Orthostatic blood pressure and its relation to cerebral autoregulation and resilience

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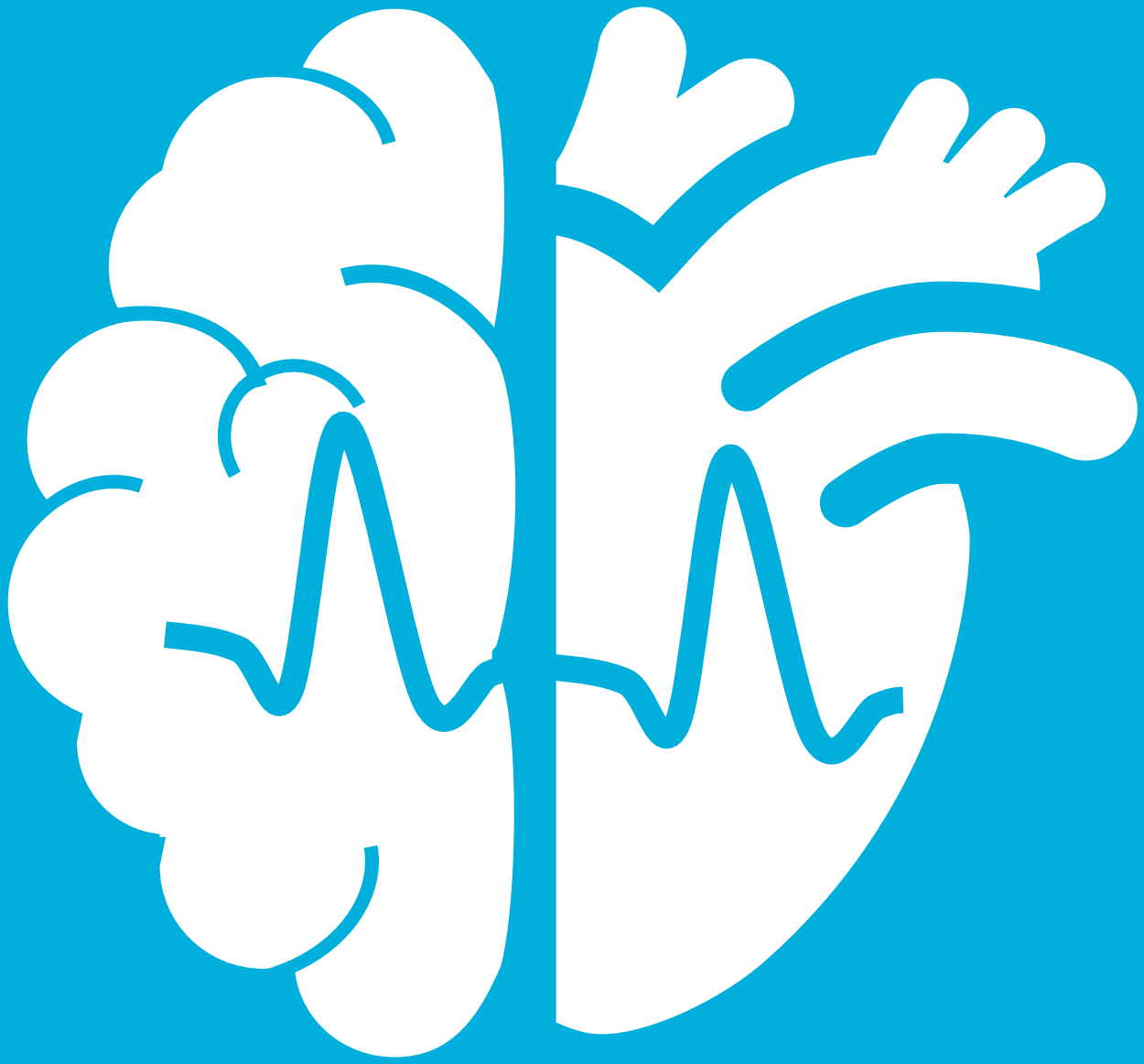
Master's thesis technical medicine



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Contents

Introduction

Blood pressure is the driving force for a sufficient supply of blood, which contains nutrients and oxygen to all organs and tissues. Mean arterial blood pressure is a regulated variable that is affected by cardiac output and total peripheral resistance [1, 2]. Cardiac output is on its turn dependent on the stroke volume and heart rate. Below, the various mechanisms and factors involved in the control of blood pressure are discussed.

Blood pressure regulation

The first mechanism that regulates blood pressure is the baroreflex. In the baroreflex, the blood pressure is sensed by mechanical stretch receptors (baroreceptors) in the aortic arch and carotid sinus [1]. If blood pressure is low the baroreflex increases the heart rate and stimulates vasoconstriction. The second mechanism is the renin-angiotensin-aldosterone system (RAAS) [3]. This mechanism acts slower and more long-term than the baroreflex. By reacting to reduced renal blood pressure, RAAS eventually leads to an increase in the extracellular fluid which increases the blood pressure [3]. The third regulatory mechanism is pressure natriuresis [2]. Here the kidneys react to a fall in the extracellular fluid by decreasing excretion of renal sodium to keep the blood pressure steady [2].

Besides these regulatory mechanisms, other factors can affect a person's blood pressure. Stress and exercise affect blood pressure, due to the changing demands of oxygen and blood in tissues and an increase in heart rate [4]. Gravitational force also affects blood pressure, by redistributing the blood if a person changes position [5]. For example, if a body changes its posture from supine to standing blood is pulled to the lower limbs. In that case, systems like the baroreflex should restabilize blood pressure [5]. If this does not happen someone has an impaired or inadequate blood pressure regulation.

Inadequate blood pressure regulation

A normal blood pressure response in older adults after standing up is a rising mean arterial pressure in the first 6 seconds [5]. This rise is due to the rise in peripheral resistance after standing up. The increase is followed by a transient dip from baseline and recovery within around 20 seconds[5]. If blood pressure does not recover back to baseline, orthostatic hypotension (OH) could be present. The definition of classical OH is a sustained systolic blood pressure (SBP) drop of 20 mmHg and/or a diastolic blood pressure (DBP) drop of 10 mmHg within three minutes after standing[6]. This blood pressure drop can cause symptoms like dizziness and instability and can lead to falling. As people age, OH gets more common with a prevalence of almost 20% in people older than 80 years[7].

Another impaired response to standing up is, an initial drop larger than 40mmHg [5, 8]. This response is called initial OH. Furthermore, there are patients with delayed blood pressure recovery. These patients have a drop in SBP larger than 20mmHg around 30 seconds after standing but this drop is not sustained, recovery happens within a minute [5, 8].

Previous studies found an association between delayed blood pressure recovery after standing and mortality[9] and Alzheimer's disease progression [10]. Also, the presence of OH increases the cardiac event risk [11]. Together this suggests that a blood pressure response after standing up contains more information about a person's overall health.

Measurements of blood pressure regulation

To use blood pressure recovery after standing up as a diagnostic tool it is important that there is consensus on how to best measure blood pressure. There are multiple ways to measure blood pressure. In a clinical setting, blood pressure is often measured with an oscillometric measurement at the brachial artery [12]. Because this method uses an inflatable cuff around the brachial artery it can only measure blood pressure intermittently. To measure a complete blood pressure response, a continuous measurement method is used.

Continuous blood pressure measurements can be done noninvasively with a finger cuff using volume- clamp photoplethysmography (PPG), like the Finapres system [8, 13]. The inflatable cuff around the finger measures the arterial pressure. By sending infrared light in the cuff, PPG can measure the blood volume in the finger artery. The cuff is used to apply varying counter pressures equal to the arterial pressure to keep blood volume constant [8, 14]. With this technique, continuous blood pressure can be measured during standing up.

Insufficient blood pressure can lead to insufficient blood flow to the brain, which can lead to symptoms like dizziness and feeling light-headed[15]. Therefore, it is also relevant to be able to measure the blood flow in the brain when exploring blood pressure regulation. One way to indirectly measure blood flow in the brain is near-infrared spectroscopy (NIRS) [16, 17]. NIRS sends near-infrared light into the cerebral tissue and measures the absorbance of this light. With this method, relative oxygenated hemoglobin (oxyHb) and deoxygenated hemoglobin (deoxyHb) concentrations can be measured. [16]

Research aim

This research focused on two different aspects of blood pressure regulation. The first part focuses on blood pressure dysregulation and blood flow to the brain in patients with OH. We examined what may be causing symptoms in some patients, while others do not experience symptoms. This was done by using simultaneously measured blood pressure and NIRS data. This part gives more insight into the physiological underlying mechanisms of blood pressure dysregulation while standing up.

The second part focuses on blood pressure recovery after standing up in relation to a patient's overall health and long-term outcomes. It was investigated whether a delayed blood pressure recovery after standing up can be a predictive factor for surgery outcomes. This study gives more insight into how a dysfunctional blood pressure regulation is related to (longer-term) outcomes.

1 | The relation of cerebral autoregulation with symptomatic and asymptomatic orthostatic hypotension

Introduction: Patients with orthostatic hypotension (OH) have a sustained blood pressure drop after standing, which can cause symptoms of dizziness. Cerebral autoregulation must ensure a sufficient blood flow to the brain, with changing blood pressures. Therefore, symptoms were hypothesized to be influenced by (inadequate) cerebral autoregulation.
Method: To examine the difference between OH and non-OH patients with and without symptoms, near-infrared spectroscopy (NIRS) and blood pressure signals were explored in time and frequency domain. Patients performed three supine stand tests and a repeated sit stand test. In time domain, initial drops and recovery values were computed based on the supine stand test data. In frequency domain transfer function analyses (TFA) with oxyHb and deoxyHb was used to quantify cerebral autoregulation. For TFA, data from supine rest and the repeated sit stand exercise was were used.
Results: 37 patients were included, in our analysis. Patients with symptoms and OH seemed to have a lower drop in oxyHb compared to the other groups (p=0.583). Furthermore, no differences were found between the groups in the TFA results.
Conclusion: OxyHb contains some information about symptoms after standing up. No differences in cerebral autoregulation were found between patients with and without symptoms.

Introduction

Orthostatic hypotension (OH) is defined as a sustained blood pressure drop of 20mmHg systolic or 10mmHg diastolic after standing up [6]. Symptoms of OH are dizziness and light-headedness. However, the majority of OH patients experiences no symptoms [18]. Symptoms are likely caused by insufficient blood flow to the brain, which should be maintained by cerebral autoregulation [15].

A constant cerebral blood flow (CBF) is needed to supply a constant level of oxygen to the brain, to prevent ischemic brain damage [19]. The mechanism that regulates CBF is cerebral autoregulation [19, 20]. Cerebral autoregulation changes the diameter of the cerebral arteries to compensate for a change in blood pressure. This principle can be explained by the Hagen-Poiseuille law which is given in equation 1.1 [19, 21].

$$Q = \frac{\pi P r^4}{8\eta l} \tag{1.1}$$

In equation 1.1, Q is the blood flow in a vessel, P is the pressure difference, r is the radius of the vessel, l is the length of the vessel and η is the viscosity of the fluid. If the pressure becomes greater the radius must

become smaller to keep the blood flow steady and vice versa.

This concept of autoregulation was first described by Lassen et al. [22]. He described CBF to be constant between certain levels of mean arterial pressure (MAP). This principle works until maximal vasoconstriction or vasodilatation is reached. If the blood pressure decreases further while there is no more dilatation possible the pressure can drop, and the vessel can collapse. If the blood pressure increases while maximal constriction is already achieved, the pressure can stretch and passively dilate the vessel which leads to an increased flow (see Figure 1.1). The fact that CBF appears constant within a range of maps is correct when looking at longer periods of time (10 minutes or more). Therefore this is referred to as static autoregulation [20].

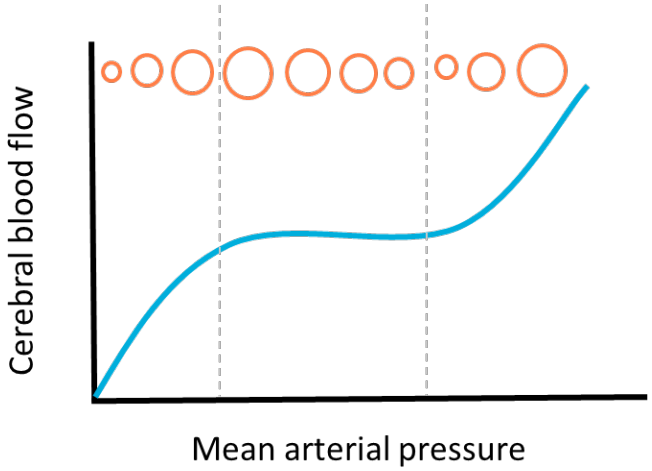


Figure 1.1: Lassen's autoregulation cure. The CBF stays constant between certain levels of blood pressure, because the cerebral arteries (the orange circles) adapt there radius.

For fast changes (seconds) in blood pressure, cerebral autoregulation appears to be working like a high pass filter [23]. This is called dynamic autoregulation. In the high frequency (HF) range (0.2-0.5Hz) CBF should follow blood pressure. While, in the low frequency (LF: 0.07 -0.2Hz) and in the very low frequency (VLF: 0.02-0.07Hz) ranges CBF should be dampened and have a phase difference compared to blood pressure [20]. Therefore, when CBF follows blood pressure changes passively in the LF and VLF ranges, this indicates poor autoregulation. However, when CBF waves are damped and have a phase difference in the lower frequencies compared to the blood pressure waves autoregulation is most likely present [20].

Transfer function analysis (TFA) can be used to asses dynamic autoregulation [24, 25]. TFA is a technique used in engineering to assess the frequency response of a system. This studies how the signal's phase and gain change from input to output in a system. Also, the coherence between the input and output signals is computed, which describes the correlation between the in- and output. If the coherence is below the significance level, the results of TFA are less reliable [25].

Ideally, to compute measures for cerebral autoregulation the CBF should be known. However, CBF cannot be measured directly. Therefore, indirect measures for CBF are often used. The cerebral blood velocity (CBV) measured with transcranial doppler is one of these [26]. Another method to estimate CBF is near-infrared spectroscopy (NIRS) [17, 27]. NIRS sends near-infrared light into the cerebral tissue and measures the absorbance of this light. Body tissues all reflect and absorb light, but each tissue has a different absorption spectrum. Above 1300 nm, water absorbs almost all light [28]. Also, light with a wavelength below 700 nm is absorbed by hemoglobin and is increasingly scattered [28]. With wavelengths between 700 nm and 1300

nm light travels through body tissue. Because the absorption spectra of oxygenated hemoglobin (oxyHb) and deoxgenated hemoglobin (deoxyHb) differ in this region, and are the main cause of light absorption, NIRS can be used to determine the relative concentration of these two [29].

Elting et al. designed a model to compute dynamic cerebral autoregulation based on TFA with oxyHb and deoxyHb [30]. OxyHb and deoxyHb can be seen as a serial system because oscillations in deoxyHb are delayed compared to oxyHb as a result of passage through the capillary system [30]. This transit time causes a linear phase difference trend in the frequency domain. Furthermore, blood flow and blood volume oscillations can create a constant phase shift. A correction for these effects needs to take place to be able to see what phase difference is caused by autoregulation alone. The dynamic cerebral autoregulation method of Elting et al. corrects for these effects by subtracting the linear phase trend in the HF range from the phase shift [30].

With the method developed by Elting et al. it should be possible to assess cerebral autoregulation with NIRS only in patients with OH. Specifically, the relation between the presence of orthostatic intolerance symptoms and cerebral autoregulation can be easily studied. It was hypothesized that cerebral autoregulation would function less in symptomatic OH patients compared to asymptomatic OH patients, resulting in a higher phase shift and lower gain in asymptomatic patients compared to symptomatic patients. This led to the following research question: *What is the relation between cerebral autoregulation measured with NIRS and symptoms in older patients with orthostatic hypotension?*

Method

In and Exclusion criteria

Geriatric outpatients of the Radboud University Medical Center were included. The following inclusion criteria were used:

- Age: above 70 years
- The patient should be instructible as assessed by the treating geriatrician
- Capable of standing up from a supine position

Patients with the following conditions were excluded:

- Neurological diseases causing an inability to walk unassisted
- Immobilization for 1 week during the last 3 months
- Orthopedic surgery during the last 6 months that results in limited mobility
- Muscle disorders causing leg muscle weakness
- Any disorder causing chronic pain or pain during walking with a pain score > 6 on a scale from 1 to 10
- Severe vision problems, causing an inability to walk unassisted
- Acute infections affecting the general condition

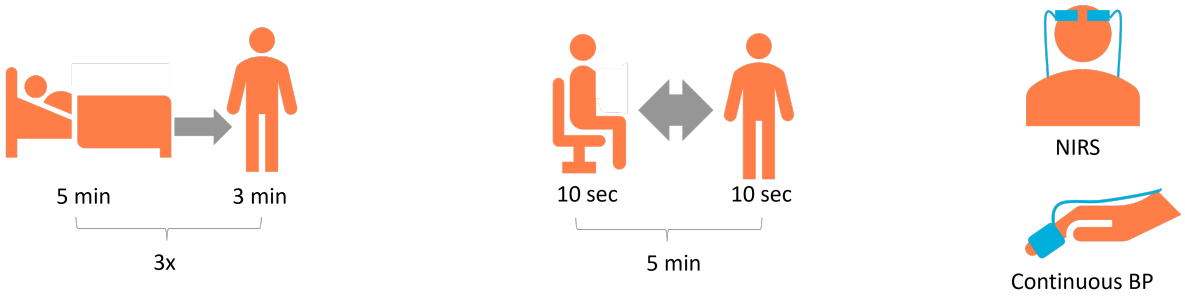
Measurement protocol

During a study visit, several assessments were done to review the overall functioning of the patient, which include the orthostatic hypotension questionnaire (OHQ) and the Short Physical Performance Battery (SPPB) [31, 32]. The OHQ consists of a six-item symptoms assessment scale and a four-item daily activity scale to assess the burden of symptoms[32]. Other baseline parameters were retrieved from the comprehensive geriatric assessment at the outpatient clinic. Based on this data the Charlson comorbidity index (CCI) and

the vascular comorbidity index (VCS) were computed [33, 34]. The CCI is a weighted index to predict the risk of death within 1 year based on specific comorbidities [35]. The VCS summarizes vascular comorbidities such as: hypertension, chronic heart failure, coronary heart disease, arrhythmia's, cerebrovascular disease, peripheral artery disease and chronic kidney disease [33, 34].

Patients were equipped with a 3-lead ECG, NIRS PortaLites (Artinis Medical Systems, Elst, The Netherlands), a continuous blood pressure device (Finapres Nova; Finapres Medical Systems, Enschede, The Netherlands) and a gyroscope. The PortaLites had a sampling frequency of 10 Hz while the blood pressure and ECG data were measured with a sampling frequency of 200Hz. The Gyroscope had a sampling frequency of 208Hz.

The patients performed a rapid supine-to-stand test three times. The patients lay down for five minutes, after which the patients were asked to stand up as fast as possible and remain standing for three minutes. Furthermore, the patient was asked to perform a repetitive sit-to-stand test. The patient switched every ten seconds from sitting to standing or vice versa for a total of five minutes. During both tests, patients were asked whether they experienced symptoms of dizziness, blurred vision, or had balance problems. Patients were classified as having symptoms when they indicated having symptoms at least once during our measurement protocol. Figure 1.2 shows a schematic overview of the measurement protocol.



(a) (b) (c)

Figure 1.2: schematic overview of measurement protocol: a) the supine to stand protocol b) shows the repeated sit stand exercise c) the measurement devices.

Data analysis

For this study the measured blood pressure, oxyHb and deoxyHb data were used. Signal preprocessing was done in MATLAB 2022a. Data were analyzed in time and frequency domain.

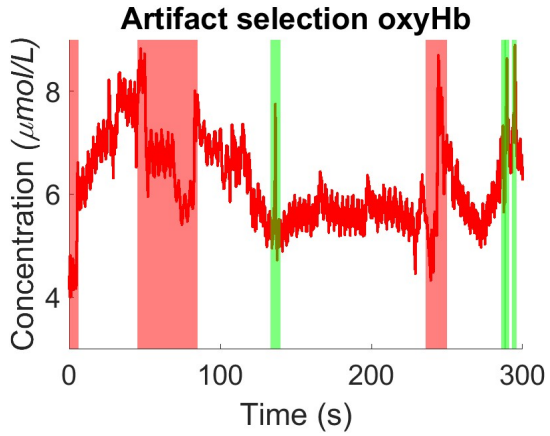
Prepossessing

The continuous blood pressure data were processed by detecting the systolic and diastolic peaks automatically [33]. The peaks were manually checked and corrected if needed, to remove noise from the data. Systolic and diastolic blood pressure data were resampled at 10Hz and filtered with a 5 second moving average filter. The blood pressure data were averaged over the three measurements.

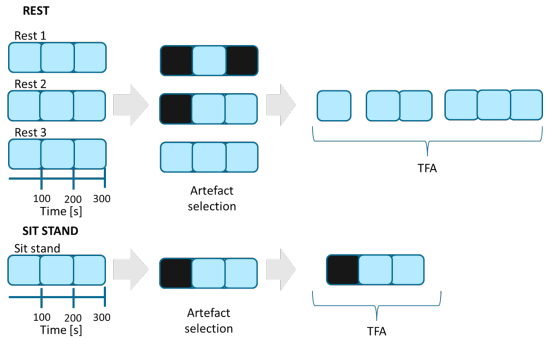
For analysis in the time domain the oxyHB and deoxyHb data quality from the supine to stand exercise was visually checked. Signals with large overshoots at the moment of standing because of movement artefacts

were excluded from further analysis. Also, signals without a visual heart beat were excluded. Artefact-free data were averaged first between left and right (if both available) and over the available measurements.

For TFA, oxyHB and deoxyHb data from the supine rest and sit stand exercise were preprocessed by selecting which parts of the data contained artefacts. An artefact smaller than 3 seconds was linearly interpolated. An artefact longer than 3 seconds was removed from the data. Removing artefacts was done by removing the complete 100 second window in the supine rest data. Large artefacts were not removed from the repeated sit-to-stand data because a minimum length of 5 minutes was needed for the computation . A schematic overview of this artefact selection can be found in Figure 1.3.



(a) Example of artefact selection.



(b) Schematic overview of difference in artefact selection between the rest data and the repeated sit-stand data.

Figure 1.3: Artefact selection overview. a) The green areas show artefacts that could be linearly interpolated. The red areas show large artefacts, around which a 100-second window was deleted. In this example, only the window between 100 and 200 seconds is without large artefacts and can thus be used. b) The black segments visualize data parts with artefacts. In rest only 100 second windows without large artefacts were used. All data segments from the repeated sit-stand were used.

Time domain analysis

For time domain analysis, different characteristics were computed for both blood pressure and oxyHb and deoxyHb: Baseline, initial drop after standing, and early and late recovery values. Baseline was taken as the average between 40 and 10 seconds before standing. Baseline was subtracted from the entire measurement before computation of the other variables. The initial drop was computed as the minimal value within 40 seconds after standing [10]. Early recovery was defined as the mean value between 55 and 60 seconds after standing. Additionally, late recovery was computed as the mean value between 80 and 180 seconds after standing [36].

Based on the blood pressure data patients were classified as having or not having OH. OH was assumed to be present if one value of the 5 second moving average SBP was 20mmHg below baseline and/or one value of the averaged DBP was 10mmHg below baseline between 60 and 175 seconds of standing.

Transfer function analysis

TFA computation was done in the DCA software based on the method of Elting et al. with oxyHb as input and deoxy Hb as output [30]. Per patient, the coherence, phase and gain plots were retrieved. The phase

and gain were only used from frequency bins that were above the coherence threshold an example can be seen in Figure 1.4.

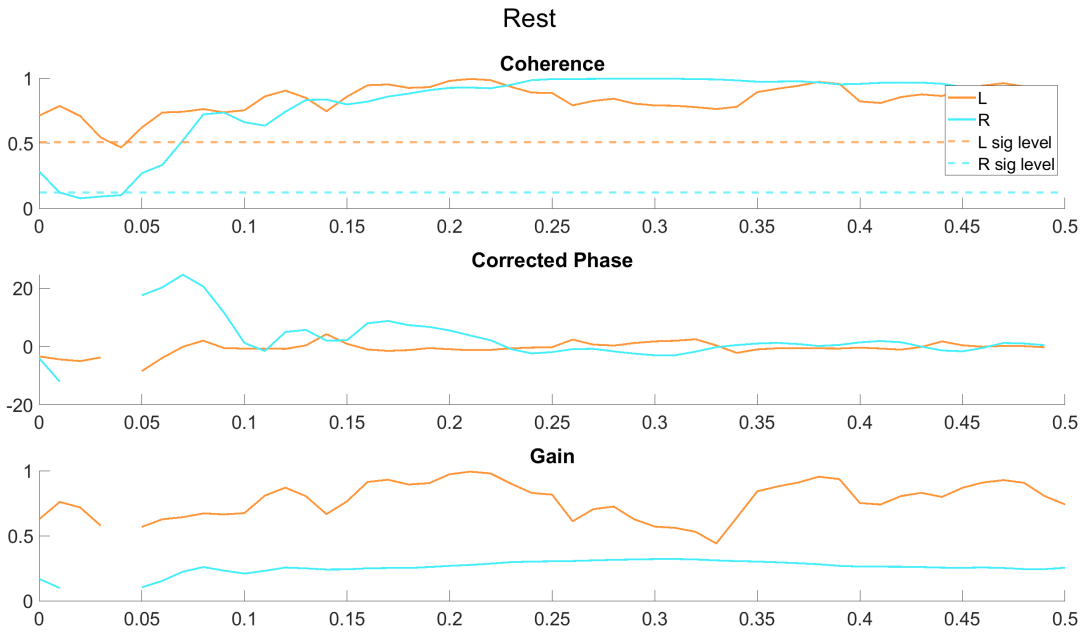


Figure 1.4: Example TFA results of 1 patient. Significance level is dependent on the data. If coherence is below significance level, phase and gain are not used for those frequency bins.

After TFA analysis the results of every data segment (thus rest 1 to 3 and sit-to-stand, left and right) were checked for usability. This was done based on the methods of Tas et al. [37]. The four exclusion criteria for segments were: no correction for transit time available, a negative mean VLF and /or LF phase shift <-10, mean VLF and/or LF phase shift > 180 or <-180 and <33% of the frequency bins were above the coherence threshold in VLF+LF and/or HF.

The mean coherence, phase shift and gain per frequency band were obtained from the software. If a patient had TFA results from both sides after segment exclusion these were averaged.

Statistical analysis

Statistical analysis was done in R studio (version 2022.02.1). Patients were divided into four groups: OH + symptoms, OH + no symptoms, no OH + symptoms and no OH+no symptoms. Data were checked for normality by plotting histograms and using the Shapiro Wilk test. If data were normally distributed within all groups an ANOVA test was used to compare the groups. If data were not normally distributed a kruskal-wallis test was used. For comparison of categorical variables the Chi-squared test was used. For post hoc testing either a Tukey test or a Wilcoxon signed-rank test was used.

Two sub-analyses were performed on the TFA data by dividing the patients into two groups. The first was a comparison between OH patients and patients without OH. In the second sub-analysis patients with and without symptoms (whether or not OH) were compared.

Results

Patient inclusion

Between November 2019 and December 2022, 41 patients were included. Data of 37 patients could be used for analyses. The distribution of patients in groups can be seen in the flowchart in Figure 1.5. There were more patients without than with OH.

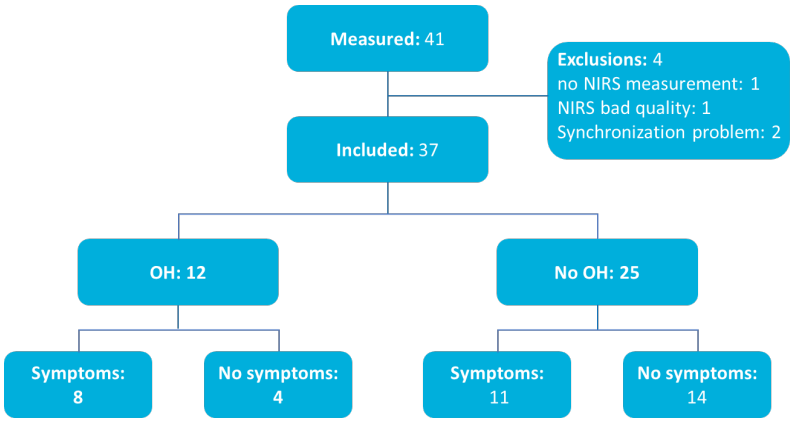


Figure 1.5: Flowchart of the barocontrol monitor study

General patient characteristics

The general characteristics of the four groups are shown in Table 1.1. This table does not show any significant differences between these groups.

Table 1.1: General characteristics

	no OH no symptoms (N=14)	no OH symptoms (N=11)	OH no symptoms (N=4)	OH symptoms (N=8)	Overall (N=37)	p-value
Age						
Median (IQR)	77.0 (5.75)	77.0 (5.00)	75.0 (2.50)	76.5 (7.00)	76.0 (5.00)	0.697[a]
Sex						0.157[b]
Female N (%)	5 (35.7%)	8 (72.7%)	2 (50.0%)	2 (25.0%)	17 (45.9%)	
BMI						
Median (IQR)	26.0 (2.79)	25.0 (4.24)	23.1 (1.69)	27.1 (6.19)	25.3 (4.12)	0.228[a]
SPPB score						
Median (IQR)	12.0 (2.00)	9.00 (3.00)	10.5 (3.00)	10.5 (3.25)	11.0 (3.00)	0.456[a]
MoCA score						
Median (IQR)	22.0 (5.50)	24.5 (2.75)	24.5 (6.25)	26.0 (2.00)	25.0 (5.25)	0.376[a]
CCI						0.598[b]
3	3 (21.4%)	1 (9.1%)	2 (50.0%)	2 (25.0%)	8 (21.6%)	
4	4 (28.6%)	6 (54.5%)	0 (0%)	2 (25.0%)	12 (32.4%)	
5	2 (14.3%)	0 (0%)	1 (25.0%)	2 (25.0%)	5 (13.5%)	
6	2 (14.3%)	3 (27.3%)	1 (25.0%)	0 (0%)	6 (16.2%)	
7	1 (7.1%)	1 (9.1%)	0 (0%)	2 (25.0%)	4 (10.8%)	
8	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	
10	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	1 (2.7%)	
VCS						0.315[b]
0	5 (35.7%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	10 (27.0%)	
1	3 (21.4%)	3 (27.3%)	3 (75.0%)	0 (0%)	9 (24.3%)	
2	3 (21.4%)	2 (18.2%)	0 (0%)	4 (50.0%)	9 (24.3%)	
3	3 (21.4%)	3 (27.3%)	0 (0%)	2 (25.0%)	8 (21.6%)	
4	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	1 (2.7%)	

OH: Orthostatic Hypotension, SPPB: Short physical performance battery, MoCA: Montreal Cognative Assessment, CCI: Charlson comorbidity index, VCS: vascular comorbidity score.

[a] kruskal wallis test, [b] chi-square test

In Table 1.2 the comparison between symptoms during the study visit with the OHQ can be seen. There were 8 patients who experienced symptoms in daily life but not during the study visit. There were also 5 patients who experienced symptoms during the study visit, but not in daily life.

Table 1.2: Orhtostatic hypotenstion questionare (OHQ)

	no OH no symptoms (N=14)	no OH symptoms (N=11)	OH no symptoms (N=4)	OH symptoms (N=8)	Overall (N=37)
total OHQ					
0	9 (64.3%)	2 (18.2%)	1 (25.0%)	3 (37.5%)	15 (40.5%)
1	4 (28.6%)	6 (54.5%)	1 (25.0%)	3 (37.5%)	14 (37.8%)
2	1 (7.1%)	1 (9.1%)	0 (0%)	1 (12.5%)	3 (8.1%)
3	0 (0%)	0 (0%)	1 (25.0%)	1 (12.5%)	2 (5.4%)
4	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	1 (2.7%)
5	0 (0%)	0 (0%)	1 (25.0%)	0 (0%)	1 (2.7%)
6	0 (0%)	1 (9.1%)	0 (0%)	0 (0%)	1 (2.7%)

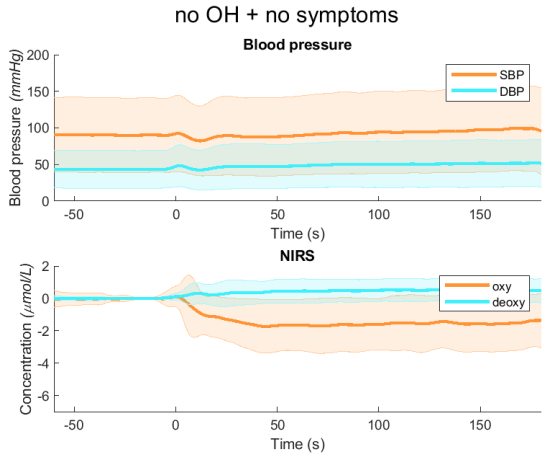
In Table 1.3 the OH classification from the Finapres and the oscillometric cuff measurement at the outpatient clinic are compared. This table shows that some patients had OH at the outpatient clinic but not during the study visit.

Table 1.3: Orthostatic hypertension (OH) classification comparison

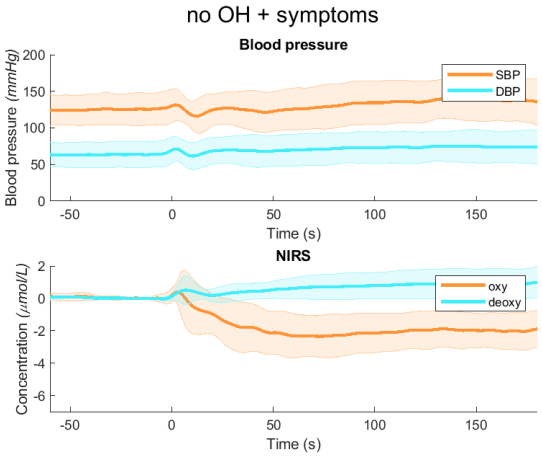
	OH oscilometric cuff	no OH oscilometric cuff
OH Finapres	10	2
no OH Finapres	8	17

Time domain analysis

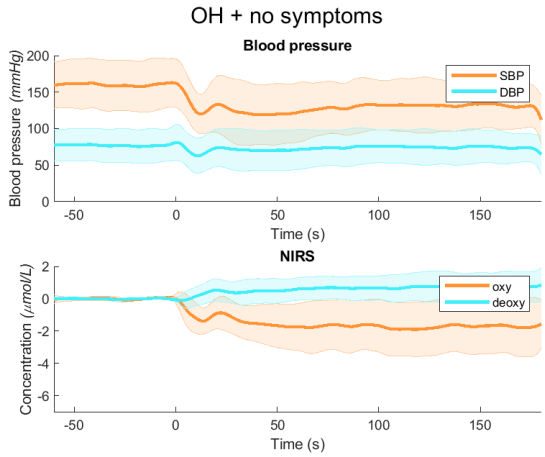
Averaged curves for blood pressure and NIRS variables can be found for each group in Figure 1.6. In the oxyHb data over time it appears as if the drop after standing is deeper in patients with symptoms compared to no symptoms in OH and non OH patients. Furthermore, the OH patients also show a delayed blood pressure recovery compared to the non OH patients.



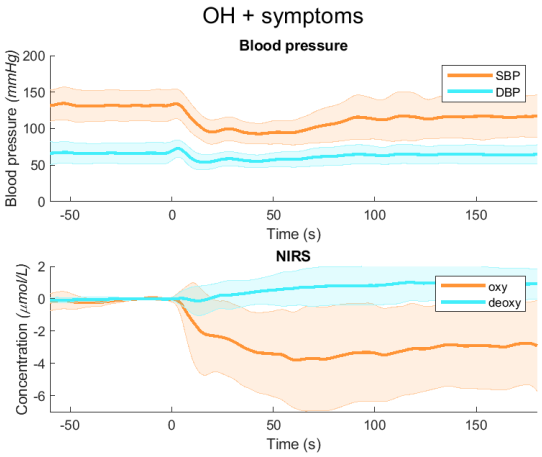
(a) no OH + no symptoms



(b) no OH + symptoms



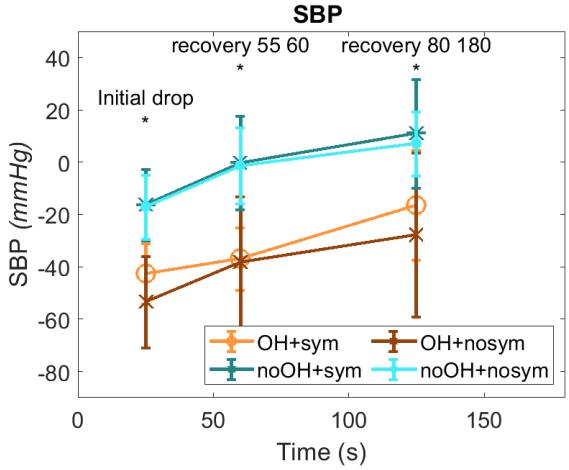
(c) OH + no symptoms



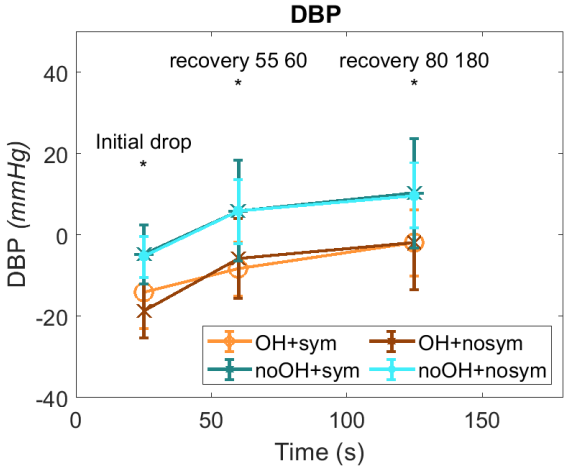
(d) OH + symptoms

Figure 1.6: Average blood pressure and Hb curves for each patient group. At time 0 seconds the participant stood up. OH: orhtostatic hypotension, SBP: systolic blood pressure, DBP: diastolic blood pressure, oxy: oxygenated hemoglobin, deoxy: deoxygenated hemoglobin

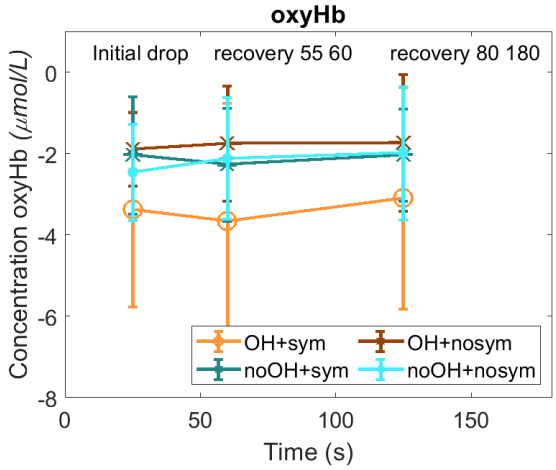
The computed variables from the blood pressure and NIRS data are shown in Figure 1.7. Patients with OH have a larger initial blood pressure drop and lower blood pressure recovery values after standing than patients without OH. However, there was no significant difference between symptoms and no symptoms. Patients with OH and symptoms had a larger initial drop in oxyHb and lower recovery values in oxyHb compared to the other groups. Yet, none of these values were significantly different.



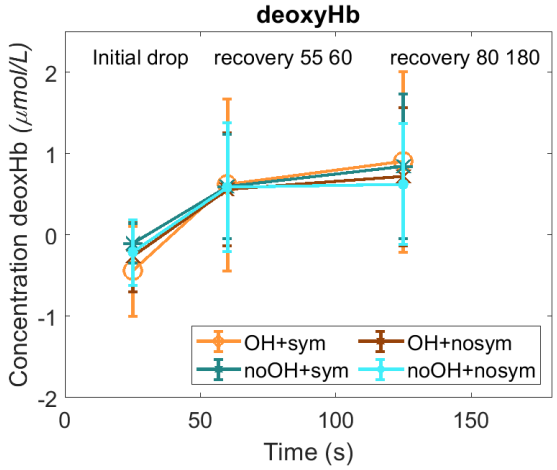
(a) SBP computed values. * = p<0.05



(b) DBP computed values. * = p<0.05



(c) oxyHb computed values. Initial drop (p=0.583), recovery 55 60 (p=0.278), recovery 80 180 (p=0.537)



(d) deoxyHb computed values. Initial drop (p=0.401), recovery 55 60 (p=0.999), recovery 80 180 (p=0.9)

Figure 1.7: Different computed variables for the oxyHb and deoxyHb values. The initial drop is the minimum within 40 seconds after standing. Recovery 55-60 seconds is the mean value between 55 and 60 seconds. Recovery 80-180 seconds is the mean value between 55 and 60 seconds. At time 0 seconds the participant stood up.

Transfer function analysis

The transfer function analysis results from the supine rest and sit stand exercise can be found in Tables 1.4 to 1.6. Missing patients are those where both left and right side were excluded after TFA analysis. It should be noted that more patients were excluded from the sit stand exercise compared to the supine rest.

No clear pattern was found in these TFA results. The only significant difference found was a lower gain

in no OH patients without symptoms compared to no OH patients with symptoms in the low frequencies. However, in the OH patient group this is the other way around. Furthermore, this pattern was not seen in the supine rest exercise.

The transfer function analysis results were also compared in sub-analyses in between two groups: OH patients versus no OH patients and patients with symptoms versus patients without symptoms. These results can be found in Appendix A.

Table 1.4: Coherence of supine rest and repeated sit stand data in very low frequency (VLF) and low frequency (LF) range

	no OH no symptoms (N=14)	**no OH symptoms (N=11)**	**OH no symptoms (N=4)**	**OH symptoms (N=8)**	**Overall (N=37)**	**p-value**
Coherence rest VLF						
Mean (SD)	0.314 (0.176)	0.271 (0.159)	0.256 (0.0544)	0.386 (0.249)	0.310 (0.178)	0.632[a]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Coherence rest LF						
Median (IQR)	0.479 (0.204)	0.300 (0.494)	0.579 (0.215)	0.629 (0.345)	0.479 (0.409)	0.539[b]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Coherence sit stand VLF						
Median (IQR)	0.612 (0.240)	0.870 (0.257)	0.646 (0.267)	0.685 (0.259)	0.658 (0.283)	0.169[b]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	
Coherence sit stand LF						
Median (IQR)	0.780 (0.284)	0.795 (0.115)	0.795 (0.0678)	0.798 (0.0217)	0.786 (0.0958)	0.215[b]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	

OH: Orthostatic hypotension
[a] ANOVA test, [b] kruskal Wallis test

Table 1.5: Phase of supine rest and repeated sit stand data in very low frequency (VLF) and low frequency (LF) range

	no OH no symptoms (N=14)	**no OH symptoms** (N=11)	**OH no symptoms** (N=4)	**OH symptoms** (N=8)	**Overall** (N=37)	**p-value**
Phase rest VLF						
Mean (SD)	36.4 (33.5)	25.0 (37.3)	2.38 (12.0)	20.5 (28.6)	25.7 (32.7)	0.399[a]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Phase rest LF						
Median (IQR)	17.3 (27.2)	4.62 (18.0)	-2.46 (4.00)	5.23 (2.64)	5.78 (17.3)	0.0789[b]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Phase sit stand VLF						
Median (IQR)	23.0 (30.7)	0.0749 (26.0)	7.58 (7.58)	18.6 (20.4)	16.2 (30.2)	0.408[b]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	
Phase sit stand LF						
Median (IQR)	8.26 (23.8)	4.62 (15.5)	2.29 (2.29)	4.69 (3.15)	5.68 (17.3)	0.5152[b]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	

OH: Orthostatic hypotension
[a] ANOVA test, [b] kruskal Wallis test

Table 1.6: Gain of supine rest and repeated sit stand data in very low frequency (VLF) and low frequency (LF) range

	no OH no symptoms (N=14)	no OH symptoms (N=11)	OH no symptoms (N=4)	OH symptoms (N=8)	Overall (N=37)	p-value
Gain rest VLF						
Median (IQR)	0.173 (0.131)	0.226 (0.147)	0.163 (0.0572)	0.262 (0.298)	0.180 (0.143)	0.979[b]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Gain rest LF						
Mean (SD)	0.255 (0.0920)	0.218 (0.0904)	0.264 (0.112)	0.347 (0.175)	0.263 (0.118)	0.226[a]
Missing	3 (21.4%)	2 (18.2%)	1 (25.0%)	2 (25.0%)	8 (21.6%)	
Gain sit stand VLF						
Median (IQR)	0.263 (0.119)	0.460 (0.407)	0.357 (0.0497)	0.313 (0.0582)	0.313 (0.144)	0.0736 [b]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	
Gain sit stand LF						
Median (IQR)	0.273 (0.117)	0.613 (0.270)	0.520 (0.0230)	0.392 (0.0526)	0.392 (0.211)	0.00469[b*]
Missing	3 (21.4%)	4 (36.4%)	2 (50.0%)	3 (37.5%)	12 (32.4%)	

OH: Orthostatic hypotension
[a] ANOVA test, [b] kruskal Wallis test, * significant p<0.05

Discussion

In the time domain OH patients show an incomplete blood pressure recovery and a larger initial drop in blood pressure compared to patients without OH. The blood pressure response, initial drop and recovery values did not differ between patients with and without symptoms. Patients with both OH and symptoms showed a trend towards greater average drop in oxyHb compared to other patient groups. However, this was not significant. No clear pattern could be found in the TFA results in the frequency domain.

Time domain

Since OH is defined as a sustained (at least until 1 minute after standing) blood pressure reduction after standing, it was expected that OH patients had a greater initial drop and lower recovery values [6]. The size of the initial drop of the OH patients, may indicate the presence of initial OH among some of the patients included in our study. Initial OH means a blood pressure drop of 40 mmHg systolic in the first 15 seconds [5]. The literature describes the presence of the same symptoms of light headedness and dizziness by iOH as by general OH [38]. Here, no difference in initial drop was seen in patients presenting symptoms compared to patients without symptoms. Therefore it is assumed that both groups included patients with iOH and iOH was not the cause of symptoms. Furthermore, the blood pressure recovery values did not differ between patients with and without symptoms. This is coherent with the fact that OH does not always explain orthostatic symptoms [39, 40]. Patients without OH can also suffer from orthostatic symptoms [40].

On average, patients with OH and symptoms tend to experience a greater drop in oxyHb after standing up. Since oxyHb is an indirect measurement of CBF, a low oxyHb could indicate a reduction in CBF [17, 27]. As the brain is depended on a constant CBF for its oxygen and glucose supply, a reduction in CBF may cause symptoms like light headedness [19]. Nonetheless, no significant results in oxyHb variables were found. However, there is supporting literature confirming the relation between oxyHb and the presentation of symptoms. One study reports that patients with orthostatic intolerance returned slower to their baseline oxygenation than controls during a head-up tilt test [41]. Another study reported that healthy controls show decreased cerebral oxygenation after a head up tilt test but to a lesser degree than patients with a history

of orthostatic syncope [42, 43]. However, this study used a history of orthostatic syncope instead of actual complaints of syncope during the measurement. They also found an acute drop in cerebral oxygenation in patients who did experienced (pre)syncope symptoms during the measurements [43]. Nevertheless, the difference between an active stand and head up tilt test should be noted as with an active stand muscles in the lower limps can be used to pomp blood in the direction of the heart [44].

Frequency domain

It was hypothesized that patients with orthostatic symptoms would show decreased cerebral autoregulation compared to those without symptoms despite the presence or absence of OH. We found no consistent pattern for the difference in autoregulation in our TFA results. In literature, ideas about orthostatic symptoms and cerebral autoregulation are described. First, it was reported that OH patients could have three different cerebral response patterns: autoregulatory failure with a flat flow-pressure curve, intact autoregulation with an expanded range, and autoregulation failure with a steep flow-pressure curve [15]. Patients with the last pattern were less able to cope with OH. These patients developed symptoms with smaller drops in blood pressure compared to patients with other cerebral autoregulation patterns[15]. In that study, TCD was used to measure autoregulation instead of NIRS. Second, literature shows that absent autoregulation during orthostasis can happen without the presence of OH [45]. Third, the relation between cerebral autoregulation with supine hypertension (elevation of blood pressure when lying down), was examined [46]. It was found that cerebral autoregulation, measured with NIRS tissue saturation index (TSI), was impaired in patients with supine hypertension [46]. Healthy patients with normal autoregulation can also experience symptoms because the speed of the onset of the blood pressure changes also limits the potential for autoregulation to buffer these changes[20]. This all suggests that there is no clear consensus on the link between orthostatic complaints, orthostatic hypotension and cerebral autoregulation. Furthermore, the measurement methods and methods for defining cerebral autoregulation differ.

Symptoms and OH classification

In this study there were no clear differences in TFA results and oxyHb variables between the four groups: no OH without symptoms, no OH with symptoms, OH without symptoms, and OH with symptoms. One possible explanation is that patients find it difficult to express the experienced symptoms as complaints might be very subjective. Now the complaints patients experienced the supine-stand test during the study visit were used to categorize patients. However, symptoms during the study visit do not necessarily match symptoms in daily life, measured with the OHQ. Therefore it could be possible to use the OHQ to divide patients into symptom categories. However, this still remains a subjective measurement and relies on the memory of the patient.

Besides an arbitrary choice for symptom classification there are also different ways to classify OH. In the clinic, an oscillometric blood pressure cuff at the brachial artery is often used [12]. However, in this study the OH classification at the clinic differed from the found OH classification based on the continuous blood pressure measurement at the study visit. However, it should be noted that for some patients there was a significant time difference between their visit to the clinic and the study visit. For future research it could be a possibility to measure the blood pressure with a cuff at the brachial artery during the study visit in addition to the continuous monitor. This could help in comparing both methods of OH classification. Nonetheless, the continuous blood pressure measurement has the advantages that it does not depend on timing and can measure a full response compared to the oscillometric cuff.

Strengths and limitations

The strength of this study is that we evaluate both OH and orthostatic symptoms in elderly people. Most studies evaluate either OH or orthostatic intolerance [36, 41]. Furthermore, our data were analyzed in time and frequency domain. Additionally, this is the first time the TFA method with NIRS was used in patients with OH.

The first limitation of this study concerns the small (n=37) sample size. Secondly, the groups are unevenly distributed. Thirdly, the sit-stand exercise had several limitations. The sit-stand exercise was only five minutes long. Therefore, no data could be excluded from the TFA. Furthermore, the sit-stand exercise created constant movement artifacts. To illustrate, the NIRS data of some patients showed oscillations that were twice as fast as was intended (0.1Hz instead of 0.05Hz). This is most likely due to head movements during this exercise. A fourth limitation, is that we only evaluated OH and symptoms during a study visits which gives us only a snapshot of information. Patients don't always experience OH or orthostatic symptoms in the same situations. For future research monitoring patients at home with NIRS and/or a continuous blood pressure device could give new and more information about the relationship between OH and orthostatic symptoms.

Conclusion

Blood pressure drop and recovery did not explain symptoms in patients with and without OH. The OxyHb signal may contain some information about symptoms after standing up. However, further research is needed to confirm the usability for OxyHb to detect symptoms after standing up. Additionally, no difference in cerebral autoregulation defined by TFA with NIRS, was found between patients with and without symptoms and with and without OH.

2 | Blood pressure response as a measure for resilience

Introduction: Resilience is the ability to recovery from a health stressor, while frailty is the increased risk of poor health outcomes. The resilience of the blood pressure control system, could be an indicator of the resilience of the entire body. Therefore, the blood pressure response after standing up could hold information about frailty, resilience and surgical outcomes. The hypotheses was that patients with an incomplete blood pressure recovery (including orthostatic hypotension (OH)) were more frail and less resilient.
Method: During a preoperative screening patients underwent a supine stand test while continuous blood pressure was measured. Principal component analysis was used to divide patients into two groups based on their blood pressure curve. Patients were also divided in tertiles based on their Comprehensive Geriatric Assessment Frailty Index (CGA-FI). Patients were followed through their electronic patient files.
Results: A 140 patients were included of which 91 had complete blood pressure data. Patients with a blood pressure recovery after standing above baseline, appeared to be more frail than patients with other blood pressure patterns, but this was not significant. Patients were the continuous blood pressure measurement failed were the most frail patients. No differences were found in surgery outcomes between groups with a different blood pressure pattern.
Conclusion: Being unable to measure the continuous blood pressure is a marker for frailty. Furthermore, our results suggest that orthostatic hypertension could be a marker of frailty, although an incomplete blood pressure is often related to frailty and mortality in literature. Therefore, it could be that orthostatic hypertension and OH can both be markers of frailty.

Introduction

The world population is aging and it is expected that the proportion of people over 60 will have doubled by 2050 compared to 2015 [47]. Aging can be described as a progressive loss of physiological integrity, leading to impaired functioning [48]. Healthy aging could be seen as maintaining the functionality that enables wellbeing in older age [49]. Since the population is getting older, it is valuable to focus on improving healthy aging. To improve healthy aging, the principles of personalized medicine, an approach to improve the delivery of therapies tailored to the needs of the individual patient, can be applied[50].

In the context of geriatrics, personalized medicine could be of help when deciding if a patients is still strong enough to undergo surgery. Certainly since the risk of morbidity and mortality after surgery increases with age [51]. The functioning of some patients improves after surgery whereas other patients show a decline after surgery. To better understand why some patients may benefit from surgery and some may not, the

concepts of frailty and resilience are important.

Although the term frailty is widely used, varying definition exists. Most often frailty is described as an increased vulnerability due to external stressors [52, 53]. Whitin the clinic, frailty is assessed using measures using measures like the comprehensive geriatric assessment frailty index (CGA-FI)[54] and the clinical frailty scale (CFS) [55]. Frailty increases the risk of mortality and postoperative complications after surgery [56].

Resilience can be described as the ability to return to an original state after a perturbation [57, 58]. In case of high resilience, a system will quickly recover, whereas a system with a low resilience shows a slow recovery or even no recovery at all (see Figure 2.1). This could also mean that a tipping point is near. A tipping point is a point for a system that separates two equilibriums. If this point is passed, the system will transition into a new equilibrium[59, 60]. The concept of resilience is widely interpretable in different fields, like ecology[61], economy [62], and the human body. Within the clinic, resilience is negatively associated with frailty. A higher resilience means often a lower frailty[53]. Physical resilience can be seen as a dynamic parameter, while frailty is more a static clinical syndrome[57].

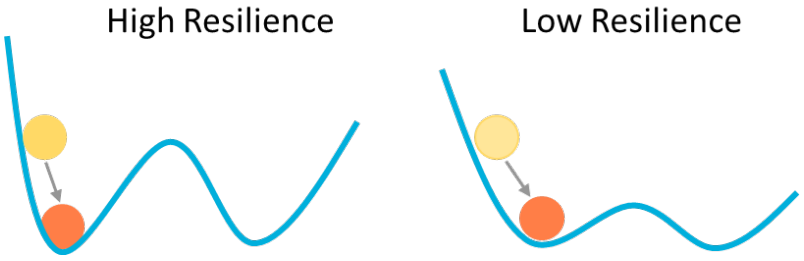


Figure 2.1: Conceptual visualisation of resilience

Within the human body resilience is the ability to recover from a stressor[63]. Multiple systems are involved in the recovery. A perturbation that can be induced to the human body is an orthostatic challenge which disturbs the blood pressure [10]. When a person stands up, the gravitational force redistributes the blood [5]. The human body must activate the blood pressure control system to restabilize the blood pressure. In the blood pressure control system the baroreceptors, the blood vessel, heart and autonomic nervus system are involved [1]. Therefore, blood pressure measurement can show the reaction and possibly the resilience of the blood pressure control system. It is assumed that the resilience of a system like the blood pressure control system also is linked to the resilience of the total body. An association between delayed blood pressure recovery after an orthostatic challenge and mortality[9, 64] and Alzheimer's disease progression was already found [10]. Surgery could be seen as a large perturbation that can possibly lead to the crossing of a tipping point. Therefore it would be useful to be able to evaluate the resilience of a patient before a surgery. However, whether the blood pressure recovery after standing holds information of surgery outcomes is unknown yet.

This study aimed to evaluate at the blood pressure recovery and its relation to resilience in geriatric patients. Additionally, the relation between blood pressure recovery and complications after surgery were of interest. Therefore, the following research question has been formulated: *Can blood pressure changes after an orthostatic challenge be a measure of resilience in geriatric outpatients and be predictive of complications after surgery?*

Method

Population

Geriatric outpatients of the Radboud University Medical Center who came for a preoperative screening were included. The following inclusion criteria were used:

- Age 60 years or over
- Patients are coming for a new problem that requires a new intake

The exclusion criteria are as follows:

- Patient is unable to follow up on instructions
- Physically unable to perform a supine-to-stand test

Measurement protocol

During a patient visit to the clinic for a comprehensive geriatric assessment a supine to stand test was done. This test consisted of five minutes of laying down, followed by five minutes of standing. During this test the blood pressure was measured continuously (Finapres Nova; Finapres Medical Systems, Enschede, The Netherlands). Also, the blood pressure was measured with an oscillometric cuff at the brachial artery on the contralateral arm in supine position and at one, three and five minutes after standing.

Furthermore, the grip strength, fatigue resistance, and grip work were assessed using a Martin Vigorimeter. These measurements assess a patient's frailty by measuring the performance of the musculoskeletal system [65]. The fatigue resistance was measured as the time in which the grip strength decreased to 50% of its maximum [66]. Grip work can be seen as an estimate of the total effort of the fatigue resistance measurement [67]. Grip work was calculated as

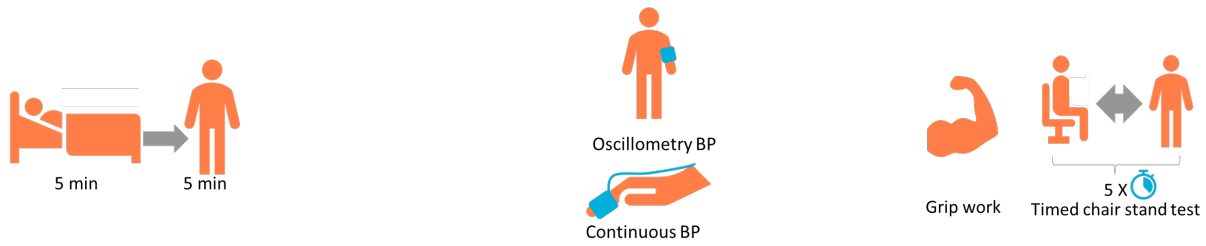
$$Grip\ work = (Grip\ strength\ x\ 0.75)\ x\ fatigue\ resistance. \tag{2.1}$$

Additionally a timed chair stand test (tcst) was performed to assess the mussel performance of the lower limbs [68, 69]. A patient was asked to stand up five times as fast as possible, without the use of his hands. The duration of this test was measured in seconds.

The clinical frailty scale (CFS) was asses by the geriatrician during the assessment. The CFS is a scale that ranges from 1 (very fit) to 9 (terminally ill) [55, 70]. Based on the geriatric consult the comprehensive geriatric assessment frailty index (CGA-FI) was computed by the researcher. The CGA-FI, consists of 21 medical history items, 22 functional status items, and 4 performance tests including the MoCA, tcst, gait speed, and dominant handgrip strength[71, 72]. Additionally, the TOPICS morbidity score was retrieved based on the geriatric consult [73]. The TOPICS morbidity score consists of 17 morbidities if a morbidity was present in the past 12 month one point was added to the score. After the measurements patients were followed passively through their electronic patient files.

Data analysis

The blood pressure data analysis was done in MATLAB 2022a. First the continuous blood pressure was preprocessed, from which several variables were retrieved. Furthermore, the blood pressure curves were used as input for a principal component analysis (PCA).



(a) (b) (c)

Figure 2.2: Schematic overview of measurement protocol. a) Rapid supine to stand protocol. b) blood pressure measurements. c) Gripwork assessment and timed chair stand test(tcst)

Preprocessing

The continuous blood pressure data were processed by detecting the systolic and diastolic peaks automatically[10]. The peaks were manually checked and corrected if needed, reducing noise in the data. Furthermore, the continuous blood pressure signals were resampled at 10Hz and filtered using a 5-second moving average filter. The data were shortened to 1 min before standing until 4 minutes after standing.

Blood pressure variables

The blood pressure data were used to compute, baseline, initial drop and four recovery values [74]. Baseline SBP and DBP were determined by taking the average value between 10 and 40 seconds before standing. The initial drop was computed by finding the minimum blood pressure value in the first 40 seconds after standing and subtracting baseline from this value. Four different recovery values were computed: orthostatic (between 50 and 60 seconds), rapid (between 30 and 60 seconds), sustained (between 60 and 120 seconds) and prolonged recovery (between 120 and 180 seconds) (See Figure, 2.3). Recovery values were computed by subtracting the baseline from mean blood pressure in the specific time interval.

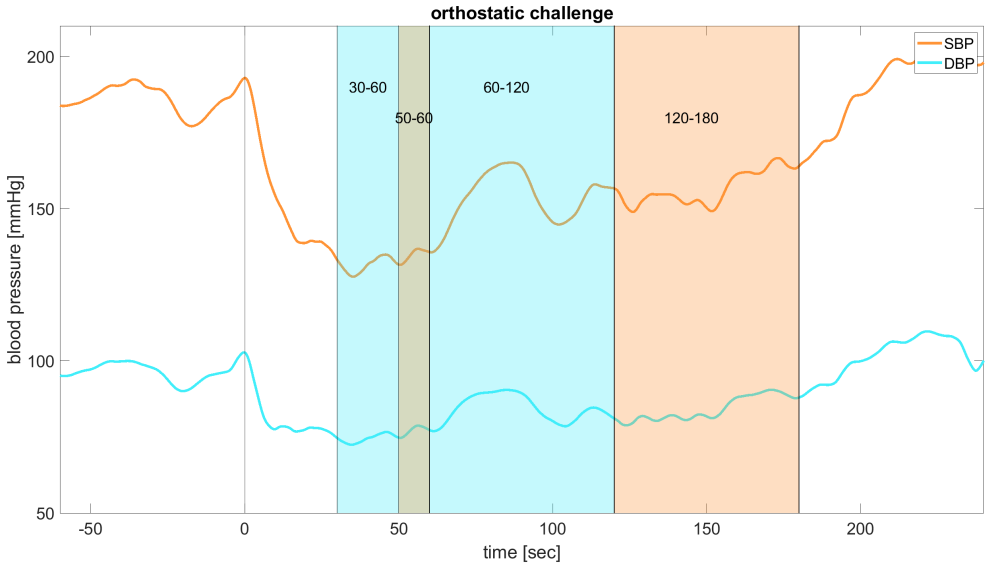


Figure 2.3: Recovery periods in the blood pressure, of an example measurement

Furthermore, the recovery time was computed as the first time after baseline were the blood pressure was equal or above baseline.

Another set of variables was computed based on the method of Lagro et al. [9]. Baseline values were seen as 100%, after which a recovery percentage was computed for the first 15 seconds after standing (see equation 2.2). The data between 15 to 60 seconds after standing was divided into 5 second intervals. The recovery percentage was computed for all these intervals, according to the following equation:

$$\%BP_{recovery0-15} = \frac{BP_{average0-15} - BP_{Baseline}}{BP_{Baseline}} \tag{2.2}$$

Furthermore, the continuous blood pressure data were used to check if patients had OH. This was done by checking if a patient's blood pressure after moving average filtering had any point 20mmHg below systolic baseline or 10mmHg below diastolic baseline after 60 seconds of standing. Additionaly, the oscillometric blood pressure data were used to check for OH. Osillometric OH was present if one of the blood pressure at 1,3 or 5 minutes after standing was 20mmHg below systolic baseline or 10mmHg below diastolic baseline,.

Principal component analysis

To divide patients in groups based on their blood pressure curve principal component analysis (PCA) was used. PCA is a statistical method for data reduction [75–77]. By reducing a large data set to a few principal components based on the variance, data gets simpler without losing much information. These principal components can be used to identify clusters in dataset, and classify groups according to these clusters[75]. The complete systolic pressure curves in percentage from baseline were given as input to the PCA function in MATLAB. The alternating least squares algorithm was used [78]. The scores of the first two principal components were used as input for k-means clustering to divide the patients into groups.

Group divisions

Different group divisions were used to analyze the data. The first group division was based on the outcomes of the PCA. Patients were divided into the following groups: PCA group 1, PCA group 2, Finapres measurement failed and Finapres not measured for a logistic reason. The second group division was similar to the first, but with three PCA groups. The third division was based on the systolic blood pressure recovery value in percentages between 55 and 60 seconds. Patients were divided into three groups: <95%, >95% <105%, and >105%. Finally, all patients with continuous blood pressure data were divided into tertiles according to their CGA-FI value.

Comparisons

For the group division based on the blood pressure the decision about surgery, surgery outcomes and measures for frailty and resilience were compared between groups. The blood pressure variables during the orthostatic challenge were compared between the CGA-FI tertiles.

Statistical analysis

Statistical analysis was done in R (Version 2022.02.1). Data were checked for normality before testing, by using histograms and the Shapiro Wilk test. If the distribution within all groups was normal an ANOVA test was used. The Kruskal Wallis test was used if the distribution within one of the groups was not normal.

Chi-squared test was used for the comparison of categorical variables. For post hoc testing either a Tukey test or a Wilcoxon signed-rank test was used.

Results

Patient inclusion

Between August 2021 and January 2022, 205 patients have visited the outpatient clinic for a preoperative assessment. From these patient, 140 have been included. However, the continuous blood pressure data were missing for 49 patients for various reasons. The flowchart of the Geriatric Resilience Registry outpatients can be seen in Figure 2.4.

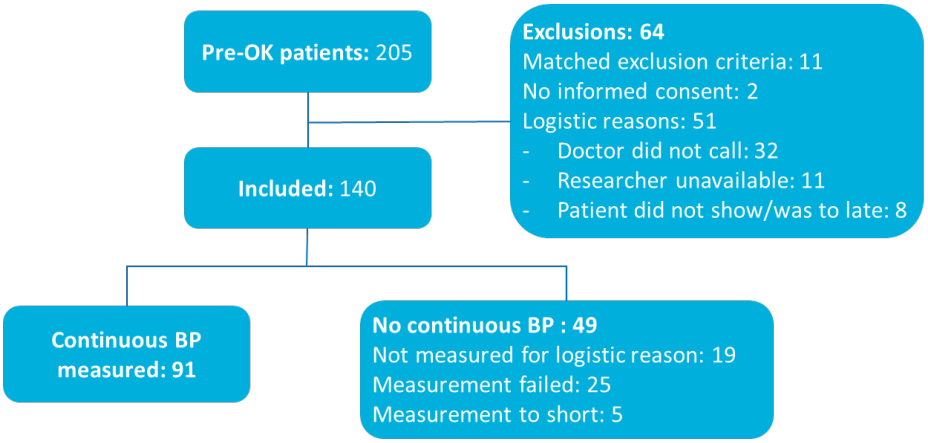


Figure 2.4: Flowchart of outpatients in the geriatric resilience registry

Principal component analysis

With PCA based on the entire systolic blood pressure curves in percentage from baseline two different group division have been made. Results on the PCA itself and the divisions can be found in Appendix B. Figure 2.5 shows the PCA division with two groups. The first PCA group shows patients with almost no recovery to patients who recover to baseline. The second PCA group shows patients who recover above the baseline blood pressure after standing. The general characteristics of these groups can be found in Table 2.1. This table shows that the delirium history and age are significantly different between groups. Post hoc testing showed no significant differences in age between the specific groups.

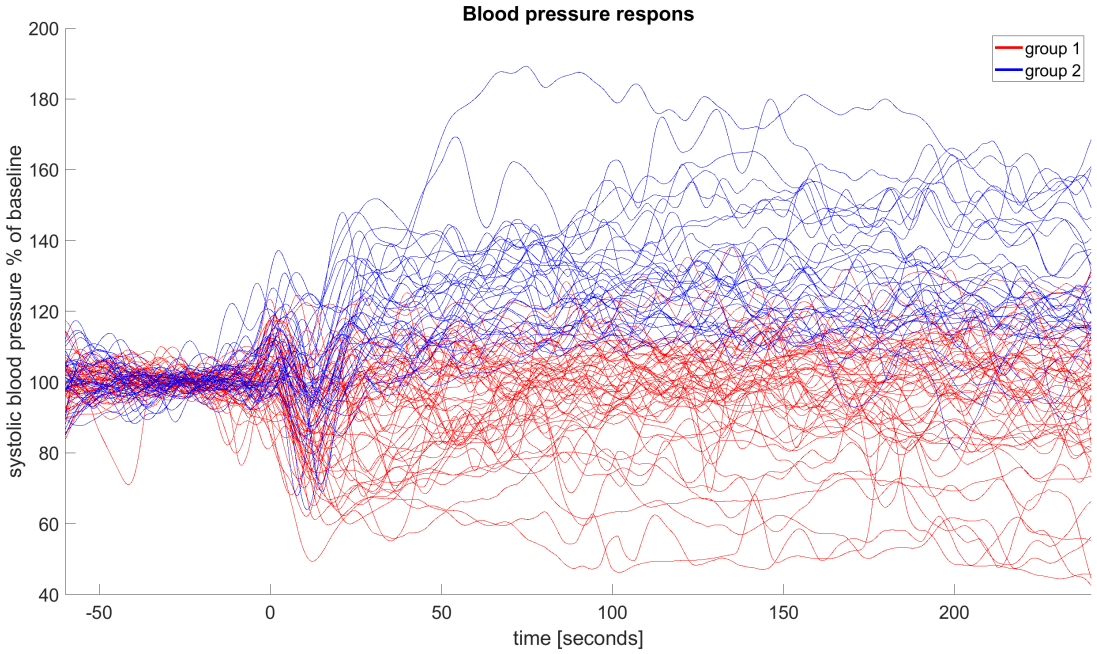


Figure 2.5: Continuous percentage of baseline systolic blood pressure of all patients divided in there principal component group.

Table 2.1: General patient characteristics per PCA group and fp not measured for different reasons

	PCA group 1 (N=56)	**PCA group 2 (N=35)**	**fp measurment failed (N=25)**	**no fp measured logistic reason (N=24)**	**Overall (N=140)**	**p-value**
Sex						0.233[a]
male N (%)	37 (66.1%)	23 (65.7%)	12 (48.0%)	17 (70.8%)	89 (63.6%)	
age						
Mean (SD)	76.5 (6.00)	76.3 (5.74)	80.4 (7.38)	79.8 (6.52)	77.7 (6.47)	0.0148[b*]
MoCA score						
Median (IQR)	25.0 (3.75)	25.5 (3.00)	23.0 (5.50)	23.0 (4.00)	25.0 (4.75)	0.297[c]
delirium history						<0.01[a*]
delirium N (%)	12 (21.4%)	0 (0%)	9 (36.0%)	5 (20.8%)	26 (18.6%)	
number of medications						
Median (IQR)	7.50 (5.50)	8.00 (6.00)	9.00 (6.00)	6.00 (4.00)	8.00 (6.00)	0.287[c]
Supine Cuff SBP						
Mean (SD)	153 (24.3)	144 (19.5)	148 (26.1)	150 (23.7)	149 (23.5)	0.283[b]
Supine Cuff DBP						
Median (IQR)	81.0 (16.0)	74.0 (20.5)	77.0 (20.0)	80.0 (11.8)	78.5 (18.0)	0.307[c]
anti-hypertensive drugs						0.637[a]
Yes N (%)	48 (85.7%)	27 (77.1%)	20 (80.0%)	18 (75.0%)	113 (80.7%)	
TOPICS morbidity score						
Median (IQR)	2.00 (2.00)	3.00 (2.00)	3.00 (3.00)	3.00 (1.25)	3.00 (2.00)	0.0585[c]

PCA: principal component analysis, fp: Finapres, MoCA: Montreal cognitive assessment, SBP: systolic blood pressure, DBP: diastolic blood pressure.
[a] Chi-square test, [b] ANOVA test, [c] Kruskal Wallis test, * significant P<0.05

The results of the frailty and resilience measures can be found in Table 2.2. All frailty and resilience variables show that the group where the Finapres measurement failed was most frail/least resilient, followed by the group with blood pressure recovery above baseline and the group with slower blood pressure recovery respectively. However this difference was only significant for the gait speed and CGA-FI. CGA-FI and gait

speed were significantly different between PCA group 1 and the group where the Finapres measurement failed.

Table 2.2: Frailty/resilience measurements per PCA group and fp not measured for different reasons

	PCA group 1 (N=56)	PCA group 2 (N=35)	fp measurement failed (N=25)	no fp measured logistic reason (N=24)	Overall (N=140)	p-value
CFS						0.233[a]
Median (IQR)	4.00 (2.00)	4.00 (1.50)	5.00 (1.00)	4.50 (1.25)	4.00 (2.00)	
CGA-FI						
Median (IQR)	0.0975 (0.0888)	0.145 (0.0860)	0.198 (0.188)	0.128 (0.134)	0.132 (0.140)	<0.01[b*]
GWA						
Median (IQR)	1800 (2000)	1640 (1280)	1310 (1200)	1810 (1580)	1680 (1770)	0.229[b]
GS						
Median (IQR)	64.5 (25.3)	58.0 (30.0)	55.0 (24.0)	60.0 (31.3)	60.0 (27.3)	0.517[b]
FR						
Median (IQR)	43.0 (45.0)	40.0 (32.6)	40.0 (35.8)	43.0 (22.8)	40.0 (40.0)	0.297[b]
tcst						
Mean (SD)	14.5 (5.23)	16.4 (12.0)	17.6 (8.81)	15.6 (4.03)	15.7 (8.06)	0.886[c]
Missing	3 (5.4%)	0 (0%)	5 (20.0%)	3 (12.5%)	11 (7.9%)	
gait speed						
Median (IQR)	1.10 (0.240)	1.00 (0.235)	0.870 (0.330)	0.900 (0.320)	1.00 (0.335)	<0.01[b*]
Missing	11 (19.6%)	8 (22.9%)	3 (12.0%)	3 (12.5%)	25 (17.9%)	

PCA: principal component analysis, fp: Finapres, CFS: clinical frailty scale, CGA-FI: comprehensive geriatric assessment frailty index, GWA: Grip work assessment, GS: grip strength, FR: fatigue resistance, tcst: timed chair stand test.
[a] Chi-square test, [b] Kruskal Wallis test, [c] ANOVA test, [*] significant p<0.05

The decision about surgery was compared between the groups, this is shown in Table 2.3. No significant differences were found for the decision about surgery between the two PCA groups and the two groups without Finapres measurements.

Table 2.3: Decision about surgery for each group

	PCA group 1 (N=56)	PCA group 2 (N=35)	fp measurement failed (N=25)	no fp measured logistic reason (N=24)	Overall (N=140)	p-value
surgery						0.662[a]
no surgery	13 (23.2%)	10 (28.6%)	10 (40.0%)	9 (37.5%)	42 (30.0%)	
surgery	30 (53.6%)	16 (45.7%)	13 (52.0%)	12 (50.0%)	71 (50.7%)	
Missing	13 (23.2%)	9 (25.7%)	2 (8.0%)	3 (12.5%)	27 (19.3%)	
surgery cancel reason						0.622[a]
to frail according to geriatrician	4 (7.1%)	4 (11.4%)	2 (8.0%)	4 (16.7%)	14 (10.0%)	
patient did not want to	6 (10.7%)	3 (8.6%)	3 (12.0%)	4 (16.7%)	16 (11.4%)	
other	3 (5.4%)	3 (8.6%)	5 (20.0%)	1 (4.2%)	12 (8.6%)	
Missing	43 (76.8%)	25 (71.4%)	15 (60.0%)	15 (62.5%)	98 (70.0%)	

PCA: principal component analysis, fp: Finapres
[a] Chi-square test

Of the 140 included patients only 71 patients underwent a surgery. The surgery outcome results can be found in Table 2.4. No significant differences were found. Some information was missing because not all patients were operated in the Radboud umc. It should be noted that only 3 patients developed a delirium after surgery and only 13 patients had any kind of complications.

The results of the patient group division with three PCA groups are stated in Appendix C. This Appendix also contains the results of the patient group division based on the recovery value around 60 seconds.

Table 2.4: Surgery outcome variables

	PCA group 1 (N=30)	PCA group 2 (N=16)	fp measurement failed (N=13)	no fp measured logistic reason (N=12)	Overall (N=71)	p-value
Surgery time						
Median (IQR)	152 (181)	164 (78.3)	115 (104)	134 (140)	141 (125)	0.412[a]
Missing	4 (13.3%)	0 (0%)	0 (0%)	0 (0%)	4 (5.6%)	
ICU admission						0.081[b]
Yes	7 (23.3%)	5 (31.3%)	8 (61.5%)	2 (16.7%)	22 (31.0%)	
Missing	4 (13.3%)	0 (0%)	0 (0%)	0 (0%)	4 (5.6%)	
admission days						
Median (IQR)	4.00 (6.00)	7.00 (6.50)	8.00 (7.00)	4.00 (7.50)	4.00 (7.00)	0.471[a]
Missing	3 (10.0%)	1 (6.3%)	0 (0%)	1 (8.3%)	5 (7.0%)	
complications						0.893[b]
Yes	4 (13.3%)	3 (18.8%)	3 (23.1%)	3 (25.0%)	13 (18.3%)	
Missing	5 (16.7%)	1 (6.3%)	1 (7.7%)	0 (0%)	7 (9.9%)	
Delirium during admission						0.585[b]
Yes	2 (6.7%)	1 (6.3%)	0 (0%)	0 (0%)	3 (4.2%)	
Missing	4 (13.3%)	1 (6.3%)	0 (0%)	0 (0%)	5 (7.0%)	

PCA: principal component analysis, fp: Finapres
[a] Kruskal Wallis test, [b] Chi-square test

Blood pressure characteristics

General characteristics of the three CGA-FI groups can be found in Table 2.5. Group 1 is the group with the lowest frailty index and thus the strongest group of patients. Group 3 has the highest frailty index and thus is the most frail patient group. The topics comorbidity score and MoCA score were both significantly different between groups. For both variables there was a significant difference between the third and first group. Furthermore, there percentage of males was greater in group 1 and 2 compared to group 3.

Table 2.5: General characteristics of patients divided in tertiles based on comprehensive geriatric assesment frailty index (CGAFI)

	1 (N=31)	**2** (N=30)	**3** (N=30)	**Overall** (N=91)	**p-value**
Sex					<0.01[a*]
male N (%)	24 (77.4%)	23 (76.7%)	13 (43.3%)	60 (65.9%)	
age					
Mean (SD)	75.3 (5.88)	76.2 (5.21)	77.8 (6.39)	76.4 (5.87)	0.13[b]
MoCA					
Median (IQR)	26.0 (2.00)	25.0 (2.00)	23.0 (10.0)	25.0 (4.00)	0.038[c*]
Missing	2 (6.5%)	1 (3.3%)	2 (6.7%)	5 (5.5%)	
delirium history					0.457[a]
delirium N(%)	6 (19.4%)	3 (10.0%)	3 (10.0%)	12 (13.2%)	
number of medications					
Median (IQR)	7.00 (4.50)	9.00 (4.00)	8.00 (7.00)	8.00 (6.00)	0.282[c]
antihypertensive drugs					0.265[a]
Yes N (%)	23 (74.2%)	27 (90.0%)	25 (83.3%)	75 (82.4%)	
TOPICS morbidity score					
Median (IQR)	2.00 (1.50)	2.00 (1.75)	3.00 (2.00)	2.00 (2.00)	<0.01[a*]
Missing	0 (0%)	0 (0%)	1 (3.3%)	1 (1.1%)	
GCA-FI					
Median (IQR)	0.0650 (0.0210)	0.118 (0.0405)	0.232 (0.131)	0.116 (0.0980)	<0.01[c*]

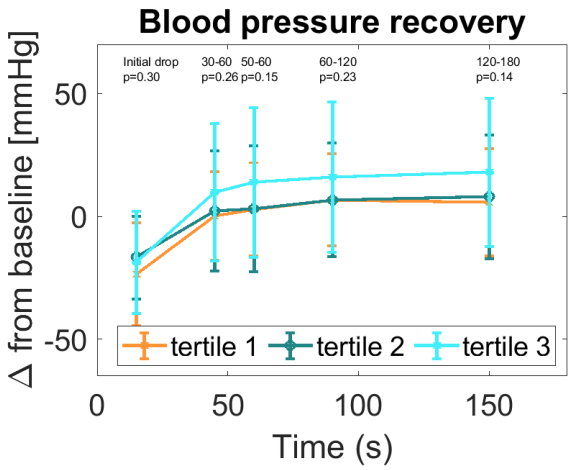
[a] Chi-square test, [b] ANOVA, [c] Chi-square test, $^{*}significantp < 0.05$
MoCA: montreal cognative assesment,

The results of the blood pressure recovery variables can be found in Table 2.6 and Figure 2.6. It is shown that the blood pressure drop was deeper after standing in the least frail group. However this was not significant. Furthermore, the recovery values of the most frail group were higher than the other two groups, but this was not significant. The most frail group appeared to recovery above the systolic baseline, while the other two groups returned to baseline.

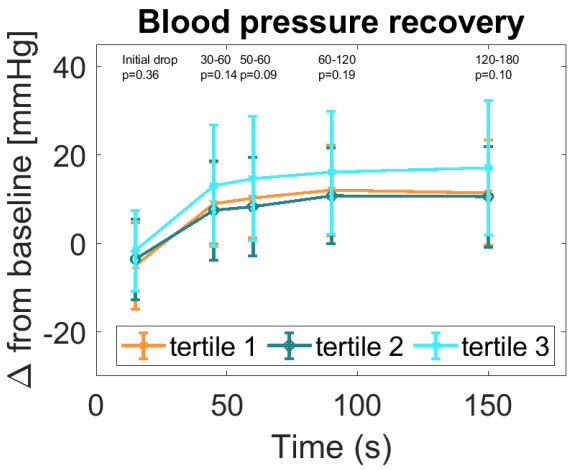
Table 2.6: Blood pressure variables of patients divided in tertiles based on comprehensive geriatric assessment frailty index (CGAFI)

	1 (N=31)	**2** (N=30)	**3** (N=30)	**Overall** (N=91)	**p-value**
OH measured with Finapres					0.3851[a]
N (%)	12 (38.7%)	11 (36.7%)	7 (23.3%)	30 (33.0%)	
baseline SBP					
Mean (SD)	126 (24.2)	125 (30.0)	116 (26.3)	122 (27.0)	0.292[b]
baseline DBP					
Mean (SD)	56.9 (15.8)	57.9 (15.7)	51.2 (15.2)	55.3 (15.7)	0.203[b]
recovery time SBP					
Median (IQR)	26.5 (41.2)	23.0 (72.7)	20.0 (21.4)	23.0 (39.3)	0.549[c]
recovery time DBP					
Median (IQR)	14.8 (12.6)	15.3 (29.7)	13.5 (18.5)	14.5 (16.2)	0.529[c]

OH: orhtostatic hypotension, SBP: systolic blood pressure, DBP: diastolic blood pressure.
[a] Chi-square test, [b] ANOVA, [c]Kruskal Wallis test

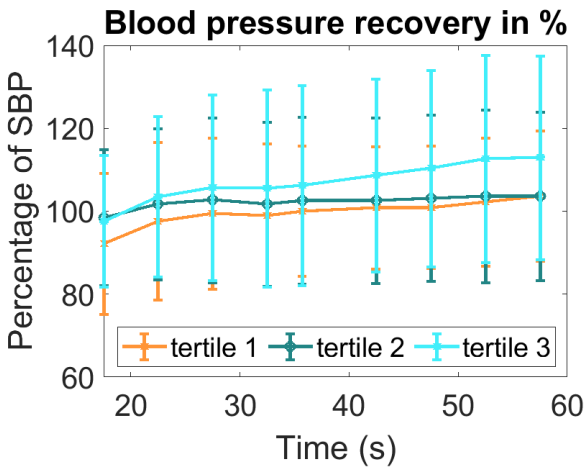


(a) Systolic blood pressure recovery values

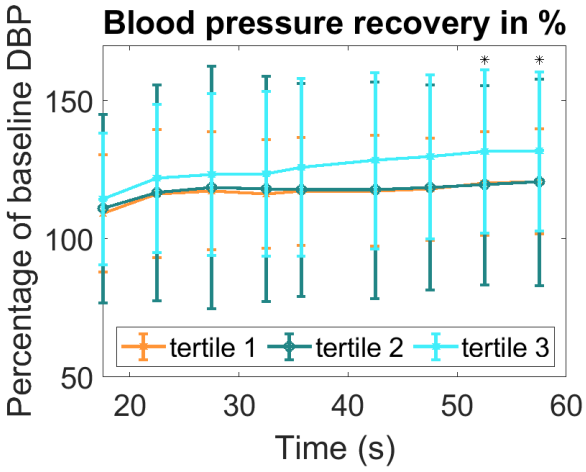


(b) Diastolic blood pressure recovery values

Figure 2.6: Mean of the blood pressure variables with standard deviation. The initial drop and recovery values for different time points (30-60 s,50-30 s, 60-120 s, 120-280 s, as indicated above the graphs) are plotted.



(a) Systolic blood pressure



(b) Diastolic blood pressure

Figure 2.7: Percentage of baseline blood pressure in the first minute after standing for three groups of geriatric clinical frailty index tertiles. The mean and standard deviation are plotted. * are significantly different between the groups ($p<0.05$).

The results of the recovery as percentage of baseline in the first minute is shown in Figure 2.7. In both the systolic and diastolic blood pressure the most frail group seems to recover above baseline instead of to baseline. However, this is only significantly different in the at the diastolic blood pressure between 50 and 60 seconds of standing (see Figure 2.7b).

OH classification

In Table 2.7 the comparison between OH classification based on the Finapres measurement and the oscillometric cuff measurement is shown. There are patients who have OH based on the cuff measurement but not on the Finapres, and vice versa.

Table 2.7: Orthostatic hypertension classification comparison

	OH oscillometric cuff	no OH oscillometric cuff
OH Finapres	43	18
no OH Finapres	11	19

Discussion

We investigated the hypothesis that patients with an incomplete blood pressure recovery after standing are more frail and have a higher risk of a complication after surgery. However, it was found that patients with a blood pressure recovery that exceeded baseline tended to be more frail than patients with another blood pressure pattern. Patients for whom the Finapres measurement did not work, were more frail than patients who returned to baseline or who stayed below baseline. Furthermore, the most frail patients had a higher DBP between 50 and 60 seconds after standing compared to the other patients. No differences between blood pressure patterns were found in surgical outcomes.

Principal component analysis

As the separation between both PCA groups is most visible at timepoints between 50 and 240 seconds after standing, it is clear this part of data the blood pressure response played a role in the division. For future research it could be interesting to see what the result of the PCA division would be if only 60 seconds after standing are used. PCA was not used before to make a group division based on blood pressure curves after standing. However, functional PCA was used on the tissue saturation index data after standing for dimensionality reduction[76]. They used the principal components scores for regression analysis and not for group division [76]. This method of using the PCA scores for regression analysis could also be used on our data in future research.

The pattern found in the frailty measures between the groups suggests that a blood pressure recovery above baseline is an indicator of frailty instead of an incomplete recovery. A blood pressure recovery above baseline is an abnormal reaction of the blood pressure regulation system. Therefore, a recovery pattern could be an indicator of frailty. Furthermore, the fact that the Finapres measurement does not work with a specific patient may also be an indicator of frailty. A reason why the Finapres does not work with a patients is inadequate blood flow to the fingers, for example due to cardiovascular diseases, on its turn related to frailty [79, 80].

Despite the contrast in the frailty index between the groups, no differences were found in surgery outcomes. However, another study found that patients with pre-operative OH stayed longer in hospital compared to patients without OH [81]. Furthermore, it was found that patients with OH had a higher incidence of postoperative nausea and vomiting compared to patients without OH [82]. This suggest that the blood pressure curves could hold information about surgery outcomes. One reason for our lack of differences in the surgery outcome was the low incidence of complications and delirium, hence more data on operated patients is needed. Furthermore, the surgeries patients underwent varied, therefore it is difficult to compare outcomes. Additionally, it is important to consider that there were also other reasons than frailty why a patient did not underwent surgery. Some patients did not want surgery based on their own considerations, while for other patients surgery was technically impossible. But the incidence of these reasons were similar between the groups, therefore the influence on the results should be minimal.

Blood pressure variables

When comparing blood pressure recovery values between the frailty groups it was found that patients who were most frail recovered further above baseline. However, only two of these recovery values were significantly different. Nonetheless, this suggests that a blood pressure above baseline may be an indicator of frailty. In the same way, the PCA group with blood pressure above baseline tended to be more frail. Because the findings of both our analyses are coherent, orthostatic hypertension may be explored in further research in addition to OH.

Orthostatic hypertension

Both our analyses indicate that frailty may be linked to a higher blood pressure after standing. This suggest that orthostatic hypertension instead of OH could be of interest when examining frailty and resilience. Another study also found a smaller initial blood pressure drop and a recovery above sitting baseline after standing in frail patients compared to non-frail patients [83]. However, there are multiple studies where blood pressure drop and incomplete recovery after standing were associated with frailty and mortality [9, 84, 85]. Research on orthostatic hypertension is less coherent than OH research, because not always the same definition was used [86]. The definitions range from any increase in blood pressure, to a DBP increase of 90 mmHg after standing [86]. Nonetheless, both OH and orthostatic hypertension are signs of abnormal autonomic control [86]. Therefore, both blood pressure responses after standing could tell us more about a patient's frailty and resilience.

Frailty versus resilience measurements

The aim of the study was to investigate blood pressure as measure of resilience. However, mostly the relationship with measures of frailty is explored. Since resilience is the ability to recovery from a perturbation, the surgery outcomes could be seen as a measure for resilience. However, no differences were found between the surgery outcomes. Since, this study lacks a follow up on the functional improvement or decline of patients, there were no other measures of resilience. The frailty measures examine more the static clinical condition of a patient[57]. Even though, frailty and resilience are negatively linked, the difference is important to consider.

Continuous versus cuff blood pressure

We used the Finapres finger blood pressure (fiAP). The measured blood pressures pressure values may differ from the oscillometric cuff measurements that are often done in the clinic. An example of the difference between both blood pressure measurements is shown in the OH classification. The difficulty with the cuff measurement is the timing of the measurement. The timing of the measurement is important because the blood pressure changes quickly after standing. For example, if a measurement is later than planed the blood pressure could already have changed, and OH could be missed. The time the cuff needs to find a blood pressure differs per patient, while often a standard measurement protocol is used. Furthermore the cuff measurement can give errors, which means the measurement needs to be re done and the timing of the measurement is incorrect. On the other hand, the timing with the Finapres measurement can be exact but the values are different from brachial artery blood pressure [87]. The fiAP is lower in older people than the brachial artery pressure because of a pressure gradient caused by flow in the restrictive vascular tree [88]. The difference between both methods is important to know to be able to interpret the results correctly.

Strengths and limitations

This study had several strengths. The most important is that continuous blood pressure as well as oscillometric blood pressure was measured. Because of the continuous blood pressure there is more information and data that can be used. Also by using the blood pressure cuff simultaneously with the Finapres the patients for whom the Finapres measurement did not work were included. Another strength of this study is that data collection was seen as a standard care procedure, enabling us to collect data of all preoperative geriatric outpatients. Additionally, this gave us a large sample size (N=140) and minimized selection bias.

Besides these strengths there were several limitations. First of all, there was no follow up with the patient after surgery. The patients were only followed through their hospital files. Therefore, we miss information about the functional decline or progress of a patient after surgery. In future research it could be useful to add a follow up with a TOPICS questionnaire and repeat the GWA, tcst and the supine to stand test. Secondly, performing a supine to stand test is difficult for some geriatric patients. Getting up with only one hand, because the other hand was in a sling for the Finapres measurement, was difficult for some patients even with help from the researcher. Therefore, the speed at which patients stood up varied. This varying speed could have influenced the blood pressure responses. Standing up more slowly, will likely lead to a lower blood pressure drop. Thirdly, only half of the patients was operated (71 of 141). Also, it is difficult to draw conclusions regarding complications if only 13 of the 71 operated patients had a complication. Fourthly, the kind of surgeries that patients underwent varied from an open aneurysm repairs to a cochlear implantation. Because of this variation it is difficult to compare surgery outcomes and complications. For future research with a larger dataset it could be possibility to separate the data per type of surgery.

Conclusion

Patients were the Finapres continuous blood pressure measurement did not worked were more frail compared to patients with a Finapres measurement. Furthermore, patients with a higher blood pressure after standing appeared to be more fail, than patients with other blood pressure patterns. Furthermore, blood pressure in the most frail patients seemed to recover above baseline. However, there was a great variation in the data. So further research is needed to see if orthostatic hypertension could be a marker for frailty. Furthermore, the blood pressure response after standing was not predictive of surgery outcomes. Further research, with more patients and a follow up, is needed before the blood pressure response after standing can be used as a screening tool for complications after surgery.

3 | General conclusion

This research focused on blood pressure regulation after standing up. In the first part it was explored if NIRS signals could help discriminate between OH patients with and without symptoms, for example by quantifying their cerebral autoregulation. In the second part the relation of resilience and frailty with the blood pressure response after standing up was explored.

Cerebral autoregulation

It was hypothesized that cerebral autoregulation could explain the difference between patients with and without symptoms after standing up. However, we found no differences in cerebral autoregulation with TFA were oxyHb was used as input and deoxyHb as output. As was found before, blood pressure drops after standing did not explain symptoms after standing. Nonetheless, oxyHb tended to drop lower in patients with OH and symptoms compared to the other groups. Even though this difference was not significant, it suggests that oxyHb holds information about the symptoms a patient can experience. In future research the relation of oxyHb with orthostatic symptoms can be studied by measuring patients with NIRS in their daily life. This to get a full scope of their experienced symptoms.

Resilience and frailty

We hypothesized that an inadequate blood pressure recovery after standing up would mean that a patient was more frail and less resilient. However it was found that blood pressure recovery above baseline may be an indicator for frailty. This could mean that in future it is important to look for orthostatic hypertension as well as OH when assessing a patients resilience of frailty. No link between blood pressure recovery after standing and surgery outcomes was found. A follow up where the functioning of a patient after surgery is evaluated is needed before blood pressure recovery after standing up can be used as a screenings tool for complications after surgery.

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A | Transfer function analysis two groups

OH vs no OH

In Tables A.1 to A.3 the TFA results of OH and no OH patients are shown. No clear differences between patients with and without OH can be seen.

Table A.1: OH vs no OH, coherence of rest data in very low frequency (VLF) and low frequency (LF) range

	no OH (N=25)	**OH (N=12)**	**Overall (N=37)**	**p-value**
Coherence rest VLF				
Mean (SD)	0.295 (0.166)	0.343 (0.209)	0.310 (0.178)	0.551[a]
Missing	5 (20.0%)	3 (25.0%)	8 (21.6%)	
Coherence rest LF				
Mean (SD)	0.479 (0.235)	0.569 (0.215)	0.507 (0.229)	0.3265[a]
Missing	5 (20.0%)	3 (25.0%)	8 (21.6%)	

[a] t-test

Table A.2: OH vs no OH, Phase of rest data in very low frequency (VLF) and low frequency (LF) range

	no OH (N=25)	**OH (N=12)**	**Overall (N=37)**	**p-value**
Phase rest VLF				
Median (IQR)	25.5 (34.2)	6.53 (17.6)	17.5 (29.2)	0.1[a]
Missing	5 (20.0%)	2 (16.7%)	7 (18.9%)	
Phase rest LF				
Median (IQR)	10.9 (29.8)	4.25 (7.00)	5.73 (17.5)	0.049[a]
Missing	5 (20.0%)	2 (16.7%)	7 (18.9%)	

[a] Wilcox test

Table A.3: OH vs no OH, Phase of rest data in very low frequency (VLF) and low frequency (LF)range

	no OH (N=25)	OH (N=12)	Overall (N=37)	p-value
Gain rest VLF				
Mean (SD)	0.213 (0.108)	0.265 (0.182)	0.229 (0.134)	0.448 [a]
Missing	5 (20.0%)	3 (25.0%)	8 (21.6%)	
Gain rest LF				
Mean (SD)	0.238 (0.0909)	0.319 (0.155)	0.263 (0.118)	0.17 [a]
Missing	5 (20.0%)	3 (25.0%)	8 (21.6%)	

[a] t-test

symptoms vs no symptoms

In Tables A.4 to A.6 the TFA results of patients with and without symptoms are shown.

Table A.4: symptoms vs no symptoms, coherence of rest data in very low frequency (VLF) and low frequency (LF) range

	no symptoms (N=18)	symptoms (N=19)	Overall (N=37)	p-value
Coherence rest VLF				
Mean (SD)	0.302 (0.158)	0.317 (0.200)	0.310 (0.178)	0.819[a]
Missing	4 (22.2%)	4 (21.1%)	8 (21.6%)	
Coherence rest LF				
Median (IQR)	0.501 (0.260)	0.398 (0.448)	0.479 (0.409)	0.32[b]
Missing	4 (22.2%)	4 (21.1%)	8 (21.6%)	

[a] t-test
[b] wilcox test

Table A.5: symptoms vs no symptoms, Phase of rest data in very low frequency (VLF) and low frequency (LF) range

	no symptoms (N=18)	symptoms (N=19)	Overall (N=37)	p-value
Phase rest VLF				
Median (IQR)	19.6 (30.2)	17.5 (31.0)	17.5 (29.2)	0.5[a]
Missing	4 (22.2%)	3 (15.8%)	7 (18.9%)	
Phase rest LF				
Median (IQR)	7.66 (25.2)	4.65 (11.0)	5.73 (17.5)	0.5[a]
Missing	4 (22.2%)	3 (15.8%)	7 (18.9%)	

[a] wilcox test

Table A.6: symptoms vs no symptoms, Gain of rest data in very low frequency (VLF) and low frequency (LF) range

	no symptoms (N=18)	**symptoms (N=19)**	**Overall (N=37)**	**p-value**
Gain rest VLF				
Mean (SD)	0.205 (0.0883)	0.252 (0.166)	0.229 (0.134)	0.148[a]
Missing	4 (22.2%)	4 (21.1%)	8 (21.6%)	
Gain rest LF				
Mean (SD)	0.257 (0.0920)	0.269 (0.141)	0.263 (0.118)	0.782[a]
Missing	4 (22.2%)	4 (21.1%)	8 (21.6%)	

[a] t-test

B | Principal component analysis results

Principal component division

For the division of the patients with continuous blood pressure measurement into two groups prinicpal component analysis was used for dimensionality reduction. The first two principal components explained 82.8% and 6.4% of the variance in the data respectively. The first prinicpal component was mostly dependent on the measurement after 30 seconds of standing. In Figure B.1 the data is plotted in the prinicpal component space. This Figure shows that the division that the kmeans clustering method made, is mostly dependent on the first prinicpal component. The position on the x axis decides which group a patients gets assigned instead of the position on the y axis.

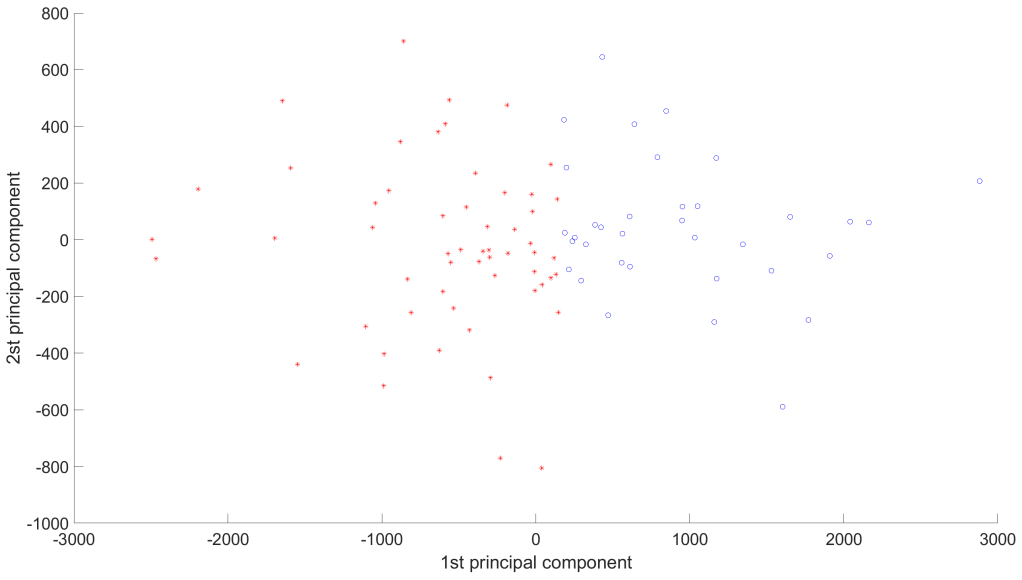

Figure B.1: Data from the systolic blood pressure curves in percentage of baseline plotted on their first and second principal component space. Red dots show the first PCA group, the blue dots show the second PCA group.

C | Blood pressure data divided into tree groups

Recovery value division

The division based on there recovery value between 55 and 60 seconds can be seen in Figure C.1. Group 1 is the group that recovered above baseline, group 2 is at baseline and group 3 is not yet recovered to baseline. Some general characteristics of these patient groups can be seen in Table C.1. This table shows that there is a significant difference between the groups for the age delirium history and supine cuff SBP. However, the age and supine cuff SBP were not significantly different between specific groups during post hoc testing. It should be noted that the groups are not evenly distributed. The baseline group is small compared to the other two groups.

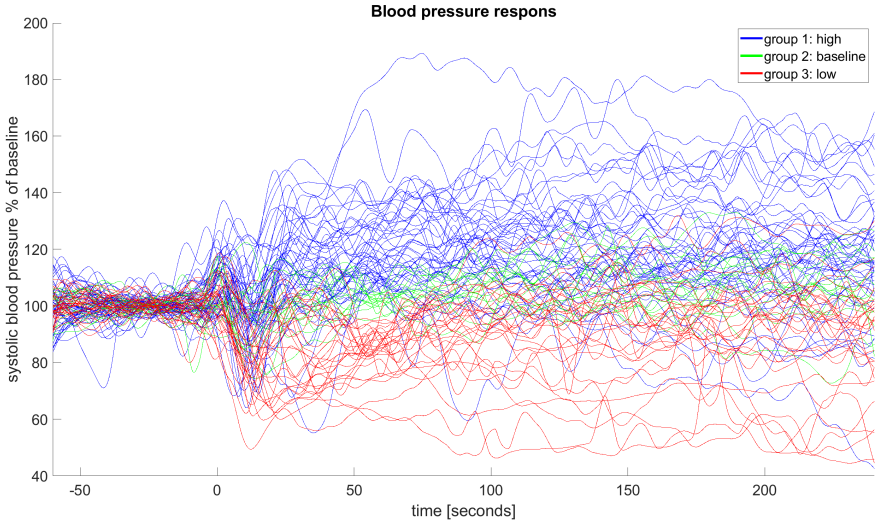

Figure C.1: Division of patients based on the recovery value between 55 and 60 seconds.

Table C.2 shows the frailty variables for the groups. Here the CGA-FI, and the gait speed are significantly different between groups. The CGA-FI is significantly different between group 3 and the measurement failed group. The gait speed is significantly different between the measurement failed group and group 1 and group. Group 3 is also significantly different from the measurement not done because of a logistic reason group. The Finapres measurement failed group is the most frail group. Additionally, it looks as if the group above baseline is more frail than the baseline and below baseline group. However, this was not significantly different.

Table C.1: General characteristics, patients with blood pressure data divided into three groups based on recovery value between 55 and 60 seconds

	group 1: High (N=49)	group 2: Baseline (N=14)	group 3: Low (N=28)	fp measurment failed (N=25)	no fp measured logistic reason (N=24)	Overall (N=140)	
Sex							0.414[a]
Male	33 (67.3%)	8 (57.1%)	19 (67.9%)	12 (48.0%)	17 (70.8%)	89 (63.6%)	
Female	16 (32.7%)	6 (42.9%)	9 (32.1%)	13 (52.0%)	7 (29.2%)	51 (36.4%)	
Age							
Mean (SD)	77.2 (6.22)	74.8 (5.65)	75.8 (5.27)	80.4 (7.38)	79.8 (6.52)	77.7 (6.47)	0.0136[b]
MoCA score							
Median (IQR)	25.0 (3.75)	24.0 (3.00)	26.0 (3.50)	23.0 (5.50)	23.0 (4.00)	25.0 (4.75)	0.468[c]
Missing	2 (3.6%)	1 (5.9%)	2 (11.1%)	2 (8.0%)	3 (12.5%)	10 (7.1%)	
delirium history							0.025[a*]
0	46 (93.9%)	12 (85.7%)	21 (75.0%)	16 (64.0%)	18 (75.0%)	113 (80.7%)	
1	3 (6.1%)	2 (14.3%)	7 (25.0%)	9 (36.0%)	5 (20.8%)	26 (18.6%)	
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.2%)	1 (0.7%)	
number of medications							
Median (IQR)	8.00 (5.00)	7.00 (3.50)	10.0 (8.00)	9.00 (6.00)	6.00 (4.00)	8.00 (6.00)	0.292[c]
Supine Cuff SBP							
Mean (SD)	146 (21.5)	144 (21.0)	159 (24.0)	148 (26.1)	150 (23.7)	149 (23.5)	0.0136[b*]
Supine Cuff DBP							
Median (IQR)	75.0 (21.0)	79.0 (15.0)	81.0 (16.3)	77.0 (20.0)	80.0 (11.8)	78.5 (18.0)	0.468[c]
anti-hypertensive drugs							0.211[a]
0	12 (24.5%)	3 (21.4%)	1 (3.6%)	5 (20.0%)	6 (25.0%)	27 (19.3%)	
1	37 (75.5%)	11 (78.6%)	27 (96.4%)	20 (80.0%)	18 (75.0%)	113 (80.7%)	
TOPICS morbidity score							
Median (IQR)	3.00 (1.00)	3.00 (2.00)	2.50 (2.25)	3.00 (3.00)	3.00 (1.25)	3.00 (2.00)	0.215[c]
Missing	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	

fp: Finapres, MoCA: Montreal cognitive assessment, SBP: systolic blood pressure, DBP: diastolic blood pressure
[a] Chi-square test, [b] ANOVA test, [c] Kruskal Wallis test, * significant p<0.05

Table C.2: Frailty characteristics, patients with blood pressure data divided into three groups based on recovery value between 55 and 60 seconds

	group 1: High (N=49)	group 2: Baseline (N=14)	group 3: Low (N=28)	fp measurment failed (N=25)	no fp measured logistic reason (N=24)	Overall (N=140)	
CFS							0.126[a]
Median (IQR)	4.00 (2.00)	3.00 (1.75)	4.00 (1.25)	5.00 (1.00)	4.50 (1.25)	4.00 (2.00)	
CGA-FI							
Median (IQR)	0.139 (0.134)	0.102 (0.0600)	0.102 (0.0778)	0.198 (0.188)	0.128 (0.134)	0.132 (0.140)	0.013[b*]
GWA							
Median (IQR)	1630 (1240)	2230 (1700)	2160 (2230)	1310 (1200)	1810 (1580)	1680 (1770)	0.230[b]
Missing	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	
Grip strength							
Median (IQR)	60.0 (24.0)	67.5 (32.8)	65.0 (29.0)	55.0 (24.0)	60.0 (31.3)	60.0 (27.3)	0.485[b]
fatigue resistance							
Median (IQR)	36.0 (28.9)	66.0 (62.2)	47.7 (44.4)	40.0 (35.8)	43.0 (22.8)	40.0 (40.0)	0.518[b]
Missing	0 (0%)	1 (7.1%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	
tcst							
Median (IQR)	13.8 (4.25)	13.6 (4.29)	12.8 (6.47)	14.6 (8.52)	16.1 (6.47)	13.7 (5.96)	0.461[b]
Missing	0 (0%)	1 (7.1%)	2 (7.1%)	5 (20.0%)	3 (12.5%)	11 (7.9%)	
gait speed							
Median (IQR)	1.00 (0.310)	1.00 (0.228)	1.10 (0.200)	0.880 (0.300)	0.900 (0.320)	1.00 (0.340)	<0.01[b*]
Missing	10 (20.4%)	4 (28.6%)	6 (21.4%)	4 (16.0%)	3 (12.5%)	27 (19.3%)	

fp: Finapres, CFS: Clinical frailty scale, CGA-FI: Comprehensive geriatric assessment frailty index, GWA: grip work assessment, tcst: ti
[a] Chi-square test, [b] Kruskal Wallis test, [c] ANOVA test, * significant p<0.05

PCA with three groups

The division in three groups based on the PCA analysis of the entire curve can be seen in Figure C.2. Group 1 is the baseline group, group 2 does not recover to baseline and group 3 recovers above baseline.

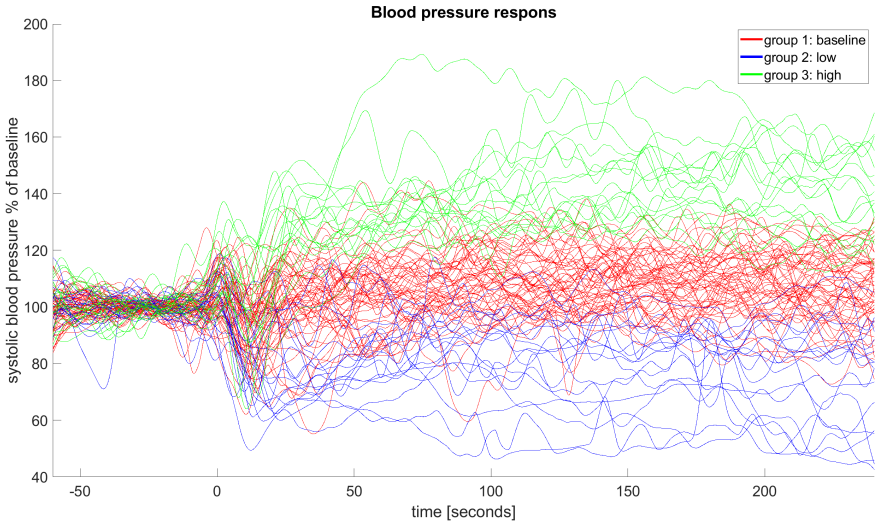

Figure C.2: Division of patients with the principal component analysis (PCA) of the entire data-set, and k means clustering.

In Table C.3 the general characteristics of the groups are shown. The groups are not evenly distributed, the baseline group is bigger than the high and low group. Furthermore, the age, delirium history and supine Cuff SBP are significantly different between the groups. However the age was not significantly different between the groups during post hoc testing. The SBP supine was significantly different between group 2 and group 3. Thus there was a significant difference between the low and the high group. The group with an inadequate blood pressure recovery had a higher supine blood pressure compared to patients who recovered above baseline.

Frailty and resilience characteristics of the groups can be found in Table C.4. The CGA-FI and gait speed are significantly different between the groups. For both these variables was the Finapres measurement failed group significantly different with group 1 and 2. In the CGA-FI it looks as if the recovery above baseline group is more frail than the other two PCA groups. However this was not significantly different. In the GWA it appears that the baseline group is the least resilient and the group that does not recovery to baseline is most resilient. These findings are not in line with each other.

Table C.3: General characteristics of three groups based on PCA of the entire measurement

	group 1: Baseline (N=56)	**group 2: Low** (N=17)	**group 3: High** (N=18)	**fp measurment failed** (N=25)	**no fp measured logistic reason** (N=24)	**Overall** (N=140)	
Sex							0.493[a]
Male	37 (66.1%)	11 (64.7%)	12 (66.7%)	12 (48.0%)	17 (70.8%)	89 (63.6%)	
Female	19 (33.9%)	6 (35.3%)	6 (33.3%)	13 (52.0%)	7 (29.2%)	51 (36.4%)	
Age							
Mean (SD)	76.4 (6.29)	75.7 (4.33)	77.1 (5.99)	80.4 (7.38)	79.8 (6.52)	77.7 (6.47)	0.028[b]
MoCA score							
Median (IQR)	25.0 (4.75)	25.5 (2.25)	25.0 (2.25)	23.0 (5.50)	23.0 (4.00)	25.0 (4.75)	0.52[c]
Missing	2 (3.6%)	1 (5.9%)	2 (11.1%)	2 (8.0%)	3 (12.5%)	10 (7.1%)	
delirium history							0.037[a]
0	48 (85.7%)	13 (76.5%)	18 (100%)	16 (64.0%)	18 (75.0%)	113 (80.7%)	
1	8 (14.3%)	4 (23.5%)	0 (0%)	9 (36.0%)	5 (20.8%)	26 (18.6%)	
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (4.2%)	1 (0.7%)	
number of medications							
Median (IQR)	8.00 (5.25)	10.0 (8.00)	7.50 (6.75)	9.00 (6.00)	6.00 (4.00)	8.00 (6.00)	0.234[c]
Supine Cuff SBP							
Mean (SD)	148 (21.2)	165 (24.2)	140 (20.8)	148 (26.1)	150 (23.7)	149 (23.5)	0.025[b*]
Supine Cuff DBP							
Median (IQR)	77.0 (18.0)	85.0 (9.00)	69.0 (17.0)	77.0 (20.0)	80.0 (11.8)	78.5 (18.0)	0.094[c]
anti-hypertensive drugs							0.674[a]
0	9 (16.1%)	2 (11.8%)	5 (27.8%)	5 (20.0%)	6 (25.0%)	27 (19.3%)	
1	47 (83.9%)	15 (88.2%)	13 (72.2%)	20 (80.0%)	18 (75.0%)	113 (80.7%)	
Topics morbidity score							
Median (IQR)	3.00 (1.00)	3.00 (3.00)	3.00 (1.75)	3.00 (3.00)	3.00 (1.25)	3.00 (2.00)	0.234[c]
Missing	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	

fp: Finapres, MoCA: Montreal cognitive assessment, SBP: systolic blood pressure, DBP: diastolic blood pressure
[a] Chi-square test, [b] ANOVA test, [c] Kruskal Wallis test, * significant p<0.05

Table C.4: Frailty characteristics of three groups based on PCA of the entire measurement

	group 1: Baseline (N=56)	**group 2: Low** (N=17)	**group 3: High** (N=18)	**fp measurment failed** (N=25)	**no fp measured logistic reason** (N=24)	**Overall** (N=140)	
CFS							0.232[a]
Median (IQR)	4.00 (1.00)	4.00 (1.00)	4.00 (2.00)	5.00 (1.00)	4.50 (1.25)	4.00 (2.00)	
CGA-FI							
Median (IQR)	0.104 (0.112)	0.115 (0.0760)	0.150 (0.103)	0.198 (0.188)	0.128 (0.134)	0.132 (0.140)	0.011[b*]
GWA							
Median (IQR)	1640 (1340)	2420 (2520)	1860 (2480)	1310 (1200)	1810 (1580)	1680 (1770)	0.528[b]
Missing	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	
Grip strength							
Median (IQR)	60.0 (27.0)	60.0 (26.0)	62.5 (30.8)	55.0 (24.0)	60.0 (31.3)	60.0 (27.3)	0.731[b]
fatigue resistance							
Median (IQR)	36.0 (42.4)	45.0 (49.7)	42.9 (45.0)	40.0 (35.8)	43.0 (22.8)	40.0 (40.0)	0.890[b]
Missing	1 (1.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.7%)	
tcst							
Median (IQR)	13.1 (4.79)	13.0 (7.87)	15.0 (4.97)	14.6 (8.52)	16.1 (6.47)	13.7 (5.96)	0.165[b]
Missing	2 (3.6%)	1 (5.9%)	0 (0%)	5 (20.0%)	3 (12.5%)	11 (7.9%)	
gait speed							
Median (IQR)	1.00 (0.300)	1.10 (0.200)	1.00 (0.400)	0.880 (0.300)	0.900 (0.320)	1.00 (0.340)	0.010[b*]
Missing	11 (19.6%)	4 (23.5%)	5 (27.8%)	4 (16.0%)	3 (12.5%)	27 (19.3%)	

fp: Finapres, CFS: Clinical frailty scale, CGA-FI: Comprehensive geriatric assessment frailty index, GWA: grip work assessment, tcst: ti
[a] Chi-square test, [b] ANOVA test, [c] Kruskal Wallis test, * significant p<0.05