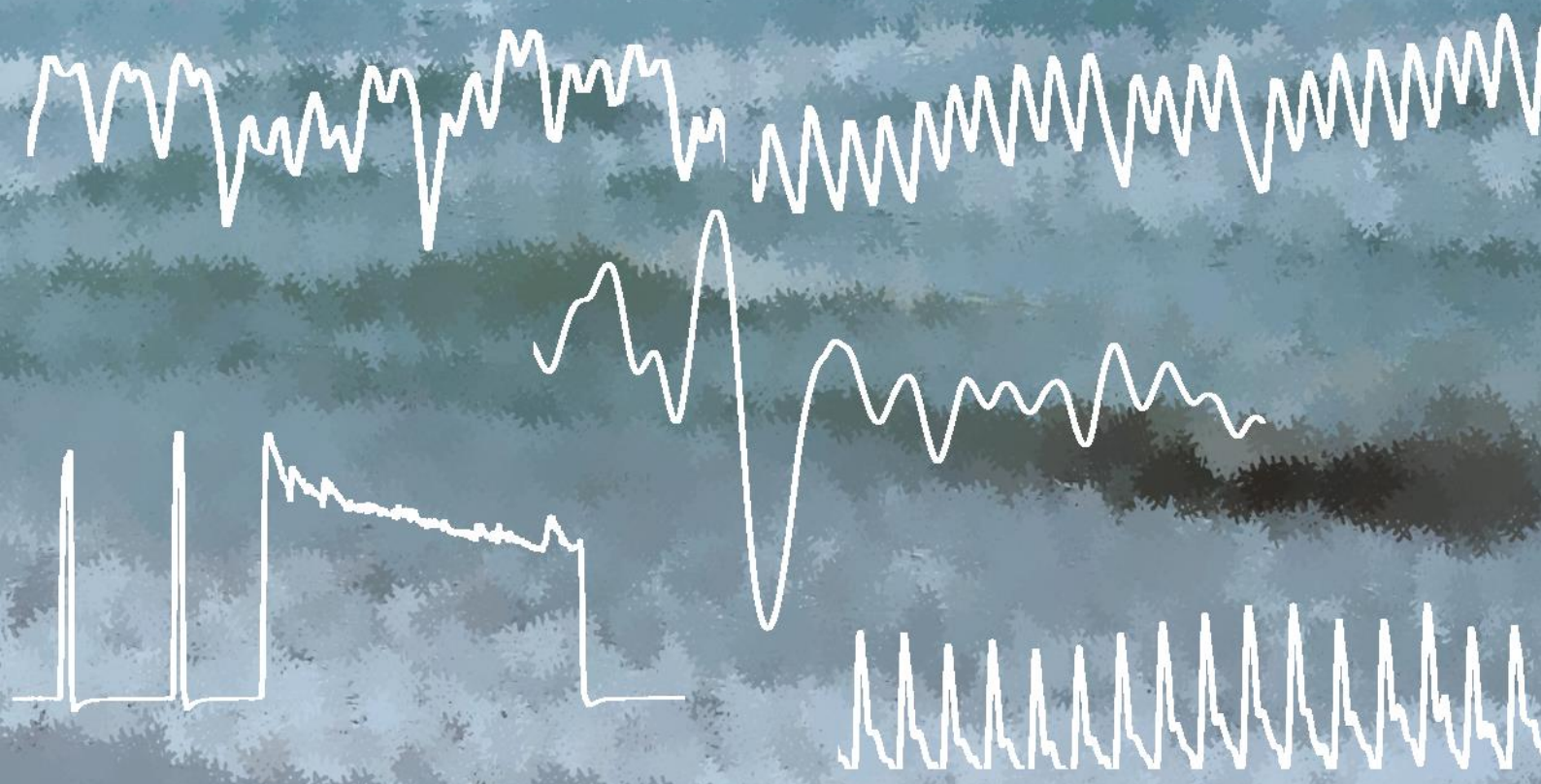
Physical resilience indicators derived from haemodynamic signals in older adults: relation to cognitive status, cognitive decline and surgical outcome

Marjolein Klop
Master's thesis Technical Medicine

Date of graduation: 10 September 2020



Graduation committee:

Chairman:	prof. dr. R.J.A. van Wezel
Clinical supervisors:	dr. J.A.H.R. Claassen
	M.L. Sanders, MSc
Technical supervisor:	prof. dr. R.J.A. van Wezel
Process supervisor:	dr. M. Groenier
External member:	dr. E. Groot Jebbink

UNIVERSITY OF TWENTE.

Radboudumc

Table of contents

Preface

This thesis is about the application of quantitative physical resilience in geriatric medicine. To me, the sea, as shown on the front page, represents a perfectly resilient system, exhibiting cyclic behaviour returning to low and high tide every 12 hours. Even in extreme situations, the sea returns to its original state again, and it can function as a buffer for other systems. On the other hand, an object floating on the waves of the sea can be pushed underwater by a wave. The larger the wave, or the perturbation, the deeper the objects goes underwater, and the longer it takes to return to the surface. Therefore, natural waves of the sea and natural perturbations might therefore a state of nature. High waves can be a forecast of stormy weather. The signals projected onto the waves of the sea may in the same way forecast or precede transitions in the human body, related to disease. That is what will be explored and evaluated in this thesis.

1. Introduction

1.1 General introduction

The ageing population leads to a higher demand for healthcare [1]. An ageing society is for example accompanied by an increased prevalence of dementia, and an increased pressure on surgical capacity, since more elderly will undergo surgery [2]. This emphasises the need for personalised healthcare and gaining more insight into the physiological processes that change in ageing adults. Frailty has already been a key concept in geriatric medicine. It is defined as an increased vulnerability to adverse outcomes. Frailty is mostly presented as a score dependent on static measures, such as comorbidity, ability to perform (instrumental) activities of daily living and grip strength. Although frailty can predict the risk of events like falls, delirium, or even death, it does not necessarily forecast recovery from a stressor like illness or surgery [3]. Therefore, more research is needed to the question why some older adults recover adequately from a stressor while others do not [4]. In clinical practice, an aiding measure to predict a patient's recovery potential will be helpful, especially before important clinical decision-making. An example is major elective surgery. While one patient undergoing surgery might have an uncomplicated hospital stay accompanied by fast discharge and recovery, the other can suffer from delirium or other complications leading to a decrease in functional and cognitive status. This variety of responses to a stimulus forms the background for the principle of physical resilience. Physical resilience, the capacity to bounce back after a stressor, is illustrated in Figure 1, showing a mountain landscape [5]. This metaphorically represents the complex system of homeostasis in the human body, simplified as a healthy and a diseased state. Two balls are shown, that lie in a valley representing a stable, healthy equilibrium. When these balls are pushed by a perturbation, for instance surgery, the light blue one (Figure 1B) is more likely to cross the hill (a tipping point) to the other valley (the diseased state) than the dark blue one (Figure 1A). Therefore, the dark blue ball is said to represent a resilient patient, and the light blue one a less resilient patient. Moreover, after a small push uphill, the dark blue ball would return to the healthy equilibrium state more quickly than the light blue ball, as the slope is steeper. This reveals an important characteristic of complex systems that are close to a tipping point: critical slowing down. It is that characteristic that is aimed to be captured using quantitative resilience measures.

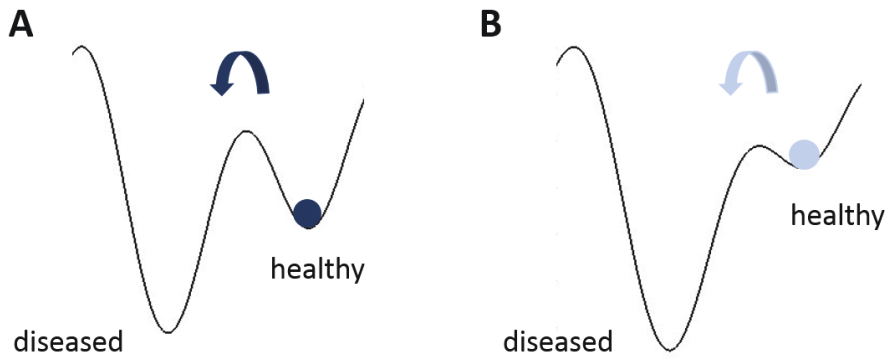


Figure 1: Illustration of the effect of a large perturbation on a ball in a landscape as a metaphor for A) a resilient patient and B) a less resilient patient.

1.2 Outline

This thesis has been split into three parts. The first two describe quantitative resilience measures concerning cognition, which were retrospectively investigated in healthy subjects, older adults with mild

cognitive impairment (MCI) and Alzheimer's Disease (AD) patients. In the last part, the resilience measures were investigated in clinical practice, describing application at the cardiothoracic surgery outpatient clinic. The thesis ends with a general conclusion, connecting the different approaches to and applications of physical resilience in geriatric medicine.

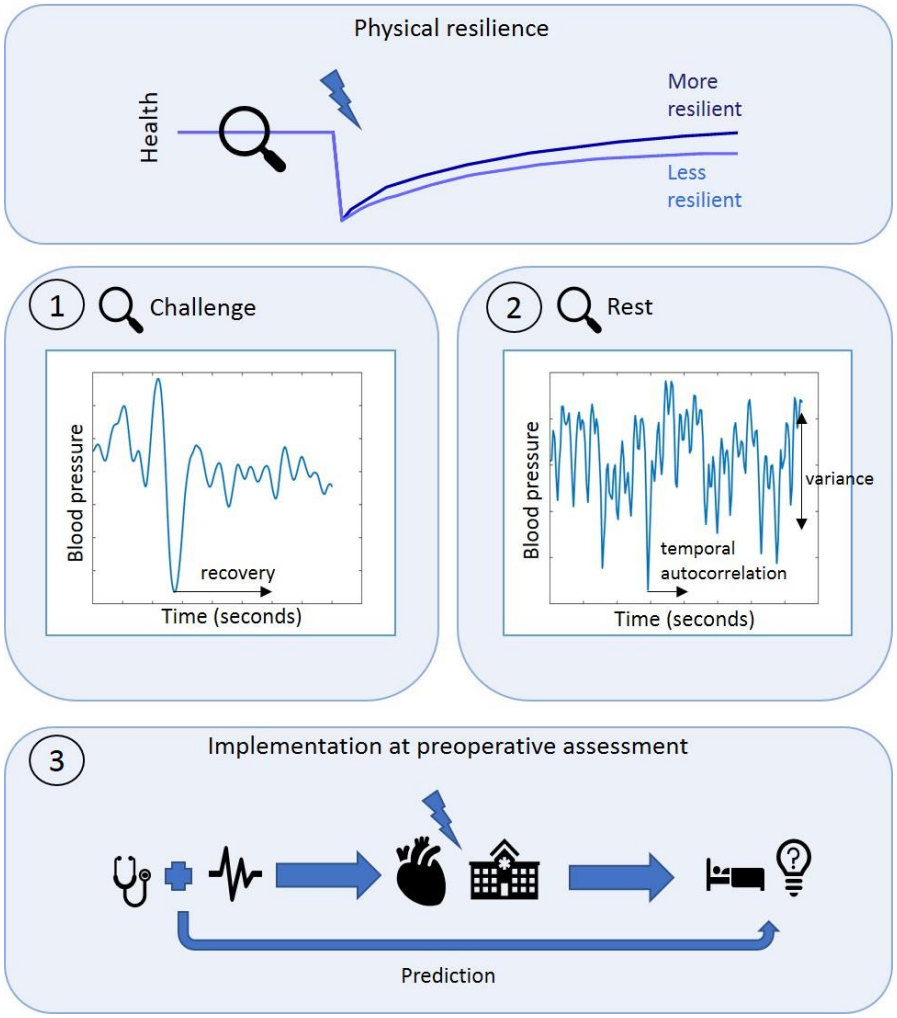


Figure 2: Graphical representation of the topics covered in this thesis.

Part 1: Association between haemodynamic orthostatic recovery and one-year change in cognitive functioning in elderly with MCI

Objective:

- Determining the relation between orthostatic recovery (slowing down of recovery) and cognitive function after one year in elderly with MCI, using blood pressure, cerebral blood flow and cerebral oxygenation measurements.

Part 2: Quantitative resilience indicators (DIORs) in relation to cognitive status

Objectives:

- Investigating the applicability of dynamical indicators of resilience (DIORs) in blood pressure signals.

- Investigating if DIORs in blood pressure signals differed between healthy subjects, older adults with MCI and AD patients.
- Determining the differences in DIORs derived from blood pressure measurements between a resting (sitting) and more activated (standing) equilibrium state, for healthy controls, participants with MCI and AD patients.
- Investigating DIORs as a predictor for cognitive decline in elderly with MCI and AD patients, and determining the overlap with orthostatic recovery as another resilience indicator.

Part 3: Resilience in patients undergoing major thoracic aortic surgery: a pilot study
Objectives:

- Assessing feasibility of implementation of resilience measurements in clinical practice.
- Exploring the relation between resilience measures and clinical outcome after surgery.

1.3 List of abbreviations

AD	Alzheimer's disease
BMI	Body mass index
BP	Blood pressure
CBF	Cerebral blood flow
CBFV	Cerebral blood flow velocity
CMO	Commissie mensgebonden onderzoek
CFS	Clinical frailty scale
CGA	Comprehensive geriatric assessment
CoV	Coefficient of variation
DBP	Diastolic blood pressure
DFV	Diastolic cerebral blood flow velocity
DIORs	Dynamical indicators of resilience
HC	Healthy controls
HHb	Deoxygenated haemoglobin
HR	Heart rate
HRV	Heart rate variability
IBI	Inter-beat interval
ICU	Intensive care unit
IQR	Interquartile range
MCI	Mild cognitive impairment
MMSE	Mini-mental state examination
MoCA	Montreal cognitive assessment
NIRS	Near-infrared spectroscopy
O_2Hb	Oxygenated haemoglobin
SBP	Systolic blood pressure
se	Standard error
SFV	Systolic cerebral blood flow velocity
SD	Standard deviation
TAC	Temporal autocorrelation
TCD	Transcranial Doppler

tHb	Total haemoglobin
TSI	Tissue saturation index
VAR	Variance
VIM	Variance independent of the mean

2. Association between haemodynamic orthostatic recovery and one-year cognitive change in elderly with MCI

Abstract

Background: Mild cognitive impairment (MCI) can be a prodromal stage to Alzheimer's Disease. Therefore, a predictor of cognitive decline is desirable in elderly with MCI. As orthostatic hypotension has already been related to cognitive decline and mortality, orthostatic recovery values of blood pressure (BP), but also cerebral blood flow (CBF) and cerebral oxygenation may have prognostic value.

Objective: To investigate the association between orthostatic haemodynamic recovery and cognitive change in older adults with MCI.

Methods: We performed a retrospective analysis on data of the NeuroExercise trial. Continuous BP, CBF and cerebral oxygenation were measured during a sit-to-stand challenge, and expressed as recovery values after the systolic BP (SBP) nadir caused by standing up, relative to sitting values. A composite cognitive function score was determined at baseline and one-year follow-up, and expressed as a z-score. We investigated the association between the change in cognitive z-score and recovery values of BP, CBF and cerebral oxygenation.

Results: 29 elderly with MCI were included, of whom 14 improved in cognition (change in cognition z-score of 0.214 (±0.167)) and 15 deteriorated (change in cognition z-score of -0.287 (±0.248)). The cognitively improved patients had higher SBP recovery values than the declined patients at approximately 35-45 seconds after the SBP drop caused by standing (p=0.017). CBF and cerebral oxygenation recovery values did not show significant differences between patient groups. Moreover, impaired SBP recovery (≤95% of baseline value) at approximately 35-45 seconds after SBP trough was associated with cognitive decline.

Conclusion: An impaired SBP response after an orthostatic challenge was related to cognitive decline in older adults with MCI. In the future, this might provide an easy prognostic tool to recognise elderly with MCI who are at risk of cognitive decline.

2.1 Introduction

Mild cognitive impairment (MCI) is defined as cognitive decline not interfering with activities of daily life. It can be a preliminary stage to dementia due to Alzheimer's Disease (AD), with progression rates of MCI (specifically amnestic MCI; MCI type that is characterised by memory loss) to AD between 10 and 41% per year [6-9]. Although the reported progression rates differ due to heterogeneity of the MCI population, elderly with MCI do have a larger risk of developing AD than the general older population. On the other hand, heterogeneity means that many older adults with MCI do not show cognitive decline or even show cognitive improvement over time. Therefore, it is important to identify elderly with MCI who are at risk of cognitive decline, or conversion to clinical AD, to gain more insight into disease progression, and possible treatment targets.

Static haemodynamic parameters, such as the value of blood pressure (BP), cerebral blood flow (CBF) and cerebral oxygenation have been studied extensively in relation to cognitive decline, with mixed results. Hypertension in mid-life is associated with cardiovascular risk factors and AD, but in late life it might not be related to AD [10]. Simultaneously, lower CBF has been associated with cognitive decline, although CBF also decreases in healthy ageing [11, 12]. Moreover, lower frontal lobe oxygenation values were found in AD patients and elderly with MCI compared to cognitively healthy older adults, in rest as well as during cognitive tasks [13]. However, these observations have not led to a short-term predictor of cognitive decline in elderly.

Another approach might be to assess physical resilience as a predictive marker for disease progression. Slowing down of recovery after a stressor may be related to decreased resilience [14, 15]. An example of a stressor is an orthostatic challenge. Standing up from a sitting or supine position leads to gravity-induced venous pooling in the lower abdomen and legs. In response to that, BP decreases, sensed by baroreceptors in the aortic arch and carotid sinus. These baroreceptors induce vagal and sympathetic activation, leading to an increased heart rate and vasoconstriction. This causes higher peripheral resistance, counteracting the BP decrease [16-18]. In the brain, a BP decline leads to additional vasodilation due to cerebral autoregulation. In this way, adequate CBF supplying oxygen is maintained [19]. Therefore, with intact autoregulatory mechanisms, CBF recovers faster than BP, and the oxygen supply follows the same course [20, 21]. The initial systolic CBF velocity (SFV) will then remain stable [22]. BP recovery is impaired in 25 to 40% of people aged >70 years, leading to orthostatic hypotension [23]. Orthostatic hypotension is classically defined as sustained systolic BP (SBP) drop ≥20 mmHg or a diastolic BP (DBP) decline ≥10 mmHg upon standing [17, 24]. It is accompanied by transient CBF and cerebral oxygenation reductions, leading to orthostatic hypotension symptoms, like syncope [25].

Different studies have already found orthostatic hypotension to be a negative health predictor in older adults. Relations have been found between orthostatic hypotension and cognitive decline, in patients with AD and in people that were cognitively healthy at the time of orthostatic hypotension measurement [26-29]. However, previous studies mainly focused on BP falls as large as in orthostatic hypotension. Only little research has been done to recovery from an orthostatic challenge, not necessarily accompanied by orthostatic hypotension. An association has been revealed between impaired BP recovery and mortality in falls clinic patients [30]. In relation to cognition, previous study results are conflicting: one study showed that diminished orthostatic recovery was associated with cognitive decline in AD patients [31], while another stated that a relation was not evident in a broad sample of community-dwelling older adults [32]. Therefore, researching the relation between orthostatic recovery and cognition in older adults with MCI could reveal if the association found in AD patients can be generalised. With respect to the CBF and oxygenation response after standing, studies that compare the orthostatic cerebral oxygenation response between older and younger patients have been performed with mixed results. A lower concentration of oxygenated haemoglobin (O_2Hb) and an increased deoxygenated haemoglobin (HHb) value after standing have been found in older compared to younger patients [33], but the opposite has been reported as well [34]. However, CBF and cerebral oxygenation recovery after an orthostatic challenge have not yet been related to cognitive change directly. Nevertheless, an initial response of the systolic blood flow velocity (SFV) without a clear drop might indicate adequate functioning of the cerebral autoregulation [22].

Our goal was to assess whether recovery of BP, CBF and cerebral oxygenation at different time windows after an orthostatic challenge is associated with cognitive change in older people with MCI. We investigated these haemodynamic responses in relation to the change in cognition after one year, determined at different cognitive domains.

2.2 Methods

2.2.1 Study design and population

This is a retrospective analysis using data from the Dutch study site (Radboud university medical centre, Nijmegen) of the NeuroExercise trial. The NeuroExercise trial investigated the effect of aerobic and non-aerobic exercise on cognition and haemodynamics in elderly with MCI. However, no effect of exercise on cognitive functioning was found [35]. 42 older adults with MCI were included in the Netherlands.

Complete inclusion and exclusion criteria have been described before in the study protocol [36]. In short, participants were diagnosed with amnestic MCI due to AD and at least 50 years old. The medical ethics committee (CMO Arnhem-Nijmegen) approved the study protocol. All participants signed written informed consent, in accordance to the Declaration of Helsinki.

This part of the study aimed to investigate the relation of BP, CBF and cerebral oxygenation recovery after an orthostatic challenge with cognitive decline. Additional exclusion criteria consisted of absence of sit-to-stand manoeuvres, absence of data on cognitive performance at one-year follow-up and inadequacy of sit-to-stand challenges. Inadequate was defined as the absence of troughs in the SBP signal or inability to stand up fluently.

2.2.2 Data collection

The orthostatic challenge was performed as follows. The participant sat in a chair and was asked to stand up. The protocol consisted of 2 minutes of sitting and 1 minute of standing, repeated three times. The third standing period lasted for 5 minutes instead of 1 minute to measure recovery during prolonged standing. During this protocol, different haemodynamic signals were measured. The beat-to-beat arterial BP was measured using volume-clamp photoplethysmography (Finapres Medical Systems, Enschede, The Netherlands) in the digital artery of the middle finger of the non-dominant hand [37, 38]. The arm was resting at heart height, supported by a sling, to prevent hydrostatic changes. The CBF velocity (CBFV) was measured in the middle cerebral artery through the left and right temporal window using transcranial Doppler (TCD; DWL Doppler Box, Compumedics Germany GmbH, Singen, Germany). The CBFV can be seen as a surrogate for the CBF, since the diameter of the middle cerebral artery is assumed to be constant [39]. CBFV values obtained from both sides were averaged unless only one signal was available. Then, the signal on that side was included for analysis. The TCD probes and NIRS electrodes were kept in place by using a headband (Spencer Technologies, Seattle, WA). O_2Hb and HHb were measured using NIRS (Oxymon, Artinis Medical Systems, The Netherlands). Again, measurements from the left and right side were averaged when both available. All measurements were obtained at 200 Hz.

2.2.3 Cognitive functioning score

Cognitive functioning was assessed as the primary outcome at baseline and after one year. This included neuropsychological tests varying over six cognitive domains, including verbal and visual learning, psychomotor and executive function, attention and working memory [40]. All test results were converted into z-scores by subtracting the mean score at baseline and dividing by the standard deviation at baseline, for both the baseline and follow-up value. These obtained z-scores were averaged per domain, after which the domain scores were averaged again to attain one cognitive function score. The difference between this score at follow-up and baseline was calculated, directly indicating cognitive decline or improvement.

2.2.4 Data analysis

Data processing was performed in MATLAB (R2018a, MathWorks Inc., Natick, USA), using custom-written semi-automatic scripts, as described previously [41]. Heart rate, SBP, DBP, SFV and diastolic CBFV (DFV) were obtained over time from the peaks and troughs. Moreover, O_2Hb and HHb concentration over time were obtained. Examples of these signals are shown in Figure 3. All physiological signals were resampled at 10 Hz, and filtered using a 5-second moving average filter [42, 43].

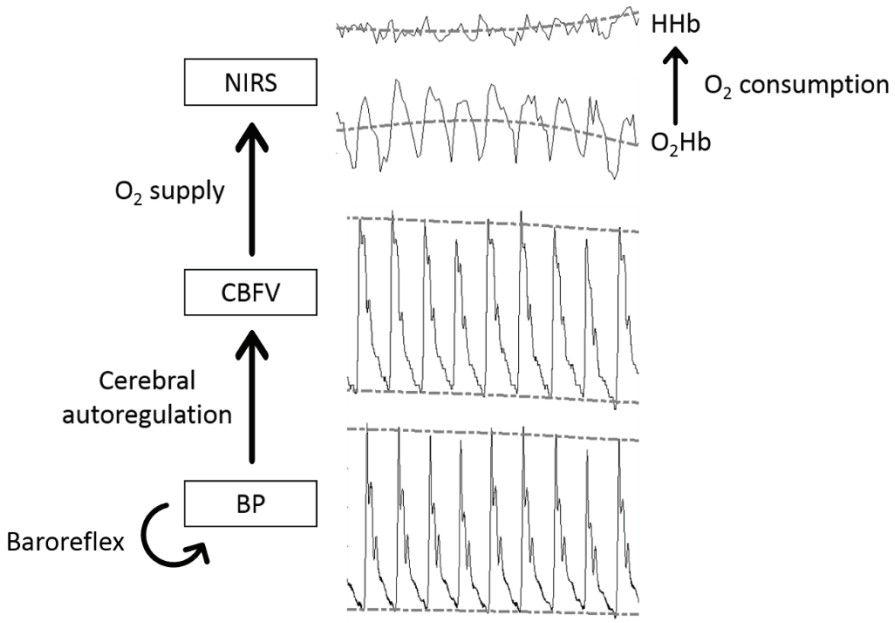


Figure 3: Example of the signals that were obtained from different measurements. Blood pressure (BP) fluctuations are conducted to cerebral blood flow velocity (CBFV) fluctuations by cerebral autoregulation, while oxygen (O_2) supply and consumption cause oxygenated (O_2Hb) and deoxygenated haemoglobin (HHb) fluctuations. BP and CBFV are expressed as both systolic and diastolic values, shown in dashed grey lines, while O_2Hb and HHb are expressed as mean values, also indicated by dashed grey lines. NIRS: near-infrared spectroscopy.

Data were visually inspected per stand. One stand was defined from 60 seconds before the nadir in SBP caused by standing, to 45 seconds after this trough. For BP analysis, a stand was removed when the SBP nadir was absent, or smaller than 10 mmHg [44]. Furthermore, stands were removed when artefacts were present, defined as physiologically implausible values for sitting BP and flat lines for cerebral oxygenation. The remaining stands were averaged per person, leading to one average orthostatic response per person. From this response, baseline and recovery values were extracted. Baseline was defined as the average of 55 to 25 seconds before the SBP nadir, as shown in the example in Figure 4. Recovery values were defined as a percentage relative to baseline, averaged over 10-second time windows. The window between 35 and 45 seconds after SBP nadir approximately corresponds to 50 to 60 seconds after standing, as used previously to describe orthostatic recovery [23, 30]. Earlier windows from 5 seconds before to 35 seconds after SBP nadir were added, for we did not expect recovery rates to be as low as at the falls clinic in earlier research [30]. The same windows were used for CBF and cerebral oxygenation.

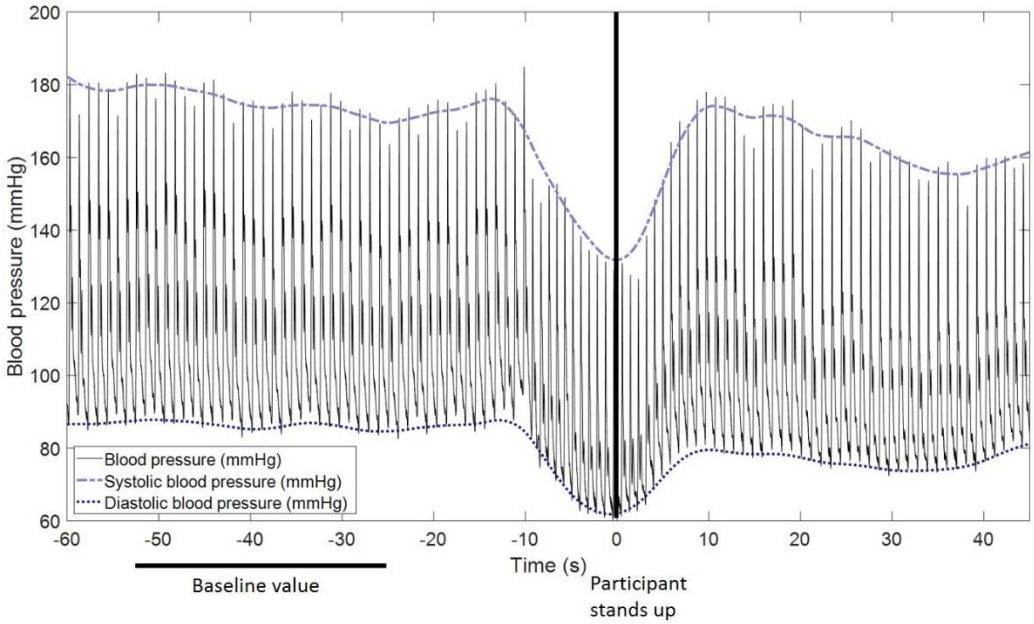


Figure 4: Example of blood pressure data of one stand for one patient. At t=0 seconds the systolic blood pressure nadir was found. Recovery values were determined at moments after this trough. Systolic and diastolic blood pressure (SBP and DBP respectively), filtered with a 5-second moving average filter are shown in a dashed light blue and dotted dark blue line respectively.

2.2.5 Statistical analysis

Recovery values for the physiological signals in all time windows were related to change in cognitive function by using linear regression. Two different models were used: one without adjustments, and another with one adjustment, as the sample size did not allow for more. Covariates of which the adjustment effect was investigated were age, gender, use of antihypertensive drugs, exercise group and the normalised number of training sessions. Subsequently, the study population was divided into a group of patients with an increased cognitive score and a group with a decreased cognitive score after one year, to compare haemodynamic recovery values. Alternatively, the study population was divided into two groups based on BP recovery values at 35-45 seconds after SBP nadir, cut off at recovery to 95% of baseline [30]. Between-group comparisons were made using independent sample t-tests or Mann-Whitney U tests for continuous variables and chi-squared or Fisher's exact tests for categorical variables, as appropriate, using an alpha level of 0.05. Continuous variables are reported as mean (standard deviation) or median (interquartile range) and categorical variables as number (%).

2.3 Results

2.3.1 Patient characteristics

38 patients performed sit-to-stand manoeuvres at baseline. Of those, 29 participants could be considered for further analysis; data from 9 patients were excluded due to absence of sit-to-stand measurements, absence of data on cognitive performance at one-year follow-up, or inadequate sit-to-stand manoeuvres. These exclusions, as well as additional exclusions due to artefacts, are specified in Figure 5. Baseline characteristics are presented in Table 1. None of these were significantly different ($p<0.05$) between patients with an increased and patients with a declined cognition score.

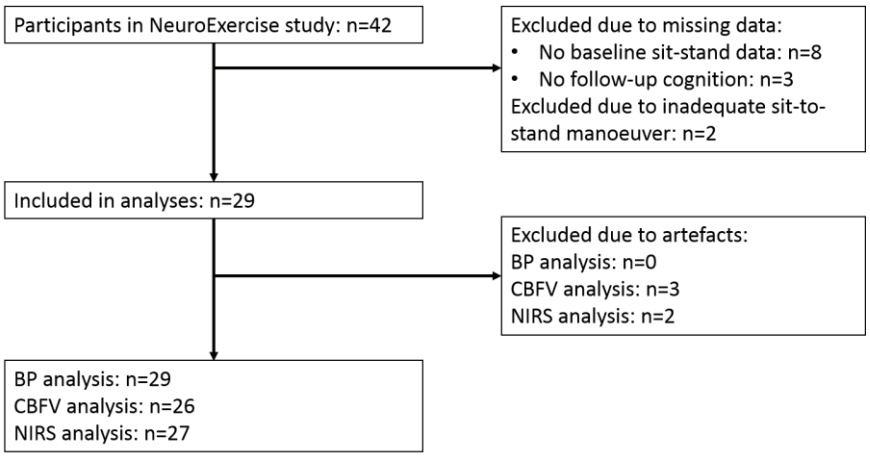


Figure 5: Flowchart describing the inclusion and exclusion of patient data due to unknown cognition progression, unavailability of haemodynamic data or artefacts. BP: blood pressure, CBFV: cerebral blood flow velocity, NIRS: near-infrared spectroscopy.

Table 1: Baseline characteristics of all included patients, the cognitively improved and the cognitively deteriorated group.

	All patients (n=29)	Improved cognition (n=14)	Deteriorated cognition (n=15)	P-value
Male	20 (69%)	10 (71%)	10 (67%)	1.000
Age (years)	68.0 (7.7)	68.8 (7.5)	67.3 (8.1)	0.444
BMI	26.0 (4.1)	27.2 (4.4)	24.9 (3.5)	0.183
Intervention group	22 (76%)	9 (64%)	13 (87%)	0.215
Aerobic exercise	11 (38%)	4 (29%)	7 (47%)	0.450
Non-aerobic exercise	11 (38%)	5 (36%)	6 (40%)	1.000
Number of training sessions	88 (70)	88 (73)	89 (69)	0.878
Cardiovascular disease	8 (28%)	4 (29%)	4 (27%)	1.000
Antihypertensive drug use	12 (41%)	6 (43%)	6 (40%)	1.000
Use beta blockers (metoprolol)	4 (14%)	3 (21%)	1 (7%)	0.329
Statin use	8 (28%)	4 (29%)	4 (27%)	1.000
Antidepressant use	1 (3%)	1 (7%)	0 (0%)	0.482
Systolic blood pressure	144 (24)	143 (14)	145 (31)	0.844
Diastolic blood pressure	85 (12)	84 (11)	85 (14)	0.861
MoCA	23.2 (2.4)	23.4 (2.6)	23.1 (2.3)	1.000
Cognition z-score	0.21 (0.67)	0.16 (0.60)	0.25 (0.75)	0.678

Data are presented as number (percentage) or mean (standard deviation). P-values result from Mann-Whitney U test or Fisher's test. BMI: body mass index, MoCA: Montreal Cognitive Assessment.

2.3.2 Orthostatic challenge

In Figure 6, the average responses to an orthostatic challenge are shown for BP, CBF and oxygenation values relative to baseline. The average finger BP at baseline was 146/70 (±SD 27/14, SBP/DBP) mmHg. SBP and DBP recovered on average to 98 (±7)% and 101 (±6)% of baseline respectively in the first 45

seconds after the SBP trough, which means DBP tended to have a higher recovery rate than SBP (p=0.095). The average SFV and DFV were 67 (±18) cm/s and 27 (±8) cm/s respectively. Responses of the SFV and DFV upon standing were different: while DFV showed a decrease upon standing, SFV did not. After 35 to 45 seconds SFV stabilised to 97 (±5)% and DFV to a significantly higher 102 (±5)% (p=0.002). O_2Hb and HHb, were only assessed relatively. The relative change at the minimum for O_2Hb was on average -1.18 (±0.61) µmol/L, and for HHb -0.08 (±0.22) µmol/L. After 35-45 seconds, O_2Hb recovered to -0.75 (±0.40) µmol/L relative to baseline, while HHb remained relatively stable (0.15 (±0.27) relative to baseline).

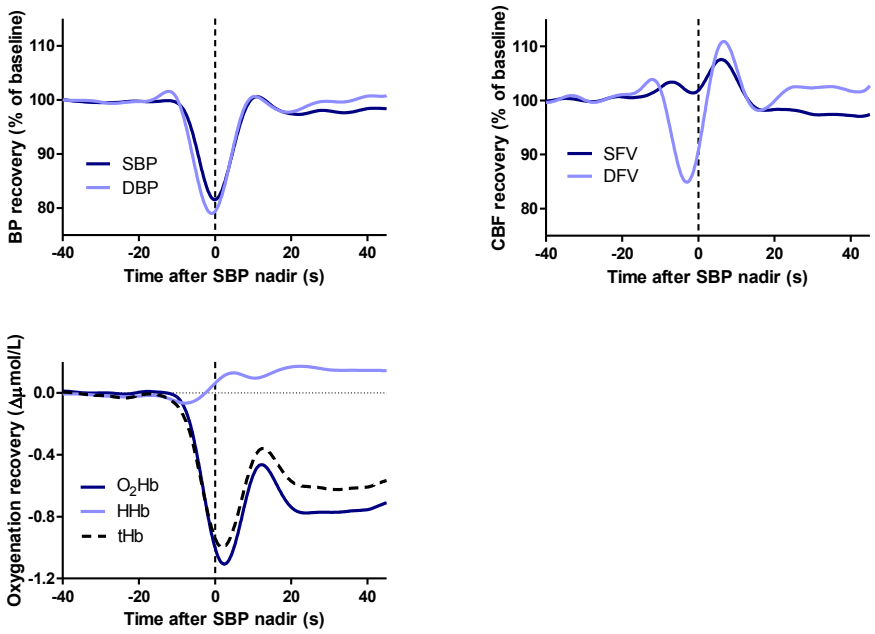


Figure 6: Responses of the blood pressure (BP), cerebral blood flow (CBF) and cerebral oxygenation measured with near-infrared spectroscopy (NIRS) to an orthostatic challenge (nadir of SBP at t=0 seconds). Lines represent mean values. DBP: diastolic blood pressure, SBP: systolic blood pressure, DFV: diastolic flow velocity, SFV: systolic flow velocity, O_2Hb: oxygenated haemoglobin, HHb: deoxygenated haemoglobin, tHb: total amount of haemoglobin.

2.3.3 Change in cognition score over one year

Change in cognitive function score after one year was on average -0.045 (±0.330). For SBP, 10 patients did not recover to 95% of the baseline value, whereas 19 patients did. Patients whose SBP recovered to more than 95% of the baseline value had a median (IQR) change in cognition of 0.078 (-0.153 to 0.230), and patients whose SBP did not recover to 95% of the baseline value had a cognition change of -0.189 (-0.354 to -0.025), p=0.033. As shown in Table A.1 in Appendix A, the number of patients in the aerobic exercise group, the number of training sessions and the baseline Montreal Cognitive Assessment (MoCA) value were higher in patients with a full SBP recovery than in patients with a partial SBP recovery. For DBP, only 6 patients did not recover to 95% of the baseline value. The cognition change did not differ significantly between the group with a full (>95%) DBP recovery and the group without (0.033 (-0.200 to 0.175) vs -0.098 (-0.245 to 0.057); p=0.609). As presented in Table A.2 in Appendix A, the baseline characteristics did not differ significantly between both groups. Linear regression analysis using the unadjusted regression model did not show a significant association between the percentage of recovery to baseline and change in cognition score after one year, both for BP and CBFV signals at all different time windows, as shown in Table A.3 in Appendix A. None of the

adjustments that were explored (age, gender, use of antihypertensive drugs, exercise group and the normalised number of training sessions) led to a ≥10% change in estimate [45]. Therefore, we refrained from adjusting for covariates.

2.3.4 Recovery analysis for improved and deteriorated group

In Figure 7 the responses of the SBP, DBP, SFV, DFV, O_2Hb and HHb after an orthostatic challenge are shown for patients whose cognition improved and patients whose cognition deteriorated. The SBP of cognitively improved patients was further recovered after 25-35 and 35-45 seconds after the SBP trough than the SBP of cognitively deteriorated patients (at 25-35 seconds a median (IQR) of 100 (96–107)% versus 96 (93–100)%; p=0.058, and at 35-45 seconds 101 (95-106)% versus 94 (92-99)%; p=0.017). The DBP recovery was 103 (99–107)% for patients whose cognition improved and 100 (94–103)% for patients whose cognition deteriorated (p=0.085) at 25-35 seconds and 102 (99-109)% versus 100 (95–102)% (p=0.111) at 35-45 seconds after the SBP trough. The early SFV values were almost equal for both groups, while the SFV seemed to stabilise at a slightly higher level for cognitively improved patients after 25 seconds after SBP nadir, although not significant (p>0.182). In addition, all cerebral oxygenation values (O_2Hb, HHb and total haemoglobin (tHb)) did not differ significantly between both groups at all time windows, although the HHb change tended to be lower in the cognitively improved group compared to the declined group, with the largest difference at 5-15 seconds after the SBP trough (-0.04 (-0.17-0.01) µmol/L versus 0.12 (-0.07-0.25) µmol/L; p=0.069). Extension of the recovery measurements to 5 minutes (Figure A.1 in Appendix A) shows that the main differences between the patients who improved in cognitive function and those who did not are reached within the first minute after standing up, comparable to what is presented in Figure 7.

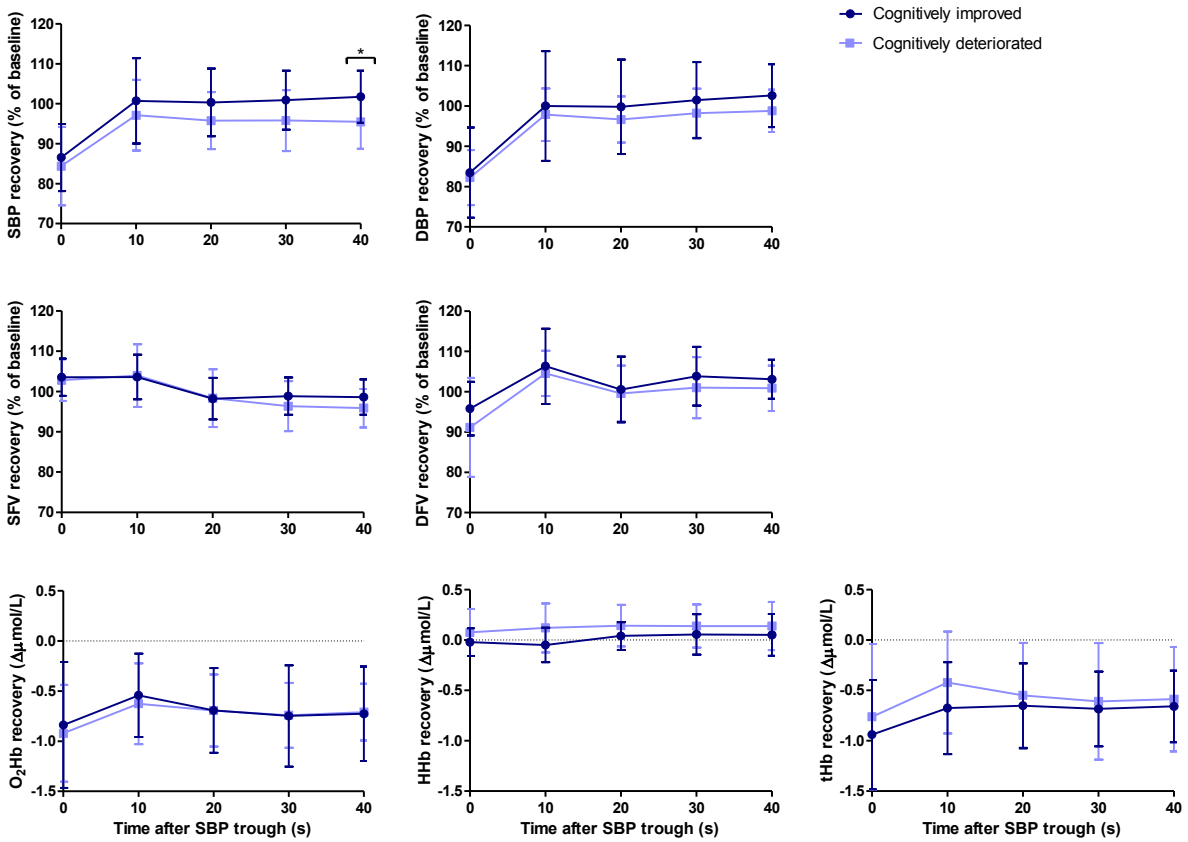


*Figure 7: Initial recovery of physiological signals (mean ±SD) after an orthostatic challenge (SBP nadir at t=0 seconds). The cognitively improved group is shown in dark blue and the cognitively deteriorated group in light blue. * indicates a significant (p<0.05) difference between the two groups.*

2.4 Discussion

The main goal of our study was to identify whether there is an association between haemodynamic recovery values after an orthostatic challenge and one-year cognitive change in elderly with MCI. We found that lower early (25-45 s after the SBP nadir) SBP recovery values, indicating incomplete recovery, were associated with cognitive decline. Other haemodynamic recovery parameters did not show a significant association with change in cognitive function after one year.

2.4.1 Orthostatic blood pressure recovery

Our BP findings correspond to earlier research in falls clinic and AD patients. These studies found an impaired orthostatic BP response at 50 to 60 seconds after standing, approximately corresponding to 35 to 45 seconds after the SBP trough defined by us, to be a predictor of mortality and cognitive decline respectively [30, 31]. Hayakawa et al. (2015) found that an impaired BP recovery at 30 seconds after standing (±15 seconds after SBP nadir) was already associated with MCI progression into AD [46]. However, they assessed a supine-to-stand manoeuvre, inducing a larger challenge, possibly enhancing differences between groups. This may explain why we did not find the same at 15 seconds after the SBP trough. In many patients the BP after standing up was higher than the sitting BP, reaching BP recovery values >100%. It is uncertain what recovery to higher than the baseline value means. As full recovery is already reached at 100%, this can explain why we did not find a strong linear relation between the percentage of BP recovery and cognitive change. Conversely, an orthostatic BP recovery >100% was not related to cognitive decline as well. This suggests there may be a certain threshold value of the BP recovery below which someone is at increased risk of cognitive decline. Above this value, full recovery is reached, in which 100% recovery and >100% recovery have a similar outcome. Earlier research by O'Hare et al. (2017) found many community-dwelling elderly aged >70 years with a higher standing than sitting BP. They did not see a worse cognitive status for patients having higher standing BP [27]. Contrarily, in another study higher standing BP was associated with cognitive decline in community-dwelling subjects of at least 65 years old [47]. However, in that study, cognitive function was assessed using the Mini-Mental State Examination, which is not comparable to our composite cognition score based on various cognitive domains.

2.4.2 Orthostatic cerebral perfusion recovery

SFV remained approximately constant upon standing in almost all patients, independent of the cognition group (improved or deteriorated cognition). DFV did follow the BP decline with a higher overshoot, probably due to active adaptation of cerebral perfusion by cerebral autoregulation, causing vasoconstriction and vasodilation in the cerebral arteries. The almost constant SFV indicates intact autoregulation, meaning that a sufficient flow of blood into the brain remained even during the acute phase of BP fall. This is supported by a study by de Heus et al. (2018) who did not find disturbed cerebral autoregulation in AD patients and elderly with MCI [41]. Different hypotheses have been posed before, linking impaired orthostatic recovery to cognitive decline. Vascular stiffening for example, as present in many older people, may lead to an increased BP variability including periods of hypotension. This can result in diminished cerebral microcirculation and repeated periods of ischemia [29, 48, 49]. Conversely, cerebral degeneration as a result of a cognitive disorder like MCI due to AD may result in autonomic dysfunction leading to orthostatic hypotension [50]. Our results cannot fully be explained by one of these hypotheses. The first hypothesis implies that hypotensive periods are joined by decreased CBF and O_2Hb. Although relative O_2Hb slightly declined upon standing, CBFV remained relatively stable during the profound drop in BP. On average, during the early BP recovery

phase (approximately after 30 to 60 seconds of standing), SFV seemed to stabilise below baseline level. In addition, O_2Hb remained below baseline levels, while HHb increased only little. Both CBFV and cerebral oxygenation recovery values indicate that oxygen supply declined, while the oxygen consumption did not increase much [33]. The first hypothesis is therefore partially supported, not immediately in the initial response to standing, but in the early recovery phase. Regarding the second hypothesis, orthostatic hypotension defined as a sustained SBP/DBP drop of 20/10 mmHg below baseline, was only present in one patient in our study population, so we cannot draw conclusions based on that.

2.4.3 Strengths and limitations

The primary goal of the NeuroExercise trial was to investigate the association between physical exercise and cognitive decline. In the original trial, no effect of physical exercise on cognitive function was found [35]. Still, physical exercise may have influenced the cognitive function score after one year. However, both participation in an exercise group and the number of training sessions completed did not differ significantly between the cognitively declined and improved group, and adjustment did not change our results. Additionally, patients having an incomplete SBP recovery (≤95%), were more often participating in the aerobic exercise group and attended more training sessions, compared to those having a full SBP recovery, as shown in Appendix A. As the effect of exercise on cognition is unknown, the difference in cognitive change between patients with a full and an incomplete SBP recovery could have been different without an exercise programme.

Our study population was heterogeneous, mainly concerning cognition score and age. On one hand, this can be seen as a limitation, but it also means the generalizability among elderly with MCI is large. Almost half of the participants improved their cognition after one year, while the other half cognitively declined. The age of our subjects ranged from 55 to 84 years, making age-related effects on orthostatic recovery possible. For example, the older the group of subjects, the greater the chance of orthostatic hypotension, and the lower the resting CBF [12, 23]. Nevertheless, in our study, there were no significant age differences in groups based on cognitive change, and in groups based on SBP or DBP recovery. Therefore, the possible age-related effects were equally represented in both groups. However, Frewen et al. (2014) reported that the association between orthostatic hypotension and cognitive performance was only present in the age group of people aged 65 and older [51]. Therefore, our heterogeneous sample, including 11 (out of 29) patients who were younger than 65, may have led to an underestimation of the associations we found.

Many previous studies performed an orthostatic supine-to-stand challenge, which has the advantage of exposing the haemodynamic system to a larger challenge than a sit-to-stand manoeuvre [23, 24, 26, 28, 30]. However, we chose to assess sit-to-stand challenges, as these are more feasible in clinical practice, often involving frail elderly and more easily to standardise. Moreover, sit-to-stand manoeuvres were used in some former studies still obtaining significant results [27, 31]. Shaw et al. (2017) have introduced different cut-off values for orthostatic hypotension based on seated instead of supine baseline values, making a sit-to-stand challenge even possible in clinical practice for diagnosing orthostatic hypotension [52]. Regarding our analysis, we chose to assess recovery from the moment of SBP nadir instead of recovery from the moment of standing up. This was done as an attempt to standardise our analysis across different subjects. Since only one marker was set when standing up, the timing of standing could vary among different participants. As the SBP drop is the actual stressor, determining recovery after this drop makes sense in terms of resilience. However, this choice makes our study slightly less comparable to previous research. In future work, we would advocate the use of

several markers upon standing, for example, one when a patient starts standing and one when he is fully standing upright. This would also allow for reconstruction of the time the patient took to stand up.

2.4.4 Conclusion

Routinely measuring the orthostatic BP response can be beneficial in older adults with MCI, since it may be a predictor of change in cognitive status. However, the exact mechanism behind the association between an inadequate orthostatic BP recovery and cognitive deterioration remains unknown, and it is uncertain whether there is a causal relation. Therefore, prevention of cognitive deterioration by diminishing BP fluctuations is not yet certain, and future research is needed to reveal the mechanisms behind this.

In conclusion, we found an impaired recovery of SBP to be associated with cognitive decline in elderly with MCI. Our research hereby confirms previous study results about the importance of BP recovery in association with cognition. However, we did not find consistent associations between orthostatic CBF or cerebral oxygenation recovery and cognition. Given our small sample size and limitations, no definite conclusions can be drawn on behalf of this.

A. Supplementary results

Table A.1: Baseline characteristics of all included patients, the SBP recovery >95% and ≤95% group.

	All patients (n=29)	SBP recovery >95% (n=19)	SBP recovery ≤95% (n=10)	P-value
Male	20 (69%)	14 (74%)	6 (60%)	0.675
Age (years)	68.0 (7.7)	69.0 (8.3)	66.2 (6.5)	0.408
BMI	26.0 (4.1)	26.1 (4.2)	25.7 (3.9)	0.836
Intervention group	22 (76%)	12 (63%)	10 (100%)	0.063
Aerobic exercise	11 (38%)	4 (21%)	7 (70%)	0.017*
Non-aerobic exercise	11 (38%)	8 (42%)	3 (30%)	0.694
Number of training sessions	88 (70)	65 (61)	132 (66)	0.049*
Cardiovascular disease	8 (28%)	5 (26%)	3 (30%)	1.000
Antihypertensive drug use	11 (38%)	8 (42%)	3 (30%)	0.694
Use of beta blockers (metoprolol)	4 (14%)	3 (16%)	1 (10%)	1.000
Statin use	7 (24%)	6 (32%)	1 (10%)	0.367
Antidepressant use	1 (3%)	0 (0%)	1 (10%)	0.344
Systolic blood pressure	144 (24)	145 (24)	142 (24)	0.801
Diastolic blood pressure	85 (12)	86 (13)	81 (11)	0.301
MoCA	23.2 (2.4)	22.7 (2.6)	24.2 (1.8)	0.046*
Cognition z-score	0.21 (0.67)	0.15 (0.64)	0.32 (0.75)	0.281

Data are presented as number (percentage) or mean (SD). Data were tested for statistical significance using Mann-Whitney U tests and Fisher's exact tests. Significant ($p<0.05$) differences are indicated with *.

Table A.2: Baseline characteristics of all included patients, the DBP recovery >95% and ≤95% group.

	All patients (n=29)	DBP recovery >95% (n=23)	DBP recovery ≤95% (n=6)	P-value
Male	20 (69%)	17 (74%)	3 (50%)	0.339
Age (years)	68.0 (7.7)	68.5 (7.7)	66.1 (8.3)	0.590
BMI	26.0 (4)	25.8 (4)	26.7 (5)	0.346
Intervention group	22 (76%)	16 (70%)	6 (100%)	0.289
Aerobic exercise	11 (41%)	7 (30%)	4 (67%)	0.164
Non-aerobic exercise	11 (38%)	9 (39%)	2 (33%)	1.000
Number of training sessions	88 (77)	65 (68)	133 (61)	0.116
Cardiovascular disease	8 (28%)	6 (26%)	2 (33%)	1.000
Antihypertensive drug use	11 (38%)	9 (39%)	2 (33%)	1.000
Using beta blockers (metoprolol)	4 (13%)	3 (17%)	1 (10%)	1.000
Statin use	7 (24%)	6 (26%)	1 (17%)	1.000
Antidepressant use	1 (3%)	0 (0%)	1 (17%)	0.303
Systolic blood pressure	144 (24)	145 (23)	141 (28)	0.787
Diastolic blood pressure	85 (12)	85 (13)	81 (11)	0.484
MoCA	23.2 (2.4)	22.9 (2.6)	24.5 (1.0)	0.086
Cognition z-score	0.21 (0.67)	0.21 (0.66)	0.22 (0.78)	0.726

Data are presented as number (percentage) or mean (SD). Data were tested for statistical significance using Mann-Whitney U tests and Fisher's exact tests. Significant ($p<0.05$) differences are indicated with *.

Table A.3: Linear regression analysis.

Predictor	Time after nadir (s)	b (±se)	β	P-value
SBP recovery	-5 to 5	0.001 (±0.007)	0.041	0.834
	5 to 15	0.002 (±0.006)	0.056	0.772
	15 to 25	0.006 (±0.008)	0.150	0.438
	25 to 35	0.009 (±0.008)	0.202	0.293
	35 to 45	0.014 (±0.008)	0.301	0.112
DBP recovery	-5 to 5	0.001 (±0.007)	0.041	0.832
	5 to 15	-0.001 (±0.006)	-0.025	0.896
	15 to 25	0.002 (±0.007)	0.059	0.761
	25 to 35	0.004 (±0.008)	0.107	0.580
	35 to 45	0.007 (±0.009)	0.139	0.472
SFV recovery	-5 to 5	-0.002 (±0.015)	-0.025	0.904
	5 to 15	-0.004 (±0.011)	-0.087	0.674
	15 to 25	0.002 (±0.012)	0.028	0.892
	25 to 35	0.020 (±0.012)	0.310	0.123
	35 to 45	0.023 (±0.014)	0.309	0.125
DFV recovery	-5 to 5	0.009 (±0.007)	0.253	0.212
	5 to 15	0.006 (±0.009)	0.134	0.514
	15 to 25	0.007 (±0.009)	0.157	0.443

	25 to 35	0.016 (±0.009)	0.343	0.086
	35 to 45	0.021 (±0.013)	0.331	0.099
O_2Hb recovery	-5 to 5	0.008 (±0.012)	0.013	0.948
	5 to 15	-0.095 (±0.167)	-0.114	0.572
	15 to 25	0.046 (±0.175)	0.052	0.796
	25 to 35	0.012 (±0.162)	0.015	0.940
	35 to 45	-0.018 (±0.176)	-0.020	0.920
HHb recovery	-5 to 5	-0.298 (±0.341)	-0.172	0.391
	5 to 15	-0.352 (±0.293)	-0.233	0.242
	15 to 25	-0.432 (±0.365)	-0.221	0.247
	25 to 35	-0.334 (±0.319)	-0.205	0.305
	35 to 45	-0.305 (±0.295)	-0.202	0.311

β: standardised regression coefficient, b: unstandardised regression coefficient, se: standard error.

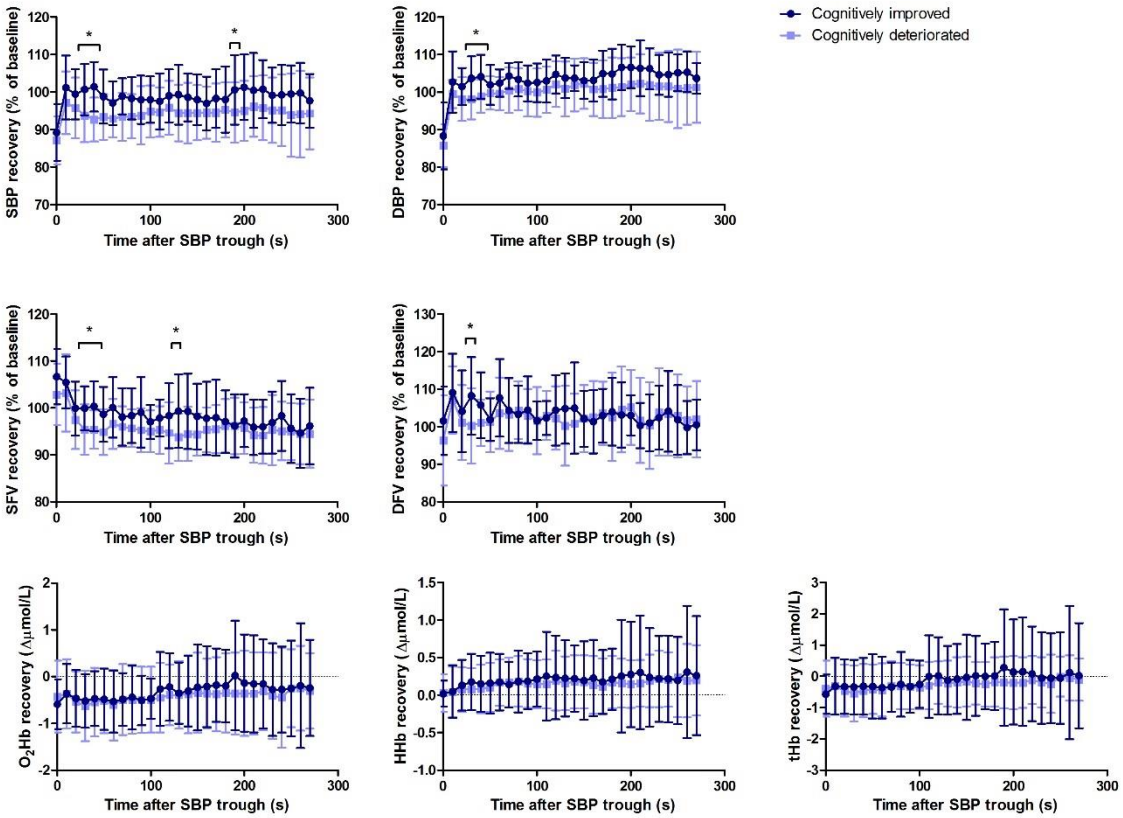


*Figure A.1: 5-minute recovery of physiological signals (mean ±SD) after an orthostatic challenge (trough of SBP at t=0 seconds). The cognitively improved group is shown in dark blue and the cognitively deteriorated group in light blue. * indicates a significant (p<0.05) difference between the two groups.*

3. Quantitative resilience indicators (DIORs) in relation to cognitive status

Abstract

Background: Dementia and mild cognitive impairment (MCI) due to Alzheimer's Disease (AD) are complex and heterogeneous diseases, and their rate of progression is hard to predict. Therefore, easy tools to aid in predicting progression and to help understanding the factors that influence the progression of MCI and AD, are desirable. Physical resilience, the ability to recover from a stressor, might be associated with cognitive decline.

Aim: To investigate the use of dynamical indicators of resilience (DIORs) in blood pressure (BP) signals, their relation to cognitive status and the possibility to be used as a predictor of cognitive decline.

Methods: Our study population consisted of 50 AD patients, 31 elderly with MCI and 41 healthy older adults (together a mean age of 70.8 ±6.4 years, 55% men). DIORs (temporal autocorrelation (TAC) and variance) were calculated from continuous sitting and standing systolic BP (SBP) and diastolic BP (DBP) measurements.

Results: In rest, AD patients showed a trend towards a higher TAC than older adults with MCI and healthy controls ($p=0.106$ for SBP and $p=0.053$ for DBP) but there was no significant difference in variance. For all participant groups, TAC increased upon standing ($p<0.022$, trend for SBP in AD patients ($p=0.083$)). The same applied to variance, although not significant for elderly with MCI. Within the groups of AD patients and participants with MCI, no consistent association was found between DIORs and cognitive decline, nor between DIORs and SBP recovery after standing up.

Conclusion: Our results indicate that DIORs can be obtained from BP signals to assess physical resilience. Higher DIORs, corresponding to lower resilience, were associated with a worse cognitive status, and DIORs were increased in standing compared to sitting BP. However, changes in resilience preceding cognitive decline might have been too subtle to capture using DIORs. Therefore, inducing larger perturbations, like during an orthostatic challenge, possibly enhancing differences in resilience, may be more useful to eventually predict dementia progression.

3.1 Introduction

Disease progression in dementia, like Alzheimer's Disease (AD), but also in a prodromal stage of mild cognitive impairment (MCI), is often heterogeneous and therefore hard to predict [6, 7, 53, 54]. A predictive factor may aid in informing patients, their families and caregivers, and might give more insight into dementia. More knowledge of factors that influence progression possibly reveals modifiable factors in preventing (fast) progression. In the past, research focussed on static measures, such as blood pressure (BP) values. However, this has not led to consistent results related to disease progression. Lately, focus in geriatric medicine is slowly shifting to a more dynamical and holistic approach, including resilience [15]. Physical resilience is defined as the ability to recover from and resist a perturbation [55-58].

Complex biological systems, such as the human body, are characterised by showing non-linear behaviour and have certain tipping points or critical transitions from one state to another [59]. In the body, the ultimate tipping point is death, but others can consist of transitions from a healthy to a diseased state. In the light of cognitive decline, such a tipping point could be a sudden fast progression of AD. Complex systems, ecosystems but also the human body, approaching a tipping point, show specific behaviour. This can be referred to as critical slowing down or slowing down of recovery. Critical slowing down can be assessed by following recovery after a stressor or perturbation, for example an orthostatic challenge, accompanied by a decline in BP. It can also be present in rest, in response to

spontaneous micro-perturbations, for example due to respiration, vasomotion and autonomic nervous activity [14, 55].

In rest, a system can exhibit critical slowing down by presenting different early warning signals. These signals are called dynamical indicators of resilience (DIORs), consisting of temporal autocorrelation (TAC), variance and cross-correlation. Higher TAC indicates longer memory in a stochastic process, meaning that a system's state is more dependent on the previous state, with a certain delay or lag. Therefore, higher TAC corresponds to a less random signal. Higher variance means that there are more and/or larger fluctuations present in a signal, and a higher cross-correlation expresses that one system is more dependent on the other system. As high resilience means that a system is only influenced little by perturbations, lower values for all DIORs are indicative of higher resilience [5, 60].

DIORs have mainly been described in ecosystem studies [5], but also in a few studies on the human body. DIORs have been assessed in long time series, such as 100 days of self-rated health, in which DIORs correlated with frailty levels [61]. In shorter time series of physiological signals, DIORs have only been applied to postural balance signals in a time series of 30 seconds. High-functioning older adults walking the Nijmegen Four Days marches were compared with less active community-dwelling elderly. TAC and variance appeared to be lower in postural balance signals captured from highly functioning and very active elderly than from less active older adults, indicating higher resilience [62]. This study illustrates the potential to use DIORs in discriminating patients with various resilience levels.

Previous studies indicate that lower physical resilience of the cardiovascular system, assessed by an orthostatic challenge, can reveal slowing down of recovery. This may precede cognitive decline in AD patients [31], but also in elderly with MCI (see Chapter 2). Therefore, the question arises whether DIORs in stationary BP signals can be predictive of cognitive decline as well. As a first step in investigating this, we assessed and compared DIORs in three cohorts of subjects: clinical AD patients, patients with MCI due to AD and healthy older adults.

3.2 Methods

3.2.1 Study design and population

This is a retrospective analysis combining data from three different trials. AD patients were recruited for the Nilvad trial [63, 64], elderly with MCI for the NeuroExercise trial (both between July 2013 and September 2017) [36] and data from healthy subjects were collected between July 2008 and June 2011. All inclusion and exclusion criteria have been described before [41]. With respect to cognitive score, AD patients were included when their Mini-Mental State Examination (MMSE) score was between 12 and 26 [65], while older adults with MCI had a Montreal Cognitive Assessment (MoCA) score between 18 and 26 [66], and healthy subjects were screened by a geriatrician to exclude cognitive impairment. Furthermore, AD patients and elderly with MCI were ≥50 years, whereas healthy subjects were aged ≥65 years. While AD patients and elderly with MCI were excluded when they had significant medical conditions, healthy controls were only included when they did not have a medical history of any cardiovascular or cerebrovascular disease, excluding all older adults with (resting and/or exercise) ECG abnormality. All participants gave written informed consent. The study protocols were approved by the medical ethics committee (CMO Arnhem-Nijmegen), and in accordance with the Declaration of Helsinki.

3.2.2 Data collection

All participants performed a 5-minute seated baseline measurement. As part of a sit-to-stand manoeuvre for AD patients and participants with MCI, and a squat-to-stand manoeuvre for healthy subjects, all participants remained standing for 5 minutes. Simultaneously, continuous BP was measured using volume-clamp photoplethysmography (Finapres Medical Systems, Enschede, The Netherlands) in the digital artery of the middle finger of the non-dominant hand.

3.2.3 Data processing

Data processing was performed using MATLAB (2018a, MathWorks Inc., Natick, USA), with custom-written semi-automatic scripts, as described previously [41]. Heart rate, systolic BP (SBP) and diastolic BP (DBP) were obtained over time from peaks and troughs in the continuous signal. BP signals were resampled at 10 Hz and detrended by using a third-order high-pass Butterworth filter (cut-off frequency 0.0025 Hz), to remove slow drifts.

Patients were excluded from the analysis when many ectopic beats were present, as these cause fast BP fluctuations, strongly influencing DIORs. Ectopic beats are not caused by a regulator, but have a cardiac origin, independent of regulatory systems. Therefore, we aimed not to capture these using DIORs. To achieve this, patients with a heart rate variability (HRV) >85 ms, in the presence of ectopic beats, were excluded, with HRV defined as follows [67]:

$$HRV = SD(IBI) = SD\left(\frac{1}{HR}\right)$$

with IBI the inter-beat interval, defined as the inverse of the heart rate, and SD the standard deviation.

3.2.4 Dynamical indicators of resilience

For analysis of sitting measurements, DIORs were determined using the entire measurement of 5 minutes. For within-group comparisons between DIORs in sitting and standing BP measurements, the first minute of both measurements was removed. The first minute of standing contains a large BP drop caused by venous pooling due to gravity and does therefore not meet the stationarity assumption underlying DIORs. Furthermore, the sitting and standing measurement should be of similar length to be able to compare DIORs obtained from both.

DIORs that were calculated were normalised TAC and variance. TAC is defined as follows:

$$TAC(k) = \mathbb{E}(X_{n+k}X_n)$$

This equation says that the autocorrelation function is the expectation of the product of signal *X* and the lagged version of signal *X* with lag *k*, independent of time. The results is one TAC value for every lag *k*, which means that the TAC can be plotted against lag *k*. TAC was calculated for lags ranging from 1 to 40 seconds, as most BP regulation takes place at this timescale. For example, baroreflexes sensing BP fluctuations and compensating for them, resonate with a period of approximately 10 seconds [68]. Moreover, the temporal resolution of the measurements allows for a minimum lag of 1 second, as approximately one heartbeat per second is present, yielding one SBP and DBP value per second. TAC was normalised between -1 and 1.

To correct for the influence of mean BP on variance, variance was also expressed as coefficient of variation (CoV) and variability independent of the mean (VIM) [48, 69, 70]. All variance parameters were scaled by scaling factor *c* such that their means were equal, making all variance measures that were used as follows:

- $variance = SD$
- $CoV = c * \frac{SD}{mean}$ (scaling factor *c*)

- $VIM = c * \frac{SD}{mean^a}$ (scaling factor c and constant a)

  Constant parameter a was determined by fitting a nonlinear curve through a plot of the SD against the mean, using iterative least squares estimation.

3.2.5 Statistical analysis

Participant characteristics were compared between groups using one-way ANOVA tests or independent samples t tests for continuous variables or chi-squared tests for categorical variables. DIORs determined from the 5-minute sitting measurement were compared between healthy subjects, elderly with MCI and AD patients, and within groups of participants with MCI and AD. Within the MCI group, DIORs of patients who improved and decreased in cognitive functioning score (z-score based on various neuropsychological tests [40], see section 2.2.3) after one year were compared, as well as patients who fully recovered (SBP >95% of baseline value) within 1 minute after an orthostatic challenge and patients with a partial recovery (≤95% of baseline value). Within the AD group, DIORs in BP signals of fast progressors (ADAS-cog score increase ≥12 after 1.5 years [31]) and slow progressors (ADAS-cog score increase <12 after 1.5 years) were compared. The AD group was also split into patients with a full and with a partial SBP recovery after standing up, similar to the MCI group. Furthermore, for all 3 groups, DIORs determined from the last 4 minutes of the sitting measurement were compared to DIORs in the last 4 minutes of the standing measurement. For all comparisons, TAC was plotted against the lag to determine the lag at which the TAC visually differed most between these groups. The value of the TAC, averaged over a 2-second window around this lag, and different variance parameters were compared. Between-group comparisons were made using one-way ANOVA tests or Kruskal-Wallis tests, as appropriate. DIORs from sitting and standing BP were compared within groups using paired t-tests or paired two-sided Wilcoxon signed-rank tests. Other within-group comparisons were tested for significance with one-sample t-tests or Mann-Whitney U tests. All statistical analyses were performed in MATLAB. P-values <0.05 were considered statistically significant.

3.3 Results

3.3.1 Baseline characteristics

In this study, 50 AD patients, 31 elderly with MCI and 41 healthy controls were included for analyses. Of those, for comparisons between sitting and standing, data were available of 46 AD patients, 24 older adults with MCI and 39 healthy subjects. Baseline characteristics are shown in Table 2. AD patients were older than healthy controls and elderly with MCI. Moreover, corresponding to original exclusion criteria, comorbidities and medication use were more prevalent in MCI participants and AD patients. Beta blockers were used by 4 elderly with MCI, but by none of the AD patients. Both SBP and DBP at screening were significantly higher in older adults with MCI than in AD patients and healthy controls.

Table 2: Baseline characteristics of healthy controls (HC), elderly with mild cognitive impairment (MCI) and Alzheimer's disease (AD) patients.

	HC (n=41)	MCI (n=31)	AD (n=50)	P-value
Male	25 (61%)	20 (65%)	22 (44%)	0.124
Age (years)	69.6 (3.7)	69.0 (8.7)	72.9 (6.1)	0.009*
BMI	26.4 (3.2)	25.9 (3.8)	24.9 (3.4)	0.100
Cardiovascular disease†	0	8 (26%)	9 (18%)	0.402
Antihypertensive drug use†	0	10 (32%)	13 (26%)	0.544
Beta blocker use	0	4 (13%)	0	NA
Statin use†	0	6 (19%)	8 (16%)	0.698
Systolic blood pressure	132 (12)	143 (22)	137 (13)	0.013*
Diastolic blood pressure	78 (9)	85 (12)	78 (6)	0.002*
MoCA	-	22.9 ± 2.5	-	NA
MMSE‡	28.7 ± 1.4	-	20.3 ± 3.5	<0.001*

Values are presented as mean (SD) or number (percentage). Test statistics used were F- and t-statistic for continuous variables and χ^2-statistic for categorical variables.

* Significant difference ($p<0.05$).

† Compared between MCI and AD group.

‡ Compared between HC and AD group.

BMI: body mass index, MoCA: Montreal Cognitive Assessment, MMSE: Mini-Mental State Examination.

3.3.2 Between-group comparisons in DIORs

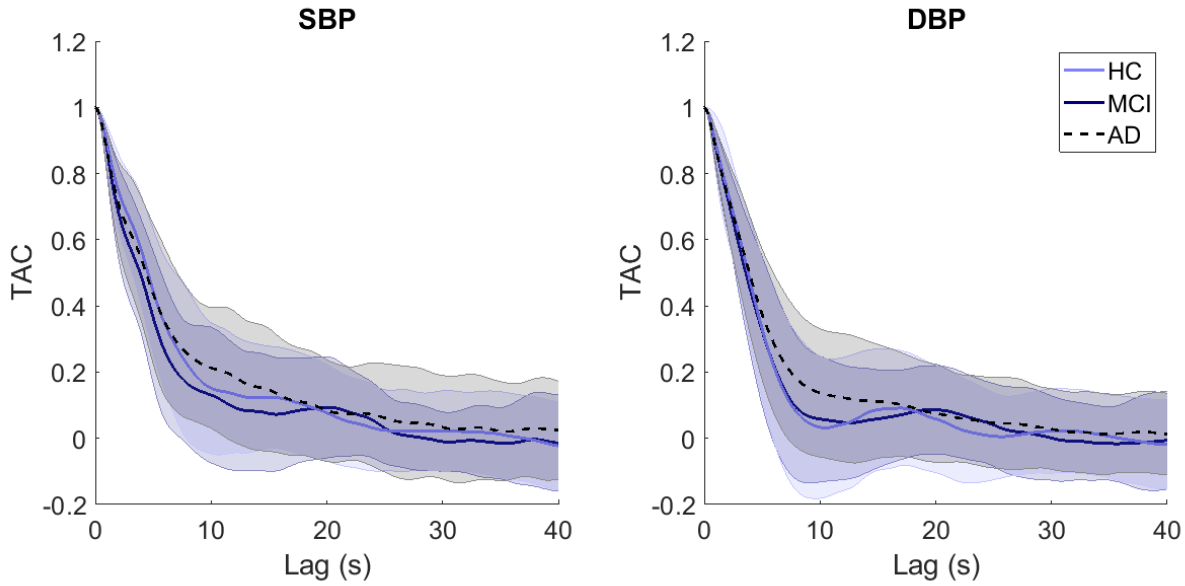


Figure 8: Temporal autocorrelation (TAC) against lags from 0 to 40 s, for healthy controls (HC; light blue line), older adults with mild cognitive impairment (MCI) (dark blue line) and Alzheimer's disease (AD) patients (black dashed line) A) determined from the systolic blood pressure (SBP) and B) determined from the diastolic blood pressure (DBP). Vertical dashed black lines indicate a lag of 10 seconds at which TAC of both SBP and DBP differs most between groups. Tested for significance using one-way ANOVA tests.

As shown in Figure 8, average TAC for both the baseline SBP and DBP differs most between groups at a lag of approximately 10 seconds, revealing slightly higher TAC for AD patients (p=0.106 for SBP and

p=0.053 for DBP). As shown in Table 3, BP variance was lower in AD patients than in elderly with MCI and healthy controls, but BP CoV and VIM did not differ between participant groups.

*Table 3: Variance (expressed as VAR: variance, CoV: coefficient of variation and VIM: variation independent of the mean) compared between healthy controls (HC), elderly with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD). Data are expressed as median (interquartile range), and significant (p<0.05) differences indicated with *. Reported p-values result from Kruskal-Wallis tests.*

	HC	MCI	AD	P-value
SBP				
VAR	6.03 (5.12-6.89)	5.70 (4.39-7.24)	5.11 (4.08-6.45)	0.086
CoV	5.94 (4.97-7.34)	5.25 (4.47-6.11)	5.27 (4.38-6.52)	0.194
VIM	6.14 (5.11-7.03)	5.62 (4.49-6.60)	5.24 (4.13-6.55)	0.125
DBP				
VAR	2.61 (2.31-3.10)	3.05 (2.55-3.65)	2.44 (2.07-3.02)	0.022*
CoV	2.40 (2.10-2.92)	2.49 (2.19-3.01)	2.62 (1.95-3.46)	0.728
VIM	2.45 (2.26-3.12)	2.94 (2.54-3.56)	2.57 (2.11-3.07)	0.100

3.3.2 DIORs compared between sitting and standing

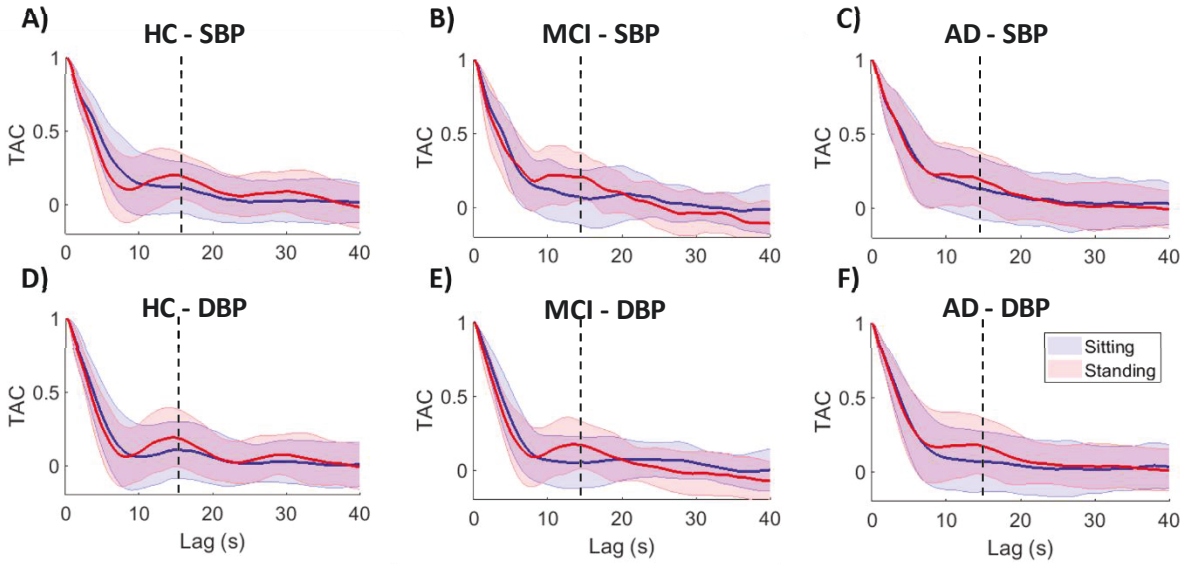


Figure 9: Temporal autocorrelation (TAC) plotted over lags from 0 to 40 s, compared between 4 minutes of sitting blood pressure in blue and 4 minutes of standing blood pressure in red. A-C show the TAC derived from the systolic blood pressure (SBP), D-F from the diastolic blood pressure (DBP). A and D are showing TAC from healthy controls (HC), B and E from elderly with mild cognitive impairment (MCI) and C and F from Alzheimer's disease (AD) patients. The dashed black vertical lines indicate a lag of 15 s, which was visually found to show the largest difference between sitting and standing TAC, in all participant groups. TAC at this lag was tested for significance using paired t-tests.

In Figure 9, TAC is shown for different lags and compared between sitting and standing BP. For all groups of subjects, TAC around a lag of 15 s in DBP signals increased significantly upon standing (for healthy subjects p=0.004, for elderly with MCI p=0.010 and for AD patients p=0.022). When determined from SBP, TAC showed a significant increase upon standing in healthy subjects and older adults with MCI, and a trend for AD patients (p=0.083; for healthy controls and elderly with MCI

p=0.015 and p=0.002 respectively). As shown in Table 4, almost all variance measures increased significantly upon standing for healthy subjects and AD patients, when calculated from both SBP and DBP. For elderly with MCI, median variance only shows a small (not significant) rise.

*Table 4: Variance measures (VAR: variance, CoV: coefficient of variation and VIM: variation independent of the mean) compared between 4-minute sitting and standing measurements for healthy controls (HC), elderly with mild cognitive impairment (MCI) and patients with Alzheimer's disease (AD). Data are expressed as median (interquartile range), and significant differences, resulting from Wilcoxon signed-rank tests, are indicated with *.*

Group of subjects		Sitting value	Standing value	P-value
HC	SBP			
	VAR	5.89 (4.92-6.79)	7.23 (5.79-9.03)	<0.001*
	CoV	5.91 (5.11-7.29)	6.76 (5.66-8.75)	0.006*
	VIM	5.82 (5.06-6.98)	6.91 (5.81-8.91)	<0.001*
	DBP			
	VAR	2.54 (2.31-2.96)	3.05 (2.57-4.21)	<0.001*
	CoV	2.52 (2.23-3.15)	3.16 (2.70-3.86)	0.016*
	VIM	2.52 (2.33-2.95)	3.07 (2.68-4.27)	<0.001*
MCI	SBP			
	VAR	5.47 (4.55-7.19)	5.88 (4.89-7.28)	0.189
	CoV	5.23 (4.56-6.22)	5.87 (4.96-7.02)	0.081
	VIM	5.51 (4.60-6.70)	6.26 (5.10-7.28)	0.317
	DBP			
	VAR	2.87 (2.60-3.33)	3.12 (2.49-3.54)	0.424
	CoV	2.80 (2.53-3.43)	3.06 (2.33-3.69)	0.732
	VIM	2.93 (2.72-3.34)	2.92 (2.51-3.82)	0.775
AD	SBP			
	VAR	4.93 (3.78-6.35)	6.17 (5.22-7.43)	0.004*
	CoV	4.86 (3.41-7.04)	5.99 (4.80-7.65)	0.009*
	VIM	5.06 (3.65-6.92)	6.20 (5.24-7.55)	0.002*
	DBP			
	VAR	2.46 (2.01-2.74)	2.97 (2.62-3.45)	0.002*
	CoV	2.34 (1.76-3.30)	2.64 (2.19-3.63)	0.083
	VIM	2.40 (2.08-3.02)	3.00 (2.66-3.39)	0.003*

3.4 Discussion

In this study, DIORs, specifically TAC and variance, derived from BP measurements were compared between subject groups with a distinct cognitive status. These groups consisted of cognitively, and also physically, healthy older adults, older adults with MCI and AD patients. TAC at lag 10 s tended to be higher for AD patients compared to participants with MCI and healthy subjects, while variance measures did not differ between participant groups. For all subject groups, TAC at lag 15 s increased upon standing, complemented by a rise in variance for AD patients and healthy controls.

3.4.1 Proximity to a tipping point

Our findings suggest that resilience measures and cognitive status might be related. This implies that the association between impaired orthostatic recovery and cognitive decline found previously in AD patients [31] and older adults with MCI (see chapter 2) may be interpreted in terms of resilience. Other studies have found cognitive status to be related to functional recovery potential, another way of describing resilience, for example after elective surgery [55, 71-73]. The similar yet weak association we found between decreased resilience in BP signals and diminished cognitive function matches this more holistic resilience approach used previously. In the proximity of a tipping point or critical transition, both an increase in DIORs in stationary, resting signals and slowing down of recovery after a stressor are expected to occur. However, we did not find any consistent association between DIORs and 1 to 1.5-year cognitive decline within the MCI and AD groups (see Appendix B). Moreover, orthostatic BP recovery, previously found to be associated with cognitive decline [31], and DIORs derived from sitting BP were not related. Our results imply that orthostatic recovery is a more sensitive measure for resilience, while DIORs in a stationary signal, with natural, spontaneous micro-perturbations, only show differences in closer proximity to a tipping point. This might explain why TAC was higher in AD patients, but did not differ between healthy controls and elderly with MCI. Moreover, the rise in DIORs upon standing supports the idea that standing causes a perturbation that (temporarily) reduces the distance to a tipping point. In this way, an orthostatic challenge might distinguish less resilient from more resilient patients when a critical transition is relatively far away.

3.4.2 Blood pressure variability

We did not find an association between cognitive status and variance measures, although previous research into BP variability indicates that higher BP variability is associated with cardiovascular disease. Cardiovascular disease is, in turn, an important risk factor for cognitive decline [74-77]. On a larger (day-to-day) timescale, BP variability has even been linked to AD progression before [48]. Our contrasting findings can be explained in several ways. Mainly medication and comorbidity could have affected the results. None of the healthy subjects used antihypertensive medication, resulting in a less suppressed, and possibly more fluctuating BP. Moreover, only MCI patients were included when using beta blockers. In the AD and MCI group, comorbidity such as cardiovascular disease could have influenced BP, as exclusion criteria were less stringent. The larger number of exclusions in the MCI and AD group due to ectopic beats illustrates this. Moreover, average BP was higher in elderly with MCI than in the other groups. However, we corrected for this influence by also considering CoV and VIM, but we did not find significant differences in these parameters either.

3.4.3 The role of baroreflexes and other regulatory mechanisms

Physiologically, BP constantly fluctuates over time, for instance, influenced by autonomic nervous activity and respiration. Simultaneously, baroreflexes try to maintain constant BP. When a BP increase is sensed by the stretching baroreceptors, stimulation of parasympathetic and inhibition of sympathetic nervous activity lowers heart rate [16]. Baroreflexes are thought to form the origin of BP waves with a period of 10 s [68, 78]. This overlaps with the TAC lag of 10-15 s we found to be relevant. Therefore, higher TAC at this lag indicates that BP in AD patients might be less strictly regulated, as 10 s waves are more dominantly present. This fits the concept of high resilience being determined by intact regulatory systems and therefore indicates that the AD group was on average less resilience than the MCI group and healthy subjects [79]. After standing up, the observed increase in TAC may be explained by an increased baroreflex activity, although most clear at lag 15s. We cut off the first minute

of standing to remove the initial BP recovery phase following the gravity-induced BP drop, yet BP might not have been fully stabilised within this first minute. This may have resulted in a non-stationary signal, whereas stationarity is one of the main assumptions underlying the DIORs approach. On the other hand, visual inspection of the BP signals during standing did not reveal a trend. Moreover, the TAC curves did not reveal periodicity of 10 s in the TAC function, advocating that even in the standing BP signals, TAC did not represent baroreflexes alone, but possibly a more complex regulatory system. Upright standing is a more active posture than sitting, in which many regulatory mechanisms play a role. These for example consist of vestibular, cognitive, somatosensory and visual system, associated with postural balance, and the skeletal muscle pump [80]. Especially the latter is thought to influence BP, by redistribution of pooled blood in the legs. There are indications that postural sway during active standing leads to BP fluctuations corresponding to sway frequencies, especially in the low frequency range (approximately 0.04-0.15 Hz) [81]. Besides baroreflexes, TAC differences between sitting and standing around lag 15 s could therefore be explained by an active muscle pump and postural sway.

3.4.4 Resilience as a predictive factor

It is, however, questionable whether the association between resilience in the cardiovascular system and cognitive changes should be expected to be strong. The majority of AD patients progresses slowly [82]. Cognitive decline might therefore not be considered a critical transition, as often the change in cognitive function is not abrupt. Nevertheless, AD patients are still likely to be closer to a critical transition than healthy older controls and older adults with MCI, as their life expectancy is shortened [83]. Moreover, autonomic dysfunction as a result of neurodegeneration in AD patients might cause dysregulation, possibly cohering with BP instability. This BP instability can be captured by an increased TAC, which we found at a 10-15 s timescale. The heterogeneity and complexity of dementia and MCI due to AD, in which many factors influence progression, complicates the predictive ability of resilience measures. This probably means that cardiovascular resilience could not be a predictive factor for cognitive decline on its own, but it may still be of added value, complemented with other possible predictors from different health domains [84].

3.4.5 Strengths and limitations

The main strength of our approach is the use of a relatively simple and short measurement, in contrast to previous questionnaire time series that were repeated for many days. Moreover, even frail older adults are likely to be able to perform an orthostatic challenge, and if not, a 5-minute baseline measurement can provide insight into a patient's resilience as well. This could even be performed supine when a patient is critically ill. However, some difficulties were faced during the analysis of our BP data. In some patients, mainly elderly with MCI, ectopic beats were present. For the cohort of healthy controls, ECG abnormalities formed one of the exclusion criteria. Therefore, the choice was made to exclude MCI and AD participants that showed many ectopic beats in their BP measurements. This does affect the results, as ectopic beats increase BP variability, and are therefore also likely to cause an increase in variance. Paradoxically, ectopic beats may induce a faster decay of TAC over larger lags, and could thus be related to lower TAC. Therefore, the explanation of ectopic beats is unclear in terms of DIORs, but a further in-depth investigation of ectopic beats is interesting for future research. Another limitation concerns different in- and exclusion criteria between groups. Elderly with MCI had a significantly higher BP, and more often used beta blockers, known to be able to cause orthostatic hypotension, indicating a less tightly regulated BP. Healthy controls did not use any BP-related medication, and were excluded when they had a medical history of cardiovascular disease. This may

have influenced variance measurements. However, TAC is less likely to be influenced by antihypertensive medication and cardiovascular comorbidities than variance, since the groups of older adults with MCI and healthy controls show considerable overlap in TAC. Medication use and comorbidity were comparable between people with MCI and AD, or even higher in MCI than in AD patients. Lastly, a 5-minute sitting measurement may have been too short to fully capture BP dynamics. For TAC we explored the 1 to 40 s (corresponding to 0.025-1 Hz) range. At lag 40 seconds the robustness of TAC estimation was already limited, as only 7 periods were present in a 5-minute signal. To be able to look at larger timescales, such as the very low frequency range (0.003-0.04 Hz), longer measurements are needed [85]. Especially the standing measurement of only 4 minutes due to removal of the first minute of BP stabilization, should preferably be longer to ascertain stationarity. In this way, DIORs and BP regulation could be assessed at different timescales.

3.4.6 Conclusion

In conclusion, TAC was slightly increased in AD patients compared to elderly with MCI and healthy controls, and both DIORs increased upon standing. The predictive value of DIORs in resting measurements for cognitive decline seemed limited. Changes in resilience preceding cognitive decline might be too subtle to capture using DIORs in sitting BP signals, so stimulus-response tests like an orthostatic challenge, or longer standing BP measurements, may be more useful to assess resilience in relation to cognitive change in future research.

B. DIORs related to cognitive decline within MCI and AD group

B.1 Results DIORs within MCI group

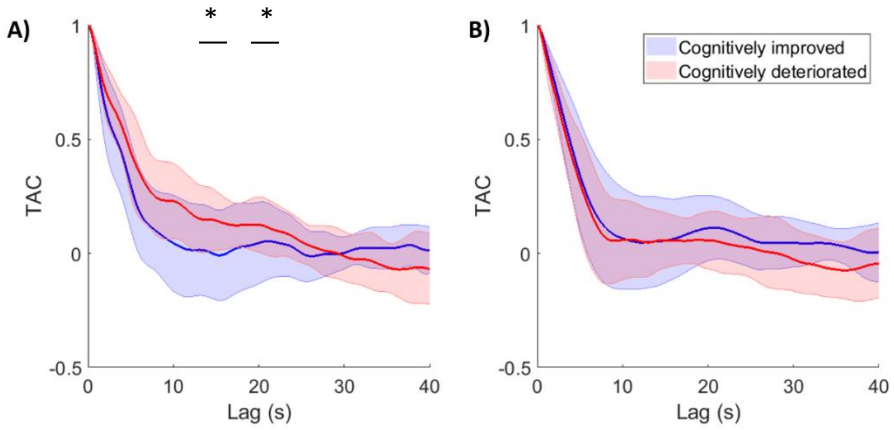


*Figure B.1: Temporal autocorrelation (TAC) plotted for different lags for elderly with MCI whose cognitive score improved (blue; n=14) and patients whose cognitive score deteriorated (red; n=15). The thick line represents the mean and the shaded area the standard deviation. For A) systolic blood pressure (SBP) and B) diastolic blood pressure (DBP). Significant difference between groups indicated with *.*

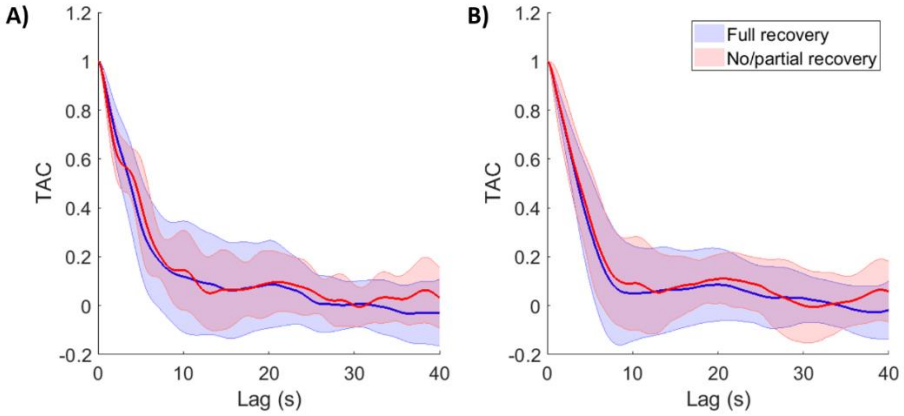


Figure B.2: Temporal autocorrelation (TAC) plotted for different lags for elderly with MCI who had a full SBP recovery (recovered to >95% of the baseline value; shown in blue; n=18) and patients whose SBP recovered incompletely in the first 60s after standing up (recovered to ≤95% of the baseline value; shown in red; n=8). The thick line represents the mean and the shaded area the standard deviation. For A) systolic blood pressure (SBP) and B) diastolic blood pressure (DBP).

Within the MCI group TAC derived from SBP did significantly differ between a group of patients who improved in cognitive score and a group that had a deteriorated cognitive score after one year (around lag 10s p=0.020 and around lag 15s p=0.006; see Figure B.1). However, for DBP this was not the case (p=0.678 at lag 10s and p=0.810 at lag 15s). Between the people with MCI that reached full (>95% of the baseline value) orthostatic SBP recovery within 60 s of standing and patients who recovered partially (≤95% of the baseline value) both TAC derived from SBP and DBP did not differ, as shown in Figure B.2. All variance parameters were not significantly different between groups based on cognitive progression after one year, although medians were higher for all variance measures for cognitively deteriorated compared to improved elderly with MCI. Variance measures did not differ between groups based on orthostatic recovery values as well, as shown in Table B.1.

*Table B.1: Variance measures (VAR: variance, CoV: coefficient of variation and VIM: variation independent of the mean) compared between mild cognitive impairment (MCI) patients whose cognitive score improved and those whose score declined. Data are expressed as median (interquartile range), and significant differences indicated with *.*

	Cognitively improved (n=14)	Cognitively deteriorated (n=15)	P-value
SBP			
VAR	5.40 (4.36-6.67)	5.67 (4.44-6.93)	0.810
CoV	5.66 (4.95-6.10)	6.08 (4.78-7.55)	0.247
VIM	5.31 (4.48-6.54)	5.62 (4.31-6.56)	0.585
DBP			
VAR	2.69 (2.38-3.17)	3.05 (2.74-3.69)	0.266
CoV	2.81 (2.38-3.14)	3.13 (2.69-3.59)	0.183
VIM	2.62 (2.21-2.97)	2.94 (2.69-3.58)	0.230
	Full orthostatic recovery (n=18)	Partial/no orthostatic recovery (n=8)	P-value
SBP			
VAR	5.85 (4.79-6.75)	5.59 (4.00-7.34)	0.697
CoV	6.00 (5.00-7.16)	5.49 (4.42-6.38)	0.374
VIM	6.05 (4.69-6.54)	5.32 (4.06-6.70)	0.781
DBP			
VAR	2.87 (2.60-3.26)	3.11 (2.54-3.56)	0.739
CoV	3.13 (2.71-3.54)	2.86 (2.62-3.47)	0.657
VIM	2.92 (2.56-3.19)	2.94 (2.47-3.40)	0.868

B.2 Results DIORs within AD group

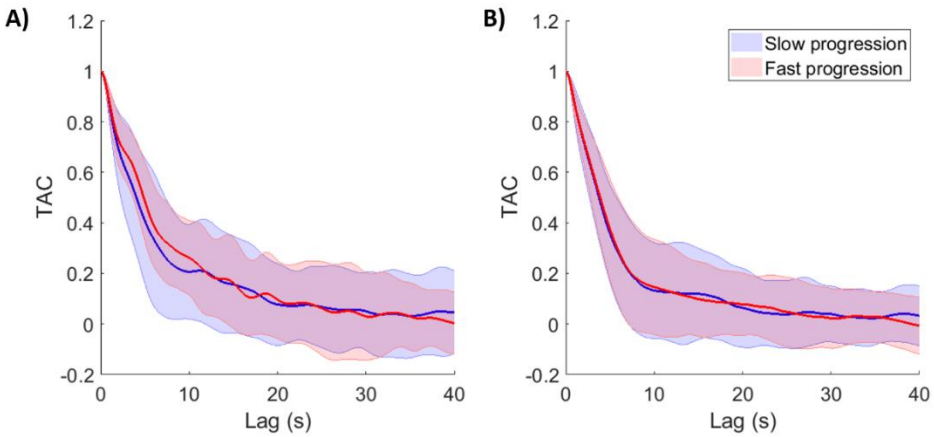


Figure B.3: Temporal autocorrelation (TAC) plotted for different lags from 0 to 40s for AD patients who progressed slowly (1.5-year difference in ADAS-cog score <12; blue; n=30) and patients who deteriorated relatively quickly (difference in ADAS-cog score after 1.5 years ≥12; red; n=17). The thick line represents the mean and the shaded area the standard deviation. For A) systolic blood pressure (SBP) and B) diastolic blood pressure (DBP).

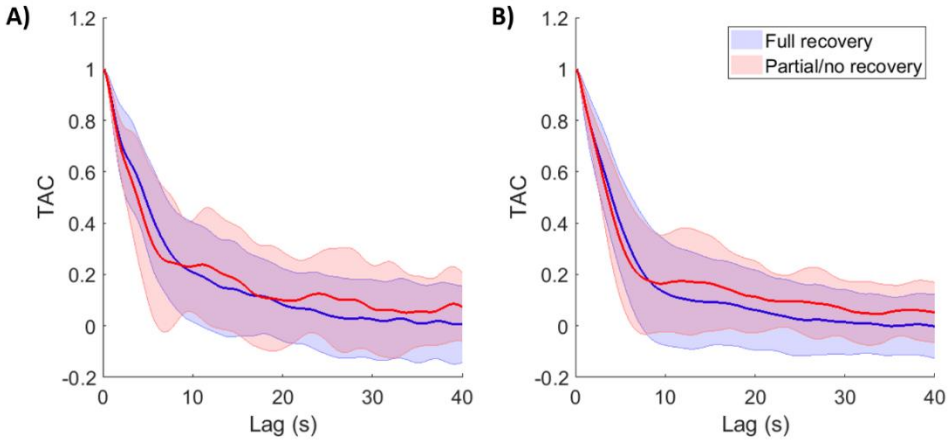


Figure B.4: Temporal autocorrelation (TAC) plotted for different lags from 0 to 40s for AD patients who had a full recovery (>95% of the sitting systolic blood pressure value) within one minute after standing (blue; n=34) and patients who had a partial or no recovery (≤95% of the systolic baseline value) within one minute after standing (red; n=15). The thick line represents the mean and the shaded area the standard deviation. For A) systolic blood pressure (SBP) and B) diastolic blood pressure (DBP).

Within the group of AD patients, none of the DIORs differed significantly between fast (ADAS-cog score change after 1.5 years ≥12) and slow progressors (ADAS-cog score change after 1.5 years <12), although the median of all variance parameters was slightly higher for fast progressors (see Figure B.3 and Table B.2). When comparing AD patients who fully recovered after an orthostatic challenge to patients who did not, TAC from both SBP and DBP seem consistently lower for patients with full SBP recovery than patients with partial SBP recovery. This was however not significant (p=0.255 at lag 10s and p=0.313 at lag 15s). Variance measures were not significantly different.

*Table B.2: Variance measures (VAR: variance, CoV: coefficient of variation and VIM: variation independent of the mean) compared between Alzheimer's Disease (AD) patients who progressed slowly and who progressed rapidly. Data are expressed as median (interquartile range), and significant differences indicated with *.*

	Slow cognitive decline (n=30)	Fast cognitive decline (n=17)	P-value
SBP			
VAR	4.80 (3.86-6.19)	5.18 (4.63-6.76)	0.236
CoV	4.80 (3.61-6.14)	5.18 (4.39-7.92)	0.264
VIM	5.18 (3.83-6.13)	5.46 (4.53-7.07)	0.217
DBP			
VAR	2.37 (2.07-2.94)	2.64 (2.04-3.02)	0.528
CoV	2.27 (1.64-2.77)	2.35 (1.82-3.26)	0.406
VIM	2.42 (2.11-2.88)	2.61 (2.09-3.15)	0.528
	Full orthostatic recovery (n=34)	Partial/no orthostatic recovery (n=15)	P-value
SBP			
VAR	5.24 (4.00-6.32)	5.13 (4.39-6.97)	0.494
CoV	4.62 (4.18-5.93)	5.93 (3.76-8.58)	0.345
VIM	5.18 (4.21-6.23)	5.43 (4.04-7.56)	0.454
DBP			
VAR	2.42 (2.12-2.95)	2.53 (2.13-3.40)	0.494
CoV	2.30 (1.72-2.81)	2.48 (1.71-3.98)	0.357
VIM	2.53 (2.11-3.06)	2.77 (2.18-4.09)	0.324

4. Resilience in patients undergoing major thoracic aortic surgery: a pilot study

Abstract

Background: Open cardiothoracic surgery, a highly complex procedure, can reveal large differences in clinical outcomes between individuals, especially among older patients. Some benefit from surgery, whereas others deteriorate cognitively or physically and do not reach their baseline health level again. Recovery after surgery can be described by the concept of physical resilience, which is a patient's ability to withstand and recover from a perturbation. Therefore, estimating resilience would be helpful to complement the already performed geriatric assessment. Patients who experience a loss of resilience show critical slowing down, which occurs even before the actual stressor. Measuring critical slowing down may help in identifying patients at risk of complications during recovery after surgery.

Aim: To investigate physical resilience measurements in clinical practice at the cardiothoracic surgery outpatient clinic.

Methods: All patients who had to undergo open thoracic aortic surgery were included. Measurements were performed during an orthostatic challenge (5 minutes of sitting followed by 3 minutes of standing) and a handgrip challenge (2x maximal grip strength, 1x sustained maximal grip strength). Meanwhile, continuous finger blood pressure and cerebral oxygenation were measured. We determined feasibility of measuring in clinical practice and quality of the acquired signals. Moreover, a preliminary analysis was performed to compare patients with a short (<10 days) and a long (>13 days) hospital stay based on orthostatic recovery values and grip strength values.

Results: We included 27 patients, who were on average 63.0 (13.3) years old, and 70% were men. Until now, 12 patients have had surgery. They stayed 13.1 (9.8) days in the hospital, of which 1.5 (0.7) days at the ICU. The in-hospital mortality was 8%. Our measurements were successfully embedded in the clinical workflow and well-tolerated by patients. Technically, 96% of all BP measurements were useful, as well as 93% of cerebral oxygenation measurements on at least one side. Preliminary results, based on duration of hospital stay, suggest blood pressure recovery upon standing may be of interest to assess resilience in future clinical research.

Conclusion: We showed feasibility of clinical application of resilience measurements at the outpatient clinic. Our analysis should be repeated when more measurements have been performed. In conclusion, this is a promising first step to a more routine use of physical resilience indicators in clinical practice.

4.1 Introduction

Thoracic aortic aneurysms are common in clinical practice, having an incidence of 7.6 per 100,000 people per year, being more prevalent in men than in women. The mean age at diagnosis is 67 years, indicating that many of the people diagnosed with a thoracic aortic aneurysm are older patients [86]. An operation is often indicated when the aneurysm size exceeds 5.5 cm [87]. The surgery procedure is complex, including heart-lung bypass, and it might include cooling of the body to decrease cerebral metabolic rate [88, 89]. However, especially in older adults, such a complex operation raises uncertainty in clinical outcome. Although operative risk increases with age, even patients aged >80 years may still benefit from surgery [90]. At the Radboudumc cardiothoracic surgery outpatient clinic, a comprehensive geriatric assessment (CGA) is done to evaluate whether the advantages of surgery outweigh the risks and whether the advantages match the patient's own goals. The assessment covers different domains, like cognition, frailty and functional status, aiming to estimate an older person's ability to recover from surgery [91].

The concept of physical resilience covers the patient's recovery potential. In this case, lower resilience means closer proximity to a tipping point. This can be related to slower recovery, reflected in a longer hospital stay or complications such as delirium. Therefore, prediction of the proximity of a tipping point, or so-called critical transition, can assist in identifying patients who are at risk of complications after surgery [5, 14]. In this study, different easy resilience measures, that have been promising in previous research, were embedded in clinical practice. These consist of BP (blood pressure) and cerebral oxygenation measurements during rest and physical challenges, potentially revealing slowing down of recovery. The challenges performed were an orthostatic challenge and a handgrip challenge, measuring maximum grip strength and grip work.

From measurements in rest, dynamical indicators of resilience (DIORs) have been calculated before. In BP signals it has previously been shown that DIORs might be indicative of resilience, although their predictive value for cognitive decline seemed limited (see Chapter 3 and Appendix B). Often, absolute BP values are lowered by medication to prevent aneurysm rupture. Therefore, absolute cerebral oxygenation values may be more suited to include in resilience estimations. Besides the already extensively used perioperative monitoring of cerebral oxygenation, baseline preoperative cerebral oxygenation values have been shown to correlate with complications after cardiothoracic surgery [92-94]. Furthermore, oxygenation values have been shown to decrease with age [95]. As resilience generally decreases with age, factors correlated with ageing, such as a declined cerebral oxygenation, may be related to resilience as well.

The orthostatic and handgrip challenge both cause a disturbance on the human body, and more specifically the cardiovascular system, as a complex system. Impaired orthostatic BP recovery has already been linked to fast cognitive decline in AD patients and to mortality in falls clinic patients. These results fit into the complex system theory of physical resilience, indicating that slowing down of recovery is related to a loss of resilience [14, 30, 31]. The response of cerebral oxygenation to an orthostatic challenge has been investigated before with mixed results. Slower recovery has been related to diseases such as depression [96]. BP and cerebral oxygenation recovery in response to a handgrip challenge have not been assessed before, to our knowledge. Sustained handgrip, as also measured in a grip work measurement causes an immediate, temporary rise in BP and cerebral oxygenation. We explored if a recovery phase is present after this rise as well, and if that can be used as a challenge in resilience research, possibly providing an alternative for the orthostatic challenge.

Additionally, the grip challenge itself can provide a resilience measure as well. Grip strength is an already frequently used measure for frailty [97]. Adding a time component to the grip strength measurement, by sustaining maximum grip as long as possible, makes the measurement more dynamical. In this way, fatiguability and physical reserve of a system are tested as well, making grip work, in contrast to grip strength, a possible resilience indicator [98]. Grip work has previously been related to dependency in activities of daily living and self-rated physical functioning in community-dwelling older adults [99, 100].

The aim of this study was to implement different simple resilience measurements in clinical practice and investigate feasibility of routine clinical use. Simultaneously, the relation between resilience indicators and outcome after major cardiothoracic surgery (thoracic aortic surgery) was assessed, as our ultimate goal is to use resilience measurements as a tool to complement standard (preoperative) assessment.

4.2 Methods

4.2.1 Study design and population

This is a preliminary analysis of a prospective study performed at the cardiothoracic surgery outpatient clinic from February 2020 onwards. The study is planned to continue at least until 2022. Consecutive patients were included in this analysis when they visited the comprehensive preoperative assessment between February and August 2020. The assessment included a visit at a cardiothoracic surgeon, anaesthesiologist, physiotherapist and cardiology nurse, complemented with a short geriatric assessment for patients aged ≥70 years or patients who were otherwise considered to be frail. All patients who were planned to undergo elective open thoracic aortic surgery were included. Exclusion criteria were being physically (inability to take a standing position from sitting) or mentally (inability to understand given instructions) unable to perform the resilience tests. The study was approved by the medical ethics committee (CMO Arnhem-Nijmegen). Written informed consent was obtained from all participants.

4.2.2 Short geriatric assessment

For patients who visited a geriatrician as part of their preoperative assessment, BP, cerebral oxygenation and handgrip measurements were complemented with:

- The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS) questionnaire, covering different domains like physical health, activities in daily life, mental health, social activities, quality of life and independence [101];
- Rosow-Breslau-Nagi questionnaire consisting of questions for (heavy) physical activities, resulting in a score between 0 and 8 (0 meaning no problems at all, 8 meaning problems at all points assessed by this questionnaire) [102];
- Life space assessment, concerning someone's action radius, score from 0 (staying in the bedroom all day) to 120 (goes outside city or village every day) [103];
- Montreal cognitive assessment (MoCA) to determine cognitive status [66];
- 5 times repeated chair-stand test and gait speed: a screening test for muscle strength in legs;
- Clinical frailty scale: phenotype-based scale of frailty between 1 (very fit) and 10 (critically ill) [104];
- CGA frailty index: frailty index proposed by Beth Israel Deaconess Medical Center, Boston, combining medical history, (instrumental) activities of daily living, Rosow-Breslau-Nagi questions, MoCA, 5 repeated chair-stands, gait speed, handgrip strength and nutritional status. This results in a value between 0 and 1 (0 meaning non-frail and 1 severely frail), for which an online calculation tool is available [105].

4.2.3 Data collection

Our measurement protocol, containing an orthostatic and grip challenge, is shown in Figure 10. For the orthostatic challenge, participants were instructed to sit still for 5 minutes, and not to talk to prevent head motion. Subsequently, they stood up and remained standing for 3 minutes. After the orthostatic challenge, patients became seated again and started the grip challenge, in which they were asked to squeeze maximally for 3 times, with their dominant hand, using a Martin vigorimeter [106]. The large bulb was used, as this size is least dependent on hand size and could be used for both tall and short men and women [107]. The third attempt, the patients were encouraged to remain squeezing until fatigue resistance was reached. Fatigue resistance is defined as the time between maximum grip strength and a 50% decrease during that attempt.

Figure 10: Clinical measurement protocol, including an orthostatic challenge (a baseline measurement consisting of 5 minutes of sitting followed by 3 minutes of standing) and a grip challenge (repeated (2x) grip strength measurement and grip work measurement, followed by 1 minute of rest). During these challenges, both blood pressure and cerebral oxygenation were measured continuously.

During the entire protocol, BP was measured continuously with volume-clamp photoplethysmography (Finapres Medical Systems, Enschede, The Netherlands) in the digital artery of the middle finger of the non-dominant hand. The non-dominant hand was held at heart height using a sling, during the entire measurement protocol. BP and grip strength were recorded in the data acquisition programme Acqknowledge (version 4, BioPac Systems Inc., Goleta, USA). Frontal lobe oxygenation was measured continuously using continuous-wave near-infrared spectroscopy (NIRS; Portalite, Artinis Medical Systems, Elst, The Netherlands), with sensors placed bilaterally on the forehead. The NIRS devices consist of three transmitters emitting light with wavelengths of 760 and 850 nm and one receiver [108]. Relative values for deoxygenated haemoglobin (HHb) and oxygenated haemoglobin (O_2Hb) were determined in Oxysoft (version 3.0, Artinis Medical Systems, Elst, The Netherlands) using the modified Lambert-Beer law, and collected at a sampling frequency of 10 Hz. The differential pathway factor was determined according to a general equation by Scholkmann et al (2013) for patients below 50 years, and set to 6.61 for patients ≥50 years [109]. Tissue saturation index (TSI) was defined as:

$$TSI = \frac{\mathrm{O_2Hb}}{\mathrm{HHb}+\mathrm{O_2Hb}} \times 100$$

with O_2Hb and HHb the absolute concentrations calculated with spatially resolved spectroscopy, making use of all transmitters included in the NIRS device. Moreover, a TSI fit factor was calculated, indicating the quality of TSI estimation. Markers were set simultaneously in Oxysoft and Acqknowledge to synchronise BP and NIRS measurements (Portasync, Artinis Medical Systems, Elst, The Netherlands).

4.2.4 Data processing

Data were processed in MATLAB (2018a, MathWorks Inc., Natick, USA). BP and NIRS data were processed in a similar way as in Section 2.2.4, except for orthostatic recovery values being calculated from the moment of starting to stand up instead of from the moment of SBP nadir. Therefore, baseline values were determined as the average value between 40 and 10 seconds before standing up. Additionally, patients were excluded when it took more than 10 seconds to perform a sit-to-stand manoeuvre, since in that case a rapid BP drop is absent [110]. In contrast to Section 2.2.4, we used different NIRS devices, in which three optode pairs were present per side, allowing for TSI calculation. The middle pair of optodes, with an inter-optode distance of 35 mm was used for analysis of relative Hb concentrations. TSI measurements were excluded according to criteria

described previously by O'Connor et al. (2020) [111]. These were a TSI change of more than 45% overall or 10% during the sitting measurement, a TSI change of less than 0.1% within the first 30 s of standing, and an average TSI fit factor (representing the agreement between different optodes) below 98%. Correspondence with the manufacturer confirmed that the TSI fit factor should be at least 98%, but preferably 99.5%. Therefore, we scored TSI quality as good (fit factor ≥99.5%), moderate (fit factor ≥98% and <99.5%) or poor (fit factor <98%). We additionally excluded TSI measurements of moderate quality on one side when on the other side a good quality measurement was available. Otherwise, moderate quality was still included. Relative O_2Hb and HHb measurements were excluded when showing unrealistically sudden shifts, caused by loosening of a device. When measurements were available from both the left and the right side, relative Hb concentrations and TSI values from both sides were averaged.

From the grip challenge, the maximum grip strength (GS_{max}) of three measurements, fatigue resistance (FR) and grip work were extracted. Grip work (GW) was estimated using [100]:

$$GW = 0.75 * GSmax * FR$$

Moreover, grip strength and grip work were calculated per kg body weight, to indirectly correct for hand size and gender [99].

4.2.5 Statistical analysis

Continuous parameters were presented as mean (SD; range from minimum to maximum value), and categorical variables as number (%). Outcome parameters were dichotomised based on length of hospital stay. Differences between these groups in preoperative parameters were explored and tested for significance ($p<0.05$) using Fisher's exact tests for categorical variables and Mann-Whitney U tests for continuous variables.

4.3 Results

4.3.1 Patient characteristics

Consecutively, 27 patients were included at the cardiothoracic surgery outpatient clinic, of whom 14 had a geriatric assessment. The included patients were on average 63.0 (13.3) years old, and 70% were men. Relatively young included patients were mostly suffering from connective tissue disease (Ehlers Danlos syndromes or Marfan's syndrome), accounting for 15% of all patients. Surgical indications varied, with an average number of 1.7 (0.8). These often consisted of a combination of a thoracic aortic aneurysm and aortic valve repair. All baseline characteristics are shown in Table 5.

Table 5: Patient characteristics. At the moment of writing this report, not all patients have had surgery yet, hence the lower number of patients with postoperative outcomes, who have been subdivided into a short and a long hospital stay group.

Characteristic	**All patients**	**Short (<10 days) hospital stay**	**Long (>13 days) hospital stay**	**P-value**
	n=27	**n=5**	**n=5**	
Age (years)	63.0 (13.3; 25-78)	51.2 (17.5)	65.6 (7.0)	0.294
Male	19 (70%)	5 (100%)	4 (80%)	1.000
BMI (kg/m^2)	27.1 (4.4; 18.4-37.7)	25.6 (4.2)	28.1 (3.9)	0.889
Connective tissue disease	4 (15%)	2 (40%)	1 (20%)	1.000
Hypertension	15 (56%)	1 (20%)	5 (100%)	0.048*
Diabetes	1 (4%)	0	0	NA

Previous cardiothoracic surgery	6 (22%)	1 (20%)	2 (40%)	1.000
Antihypertensive drug use	22 (81%)	4 (80%)	4 (100%)	1.000
Beta blocker use	17 (63%)	3 (60%)	3 (60%)	1.000
SBP at screening (mmHg)‡	130.5 (26.5; 87-190)	139.0 (24.4)	123.5 (9.5)	0.222
DBP at screening (mmHg)‡	80.5 (11.7; 49-98)	80.2 (10.2)	87.5 (7.7)	0.492
Geriatric assessment	14 (52%)	1 (20%)	3 (60%)	0.524
Clinical frailty score†	3.0 (1.2; 1-6)			
CGA frailty index†	0.133 (0.095; 0.020-0.372)			
Gait speed (m/s)†	1.0 (0.25; 0.5-1.3)			
5x chair-stand (s)†	13.1 (3.9; 9.0-22.5)			
MoCA score†	24.6 (2.8; 20-29)			
Rosow-Breslau-Nagi score†	1.3 (2.0; 0-5)			
Life space assessment†	89.8 (28.0; 11-120)			
Number of surgical indications	1.7 (0.8; 1-4)	1.6 (0.5)	1.4 (0.5)	1.000
Aortic root aneurysm	4 (15%)	3 (60%)	0 (0%)	0.167
Aortic arch aneurysm	2 (7%)	0	0	NA
Ascending TAA	7 (26%)	1 (20%)	1 (20%)	1.000
Descending TAA	4 (15%)	0	0	NA
TAAA	6 (22%)	0 (0%)	3 (60%)	0.167
Thoracic aortic type B dissection	2 (7%)	0	1 (20%)	1.000
Aortic valve stenosis	9 (33%)	2 (40%)	1 (20%)	1.000
Aortic valve insufficiency	2 (7%)	1 (20%)	0 (0%)	1.000
Vasculitis	1 (4%)	0 (0%)	1 (20%)	1.000
Suspected thymoma	1 (4%)	1 (20%)	0 (0%)	1.000
Subclavian artery aneurysm	1 (4%)	0	0	NA
Atrial fibrillation	2 (7%)	0	0	NA
Coronary artery disease	3 (11%)	0	0	NA
Hypertrophic cardiomyopathy	1 (4%)	0	0	NA

SBP: systolic blood pressure, DBP: diastolic blood pressure, CGA: comprehensive geriatric assessment, MoCA: Montreal cognitive assessment, TAA: thoracic aortic aneurysm, TAAA: thoracoabdominal aortic aneurysm. Continuous variables are presented as mean (SD; range) and tested using Mann-Whitney U tests, categorical variables are presented as number (%) and tested for significant using Fisher's exact test.

* Significant differences between short-stay group and group with longer duration of hospital stay.

† Only available for patients who had a geriatric assessment (n=14).

‡ Measured at the preoperative visit, using an oscillometric device, missing for one patient.

4.3.2 Preliminary results

Outcome after surgery, as was available for 12 patients, is presented in Table 6. On average (SD), the hospital stay after surgery was 13.1 (9.8) days, with an ICU stay of 1.5 (0.7) days. Different complications occurred during the hospital stay, most often consisting of fever caused by a pulmonary or urinary tract infection, or atrial fibrillation needing medical treatment (arrhythmia). An uncomplicated recovery at the hospital was associated with a short hospital stay of 5-9 days. As already shown in Table 5, baseline characteristics did not differ significantly between patients with a short and with a long hospital stay, except for having a history of hypertension.

Table 6: Outcome parameters (n=12).

Parameter	Value
Duration of hospital stay (days)†‡	13.1 (9.8; 5-37)
Duration of ICU stay (days)‡	1.5 (0.7; 1-3)
Complications during hospital stay	
Delirium	2 (17%)
Infection	4 (33%)
Arrhythmia	3 (25%)
Cerebrovascular accident	2 (17%)
Kidney complication	1 (8%)
Gastro-intestinal complication	1 (8%)
In-hospital mortality	1 (8%)

Continuous variables are presented as mean (SD; range), categorical variables are presented as number (%).

† Unknown for patients who went to the cardiology department of another hospital after discharge from the Radboudumc, and have not had a follow-up consult by phone yet (n=2).

‡ Patients who deceased during ICU stay were not included for this parameter (n=1).

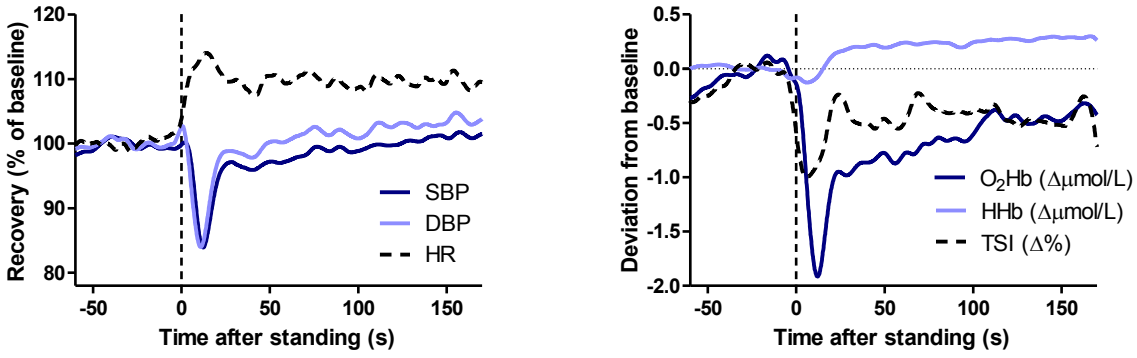


Figure 11: Orthostatic challenge, shown as mean value over time for A) systolic and diastolic blood pressure (SBP (dark blue) and DBP (light blue) respectively) and heart rate (HR, shown in dashed black), n=26 and for B) oxygenated and deoxygenated haemoglobin (O_2Hb (dark blue) and HHb (light blue) respectively) and tissue saturation index (TSI; shown in dashed black), n=25. All trajectories are shown relative to the baseline value at 40 to 10 s before standing up. At t=0 s patients stood up.

In Figure C.1 in Appendix C, a flowchart describing the exclusion of subjects and signal quality is presented. In Figure 11, the course during an orthostatic challenge is shown for all physiological signals that were measured, relative to the baseline sitting value. One patient was excluded for not being able

to stand up within 10 seconds. Standing up took between 1.2 and 5.4 seconds with a mean (SD) of 2.5 (1.0) seconds. Upon standing, both SBP and DBP decrease, coming from a mean (SD) absolute finger SBP/DBP of 122/68 (26/17) mmHg. BP reaches a nadir in approximately 10-15 seconds. After the initial drop, BP rises again and recovers slowly to baseline values. Heart rate increases immediately upon standing and stabilises above baseline values. On average, relative O_2Hb shows a drop upon standing, while relative HHb shows a small increase. TSI decreased upon standing, starting from an average baseline TSI of 73.4 (5.6)%. The TSI responses were heterogeneous, having a standard deviation of at least 2% during the entire orthostatic challenge. Between patients with a fast hospital discharge and patients who had a longer stay, slightly different average BP and cerebral oxygenation trajectories could be observed (shown in Figure 12), but none of these were significantly different (p>0.309). Baseline TSI values did not differ significantly between both groups (73.9 (7.9)% versus 75.2 (3.6)%; p=1.000).

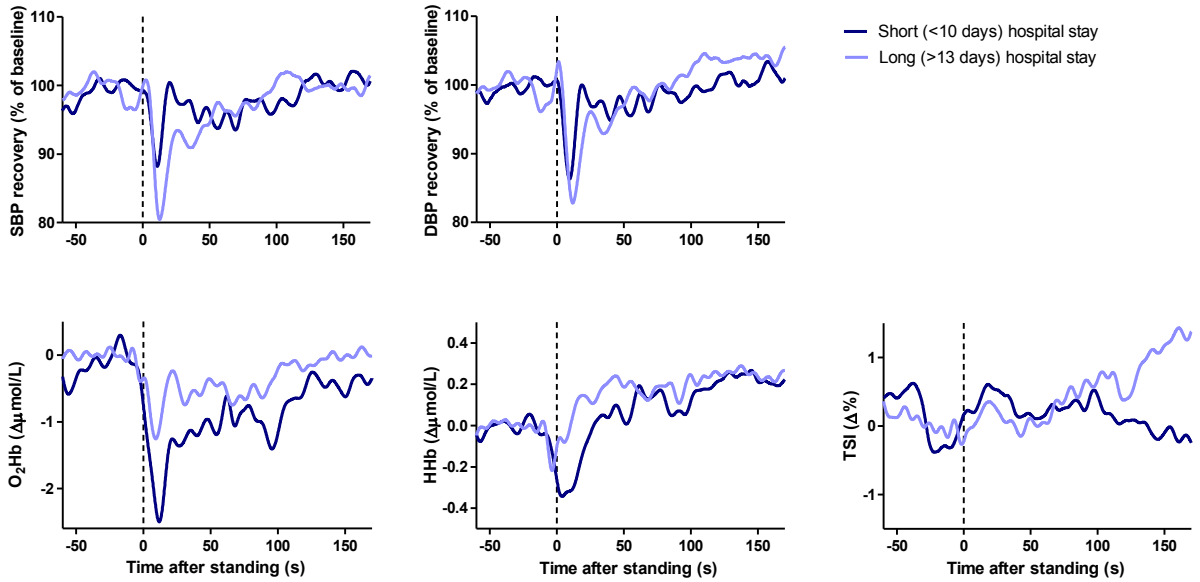


Figure 12: Preliminary results showing average responses upon standing of patients who had a relatively short hospital stay (<10 days; n=5; in dark blue) and patients with a relatively long stay (>13 days; n=5; in light blue). The upper figures show the systolic blood pressure (SBP) and diastolic blood pressure (DBP) response, and the lower figures the relative change in oxygenated and deoxygenated haemoglobin (O_2Hb and HHb respectively) and change in tissue saturation index (TSI) after standing.

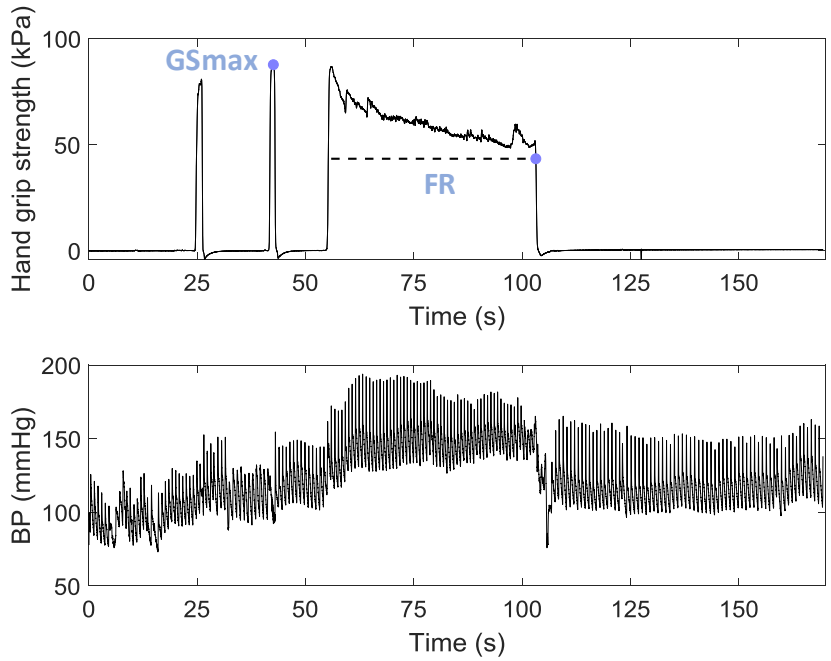


Figure 13: Example of grip challenge for one patient: the patient squeezed two times maximally, followed by a grip work measurement, combining maximum grip strength and endurance. Maximum grip strength (GSmax) and fatigue resistance (FR) are indicated by blue dots.

In Figure 13, an example of the grip challenge is shown, representing squeezing maximally twice, and the third attempt represents the grip work measurement of squeezing maximally and sustaining as long as possible (until fatigue resistance is reached). Simultaneous continuous BP recording shows an increase in SBP as well as DBP during sustained grip. Some abrupt changes in BP can be seen, occurring while starting to squeeze and releasing grip strength. In Table 7, average values of the grip strength measurements are shown for all patients, but also split based on duration of hospital stay. Maximum grip strength showed a trend to be higher for patients with a short hospital stay compared to those who stayed longer at the hospital, but corrected for body weight this trend disappeared.

Table 7: Outcome parameters resulting from the grip challenge.

Parameter	**Value** n=27	**Short (<10 days) hospital stay** n=5	**Long (>13 days) hospital stay** n=5	**P-value**
Maximum grip strength (kPa)	82.6 (28.3; 38.0-138.4)	106.9 (17.7)	74.7 (26.1)	0.056
Maximum grip strength/kg body weight (kPa/kg)	0.97 (0.28; 0.44-1.55)	1.2 (0.27)	0.87 (0.29)	0.222
Fatigue resistance (s)*	43.3 (26.1; 5.7-94.0)	53.5 (30.0)	36.5 (26.1)	0.421
Estimated grip work ($\times 10^3$ kPa s)*	2.47 (1.60; 0.20-5.00)	3.86 (1.82)	1.93 (1.41)	0.095
Estimated grip work/kg bodyweight (kPa s/kg)*	30.0 (20.4; 2.5-67.3)	45.1 (23.2)	22.4 (17.1)	0.222

Data are presented as mean (SD; range)

*11 patients did not sustain until their grip strength dropped to 50%; the time until they loosened handgrip was taken as fatigue resistance.

4.3.3 Feasibility of clinical implementation

Quantitative resilience measurements were successfully implemented in the workflow at the cardiothoracic surgery preoperative outpatient clinic. Per patient, the preoperative visit took approximately 30 minutes to shortly explain the measurements, sign informed consent forms and perform the orthostatic and grip challenge. Without a need for informed consent, the measurements themselves could be performed in 15-20 minutes. Follow-up measurements were planned simultaneously with the three-month follow-up visit patients had at the cardiothoracic surgeon and took 15-20 minutes. However, in practice, not all patients who were referred from hospitals relatively far away came to the Radboudumc for a follow-up visit. Therefore, we could only perform follow-up by phone, leading to missing follow-up measurements. Of all patients that were eligible for inclusion, 95% were willing to participate, and measurements were well-tolerated. Patients scaled them on average (SD) 2.0 (1.2) on a scale from 1 to 10 (1 not burdensome at all; 10 very burdensome and tiring). Technically, measuring in a clinical setting with time constraints had some consequences. BP measurements were available in all patients. In 4 patients, relative O_2Hb and HHb were only available on one side, mainly due to temporarily loosening of one NIRS device, leading to sudden shifts. TSI was only available on one side in 5 patients, and quality was moderate on one side in 16 patients, leading to exclusion of TSI on one side in 21 patients. For 4 patients, TSI quality was moderate on both sides. However, these measurements were still included, as TSI values and courses were reasonable. Altogether, cerebral oxygenation measurements were only excluded for one patient due to loosening of the device, but signal quality did not influence the number of exclusions. This is specified in Figure C.1 in Appendix C. During the grip challenge, 11 patients did not sustain until fatigue resistance was reached, for various reasons. These reasons ranged from muscle cramp or pain to instructions to stop squeezing accidentally given too early. However, we still considered time until letting go of grip strength to be the fatigue resistance. Geriatricians' opinion on feasibility of standard application of orthostatic BP and grip measurements is dependent on the availability of interpretable outcome measures. These ideally consist of a list of individual values relative to reference values for patients of that gender and age, saying if and to what extent a patient's performance is above or below what could have been expected. When such easily interpretable outcome values become available, clinicians see added value of these measurements in practice. For orthostatic BP measurements, cut-off values for orthostatic hypotension (BP drop of (SBP/DBP) ≥20/10 mmHg) or diminished orthostatic recovery (≤95% of baseline value) are already available [24, 30]. For handgrip strength and work, the aim is to collect reference data for patients of different gender and age groups, but these are not available yet.

4.4 Discussion

Clinical implementation of quantitative resilience measures was successful and feasible. Patients were able to perform the orthostatic and grip challenge, and these were well-tolerated. Preliminary results show that we retrieved data of sufficient quality of orthostatic BP and relative cerebral oxygenation, and grip measurements.

4.4.1 Orthostatic challenge

For all patients, BP measurements and relative O_2Hb and HHb measurements during sitting and standing could be retrieved, and showed realistic courses upon standing, comparable with previous literature [18, 30, 112]. TSI values seemed slightly less reliable, although on average their course upon standing was comparable to what has been described in previous research, showing a decrease followed by an overshoot and recovery phase [96, 112]. Left-right differences were large, and many

TSI measurements (on one side) had to be excluded. This could have been caused by a need for recalibration. Nevertheless, regarding BP and relative oxygenation values, the orthostatic challenge was technically feasible to determine resilience. In contrast to our research in elderly with MCI (see Chapter 2), we determined recovery from the moment of standing up, which was defined as the moment the patient started to stand up and heart rate increased. We set two different markers, when starting to stand and when an upright position was fully assumed. In that way, we were able to determine if a sit-to-stand manoeuvre took so long that the actual challenge (the BP drop) was not there. This was the case for only one of our included patients.

4.4.2 Grip challenge

The use of grip strength and grip work measurements appeared to be feasible in a preoperative outpatient clinic setting. Grip strength values, ranging from 43.5 kPa in a small woman to 138 kPa in a taller man, were comparable to known values from previous studies [113, 114]. However, fatigue resistance values should be interpreted with caution, as for various reasons some of our patients did not reach fatigue resistance, and average values are therefore lower than reported previously [100, 113]. These patients were not excluded, as muscle cramp after a few seconds or a mental component could give an indication of fatigability, and therefore contains valuable information. BP measurements during the grip challenge were distorted in most patients. Although patients were squeezing the bulb with their dominant hand, and the BP device was attached to the non-dominant hand, the distortion may have been caused by muscle tension or movements of the non-dominant hand. The abrupt changes in BP caused by exerting force make intermediate calibrations of the BP signal necessary to prevent stabilization of the measurement at an erroneous BP level [37]. However, the built-in calibration function was turned off during the entire measurement, to prevent calibration artefacts. Moreover, releasing pressure on the handgrip balloon led to an immediate fall in BP. No recovery phase was visible to be used as resilience measure. Instead of using BP and oxygenation recovery after a stressor, these measurements might still be useful. Assessing the difference between BP and cerebral oxygenation values before and during squeezing might be a measure for autonomic function. Ewing's standard battery, a set of tests to determine cardiovascular autonomic dysfunction, uses this. Changes in diastolic BP caused by sustained exertion of force are then thought to reflect autonomic function [50, 115].

4.4.3 Clinical value

Some of the resilience measures that were implemented are already being introduced in clinical practice, especially in geriatric medicine. At the geriatric outpatient clinic, a routine orthostatic BP measurement is already performed, as a screening tool for orthostatic hypotension. BP is then measured while lying, and at 1, 3 and 5 minutes of standing, using an oscillometric device. This measurement could easily be replaced by our orthostatic challenge protocol, when extending the standing measurement to 5 minutes and replace sitting by lying. In this way, two different questions could be answered on an individual basis. The first one concerns a more reliable diagnosis of orthostatic hypotension [23]. As the entire BP curve upon standing is known, complaints such as dizziness and light-headedness may be explained more easily. Eventually, even more insight into these complaints could be given by supplementing the BP measurement with a cerebral oxygenation measurement as used in our study or another measure of cerebral perfusion. Second, a diminished or delayed BP recovery, defined as not reaching 95% BP recovery after an orthostatic challenge, might provide additional insight into the patient's resilience [30]. Apart from the orthostatic challenge, grip

strength, fatigue resistance and grip work are already being implemented at the outpatient clinic, to determine muscle strength and fatigability. Robust reference values per age group and gender are only available for grip strength, and not yet for fatigue resistance and grip work. Nevertheless, routine use of grip strength and grip work measurements could aid in collecting a large dataset to provide a more extensive set of reference values. Moreover, international collaboration with other researchers who are also collecting grip work data is set up to provide a reference dataset for clinicians.

4.4.4 Recommendations

Preliminary results between two groups based on the duration of hospital stay are not interpretable yet, as this duration was known for only 10 patients. Our preliminary results were compared between two groups, based on the duration of hospital stay. For now, the division was made between a completely uncomplicated stay and a stay with minor or major complications. When a larger study sample becomes available, it would be more sufficient to distinguish different groups: a group having no or minor complications and a group with major complications. In this way, identification of patients at risk of major complications, which is clinically most relevant, could be investigated, to be able to offer them a prehabilitation programme, or even refrain from surgery at all. Moreover, baseline characteristics such as surgical indication and procedures, age and comorbidity varied widely among the included patients, emphasizing the necessity of a large study sample. Preoperative parameters retrieved from continuous BP, cerebral oxygenation and handgrip measurements, could be linked to various adverse outcomes separately. It should be investigated what additional predictive value our resilience measurements have above the conventional frailty estimation in older adults, and above already known baseline characteristics.

As a next step, the follow-up data, until now consisting of medical records and follow-up measurements at approximately 3 months after surgery, can be complemented with more visits during hospital stay. Additionally, our research could be combined with other studies performing questionnaires after ICU admission, a study population overlapping with ours, for example regarding quality of life. In this way, more insight could be gained into the extent of recovery of different outcome measures to or preferably above the preoperative state, and the individual recovery curve could be assessed as accurately as possible.

Therefore, our main recommendation is to continue performing these measurements in clinical practice at the cardiothoracic outpatient clinic, to directly apply them. The retrieved information could be used in the advice to the treating surgeon and the patient and caregivers. Moreover, measurements could be introduced more routinely in clinical practice, starting with the geriatric outpatient clinic, at which a similar orthostatic challenge is already performed. This broad use of resilience measurements can lead to a large and heterogeneous, but therefore also representative, cohort to further establish the concept of physical resilience. Eventually, evaluation of resilience prior to surgery may aid the information given to patients and caregivers. Patients could use the time before surgery to optimally prepare themselves by improving their resilience, for instance by staying active or reduce alcohol use. Receiving feedback on their personal extent of resilience may aid in following these guidelines.

4.4.5 Conclusion

In conclusion, this clinically embedded study answers the need for gaining more insight into processes underlying recovery from surgery, especially in elderly. We showed feasibility of clinical use of resilience measurements based on haemodynamic signals and grip strength.

C. Exclusion of subjects and signal quality

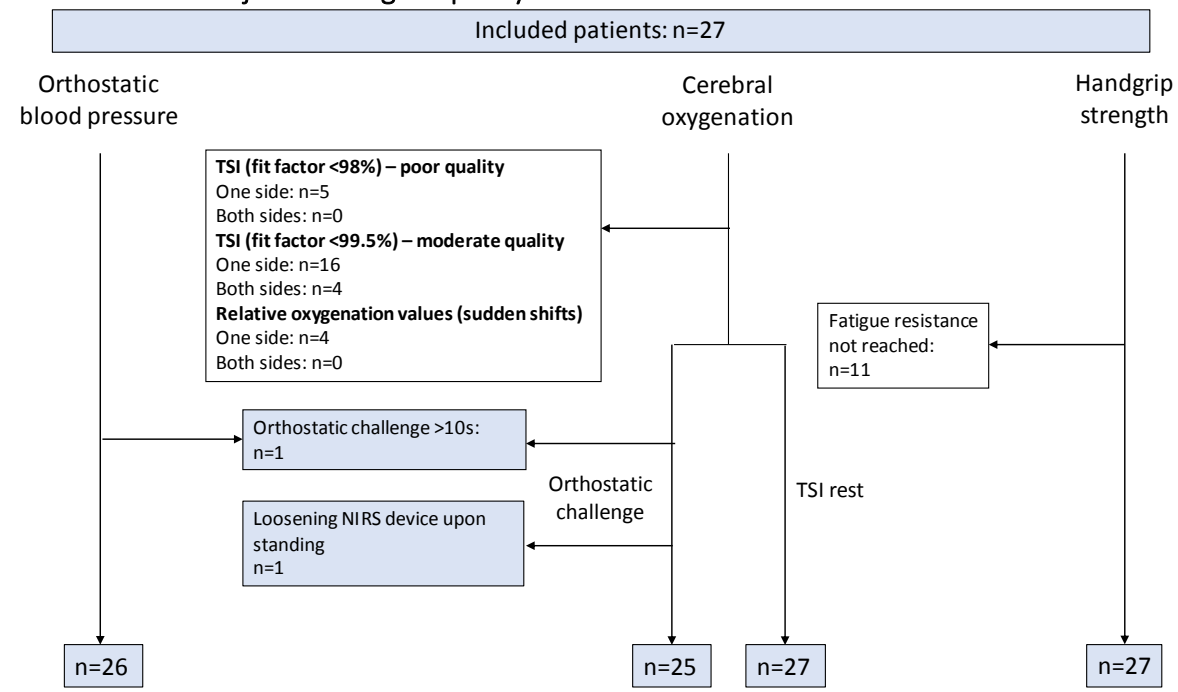


Figure C.1: Flowchart describing exclusion of subjects (in light blue) for orthostatic blood pressure, cerebral oxygenation (both orthostatic and rest) and handgrip strength measurements. Moreover, signal quality has been indicated. For TSI, signals of good quality (TSI fit factor >99.5%) were used when available averaged from both sides. When TSI on only one side was of good quality, the other side was removed. When no TSI of good quality was present, TSI with moderate quality was used, either averaged when present on both sides, or of only one side. Patients who did not reach fatigue resistance, were not excluded. Eventually, orthostatic blood pressure recovery could be analysed for 26 patients, orthostatic cerebral oxygenation recovery for 25 patients, and resting TSI and handgrip for all 27 patients. TSI: tissue saturation index, NIRS: near-infrared spectroscopy.

5. General conclusion

In this thesis, different methods to quantify resilience have been investigated. These were used to determine the relation between resilience and cognitive status, and whether quantitative resilience measures could be predictive of cognitive decline. Ultimately, clinical implementation of these quantitative resilience measures was performed and evaluated.

In relation to cognitive decline, results suggest that challenging the human body may be necessary to assess resilience in relative remoteness of a critical transition in rest. We mainly focussed on acquiring resilience measures from continuous BP measurements, as these seem most robust, and only little influenced by artefacts. CBF and NIRS measurements were investigated as well during an orthostatic challenge in relation to cognitive decline. However, the added value of these, being both cerebral perfusion measures, in addition to BP measurements remains unknown. Cerebral perfusion is even more tightly regulated than BP, by means of cerebral autoregulation. Therefore, both CBF and cerebral oxygenation show a smaller drop after standing than BP. This may imply that the challenge of standing on CBF and cerebral oxygenation is smaller than on BP, which may make BP more suitable for capturing loss of resilience.

Altogether, our results imply that challenging the body as a complex system can provide more insight into functioning and dysfunction of subsystems, in this case the cardiovascular system. For now, resilience obtained from BP and handgrip measurements seems most appropriate for routine implementation in clinical practice, mainly because of the easy and fast execution and relatively straightforward interpretation. In the future, research consisting of routinely collecting time series of physiological data, whether or not directly embedded in clinical practice, may provide new insights into the role of resilience in estimating physical reserve and recovery potential around treatment.

6. References

1. *An Aging Population And Growing Disease Burden Will Require ALarge And Specialized Health Care Workforce By 2025.* Health Affairs, 2013. **32**(11): p. 2013-2020.
2. Etzioni, D.A., et al., *The aging population and its impact on the surgery workforce.* Ann Surg, 2003. **238**(2): p. 170-7.
3. Whitson, H.E., et al., *Physical Resilience: Not Simply the Opposite of Frailty.* Journal of the American Geriatrics Society, 2018. **66**(8): p. 1459-1461.
4. Varadhan, R., J.D. Walston, and K. Bandeen-Roche, *Can a Link Be Found Between Physical Resilience and Frailty in Older Adults by Studying Dynamical Systems?* Journal of the American Geriatrics Society, 2018. **66**(8): p. 1455-1458.
5. Scheffer, M., et al., *Early-warning signals for critical transitions.* Nature, 2009. **461**(7260): p. 53-59.
6. Gauthier, S., et al., *Mild cognitive impairment.* The Lancet, 2006. **367**(9518): p. 1262-1270.
7. Albert, M.S., et al., *The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroupson diagnostic guidelines for Alzheimer's disease.* Alzheimer's & dementia : the journal of the Alzheimer's Association, 2011. **7**(3): p. 270-279.
8. Csukly, G., et al., *The Differentiation of Amnestic Type MCI from the Non-Amnestic Types by Structural MRI.* Front Aging Neurosci, 2016. **8**: p. 52.
9. Mitchell, A.J. and M. Shiri-Feshki, *Temporal trends in the long term risk of progression of mild cognitive impairment: a pooled analysis.* J Neurol Neurosurg Psychiatry, 2008. **79**(12): p. 1386-91.
10. Lennon, M.J., et al., *Midlife Hypertension and Alzheimer's Disease: A Systematic Review and Meta-Analysis.* J Alzheimers Dis, 2019. **71**(1): p. 307-316.
11. Wolters, F.J., et al., *Cerebral Perfusion and the Risk of Dementia: A Population-Based Study.* Circulation, 2017. **136**(8): p. 719-728.
12. den Abeelen, A.S., et al., *Impaired cerebral autoregulation and vasomotor reactivity in sporadic Alzheimer's disease.* Curr Alzheimer Res, 2014. **11**(1): p. 11-7.
13. Yeung, M.K. and A.S. Chan, *Functional near-infrared spectroscopy reveals decreased resting oxygenation levels and task-related oxygenation changes in mild cognitive impairment and dementia: A systematic review.* Journal of Psychiatric Research, 2020. **124**: p. 58-76.
14. Olde Rikkert, M.G., et al., *Slowing Down of Recovery as Generic Risk Marker for Acute Severity Transitions in Chronic Diseases.* Crit Care Med, 2016. **44**(3): p. 601-6.
15. Olde Rikkert, M.G.M. and R.J.F. Melis, *Rerouting Geriatric Medicine by Complementing Static Frailty Measures With Dynamic Resilience Indicators of Recovery Potential.* 2019. **10**(723).
16. Kaufmann, H., L. Norcliffe-Kaufmann, and J.-A. Palma, *Baroreflex Dysfunction.* New England Journal of Medicine, 2020. **382**(2): p. 163-178.
17. Low, P.A. and V.A. Tomalia, *Orthostatic Hypotension: Mechanisms, Causes, Management.* Journal of clinical neurology (Seoul, Korea), 2015. **11**(3): p. 220-226.
18. van Wijnen, V.K., et al., *Noninvasive beat-to-beat finger arterial pressure monitoring during orthostasis: a comprehensive review of normal and abnormal responses at different ages.* J Intern Med, 2017. **282**(6): p. 468-483.
19. Payne, S., *Cerebral Autoregulation: Control of Blood Flow in the Brain*. 2016: Springer International Publishing.
20. Kim, Y.S., et al., *Effects of aging on the cerebrovascular orthostatic response.* Neurobiol Aging, 2011. **32**(2): p. 344-53.
21. Lieshout, J.J.V., et al., *Syncope, cerebral perfusion, and oxygenation.* Journal of Applied Physiology, 2003. **94**(3): p. 833-848.
22. Rosengarten, B. and M. Kaps, *Peak Systolic Velocity Doppler Index Reflects Most Appropriately the Dynamic Time Course of Intact Cerebral Autoregulation.* Cerebrovascular Diseases, 2002. **13**(4): p. 230-234.

23. Finucane, C., et al., *Age-Related Normative Changes in Phasic Orthostatic Blood Pressure in a Large Population Study.* Circulation, 2014. **130**(20): p. 1780-1789.
24. Freeman, R., et al., *Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome.* Clin Auton Res, 2011. **21**(2): p. 69-72.
25. Harms, M.P., et al., *Orthostatic tolerance, cerebral oxygenation, and blood velocity in humans with sympathetic failure.* Stroke, 2000. **31**(7): p. 1608-14.
26. Cremer, A., et al., *Orthostatic Hypotension and Risk of Incident Dementia: Results From a 12-Year Follow-Up of the Three-City Study Cohort.* Hypertension, 2017. **70**(1): p. 44-49.
27. O'Hare, C., et al., *Cognitive Status, Gray Matter Atrophy, and Lower Orthostatic Blood Pressure in Older Adults.* J Alzheimers Dis, 2017. **57**(4): p. 1239-1250.
28. Wolters, F.J., et al., *Orthostatic Hypotension and the Long-Term Risk of Dementia: A Population-Based Study.* PLoS Med, 2016. **13**(10): p. e1002143.
29. Rawlings, A.M., et al., *Association of orthostatic hypotension with incident dementia, stroke, and cognitive decline.* Neurology, 2018. **91**(8): p. e759-e768.
30. Lagro, J., et al., *Impaired Systolic Blood Pressure Recovery Directly After Standing Predicts Mortality in Older Falls Clinic Patients.* The Journals of Gerontology: Series A, 2013. **69**(4): p. 471-478.
31. de Heus, R.A.A., et al., *Orthostatic Blood Pressure Recovery Is Associated With the Rate of Cognitive Decline and Mortality in Clinical Alzheimer's Disease.* The Journals of Gerontology: Series A, 2020.
32. Feeney, J., N. O'Leary, and R.A. Kenny, *Impaired orthostatic blood pressure recovery and cognitive performance at two-year follow up in older adults: The Irish Longitudinal Study on Ageing.* Clin Auton Res, 2016. **26**(2): p. 127-33.
33. Mehagnoul-Schipper, D.J., et al., *Cerebral oxygenation declines in healthy elderly subjects in response to assuming the upright position.* Stroke, 2000. **31**(7): p. 1615-20.
34. Kim, Y.-S., et al., *Effects of aging on the cerebrovascular orthostatic response.* Neurobiology of Aging, 2011. **32**(2): p. 344-353.
35. Sanders, M.L., et al., *NeuroExercise: The effect of a 12-month exercise intervention on cognition in mild cognitive impairment - A multicenter randomized controlled trial.* Medicine & Science in Sports & Exercise, under review.
36. Devenney, K.E., et al., *The effects of an extensive exercise programme on the progression of Mild Cognitive Impairment (MCI): study protocol for a randomised controlled trial.* BMC Geriatr, 2017. **17**(1): p. 75.
37. Imholz, B.P., et al., *Fifteen years experience with finger arterial pressure monitoring: assessment of the technology.* Cardiovasc Res, 1998. **38**(3): p. 605-16.
38. Sammons, E.L., et al., *Influence of noninvasive peripheral arterial blood pressure measurements on assessment of dynamic cerebral autoregulation.* J Appl Physiol (1985), 2007. **103**(1): p. 369-75.
39. Aaslid, R., T.M. Markwalder, and H. Nornes, *Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries.* J Neurosurg, 1982. **57**(6): p. 769-74.
40. Lezama, G.F., et al., *Neuropsychological Assessment*. 2004: Oxford University Press.
41. de Heus, R.A.A., et al., *Dynamic Regulation of Cerebral Blood Flow in Patients With Alzheimer Disease.* Hypertension, 2018. **72**(1): p. 139-150.
42. van der Velde, N., et al., *Measuring orthostatic hypotension with the Finometer device: is a blood pressure drop of one heartbeat clinically relevant?* Blood Press Monit, 2007. **12**(3): p. 167-71.
43. Romero-Ortuno, R., et al., *Continuous noninvasive orthostatic blood pressure measurements and their relationship with orthostatic intolerance, falls, and frailty in older people.* J Am Geriatr Soc, 2011. **59**(4): p. 655-65.
44. Claassen, J.A., *Orthostatische hypotensie bij de oudere patiënt.* Nederlands Tijdschrift voor Geneeskunde, 2018. **162**: p. D1943.

45. VanderWeele, T.J., *Principles of confounder selection.* European Journal of Epidemiology, 2019. **34**(3): p. 211-219.
46. Hayakawa, T., et al., *Orthostatic Blood Pressure Behavior in People with Mild Cognitive Impairment Predicts Conversion to Dementia.* J Am Geriatr Soc, 2015. **63**(9): p. 1868-73.
47. Curreri, C., et al., *Orthostatic Changes in Blood Pressure and Cognitive Status in the Elderly.* Hypertension, 2016. **68**(2): p. 427-435.
48. Heus, R.A.A.d., et al., *Blood Pressure Variability and Progression of Clinical Alzheimer Disease.* 2019. **74**(5): p. 1172-1180.
49. Robertson, A.D., et al., *Orthostatic hypotension and dementia incidence: links and implications.* Neuropsychiatr Dis Treat, 2019. **15**: p. 2181-2194.
50. Femminella, G.D., et al., *Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature.* J Alzheimers Dis, 2014. **42**(2): p. 369-77.
51. Frewen, J., et al., *Cognitive performance in orthostatic hypotension: findings from a nationally representative sample.* J Am Geriatr Soc, 2014. **62**(1): p. 117-22.
52. Shaw, B.H., et al., *Optimal diagnostic thresholds for diagnosis of orthostatic hypotension with a 'sit-to-stand test'.* J Hypertens, 2017. **35**(5): p. 1019-1025.
53. Haaksma, M.L., et al., *Predicting Cognitive and Functional Trajectories in People With Late-Onset Dementia: 2 Population-Based Studies.* Journal of the American Medical Directors Association, 2019. **20**(11): p. 1444-1450.
54. Melis, R.J.F., M.L. Haaksma, and G. Muniz-Terrera, *Understanding and predicting the longitudinal course of dementia.* Curr Opin Psychiatry, 2019. **32**(2): p. 123-129.
55. Gijzel, S.M.W., et al., *Resilience in Clinical Care: Getting a Grip on the Recovery Potential of Older Adults.* 2019. **67**(12): p. 2650-2657.
56. Whitson, H.E., et al., *Physical Resilience in Older Adults: Systematic Review and Development of an Emerging Construct.* J Gerontol A Biol Sci Med Sci, 2016. **71**(4): p. 489-95.
57. Katura, T., et al., *Quantitative evaluation of interrelations between spontaneous low-frequency oscillations in cerebral hemodynamics and systemic cardiovascular dynamics.* NeuroImage, 2006. **31**(4): p. 1592-1600.
58. Yoshimoto, T., et al., *Frequency components of systolic blood pressure variability reflect vasomotor and cardiac sympathetic functions in conscious rats.* The Journal of Physiological Sciences, 2011. **61**(5): p. 373-383.
59. Chen, L., et al., *Detecting early-warning signals for sudden deterioration of complex diseases by dynamical network biomarkers.* Scientific Reports, 2012. **2**(1): p. 342.
60. Scheffer, M., et al., *Anticipating Critical Transitions.* Science, 2012. **338**(6105): p. 344.
61. Gijzel, S.M.W., et al., *Dynamical Resilience Indicators in Time Series of Self-Rated Health Correspond to Frailty Levels in Older Adults.* The Journals of Gerontology: Series A, 2017. **72**(7): p. 991-996.
62. Gijzel, S.M.W., et al., *Dynamical Indicators of Resilience in Postural Balance Time Series Are Related to Successful Aging in High-Functioning Older Adults.* The Journals of Gerontology: Series A, 2018. **74**(7): p. 1119-1126.
63. Lawlor, B., et al., *NILVAD protocol: a European multicentre double-blind placebo-controlled trial of nilvadipine in mild-to-moderate Alzheimer's disease.* BMJ Open, 2014. **4**(10): p. e006364.
64. Meulenbroek, O., et al., *European multicentre double-blind placebo-controlled trial of Nilvadipine in mild-to-moderate Alzheimer's disease—the substudy protocols: NILVAD frailty; NILVAD blood and genetic biomarkers; NILVAD cerebrospinal fluid biomarkers; NILVAD cerebral blood flow.* 2016. **6**(7): p. e011584.
65. Folstein, M.F., S.E. Folstein, and P.R. McHugh, *"Mini-mental state". A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res, 1975. **12**(3): p. 189-98.
66. Nasreddine, Z.S., et al., *The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment.* J Am Geriatr Soc, 2005. **53**(4): p. 695-9.

67. Electrophysiology, T.F.o.t.E.S.o.C.t.N.A.S.o.P., *Heart Rate Variability.* Circulation, 1996. **93**(5): p. 1043-1065.
68. Swenne, C.A., *Baroreflex sensitivity: mechanisms and measurement.* Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation, 2013. **21**(2): p. 58-60.
69. Rothwell, P.M., et al., *Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension.* The Lancet, 2010. **375**(9718): p. 895-905.
70. van de Leemput, I.A., et al., *Critical slowing down as early warning for the onset and termination of depression.* Proceedings of the National Academy of Sciences, 2014. **111**(1): p. 87-92.
71. Lawrence, V.A., et al., *Functional independence after major abdominal surgery in the elderly.* J Am Coll Surg, 2004. **199**(5): p. 762-72.
72. Maxwell, C.A., et al., *Preinjury physical frailty and cognitive impairment among geriatric trauma patients determine postinjury functional recovery and survival.* J Trauma Acute Care Surg, 2016. **80**(2): p. 195-203.
73. Seematter-Bagnoud, L., et al., *Predictors of functional recovery in patients admitted to geriatric postacute rehabilitation.* Arch Phys Med Rehabil, 2013. **94**(12): p. 2373-80.
74. Parati, G., *Blood pressure variability: its measurement and significance in hypertension.* J Hypertens Suppl, 2005. **23**(1): p. S19-25.
75. Parati, G., et al., *Assessment and management of blood-pressure variability.* Nature reviews. Cardiology, 2013. **10**: p. 143-55.
76. Newman, A.B., et al., *Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the Cardiovascular Health Study cohort.* J Am Geriatr Soc, 2005. **53**(7): p. 1101-7.
77. Xia, Y., et al., *Influence of beat-to-beat blood pressure variability on vascular elasticity in hypertensive population.* Scientific Reports, 2017. **7**(1): p. 8394.
78. Di Rienzo, M., et al., *Baroreflex contribution to blood pressure and heart rate oscillations: time scales, time-variant characteristics and nonlinearities.* Philos Trans A Math Phys Eng Sci, 2009. **367**(1892): p. 1301-18.
79. Varadhan, R., et al., *Stimulus-response paradigm for characterizing the loss of resilience in homeostatic regulation associated with frailty.* Mechanisms of ageing and development, 2008. **129**(11): p. 666-670.
80. Verma, A.K., et al., *Skeletal Muscle Pump Drives Control of Cardiovascular and Postural Systems.* Scientific Reports, 2017. **7**(1): p. 45301.
81. Shaffer, F. and J.P. Ginsberg, *An Overview of Heart Rate Variability Metrics and Norms.* Frontiers in public health, 2017. **5**: p. 258-258.
82. Haaksma, M.L., et al., *Cognitive and functional progression in Alzheimer disease: A prediction model of latent classes.* Int J Geriatr Psychiatry, 2018. **33**(8): p. 1057-1064.
83. Zanetti, O., S.B. Solerte, and F. Cantoni, *Life expectancy in Alzheimer's disease (AD).* Arch Gerontol Geriatr, 2009. **49 Suppl 1**: p. 237-43.
84. Uleman, J.F., et al., *Mapping the multicausality of Alzheimer's disease through group model building.* GeroScience, 2020.
85. Leor-Librach, R.J., et al., *A common origin of the very low frequency heart rate and blood pressure variability--a new insight into an old debate.* Auton Neurosci, 2002. **96**(2): p. 140-8.
86. Quintana, R.A. and W.R. Taylor, *Introduction to the Compendium on Aortic Aneurysms.* Circulation Research, 2019. **124**(4): p. 470-471.
87. Booher, A.M. and K.A. Eagle, *Diagnosis and management issues in thoracic aortic aneurysm.* American Heart Journal, 2011. **162**(1): p. 38-46.e1.
88. Peterss, S., et al., *Patient management in aortic arch surgery†.* Eur J Cardiothorac Surg, 2017. **51**(suppl 1): p. i4-i14.
89. Tian, D.H., B. Croce, and A. Hardikar, *Aortic arch surgery.* Ann Cardiothorac Surg, 2013. **2**(2): p. 245.

90. Peterss, S., et al., *Elective surgery for ascending aortic aneurysm in the elderly: should there be an age cut-off?* Eur J Cardiothorac Surg, 2017. **51**(5): p. 965-970.
91. Kumar, C., B. Salzman, and J.L. Colburn, *Preoperative Assessment in Older Adults: A Comprehensive Approach.* Am Fam Physician, 2018. **98**(4): p. 214-220.
92. Heringlake, M., M.D., et al., *Preoperative Cerebral Oxygen Saturation and Clinical Outcomes in Cardiac Surgery.* Anesthesiology: The Journal of the American Society of Anesthesiologists, 2011. **114**(1): p. 58-69.
93. Wen, S., et al., *A pilot study using preoperative cerebral tissue oxygen saturation to stratify cardiovascular risk in major non-cardiac surgery.* Anaesth Intensive Care, 2017. **45**(2): p. 202-209.
94. Scheeren, T.W., P. Schober, and L.A. Schwarte, *Monitoring tissue oxygenation by near infrared spectroscopy (NIRS): background and current applications.* J Clin Monit Comput, 2012. **26**(4): p. 279-87.
95. Newman, L., et al., *Age and sex differences in frontal lobe cerebral oxygenation in older adults-Normative values using novel, scalable technology: Findings from the Irish Longitudinal Study on Ageing (TILDA).* Arch Gerontol Geriatr, 2020. **87**: p. 103988.
96. Briggs, R., et al., *The association between frontal lobe perfusion and depressive symptoms in later life.* The British Journal of Psychiatry, 2019. **214**: p. 1-7.
97. Fried, L.P., et al., *Frailty in Older Adults: Evidence for a Phenotype.* The Journals of Gerontology: Series A, 2001. **56**(3): p. M146-M157.
98. Murphy, S.L., S.L. Schepens, and A.L. Kratz, *Fatigability as a measure of physical resilience in older adults.* Innovation in Aging, 2017. **1**(suppl_1): p. 405-405.
99. Bautmans, I., et al., *Handgrip performance in relation to self-perceived fatigue, physical functioning and circulating IL-6 in elderly persons without inflammation.* BMC Geriatrics, 2007. **7**(1): p. 5.
100. Bautmans, I., et al., *Grip work estimation during sustained maximal contraction: Validity and relationship with dependency and inflammation in elderly persons.* The journal of nutrition, health & aging, 2011. **15**(8): p. 731-736.
101. Lutomski, J.E., et al., *The Development of the Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS): A Large-Scale Data Sharing Initiative.* PLOS ONE, 2013. **8**(12): p. e81673.
102. Alexander, N.B., et al., *Self-reported walking ability predicts functional mobility performance in frail older adults.* J Am Geriatr Soc, 2000. **48**(11): p. 1408-13.
103. Stalvey, B.T., et al., *The Life Space Questionnaire: A Measure of the Extent of Mobility of Older Adults.* Journal of Applied Gerontology, 1999. **18**(4): p. 460-478.
104. Rockwood, K., et al., *A global clinical measure of fitness and frailty in elderly people.* CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 2005. **173**(5): p. 489-495.
105. *Beth Israel Deaconess Medical Center For providers: online tool to calculate frailty index (FI)*. [cited 2020 7]; Available from: https://www.bidmc.org/research/research-by-department/medicine/gerontology/calculator.
106. Sipers, W.M., et al., *The Martin Vigorimeter Represents a Reliable and More Practical Tool Than the Jamar Dynamometer to Assess Handgrip Strength in the Geriatric Patient.* J Am Med Dir Assoc, 2016. **17**(5): p. 466.e1-7.
107. Desrosiers, J., et al., *Comparison of the Jamar dynamometer and the Martin vigorimeter for grip strength measurements in a healthy elderly population.* Scand J Rehabil Med, 1995. **27**(3): p. 137-43.
108. Scholkmann, F., et al., *A review on continuous wave functional near-infrared spectroscopy and imaging instrumentation and methodology.* Neuroimage, 2014. **85 Pt 1**: p. 6-27.
109. Scholkmann, F. and M. Wolf, *General equation for the differential pathlength factor of the frontal human head depending on wavelength and age*. J Biomed Opt, 2013. **18**(10): p. 105004.

110. O'Connor, J.D., et al., *Impact of Standing Speed on the Peripheral and Central Hemodynamic Response to Orthostasis.* Hypertension, 2020. **75**(2): p. 524-531.
111. O'Connor, J.D., et al., *Functional Analysis of Continuous, High-Resolution Measures in Aging Research: A Demonstration Using Cerebral Oxygenation Data From the Irish Longitudinal Study on Aging.* Frontiers in Human Neuroscience, 2020. **14**(261).
112. Mol, A., et al., *Sensitivity and reliability of cerebral oxygenation responses to postural changes measured with near-infrared spectroscopy.* European journal of applied physiology, 2019. **119**(5): p. 1117-1125.
113. Bautmans, I. and T. Mets, *A fatigue resistance test for elderly persons based on grip strength: reliability and comparison with healthy young subjects.* Aging Clin Exp Res, 2005. **17**(3): p. 217-22.
114. Desrosiers, J., et al., *Normative data for grip strength of elderly men and women.* Am J Occup Ther, 1995. **49**(7): p. 637-44.
115. Ewing, D.J., et al., *The Value of Cardiovascular Autonomic Function Tests: 10 Years Experience in Diabetes.* Diabetes Care, 1985. **8**(5): p. 491.

Dankwoord

Hiermee is het einde van mijn opleiding Technische Geneeskunde bereikt. De afgelopen zes jaar hebben me veel geleerd, zowel medisch als technisch, maar vooral over mezelf. Afgelopen week hoorde ik het nummer 'De overkant' dat mij deed denken aan de brug over de IJssel bij Deventer die voor mij het midden tussen thuis (Enschede) en thuisthuis (Woudenberg) symboliseerde. De vier warme, fijne jaren in Enschede met alle goede herinneringen kwamen hierdoor weer boven. Ook de tijd in Nijmegen heb ik als een bijzondere periode ervaren, en ik ben blij dat ik hier nog even kan blijven. Op de Geriatrie heb ik me het afgelopen jaar helemaal op mijn plek gevoeld, en ik heb ook hier de kans heb gekregen me op onderzoeksgebied en klinisch en persoonlijk vlak te ontwikkelen.

Ik wil daarom graag iedereen op de afdeling Geriatrie in het Radboudumc bedanken voor de leuke, leerzame stage, en natuurlijk voor alle gezelligheid tussendoor! In het bijzonder mijn begeleiders, Jurgen en Marit. Jurgen, dankjewel voor je enthousiasme over vrijwel alles wat ik je liet zien, de vele ideeën en mogelijkheden die je zag. Je positiviteit en optimisme gaven me het vertrouwen dat wat we wilden ook daadwerkelijk zou lukken en lieten me inzien dat ik me geen zorgen hoefde te maken of het allemaal wel goed zou komen. Marit, dankjewel dat ik altijd met alles bij jou terecht kon, van feedback op onderzoeksgebied tot meedenken op het vlak van mijn persoonlijke ontwikkeling. Natuurlijk ook bedankt voor je gezelligheid tijdens de dinsdagen waarop we de laatste tijd onze metingen weer uitvoerden, en het mij erdoorheen slepen als ik heel hard eten nodig had. Daarnaast wil ik Jerrald en René bedanken. Jerrald, thanks for helping me with and spreading your enthusiasm about DIORs. René, bedankt voor het meedenken over mijn statistische analyses en voor je kritische vragen, die me soms wat aan het twijfelen brachten, maar ook voor nieuwe stof tot nadenken zorgden.

De stagiaires met wie ik op een kamer zat voor de coronacrisis, Lidwine, Sevilay, Nick en Sanne, jullie wil ik graag bedanken voor de gezelligheid, het ieder uur (of soms nog vaker) meedoen aan mijn koffie/theerondje en het meedenken met en aanhoren van mijn frustraties als dingen even niet lukten zoals ik wilde.

Mijn begeleiders vanuit de Universiteit Twente wil ik ook bedanken. Marleen, dankjewel voor het luisteren tijdens de intervisies en de verdiepende vragen waarmee je me meer inzicht in mezelf en mijn (soms wat onrealistische) overtuigingen. Daarmee heb je bijgedragen aan het vergroten van mijn vertrouwen in mijn eigen kunnen. Richard, bedankt voor je technische input, het meedenken met problemen in de analyses waar ik tegen aanliep en het helpen inperken van de hoeveelheid onderzoeksvragen waar ik in eerste instantie mee aankwam.

Mijn studietijd was natuurlijk nooit zo fijn geweest zonder mijn lieve TG-vriendinnen. Annabel, Anne, Deborah, Denise, Lianne, Maritta, Nynke en Tess, we hebben al weer ons zesjarig vriendschapsjubileum gehad, terwijl onze een-, twee en driemaandelijkse jubilea nog zo kortgeleden lijken. Ik vind het heel fijn dat we altijd op elkaars steun kunnen rekenen, van oneindige snaaisessies met koekjes, pepernoten, paaseitjes en nog veel meer in de collegezaal, tot al onze vakanties samen, dankjulliewel dat jullie de afgelopen zes jaar zo speciaal hebben gemaakt. Hopelijk kunnen we onze Spaanse avonturen uit het eerste jaar snel herbeleven! Maritta, nog een extra bedankje voor jou. Ik vond het heel bijzonder hoe we het afgelopen jaar bijna tegelijkertijd steeds hetzelfde meemaakten en zoveel herkenning en steun konden vinden bij elkaar. We hebben elkaar af en toe door TG-vakken, maar ook ons afstuderen heen gesleept, en dat zal in onze komende PhD-jaren niet

veranderen. Esther en Lea, mijn Amersfoortse vriendinnen, jullie wil ik bedanken voor de gezellige lunch- en koffiedates, waarbij ik met jullie ook over totaal andere dingen dan stage en TG kon praten!

Als laatste wil ik natuurlijk mijn familie bedanken. Esther, dankjewel voor je steun en bijdrage aan mijn werk door me steeds weer (soms met een zucht) feedback te geven en te helpen met mijn statistiekvragen, en me daarnaast te verbieden om ook maar even door te werken in de weekenden dat we samen bij onze ouders waren. Papa en mama, dankjulliewel dat Woudenberg altijd als mijn thuis is blijven voelen, de laatste tijd zelfs letterlijk doordat ik weer bij jullie kwam wonen. Jullie hebben me altijd een veilige haven en alle mogelijke steun geboden. En als laatste, de belangrijkste 'oudere' in mijn leven, oma, bedankt voor alle gezellige zaterdagochtenden en het geven van de inspiratie om als eerste M2-stage voor de afdeling Geriatrie te kiezen. Drie jaar geleden was u er na de bacheloruitreiking nog van overtuigd dat u mijn mastercolloquium niet meer zou meemaken. Ik heb u ervan overtuigd dat dat wel zo zou zijn, en gelukkig heb ik gelijk gekregen. Dat maakt het extra jammer dat we niet met zijn allen in Enschede kunnen zijn. Laten we daarom nu vast afspreken dat u over (hopelijk) vier jaar mijn verdediging zult bijwonen!