Quantification of Physical Resilience in Older Adults Using Continuous Blood Pressure Signals

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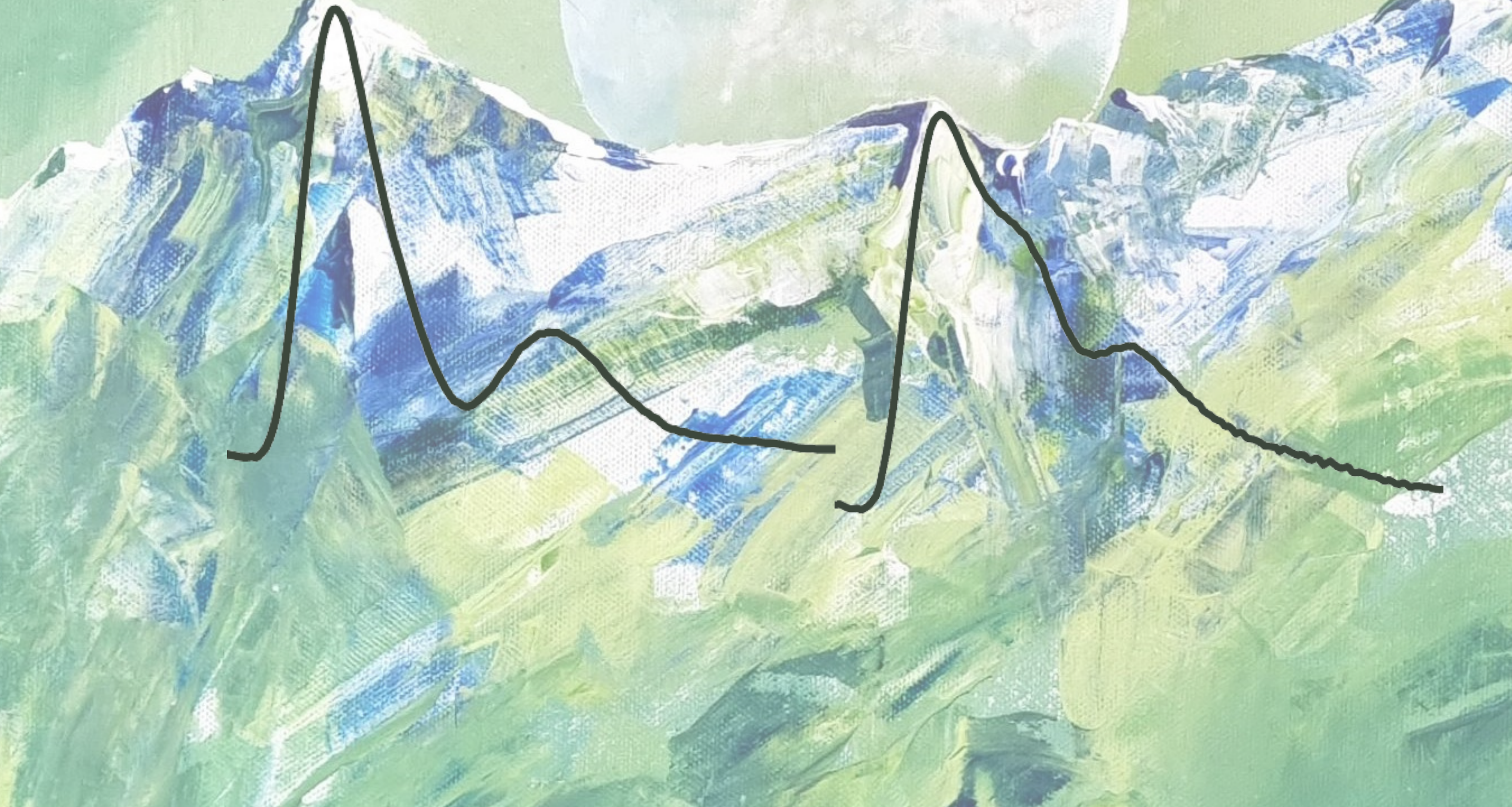

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PREFACE

In front of you lies the result of my ten-month internship at the department of Geriatrics of the Radboudumc, for the third year of my master Technical Medicine. On the front page, you find a painting made by Mirjam Verbeek. I was looking for an image representing the concept of resilience in combination with blood pressure. These mountains visualise a resilience landscape, with peaks and throughs, and steep and flat slopes. In my opinion, the blood pressure waveforms match perfectly with the shape of the mountains. Combined, this makes an ideal representation of the theme of my thesis.

After presenting my work during my colloquium, I will hopefully receive the title 'Master of Science' and continue to learn and use my knowledge for technical solutions to medical problems. The last year, I have worked on this thesis with great pleasure. Therefore, I would like to thank a few people. First, is my graduation committee. Jurgen, thank you for offering me a graduation internship, your guidance throughout the world of geriatric medicine, bringing up new ideas and always supporting me in working independently on this graduation project. Marjolein, thank you for being always available to listen and support me, for being a real technical physician supervisor, providing support on both a technical and medical level, trusting me in the execution of your measurements and of course also for the moments of relaxation. Richard, thank you for watching over my progress, letting me know that it is okay to make my own choices and providing me with useful tips for academic writing. Dick, thank you for your enthusiasm about being my external member. Ruby, thank you for your guidance over the last two years, letting me learn a lot about myself and others and motivating me to keep growing on a personal level.

The second chapter of this thesis consists of the preliminary results of a clinical study: the Geriatric Resilience Registry. Thanks to Myrthe, René, Marjolein, Jurgen, Anne and Yvet for setting up this study with me. Thanks to Inge for your input about and facilitating the logistical aspect of this study at the outpatient clinic. Thanks to Marjolein, Maaike, Nina, Odette, and Anne for their help with the inclusion of geriatric patients.

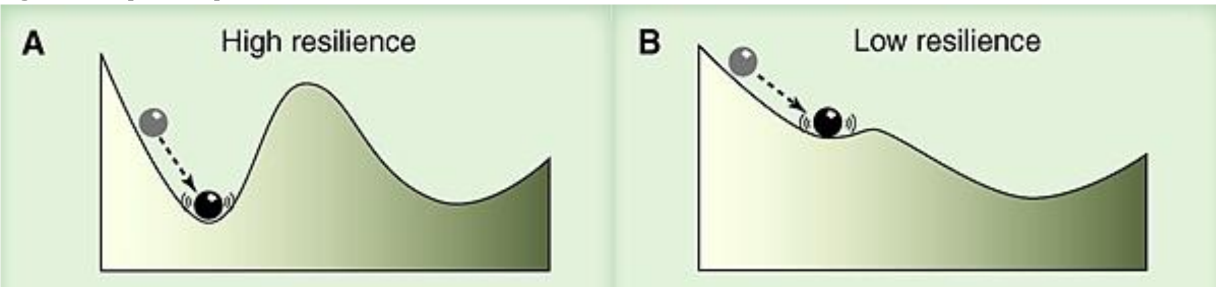
In general, I would like to thank everyone at the geriatric department for making me feel at home and treating me as a full-fledged colleague. I really enjoyed my time at the department, which is mainly caused by the pleasant atmosphere, being able to ask everyone for input or help and having colleagues to walk and relax with during breaks. Last but not least, thanks to my family and friends for supporting me and taking my mind off my graduation internship.

I hope you enjoy reading this thesis.

1. GENERAL INTRODUCTION

Resilience is a broad concept that can be applied in many different fields, such as psychology, ecological and environmental sciences, social sciences and even economy and business systems. Resilience is described as the capacity of a system to recover and adapt to unexpected disturbances of that system and find a new way of functioning. (Ungar, 2018; Xu & Kajikawa, 2018) All these different systems exist in a dynamic, constantly changing equilibrium. Whenever a challenge comes along, this equilibrium might be disturbed. Depending on the stability of the equilibrium, this challenge can be very small or has to be large in order to disturb it. When this happens, a tipping point is crossed and the steady state changes into a different equilibrium. The stability of such a system is called resilience, and is graphically represented in Figure 1. (Scheffer et al., 2018) A recent, ongoing example of a disturbance on many different systems is the COVID-19 pandemic. On a small scale it disturbs a person's physical health and mental wellbeing but on a broader level the national and global economy, social networks, and health systems. Depending on the level of resilience of each system, and the influence of the pandemic on this system, a tipping point might be crossed and a new equilibrium has to be found. (Ramos & Hynes, 2020)

Figure 1: Graphical representation of resilience



A: High resilient landscape, a large perturbation is needed to disturb the stable equilibrium. B: low resilient landscape, only a small perturbation is needed to disturb the fragile equilibrium. (Scheffer et al., 2012)

The concept of resilience is also applicable to the mental and physical health of individual human beings. Especially in elderly, this theory has gained interest over the past years. In current medical practice, most measures are static indicators of health. An estimation of the resilience of a person would allow for the prediction of near tipping points and stability of the equilibrium, which could help in the prevention of diseased states. In elderly care, the question of whether to perform surgery on a patient is a very common one. When taking into account the concept of resilience, this could help us to tailor treatment plans by predicting how large a disturbance can be without pushing the person over a tipping point and disrupting their steady state. This changed state could be less functionality, less independence or even death. (Olde Rikkert & Melis, 2019; Scheffer et al., 2018)

Blood pressure (BP) homeostasis is another example of a health-related concept that can be seen as an equilibrium state in the light of resilience, held in balance by different mechanisms. When, for example, standing up disturbs this system, these mechanisms will come into action and the system will recover back to the steady state. Standing up results in a shift of blood volume towards the lower body, caused by gravity and vasodilation. This leads to a lower venous return and therefore a decrease in BP. Hereafter, the baroreceptors will sense this drop in BP and induce an increased heart rate and vasoconstriction to return the BP to its steady state. (Claassen et al., 2021; Saal et al., 2016; V. K. Van Wijnen et al., 2017) When the drop in BP is too large, or the equilibrium too fragile, a tipping point is reached and a person can experience symptoms of dizziness or even syncope. (Claassen et al., 2021) Multiple studies targeting BP recovery after standing up found associations of impaired recovery patterns with negative clinical outcome measures. (De Heus et al., 2020; Finucane et al., 2017; Lagro et al., 2014; Mol et al., 2021)

To measure BP recovery, a continuous beat-to-beat signal is recorded. In previous research, the focus was on analysing the systolic blood pressure (SBP) and diastolic blood pressure (DBP) values. (De Heus et al., 2020; Mol et al., 2021) This means the BP course between these peaks and troughs is not taken into account, while this could contain valuable information. The full BP signal can be analysed using waveform morphologies, which has been done in earlier studies using signals from intracranial pressure, arterial BP or photoplethysmography (PPG). (Hu et al., 2009; Reisner et al., 2008; Townsend et al., 2015) This approach could also be used in beat-to-beat BP monitoring to reveal information about a person's cardiovascular status and possibly contain extra information about resilience.

The aim of this study was (1) to address the feasibility and added value of quantification of resilience in clinical practice using BP recovery after standing up and (2) to investigate the analysis of waveform morphologies in continuous BP signals. This thesis consists of two separate chapters targeting the mentioned aims. Thereafter, a general conclusion will be drawn on the topic of quantifying resilience.

1.2 List of Abbreviations

AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale-Cognitive Subscale
AUC	Area Under the Curve
BMI	Body Mass Index
BP	Blood Pressure
CGA-FI	Complete Geriatric Assessment Frailty Index
CFS	Clinical Frailty Scale
DBP	Diastolic Blood Pressure
Fmax	Maximal grip strength
FR	Fatigue Resistance
GRR	Geriatric Resilience Registry
GW	Grip Work
HR	Heartrate
MoCA	Montreal Cognitive Assessment
OH	Orthostatic Hypotension
PPG	Photoplethysmography
PPT	Peak-to-Peak Time
RI	Reflection Index
SBP	Systolic Blood Pressure
SSF	Slope Sum Function

2. Quantitative resilience measures in geriatric pre-operative outpatients: an assessment of clinical outcome and feasibility

Abstract

Background: Resilience is defined as a person's ability to bounce back after a stressor. In geriatric medicine, quantifying resilience could be of added value to support clinical decision making. Blood pressure (BP) recovery, measured using volume-clamp photoplethysmography after an orthostatic challenge, is known to associate with different outcomes related to resilience. Grip work (GW) is another concept that is known to associate with frailty. This study aims to assess both usability and feasibility of quantitative resilience measures, such as BP recovery and GW, and explore associations with cross-sectional outcome measures targeting frailty.

Methods: Patients visiting the pre-operative outpatient geriatric clinic were included. A supine-to-stand test including continuous BP monitoring, a GW measurement and a timed chair-stand-test were executed. Outcome measures were the comprehensive geriatric assessment frailty index, clinical frailty scale and decision about surgery, and were derived from patient files. Initial BP drop and recovery at different time windows were derived from B signals. These variables, as well as grip strength and GW, were tested for association with the outcome measures using linear and logistic regression. The feasibility of the measurements in clinical practice was assessed by interviewing geriatricians and collecting experiences during our study.

Results: At the moment of analysis, 39 patients were included in our study. Continuous BP data were recorded in thirty patients. Our results showed that BP recovery and initial drop after standing up were not significantly associated with any of our outcome measures. GW was significantly associated with all three outcome measures and was in all cases more strongly associated than grip strength. Measurements have shown to be feasible in clinical practice, taking into account a few practical and technical improvements that should be made.

Conclusion: We showed that quantitative resilience measures are feasible to implement at the geriatric outpatient clinic. More data with a longer follow-up period are needed for definitive conclusions, but GW showed to be a promising marker of resilience.

2.1 Introduction

With a rising ageing population, care for the elderly is gaining awareness. In elderly care, special attention for a patient's mental, physical, and social situation is required. Information should be gathered about quality of life and independence level in daily living. Frailty is a widely used term to describe a loss of reserves in these multiple dimensions. It describes how vulnerable a person is, and can be classified using a clinical frailty scale. (Clegg et al., 2013; Hale et al., 2019; Rockwood et al., 2005) Another way to look at the vulnerability of a person is by using the concept of physical resilience. In contrast to frailty, resilience is a dynamic indicator that describes a person's ability to bounce back after a stressor. Currently, resilience is often used to describe the mental capacity to recover from a perturbation. Questionnaires exist that target people's beliefs, meaning in life and social support system. (Kohler et al., 2020; Li & Ow, 2020; MacLeod et al., 2016; Smith et al., 2008) Physical resilience is a concept that conceptualizes a person's balance in a broad sense and targets homeostasis. When a person is highly resilient, chances of a good outcome after for example a hip surgery are high. When a person has low resilience, there is a high risk of getting complications during or after surgery, or ending up at a lower quality of life than before the surgery. (Hale et al., 2019)

The theory of resilience considers a person in a dynamic state. While we live, we come across multiple stressors, after which we bounce back and recover to our original state. When the stressor is large, it might take longer to recover from this. When the stressor is too large, a person can pass a so-called 'tipping point', after which he is not able to bounce back anymore. This can lead to a diseased state, or in the most extreme case to death. For a highly resilient person, the stressor has to be large to cause the shift over a tipping point.

For a low resilient person, this balance can be fragile, will be more easily disturbed and will take longer to recover back to the healthy state. In this model of physical resilience, a large perturbation can be represented by for example surgery or intensive care admission. Medium perturbations could for example be a fever or fall. Our body has to deal with very small perturbations every day multiple times, like standing up. (Hale et al., 2019; Olde Rikkert & Melis, 2019; Scheffer et al., 2018)

An orthostatic challenge is an example of such a small perturbation, which is standing up after a few minutes of lying down. This challenge causes a downward shift in blood volume caused by gravity, followed by a decrease in venous return which results in a drop in BP. While standing, we tighten our muscles and the baroreflex comes into action, resulting in a higher heart rate and an increase in vascular resistance. Hereafter, the BP normalizes again. A large drop in BP can cause light-headedness and may lead to falls. (Claassen et al., 2021; Saal et al., 2016) A sustained drop within three minutes after standing up of ≥20 mmHg for SBP and/or ≥10 mmHg for DBP, is defined as orthostatic hypotension (OH). (Freeman et al., 2011) To diagnose OH, the orthostatic challenge is routinely performed at the geriatric outpatient clinic. During this manoeuvre, the BP is measured intermittently before and at 1, 3 and 5 minutes after standing up. Besides this definition of 'classic' OH, other forms of a suboptimal BP course during this manoeuvre can be defined. A very deep initial drop in BP, that can recover fast, is called initial OH. This could result in a normal BP value one minute after standing up but can lead to complaints immediately after standing. Another option is that the BP does not decrease as much as in classic OH but does take a very long time before recovering back to normal. In that case, we say that there is a delayed recovery of BP. (Finucane et al., 2019; Veera K. Van Wijnen et al., 2018)

To diagnose the different patterns of orthostatic BP responses, it is necessary to use a continuous BP monitoring device. When using intermittent BP measurements, it is difficult to state which part of the orthostatic response is captured. Continuous BP measurements allow for monitoring the complete BP response, including the initial drop and recovery phase. (Finucane et al., 2019; Moloney et al., 2021) The technique of volume-clamp PPG, first described by Peñáz (Peñáz, 1973), makes it possible to measure beat-to-beat BP. An often-used medical device that uses this technique is the Finapres (Finapres Medical Systems, Amsterdam, The Netherlands). The Finapres uses an inflatable cuff around the finger to measure finger arterial pressure. This cuff contains an infrared light that uses PPG to measure the blood volume in the finger artery. After calibration, the finger artery is clamped to a certain volume by applying varying counter pressure. This pressure increases and decreases based on the blood volume inside the artery as determined by PPG. The waveform of the cuff pressure needed to keep the blood vessel diameter constant is similar to the arterial BP. The received finger arterial pressure can be translated into a brachial artery pressure waveform by an algorithm, which requires one BP measurement at the brachial artery. (Ameloot et al., 2015; Bartels & Thiele, 2015; Langewouters et al., 1998; Rastegar et al., 2019; Reisner et al., 2008; V. K. Van Wijnen et al., 2017)

Several studies using continuous BP monitoring have revealed associations between OH or impaired BP recovery and negative outcomes. A study showed that classic OH is strongly associated with mortality, disability, and hospitalization in the highest frailty degree, and may therefore represent a new marker of clinical frailty. (Liguori et al., 2018) Other researchers found that initial OH is associated with falls and frailty. (Romero-Ortuno et al., 2011) Multiple studies have assessed the significance of impaired BP recovery and found independently that this was associated with physical performance, frailty and number of falls in geriatric outpatients (Mol et al., 2021), mortality in older falls clinic patients (Lagro et al., 2014), falls in older adults (Finucane et al., 2017), and rate of cognitive decline and mortality in clinical Alzheimer's disease (De Heus et al., 2020).

Grip work (GW) is another parameter of interest in studies targeting the quantification of resilience or frailty in elderly. GW was introduced by Bautmans et al. to measure the dynamic performance of an individual and thereby estimate recovery capacity. GW is an extension of the concept of grip strength, not only taking into account maximum strength but also muscle fatigability. It is defined as the area under the curve of grip strength over time. The time it takes an individual to decrease to 50% of the initial grip strength is called fatigue resistance. (Bautmans et al., 2007, 2011) Research showed that fatigue resistance and GW are significantly associated with independence of daily living, self-perceived fatigue and circulating markers of inflammation within different populations of elderly. (Bautmans et al., 2007; Beyer et al., 2012; De Dobbeleer et al., 2017) Moreover, pre-frail community-dwelling elderly have a significantly lower GW when compared to robust elderly from the same population. (Knoop et al., 2021)

Our study aims to examine BP recovery and GW as markers of resilience in clinical practice. From the previously reported studies, it can be concluded that BP recovery after an orthostatic challenge, measured with continuous BP monitoring, is associated with several negative outcome measures. Moreover, GW could be used to assess frailty in elderly. The question that remains is how these measurements can be used as quantitative resilience measures in daily care. Therefore, the Geriatric Resilience Registry (GRR) was set up, a study that assesses several functional measurements in the scope of the recovery capacity of elderly. Our substudy of the GRR targets the relation between BP responses and GW with frailty and resilience in the geriatric pre-operative outpatient clinic. The hypothesis is that patients with a lower initial drop in BP, a slower recovery of BP and a lower GW, score as more frail on several clinical cross-sectional outcome measures and show less recovery potential after surgery. Moreover, our study examined the feasibility of executing these quantitative resilience measures in clinical practice.

2.2 Materials and methods

2.2.1 Study Design and population

This study was part of the GRR, a registry study in geriatric in- and outpatients designed for the development and validation of quantitative resilience measures to study intrinsic capacity and recovery capacity of older patients. The study was submitted to the Medical Ethics Committee (CMO Arnhem-Nijmegen) and was exempt from formal approval because the study did not fall within the remit of the "Medical Research Involving Human Subjects Act". The study was also exempt from the need to obtain explicit written informed consent, because of the low additional burden of our measurements. Despite this, oral informed consent was asked from each participant. The study was carried out according to the Declaration of Helsinki.

Our substudy had a cross-sectional design and included patients that visited the geriatric pre-operative outpatient clinic for a three-hour assessment by a geriatrician. The aim of this visit was to assess the possibilities and challenges regarding the proposed surgery. Patients were eligible for this study if they were 65 years or over. Exclusion criteria were being physically unable to sit and stand up or inability to understand and follow up instructions. The measurements were executed by a trained researcher as part of standard clinical care. Inclusions for this study started in August 2021 and were planned to continue throughout 2022.

2.2.2 Data collection

The following patient characteristics were extracted from the medical records: age, sex, height, weight, medical history, medication, smoking habits, alcohol consumption, independence of daily living and the medical speciality the patient was referred by.

A standardized test battery of quantitative resilience measurements was executed at each eligible patient visiting the pre-operative outpatient clinic. This test battery consisted of a supine-to-stand challenge, a GW measurement, and a timed chair-stand test, which will be elaborated on below. Other medical information, derived during the comprehensive geriatric assessment by the geriatrician, was obtained from patient files. This study procedure is schematically depicted in Figure 2.

Figure 2: Schematic representation of the quantitative resilience measures

Quantitative resilience measures consist of a supine-to-stand test, with 5 minutes of lying supine and 5 minutes of remaining in a standing position, a grip work measurement, and a timed chair-stand-test. Other patient characteristics as assessed during the pre-operative assessment were derived from the electronic patient file.

Supine-to-stand challenge

The supine-to-stand test consisted of 5 minutes of lying down, followed by standing up and remaining in a standing position for 5 minutes. During this orthostatic manoeuvre, continuous BP measurements were executed using volume-clamp PPG (Finapres Medical Systems, Amsterdam, The Netherlands) at the middle or index finger of the hand. Patients were asked to hold their hand at heart level during the test and were supported in this by an arm sling. Moreover, oscillometric BP measurements at the brachial artery of the contralateral arm were executed during supine posture, as well as at 1, 3 and 5 minutes after standing up. This was in accordance with the current standard of clinical care.

Grip work measurement

The GW measurement was executed using the large bulb of a Martin Vigorimeter. The assessment followed the protocol as introduced by Bautmans et al. (Bautmans et al., 2011) The total measurement consisted of three maximum grip strength measures and one fatigue resistance test of the dominant hand. For clinical purposes, the maximum grip strength was also assessed in the non-dominant hand. To determine maximum grip strength, the highest of three attempts was noted, with a rest period of 30 seconds between successive attempts.

To measure fatigue resistance (FR), patients were asked to squeeze the bulb using maximum strength and to maintain this as long as possible. During the procedure, it was verified that the starting strength (Fmax) corresponded to at least 80% of the maximum grip strength as measured before. Patients were verbally motivated by the researcher to maintain sufficient grip strength as long as possible. When the grip strength was decreased to 50% of the patient's maximum grip strength, they were told to let go and the time in seconds was captured. Grip work was estimated using the formula GW = Fmax*0.75*FR. (Bautmans et al., 2011)

Timed chair-stand-test

Patients were asked to stand up from a chair and get back to a seating position 5 times in a row as fast as possible. Arms should be folded in front of the chest and could not be used to support the standing up. (M & DJ, 1985) The time was recorded during this test. When a patient was not able to stand up without using the arms, support from the arms was allowed or support was provided by the researcher. This was noted in the measurement file.

2.2.3 Outcome parameters

During the geriatric assessment, multiple questionnaires were taken by the geriatrician as part of clinical practice, targeting frailty, resilience, quality of life and independence in daily living. These questionnaires, together with other information obtained from patient files, were used to derive the outcome measures for this study. The primary outcome measure was the comprehensive geriatric assessment frailty index (CGA-FI).[1] (Jones et al., 2005) The CGA-FI can range from 0 to 1, where higher values indicate more frailty. It is a multidomain index, covering medical history, functional status, nutritional status, and performance on several tests. These tests are the Montreal cognitive assessment (MoCA), gait speed and the earlier described timed chair-stand test and handgrip strength. The Clinical Frailty Scale (CFS) as determined by the geriatrician was used as a secondary outcome measure. (Rockwood et al., 2005)

[1] https://www.bidmc.org/research/research-by-department/medicine/gerontology/calculator

Moreover, the concluding advice of the pre-operative assessment was used as an outcome measure, named 'decision about surgery'. Before visiting the geriatric department, the clinical indication of the surgery was already established by the referring specialist. At the end of the assessment, the geriatrician gives advice about the feasibility and risks of the surgery, based on estimated frailty and resilience as well as the quality of life for that specific patient. Eventually, the patient decides, together with the medical team, whether he wants to pursue the surgery or not. For use in this study, the decision about surgery was estimated by the researcher as yes or no. In cases when no definitive decision was registered in the patient file yet, the choice most inclined to was derived from the patient file and used as an outcome measure. A decision to refrain from surgery could either be made by the patient, the geriatrician, or the referring specialist.

Patients were followed up passively using electronic patient files. Information about executed surgeries, unexpected hospital admissions and mortality data were collected. If the patient did undergo surgery, outcome measures from their surgery and hospitalization were collected. These outcome measures include the occurrence of complications after surgery, the occurrence of delirium and length of hospital stay.

2.2.4 Data Analysis

BP signals were processed in MATLAB 2018a using semiautomated custom-written scripts as described previously. (De Heus et al., 2018) This data processing leads to an SBP and DBP over time, retrieved by connecting all peaks and throughs. Signals were resampled at 10 Hz and filtered using a 5-second moving average filter.

The baseline SBP and DBP were defined as the average value between 10 and 40 seconds before standing up from a supine position. Multiple outcome measures were defined using the continuous BP signals. First, the initial drop in BP was detected, defined as the minimum BP value in the first 40 seconds after standing up. This was represented as a difference from baseline according to:

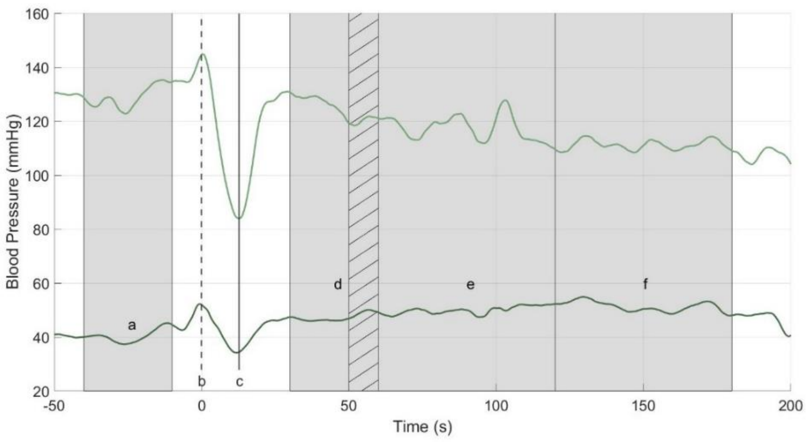
$$\mathbf{BP_{initial\ drop} = BP_{baseline} - BP_{minimum\ within\ 40\ seconds\ after\ standing}}$$

Thereafter, multiple values of BP recovery were extracted from the continuous BP data. Orthostatic recovery was defined as the average BP value between 50 and 60 seconds after standing up. Other recovery values were defined as rapid recovery, from 30 to 60 seconds after standing up, sustained recovery from 60 to 120 seconds after standing up and prolonged recovery from 120 to 180 seconds after standing up. (De Heus et al., 2020; Mol et al., 2021) These recovery measures were presented as the absolute differences from baseline according to:

$$\mathbf{BP_{recovery} = BP_{baseline} - mean(BP_{time\ window})}$$

An example of continuous BP data from a supine-to-stand challenge with the defined outcome measures is depicted in Figure 3.

Figure 3: Example of processed continuous blood pressure data during a supine-to-stand challenge



a=baseline; b=moment of standing up; c=initial drop; d=rapid recovery; e=sustained recovery; f=prolonged recovery; hatched area=orthostatic recovery. The dark green line is diastolic blood pressure, the lighter green line is systolic blood pressure.

2.2.5 Statistical analysis

IBM SPSS Statistics 25 was used for statistical analysis. Baseline characteristics and outcome measures were tested for normality using a Shapiro-Wilk test. Normally distributed variables were presented using the mean and standard deviation. Not normally distributed variables were presented using the median and interquartile range. Categorical and dichotomous variables were presented by the number of patients and the percentage of the total sample.

Linear and logistic regression models were used to analyse the associations between the quantitative resilience measures and the outcome measures. These models consisted of 7 different independent variables and 3 different dependent variables, combined pairwise. All variables are displayed in Table 1. For CGA-FI and CFS as dependent variables, linear regression was used. For 'decision about surgery' as the dependent variable, logistic regression was used.

Table 1: Variables used for several linear regression analyses

Independent variables	Dependent variables
BP initial drop	CGA-FI
BP recovery orthostatic (50 – 60 sec)	CFS
BP recovery rapid (30 – 60 sec)	Decision about surgery
BP recovery sustained (60 – 120 sec)	
BP recovery prolonged (120-180 sec)	
Grip strength	
Grip work	

BP, blood pressure; CGA-FI, comprehensive geriatric assessment frailty index; CFS, clinical frailty scale.

As a secondary outcome measure, it was determined whether the continuous BP signal led to other classifications of OH than the oscillometric BP measurements. From the continuous BP data, the measure of BP recovery orthostatic was used to diagnose OH if a drop in SBP of ≥ 20 mmHg or DBP of ≥ 10 mmHg was present at this moment. From the oscillometric measurements at the brachial artery, the difference between supine measurement and approximately 1 minute after standing up was used with the same cut-off values. The difference in diagnosis results between both measurement methods was tested for significance using a Fisher's test.

2.2.6 Feasibility

The applicability of quantitative resilience measures at the outpatient clinic was assessed and improved. Geriatricians were interviewed individually or in small groups to get their input on the implementation of our measures in clinical practice. The interview took place after the geriatrician experienced the execution of the measurements by the researcher at the geriatric outpatient clinic during our study. The interview focussed on multiple questions:

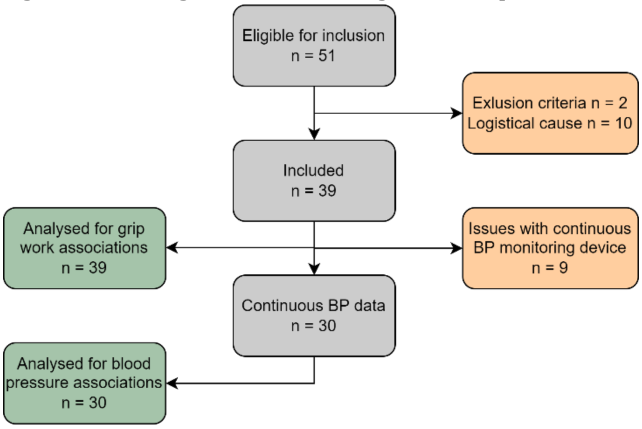
- What is for you the added value of quantitative resilience measures such as BP recovery and GW during a pre-operative geriatric assessment?
- Would you be willing to learn and execute the continuous BP and GW measurement yourself during an appointment? Why?
- What are the downsides you experience of the currently used intermittent brachial BP measurements during an orthostatic manoeuvre?

With our experience gained during the execution of this study and evaluations with various people, the use of quantitative resilience measures in clinical practice was evaluated. Attention was drawn towards the logistical organization, technical difficulties, training of proficient staff and patients' and doctors' experiences.

2.3 Results

Thirty-nine geriatric pre-operative outpatients from the Radboudumc were included in our substudy in the period between mid-august and the end of December 2021. A flow diagram is provided in Figure 4.

Figure 4: Flow diagram of inclusion of geriatric outpatients



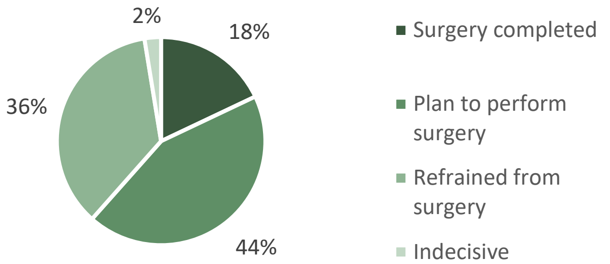
Baseline characteristics, including missing cases per variable, can be found in Table 2. Normal distribution has been tested using Shapiro-Wilk and characteristics are presented accordingly. A graphical representation of the decision about surgery of our population is shown in Figure 5.

Table 2: Baseline patient characteristics

Characteristics	n	Value
Sociodemographic		
Age (years), mean (SD)	39	78 (6,5)
Female gender, n (%)	39	16 (41)
Health characteristics		
BMI (kg/m^2), median (IQR)	38	26.9 (8.2)
Currently smoking, n (%)	39	7 (18)
Excessive alcohol use, n (%) [a]	39	2 (5)
Total MoCA score, mean (SD)	36	23.7 (4.0)
History of delirium, n (%)	39	8 (21)
Hypertension, n (%)	39	24 (62)
Number of medications in use, median (IQR)	39	7 (7)
Antihypertensive drug use, n (%)	39	31 (80)
Cases of OH, n (%) [b]	38	12 (31)
Quantitative resilience measures		
Grip strength (kPa), median (IQR)	39	50.0 (26.0)
Fatigue resistance (sec), median (IQR)	39	31.7 (23.8)
Grip work (kPa*sec), median (IQR)	39	1460 (1102)
Timed chair stand test (sec), median (IQR)	35	15.0 (6.7)
SBP supine (mmHg), mean (SD)[b]	39	150 (24)
DBP supine (mmHg), mean (SD)[b]	39	79 (11)
HR supine (mmHg), median (IQR)[b]	39	68 (16)
SBP 1 minute (mmHg), mean (SD)[b]	38	136 (29)
DBP 1 minute (mmHg), mean (SD)[b]	38	75 (14)
HR 1 minute (mmHg), mean (SD)[b]	38	82 (17)
Outcome measures		
Clinical frailty scale, median (IQR)	39	4 (2)
CGA-FI, median (IQR)	39	0.108 (0.093)
Decision about surgery: yes/most likely, n (%)	38	24 (62)

BP, Blood Pressure; SD, standard deviation; BMI, body mass index; IQR, interquartile range; OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CGA-FI, comprehensive geriatric assessment frailty index.
[a] Excessive alcohol use was defined as more than 24 units per week for men and more than 14 units per week for women.
[b] Blood pressure as measured by oscillometric brachial cuff measurements.

Figure 5: Pie chart visualizing decision about surgery



The first category contains patients that already underwent surgery, the second category patients that are likely to undergo surgery in the near future. These two categories together were stated as 'yes', regarding their decision about surgery. The third category contains patients that refrained from surgery. The last category consists of one patient for whom it could not be determined whether surgery was likely to happen or not.

During follow up, one patient died during an unexpected hospital admission due to COVID-19. Two other patients were admitted to the Radboudumc for other emergent reasons than the surgery they were screened for. Seven patients have had surgery so far and have all been discharged.

2.3.1 Continuous BP data

From thirty patients, continuous BP data were successfully measured using volume-clamp PPG (Finapres Medical Systems, Amsterdam, The Netherlands). Baseline characteristics stratified by a successful (n=30) or unsuccessful (n=9) continuous BP measurement are available in Appendix A, Table A.1. These groups showed to only differ significantly on the number of medications that were used and were comparable on all other characteristics. From the patients with continuous BP data, one patient did not complete the full 5 minutes of standing, due to a collapse approximately 2 minutes after standing up. This collapse was caused by a decreasing BP, as could be seen in the continuous BP data.

Continuous BP data were screened for usability before analysis. After pre-processing and filtering these signals, SBP and DBP were used to derive outcome measures. The results can be found in Table 3.

Table 3: Results of continuous blood pressure (BP) data analysis from 30 patients

Characteristic	N	Value
Baseline BP (mmHg)	30	
Systolic, mean (SD)		125.3 (26.0)
Diastolic, mean (SD)		54.3 (13.7)
Initial drop in BP (mmHg)	30	
Systolic, median (IQR)		14.5 (36.2)
Diastolic, mean (SD)		5.3 (9.2)
BP recovery orthostatic (mmHg)	30	
Systolic, mean (SD)		-0.4 (21.3)
Diastolic, mean (SD)		-8.0 (7.9)
BP recovery rapid (mmHg)	30	
Systolic, mean (SD)		1.8 (19.6)
Diastolic, mean (SD)		-6.8 (8.2)
BP recovery sustained (mmHg)	30	
Systolic, mean (SD)		-1,9 (21.4)
Diastolic, mean (SD)		-8.2 (8.8)
BP recovery prolonged (mmHg)	29	
Systolic, mean (SD)		-2,2 (17.1)
Diastolic, mean (SD)		-8.2 (10.4)

BP, blood pressure; OH, orthostatic hypotension

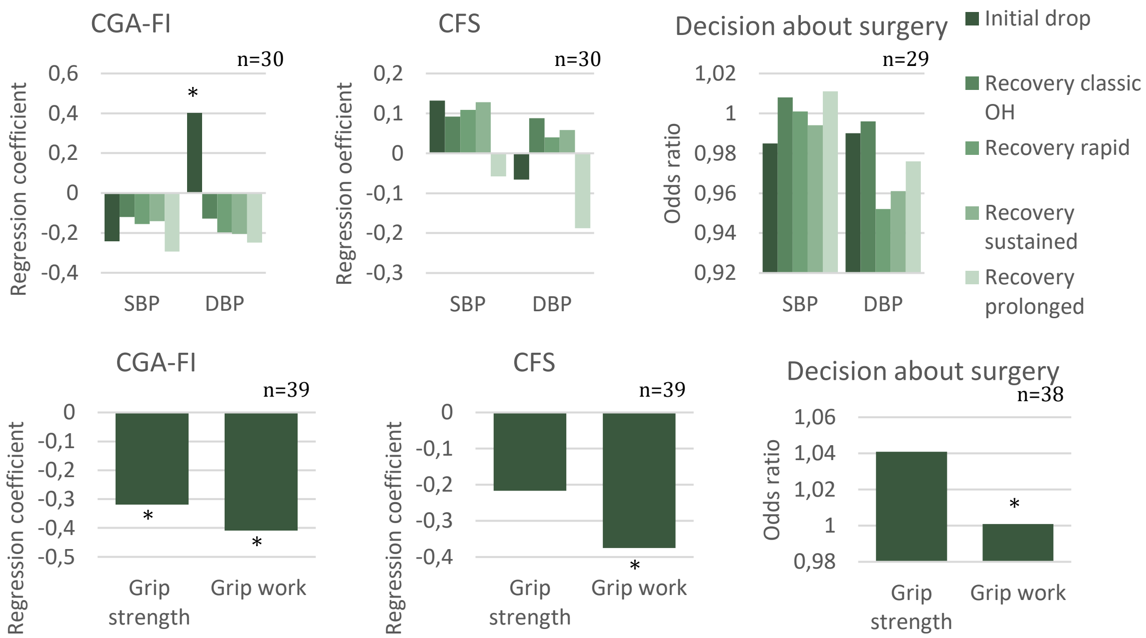
Initial drop and recovery values are represented as an absolute difference from baseline. The initial drop is defined as the lowest BP value within 40 seconds after standing up. BP recovery orthostatic is defined as 50-60 seconds after standing up. BP recovery rapid represents 30-60 seconds after standing up. BP recovery sustained is defined as 60-120 seconds after standing up. BP recovery prolonged is defined as 120-180 seconds after standing up.

Except for SBP initial drop, all BP variables were normally distributed according to a Shapiro-Wilk test. The absolute value for BP at baseline cannot be interpreted in the same way as oscillometric brachial measurements since the continuous measuring device has not been calibrated with a brachial cuff measurement and height correction was not used in our protocol. Therefore, the other BP characteristics are presented as absolute deviation from baseline. A negative value represents an increase in BP compared to baseline. On average, SBP showed little deviation from baseline at the different recovery moments. DBP showed increases in BP at all recovery moments. Especially the SBP has a very large standard deviation, meaning our population had a wide variety of BP responses to standing up.

2.3.2 Regression analysis

Figure 6 shows the associations between BP initial drop, BP recovery at different time intervals, grip strength and GW with our three different outcome measures. The detailed data including significance levels can be found in Appendix B. From all models containing BP, linear regression only showed a significant association between diastolic initial drop and CGA-FI. Logistic regression showed no significant association between any BP characteristics and decision about surgery. Grip strength was significantly associated with CGA-FI. In linear and logistic regression, GW showed a significant association with all three outcome measures.

Figure 6: Regression analysis of blood pressure and grip work with outcome measures



CGA-FI, complete geriatric assessment frailty index; CFS, clinical frailty scale; OH, orthostatic hypotension. Initial drop = minimum BP within 40 seconds after standing up. Recovery orthostatic = 50-60 seconds after standing up. Recovery rapid = 30-60 seconds after standing up. Recovery sustained = 60-120 seconds after standing up. Recovery prolonged = 120-180 seconds after standing up.
Bars indicate the standardized regression coefficients/odds ratios. Significant results have been marked with an asterisk.

2.3.4 Diagnosis of orthostatic hypotension

The diagnosis of OH was reviewed as a secondary outcome measure. For patients that had both continuous BP data and oscillometric brachial cuff measurements, their diagnosis with the different measurement methods was compared and can be found in Table 4. Our results show that brachial cuff measurements led to more diagnoses of OH in our sample than continuous BP measurements (9 vs 6). Five patients had OH according to the brachial cuff measurements but were not diagnosed using the continuous BP data. Two patients had OH according to continuous data but were not diagnosed according to brachial cuff measurements. This difference was significant (p = 0.049) according to a Fisher's exact test.

Table 4: Diagnoses of orthostatic hypotension (OH) according to continuous blood pressure data and oscillometric brachial cuff measurements

	Not OH continuous	OH continuous	Total
Not OH oscillometric	19	2	21
OH oscillometric	5	4	9
Total	24	6	30

OH, Orthostatic Hypotension.
Oscillometric OH was diagnosed when a drop of ≥20 mmHg in systolic or a drop of ≥10 mmHg in diastolic blood pressure was present at 1 minute compared to supine. In continuous blood pressure data, OH was diagnosed with the same cut-off values at the window of 50-60 seconds after standing up.

2.3.5 Feasibility

Since the end of August, we implemented our quantitative resilience measures as standard clinical care at the preoperative outpatient clinic of the Radboudumc. Patients were first seen by the geriatrician, after which an electrocardiogram was made, and the resilience measures were executed. A researcher was available on call whenever the patient was ready. After executing the measurements, the results were also communicated to the geriatrician, to support clinical decision making. Before the inclusion period of our study started, patients already executed an orthostatic challenge, only with intermittent BP measurements. A maximum grip strength measurement was also already part of clinical care, where we added the GW measurement and a more elaborate measurement protocol for maximal strength. The timed chair test was newly introduced.

In total, 51 patients were seen at the pre-operative geriatric outpatient clinic within the period of inclusion for this study. 39 patients executed the quantitative resilience measures and were included in our study. Of the twelve patients that did not execute our measurements, two were not able to stand up and therefore not measured. In ten other cases, there were logistic problems with the execution. For example, there was no researcher available due to other obligations or there were communication issues that led to missed calls for the researcher. These problems occurred mostly at the beginning of our inclusion period. After a while, the quantitative resilience measures were successfully implemented in daily clinical care.

Geriatricians were consulted for their opinion on the feasibility and implementation of these measurements in clinical care. Overall, they were satisfied with the way the measurements were implemented and executed. One downside they experienced was the fact that the measurements made the planning of the consult more complicated. It takes time to execute the measurements which means that sometimes the geriatricians had to wait until the researcher was finished. Besides that, geriatricians agreed that the feedback about the results of the measurements could be improved. It would be helpful if the electronic patient file could be adapted to our measurements, so the results can easily be interpreted and entered into patient files. The interpretation of the measurements was the third and last point of improvement. Right now, mostly the orthostatic manoeuvre and grip strength are used in clinical practice and can therefore be interpreted according to standard measures by the geriatricians. The extra measurements we added, such as continuous BP measurements and GW were experienced as more difficult to interpret.

Other downsides or problems our researchers encountered during the study were mostly technical issues. Especially the Finapres device often had problems that slowed down the researchers or even led to not recording continuous BP at all. In total, continuous BP data could not be measured successfully in nine out of 39 included patients. In two cases, this was caused by a fault made by the researchers that can be prevented in the future. In the other seven cases, the Finapres gave error warnings and could not be used to measure BP correctly. After rebooting and a few troubleshooting attempts, researchers decided to only measure brachial BP, partly due to time issues. Even in patients with a successful measurement of continuous BP, the device had to be restarted multiple times before sufficient data quality was reached. Before implementing continuous BP measurements in further clinical care, these kinds of technical issues should be resolved.

The GW measurements were easy to execute for every patient. For some patients, the protocol of four maximum squeezes led to less grip strength in the actual GW measurement. Overall, GW measurements would be very feasible to implement in an outpatient clinic.

2.4 Discussion

Our study included 39 geriatric outpatients that visited the Radboudumc for a pre-operative assessment. GW was significantly associated with three different outcome measures; CGA-FI, as determined based on the assessment, CFS, established by the geriatrician and decision about surgery, interpreted by the researcher from patient files. Grip strength was only significantly associated with CGA-FI. From a supine-to-stand challenge in thirty patients, continuous monitored BP data did not reveal significant associations between initial drop or multiple recovery values and the outcome measures.

From our linear regression analysis comparing BP initial drop and recovery with outcome measures, only DBP initial drop was significantly associated with CGA-FI. However, this result should be interpreted with care since we executed many tests using BP where only one showed a significant result. A recent study with a similar protocol and analysis showed that SBP recovery was associated with frailty and that DBP recovery was associated with physical performance, frailty and falls. (Mol et al., 2021) This study consisted of 168 geriatric outpatients and used different outcome measures than we did. Another study showed that orthostatic BP recovery is associated with the rate of cognitive decline and mortality in Alzheimer's patients. (De Heus et al., 2020) BP recovery has also shown to be associated with unexplained and injurious falls. (Finucane et al., 2017) Moreover, OH, as measured with oscillometric brachial cuff measurements, is associated with mortality, disability and hospitalization and may therefore be a marker of clinical frailty. (Liguori et al., 2018) Possibly, our sample was too small with only thirty patients with continuous BP data to analyse.

Continuous BP measurements are believed to be of added value for diagnosing OH. (Finucane et al., 2014; Romero-Ortuno et al., 2011) In some populations, such as patients with unexplained syncope or orthostatic intolerance, continuous BP measurements could reveal initial OH that could not have been diagnosed with intermittent BP measurements. (Van Twist et al., 2018) However, in our study, the analysis of continuous BP data missed five cases of OH that were diagnosed with the brachial cuff measurement. On the other hand, two cases were diagnosed that would have been missed with only the brachial cuff measurement. We used only the timeframe of 50-60 seconds to diagnose OH, while the official diagnosis calls for a sustained drop in BP. Therefore, other researchers used a more strict definition where the drop in BP should be present at all timeframes between 1 and 3 minutes after standing up, before being classified as OH. (Finucane et al., 2014, 2019) In both brachial cuff and continuous BP measurements, the time points at which OH is classified are of great importance due to fluctuations in BP. For the brachial cuff measurements, we saw in our sample that some of the OH diagnoses, that were not diagnosed according to continuous data, were most likely measured during the initial drop in BP. In these cases, the diagnosis of OH by brachial cuff measurements was inaccurate. However, it is hard to say at which moment exactly the brachial cuff measured BP. Until the continuous BP measurement procedure is optimized, it would be advised to use both BP measurement methods for a correct diagnosis of OH.

In literature, no consensus is reached on how to analyse continuous BP data. Many different timepoints and windows of BP recovery and initial drop can be found in literature. Besides that, some studies use the absolute difference in BP like we did, while others use percentual differences from baseline. (De Heus et al., 2020; Finucane et al., 2014, 2019; Mol et al., 2021) In our study, we chose to use absolute differences in BP, since this conforms mostly to the definition of OH. Besides that, absolute differences are more likely to correspond with possible symptoms of OH experienced by the patient. Furthermore, the analysis of continuous BP data is rather laborious. With the currently used pre-processing method, each signal had to be checked for detection of systolic and diastolic peaks. When clear extrasystoles or artefacts were present, these peaks were not detected. If a longer period of noise was present, no peaks were detected, and the signal was interpolated from the last detected peak until the first following peak. In some cases, this might not represent the actual BP course of the patient.

Our other quantitative resilience measure, GW, was introduced by Bautmans et al. to reflect muscle endurance in elderly. (Bautmans et al., 2011) Recent research showed that pre-frail community-dwelling elderly have a lower GW than robust elderly. (Knoop et al., 2021) Grip strength has proven to be a marker of clinical frailty in multiple studies and is already used in standard clinical care. (Dudzińska-Griszek et al., 2017; Syddall et al., 2003) GW contains grip strength but is extended with an aspect of fatiguability by measuring sustained grip strength. In our study, GW was more strongly associated with all our outcome measures than grip strength. Since grip strength is one of the parameters of the CGA-FI, it was expected that an association would be found. However, GW still showed a stronger association, meaning the addition of muscle fatiguability is valuable. No previous literature could be found that examined this association in a heterogeneous geriatric outpatient sample.

We implemented the supine-to-stand test with continuous BP measurements as a part of standard clinical care, compared to only oscillometric brachial cuff measurements executed before. Because we used a clinical setting, our results are an adequate reflection of daily clinical practice. However, a downside to this is that the supine-to-stand test protocol was suboptimal in many cases. For nine of our patients, no continuous BP data was available. Seven times, this was caused by the inability of the measurement device to reach sufficient data quality. This group only differed significantly from the group with successful continuous BP data on the number of medications used. Therefore, these patients were believed to be a random sample and have no influence on our conclusions. A recent study showed a similar portion of unsuccessful measurements with Finapres in a sample of 29 geriatric inpatients. Possible reasons for the failure of continuous BP measurement in a geriatric population are high vessel stiffness, peripheral vascular disease and cold or arthritic fingers. (Tran et al., 2022) Finucane et al. described a practical guide to active stand testing and analysis using continuous beat-to-beat non-invasive BP monitoring. (Finucane et al., 2019) Our measurement approach was quite similar to theirs, but due to the clinical setting of our measurements, our approach was less standardized. For example, time of day, caffeine or nicotine intake or medication use cannot be controlled in clinical practice. In some cases, patients provoked artefacts by talking, coughing, or tightening their fingers. Advised improvements that could be made to our protocol are the addition of the height correction system, carrying out a practice stand and instructing the patient to keep the arm with measurements device stable during standing up.

Getting from a supine to a standing position with one hand fixed in a sling and a BP measurement device attached to it was a challenge for our geriatric population, which is believed to have influenced our results. Patients were assisted in standing up by the researcher, but this still led to long transition times. In these patients with long stand-up times, the initial drop in BP is likely to be smaller than in patients with fast stand-ups. (Van Twist et al., 2021) Since more frail patients probably need longer to stand up, and more physical effort, their drop in BP is likely to decrease. This could countereffect the possible association between BP drop or recovery and frailty. (Van Twist et al., 2021) Moreover, the marker for the moment of standing might have been misplaced in these cases where the researcher also had to assist the patient. A sit-to-stand challenge would be easier and faster to execute, but also results in less drop in BP and is not the official protocol to diagnose OH.

To develop quantitative resilience measures, it would be ideal to use a large, heterogeneous population with a long follow-up period. In the geriatric resilience registry, a wide variety of geriatric patients is included to be able to develop quantitative resilience measures that can be used in clinical practice on a broad scale. Our substudy contains all eligible pre-operative outpatients that had an appointment at the Radboudumc, which led to a heterogenic sample. Our current analysis was only cross-sectional since only 7 of our included patients have had surgery, which is not enough for any valuable analyses. An intervention such as a surgery could be analysed as a disturbance of the system, after which recovery of the patient can be monitored. In the future, a larger sample of our population will have had surgery and outcome measures can be compared with the resilience measures quantified at baseline.

Three different outcome measures were used in our study. The CGA-FI was chosen as the primary outcome measure since this is a multi-domain scale believed to cover many aspects that influence resilience. During this study, the CGA-FI was calculated by the researcher. To improve repeatability, the calculation of CGA-FI could be automated in the future with information from the electronic patient file. The CFS is widely used as an indicator of frailty. However, this outcome remains an arbitrary estimation made by the geriatrician. The outcome measure 'decision about surgery', in our study was an estimation made by the researcher, based on information from patient files. It would be more reliable to wait until the choice of surgery was completely fixed, or until surgery was planned or even executed. However, due to time issues, this was not possible yet. Another possible outcome measure would be a frailty index based on TOPICS-MDS data. In our population, this information was not available for everyone and let to a too-small sample size for now. However, frailty has proven to be able to be captured from TOPICS-MDS data. (Shaw et al., 2019)

Our resilience measures showed to be feasible in clinical practice, but improvement is possible. By reviewing our protocol, changes can be made that increase the success rate of continuous BP monitoring and the quality of data. When the added value of continuous BP monitoring is acknowledged by clinical staff, the extra time to set up the measurement will be better accepted. GW is easy to execute and correlates more strongly with our outcome measures than grip strength, which is currently used. Besides that, it only takes little extra time, so it was easy to implement this measurement in clinical practice. Other advantages are the fact that everybody can learn to take the measurements and all patients from our sample could execute them. Besides that, the relation with resilience is still unclear but is exactly what is targeted in this study. Therefore, the feedback of our results to clinical staff might be a bit preliminary but could still be valuable to get more insight into the physical strength of patients. Moreover, we think it is helpful to already use these measures in clinical care, so physicians can get used to working with these data.

2.5 Conclusion

In our substudy of the geriatric resilience registry, 39 pre-operative outpatients were included. In nine patients, no successful continuous BP measurement could be executed. SBP and DBP values for initial drop and recovery during an orthostatic challenge did not associate with the used outcome measures targeting frailty. Longer transition times in more frail elderly were believed to undo a possible association since they cause a lower drop in BP. GW showed significant associations with all outcome measures and was found to be of added value to grip strength. Analysis of more patients, as well as post-surgery follow-up outcome measures indicating resilience, are needed for conclusive results about both associations.

APPENDIX A: SUPPLEMENTARY RESULTS BASELINE CHARACTERISTICS

Table A.1: Baseline characteristics of stratified samples by successful (n=30) and unsuccessful (n=9) continuous monitoring of blood pressure during supine-to-stand test

Characteristics	Sample with cont. BP (n=30)	Sample without cont. BP (n=9)	P-value
Sociodemographic			
Age (years), mean (SD)	77 (6.6)	80 (5,9)	0.22
Female gender, n (%)	12 (40)	4 (44)	0.81
Health characteristics			
BMI (kg/m^2), median (IQR)	27.1 (7.9) [1]	23.9 (7.5)	0.16
Currently smoking, n (%)	6 (20)	1 (11)	0.78
Excessive alcohol use, n (%) [a]	2 (7)	0	0.68
Total MoCA score, mean (SD)	23.5 (4.3) [3]	24.3 (3.2)	0.59
History of delirium, n (%)	7 (23)	1 (11)	0.43
Hypertension, n (%)	19 (63)	5 (56)	0.67
Number of medications in use, median (IQR)	9.5 (9)	4 (3)	0.01 *
Antihypertensive drug use, n (%)	25 (83)	6 (67)	0.28
Cases of OH, n (%) [b]	9 (30)	3 (33) [1]	0.69
Quantitative resilience measures			
Grip strength (kPa), median (IQR)	51 (22.8)	50.0 (28.0)	0.89
Fatigue resistance (sec), median (IQR)	33.3 (25.0)	26.0 (18.6)	0.29
Grip work (kPa*sec), median (IQR)	1494 (1097)	825 (1179)	0.41
Timed chair stand test (sec), median (IQR)	14.4 (6.7) [2]	15.0 (7.8) [2]	0.43
SBP supine (mmHg), mean (SD)[b]	150 (25)	152 (22)	0.85
DBP supine (mmHg), mean (SD)[b]	79 (11)	77 (11)	0.59
HR supine (mmHg), median (IQR)[b]	67 (16)	69 (18)	0.57
SBP 1 minute (mmHg), mean (SD)[b]	137 (28)	133 (35) [1]	0.72
DBP 1 minute (mmHg), mean (SD)[b]	75 (14)	74 (14) [1]	0.94
HR 1 minute (mmHg), mean (SD)[b]	80 (15)	87 (23) [1]	0.31
Outcome measures			
Clinical frailty scale, median (IQR)	4 (2)	4 (2)	0.93
CGA-FI, median (IQR)	0.112 (0.094)	0.108 (0.133)	0.75
Decision about surgery: yes/most likely, n (%)	20 (67) [1]	4 (44)	0.18

BP, Blood Pressure; SD, standard deviation; BMI, body mass index; IQR, interquartile range; OH, orthostatic hypotension; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; CGA-FI, comprehensive geriatric assessment frailty index.
[a] Excessive alcohol use was defined as more than 24 units per week for men and more than 14 units per week for women.
[b] Blood pressure as measured by oscillometric brachial cuff measurements.
[1] Missing data for 1 case from this sample. The number in superscript represents the number of missing cases respectively.
Normally distributed variables in the total sample (n=39) were presented as mean and standard deviation, groups were compared using an independent samples t-test. Not normally distributed variables were presented as median and interquartile range, groups were compared using a Mann-Whitney U test. Categorical and dichotomous variables were presented as number and percentage of the sample, groups were compared using a chi-square test.

Appendix B: Supplementary results of regression analysis

Table B.1: results of linear regression with Comprehensive Geriatric Assessment frailty index (CGA-FI) as dependent variable (n=30)

Independent variable	Coefficient B	Standard beta	P-value	Coefficient B	Standard beta	P-value
	SBP			DBP		
Initial drop	-.001	-.24	.20	-.005	.40	.03*
Recovery orthostatic	-.001	-.12	.53	-.002	-.13	.50
Recovery rapid	-.001	-.16	.41	-.003	-.20	.30
Recovery sustained	-.001	-.14	.46	-.003	-.21	.27
Recovery prolonged	-.002	-.29	.12	-.003	-.25	.20
Grip strength (n=39)	-.002	-.32	.05*			
Grip work (n=39)	-.00004	-.41	.01*			

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

Table B.2: Results of linear regression with Clinical Frailty Scale (CFS) as dependent variable (n=30)

Independent variable	Coefficient B	Standard beta	P-value	Coefficient B	Standard beta	P-value
	SBP			DBP		
Initial drop	.010	.13	.49	-.01	-.07	.73
Recovery orthostatic	.006	.09	.63	.02	.09	.65
Recovery rapid	.008	.11	.57	.01	.04	.84
Recovery sustained	.009	.13	.50	.01	.06	.76
Recovery prolonged	-.005	-.06	.77	-.02	-.19	.54
Grip strength (n=39)	-.019	-.22	.18			
Grip work (n=39)	-.001	-.38	.02*			

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

Table B.3: Results of logistic regression with 'Decision about surgery (yes/no)' as dependent variable (n=29)

Independent variable	Coefficient B	Odds ratio (Exp B)	P-value	Coefficient B	Odds ratio (Exp B)	P-value
	SBP			DBP		
Initial drop	-.015	.99	.48	-.010	.99	.81
Recovery orthostatic	.008	1.01	.66	-.004	1.00	.93
Recovery rapid	.001	1.00	.95	-.049	.95	.37
Recovery sustained	-.006	.99	.74	-.040	.96	.40
Recovery prolonged	.011	1.01	.68	-.024	.98	.56
Grip strength (n=38)	.040	1.04	.13			
Grip work (n=38)	.001	1.00	.04*			

SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

3. An explorative study targeting change in blood pressure waveform morphology as a response to orthostatic stress in Alzheimer patients

Abstract

Background: Orthostatic blood pressure (BP) recovery is known to associate with the rate of cognitive decline and mortality in patients with Alzheimer's disease (AD). Many data points obtained from the continuously measured BP signal are normally ignored during analysis. Waveform morphology of BP signals could provide patient-specific information about cardiac function and arterial stiffness, which are also risk factors for the progression of AD. Our explorative research aimed to assess whether waveform characteristics can be used to make a better prediction of cognitive decline in patients with AD.

Methods: Participants from the cerebral blood flow substudy of the Nilvad trial were included in this study. The Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) was assessed four times within 1.5 years. The average increase in ADAS-cog score per year was used as an outcome measure for cognitive decline. Participants performed a sit-to-stand challenge, during which BP was monitored continuously. From continuous BP data, waveforms were selected in time windows of ten seconds at baseline and 15, 30 and 60 seconds after standing up. From average waveforms, the area under the curve, peak-to-peak time and reflection index were determined to quantify waveform morphology. These parameters were compared within individuals before and after standing up. Besides that, the change in parameters upon standing was tested for association with cognitive decline.

Results: 52 participants were included in our analysis. At 60 seconds after standing up, all waveform characteristics deviated significantly from baseline. None of these deviations was significantly associated with cognitive decline.

Conclusion: Our analysis of continuous BP data retrieved from a sit-to-stand challenge of participants with AD showed no associations between change in waveform morphology and cognitive decline. We showed that different waveform characteristics change significantly as a response to orthostatic stress.

3.1 Introduction

The number of people diagnosed with probable Alzheimer's Disease (AD) is increasing, and much research is conducted targeting not only the cure but also the development and progression of AD. Since the progression of AD varies much between and within people, it is difficult to predict progression. This makes it hard for patients and their relatives to cope with their disease. If AD progression could be estimated patient-specific at baseline, this would allow for better care and more accurate information for these patients and their families. A prediction of the rate of cognitive decline in AD patients should cover multidomain aspects. (Haaksma et al., 2019; Melis et al., 2019) Therefore, the concept of resilience could be feasible to realize this. Earlier research showed that orthostatic BP recovery, as a measure of resilience, was associated with the rate of cognitive decline and mortality in patients with AD. (De Heus et al., 2020)

When determining BP recovery from continuous BP signals many data points are ignored since only the course of SBP and DBP is analysed. Regarding other research topics, it is very common to analyse waveform morphologies from e.g. intracranial pressure (Hu et al., 2009), arterial BP (Almeida et al., 2013; Moxham, 2003; Townsend et al., 2015) or PPG signals (Bartels & Thiele, 2015; De Heus et al., 2018; Reisner et al., 2008). The photoplethysmogram that is received when measuring beat-to-beat BP is similar in morphology and physiological cause to an arterial BP waveform. (Reisner et al., 2008) This waveform can provide patient-specific information about cardiac function and arterial stiffness. (Allen & Murray, 2003; Charlton et al., 2019) Since vascular stiffness is associated with faster progression of dementia, independently of hypertension as a known risk factor, the waveform could give us valuable information. (Hajjar et al., 2016; Pase et al., 2012)

Waveform morphology analysis of PPG signals has been examined in different studies. Whereas PPG signals as used for beat-to-beat BP monitoring are measured at the finger, other measurement sites could also be used for PPG, such as the wrist, arm, earlobe, or forehead. Research has shown that each measurement site results in a different morphology of the PPG waveform. (Hartmann et al., 2019) When measured at the finger, an elevation of the hand can also cause morphological changes in PPG signals, hypothesized to be caused by changes in vascular resistance. (Hickey et al., 2015) Besides that, research showed that several features of the PPG signal change as a result of a shift in central blood volume, induced by a head-up tilt table test. (Aarotale et al., 2020) This test causes orthostatic stress, which is also caused by actively standing up. Multiple studies have shown that orthostatic stress induces changes in PPG waveform morphology. They each used several waveform characteristics to quantify waveform morphology, such as the area under the curve (AUC), height and width of a pulse or the time delay between the systolic and diastolic peak. (Linder et al., 2006; Millasseau et al., 2006; Palasz et al., 2020; Zaidi & Collins, 2016) It was shown that these variables decrease when comparing a standing to a supine position (Zaidi & Collins, 2016), but also that change in waveform morphology followed by standing up is heterogeneous (Linder et al., 2006).

With explorative research, we aim to assess whether waveform characteristics can be used to make a better prediction of cognitive decline in AD patients. We used continuous beat-to-beat BP signals from a supine-to-stand test in patients diagnosed with AD and quantified waveform morphology by extracting multiple characteristics that have been used in earlier research. Not only the waveform morphologies at baseline can be valuable, but also the response of the vascular system to standing up. When rising, hemodynamic changes occur caused by a blood volume shift. Hereafter, influenced by aspects such as intravascular volume status, arterial stiffness and BP, waveform morphology is believed to change. It is hypothesized that patients with fast progression of AD have less capacity to adapt to the volume change caused by standing up since earlier research showed that both orthostatic BP recovery and BP variability are associated with cognitive decline. (De Heus et al., 2020, 2021) Therefore, we expect that patients with fast progression of AD will show more change in waveform morphology upon standing up, and thus more change in the three waveform characteristics used to quantify waveform morphology.

3.2 Methods

3.2.1 Study design and population

Data for this study were derived from the Nilvad trial (NCT02017340), which is a randomized controlled trial in which the effect of nilvadipine was investigated on cognitive and functional outcomes in 511 people with mild-to-moderate AD. This study concluded that nilvadipine did not affect disease progression. For our analysis of continuous BP measurements, the cerebral blood flow substudy of the Nilvad trial, performed at the Radboudumc, was used. This substudy contains 58 participants, aged 50 and older and diagnosed with probable AD. (De Heus et al., 2020; Lawlor et al., 2018; Meulenbroek et al., 2016)

3.2.2 Data collection

Blood Pressure Measurement

Participants were asked to perform a sit-to-stand test. During this test, continuous BP measurements were performed at the index or middle finger of the non-dominant hand using volume-clamp PPG (Finapres Medical Systems, Amsterdam, The Netherlands). Participants were asked to hold their hand at heart level during the test, supported by an arm sling. Before the measurement started, participants already sat for 5 minutes. Hereafter, the measurement started with 2 minutes of sitting, followed by standing up calmly and 1 minute of standing. This was repeated 2 times, so in total 3 sit-to-stand manoeuvres were executed. After the last sit-to-stand transition, participants were asked to remain standing for 5 minutes. To assess the presence of OH from this sit-to-stand test, a cut-off value of 15 mmHg in SBP drop or 7 mmHg in DBP drop was used (Shaw et al., 2017).

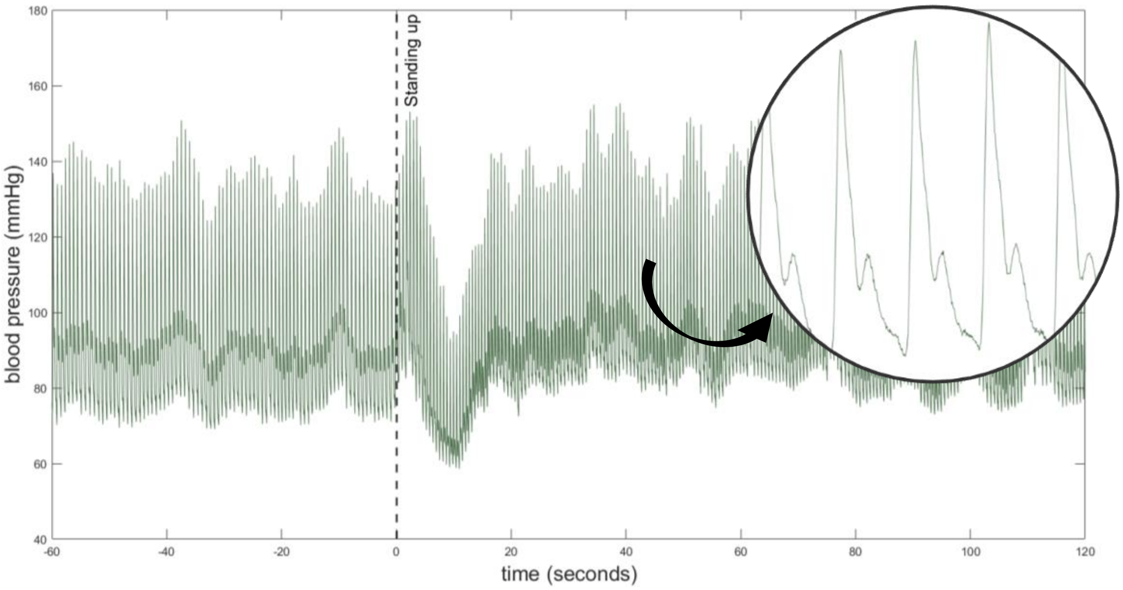
Cognitive Assessment

Participants were scored on the 12-item Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog), which covers multiple cognitive domains and ranges from 0 to 80 points. More points indicate worse cognitive performance. Assessments were done at baseline and after 13, 52 and 78 weeks. If less than three of these measurements were available, participants were excluded for further analysis. To express cognitive decline, a linear function was fit through these datapoints of ADAS-cog score at the different time points. The slope of this line was used as an outcome of cognitive decline to correct for possible deviations in individual test scores at each time point and can be interpreted as the average increase in ADAS-cog score per year. Moreover, all-cause mortality data were collected via the database of the Dutch municipal records with a minimum follow-up period of 4 years.

3.2.3 Data analysis

Continuous BP data of a sit-to-stand test as measured at baseline were used for analysis. The raw BP signals were used, in combination with markers for moments of sitting and standing up as defined by De Heus et al. (De Heus et al., 2018, 2020) Further analysis was performed using custom-written scripts in MATLAB R2020b. An example of the used BP data is depicted in Figure 7.

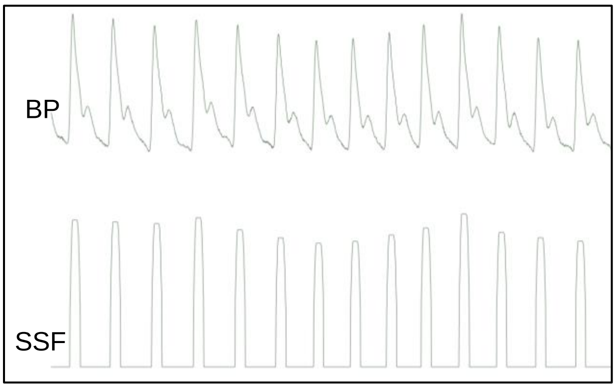
Figure 7: Continuous blood pressure data of a sit-to-stand challenge



Time series data as measured with volume-clamp photoplethysmography consist of many compressed waveforms, as depicted in the enlarged window. The dashed line represents the moment of standing up after a period of sitting.

From the available data, only the third sit-to-stand manoeuvre was used, since the evaluation of BP recovery around 1 minute was of interest for this study. First, the data of interest were selected and defined as 60 seconds before the third time of standing up until 120 seconds after standing up. Hereafter, this data of interest was split up into separate waveforms. This was done by detecting the onset of each waveform using a slope sum function (SSF) as described by Zong et al. (Zong & Mark, 2003) The relation between a BP signal and its SSF is visualized in Figure 8. First, a second-order low-pass Butterworth filter with a cut-off frequency of 16 Hz was applied to remove high-frequency noise that could affect pulse onset detection. Hereafter, the slope between each sample was calculated. When this slope was negative, it was set to 0. When this slope was positive it was kept at its value. To maximize the SSF, the sum of the signal was calculated using windows of 160 milliseconds. Hereafter, a decision rule was applied. A threshold of 150% from the mean SSF was chosen to only detect correct onsets. Finally, a refractory period of 240 milliseconds, which would correspond with an improbable heart rate of 250 beats/min, was set where no new onsets could be detected to avoid double pulse detection. (Zong & Mark, 2003)

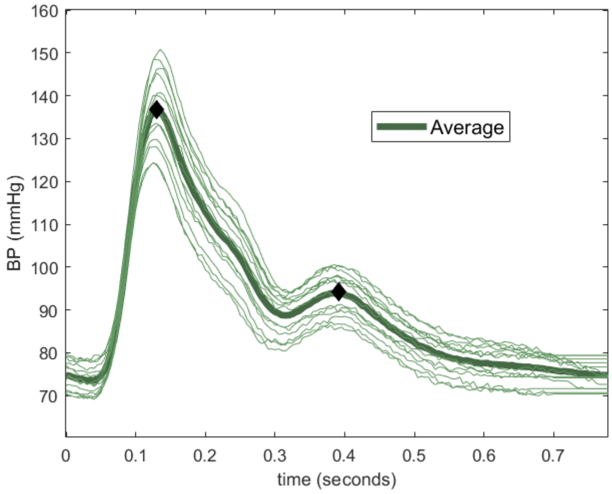
Figure 8: Blood pressure signal and its corresponding Slope Sum Function



BP, Blood Pressure; SSF, Slope Sum Function
The upper continuous blood pressure signal consists of consecutive pulses. To improve pulse onset detection, a slope sum function was implemented, of which an example is shown below.

For analysis of these detected waveforms, the following timepoints of interest were selected: baseline, 15, 30 and 60 seconds after standing up. The baseline started at 40 seconds before standing up. For a time window of 10 seconds starting at the timepoint of interest, all waveforms were selected and the average was calculated. Thereafter, the systolic and diastolic peak were detected from this average waveform. An example of such an averaged waveform with detected peaks can be seen in Figure 9.

Figure 9: Consecutive waveforms within 10 seconds with their average and detected peaks

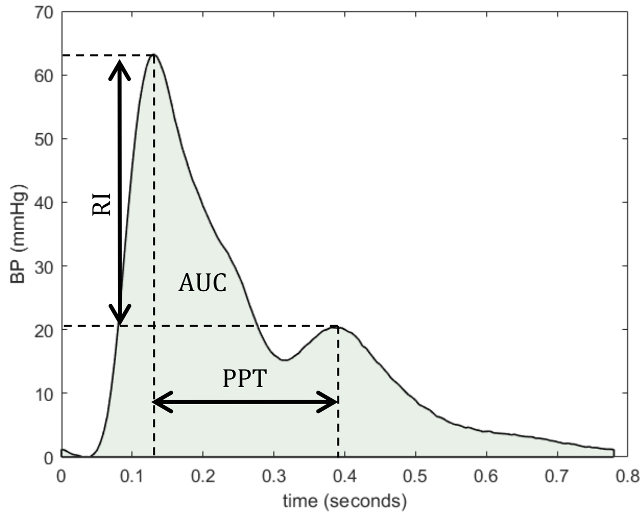


The thin green lines represent individual waveforms within ten seconds of interest. Their average is depicted as the thick green line. Detected systolic and diastolic peaks are shown as black diamonds.

Selected and averaged waveforms, as well as detected peaks, were verified by visual inspection. If one waveform within the time window visually deviated a lot from the other waveforms, the continuous BP data were reviewed to track down the cause of this deviation. If a clear artefact or an extrasystole was seen in this continuous data, this specific waveform was excluded from the average. Possible undetected or falsely detected peaks were corrected. In the case of an M-shaped systolic peak, the peak with the highest amplitude was defined as the systolic peak.

Outcome parameters were calculated from each average waveform. They were chosen based on parameters used in earlier research. (Almeida et al., 2013; Hartmann et al., 2019; Millasseau et al., 2006; Moxham, 2003; Palasz et al., 2020; Townsend et al., 2015; Zaidi & Collins, 2016) The parameters were chosen with the aim of quantifying the morphology of the waveform. The outcome parameters used were the area under the curve (AUC), peak-to-peak time (PPT) and reflection index (RI), visualized in Figure 10. For calculation of the AUC and RI, the waveform was normalized to a baseline of 0 mmHg, to prevent influence from the absolute BP values on these parameters.

Figure 10: Normalised waveform with used waveform characteristics.



RI = reflection index; AUC = area under the curve; PPT = peak-to-peak time.

AUC was calculated using MATLAB's function *trapz* according to:

$$\text{AUC} = \sum_{\text{t=pulse onset}}^{\text{next pulse onset}} \text{BPsignal}$$

PPT was defined as the difference between the systolic peak and diastolic peak in seconds:

$$\text{PPT} = \frac{\text{peak}_{\text{diastolic}} - \text{peak}_{\text{systolic}}}{\text{Sample frequency}}$$

RI was defined as the ratio between the systolic peak and the diastolic peak:

$$\text{RI} = \frac{\text{peak}_{\text{diastolic}}}{\text{peak}_{\text{systolic}}}$$

3.2.4 STATISTICAL ANALYSIS

BASELINE AND WAVEFORM CHARACTERISTICS

IBM SPSS Statistics 25 was used for statistical analysis. Baseline and waveform characteristics were tested for normality using a Shapiro-Wilk test. Normally distributed variables were presented using the mean and standard deviation. Not normally distributed variables were presented using the median and interquartile range. Categorical and dichotomous variables were presented by the number of participants and the percentage of the total sample.

CHANGES IN WAVEFORM CHARACTERISTICS IN RESPONSE TO ORTHOSTATIC MANOEUVRE

As a first step, absolute changes in waveform characteristics within an individual at each time point after standing up were compared with baseline as follows:

$$\Delta\ \text{Characteristic} = |\text{Characteristic}_{\text{baseline}} - \text{Characteristic}_{\text{time X}}|$$

In the case of normal distribution of these deltas, a paired t-test was used, otherwise, a Wilcoxon signed-rank test was used to test for significant differences. For each parameter separately, the timepoint after standing up with the highest average deviation from baseline was defined. The time point that showed the largest deviation in the most characteristics was used for further analysis, given that this difference was significant ($p<0.05$). If this did not provide a definitive answer, the level of significance was considered as well.

Association between waveform morphology and cognitive decline

Hereafter, we evaluated whether waveform characteristics at baseline are associated with cognitive decline. After visual inspection of the data using a scatterplot, a linear regression model was used to assess possible associations. For each waveform parameter, a separate model was made. All models included cognitive decline, expressed as the average increase in ADAS-cog score over one year, as an outcome. The following general linear regression equation was used:

$$\text{Cognitive decline} = \beta_0 + \beta_1 \cdot \text{Characteristic}$$

Moreover, we assessed whether the change in waveform characteristics caused by standing up is associated with cognitive decline. The absolute change of each parameter from baseline to the timepoint of interest as determined earlier was used in this analysis. These delta values were first visually inspected when compared to cognitive decline using a scatterplot. Thereafter, we used linear regression to investigate possible associations between change in waveform upon standing and cognitive decline, according to the following equation:

$$\text{Cognitive decline} = \beta_0 + \beta_1 \cdot \Delta\ \text{Characteristic}$$

Additionally, we investigated whether these waveform characteristics together can predict cognitive decline in AD patients. A random forest was used since this algorithm showed good accuracy in earlier research using machine learning for arterial pressure waveform analysis. (Almeida et al., 2013) A random forest is an unsupervised machine learning method used for the classification of samples based on several features. The classifier consists of multiple decision trees, of which the majority vote is used to classify a sample. Each decision tree is created using a bootstrap sample of the data set and a randomly drawn sample of features, which is called bootstrap aggregating (bagging). This increases accuracy and prevents overfitting of the classifier. Besides that, bagging eliminates the need of using a separate test data set, since the out-of-bag data can provide for an error estimate of the random forest model. (Breiman, 2001; Dauwan et al., 2016)

The classifier was designed using R 4.0.3 and RStudio Version 1.4.1103. To use a binary classification method, two classes were defined based on AD progression. Fast progressors had an increase in ADAS-cog score of ≥ 8 in one year and slow progressors of < 8. (De Heus et al., 2020) The waveform characteristics at baseline, the delta of each characteristic, together with sex and age, were included as features to classify fast and slow progressors of AD. The importance of variables was presented by the normalized mean decrease Gini per feature. (Dauwan et al., 2016) If the random forest would result in a low error rate when classifying fast and slow progressors of AD, this would suggest that the use of artificial intelligence on this topic would be promising for future research.

Association between changes in waveform morphology and orthostatic recovery

From the research of De Heus et al., data were available about the orthostatic recovery of our sample. Orthostatic recovery was defined as the difference between baseline and mean BP at 50-60 seconds after standing up, where the baseline was the average BP between 40 and 10 seconds before standing up. Orthostatic recovery was expressed as a percentage from baseline. (De Heus et al., 2020) To assess if participants with worse recovery of BP showed more change in waveform morphology, linear regression was used according to the following equation:

$$\text{Orthostatic recovery} = \beta_0 + \beta_1 \cdot \Delta\ \text{Characteristic}$$

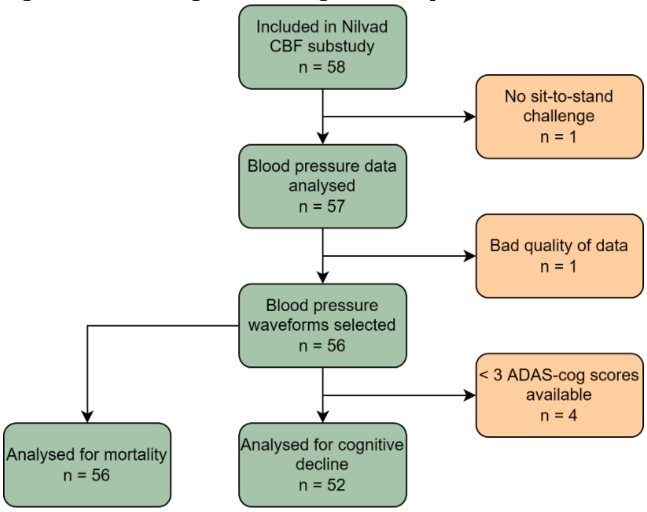
Association between changes in waveform morphology and mortality

Since earlier research with these data showed that orthostatic BP recovery was associated with mortality, we explored associations with this outcome measure as well. (De Heus et al., 2020). Logistic regression was used to assess associations between change in waveform characteristics with mortality. Mortality was determined through the database of the Dutch municipal records in March 2019 for all participants, resulting in a minimum follow-up period of 4 years.

3.3 Results

After the exclusion of two participants, 56 participants remained for analysis. For cognitive decline analysis, four more patients were excluded resulting in a sample of 52 participants. Reasons for exclusion are shown in Figure 11.

Figure 11: Flow diagram showing inclusion procedure



CBF = cerebral blood flow; ADAS-cog = Alzheimer's Disease Assessment Scale - cognitive subscale.

Baseline characteristics of the 56 included participants can be found in Table 5. Characteristics of the 52 participants used for cognitive decline analysis can be found in Appendix C, Table C.1. Continuous variables were tested for normality and presented accordingly. During the sit-to-stand manoeuvre, one participant experienced dizziness and two participants experienced other orthostatic symptoms.

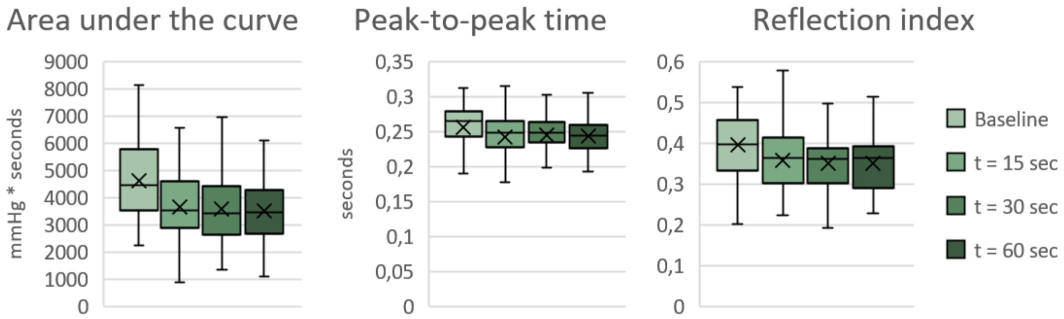
Table 5: Participant characteristics (n=56)

Characteristics	Value	
Sociodemographic		
Age (years), mean (SD)[a]	73.1 (6.1)	
Female gender, n (%)	32 (57.1)	
Health characteristics		
BMI (kg/m^2), mean (SD)[a]	24.8 (3.7)	
Intervention group Nilvadipine, n (%)	29 (51.8)	
Antihypertensive drug use, n (%)[a]	16 (28.6)	
History of cardiovascular disease, n (%)[a]	9 (16.1)	
Cognitive measures		
ADAS-cog score at baseline, median (IQR)[a]	30 (11)	
Cognitive decline (Δ ADAS-cog/year), median (IQR)	4.4 (8.2)	
Blood pressure measures		
Sitting SBP (mmHg), mean (SD)[a]	135.8 (13.0)	
Δ SBP after standing (mmHg), mean (SD)[a]	-0.1 (8.5)	
Sitting DBP (mmHg), median (IQR)[a]	80 (9.0)	
Δ DBP after standing (mmHg), median (IQR)[a]	0.0 (3.8)	
Orthostatic hypotension, n (%)[a]	5 (8.9)	
Orthostatic recovery SBP (%), mean (SD)[a b]	97.8 (9.0)	n=51
Orthostatic recovery DBP (%), median (IQR)[a b]	102.8 (8.4)	n=51

BMI, body mass index; ADAS-cog, Alzheimer's disease Assessment Scale-cognitive subscale; SBP, systolic blood pressure; DBP, diastolic blood pressure.
Cognitive decline was defined by a linear fit through four ADAS-cog assessments over 1.5 years.
a = as measured at baseline, before starting Nilvadipine intervention or placebo.
b = as available from De Heus et al. BP at 50-60 seconds after standing up as a percentage from baseline. (De Heus et al., 2020)

The characteristics determined from the average waveforms at each timepoint from all 56 participants are visualized as boxplots in Figure 12. Exact values can be found in Appendix C, Table C.2.

Figure 12: Boxplots of waveform characteristics at baseline and three time points after standing up (n=56)



The left graph shows Area Under the Curve (AUC), the middle graph Peak-to-Peak Time (PPT), the right graph Reflection Index (RI) as derived from blood pressure waveforms at baseline and t = 15, t = 30 and t = 60 after standing up.

3.3.1 Changes in waveform characteristics in response to orthostatic manoeuvre

With a paired sample t-test, it was examined whether waveform characteristics differed significantly from baseline at the time points of 15, 30 and 60 seconds after standing up. The results can be found in Table 6. At 60 seconds after standing up, all characteristics were significantly changed within a participant when compared to baseline. At 15 and 30 seconds after standing up, AUC and RI showed significant changes. Since 60 seconds after standing showed the most significant results and largest absolute differences, this time point was chosen for further analysis.

Table 6: Paired sample t-test results of change in all waveform characteristics compared to baseline (n=56)

Characteristic	Baseline compared with	Mean difference	P-value
AUC	t = 15	994	< 0.001***
	t = 30	1050	< 0.001***
	t = 60	1106	< 0.001***
PPT	t = 15	0.011	0.051
	t = 30	0.009	0.060
	t = 60	0.011	0.036*
RI	t = 15	0.037	< 0.001***
	t = 30	0.045	< 0.001***
	t = 60	0.045	< 0.001***

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index.
* Indicates significance level of p < 0.05. ** Indicates significance level of p < 0.01. *** Indicates significance level of p < 0.001.

3.3.2 Association between waveform characteristics at baseline and cognitive decline

To explore possible associations between waveform characteristics at baseline and cognitive decline, linear regression analysis was performed. The results can be found in Table 7. In each regression model, either AUC, PPT or RI was used as the independent variable. In all cases, cognitive decline was used as the dependent variable. Our regression analysis showed that PPT at baseline was significantly associated with cognitive decline.

Table 7: Results of linear regression with cognitive decline as the dependent variable and each baseline characteristic as the independent variable (n=52)

Independent variable	Unstandardized Coefficients B	Standardized Coefficients Beta	P-value
$AUC_{baseline}$	-0.00012	-0.02	0.88
$PPT_{baseline}$	-58.56	-0.30	0.03*
$RI_{baseline}$	20.88	0.21	0.14

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index.
* Indicates significance level of p < 0.05.

3.3.4 Association between changes in waveform characteristics in response to orthostatic manoeuvre and cognitive decline

The absolute change in waveform characteristics was defined as the difference between baseline and t=60. This resulted in a mean delta AUC of 1163 (± 810) mmHg*sec, a mean delta PPT of 0.031 (± 0.024) sec and a mean delta RI of 0.050 (± 0.043) over all participants.

To investigate the possible association of these changes in waveform characteristics with cognitive decline, linear regression was used. In this analysis, delta AUC, delta PPT or delta RI was used as the independent variable and cognitive decline was used as the dependent variable. None of these linear regression models showed a significant association with cognitive decline. Results can be found in Table 8.

Table 8: Results of linear regression with cognitive decline as the dependent variable and delta of each characteristic as the independent variable (n=52)

Independent variable	Unstandardized Coefficients B	Standardized Coefficients Beta	P-value
Δ AUC	-0.001	-0.06	0.68
Δ PPT	65.59	0.21	0.13
Δ RI	-20.60	-0.12	0.40

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index.

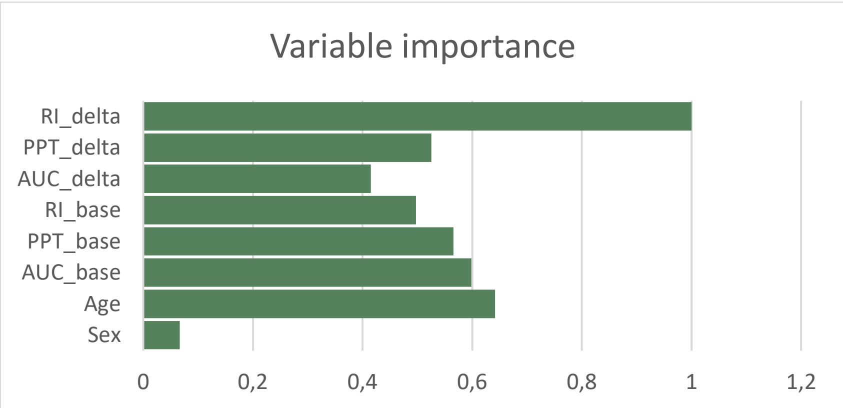
3.3.5 Random forest classifier

The random forest classifier contained the baseline value of all characteristics and delta AUC, delta PPT and delta RI as features, as well as age and sex. The random forest consisted of five hundred trees and three variables were tried at each split. This resulted in an out-of-bag estimate of error rate of 28.85 per cent. The sensitivity of the classifier was 25.00 per cent, specificity was 91.67 per cent. The confusion matrix of the classifier can be found in Table 9, the calculated variable importance is displayed in Figure 13. In this random forest, delta RI had the biggest influence on the final classification of fast or slow progressors. Sex had the least influence on the final classification.

Table 9: Confusion matrix of random forest classifier (n=52)

	Predicted fast progressor	Predicted slow progressor	Class error
Fast progressor	4	12	0.75
Slow progressor	3	33	0.08

Figure 13: Normalized variable importance of each feature

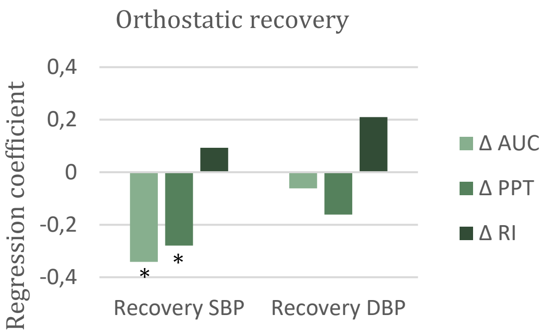


RI, Reflection Index; PPT, Peak-To-Peak time; AUC, Area Under the Curve.
Variable importance was calculated as the normalized mean decrease Gini per feature. (Dauwan et al., 2016)

3.3.6 Association between changes in waveform morphology and orthostatic recovery

From 51 participants of our sample, orthostatic recovery values were available. Linear regression showed significant associations between delta AUC and delta PPT with recovery SBP. Other associations were not significant. Normalized regression coefficients are visualized in Figure 14. Exact results can be found in Appendix C, Table C.3 and C.4, for respectively SBP and DBP recovery.

Figure 14: Results of linear regression analysis between waveform characteristics and orthostatic recovery (n=51)



AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.
* Indicates significance level of $p < 0.05$.

3.3.7 Association between changes in waveform morphology and mortality

Analysis with mortality as an outcome measure was executed using all 56 participants. During the follow-up period of the study, 21 (37.5%) participants from our sample died. The results of the logistic regression analysis can be found in Table 10. We found that none of the changes in waveform characteristics as a response to orthostatic stress was significantly associated with mortality after a 4-year follow-up period.

Table 10: Results of logistic regression analysis (n=56)

Independent variable	Coefficient B	Odds ratio (Exp B)	P-value
Δ AUC	-0.00032	1.00	.39
Δ PPT	9.94	20658.90	.39
Δ RI	1.44	4.21	.82

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index

3.4 Discussion

This study explored the value of waveform morphology assessment in relation to cognitive decline in patients with mild-to-moderate AD, who participated in the cerebral blood flow substudy of the Nilvad trial. In our explorative analysis, we used three different waveform characteristics to approximate the morphology of waveforms at baseline and after standing up. We found that these waveform characteristics within an individual change significantly when participants were exposed to orthostatic stress. We only found a significant association of peak-to-peak time at baseline with cognitive decline. Change in waveform characteristics caused by standing up had no significant association with cognitive decline or mortality.

In this study, we wanted to assess the morphology of BP waveforms by quantification of waveform characteristics. To keep the analysis manageable and interpretable, only a select number of parameters were chosen based on the literature. This resulted in an approximation of the waveform morphology, but many other parameters could have been used and might be of value. To calculate PPT and RI, two peaks were detected in each waveform. For most waveforms, peaks were clearly visible. However, for some waveforms discussion arose about the detected peaks. Some systolic peaks were ambiguous since they were M-shaped and actually consisted of two peaks. After consultation with a geriatrician, it was decided to always use the peak with the highest amplitude, independent of it being the first or second peak of the M-shaped systolic peak. In a few other cases, the second or diastolic peak was harder to detect. Manual selection of the peak was applied in these cases, which decreased the repeatability of the calculation of PPT and RI.

We found that the used waveform characteristics change significantly in response to orthostatic stress, which is in agreement with earlier research. (Aarotale et al., 2020; Linder et al., 2006; Palasz et al., 2020; Zaidi & Collins, 2016) Since the heart rate in most participants increases when standing up, a part of the decrease in AUC was caused by a higher heart rate as waveforms were not normalized over the time axis. The changes in PPT and RI were not influenced by heart rate. Our research was the first to show such a change in quantified waveform morphology as a response to orthostatic stress in a cohort of Alzheimer patients.

Moreover, our results showed a significant association of PPT at baseline with cognitive decline when using linear regression. However, the other two characteristics at baseline as well as the delta of all characteristics showed no significant association. When looking at scatterplots of our data, we saw that one specific sample had a very high score for cognitive decline, and had a low PPT. This result could have biased the linear regression. When leaving this sample out, the P-value was no longer below our significance level of 0.05. Larger sample sizes, with more participants with high rates of cognitive decline, could provide clarity about this possible association.

In our study sample, only five people were classified as OH patients, based on the BP data from the sit-to-stand challenge with its according cut-off values. (Shaw et al., 2017) This is only a prevalence of 9.6% of OH in our sample, whereas a systematic review concluded on a prevalence of one in five community-dwelling older people and almost one in four older people in long-term care. (Saedon et al., 2020) Our population was however selected on the absence of (severe) OH and the use of beta-blockers was an exclusion criterion for the Nilvad trial. This could mean that our population of AD patients on average had fewer cardiovascular problems, and therefore showed less OH than a random sample population would have. This could also have resulted in a less perceived change in waveform morphology as a response to orthostatic stress. Another explanation for our low OH prevalence could be the fact that a sit-to-stand challenge was used instead of the normally used supine-to-stand test. However, the accordingly used cut-off values should have accounted for this difference.

The random forest classifier resulted in an out-of-bag estimate of error rate of 28.85 per cent. However, the error rate in the fast progressor group was much higher (75%) than that of the slow progressor group (8%). An explanation for this is the fact that our dataset was imbalanced in the presence of fast (n=16) and slow (n=36) progressors of AD. This influences the classifier since the classification of 'slow' is by definition more likely to be true. A median split of fast and slow progressors led to a higher error rate of the classifier. Using our current sample and analysis approach, a random forest classifier could not provide accurate classification.

Additionally, we found that orthostatic recovery of SBP was significantly associated with a change in two out of three waveform characteristics. It remains unclear why specifically AUC and PPT showed significant associations, and why DBP response showed no significant results. Orthostatic recovery was associated with cognitive decline in the same cohort of patients. (De Heus et al., 2020) It is hypothesized that patients with worse orthostatic recovery, have less capacity to adapt to change and therefore show more change in quantified waveform morphology in two out of three used parameters.

To assess cognitive decline, we used a linear fit through measured ADAS-cog scores at weeks 0, 13, 52 and 78. In many cases, progression did not follow an increasing pattern but showed both higher and lower scores throughout time. Where earlier studies only used the difference between baseline and 1,5 years (De Heus et al., 2020), we tried to account for variability in the assessment moment by our approach. Our linear method also handled missing data of ADAS-cog score, which led to fewer exclusions. However, the reason for this missing data was not taken into account. For two participants, the ADAS-cog score at 78 weeks was missing due to severe progression. Since these participants showed a sudden increase after the last available data point of 52 weeks, this severe progression was not directly reflected in their score for cognitive decline. Besides them, many participants with all four data points did not show linear progression in ADAS-cog scores. Therefore, it might be valuable to be able to predict tipping points in Alzheimer progression. For this, more insight into the heterogeneous aetiology and pathophysiology of AD is needed.

3.4.1 Future perspectives

We saw that quantified waveform morphology changed as a result of applied orthostatic stress by a sit-to-stand challenge. However, the amount of change was not related to cognitive decline or mortality. It might be interesting to look at changes in waveform morphology with a bigger stressor, such as a supine-to-stand test or a head-up tilt table test. Many recent studies measure continuous BP data during such challenges, so it would be feasible to assess the waveform morphology of this data supplementary to the currently analysed SBP and DBP over time.

We hypothesized that AD patients would have less capacity to adapt to change and would therefore show more change in waveform morphology. Maybe the comparison of the change in waveform morphology with cognitive decline and mortality is too distinctive. Waveform morphology has proven to be related to arterial stiffness, but its application is still a point of debate. (Allen & Murray, 2003; Charlton et al., 2019) Besides that, the role of arterial stiffness and vascular condition in general in the progression of AD remains unclear. OH assessed in midlife was significantly associated with incident dementia, but underlying pathways have not been unravelled yet. (Rawlings et al., 2018) Before taking the step to cognitive decline or mortality, waveform analysis of continuous BP data should be examined in the scope of cardiovascular function.

Where we used three parameters to quantify waveform morphology, there are many more ways to incorporate waveform analysis. For example pulse decomposition analysis has been proven useful for the analysis of PPG and central arterial BP signals. (Baruch et al., 2011, 2014; Fleischhauer et al., 2020) A study by Stoner et al. showed that pulse waveform separation assessing the arterial wave reflection can be used to research the cardiovascular response to an orthostatic challenge. (Stoner et al., 2018) Moreover, machine learning techniques could be used to assess arterial pressure waveforms. (Almeida et al., 2013) Other researchers developed a mathematical method (symmetric projection attractor reconstruction) to quantify changes in raw waveform data. They mostly aim to use all of the data captured when measuring a continuous signal, instead of only using averages. (Aston et al., 2018; Nandi et al., 2018)

3.5 Conclusion

Our analysis of continuous BP data retrieved from a sit-to-stand challenge of 56 participants participating in the Nilvad trial aimed to use individual BP waveform characteristics to predict cognitive decline or mortality. We showed that our method of waveform analysis showed a significant change in waveform morphology as a result of orthostatic stress. However, only the baseline value of one characteristic showed an association with cognitive decline. With future research, the waveform morphology could give us more insight into the role of arterial stiffness in the progression of AD.

APPENDIX C: SUPPLEMENTARY RESULTS

Table C.1: Baseline characteristics for the sample used for analyses with cognitive decline as an outcome measure (n=52)

Characteristics	Cognitive decline analysis	
Sociodemographic		
Age (years), mean (SD)[a]	73.4 (6.1)	
Female gender, n (%)	30 (57.7)	
Health characteristics		
BMI (kg/m^2), mean (SD)[a]	24.7 (3.6)	
Intervention group Nilvadipine, n (%)	26 (50)	
Antihypertensive drug use, n (%) [a]	16 (30.8)	
History of cardiovascular disease, n (%) [a]	9 (17.3)	
Cognitive measures		
ADAS-cog score at baseline, median (IQR)[a]	30 (11)	
Cognitive decline (Δ ADAS-cog/year), median (IQR)	4.4 (8.2)	
Blood pressure measures		
Sitting SBP (mmHg), mean (SD)[a]	135.6 (13.4)	
Δ SBP after standing (mmHg), mean (SD)[a]	0.0 (8.7)	
Sitting DBP (mmHg), median (IQR)[a]	80.0 (7.0)	
Δ DBP after standing (mmHg), median (IQR)[a]	0.0 (4.8)	
Orthostatic hypotension, n (%) [a]	5 (9.6)	
Orthostatic recovery SBP (%), mean (SD)[a b]	97.8 (9.0)	n=51
Orthostatic recovery DBP (%), median (IQR)[a b]	102.8 (8.4)	n=51

BMI, Body Mass Index; ADAS-cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure

Table C.2: Waveform characteristics as determined from average waveforms within windows of 10 seconds at different timepoints (n=56)

	AUC (mmHg*seconds)	PPT (seconds)	RI
Baseline	4618 ± 1368	0.254 ± 0.040	0.396 ± 0.075
t = 15	3624 ± 1247	0.243 ± 0.043	0.359 ± 0.079
t = 30	3568 ± 1269	0.245 ± 0.031	0.351 ± 0.074
t = 60	3512 ± 1233	0.243 ± 0.029	0.351 ± 0.079

AUC = area under the curve; PPT = peak-to-peak time; RI = reflection index. Values are presented as mean ± standard deviation.

Table C.3: Results of linear regression analysis with the orthostatic recovery of systolic blood pressure as dependent variable (n=51)

Independent variable	Coefficient B	Standard beta	P-value
Δ AUC	-.004	-.342	.01*
Δ PPT	-105.18	-.280	.05*
Δ RI	19.37	.093	.52

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index

* Indicates significance level of $p < 0.05$.

Table C.4: Results of linear regression analysis with orthostatic recovery of diastolic blood pressure as dependent variable (n=51)

Independent variable	Coefficient B	Standard beta	P-value
Δ AUC	-.001	-.061	.67
Δ PPT	-49.52	-.161	.26
Δ RI	36.11	.210	.14

AUC, Area Under the Curve; PPT, Peak-to-Peak Time; RI, Reflection Index

4. General conclusion

In this thesis, continuous BP measurements have been used to quantify and analyse resilience in different populations. The first part consisted of a clinical study, the GRR, aiming to develop quantitative resilience measurements for use in clinical practice. Geriatric pre-operative outpatients were included and performed a physical test battery consisting of a supine-to-stand test, GW measurement and timed chair-stand-test. Our cross-sectional analysis showed associations between GW and clinical outcome measures, but no significant associations were found between BP recovery and these outcomes. It is believed that long transition times induced by frailty counter affected a possible association. The second part consisted of an explorative analysis, using data from the cerebral blood flow substudy of the Nilvad trial. Waveform characteristics of continuous BP data from a supine-to-stand test from Alzheimer patients were analysed and compared with their rate of cognitive decline. No significant association with cognitive decline was found, but waveform characteristics did change significantly within the individuals as a response to orthostatic stress.

Quantifying resilience remains a difficult, challenging, and interesting task. Ideally, long follow-up periods and large heterogeneous cohorts should be analysed. Our research showed that GW is a promising and easy to implement measure that associates with different measures of frailty. When including more patients and maintaining longer follow-up periods of our sample after surgery, GW and BP recovery can be re-assessed to draw definitive conclusions. We also showed that waveform morphology changes as a result of orthostatic stress in Alzheimer patients. Since waveform morphology is believed to include information about a patient's vascular status, this type of analysis could also be performed in continuous BP signals from other samples. Associations with arterial stiffness and possibly resilience could be assessed.

With the current state of research, it is too soon to use BP recovery as a measure of resilience. Many different studies have been performed and reported different results. In the end, the determination of a person's resilience is a complex task, containing many different aspects. BP recovery could play a role in this but should be combined with other measures targeting resilience, such as GW. Besides that, waveform morphology of continuous BP signals could give us more insight in cardiovascular status on a patient-specific level. In an ideal situation, a standardized test battery containing multiple physical tests, supplemented with patient characteristics, can quantify resilience, and support clinical decision making.

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