1* | <0.001 | 3.4 | *0.1* | <0.001 | 3.1 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 65.7 | *0.8* | 64.5 | *1.2* | <0.001 | 67.0 | *0.8* | <0.001 | 70.2 | *0.9* | <0.001 | <0.001 |
| SD time sample | 10.7 | *1.2* | 12.1 | *0.7* | <0.001 | 10.3 | *0.6* | <0.001 | 13.2 | *1.1* | <0.001 | <0.001 |

**Table 46 Continuous estimates of ARI Pre-HUT (Mean of left and right MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group* **)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test (*p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 46.9 | *0.7* | 47.7 | *0.5* | <0.001 | 47.6 | *0.8* | <0.001 | 38.0 | *0.4* | <0.001 | <0.001 |
| SD time sample | 14.3 | *1.5* | 14.8 | *0.7* | 0.436 | 10.9 | *0.4* | <0.001 | 6.2 | *0.8* | <0.001 | <0.001 |
| **MAP (mmHg)** | 93.9 | *0.8* | 96.4 | *0.8* | <0.001 | 96.3 | *1.1* | <0.001 | 96.9 | *0.7* | <0.001 | <0.001 |
| SD time sample | 13.7 | *1.0* | 19.7 | *0.9* | <0.001 | 11.6 | *1.1* | <0.001 | 16.7 | *0.9* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 116.7 | *1.2* | 124.8 | *1.4* | <0.001 | 100.9 | *1.3* | <0.001 | 122.0 | *0.9* | <0.001 | <0.001 |
| SD time sample | 56.4 | *0.7* | 56.4 | *0.6* | 0.674 | 67.3 | *1.1* | <0.001 | 51.4 | *0.7* | <0.001 | <0.001 |
| **ARI Right** | 4.4 | *0.2* | 3.6 | *0.1* | <0.001 | 3.8 | *0.1* | <0.001 | 4.8 | *0.3* | <0.001 | <0.001 |
| SD time sample | 3.0 | *0.1* | 2.7 | *0.1* | <0.001 | 3.4 | *0.1* | <0.001 | 3.2 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 64.7 | *0.7* | 64.6 | *1.4* | 0.292 | 67.5 | *0.9* | <0.001 | 69.1 | *0.9* | <0.001 | <0.001 |
| SD time sample | 10.5 | *1.1* | 12.1 | *1.0* | <0.001 | 10.4 | *0.7* | 0.314 | 12.3 | *1.1* | <0.001 | <0.001 |



**Table 47 Continuous estimates of ARI Pre-HUT (Right MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (14) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 43.9 | *0.8* | 47.4 | *0.7* | <0.001 | 44.4 | *0.6* | <0.001 | 40.5 | *0.6* | <0.001 | <0.001 |
| SD time sample | 13.1 | *1.6* | 15.8 | *1.3* | <0.001 | 14.0 | *0.5* | 0.032 | 8.0 | *0.8* | <0.001 | <0.001 |
| **MAP (mmHg)** | 90.6 | *0.8* | 94.6 | *1.0* | <0.001 | 93.8 | *1.0* | <0.001 | 98.1 | *1.0* | <0.001 | <0.001 |
| SD time sample | 8.7 | *0.8* | 19.7 | *1.1* | <0.001 | 12.1 | *0.9* | <0.001 | 14.9 | *1.1* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 113.5 | *0.8* | 121.4 | *1.7* | <0.001 | 95.8 | *1.2* | <0.001 | 118.2 | *1.6* | <0.001 | <0.001 |
| SD time sample | 48.3 | *1.0* | 55.4 | *0.7* | <0.001 | 65.9 | *1.0* | <0.001 | 58.8 | *0.8* | <0.001 | <0.001 |
| **ARI Left** | 5.9 | *0.4* | 2.8 | *0.1* | <0.001 | 3.7 | *0.2* | <0.001 | 4.7 | *0.3* | <0.001 | <0.001 |
| SD time sample | 2.1 | *0.2* | 2.9 | *0.1* | <0.001 | 3.3 | *0.1* | <0.001 | 3.0 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 66.7 | *1.1* | 64.3 | *1.3* | <0.001 | 66.5 | *1.1* | 0.083 | 71.2 | *1.4* | <0.001 | <0.001 |
| SD time sample | 11.0 | *1.6* | 12.1 | *0.9* | <0.001 | 10.2 | *0.9* | 0.004 | 14.2 | *1.2* | <0.001 | <0.001 |

**Table 48 Continuous estimates of ARI Pre-HUT (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 42.3 | *1.6* | 44.0 | *1.7* | <0.001 | 42.1 | *1.5* | 0.287 | 37.7 | *1.9* | <0.001 | <0.001 |
| SD time sample | 12.2 | *1.2* | 14.2 | *1.4* | <0.001 | 11.1 | *0.9* | <0.001 | 8.4 | *0.8* | <0.001 | <0.001 |
| **MAP (mmHg)** | 16.1 | *1.2* | 20.4 | *3.2* | <0.001 | 18.5 | *1.9* | <0.001 | 22.0 | *1.1* | <0.001 | <0.001 |
| SD time sample | 85.1 | *1.3* | 87.7 | *2.3* | <0.001 | 90.4 | *2.0* | <0.001 | 88.6 | *1.8* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 105.2 | *4.5* | 109.5 | *6.9* | <0.001 | 93.6 | *6.8* | <0.001 | 110.2 | *4.5* | <0.001 | <0.001 |
| SD time sample | 52.1 | *3.2* | 53.9 | *4.1* | 0.004 | 59.7 | *4.5* | <0.001 | 55.5 | *1.6* | <0.001 | <0.001 |
| **ARI** | 5.7 | *0.5* | 3.5 | *0.4* | <0.001 | 4.2 | *0.4* | <0.001 | 4.3 | *0.2* | <0.001 | <0.001 |
| SD time sample | 2.9 | *0.2* | 3.2 | *0.4* | <0.001 | 3.4 | *0.3* | <0.001 | 3.2 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 70.0 | *1.7* | 67.3 | *1.7* | <0.001 | 70.2 | *1.3* | 0.571 | 73.7 | *2.2* | <0.001 | <0.001 |
| SD time sample | 12.3 | *1.0* | 13.0 | *1.3* | <0.001 | 11.2 | *0.8* | <0.001 | 15.0 | *4.5* | <0.001 | <0.001 |

**Table 49 Continuous estimates of ARI HUT 1 minute (Mean of right and left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 43.2 | *2.3* | 44.7 | *2.0* | <0.001 | 43.2 | *2.0* | 0.951 | 36.8 | *1.5* | <0.001 | <0.001 |
| SD time sample | 13.1 | *1.6* | 13.0 | *1.1* | 0.651 | 10.8 | *1.0* | <0.001 | 8.0 | *0.9* | <0.001 | <0.001 |
| **MAP (mmHg)** | 93.4 | *3.8* | 92.1 | *3.6* | <0.001 | 92.5 | *4.6* | <0.001 | 91.8 | *4.2* | 0.009 | 0.001 |
| SD time sample | 22.5 | *4.2* | 19.8 | *1.8* | <0.001 | 18.5 | *5.1* | <0.001 | 22.5 | *2.1* | 0.096 | <0.001 |
| **$tCO_2$ (mmHg)** | 108.4 | *6.5* | 114.5 | *6.4* | <0.001 | 92.5 | *6.5* | <0.001 | 110.8 | *5.7* | 0.005 | <0.001 |
| SD time sample | 55.8 | *4.3* | 52.7 | *3.1* | <0.001 | 63.2 | *6.4* | <0.001 | 52.5 | *1.6* | <0.001 | <0.001 |
| **ARI Right** | 5.6 | *0.6* | 3.6 | *0.4* | <0.001 | 3.7 | *0.5* | <0.001 | 4.1 | *0.3* | <0.001 | <0.001 |
| SD time sample | 3.1 | *0.2* | 3.2 | *0.3* | 0.609 | 3.5 | *0.3* | <0.001 | 3.2 | *0.2* | 0.001 | <0.001 |
| **Heart Rate (bpm)** | 68.4 | *2.8* | 67.3 | *2.0* | 0.001 | 70.5 | *2.1* | <0.001 | 71.7 | *2.9* | <0.001 | <0.001 |
| SD time sample | 12.0 | *1.1* | 13.2 | *1.6* | <0.001 | 11.0 | *1.2* | <0.001 | 15.2 | *9.1* | <0.001 | <0.001 |

**Table 50 Continuous estimates of ARI HUT 1 minute (Right MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (14) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 43.0 | *2.2* | 44.0 | *1.3* | 0.001 | 39.4 | *1.8* | <0.001 | 38.4 | *2.3* | <0.001 | <0.001 |
| SD time sample | 11.5 | *1.6* | 16.6 | *1.3* | <0.001 | 11.5 | *1.2* | 0.977 | 8.7 | *1.0* | <0.001 | <0.001 |
| **MAP (mmHg)** | 88.5 | *4.0* | 88.4 | *3.0* | 0.970 | 88.8 | *4.2* | 0.943 | 94.0 | *3.2* | <0.001 | <0.001 |
| SD time sample | 14.1 | *2.5* | 19.4 | *2.8* | <0.001 | 19.3 | *5.2* | <0.001 | 22.4 | *2.4* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 105.9 | *7.0* | 108.9 | *6.3* | 0.011 | 87.4 | *6.6* | <0.001 | 109.2 | *4.0* | <0.001 | <0.001 |
| SD time sample | 48.1 | *4.6* | 50.5 | *3.2* | 0.002 | 61.5 | *5.8* | <0.001 | 58.5 | *2.2* | <0.001 | <0.001 |
| **ARI Left** | 5.4 | *0.4* | 3.5 | *0.7* | <0.001 | 4.1 | *0.9* | <0.001 | 4.4 | *0.4* | <0.001 | <0.001 |
| SD time sample | 2.9 | *0.4* | 2.9 | *0.4* | 0.693 | 3.6 | *0.3* | <0.001 | 3.2 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 70.5 | *2.7* | 67.0 | *1.9* | <0.001 | 69.9 | *2.1* | 0.089 | 75.9 | *2.2* | <0.001 | <0.001 |
| SD time sample | 12.6 | *1.6* | 13.3 | *1.7* | 0.009 | 11.2 | *1.1* | <0.001 | 14.7 | *1.3* | <0.001 | <0.001 |



**Table 51 Continuous estimates of ARI HUT 1 minute (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 41.3 | *1.0* | 41.6 | *1.1* | 0.009 | 40.5 | *0.7* | <0.001 | 35.4 | *0.8* | <0.001 | <0.001 |
| SD time sample | 11.0 | *1.3* | 14.0 | *1.4* | <0.001 | 10.0 | *0.6* | <0.001 | 8.3 | *0.7* | <0.001 | <0.001 |
| **MAP (mmHg)** | 84.9 | *1.0* | 85.2 | *2.3* | 0.491 | 90.5 | *1.6* | <0.001 | 85.3 | *1.1* | 0.055 | <0.001 |
| SD time sample | 15.0 | *1.2* | 20.9 | *2.2* | <0.001 | 20.1 | *2.1* | <0.001 | 20.4 | *0.8* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 99.9 | *1.8* | 102.9 | *4.7* | <0.001 | 88.8 | *2.9* | <0.001 | 102.0 | *1.3* | <0.001 | <0.001 |
| SD time sample | 47.2 | *1.6* | 49.8 | *2.7* | <0.001 | 58.7 | *3.4* | <0.001 | 53.4 | *1.1* | <0.001 | <0.001 |
| **ARI** | 5.1 | *0.7* | 5.1 | *0.2* | 0.233 | 4.8 | *0.5* | <0.001 | 4.8 | *0.4* | <0.001 | <0.001 |
| SD time sample | 2.6 | *0.1* | 2.7 | *0.2* | <0.001 | 2.8 | *0.3* | <0.001 | 2.9 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 75.1 | *1.3* | 69.8 | *1.6* | <0.001 | 73.9 | *0.7* | <0.001 | 76.2 | *1.2* | <0.001 | <0.001 |
| SD time sample | 13.1 | *3.1* | 12.3 | *1.2* | <0.001 | 11.2 | *0.8* | <0.001 | 14.3 | *1.5* | <0.001 | <0.001 |



**Table 52 Continuous estimates of ARI HUT 2 minute (Mean of right and left MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (21) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 41.8 | *1.0* | 42.0 | *1.0* | 0.194 | 42.1 | *0.8* | 0.047 | 35.2 | *0.7* | <0.001 | <0.001 |
| SD time sample | 11.6 | *1.5* | 13.7 | *1.2* | <0.001 | 9.4 | *0.7* | <0.001 | 7.5 | *0.7* | <0.001 | <0.001 |
| **MAP (mmHg)** | 84.7 | *1.5* | 86.0 | *3.2* | 0.142 | 92.2 | *1.3* | <0.001 | 83.1 | *0.9* | <0.001 | <0.001 |
| SD time sample | 17.4 | *1.8* | 20.7 | *2.9* | <0.001 | 20.7 | *1.6* | <0.001 | 21.8 | *1.1* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 100.7 | *2.0* | 107.2 | *2.6* | <0.001 | 89.7 | *1.4* | <0.001 | 102.1 | *1.3* | <0.001 | <0.001 |
| SD time sample | 50.8 | *1.4* | 49.3 | *0.7* | <0.001 | 61.6 | *1.0* | <0.001 | 51.5 | *1.2* | <0.001 | <0.001 |
| **ARI Right** | 5.1 | *0.9* | 5.4 | *0.5* | 0.127 | 4.7 | *0.7* | <0.001 | 4.9 | *0.5* | 0.029 | <0.001 |
| SD time sample | 2.7 | *0.3* | 2.4 | *0.3* | <0.001 | 2.8 | *0.4* | 0.682 | 3.0 | *0.3* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 73.8 | *1.7* | 69.5 | *1.5* | <0.001 | 73.8 | *0.9* | 0.781 | 74.0 | *1.6* | 0.369 | <0.001 |
| SD time sample | 13.1 | *3.1* | 12.4 | *1.6* | 0.042 | 10.7 | *1.1* | <0.001 | 14.5 | *2.6* | <0.001 | <0.001 |

**Table 53 Continuous estimates of ARI HUT 2 minute (Right MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (14) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 40.5 | *1.0* | 42.5 | *1.1* | <0.001 | 38.1 | *0.7* | <0.001 | 35.5 | *1.0* | <0.001 | <0.001 |
| SD time sample | 9.7 | *1.1* | 15.4 | *0.9* | <0.001 | 11.0 | *0.4* | <0.001 | 9.0 | *1.4* | <0.001 | <0.001 |
| **MAP (mmHg)** | 85.0 | *1.2* | 82.8 | *1.9* | 0.003 | 90.1 | *1.1* | <0.001 | 87.5 | *1.6* | <0.001 | <0.001 |
| SD time sample | 12.1 | *2.3* | 21.3 | *2.9* | <0.001 | 21.0 | *1.9* | <0.001 | 19.0 | *0.8* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 98.1 | *2.3* | 102.7 | *1.8* | <0.001 | 85.1 | *1.2* | <0.001 | 101.8 | *1.8* | <0.001 | <0.001 |
| SD time sample | 42.1 | *1.6* | 47.5 | *1.1* | <0.001 | 59.7 | *1.0* | <0.001 | 55.2 | *1.2* | <0.001 | <0.001 |
| **ARI Left** | 5.5 | *0.4* | 5.0 | *0.3* | <0.001 | 4.8 | *0.4* | <0.001 | 4.6 | *0.6* | <0.001 | <0.001 |
| SD time sample | 2.4 | *0.2* | 2.9 | *0.2* | <0.001 | 3.1 | *0.2* | <0.001 | 2.9 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 76.3 | *1.4* | 69.2 | *1.6* | <0.001 | 73.6 | *0.9* | <0.001 | 78.4 | *1.4* | <0.001 | <0.001 |
| SD time sample | 12.9 | *1.1* | 12.5 | *1.5* | <0.001 | 11.3 | *1.0* | <0.001 | 14.2 | *1.6* | <0.001 | <0.001 |



**Table 54 Continuous estimates of ARI HUT 2 minute (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | **Asymptomatic No OH (16)** | | **Symptomatic No OH (11)** | | **Mann Whitney U Test** *(p-value)* | **Asymptomatic OH (14)** | | **Mann Whitney U Test** *(p-value)* | **Symptomatic OH (18)** | | **Mann Whitney U Test** *(p-value)* | **Kruskal-Wallis Test** *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 38.2 | *0.7* | 36.3 | *0.8* | <0.001 | 38.2 | *0.9* | 0.618 | 34.4 | *1.9* | <0.001 | <0.001 |
| SD time sample | 10.8 | *0.7* | 13.6 | *0.8* | <0.001 | 10.5 | *0.7* | 0.040 | 9.1 | *0.6* | <0.001 | <0.001 |
| **MAP (mmHg)** | 81.9 | *1.1* | 83.1 | *1.0* | <0.001 | 82.0 | *1.0* | 0.289 | 87.8 | *3.1* | <0.001 | <0.001 |
| SD time sample | 15.5 | *1.0* | 19.9 | *0.6* | <0.001 | 24.2 | *2.6* | <0.001 | 21.3 | *0.9* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 97.9 | *1.1* | 97.5 | *0.9* | 0.041 | 102.5 | *2.0* | <0.001 | 97.2 | *1.0* | <0.001 | <0.001 |
| SD time sample | 48.9 | *1.6* | 51.3 | *0.6* | <0.001 | 49.1 | *1.9* | 0.185 | 61.3 | *4.4* | <0.001 | <0.001 |
| **ARI** | 4.6 | *0.3* | 3.4 | *0.2* | <0.001 | 4.0 | *0.1* | <0.001 | 5.0 | *0.3* | <0.001 | <0.001 |
| SD time sample | 2.9 | *0.1* | 3.0 | *0.1* | <0.001 | 2.6 | *0.1* | <0.001 | 3.2 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 77.3 | *0.9* | 75.1 | *0.6* | <0.001 | 73.5 | *1.5* | <0.001 | 76.4 | *2.5* | 0.458 | <0.001 |
| SD time sample | 15.3 | *1.1* | 15.1 | *1.0* | 0.317 | 12.5 | *1.2* | <0.001 | 15.9 | *1.1* | 0.001 | <0.001 |

**Table 55 Continuous estimates of ARI prior to end of HUT (Mean of right and left MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (12) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (20) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 38.3 | *0.8* | 37.8 | *1.1* | 0.002 | 39.6 | *1.0* | <0.001 | 35.0 | *0.5* | <0.001 | <0.001 |
| SD time sample | 10.8 | *0.8* | 15.9 | *0.9* | <0.001 | 10.3 | *1.3* | 0.003 | 8.5 | *0.9* | <0.001 | <0.001 |
| **MAP (mmHg)** | 83.7 | *0.9* | 87.3 | *1.4* | <0.001 | 84.2 | *1.5* | 0.013 | 87.4 | *1.2* | <0.001 | <0.001 |
| SD time sample | 15.1 | *0.8* | 17.4 | *1.3* | <0.001 | 28.6 | *1.2* | <0.001 | 22.4 | *1.0* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 97.9 | *1.0* | 99.9 | *1.8* | <0.001 | 107.4 | *2.1* | <0.001 | 90.9 | *1.0* | <0.001 | <0.001 |
| SD time sample | 50.6 | *1.1* | 51.1 | *0.8* | <0.001 | 49.9 | *1.5* | <0.001 | 63.8 | *1.1* | <0.001 | <0.001 |
| **ARI Right** | 4.8 | *0.1* | 2.7 | *0.3* | <0.001 | 4.0 | *0.4* | <0.001 | 5.2 | *0.2* | <0.001 | <0.001 |
| SD time sample | 2.9 | *0.0* | 3.0 | *0.2* | <0.001 | 2.4 | *0.3* | <0.001 | 3.4 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 77.1 | *0.8* | 77.2 | *0.9* | 0.260 | 71.9 | *1.3* | <0.001 | 77.1 | *1.5* | 0.649 | <0.001 |
| SD time sample | 15.6 | *1.3* | 16.4 | *1.8* | 0.054 | 11.8 | *1.2* | <0.001 | 16.2 | *1.6* | 0.019 | <0.001 |

**Table 56 Continuous estimates of ARI prior to end of HUT (Right MCA***; Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (16) | | Symptomatic No OH (11) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (18) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 38.1 | *0.4* | 37.4 | *1.6* | 0.551 | 35.5 | *1.1* | <0.001 | 33.8 | *3.9* | <0.001 | <0.001 |
| SD time sample | 10.6 | *0.6* | 15.4 | *2.1* | <0.001 | 10.9 | *0.6* | <0.001 | 9.8 | *1.2* | <0.001 | <0.001 |
| **MAP (mmHg)** | 79.6 | *1.7* | 82.3 | *1.0* | 0.002 | 79.0 | *1.0* | 0.001 | 88.2 | *6.3* | <0.001 | <0.001 |
| SD time sample | 15.7 | *2.4* | 22.7 | *0.3* | <0.001 | 22.9 | *1.4* | <0.001 | 20.2 | *1.0* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 99.3 | *2.0* | 95.7 | *0.4* | 0.001 | 95.3 | *1.4* | <0.001 | 103.6 | *1.8* | <0.001 | <0.001 |
| SD time sample | 45.3 | *1.7* | 53.1 | *0.6* | <0.001 | 50.7 | *1.3* | <0.001 | 58.8 | *8.0* | <0.001 | <0.001 |
| **ARI Left** | 3.9 | *0.2* | 3.3 | *0.0* | <0.001 | 4.1 | *0.2* | <0.001 | 4.8 | *0.6* | <0.001 | <0.001 |
| SD time sample | 2.8 | *0.2* | 3.3 | *0.0* | <0.001 | 3.0 | *0.1* | <0.001 | 3.0 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 78.3 | *1.3* | 75.0 | *0.5* | <0.001 | 72.8 | *1.0* | <0.001 | 75.7 | *4.6* | 0.003 | <0.001 |
| SD time sample | 15.0 | *1.4* | 13.7 | *0.6* | 0.007 | 12.8 | *1.5* | <0.001 | 15.5 | *1.8* | 0.261 | <0.001 |



**Table 57 Continuous estimates of ARI prior to end of HUT (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (16) | | Symptomatic No OH (11) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (18) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 40.5 | *1.1* | 44.2 | *0.8* | <0.001 | 41.5 | *1.6* | 0.001 | 38.8 | *1.5* | <0.001 | <0.001 |
| SD time sample | 11.2 | *1.0* | 13.3 | *1.5* | <0.001 | 10.7 | *1.3* | <0.001 | 11.1 | *1.6* | 0.479 | <0.001 |
| **MAP (mmHg)** | 84.2 | *3.4* | 90.2 | *2.2* | <0.001 | 84.8 | *2.9* | 0.051 | 90.7 | *6.2* | <0.001 | <0.001 |
| SD time sample | 18.3 | *1.8* | 19.7 | *0.6* | <0.001 | 18.3 | *3.1* | 0.321 | 21.9 | *2.2* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 105.4 | *4.2* | 110.3 | *2.3* | <0.001 | 108.5 | *3.7* | <0.001 | 103.8 | *6.5* | 0.007 | <0.001 |
| SD time sample | 51.2 | *1.9* | 48.7 | *0.8* | <0.001 | 45.4 | *1.5* | <0.001 | 62.9 | *5.3* | <0.001 | <0.001 |
| **ARI** | 4.9 | *0.2* | 5.0 | *0.3* | 0.269 | 4.2 | *0.4* | <0.001 | 4.7 | *0.6* | <0.001 | <0.001 |
| SD time sample | 2.7 | *0.1* | 2.7 | *0.2* | 0.685 | 2.9 | *0.1* | <0.001 | 3.1 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 69.9 | *2.7* | 63.6 | *0.9* | <0.001 | 66.3 | *2.4* | <0.001 | 72.6 | *4.1* | <0.001 | <0.001 |
| SD time sample | 11.4 | *5.4* | 12.8 | *1.5* | <0.001 | 10.8 | *5.1* | 0.006 | 14.7 | *1.2* | <0.001 | <0.001 |

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**Table 58 Continuous estimates of ARI post-HUT 1 minute (Mean of right and left MCA**; *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group*)

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (12) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (20) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 41.6 | *1.3* | 43.2 | *1.4* | <0.001 | 43.3 | *1.2* | <0.001 | 38.7 | *1.5* | <0.001 | <0.001 |
| SD time sample | 12.1 | *1.1* | 13.9 | *2.6* | <0.001 | 10.8 | *1.8* | <0.001 | 10.2 | *2.6* | <0.001 | <0.001 |
| **MAP (mmHg)** | 86.8 | *6.1* | 88.1 | *3.9* | 0.236 | 84.6 | *3.5* | 0.031 | 88.9 | *5.3* | 0.004 | <0.001 |
| SD time sample | 19.2 | *2.3* | 19.5 | *1.0* | 0.216 | 17.9 | *4.9* | <0.001 | 23.3 | *3.3* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 105.4 | *7.0* | 107.4 | *4.1* | 0.041 | 112.3 | *6.0* | <0.001 | 99.2 | *11.0* | <0.001 | <0.001 |
| SD time sample | 54.7 | *3.6* | 49.2 | *1.3* | <0.001 | 43.2 | *2.0* | <0.001 | 64.5 | *3.6* | <0.001 | <0.001 |
| **ARI Right** | 5.0 | *0.3* | 4.8 | *0.5* | 0.221 | 3.8 | *0.6* | <0.001 | 4.8 | *0.7* | 0.007 | <0.001 |
| SD time sample | 2.7 | *0.2* | 2.8 | *0.1* | 0.015 | 2.7 | *0.2* | 0.639 | 3.1 | *0.3* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 69.8 | *3.7* | 66.1 | *1.6* | <0.001 | 66.4 | *3.0* | <0.001 | 73.6 | *3.3* | <0.001 | <0.001 |
| SD time sample | 11.2 | *1.7* | 12.2 | *2.3* | 0.016 | 9.3 | *1.2* | <0.001 | 15.1 | *1.5* | <0.001 | <0.001 |

**Table 59 Continuous estimates of ARI post-HUT 1 minute (Right MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (16) | | Symptomatic No OH (11) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (18) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 40.3 | *1.3* | 44.4 | *0.9* | <0.001 | 37.8 | *1.0* | <0.001 | 38.2 | *2.3* | <0.001 | <0.001 |
| SD time sample | 11.9 | *1.1* | 12.5 | *0.8* | <0.001 | 8.8 | *1.1* | <0.001 | 12.1 | *2.1* | 0.068 | <0.001 |
| **MAP (mmHg)** | 83.1 | *6.1* | 92.3 | *1.2* | <0.001 | 82.6 | *3.3* | 0.766 | 92.7 | *8.5* | <0.001 | <0.001 |
| SD time sample | 18.4 | *2.9* | 19.8 | *0.5* | <0.001 | 17.0 | *2.0* | <0.001 | 20.7 | *2.1* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 108.2 | *7.3* | 113.2 | *1.2* | <0.001 | 103.0 | *5.6* | <0.001 | 108.0 | *4.0* | 0.622 | <0.001 |
| SD time sample | 48.9 | *3.0* | 48.4 | *0.9* | 0.561 | 47.6 | *1.8* | 0.002 | 63.0 | *8.5* | <0.001 | <0.001 |
| **ARI Left** | 5.1 | *0.6* | 5.0 | *0.5* | 0.066 | 4.5 | *0.4* | <0.001 | 4.6 | *0.5* | <0.001 | <0.001 |
| SD time sample | 2.5 | *0.4* | 2.9 | *0.3* | <0.001 | 3.0 | *0.2* | <0.001 | 3.1 | *0.2* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 70.2 | *3.3* | 61.1 | *1.7* | <0.001 | 68.3 | *5.3* | <0.001 | 72.8 | *4.7* | 0.001 | <0.001 |
| SD time sample | 10.9 | *1.5* | 13.6 | *1.9* | <0.001 | 11.7 | *14.2* | <0.001 | 14.6 | *1.3* | <0.001 | <0.001 |

**Table 60 Continuous estimates of ARI post-HUT 1 minute (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group*)

| | Asymptomatic No OH (16) | | Symptomatic No OH (11) | | Mann Whitney U Test *(p-value))* | Asymptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (18) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV (cm/s)** | 41.6 | *0.8* | 43.6 | *0.2* | <0.001 | 41.2 | *1.1* | <0.001 | 41.7 | *1.3* | 0.132 | <0.001 |
| SD time sample | 12.0 | *1.2* | 11.8 | *0.5* | <0.001 | 10.5 | *1.0* | <0.001 | 11.7 | *1.0* | 0.001 | <0.001 |
| **MAP (mmHg)** | 97.3 | *1.6* | 92.3 | *0.2* | <0.001 | 90.4 | *1.2* | <0.001 | 98.8 | *2.1* | <0.001 | <0.001 |
| SD time sample | 16.9 | *1.1* | 19.6 | *0.4* | <0.001 | 14.8 | *0.8* | <0.001 | 19.5 | *1.1* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 122.7 | *2.5* | 112.8 | *0.3* | <0.001 | 118.1 | *2.0* | <0.001 | 113.5 | *4.2* | <0.001 | <0.001 |
| SD time sample | 56.1 | *0.9* | 49.4 | *0.4* | 0.025 | 45.4 | *0.6* | <0.001 | 62.6 | *3.7* | 0.100 | <0.001 |
| **ARI** | 4.9 | *0.3* | 4.9 | *0.1* | <0.001 | 4.1 | *0.4* | <0.001 | 4.8 | *0.4* | 0.051 | <0.001 |
| SD time sample | 2.7 | *0.2* | 3.0 | *0.0* | <0.001 | 2.8 | *0.2* | 0.613 | 2.8 | *0.1* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 64.7 | *0.8* | 62.5 | *0.7* | <0.001 | 62.2 | *0.9* | <0.001 | 65.5 | *2.1* | <0.001 | <0.001 |
| SD time sample | 11.3 | *0.7* | 13.0 | *1.4* | 0.523 | 10.5 | *1.0* | <0.001 | 14.0 | *1.5* | 0.087 | <0.001 |

**Table 61 Continuous estimates of ARI post-HUT 2 minute (Mean of right and left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (12) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (20) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Right (cm/s)** | 42.1 | *0.9* | 43.6 | *0.4* | <0.001 | 42.6 | *0.7* | <0.001 | 40.4 | *0.6* | <0.001 | <0.001 |
| SD time sample | 12.0 | *1.3* | 11.0 | *1.0* | 0.013 | 12.4 | *1.4* | 0.024 | 10.3 | *1.7* | <0.001 | <0.001 |
| **MAP (mmHg)** | 100.0 | *1.1* | 92.3 | *0.5* | <0.001 | 91.6 | *1.8* | <0.001 | 102.2 | *1.0* | <0.001 | <0.001 |
| SD time sample | 17.4 | *1.3* | 19.4 | *0.6* | <0.001 | 12.8 | *0.9* | <0.001 | 19.9 | *1.2* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 122.1 | *1.8* | 112.2 | *0.6* | <0.001 | 123.7 | *2.8* | <0.001 | 109.3 | *7.5* | <0.001 | <0.001 |
| SD time sample | 59.9 | *1.1* | 50.6 | *0.5* | <0.001 | 41.6 | *0.8* | <0.001 | 72.0 | *3.2* | <0.001 | <0.001 |
| **ARI Right** | 5.0 | *0.3* | 5.1 | *0.1* | 0.106 | 3.6 | *0.4* | <0.001 | 4.9 | *0.5* | 0.552 | <0.001 |
| SD time sample | 2.7 | *0.2* | 2.7 | *0.1* | 0.279 | 2.7 | *0.3* | 0.044 | 2.8 | *0.1* | 0.001 | <0.001 |
| **Heart Rate (bpm)** | 64.6 | *1.0* | 64.6 | *1.0* | 0.890 | 61.0 | *1.4* | <0.001 | 67.4 | *1.5* | <0.001 | <0.001 |
| SD time sample | 11.2 | *1.3* | 11.4 | *2.2* | 0.945 | 10.0 | *1.0* | <0.001 | 14.2 | *2.0* | <0.001 | <0.001 |

**Table 62 Continuous estimates of ARI post-HUT 2 minute (Right MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | Asymptomatic No OH (16) | | Symptomatic No OH (11) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (18) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **CBFV Left (cm/s)** | 41.5 | *0.7* | 44.4 | *0.9* | <0.001 | 39.0 | *0.7* | <0.001 | 39.9 | *0.6* | <0.001 | <0.001 |
| SD time sample | 12.5 | *1.2* | 12.5 | *0.8* | 0.264 | 7.9 | *0.7* | <0.001 | 14.6 | *0.6* | <0.001 | <0.001 |
| **MAP (mmHg)** | 95.4 | *1.3* | 92.3 | *1.2* | <0.001 | 88.7 | *1.5* | <0.001 | 101.4 | *1.4* | <0.001 | <0.001 |
| SD time sample | 16.2 | *1.4* | 19.8 | *0.5* | <0.001 | 16.4 | *1.2* | 0.351 | 17.8 | *1.3* | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 124.6 | *1.7* | 113.2 | *1.2* | <0.001 | 113.0 | *2.4* | <0.001 | 126.2 | *2.3* | <0.001 | <0.001 |
| SD time sample | 52.5 | *1.1* | 48.4 | *0.9* | <0.001 | 49.7 | *1.0* | <0.001 | 61.9 | *1.3* | <0.001 | <0.001 |
| **ARI Left** | 4.8 | *0.5* | 5.0 | *0.5* | 0.003 | 4.5 | *0.6* | <0.001 | 4.4 | *0.6* | 0.002 | <0.001 |
| SD time sample | 2.6 | *0.4* | 2.9 | *0.3* | <0.001 | 2.9 | *0.3* | <0.001 | 2.9 | *0.3* | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 65.0 | *1.2* | 61.1 | *1.7* | <0.001 | 63.9 | *1.3* | <0.001 | 67.9 | *1.4* | <0.001 | <0.001 |
| SD time sample | 11.7 | *0.9* | 13.6 | *1.9* | <0.001 | 10.3 | *0.9* | <0.001 | 15.1 | *2.0* | <0.001 | <0.001 |

**Table 63 Continuous estimates of ARI post-HUT 2 minute (Left MCA;** *Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group*)

| | Asymptomatic No OH (14) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -3.1 | *-1.4* | -3.6 | *-1.6* | 0.023 | -3.8 | *-1.7* | 0.003 | -1.6 | *-1.9* | <0.001 | <0.001 |
| Change in SD time sample | -1.5 | *-1.9* | -1.1 | *-2.2* | 0.102 | -1.3 | *-1.1* | 0.123 | 1.3 | *-1.1* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -7.2 | *-1.3* | -7.8 | *-2.3* | 0.012 | -4.6 | *-2.2* | <0.001 | -9 | *-2* | <0.001 | <0.001 |
| Change in SD time sample | 4.8 | *-1.4* | 0.7 | *-3.3* | <0.001 | 6.6 | *-1.8* | <0.001 | 6.2 | *-1.6* | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -10.2 | *-4.2* | -13.9 | *-7.7* | <0.001 | -4 | *-8.2* | <0.001 | -10 | *-4.8* | 0.745 | <0.001 |
| Change in SD time sample | -0.4 | *-3.3* | -1.7 | *-4.7* | <0.001 | -7.4 | *-4.1* | <0.001 | 0.4 | *-2* | 0.071 | <0.001 |
| **Change in combined ARI** | 0.5 | *-0.5* | 0.3 | *-0.4* | 0.007 | 0.5 | *-0.5* | 0.846 | -0.5 | *-0.3* | <0.001 | <0.001 |
| Change in SD time sample | 0.4 | *-0.2* | 0.4 | *-0.4* | 0.892 | 0.1 | *-0.3* | <0.001 | 0.1 | *-0.2* | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 4.3 | *-1.8* | 2.9 | *-2.6* | <0.001 | 3.1 | *-1.4* | <0.001 | 3.5 | *-2.5* | 0.020 | <0.001 |
| Change in SD time sample | 1.8 | *-1.5* | 0.9 | *-1.2* | <0.001 | 0.9 | *-1* | <0.001 | 1.7 | *-4.6* | 0.010 | <0.001 |

**Table 64 Changes in mean time varying estimates at 1 minute of HUT (***Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group***)**

| | **Asymptomatic No OH (16)** | | **Symptomatic No OH (16)** | | **Mann Whitney U Test** *(p-value))* | **Asymptomatic OH (16)** | | **Mann Whitney U Test** *(p-value)* | **Symptomatic OH (14)** | | **Mann Whitney U Test** *(p-value)* | **Kruskal-Wallis Test** *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -3.9 | *-1.1* | -5.9 | *-1.3* | <0.001 | -5.6 | *-0.8* | <0.001 | -3.9 | *-0.7* | 0.357 | <0.001 |
| Change in SD time sample | -2.6 | *-2.2* | -1.3 | *-2* | <0.001 | -2.5 | *-0.6* | 0.266 | 1.2 | *-1.1* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -7.6 | *-1.5* | -10.3 | *-2* | <0.001 | -4.6 | *-1.5* | <0.001 | -12.2 | *-1.4* | <0.001 | <0.001 |
| Change in SD time sample | 3.7 | *-1.4* | 1.2 | *-1.8* | <0.001 | 8.3 | *-1.6* | <0.001 | 4.6 | *-1.3* | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -13.5 | *-5.3* | -20.3 | *-5.8* | <0.001 | -9.6 | *-3.5* | <0.001 | -18.1 | *-1.6* | <0.001 | <0.001 |
| Change in SD time sample | -6.6 | *-4.7* | -6.1 | *-2.6* | 0.001 | -8 | *-2.9* | <0.001 | -1.8 | *-1.2* | <0.001 | <0.001 |
| **Change in combined ARI** | 0 | *-1* | 1.9 | *-0.3* | <0.001 | 1.1 | *-0.6* | <0.001 | 0 | *-0.6* | 0.892 | <0.001 |
| Change in SD time sample | 0 | *-0.3* | -0.1 | *-0.2* | <0.001 | -0.6 | *-0.3* | <0.001 | -0.2 | *-0.2* | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 9.3 | *-1.6* | 5.3 | *-2.5* | <0.001 | 6.8 | *-1* | <0.001 | 6 | *-1.6* | <0.001 | <0.001 |
| Change in SD time sample | 2.5 | *-3.2* | 0.2 | *-1.4* | <0.001 | 0.9 | *-1* | <0.001 | 1.1 | *-1.8* | <0.001 | <0.001 |

**Table 65 Changes in mean time varying estimates at 2 minutes of HUT** *(Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (17) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (12) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (20) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | | **Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -7.2 | *-0.7* | -10.9 | *-0.8* | <0.001 | -8.3 | *-1.4* | 0.001 | -7.7 | *-3.9* | <0.001 | <0.001 |
| Change in SD time sample | -2.4 | *-1.4* | -0.9 | *-0.9* | 0.003 | -2.6 | *-1.6* | <0.001 | -0.7 | *-4.6* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -11 | *-2.2* | -11.7 | *-1.1* | <0.001 | -13.2 | *-1.1* | <0.001 | -9.1 | *-3.7* | <0.001 | <0.001 |
| Change in SD time sample | 3.9 | *-1* | -0.2 | *-1.3* | <0.001 | 10.6 | *-3.2* | <0.001 | 4.4 | *-2.3* | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -12.8 | *-7.3* | -24.4 | *-1.4* | <0.001 | -2.3 | *-11.4* | <0.001 | -24 | *-2.4* | <0.001 | <0.001 |
| Change in SD time sample | -7.2 | *-6.7* | -4.8 | *-0.8* | 0.692 | -14.6 | *-6.2* | <0.001 | 6.1 | *-4.5* | <0.001 | <0.001 |
| **Change in combined ARI** | -0.3 | *-0.6* | 0.1 | *-0.2* | <0.001 | 0.4 | *-0.2* | <0.001 | 0.7 | *-0.8* | <0.001 | <0.001 |
| Change in SD time sample | 0.1 | *-0.4* | 0.1 | *-0.1* | <0.001 | -0.6 | *-0.2* | <0.001 | 0.2 | *-0.2* | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 11.4 | *-1.1* | 10.6 | *-1.1* | <0.001 | 6.7 | *-1.6* | <0.001 | 8.5 | *-3.3* | <0.001 | <0.001 |
| Change in SD time sample | 4.6 | *-1.5* | 2.9 | *-1.1* | <0.001 | 1.9 | *-1.8* | <0.001 | 3.2 | *-1.4* | <0.001 | <0.001 |

**Table 66 Changes in mean time varying estimates pre-end of HUT (***Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (14) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **% of Mean** | ***SD*** | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -6.8 | *-3.2* | -7.5 | *-3.4* | 0.095 | -8.3 | *-3.6* | 0.006 | -4.2 | *-4.7* | <0.001 | <0.001 |
| Change in SD time sample | -10.1 | *-13.7* | -6.5 | *-13.9* | 0.054 | -10.0 | *-8.9* | 0.419 | 20.1 | *-16.8* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -7.9 | *-1.3* | -8.2 | *-2.4* | 0.101 | -4.8 | *-2.3* | <0.001 | -9.2 | *-2.0* | <0.001 | <0.001 |
| Change in SD time sample | 43.2 | *-14.6* | 3.7 | *-16.7* | <0.001 | 55.7 | *-16.1* | <0.001 | 40.0 | *-11.7* | 0.233 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -8.9 | *-3.6* | -11.2 | *-6.1* | 0.001 | -4.0 | *-8.3* | 0.002 | -8.3 | *-3.9* | 0.341 | <0.001 |
| Change in SD time sample | -0.8 | *-6.3* | -3.0 | *-8.3* | 0.001 | -11.1 | *-6.2* | <0.001 | 0.7 | *-3.5* | 0.066 | <0.001 |
| **Change in combined ARI** | 10.4 | *-9.4* | 10.0 | *-13.5* | 0.690 | 13.3 | *-13.6* | 0.018 | -9.8 | *-6.6* | <0.001 | <0.001 |
| Change in SD time sample | 15.8 | *-7.1* | 14.4 | *-16.3* | 0.546 | 1.6 | *-9.0* | <0.001 | 4.0 | *-6.0* | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 6.6 | *-2.7* | 4.5 | *-4.1* | 0.001 | 4.7 | *-2.1* | <0.001 | 5.0 | *-3.6* | 0.003 | <0.001 |
| Change in SD time sample | 17.9 | *-15.4* | 7.5 | *-10.1* | <0.001 | 9.3 | *-10.3* | <0.001 | 13.6 | *-34.9* | <0.001 | <0.001 |

**Table 67 Percentage mean change from pre-HUT at 1 minute of HUT** *(Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (16) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **% of Mean** | ***SD*** | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -8.7 | *-2.5* | -12.5 | *-2.7* | <0.001 | -11.7 | *-2.1* | <0.001 | -9.9 | *-1.7* | <0.001 | <0.001 |
| Change in SD time sample | -18.4 | *-16.1* | -7.8 | *-12.8* | <0.001 | -19.1 | *-5.3* | 0.196 | 18.1 | *-16.5* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -8.0 | *-1.4* | -10.8 | *-2.1* | <0.001 | -5.3 | *-2.2* | <0.001 | -12.6 | *-1.4* | <0.001 | <0.001 |
| Change in SD time sample | 34.6 | *-12.4* | 5.9 | *-9.4* | <0.001 | 64.3 | *-20.9* | <0.001 | 29.4 | *-9.3* | 0.233 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -13.1 | *-1.8* | -16.4 | *-4.5* | <0.001 | -8.6 | *-4.7* | <0.001 | -15.1 | *-1.3* | 0.341 | <0.001 |
| Change in SD time sample | -9.9 | *-3.6* | -10.9 | *-4.6* | <0.001 | -13.7 | *-6.8* | 0.100 | -3.2 | *-2.2* | 0.066 | <0.001 |
| **Change in combined ARI** | -3.9 | *-13.3* | 60.1 | *-11.4* | <0.001 | 32.7 | *-18.4* | <0.001 | 0.9 | *-13.3* | <0.001 | <0.001 |
| Change in SD time sample | 2.5 | *-5.8* | -3.1 | *-6.9* | <0.001 | -17.7 | *-9.1* | <0.001 | -5.3 | *-5.8* | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | 14.4 | *-2.5* | 8.4 | *-4.0* | <0.001 | 10.3 | *-1.8* | <0.001 | 8.6 | *-2.4* | 0.003 | <0.001 |
| Change in SD time sample | 24.4 | *-28.2* | 2.1 | *-11.5* | <0.001 | 11.0 | *-11.5* | <0.001 | 8.8 | *-12.6* | <0.001 | <0.001 |

**Table 68 Percentage mean change from pre-HUT at 2 minutes of HUT** *(Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (16) | | Symptomatic No OH (16) | | Mann Whitney U Test *(p-value)* | Asymptomatic OH (16) | | Mann Whitney U Test *(p-value)* | Symptomatic OH (14) | | Mann Whitney U Test *(p-value)* | Kruskal-Wallis Test *(p-value)* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **% of Mean** | ***SD*** | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | **% of Mean** | ***SD*** | | |
| **Change in combined CBFV (cm/s)** | -15.8 | *-1.7* | -22.9 | *-1.8* | <0.001 | -17.8 | *-3.1* | <0.001 | -17.6 | *-8.0* | 0.680 | <0.001 |
| Change in SD time sample | -17.7 | *-9.1* | -5.9 | *-6.3* | <0.001 | -19.4 | *-13.4* | 0.730 | 3.8 | *-45.5* | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -11.9 | *-2.4* | -12.2 | *-1.1* | 0.025 | -13.8 | *-1.2* | <0.001 | -9.5 | *-3.8* | 0.008 | <0.001 |
| Change in SD time sample | 34.3 | *-8.8* | -1.0 | *-7.0* | <0.001 | 64.6 | *-25.5* | <0.001 | 32.5 | *-15.8* | 0.320 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -11.2 | *-6.3* | -20.0 | *-1.5* | <0.001 | -2.9 | *-11.3* | <0.001 | -22.4 | *-4.1* | <0.001 | <0.001 |
| Change in SD time sample | -13.1 | *-11.7* | -8.6 | *-1.5* | 0.594 | -25.1 | *-11.6* | <0.001 | 10.1 | *-7.6* | <0.001 | <0.001 |
| **Change in combined ARI** | -5.0 | *-12.5* | 2.0 | *-7.0* | 0.001 | 10.6 | *-5.1* | <0.001 | 17.3 | *-21.0* | <0.001 | <0.001 |
| Change in SD time sample | 3.9 | *-14.9* | 5.3 | *-4.0* | 0.009 | -20.6 | *-8.3* | <0.001 | 6.4 | *-5.7* | 0.183 | <0.001 |
| **Change in Heart Rate (bpm)** | 17.3 | *-1.7* | 16.2 | *-1.7* | 0.001 | 10.3 | *-2.4* | <0.001 | 12.4 | *-4.9* | <0.001 | <0.001 |
| Change in SD time sample | 44.2 | *-15.5* | 24.4 | *-9.0* | <0.001 | 15.8 | *-15.4* | <0.001 | 28.6 | *-12.8* | <0.001 | <0.001 |

**Table 69 Percentage mean change from pre-HUT at end of HUT** *(Mann Whitney U to compare each group with the Control, i.e. Asymptomatic No OH; Kruskal-Wallis Test to examine for variances across group)*

| | Asymptomatic No OH (17) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=3)*** | | ***Asymptomatic HUT (n=14)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Mean combined CBFV (cm/s)** | 42.3 | *1.2* | 46.1 | *0.8* | <0.001 |
| SD time sample | 13.8 | *1.3* | 13.6 | *1.7* | <0.001 |
| **MAP (mmHg)** | 95 | *1.8* | 89.4 | *1.2* | <0.001 |
| SD time sample | 4.8 | *2.5* | 8.9 | *0.9* | <0.001 |
| **$tCO_2$ (mmHg)** | 87.5 | *1.8* | 120.6 | *1.0* | <0.001 |
| SD time sample | 60.0 | *1.7* | 41.8 | *1.2* | <0.001 |
| **Mean combined ARI** | 5.5 | *0.8* | 5.0 | *0.1* | <0.001 |
| SD time sample | 2.1 | *0.5* | 2.6 | *0.1* | <0.001 |
| **Heart Rate (bpm)** | 68.4 | *3.8* | 66.3 | *1.3* | <0.001 |
| SD time sample | 4.8 | *2.9* | 11.8 | *1.7* | <0.001 |

**Table 70 Pre-HUT values for those who were symptomatic versus asymptomatic during HUT within Asymptomatic No OH group**

| | Asymptomatic No OH (17) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=3)*** | | ***Asymptomatic HUT (n=14)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in mean combined CBFV (cm/s)** | -6.3 | 3.3 | -7.6 | 0.9 | <0.001 |
| Change in SD time sample | -5.2 | 2.4 | -3.2 | 1.8 | <0.001 |
| **Change in MAP (mmHg)** | -14.7 | 4.1 | -9.8 | 1.5 | <0.001 |
| Change in SD time sample | 20.8 | 4.6 | 2.0 | 1.3 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -2.9 | 2.2 | -15.7 | 1.8 | <0.001 |
| Change in SD time sample | 4.0 | 2.1 | -0.8 | 1.9 | <0.001 |
| **Change in mean combined ARI** | -2.6 | 1.3 | -0.5 | 0.3 | <0.001 |
| Change in SD time sample | -0.5 | 0.5 | 0.4 | 0.1 | <0.001 |
| **Change in Heart Rate (bpm)** | 4.8 | 5.0 | 13.3 | 1.6 | <0.001 |
| Change in SD time sample | 10.8 | 3.0 | 4.9 | 2.2 | <0.001 |

**Table 71 Comparison of mean changes between pre-HUT and pre-End HUT of those who were symptomatic versus asymptomatic during HUT within Asymptomatic No OH group**

| | Symptomatic No OH (16) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT(n=6)*** | | ***Asymptomatic HUT(n=10)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Mean combined CBFV (cm/s)** | 59.5 | *1.4* | 41.9 | *0.4* | <0.001 |
| SD time sample | 19.5 | *1.5* | 8.4 | *0.3* | <0.001 |
| **MAP (mmHg)** | 88.0 | *1.7* | 95.1 | *1.2* | <0.001 |
| SD time sample | 19.1 | *1.6* | 20.1 | *0.7* | <0.001 |
| **$tCO_2$ (mmHg)** | 99.6 | *3.1* | 129.6 | *1.2* | <0.001 |
| SD time sample | 51.0 | *1.2* | 52.5 | *0.7* | <0.001 |
| **Mean combined ARI** | 3.6 | *0.0* | 3.0 | *0.2* | <0.001 |
| SD time sample | 3.3 | *0.2* | 2.4 | *0.0* | <0.001 |
| **Heart Rate (bpm)** | 68.7 | *2.4* | 62.5 | *1.1* | <0.001 |
| SD time sample | 12.0 | *0.6* | 11.0 | *1.3* | <0.001 |

**Table 72 Pre-HUT values for those who were symptomatic versus asymptomatic during HUT within Symptomatic No OH group**

| | Symptomatic No OH (16) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT(n=6)*** | | ***Asymptomatic HUT(n=10)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in mean combined CBFV (cm/s)** | -14.7 | 1.5 | -7.6 | 0.9 | <0.001 |
| Change in SD time sample | 3.2 | 1.1 | -3.2 | 1.8 | <0.001 |
| **Change in MAP (mmHg)** | -28.7 | 2.5 | -6.3 | 3.1 | <0.001 |
| Change in SD time sample | 19.0 | 2.6 | 5.8 | 3.1 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -25.2 | 3.7 | 28.8 | 4.4 | <0.001 |
| Change in SD time sample | -15.0 | 2.4 | -14.4 | 3.1 | 0.196 |
| **Change in mean combined ARI** | -0.4 | 0.1 | -0.5 | 0.3 | <0.001 |
| Change in SD time sample | -1.2 | 0.1 | 0.4 | 0.1 | <0.001 |
| **Change in Heart Rate (bpm)** | -1.3 | 2.5 | 8.6 | 2.4 | <0.001 |
| Change in SD time sample | 3.0 | 1.2 | 2.0 | 2.9 | <0.001 |

**Table 73 Comparison of mean changes between pre-HUT and pre-End HUT of those who were symptomatic versus asymptomatic during HUT within Symptomatic OH group**

| | Asymptomatic OH (16) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT(n=5)*** | | ***Asymptomatic HUT(n=11)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Mean combined CBFV (cm/s)** | 51.3 | *0.9* | 46.1 | *0.8* | <0.001 |
| SD time sample | 8.8 | *0.6* | 13.6 | *1.7* | <0.001 |
| **MAP (mmHg)** | 100.3 | *1.0* | 89.4 | *1.2* | <0.001 |
| SD time sample | 10.7 | *1.6* | 8.9 | *0.9* | <0.001 |
| **$tCO_2$ (mmHg)** | 130.1 | *1.6* | 120.6 | *1.0* | <0.001 |
| SD time sample | 58.3 | *1.2* | 41.8 | *1.2* | <0.001 |
| **Mean combined ARI** | 4.2 | *0.2* | 5.0 | *0.1* | <0.001 |
| SD time sample | 3.4 | *0.1* | 2.6 | *0.1* | <0.001 |
| **Heart Rate (bpm)** | 68.3 | *0.9* | 66.3 | *1.3* | <0.001 |
| SD time sample | 10.2 | *0.6* | 11.8 | *1.7* | <0.001 |

**Table 74 Pre-HUT values for those who were symptomatic versus asymptomatic during HUT within Asymptomatic OH group**

| | Asymptomatic OH (16) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT(n=5)*** | | ***Asymptomatic HUT(n=11)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in mean combined CBFV (cm/s)** | -7.4 | 2.7 | -8.8 | 0.6 | <0.001 |
| Change in SD time sample | -10.4 | 2.2 | 3.0 | 0.6 | <0.001 |
| **Change in MAP (mmHg)** | -12.1 | 8.3 | -4.3 | 2.0 | <0.001 |
| Change in SD time sample | -13.6 | 4.8 | -2.0 | 2.4 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 2.4 | 12.0 | -26.7 | 2.0 | <0.001 |
| Change in SD time sample | -44.5 | 4.4 | 5.1 | 1.4 | <0.001 |
| **Change in mean combined ARI** | -1.1 | 0.4 | 1.1 | 0.6 | <0.001 |
| Change in SD time sample | -1.0 | 0.3 | 0.4 | 0.2 | <0.001 |
| **Change in Heart Rate (bpm)** | 8.9 | 3.7 | 14.0 | 1.7 | <0.001 |
| Change in SD time sample | -7.5 | 2.9 | 7.0 | 2.7 | <0.001 |

**Table 75 Comparison of mean changes between pre-HUT and pre-End HUT of those who were symptomatic versus asymptomatic during HUT within Symptomatic No OH group**

| | Symptomatic OH (20) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=9)*** | | ***Asymptomatic HUT (n=11)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Mean combined CBFV (cm/s)** | 39.8 | *0.6* | 38.9 | *0.6* | <0.001 |
| SD time sample | 8.1 | *0.9* | 6.1 | *0.6* | <0.001 |
| **MAP (mmHg)** | 91.8 | *1.9* | 97.9 | *1.3* | <0.001 |
| SD time sample | 11.4 | *2.1* | 11.8 | *0.6* | <0.001 |
| **$tCO_2$ (mmHg)** | 111.7 | *2.1* | 115.9 | *1.8* | <0.001 |
| SD time sample | 55.0 | *1.2* | 61.6 | *1.0* | <0.001 |
| **Mean combined ARI** | 4.7 | *0.3* | 4.6 | *0.4* | <0.001 |
| SD time sample | 3.2 | *0.1* | 2.9 | *0.1* | <0.001 |
| **Heart Rate (bpm)** | 68.4 | *2.0* | 72.1 | *1.8* | <0.001 |
| SD time sample | 12.8 | *0.6* | 15.3 | *1.9* | <0.001 |

**Table 76 Pre-HUT values for those who were symptomatic versus asymptomatic during HUT within Symptomatic OH group**

| | Symptomatic OH (20) | | | | Mann Whitney U Test *(p-value)* |
|---|---|---|---|---|---|
| | ***Symptomatic HUT (n=9)*** | | ***Asymptomatic HUT (n=11)*** | | |
| | **Mean** | ***SD*** | **Mean** | ***SD*** | |
| **Change in mean combined CBFV (cm/s)** | -5.7 | 0.8 | -4.6 | 0.9 | <0.001 |
| Change in SD time sample | 1.5 | 0.8 | 0.5 | 0.7 | <0.001 |
| **Change in MAP (mmHg)** | -4.7 | 2.5 | -15.2 | 2.6 | <0.001 |
| Change in SD time sample | 10.5 | 2.1 | 5.9 | 1.8 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 6.5 | 3.2 | -23.6 | 2.1 | <0.001 |
| Change in SD time sample | -2.5 | 1.5 | -9.9 | 2.5 | <0.001 |
| **Change in mean combined ARI** | -0.5 | 0.5 | 1.6 | 0.4 | <0.001 |
| Change in SD time sample | -0.5 | 0.2 | 0.3 | 0.1 | <0.001 |
| **Change in Heart Rate (bpm)** | 8.2 | 3.6 | 9.0 | 1.8 | <0.001 |
| Change in SD time sample | 2.7 | 2.2 | 0.1 | 2.3 | <0.001 |

**Table 77 Comparison of mean changes between pre-HUT and pre-End HUT of those who were symptomatic versus asymptomatic during HUT within Symptomatic OH group**

| *Right side* | **No PPH - placebo** | | **No PPH - glucose** | | **Wilcoxon Signed Ranks** (p-value) | **PPH - placebo** | | **PPH - glucose** | | **Wilcoxon Signed Ranks** (p-value) | **Mann Whitney U** *(p-value)* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | | Mean | *SD* | Mean | *SD* | | **Placebo** | **Glucose** |
| **ARI** | 5.32 | *0.97* | 4.78 | *1.59* | 0.064 | 4.98 | *1.51* | 5.11 | *1.55* | 0.328 | 0.821 | 0.361 |
| **Coherence Low Frequency** (<0.07Hz) | 0.44 | *0.17* | 0.34 | *0.11* | 0.152 | 0.31 | *0.15* | 0.30 | *0.15* | 0.657 | 0.041 | 0.239 |
| **Gain Low Frequency** (<0.07Hz) | 0.44 | *0.19* | 0.38 | *0.07* | 0.507 | 0.34 | *0.14* | 0.34 | *0.13* | 0.859 | 0.201 | 0.381 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.70 | *0.29* | 0.55 | *0.36* | 0.133 | 0.65 | *0.29* | 0.65 | *0.28* | 0.929 | 0.683 | 0.491 |
| **Step Response Recovery (%)** | 76.1 | *13.8* | 68.4 | *25.6* | 0.221 | 72.8 | *21.3* | 80.9 | *38.4* | 0.594 | 0.586 | 0.468 |

**Table 78 Baseline ARI (Tiecks model) Right Middle Cerebral Artery**

| *Left side* | **No PPH - placebo** | | **No PPH - glucose** | | **Wilcoxon Signed Ranks** (p-value) | **PPH - placebo** | | **PPH - glucose** | | **Wilcoxon Signed Ranks** (p-value) | **Mann Whitney U (p-value)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | *SD* | Mean | *SD* | | Mean | *SD* | Mean | *SD* | | **Placebo** | **Glucose** |
| **ARI** | 4.67 | *1.60* | 4.62 | *2.19* | 0.777 | 5.43 | *2.02* | 5.34 | *1.56* | 0.836 | 0.154 | 0.422 |
| **Coherence Low Frequency** (<0.07Hz) | 0.41 | *0.18* | 0.33 | *0.14* | 0.215 | 0.34 | *0.18* | 0.30 | *0.13* | 0.796 | 0.135 | 0.567 |
| **Gain Low Frequency** (<0.07Hz) | 0.46 | *0.18* | 0.38 | *0.13* | 0.267 | 0.40 | *0.29* | 0.30 | *0.16* | 0.469 | 0.175 | 0.142 |
| **Phase Low Frequency** (<0.07Hz) **(radians)** | 0.49 | *0.55* | 0.55 | *0.34* | 0.349 | 0.67 | *0.59* | 0.46 | *0.35* | 0.255 | 0.347 | 0.403 |
| **Step Response Recovery (%)** | 70.1 | *21.2* | 70.9 | *40.4* | 0.647 | 101.9 | *57.1* | 84.5 | *37.6* | 0.642 | 0.036 | 0.317 |

**Table 79 Baseline ARI (Tiecks model) Left Middle Cerebral Artery**

| | No PPH – placebo (n=17) | | No PPH – glucose (n=17) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=12) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 43.7 | *8.8* | 46.4 | *6.6* | 0.287 | 43.3 | *11.4* | 42.1 | *7.1* | 0.695 | 0.616 | 0.166 |
| **CBFV Left (cm/s)** | 43.4 | *8.2* | 45.1 | *8.4* | 0.523 | 44.7 | *9.1* | 45.1 | *9.3* | 0.875 | 0.499 | 0.811 |
| **Mean CBFV (cm/s)** | 43.5 | *7.1* | 45.8 | *6.5* | 0.795 | 44.0 | *9.0* | 43.6 | *7.0* | 1.000 | 0.664 | 0.891 |
| **Systolic CBFV Right (cm/s)** | 68.5 | *11.1* | 72.5 | *11.1* | 0.332 | 68.3 | *17.4* | 62.3 | *10.7* | 0.272 | 0.777 | 0.030 |
| **Systolic CBFV Left (cm/s)** | 66.9 | *12.9* | 69.7 | *13.5* | 0.619 | 64.2 | *17.2* | 68.0 | *16.9* | 0.754 | 0.616 | 1.000 |
| **Mean Systolic CBFV (cm/s)** | 67.7 | *9.8* | 71.1 | *10.9* | 0.723 | 66.3 | *11.3* | 65.2 | *12.2* | 0.735 | 0.901 | 0.784 |
| **Diastolic CBFV Right (cm/s)** | 27.4 | *6.5* | 28.7 | *4.4* | 0.227 | 26.8 | *9.1* | 27.3 | *4.6* | 0.583 | 0.499 | 0.471 |
| **Diastolic CBFV Left (cm/s)** | 27.3 | *5.6* | 28.7 | *5.8* | 0.554 | 24.8 | *10.2* | 28.7 | *5.1* | 0.272 | 0.679 | 0.586 |
| **Mean Diastolic CBFV (cm/s)** | 27.3 | *5.4* | 28.7 | *4.7* | 0.723 | 25.8 | *7.6* | 28.0 | *4.2* | 0.735 | 0.757 | 0.471 |
| **SBP (mmHg)** | 134.1 | *16.0* | 138.2 | *20.3* | 0.868 | 152.2 | *24.2* | 139.9 | *23.5* | 0.347 | 0.034 | 0.744 |
| **DBP (mmHg)** | 71.8 | *14.6* | 73.2 | *10.5* | 0.831 | 81.0 | *21.3* | 79.6 | *17.2* | 0.638 | 0.283 | 0.499 |
| **MAP (mmHg)** | 92.6 | *13.0* | 94.9 | *11.5* | 0.723 | 106.4 | *20.1* | 102.4 | *19.1* | 0.388 | 0.053 | 0.394 |
| **Heart Rate (bpm)** | 66.2 | *5.5* | 61.7 | *5.3* | 0.025 | 62.5 | *4.4* | 63.4 | *5.3* | 0.638 | 0.073 | 0.370 |
| **$tCO_2$ (mmHg)** | 48.2 | *63.5* | 47.3 | *63.6* | 0.981 | 73.4 | *70.4* | 101.0 | *64.3* | 0.239 | 0.527 | 0.053 |

**Table 80 Group Measurements pre-HUT (***i.e.1 minute prior to HUT; For this time point the Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase, Mean CBFV =combined right and left CBFV***)**

| | **No PPH – placebo (n=17)** | | **No PPH – glucose (n=17)** | | **Wilcoxon Signed Ranks Test** (p-values) | **PPH – placebo (n=12)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-values) | **Mann Whitney U test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 38.6 | *9.5* | 41.0 | *8.9* | 0.687 | 40.0 | *11.9* | 38.9 | *9.3* | 0.875 | 0.879 | 0.616 |
| **CBFV Left (cm/s)** | 39.1 | *8.5* | 42.2 | *8.6* | 0.407 | 41.3 | *7.4* | 44.8 | *12.3* | 0.347 | 0.303 | 0.499 |
| **Mean CBFV (cm/s)** | 38.8 | *7.8* | 41.6 | *8.3* | 0.554 | 40.7 | *8.6* | 41.9 | *8.7* | 0.128 | 0.494 | 0.584 |
| **Systolic CBFV Right (cm/s)** | 59.3 | *15.0* | 62.6 | *12.3* | 0.492 | 59.7 | *15.2* | 58.8 | *14.6* | 0.754 | 0.948 | 0.444 |
| **Systolic CBFV Left (cm/s)** | 59.9 | *11.7* | 64.1 | *11.5* | 0.246 | 62.0 | *10.9* | 67.2 | *20.5* | 0.480 | 0.556 | 0.711 |
| **Mean Systolic CBFV (cm/s)** | 59.6 | *11.7* | 63.3 | *10.9* | 0.687 | 60.9 | *11.4* | 63.0 | *14.8* | 0.237 | 0.534 | 0.632 |
| **Diastolic CBFV Right (cm/s)** | 25.2 | *7.4* | 27.1 | *6.6* | 0.586 | 26.8 | *9.7* | 25.8 | *6.0* | 0.875 | 0.777 | 0.679 |
| **Diastolic CBFV Left (cm/s)** | 25.8 | *6.4* | 28.1 | *6.3* | 0.309 | 27.6 | *6.2* | 29.3 | *6.9* | 0.638 | 0.394 | 0.647 |
| **Mean Diastolic CBFV (cm/s)** | 25.5 | *6.0* | 27.6 | *6.2* | 0.569 | 27.2 | *7.2* | 27.5 | *4.9* | 0.310 | 0.318 | 0.811 |
| **SBP (mmHg)** | 117.2 | *21.9* | 123.5 | *22.5* | 0.381 | 129.7 | *18.1* | 123.4 | *30.5* | 0.308 | 0.370 | 0.679 |
| **DBP (mmHg)** | 75.1 | *13.4* | 72.8 | *17.0* | 0.586 | 80.4 | *24.0* | 78.6 | *21.6* | 0.530 | 0.419 | 0.711 |
| **MAP (mmHg)** | 88.3 | *14.3* | 88.6 | *16.5* | 0.906 | 98.0 | *22.5* | 95.5 | *26.1* | 0.530 | 0.325 | 0.647 |
| **Heart Rate (bpm)** | 70.5 | *7.2* | 67.4 | *6.1* | 0.227 | 66.7 | *6.8* | 68.6 | *5.4* | 0.480 | 0.195 | 0.777 |
| **$tCO_2$ (mmHg)** | 42.6 | *57.0* | 44.6 | *59.2* | 0.868 | 58.8 | *53.2* | 85.9 | *54.1* | 0.272 | 0.777 | 0.107 |

**Table 81 Group Measurements at 1 minute of HUT** *(For this time point the Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase)*

| | **No PPH – placebo (n=17)** | | **No PPH – glucose (n=17)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=12)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 40.0 | *8.8* | 39.6 | *8.7* | 0.981 | 38.4 | *10.1* | 39.7 | *10.5* | 0.875 | 0.412 | 0.879 |
| **CBFV Left (cm/s)** | 40.2 | *8.5* | 42.2 | *10.0* | 0.381 | 40.8 | *6.6* | 43.0 | *13.0* | 1.000 | 0.877 | 0.679 |
| **Mean CBFV (cm/s)** | 40.1 | *7.2* | 40.9 | *8.5* | 0.868 | 39.6 | *7.2* | 41.3 | *9.9* | 0.779 | 0.710 | 0.931 |
| **Systolic CBFV Right (cm/s)** | 62.6 | *12.3* | 61.1 | *12.7* | 0.723 | 58.5 | *13.3* | 59.5 | *15.3* | 0.875 | 0.276 | 0.711 |
| **Systolic CBFV Left (cm/s)** | 61.5 | *11.9* | 65.0 | *15.6* | 0.554 | 62.2 | *10.7* | 64.9 | *22.9* | 0.695 | 0.842 | 0.983 |
| **Mean Systolic CBFV (cm/s)** | 62.0 | *10.1* | 63.0 | *12.6* | 0.831 | 60.4 | *10.1* | 62.2 | *16.2* | 0.889 | 0.757 | 0.986 |
| **Diastolic CBFV Right (cm/s)** | 25.8 | *8.0* | 25.6 | *6.0* | 0.831 | 25.1 | *7.9* | 26.7 | *6.9* | 0.480 | 0.521 | 0.616 |
| **Diastolic CBFV Left (cm/s)** | 26.4 | *6.7* | 27.2 | *6.3* | 0.523 | 26.7 | *5.6* | 28.6 | *7.4* | 0.695 | 0.774 | 0.419 |
| **Mean Diastolic CBFV (cm/s)** | 26.1 | *6.4* | 26.4 | *5.8* | 0.831 | 25.9 | *6.1* | 27.6 | *6.1* | 0.674 | 0.576 | 0.931 |
| **SBP (mmHg)** | 127.4 | *27.6* | 129.8 | *16.6* | 0.723 | 126.7 | *21.8* | 123.2 | *24.1* | 0.754 | 0.363 | 0.325 |
| **DBP (mmHg)** | 71.1 | *17.7* | 75.5 | *16.4* | 0.868 | 79.0 | *23.7* | 80.3 | *21.4* | 0.814 | 0.707 | 0.527 |
| **MAP (mmHg)** | 87.4 | *17.7* | 92.1 | *14.7* | 0.407 | 95.6 | *22.5* | 95.2 | *23.0* | 0.814 | 0.707 | 0.711 |
| **Heart Rate (bpm)** | 69.9 | *8.4* | 69.3 | *6.7* | 0.906 | 68.0 | *7.6* | 73.3 | *14.1* | 0.347 | 0.550 | 0.647 |
| **$tCO_2$ (mmHg)** | 45.0 | *59.4* | 42.5 | *56.2* | 0.831 | 59.3 | *54.5* | 93.7 | *58.3* | 0.099 | 0.912 | 0.059 |

**Table 82 Groups Measurements at 3 minutes of HUT** *(For this time point the Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase)*

| | **No PPH – placebo (n=17)** | | **No PPH – glucose (n=19)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=13)** | | **PPH – glucose (n=15)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 38.7 | *8.2* | 35.4 | *7.8* | 0.124 | 35.5 | *6.6* | 34.5 | *6.2* | 0.552 | 0.320 | 0.918 |
| **CBFV Left (cm/s)** | 35.8 | *10.0* | 37.1 | *8.8* | 0.554 | 35.0 | *6.6* | 37.6 | *8.4* | 0.600 | 0.934 | 0.681 |
| **Mean CBFV (cm/s)** | 37.3 | *8.4* | 36.3 | *7.5* | 0.687 | 35.3 | *5.6* | 36.1 | *5.2* | 0.176 | 0.711 | 0.973 |
| **Systolic CBFV Right (cm/s)** | 60.3 | *11.1* | 54.9 | *11.9* | 0.149 | 54.9 | *10.1* | 55.1 | *10.1* | 0.861 | 0.183 | 1.000 |
| **Systolic CBFV Left (cm/s)** | 54.9 | *13.9* | 58.7 | *11.2* | 0.435 | 53.4 | *8.3* | 59.8 | *14.1* | 0.249 | 1.000 | 0.681 |
| **Mean Systolic CBFV (cm/s)** | 57.6 | *11.1* | 56.8 | *10.4* | 0.723 | 54.2 | *7.1* | 57.5 | *9.5* | 0.735 | 0.509 | 0.706 |
| **Diastolic CBFV Right (cm/s)** | 26.4 | *5.6* | 24.1 | *5.0* | 0.163 | 23.6 | *4.8* | 22.7 | *5.8* | 0.552 | 0.113 | 0.242 |
| **Diastolic CBFV Left (cm/s)** | 24.7 | *7.0* | 28.1 | *10.0* | 0.149 | 23.9 | *6.0* | 24.9 | *6.9* | 0.807 | 0.805 | 0.286 |
| **Mean Diastolic CBFV (cm/s)** | 25.6 | *5.8* | 26.1 | *6.3* | 0.653 | 23.7 | *4.7* | 23.8 | *5.2* | 0.063 | 0.457 | 0.430 |
| **SBP (mmHg)** | 121.9 | *24.9* | 120.8 | *19.3* | 0.906 | 128.4 | *31.1* | 122.9 | *26.7* | 0.507 | 0.385 | 0.758 |
| **DBP (mmHg)** | 75.0 | *15.4* | 73.2 | *12.2* | 0.943 | 74.8 | *16.2* | 73.2 | *17.1* | 0.807 | 0.320 | 0.560 |
| **MAP (mmHg)** | 89.3 | *16.3* | 88.1 | *12.9* | 0.723 | 93.2 | *20.2* | 91.8 | *15.3* | 0.507 | 0.113 | 0.286 |
| **Heart Rate (bpm)** | 76.9 | *10.1* | 75.7 | *10.0* | 0.943 | 71.7 | *9.0* | 74.7 | *12.3* | 0.861 | 0.263 | 0.202 |
| **$tCO_2$ (mmHg)** | 117.0 | *29.9* | 117.7 | *21.1* | 0.984 | 105.2 | *52.4* | 81.9 | *52.3* | 0.101 | 0.869 | 0.043 |

**Table 83 Group Measurements prior to End HUT** *(i.e.1 minute prior to the end of HUT; For this time point the Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase))*

| | No PPH – placebo (n=17) | | No PPH – glucose (n=17) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=12) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change CBFV Right (cm/s)** | -5.1 | *6.8* | -5.4 | *5.7* | 0.492 | -3.3 | *4.5* | -3.2 | *4.9* | 0.937 | 0.419 | 0.325 |
| **Change CBFV Left (cm/s)** | -4.3 | *6.9* | -3.0 | *5.7* | 0.356 | -3.4 | *6.4* | -0.3 | *9.2* | 0.308 | 0.616 | 0.556 |
| **Change Mean CBFV (cm/s)** | -4.7 | *6.4* | -4.2 | *5.2* | 0.795 | -3.3 | *5.0* | -1.7 | *6.3* | 0.735 | 0.534 | 0.179 |
| **Change Systolic CBFV Right (cm/s)** | -9.2 | *11.3* | -9.8 | *9.2* | 0.554 | -8.6 | *9.7* | -3.5 | *7.6* | 0.239 | 0.586 | 0.059 |
| **Change Systolic CBFV Left (cm/s)** | -7.0 | *10.8* | -5.7 | *8.9* | 0.407 | -2.2 | *14.5* | -0.9 | *13.2* | 0.638 | 0.679 | 0.347 |
| **Change Mean Systolic CBFV (cm/s)** | -8.1 | *10.8* | -7.7 | *8.3* | 0.981 | -5.4 | *5.6* | -2.2 | *9.7* | 0.398 | 0.951 | 0.023 |
| **Change Diastolic CBFV Right (cm/s)** | -2.2 | *6.3* | -1.6 | *4.4* | 0.795 | 0.0 | *2.8* | -1.5 | *3.2* | 0.388 | 0.283 | 0.983 |
| **Change Diastolic CBFV Left (cm/s)** | -1.5 | *5.2* | -0.6 | *4.3* | 0.795 | 2.9 | *10.3* | 0.6 | *5.7* | 0.695 | 0.211 | 0.679 |
| **Change Mean Diastolic CBFV (cm/s)** | -1.9 | *5.2* | -1.1 | *4.2* | 0.906 | 1.4 | *5.7* | -0.4 | *3.8* | 0.237 | 0.147 | 0.286 |
| **Change SBP (mmHg)** | -16.9 | *21.8* | -14.6 | *24.7* | 0.523 | -22.5 | *20.9* | -16.5 | *22.8* | 0.433 | 0.711 | 0.527 |
| **Change DBP (mmHg)** | 3.3 | *12.3* | -0.4 | *12.5* | 0.758 | -0.6 | *11.8* | -1.0 | *11.9* | 0.937 | 0.227 | 0.556 |
| **Change MAP (mmHg)** | -4.3 | *11.6* | -6.2 | *14.1* | 0.831 | -8.3 | *13.1* | -6.9 | *14.4* | 0.638 | 0.471 | 0.419 |
| **Change Heart Rate (bpm)** | 4.3 | *4.6* | 5.8 | *4.4* | 0.227 | 4.2 | *7.4* | 5.2 | *5.5* | 0.754 | 0.913 | 0.879 |
| **Change $tCO_2$ (mmHg)** | -5.5 | *10.8* | -2.7 | *9.7* | 0.981 | -14.6 | *20.7* | -15.2 | *20.6* | 1.000 | 0.394 | 0.227 |

**Table 84 Differences between pre-HUT and 1 minute HUT (***i.e. The difference between 1 minute prior to HUT and 1 minute HUT; Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase)*

| | No PPH – placebo (n=17) | | No PPH – glucose (n=17) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=12) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change CBFV Right (cm/s)** | -3.7 | *9.3* | -6.8 | *5.5* | 0.136 | -4.9 | *4.4* | -2.4 | *5.9* | 0.272 | 0.283 | 0.166 |
| **Change CBFV Left (cm/s)** | -3.2 | *9.3* | -2.9 | *6.6* | 0.758 | -3.9 | *6.1* | -2.2 | *7.1* | 0.695 | 0.948 | 0.744 |
| **Change Mean CBFV (cm/s)** | -3.4 | *6.6* | -4.9 | *5.3* | 0.193 | -4.4 | *4.5* | -2.3 | *5.5* | 0.735 | 0.455 | 0.319 |
| **Change Systolic CBFV Right (cm/s)** | -5.9 | *10.1* | -11.4 | *8.9* | 0.062 | -9.8 | *7.7* | -2.9 | *8.0* | 0.084 | 0.245 | 0.018 |
| **Change Systolic CBFV Left (cm/s)** | -5.4 | *14.9* | -4.7 | *12.3* | 0.093 | -2.0 | *16.5* | -3.1 | *11.2* | 0.875 | 0.647 | 0.647 |
| **Change Mean Systolic CBFV (cm/s)** | -5.7 | *9.5* | -8.1 | *9.9* | 0.795 | -5.9 | *6.9* | -3.0 | *8.3* | 0.612 | 0.619 | 0.147 |
| **Change Diastolic CBFV Right (cm/s)** | -1.6 | *8.5* | -3.1 | *5.5* | 0.210 | -1.7 | *3.5* | -0.6 | *4.4* | 0.583 | 0.370 | 0.283 |
| **Change Diastolic CBFV Left (cm/s)** | -0.9 | *6.4* | -1.5 | *5.9* | 0.758 | 2.0 | *11.2* | -0.1 | *4.6* | 0.695 | 0.777 | 0.586 |
| **Change Mean Diastolic CBFV (cm/s)** | -1.3 | *5.9* | -2.3 | *5.4* | 0.102 | 0.1 | *6.7* | -0.3 | *4.0* | 0.735 | 0.147 | 0.515 |
| **Change SBP (mmHg)** | -6.7 | *18.9* | -8.4 | *17.7* | 0.723 | -25.5 | *19.5* | -16.7 | *21.6* | 0.182 | 0.027 | 0.394 |
| **Change DBP (mmHg)** | -0.8 | *9.4* | 2.3 | *10.9* | 0.687 | -2.0 | *11.9* | 0.7 | *10.5* | 0.583 | 0.527 | 0.913 |
| **Change MAP (mmHg)** | -5.2 | *10.8* | -2.8 | *12.4* | 0.619 | -10.8 | *12.4* | -7.2 | *13.1* | 0.433 | 0.227 | 0.647 |
| **Change Heart Rate (bpm)** | 3.8 | *4.2* | 7.6 | *5.0* | 0.028 | 5.5 | *7.8* | 9.9 | *15.3* | 0.346 | 0.811 | 0.499 |
| **Change $tCO_2$ (mmHg)** | -3.2 | *6.9* | -4.8 | *10.0* | 0.538 | -14.1 | *21.2* | -7.3 | *21.0* | 0.182 | 0.152 | 0.499 |

**Table 85 Differences between pre-HUT and 3 minutes HUT (***i.e. The difference between 1 minute prior to HUT and 3 minute HUT; Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase)*

| | No PPH – placebo (n=17) | | No PPH – glucose (n=19) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=13) | | PPH – glucose (n=15) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change CBFV Right (cm/s)** | -5.0 | *7.6* | -12.4 | *7.4* | 0.020 | -6.1 | *18.9* | -11.0 | *17.0* | 0.657 | 0.919 | 0.547 |
| **Change CBFV Left (cm/s)** | -8.3 | *8.2* | -9.0 | *5.6* | 0.776 | -4.5 | *12.8* | -10.1 | *22.0* | 0.477 | 0.610 | 0.711 |
| **Change Mean CBFV (cm/s)** | -6.7 | *6.1* | -10.7 | *5.6* | 0.427 | -5.3 | *14.8* | -10.5 | *17.7* | 0.310 | 0.209 | 0.539 |
| **Change Systolic CBFV Right (cm/s)** | -8.4 | *10.7* | -19.0 | *13.0* | 0.011 | -9.8 | *26.1* | -14.3 | *26.9* | 0.722 | 0.919 | 0.378 |
| **Change Systolic CBFV Left (cm/s)** | -13.4 | *13.8* | -11.8 | *11.2* | 0.910 | -6.9 | *20.1* | -14.7 | *37.4* | 0.477 | 0.610 | 0.611 |
| **Change Mean Systolic CBFV (cm/s)** | -10.9 | *10.1* | -15.4 | *11.1* | 0.460 | -8.4 | *21.4* | -14.5 | *29.8* | 0.612 | 0.349 | 0.567 |
| **Change Diastolic CBFV Right (cm/s)** | -1.0 | *6.7* | -5.6 | *4.5* | 0.015 | -2.2 | *13.0* | -6.0 | *10.8* | 0.424 | 0.799 | 0.746 |
| **Change Diastolic CBFV Left (cm/s)** | -3.0 | *6.4* | -1.1 | *10.1* | 0.955 | -0.4 | *8.3* | -4.5 | *13.2* | 0.328 | 0.540 | 0.781 |
| **Change Mean Diastolic CBFV (cm/s)** | -2.0 | *5.5* | -3.4 | *6.2* | 0.955 | -1.3 | *9.8* | -5.2 | *10.6* | 0.128 | 0.455 | 0.838 |
| **Change SBP (mmHg)** | -11.1 | *26.0* | -17.0 | *21.3* | 0.570 | -12.1 | *57.7* | -32.7 | *48.8* | 0.657 | 1.000 | 0.430 |
| **Change DBP (mmHg)** | 0.8 | *17.7* | 0.2 | *9.6* | 0.609 | 5.0 | *31.7* | -11.4 | *27.4* | 0.328 | 1.000 | 0.353 |
| **Change MAP (mmHg)** | -4.8 | *18.5* | -6.7 | *11.5* | 0.650 | -2.0 | *38.9* | -19.0 | *33.8* | 0.534 | 1.000 | 0.643 |
| **Change Heart Rate (bpm)** | 10.5 | *9.7* | 14.2 | *9.6* | 0.100 | 16.6 | *19.1* | 8.1 | *28.1* | 1.000 | 0.574 | 0.487 |
| **Change $tCO_2$ (mmHg)** | 80.7 | *63.5* | 73.6 | *68.1* | 0.460 | 11.4 | *70.0* | -34.3 | *84.7* | 0.155 | 0.018 | 0.002 |

**Table 86 Differences between pre-HUT and prior to end of HUT** *(i.e. The difference between 1 minute prior to HUT and 1 minute prior to the end of HUT; Wilcoxon Signed Ranks used to compare placebo and glucose phase within each group, Mann-Whitney used to compare No PPH and PPH Group for each phase)*

| | **No PPH - placebo (n=15)** | | **No PPH – glucose (n=14)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=12)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U Test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV (cm/s)** | 32.9 | *1.8* | 43.2 | *1.6* | <0.001 | 36.0 | *3.2* | 39.1 | *1.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 7.8 | *2.2* | 7.6 | *1.2* | 0.587 | 9.2 | *2.5* | 10.9 | *1.1* | <0.001 | 0.001 | <0.001 |
| **MAP (mmHg)** | 88.1 | *2.9* | 95.4 | *2.6* | <0.001 | 84.0 | *3.7* | 86.2 | *4.9* | 0.021 | <0.001 | <0.001 |
| SD time sample | 13.8 | *3.6* | 16.8 | *2.3* | <0.001 | 18.1 | *2.3* | 14.2 | *3.7* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 50.5 | *12.4* | 50.9 | *2.1* | <0.001 | 81.7 | *9.2* | 89.9 | *3.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 61.7 | *7.9* | 55.4 | *3.1* | <0.001 | 33.8 | *8.0* | 33.3 | *5.2* | 0.390 | <0.001 | <0.001 |
| **ARI** | 4.9 | *1.5* | 4.9 | *1.6* | 0.962 | 4.7 | *1.2* | 4.7 | *0.6* | 0.962 | 0.337 | 0.003 |
| SD time sample | 2.8 | *0.4* | 2.4 | *0.2* | <0.001 | 2.6 | *0.4* | 2.4 | *0.5* | 0.001 | 0.002 | 0.042 |
| **Heart Rate (bpm)** | 72.0 | *1.6* | 66.3 | *2.2* | <0.001 | 67.4 | *2.1* | 63.5 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 5.8 | *1.4* | 13.7 | *1.0* | <0.001 | 6.5 | *2.4* | 5.7 | *2.2* | 0.019 | 0.046 | <0.001 |

**Table 87 Continuous estimates of CBFV, MAP, $TCO_2$ ARI and HR Pre-HUT (Mean of left and right MCA)**

| | **No PPH - placebo (n=15)** | | **No PPH – glucose (n=14)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=12)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U Test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 30.7 | *3.0* | 42.5 | *2.2* | <0.001 | 33.7 | *2.3* | 36.9 | *2.0* | <0.001 | <0.001 | <0.001 |
| SD time sample | 8.6 | *3.1* | 8.1 | *1.1* | 0.171 | 8.7 | *3.2* | 10.6 | *1.3* | <0.001 | 0.885 | <0.001 |
| **MAP (mmHg)** | 85.4 | *4.5* | 87.4 | *3.3* | 0.004 | 86.7 | *2.3* | 84.8 | *2.8* | <0.001 | 0.001 | <0.001 |
| SD time sample | 15.0 | *3.5* | 18.2 | *3.9* | <0.001 | 21.9 | *1.6* | 11.5 | *2.5* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 47.3 | *3.6* | 56.8 | *1.8* | <0.001 | 65.5 | *3.7* | 63.7 | *3.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 62.7 | *6.2* | 54.2 | *2.3* | <0.001 | 45.4 | *3.0* | 43.1 | *2.6* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 4.9 | *0.9* | 4.3 | *0.9* | <0.001 | 4.5 | *1.5* | 5.9 | *1.0* | <0.001 | 0.001 | <0.001 |
| SD time sample | 3.3 | *0.2* | 3.2 | *0.3* | 0.038 | 2.6 | *0.5* | 2.1 | *1.0* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 71.8 | *1.9* | 65.5 | *2.3* | <0.001 | 67.5 | *2.5* | 63.3 | *3.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 7.2 | *1.2* | 6.4 | *1.3* | <0.001 | 6.2 | *2.9* | 5.6 | *3.1* | 0.038 | <0.001 | <0.001 |

**Table 88 Continuous estimates of CBFV, MAP, $TCO_2$ ARI and HR Pre-HUT (Right MCA)**

| | **No PPH - placebo (n=15)** | | **No PPH – glucose (n=14)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=12)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U Test (p-value)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 34.3 | *2.7* | 43.8 | *1.7* | <0.001 | 41.4 | *1.9* | 40.7 | *1.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 6.7 | *3.1* | 7.2 | *2.1* | 0.043 | 9.0 | *1.6* | 11.4 | *1.4* | <0.001 | 0.077 | <0.001 |
| **MAP (mmHg)** | 89.8 | *4.2* | 103.5 | *4.9* | <0.001 | 77.3 | *3.0* | 93.0 | *4.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 11.5 | *5.1* | 15.4 | *5.1* | <0.001 | 11.0 | *3.0* | 20.3 | *3.4* | <0.001 | 0.006 | <0.001 |
| **$tCO_2$ (mmHg)** | 45.4 | *3.6* | 45.0 | *3.1* | 0.468 | 109.6 | *4.5* | 118.8 | *6.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 64.5 | *6.1* | 56.7 | *4.3* | <0.001 | 12.1 | *4.4* | 28.9 | *2.8* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 5.3 | *2.3* | 5.4 | *2.4* | <0.001 | 4.1 | *0.7* | 3.4 | *1.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.3 | *0.8* | 1.6 | *0.6* | <0.001 | 2.7 | *0.4* | 2.7 | *0.5* | 0.105 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 73.0 | *1.2* | 67.2 | *2.8* | <0.001 | 66.4 | *2.9* | 63.6 | *2.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 3.8 | *1.1* | 21.0 | *1.6* | <0.001 | 6.4 | *3.5* | 6.0 | *2.9* | 0.735 | <0.001 | <0.001 |

**Table 89 Continuous estimates of CBFV, MAP, $TCO_2$ ARI and HR Pre-HUT (Left MCA)**

| | **No PPH – placebo (n=13)** | | **No PPH – glucose (n=13)** | | **Wilcoxon Signed Ranks Test** (p-value) | **PPH – placebo (n=11)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-value) | **Mann Whitney U Test** (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV (cm/s)** | 35.0 | *2.5* | 40.7 | *1.2* | <0.001 | 38.1 | *1.8* | 38.5 | *2.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 10.6 | *1.7* | 5.7 | *1.1* | <0.001 | 6.7 | *1.2* | 9.7 | *1.2* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 86.7 | *2.1* | 96.8 | *3.9* | <0.001 | 89.5 | *2.7* | 89.5 | *1.8* | 0.004 | <0.001 | <0.001 |
| SD time sample | 11.0 | *1.3* | 18.8 | *4.4* | <0.001 | 16.7 | *2.7* | 13.0 | *1.5* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 55.9 | *4.8* | 49.6 | *1.4* | <0.001 | 83.8 | *14.3* | 112.7 | *12.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 58.0 | *4.9* | 54.2 | *1.8* | <0.001 | 37.4 | *8.7* | 24.0 | *8.0* | <0.001 | <0.001 | <0.001 |
| **ARI** | 5.5 | *1.5* | 4.0 | *1.2* | <0.001 | 4.7 | *1.1* | 5.4 | *0.5* | 0.155 | <0.001 | <0.001 |
| SD time sample | 2.1 | *0.3* | 2.1 | *0.2* | 0.216 | 2.2 | *0.5* | 2.0 | *0.5* | 0.988 | 0.100 | 0.805 |
| **Heart Rate (bpm)** | 69.2 | *2.9* | 68.7 | *1.0* | 0.171 | 67.9 | *2.0* | 67.2 | *3.9* | 0.053 | <0.001 | 0.014 |
| SD time sample | 6.5 | *2.4* | 5.8 | *1.2* | 0.015 | 6.3 | *2.2* | 9.6 | *5.3* | 0.006 | 0.940 | 0.003 |

**Table 90 Continuous estimates of CBFV, MAP, $TCO_2$, ARI and HR HUT 1 minute (Mean of right and left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-value) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-value) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 32.4 | *1.6* | 40.8 | *2.5* | <0.001 | 42.6 | *1.7* | 36.5 | *1.6* | 0.001 | <0.001 | 0.024 |
| SD time sample | 8.4 | *3.2* | 3.8 | *1.9* | <0.001 | 6.5 | *1.7* | 8.7 | *1.4* | <0.001 | 0.001 | <0.001 |
| **MAP (mmHg)** | 92.7 | *1.2* | 104.3 | *6.3* | <0.001 | 82.8 | *1.8* | 87.5 | *2.7* | 0.041 | <0.001 | <0.001 |
| SD time sample | 9.4 | *1.0* | 17.1 | *5.7* | <0.001 | 9.9 | *2.1* | 5.5 | *2.4* | 0.030 | <0.001 | 0.001 |
| **$tCO_2$ (mmHg)** | 48.2 | *1.2* | 44.0 | *1.8* | <0.001 | 116.6 | *2.5* | 70.3 | *3.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 69.0 | *1.8* | 55.5 | *2.5* | <0.001 | 11.5 | *3.0* | 47.6 | *2.4* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 0.7 | *0.6* | 3.3 | *1.2* | <0.001 | 4.8 | *0.5* | 6.7 | *0.4* | 0.276 | <0.001 | <0.001 |
| SD time sample | 1.1 | *0.5* | 2.2 | *0.4* | <0.001 | 1.7 | *0.5* | 1.3 | *0.4* | 0.441 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 73.0 | *0.6* | 68.2 | *1.4* | <0.001 | 67.2 | *3.3* | 64.4 | *4.6* | 0.267 | <0.001 | 0.017 |
| SD time sample | 3.5 | *0.9* | 3.9 | *2.1* | 0.244 | 7.2 | *3.6* | 5.5 | *4.9* | 0.005 | 0.015 | 0.523 |

**Table 91 Continuous estimates of CBFV, MAP, $TCO_2$, ARI and HR HUT 1 minute (Right MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 36.5 | *2.7* | 40.9 | *1.1* | <0.001 | 36.8 | *2.0* | 31.9 | *1.0* | <0.001 | <0.001 | <0.001 |
| SD time sample | 9.1 | *2.7* | 7.3 | *0.9* | <0.001 | 7.9 | *2.7* | 14.8 | *1.7* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 81.1 | *1.8* | 92.9 | *3.9* | <0.001 | 90.6 | *1.2* | 98.6 | *1.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 17.2 | *2.4* | 18.8 | *4.9* | <0.001 | 22.1 | *2.0* | 14.0 | *2.2* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 42.6 | *1.5* | 55.1 | *1.8* | <0.001 | 68.3 | *2.1* | 126.7 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 60.7 | *1.9* | 53.0 | *2.0* | <0.001 | 48.7 | *1.3* | 22.8 | *2.8* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 3.9 | *1.7* | 4.7 | *0.4* | <0.001 | 4.2 | *1.0* | 6.9 | *0.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 3.1 | *0.5* | 2.3 | *0.2* | <0.001 | 3.6 | *0.2* | 1.4 | *0.6* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 71.8 | *2.0* | 69.9 | *1.3* | <0.001 | 67.1 | *2.5* | 73.6 | *3.8* | <0.001 | <0.001 | <0.001 |
| SD time sample | 7.4 | *1.9* | 8.4 | *1.4* | 0.026 | 5.2 | *3.4* | 18.3 | *5.5* | <0.001 | <0.001 | 0.910 |

**Table 92 Continuous estimates of CBFV, MAP, $TCO_2$, ARI and HR HUT 1 minute (Left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Combined CBFV (cm/s)** | 35.3 | *1.8* | 42.0 | *1.9* | <0.001 | 40.9 | *1.5* | 34.4 | *0.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 9.2 | *1.9* | 6.5 | *1.0* | <0.001 | 6.3 | *1.4* | 12.1 | *1.1* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 83.8 | *1.5* | 100.8 | *5.8* | <0.001 | 85.9 | *1.3* | 92.7 | *1.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 13.2 | *2.7* | 17.9 | *6.3* | <0.001 | 17.6 | *1.8* | 9.7 | *1.6* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 51.6 | *6.0* | 51.0 | *1.9* | 0.156 | 91.2 | *2.8* | 100.4 | *3.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 59.8 | *5.1* | 56.3 | *2.6* | <0.001 | 32.5 | *2.3* | 36.2 | *3.2* | <0.001 | <0.001 | <0.001 |
| **Combined ARI** | 4.3 | *0.7* | 4.6 | *0.9* | 0.310 | 5.4 | *0.7* | 7.0 | *0.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.4 | *0.7* | 2.5 | *0.4* | 0.200 | 2.6 | *0.2* | 1.3 | *0.1* | <0.001 | 0.038 | <0.001 |
| **Heart Rate (bpm)** | 70.8 | *2.6* | 69.2 | *1.3* | <0.001 | 66.9 | *2.4* | 69.2 | *2.7* | 0.001 | <0.001 | 0.116 |
| SD time sample | 5.7 | *1.3* | 6.2 | *1.6* | <0.001 | 5.8 | *2.1* | 11.6 | *3.6* | <0.001 | 0.864 | <0.001 |

**Table 93 Continuous estimates of ARI HUT 2 minute (Mean of right and left MCA)**

| | **No PPH – placebo (n=13)** | | **No PPH – glucose (n=13)** | | **Wilcoxon Signed Ranks Test** (p-values) | **PPH – placebo (n=11)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-values) | **Mann Whitney U Test (p-value)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 36.5 | *2.7* | 40.9 | *1.1* | <0.001 | 36.8 | *2.0* | 31.9 | *1.0* | <0.001 | 0.713 | <0.001 |
| SD time sample | 9.1 | *2.7* | 7.3 | *0.9* | <0.001 | 7.9 | *2.7* | 14.8 | *1.7* | <0.001 | 0.002 | <0.001 |
| **MAP (mmHg)** | 81.1 | *1.8* | 92.9 | *3.9* | <0.001 | 90.6 | *1.2* | 98.6 | *1.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 17.2 | *2.4* | 18.8 | *4.9* | 0.076 | 22.1 | *2.0* | 14.0 | *2.2* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 42.6 | *1.5* | 55.1 | *1.8* | <0.001 | 68.3 | *2.1* | 126.7 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 60.7 | *1.9* | 53.0 | *2.0* | <0.001 | 48.7 | *1.3* | 22.8 | *2.8* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 3.9 | *1.7* | 4.7 | *0.4* | <0.001 | 4.2 | *1.0* | 6.9 | *0.9* | <0.001 | 0.117 | <0.001 |
| SD time sample | 3.1 | *0.5* | 2.3 | *0.2* | <0.001 | 3.6 | *0.2* | 1.4 | *0.6* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 71.8 | *2.0* | 69.9 | *1.3* | <0.001 | 67.1 | *2.5* | 73.6 | *3.8* | <0.001 | <0.001 | <0.001 |
| SD time sample | 7.4 | *1.9* | 8.4 | *1.4* | <0.001 | 5.2 | *3.4* | 18.3 | *5.5* | <0.001 | <0.001 | <0.001 |

**Table 94 Continuous estimates of ARI HUT 2 minute (Right MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 31.4 | *1.4* | 43.0 | *3.4* | <0.001 | 45.0 | *1.9* | 36.7 | *1.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 9.2 | *2.6* | 5.7 | *1.9* | <0.001 | 4.6 | *1.3* | 9.5 | *1.0* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 85.5 | *1.6* | 108.8 | *8.5* | <0.001 | 81.1 | *1.5* | 87.2 | *1.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 16.2 | *1.6* | 17.1 | *8.2* | 0.074 | 13.0 | *1.7* | 4.0 | *2.0* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 48.5 | *1.1* | 46.9 | *2.7* | 0.025 | 114.6 | *2.1* | 72.5 | *1.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 69.7 | *2.2* | 59.5 | *3.7* | <0.001 | 16.0 | *3.1* | 49.5 | *1.5* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 2.4 | *0.6* | 4.4 | *1.9* | <0.001 | 6.7 | *0.8* | 7.1 | *0.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.4 | *0.6* | 2.8 | *0.8* | 0.310 | 1.7 | *0.3* | 1.2 | *0.5* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 74.1 | *0.9* | 68.4 | *1.8* | <0.001 | 66.8 | *3.4* | 65.5 | *3.0* | 0.014 | <0.001 | <0.001 |
| SD time sample | 4.2 | *0.8* | 4.1 | *2.5* | <0.001 | 6.5 | *4.2* | 4.2 | *2.7* | <0.001 | <0.001 | 0.920 |

**Table 95 Continuous estimates of ARI HUT 2 minute (Left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | **Placebo** | **Glucose** |
| **Combined CBFV (cm/s)** | 35.1 | 0.8 | 38.8 | 4.4 | <0.001 | 37.5 | 1.0 | 39.7 | 2.9 | <0.001 | <0.001 | 0.335 |
| SD time sample | 12.6 | 1.0 | 8.4 | 1.3 | <0.001 | 7.5 | 1.3 | 9.0 | 0.9 | <0.001 | <0.001 | 0.030 |
| **MAP (mmHg)** | 89.3 | 1.6 | 94.3 | 2.3 | <0.001 | 99.7 | 5.6 | 95.9 | 4.0 | <0.001 | <0.001 | 0.021 |
| SD time sample | 14.2 | 0.9 | 16.4 | 2.4 | <0.001 | 17.0 | 1.6 | 12.8 | 1.3 | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 127.9 | 1.3 | 115.7 | 1.7 | <0.001 | 119.0 | 3.8 | 102.5 | 4.0 | <0.001 | <0.001 | <0.001 |
| SD time sample | 24.5 | 0.8 | 38.1 | 4.7 | <0.001 | 46.4 | 10.7 | 47.0 | 9.7 | 0.003 | <0.001 | <0.001 |
| **Combined ARI** | 4.4 | 0.4 | 4.9 | 0.3 | <0.001 | 4.8 | 0.5 | 5.0 | 0.5 | 0.001 | <0.001 | 0.073 |
| SD time sample | 2.9 | 0.1 | 3.1 | 0.2 | <0.001 | 2.9 | 0.2 | 3.0 | 0.2 | 0.004 | 0.122 | <0.001 |
| **Heart Rate (bpm)** | 60.0 | 1.1 | 67.8 | 2.8 | <0.001 | 64.8 | 2.0 | 67.5 | 1.8 | <0.001 | <0.001 | 0.681 |
| SD time sample | 21.3 | 0.5 | 7.1 | 0.8 | <0.001 | 14.5 | 3.1 | 10.2 | 1.8 | <0.001 | <0.001 | 0.111 |

**Table 96 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI prior to end of HUT (Mean of right and left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 32.7 | *1.7* | 37.6 | *0.6* | <0.001 | 39.0 | *0.7* | 37.1 | *1.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 15.8 | *1.7* | 7.2 | *0.5* | <0.001 | 6.7 | *0.7* | 8.2 | *1.0* | 0.188 | <0.001 | <0.001 |
| **MAP (mmHg)** | 89.4 | *3.0* | 98.2 | *1.3* | <0.001 | 101.5 | *1.0* | 83.8 | *2.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 14.4 | *1.5* | 11.6 | *1.0* | <0.001 | 18.0 | *1.3* | 16.3 | *2.5* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 122.0 | *2.4* | 93.8 | *1.6* | <0.001 | 114.1 | *1.4* | 118.5 | *3.0* | <0.001 | <0.001 | <0.001 |
| SD time sample | 28.9 | *1.1* | 55.7 | *1.2* | <0.001 | 52.8 | *0.8* | 18.9 | *3.3* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 3.3 | *0.6* | 4.9 | *0.6* | <0.001 | 4.9 | *0.3* | 4.3 | *0.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 3.0 | *0.2* | 2.7 | *0.1* | <0.001 | 3.0 | *0.1* | 3.3 | *0.2* | <0.001 | 0.335 | <0.001 |
| **Heart Rate (bpm)** | 59.9 | *2.1* | 67.5 | *1.6* | <0.001 | 64.7 | *1.6* | 68.1 | *3.8* | <0.001 | <0.001 | 0.931 |
| SD time sample | 19.8 | *1.0* | 11.8 | *2.5* | <0.001 | 11.7 | *1.5* | 9.9 | *2.3* | 0.709 | <0.001 | <0.001 |

**Table 97 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI prior to end of HUT (Right MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 37.8 | *0.6* | 35.3 | *2.0* | <0.001 | 33.7 | *1.1* | 47.7 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 10.1 | *1.0* | 11.2 | *2.4* | <0.001 | 6.2 | *1.0* | 10.7 | *0.4* | <0.001 | <0.001 | 0.272 |
| **MAP (mmHg)** | 88.2 | *1.6* | 84.0 | *1.8* | <0.001 | 108.7 | *1.4* | 101.4 | *2.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 13.9 | *1.1* | 13.9 | *2.6* | 0.591 | 18.6 | *1.9* | 14.2 | *2.0* | <0.001 | <0.001 | 0.400 |
| **$tCO_2$ (mmHg)** | 132.0 | *2.6* | 117.0 | *2.3* | <0.001 | 116.8 | *2.3* | 108.8 | *3.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 19.6 | *1.9* | 15.7 | *3.7* | <0.001 | 61.5 | *0.9* | 54.9 | *1.9* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 4.7 | *0.9* | 4.8 | *0.5* | <0.001 | 5.4 | *0.5* | 5.7 | *0.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.7 | *0.2* | 3.1 | *0.5* | 0.003 | 3.1 | *0.2* | 3.0 | *0.5* | <0.001 | <0.001 | 0.246 |
| **Heart Rate (bpm)** | 60.9 | *1.6* | 69.9 | *4.1* | <0.001 | 68.6 | *1.3* | 66.0 | *2.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 22.9 | *0.6* | 7.0 | *3.2* | <0.001 | 11.4 | *1.0* | 8.8 | *2.4* | <0.001 | <0.001 | 0.001 |

**Table 98 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI prior to end of HUT (Left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | **Placebo** | **Glucose** |
| **Combined CBFV (cm/s)** | 36.6 | 1.5 | 44.6 | 0.9 | <0.001 | 37.7 | 0.6 | 37.8 | 1.6 | 0.525 | <0.001 | <0.001 |
| SD time sample | 12.7 | 1.2 | 10.0 | 0.5 | <0.001 | 6.4 | 0.8 | 8.7 | 1.5 | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 91.7 | 0.8 | 96.1 | 1.0 | <0.001 | 105.0 | 2.1 | 95.6 | 2.4 | <0.001 | <0.001 | <0.001 |
| SD time sample | 16.2 | 0.7 | 12.6 | 0.6 | <0.001 | 17.9 | 1.0 | 11.6 | 1.0 | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 128.2 | 1.2 | 117.4 | 1.1 | <0.001 | 116.6 | 2.2 | 104.8 | 6.1 | <0.001 | <0.001 | <0.001 |
| SD time sample | 24.3 | 1.2 | 34.5 | 1.0 | <0.001 | 55.8 | 4.5 | 41.1 | 9.2 | <0.001 | <0.001 | <0.001 |
| **Combined ARI** | 4.8 | 0.7 | 5.5 | 0.4 | <0.001 | 4.3 | 0.6 | 4.8 | 0.4 | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.6 | 0.4 | 2.9 | 0.5 | <0.001 | 2.9 | 0.2 | 2.5 | 0.2 | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 58.6 | 0.8 | 65.0 | 1.3 | <0.001 | 65.9 | 1.4 | 66.9 | 1.1 | <0.001 | <0.001 | <0.001 |
| SD time sample | 21.1 | 0.4 | 7.1 | 0.8 | <0.001 | 11.5 | 1.4 | 8.5 | 2.2 | <0.001 | <0.001 | <0.001 |

**Table 99 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 1 minute (Mean of right and left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 35.9 | *2.6* | 40.3 | *1.5* | <0.001 | 39.6 | *0.7* | 37.5 | *0.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 14.7 | *2.4* | 9.5 | *0.8* | <0.001 | 6.9 | *0.4* | 7.2 | *0.4* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 93.7 | *0.8* | 88.2 | *0.8* | <0.001 | 102.7 | *0.8* | 99.5 | *1.0* | <0.001 | <0.001 | <0.001 |
| SD time sample | 18.0 | *1.2* | 12.6 | *0.6* | <0.001 | 17.5 | *0.8* | 11.2 | *0.6* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 122.3 | *1.0* | 125.0 | *1.4* | <0.001 | 116.3 | *1.2* | 94.5 | *1.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 27.9 | *1.3* | 12.8 | *1.3* | <0.001 | 53.2 | *0.8* | 56.7 | *0.9* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 3.9 | *0.9* | 5.5 | *0.8* | <0.001 | 4.5 | *0.7* | 5.0 | *0.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 3.0 | *0.4* | 2.6 | *0.4* | <0.001 | 2.8 | *0.3* | 2.4 | *0.1* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 58.8 | *1.1* | 63.1 | *0.9* | <0.001 | 64.4 | *1.3* | 67.4 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 19.4 | *0.4* | 7.3 | *0.8* | <0.001 | 11.2 | *0.9* | 10.8 | *2.4* | 0.307 | <0.001 | <0.001 |

**Table 100 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 1 minute (Right MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 37.4 | *0.9* | 38.0 | *3.3* | 0.396 | 35.6 | *1.0* | 49.0 | *1.3* | <0.001 | <0.001 | <0.001 |
| SD time sample | 10.7 | *0.7* | 11.2 | *2.9* | 0.481 | 5.8 | *1.2* | 10.5 | *0.5* | <0.001 | <0.001 | 0.187 |
| **MAP (mmHg)** | 89.7 | *1.1* | 88.9 | *1.6* | 0.042 | 108.3 | *0.7* | 103.9 | *1.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 14.3 | *0.9* | 12.1 | *2.0* | <0.001 | 18.4 | *1.1* | 12.5 | *1.1* | <0.001 | <0.001 | 0.232 |
| **$tCO_2$ (mmHg)** | 134.1 | *1.7* | 122.0 | *1.6* | <0.001 | 116.0 | *1.0* | 109.7 | *1.4* | <0.001 | <0.001 | <0.001 |
| SD time sample | 20.8 | *1.6* | 14.6 | *2.7* | <0.001 | 60.5 | *0.9* | 56.2 | *1.4* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 5.7 | *0.6* | 4.5 | *0.8* | <0.001 | 4.1 | *0.8* | 5.6 | *0.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.2 | *0.7* | 2.5 | *0.4* | <0.001 | 3.1 | *0.3* | 3.2 | *0.6* | 0.032 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 59.2 | *0.9* | 66.5 | *1.3* | <0.001 | 67.9 | *1.1* | 65.7 | *1.8* | <0.001 | <0.001 | 0.002 |
| SD time sample | 22.9 | *0.7* | 4.7 | *1.5* | <0.001 | 11.2 | *0.7* | 7.0 | *1.4* | <0.001 | <0.001 | <0.001 |

**Table 101 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 1 minute (Left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | ***Mean*** | ***SD*** | ***Mean*** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV (cm/s)** | 37.6 | *0.8* | 43.4 | *2.5* | <0.001 | 37.3 | *0.5* | 38.5 | *3.4* | 0.132 | 0.050 | <0.001 |
| SD time sample | 10.9 | *0.9* | 8.7 | *0.8* | <0.001 | 6.7 | *1.0* | 8.7 | *1.3* | <0.001 | <0.001 | 0.057 |
| **MAP (mmHg)** | 92.4 | *1.1* | 95.9 | *1.5* | <0.001 | 103.8 | *2.4* | 95.4 | *3.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 16.9 | *1.1* | 13.9 | *1.5* | <0.001 | 17.6 | *2.5* | 11.8 | *1.5* | <0.001 | 0.002 | <0.001 |
| **$tCO_2$ (mmHg)** | 128.3 | *1.5* | 117.6 | *1.3* | <0.001 | 113.3 | *3.7* | 107.7 | *5.2* | <0.001 | <0.001 | <0.001 |
| SD time sample | 24.3 | *1.4* | 35.9 | *1.0* | <0.001 | 53.4 | *4.8* | 39.7 | *9.6* | <0.001 | <0.001 | <0.001 |
| **ARI** | 5.4 | *0.5* | 5.3 | *0.6* | 0.006 | 4.6 | *0.3* | 5.0 | *0.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.7 | *0.2* | 2.5 | *0.3* | <0.001 | 3.0 | *0.2* | 2.7 | *0.4* | <0.001 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 58.3 | *1.0* | 64.8 | *1.2* | <0.001 | 66.1 | *1.3* | 66.5 | *1.3* | 0.069 | <0.001 | <0.001 |
| SD time sample | 21.0 | *0.8* | 7.7 | *1.2* | <0.001 | 11.7 | *1.7* | 8.6 | *1.7* | <0.001 | <0.001 | <0.001 |

**Table 102 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 2 minute (Mean of right and left MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Right (cm/s)** | 38.1 | *1.3* | 41.3 | *0.9* | <0.001 | 38.6 | *0.8* | 37.3 | *0.6* | <0.001 | 0.014 | <0.001 |
| SD time sample | 11.3 | *1.5* | 8.2 | *1.3* | <0.001 | 7.6 | *1.1* | 7.5 | *0.5* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 94.7 | *0.9* | 89.5 | *1.3* | <0.001 | 101.9 | *1.3* | 98.2 | *1.1* | <0.001 | <0.001 | <0.001 |
| SD time sample | 19.3 | *0.6* | 13.7 | *0.8* | <0.001 | 16.7 | *1.1* | 11.2 | *1.1* | <0.001 | <0.001 | <0.001 |
| **$tCO_2$ (mmHg)** | 122.3 | *1.2* | 126.6 | *1.8* | <0.001 | 113.6 | *2.4* | 93.2 | *0.9* | <0.001 | <0.001 | <0.001 |
| SD time sample | 27.2 | *1.3* | 16.4 | *2.3* | <0.001 | 51.3 | *1.3* | 55.7 | *0.7* | <0.001 | <0.001 | <0.001 |
| **ARI Right** | 5.6 | *0.6* | 4.6 | *0.8* | <0.001 | 4.6 | *0.4* | 5.8 | *0.3* | 0.543 | <0.001 | <0.001 |
| SD time sample | 2.8 | *0.5* | 2.8 | *0.2* | 0.264 | 3.0 | *0.2* | 2.4 | *0.3* | <0.001 | 0.122 | <0.001 |
| **Heart Rate (bpm)** | 58.0 | *1.3* | 63.8 | *1.2* | <0.001 | 64.6 | *1.1* | 67.2 | *1.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 19.1 | *0.5* | 7.7 | *0.9* | <0.001 | 11.2 | *1.0* | 11.4 | *2.2* | 0.613 | <0.001 | <0.001 |

**Table 103 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 2 minute (Right MCA)**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **CBFV Left (cm/s)** | 37.0 | *0.6* | 36.7 | *3.0* | 0.389 | 36.1 | *0.7* | 48.5 | *1.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 10.6 | *0.6* | 9.5 | *1.9* | <0.001 | 5.6 | *0.8* | 10.1 | *0.9* | <0.001 | <0.001 | <0.001 |
| **MAP (mmHg)** | 90.3 | *1.8* | 90.1 | *1.5* | 0.953 | 106.4 | *3.4* | 101.1 | *1.7* | <0.001 | <0.001 | <0.001 |
| SD time sample | 14.5 | *2.1* | 11.8 | *1.5* | <0.001 | 18.6 | *4.5* | 12.7 | *1.9* | <0.001 | <0.001 | 0.001 |
| **$tCO_2$ (mmHg)** | 134.3 | *2.3* | 123.0 | *2.5* | <0.001 | 111.7 | *4.5* | 107.3 | *1.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 21.4 | *2.6* | 17.0 | *2.6* | <0.001 | 57.5 | *4.1* | 54.7 | *1.3* | <0.001 | <0.001 | <0.001 |
| **ARI Left** | 5.3 | *0.6* | 3.5 | *0.8* | <0.001 | 4.2 | *0.7* | 6.9 | *0.5* | <0.001 | <0.001 | <0.001 |
| SD time sample | 2.7 | *0.4* | 3.2 | *0.3* | <0.001 | 3.0 | *0.4* | 2.1 | *0.3* | 0.844 | <0.001 | <0.001 |
| **Heart Rate (bpm)** | 58.7 | *1.4* | 66.1 | *1.8* | <0.001 | 67.9 | *1.5* | 65.3 | *1.6* | <0.001 | <0.001 | <0.001 |
| SD time sample | 22.8 | *1.4* | 6.5 | *2.0* | <0.001 | 11.5 | *1.3* | 6.5 | *1.4* | <0.001 | <0.001 | 0.572 |

**Table 104 Continuous estimates of CBFV, MAP, $TCO_2$, HR and ARI post-HUT 2 minute (Left MCA)**

| | **No PPH – placebo (n=13)** | | **No PPH – glucose (n=13)** | | **Wilcoxon Signed Ranks Test** (p-values) | **PPH – placebo (n=11)** | | **PPH – glucose (n=12)** | | **Wilcoxon Signed Ranks Test** (p-values) | **Mann Whitney U Test (p-value)** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change in CBFV (cm/s)** | 2.2 | *3.2* | -2.4 | *1.9* | <0.001 | 2.2 | *3.2* | -29.6 | *1.6* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 2.9 | *2.8* | -1.9 | *1.6* | <0.001 | -2.5 | *2.6* | 27.2 | *2.9* | <0.001 | 0.279 | <0.001 |
| **Change in MAP (mmHg)** | -1.2 | *3.8* | 1.4 | *4.9* | <0.001 | 5.6 | *3.0* | -0.1 | *4.0* | <0.001 | <0.001 | 0.443 |
| Change in SD time sample | -2.6 | *3.5* | 2.0 | *4.6* | <0.001 | -1.4 | *2.4* | -3.0 | *2.5* | 0.622 | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 6.9 | *11.7* | -1.3 | *2.5* | <0.001 | 2.1 | *10.0* | 20.4 | *15.1* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -4.4 | *6.3* | -1.3 | *3.7* | <0.001 | 3.6 | *6.5* | -12.4 | *6.9* | <0.001 | <0.001 | <0.001 |
| **Change in ARI** | 0.5 | *2.6* | -0.9 | *2.6* | <0.001 | 0.0 | *2.1* | 1.2 | *0.5* | 0.658 | 0.098 | 0.001 |
| Change in SD time sample | -0.8 | *0.5* | -0.3 | *0.4* | <0.001 | -0.4 | *0.8* | -0.8 | *0.6* | 0.363 | 0.352 | <0.001 |
| **Change in Heart Rate (bpm)** | -2.9 | *3.7* | 2.3 | *2.0* | <0.001 | 0.5 | *2.8* | 3.7 | *4.1* | 0.010 | <0.001 | 0.001 |
| Change in SD time sample | 0.9 | *2.8* | -7.9 | *1.5* | <0.001 | -0.1 | *3.2* | 4.0 | *6.3* | 0.006 | <0.001 | <0.001 |

**Table 105 Changes in time varying estimates at 1 minute of HUT**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change in CBFV (cm/s)** | 2.4 | *2.6* | -1.2 | *2.4* | <0.001 | 4.9 | *3.6* | -4.9 | *1.1* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 1.4 | *3.2* | -1.2 | *1.4* | <0.001 | -2.9 | *2.3* | 0.7 | *1.6* | <0.001 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -4.3 | *3.7* | 5.4 | *6.2* | <0.001 | 1.9 | *3.9* | 3.1 | *3.7* | 0.238 | <0.001 | 0.028 |
| Change in SD time sample | -0.6 | *3.2* | 1.1 | *5.8* | <0.001 | -0.5 | *2.0* | -6.4 | *2.5* | <0.001 | 0.723 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -1.2 | *12.5* | -0.1 | *3.1* | <0.001 | -9.6 | *8.8* | -8.0 | *5.9* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -1.9 | *8.4* | -0.8 | *4.0* | <0.001 | -1.3 | *7.4* | -0.3 | *4.2* | 0.001 | 0.988 | 0.497 |
| **Change in ARI** | -0.6 | *2.0* | -0.3 | *1.7* | 0.167 | 0.7 | *1.5* | 2.9 | *0.5* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -0.4 | *0.8* | 0.1 | *0.4* | <0.001 | 0.0 | *0.5* | -1.5 | *0.1* | <0.001 | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | -1.1 | *3.4* | 2.8 | *2.4* | <0.001 | -0.5 | *3.4* | 5.9 | *2.9* | <0.001 | 0.178 | <0.001 |
| Change in SD time sample | -0.1 | *1.9* | -7.5 | *2.3* | <0.001 | -0.7 | *4.0* | 5.9 | *4.1* | <0.001 | 0.125 | <0.001 |

**Table 106 Changes in time varying estimates at 2 minutes of HUT**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Mean** | ***SD*** | **Mean** | ***SD*** | | **Placebo** | **Glucose** |
| **Change in combined CBFV (cm/s)** | 1.9 | *1.7* | -4.4 | *5.5* | <0.001 | 1.5 | *2.7* | 0.6 | *3.5* | 0.081 | 0.034 | 0.167 |
| Change in SD time sample | 6.1 | *2.3* | 0.7 | *1.4* | <0.001 | -1.6 | *3.1* | -1.9 | *1.2* | 0.485 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | 1.2 | *4.5* | -1.2 | *2.5* | 0.001 | 15.8 | *4.2* | 9.7 | *7.9* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -0.9 | *3.5* | -0.5 | *3.3* | 0.009 | 1.1 | *2.4* | -1.4 | *4.1* | 0.534 | 0.192 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 80.7 | *4.5* | 64.8 | *2.9* | <0.001 | 37.4 | *8.1* | 12.6 | *4.2* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -40.0 | *7.1* | -17.3 | *5.5* | <0.001 | 12.6 | *9.6* | 13.8 | *13.0* | 0.137 | <0.001 | <0.001 |
| **Change in combined ARI** | -1.8 | *0.6* | 0.0 | *1.4* | <0.001 | 0.1 | *1.2* | 0.3 | *0.7* | 0.080 | <0.001 | 0.001 |
| Change in SD time sample | 0.3 | *0.2* | 0.7 | *0.4* | <0.001 | 0.3 | *0.5* | 0.5 | *0.6* | <0.001 | 0.758 | 0.027 |
| **Change in Heart Rate (bpm)** | -11.3 | *1.6* | 1.5 | *4.4* | <0.001 | -2.6 | *2.3* | 4.0 | *2.6* | <0.001 | <0.001 | 0.732 |
| Change in SD time sample | 16.2 | *1.4* | -6.6 | *1.2* | <0.001 | 8.0 | *4.3* | 4.5 | *2.9* | <0.001 | <0.001 | <0.001 |

**Table 107 Changes in time varying estimates at end of HUT**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % of Mean | SD | % of Mean | SD | | % of Mean | SD | % of Mean | SD | | Placebo | Glucose |
| **Change in combined CBFV (cm/s)** | -7.4 | 5.9 | -5.5 | 4.3 | <0.001 | 6.8 | 10.4 | -74.8 | 4.2 | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -26.5 | 24.7 | -23.5 | 19.2 | 0.199 | -22.9 | 21.6 | 242.9 | 45.5 | <0.001 | 0.424 | <0.001 |
| **Change in MAP (mmHg)** | 1.6 | 5.6 | 1.5 | 5.1 | 0.121 | 6.7 | 3.8 | 0.4 | 4.4 | <0.001 | <0.001 | 0.495 |
| Change in SD time sample | 17.7 | 35.0 | 13.6 | 28.2 | 0.001 | -7.2 | 13.9 | -16.8 | 13 | 0.065 | <0.001 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | -2.4 | 5.2 | -2.4 | 4.8 | 0.039 | 2.4 | 12.5 | 25 | 15.5 | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -2.3 | 6.3 | -2 | 6.5 | 0.050 | 12.7 | 24.3 | -37.6 | 18.3 | <0.001 | <0.001 | <0.001 |
| **Change in combined ARI** | -1.4 | 61.3 | 1.6 | 65.2 | 0.100 | 9.2 | 39.2 | 28.4 | 10.6 | 0.854 | 0.046 | 0.001 |
| Change in SD time sample | -9.9 | 15.0 | -10.6 | 16.6 | 0.089 | -10.5 | 30 | -29.6 | 20.8 | 0.831 | 0.397 | <0.001 |
| **Change in Heart Rate (bpm)** | 3.3 | 2.8 | 3.6 | 3.1 | <0.001 | 0.8 | 4.1 | 6.5 | 6.5 | 0.003 | <0.001 | <0.001 |
| Change in SD time sample | -146.4 | 43.2 | -57.7 | 9.5 | <0.001 | 9.9 | 51.2 | 110.9 | 143 | 0.002 | <0.001 | <0.001 |

**Table 108 Percentage change from pre-HUT at 1 minute of HUT *(-% = negative percentage change from pre-HUT)***

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % of Mean | SD | % of Mean | SD | | % of Mean | SD | % of Mean | SD | | Placebo | Glucose |
| **Change in combined CBFV (cm/s)** | 7.7 | *8.1* | -2.6 | *5.6* | <0.001 | 14.6 | *12.1* | -12.4 | *2.6* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | 29.6 | *53.5* | -13.7 | *16.8* | <0.001 | -28.5 | *19.6* | 7.5 | *15.0* | <0.001 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | -4.8 | *4.1* | 5.7 | *6.5* | <0.001 | 2.5 | *4.7* | 3.6 | *4.3* | 0.140 | <0.001 | 0.075 |
| Change in SD time sample | -0.9 | *22.3* | 7.0 | *32.1* | 0.036 | -1.7 | *11.9* | -38.8 | *12.0* | <0.001 | 0.777 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 6.0 | *20.1* | 0.5 | *6.1* | 0.022 | 13.2 | *13.7* | 8.9 | *6.9* | 0.001 | 0.024 | <0.001 |
| Change in SD time sample | -1.6 | *14.6* | 1.8 | *7.5* | <0.001 | 0.2 | *18.4* | -0.2 | *11.4* | <0.001 | 0.146 | 0.719 |
| **Change in combined ARI** | 2.3 | *50.2* | 6.4 | *43.5* | 0.088 | 23.4 | *37.2* | 69.2 | *15.5* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -12.5 | *28.8* | 6.1 | *16.8* | <0.001 | 5.5 | *23.1* | -52.3 | *3.9* | <0.001 | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | -1.5 | *4.8* | 4.4 | *3.7* | <0.001 | -0.6 | *5.0* | 9.3 | *4.7* | <0.001 | 0.208 | <0.001 |
| Change in SD time sample | 3.2 | *31.7* | -53.8 | *13.4* | <0.001 | 4.3 | *67.8* | 124.5 | *100.6* | <0.001 | 0.069 | <0.001 |

**Table 109 Percentage change from pre-HUT at 2 minute of HUT**

| | No PPH – placebo (n=13) | | No PPH – glucose (n=13) | | Wilcoxon Signed Ranks Test (p-values) | PPH – placebo (n=11) | | PPH – glucose (n=12) | | Wilcoxon Signed Ranks Test (p-values) | Mann Whitney U Test (p-value) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **% of Mean** | **SD** | **% of Mean** | **SD** | | **% of Mean** | **SD** | **% of Mean** | **SD** | | **Placebo** | **Glucose** |
| **Change in combined CBFV (cm/s)** | 6.0 | *5.5* | -13.8 | *16.5* | <0.001 | 4.0 | *7.2* | -4.3 | *3.9* | <0.001 | 0.001 | <0.001 |
| Change in SD time sample | 110.6 | *61.6* | 9.9 | *16.8* | <0.001 | -21.2 | *42.2* | -31.6 | *14.9* | 0.012 | <0.001 | <0.001 |
| **Change in MAP (mmHg)** | 1.5 | *5.3* | -1.3 | *2.7* | 0.001 | 18 | *5.7* | 15.2 | *10.8* | 0.006 | <0.001 | <0.001 |
| Change in SD time sample | -2.4 | *20.7* | -1.6 | *25.4* | 0.120 | -6.1 | *14.4* | 18.3 | *29.7* | <0.001 | 0.068 | <0.001 |
| **Change in $tCO_2$ (mmHg)** | 171.9 | *22.7* | 129.1 | *21.9* | <0.001 | 58.9 | *15.6* | 15.4 | *6.0* | <0.001 | <0.001 | <0.001 |
| Change in SD time sample | -61.7 | *3.9* | -31.3 | *12.2* | <0.001 | 35.4 | *34.1* | 35.7 | *35.9* | 0.956 | <0.001 | <0.001 |
| **Change in combined ARI** | -29.0 | *9.2* | -8.2 | *32.2* | 0.254 | 6.6 | *31.5* | 8.4 | *18.2* | 0.271 | <0.001 | <0.001 |
| Change in SD time sample | 12.8 | *7.3* | 25 | *14.2* | <0.001 | 9.7 | *18.8* | 19.5 | *22.2* | <0.001 | <0.001 | <0.001 |
| **Change in Heart Rate (bpm)** | -15.8 | *2.1* | 1.9 | *6.2* | <0.001 | -3.8 | *3.4* | 2.1 | *4.0* | <0.001 | 0.067 | <0.001 |
| Change in SD time sample | 332.0 | *78.7* | -82.1 | *33.8* | <0.001 | 79.6 | *43.0* | 145.3 | *77.7* | <0.001 | 0.158 | <0.001 |

**Table 110 Percentage change from pre-HUT at end of HUT**

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