The influence of age, sex, frailty, and progressive strength training on short-term integrative dynamic cardiovascular and autonomic compensatory responses to orthostatic stress.

by

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ABSTRACT

Background: The cardiovascular and autonomic systems regulate blood pressure (BP) during postural changes, preventing orthostatic hypotension (OH), linked to dizziness, falls, and mortality. OH is influenced by age, sex, and frailty, yet short-term compensatory mechanisms are underexplored. Aging impairs BP regulation; females show higher OH prevalence due to lower cardiac baroreflex gain (CBG) and greater parasympathetic activity. Frailty further compromises these systems. This thesis includes a systematic review and experimental studies examining whether age, sex, and frailty affect responses to orthostatic stress and if progressive strength training (PST) improves these responses. **Methods**: Participants underwent two active standing tests: sitting (5 min) or lying (10 min), followed by up to 7 minutes standing. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and HR were measured at baseline, immediately on standing, and throughout four specific phases after standing: phase 1 (0-30s), phase 2 (30-60s), phase 3 (60-180s), and phase 4 (300-420s). CO-SVR matching was evaluated to assess BP regulation timing. Heart rate variability (HRV) at baseline was analyzed in time and frequency domains. CPM was measured by the ratio between HR at the 30^{th} beat and the 15^{th} beat (HR 30:15) on standing. CBG was determined as the ratio of HR and SBP changes (ΔHR/ΔSBP) at specific phase time points (30s, 60s, 180s, and 420s). **Results**: This research demonstrated that frail older adults experience greater BP drops and slower recovery after standing, reflecting impaired cardiovascular regulation (Chapter 4). Older adults showed delayed BP regulation, lower short-term compensatory responses, HRV indexes, and CBG compared to young adults (Chapters 5-6). Despite similar BP regulation, older females relied more on SVR and males on CO, with no significant sex differences in autonomic responses (Chapters 7-8). Pre-frail and frail individuals exhibited delayed BP recovery and reduced HRV indexes (Chapters 9-10). Finally, a 12-week PST improved BP regulation timing and countered frailty, though it did not significantly affect autonomic modulation (Chapter 11).

Conclusion: Age, sex, and frailty influence short-term cardiovascular and autonomic responses to orthostatic stress and support PST to enhance BP regulation and counteract frailty in older adults.

Keywords: Cardiovascular system, Autonomic nervous system, Orthostatic hypotension, Frailty, Sex, Older adults.

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CONTRIBUTION OF AUTHORS

All co-authors listed in each manuscript contributed to various aspects of the work, including conception, design, data analysis, content review, and feedback.

I was responsible for the conception, design, data analysis, interpretation, and writing of each study.

From Chapters 4 to 12, Dr. Rodrigo Villar and Dr. Todd Duhamel contributed to the conception, design, data interpretation, and review of the manuscript content.

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ABBREVIATIONS

1-RM: One repetition maximum

BMI: Body mass index

CBG: Cardiac baroreflex gain

CERT: Consensus on exercise reporting template

CO: Cardiac output

CI: Confidence interval

CPM: Cardiac parasympathetic modulation

CSEP: Canadian Society for Exercise Physiology

DBP: Diastolic blood pressure

DBPR: Delayed blood pressure recovery

ECG: Electrocardiogram

FFT: Fast Fourier Transform

FI: Frailty index

FITT-PV: Frequency, intensity, time, type, progression, and volume

HF: High frequency

HR: Heart Rate

HRV: Heart rate variability

IOH: Initial orthostatic hypotension

LF/HF: Low frequency to high-frequency ratio

LF: Low-frequency

MAP: Mean arterial pressure

NBP: Normal Blood Pressure

OH: Orthostatic hypotension

OI: Orthostatic intolerance

PRISMA: Preferred reporting items for systematic reviews and meta-analyses

PST: Progressive strength training

RMSSD: Root mean square of successive differences

SAGER: Sex and gender equity in research

SBP: Systolic blood pressure

SD: Standard deviation

SDRR: Standard deviation of RR intervals

SOH: Sustained orthostatic hypotension

STROBE: Strengthening the reporting of observational studies in epidemiology

SV: Stroke volume

SVR: Systemic vascular resistance

TREND: Transparent reporting of evaluations with non-randomized designs

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1. Chapter 1

Introduction

For maintaining human life, the dynamic control and regulation of the cardiovascular and autonomic systems are crucial to ensure homeostasis and functionality in response to external challenges[1]. For example, the orthostatic stress caused by postural transitions, such as getting up from a bed or chair, triggers a series of rapid adaptive responses in both systems[2]. These responses are vital for counteracting the sudden and significant drop in blood pressure and the immediate reduction in cerebral blood flow that occurs during such transitions[1,2]. Failure to regulate these responses accurately leads to homeostatic dysregulation, which exposes people to orthostatic hypotension (OH)[3]. This condition is characterized by a drop in blood pressure within the first few seconds or minutes after standing[3]. This homeostatic dysregulation may explain why OH is more prevalent in older adults[4], females[5], and individuals living with frailty[6]. Additionally, OH can compromise daily activities, leading to a "deconditioning vicious cycle[7], where people may adopt more sedentary behavior choices, resulting in extended periods of low-energy activities like sitting and lying down[8]. Also, this cycle results in physical inactivity[7], which refers to insufficient engagement in moderate-to-vigorous physical activity (at least 150 minutes per week)[8]. This increase in sedentary behavior in combination with a lack of physical activity negatively impacts individuals' health, well-being, and overall quality of life[7].

It is well known that the global population is aging rapidly[9], leading to an increase in disorders such as autonomic (baroreceptor sensitivity) and cardiovascular (blood pressure dysregulation) among many others. Blood pressure (BP) dysregulation might become more prevalent when people are challenged by postural transition (e.g., lie-to-stand)[10,11]. This BP dysregulation associated with aging may explain why older adults have frequent episodes of a sudden drop in blood pressure when standing upright (orthostatic hypotension (OH))[12]. Nearly 30% of this population is affected by OH, but one-third are asymptomatic[13]. The problem is that OH increases the likelihood of balance impairment, and postural instability in the first few seconds following standing upright, falls, and increases the risk of mortality[14,15]. When associated with comorbidities (e.g., hypertension), medication (e.g., beta-blockers), and dehydration, OH may cause dizziness, blackouts, blurred vision, dyspnea, angina pectoris, paracervical and lumbar pain, weakness, and nausea[4]. Several factors contribute to why older adults are more

affected by this condition. For example, the decrease in cardiac function with aging leads to a decrease in diastolic filling due to a reduction in preload[16]. This reduction in the preload can cause a reduction in venous return and consequently cardiac output, making older adults take longer to stabilize their blood pressure[17]. Moreover, older adults have lower heart rate variability (HRV) indexes, indicating that their bodies are less effective at managing situations that require adaptive and quicker responses (e.g., postural transition)[18].

Biological sex is another important component of autonomic and cardiovascular regulation that must be considered. For example, females are more prone to OH due to higher parasympathetic activity and less sympathetic activation in response to cardiac stress[19]. Additionally, females have reduced short-term compensatory recovery responses to regulate BP, as shown by a slower and smaller increase in heart rate (HR), resulting in a longer time for BP to recover due to higher vagal activity, smaller hearts, and lower stroke volume (SV)[19,20]. As a result, there is a lower total amount of blood in the circulation (cardiac output - CO), resulting in a lower volume of blood returning to the heart (venous return)[16]. This slower regulation of cardiac filling is associated with a prolonged BP regulation[16]. Females also have a lower systemic vascular resistance (SVR) than males, as demonstrated by attenuated vasoconstrictor effects on the vessels during autonomic stress[19].

Frailty is another critical component associated with autonomic and cardiovascular regulation. It is a prevalent geriatric syndrome observed in clinical practice and recognized as an emerging condition related to aging[21]. This syndrome includes clinical indicators related to sedentary behavior (prolonged time in low-energy activity, such as sitting), low physical activity levels (<150 minutes per week of moderate-to-vigorous physical activity), fatigue, weight loss, and impaired physical function[22]. The homeostatic ability to maintain BP after standing is diminished in people with frailty[6]. This may explain why OH is particularly high in older adults who are pre-frail or frail. This homeostatic dysfunction is linked to a decline in the physiological systems, which is a hallmark of frailty[6]. This homeostatic dysfunction, particularly in BP regulation for those living with frailty, seems to be related to impaired baroreceptor sensitivity (BRS)[23], which is responsible for maintaining BP homeostasis, and reduced sympathetic activity. The combination of impaired BRS and decreased sympathetic activity results in blunted HR responses (smaller increases in HR), decreased SVR (reduced vasoconstriction), reduced CO, and consequently slower stabilization of BP after standing[24].

As it is considered a dynamic syndrome, frailty can be counteracted if there is early intervention[25]. Emerging evidence is pointing that frailty may be counteracted with exercise[26,27]. However, most of the literature does not follow the frequency, intensity, time, type, progression, and volume (FITT-PV) principle. Such a principle is key to an efficient workout plan[28–30]. Also, there is no consensus on a specific exercise prescription guideline for this population[31] as exists for older adults. Furthermore, there is limited research on how strength training affects autonomic and cardiovascular responses to orthostatic challenges and improvements in OH etiology symptoms[32]. The results presented are inconclusive and require further investigation. Whether progressive strength training can positively impact orthostatic responses and the short-term dynamic integrative autonomic and cardiovascular regulation in frail older adults is still poorly understood.

2. Chapter 2

Literature Review

2.1 Autonomic and Cardiovascular Responses to Orthostatic Stress and Its Consequences

Orthostatic stress is a daily challenge that people face when changing posture from lying down or sitting to standing up or during extended periods of standing[33]. When someone moves from a lying or sitting position to standing, gravity pulls about 500 to 700 ml of blood down into the lower limbs, away from the chest[7]. This shift causes the veins in the lower body to temporarily expand, or vasodilate, to accommodate this extra blood[7]. This action results in a rapid decrease in central blood volume and, therefore, leads to a reduction in ventricular preload, stroke volume, and blood pressure[34]. A well-coordinated set of neural regulatory systems is quickly activated upon standing to maintain sufficient blood flow to vital organs like the brain[16] (Figure 2.1).

The sympathetic nervous system responds rapidly, driven mainly by mechanoreceptors (baroreceptors)[24]. The activation of arterial baroreceptors which are located in the carotid sinus and the aortic arch, transmit impulses via the carotid sinus and aortic depressor nerves to the brainstem in the nucleus of the solitary tract[24]. This activation of arterial baroreceptors triggers the cardiac accelerator and vasomotor centers (both connected to the sympathetic nervous system) and the inhibition of the cardiac inhibitory center (vagus nerve connected to the parasympathetic nervous system)[24]. The cardioaccelerator center stimulates cardiac function by increasing the contractility of the myocardium, resulting in an increase in HR and SV through sympathetic stimulation of the cardiac accelerator nerve, increasing CO (CO = SV x HR)[24]. Additionally, the vasomotor center sends signals to blood vessels, resulting in contraction[16]. This contraction leads to a decrease in the diameter and radius of those vessels, increasing SVR[16]. As CO and SVR increase, blood pressure returns to normal values[9](Figure 1). However, if these autonomic and cardiovascular responses are not well-regulated, homeostasis control, function maintenance, and quick adaptive responses to orthostatic challenges will be compromised and might lead to orthostatic hypotension (OH). One important method for assessing autonomic regulation during orthostatic stress is through the analysis of heart rate variability (HRV), a non-invasive marker of autonomic nervous system activity and adaptability.

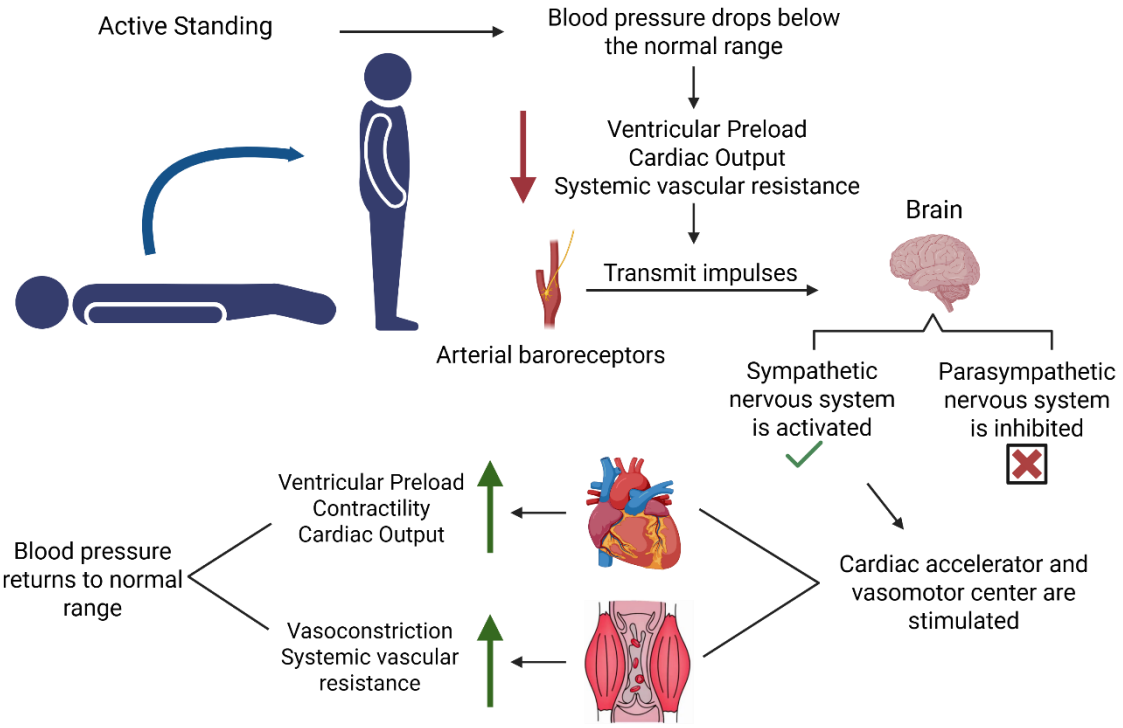

Figure 2.1 Autonomic and cardiovascular regulation to orthostatic stress.

2.2. Heart Rate Variability – Physiology and Definition

2.2.1. Cardiac and Autonomic Physiology

The heart, a muscular pump composed primarily of cardiac muscle tissue, plays a critical role in maintaining circulatory homeostasis[16]. It generates rhythmic contractions that enable the propulsion of blood throughout the vascular system, ensuring adequate oxygen and nutrient delivery to peripheral tissues[16]. The heart's activity is inherently myogenic, meaning it originates from the heart muscle itself rather than from external nerve stimulation[16]. This intrinsic electrical activity is generated by specialized pacemaker cells located in the sinoatrial (SA) node, which spontaneously depolarize to initiate each heartbeat[16]. Although this automaticity allows the heart to beat independently, its rate and rhythm are controlled by the autonomic nervous system (ANS) to meet the body's physiological demands[16].

The ANS consists of two primary branches: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS), which work in a coordinated but opposing manner to regulate cardiac function[35]. The SNS prepares the body for action by increasing heart rate (HR) (chronotropic), enhancing conduction velocity (dromotropic), and increasing myocardial contractility (inotropic), primarily through the release of

norepinephrine acting on β_1-adrenergic receptors in the heart[35]. Conversely, the PNS, through the vagus nerve, promotes a state of rest by slowing HR through the release of acetylcholine, which acts on muscarinic receptors at the sinoatrial (SA) node to reduce pacemaker firing[35]. These branches differ not only in function but also in latency of action. The PNS exerts its effects almost instantaneously, typically within less than one second, due to the rapid synaptic transmission and proximity of parasympathetic fibers to the heart[36]. In contrast, the SNS has a longer onset, taking over 5 seconds, as its effects rely on a slower cascade involving neurotransmitter release, receptor activation, and intracellular signaling[36]. This balance, referred to as autonomic tone, is not static but varies continuously[37]. One of the key markers of this variability is heart rate variability (HRV), which reflects the beat-to-beat fluctuations in HR as controlled by the sympathetic-parasympathetic balance[37]. Thus, HRV is an indirect indicator of autonomic regulation of cardiac function.

2.2.2. Heart Rate Variability: Definition, Measurement, and Function

Heart rate variability refers to the physiological variations in the intervals between consecutive heartbeats, typically measured as the time between successive R-waves in the electrocardiogram (ECG), known as R-R intervals[38] (Figure 2.2). These fluctuations are influenced by multiple physiological mechanisms, including respiratory sinus arrhythmia, baroreflex function, thermoregulation, and circadian rhythms[36].

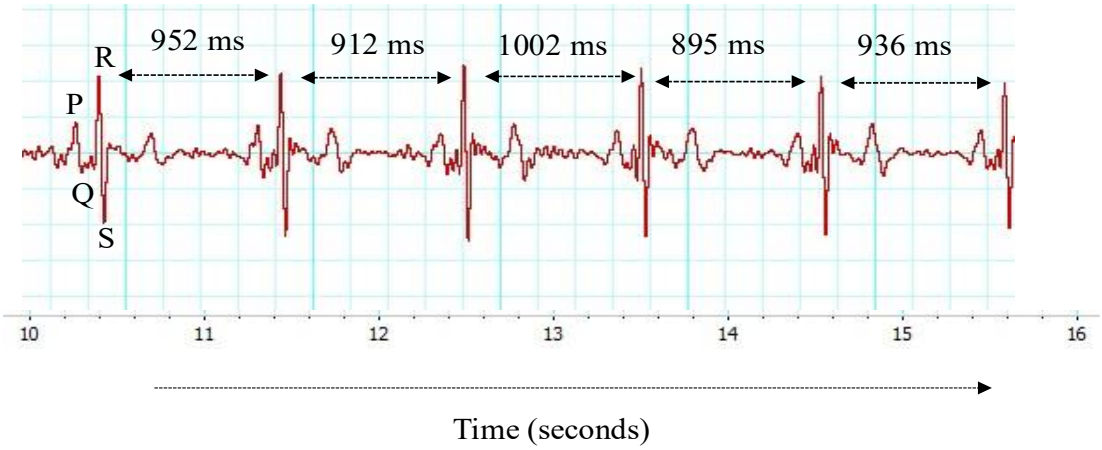

Figure 2.2 A representation of five consecutive heartbeats illustrates the key features of heart rate variability (HRV). The figure highlights the R-R intervals, measured between successive R peaks of the QRS complexes, reflecting the variation in time between individual heartbeats (inter-beat intervals).

HRV can be analyzed through two primary methods: time-domain and frequency-domain analyses. Time-domain measures quantify the amount of variability in successive

R-R intervals over time, using simple statistical calculations. Some indices are the R-R intervals, the standard deviation of R-R intervals (SDRR), and the root mean square of successive differences (RMSSD)[39] (Table 2.1). These metrics are typically calculated from ECG recordings over durations ranging from a few minutes (short-term HRV) to 24 hours (long-term HRV)[39].

The frequency-domain analysis involves transforming the R-R interval time series into its constituent frequencies using spectral methods such as the Fast Fourier Transform (FFT)[40]. This approach decomposes the HR signal into different frequency bands: The low-frequency (LF) band (0.04-0.15 Hz) is influenced by both sympathetic and parasympathetic inputs. The high-frequency (HF) band, typically 0.15-0.40 Hz, which reflects parasympathetic modulation and is closely tied to respiratory sinus arrhythmia[40]. The LF/HF ratio is commonly interpreted as a marker of sympathovagal balance[40] (Table 2.1). Frequency-domain measures offer information on how autonomic branches modulate HR across various physiological rhythms, particularly during stress (e.g., postural changes)[41].

Table 2.1 Heart Rate Variability indices and definition.

Heart rate variability indices	Definition
Time domain	
R-R intervals	Time between two consecutive R-waves on the ECG; used to calculate HRV by capturing beat-to-beat fluctuations in heart rate, primarily reflecting autonomic modulation.
SDRR	The standard deviation of all normal R-R intervals over a given time period reflects overall HRV, including both sympathetic and parasympathetic influences. Low values suggest increased sympathetic dominance.
RMSSD	The root mean square of successive differences between adjacent R-R intervals; primarily reflects short-term, high-frequency variations and is considered a marker of parasympathetic (vagal) activity.
Frequency domain	
LF (low frequency power) (0.04-0.15 Hz)	Power in the low-frequency band; reflects a combination of sympathetic and parasympathetic activity, often associated with baroreflex function.
HF (high frequency power) (0.15-0.45 Hz)	Power in the high-frequency band; is associated with parasympathetic activity and typically corresponds with respiratory sinus arrhythmia.
LF/HF Ratio	The ratio of low- to high-frequency power is commonly interpreted as an index of sympathovagal balance. A low ratio represents parasympathetic dominance.

HRV serves as a non-invasive biomarker of ANS and cardiovascular function[36,37]. Rather than a single value, HRV encompasses multiple indices, each reflecting different

aspects of autonomic control (Table 2.1)[36,37]. Alterations in these indices, particularly reductions in parasympathetic-related measures (e.g., RMSSD, HF), have been associated with increased morbidity and mortality in various clinical populations, including individuals with cardiovascular disease[36,37]. Given HRV's sensitivity to autonomic dysfunction, it has become an important tool in understanding conditions like orthostatic hypotension (OH), where impaired autonomic regulation leads to inadequate cardiovascular adjustments during postural changes.

2.3. Orthostatic Hypotension, Its Consequences, and Prevalence

OH is traditionally defined as a sustained decrease in systolic blood pressure of at least 20 mmHg or diastolic blood pressure of 10 mmHg within three minutes of standing or head-up tilt test[42]. OH can be asymptomatic or accompanied by symptoms such as blurred vision, weakness, lightheadedness, and falls, which might vary over time in the same person[42]. OH can be classified as non-neurogenic and neurogenic[43]. Non-neurogenic is generally related to reduced blood volume, cardiac function, use of pharmacological agents, and advanced age[7]. Neurogenic is related to the failure of the autonomic nervous system[43]. OH is a predictor of adverse health outcomes and is considered an independent risk factor for mortality[7]. OH is also associated with several chronic conditions, including stroke, myocardial infarction, coronary heart disease, syncope, and frailty[6,44,45]. Despite its serious health implications, the specific pathophysiological mechanisms by which OH compromises autonomic and cardiovascular regulation are still poorly understood.

OH is one of the most common disorders of blood pressure, and the prevalence is between 5% to 30% in healthy community-dwelling older adults and increases with age[33]. Additionally, OH is prevalent in 50% to 68% of older adults living in nursing and retirement homes[46]. The high prevalence of OH in this population might be associated with decreased baroreflex sensitivity, increased vascular stiffness, increased parasympathetic activity, decreased α-1-adrenergic vasoconstrictor response to sympathetic stimuli, decreased left ventricular diastolic filling, and, at the highest stage, increased mortality rates[24,33,47].

OH may cause orthostatic intolerance (OI), a disorder where the body fails to make the necessary homeostatic adjustments to the upright position[48]. OI is correlated with the magnitude of the BP drop and is followed by symptoms such as dizziness, light-headedness, loss of consciousness, and falls, all related to cerebral hypoperfusion[48]. To

better understand the underlying mechanisms of OH and how it might contribute to OI, short-term orthostatic blood pressure recovery responses have been identified[49]. This identification aims to assess the hemodynamic changes underlying this spectrum of OH, providing the physiological processes involved in response to postural change. Table 2.2 provides a description of the short-term orthostatic blood pressure recovery patterns[49].

Table 2.2 Short-term (180 seconds) orthostatic blood pressure recovery patterns.

Orthostatic BP recovery patterns	Definition
Normal BP recovery	Recovery of SBP to baseline values not exceeding a decrease of more than 20 mmHg at 30 seconds of standing
Initial orthostatic hypotension (IOH)	Transient decrease > 40 mmHg in SBP within 15 s of active standing, with complete BP recovery within 30 seconds of standing.
Delayed BP recovery	Delayed recovery of systolic BP to baseline values of more than 20 mmHg at 30 seconds of standing but not meeting the criteria of sustained orthostatic hypotension.
Sustained OH	A sustained decrease in systolic BP of ≥ 20 mmHg in the first 60 and 180 seconds of standing. With the presence of supine hypertension (supine systolic SBP ≥ 160 mmHg)

BP: blood pressure; SBP: systolic blood pressure; OH: orthostatic hypotension.

2.4. Aging and Its Effect on the Integrated Dynamic Autonomic and Cardiovascular Systems

It is known that the number of older adults is increasing rapidly worldwide. Average life expectancy is estimated to increase from 60 to 80 years from 1950 to 2050[50]. Statistics project that 25% of individuals will be 60 years of age or older worldwide by mid-century[9]. In 2022, the life expectancy in Canada was reported as 79.1 years for males and 84.5 years for females[50]. Long-term projections suggest that this trend of increasing life expectancy will continue. In 1971, older adults 65 years old and over accounted for approximately 8% of the Canadian population[50]. However, by 2080, 25% of the Canadian population is projected to be older adults 65 and over[50]. It has been observed that this growing aging population has led to a significant increase in spending requirements for healthcare[51].

Aging causes the body to undergo many changes that affect its structure and physiological function[52]. Because of these changes, it becomes harder for older adults to maintain stable control of their physiological systems when faced with stress (e.g.,

orthostatic stress)[53]. As people age, physiological systems that collaborate with physiological control and regulation, such as the autonomic and cardiovascular systems, may not work properly or fast enough.

2.4.1. Aging is Related to Orthostatic Hypotension

After a change in posture (lie-to-stand or sit-to-stand), certain physiological adaptations take place that control blood pressure[49]. For example, in a healthy young person, there is a faster, abrupt increase in HR immediately after the drop in BP and stabilization of BP values a few seconds after assuming the standing position[49]. However, this adaptation is dysregulated in older adults, which might increase the possibility of OH[49]. With age, there is a progressive decline in baroreceptor activation, which can lead to an inadequate short-term compensatory HR response for BP control[24]. Figure 2.3 illustrates the BP response in younger and older adults.

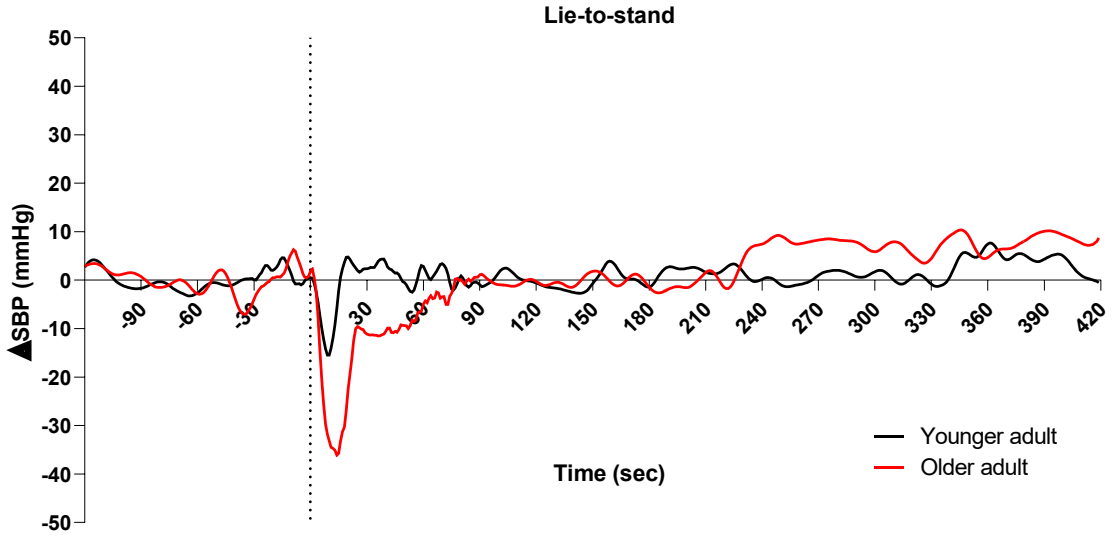

Figure 2.3. Systolic blood pressure response of a younger adults (black line) and a older adult (red line) after an active standing orthostatic stress challenge. This example data was collected by Dihogo Gama de Matos.

One of the reasons for the baroreceptor sensitivity decline is the stiffness of the carotid arteries and the aorta, where these receptors are located[24]. As a result, there is a decrease in the cardiac cholinergic response and a delay in sympathetic activation[24]. Another reason that can be observed is a decrease in diastolic filling due to a decrease in cardiac compliance and preload[16]. As there is a delay in short-term compensatory cardio acceleration, the reduction in preload is observed, causing a reduction in CO[16]. In addition, upon assuming the upright position, there is initially a transient drop in BP accompanied by a decrease in peripheral vascular resistance due to blood pooling and vasodilation. This is followed by a baroreflex-mediated increase in HR and peripheral

vascular resistance, which together helps to regulate blood pressure[16]. However, this peripheral vascular resistance response is reduced in older adults, leading to a limited increase in peripheral vasoconstriction[16]. Such dysregulation can result in OH, commonly observed in older adults, due to the inadequacy of these short-term compensatory recovery response mechanisms mentioned previously. Therefore, age is a risk factor for the development of OH due to the physiological changes that occur over time, particularly for those living a sedentary behavior lifestyle, which may be sex dependent.

2.5 Sex Differences in the Integrated Dynamic Autonomic and Cardiovascular Responses

Health research involving females has been neglected for decades[54]. Although advances and improvements in knowledge have taken place in the last 10 years, there is still much room for improvement, as females are still under-represented in research, as shown by the more significant number of male-only studies[55]. Historically, there has been a long-standing prejudice to use predominantly males in scientific research rather than females[55]. About 2 decades ago, the Institute of Medicine's 2001 report, "Exploring the Biological Contribution of Sex," emphasized the significance of sex in every aspect of cellular function and physiology, from birth to death[56]. Therefore, it is essential to distinctly define the physiological principles and regulatory mechanisms for females and males[57]. This approach will enable the translation of basic scientific discoveries into clinical research, leading to individualized, evidence-based medical strategies and practical guidelines.

Physiological differences between females and males are evident in health[58,59] as well as in various diseases and, thereby, influence simple daily activities, such as postural transitions[60]. The interpretation of historical research that has examined responses to postural changes is often based on studies that recruited exclusively male or mixed-sex samples, with few studies incorporating sex into their analysis[61]. Therefore, addressing sex differences in physiology requires focusing on the fundamental systems and mechanisms of physiological control and regulation in both sexes. This approach should be systematic, covering the earliest aspects of sexual differentiation development to the neuroanatomical and neurophysiological elements of brain function[58,59]. To improve the health of both sexes, scientists and physicians must consider these differences as fundamental physiological mechanisms to be studied.

2.5.1. Sex Differences and Orthostatic Hypotension

Orthostatic hypotension is a condition that affects males and females through different mechanisms[5], with a higher prevalence in females[62]. Females are more likely to experience recurrent episodes of syncope, potentially due to differences in cardiovascular and autonomic regulation[62]. It has been observed that this syncope is associated with the menstrual cycle, which affects female sex hormones[63]. Also, because females tend to have more parasympathetic activity, they have reduced compensatory recovery response to a drop in BP and low blood perfusion and flow to the brain, resulting in an increased incidence of falling[19]. During the premenopausal phase, females show a higher amount of estrogen, which influences the effectiveness of the renin-angiotensin system[64]. The estrogen can reduce the plasma renin activity and also influence the release of other hormones, epinephrine, and norepinephrine, which help in BP regulation[64]. Figure 2.4 presents the BP response in an older female compared with an older male.

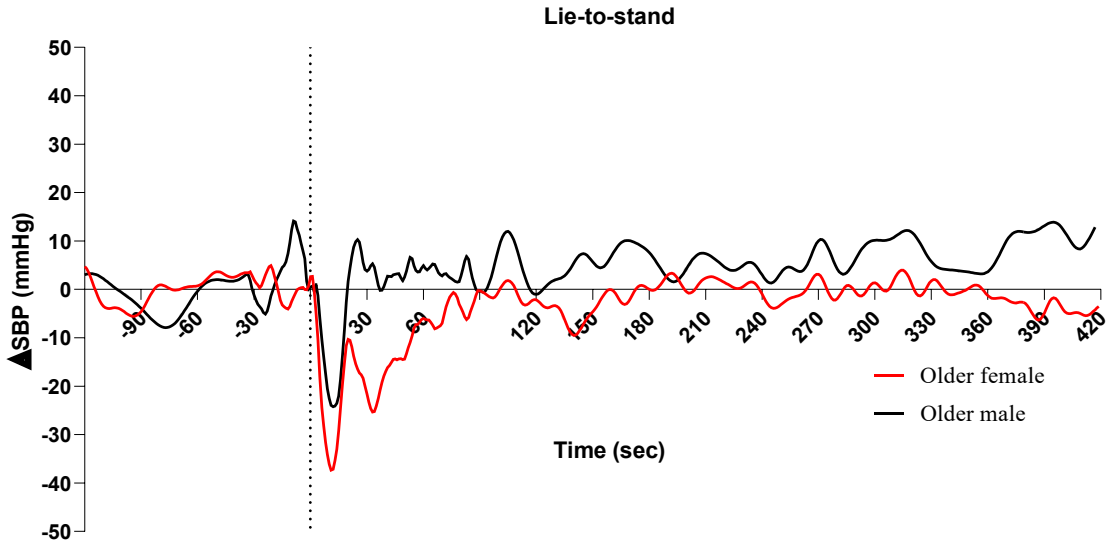

Figure 2.4. Systolic blood pressure response of an older female (red line) and an older male (black line) after an active standing orthostatic stress challenge. This example data was collected by Dihogo Gama de Matos.

Females also have less baroreceptor sensitivity to respond to an orthostatic challenge (e.g., postural transition).[37] Baroreceptors are mechanoreceptors located in the carotid sinus and in the aortic arch that allow the transmission of information about a drop in BP to the autonomic nervous system[65]. After a transition to an upright posture, information should be sent from the baroreceptors to the brain to start a quick response to counteract the transient cerebral hypoperfusion and reduced brain blood flow[65]. The acute response is to alter SVR to help venous return and increase the CO to bring BP to

the normal range[66]. Females also have a lower center of gravity (center of mass), which may be associated with increased pooling of blood in the lower extremities, with a concomitant decrease in blood volume in the thoracic region and reduction in the central venous pressure[67]. As a result, venous return and cardiac filling are impacted, affecting blood redistribution to the heart[67].

In contrast, during orthostatic stress, males might have better adaptive adjustments due to more sympathetic activation, leading to faster and higher HR responses[68]. Also, males have bigger hearts and higher SVR, which can provide enough SV and venous return to support CO response during active standing[69]. Based on the above information, it seems that females are less effective in the compensatory recovery mechanisms of controlling BP than males. Understanding the appropriate autonomic and cardiovascular responses and differences between sexes is crucial. Ignoring the role of sex in the context of postural transitions can result in the spread of inaccurate information about the underlying mechanisms. Therefore, it is key to develop a more comprehensive understanding of this integrative regulation and the influence of sex on these regulatory processes, particularly in situations of physiological stress.

2.6. Frailty and Its Impact on the Integrated Dynamic Autonomic and Cardiovascular Responses

Frailty is an emerging global health challenge with significant consequences for clinical practice and public health[21]. It is a condition that causes a loss of function across several physiological systems that leads to a decline in homeostasis and represents the difference between chronological age and biological age[70,71]. It has been estimated that over 51% of community-dwelling adults aged 65 years and over are pre-frail and frail[72]. Those frail older adults are more likely to experience negative outcomes, such as the inability to recover after a sudden drop in BP, hospitalization, institutionalization, falls, morbidity, or death[70]. To illustrate that, Figure 2.5 shows the BP response after postural transition of three participants: one classified as non-frail, the second one classified as pre-frail, and the third one classified as frail. This suggests that this participant may have an increased likelihood of experiencing symptoms of OI, such as dizziness, lightheadedness, or blurred vision. In contrast, the non-frail participant exhibited a smaller SBP drop of 24 mmHg and returned to baseline levels within 30 seconds, showing a more stable cardiovascular response to postural changes.

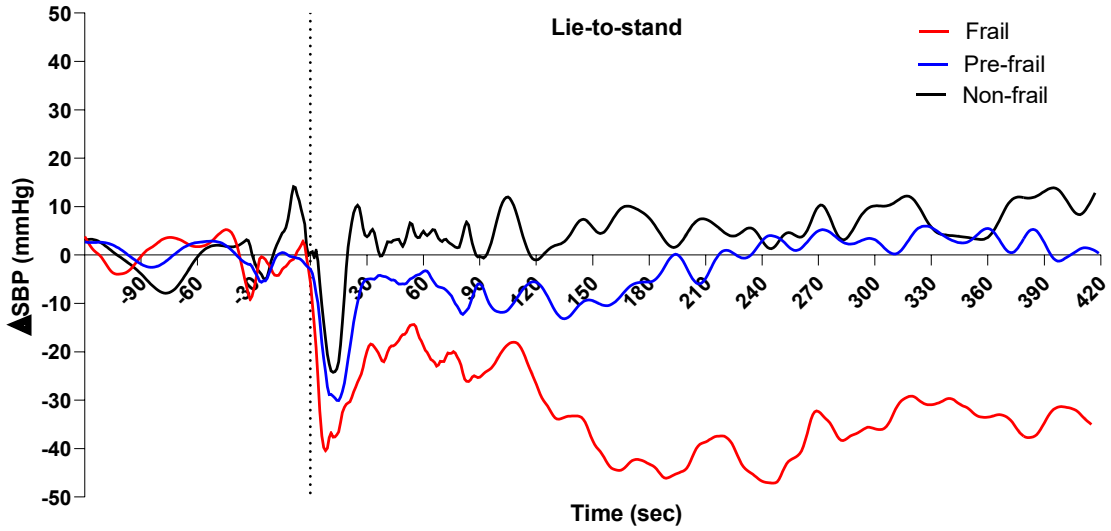

Figure 2.5. Systolic blood pressure response of a non-frail (black line), pre-frail (blue line), and frail (red line) after an active standing orthostatic stress challenge. This example data was collected by Dihogo Gama de Matos.

Research has reported that frailty is highly associated with aging[73]. However, this association cannot be explained directly by chronological age because frailty is more related to biological age[74]. Rather, frailty is directly attributed to the decline of physiological factors[21], such as muscle loss and strength, and decline in the autonomic, cardiovascular, respiratory, musculoskeletal, immune, and endocrine systems[75–77]. Therefore, it is important when studying the pathogenesis of frailty that our attention is paid to the physiological decline regardless of chronological age.

2.6.1. Frailty and Orthostatic Hypotension

In older adults, frailty is strongly associated with OH, showing significant autonomic and cardiovascular regulation issues (e.g., delayed baroreceptor response and reduced HR response) after active standing[45]. The physiological decline characteristic of frailty becomes a key factor in the predisposition to OH[45]. Autonomic dysfunction, evidenced by reduced heart rate variability (HRV) indexes and impaired sensitivity of baroreceptors, compromises the body's ability to adjust to external stressors, such as postural changes[18]. An effective autonomic nervous system (ANS) response is crucial for maintaining homeostasis in all physiological functions[18]. However, frail adults show progressive homeostatic dysregulation that affects the ANS, limiting the ability to respond quickly to drops in BP[18]. Baroreceptors, which normally detect changes in BP, become less sensitive with age and probably frailty, leading to delayed or inadequate compensatory recovery responses[24].

Frailty is also associated with a reduced ability to control and regulate BP due to a limited functioning of the cardiovascular system (e.g., a reduced CO) and a lower capacity for vasoconstriction of the blood vessels[78]. Vasoconstriction is essential for maintaining BP and ensuring sufficient blood flow and cerebral perfusion to the brain when standing[9]. In frail individuals, this mechanism is probably impaired, which will result in insufficient cerebral perfusion, a hallmark of OH[6]. This inadequate blood flow and perfusion to the brain can lead to symptoms (e.g., dizziness, lightheadedness) and consequently an increased risk of falls[7]. These deficits increase the overall physiological decline of frail individuals, making the maintenance of homeostasis increasingly challenging[46]. Consequently, interventions targeting this physiological decline, such as exercise, can play a key role in improving frailty and the associated risks.

2.7. Exercise, Frailty and Orthostatic Hypotension

It has been recommended that strength training (ST) should be part of a frailty prevention strategy[79]. There is strong evidence that ST can promote neuromuscular, autonomic, and cardiovascular improvements, which are systems associated with the gradual loss of function in people living with frailty[80]. ST can improve muscle mass, strength, and functional capacity and reduce the risk of frailty in older adults[80]. ST can increase the activation of motor neurons, helping to increase the recruitment of muscle fibers and leading to an improvement in motor coordination during functional movements (e.g., walking)[81]. There is also evidence to show that ST can improve HRV indexes and BRS responses, which are key to BP control during external stress (e.g., postural transition)[82].

People living with frailty have lower HRV indexes and blunted baroreceptor sensitivity, being more exposed to abrupt drops in BP, increasing the chances of OI, and an elevated risk of falls[23]. Evidence shows that ST improves resting SBP and DBP values and CO[83], which improves coping with orthostatic stress (e.g., postural transition). During orthostatic stress challenges, tissues and organs require more oxygen, and increasing CO ensures that enough oxygen-rich blood reaches these tissues, supporting their function[83]. These improvements in hemodynamic responses can lead to a reduction in cardiovascular disease (~10%) and stroke (~15%), which are highly associated with frailty[83].

It seems that it is a prospective area to study the effects of strength training on improving the autonomic and cardiovascular systems in the control of OH. Research shows that ST can improve the autonomic and cardiovascular systems[84]. However, to the

best of my knowledge, only one study analyzed the effects of ST on OH[32]. The authors investigated the effects of an 8-week ST program on OH in older adults. A subset of 24 individuals (age 71.0 ± 5.8 years) from a total sample of 53 participants met at least one criterion for OH, and they were included in the analysis. The ST protocol involved three weekly sessions targeting both upper and lower body muscles at 80% of each participant's one-repetition maximum (1-RM). Pre and post-test assessments were taken using the auscultatory method to measure SBP and DBP, and the palpation technique to assess HR at the 2nd minute of supine (lying down), sitting, and standing. The protocol included 10 minutes in the supine position, 5 minutes sitting, and 2 minutes standing. The results of the mentioned study[32] showed a slight change in resting DBP, increasing from 78.8 ± 10 mm Hg to 82.0 ± 10.1 mm Hg after training. SBP in the sitting position decreased from 147.1 ± 14.0 mm Hg to 143.2 ± 15.8 mm Hg, and standing HR increased from 71 ± 6 bpm to 76 ± 10 bpm. However, these findings do not provide evidence that ST may positively affect BP regulation and HR responses during postural changes. Moreover, other important variables related to OH, such as CO, SV, SVR, and baroreceptor sensitivity, were not measured. Therefore, more research is needed to analyze how ST can counteract frailty and improve the short-term integrated autonomic and cardiovascular responses to orthostatic stress, OH, and OI.

As an illustration of this research gap, Figure 2.6 presents data from the current thesis showing BP responses across pre-test, 8 weeks, and 12 weeks of progressive strength training (PST). This figure highlights the physiological adaptations over time and provides direct evidence of the dynamic effects of training on orthostatic BP regulation in older adults.

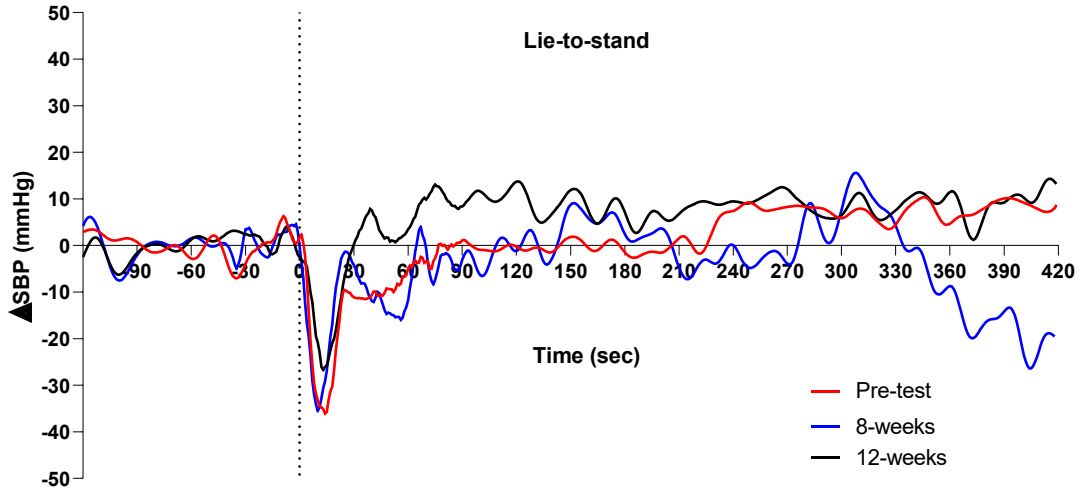

Figure 2.6. Systolic blood pressure responses at pre-test, 8 weeks, and 12 weeks of progressive strength training (PST) during an active standing orthostatic stress challenge. Example data collected by Dihogo Gama de Matos.

3. Chapter 3

Statement of the Problem and Knowledge Gaps

The world population is aging. Currently, 10% of the global population is older adults, and these numbers are still growing[85]. By 2050, it is expected that ~20% of the entire world's population will comprise older adults over 65 years[85]. With this predicted growth in the older adult population, the number of older adults living with frailty, OH and OI will increase in both males and females, as they are all associated. Therefore, it is crucial to understand how the short-term integrated dynamic autonomic and cardiovascular responses are influenced by age, sex, and frailty.

In physiology research, females are under-represented, as shown by the greater number of male-only studies[61]. The aging process differs significantly between sexes, where cardiovascular anatomy, hemodynamics, and autonomic nervous system differences have been identified[1]. For example, young females' BP is usually lower compared to males at a similar age[1]. Females tend to have more episodes of OH than males[86]. In response to cardiovascular stress, females tend to have slower short-term compensatory responses (e.g., an increase in CO) due to their smaller hearts[87]. Females also have lower sympathetic activity but higher parasympathetic activity compared to males[88]. Furthermore, older females experience reduced arterial elasticity as estrogen levels decrease, leading to increased arterial stiffness, which compromises vasoconstriction, a key mechanism for BP regulation. Given these significant sex-based differences, it is imperative to include and analyze females in studies focused on integrated dynamic autonomic and cardiovascular regulation, OH and OI.

Frailty is characterized by a decline in the biological functional reserve to tolerate stressors and increases the risk for several physiological functional deficits (e.g., baroreceptor sensitivity)[23] which is the hallmark of OH. Emerging evidence suggests that frailty may be counteracted by exercise[26,27]. However, there is a lack of studies that adhere to the FITT-PV criteria (frequency, intensity, time, type, progression, and volume) in addressing frailty and do not follow a specific exercise prescription guideline for this population[31]. Additionally, only one study has examined the effects of strength training (ST) on orthostatic hypotension (OH) in older adults[32]. Therefore, with limited evidence on the effects of ST following the FITT-PV criteria and its potential to improve the

autonomic and cardiovascular systems in frail older adults, there is a novel opportunity to assess these existing gaps.

Figure 3.1 provides a summary of my thesis framework. The figure illustrates a disturbance caused by active standing that generates an imbalance in BP regulation, which can lead to autonomic and cardiovascular dysregulation. This homeostatic dysregulation significantly increases the likelihood of developing OH and OI. Three key factors influence the risk of OH and OI: age, sex, and frailty. For example, older adults are more prone to have OH due to arterial stiffness, making harder for the cardiovascular system to adjust to changes in posture. Females are at greater risk of OH because they tend to have lower HRV indexes, which can limit the body ability to respond quickly to external stress (e.g., postural transition). Frailty, which is accompanied by diminished baroreceptor sensitivity, reduces the body's ability to detect drops in BP when standing, taking longer to recover after this maneuver. Progressive strength training (PST) emerges as a possible solution to counteract frailty and improve short-term compensatory regulation, decreasing the incidence of OH and OI. Strength training can help counteract the effects of frailty, strengthening muscles that help to improve venous return, which supports BP regulation during postural changes. Also, PST can improve baroreceptor responses by detecting changes in BP quickly. As a result, PST could impact the regulation of both autonomic and cardiovascular systems, helping BP regulation and reducing the incidence of OH and OI.

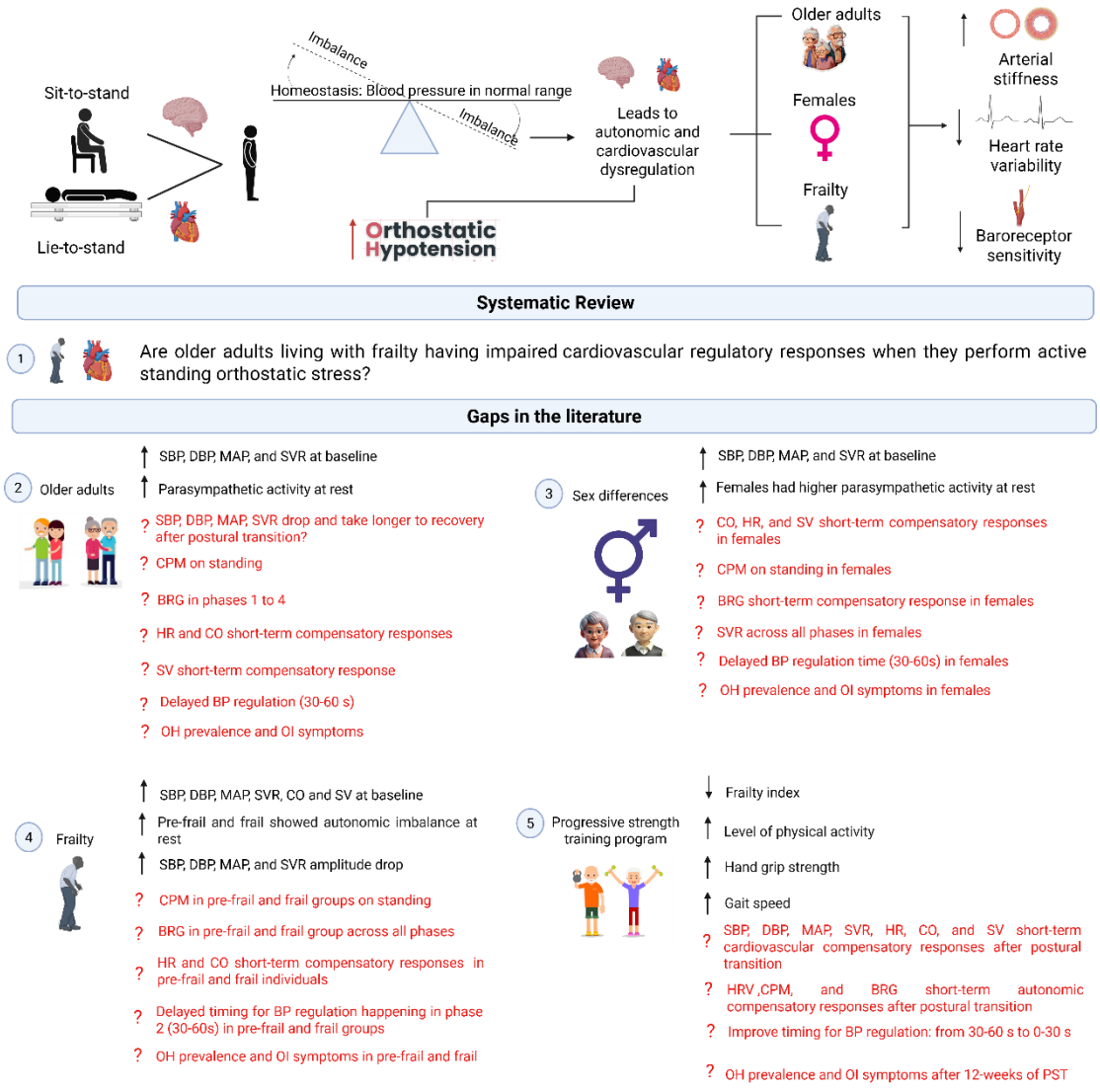

Figure 3.1 Thesis framework. The numbers represent the key studies of my thesis (1 to 5). Black words represent existing information in literature, and red words represent current gaps in literature.

3.1 General Research Question and Thesis Objective

This chapter presents the general research question and objectives. Based on a thorough review of the literature, it was observed that the integrated dynamic regulation of the autonomic and cardiovascular systems during orthostatic stress might be more affected by age, sex, and frailty. Therefore, the general research question for the overall thesis is *"How do age, sex, frailty, and progressive strength training influence the integrative dynamic autonomic and cardiovascular regulation during active standing orthostatic stress maneuvers?"*. To address this overall research question, the general objective of the thesis is *to analyze how age, sex, frailty, and progressive strength training impact the short-term integrative dynamic autonomic and cardiovascular regulation during sit-to-stand and lie-to-stand postural transitions*. This investigation began with a systematic review to synthesize existing evidence on the impact of frailty on blood pressure regulation following standing, which guided the design and rationale for the subsequent experimental studies, particularly those focusing on frailty-related impairments. The specific objectives and hypotheses will be presented in their respective study chapters (4-12).

3.2 Organization and objectives of this thesis

I have chosen to write this thesis in paper format (group-based/sandwich) as outlined by the Faculty of Graduate Studies (FGS) at the University of Manitoba. Therefore, this thesis is organized into 12 chapters, as follows:

Chapter 1 provides introductory information about cardiovascular and autonomic regulation, along with the consequences of their dysregulation, particularly in the context of postural transitions. It highlighted age, sex, and frailty as primary factors associated with impaired physiological responses and discussed how these conditions contribute to increased vulnerability to OH and OI symptoms. The chapter also addressed the potential role of progressive strength training in mitigating these impairments. Lastly, it identified important gaps in the literature related to physiological dysregulation across these populations, which provided the rationale for the studies included in this thesis.

Chapter 2 reviews the literature on cardiovascular and autonomic responses to orthostatic stress and the consequences of dysregulation in these systems. Impaired regulation can lead to OH, a common condition in older adults characterized by a drop in BP upon standing. Age, sex, and frailty are key factors associated with increased risk of OH and OI symptoms due to reduced cardiovascular and autonomic function. This

chapter also presents evidence on the role of progressive strength training (PST) in improving BP regulation and reducing OH and OI-related symptoms.

Chapter 3 provides an overview of the statement of the problems, knowledge gaps found in the literature, and the general thesis research question and objectives.

Chapter 4 was a systematic review to determine whether older adults living with frailty have impaired cardiovascular regulatory responses during active-standing orthostatic stress.

Chapter 5 determined how age impacts the short-term cardiovascular compensatory responses and blood pressure regulation timing during sit-to-stand and lie-to-stand transitions.

Chapter 6 assessed whether age impacts autonomic regulation during active standing orthostatic stress.

Chapter 7 examined whether older females and males differ in the short-term cardiovascular responses and the timing of BP regulation following active standing orthostatic stress.

Chapter 8 investigated whether there are sex differences in autonomic responses during sit-to-stand and lie-to-stand transitions in older adults.

Chapter 9 compared the short-term cardiovascular compensatory responses and BP regulation timing among non-frail, pre-frail, and frail older adults following an active standing orthostatic stress challenge.

Chapter 10 evaluated whether autonomic responses differ between frailty levels and whether these differences are associated with OI-related symptoms.

Chapter 11 tested whether a 12-week progressive strength training program reduces frailty status and improves short-term cardiovascular and autonomic compensatory responses and the timing of BP regulation in pre-frail and frail older adults.

Chapter 12 is a discussion and synthesis of the thesis research.

There is some overlap in the background information and methodological approach presented in Chapters 5 through 12. This repetition was necessary to ensure each chapter, structured as an independent manuscript, remained clear and complete for submission and publication.

4. Chapter 4

Cardiovascular regulation during active standing orthostatic stress in older adults living with frailty: a systematic review

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This manuscript represents the first study of my doctoral thesis and was written solely by me, Dihogo de Matos. It is a systematic review that synthesizes current evidence on the cardiovascular regulatory responses of older adults living with frailty during active standing orthostatic stress. This topic was selected based on its clinical relevance and the critical knowledge gap regarding cardiovascular function in frail older populations during orthostatic stress. The methodology, including the search strategy, screening, data extraction, and quality assessment, was conducted with guidance from my supervisors and supported by an experienced librarian. However, I was responsible for conceptualizing the study, developing the protocol, and drafting and revising the manuscript. This chapter provides a foundational understanding of how frailty affects short-term cardiovascular compensation during postural changes and frames the rationale for the subsequent experimental studies included in this thesis.

Publication Status

This study was published in the Archives of Gerontology and Geriatrics on May 16th, 2025.

Abstract

Background: Orthostatic hypotension (OH) is a relevant cardiovascular disorder associated with frailty and delayed cardiovascular regulatory responses, contributing to cardiovascular dysregulation. This dysregulation affects blood pressure (BP) control, increasing the risk of falls and mortality. This systematic review aimed to determine whether older adults living with frailty have impaired cardiovascular regulatory responses during active standing orthostatic stress.

Methods: MEDLINE (from 1946), PUBMED (from 1966), EMBASE (from 1974), CINAHL (from 1963), and SCOPUS (from 2004) were systematically searched for studies on cardiovascular regulation during active standing orthostatic stress in older adults living with frailty. The selection of studies involved the following criteria: ≥ 60 years, OH classification, continuous monitoring of beat-by-beat BP, active standing, and frailty status. The nine-point Newcastle-Ottawa Scale was used to assess the study quality.

Results: Of 7441 articles identified, 5 articles were included, but 3 independent data sets were extracted due to two studies reporting the same participants' cohort, resulting in an analysis of 726 participants (79±5 years, 41.7% males). Frailty was associated with a greater drop in BP (-61 mmHg), blunted HR (Frail: 8 bpm; non-frail: 16 bpm), and longer recovery after active standing, occurring between 30-60 s instead of 0-30 s (healthy systems). OH prevalence ranged from 3 to 98%, being higher in frail people.

Conclusions: Older adults living with frailty experience a greater drop in BP, a blunted HR response, and prolonged recovery time following active-standing orthostatic stress. This cardiovascular dysregulation contributes to the highest prevalence of OH among frail individuals.

Keywords: blood pressure regulation, heart rate, postural transition, orthostatic hypotension, orthostatic intolerance.

Introduction

Orthostatic hypotension (OH) and frailty are two common geriatric syndromes that lead to reduced capability to respond to stressors (e.g., postural transition). Both OH and frailty share many overlapping physiological causes. Traditionally, OH is defined as a drop in systolic blood pressure (SBP) of at least 20 mmHg and/or a drop in diastolic blood pressure (DBP) of at least 10 mmHg within 3 minutes after standing, reflecting an impaired hemodynamic homeostasis[42]. Technological advancements and beat-to-beat data collection and analysis have allowed additional OH classifications, including initial orthostatic hypotension (IOH) and delayed orthostatic hypotension (DOH) based on the timing of the BP drop[42]. OH may be asymptomatic or accompanied by symptoms such as blurred vision, weakness, lightheadedness, dizziness, and falls, and can vary with time in the same person[42]. Frailty may influence the symptomatic expression of OH by further compromising cardiovascular compensatory responses, potentially increasing the likelihood and severity of symptoms[6]. Nonetheless, asymptomatic presentations remain possible in frail individuals, which poses a diagnostic challenge and may delay clinical intervention[15]. This condition is one of the most common disorders of blood pressure (BP), and the prevalence is between 5% to 30% in healthy community-dwelling older adults (≥ 60 years) and increases with age[7,33]. The high prevalence of OH in this population may be associated with decreased baroreflex sensitivity, increased vascular stiffness, increased parasympathetic activity, decreased α-1-adrenergic vasoconstrictor response to sympathetic stimuli, and decreased left ventricular diastolic filling[7,24,33,47].

Frailty is a prevalent syndrome observed in clinical practice, recognized as an emerging condition associated with biological aging, as it might be manifested in people across all age groups[22]. Frailty causes loss across several physiological systems (e.g., autonomic nervous system, cardiovascular system) and increases susceptibility to external stressors (e.g., postural transition)[21]. Frailty is linked to negative health outcomes (e.g., heart disease), limitations in performing everyday tasks (e.g., getting up from a bed or chair), falls, hospitalizations, and mortality[6].

While OH and frailty impact each other, the existing literature predominantly addresses the prevalence of OH within populations who have varying levels of frailty. However, the underlying physiological mechanisms that link OH and frailty are still poorly understood. For example, Kocyigit et al.,[89] reported that the prevalence of OH was 30.7% among older adults with frailty ($n = 497$). Liguori et al.,[90] showed a prevalence of OH ranging from 9% to 66% according to frailty status ($n = 510$), where a higher

prevalence of OH was associated with higher levels of frailty. Although the association between OH and frailty has been observed, evidence of cardiovascular regulation after active-standing orthostatic stress in the frailty population affected by OH is limited and scarce. Therefore, the objective of this systematic review was to analyze whether older adults living with frailty have impaired cardiovascular regulatory responses, characterized by attenuated or delayed BP or heart rate (HR) adjustments, during active-standing orthostatic stress.

Methods

A PICO approach was used to define the primary research questions and help to formulate the search strategy: (P) Population - adults aged 60 years or older living with frailty; (I) Intervention - active standing orthostatic stress; (C) Comparison - cardiovascular responses during active standing orthostatic stress in non-frail, pre-frail, and frail older adults; and (O) Outcomes - understand how cardiovascular systems respond to orthostatic stress challenges. Therefore, the research question is: "*Are older adults living with frailty having impaired cardiovascular regulatory responses when they perform active standing orthostatic stress?*"

The systematic review protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42022268613)[91] and was organized following the Preferred Reporting Items for Systematic Review (PRISMA) guidelines[92] (Appendix 1). MEDLINE (from 1946), PUBMED (from 1966), EMBASE (from 1974), CINAHL (from 1963), and SCOPUS (from 2004) were systematically searched until January 9th, 2025, and investigating the cardiovascular regulation in older adults living with frailty (adults aged 60 years or older) during active standing (lie-to-stand or sit-to-stand). The search strategy is presented in Appendix 1 and includes keywords "orthostatic hypotension", "frailty", "older adults", "aging", "blood pressure", "postural transition", and "active standing". Also, a manual forward search was conducted to identify additional relevant studies that may have been missed during the initial search. The search strategy was developed in consultation with an experienced librarian (JW), and a pilot test was performed to determine if the search captured papers that we expected to be identified.

Study selection

All identified articles were organized and managed using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia). After removing the duplicates, 6491 titles and abstracts were screened by two independent reviewers (DGM and JLS) to determine their eligibility. Disagreements between the two reviewers were resolved by a third reviewer (RV).

Eligibility criteria

The articles were considered eligible if they met the following criteria: 1) adults aged 60 years or older, 2) orthostatic hypotension classification (initial orthostatic hypotension (IOH), classical orthostatic hypotension (COH), and delayed orthostatic hypotension (DOH)), 3) frailty classification using one of the existing criteria, based on validated and objective frailty measures (e.g., Fried Phenotype[22], Frailty Index[93], Clinical Frailty Scale[94]), with the inclusion of two or three frailty categories (non-frail and pre-frail, or pre-frail and frail, or non-frail, pre-frail, and frail) in the same study. In studies applying the Fried Phenotype, individuals were classified based on 5 criteria (unintentional weight loss, exhaustion, low physical activity, slow walking speed, weakness), one point for each criterion. Individuals are classified as non-frail (0 points), pre-frail (1-2 points), or frail (3-5 points). The Frailty Index provided a continuous score (0 to 1) based on accumulated deficits, typically using established thresholds (e.g., > 0.25 for frailty). The Clinical Frailty Scale categorized severity on a 9-point scale, with scores from 1 to 3 indicating non-frail, 4 to 6 reflecting varying degrees of vulnerability or mild-to-moderate frailty, and scores ≥ 7 representing severe frailty. 4) BP beat-by-beat monitoring, 5) active standing orthostatic stress, and 6) articles published in English. Reviews, meta-analyses, conference abstracts, editorials, and letters to the editor were not included in this systematic review. No exclusion criteria were applied. In case included studies used data from the same cohort (database), we decided to report only once to avoid overrepresentation.

Data extraction

The following data were extracted by two independent authors (DGM and RV): first author, year of publication, country, population, and settings (e.g., geriatric clinic), age, sex, study design, OH classification, frailty and OH prevalence, OH protocol (e.g., duration, period before and after active standing), BP measurement (e.g., manual; beat-

by-beat), and type of device used to measure BP (e.g., sphygmomanometer, Finometer - Finapress).

The OH definition used was according to the American Autonomic Society[42] as follows: initial orthostatic hypotension (IOH) - transient BP decrease > 40 mmHg SBP and/or > 20 mmHg DBP within 15 s of active standing; classic orthostatic hypotension (COH) - sustained reduction in SBP ≥ 20 mmHg or DBP ≥ 10 mmHg within 3 min of standing or head-up tilt test (HUT); delayed orthostatic hypotension (DOH) - sustained reduction in BP beyond 3 min of standing or HUT. If another definition for OH was used, it must have been explained in detail.

Study quality and risk of bias assessment

The quality and bias of each included article were assessed by two independent reviewers (DGM and JLS) using the nine-point Newcastle-Ottawa Scale (NOS)[95] for cross-sectional studies, having a higher score lowers the risk of bias. If a disagreement occurred, a third reviewer (RV) resolved this disagreement. Articles with a NOS score between 0 and 3 points were classified as low quality, 4-6 as moderate quality, and 7-9 as high quality[95]. A meta-analysis could not be performed due to the heterogeneity across the studies.

Results

Study selection and search strategy

Figure 4.1 shows 7441 studies identified, screened, and selected as illustrated in the PRISMA flowchart. Of these studies, 950 were duplicates and were removed, and 6491 were screened by title and abstract, leaving 542 potentially eligible articles. After reviewing these articles, another 537 did not meet the inclusion criteria due to the reasons described in Figure 4.1, and the 5 studies remaining were included in this systematic review.

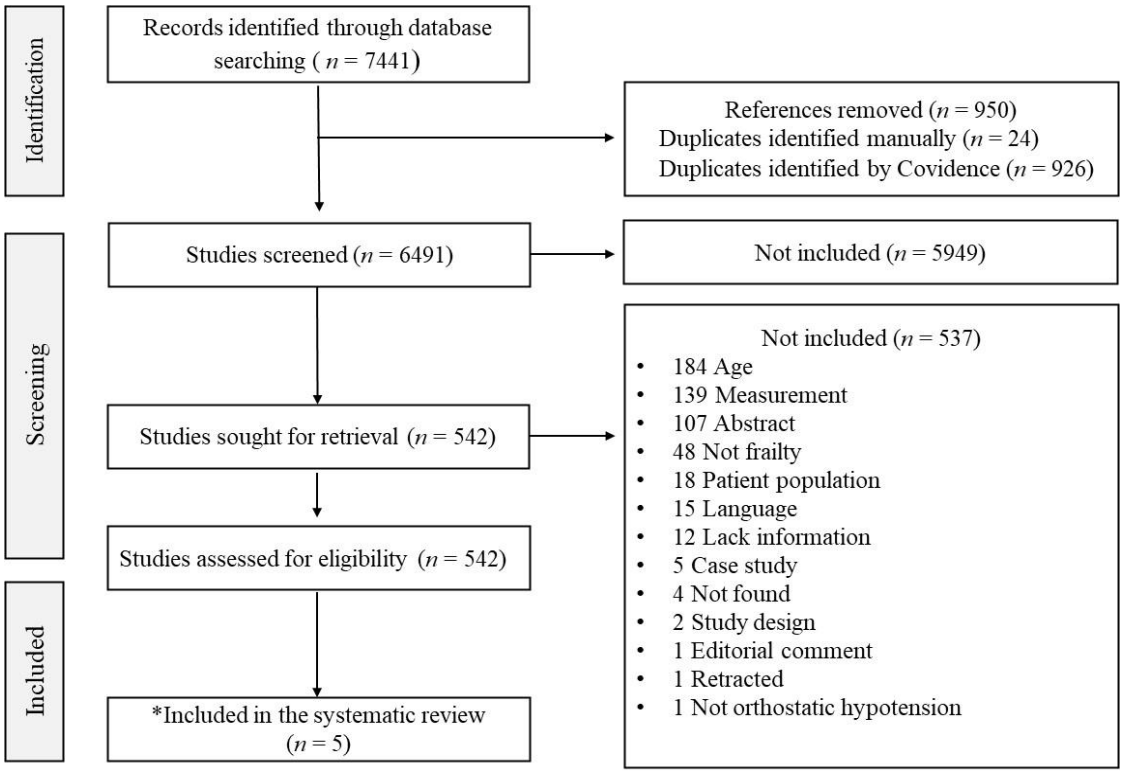

Figure 4.1 Flow diagram of the selected studies for the systematic review according to the Preferred Reporting Items for Systematic Reviews (PRISMA). **Five papers were included in the review, but data from three independent datasets were used due to data originating from the same cohort in two studies.*

Study quality assessment

Table 4.1 shows the risk of bias quality assessments included in the systematic review using the nine-point Newcastle-Ottawa Scale adapted for cross-sectional studies. Two studies were classified as high-quality[96,97], two as moderate quality[6,98], and one as low-quality[53].

Table 4.1 Risk of bias quality assessment using the Newcastle-Ottawa Scale.

First Author, Year of publication	Mol et al.,[96]	Mol et al.,[99]	Romero-Ortuno et al., [98]	Romero-Ortuno et al., [6]	Shaw et al., [53]
Representativeness of the sample	1	1	1	1	1
Sample size*	NA	NA	NA	NA	NA
Selection of the sample	1	1	1	1	1
Ascertainment of the exposure (continuous BP)	1	1	1	1	1
Groups comparison	2	2	2	2	1
OH definition	1	1	1	1	-
Statistical test	1	1	-	-	-
Total score	**7**	**7**	**6**	**6**	**4**
Quality	**High**	**High**	**Moderate**	**Moderate**	**Low**

Score 0-3: low quality, 4-6: moderate quality, 7-9: high quality. NA = information not available. *Sample size calculation was not reported in any of these studies.

Participants and study characteristics

Table 4.2 summarizes the study and participant characteristics. Overall, 726 participants were included: geriatric outpatients characterized as older adults who require medical care and management focused on age-related conditions and functional decline (n = 168), community-dwelling individuals (n = 442), and people living in long-term care facilities (n = 116) with a mean (SD) age of 79.2 ± 5 years (41.7% males). Among the five included articles, two by Mol et al.,[96,99] and two by Romero-Ortuno et al.,[6,98] used data from the same cohort to report their findings. To avoid overrepresentation, we decided to extract only one dataset from each pair of articles, resulting in three independent datasets.

Table 4.2 Study characteristics of the included articles.

Study characteristics	Mol et al.,[96,99]	Romero-Ortuno et al.,[6,98]	Shaw et al.,[53]
N	168	442	116
Age (years)	81.4 ± 4	72.1 ± 7.1	84.2 ± 0.9
Female (%)	55.4	71.7	66
Population/setting	GOPA	CDOA	LTCF
Study design	CS	CS	CS
Protocol at rest/baseline (minutes)	5	10	15
Protocol standing/sitting (minutes)	3	3	15

GOPA = geriatric outpatients; CDOA = community-dwelling older adults; LTCF = long-term care facilities; CS = cross-sectional study.

Classification and prevalence of frailty

Among the five articles included in this review, representing three independent samples, two datasets (66%) used the Fried phenotype criteria, classifying participants into non-frail, pre-frail, and frail[6,96–98]. The other study used a Frailty Index based on the Full Resident Assessment Instrument-Minimum Data Set (FI-MDS) as the frailty classification method[53]. The prevalence of frailty varies across different populations and settings. Among the studies analyzed[6,53,96–98], the total sample sizes ranged from 116 to 442 individuals. Non-frail individuals represented 15% to 45% of the population, pre-frail 40% to 52%, and frail ranged from 7% to 68%, likely reflecting differences in the study populations (e.g., community-dwelling and long-term care) and frailty assessment tools (e.g., Frailty Phenotype, Frailty Index), and inclusion/exclusion criteria.

Cardiovascular regulation after active standing and its association with frailty

The cardiovascular regulation showed differences in SBP, DBP, and HR responses after active standing across frailty classifications[53,96,99]. Non-frail individuals exhibited smaller drops in SBP and DBP and higher HR responses[6,98]. SBP drops ranged from -6.1 ± 3.3 mmHg to -34.1 ± 17.3 mmHg. DBP dropped from -14.2 ± 7.2 mmHg to -23.0 ± 11.4 mmHg. HR increases ranged from 6 ± 1 to 16 ± 7 bpm[6,98]. Pre-frail individuals demonstrated a larger drop in SBP (-35.2 ± 9.8 mmHg to -37.2 ± 18.8 mmHg) and DBP (-23.4 ± 9.0 mmHg to -24.7 ± 12.0 mmHg) than non-frail individuals. The increase in HR (14 ± 11 to 15 ± 10 bpm) was similar to the highest values reported among the non-frail individuals (16 ± 7 bpm)[6,98]. Individuals classified as frail exhibited the most pronounced drop in SBP (-17.8 ± 4.2 mmHg to -61.6 ± 11.6 mmHg) and DBP (-22.8 ±

14.0 mmHg to -36.6 ± 11.4 mmHg)[53]. The HR responses were blunted, with an increase ranging from 8 ± 2 to 13 ± 7 bpm[53]. Individuals classified as frail also showed a delayed short-term compensatory recovery in SBP, which occurred within 30–60 seconds after active standing[97].

Orthostatic hypotension classification and prevalence

All five studies[6,53,96–98], representing three independent datasets, have used the traditional American Autonomic Society's[42] classification criteria for OH (a transient drop of SBP > 20 mmHg and DBP > 10 mmHg). However, none of the studies specified the overall prevalence of OH within the frail population. Rather, two studies reported the prevalence of IOH (61%) and COH (24%)[53,96] and only one study (independent sample) reported DOH[53] because the active standing orthostatic stress protocol lasted longer than 3 minutes after the transition.

Table 4.3 summarizes studies highlighting the prevalence of OH, frailty status, and OH related to frailty status. Although Romero-Ortuno et al.,[6,98] and Mol et al.,[96,99] used the same sample, the prevalence of OH and frailty was reported separately to enhance clarity. Romero-Ortuno et al.[98] analyzed orthostatic BP responses during lie-to-stand, categorizing the responses into three distinct clusters. Cluster 1 was characterized by a small SBP drop (< 20 mmHg) and subsequent overshoot (above SBP baseline values). Cluster 2 was characterized by a moderate SBP drop (≥ 20 mmHg and ≤ 40 mmHg). Cluster 3 was characterized by a large SBP drop (> 40 mmHg). The prevalence of OH and frailty status was reported for each cluster. In another study using the same cohort, Romero-Ortuno et al.[6] reported the prevalence of IOH and COH among non-frail, pre-frail, and frail individuals. Mol et al.[96] reported the incidence of IOH and OH but not frailty. In contrast, Mol et al.[99] reported only the incidence of OH and frailty status (based on the Fried frailty phenotype) but not the incidence of OH specifically among frail individuals. The studies of Romero-Ortuno et al.,[6,98] and Mol et al.,[96,99] did not report DOH due to the duration of the protocol (3 minutes standing). Shaw et al.[53] reported the prevalence of IOH, COH, and DOH in non-frail and frail individuals, but not pre-frail individuals.

Table 4.3 Summary of studies reporting prevalence of orthostatic hypotension and frailty status.

			Classification	
Study	**Clusters**	**IOH (%)**	**COH (%)**	**DOH (%)**
Romero-Ortuno et al, 2011a*	1	3.6	80.4	NR*
	2	17.4	98.3	NR*
	3	43.5	100	NR*
Study	**Clusters**	**Non-frail (%)**	**Pre-frail (%)**	**Frail (%)**
Romero-Ortuno et al, 2011a*	1	50.9	42.9	6.2
	2	44.1	49.2	6.7
	3	39.1	52.2	8.7
Study	**Groups**	**IOH (%)**	**COH (%)**	**DOH (%)**
Romero-Ortuno et al, 2011b	Non-frail	12.7	92.4	NR*
	Pre-frail	22.6	96.2	NR*
	Frail	38.7	90.3	NR*
Study	**Groups**	**IOH (%)**	**OH (%)****	**DOH (%)**
Mol et al., 2020a*	-	36.3	14.3	NR*
Study	**Groups**	**Non-frail (%)**	**Pre-frail (%)**	**Frail (%)**
Mol et al., 2020a	-	38.5	41.9	19.6
Study	**Groups**	**IOH (%)**	**OH (%)****	**DOH (%)**
Mol et al., 2020b*	-	NR*	67.1	NR*
Study	**Groups**	**Non-frail (%)**	**Pre-frail (%)**	**Frail (%)**
Mol et al., 2020b	-	15.6	53.2	33.1
Study	**Groups**	**IOH (%)**	**COH (%)**	**DOH (%)**
Shaw et al. 2019	Non-frail	4	32	48
	Pre-Frail	NR*	NR*	NR*
	Frail	15	56	49

Cluster 1: small SBP drop (< 20 mmHg) and subsequent overshoot; Cluster 2: moderate SBP drop (≥ 20 mmHg and ≤ 40 mmHg); Cluster 3: large SBP drop (> 40 mmHg); IOH: initial orthostatic hypotension; COH: classical orthostatic hypotension; DOH: delayed orthostatic hypotension; NR: not reported. *DOH was not reported in these studies due to the protocol duration (3 minutes long). **Mol et al.,[96,99] defined OH as a sustained SBP drop of more than 20 mmHg and/or a DBP drop of more than 10 mmHg occurring within 3 min after standing up. The percentages reported in this Table for Mol et al.,[96,99] were based on the values joining two cohorts as described by these studies. Romero-Ortuno et al.,[6,98] and Mol et al.,[96,99] used the same data sets in these publications.

Discussion

The systematic review confirmed that older adults living with frailty have impaired cardiovascular regulatory responses during active standing orthostatic stress, leading them to be more susceptible to OH. Specifically, the review provides a more accurate quantification of the magnitude of SBP and DBP drop and short-term

compensatory recovery. Individuals classified as frail exhibit a more pronounced drop in SBP, DBP, and delayed short-term compensatory response, occurring within 30 to 60 s following active standing compared to non-frail older adults. Conversely, non-frail older adults are more likely to experience smaller SBP and DBP drops and faster short-term compensatory responses. These findings show that older adults living with frailty are more prone to cardiovascular dysregulation and more susceptible to OH. Additionally, older adults living with frailty exhibit a blunted HR increase following active standing compared to non-frail older adults, suggesting a diminished autonomic compensatory response. This impaired cardiovascular adjustment likely contributes to the higher prevalence of OH among frail older adults, particularly IOH and COH.

It is worth mentioning that two studies had 3 minutes of baseline, the other two studies had 10 minutes of baseline, and one had 15 minutes of baseline, which may have influenced BP regulation before standing. Longer rest periods allow baroreflex activity, vascular tone, and blood volume distribution to reach stabilization in the supine position[42], potentially leading to more consistent baseline measurements and minimizing transient hemodynamic fluctuations that can affect the initial orthostatic response[4,44]. After the active standing maneuver, four studies employed 3 minutes, and one study used 15 minutes for continuous beat-to-beat monitoring of short-term compensatory responses. Due to these differences in active standing orthostatic stress protocols, only one study reported DOH[53]. These differences emphasize the need for better assessment protocol standardization in future studies to ensure comparability and the ability to detect all types of OH, allowing for more comprehensive diagnostic and prognostic.

Potential mechanisms involved

During postural transitions, such as moving from lying or sitting to standing, the body must rapidly adjust to counteract gravitational forces that cause ~500–700 ml of blood to pool in the lower limbs[7,33]. This pooling reduces central blood volume, ventricular preload, stroke volume, and BP, requiring a rapid compensatory response to maintain cerebral blood flow and perfusion[16,100]. In healthy individuals, BP typically stabilizes within 30 seconds due to the activation of baroreceptors and subsequent neural regulation[24]. However, the findings of this systematic review revealed that among older adults with frailty, BP stabilization is significantly delayed, often extending beyond the first minute after standing, indicating impaired cardiovascular compensatory responses.

The short-term compensatory recovery response to orthostatic stress also involves an immediate transient increase in HR to offset the drop in BP[24]. This response is primarily driven by baroreceptor activation, which stimulates the sympathetic nervous system to enhance cardiac output[24]. In older adults living with frailty, as demonstrated in this systematic review, HR compensatory response was lower compared to non-frail individuals. This attenuated HR increase contributes to an inadequate compensatory response to counteract the initial sudden drop in BP, revealing the vulnerability of this population to OH.

Clinical relevance and practical applications

Understanding how older adults with frailty respond to orthostatic stress is critical for assessing their ability to regulate BP and recover from drops in SBP. Identifying impairments such as delayed BP recovery, excessive BP drops, and blunted HR responses can help predict risks of falls, syncope, and other adverse health outcomes. This knowledge supports the development of targeted interventions to improve cardiovascular regulation and postural stability, which will directly contribute to a better quality of life and reduced morbidity in this population.

Interventions such as exercise can enhance the cardiovascular responses among older adults with frailty during orthostatic challenges like sit-to-stand and lie-to-stand transitions. Exercise could improve vascular function by reducing arterial stiffness and enhancing vasoconstriction, which helps direct blood flow to the heart and brain[84,101]. Exercise also strengthens heart muscle contractility and supports increased cardiac output, which is essential for maintaining BP during positional changes[16].

Another possibility is the use of compression aids, such as compression socks, that might help reduce blood pooling in the lower limbs and may support more stable BP during transitions[102–104]. Additionally, leg-crossing for approximately one minute, which involves the contraction of agonist and antagonist muscles, might improve venous return and reduce orthostatic dizziness by enhancing blood flow back to the heart and brain[105,106]. However, the feasibility of these strategies may vary depending on the individual's functional capacity, frailty severity, and care settings. In institutionalized or severely frail individuals, these interventions may be impractical or unsafe without close supervision. Therefore, future studies should explore the effectiveness and adaptability of such interventions across different levels of frailty and in various care settings. Tailored

approaches, potentially including medication review, hydration support, and nutritional interventions, may be more appropriate in these populations.

Strengths and Limitations

The strength of this systematic review is that it is the first to specifically analyze cardiovascular responses to active standing orthostatic stress in older adults living with frailty, using a standard definition of OH (IOH, COH, DOH)[42] in sample populations of older adults aged 60 years or older. Although the inclusion criterion was set at ≥ 60 years, the actual sample populations in the included studies were composed of much older adults, which can be seen as a strength. This focus on an older demographic enhances the relevance of the findings for individuals at greater risk of cardiovascular dysregulation. However, a limitation of this review is a lack of experimental studies that included the beat-by-beat BP measurements, frailty assessments, orthostatic hypotension classification, and the active standing orthostatic stress test protocol, which did not allow a meta-analysis to be conducted to statistically combine the results for a more comprehensive conclusion. Another important limitation is the heterogeneity in frailty assessment tools and baseline durations, which may have contributed to variability in the reported findings. In addition, comorbid conditions such as sarcopenia, malnutrition, dehydration, and polypharmacy may influence both frailty and orthostatic blood pressure regulation. However, these variables were not consistently reported and thus could not be systematically analyzed in this review.

Additionally, key variables essential for understanding short-term compensatory responses and cardiovascular regulation, such as stroke volume, cardiac output, and systemic vascular resistance, were not reported in the included studies, limiting the analysis of the underlying physiological mechanisms regulating BP in this population. Therefore, future studies should investigate further autonomic and cardiovascular variables to improve our understanding of the underlying pathophysiological mechanism of frailty under orthostatic stress challenges.

Conclusion

The results of this systematic review were drawn from 3 independent samples, indicating an association between cardiovascular dysregulation and frailty levels. These findings highlight those individuals with higher levels of frailty experience larger drops in SBP and DBP, slower short-term compensatory responses following active standing orthostatic stress, and blunted HR (less increase) responses compared to less frail older

adults. These findings also suggest that cardiovascular dysregulation contributes to the predisposition of older adults living with frailty to OH. Future research should focus on investigating cardiovascular regulatory responses in younger older adults (e.g., 60 - 65 years old) to better understand the early impact of frailty on orthostatic stress. This age group is particularly interesting because it often represents a transitional stage where early physiological decline and subclinical frailty emerge. Studying this population may improve early detection of altered cardiovascular responses and inform preventive strategies before more advanced frailty becomes clinically apparent. This would help determine whether similar impairments occur in the early stages of frailty and how cardiovascular dysregulation evolves as frailty progresses, guiding diagnostic and earlier intervention strategies.

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We would like to sincerely thank Janice Winkler (librarian) for her support and expertise throughout the development of this systematic review.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

The findings of this systematic review confirm that older adults living with frailty exhibit impaired cardiovascular regulation in response to active-standing orthostatic stress. This is evidenced by exaggerated drops in SBP and DBP, delayed short-term recovery, and blunted HR responses. These results suggest that frailty compromises the hemodynamic compensatory responses and increases the risk of OH. The review also highlights the heterogeneity of protocols and frailty assessment tools across studies, limiting the comparability of results. Importantly, the lack of key physiological measurements, such as cardiac output and systemic vascular resistance, highlights a gap in the literature. These findings informed the design of the experimental studies in this thesis, which further explore cardiovascular and autonomic mechanisms in frail populations under controlled conditions.

5. Chapter 5

Short-term cardiovascular compensatory responses in younger and older adults under varying levels of orthostatic stress

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This manuscript represents the second study of my doctoral thesis. It explores the age-related differences in short-term cardiovascular compensatory responses to orthostatic stress, comparing younger and older adults during sit-to-stand and lie-to-stand transitions. I designed the experimental protocol, recruited participants, conducted all assessments, and analyzed the data. This study was motivated by the need to understand how postural transitions of different gravitational levels affect blood pressure regulation in older adults. The manuscript adopts a novel phase-specific approach to evaluate the timing and magnitude of cardiovascular regulation and introduces the concept of CO-SVR matching to infer the timing of blood pressure regulation.

Publication Status

This study will be submitted to Age and Ageing.

Abstract

The cardiovascular system of older adults is significantly impacted by age, contributing to blood pressure (BP) dysregulation, particularly during postural transitions. This study compared short-term cardiovascular compensatory responses of younger adults (YA) and older adults (OA) during sit-to-stand and lie-to-stand. The incidence of orthostatic hypotension (OH) and orthostatic intolerance (OI) was also compared between the two age groups. Participants underwent two active standing orthostatic stress tests, involving 5 minutes of sitting or 10 minutes of lying, followed by up to 7 minutes of standing. Beat-to-beat cardiovascular parameters were assessed using Finometer-Finapress. An electrocardiogram determines heart rate (HR). Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and HR were measured at baseline, immediately on standing, and throughout four specific phases after standing: phase 1 (0-30s), phase 2 (30-60s), phase 3 (60-180s), and phase 4 (300-420s). CO-SVR matching was evaluated to assess BP regulation timing. Compared to YA, OA exhibited higher SBP, DBP, MAP, and SVR but lower HR, CO, and SV at baseline. Immediately on standing, OA experienced a greater drop in SBP, DBP, MAP, and SVR, blunted HR, reduced CO, and higher SV. The short-term compensatory responses were delayed (30-60s), particularly in lie-to-stand due to a transient mismatch between CO and SVR. OA showed higher OH prevalence (84%) and OI symptoms (14%). In conclusion, OA exhibited short-term compensatory cardiovascular dysregulation, particularly in lie-to-stand, and a higher prevalence of OH and OI symptoms than YA.

Keywords: systolic blood pressure, diastolic blood pressure, older adults, active standing, orthostatic hypotension, orthostatic intolerance.

Introduction

The stress induced by performing daily activities, such as getting up from bed or a chair, requires rapid, integrated, dynamic, adaptive cardiovascular responses[49]. These responses are essential to counteract the sudden, abrupt, transient, and significant drop in blood pressure (BP) and the immediate reduction in cerebral blood perfusion and flow that happens on standing[49]. Effective dynamic control and regulation of the cardiovascular system is mandatory for maintaining homeostasis and functionality when facing external challenges[107]. Failure to properly regulate these responses can result in homeostatic dysregulation[107], common with advancing age. This physiological dysregulation may explain why older adults experience more frequent episodes of sudden BP drops on standing, a condition known as orthostatic hypotension (OH)[90].

OH is characterized by the reduction of systolic (SBP) and diastolic (DBP) blood pressure within seconds after standing[42]. Typically, OH is defined as a sustained drop in blood pressure of at least 20 mmHg in SBP or 10 mmHg in DBP, within 3 minutes of standing or head-up tilt test[42]. OH can be asymptomatic, or accompanied by symptoms such as lightheadedness, blurred vision, dizziness, and fainting[42]. In older adults, OH is strongly associated with impaired cardiovascular responses, including delayed BP recovery[108], blunted HR[109] (less increase on standing), and diminished vascular responses[110], compromising BP regulation during postural transitions. Also, these compromised responses contribute to orthostatic intolerance (OI) symptoms (e.g., lightheadedness, dizziness)[42].

Despite previous studies identifying these physiological dysfunctions[108–110], most research has focused on single measurements or specific time points[111–113], limiting the understanding of the dynamic nature of the cardiovascular adjustments that occur from the first seconds to the later minutes after postural transitions. To date, no study has analyzed cardiovascular responses across specific phases after active standing orthostatic stress (phase 1: 0-30 s; phase 2: 30-60 s; phase 3: 60-180 s; phase 4: 300-420 s). The proposed phase-specific analysis is critical, as it allows for the identification of the impairments' time course, providing information about when and how the cardiovascular system regulates or not BP.

Another age-related critical factor is the possible mismatch between cardiac output (CO) and systemic vascular resistance (SVR) after active standing orthostatic stress[49]. Typically, in a healthy system (younger adults), CO transiently increases due to the blood shifting to the thorax as a result of vasoconstriction in the legs[49]. While there is

an increase in CO in the first seconds after standing, BP transiently decreases due to a significant drop in SVR[49]. After ~15-20 seconds of standing, there is a match/balance demonstrated by the same percentage of increase in CO and drop in SVR, leading to BP recovery through these compensatory responses[49]. While this temporal sequence is established in younger adults, a description of this matching/balance in older adults is still scarce in the literature. Therefore, it is necessary to investigate this matching process to better understanding of the dynamic short-term compensatory responses in older adults because these responses are crucial for BP control and regulation.

This study aims to describe and compare short-term cardiovascular compensatory responses between younger adults (18–30 years) and older adults (60–79 years) during sit-to-stand and lie-to-stand. More specifically, it examines baseline, immediate on standing, and short-term compensatory changes in SBP, DBP, MAP, CO, HR, SV, and SVR during two transitions: (a) sit-to-stand (low orthostatic stress) and (b) lie-to-stand (high orthostatic stress). These short-term compensatory responses were analyzed across four specific phases after standing: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s). This study also compared CO-SVR matching between the two age groups in both transitions. As a secondary objective, it evaluates the incidence of OH and OI-related self-reported symptoms. To achieve our aims, five specific hypotheses were designed. **Hypothesis 1**: at baseline, older adults will have an elevated SBP, DBP, MAP, SVR, and lower HR, CO, and SV. **Hypothesis 2:** immediately on standing, older adults will have a greater transient drop and slower SBP, DBP, MAP, and SVR responses, a transiently blunted and slower increase in HR and CO, and a higher SV response. **Hypothesis 3:** Short-term compensatory responses, older adults will demonstrate reduced and delayed SBP, DBP, MAP, SVR, HR, and CO responses, particularly in phases 1 (0-30 s) and 2 (30-60 s). However, no differences are anticipated in phases 3 (60-180 s) and 4 (300-420 s). At this point, the compensatory responses should be enough to bring cardiovascular parameters to more stable values. Also, SV responses will be higher in older adults across all phases due to their reliance on this variable to compensate for the blunted HR response. **Hypothesis 4:** Regarding CO and SVR matching, older adults will demonstrate a delayed match response, occurring at phase 2 (30-60 s) instead of phase 1 (0-30 s). **Hypothesis 5:** Older adults will have a higher prevalence of OH and OI symptoms than younger adults. These responses will be due to age-related delayed activation of the compensatory vasoconstrictor and venous return responses, higher arterial stiffness, and transient chronotropic insufficiency.

Methods

Study Design

This is an observational cross-sectional study that used the Strengthening Reporting of Observational Studies in Epidemiology (STROBE)[114] (Appendix 2) and the Sex and Gender Equity in Research (SAGER)[115] (Appendix 3) as reporting guidelines.

Settings

This study was conducted at the Applied Research Centre, Faculty of Kinesiology and Recreation Management, University of Manitoba, from August 2022 until August 2023. The study received approval from the University of Manitoba Health Research Ethics Board (approval number - HE2022-0058).

Participants

Participants were recruited using a convenience sampling strategy from Dr. Todd Duhamel's database (University of Manitoba), which contains ~1000 females who volunteered in the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts study. Centre on Aging database (University of Manitoba), visits to Men's Shed, and retirement/care homes located in the city of Winnipeg were also used to further recruit older adults. Phone calls, emails, social media platforms (Facebook, Instagram, X), ads, flyers, and posters were used as recruitment strategies, particularly for younger adults. People interested in participating contacted researchers by email or phone.

Participants were included in the study if they were younger (18-30 yrs) or older (60-79 yrs) adults and identified their sex at birth as female or male. Participants were excluded if they had ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, psychiatric disorders, severe cognitive impairment, or pregnancy.

The participants underwent sit-to-stand (experiment 1) and lie-to-stand (experiment 2) orthostatic stress challenges (Figure 5.1) in a randomized and counterbalanced order. Variables regarding baseline, immediate responses on standing, dynamic short-term cardiovascular compensatory responses (phases 1-4), CO and SVR matching, and OH and OI symptoms prevalence were compared between younger adults and older adults in experiments 1 and 2.

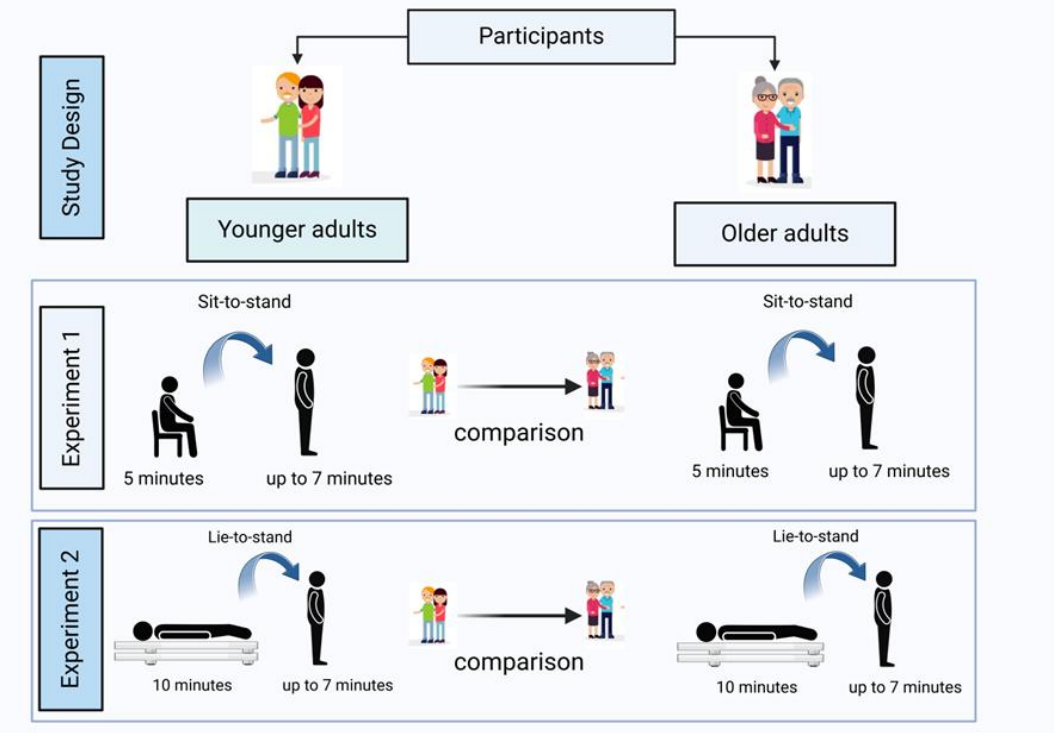


Figure 5.1 Illustration of the research design and experimental conditions (1 and 2).

Data Collection

Participants received pre-instructions 48 hours before the lab visit. On the day of this visit, they read and signed an informed consent form after having all their questions and/or concerns addressed by the researchers. Prior to testing, measurements of resting HR and BP were taken by a trained researcher to ensure participants' safety, following the procedures adopted by the Canadian Society for Exercise Physiology (CSEP) guidelines[31].

After consent and familiarization, participants underwent active standing orthostatic stress challenges with non-invasive beat-by-beat BP monitoring (Finometer^{TM} Pro Device, Finapress Medical System BV, Amsterdam, The Netherlands). Baseline SBP and DBP were measured while participants were at rest using a digital BP monitor (ARSIMAI, BSX516, Munster, Germany). At baseline, mean arterial pressure (MAP) was calculated using the formula: MAP = (2/3 × DBP) + (1/3 × SBP). Immediately after the test, participants were asked if they experienced any symptoms (e.g., dizziness, light-headedness) to indicate the presence of OI-related symptoms. The study was performed in a quiet room with a temperature of 22.0 ± 1.0°C and humidity and barometric pressure at ambient between 8:30 and 11:30 am on weekdays to minimize circadian cycle influence.

Demographic and Anthropometric Measurements

Demographic (sex assigned at birth, age, and date of birth), anthropometric, and body composition measurements were collected to characterize the sample. Measurements included body mass (kg) and height (m) assessed using an InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA) and a SECA mobile stadiometer (SECA, Frankfurt, Germany), respectively. Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by the square of their height in meters (kg/m^2)[116]. Medication used among older adults was recorded but not controlled (Appendix 4). None of the participants reported being on hormone replacement therapy.

Orthostatic Hypotension Classification

Orthostatic hypotension (OH) was classified into four categories based on BP response during active standing orthostatic stress. A normal BP (NBP) response was characterized by SBP returning to baseline without a drop exceeding 20 mmHg within 30 seconds of standing. Initial orthostatic hypotension (IOH) was defined as a transient drop of SBP > 40 mmHg within the first 15 seconds after standing, with complete SBP recovery within 30 seconds of standing. Delayed BP recovery (DBPR) was identified when SBP drops more than 20 mmHg and takes longer than 30 seconds to return to baseline values without meeting the criteria for sustained orthostatic hypotension (SOH). SOH was defined as a sustained SBP decrease of $\geq$ 20 mmHg between 60 and 180 seconds after standing, accompanied by supine hypertension (supine SBP $\geq$ 160 mmHg)[49].

Assessment of Cardiovascular Responses

HR was recorded continuously on a beat-by-beat basis using a 3-lead electrocardiogram (ECG) module (Finapres Medical System, Arnhem, The Netherlands) at a sampling frequency of 1 kHz, with HR derived from R-R intervals. Continuous non-invasive beat-by-beat measurements of SBP, DBP, and MAP were obtained from the arterial pressure signal (photoplethysmography) at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments. CO was estimated using a model flow algorithm (Finometer, Finapres Medical System, Arnhem, The Netherlands)[118]. Stroke volume (SV) was calculated as CO divided by HR

multiplied by 1000 (SV = CO/HR × 1000). Systemic vascular resistance (SVR) was derived by dividing MAP by CO (SVR = MAP/CO).

Sample Size

The sample size was determined a priori using the G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119], based on data from an internal pilot study with 16 participants (8/group). The power analysis utilized a t-test with the difference between two independent group means (younger adults *vs* older adults) obtained from the amplitude over or undershoot measured within 30 seconds after the drop (nadir) during sit-to-stand and lie-to-stand, with an α level set at 0.05. For sit-to-stand, the analysis demonstrated an actual power of 0.80 and an effect size of 0.69, based on the mean ± SD values for the younger adults (6.83 ± 6.96 mmHg) and older adults (2.36 ± 5.93 mmHg), resulting in an estimated total sample of 54 participants (27/group). For lie-to-stand, the analysis showed an actual statistical power of 0.83 and an effect size of 1.21 using a mean ± SD of the younger adults (6.21 ± 4.6 mmHg) and older adults (0.13 ± 5.41 mmHg), resulting in an estimated total sample size of 20 participants (10/group).

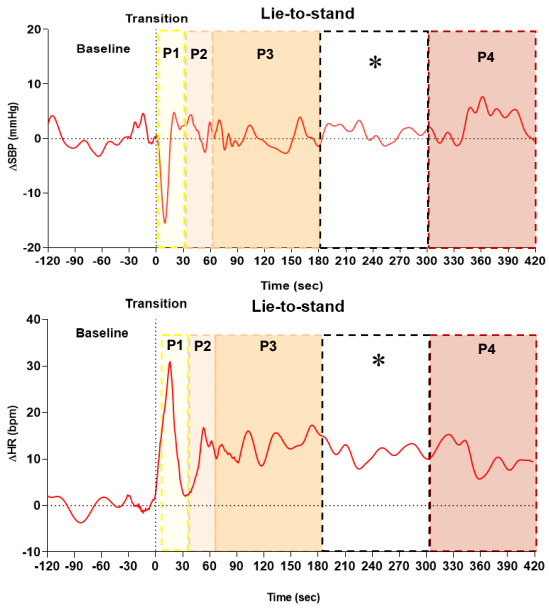
Data Analysis

Data from the Finometer were acquired and processed on a beat-by-beat basis using LabChart 8.0 (ADInstruments, Colorado Springs, CO, USA). ECG data were filtered with a 5-30 Hz bandpass to detect R peaks, except for the 30 seconds before and 90 seconds after standing, during which the raw signal was preserved, and Finometer calibration was manually disabled. When ECG traces were of poor quality, analysis was performed on the pressure waveform peaks. BP was calibrated using standard procedures described by the company, followed by a manual calibration (automated BP monitor - ARSIMAI, BSX516, Munster, Germany). Data was saved and transferred to a custom Matlab app for further analyses (Matlab R2024; The MathWorks Inc, Natick, MA, USA). In the Matlab app, noise and motion artifacts were removed using a median filter followed by a low-pass filter (cutoff = 0.05 rad/sample based on scalogram analysis) and a 5-second moving average to smooth the signal and extract parameters of interest[96,120]. Then, the data was interpolated and corrected for delays introduced by resampling at 1 Hz.

Variables Extracted and Analyzed During Active Standing

Baseline values were determined as the average of the 2 minutes before standing. In the first 30 seconds after standing, the lowest values of SBP, DBP, MAP, and SVR (drop) and the highest values of HR, CO, and SV were analyzed. Short-term

cardiovascular compensatory responses were defined as the highest point reached after the drop. These responses were divided into four phases: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s), reflecting cardiovascular regulation after active standing orthostatic stress. This phased approach is based on expected physiological responses in healthy adults (reference) and OH classifications[121,122]. Such an approach enables a detailed assessment of adaptive responses and age-related differences in cardiovascular regulation (Figure 5.2).



Phases	Time	Expected physiological responses
1	0-30 s	• Baroreceptor activation • Abruptly transient increase in HR • BP drops and then, overshooting over the baseline • Matching in CO and SVR • Slight decrease in SV
2	30-60 s	• Parasympathetic nervous system is activated • BP begins to drop • CO and HR decrease • Increase in SVR and SV
3	60-180 s	• BP, CO, SVR, and SV return to similar levels as baseline • HR remains elevated above the supine levels
4	300-420 s	• BP, CO, SVR, and SV remain close to the baseline measurement • HR stays above the baseline measurement

Figure 5.2 Example of systolic blood pressure (ΔSBP, top) and heart rate (ΔHR, bottom) responses to lie-to-stand divided into 4 phases. Phase 1: 0-30 s, phase 2: 30-60 s, phase 3: 60-180 s, and phase 4: 300-420 s after transition. *The white area (180-300 s) represents a stabilization phase similar to phase 3, and it is unrelated to any OH classification; thus, it was not included in the analysis. However, phase 4 continues in the analysis as it represents a higher prevalence of delayed orthostatic hypotension[123,124].

Statistical Analysis

The normality of the data was assessed using the Shapiro-Wilk test. Continuous variables (e.g., SBP, DBP) with a parametric distribution were reported as mean ± SD, along with the 95% confidence interval (95% CI). Non-parametric continuous variables were reported as median with interquartile range (IQR) and minimum and maximum values. For sample characterization, continuous data (e.g., height, body mass) were presented as mean ± SD, 95% CI, minimum, and maximum values, while categorical data were reported as absolute numbers and relative percentages. The Chi-square test was used to compare categorical variables.

For comparison data between groups (younger *vs*. older), the unpaired Student's independent t-test was conducted for sit-to-stand and lie-to-stand on the continuous variables (e.g., SBP, DBP). For non-parametric data, the Mann-Whitney U test was applied. To adjust for multiple hypothesis testing, the *p*-values were corrected using the Benjamini-Hochberg adjustment[125], with the false discovery rate (FDR) set at 0.05. Significant results were reported based on the corrected *p*-values, highlighting the tests that met the adjusted threshold of $p < 0.05$.

For the continuous variables, the effect size[126] between the differences was checked by Cohen's *d* (parametric data) and by the *R* coefficient (non-parametric data)[127]. Effect size was classified as low (≤ 0.05), medium (0.06-0.25), high (0.26-0.50) and very high (> 0.50)[126]. Correlations between CO and SVR at 0-30 s (phase 1), 30-60 s (phase 2), 60-180 s (phase 3), and 300-420 s (phase 4) were analyzed using Pearson or Spearman correlation, depending on the data distribution. Correlation magnitudes were interpreted as small (r = 0.10-0.29), medium (r = 0.30-0.49), and large ($r \geq 0.50$)[126]. All analyses were conducted using R® (Version 4.1.1, Vienna, Austria).

Results

Eligibility was determined using a customized screening questionnaire designed by our research laboratory. In the sit-to-stand transition, data from 12 participants were excluded from the analysis, where the final sample size was 28 younger adults and 48 older adults. In the lie-to-stand, 11 participants were excluded from the analysis, resulting in a final sample size of 27 younger adults and 50 older adults. Data was excluded due to poor signal quality (e.g., noisy, motion artifacts) (Figure 5.3).

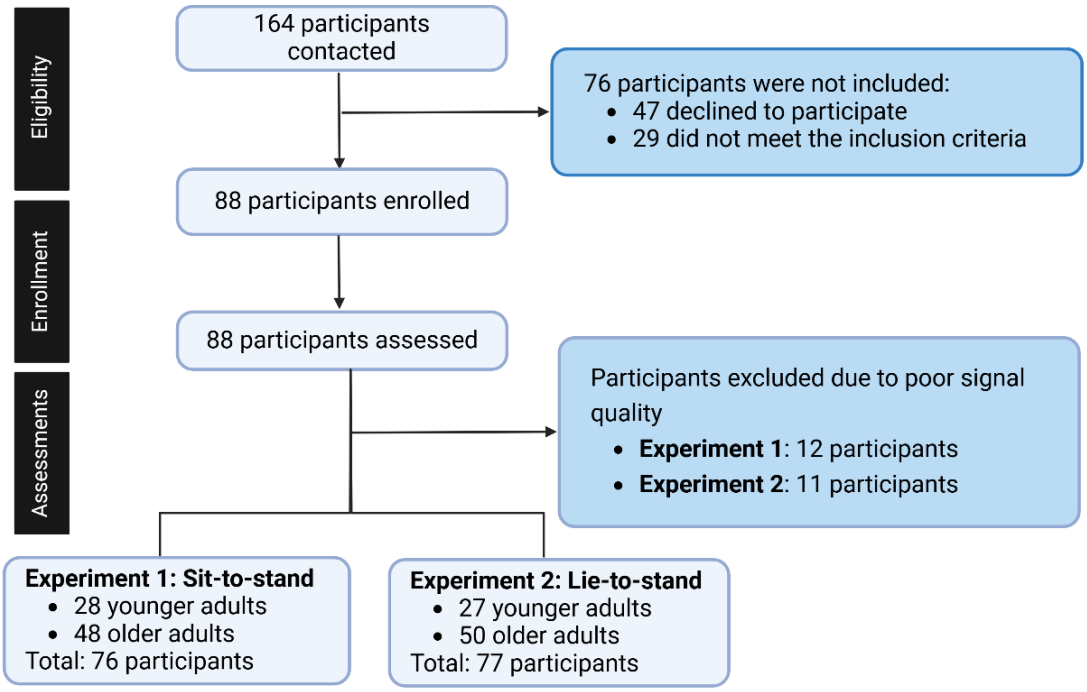


Figure 5.3 Recruitment flow chart of the study.

In terms of sex distribution, 70% of the older adults were female and 30% were older males, while the younger adults sample consisted of 50% females and 50% males. Anthropometric data showed that older adults had a higher BMI and were shorter than younger adults, but there were no statistically significant differences in body mass. Regarding OH, older adults were more likely to experience initial orthostatic hypotension (IOH), delayed blood pressure recovery (DBPR), and OI-related symptoms compared to younger adults (Table 5.1).

Table 5.1 Sample characteristics of younger adults and older adults.

Variable	Younger adults			Older adults			*p*
Sex	*n*	%		*n*	%		
Experiment 1	---	----	----	----	----	----	----
Female	14	50	----	34	70↑	----	**<0.001***
Male	14	50↑	----	14	30	----	**<0.001***
Experiment 2	---	----	----	----	----	----	----
Female	13	48↑	----	35	70↑	----	**<0.001***
Male	14	52↑	----	15	30	----	**<0.001***
Anthropometric data	Mean ± SD	CI 95%	Min; Max	Mean ±	CI 95%	Min; Max	
Age (years)	21.0 ± 2.3	20.8; 22.6	18.0; 28.0	70.5 ± 3.9↑	69.3; 71.5	63.0; 78.0	**<0.001***
Height (m)	1.73 ± 0.07	1.69; 1.76	1.56; 1.86	1.64 ± 0.08↓	1.62; 1.66	1.46; 1.84	**<0.001***
Body mass	67.6 ± 11.9	62.9-72.2	42.6; 90.5	73.7 ± 15.4	69.4; 78.0	42.5; 110.0	0.07
BMI (kg/m^2)	22.6 ± 3.38	21.3-23.9	16.5; 30.4	27.3 ± 5.6↑	25.8; 28.9	17.1; 48.4	**<0.001***
OH Classification**	*n* = 27	%	----	*n* = 50	%	----	
NBP	23	85	----	8	16↓	----	**<0.001***
IOH	0	0	----	11	22↑	----	**<0.001***
DBPR	4	15	----	31	62↑	----	**<0.001***
SOH	0	0		0	0	----	----
OI symptoms#	*n* = 27	%	----	*n* = 50	%	----	
No	27	100	----	43	86↓	----	**0.041***
Yes	0	0	----	7	14↑	----	

Mean ± Standard deviation (SD); *n*: number of participants; 95% CI: 95% confidence interval; Min-Max: Minimum; Maximum; BMI: body mass index; OH: orthostatic hypotension; NBP: normal blood pressure; IOH: initial orthostatic hypotension; DBPR: delayed blood pressure recovery; SOH: sustained orthostatic hypotension. ↓ lower than; ↑ Higher than. **Orthostatic hypotension (OH) classification followed the criteria of Van Wijnen et al.[49], focusing on beat-by-beat SBP measurements during the lie-to-stand transition. #Orthostatic intolerance (OI) symptoms were evaluated during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. *Statistically significant differences.

Baseline Responses During Active Standing Orthostatic Stress

At baseline during sit-to-stand, older adults exhibited higher SBP, DBP, MAP, and SVR, while HR, CO, and SV were lower compared to younger adults (Table 5.2). During lie-to-stand, older adults exhibited higher SBP, DBP, MAP, and SVR, while CO and SV were lower compared to younger adults, with no differences in HR (Table 5.3).

Immediately Upon Standing Responses During Active Standing Orthostatic Stress

Immediately on sit-to-stand, older adults experienced a greater drop in SBP, DBP, MAP, SVR, lower HR and CO peak, and larger SV peak values compared to younger adults (Table 5.2). After lie-to-stand, older adults experienced a greater drop in SBP, DBP, MAP, and SVR, lower HR peak, higher SV peak, and no differences in CO peak values (Table 5.3).

Short-term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress Across Phases

During sit-to-stand, SBP, DBP, and MAP short-term cardiovascular compensatory responses showed no statistically significant differences between older adults and younger adults during phases 1 (0-30 s) and 2 (30-60 s). However, older adults exhibited higher values in phases 3 (60-180 s) and 4 (300-420 s), except for DBP. Older adults also had lower SVR values in phases 1 and 2, but no differences in phases 3 and 4. In older adults, HR had lower values and SV had higher values across all phases compared to younger adults. CO values were lower in phases 1 and 4, but no differences were observed in phases 2 and 3 (Table 5.2).

Table 5.2 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses during sit-to-stand between younger adults and older adults across phases.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Younger adults	111.6 ± 9.1 (108; 115)	-8.4 | 6.4 (2.6; 43.8)	4.8 | 4.0 (-5.1; 22.0)	2.6 ± 4.6 (0.8; 4.4)	1.8 | 3.3 (-3.3; 20.0)	-1.0 ± 3.6 (-2.4; 0.4)
	Older adults	129.5 ± 12.9↑ (126; 133)	-20.4 | 11.0↑ (5.4; 41.0)	2.7 | 9.7 (-15.7; 21.9)	3.3 ± 1.1 (5.5; 7.6)	2.1 | 7.8↑ (-15.0; 22.4)	3.4 ± 2.2↑ (1.5; 5.3)
	Adj *p*	**0.003***	**0.003***	0.23	0.6	**0.003***	**0.003***
	ES	1.5	1.1	-0.3	0.1	0.76	0.8
DBP (mmHg)	Younger adults	76 | 6 (54; 82)	-7.8 | 4.4 (3.4; 28.3)	2.8 | 3.0 (-9.7; 8.2)	1.5 | 2.7 (-8.5; 6.7)	2.3 | 2.7 (-8.9; 11.4)	1.1 | 2.2 (-12.0; 6.2)
	Older adults	80 | 10↑ (56; 92)	-13.0 | 6.7↑ (5.5; 27.7)	0.6 | 3.8 (-11.8; 7.6)	1.2 | 3.0 (-9.9; 10.9)	3.3 | 37 (-9.3; 13.6)	2.0 | 4.1 (-11.6; 11.3)
	Adj *p*	**0.029***	**0.035***	0.23	0.30	0.11	0.2
	ES	0.3	0.5	0.3	0.1	0.11	0.2
MAP (mmHg)	Younger adults	87 ± 5.05 (85.1; 89)	-7.7 | 4.4 (3.4; 28.3)	2.1 | 3.6 (-6.3; 10.4)	2.8 | 3.0 (-9.7; 8.2)	2.4 | 2.7 (-8.2; 11.7)	-0.1 | 4.3 (-13.7; 3.9)
	Older adults	95.5 ± 8.52↑ (93.2; 97.9)	-13.3 | 6.7↑ (5.5; 27.7)	1.3 | 4.3 (-12.0; 9.1)	0.6 | 3.8 (-11.8; 7.8)	3.3 | 3.7↑ (-9.3; 13.6)	1.9 | 4.3↑ (-12.6; 10.6)
	Adj *p*	**0.002***	**0.023***	0.11	0.9	**0.012***	**0.008***
	ES	1.1	0.7	0.2	0.01	0.36	0.4
SVR ($mmHg.min^{-1}L^{-1}$)	Younger adults	20.6 | 6.5 (13.8; 31.1)	-7.0 | 2.7 (2.7; 11.6)	0.7 ± 1.8↑ (-0.0; 1.4)	1.6 ± 1.7 (0.9; 2.3)	1.7 | 2.1 (-1.8; 6.9)	0.2 | 1.7 (-1.9; 3.3)
	Older adults	25.8 | 8.4↑ (18.2; 49.8)	-11.3 | 6.6↑ (5.3; 21.5)	-2.0 ± 3.3 (-2.9; -1.0)	-1.3 ± -2.1↓ (-0.5; 2.7)	0.5 | 5.7 (-6.1; 11.4)	-0.4 | 5.4 (-7.9; 9.3)
	Adj *p*	**0.0017***	**0.0017***	**0.0017***	**0.0017***	0.23	0.4
	ES	0.6	0.7	-0.9	-1.2	0.1	0.1

HR (bpm)	Younger adults	71.9 ± 10.2 (68.0; 75.9)	29.2 ± 5.3 (27.1; 31.3)	29.2 ± 5.3 (27.1; 31.3)	11.7 ± 8.3 (8.5; 15.0)	18.0 ± 7.8 (15.0; 21.1)	14.1 ± 5.5 (11.9; 16.3)
	Older adults	64.5 ± 61.8↓ (67.1; 9.0)	12.3 ± 4.4↓ (11.0; 13.6)	12.3 ± 4.4↓ (11.0; 13.6)	7.0 ± 5.9↓ (8.1; 3.8)	9.3 ± 3.9↓ (8.1; 10.5)	7.5 ± 4.2↓ (6.2; 8.7)
	Adj *p*	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***	**0.001***
	ES	-0.8	-3.5	-3.5	-0.8	-1.5	-1.4
CO ($L.min^{-1}$)	Younger adults	5.4 ± 1.2 (5.0; 6.0)	2.0 | 1.3 (0.7; 4.5)	2.0 | 1.3 (0.7; 4.5)	0.3 ± 0.4 (0.1; 0.6)	0.4 ± 0.5 (0.2; 0.7)	-0.1 ± 0.4 (-0.2; 0.1)
	Older adults	3.5 ± 0.8↓ (3.3; 3.8)	1.6 | 0.8↓ (0.5; 4.7)	1.6 | 0.8↓ (0.5; 4.7)	2.2 ± 0.9 (1.9; 2.6)	0.5 ± 0.4 (0.4; 0.7)	0.1 ± 0.4↑ (0.0; 0.3)
	Adj *p*	**0.035***	**0.005***	**0.005***	0.11	0.4	**0.028***
	ES	-1.9	0.4	0.4	0.4	0.2	0.5
SV (mL)	Younger adults	77.3 ± 18.3 (70.2; 84.4)	9.1 ± 7.8 (6.0; 12.2)	-3.7 | 9.2 (-30.8; 14.0)	-8.1 ± 7.1 (-10.9; -5.3)	-10.0 | 1.1 (8.6; -28.7)	-22.3 | 11.5 (-46.9; -7.5)
	Older adults	55.9 ± 14.4↓ (51.7; 60.1)	13.6 ± 8.1↑ (11.2; 16.0)	3.8 | 9.5↑ (-7.2; 53.1)	0.1 ± 8.1↑ (-2.2; 2.5)	-3.9 | 7.4↑ (-25.8; 28.3)	-15.0 | 12.2↑ (-42.6; 30.0)
	Adj *p*	**0.0014***	**0.02***	**0.0014***	**0.0014***	**0.0014***	**0.011***
	ES	-1.3	0.6	0.5	1.0	0.6	0.35

Mean ± Standard Deviation (SD) with 95% Confidence Interval for the mean; |: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than; ↑ higher than. *Statistically significant differences between younger adults and older adults. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

During lie-to-stand, older adults' SBP, DBP, MAP, and SVR short-term compensatory responses were lower in phases 1 and 2, but similar in phases 3 and 4 than younger adults. However, HR values were lower, and SV values were higher in phases 1-3 but not in phase 4 in older adults. No statistically significant differences were observed in CO across all phases between older adults and younger adults (Table 5.3).

Table 5.3 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses during lie-to-stand between younger adults and older adults across phases.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Younger adults	111.6 ± 9.1 (108; 115)	-15.1 ± 6.6 (12.4; 17.7)	5.9 ± 4.9 (4.0; 7.9)	3.2 | 6.0 (-6.4; 9.7)	2.5 | 4.1 (-2.2; 8.3)	-0.9 | 3.5 (-4.1; 4.2)
	Older adults	129.5 ± 12.9↑ (126; 133)	-31.7 ± 12.4↑ (28.1; 35.3)	-2.5 ± 10.7↓ (-15.7; 21.9)	-1.2 | 9.0↓ (-29.1; 21.4)	2.6 | 8.0 (-23.2; 27.1)	-1.2 | 11.9 (-32.8; 19.9)
	Adj *p*	**0.003***	**0.0035***	**0.035***	**0.007***	0.5	0.23
	ES	1.5	1.5	-0.9	0.4	0.1	0.2
DBP (mmHg)	Younger adults	76 | 6 (54; 82)	-11.2 | 4.0 (2.5; 17.9)	4.0 | 3.8 (-2.6; 14.0)	3.0 | 3.1 (-2.4; 10.6)	4.3 | 2.8 (0.6; 14.0)	2.4 | 2.0 (-0.3; 10.3)
	Older adults	80 | 10↑ (56; 92)	-19.5 | 5.9↑ (0.0; 34.6)	0.1 | 7.0↓ (-9.8; 21.7)	1.2 | 5.8↓ (-10.0; 27.1)	2.5 | 6.6 (-7.6; 32.5)	2.8 | 6.0 (-8.2; 28.3)
	Adj *p*	**0.029***	**0.0017***	**0.0017***	**0.004***	0.46	0.9
	ES	0.3	0.8	0.6	0.4	0.1	0.01
MAP (mmHg)	Younger adults	87 ± 5.05 (85.1; 89)	-10.7 ± 5.5 (9.2; 12.1)	4.2 ± 3.2 (3.0; 5.5)	3.0 | 3.1 (-2.4; 10.6)	4.4 | 2.8 (0.6; 4.0)	1.7 | 8.6 (-14.5; 21.9)
	Older adults	95.5 ± 8.52↑ (93.2; 97.9)	-19.8 ± 6.9 ↑ (17.8; 21.8)	0.5 ± 3.9↓ (-0.6; 1.6)	-1.6 | 7.3↓ (-16.8; 20.9)	2.6 | 6.6 (-7.6; 32.5)	2.2 | 8.6 (-14.5; 21.9)
	Adj *p*	**0.002***	**0.0014***	**0.0014***	**0.0014***	0.58	0.90
	ES	1.1	1.8	-1.1	0.5	0.1	0.01
SVR ($mmHg.min^{-1}.L^{-1}$)	Younger adults	19.4 ± 3.6 (18.0; 20.9)	-6.4 | 3.2 (3.1; 2.3)	2.4 | 4.9 (-2.7; 11.0)	3.6 | 4.8 (-2.0; 10.0)	4.4 | 3.9 (-2.3; 10.0)	1.7 | 3.7 (-4.3; 7.2)
	Older adults	27.8 ± 7.0↑ (25.8; 29.8)	-12.5 | 5.2↑ (4.9; 25.3)	-1.7 | 4.1↓ (-13.1; 19.5)	-0.8 | 4.1↓ (-11.9; 24.9)	2.7 | 6.4 (-11.1; 40.8)	0.2 | 6.8 (-13.3; 40.5)
	Adj *p*	**0.0017***	**0.0017***	**0.0017***	**0.0017***	0.14	0.7
	ES	1.4	0.9	0.6	0.5	0.2	0.03

HR (bpm)	Younger adults	66.4 ± 9.8 (62.5; 70.2)	35.4 | 8.1↑ (25.8; 53.7)	35.4 | 8.1 (25.8; 53.7)	16.7 | 12.5 (-1.9; 47.8)	21.7 | 12.0 (11.5; 44.7)	18.8 | 9.0 (3.8; 35.5)
	Older adults	62.6 ± 8.8 (60.0; 65.1)	16.2 | 5.8 (5.6; 40.4)	16.2 | 5.8↓ (5.6; 40.4)	10.9 | 6.8↓ (0.4; 41.3)	13.5 | 8.2↓ (4.5; 42.8)	9.1 | 7.1↓ (1.8; 32.1)
	Adj *p*	0.08	**0.0014***	**0.0014***	**0.0081***	**0.0014***	**0.0014***
	ES	-0.4	0.9	0.9	0.4	0.7	0.7
CO ($L.min^{-1}$)	Younger adults	5.5 | 1.3↑ (3.9; 9.0)	1.7 | 1.0 (0.7; 5.4)	1.7 | 1.0 (0.7; 5.3)	0.1 ± 0.8 (-0.2; 0.4)	0.1 ± 0.6 (-0.0; 0.4)	-0.2 | 0.8 (-1.5; 1.3)
	Older adults	3.4 | 1.0 (2.2; 5.6)	1.7 | 1.5 (0.3; 6.0)	1.7 | 1.5 (0.3; 6.0)	0.4 ± 0.6 (0.2; 0.6)	0.5 ± 0.5 (0.4; 0.7)	-0.0 | 0.7 (-2.7; 1.0)
	Adj *p*	**0.035***	0.4	0.4	0.17	0.17	0.28
	ES	0.8	0.1	0.1	0.4	0.3	0.1
SV (mL)	Younger adults	85.3 | 22.9↑ (61.8; 122.2)	-0.1 | 16.7 (-27.7; 21.6)	-16.8 | 11.2 (-37.9; 3.1)	-19.6 ± 8.5 (-23.0; -16.3)	-23.1 ± 8.5 (-26.5; -19.7)	-19.4 | 16.4 (-42.6; -0.3)
	Older adults	55.7 | 14.9 (35.4; 93.1)	10.5 | 10.7↑ (-5.4; 49.7)	3.9 | 11.0↑ (-18.0; 33.8)	-5.5 ± 7.9↑ (-7.8; -3.2)	-8.4 ± 7.1↑ (-10.8; -6.0)	-17.5 | 24.4 (-55.7; 3.7)
	Adj *p*	**0.0011***	**0.0011***	**0.0011***	**0.0011***	**0.0011***	0.8
	ES	0.8	0.5	0.85	1.7	1.7	0.03

Mean ± Standard Deviation (SD) with 95% Confidence Interval for the mean; |: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than; ↑ higher than. *Statistically significant differences between younger adults and older adults. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

Figure 5.4 illustrates the correlation coefficients (r), 95% confidence interval (CI 95%), and *p*-values for CO and SVR responses of younger adults and older adults across four specific phases. In sit-to-stand, younger adults demonstrated a non-significant correlation between CO and SVR in phase 1 (r = -0.234, 95% CI -0.569; 0.137, p = 0.2). However, a significant, large negative correlation was observed from phases 2-4 (phase 2: r = -0.652, 95% CI -0.825; -0.369, $p < 0.001$, phase 3: r = -0.603, 95% CI -0.797; -0.296, $p < 0.001$), and phase 4: r = -0.837, 95% CI -0.922; -0.674, $p < 0.001$). Older adults demonstrated a significant negative correlation of varying magnitudes between CO and SVR across all phases of the sit-to-stand transition. Specifically, the correlation was of medium magnitude in phase 1 (r = -0.366, 95% CI -0.534; -0.011, p = 0.01) and phase 3 (r = -0.533, 95% CI -0.710; -0.293, $p < 0.001$), while large negative correlations were observed in phase 2 (r = -0.824, 95% CI -0.898; -0.704, $p < 0.001$) and phase 4 (r = -0.859, 95% CI -0.919; -0.761, $p < 0.001$) (Figure 5.4).

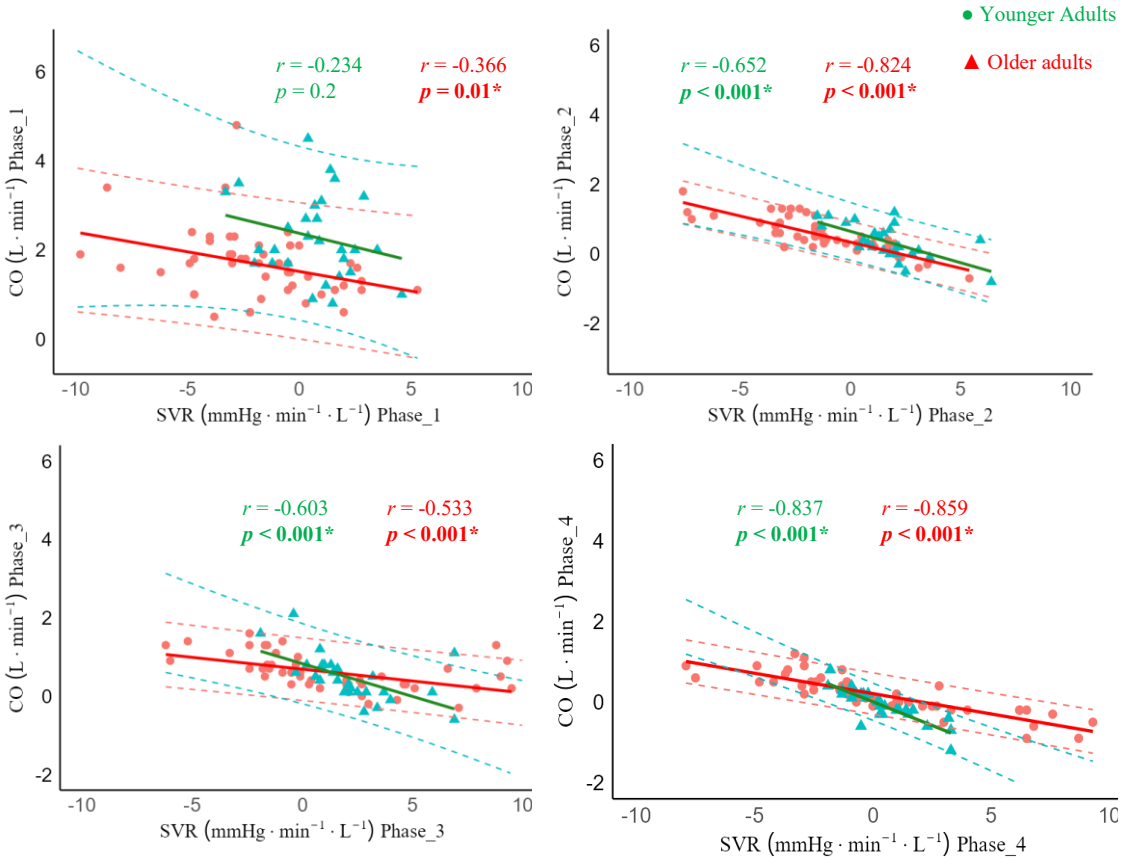


Figure 5.4 Cardiac output and systemic vascular resistance correlation during sit-to-stand in younger adults and older adults.

Figure 5.5 illustrates the correlation coefficients (r), 95% confidence interval (CI 95%), and *p*-values for CO and SVR responses of younger adults and older adults across four specific phases. In the lie-to-stand transition, younger adults showed significant negative correlations between CO and SVR across all phases. The correlation was of medium magnitude in phase 1 (r = -0.409, 95% CI -0.683; -0.034, p = 0.03), and of large magnitude in phases 2 (r = -0.784, 95% CI -0.897; -0.575, $p < 0.001$), 3 (r = -0.806, 95% CI -0.908; -0.614, $p < 0.001$), and 4 (r = -0.927, 95% CI -0.966; -0.844, $p < 0.001$). Unlike younger adults, the correlation between CO and SVR in older adults was not statistically significant in phase 1 (r = -0.197, 95% CI -0.430; 0.118, p = 0.10). However, statistically significant negative correlations of large magnitude were observed in phase 2 (r = -0.724, 95% CI -0.804; -0.486, $p < 0.001$), phase 3 (r = -0.719, 95% CI -0.834; -0.553, $p < 0.001$), and phase 4 (r = -0.908, 95% CI -0.824; -0.531, $p < 0.001$).

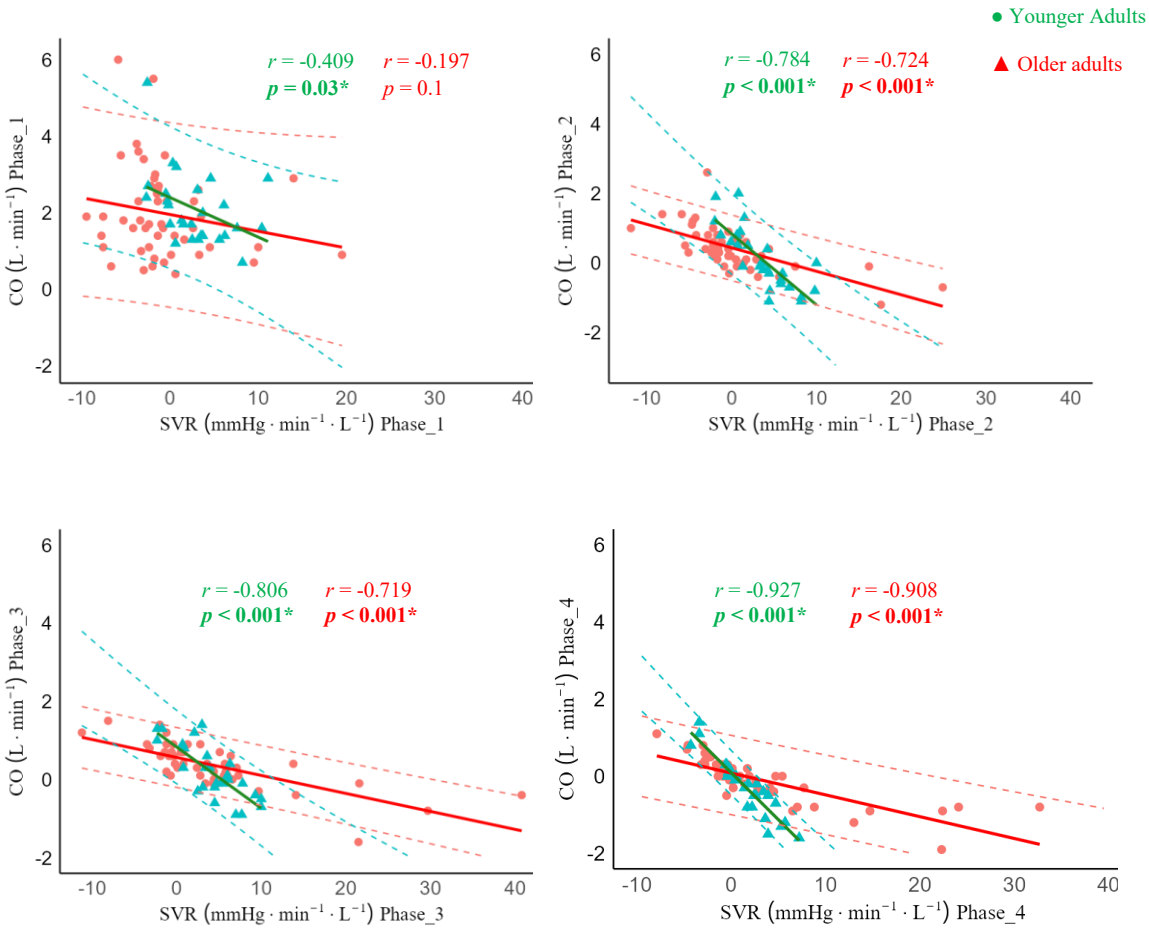


Figure 5.5 Cardiac output and systemic vascular resistance correlation during lie-to-stand transition in younger adults and older adults.

Discussion

Although other studies have examined the effect of age on short-term cardiovascular compensatory responses[109,110], our study is the first to examine phase-specific short-term cardiovascular compensatory responses in younger adults and older adults during sit-to-stand and lie-to-stand. The main findings of this study indicate that compared to young adults, older adults showed: (i) at baseline, had higher SBP, DBP, MAP, and SVR and lower HR, CO, and SV; (ii) immediately on standing, older adults experienced a greater drop in SBP, DBP, MAP, and SVR, blunted HR and CO but higher SV responses; and (iii) blunted short-term compensatory responses in early phases (phases 1 and 2) in SBP, DBP, MAP, SVR, CO, and HR. Older adults also showed a lower HR and CO peak response and a larger SV compensatory response throughout phases 1 to 4 compared to younger adults. Regarding the matching between CO and SVR, which reflects the timing of BP regulation, older adults exhibited significant negative correlations across all phases (phases 1-4) during sit-to-stand and phases 2-4 during lie-to-stand. These findings indicated that under lower gravitational stress, older adults were able to regulate BP within 30 seconds of transitioning to an upright position, while during lie-to-stand transition (higher gravitational stress), older adults took longer (30-60 s) to regulate BP. Older adults also showed a higher prevalence of OH (84%) and OI symptoms (14%) compared to younger adults.

Baseline Responses During Active Standing Orthostatic Stress

Consistent with the hypotheses, older adults exhibited higher SBP, DBP, MAP, and SVR at baseline compared to younger adults in both conditions. These findings align with previous research on age-related differences in cardiovascular responses, showing that baseline BP and SVR were higher in older adults than younger adults[111,112]. However, Hart et al.,[128] reported no differences in baseline SVR between age groups. Also, in the current study, baseline HR was lower in older adults during sit-to-stand but not different during lie-to-stand between age groups. These results align with Grassler et al.,[129] who reported lower baseline HR in older adults during sitting, and with Wieling et al.,[109] and Houghton et al.,[130] who found no significant differences in baseline HR in the supine position. Baseline CO and SV were lower in older adults than younger adults in both postural transitions, consistent with previous studies demonstrating age-related declines in CO and SV[112,130]. However, Hart et al.,[128] did not find statistical differences in baseline CO between older adults and younger adults in the supine position.

These results highlight age-related physiological changes. The higher baseline SBP, DBP, and MAP in older adults are consistent with increased arterial stiffness (elevated SVR) and reduced aortic reservoir capacity[16], which limits the aorta's ability to expand and store blood during systole, leading to elevated pressure on the heart during each contraction[16]. Additionally, higher SVR in older adults reflects increased vasoconstriction, vascular resistance, and reduced vascular compliance[16]. Lower baseline CO and SV further support age-related declines in myocardial contractility, impaired diastolic filling (preload), reduced ventricular compliance, and limited cardiac performance[16].

Immediately on Active Standing Orthostatic Stress Responses

Immediately on standing, older adults exhibited greater drops in SBP, DBP, and MAP in both transitions compared to younger adults. These results are partially supported by Smith and Fasler[113], but in contrast with Kawaguchi et al.[111]. Smith and Fasler[113] observed that older adults had a larger SBP drop compared to young adults, with no differences in DBP, after a slow 70° head-up tilt. Kawaguchi et al.[111] reported no statistically significant differences in SBP, DBP, and MAP drop during sit-to-stand between older adults and younger adults using an automated blood pressure monitor.

In the current study, SVR drop was more pronounced in older adults (sit-to-stand: 44% and lie-to-stand: 45%) than in younger adults (sit-to-stand and lie-to-stand: 33%) following the active standing orthostatic stress. This finding contrasts with Vargas[110] and Wieling et al.[109]. Vargas[110] reported that older adults had a smaller percentage change in SVR from baseline to 70º head-up tilt (22% ± 27%) compared to younger adults (62 ± 33%). However, Wieling et al.[109] reported no statistical differences in SVR changes during lie-to-stand between older adults (17 ± 24%) and younger adults (25 ± 10%).

The present study also found that HR peak value was lower (blunted response) in older adults than in younger adults in both conditions, consistent with the results from Wieling et al.[109], Vargas[110], and Smith et al.[112]. Wieling et al.[109] observed significant differences between age groups at one minute after lying to standing. Vargas[110] reported that older adults had a smaller percentage change in HR after a 70º head-up tilt. Smith et al.[112] demonstrated that HR increases were consistently lower in older males than younger adults across tilt angles (10º, 20º, 30º, 45º, and 70º).

This study also found that older adults had a reduced CO peak value during sit-to-stand but not lie-to-stand. These findings agree with Wieling et al.[109] and Kim et al[131],

both of whom reported no significant differences in CO peak between older adults and younger adults. Additionally, older adults demonstrated a higher SV peak during both active standing orthostatic stress challenges, as previously described by Wieling et al.[109] and Vargas[110]. Wieling et al.[109] found that older adults had a smaller percentage decrease in SV at 1 minute after standing compared to younger adults. Similarly, Vargas[110] reported that older adults had a smaller percentage drop in SV after a 70º head-up tilt.

The greater SBP, DBP, and MAP drop in older adults reflects age-related impairments in vascular compliance and increased arterial stiffness, reducing BP regulation during postural transitions [24]. The pronounced SVR drop and delayed vasoconstrictive response suggest greater blood pooling in the lower extremities, compromising the body's ability to maintain vascular tone[16,24]. The blunted HR response in older adults may be attributed to reduced β_1-adrenergic receptor sensitivity and slower parasympathetic withdrawal, limiting autonomic adjustments to orthostatic stress[132]. The reduced CO response indicates impaired baroreflex sensitivity and a diminished ability to adjust HR and SV to meet increased CO demands[132]. Despite a lower baseline SV, older adults demonstrated a higher SV peak during both transitions, likely a compensatory response to counteract reduced BP and CO, as well as delayed vasoconstriction[16,24].

Short-term Cardiovascular Compensatory Responses Across Phases During Active Standing Orthostatic Stress

The short-term cardiovascular compensatory phases (1-4) and expected physiological responses are described in Figure 5.2. To date, no studies have directly compared the short-term time course of cardiovascular compensation between older and younger adults following active standing orthostatic stress. Therefore, this discussion primarily draws from a few studies that examined these responses separately in each age group, as well as studies using passive maneuvers (head-up tilt - HUT), despite the inherent differences between active and passive postural transitions.

In this study, SBP, DBP, and MAP responses during sit-to-stand did not differ between older and younger adults within the first 30 seconds (phase 1). However, during lie-to-stand, older adults showed a slower BP recovery, taking over 30 s (phase 2) to return to initial values. Consistent with our results, Ten Harkel et al.[133] found that SBP and DBP returned to baseline within 20 seconds in younger males (22-40 years old) after lie-to-stand. Finucane et al.[108] investigated 4475 middle-aged and older adults (62.8 ± 9.2 years) during lie-to-stand and reported delayed SBP stabilization, within 20-30 s in males

and within 30 s in females aged 50-69 years, but up to 60 s in males and 90 s in females aged ≥ 70 years. Similarly, DBP stabilization occurred within 40 s for those aged 50-69 years, but did not return to baseline in those aged ≥ 70 years. Additionally, Heitterachi et al.[134] reported that older adults with delayed SBP recovery (> 30 s) had an increased risk of falls and mortality.

In this study, during phases 1 (0-30 s) and 2 (30-60 s), older adults exhibited diminished SVR response compared to younger adults in both conditions, consistent with the results from Smith et al.[112], Kim et al[131], and Wieling et al.[109]. Smith et al.[112] examined hemodynamic responses in older and younger males during a progressive HUT (10º, 20º, 30º, 45º, and 70º). They reported that at 20º, older males had significantly lower SVR values than younger males, with no differences observed at the subsequent tilt angles. Kim et al[131] reported no differences in SVR percentage increase between older and younger adults after lie-to-stand. Wieling et al.[109] observed that the SVR percentage increase after lie-to-stand was higher in both groups, with no significant differences at 1 min, 2 min, and 5 min.

In the current study, older adults demonstrated a blunted HR short-term compensatory response across all phases during both active standing orthostatic stress, consistent with the findings by Wieling et al.[109] and Kim et al[131]. Wieling et al.[109] reported that older adults exhibited a lower HR (blunted compensatory response) after transitioning from supine to standing at 1, 2, and 5 minutes after transition compared to younger adults. Similarly, Kim et al[131] observed that 5 minutes after standing, older adults had a smaller increase in HR than younger adults. In contrast, older and younger adults had similar CO compensatory responses across all phases. Interestingly, older adults showed a higher SV compensatory response in all phases (1 to 4) during sit-to-stand and in phases 1 to 3 during lie-to-stand. Consistent with our results, Wieling et al.[109] reported no significant differences in CO percentage change between older and younger adults at 1 and 2 minutes after lie-to-stand. However, at 5 minutes, older adults exhibited a greater percentage drop in CO than younger adults. Wieling et al.[109] also showed a smaller SV percentage drop at 1, 2, and 5 minutes after lie-to-stand in older adults compared to younger adults.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

During postural transitions, the matching between CO and SVR is essential for MAP maintenance and ensures sufficient cerebral blood flow[16,24]. This is the first study to investigate the correlation between CO and SVR across specific phases, aiming to determine the timing of BP regulation relative to baseline values. Given the novelty of this analysis, the discussion focuses on the physiological aspects of cardiovascular responses. During sit-to-stand, older adults exhibited a significant negative correlation between CO and SVR across all phases, whereas younger adults showed this correlation from phases 2 to 4. In lie-to-stand, older adults showed a significant negative correlation from phases 2 to 4, while younger adults displayed this correlation across all phases.

These findings indicate that older adults regulate BP within 30 s (phase 1) during sit-to-stand, demonstrating that older adults can still compensate under a lower gravitational stress challenge. However, in lie-to-stand (higher gravitational stress challenge), older adults exhibit delayed BP regulation, achieving matching between CO-SVR after 30 s (phase 2). This delayed response may reflect the diminished efficiency of cardiovascular and autonomic compensatory responses, including slower baroreflex activation[24], delayed vasoconstriction[16] and reduced autonomic response[132]. Consequently, older adults have impaired cardiovascular responses to rapidly counteract the significant offset and sudden BP drop, and blood pooling in the lower extremities, particularly under higher orthostatic stress (e.g., lie-to-stand).

These physiological impairments align with the higher prevalence of OH (84%) and OI symptoms (14%) observed in older adults reported in this study. The increased gravitational challenge further disrupts CO-SVR matching, prolonging BP stabilization time. The delayed compensatory responses in older adults highlight their reduced cardiovascular regulatory responses, making them more susceptible to orthostatic impairments and related symptoms.

Limitations

This study has limitations that should be considered when interpreting the findings. Medication used among older adults was recorded but not controlled (Appendix 4), which could have influenced cardiovascular responses during active orthostatic stress. Many older adults take antihypertensives, beta-blockers, or diuretics, which may affect HR, BP, and vascular resistance[3]. In this study, 27% of participants were on calcium

channel blockers (n = 14), 13% on beta-blockers (n = 7), 10% on diuretics (n = 5), 8% on ACE inhibitors (n = 4), and 8% on angiotensin receptor blockers (n = 4). While these medications may have impacted compensatory responses under investigation, they also reflect real-world conditions, making the findings more applicable to the community-dwelling older population.

In young female participants, the menstrual cycle phase was not controlled. However, its impact on cardiovascular responses remains controversial in the literature. Studies have suggested that estrogen levels influence vascular tone[24,135] and hemodynamic responses during postural transitions[136,137]. Conversely, other studies report no significant effects on hemodynamic responses[138,139]. Therefore, whether and how the menstrual cycle affected our results, and the extent of this influence, remains uncertain. However, it is unlikely to have substantially altered the overall findings of this study. Sex differences and frailty are potential confounders that should be acknowledged as limitations. Future research should explore how these factors impact cardiovascular responses during active standing orthostatic stress.

Conclusion

This study identified significant differences in cardiovascular responses to active standing orthostatic stress between older and young adults. Older adults experienced a more pronounced drop in BP and SVR, along with delayed short-term compensatory responses, indicating impairments in cardiovascular regulation. Older adults also showed a blunted HR compensatory response during both transitions. Despite this, SV was higher in older adults, indicating a greater reliance on SV as a compensatory response to attenuate BP drops. Regarding BP stabilization, older adults required more time under higher gravitational orthostatic stress, but not under lower stress, achieving regulation between 30 and 60 s after standing. Furthermore, the incidence of orthostatic hypotension (84%) and orthostatic intolerance-related self-reported symptoms (14%) was higher in older adults. These findings highlight the impact on short-term cardiovascular compensatory responses in older adults under varying levels of active standing orthostatic stress.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study revealed that older adults exhibit impaired and delayed short-term cardiovascular compensatory responses to active standing orthostatic stress, particularly during the higher gravitational stress (lie-to-stand transition). Compared to younger adults, older adults showed a more pronounced drop in BP and SVR, blunted HR and CO responses, and greater reliance on SV to support BP recovery. The delayed CO-SVR matching response observed in older adults indicates a slower regulatory adjustment, especially under higher gravitational stress. These results provide insight into the physiological basis of the increased prevalence of orthostatic hypotension and orthostatic intolerance symptoms in older populations. With the characterization of the phase-specific nature of compensatory responses, this study advances our understanding of age-related cardiovascular dysregulation and sets the stage for future work aimed at improving cardiovascular compensatory responses in older adults through targeted interventions, such as exercise.

6. Chapter 6

Short-term autonomic responses in older adults under different orthostatic stress conditions

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This manuscript constitutes the third study of my doctoral thesis, and it investigates age-related differences in autonomic regulation during postural transitions by comparing heart rate variability (HRV) indexes, cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG) in younger and older adults. The study was designed to build on previous chapters by providing a more detailed analysis of autonomic function during active standing. I was responsible for developing the study design, recruiting participants, collecting and analyzing data, and drafting and revising the manuscript. The inclusion of CPM analysis and phase-specific assessments of BRG offers a novel contribution to the field by capturing the temporal dynamics of autonomic regulation, an area previously underexplored in aging research.

Publication Status

This study will be submitted to Experimental Gerontology.

Abstract

Older adults demonstrate progressive declines in autonomic function, resulting in altered autonomic balance. These changes can affect the dynamic interplay between sympathetic and parasympathetic modulation, compromising short-term compensatory responses to active standing. This study aimed to compare heart rate variability (HRV) indexes at baseline, cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG) between younger adults (YA, 18-30 years) and older adults (OA, 60-79 years) following active standing. A secondary objective was to analyze the incidence of orthostatic intolerance (OI) symptoms. Participants completed sit-to-stand and lie-to-stand maneuvers with continuous beat-to-beat blood pressure and heart rate (HR, electrocardiogram). HRV indexes at baseline was analyzed in both time and frequency domains. CPM was measured by the ratio between HR at the 30th beat and the 15th beat (HR 30:15) on standing. CBG was determined as the ratio of HR and SBP changes (ΔHR/ΔSBP) at specific phase time points (30s, 60s, 180s, and 420s). At baseline, OA exhibited reduced Standard Deviation of RR intervals (SDRR), Root Mean Square of Successive Differences (RMSSD), low-frequency (LF), and high-frequency (HF) power, and elevated LF/HF ratio, indicating a shift toward sympathetic dominance. During active standing orthostatic stress, OA demonstrated higher CPM and lower CBG in later phases (phases 2-4). Also, OA reported more symptoms (14%) of OI than YA (0%). In conclusion, these findings indicate that aging is associated with autonomic short-term compensatory response impairments characterized by reduced HRV indexes, higher CPM, and lower CBG, leading to diminished autonomic regulation under active-standing orthostatic stress and a higher incidence of OI symptoms.

Keywords: Heart rate variability, cardiac parasympathetic modulation, cardiac baroreflex gain, older adults, active standing.

Introduction

Transitioning from supine or sitting to a standing upright posture is marked by a rapid transient drop in blood pressure (BP), generating a stimulus for the autonomic nervous system (ANS) to compensate for this BP drop[7,33]. This hemodynamic challenge activates compensatory mechanisms, including an increase in sympathetic activity and a reduction in parasympathetic tone[140]. These responses facilitate vasoconstriction and an increase in heart rate (HR), contributing to the rapid short-term compensatory BP response and maintenance of cerebral perfusion and brain blood flow[24,132].

With the aging process, the ANS undergoes a gradual decline that impacts its response during postural transitions[141]. This age-related autonomic change is characterized by compromised baroreceptor sensitivity to activate the sympathetic nervous system[35]. Also, the decline in vagal tone further limits the rapid withdrawal of parasympathetic influence necessary for a timely HR increase[132]. Additionally, decreased responsiveness of adrenergic receptors in the heart and vasculature contributes to a less effective sympathetic output[35]. Changes in chemoreceptor function and a decline in muscle pump further contribute to the inability to counteract orthostatic stress[35,132]. A delayed onset of these mechanisms can result in prolonged hypotension during postural transitions, elevating the risk of dizziness, blurry vision, and falls[132].

Heart rate variability (HRV) is a key marker of autonomic balance that reflects the interplay between sympathetic and parasympathetic activity[38]. In older adults, HRV indexes are generally reported to be reduced, indicating diminished parasympathetic modulation and impaired autonomic response[38]. Although studies suggest a decline in HRV indexes with aging[142,143], the literature remains inconclusive, as some findings indicate that HRV indexes, such as root mean square successive difference (RMSSD) and standard deviation of R-R intervals (SDRR), may be preserved in healthy older individuals[144,145].

Another factor associated with age is the deterioration of the ΔHR 30:15 ratio, which is cardiac parasympathetic modulation (CPM)[146], that provides an index of parasympathetic withdrawal. Despite its established relevance in assessing autonomic function[146], its role in BP regulation during active standing orthostatic stress has not been thoroughly investigated in older adults. To date, no studies have specifically compared the autonomic responses of younger and older adults using CPM analysis during lower and higher active standing orthostatic stress (sit-to-stand and lie-to-stand, respectively).

With age, baroreceptors (primary sensors for BP fluctuations) impaired function contributes significantly to the overall reduction in autonomic responses[12]. Evidence has shown that, in older adults, BP regulation can be challenging during standing due to the decline in baroreceptor sensitivity response[12,147,148]. Although existing literature has emphasized the key role of baroreceptors in hemodynamic regulation, studies have yet to investigate their response across specific time intervals following active standing orthostatic stress. To address this gap, our study will analyze cardiac baroreflex gain (CBG) in four distinct specific phase time points 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4), providing information about whether ANS can regulate BP or not (impaired function).

This study aims to **(1)** describe and compare HRV indexes at baseline, **(2)** CPM response immediately on standing (HR 30:15), and **(3)** CBG responses at 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4): when transitioning from (1) sit-to-stand (lower orthostatic stress challenge) and (2) lie-to-stand (higher orthostatic stress challenge). It also aims to **(4)** compare the incidence of orthostatic intolerance (OI) related symptoms between younger adults and older adults. This study was divided into 4 hypotheses, as follows: compared to younger adults, older adults will show: **(i)** a lower HRV indexes (time and frequency domains); **(ii)** greater CPM (HR 30:15) on standing, (**iii**) reduced CBG, particularly at 30 s (phase 1) and 60 s (phase 2), but no differences are anticipated at 180 s (phase 3) and 420 s (phase 4). At this point, the CBG responses are sufficient to bring hemodynamic parameters to more stable values. **(iv)** It is also hypothesized that older adults will report a higher incidence of OI symptoms than younger adults. The observed responses in older adults can be attributed to age-related deterioration in autonomic regulatory mechanisms, an imbalance between sympathetic and parasympathetic influences, increased CPM, and a reduction in baroreceptor-mediated autonomic control, resulting in a higher incidence of OI-related symptoms.

Methods

Study Design

This is an observational cross-sectional study that adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[114] (Appendix 5) and the Sex and Gender Equity in Research (SAGER)[115] (Appendix 6) reporting guidelines.

Settings

This study took place at the Applied Research Centre within the Faculty of Kinesiology and Recreation Management at the University of Manitoba between August 2022 and August 2023. Ethical approval was granted by the University of Manitoba Health Research Ethics Board (approval number - HE2022-0058).

Participants

A convenience sampling strategy was employed to recruit participants. Older adults were drawn from Dr. Todd Duhamel's database at the University of Manitoba - which comprises ~1,000 females who previously participated in the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts study - as well as from the Centre on Aging database (University of Manitoba), and in-person visits to Men's Shed and retirement or care homes in Winnipeg. For younger adults, recruitment was done by telephone, email, social media platforms (including Facebook, Instagram, and X), advertisements, flyers, posters, and word of mouth.

The sample included both male and female participants divided into two distinct age groups: younger adults (18-30 years) and older adults (60-79 years). Eligibility required that individuals have these specific age ranges and identify their sex at birth as either female or male. Participants with a history of cardiovascular conditions, such as ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, psychiatric disorders, and severe cognitive impairment, or who were pregnant, were excluded from the study.

Eighty-eight participants underwent active standing orthostatic stress challenges in two experimental conditions: sit-to-stand (Experiment 1) and lie-to-stand (Experiment 2) (Figure 6.1).

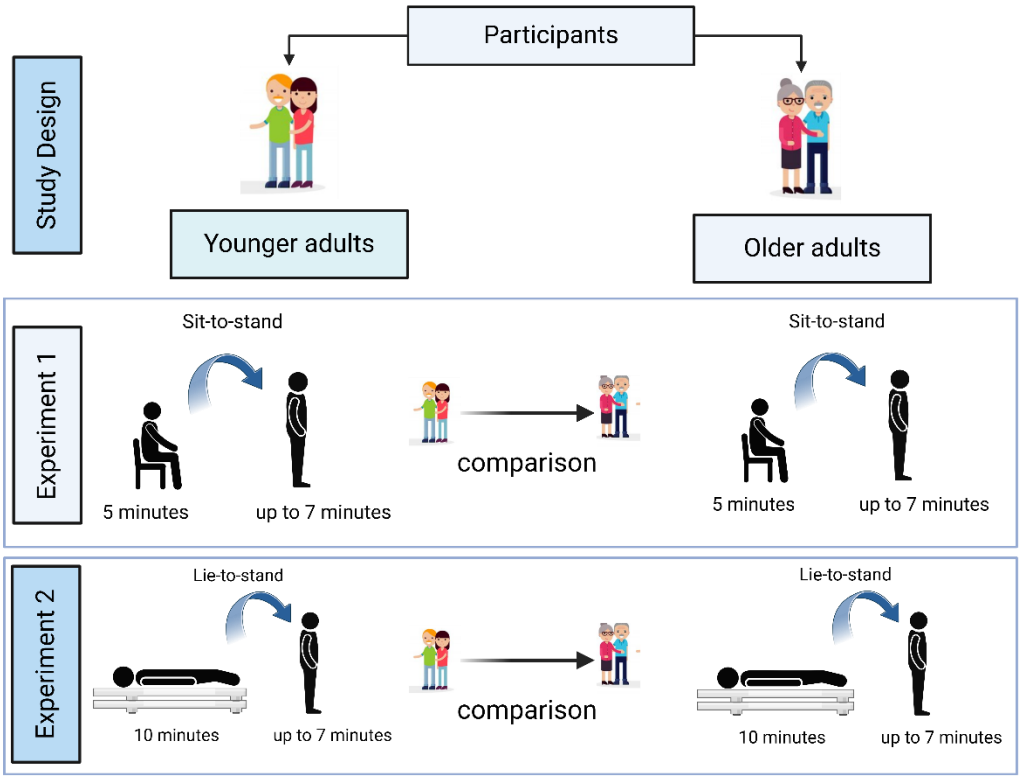

Figure 6.1 Illustration of the research design and experimental conditions (1 and 2).

Data Collection

Participants were given preparatory instructions 48 hours before their appointment. Upon arrival, they read and signed an informed consent form. Before the assessments, a trained researcher measured resting HR and BP to verify that each participant met the safety criteria outlined by the Canadian Society for Exercise Physiology (CSEP) guidelines[31].

After obtaining informed consent and completing familiarization procedures, participants performed two active standing orthostatic stress tests (sit-to-stand and lie-to-stand) with BP measured continuously on a beat-by-beat basis using a Finometer^{TM} Pro Device (Finapress Medical System BV, Amsterdam, The Netherlands). Immediately following the test, participants were questioned about any symptoms such as dizziness or light-headedness to assess orthostatic intolerance (OI). All assessments were conducted in a quiet room maintained at 22.0 ± 1.0°C with humidity and barometric pressure at ambient. Testing occurred on weekdays between 8:30 and 11:30 am to minimize circadian cycle influences. The order of the sit-to-stand and lie-to-stand conditions was randomized and counterbalanced among participants.

Demographic and Anthropometric Measurements

Demographic information, including sex assigned at birth, age, and date of birth, was collected to characterize the sample. In addition, anthropometric and body composition assessments were conducted. Body mass (kg) was measured using an InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA), and height (m) was measured using a mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was determined using the standard formula: body mass (kg) divided by height (m) squared[116].

Assessment of Heart Rate Variability, Cardiac Parasympathetic Modulation, and Cardiac Baroreflex Gain

HRV, CPM, and CBG were obtained by extracting information from the electrocardiogram (ECG) and Finometer (Finapres Medical System, Arnhem, The Netherlands)[117] and recorded using LabChart 8.0 (ADInstruments, Colorado Springs, USA) at a sampling frequency of 1 kHz. The ECG signals were subjected to a 5-30 Hz bandpass filter for R peak detection, except during the 30 seconds before and 90 seconds after standing, when the raw signal was preserved and Finometer calibration was manually disabled. Cardiovascular parameters during the sit-to-stand and lie-to-stand tests were analyzed with a custom macro for R-R interval detection; in instances of poor ECG quality, the analysis relied on the peaks from the pressure waveform instead. The R-R intervals obtained from the ECG served as the basis for HR calculation.

Arterial pressure was recorded non-invasively via photoplethysmography at the middle finger of the left hand (Finometer - Finapres Medical System, Arnhem, The Netherlands)[117]. BP calibration was initially performed using the manufacturer's standard protocol and subsequently refined through manual calibration with an automated BP monitor (ARSIMAI, BSX516, Munster, Germany). Approximately five minutes before each procedure, finger and brachial pressures were adjusted using the return-to-flow calibration. Finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments.

Systolic blood pressure (SBP) and HR data were then stored and transferred to a custom Matlab application (Matlab R2024; The MathWorks Inc, Natick, MA, USA). Once the data were imported from LabChart into the Matlab application, noise and motion artifacts were disregarded using a two-step filtering process. Initially, a median filter was applied, followed by a low-pass

filter with a cutoff frequency of 0.05 rad/sample, as determined by scalogram analysis. Lastly, a 5-second moving average filter was employed to smooth the signal and isolate the parameters of interest[96,120]. Following data import, interpolation was applied to correct for delays induced by resampling at 1 Hz. The onset of active standing was defined as time zero, with baseline values assigned as negative and positive values representing short-term compensatory responses.

Heart Rate Variability

Heart rate variability (HRV) was obtained by continuous beat-by-beat measurements during supine position using a three-lead electrocardiogram (ECG) module collected at a 1 kHz sampling rate (Finometer, Finapres Medical System, Arnhem, The Netherlands) according to guidelines from the *European Society of Cardiology and the North American Society of Pacing Electrophysiology*[149]. HRV data were analyzed in time and frequency domains using at least 5 minutes or a window of ≥ 256 beats. The HRV data was preprocessed through the HRV module (LabChart 8, ADInstruments, Colorado Springs, USA). The module detects and extracts RR intervals and automatically differentiates between normal and ectopic beats. In the time domain, mean RR intervals, the standard deviation of RR intervals (SDRR), and the root mean square of successive RR intervals (RMSSD) were assessed to evaluate the sympathetic and parasympathetic activity. Spectral analysis of frequency domain variables was calculated using the Fast Fourier transform model. Low-frequency (LF) (0.04-0.15 Hz) and high-frequency (HF) (0.15-0.45 Hz) spectral components were collected in absolute values of power (ms^2). The low-frequency/high-frequency ratio (LF/HF) was calculated from the absolute values of LF and HF.

Cardiac Parasympathetic Modulation

Cardiac parasympathetic modulation (CPM) was measured using the HR 30:15 ratio of the longest RR-interval around the 30th heartbeat and the slowest RR-interval around the 15th heartbeat after standing[146]. The HR used for the CPM calculation was obtained from the R-R intervals (ECG-module, Finometer, Finapres Medical System, Arnhem, The Netherlands). This measurement is generally used in clinical settings to assess the autonomic cardiovascular reflex function and detect early signs of autonomic dysfunctions[150,151]. It provides insight into the heart's ability to respond to stress (e.g., postural transition), which could support the diagnosis of conditions that can affect cardiovascular stability, mainly in people with underlying health issues[150,151].

Cardiac Baroreflex Gain

Cardiac baroreflex gain (CBG) was adapted from the proposed method by the Autonomic Disorders Consortium[152] by calculating the change in HR divided by the drop in SBP (ΔHR/ΔSBP ratio) divided into four distinct specific phase time points: 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4) after active standing orthostatic stress, expressed as $bpm.mmHg^{-1}$ [152]. The selected time points were chosen to capture key phases of autonomic regulation following active standing. Phase 1 represents the immediate compensatory response to counteract the initial BP drop. Phase 2 reflects early stabilization through sustained sympathetic activation. Phases 3 and 4 assess autonomic dysregulation linked to late BP regulation[24,65]. Also, this phased time-specific assessment of adaptive CBG responses identifies differences in autonomic regulation during the short-term compensatory responses. The HR used for this calculation was obtained from the R-R intervals (ECG - module, Finometer, Finapres Medical System, Arnhem, The Netherlands). SBP was obtained from the arterial pressure non-invasively via photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Calibration procedures (return-to-flow and finger and brachial arterial pressures adjustments), appropriate cuff size, and height correction system adjustments were the same as previously described. CBG assessment is typically used in clinical settings for evaluating BP regulation during active standing, identifying issues with autonomic control that could lead to orthostatic intolerance (e.g., dizziness)[153].

Sample Size

The sample size was determined a priori using the G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119], based on data obtained from an internal pilot with 16 participants and equal distribution between groups. A t-test (two independent means) comparing the differences in the CPM (HR 30:15), derived from the minimum and maximum HR observed around the 30th and 15th beats after standing, with an α level of 0.05. For the sit-to-stand experiment, the analysis indicated a statistical power of 0.81 and an effect size of 1.17, based on mean ± SD values of 0.87 ± 0.06 for younger adults and 0.93 ± 0.04 for older adults, which resulted in an estimated total sample of 20 participants (10 per group). In the lie-to-stand experiment, the estimated power was 0.80 with an effect size of 1.74, using mean ± SD values of 0.82 ± 0.07 for younger adults and 0.91 ± 0.02 for older adults, resulting in a total of 10 participants (5 per group).

Statistical Analysis

Data normality was evaluated using the Shapiro-Wilk test. Variables with a parametric distribution were expressed as mean ± standard deviation (SD) along with the corresponding 95% confidence interval (95% CI), while non-parametric variables were summarized as the median with interquartile range (IQR) and their minimum and maximum values. For sample characterization, continuous data were presented using these descriptive statistics, and categorical data were reported as absolute numbers and relative percentages. Additionally, the Chi-Square test was utilized to assess differences in categorical variables.

An unpaired Student t-test was used to compare differences between the younger adults and older adults for both the sit-to-stand and lie-to-stand conditions, while the Mann-Whitney U test was applied to non-parametric data. To control for multiple comparisons, *p*-values were adjusted using the Benjamini-Hochberg procedure with a false discovery rate of 0.05, thereby limiting the expected proportion of false positives among significant findings[125]. Significant results were reported based on the corrected *p*-values, highlighting the tests that met the adjusted threshold of $p < 0.05$.

Effect sizes were calculated using Cohen's *d* for parametric data[126] and by the *R* coefficient (non-parametric data)[127] with classifications set as low (≤ 0.05), medium (0.06-0.25), high (0.26-0.50), and very high (> 0.50)[126]. All analyses were done using R® (Version 4.1.1, Vienna, Austria).

Results

Figure 6.2 illustrates the recruitment flowchart. Eligibility was assessed using a screening questionnaire developed by our research team to evaluate each participant's health status. Due to poor signal quality, 13 participants were excluded from Experiment 1 and 12 from Experiment 2. As a result, Experiment 1 included 26 younger adults and 49 older adults, while Experiment 2 consisted of 26 younger adults and 50 older adults. HRV indexes at baseline, CPM (HR 30:15) immediately on standing, and CBG at 30 s, 60 s, 180 s, and 420 s were compared between younger adults and older adults in experiments 1 and 2.

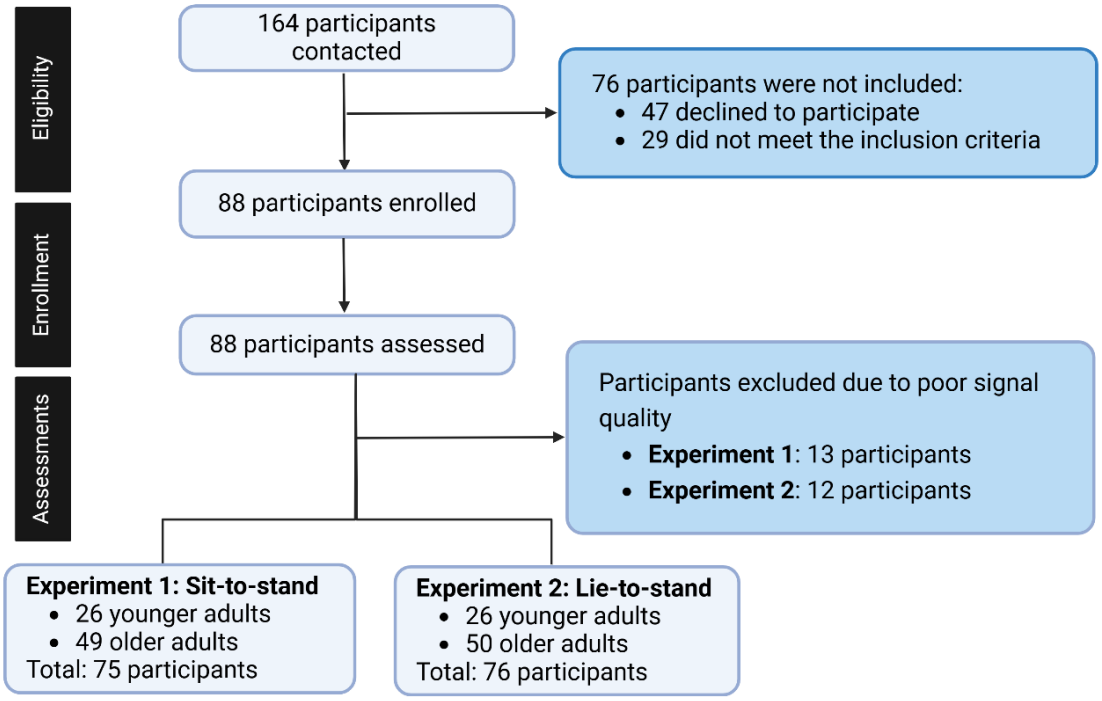

Figure 6.2 Recruitment flow chart of the study.

Table 6.1 summarizes the characteristics of younger adults (18 - 30 years) and older adults (60 - 79 years) for sex distribution, anthropometric measurements, and the incidence of OI-related self-reported symptoms. Younger adults had an equal distribution of females and males in both experiments. For experiment 1, 71.5% of the older adults were female, and 28.5% were male, whereas in experiment 2, 70% were female and 30% were male. Older adults exhibited a higher body mass index (BMI), and shorter stature compared to younger adults, although no significant differences in body mass were observed. Additionally, older adults were more likely to experience OI symptoms than younger adults.

Table 6.1 Sample characteristics of younger adults and older adults.

Variable	Younger adults			Older adults			*p*
Sex	*n*	%		*n*	%		
Experiment 1	----	----	----	----	----	----	----
Female	13	50	----	35	71.5↑	----	**<0.001***
Male	13	50	----	14	28.5	----	**<0.001***
Experiment 2	----	----	----	----	----	----	----
Female	13	50	----	35	70↑	----	**<0.001***
Male	13	50	----	15	30	----	**<0.001***
Anthropometric data	Mean ± SD	CI 95%	Min; Max	Mean ±	CI 95%	Min; Max	
Age (years)	21.0 ± 2.3	20.8; 22.6	18.0; 28.0	70.5 ± 3.9↑	69.3; 71.5	63.0; 78.0	**<0.001***
Height (m)	1.73 ± 0.07	1.69; 1.76	1.56; 1.86	1.64 ± 0.08↓	1.62; 1.66	1.46; 1.84	**<0.001***
Body mass	67.6 ± 11.9	62.9-72.2	42.6; 90.5	73.7 ± 15.4	69.4; 78.0	42.5; 110.0	0.07
BMI (kg/m^2)	22.6 ± 3.38	21.3-23.9	16.5; 30.4	27.3 ± 5.6↑	25.8; 28.9	17.1; 48.4	**<0.001***
OI symptoms[#]	*n*	%	----	*n*	%	----	
No	26	100↑	----	43	86	----	**0.041***
Yes	0	0	----	7	14↑	----	

Mean ± Standard deviation (SD); *n*: number of participants; 95% CI: 95% confidence interval; Min-Max: Minimum; Maximum; BMI: body mass index; ↓ lower than; ↑ higher than. [#]Orthostatic intolerance (OI) symptoms were evaluated during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. *Statistically significant differences.

Heart Rate Variability at Baseline in Supine Position

Table 6.2 presents the autonomic responses of HRV indexes in the time and frequency domains comparing younger adults and older adults at baseline in the supine position. There were no statistically significant differences in RR intervals between groups. However, older adults exhibited lower SDRR and RMSSD (time domain), lower LF and HF, and higher LF/HF ratio (frequency domain) compared with younger adults.

Table 6.2 Comparison of time and frequency domain heart rate variability (HRV) analyses at baseline in the supine position comparing younger adults and older adults.

HRV (time domain)				
	Younger adults	Older	*p*	ES
RR (ms)	888.7 | 316.6 (977.9; 1.01)	825.0 | 898.8 (999.7; 1.01)	0.213	-0.480
SDRR (ms)	63.9 ± 24.0 (54.1; 73.6)	36.0 ± 15.9↓ (31.5; 40.6)	**<0.001***	-1.462
RMSSD (ms)	77.7 | 51.2 (20.9; 141.0)	24.9 | 19.2↓ (7.2; 86.2)	**<0.001***	-1.758
HRV (frequency domain)				
	Younger adults	Older	*p*	ES
LF (ms)	1060.0 | 1417.7 (95.8; 5352.0)	342.3 | 460.1↓ (31.4; 2226.0)	**<0.001***	-1.029
HF (ms)	2893.0 | 3984.7 (1.0; 9555.0)	402.5 | 640.0↓ (13.1; 5756.0)	**<0.001***	-1.322
LF/HF	0.4 | 0.2 (0.0; 0.8)	0.7 | 0.9↑ (0.1; 3.6)	**0.002***	1.306

|: Interquartile range with Minimum and Maximum; HRV: heart rate variability; ES: Effect size; RR: Average interval between consecutive heartbeats (RR-intervals); SDRR: Standard Deviation of RR intervals; RMSSD**:** Root Mean Square of Successive Differences between RR intervals; LF: Low-Frequency power; HF: High-Frequency power; LF/HF: Low-Frequency to High-Frequency power ratio: HR: heart rate. ↓ lower than; ↑ higher than. *Statistically significant differences.

Cardiac Parasympathetic Modulation Responses During Active Standing Orthostatic Stress

Figure 6.3 shows the CPM comparison between younger adults and older adults during the sit-to-stand and lie-to-stand transitions. During the sit-to-stand test, CPM was exhibited as median values with interquartile range. Older adults had a significantly lower CPM (1.07, IQR: 0.08) compared to younger adults (1.18, IQR: 0.16) ($p < 0.001$). During the lie-to-stand test, CPM was expressed as a mean ± SD. Older adults showed a lower CPM of 1.07 ± 0.09 than younger adults (1.28 ± 0.16; $p < 0.001$).

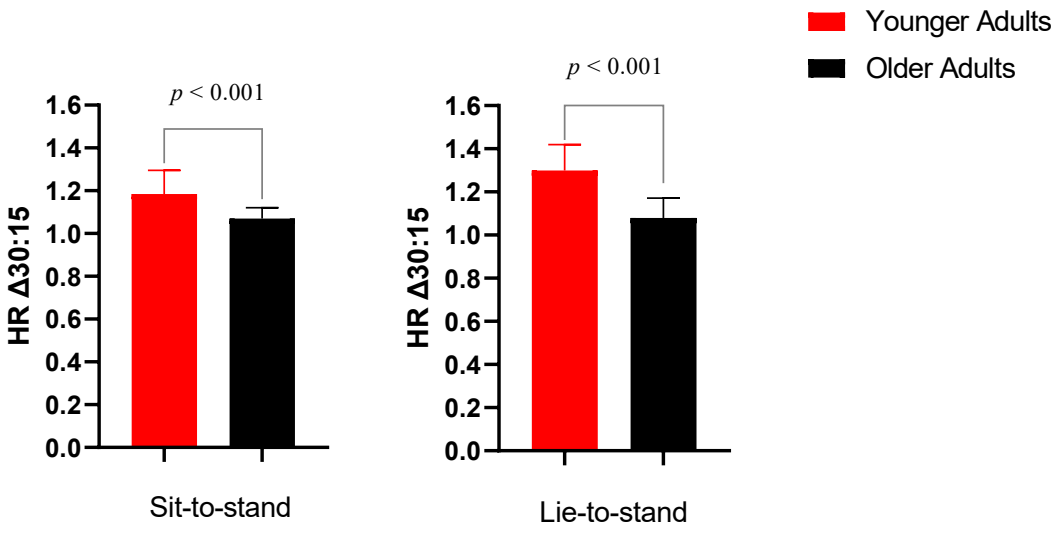

Figure 6.3 Cardiac parasympathetic modulation (CPM) comparison between younger adults and older adults during the sit-to-stand and lie-to-stand transitions.

Cardiac Baroreflex Gain Responses During Active Standing Orthostatic Stress Across Specific Phase Time Points

In the sit-to-stand transition, no differences in phase 1 (0-30 s) were observed between groups. However, older adults showed lower CBG values from phases 2-4 (30-420 s). In the lie-to-stand, older adults showed lower CBG values in phases 3 (60-180 s) and 4 (300-420 s), but no differences in phases 1 (0-30 s) and 2 (30-60 s) (Table 6.3).

Table 6.3 Comparison of the short-term cardiac baroreflex gain during sit-to-stand and lie-to-stand between younger adults and older adults across phases.

		Sit-to-Stand			
Variable	**Group**	**Phase 1**	**Phase 2**	**Phase 3**	**Phase 4**
CBG (bpm.mmHg^{-1})	Younger adults	0.6 | 0.2 (0.4; 1.1)	0.6 | 0.2 (0.4; 1.1)	0.7 | 0.1 (0.5; 1.1)	0.7 | 0.2 (0.5; 1.0)
	Older adults	0.5 | 0.1 (0.3; 0.9)	0.5 | 0.1↓ (0.3; 0.9)	0.5 | 0.1↓ (0.3; 0.8)	0.6 | 0.9↓ (0.3; 0.8)
	Adj *p*	0.10	**0.0013***	**0.0013***	**0.0013***
	ES	0.2	0.4	0.7	0.7
		Lie-to-Stand			
Variable	**Group**	**Phase 1**	**Phase 2**	**Phase 3**	**Phase 4**
CBG (bpm.mmHg^{-1})	Younger adults	0.5 | 0.1 (0.4; 1.4)	0.6 | 0.1 (0.4; 1.2)	0.6 | 0.2 (0.5; 1.1)	0.7 | 0.1 (0.4; 1.2)
	Older adults	0.5 | 0.1 (0.3; 1.0)	0.5 | 0.1 (0.3; 1.1)	0.5 | 0.1↓ (0.3; 0.9)	0.5 | 0.1↓ (0.3; 1.0)
	Adj *p*	0.6	0.06	**0.002***	**0.002***
	ES	0.07	0.3	0.5	0.7

|: Interquartile range with Minimum and Maximum; CBG: cardiac baroreflex gain; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than. *Statistically significant differences between younger adults and older adults.

Discussion

This study examines the phase-specific autonomic short-term compensatory responses in younger adults and older adults during two distinct active-standing orthostatic stress tests: sit-to-stand and lie-to-stand. To our knowledge, this is among the first studies to compare CPM and CBG across distinct specific phase time points of younger and older adults following active-standing orthostatic stress. The main findings of this study indicate that older adults had reduced autonomic activity measured through HRV indexes, lower CPM, lower CBG from phases 2-4, and higher symptoms of OI.

Heart Rate Variability Responses

In the time domain analysis, there were no statistically significant differences between older adults and younger adults in RR intervals during both transitions. Kawaguchi et al.[111] reported no statistically significant differences in RR intervals at baseline between older adults and younger adults, supporting the results of the current study. Additionally, in this study, older adults exhibited lower SDRR and RMSSD compared to younger adults in both conditions, which corroborated the results of Grassler et al.[129] and Kawaguchi et al.[111].

The reduced SDRR and RMSSD observed in older adults in our study indicate a decline in HRV indexes, which is commonly associated with diminished parasympathetic modulation[38]. Our data shows significantly lower SDRR and RMSSD values in older adults compared to younger adults, supporting the understanding of reduced vagal tone in older adults[154]. This diminished vagal tone is particularly relevant during postural transitions, where parasympathetic withdrawal and sympathetic activation must occur in a coordinated manner to maintain autonomic regulation[38].

In the frequency domain, our results showed that older adults exhibited lower LF and HF power compared to younger adults in both postural transitions, along with a higher LF/HF ratio. These findings align with those of Grassler et al.[129], who reported significantly reduced LF and HF power in older adults compared to younger adults. Similarly, Kawaguchi et al.,[111] also observed that older adults had lower LF and HF compared to younger individuals, along with a higher LF/HF ratio in older adults than in younger adults. The reduction in LF and HF power in older adults suggests an overall decline in autonomic activity[38]. A lower LF indicates reduced sympathetic modulation

and diminished baroreflex sensitivity, while a lower HF reflects impaired parasympathetic activity[155]. The higher LF/HF ratio observed in older adults' points to a shift towards sympathetic dominance and reduced vagal tone. This shift is associated with reduced CBG and a greater likelihood of OI, as observed in our results.

Cardiac Parasympathetic Modulation

The Δ30:15 ratio, a marker of parasympathetic (vagal) reflex engagement, was analyzed in this study, being the first comparison of this variable between older adults and younger adults. In both conditions, older adults exhibited a lower CPM compared to younger adults. The reduced Δ30:15 ratio observed in older adults in our study suggests a slower withdrawal of parasympathetic tone and delayed activation of the sympathetic nervous system during active standing orthostatic stress. This autonomic imbalance impairs the rapid cardiovascular adjustments necessary to maintain adequate perfusion pressure, particularly during the early phases of orthostatic stress[16,24]. The reduced ability to promptly engage in sympathetic activity compromises HR and vascular resistance responses[132]. This might contribute to greater transient drops in BP and increase the risk of OH and OI-related symptoms in older individuals[16].

Cardiac Baroreflex Gain Responses Across Specific Phase Time Points During Active Standing Orthostatic Stress

It was observed in this study that older adults exhibited significantly lower CBG compared to younger adults from phases 2 to 4 (30 s to 420 s) during sit-to-stand and from phases 3 and 4 (180 s - 420 s) during lie-to-stand. Evidence demonstrates consistent results reporting that older adults had lower CBG compared to younger adults at the 5th minute after lie-to-stand[131] using a sequence method analysis[156], and the Valsalva maneuver[157].

In the present study, the observed decline in CBG among older adults during the later phases of both sit-to-stand and lie-to-stand transitions is primarily driven by age-related impairments in baroreceptor function, arterial compliance, and autonomic regulation[12]. Age is associated with increased arterial stiffness, particularly in the carotid sinus and aortic arch, which reduces the mechanosensitivity of baroreceptors and impairs their ability to detect and respond to acute fluctuations in BP[24]. This diminished mechanotransduction results in a blunted baroreflex response, as evidenced by Monahan et al.,[157] who demonstrated a strong positive relationship between carotid artery compliance and cardiovagal baroreflex sensitivity. Additionally, age-related alterations

in neural integration within the nucleus tractus solitarius (NTS) and reduced vagal efferent responsiveness contribute to delayed and attenuated HR adjustments during postural stress[35]. The findings by Lai et al.[156] and Kim et al.[158] further support this physiological mechanism, highlighting significantly lower baroreflex sensitivity in older adults compared to younger individuals.

Symptoms of Orthostatic Intolerance

The comparison of OI symptoms between younger adults and older adults is limited in the literature, making direct age-group analyses challenging. In this study, older adults exhibited a higher prevalence of OI symptoms (14%) compared to younger adults (0%). Given the scarcity of direct comparisons, the discussion will focus on the physiological mechanisms underlying this difference. The higher OI-related symptoms indicate an age-related decline in cardiovascular-autonomic regulation. This disparity suggests that age is associated with impairments in baroreflex sensitivity[156], reduced parasympathetic modulation[35], and diminished vascular response[16], all of which contribute to compromised hemodynamic stability during postural transitions. The increased susceptibility to OI symptoms in older adults may reflect attenuated compensatory mechanisms, including delayed vasoconstriction and inadequate cardiac output adjustments[16,24], leading to transient cerebral hypoperfusion and symptomatic manifestations. This impairment contributes to the higher prevalence of OI-related symptoms in older adults, as a reduced autonomic response can delay cardiovascular adjustments, increasing susceptibility to dizziness or lightheadedness upon standing, which likely increases the risk of fainting and falls.

Limitations

Some limitations could be observed when analyzing the findings. Although HRV was assessed using both time- and frequency-domain measures, these analyses were conducted only at baseline, which may not fully observe the autonomic fluctuations in active standing orthostatic stress. The use of short-term or ultra-short HRV analyses could provide additional insights into the dynamic interplay between sympathetic and parasympathetic modulation in response to active standing orthostatic stress. Future studies may incorporate these approaches and could offer a more detailed characterization of autonomic regulation.

CBG was assessed at specific time points (30 s, 60 s, 180 s, and 420 s), which may not fully show the continuous fluctuations in baroreflex function throughout the active

standing orthostatic stress. While this approach provides information on the short-term compensatory responses at key times during active standing orthostatic stress, it may not account for transient variations or phase-dependent adaptations. Alternative methodologies, such as the sequence method[153], which detects spontaneous changes in SBP and RR intervals to estimate baroreflex sensitivity in real-time, or transfer function analysis[153], which evaluates baroreflex function across different frequency bands, could offer a more comprehensive representation of baroreflex regulation.

Conclusion

In conclusion, older adults had their autonomic regulation significantly affected by active standing orthostatic stress than younger adults. Older adults demonstrated higher parasympathetic activity measured through HRV indexes, lower CPM, reduced CBG, and higher symptoms of OI during active standing orthostatic stress. These findings indicate that autonomic compensatory mechanisms are impaired in older adults, leading to a reduced ability to regulate BP and maintain cerebral perfusion during postural transitions. This impairment likely contributes to the higher prevalence of OI symptoms in older adults (14%) compared to younger adults (0%), as the diminished autonomic response may result in delayed cardiovascular adjustments, increasing susceptibility to dizziness or lightheadedness on standing.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study demonstrated that age is associated with significant impairments in autonomic short-term compensatory responses to orthostatic stress. Older adults exhibited reduced HRV indexes, lower CPM, and decreased CBG, particularly in the later recovery phases, compared to younger adults. These results suggest a shift toward sympathetic dominance and diminished baroreflex sensitivity in older adults, contributing to impaired regulation of HR and BP during postural transitions. Notably, older adults also had a higher incidence of orthostatic intolerance symptoms. The integration of HRV, CPM, and BRG analyses enhances our understanding of the mechanisms underlying autonomic dysregulation in older adults. These findings support the need for targeted interventions to improve autonomic function and reduce the risk of orthostatic-related impairments in older populations.

7. Chapter 7

Two paths, one outcome: sex-specific short-term cardiovascular compensatory responses of older adults on standing

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This chapter focuses on sex-specific differences in cardiovascular short-term compensatory responses to orthostatic stress in older adults. Building on the findings of previous chapters, this study compares older female and male participants during sit-to-stand and lie-to-stand transitions, with a detailed phase-specific analysis of blood pressure regulation, cardiac output, stroke volume, systemic vascular resistance, and cardiac-autonomic matching. I was responsible for designing the study, conducting all participant assessments, performing data analysis, and drafting and revising the manuscript. This work advances the understanding of how sex interact to influence hemodynamic responses during postural transitions and provides a critical perspective on the physiological diversity within older populations.

Publication Status

This study will be submitted to Clinical Geriatric Medicine.

Abstract

This study compared short-term cardiovascular compensatory responses in female and male older adults during postural transitions. The prevalence of orthostatic hypotension (OH) and orthostatic intolerance-related (OI) symptoms were also compared between sexes. Participants underwent two active standing orthostatic stress tests, involving 5 minutes of sitting or 10 minutes of lying, followed by up to 7 minutes of standing. Continuous beat-to-beat systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR) (Finometer-Finapress), and heart rate (HR, electrocardiogram) at baseline, immediately on standing, and across four specific phases: phase 1 (0-30s), phase 2 (30-60s), phase 3 (60-180s), phase 4 (300-420s) were measured. The timing of BP regulation was assessed through CO-SVR correlation. Baseline SBP, DBP, MAP, SVR, and HR were similar between sexes, but CO and SV were lower in females. On standing, SBP, DBP, MAP, and SVR drops were similar between sexes, but females exhibited lower CO and SV peak values in both transitions. In females, CO remained lower across all phases (1-4), but DBP (phase 4) and SVR (phases 3-4) were higher than in males. BP stabilization occurred within 30-60s in females and 0-30s in males, particularly under higher orthostatic stress. The prevalence of OH and OI symptoms was not different between sexes. In conclusion, despite similar BP responses between sexes, older females exhibit lower CO and SV, compensated by higher SVR, whereas males rely more on CO adjustments, showing sex-specific regulatory mechanisms in orthostatic BP control.

Keywords: Older females, older males, orthostatic stress, blood pressure regulation, sex differences

Introduction

Standing up from a bed or chair is one of the most frequent daily movements[159], with individuals performing approximately 50–60 sit-to-stand transitions each day[160,161]. Although this may seem simple, it poses a significant challenge to the body's ability to maintain physiological homeostasis[162]. Failure to quickly adapt to such activities can lead to serious life-threatening and hazardous conditions, including chronic diseases and falls[19]. For example, standing up abruptly can cause a sudden drop in blood pressure (BP), known as orthostatic hypotension (OH)[19]. This leads to reduced cerebral perfusion and blood flow to the brain, which can result in orthostatic intolerance[163] (e.g., dizziness, nausea, and fainting). The dynamic adaptive integrative responses of the body's physiological systems to these activities are crucial for survival, as they require complex adjustments to meet the physiological demands and maintain necessary function, which is probably sex-dependent.

Generally, females are more prone to OH than males[19]. This susceptibility is partly due to sex-related differences in BP regulation, which is observed in the cardiovascular system. Females typically have smaller hearts, which correlates with lower cardiac output (CO) and diminished venous return[164]. Venous return is crucial for maintaining BP regulation, and its reduction is a key factor contributing to the higher incidence of OH, particularly in young females compared to age-matched males[164]. While OH is generally more prevalent with advancing age, age-related physiological adaptations may influence its manifestation in older adults. Interestingly, research by Edgell et al.[165] suggests that older females may exhibit higher venous return compared to their younger counterparts, potentially explaining a lower incidence of OH in older females. Moreover, the literature presents inconsistent findings regarding systemic vascular resistance (SVR)[5,122]. Some studies have reported that older females exhibit higher SVR at rest compared to older males[122]. In contrast, other research has found no significant sex differences in SVR among older adults[5].

Several hypotheses have been proposed to elucidate the differences in cardiovascular regulation between females and males and why females experience a higher incidence of OH[19,122]. However, the literature is scarce regarding the association between short-term cardiovascular compensatory responses after orthostatic stress in subsequent time intervals and sex differences[121]. Previous research comparing older females and males has analyzed BP recovery responses at specific 10-second epochs during the sit-to-stand transition as the orthostatic stress challenge[5]. However, despite

assessing BP at specific time points, that study did not evaluate key hemodynamic variables such as SV and CO, which are essential for understanding the integrated cardiovascular response to postural transitions. Moreover, the lie-to-stand transition was not analyzed, which limits the broader applicability of the findings due to the distinct physiological demands this posture change imposes compared to sit-to-stand, reducing the generalizability across different types of orthostatic stress. Therefore, it is still unclear whether and why older females have higher OH and if this is due to attenuated responsiveness in the cardiovascular responses that underlie BP regulation under orthostatic challenges.

In older adults, the match between CO and SVR after postural transitions may differ between females and males. Normally, CO increases as blood shifts to the thorax, while a drop in SVR leads to a temporary decrease in BP[49]. In healthy young adults, this thoracic blood pooling results from leg vasoconstriction and contributes to a transient rise in CO that helps stabilize BP[49]. Around 15-20 seconds after standing, BP recovers as CO and SVR adjustments match[49]. However, whether this matching process differs between older females and males remains poorly understood. Comparing these sex-specific recovery responses is essential for understanding the time that BP regulates in older females and males.

This study aims to describe and compare the short-term cardiovascular responses between community-dwelling older females and males (60–79 years) during postural transitions. **(1)** Baseline values, **(2)** cardiovascular responses immediately on standing, and **(3)** short-term compensatory changes in SBP, DBP, MAP, CO, HR, SV, and SVR were assessed during sit-to-stand (lower orthostatic stress) and lie-to-stand (higher orthostatic stress). The short-term cardiovascular compensatory responses were analyzed across four specific phases: phase 1 (0–30 s), phase 2 (30–60 s), phase 3 (60–180 s), and phase 4 (300–420 s). This study also examines **(4)** CO-SVR matching between groups in both transitions and **(5)** the incidence of OH and OI-related symptoms. The hypotheses are divided into five specific points. **(i)** Baseline: females will show higher SBP, DBP, MAP, and SVR than males due to reduced estrogen, compromising vascular function, increased arterial stiffness, and diminished vascular compliance. HR will be higher in older females, possibly compensating for a lower SV to maintain CO. **(ii)** Immediately on standing: older females will have a greater transient drop in SBP, DBP, MAP, and SVR and lower HR, CO, and SV peak values compared to males due to impaired vasoconstriction and increased vascular stiffness. **(iii)** Short-term cardiovascular

compensatory responses: older females will have reduced SBP, DBP, MAP, and SVR in phase 1 (0-30 s) due to delayed compensatory responses (e.g., vasoconstriction and venous return) than males. No significant differences are expected from phases 2 to 4, as cardiovascular compensatory responses stabilize by phase 2. In older females, CO, HR, and SV responses will be lower and delayed in phases 1 and 2 compared to males, reflecting greater parasympathetic dominance and slower sympathetic activation. No significant differences are expected in phases 3 and 4, as sympathetic drive and venous return normalize CO, HR, and SV responses. **(iv)** CO and SVR matching will be delayed in older females, occurring in phase 2 (30-60 s) instead of phase 1 as compared to males due to increased vascular stiffness. **(v)** Older females will exhibit a higher incidence of OH and symptoms of OI than males.

Methods

Study design

This observational cross-sectional study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[114] (Appendix 7) and the Sex and Gender Equity in Research (SAGER)[115] (Appendix 8) reporting guidelines.

Settings

The study took place at the Applied Research Centre, University of Manitoba, between August 2022 and August 2023. Ethical approval was granted by the University of Manitoba Health Research Ethics Board (approval number HE2022-0058).

Participants

Participants were selected using a convenience sampling method. Older adults with different frailty levels were sourced from several channels, including Dr. Todd Duhamel's database at the University of Manitoba, which comprises ~1000 females from the Women's Advanced Risk-assessment in Manitoba (WARM) Hearts study - the Centre on Aging database, Men's Shed, and retirement or care facilities in Winnipeg. Individuals interested in joining the study contacted the research team directly via email or phone.

The sample was composed of age-matched older females and males (60-79 years old) who underwent sit-to-stand (experiment 1) and lie-to-stand (experiment 2) orthostatic stress challenges in a randomized and counterbalanced order (Figure 7.1). Variables regarding baseline, immediate responses on standing, dynamic short-term cardiovascular compensatory responses (phases 1-4), CO and SVR matching, and OH prevalence and OI-related symptoms were compared between older females and males in

experiments 1 and 2. Exclusion criteria included a history of ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, psychiatric disorders, and severe cognitive impairment. Medications were recorded but not controlled (Appendix 4). All participants reported not doing hormone replacement therapy.

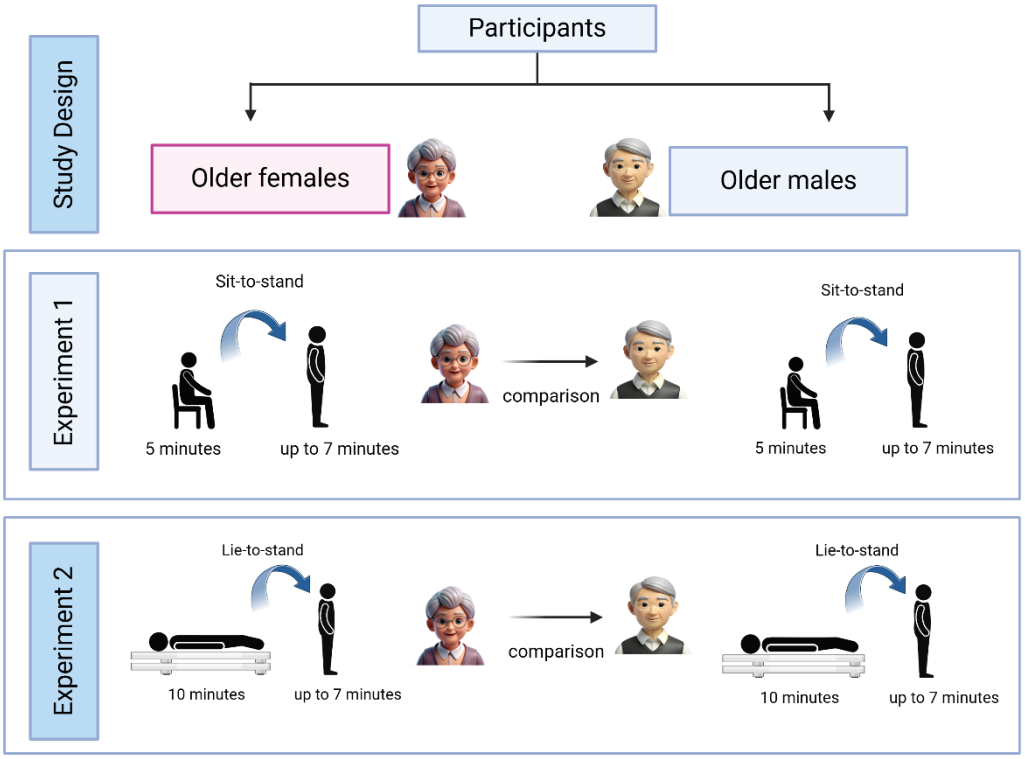


Figure 7.1 A framework for comparative research design involving two groups.

Data Collection

Participants received preliminary instructions 48 hours prior to their laboratory visit. Upon arrival, and after all inquiries were satisfactorily addressed by the research team, participants provided written informed consent. A trained researcher then measured resting HR and BP following the Canadian Society for Exercise Physiology (CSEP) guidelines[31]. Baseline SBP, DBP, and HR were measured using a digital BP monitor (ARSIMAI, BSX516, Munster, Germany). Following consent and familiarization, participants completed active standing orthostatic stress tests with non-invasive, beat-by-beat BP monitoring using a Finometer^{TM} Pro Device (Finapress Medical System BV, Amsterdam, The Netherlands). Immediately after testing, participants were asked to report any symptoms, such as dizziness or light-headedness, to assess for OI. All procedures were conducted in a quiet room maintained at 22.0 ± 1.0°C, with barometric

pressure and humidity at ambient. The orthostatic stress tests were scheduled on weekdays between 8:30 and 11:30 a.m. to minimize the influence of the circadian cycle.

Demographic and Anthropometric Measurements

To characterize the sample, demographic information (including sex assigned at birth, age, and date of birth), along with anthropometric and body composition data, were collected. Body mass (kg) was measured using an InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA), and height (m) was determined with a SECA mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by the square of their height in meters (kg/m^2)[116].

Definition of Short-Term Orthostatic Blood Pressure Recovery Responses

OH was classified into four types based on BP response during active standing, as proposed by Van Wijnen et al.[49], using beat-to-beat data. Normal BP recovery (NBP) was defined as SBP returning to baseline without a drop exceeding 20 mmHg within the first 30 seconds after standing. Initial orthostatic hypotension (IOH) was characterized by a transient SBP drop of > 40 mmHg within the first 15 seconds, followed by full recovery within 30 seconds. Delayed BP recovery (DBPR) was diagnosed when SBP required more than 30 seconds to return to baseline, with a drop exceeding 20 mmHg without meeting the criteria for sustained orthostatic hypotension (SOH). SOH was classified as a sustained SBP reduction of ≥ 20 mmHg between 60 and 180 seconds after standing, accompanied by supine hypertension (supine SBP ≥ 160 mmHg)[49].

Assessment of Cardiovascular Responses

HR was continuously recorded on a beat-by-beat basis using a 3-lead electrocardiogram (ECG) module (Finapres Medical System, Arnhem, The Netherlands) at a sampling frequency of 1 kHz, with HR calculated from R-R intervals (Labchart 8.0, ADInstruments, Colorado Springs, CO, USA). Cardiovascular responses were measured noninvasively using a cardiovascular monitor that assessed arterial pressure at the finger (Finometer, Finapres Medical System, Arnhem, The Netherlands). Continuous beat-by-beat measurements of SBP, DBP, and MAP were obtained from the arterial pressure signal using photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Calibration was performed ~5 minutes before each procedure using the return-to-flow method to align finger pressure with brachial pressure. Finger circumference was measured to select the appropriate cuff

size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments. CO was estimated using a model flow algorithm (Finometer, Finapres Medical System, Arnhem, The Netherlands)[118]. SV was calculated by dividing CO by HR and multiplying by 1000 (SV = CO/HR × 1000). SVR was calculated by dividing MAP by CO, as expressed by the formula SVR = MAP/CO.

Sample Size

The sample size was estimated a priori using G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119]. A *post-hoc* power analysis (a posteriori) was conducted with the total sample to assess the power of the sample size for analyzing sex differences in postural transitions. These measurements were obtained from the amplitude over or undershoot measured within 30 seconds after the drop (nadir). For sit-to-stand, the mean and standard deviation (SD) values for the older females were (2.5 ± 6.14 mmHg) and for older males (5.1 ± 6.14 mmHg), having an effect size of 0.35 and an achieved power of 0.29. For lie-to-stand, older females had (-2.6 ± 9.79 mmHg) and older males (-2.7±11.1 mmHg), with an effect size of 0.009 and an achieved power of 0.05.

Data Analysis

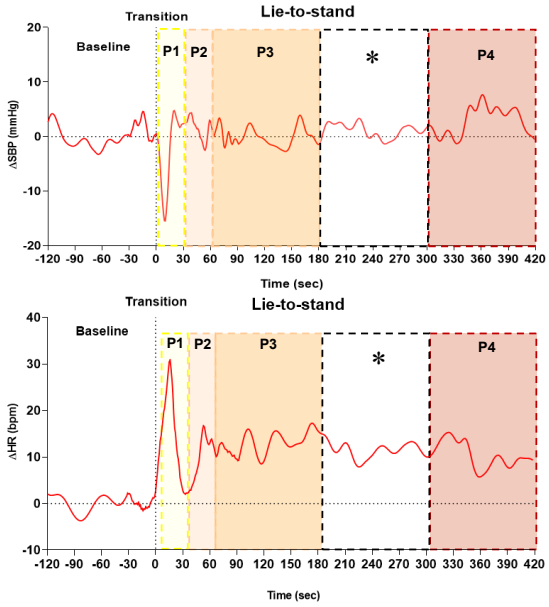
Data from the Finometer were recorded and processed on a beat-by-beat basis using LabChart 8.0 (ADInstruments, Colorado Springs, CO, USA). ECG data were filtered with a 5–30 Hz bandpass for R-peak detection, except during the 30 seconds before and 90 seconds after standing, when the raw signal was preserved, and Finometer calibration was manually disabled. Cardiovascular variables during the lie-to-stand and sit-to-stand transitions were analyzed using a custom macro for R-R interval detection. For poor-quality ECG traces, analysis was performed on the finger pressure waveform following the same detection principles. BP was calibrated using the Finometer standard procedure, followed by manual calibration with an automated BP monitor (ARSIMAI, BSX516, Munster, Germany) to correct any discrepancies. CO was calculated using the model flow algorithm[118], and the data were exported to a custom Matlab app (Matlab R2024; The MathWorks Inc, Natick, MA, USA) for further analysis.

After importing LabChart data into the Matlab app, noise and motion artifacts were removed using a median filter followed by a low-pass filter with a cut-off frequency of 0.05 rad/sample based on scalogram analysis. A 5-second moving average filter was

applied to smooth the data and extract the parameters of interest[96,120]. The data were then interpolated and corrected for delays caused by resampling at 1 Hz.

Variables Extracted and Analyzed During Active Standing Orthostatic Stress

Baseline measurements were obtained by averaging data from two minutes before standing up. Within the initial 30 seconds of standing, the lowest values for SBP, DBP, MAP, and TPR (Δ drop) and the highest values for HR, CO, and SV (Δ peak) were identified. The subsequent short-term compensatory responses were characterized by the highest values reached following the drop (nadir) and divided into four specific phases: phase 1 (0–30 s), phase 2 (30–60 s), phase 3 (60–180 s), and phase 4 (300–420 s), showing the cardiovascular regulation following active standing. This phased framework aligns with established physiological responses in healthy adults and OH classifications[121,122], facilitating a more comprehensive evaluation of adaptive responses and sex-related responses in cardiovascular regulation (Figure 7.2).



Phases	Time	Expected physiological responses
1	0-30 s	• Baroreceptor activation • Abruptly transient increase in HR • BP drops and then, overshooting over the baseline • Matching in CO and SVR • Slight decrease in SV
2	30-60 s	• Parasympathetic nervous system is activated • BP begins to drop • CO and HR decrease • Increase in SVR and SV
3	60-180 s	• BP, CO, SVR, and SV return to similar levels as baseline • HR remains elevated above the supine levels
4	300-420 s	• BP, CO, SVR, and SV remain close to the baseline measurement • HR stays above the baseline measurement

Figure 7.2 Illustration of systolic blood pressure (ΔSBP, top) and heart rate (ΔHR, bottom) responses during the lie-to-stand transition, split into four phases: phase 1 (0–30 s), phase 2 (30–60 s), phase 3 (60–180 s), and phase 4 (300–420 s) after transition. The unshaded interval (180-300 s) represents a stabilization period similar to phase 3, therefore, it was excluded from the analysis. However, phase 4 continues in the analysis as it represents a higher incidence of delayed orthostatic hypotension[123,124].

Statistical Analysis

The Shapiro-Wilk test was used to assess data normality. Continuous variables with a parametric distribution were reported as mean ± SD and 95% confidence interval (95% CI), while non-parametric continuous variables were presented as median,

interquartile range (IQR), and minimum and maximum values. For sample characterization, continuous variables were summarized as mean, SD, 95% confidence interval (CI), and minimum and maximum values. Categorical data were presented as absolute numbers and percentages. Fisher's exact test was used to compare categorical variables. An unpaired Student's t-test was used to compare the groups when data followed a parametric distribution. For non-parametric data, the Mann-Whitney U test was applied. Multiple hypothesis testing was adjusted using the Benjamini-Hochberg procedure, with a false discovery rate (FDR) of 0.05 to control for false positives.[125] Significant results were reported based on corrected *p*-values with significance set at < 0.05. The effect size was calculated for continuous variable measurements[126]. For parametric data, Cohen's *d* was used, while the *R* coefficient was applied for non-parametric data[127]. Effect sizes were categorized as low (≤ 0.05), medium (0.06-0.25), high (0.26-0.50), and very high (> 0.50). Correlations between CO and SVR in phases 1 (0-30 s), 2 (30-60 s), 3 (60-180 s), and 4 (300-420 s) were analyzed using Pearson or Spearman correlation, depending on data distribution. Correlation magnitudes were interpreted as small ($r = 0.10$-0.29), medium ($r = 0.30$-0.49), and large ($r \geq 0.50$)[126]. All statistical analyses were performed in R® (Version 4.1.1, Vienna, Austria).

Results

Eligibility criteria were assessed using a screening tool developed by our research team to evaluate participants' health profiles. Due to poor signal quality, data from 11 participants were excluded from the analysis in the sit-to-stand transition, where the final sample size was 49 participants (14 older males and 35 older females). In the lie-to-stand transition, 10 participants were excluded, resulting in a final sample size of 50 participants (35 older females and 15 older males) (Figure 7.3).

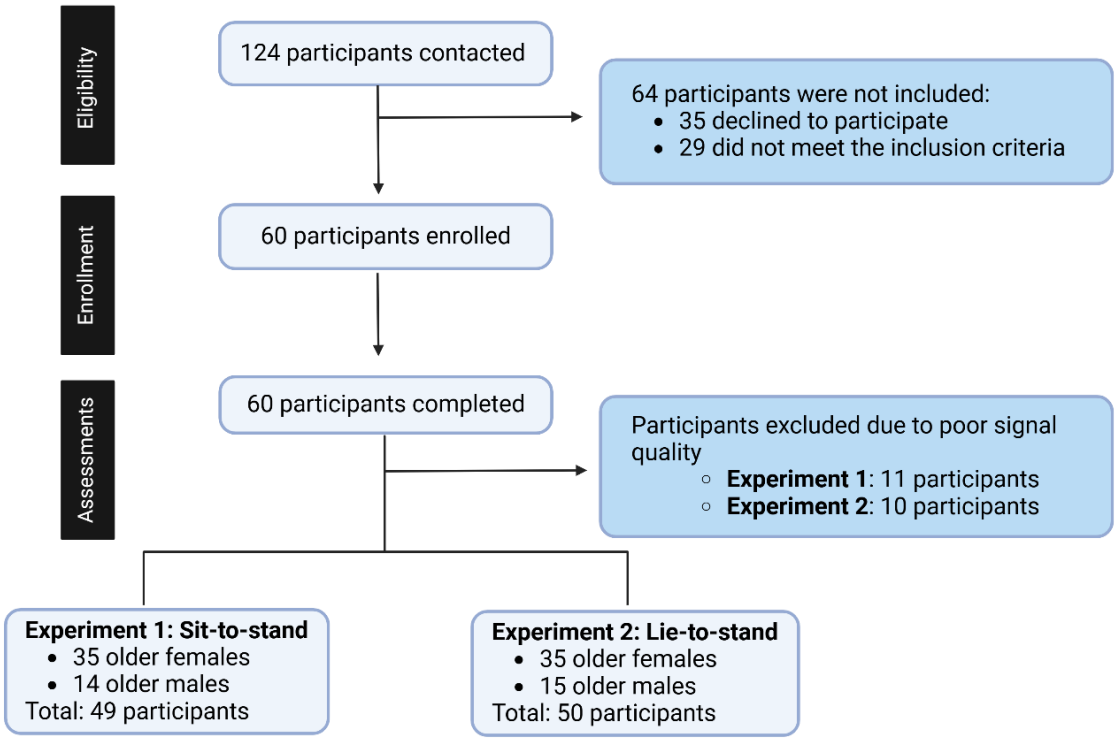


Figure 7.3 Recruitment flow chart of the study.

Older females were shorter and had lower body mass compared to older males. BMI did not differ between groups. Regarding cardiovascular variables, baseline SBP, DBP, and HR did not differ between sexes. In terms of OH classification, the distribution of NBP, IOH, and DOH was similar between groups. Neither older females nor older males were classified with SOH. The prevalence of OI symptoms did not differ between older females and males (Table 7.1).

Table 7.1 Sample characteristics of older females and older males (60-79 years old).

Variable	Female			Male			*p*
Antropometric	Median |	Min	Max	Median |	Min	Max	
Age	71 | 6	63.0	78.0	72 | 5.5	64.0	77.0	0.3
Height (m)	1.6 | 0.1↓	1.5	1.7	1.7 | 0.1	1.5	1.8	**<0.001***
Body mass (kg)	67.2 | 17.7↓	42.5	109.0	82.8 | 10.3	68.4	110.0	**<0.001***
BMI	25.7 | 7.4	17.1	48.4	27.9 | 4.4	24.5	36.6	0.06
Hemodynamic							
Rest SBP	128 | 20	108	154	130 | 21	110	150	0.7
Rest DBP	78 | 14	56	92	80 | 4	72	90	0.3
Rest HR	68 | 12	52	92	64 | 16	52	92	0.06
*OH Classification***	*n* = 35	%	----	*n* = 15	%	----	
NBP	6	17	----	2	13.4	----	1.0
IOH	8	23	----	3	20	----	1.0
DOH	21	60	----	10	66.6	----	0.8
SOH	0	0	----	0	0	----	---
OI symptoms#	*n* = 35	%	----	*n* = 15	%	----	
No	31	87	----	12	75	----	0.41
Yes	4	13	----	3	25	----	

|: Interquartile range with Minimum and Maximum; 95% CI: 95% confidence interval; Min-Max: Minimum; Maximum; BMI: body mass index; OH: orthostatic hypotension; NBP: normal blood pressure; IOH: initial orthostatic hypotension; DBPR: delayed blood pressure recovery; SOH: sustained orthostatic hypotension. ↓lower than. **OH classification was based on the criteria outlined by Van Wijnen et al.[49], specifically analyzing SBP during the lie-to-stand transition. #Orthostatic intolerance (OI) symptoms were assessed during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. *Statistically significant differences.

Baseline Responses During Active Standing Orthostatic Stress

At baseline, in both transitions, no differences were observed between older females and males for SBP, DBP, MAP, SVR, and HR. However, older females exhibited lower CO and SV compared to males (Tables 7.2 and 7.3).

Immediately On Standing Responses During Active Standing Orthostatic Stress

In sit-to-stand, SBP, DBP, MAP, SVR, and HR amplitude changes were similar between groups, while older females showed a lower CO and SV peak compared to older males (Table 7.2). After lie-to-stand, there were no statistically significant differences in SBP, DBP, MAP, SVR, HR, CO, or SV between older females and males. Both groups demonstrated similar responses in the amplitude drop or peak values (Table 7.3).

Short-term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress Across Phases

During sit-to-stand responses, SBP, MAP, HR, and SV were similar between older females and males across all phases. For DBP, no differences were observed from phases 1 through 3, but older females demonstrated a higher DBP response in phase 4 than older males. SVR responses were similar in phases 1 and 2, whereas older females exhibited significantly greater compensatory responses in phases 3 and 4 compared to older males. CO was lower in older females across all phases, reflecting a smaller compensatory response compared to older males (Table 7.2).

Table 7.2 Comparison of baseline, amplitudes, and short-term cardiovascular compensatory responses across phases during sit-to-stand between older females and males.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Older females	125.2 | 12.4 (102.3; 148.3)	20.3 | 12.8 (8.6; 39.7)	1.5 | 9.0 (-15.7; 21.9)	2.6 | 7.7 (-15.0; 20.1)	6.6 | 8.9 (-12.5; 21.8)	3.8 | 8.4 (-13.0; 18.3)
	Older males	131.6 | 20.4 (108.4; 147.4)	20.0 | 8.7 (5.4; 41.0)	4.5 | 8.0 (-4.5; 16.2)	1.9 | 10.3 (-4.8; 22.5)	6.2 |6.5 (-1.1; 18.2)	2.0 | 8.3 (-8.6; 14.9)
	Adj *p*	0.7	0.81	0.7	0.81	0.9	0.81
	ES	0.18	0.05	0.18	0.06	0.01	0.12
DBP (mmHg)	Older females	77.0 | 15.8 (57.6; 91.1)	12.6 | 8.3 (5.5; 23.4)	0.6 | 4.3 (-11.8; 7.2)	1.5 | 3.1 (-9.9; 7.1)	3.6 | 3.8 (-9.3; 13.6)	3.1 | 2.9↑ (-11.6; 11.2)
	Older males	79.4 | 7.8 (69.2; 89.3)	14.8 | 8.2 (9.4; 27.7)	0.5 | 2.6 (-6.8; 7.6)	0.4 | 3.7 (-4.3; 10.9)	1.8 | 3.7 (-1.1; 12.1)	-0.1 | 1.7 (-3.0; 5.9)
	Adj *p*	0.8	0.23	0.8	0.8	0.23	**0.014***
	ES	0.12	0.27	0.06	0.25	0.31	0.58
MAP (mmHg)	Older females	96.0 | 13.4 (76.2; 116.6)	15.9 | 11.0 (7.8; 29.8)	1.3 | 4.8 (-12.0; 9.1)	1.8 | 4.5 (-12.2; 9.6)	4.6 | 4.1 (-8.1; 16.1)	3.0 | 3.7 (-12.6; 10.7)
	Older males	98.3 | 7.3 (85.1; 110.8)	17.7 | 7.9 (12.2; 31.4)	1.5 | 3.2 (-4.3; 6.9)	0.2 | 4.5 (-2.9; 12.4)	3.4 | 3.4 (1.0; 12.9)	0.8 | 2.4 (-2.8; 8.9)
	Adj *p*	0.52	0.52	0.58	0.58	0.52	0.14
	ES	0.2	0.2	0.1	0.1	0.2	0.43
SVR ($mmHg.min^{-1}L^{-1}$)	Older females	27.1 | 10.8 (18.2; 49.7)	11.4 | 7.3 (5.2; 21.5)	-1.7 | 4.0 (-10.3; 5.3)	-1.2 | 3.3 (-7.4; 5.4)	2.3 | 6.6↑ (-6.1; 11.4)	1.0 | 5.0↑ (-7.8; 9.3)
	Older males	24.7 | 3.5 (18.4; 40.5)	10.6 | 6.1 (7.3; 21.4)	-2.8 | 3.2 (-8.5; 2.3)	-2.5 | 1.9 (-7.5; 2.0)	-1.1 | 2.0 (-5.1; 4.6)	-2.5 | 2.1 (-4.9; -0.0)
	Adj *p*	0.14	1.0	0.46	0.08	**0.018***	**0.007***
	ES	0.3	0.1	0.14	0.4	0.51	0.6

HR (bpm)	Older females	65.3 | 9.7 (49.2; 78.1)	12.4 | 4.6 (5.4; 19.7)	12.4 | 4.6 (5.4; 24.9)	6.9 | 5.2 (1.9; 19.2)	9.5 | 4.3 (4.2; 20.0)	6.8 | 4.7 (2.7; 19.1)
	Older males	58.8 | 16.6 (50.2; 92.4)	10.6 | 8.3 (3.7; 24.5)	10.6 | 8.3 (3.7; 24.5)	6.1 | 4.7 (0.7; 12.1)	9.0 | 6.6 (1.8; 16.6)	5.2 | 6.6 (0.2; 16.3)
	Adj *p*	0.5	0.5	0.5	0.5	0.5	0.5
	ES	0.2	0.11	0.11	0.1	0.1	0.2
CO ($L.min^{-1}$)	Older females	3.5 | 1.0↓ (1.9; 5.1)	1.3 | 0.7↓ (0.5; 2.4)	1.3 | 0.7↓ (0.5; 2.4)	0.4 | 0.4↓ (-0.7; 1.2)	0.3 | 0.4↓ (-0.2; 1.3)	0.0 | 0.5↓ (-0.9; 1.1)
	Older males	3.8 | 0.5 (2.5; 5.7)	2.1 | 0.6 (1.1; 4.7)	2.1 | 0.6 (1.1; 4.7)	0.7 | 0.8 (0.2; 1.8)	0.6 | 0.7 (0.1; 1.6)	0.4 | 0.4 (-0.0; 1.2)
	Adj *p*	**0.02***	**0.023***	**0.001***	**0.008***	**0.02***	**0.005***
	ES	0.44	0.7	0.7	0.5	0.4	0.56
SV (mL)	Older females	52.9 | 15.2↓ (31.0; 87.4)	9.9 | 6.6↓ (-1.5; 31.5)	2.8 | 8.7 (-7.2; 25.9)	-1.4 | 8.5 (-21.1; 12.4)	-4.4 | 7.6 (-25.8; 28.3)	-14.3 | 11.7 (-38.4; 30.0)
	Older males	68.9 | 20.3 (41.9; 78.6)	19.7 | 7.8 (8.6; 36.5)	7.6 | 10.7 (-7.1; 53.2)	4.3 | 7.5 (-7.4; 23.0)	-0.5 | 12.0 (-13.1; 21.5)	-17.5 | 13.1 (-42.7; -7.4)
	Adj *p*	**0.021***	**0.0035***	0.052	0.07	0.2	0.2
	ES	0.49	0.74	0.37	0.40	0.33	0.24

|: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than; ↑ higher than. *Statistically significant differences between older females and older males. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

During lie-to-stand responses, SBP, DBP, MAP, SVR, HR, and SV responses were similar between older females and males across all phases. CO responses were also similar in phases 1, 2, and 4. However, in phase 3, older females exhibited a smaller CO response compared to older males (Table 7.3)

Table 7.3 Comparison of baseline, amplitudes, and short-term cardiovascular compensatory responses across phases during lie-to-stand between older females and males across phases.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Older Females	127.4 | 16.9 (105.9; 157.5)	31.9 | 17.8 (11.1; 59.1)	-0.1 | 14.6 (-25.2; 13.7)	-0.4 | 9.9 (-29.1; 21.4)	4.8 | 8.7 (-23.2; 27.1)	4.7 | 10.0 (-32.8; 19.8)
	Older Males	127.4 | 21.3 (105.4; 162.0)	28.2 | 9.4 (18.7; 49.7)	-2.9 | 10.4 (-23.1; 17.5)	-2.1 | 7.2 (-20.5; 12.3)	1.1 | 3.2 (-10.2; 11.8)	-1.7 | 8.6 (-8.7; 12.7)
	Adj *p*	0.9	0.7	0.9	0.7	0.35	0.35
	ES	0.03	0.1	0.01	0.1	0.2	0.3
DBP (mmHg)	Older Females	78.2 | 11.5 (52.7; 96.9)	19.2 | 8.2 (8.2; 34.6)	0.7 | 7.9 (-9.1; 21.7)	1.5 | 6.0 (-8.3; 27.1)	4.2 | 6.2 (-7.6; 32.5)	4.0 | 7.6 (-8.2; 28.3)
	Older Males	79.3 | 4.8 (69.4; 95.1)	20.1 | 2.7 (12.7; 32.8)	-0.6 | 5.3 (-9.8; 7.6)	-0.9 | 4.3 (-10.0; 8.3)	1.6 | 3.3 (-0.4; 8.1)	0.5 | 3.9 (-2.0; 6.7)
	Adj *p*	0.7	0.7	0.7	0.23	0.23	0.23
	ES	0.11	0.14	0.06	0.27	0.32	0.31
MAP (mmHg)	Older Females	97.6 | 11.6 (71.8; 118.1)	25.3 | 9.3 (7.6; 46.4)	-1.0 | 11.4 (-13.9; 11.8)	-0.1 | 9.1 (-16.8; 20.9)	4.3 | 10.4 (-12.2; 26.8)	3.8 | 9.7 (-14.5; 21.9)
	Older Males	99.1 | 10.5 (81.9; 121.3)	24.9 | 5.5 (18.1; 39.8)	-1.9 | 7.1 (-17.5; 11.3)	-2.4 | 3.8 (-15.2; 11.9)	1.0 | 4.0 (-3.7; 8.1)	-0.9 | 3.7 (-4.1; 8.3)
	Adj *p*	0.9	0.9	0.9	0.7	0.7	0.35
	ES	0.06	0.02	0.04	0.19	0.23	0.35
SVR ($mmHg.min^{-1}L^{-1}$)	Older Females	28.3 | 6.6 (15.2; 44.6)	12.9 | 5.9 (4.9; 25.3)	-1.6 | 6.2 (-13.1; 19.5)	0.0 | 5.1 (-11.9; 24.9)	4.3 | 6.8 (-11.1; 40.7)	2.6 | 8.1 (-13.3; 40.5)
	Older Males	24.3 | 7.7 (17.5; 33.0)	11.9 | 3.4 (8.7; 17.5)	-1.6 | 2.3 (-5.9; 0.5)	-1.9 | 2.6 (-5.9; 0.8)	-0.1 | 1.7 (-1.9; 13.8)	-0.8 | 1.6 (-3.2; 6.9)
	Adj *p*	0.12	0.35	0.4	0.07	0.07	0.07
	ES	0.32	0.16	0.14	0.37	0.41	0.43

HR (bpm)	Older Females	63.0 | 9.9 (46.2; 78.9)	16.5 | 4.9 (5.6; 24.9)	16.5 | 4.9 (5.6; 24.9)	10.7 | 6.6 (0.4; 20.7)	12.3 | 7.7 (4.5; 24.5)	8.7 | 7.3 (1.8; 17.2)
	Older Males	56.8 | 15.0 (46.0; 89.9)	14.3 | 8.7 (10.3; 40.4)	14.3 | 8.7 (10.3; 40.4)	12.5 | 7.9 (3.3; 41.3)	15.5 | 6.4 (5.5; 42.8)	9.4 | 5.2 (2.5; 32.1)
	Adj *p*	0.7	0.9	0.9	0.9	0.9	0.9
	ES	02	0.1	0.02	0.01	0.16	0.03
CO ($L.min^{-1}$)	Older Females	3.3 | 0.7↓ (2.2; 5.6)	1.6 | 1.3 (0.3; 5.4)	1.6 | 1.3 (0.3; 5.4)	0.2 | 0.7 (-1.2; 1.4)	0.2 | 0.6↓ (-1.6; 1.5)	-0.19 | 0.9 (-2.7; 1.0)
	Older Males	4.2 | 1.2 (3.0; 4.9)	2.2 | 1.3 (0.8; 6.0)	2.2 | 1.3 (0.8; 6.0)	0.5 | 0.6 (-0.0; 2.6)	0.5 | 0.5 (0.0; 1.3)	0.2 | 0.2 (-0.8; 0.8)
	Adj *p*	**0.04***	0.1	0.1	0.07	**0.035***	0.07
	ES	0.4	0.25	0.25	0.35	0.44	0.37
SV (mL)	Older Females	51.8 | 14.8↓ (35.4; 83.9)	8.3 | 8.3 (-5.4; 26.4)	4.7 | 10.7 (-18.0; 14.5)	-7.1 | 8.5 (-24.6; 10.9)	-7.5 | 9.4 (-31.0; 11.2)	-16.4 | 22.7 (-54.1; 3.7)
	Older Males	66.5 | 24.4 (43.9; 93.1)	10.5 | 25.8 (2.2; 49.7)	2.7 | 11.0 (-14.4; 33.9)	-4.0 | 8.6 (-21.7; 14.7)	-6.8 | 12.0 (-24.4; 1.5)	-25.5 | 33.9 (-55.8; 1.3)
	Adj *p*	**0.0014***	0.18	0.7	0.28	0.58	0.28
	ES	0.55	0.3	0.05	0.2	0.12	0.21

|: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than; ↑ higher than. *Statistically significant differences between older females and older males. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

In sit-to-stand (Figure 7.4), older females showed a non-significant correlation between CO and SVR in phase 1 (r = -0.322, 95% CI -0.562; 0.069, and p = 0.063). However, older females showed a significant negative correlation in the following phases: a large correlation in phase 2 (r = -0.798, 95% CI -0.916; -0.695, and p < 0.001), a moderate correlation in phase 3 (r = -0.494, 95% CI -0.672; -0.110, and p = 0.003), and large correlation in phase 4 (r = -0.920, 95% CI -0.930; -0.742, and p < 0.001). Older males showed no significant correlation between CO and SVR in phase 1 (r = -0.415, 95% CI -0.781; 0.127, and p = 0.141). However, a large and significant correlation was observed in phase 2 (r = -0.785, 95% CI -0.932; -0.456, and p = 0.001), phase 3 (r = -0.736, 95% CI -0.904; -0.300, and p = 0.004), and phase 4 (r = -0.842, 95% CI -0.925; -0.416, and p < 0.001).

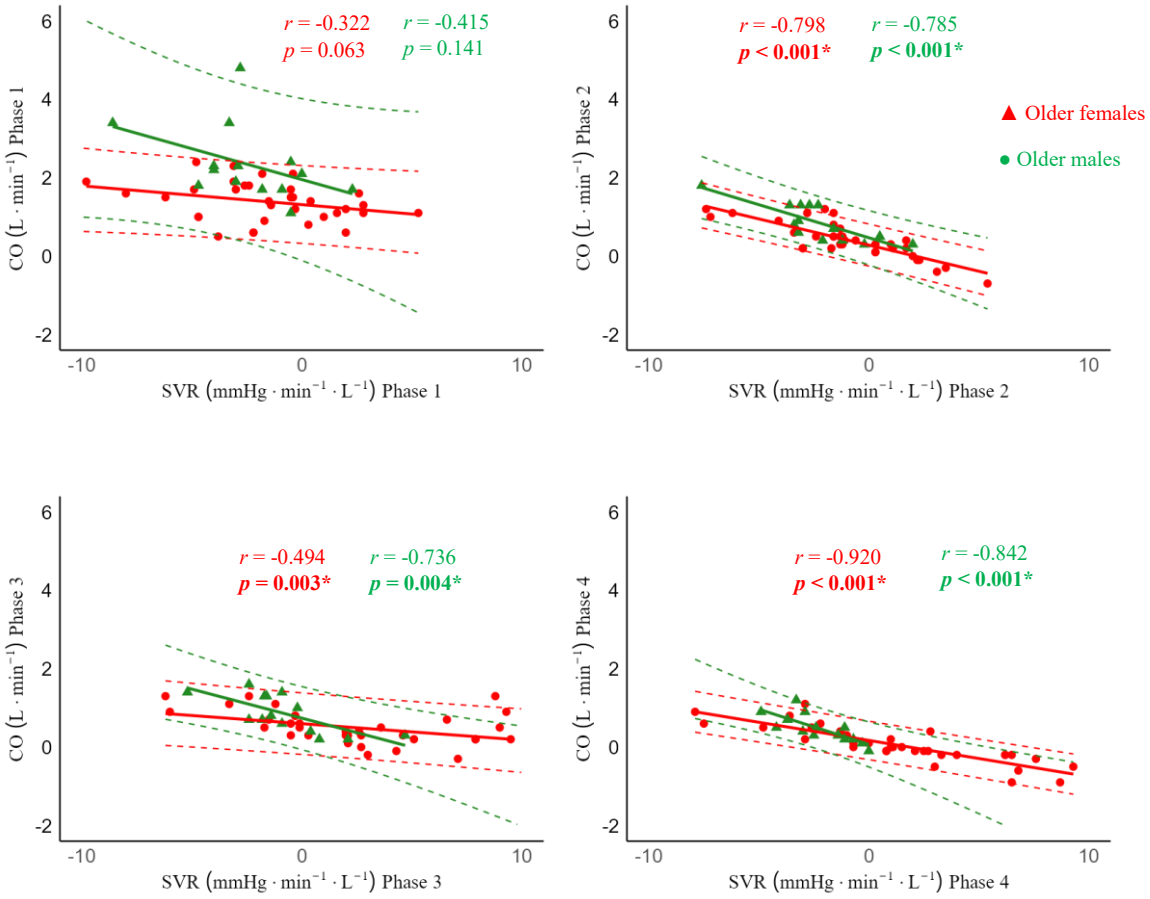


Figure 7.4 Cardiac output and systemic vascular resistance correlation during sit-to-stand in female and male older adults.

In lie-to-stand (Figure 7.5), older females demonstrated no statistically significant correlation in phase 1 (r = -0.08, 95% CI -0.420; 0.251, and p = 0.6), but large and significant negative correlations in phase 2 (r = -0.721, 95% CI -0.873; -0.565, and p < 0.001), phase 3 (r = -0.747, 95% CI -0.869; -0.553, and p < 0.001), and phase 4 (r = -0.877, 95% CI -0.830; -0.449, and p < 0.001). Older males exhibited a large and significant negative correlation in phase 1 (r = -0.536, 95% CI -0.878; -0.230, and p = 0.04), phase 2 (r = -0.693, 95% CI -0.830; -0.06, and p < 0.005), and phase 3 (r = -0.693, 95% CI -0.955; -0.638, and p = 0.005), but no differences in phase 4 (r = -0.364, 95% CI -0.726; -0.208, and p = 0.2).

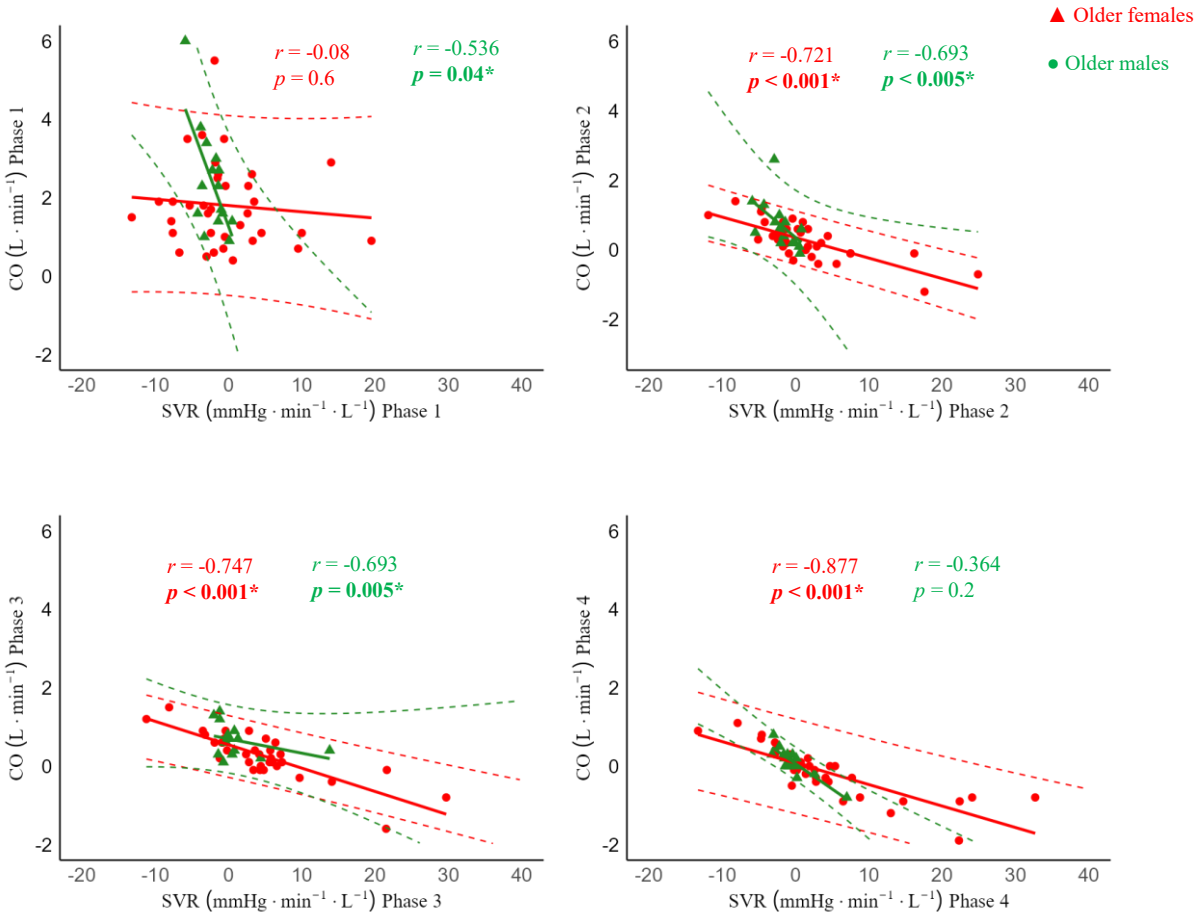


Figure 7.5 Cardiac output and systemic vascular resistance correlation during lie-to-stand transition in female and male older adults.

Discussion

To our knowledge, this is one of the first studies to analyze phase-specific short-term cardiovascular compensatory responses in community-dwelling older females and males under two distinct active standing orthostatic stress. This research aimed to describe and compare the dynamic cardiovascular adjustments during sit-to-stand and lie-to-stand. At baseline, in both transitions, SBP, DBP, MAP, SVR, and HR were similar between sexes, but older females exhibited lower CO and SV than older males. Immediately on standing, both groups experienced similar drops in BP, and similar increases in HR, but CO and SV values were lower in older females than in males. Throughout the phases of the short-term cardiovascular compensatory responses during sit-to-stand, SBP, MAP, HR, and SV values were not significantly different between sexes. However, CO values were lower in all phases, SVR values were higher in phases 3 and 4, and DBP was higher in phase 4 in older females compared to older males. During lie-to-stand, older females exhibited lower CO than older males in phases 2, 3, and 4, with no significant differences between the other variables.

The match between CO and SVR, which may indicate the timing of BP regulation, exhibited similar responses during sit-to-stand. However, older females primarily compensated through increased SVR, while older males relied more on CO. In sit-to-stand, older females and males did not show significant correlations in phase 1, but significant negative correlations from phases 2 to 4, indicating that 30-60 s were required for BP regulation. In lie-to-stand, older males exhibited significant negative correlations across all phases (1-4), except phase 3. Females showed significant negative correlations from phases 2-4. This result indicates that older females had a delayed matching response (30-60 s) under higher orthostatic gravitational stress (lie-to-stand) than older males. However, this response was not different between sexes under lower gravitational orthostatic stress (sit-to-stand). Additionally, older females and males did not demonstrate significant differences regarding OH and OI symptoms.

Baseline Responses During Active Standing Orthostatic Stress

In the present study, older females had lower CO and SV values at baseline in both conditions, but no significant differences were observed in SBP, DBP, MAP, SVR, and HR. These findings align with Sachse et al.[5] study that reported no statistical differences between older females and males in SBP, DBP, and MAP at baseline. Our findings partially corroborate those of Romero-Ortuno et al.[122] who reported no

statistically significant differences in SBP, DBP, MAP, HR, and CO between older females and males at baseline, but older females had a lower SV and a higher SVR than older males.

One possible physiological explanation for the similar baseline BP values between older females and males, despite females having lower CO and SV, is the compensatory response of SVR[16]. Since BP is determined by the interaction of CO and SVR (BP = CO × SVR), a reduction in CO can be counterbalanced by an increase in SVR to maintain similar SBP, DBP, and MAP[16]. Previous studies suggest that older females exhibit a higher SVR than older males at baseline, which could explain why their BP remains comparable despite lower SV and CO[122]. Additionally, sex-related variations in vascular function and autonomic regulation may contribute to this balance. As age advances, estrogen decline in females and testosterone reduction in males lead to vascular adaptations, including increased arterial stiffness and altered sympathetic and parasympathetic activity[166]. These changes may minimize sex differences in resting BP by promoting compensatory responses such as enhanced vasoconstriction and baroreflex sensitivity[1,166]. Consequently, while CO and SV are lower in older females, their vascular adaptations may allow for a similar resting BP compared to older males.

Immediately On Standing Responses During Active Standing Orthostatic Stress

No significant sex differences were observed in all variables in both postural transitions, except that older females exhibited lower CO and SV peak values than older males in sit-to-stand. Similar to our findings, Sachse et al.[5] showed that SBP, DBP, MAP, and SVR responses in older females and males were similar at 0-10 s when they transitioned from sitting to standing. Also, corroborating our findings, Romero-Ortuno et al.[122] did not find significant differences between older females and males in SBP, DBP, MAP, and SVR drop, and HR, CO, and SV peak responses in lie-to-stand. In contrast with the present study, Mellingsæter et al.[166] compared the hemodynamic responses of older females and males during the head-up tilt test (HUT) at 30º and 70º. Although HUT is a passive method and differs from the active standing protocol used in the present study, it can provide insights regarding hemodynamic responses and cardiovascular regulation to orthostatic stress. The authors reported that at a 30º HUT, older females exhibited lower SBP and MAP, and higher SVR compared to older males, while no significant differences were observed in HR. At a 70º HUT, the only significant difference was observed in SVR,

with older females maintaining a higher response than older males, whereas SBP, DBP, MAP, and HR remained similar between sexes.

Older females and males had similar SVR drop and HR peak values following both postural transitions, suggesting that the baroreflex-mediated vasoconstrictor response and cardiac autonomic regulation were similar in both sexes[24,35]. This indicates that, despite known sex differences in cardiovascular function[1], older females and males demonstrated similar responses to modulate vascular tone and HR to maintain BP homeostasis on standing[16]. However, the lower CO and SV peaks observed in older females during the sit-to-stand transition suggest sex-specific differences related to left ventricular compliance, total blood volume, and venous return dynamics[1]. These physiological differences show the importance of considering sex-related cardiovascular adaptations in older adults, particularly when assessing active standing orthostatic stress.

Short-Term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress

During sit-to-stand short-term cardiovascular compensatory responses, older females and males exhibited similar responses in SBP, MAP, HR, and SV, with no significant differences between groups. DBP was similar between sexes in phases 1 to 3, but it was higher in older females in phase 4 than in older males. SVR showed no significant differences in phases 1 and 2, whereas older females exhibited a higher SVR in phases 3 and 4 than older males. CO was lower in older females than in males across all phases. Similarly, during the lie-to-stand transition, no significant sex differences were observed in SBP, DBP, MAP, SVR, HR, and SV. CO was similar in phases 1, 2, and 4, but lower in phase 3 in older females than in males. These findings are partially supported by Romero-Ortuno et al.[122] who reported no significant sex differences in SBP, DBP, MAP, and HR within 2 minutes from lie-to-standing. However, their study found that older females had a lower SV and a higher SVR than older males, which differs from our results. We found no statistically significant differences in SV and SVR in phases 1 and 2. Similarly, Sachse et al.[5] demonstrated no significant differences in SBP, DBP, MAP, HR, and SVR across five distinct phases (0-10 s, 10-20 s, 20-30 s, 180-190 s, and 290-300 s) following sit-to-stand, supporting our findings for these specific variables.

The lack of statistically significant differences in SBP, DBP, MAP, SVR drop, and HR peak responses between older females and males during active-standing orthostatic stress suggests that both sexes were capable of regulating BP. This

resemblance is likely driven by baroreflex function and sympathetic activation, which trigger vasoconstriction and HR increases to regulate BP[16,24]. Females, who generally have lower SV and CO due to smaller left ventricular dimensions and lower total blood volume[16,24], may rely more on SVR to regulate BP[1]. In contrast, males, who typically exhibit higher SV and CO[1], might depend more on cardiac adjustments to counteract postural BP changes. These differences suggest that while both sexes demonstrate similar BP responses, older females may rely more on vascular compensatory mechanisms, whereas older males benefit from greater cardiac response in maintaining hemodynamic stability[1].

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

During postural transitions, the matching between CO and SVR plays a crucial role in maintaining BP regulation and ensuring adequate cerebral perfusion[16,24]. This is the first study to investigate the correlation between CO and SVR across specific phases to determine the possible timing of BP regulation relative to baseline values in female and male older adults.

In sit-to-stand, older females and males showed no statistically significant correlation between CO and SVR in phase 1 (0-30 s), indicating an initial mismatch in cardiovascular regulation, likely due to the rapid gravitational shift of blood volume on standing. However, significant negative correlations were found in phases 2-4, indicating an increase in vascular resistance and CO to regulate BP[24]. This delay but progressive adjustment may reflect the time-dependent activation of sympathetic mechanisms required to counteract the transient hypotensive effect of standing[16].

During lie-to-stand, older females exhibited no significant correlation between CO and SVR in phase 1, demonstrating a delayed response to higher orthostatic stress challenge. The significant correlations observed in phases 2-4 indicate that cardiovascular adjustments eventually occurred, likely driven by delayed vasoconstriction and venous return[24]. In contrast, older males demonstrated a significant correlation in phase 1 (0-30 s), indicating a faster CO-SVR matching than older females due to a more immediate vascular response[54]. This earlier adaptation in older males may be attributed to a more rapid activation of sympathetic vasoconstriction[54], allowing for a faster redistribution of blood volume and control of arterial pressure.

Prevalence of Orthostatic Hypotension and Orthostatic Intolerance Symptoms

Significant differences in the prevalence of OH and OI symptoms between the sexes were not observed as we previously hypothesized, corroborating with Mendez et al.[86], Harris et al.[167] and Romero-Ortuno et al.[122] studies. The similar prevalence of OH and OI-related symptoms among older adults suggests that age-related cardiovascular changes may attenuate the sex-specific physiological differences[168,169]. With advancing age, both females and males experience a decline in baroreceptor sensitivity[35], leading to a reduced ability to regulate BP on standing[122]. This decline is associated with arterial stiffening, which diminishes the responses of mechanoreceptor-mediated vascular adjustments and β-adrenergic receptors, which impairs CO modulation[16,24,35]. As a result, OH prevalence and OI symptoms are similar between older females and males.

Limitations

Despite the strengths of this study, some limitations were observed. The sample size was relatively small, which may have limited the statistical power to detect sex-related differences in postural BP regulation. Also, the study included more females (70%) than males (30%), which could have influenced the variability in responses and the ability to detect sex-specific differences. Future studies with larger and more balanced samples are needed to improve statistical power and enhance the generalizability of these findings.

Medication used among older adults was documented rather than controlled (Appendix 4), which may have affected the cardiovascular responses during active orthostatic stress. Several older adults are prescribed drugs such as antihypertensives, beta-blockers, or diuretics that can affect HR, BP, and vascular resistance[3]. In our sample of females, 29% were on calcium channel blockers (n = 10), 11% on beta-blockers (n = 4), 9% on diuretics (n = 3), 9% on ACE inhibitors (n = 3), and 11% on angiotensin II receptor blockers (n = 4). In males, 27% were on calcium channel blockers (n = 4), 20% on beta-blockers (n = 3), 13% on diuretics (n = 2), and 6% on ACE inhibitors (n = 1). Although these medications could have influenced the compensatory responses under investigation, they also reflect the real-world clinical conditions of community-dwelling older adults, thereby enhancing the applicability of our findings.

Another limitation is that CO and SV were not normalized to height, body mass, or body surface area, which are physiological parameters that differ between sexes. Considering that females generally present with smaller body size and cardiac

dimensions, the lack of normalization may have contributed to disparities in absolute cardiovascular values, potentially influencing the interpretation of lower/higher responses observed in females.

Conclusion

In conclusion, SBP, DBP, MAP, SVR, and HR were similar at baseline and during recovery phases; older females exhibited lower CO and SV, suggesting reduced cardiac filling. Despite similar BP regulation, older females relied more on vascular adjustments (higher SVR), whereas older males demonstrated a greater CO response. Regarding timing for BP stabilization, correlation analysis indicated that the CO-SVR matching for older females occurred within 30-60 s and for older males within 0-30 s, particularly under higher orthostatic stress (lie-to-stand). Also, the prevalence of OH and symptoms of OI were similar between sexes. These findings highlight that while older females and males showed similar BP responses, they rely on different physiological mechanisms to regulate BP (two paths, one outcome).

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study revealed that while BP responses were generally similar between older females and males during postural transitions, the underlying physiological mechanisms differed. Older females showed lower CO and SV responses, but higher SVR, particularly during later recovery phases (phases 3 and 4). In contrast, older males relied more on cardiac adjustments. The timing of BP regulation, assessed through CO-SVR correlation, was delayed in females under higher orthostatic stress, suggesting sex-specific compensatory dynamics. Despite these physiological differences, the prevalence of OH and OI symptoms did not differ between sexes. These findings show the importance of considering sex as a biological variable in aging research and suggest that interventions to prevent orthostatic complications may need to be tailored accordingly by sex.

8. Chapter 8

Different at baseline, similar in regulation: Sex differences in autonomic tone but not in short-term compensatory responses

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This chapter investigates sex differences in autonomic short-term compensatory responses to orthostatic stress in community-dwelling older adults. Specifically, it examines heart rate variability (HRV), cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG) across time phases during sit-to-stand and lie-to-stand transitions. I was responsible for designing the study, recruiting and assessing participants, analyzing the data, and preparing the manuscript. This work builds upon the previous chapter by focusing on autonomic rather than hemodynamic sex differences, offering a comprehensive view of how biological sex modulates autonomic regulation under orthostatic stress in older adults.

Publication Status

This study will be submitted to Geriatrics and Gerontology International.

Abstract

Postural transitions require rapid autonomic adjustments to maintain blood pressure (BP) stability, cerebral perfusion, and cerebral blood flow. However, sex differences in short-term autonomic compensatory responses remain poorly understood, particularly in community-dwelling older adults. This observational cross-sectional study aimed to describe and compare heart rate variability (HRV) indexes, cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG) between older females and males (60-79 years) following active standing orthostatic stress. A secondary objective was to analyze the incidence of orthostatic intolerance (OI) symptoms. Participants underwent active standing tests from a seated and supine position to stand-up to 7 minutes, with non-invasive continuous beat-to-beat blood pressure (Finometer-Finapress) and heart rate (HR, electrocardiogram) monitoring. Heart rate variability (HRV) was assessed through time and frequency domain analyses at rest. Cardiac parasympathetic modulation (CPM) was determined using the 30^{th} beat and the 15^{th} beat (HR 30:15) on standing. Cardiac baroreflex gain (CBG) was calculated as the ratio of HR change to systolic blood pressure (SBP) drop (ΔHR/ΔSBP) at specific phase time points (30s, 60s, 180s, and 420s). HRV analysis showed that older females had a lower standard deviation of R-R intervals (SDRR) and a low frequency/high frequency (LF/HF) ratio than older males, indicating greater parasympathetic dominance in older females. CPM and CBG responses and OI symptoms were similar between the sexes. These findings indicate that older females demonstrate a more pronounced parasympathetic influence at baseline than older males, but both older females and males exhibit similar CPM and CBG short-term compensatory responses in both postural transitions.

Keywords: Cardiac baroreflex gain, heart rate variability, cardiac parasympathetic modulation, postural transitions, older adults.

Introduction

The simple movement of standing from a chair or bed imposes a significant challenge to the autonomic nervous system (ANS)[35,170]. This transition causes a sudden gravitational shift of blood toward the lower extremities, requiring the ANS to adjust rapidly sympathetic and parasympathetic activity to maintain blood pressure (BP) cerebral perfusion, and cerebral blood flow[35,132]. This process involves baroreflex, sympathetic activation, and parasympathetic withdrawal[132]. Baroreceptor activity detects drops in arterial pressure and triggers a compensatory autonomic response (e.g., an increase in heart rate (HR))[132]. Sympathetic activation induces an increase in vasoconstriction responses, while parasympathetic withdrawal facilitates HR acceleration, ensuring sufficient blood flow to the brain[132]. These autonomic responses to an orthostatic stress challenge are sex-specific[35].

Sex differences in autonomic regulation during postural transitions have been reported in the literature[5,171]. Females tend to exhibit higher baseline parasympathetic activity and lower sympathetic drive compared to males[19], which may influence their ability to adjust to sudden postural changes. Additionally, sex hormones play a crucial role in autonomic function, with estrogen promoting vagal tone and testosterone enhancing sympathetic activity[19,64]. The decline in estrogen after menopause alters autonomic balance, potentially contributing to slower baroreflex responses[19,172] and increased susceptibility to orthostatic intolerance (OI) in older females[19]. In contrast, older males often maintain a relatively higher sympathetic outflow, which may facilitate faster autonomic adjustments but also increase cardiovascular strain[19,171].

Key autonomic markers, such as heart rate variability (HRV), cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG), may differ between older females and males, influencing their ability to regulate autonomic responses effectively under orthostatic stress challenges (postural transitions). HRV, a measure of autonomic balance, often shows greater parasympathetic dominance in females and a more pronounced shift toward sympathetic modulation in males. However, the literature shows conflicting results regarding these sex differences as they age[5,166]. For example, Mellingsaeter et al.[166] reported that older females have a lower low-frequency/high-frequency ratio (LF/HF ratio), an index of sympathovagal balance, at rest compared to older males. Conversely, Sachse et al.[5] observed that older females exhibit higher sympathetic activity than older males, pointing to complex changes in autonomic regulation across the lifespan.

CPM is essential for keeping the balance between the parasympathetic and sympathetic nervous system[173]. The literature has shown that females typically exhibit higher parasympathetic activity[19], which could contribute to a reduced CPM. However, despite the importance of CPM in autonomic regulation, no study has examined sex differences in CPM following active standing orthostatic stress in older adults. This gap in the literature limits the understanding of how sex modulates autonomic compensation mechanisms, particularly in response to postural challenges.

Typically CBG, which reflects the sensitivity of the baroreflex response, is reduced in older adults[19]. However, the extent of decline seems to be sex-dependent[172]. While some studies suggest that females exhibit lower baroreceptor function than males[138,174], others report no significant sex-based differences[175,176]. This divergence in the literature highlights the complexity of sex-specific autonomic regulation and shows the need for further analysis to clarify these differences. Also, to date, no study has examined sex-specific CBG responses across specific time intervals following active standing orthostatic stress. Therefore, our study will assess CBG at the 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4), enabling a time-course analysis of the role of the autonomic system in regulating BP and sex-specific differences following active standing orthostatic stress.

Given these gaps in the literature, this study aims to describe and compare sex-specific differences in **(1)** HRV indexes at baseline in supine position, **(2)** CPM response immediately on standing, **(3)** CBG responses at 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4), when transitioning from (1) sit-to-stand (low orthostatic stress challenge) and (2) lie-to-stand (high orthostatic stress challenge) in subsequent time intervals (phases 1-4). A secondary objective is **(4)** to compare the incidence of OI-related symptoms between older females and males. It is hypothesized that older females, when compared to older males, will exhibit **(i)** lower HRV indexes at baseline, indicating parasympathetic dominance; **(ii)** lower CPM immediately on standing, indicating stronger parasympathetic control of HR; **(iii)** lower CBG during phases 1 and 2, due to higher vagal activity and vascular stiffness, impairing baroreceptor sensitivity. No differences are expected in phases 3 and 4 as sympathetic activation balances parasympathetic and sympathetic activity, and **(iv)** older females will report a higher incidence of OI symptoms than older males.

Methods

Study design

This observational cross-sectional study used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) report guideline[114] (Appendix 9) and the Sex and Gender Equity in Research (SAGER) report guideline[115] (Appendix 10).

Settings

The research was conducted at the Applied Research Centre, University of Manitoba, from August 2022 to August 2023. Ethical approval was obtained from the University of Manitoba Health Research Ethics Board (approval number HE2022-0058).

Participants

A convenience sampling approach was used to recruit participants. Older adults were selected from Dr. Todd Duhamel's database at the University of Manitoba, which includes approximately 1,000 females who previously participated in the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts study. Additional recruitment sources included the Centre on Aging database, in-person visits to Men's Shed, and retirement or care facilities in Winnipeg.

The study sample consisted of age-matched older (aged 60-79 years) females and males who participated in sit-to-stand and lie-to-stand orthostatic stress challenges. Eligibility criteria required individuals to be within these age ranges and to identify their sex at birth as either female or male. Exclusion criteria included a history of cardiovascular conditions such as ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, psychiatric disorders, and severe cognitive impairment. Medications were recorded but not controlled (Appendix 4). All of the participants reported that they were not on hormone replacement therapy. Participants underwent orthostatic stress challenges in two experimental conditions: sit-to-stand (Experiment 1) and lie-to-stand (Experiment 2) (Figure 8.1).

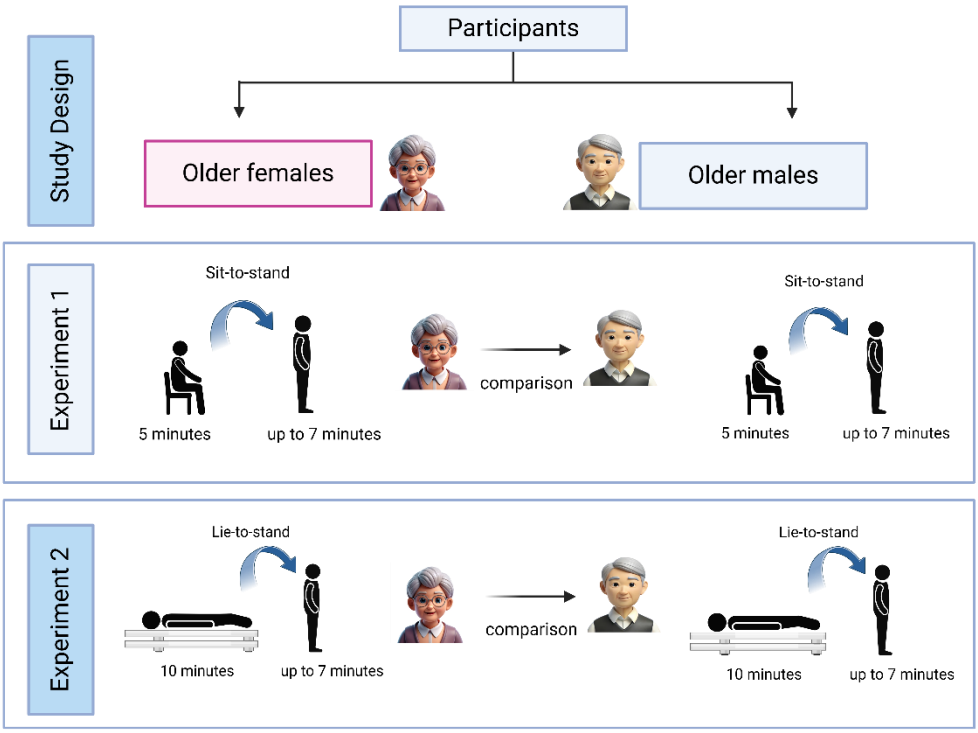

Figure 8.1 A framework for comparative research design involving two groups.

Data Collection

Participants received preparatory instructions 48 hours prior to their laboratory visit. Upon arrival, they reviewed and signed an informed consent form. Before the assessments, a researcher measured resting HR and BP to ensure that each participant met the safety criteria established by the Canadian Society for Exercise Physiology (CSEP) guidelines[31].

Following informed consent and familiarization procedures, participants underwent active standing orthostatic stress tests, with BP continuously monitored on a beat-by-beat basis using a Finometer^{TM} Pro Device (Finapress Medical System BV, Amsterdam, The Netherlands). Immediately after testing, participants were assessed for OI by reporting symptoms such as dizziness, faintness, or light-headedness. All assessments were conducted in a quiet room maintained at a controlled temperature of 22.0 ± 1.0°C, with humidity and barometric pressure at ambient. Testing sessions were scheduled on weekdays between 8:30 and 11:30 am to minimize circadian cycle influences. The order of the sit-to-stand and lie-to-stand conditions was randomized and counterbalanced to minimize potential order effects.

Demographic and Anthropometric Measurements

To characterize the sample, demographic data - including sex assigned at birth, age, and date of birth - were collected alongside anthropometric and body composition measurements. Body mass was assessed in kilograms (kg) using an InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA), while height was measured in meters (m) with a SECA mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was determined using the standard formula: body mass (kg) divided by height (m) squared[116].

Assessment of Heart Rate Variability, Cardiac Parasympathetic Modulation, Cardiac Baroreflex Gain

HRV, CPM, and CBG were derived from the electrocardiogram (ECG) and Finometer (Finapres Medical System, Arnhem, The Netherlands)[117] and recorded using LabChart 8.0 (AD Instruments, Colorado Springs, USA) at a sampling frequency of 1 kHz. The ECG signals were processed using a bandpass filter (5–30 Hz) for R-peak identification, except during the 30 seconds preceding and 90 seconds following the standing transition, where the raw signal was retained, and Finometer calibration was manually turned off. Cardiovascular variables recorded during the sit-to-stand and lie-to-stand tests were analyzed using a custom macro designed for R-R interval detection. In cases where ECG quality was insufficient, peak detection was based on the pressure waveform instead. The R-R intervals derived from the ECG were used for HR calculation.

Arterial pressure was measured non-invasively using photoplethysmography at the middle finger of the left hand (Finometer - Finapres Medical System, Arnhem, The Netherlands)[117]. BP calibration was initially conducted following the manufacturer's standard procedures and subsequently done manually with an automated BP monitor (ARSIMAI, BSX516, Munster, Germany). Approximately 5 minutes before each test, calibration via the return-to-flow method was used to adjust finger arterial pressure to brachial arterial pressure. Additionally, finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments.

SBP and HR data were recorded and subsequently transferred to a custom Matlab application (Matlab R2024; The MathWorks Inc, Natick, MA, USA). Upon importing the data from LabChart into the Matlab application, a multi-step signal processing approach

was implemented to enhance data quality. Initially, noise and motion artifacts were removed through a two-stage filtering process: a median filter was applied first, followed by a low-pass filter with a cutoff frequency of 0.05 rad/sample, as determined by scalogram analysis. A 5-second moving average filter was used, ensuring the extraction of parameters of interest[96,120]. After the processing analysis step, interpolation techniques were employed to correct for resampling-induced delays at 1 Hz. The onset of active standing was designated as time zero, with baseline values presented as negative values and short-term compensatory responses as positive values.

Heart Rate Variability

Heart Rate Variability **(**HRV) was assessed through continuous beat-by-beat recordings in the supine position using a three-lead electrocardiogram (ECG) module (Finometer, Finapres Medical System, Arnhem, The Netherlands) at a 1 kHz sampling rate, following the guidelines established by the *European Society of Cardiology and the North American Society of Pacing Electrophysiology*[149]. HRV data were analyzed using the HRV module in LabChart 8 (ADInstruments, Colorado Springs, USA). This module automatically detects and extracts R-R intervals while distinguishing between normal and ectopic beats. In the time domain, HRV parameters were analyzed, including the mean R-R interval, the standard deviation of R-R intervals (SDRR), and the root mean square of successive R-R interval differences (RMSSD). Spectral analysis of frequency domain variables was performed using the Fast Fourier Transform model, with low-frequency (LF, 0.04-0.15 Hz) and high-frequency (HF, 0.15-0.45 Hz) spectral components expressed as absolute power values (ms^2). Additionally, the low-frequency to high-frequency ratio (LF/HF) was calculated based on the absolute power values of LF and HF.

Cardiac Parasympathetic Modulation

Cardiac parasympathetic modulation (CPM) was evaluated using the Δ30:15 HR ratio, which represents the ratio of the maximum (tachycardia) and minimum (bradycardia) HR occurring around the 15^{th} and 30^{th} heartbeats after standing[146]. HR data for this calculation were extracted from R-R intervals recorded via the ECG module (Finometer, Finapres Medical System, Arnhem, The Netherlands). This measure is widely utilized in clinical settings to assess autonomic cardiovascular reflex function and to identify early signs of autonomic dysfunction[150,151]. It provides valuable insight into the heart's adaptive response to stressors, such as postural transitions, and can aid in

diagnosing conditions that impact cardiovascular stability, particularly in individuals with underlying health concerns[150,151].

Cardiac Baroreflex Gain

Cardiac baroreflex gain (CBG) was determined using the method proposed by the Autonomic Disorders Consortium[152] calculated as the ratio of HR change to SBP drop (ΔHR/ΔSBP) at 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4) following active standing orthostatic stress, expressed in $bpm.mmHg^{-1}$ [152]. The selected time points were chosen to capture key phases of autonomic regulation following active standing. Phase 1 represents the immediate compensatory response to counteract the initial BP drop. Phase 2 reflects early stabilization through sustained sympathetic activation. Phases 3 and 4 assess autonomic dysregulation linked to late BP regulation[24,65]. HR data for this calculation were derived from R-R intervals recorded via the ECG module (Finometer, Finapres Medical System, Arnhem, The Netherlands). SBP was obtained through non-invasive photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Calibration procedures, including return-to-flow adjustments, adjustments of finger and brachial arterial pressures, cuff size selection, and height correction, followed the previously outlined protocol. CBG evaluation is commonly employed in clinical settings to assess BP regulation during active standing and to identify autonomic dysfunction that may contribute to OI-related symptoms, such as dizziness[153].

Sample Size

The sample size was estimated using G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119] based on data from a pilot study with 20 participants (10 per group). The power analysis utilized a t-test with the difference between two independent group means (older females *vs* older males) for experiments 1 and 2, with an alpha level set at 0.05. These measurements were obtained from the differences in the Δ30:15 HR ratio, derived from the minimum and maximum HR observed around the 30^{th} and 15^{th} beats after standing. For experiment 1 (sit-to-stand), the analysis demonstrated an actual power of 0.8 and an effect size of 1.21, based on the mean and standard deviation (SD) values for the older females (0.93 ± 0.03) and older males (0.88 ± 0.05). Therefore, the estimated total sample for this experiment is 22 participants (11 in each group). For experiment 2 (lie-to-stand), the analysis showed an actual statistical power of 0.8 and an effect size of 0.17, calculated using a mean and standard deviation (SD) of the older

females (0.91 ± 0.04) and older males (0.90 ± 0.07). The estimated total sample size for this experiment and expected effect size is 976 participants (488 in each group).

Statistical Analysis

The Shapiro-Wilk test was applied to evaluate the normality of the data. Continuous variables following a parametric distribution were expressed as mean ± SD and 95% confidence interval (95% CI). Non-parametric continuous variables were reported as median, interquartile range (IQR), and minimum and maximum values. For sample characterization, continuous measures such as height and weight were summarized using mean, SD, 95% CI, and range (minimum and maximum). Categorical variables were presented as absolute frequencies and percentages, and comparisons between groups were conducted using the Chi-square test.

An unpaired Student's *t*-test was employed to compare continuous variables between older females and older males for each postural transition (sit-to-stand and lie-to-stand) when the data followed a parametric distribution. In cases where data exhibited non-parametric distribution, the Mann-Whitney *U* test was utilized. To account for multiple hypothesis testing, particularly for CBG, the Benjamini-Hochberg procedure was applied, maintaining a false discovery rate (FDR) of 0.05 to minimize the risk of false-positive results[125]. Significant results were reported based on corrected *p*-values ($p < 0.05$).

The effect size was calculated for continuous variables and HRV measurements[126]. For parametric data, Cohen's *d* was used, while the *R* coefficient was applied for non-parametric data[127]. Effect size was classified as low (≤ 0.05), medium (0.06-0.25), high (0.26-0.50) and very high (> 0.50). All statistical analyses were performed in R® (Version 4.1.1, Vienna, Austria).

Results

Figure 8.2 presents the recruitment flowchart. Eligibility was determined through a screening questionnaire designed by our research team to assess each participant's health status and ensure compliance with the study's inclusion and exclusion criteria. Sixty participants were recruited, but due to poor signal quality, 11 participants were excluded from Experiment 1 and 10 from Experiment 2. As a result, experiment 1 included 35 older females and 14 older males ($n = 49$) and experiment 2 consisted of 35 older females and 15 older males ($n = 50$).

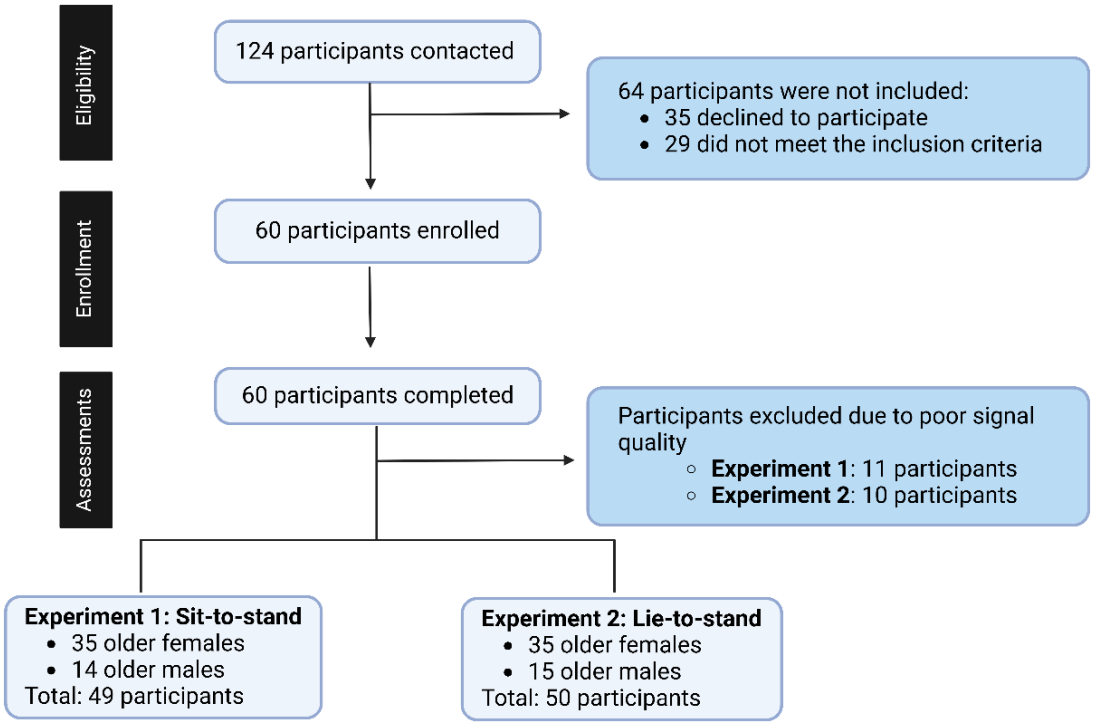

Figure 8.2 Recruitment flow chart of the study.

Table 8.1 provides an overview of the characteristics of older females and older males (60–79 years), including anthropometric measurements, hemodynamic variables, and the prevalence of OI-related symptoms. Age and hemodynamics measurements were similar between groups. Older females are shorter and have lower body mass than older males. BMI and the incidence of OI symptoms did not differ between the groups.

Table 8.1 Sample characteristics of older females and older males (60-79 years old).

Variable	Female			Male			*p*
Antropometric	Median |	Min	Max	Median |	Min	Max	
Age	71 | 6	63.0	78.0	72 | 5.5	64.0	77.0	0.3
Height (m)	1.6 | 0.1↓	1.5	1.7	1.7 | 0.1	1.4	1.8	**<0.001***
Body mass (kg)	67.2 | 17.7↓	42.5	109.0	82.8 | 10.3	68.4	110.0	**<0.001***
BMI	25.7 | 7.4	7.4	17.1	27.9 | 4.4	24.5	36.6	0.06
Hemodynamic							
Rest SBP	128 | 20	108	154	130 | 21	110	150	0.7
Rest DBP	78 | 14	56	92	80 | 4	72	90	0.3
Rest HR	68 | 12	52	92	64 | 16	52	92	0.06
OI symptoms[#]							
No	31	---	----	12	---	----	0.42
Yes	4	---	----	3	---	----	

|: Interquartile range with Minimum (Min) and Maximum (Max); BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate. ↓ lower than. [#]Orthostatic intolerance (OI) symptoms were assessed during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. *Statistically significant differences between groups.

Heart Rate Variability at Baseline in the Supine Position

Table 8.2 presents HRV in the time and frequency domains in older females and males at baseline in the supine position. In the time-domain HRV analysis, SDRR values were lower in females compared to males, while RR intervals and RMSSD were similar between groups. In the frequency-domain analysis, despite no differences in LF power and HF power between females and males, females exhibited a lower LF/HF ratio than males.

Table 8.2 Comparison of Heart Rate Variability parameters in time and frequency domains in older females and older males.

HRV (time domain)				
Variables	Older females	Older males	*p*	ES
RR (ms)	859.1 | 911.4 (999.7; 1.0)	605.4 | 1.1 (886.7; 1.0)	0.5	0.1
SDRR (ms)	34.4 | 22.6 ↓ (10.8; 66.4)	40.8 | 23.5 (7.6; 73.0)	**0.01***	0.44
RMSSD (ms)	24.9 | 17.3 (8.4; 81.3)	27.6 | 24.6 (7.2; 86.1)	0.8	0.03
HRV (frequency domain)				
Variables	Older females	Older males	*p*	ES
LF (ms)	320.0 | 406.3 (31.4; 2123.0)	506.8 | 1185.4 (41.4; 2226.0)	0.2	0.23
HF (ms)	402.5 | 556.1 (13.2; 5756.0)	411.9 | 697.8 (22.4; 5442.0)	0.5	0.12
LF/HF (au)	0.5 | 0.6 ↓ (0.1; 2.3)	1.5 | 0.9 (0.2; 3.6)	**<0.001***	0.64

|: Interquartile range with Minimum and Maximum; ES: Effect size, HRV: heart rate variability; RR: Average interval between consecutive heartbeats (RR-intervals); SDRR: Standard Deviation of RR intervals; RMSSD**:** Root Mean Square of Successive differences between RR intervals; LF: Low-Frequency power; HF: High-Frequency power; LF/HF: Low Frequency to High-Frequency power ratio: HR: heart rate. *Statistically significant differences between groups. ↓ lower than.

Cardiac Parasympathetic Modulation

Table 8.3 shows the comparison of CPM between older females and males assessed through the HR Δ30:15 ratio. No significant differences were observed between older females and males in both postural transitions.

Table 8.3 Comparison of cardiac parasympathetic modulation between older females and older males.

Cardiac parasympathetic modulation				
Sit-to-stand				
	Older females	Older males	*p*	ES
HR Δ 30:15	1.07 | 0.06 (0.96; 1.15)	1.11 | 0.10 (0.96; 1.30)	0.3	0.21
Lie-to-stand				
	Older females	Older males	*p*	ES
HR Δ 30:15	1.08 | 0.10 (0.91; 1.26)	1.08 | 0.10 (0.87; 1.38)	0.5	0.1

|: Interquartile range with Minimum and Maximum; Adj *p*: adjusted *p*-value; ES: effect size.

Short-Term Cardiac Baroreflex Gain Compensatory Responses During Sit-to-Stand Orthostatic Stress Across Phases

Table 8.4 presents the short-term compensatory responses of CBG. There were no statistically significant differences between older females and males across all phases in both conditions.

Table 8.4 Comparison of the short-term baroreceptor compensatory gain during sit-to-stand between older females and older males across phases.

Sit-to-Stand					
Variable	**Group**	**Phase 1**	**Phase 2**	**Phase 3**	**Phase 4**
CBG bpm.mmHg^{-1}	Older females	0.5 | 0.1 (0.3; 0.9)	0.6 | 0.1 (0.3; 0.8)	0.5 | 0.1 (0.3; 0.7)	0.5 | 0.0 (0.4; 0.8)
	Older males	0.4 | 0.2 (0.3; 0.7)	0.5 | 0.2 (0.3; 0.7)	0.5 | 0.1 (0.3; 0.7)	0.5 | 0.1 (0.3; 0.8)
	Adj *p*	0.2	0.2	0.3	0.3
	ES	0.34	0.30	0.21	0.18
Lie-to-Stand					
Variable	**Group**	**Phase 1**	**Phase 2**	**Phase 3**	**Phase 4**
CBG bpm.mmHg^{-1}	Older Females	0.6 | 0.1 (0.3; 0.9)	0.5 | 0.1 (0.3; 0.9)	0.5 | 0.1 (0.3; 0.8)	0.5 | 0.1 (0.3; 0.7)
	Older Males	0.5 | 0.3 (0.3; 1.0)	0.5 | 0.3 (0.3; 1.1)	0.5 | 0.1 (0.3; 0.9)	0.5 | 0.2 (0.3; 0.9)
	Adj *p*	0.9	0.9	0.9	0.9
	ES	0.08	0.01	0.04	0.04

|: Interquartile range with Minimum and Maximum; CBG: cardiac baroreflex gain; Adj *p*: adjusted *p*-value; ES: effect size.

Discussion

To the best of our knowledge, this study was among the first in the literature to analyze phase-specific autonomic short-term compensatory responses in community-dwelling older females and males under two distinct orthostatic stress conditions. It aimed to compare autonomic regulation during sit-to-stand and lie-to-stand in older females and males. Autonomic responses showed that older females had a higher parasympathetic influence during baseline than older males. However, CPM and CBG responses and OI-related symptoms were similar between the sexes.

Heart Rate Variability (HRV) Responses at Baseline

In the time domain analysis, older females had lower SDRR than older males, while no statistical significance was found in RR intervals and RMSSD in this study. Stein et al.[177] reported no differences in RR intervals, SDRR, and RMSSD in older females and males using HRV extracted from 24-hours Holter recording, which partially agrees with our results. Additionally, in the frequency domain analysis in this study, no statistical differences were found in LF and HF, while older females had a lower LF/HF ratio than older males. Stein et al.[177] demonstrated that older females had similar results in LF and HF compared to older males, while the LF/HF ratio was significantly lower in older females, corroborating our findings. Mellingsæter et al.[166] reported that older females exhibited higher HF, lower LF, and a reduced LF/HF ratio compared to older males during 5 min at a supine position, which partially agrees with our results. These results highlight physiological differences in autonomic regulation between older females and males. Lower SDRR and higher LF/HF ratio indicate overall parasympathetic activity in females[24,171,178]. These sex-related differences in autonomic regulation suggest underlying differences in baroreflex sensitivity, vascular compliance, or cardiac autonomic modulation, with females potentially exhibiting greater reliance on sympathetic activation to maintain hemodynamic regulation[19,35,171].

Cardiac Parasympathetic Modulation Responses During Active Standing Orthostatic Stress

CPM values were similar between older females and males in both transitions, represented by the HR30:15 ratio, an indicator of parasympathetic (vagal) reflex function. The similarities between the sexes in CPM suggest that, despite known age-related declines in baroreceptor sensitivity, both α-adrenergic and β_1-adrenergic receptor-mediated autonomic responses may remain similar between older females and males[35,179].

While sex differences in the distribution of these receptors have been reported, with males typically exhibiting greater α-adrenergic receptor-mediated vasoconstriction and females having higher β_2-adrenergic receptor density and sensitivity, particularly in younger populations[179,180], these differences may diminish with age[35]. Postmenopausal hormonal changes significantly impact vascular regulation[181], as the decline in estrogen reduces β_2-adrenergic receptor-mediated vasodilation and increases sympathetic nerve activity, leading to greater vascular stiffness and attenuated baroreflex sensitivity[182]. Additionally, endothelial function declines due to reduced nitric oxide bioavailability and impaired local vasodilatory control, further altering autonomic regulation[183]. The α_1-adrenergic receptors primarily mediate vasoconstriction[35], supporting BP regulation upon standing, while β_1-adrenergic receptors facilitate HR modulation[35].

This similar HR30:15 ratio implies that parasympathetic withdrawal and sympathetic activation are not different between older females and males. Furthermore, while nitric oxide bioavailability is typically higher in premenopausal females due to estrogen's vasodilatory effects[183], this advantage diminishes after menopause, potentially contributing to the observed similarities in CPM. The interaction between nitric oxide-mediated vasodilation and sympathetic vasoconstriction may become more similar between sexes among older adults[183], preventing significant sex-related differences in autonomic cardiovascular reflex function.

Short-term Cardiac Baroreflex Gain Compensatory Responses During Active Standing Orthostatic Stress

During the short-term compensatory responses in the sit-to-stand and lie-to-stand transitions, older females and males demonstrated no statistically significant differences in CBG across all phases. Consistent with our findings, Mellingsæter et al.[166] also reported no significant sex-based differences in baroreceptor responses (baroreflex function) in older adults using the sequence method (spontaneous fluctuations in BP and HR). Tank et al.[176] also found no significant sex differences in CBG after 20 min in the supine position in older adults using cross-spectral analysis (relationship between BP and HRV in different frequency domains). Contrary to our results, Okada et al.[184] reported that older females exhibited a lower baroreceptor response compared to their male counterparts during 6-minute spontaneous breathing (sequence method).

The absence of significant differences in CBG observed between older females and males suggests that different autonomic mechanisms involved in BP regulation, such

as arterial baroreflex function and sympathetic outflow[24,35], may be more similar across sexes as they age. While younger females typically exhibit greater parasympathetic modulation and lower sympathetic outflow than males[24], this advantage diminishes with age due to the decline in estrogen and progesterone post-menopause[35]. The loss of estrogen is associated with increased sympathetic nerve activity[35], reduced β_2-adrenergic receptor-mediated vasodilation, and impaired baroreflex sensitivity[183], potentially reducing sex-related differences in CBG. Additionally, age-related endothelial dysfunction, characterized by reduced nitric oxide bioavailability and increased vascular stiffness, may further contribute to the observed similarities in baroreflex responses between sexes[182]. The renin-angiotensin-aldosterone system (RAAS), which plays a critical role in vascular tone regulation, also becomes dysregulated with age[183], potentially influencing BP control mechanisms similarly in both sexes. The similar CBG responses between older females and males indicate that autonomic regulatory mechanisms, including α_1-adrenergic vasoconstriction and β_1-adrenergic cardiac modulation, may become more similar between older females and males.

Orthostatic Intolerance Symptoms

No significant differences were found between older females and males in the OI-related symptoms, consistent with Romero-Ortuno et al.[122] and in contrast with Fu et al.[185]. Fu et al.[185] showed that females had more OI symptoms than males. The similarities in OI symptoms between post-menopause older females and males suggest that impairments in autonomic regulation are more influenced by age per se than sex[24,35]. As age advances, baroreceptor sensitivity declines, reducing the ability to detect BP fluctuations during postural transitions[35]. Older females and males also experience a blunted sympathetic response, leading to slower HR adjustments[132]. Vascular stiffness increases with age, limiting arterial compliance and delaying compensatory vasoconstriction[16]. However, these responses seem to be less affected by sex in older adults, which may partially explain the similar prevalence of OI symptoms in both sexes reported in the current study.

Limitations

Despite the study's strengths, some limitations should be considered. While HRV was evaluated using both time- and frequency-domain analyses, assessments were limited to baseline, potentially overlooking autonomic fluctuations during active-standing orthostatic stress. Incorporating short-term or ultra-short HRV analyses, or non-linear

methods, could enhance understanding of the dynamic interaction between sympathetic and parasympathetic modulation throughout postural transitions[38]. Future research integrating these approaches may provide a more comprehensive assessment of autonomic regulation. Furthermore, CBG was measured at particular time points (30s, 60s, 180s, and 420s), which may not fully capture the continuous changes in baroreflex function during active standing. While this method allows for an evaluation of short-term compensatory responses at critical phases, it may not reflect transient variations or phase-specific adaptations. Alternative techniques, such as the sequence method[153], which identifies spontaneous changes in SBP and RR intervals to estimate real-time baroreflex sensitivity or transfer function analysis[153], which assesses baroreflex function across different frequency ranges, could offer a more detailed representation of baroreflex regulation.

The relatively small sample size may have reduced the statistical power to identify sex-related differences in BP regulation during postural changes. A posteriori analyses revealed reduced statistical power in both experiments, with an achieved power of 0.29 for the sit-to-stand (Experiment 1) and 0.05 for the lie-to-stand transition (Experiment 2) The disproportionate representation of females (70%) compared to males (30%) could have affected response variability and limited the detection of sex-specific differences. Future research with larger, more sex-balanced samples is recommended to strengthen statistical power and improve the generalizability of the results.

A significant proportion of older adults are prescribed antihypertensive medications, such as β-blockers and diuretics, which can influence heart rate, blood pressure, and vascular resistance[3]. In the present study, among females, 29% were taking calcium channel blockers (n = 10), 11% β-blockers (n = 4), 9% diuretics (n = 3), 9% ACE inhibitors (n = 3), and 11% angiotensin receptor blockers (n = 4). Among males, 27% were using calcium channel blockers (n = 4), 20% β-blockers (n = 3), 13% diuretics (n = 2), and 6% ACE inhibitors (n = 1). Although these medications may have influenced the short-term compensatory responses observed, their prevalence reflects the common pharmacological management of community-dwelling older adults, enhancing the external validity of the study. The use of β-blockers in both females and males could have attenuated β-adrenergic signaling, potentially impacting β_1 and β_2-adrenergic receptor-mediated responses involved in cardiovascular regulation. This is particularly relevant when interpreting findings related to autonomic modulation and sex differences.

Additionally, the study did not account for frailty status, which may influence autonomic responses to postural transitions. Frailty is associated with impaired baroreflex sensitivity[65], reduced HRV indexes[41], and diminished vascular responsiveness[6], all of which could impact CBG response. Given the heterogeneity in physiological adaptations among older adults, future studies should consider stratifying participants by frailty levels to determine whether autonomic responses differ across frailty stages.

Conclusion

Sex differences influence autonomic responses at baseline, but do not influence the CPM (HR 30:15) on standing, CBG at specific time points in older adults, and self-reported OI-related symptoms. HRV indexes analysis revealed that older females exhibited greater parasympathetic modulation, suggesting more reliance on parasympathetic responses at baseline (lying position) than older males. However, cardiac parasympathetic modulation and baroceptor gain responses were not influenced by sex during active orthostatic stress challenges.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study demonstrated that older females and males differ in baseline autonomic tone but exhibit similar short-term autonomic compensatory responses during orthostatic challenges. Older females had lower LF/HF ratios and reduced SDRR at rest, suggesting greater parasympathetic dominance. However, no significant differences were observed in CPM or CBG responses during the postural transitions, indicating similar capacity for autonomic adjustment despite baseline differences. Additionally, OI symptoms were similar between the sexes. The study highlights the importance of considering both baseline tone and phase-specific responses when evaluating autonomic function and reinforces the need for sex-based analysis, yet individualized interventions in older populations.

9. Chapter 9

Frailty status influences the temporal dynamics of blood pressure and cardiovascular regulation: Time Matters

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This chapter examines the impact of frailty status on cardiovascular short-term compensatory responses during orthostatic stress, comparing non-frail, pre-frail, and frail older adults. This study builds upon previous chapters by extending the analysis to a clinically relevant continuum of aging, using a frailty-specific framework. I was responsible for conceptualizing the research question, recruiting participants, collecting data, performing statistical analyses, and drafting the manuscript. The study adopts a phase-based approach to postural transitions and provides critical insight into the interaction between frailty and cardiovascular regulation, emphasizing the need for targeted assessment and intervention strategies in vulnerable older populations.

Publication Status

This study will be submitted to Archives of Geriatric and Gerontology.

Abstract

Frail individuals tend to experience greater drops in blood pressure (BP) on standing. However, how they regulate BP, cardiovascular responses, and the timing of this regulation remain poorly understood. This study aimed to describe and compare short-term cardiovascular compensatory responses in older adults living with frailty during postural transitions. Systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and heart rate (HR) were assessed at baseline, immediately on standing, and across four specific phases: phase 1 (0-30s), phase 2 (30-60s), phase 3 (60-180s), and phase 4 (300-420s). CO-SVR matching was used to determine BP regulation timing. The prevalence of orthostatic hypotension (OH) and orthostatic intolerance (OI) symptoms were compared among frail individuals. Participants completed two active standing tests, with 5 minutes of sitting or 10 minutes of lying, followed by up to 7 minutes of standing. Continuous beat-to-beat BP was measured using a Finometer-Finapress, and HR was recorded with an electrocardiogram. Baseline hemodynamics were similar across groups, except for lower HR in non-frail individuals. BP and SVR drop on standing were similar between groups, while the non-frail group exhibited a higher CO peak on standing and greater CO and SV in phase 1. Correlation analysis showed BP regulation occurred within 30s in non-frail, 30-60s in pre-frail, and 60-180s in frail individuals under higher orthostatic stress. OH and OI prevalence were similar across groups. In conclusion, frailty status influences BP regulation, with delayed compensatory responses.

Keywords: older adults, frailty, orthostatic hypotension, systolic blood pressure, systemic vascular resistance

Introduction

The maintenance of human life relies on the dynamic regulation of the cardiovascular system, ensuring homeostatic regulation in the face of external stressors[186]. Transitioning from a seated or lying position to standing (active standing) triggers a range of rapid cardiovascular adjustments[7]. These responses are essential to counteract the sudden and substantial drop in blood pressure (BP) and the immediate decrease in cerebral perfusion associated with active standing[7]. Failure in these regulatory mechanisms can impair daily functioning and may contribute to adverse health outcomes (e.g., BP dysregulation)[16]. Such homeostatic dysregulation becomes more pronounced in older adults living with frailty[6], potentially explaining the increased incidence of orthostatic hypotension (OH), a transient and pronounced drop in BP on standing[6]. OH is frequently accompanied by orthostatic intolerance (OI) symptoms, such as lightheadedness, dizziness, or blurry vision[186], which tend to be more prevalent in older adults living with frailty[15].

Frailty is a common clinical syndrome characterized by a decline in multiple physiological systems, often associated with biological aging but manifested in people across all age groups[22]. Older adults living with frailty have functional limitations in daily activities (e.g., rising from a seated or lying position), leading to a higher likelihood of falls, frequent hospitalizations, and increased mortality[6]. Therefore, the pathophysiology of frailty is linked to an imbalance in physiological regulation, where cardiovascular dysfunction serves as a key contributing factor[10].

The cardiovascular system is critical to maintaining BP control, especially during physiological stress such as postural changes[7]. In a healthy system, a sudden drop in BP triggers baroreceptor activation, which stimulates the sympathetic nervous system, resulting in an abrupt transient increase in heart rate (HR) and, consequently, increasing cardiac output (CO)[16]. Also, the vasomotor center is activated, leading to increased systemic vascular resistance (SVR), bringing BP to a normal range[9]. However, in a frail population, these responses might be impaired, causing a delayed recovery from a drop in BP[6], blunted HR response[97], and reduced vascular responses[6], leading to a compromised BP regulation after standing. While it is known that the frail population may take longer to recover after a drop in BP[6], the association between frailty and short-term cardiovascular responses after lower (sit-to-stand) and higher orthostatic stress (lie-to-stand) is still limited and requires further investigation.

Mol et al.[97] demonstrated that BP recovery at 15 - 30 s, 30 - 60 s, 60 - 120 s, and 120 - 180 s after lie-to-stand is associated with clinical symptoms, such as dizziness and lightheadedness in community-dwelling older adults (≥ 65 years). While this study provided important insights, it did not examine the first 15 seconds following the transition to an upright position and key short-term compensatory variables, including SVR, HR, CO, and stroke volume (SV). The first 15 s time window is particularly important as initial orthostatic hypotension (IOH) typically manifests within this period, making its analysis essential for understanding transient cardiovascular responses. Shaw et al.[53] also reported an association between frailty and orthostatic hypotension (OH), highlighting impaired BP regulation in frail individuals. However, their analysis did not include pre-frail individuals, nor did it assess critical short-term compensatory responses (SVR, CO, and HR), leaving gaps in understanding the cardiovascular regulation across different frailty stages.

In healthy individuals, standing causes gravitational blood pooling in the lower extremities, which reduces venous return and stroke volume[49]. This leads to a transient drop in CO and BP, as SVR does not initially compensate for the shift[49]. Within 15-20 seconds, baroreflex-mediated mechanisms trigger a compensatory response, involving an increase in HR and peripheral vasoconstriction, which together elevate CO and SVR to stabilize BP[49,109]. While this regulatory sequence is well-established in younger adults, it remains unclear whether this CO-SVR matching is impaired in individuals living with frailty, potentially contributing to delayed or inadequate hemodynamic short-term compensatory response. Investigating this CO-SVR matching process in pre-frail and frail individuals is essential to understanding short-term cardiovascular compensatory responses, as these responses play a crucial role in BP regulation, particularly in older adults living with frailty, due to the strong association between frailty and aging[6,109].

This study aims to describe and compare SBP, DBP, MAP, CO, HR, SV, and SVR responses **(1)** at baseline, **(2)** immediately on standing, **(3)** during short-term cardiovascular compensatory responses, and **(4)** match between CO and SVR between non-frail, pre-frail, and frail individuals. These variables were analyzed during (a) sit-to-stand (lower orthostatic stress challenge) and (b) lie-to-stand (higher orthostatic stress challenge). Additionally, the short-term cardiovascular compensatory responses were divided into four specific phases, as follows: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), phase 4 (300-420 s). A secondary objective **(5)** was to compare the incidence of OH and OI-related symptoms among frail individuals (non-frail, pre-frail and frail).

This study was divided into five different hypotheses. **(i)** At baseline. Pre-frail and frail individuals will have higher SBP, DBP, MAP, SVR, and HR, and lower SV and CO than the non-frail group due to reduced vascular compliance, vascular resistance and impaired blood circulation. **(ii)** Immediately on standing. Pre-frail and frail individuals are expected to experience a greater transient drop in SBP, DBP, MAP, and SVR and lower HR, CO, and SV peaks following the postural transitions compared to non-frail individuals due to increased vascular stiffness and impaired vasoconstriction. **(iii)** Short-term cardiovascular compensatory responses. During the early phases of compensatory responses (phase 1: 0-30 s and phase 2: 30-60 s), pre-frail and frail individuals are expected to show lower and delayed SBP, DBP, MAP, SVR, HR, CO, and SV responses due to impaired compensatory responses, such as vasoconstriction. However, in the later phases (phases 3 and 4), no significant differences are expected, as compensatory responses stabilize in phase 2. **(iv)** CO and SVR matching. A delayed matching between CO and SVR is expected in pre-frail and frail individuals, occurring in phase 2 (30–60 s) instead of phase 1 (0–30 s). These impaired responses are attributed to the frail-related decline in the activation of compensatory vasoconstriction and venous return mechanisms, diminished vascular compliance, increased arterial stiffness, and transient limitations in chronotropic capacity. **(v)** Prevalence of OH and OI. Pre-frail and frail groups will have a higher incidence of OH and OI symptoms than the non-frail group.

Methods

Study design

This is an observational case-control study that used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[114] (Appendix 11) and the Sex and Gender Equity in Research (SAGER)[115] (Appendix 12) as reporting guidelines.

Settings

This research was carried out at the Applied Research Centre within the Faculty of Kinesiology and Recreation Management at the University of Manitoba between August 2022 and August 2023. Ethical approval for the study was granted by the University of Manitoba Health Research Ethics Board under the protocol number HE2022-0058.

Participants

Participants were selected through a convenience sampling approach. Older adults with varying frailty levels were recruited from multiple sources, including Dr. Todd Duhamel's database at the University of Manitoba, which consists of approximately 1,000 female volunteers from the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts study. Additional recruitment sources included the Centre on Aging database at the University of Manitoba, the Men's Shed organization, and various retirement and care homes in Winnipeg. Individuals interested in participating reached out to researchers via email or phone.

The study sample comprised age-matched males and females (60 to 79 years) who underwent orthostatic stress assessments, including sit-to-stand and lie-to-stand transitions (Figure 9.1). Eligibility criteria required participants to be within this age range and to have been assigned female or male at birth. Exclusion criteria were a history of cardiovascular conditions such as ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, or congestive heart failure, along with psychiatric disorders or severe cognitive impairment. Medication was recorded but not controlled (Appendix 4). All participants reported that they were not on hormone replacement therapy.

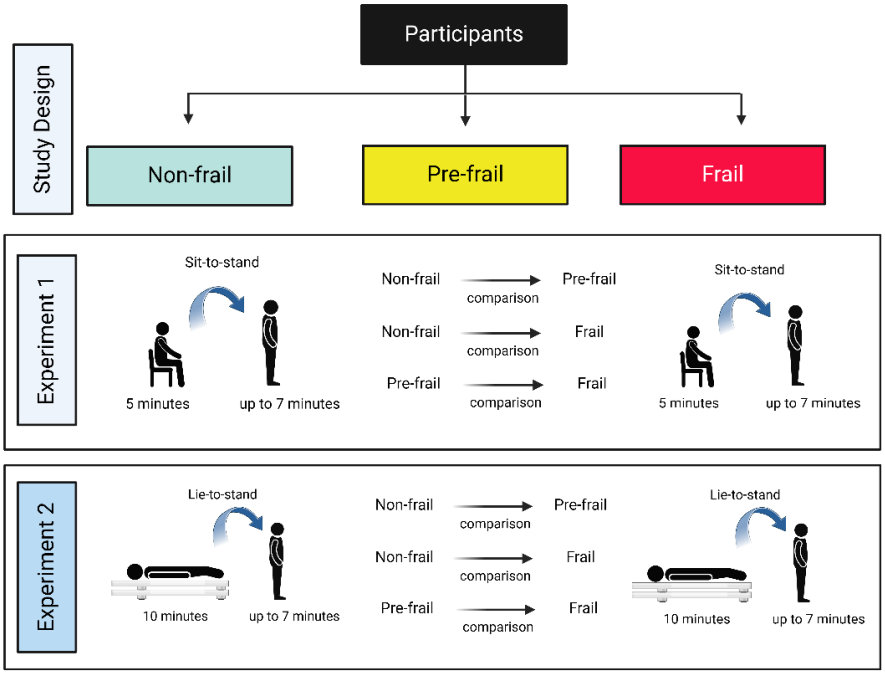


Figure 9.1 A structure for comparative research design of three distinct groups.

Data Collection

Participants were provided with pre-instructions 48 hours before their scheduled laboratory visit. Upon arrival, they reviewed and signed an informed consent form after having their questions or concerns clarified by the research team. Before testing, a trained researcher measured resting HR and BP to confirm the participant's safety for study participation. These procedures adhered to the guidelines established by the Canadian Society for Exercise Physiology (CSEP)[31].

Following the consent process and familiarization, participants underwent active standing orthostatic stress tests with continuous non-invasive beat-by-beat blood pressure monitoring using the Finometer™ Pro device (Finapress Medical System BV, Amsterdam, The Netherlands). Resting SBP and DBP were measured with a digital blood pressure monitor (ARSIMAI, BSX516, Munster, Germany). Immediately after completing the test, participants were asked about any symptoms such as dizziness or light-headedness to assess the presence of orthostatic intolerance (OI) symptoms. The study was conducted in a quiet room with a controlled temperature of 22.0 ± 1.0ºC, while humidity and barometric pressure remained at ambient. The orthostatic stress tests took place between 8:30 and 11:30 a.m. on weekdays to minimize circadian cycle influences. The test order was randomized and counterbalanced between the sit-to-stand and lie-to-stand conditions to account for potential order effects.

Demographic, Anthropometric Measurements, and Frailty Index

Demographic information, including sex assigned at birth, age, and date of birth, along with anthropometric and body composition measurements, was collected to characterize the study sample. Body mass (kg) was assessed using the InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA), while height (m) was measured with a SECA mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was calculated by dividing a participant's body mass in kilograms by the square of their height in meters (kg/m^2)[116]. The Frailty Index (FI) (Appendix 13) was used to screen and classify the participants into non-frail (≤ 0.08), pre-frail (> 0.08 to 0.25), and frail (≥ 0.25) categories as recommended[187].

Definition of Short-Term Orthostatic Blood Pressure Recovery Responses

Orthostatic hypotension (OH) was grouped into four classifications based on SBP response during the active standing orthostatic stress test (lie-to-stand). A normal BP (NBP) response was defined as SBP returning to baseline without a drop exceeding 20

mmHg within 30 seconds of standing. Initial orthostatic hypotension (IOH) was characterized by a transient SBP drop of more than 40 mmHg within the first 15 seconds after standing, followed by complete recovery within 30 seconds. Delayed BP recovery (DBPR) was identified when SBP decreased by more than 20 mmHg and took longer than 30 seconds to return to baseline, without meeting the criteria for sustained orthostatic hypotension (SOH). SOH was defined as a sustained SBP reduction of ≥ 20 mmHg occurring between 60 and 180 seconds after standing, accompanied by supine hypertension (supine SBP ≥ 160 mmHg)[49].

Assessment of Cardiovascular Responses

Heart rate (HR) was continuously recorded on a beat-by-beat basis using a 3-lead electrocardiogram (ECG) module (Finapres Medical System, Arnhem, The Netherlands) with a sampling frequency of 1 kHz, with HR derived from R-R intervals. Additionally, continuous non-invasive beat-by-beat measurements of SBP, DBP, and MAP were obtained from the arterial pressure signal using photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. The device was calibrated approximately five minutes before each procedure using the return-to-flow method to align finger pressure with brachial pressure. Finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments. Cardiac output (CO) was estimated using a model flow algorithm (Finometer, Finapres Medical System, Arnhem, The Netherlands)[118]. Stroke volume (SV) was calculated using the formula: SV = (CO/HR) × 1000, where cardiac output (CO) was divided by heart rate (HR) and multiplied by 1000. Systemic vascular resistance (SVR) was determined by dividing mean arterial pressure (MAP) by CO (SVR = MAP/CO).

Data Analysis

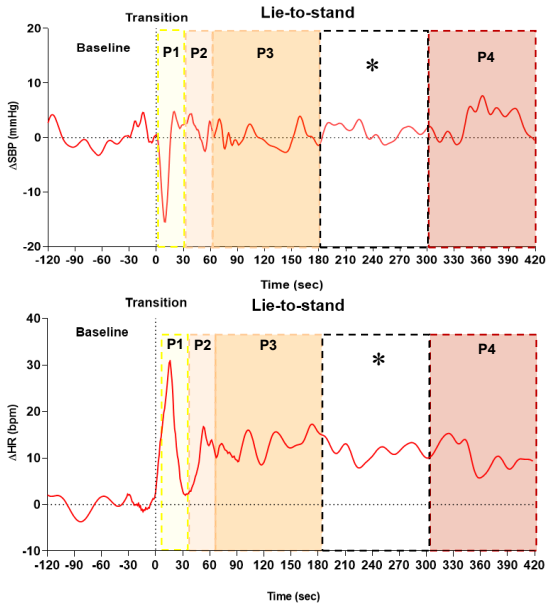
Data from the Finometer-Finapress were acquired and processed on a beat-by-beat basis using LabChart 8.0 (ADInstruments, Colorado Springs, CO, USA). Electrocardiogram (ECG) signals were filtered using a 5 - 30 Hz bandpass to detect R peaks, except for the 30 seconds before and 90 seconds after standing, during which the raw signal was retained, and Finometer calibration was manually disabled. Cardiovascular variables during the sit-to-stand and lie-to-stand transitions were analyzed using a custom macro designed for R-R interval detection. In cases where ECG traces

were of poor quality, analysis was conducted using pressure waveform peaks. BP calibration followed standard company procedures, supplemented by manual calibration using an automated BP monitor (ARSIMAI, BSX516, Munster, Germany). All data were saved and subsequently transferred to a custom Matlab application (Matlab R2024; MathWorks Inc, Natick, MA, USA) for further analysis.

After importing data from LabChart into the custom Matlab application (Matlab R2022b, MathWorks, Inc., USA), noise and motion artifacts were removed using a median filter, followed by a low-pass filter with a cutoff of 0.05 rad/sample, determined through scalogram analysis. To further refine the signal, a 5-second moving average filter was applied, allowing for signal smoothing and extraction of key parameters[96,120]. Data were interpolated and adjusted to correct for delays introduced by resampling at 1 Hz.

Variables Extracted and Analyzed During Active Standing Orthostatic Stress

Baseline measurements were determined by averaging data from the two minutes preceding the transition to standing. Within the first 30 seconds post-stand, the lowest values for SBP, DBP, MAP, and SVR (drop) and the highest values for HR, CO, and SV (peak) were identified. The subsequent short-term cardiovascular compensatory responses were assessed based on the highest values reached following the drop. These responses were divided into four specific phases: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s), representing the progression of cardiovascular adjustments after active standing. This classification aligns with recognized physiological responses in healthy adults and established OH criteria[121,122], enabling a comprehensive analysis of adaptive responses and frailty-related differences in cardiovascular regulation (Figure 9.2).



Phases	Time	Expected physiological responses
1	0-30 s	• Baroreceptor activation • Abruptly transient increase in HR • BP drops and then, overshooting over the baseline • Matching in CO and SVR • Slight decrease in SV
2	30-60 s	• Parasympathetic nervous system is activated • BP begins to drop • CO and HR decrease • Increase in SVR and SV
3	60-180 s	• BP, CO, SVR, and SV return to similar levels as baseline • HR remains elevated above the supine levels
4	300-420 s	• BP, CO, SVR, and SV remain close to the baseline measurement • HR stays above the baseline measurement

Figure 9.2 An illustration depicting systolic blood pressure (ΔSBP, top) and heart rate (ΔHR, bottom) responses during the lie-to-stand transition, segmented into four phases: phase 1 (0–30 s), phase 2 (30–60 s), phase 3 (60–180 s), and phase 4 (300–420 s) post-transition. *The unshaded interval (180-300 s) represents a stabilization period similar to phase 3, therefore, it was excluded from the analysis. However, phase 4 continues in the analysis as it represents a higher incidence of delayed orthostatic hypotension[123,124].

Sample Size

The sample size for this study was calculated using G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119], utilizing an internal pilot study data with 15 participants (5 per group). The power analysis used the F-test ANOVA for fixed effects, omnibus, and one-way. The values were obtained from the amplitude over or undershoot measured within 30 seconds after the nadir across three groups (non-frail, pre-frail, and frail) for two conditions (sit-to-stand and lie-to-stand). For sit-to-stand, the analysis demonstrated an actual power of 0.8 and an effect size of 0.21, with an SD σ within groups (9.21) and each group mean: non-frail 3.19, pre-frail 7.9, and frail 4.86. Therefore, the estimated total sample for this experiment is 219 participants (73 in each group). For lie-to-stand, the analysis showed an actual power of 0.84 and an effect size of 0.67, with an SD σ within groups (8.56) and each group mean, non-frail 3.12, pre-frail -10.69, and frail -0.88. The estimated total sample for this experiment is 27 participants (9 in each of the 3 groups).

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables following a parametric distribution were reported as mean ± SD and the 95% confidence interval (95% CI). For non-parametric data, the median, interquartile range, and minimum and maximum values were provided. To describe the sample characteristics, continuous data were summarized using the mean, SD, 95% CI, and range (minimum and maximum). Categorical data were expressed in absolute numbers and percentages. Categorical variables were analyzed using Pearson's Chi-square test. The one-way ANOVA was used for the comparisons between non-frail, pre-frail, and frail groups for parametric continuous data, and the Kruskal-Wallis test was used for non-parametric data. Bonferroni *post-hoc* was applied if significant differences were observed. To account for multiple hypothesis testing, *p*-values were adjusted using the Benjamini-Hochberg correction[125], with the false discovery rate (FDR) set at 0.05. Significant results were reported based on the corrected *p*-values set as < 0.05. Correlations between CO and SVR during different phases (0-30 s, 30-60 s, 60-180 s, and 300-420 s) were assessed using Pearson or Spearman correlation, depending on the data distribution. Correlation magnitudes were interpreted as small ($r = 0.10$-0.29), medium ($r = 0.30$-0.49), and large ($r \geq 0.50$)[126]. All statistical analyses were conducted using R® (Version 4.1.1, Viana, Austria).

Results

The recruitment process is illustrated in Figure 9.3. Participant eligibility was determined through a screening questionnaire designed by the research team to assess health status and verify adherence with the study's inclusion and exclusion criteria. A total of 60 individuals were recruited. However, data from 11 participants were excluded from Experiment 1 (sit-to-stand) and 10 from Experiment 2 (lie-to-stand) due to poor signal quality (e.g., noise and motion artifacts). As a result, the final sample consisted of 49 participants for Experiment 1, including 28 non-frail, 13 pre-frail, and 8 frail older adults, while Experiment 2 comprised 50 participants, with 28 non-frail, 14 pre-frail, and 8 frail individuals.

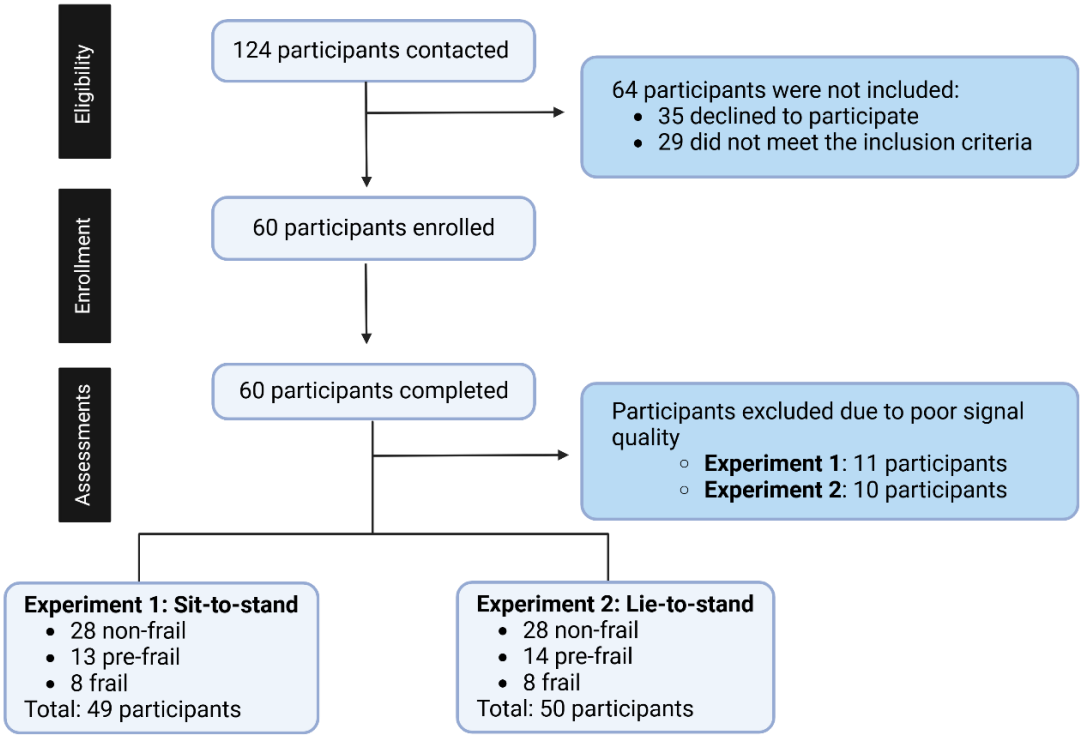


Figure 9.3 Recruitment flow chart of the participants.

Anthropometric measurements, including height, body mass, and BMI, were similar among the groups with no statistically significant differences. SBP and DBP resting parameters were similar between the groups, while resting HR was significantly higher in the frail group compared to the pre-frail and non-frail groups. No differences were observed between the non-frail and pre-frail groups regarding resting HR. The proportion of participants that met OH classification criteria and the prevalence of OI symptoms did not differ significantly between groups. Neither non-frail, pre-frail, nor frail individuals met the SOH classification (Table 9.1).

Table 9.1 Sample characteristics of participants by Frailty status.

Variables	Non-frail		Pre-frail		Frail		*p*
Sit-to-stand	***n***	%	***n***	**%**	***n***	**%**	
Females	16	57	12	92	6	75	0.07
Males	12	43	1	8	2	25	
Lie-to-stand	***n***	%	***n***	**%**	***n***	**%**	
Females	16	57	13	93	6	75	0.056
Males	12	43	1	7	2	25	
Anthropometric	**Median |**	**Min; Max**	**Median |**	**Min; Max**	**Median |**	**Min; Max**	***p***
Age	70 | 6.7	63.0; 77.0	70.5|5.5	63.0; 78.0	73.5|3.7	68.0; 76.0	0.3
Height (m)	1.6 | 0.1	1.4; 1.8	1.5|0.1	1.5; 1.8	1.6|0.1	1.5; 1.7	0.2
Body mass (kg)	74.1 | 21.3	46.6; 110.0	73.6|19.6	50.8; 95.2	77,,.0|14.3	42.5; 109.0	0.4
BMI	26.7 | 5.6	17.1; 36.6	26.1|7.3	19.3; 37.7	29.0|2.8	17.9; 48.4	0.5
Hemodynamic	**Median |**	**Min; Max**	**Median |**	**Min; Max**	**Median |**	**Min; Max**	***p***
Rest SBP	126 | 20.0	108.0; 154.0	130 | 19.2	110.0; 150.0	140.0 | 12.7	118.0; 150.0	0.1
Rest DBP	78 | 7.5	56.0; 92.0	82 | 10.0	60.0; 92.0	84.0 | 11.0	66.0; 90.0	0.2
Rest HR	64 | 12.2	52.0; 84.0	74 | 7.2	62.0; 90.0	75.5 | 14.5↑	64.0; 92.0	**0.002***
OH Classification**	***n***	%	***n***	**%**	***n***	**%**	
NBP	5	18	1	7.2	2	25	0.5
IOH	5	18	3	21.4	3	37.5	0.7
DOH	18	64	10	71.4	3	37.5	0.1
SOH	--	--	--	--	--	--	--
OI symptoms[#]**	***n***	**%**	***n***	**%**	***n***	**%**	***p***
No	25	89	11	78	7	87	0.3
Yes	3	11	3	22	1	13	

|: Interquartile range with Minimum (Min) and Maximum (Max); BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; ↑: higher than; **OH classification was based on the criteria outlined by Van Wijnen et al.[49], specifically analyzing SBP during the lie-to-stand transition. [#]Orthostatic intolerance (OI) symptoms were assessed during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. *Statistically significant differences.

Baseline Responses During Active Standing Orthostatic Stress

At baseline, SBP, DBP, MAP, SVR, and CO were similar across all groups in both conditions. HR was lower in the non-frail group in both conditions compared to the pre-frail and frail groups, with no significant differences between the pre-frail and frail groups. SV was similar among the groups during the sit-to-stand transition. However, SV was higher in lie-to-stand in the non-frail group compared with the pre-frail and frail groups, with no significant differences between the pre-frail and frail groups (Tables 9.2 and 9.3).

Immediately on Standing Responses During Active Standing Orthostatic Stress

The groups exhibited a similar response immediately on standing, with no significant differences in all variables in sit-to-stand (Table 9.2). During the lie-to-stand transition, SBP, DBP, MAP, SVR, HR, and SV were similar across all groups. However, the CO peak was higher in the non-frail group compared to the pre-frail and frail groups, with no significant differences between the latter two groups (Table 9.3).

Short-Term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress Across Phases

Sit-to-stand

The short-term compensatory responses were similar between groups in all variables and phases, with no statistically significant differences (Table 9.2).

Table 9.2 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses during sit-to-stand between non-frail, pre-frail, and frail groups.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Non-frail	121.4|18.0 (102.3; 147.4)	20.8|12.4 (5.4; 41.1)	4.5|7.6 (-10.1; 16.2)	2.1|6.6 (-15.0; 22.4)	6.8|5.9 (-12.5; 20.7)	3.3|6.4 (-8.6; 13.4)
	Pre-frail	127.7|8.3 (103.7; 148.3)	17.7|11.1 (8.7; 30.6)	1.5|7.6 (-11.4; 21.9)	3.6|6.2 (-10.2; 20.1)	5.7|12.7 (-7.9; 21.8)	4.0|13.3 (-13.0; 15.0)
	Frail	132.2|12.7 (119.9; 143.3)	21.1|8.4 (14.9; 37.4)	-1.5|8.7 (-15.7; 25.6)	1.1|9.0 (-7.2; 22.2)	5.7|11.9 (-5.0; 27.3)	2.1|10.7 (-1.8; 23.3)
	Adj *p*	0.46	0.46	0.52	0.9	0.9	0.46
	ES	0.05	0.06	0.05	0.01	0.01	0.1
DBP (mmHg)	Non-frail	76.8|10.8 (58.7; 88.9)	13.8|8.8 (6.0; 27.7)	0.8|2.9 (-6.8; 7.6)	1.0|2.6 (-4.3; 10.9)	3.0|3.0 (-1.1; 13.6)	1.3|3.7 (-3.0; 9.2)
	Pre-frail	75.5|17.2 (57.6; 91.1)	12.3|7.3 (5.5; 22.3)	0.8|4.6 (-11.8; 7.1)	1.8|4.3 (-9.9; 6.9)	3.5|4.4 (-9.3; 12.4)	2.4|4.6 (-11.6; 9.8)
	Frail	83.5|9.1 (66.2; 89.3)	12.1|5.8 (6.7; 17.3)	-0.7|3.7 (-5.0; 13.6)	0.8|2.8 (-3.5; 13.1)	3.3|5.0 (-0.2; 25.8)	2.7|6.5 (-1.9; 17.0)
	Adj *p*	0.35	0.7	0.84	0.9	0.9	0.84
	ES	0.07	0.05	0.03	0.01	0.01	0.02
MAP (mmHg)	Non-frail	96.1|12.5 (78.3; 110.7)	17.7|11.8 (7.8; 31.4)	1.6|3.4 (-6.0; 6.9)	1.2|4.5 (-2.9; 12.4)	4.5|3.1 (-3.1; 14.7)	1.7|3.4 (-2.5; 9.4)
	Pre-frail	93.8|15.2 (76.2; 116.6)	15.6|5.0 (8.4; 24.9)	1.8|4.4 (-12.0; 9.1)	2.5|5.6 (-12.2; 9.6)	4.5|7.8 (-8.1; 16.2)	3.8|6.5 (-12.6; 10.7)
	Frail	98.2|6.1 (91.6; 110.8)	16.5|5.4 (11.0; 22.4)	-2.0|7.0 (-9.7; 16.9)	0.3|5.9 (-5.1; 15.4)	3.8|7.6 (-1.9; 30.6)	1.8|8.4 (-1.0; 21.1)
	Adj *p*	0.7	0.7	0.7	0.9	0.9	0.9
	ES	0.05	0.05	0.03	0.01	0.01	0.01

SVR ($mmHg.min^{-1}L^{-1}$)	Non-frail	25.4|7.7 (18.2; 41.7)	11.5|7.4 (5.2; 21.5)	-2.0|3.0 (-8.6; 5.4)	-1.4|2.8 (-7.6; 5.4)	2.0|4.5 (-5.2; 11.4)	-0.5|4.8 (-4.9; 9.3)
	Pre-frail	27.7|7.6 (18.4; 49.8)	11.7|5.6 (5.5; 20.6)	-2.6|4.4 (-10.3; 2.8)	-2.8|4.3 (-7.4; 2.2)	-0.4|5.0 (-6.1; 9.1)	-0.6|4.0 (-7.9; 6.8)
	Frail	25.6|5.9 (19.3; 49.8)	8.5|3.1 (7.3; 16.6)	-0.4|1.8 (-3.9; 1.6)	-1.2|3.9 (-3.5; 3.5)	1.3|8.0 (-1.5; 9.5)	0.4|5.3 (-2.8; 8.7)
	Adj *p*	0.8	0.56	0.52	0.52	0.52	0.7
	ES	0.01	0.04	0.05	0.06	0.05	0.02
HR ($beats.min^{-1}$)	Non-frail	60.2|9.6↓*§ (49.2; 74.5)	11.2|5.2 (4.4; 24.5)	11.2|5.1 (4.4; 24.5)	5.3|4.9 (0.7; 12.1)	8.1|4.6 (1.8; 18.8)	5.4|4.4 (0.2; 18.4)
	Pre-frail	68.1|7.1 (56.2; 78.1)	14.0|6.2 (8.0; 21.1)	14.0|6.2 (8.0; 21.1)	8.1|5.0 (2.6; 14.2)	9.5|5.1 (4.2; 17.0)	8.1|5.3 (3.0; 16.3)
	Frail	72.3|18.3 (55.0; 92.4)	10.8|6.3 (3.7; 19.7)	10.8|6.3 (3.7; 19.7)	7.7|5.1 (2.0; 19.2)	9.9|3.1 (4.6; 20.0)	7.9|3.9 (4.2; 19.1)
	Adj *p*	**0.03**	0.4	0.4	0.17	0.4	0.14
	ES	0.2	0.03	0.03	0.07	0.05	0.1
CO ($L.min^{-1}$)	Non-frail	3.7|1.2 (2.0; 5.1)	1.7|0.8 (0.5; 4.8)	1.7|0.8 (0.5; 4.7)	0.5|0.4 (-0.7; 1.8)	0.4|0.6 (-0.1; 1.6)	0.1|0.6 (-0.9; 1.2)
	Pre-frail	3.5|0.5 (2.0; 4.7)	1.3|0.8 (0.5; 2.2)	1.3|0.8 (0.5; 2.2)	0.4|0.7 (-0.1; 1.2)	0.5|0.5 (0.1; 1.3)	0.1|0.5 (-0.6; 1.1)
	Frail	3.8|0.6 (1.9; 5.7)	1.3|0.5 (0.5; 2.3)	1.3|0.5 (0.5; 2.3)	0.4|0.4 (-0.2; 1.4)	0.4|0.8 (-0.2; 1.3)	0.1|0.5 (-0.9; 0.9)
	Adj *p*	0.52	0.23	0.23	0.9	0.84	0.9
	ES	0.04	0.09	0.09	0.01	0.01	0.01

SV (mL)	Non-frail	57.1|22.5 (31.0; 87.4)	15.9|12.9 (3.9; 36.5)	6.5|11.7 (-7.2; 53.2)	1.9|9.1 (-21.1; 23.1)	-3.9|7.2 (-25.8; 21.6)	-4.4|11.2 (-23.7; 16.6)
	Pre-frail	50.1|8.4 (31.3; 67.8)	9.8|6.8 (-1.5; 22.9)	3.8|9.0 (-6.7; 11.3)	-0.6|6.8 (-11.0; 9.6)	-3.6|6.1 (-13.2; 7.0)	-2.1|10.0 (-15.5; 6.3)
	Frail	58.0|20.7 (32.8; 69.7)	11.4|6.6 (1.7; 19.4)	1.4|6.7 (-4.5; 13.1)	-2.0|6.3 (-11.6; 10.5)	-6.6|10.8 (-19.2; 8.9)	-5.5|7.5 (-20.7; 6.9)
	Adj *p*	0.21	0.14	0.35	0.42	0.58	0.6
	ES	0.1	0.13	0.06	0.04	0.03	0.02

|: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; ↓ lower than; Adj *p*: adjusted *p*-value; ES: effect size. *Statistically significant differences between non-frail and frail. §Statistically significant differences between non-frail and pre-frail. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Lie-to-stand

SBP, DBP, MAP, SVR, and HR short-term cardiovascular compensatory responses were similar across all phases and groups in the lie-to-stand transition. However, in phase 1, CO and SV peak values were higher in the non-frail group than in the pre-frail and frail groups, with no statistically significant differences between pre-frail and frail groups. No significant differences were observed between the groups from phases 2 through 4 (Table 9.3).

Table 9.3 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses during lie-to-stand between non-frail, pre-frail, and frail.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Non-frail	125.9|20.9 (105.4; 151.7)	27.8|17.8 (6.1; 29.1)	2.2|12.2 (-25.2; 17.5)	-0.1|8.9 (-29.1; 17.3)	3.0|10.8 (-23.2; 24.7)	4.5|13.2 (-32.8; 19.3)
	Pre-frail	129.2|19.2 (105.9; 154.7)	34.2|10.6 (12.5; 51.8)	-6.2|8.2 (-20.4; 5.8)	-3.8|4.9 (-18.2; 4.9)	1.8|6.6 (-8.8; 8.7)	-4.5|11.5 (-12.1; 7.4)
	Frail	135.2|23.4 (111.7; 162.0)	28.1|20.9 (11.1; 49.7)	-2.4|16.5 (-23.1; 7.6)	-3.4|12.3 (-20.5; 21.4)	6.5|7.2 (-5.3; 27.1)	6.4|11.3 (-8.0; 35.2)
	Adj *p*	0.58	0.6	0.2	0.52	0.46	0.2
	ES	0.02	0.02	0.12	0.05	0.05	0.11
DBP (mmHg)	Non-frail	77.3|9.8 (58.7; 90.6)	20.1|5.3 (9.8; 34.6)	1.3|5.5 (-6.7; 16.4)	1.5|5.5 (-7.5; 16.6)	2.2|6.6 (-7.6; 23.4)	3.6|6.0 (-5.4; 19.9)
	Pre-frail	79.1|14.7 (52.7; 96.9)	20.1|7.5 (9.4; 28.1)	-3.9|5.6 (-9.1; 3.1)	-0.1|6.9 (-8.3; 4.3)	2.5|4.5 (-6.1; 9.8)	1.0|4.7 (-8.2; 14.1)
	Frail	80.6|7.2 (71.4; 96.8)	16.4|8.3 (8.2; 28.6)	-1.7|15.1 (-9.8; 21.7)	1.3|12.3 (-10.0; 27.1)	7.6|13.0 (0.1; 32.5	5.4|13.2 (-2.0; 28.3)
	Adj *p*	0.35	0.35	0.24	0.4	0.35	0.35
	ES	0.04	0.05	0.1	0.03	0.04	0.06
MAP (mmHg)	Non-frail	98.1|10.5 (81.9; 115.2)	23.8|5.4 (13.1; 46.4)	0.6|7.2 (-13.9; 14.4)	-1.5|7.3 (-16.8; 15.4)	3.8|7.9 (-12.2; 23.5)	2.6|9.3 (-14.6; 20.0)
	Pre-frail	99.1|14.7 (71.8; 118.1)	27.6|8.5 (10.5; 37.7)	-6.3|5.0 (-13.8; 2.6)	-3.2|7.2 (-11.8; 3.3)	1.8|8.0 (-5.1; 10.2)	-1.6|6.1 (-13.3; 5.7)
	Frail	97.7|12.1 (92.5; 121.3)	24.8|16.3 (7.6; 38.3)	-2.4|16.1 (-17.5; 11.9)	1.8|12.4 (-15.2; 20.9)	7.7|15.2 (-2.4; 33.6)	6.8|14.4 (-4.1; 29.3)
	Adj *p*	0.6	0.46	0.28	0.28	0.28	0.28
	ES	0.01	0.02	0.1	0.06	0.06	0.1

SVR ($mmHg.min^{-1}L^{-1}$)	Non-frail	26.6|7.9 (15.5; 40.6)	13.1|4.1 (8.5; 25.3)	-1.3|2.9 (-7.6; 31.6)	-0.3|3.9 (-5.9; 38.4)	2.4|6.0 (-3.1; 43.4)	0.2|7.3 (-4.6; 38.1)
	Pre-frail	29.5|5.9 (21.5; 44.6)	13.6|5.3 (6.9; 22.5)	-3.3|5.6 (-13.1; 4.5)	-1.7|5.2 (-11.9; 7.5)	2.7|7.2 (-11.1; 7.3)	-0.2|5.3 (-13.3; 40.6)
	Frail	26.8|10.7 (15.2; 39.1)	10.0|1.7 (4.9; 14.3)	-0.4|13.4 (-6.7; 19.5)	1.3|9.3 (-5.4; 24.9)	5.0|13.5 (-1.2; 29.8)	3.5|13.2 (-3.2; 22.4)
	Adj *p*	0.14	0.07	0.11	0.14	0.5	0.35
	ES	0.06	0.17	0.12	0.1	0.03	0.04
HR ($beats.min^{-1}$)	Non-frail	58.3|12.1↓*§ (46.0; 72.5)	16.3|5.8 (5.6; 32.0)	16.3|5.8 (5.6; 32.0)	10.0|6.7 (0.4; 20.7)	13.0|8.0 (5.5; 19.7)	8.2|6.1 (2.5; 16.5)
	Pre-frail	66.2|4.5 (53.3; 78.9)	17.5|6.3 (8.9; 40.4)	17.5|6.3 (8.9; 40.4)	16.0|6.5 (2.3; 41.3)	16.5|6.9 (4.5; 42.8)	11.7|6.0 (1.8; 32.1)
	Frail	69.8|15.3 (57.5; 89.9)	13.6|4.7 (12.1; 24.0)	13.6|4.7 (12.1; 24.0)	12.7|6.7 (8.1; 17.0)	11.9|5.8 (5.6; 18.6)	7.9|7.5 (3.8; 17.2)
	Adj *p*	**0.03**	0.5	0.5	0.18	0.28	0.28
	ES	0.22	0.03	0.03	0.09	0.06	0.05
CO ($L.min^{-1}$)	Non-frail	3.6|1.0 (2.2; 5.4)	2.3|1.3↑*§ (0.8; 6.0)	2.3|1.3↑*§ (0.8; 6.0)	0.5|0.6 (-0.7; 2.6)	0.4|0.6 (-1.3; 1.4)	-0.1|1.0 (-2.7; 0.8)
	Pre-frail	3.3|0.6 (2.2; 4.2)	1.3|0.9 (0.5; 2.3)	1.3|0.9 (0.5; 2.3)	0.3|0.7 (-0.1; 1.4)	0.3|0.7 (-0.1; 1.5)	-0.1|0.5 (-1.2; 1.1)
	Frail	3.8|1.6 (2.3; 5.6)	0.9|0.7 (0.3; 3.0)	0.9|0.7 (0.3; 3.0)	0.1|0.7 (-1.2; 0.5)	0.2|0.6 (-1.6; 0.6)	0.1|1.0 (-1.9; 0.3)
	Adj *p*	0.1	**0.003**	**0.003**	0.14	0.23	0.3
	ES	0.06	0.3	0.3	0.08	0.06	0.04

SV (mL)	Non-frail	60.5|15.9↑*§ (39.8; 93.2)	12.3|13.5 (2.2; 49.8)	5.1|7.2↑*§ (-14.4; 33.9)	-5.7|9.2 (-21.7; 14.7)	-7.7|12.5 (-30.9; 5.9)	-9.1|13.0 (-26.0; 10.4)
	Pre-frail	49.9|13.1 (35.4; 62.5)	8.3|5.7 (1.1; 17.0)	1.7|9.7 (-13.8; 8.5)	-6.4|6.5 (-14.3; 11.0)	-6.7|5.2 (-20.4; 11.2)	-6.9|8.9 (-18.1; 9.9)
	Frail	51.8|17.2 (41.3; 84.0)	6.2|5.5 (-5.4; 24.4)	-2.9|9.9 (-18.0;5.3)	-7.2|10.4 (-24.6; 9.9)	-6.3|9.9 (-27.5; 2.0)	-3.1|6.2 (-29.6; 0.7)
	Adj *p*	**0.023**	0.07	**0.014**	0.7	0.7	0.56
	ES	0.18	0.13	0.25	0.01	0.01	0.03

|: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; ↑ higher than; Adj *p*: adjusted *p*-value; ES: effect size. *Statistically significant differences between non-frail and frail. §Statistically significant differences between non-frail and pre-frail. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

In the sit-to-stand transition (Figure 9.4), the non-frail group showed a significant negative correlation between CO and SVR in all phases. A medium correlation in phase 1 (r = -0.465, 95% CI -0.699; -0.047, p = 0.01), and a large correlation in phase 2 (r = -0.810, 95% CI -0.941; -0.729, p < 0.001), phase 3 (r = -0.622, 95% CI -0.767; -0.193, p < 0.001), and phase 4 (r = -0.964, 95% CI -0.951; -0.771, p < 0.001). The pre-frail group showed no statistically significant correlation in phase 1 (r = -0.374, 95% CI -0.760; -0.239, p = 0.2). However, a large and significant negative correlation was observed from phases 2-4 (phase 2: r = -0.841, 95% CI -0.966; -0.660, p < 0.001, phase 3: r = -0.901, 95% CI -0.923; -0.353, p < 0.001), and phase 4: (r = -0.890, 95% CI -0.955; -0.571, p < 0.001). In the frail group, the CO and SVR correlation was not statistically significant in phase 1 (r = -0.333, 95% CI -0.894; 0.300, p = 0.4) and phase 3 (r = -0.310, 95% CI -0.804; -0.567, p = 0.4). However, a large and significant negative correlation was observed in phase 2 (r = -0.857, 95% CI -0.979; -0.471, p = 0.01) and phase 4 (r = -0.738, 95% CI -0.965; -0.249, p = 0.04).

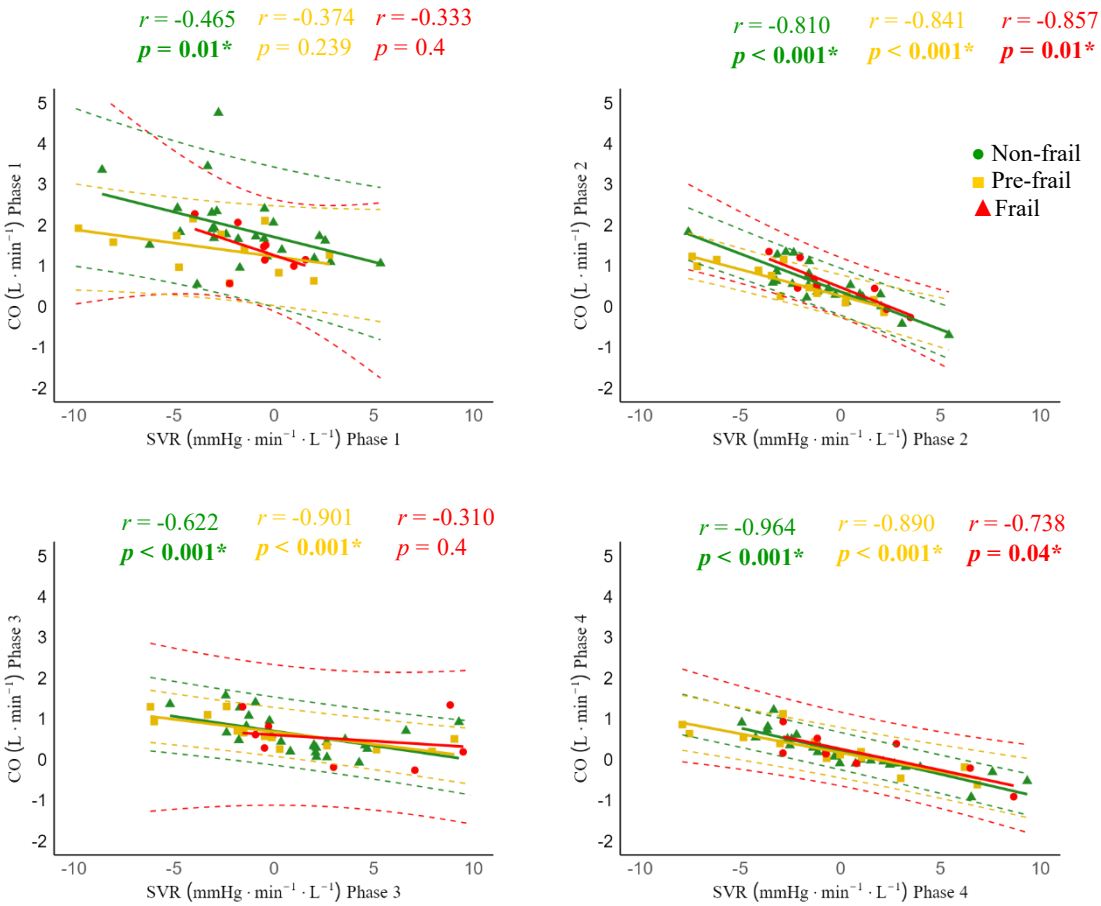


Figure 9.4 Cardiac output and systemic vascular resistance correlation during sit-to-stand in non-frail, pre-frail, and frail older adults.

In the lit-to-stand transition (Figure 9.5), the non-frail group showed a large significant correlation between CO and SVR in all phases: phase 1 (r = -0.580, 95% CI -0.657; -0.018, p = 0.001), phase 2 (r = -0.798, 95% CI -0.887; -0.287, p < 0.001), phase 3 (r = -0.677, 95% CI -0.882; -0.5448, p < 0.001), and phase 4 (r = -0.900, 95% CI -0.918; -0.319, p < 0.001). The pre-frail group showed no significant correlation in phase 1 (r = -0.549, 95% CI -0.784; -0.182, p = 0.06). Unlike phase 1, a large and significant negative correlation was observed from phases 2 to 4 (phase 2: r = -0.808, 95% CI -0.915; -0.307, p = 0.001, phase 3: r = -0.775, 95% CI -0.956; -0.575, p = 0.003), and phase 4: (r = -0.956, 95% CI -0.960; -0.604, p < 0.001). In the frail group, there was no significant correlation in phase 1 (r = -0.095, 95% CI -0.516; 0.828, p = 0.8) and phase 2 (r = -0.690, 95% CI -0.966; -0.268, p = 0.06). However, large and significant negative correlations were observed in phase 3 (r = -0.738, 95% CI -0.975; -0.398, p = 0.046) and phase 4 (r = -0.929, 95% CI -0.983; -0.559, p = 0.002).

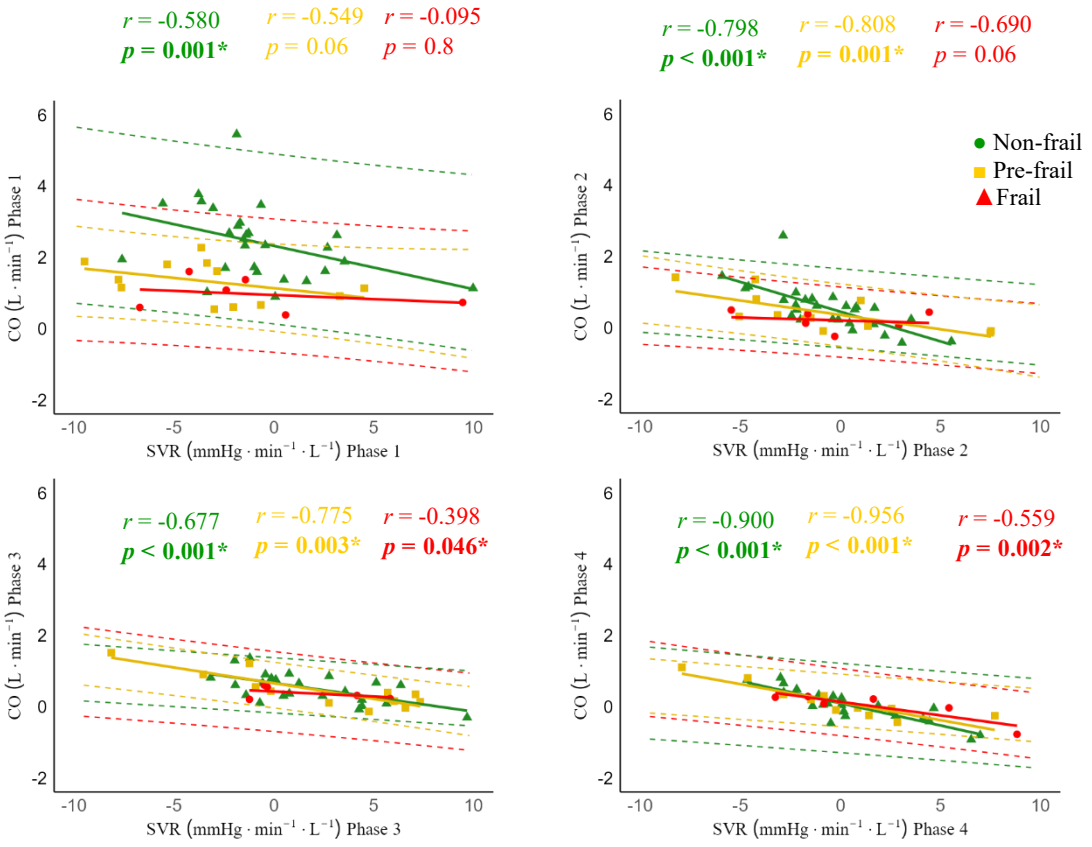


Figure 9.5 Cardiac output and systemic vascular resistance correlation during lie-to-stand in non-frail, pre-frail, and frail older adults.

Discussion

This is one of the first studies to analyze phase-specific short-term cardiovascular compensatory responses in community-dwelling non-frail, pre-frail, and frail older adults under two distinct active-standing orthostatic stress. It aimed to describe and compare the dynamic integrative cardiovascular regulation during sit-to-stand and lie-to-stand transitions. At baseline, SBP, DBP, MAP, SVR, and CO were similar across all groups in both conditions. HR was lower in the non-frail group in both conditions, while SV was higher in the non-frail group in the lie-to-stand transition. In lie-to-stand, the CO peak value was higher in the non-frail group, but no statistical differences were observed in the other variables. Additionally, CO and SV were higher in phase 1 in the non-frail group, while SBP, DBP, MAP, SVR, and HR were similar across all phases and groups. The CO and SVR correlation (matching), which indicates the timing of BP regulation, showed different responses among groups. The non-frail group showed a significant negative correlation in all phases in sit-to-stand and lie-to-stand transitions. The pre-frail group showed a significant negative correlation from phases 2-4 in both transitions. The frail group showed a significant negative correlation in phases 2 and 4 in the sit-to-stand transition, and in phases 3 and 4 in the lie-to-stand transition. These results indicate that non-frail individuals reach BP stabilization within 30 s, while pre-frail and frail groups require more time for BP regulation under different levels of orthostatic stress, reaching BP stabilization within 60 s and 180 s, respectively. The three groups showed similarities in OH prevalence and OI self-reported symptoms.

Baseline Responses During Active Standing Orthostatic Stress

No statistical differences were found at baseline in SBP, DBP, MAP, SVR, and CO across all groups in both conditions. HR was lower in the non-frail group in both transitions, while SV was higher in the lie-to-stand transition. Romero-Ortuno et al.[6] reported that SBP and DBP were similar between non-frail, pre-frail, and frail, while HR was lower in the non-frail group at baseline, supporting our results. Chen et al.[188] also showed that baseline SBP and DBP were not different between non-frail and pre-frail groups, which aligns with our results. Corroborating partially with our findings, Shaw et al.[53] did not find statistical differences between non-frail and frail in SBP and DBP at baseline. In contrast with our data, the authors reported no statistical differences in HR at baseline between non-frail and frail individuals.

No statistically significant differences in SBP, DBP, MAP, SVR, and CO baseline values across all groups in both conditions indicate that under resting supine, cardiovascular parameters remain similar regardless of frailty status. However, the lower HR observed in the non-frail group likely reflects greater vagal modulation and autonomic balance, indicative of well-regulated cardiac function at baseline[24,35]. Greater vagal modulation and autonomic balance are advantageous because they support rapid cardiovascular regulation during orthostatic challenges, reducing the likelihood of exaggerated HR peak or BP fluctuations[35]. Additionally, the higher SV in the non-frail group during the lie-to-stand transition suggests less disturbance in SV. Higher SV supports adequate cardiovascular responses and helps maintain cerebral perfusion and blood flow to the brain during postural changes[189]. SV maintenance during these transitions is particularly important to prevent an excessive decline in CO and systemic perfusion during standing, assisting in faster cardiovascular regulation[141].

Immediately On Standing Responses During Active Standing Orthostatic Stress

In the sit-to-stand transition, there were no statistically significant differences in all variables between the three groups. In the lie-to-stand transition, SBP, DBP, MAP, SVR, HR, and SV were similar across all groups, while the CO peak value was higher in the non-frail group. Shaw et al.[53] did not find statistically significant differences in SBP and HR between non-frail and frail individuals immediately on standing, corroborating our findings. Romero-Ortuno et al.[6] did not find statistical differences in the lie-to-stand transition in SBP and DBP between non-frail, pre-frail, and frail individuals, supporting our results. However, HR peak value was higher in the non-frail group than in the pre-frail and frail groups, contrasting our findings.

Similar cardiovascular responses across all groups in a lower level of orthostatic stress (sit-to-stand) suggest that the BP regulation immediately on standing is primarily maintained through autonomic reflexes, such as baroreceptor activation, which rapidly adjusts HR and vascular resistance to counteract the effects of postural changes[35]. The higher CO peak value observed in the non-frail group in a higher level of orthostatic stress (lie-to-stand) may indicate a more pronounced cardiac contribution to BP regulation[16], likely reflecting an enhanced SV and HR in response to orthostatic stress[16]. This implies that non-frail older adults may have a more effective compensatory response, relying on increased CO to maintain perfusion[17], which is limited among frail older adults.

Short-Term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress

In the sit-to-stand transition, there were no statistically significant differences across the analyzed phases (1-4) for all groups (non-frail, pre-frail, and frail). In the lie-to-stand transition, CO and SV peak values in phase 1 in the non-frail group were higher compared to the pre-frail and frail groups, with no differences for other variables across all phases and groups. Similar to our findings, Romero-Ortuno et al.[6] did not find statistical significance in the lie-to-stand transition in SBP and DBP at 30, 60, and 120 s from baseline. However, in contrast with our results, the authors showed that HR at 30 s was higher in the non-frail group, while no statistical differences were found at 120 s. Mol et al.[96] observed significant associations between SBP and DBP responses within the first 15 seconds and from 15 to 180 seconds after standing and frailty status. Kocyigit et al.[89] reported correlations between frailty classification (non-frail, pre-frail, frail) and SBP and DBP values at 1, 3, and 5 minutes after the head-up tilt test, with the frail group showing higher correlation coefficients across all time points. Although these studies did not directly assess compensatory responses, they suggest a potential link between delayed BP regulation and frailty.

No differences in the short-term cardiovascular compensatory responses across frailty status during the sit-to-stand transition indicate that a lower orthostatic stress challenge was not sufficient to disturb cardiovascular regulation among frail community-dwelling older adults. The higher CO and SV peaks in phase 1 (0-30 s) observed in the non-frail group during the lie-to-stand transition may indicate a more immediate cardiovascular response, likely driven by an effective Frank-Starling mechanism and autonomic regulation[16]. This early response in SV and CO suggests a greater redistribution of blood flow, allowing for rapid compensation against the gravitational displacement of blood[16,35]. The similar responses observed in other variables across all phases and groups show that vascular adjustments, including SVR, may follow a similar response in these specific time points, independently of frailty status.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

This study is the first to examine the correlation between CO and SVR across specific phases, aiming to identify the potential timing of BP regulation relative to baseline values in older adults living with frailty. The matching between CO and SVR is

crucial for BP regulation and ensuring adequate cerebral perfusion[16,24] during postural transitions.

The non-frail group showed a significant negative correlation between CO and SVR across all phases in both transitions. This indicates that non-frail individuals regulated BP within 30 s (phase 1) under lower and higher gravitational stress. The pre-frail group exhibited no significant correlation in phase 1 (0-30 s), but a significant negative correlation from phases 2 to 4 in both transitions. These results indicate that CO and SVR matching occurred within 30-60 s (phase 2), which is longer than in the non-frail group. In the sit-to-stand transition, the frail group showed no significant correlation in phase 1 (0-30 s), a negative correlation in phase 2 (30-60 s), a loss of a significant correlation in phase 3 (60-180 s), and the negative correlation was reported again in phase 4 (300-420 s). In the lie-to-stand transition, the frail group correlations were observed in phases 3 and 4, but not in phases 1 and 2. These findings indicate that frail community-dwelling older adults have more difficulty regulating BP and also have delayed responses compared with pre-frail and non-frail older adults. Additionally, frail older adults demonstrated higher BP instability requiring more time to regulate BP, varying from 30 s to 180 s depending on the gravitational stress challenge (lower or higher). These findings indicated that not only are the values of the variables important, but also that the time of responses also matters.

The delayed BP regulation observed in pre-frail and frail individuals may be attributed to impairments in baroreflex sensitivity, reduced vascular compliance, and diminished autonomic responsiveness[16,35]. These factors can lead to prolonged compensatory vasoconstriction and CO regulation required to stabilize BP following postural transitions[16,24]. Additionally, a decline in cardiovagal function and reduced β-adrenergic responsiveness in frail individuals may further contribute to the delayed integration of cardiovascular responses[16,24,35], increasing susceptibility to BP dysregulation.

Prevalence of Orthostatic Hypotension and Orthostatic Intolerance Symptoms

No significant differences were observed between groups in the proportion of participants who met the criteria for OH. Similarly, the proportion of non-frail, pre-frail, and frail individuals self-reporting OI symptoms did not differ significantly (11%, 22%, and 13%, respectively). In contrast with our results, Romero Ortuno et al.[6] showed no statistical difference in DOH and a higher prevalence of IOH in frail than non-frail and

pre-frail. Also, the authors reported higher OI symptoms in the frail group than in the non-frail and pre-frail groups. Also, not aligned with our findings, Kocyigit et al.[89] reported a higher prevalence of OH in frail individuals than in non-frail individuals.

The similar prevalence of OH and OI symptoms across all groups suggests that the occurrence of these conditions may not be solely dependent on frailty status but rather influenced by other physiological factors such as autonomic function[35], vascular compliance[16], and circulatory control[35]. This finding suggests that factors beyond frailty status, such as individual variations in baroreflex sensitivity[65], blood volume regulation[16], and neurovascular control[35] may play a more critical role in the development of OH and OI symptoms.

Limitations

Despite the strengths raised in the above discussion, this study has some limitations. The frail group was relatively small, representing 16% of the total sample, which may have reduced the statistical power to detect significant differences between groups and limited the applicability of the findings. A small sample size increases the risk of type II errors, potentially hiding physiologically meaningful differences in BP regulation. Similar to our sample, Romero-Ortuno et al.[6] also had a limited frail group, representing only 7% of their total sample (n = 31). However, the consistency of our results with existing literature reinforces the reliability of the observed findings. However, we recognize that future studies should focus on increasing the frail community-dwelling older adults' participation in research.

The use of medication among older adults was recorded but not controlled (Appendix 4), potentially influencing cardiovascular responses during active orthostatic stress. Many older individuals are prescribed hypertensive medications, such as beta-blockers and diuretics, which can alter HR, BP, and vascular resistance[3]. In the non-frail group, 36% of the individuals used calcium channel blockers (n = 10), 18% beta-blockers (n = 5), 9% diuretics (n = 3), and 36% ACE inhibitors (n = 10). Among pre-frail individuals, 40% used calcium channel blockers (n = 8), 10% beta-blockers (n = 2), 20% diuretics (n = 4), and 30% angiotensin receptor blockers (n = 6). In frail older adults, 42% used calcium channel blockers (n = 5), 33% beta-blockers (n = 4), 17% diuretics (n = 2), and 8% angiotensin receptor blockers (n = 1). While these medications may have affected the short-term cardiovascular compensatory responses observed in this study, they also

represent the typical clinical profile of community-dwelling older adults with frailty, strengthening the relevance of our findings.

Also, sex distribution was not balanced across frailty categories, which may have influenced the results. Previous research has demonstrated sex-related differences in cardiovascular function, vascular responsiveness, and hormonal regulation[1,63,190,191], which can affect cardiovascular adjustments to postural changes. As such, the observed differences in cardiovascular responses may partly reflect underlying sex-based physiological variability rather than frailty status alone.

Conclusion

This study highlights phase-specific differences in short-term cardiovascular compensatory responses during postural transitions in non-frail, pre-frail, and frail community-dwelling older adults. While baseline cardiovascular parameters were similar between groups, the short-term compensatory responses in the non-frail group exhibited higher CO on standing and greater CO and SV peaks in phase 1 (0-30 s). BP regulation timing varied with frailty status, with delayed responses observed in pre-frail (30-60 s) and frail (60-180 s) older adults, particularly under higher orthostatic stress. Despite these differences, OH and OI prevalence remained similar across groups. These findings indicate that frailty influences the efficiency of BP regulation, and the time of these responses matters, which may have implications for fall risk and cardiovascular dysfunction in older adults living with frailty.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study revealed that frailty is associated with progressively impaired cardiovascular short-term compensatory responses during postural transitions. Compared to non-frail and pre-frail participants, frail older adults exhibited more pronounced drops in BP and lower CO peak. The timing of BP regulation varied by frailty status, with delayed responses observed in pre-frail individuals during 30-60 seconds (phase 2) and in frail individuals during 60-180 seconds (phase 3), particularly under higher orthostatic stress. These alterations suggest that frailty compromises both cardiac and vascular mechanisms needed to maintain hemodynamic stability under orthostatic stress. The results demonstrated the clinical relevance of frailty assessment in predicting orthostatic intolerance and its consequences, such as falls and reduced functional capacity. This chapter adds to the thesis by demonstrating that cardiovascular dysregulation in older adults is not uniform but varies significantly with frailty status, reinforcing the importance of early detection and personalized intervention in the older frail population.

10. Chapter 10

Increased autonomic dysregulation at baseline and enhanced parasympathetic modulation on standing in frail older adults during active orthostatic stress

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Preface to the Manuscript Written Exclusively by Dihogo de Matos

This manuscript examines the effects of frailty on short-term autonomic compensatory responses to active standing orthostatic stress, with a particular focus on heart rate variability (HRV), cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG). The study was designed to build upon the earlier chapters by adding a time-phase perspective to the analysis of autonomic regulation across non-frail, pre-frail, and frail older adults. I was responsible for designing the study, conducting participant recruitment and assessment, performing all analyses, and writing the manuscript. This work contributes a novel phase-specific approach to characterizing autonomic adaptation in frailty, offering valuable insights for clinical and research applications in geriatric populations.

Publication Status

This study will be submitted to The Journal of Frailty & Aging.

Abstract

Frailty is associated with autonomic dysfunction, which may impair autonomic regulation during active standing orthostatic stress. However, limited research has examined short-term autonomic compensatory responses to active standing orthostatic stress across different phases and levels of frailty. This study aimed to describe and compare frailty-specific differences in heart rate variability (HRV) indexes at baseline, cardiac parasympathetic modulation (CPM) immediately on standing, and cardiac baroreflex gain (CBG) responses at specific time points during postural transitions. Additionally, the incidence of orthostatic intolerance (OI) symptoms was assessed across frailty groups. This observational study included older adults (60-79 years) classified as non-frail, pre-frail, or frail based on the frailty index. HRV was assessed in the supine position in the time and frequency domains. CPM was obtained using the 30^{th} beat and the 15^{th} beat (HR 30:15), evaluating vagal control over HR. CBG was measured as the ratio of HR change to systolic blood pressure (SBP) drop (ΔHR/ΔSBP) at four specific phases (0-30 s, 30-60 s, 60-180 s, and 300-420 s). Orthostatic intolerance (OI) symptoms were self-reported post-test. Pre-frail and frail individuals exhibited an imbalance between parasympathetic and sympathetic activity at baseline. The pre-frail group showed lower CPM following active standing, while the frail group had a higher CBG response in phase 1 of the lie-to-stand transition. No significant differences in OI symptoms were observed between groups. In conclusion, autonomic regulation is affected by frailty at baseline and during postural transitions. Pre-frail and frail individuals presented altered autonomic balance, with distinct short-term compensatory response dysfunction.

Keywords: frailty, heart rate variability, cardiac parasympathetic modulation, cardiac baroreflex gain

Introduction

Homeostatic dysregulation compromises the rapid adjustments in the integrative autonomic and cardiovascular regulatory mechanisms[18]. The autonomic nervous system plays a critical role in homeostasis maintenance[143]. However, if these systems are not well integrated, people could have episodes of a sudden drop in blood pressure when standing upright, known as orthostatic hypotension (OH)[12]. OH increases the likelihood of falls and postural instability during the first few seconds following standing upright[186], and is also associated with frailty[6]. OH often presents with orthostatic intolerance (OI) symptoms (e.g., dizziness or lightheadedness)[186] which are commonly reported among frail individuals[15].

Frailty is a global challenge with significant consequences for clinical practice and public health[21]. Frailty is linked to difficulties in performing everyday tasks as well as negative health outcomes (e.g., heart diseases, falls, and disability)[192]. It is a condition that causes a loss of function across several physiological systems, as well as an increased susceptibility to stressors[21]. The underlying pathophysiology of frailty is associated with a dynamic, dysregulated physiological system in which autonomic dysfunction plays a critical role.

The autonomic nervous system (ANS) is critical to maintaining body homeostasis. Its proper function is crucial for the regulation of physiological responses, such as blood pressure (BP) control and regulation, and heart rate (HR) adjustments during stress[18]. A key indicator of ANS health is heart rate variability (HRV), which reflects the system's ability to adapt to sudden physiological demands[18]. Studies investigating HRV in frail populations have inconsistent results. Katayama et al.[41] reported an increased power in the low-frequency band and a decreased power in the high-frequency band. Conversely, research by Chaves et al.[193] demonstrated opposite results regarding HRV analysis. The authors also found that lower physiological complexity in HRV indexes is significantly associated with higher levels of frailty, reflecting a loss of ANS adaptive capacity. These conflicting findings highlight the complexity of the autonomic responses in frailty and show the need for further research to elucidate ANS responses in the frailty population.

Cardiac parasympathetic modulation (CPM) is essential for maintaining autonomic balance by regulating the interaction between the parasympathetic and sympathetic nervous systems on standing[146]. Evidence suggests that frail individuals may exhibit increased parasympathetic activity[41], potentially leading to lower CPM. However, studies on the effects of frailty on CPM following active standing orthostatic stress in

community-dwelling older adults remain scarce. This gap in the literature limits the understanding of how frailty influences autonomic compensatory responses after postural transitions.

Cardiac baroreflex gain (CBG) is typically reduced in frail individuals[23], which increases the possibility of homeostatic dysregulation. Existing literature provides some evidence on the effects of frailty on CBG following postural transitions[23,96]. However, no studies have specifically examined CBG across specific phases following active-standing orthostatic stress. This study will address this gap by evaluating CBG across four phases: 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4), allowing for a specific time-course analysis of autonomic regulation and potential frailty-specific differences following active standing orthostatic stress. The selected time points were chosen to capture key phases of autonomic regulation following active standing. Phase 1 represents the immediate compensatory response to counteract the initial BP drop. Phase 2 reflects early stabilization through sustained sympathetic activation. Phases 3 and 4 assess autonomic dysregulation linked to late BP regulation[24,65].

This study aims to describe and compare frailty-specific differences in HRV indexes at baseline in the supine position, CPM response immediately on standing, and CBG responses at 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4) after sit-to-stand and lie-to-stand. Additionally, the study seeks to compare the incidence of OI-related symptoms among non-frail, pre-frail, and frail individuals. It is hypothesized that compared with the non-frail group, the pre-frail and frail groups will have: **(1)** lower HRV indexes at baseline. **(2)** Decreased CPM, suggesting a greater dominance of parasympathetic activity to regulate HR. **(3)** Lower CBG in phases 1 (0-30 s) and 2 (30-60 s) due to higher vagal activity. No differences are expected in phases 3 (60-180 s) and 4 (300-420 s) because, at this point, the sympathetic response has been activated, triggering the baroreceptor response. No differences are anticipated between community-dwelling pre-frail and frail individuals, as both groups exhibit impaired cardiac baroreflex gain due to lower autonomic response. It is also hypothesized that pre-frail and frail groups will have higher OI self-reported symptoms than the non-frail group.

Methods

Study Design

This is an observational case-control study that used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[114] (Appendix 14) and the Sex and Gender Equity in Research (SAGER)[115] (Appendix 15) reporting guidelines.

Settings

This research was conducted at the Applied Research Centre in the Faculty of Kinesiology and Recreation Management, University of Manitoba, from August 2022 to August 2023. Ethical approval was obtained from the University of Manitoba Health Research Ethics Board (approval number: HE2022-0058).

Participants

A convenience sampling method was employed to recruit participants. Older adults were drawn from Dr. Todd Duhamel's database at the University of Manitoba, which comprises around 1,000 females who had previously taken part in the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts study. Additional recruitment efforts involved the Centre on Aging database, in-person outreach at Men's Shed, and engagement with retirement and care facilities in Winnipeg.

The study sample included age-matched older males and females (aged 60 - 79 years) who participated in orthostatic stress challenges: sit-to-stand and lie-to-stand (Figure 10.1). Eligibility criteria required participants to be within this age range and to have been assigned male or female at birth. Individuals were excluded if they had a history of cardiovascular conditions, including ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass surgery, or congestive heart failure, as well as psychiatric disorders or severe cognitive impairment. Medications were recorded but not controlled (Appendix 4). All participants reported not doing hormone replacement therapy.

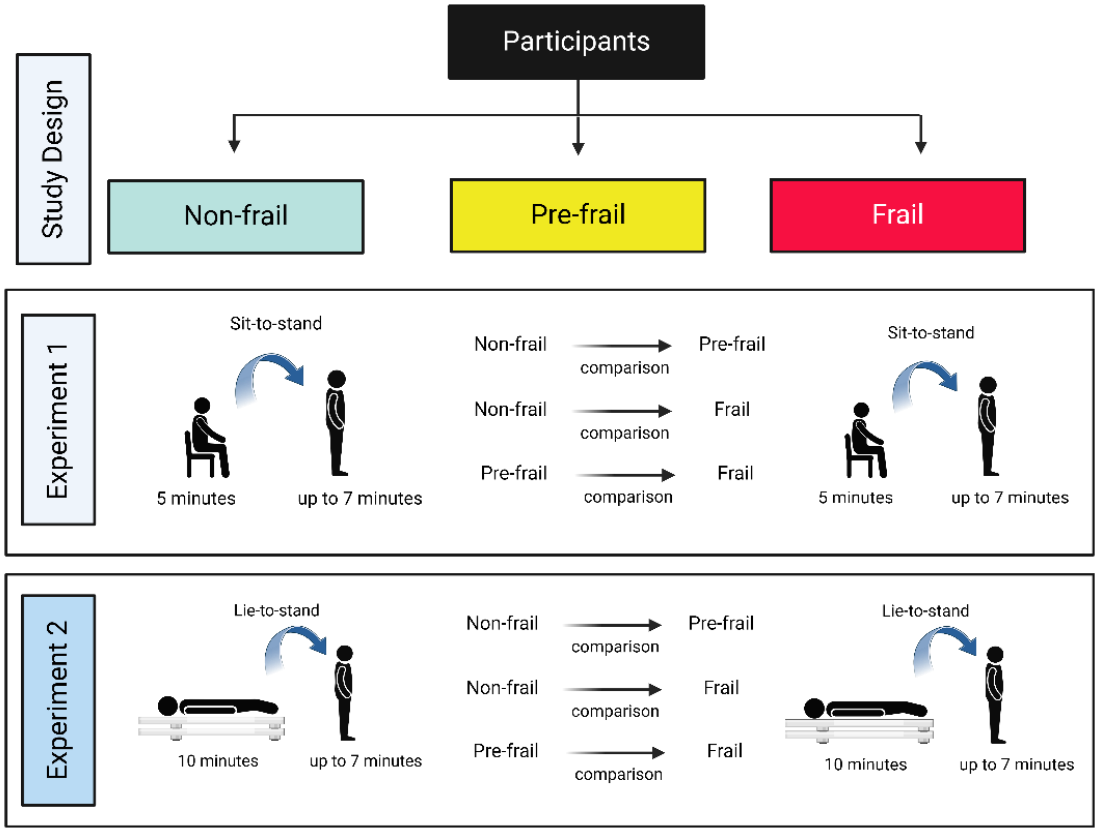

Figure 10.1 A structure for comparative research design of three distinct groups.

Data Collection

Participants received pre-instructions 48 hours before their laboratory visit. Upon arrival, they reviewed and signed an informed consent form. Before the assessments, a researcher measured resting HR and BP to confirm that each participant met the safety criteria outlined by the Canadian Society for Exercise Physiology (CSEP) guidelines[31].

Participants performed active standing orthostatic stress tests after completing the informed consent process and familiarization procedures. During the tests, BP was continuously recorded on a beat-by-beat basis using a Finometer™ Pro device (Finapres Medical System BV, Amsterdam, The Netherlands). Orthostatic intolerance (OI) was assessed immediately following the tests by asking participants to report symptoms such as dizziness, faintness, or light-headedness. All assessments took place in a quiet room maintained at a controlled temperature of 22.0 ± 1.0°C and at ambient humidity and barometric pressure. Testing sessions were scheduled on weekdays between 8:30 and 11:30 a.m. to minimize circadian cycle influences. Sit-to-stand and lie-to-stand conditions were randomized and counterbalanced to reduce potential order effects.

Demographic, Anthropometric Measurements, and Frailty Index

To describe the sample, demographic information - including sex assigned at birth, age, and date of birth - was collected along with anthropometric and body composition measurements. Body mass (kg) was measured using an InBody 270 device (©2015 InBody Co., Ltd, Cerritos, CA, USA), while height (m) was assessed with a SECA mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was calculated by dividing a participant's weight in kilograms by the square of their height in meters (kg/m^2)[116]. The Frailty Index (FI) (Appendix 13) was used to screen and classify the participants into non-frail (≤ 0.08), pre-frail (> 0.08 to 0.25), and frail (≥ 0.25) categories as recommended[187]. For example, an individual with 6 deficits out of 40 would have an FI of 0.15 (6/40), which will be classified as pre-frail.

Assessment of Heart Rate Variability, Cardiac Parasympathetic Modulation, Cardiac Baroreflex Gain

HRV, CPM, and CBG were derived from the electrocardiogram (ECG) and Finometer (Finapres Medical System, Arnhem, The Netherlands)[117] and recorded using LabChart 8.0 (AD Instruments, Colorado Springs, USA) at a sampling frequency of 1 kHz. ECG signals were processed with a bandpass filter (5–30 Hz) for R-peak detection, except during the 30 seconds before and 90 seconds after the standing transition, where the raw signal was maintained, and Finometer calibration was manually disabled. Cardiovascular parameters recorded during the sit-to-stand and lie-to-stand tests were analyzed using a custom macro developed for R-R interval detection using Lachart 8 (ADInstruments, Colorado Springs, CO, USA). The R-R intervals obtained from the ECG were used to calculate HR using automated peak detection (Lachart 8, ADInstruments, Colorado Springs, CO, USA). When the ECG signal quality was insufficient, peak detection was performed using the pressure waveform instead.

Arterial pressure was assessed non-invasively using photoplethysmography at the middle finger of the left hand (Finometer - Finapres Medical System, Arnhem, The Netherlands)[117]. BP calibration was first performed according to the manufacturer's standard procedure and then manually adjusted using an automated BP monitor (ARSIMAI, BSX516, Münster, Germany). To ensure consistency between finger and brachial pressures, the device was calibrated using the return-to-flow method approximately five minutes before each test. Finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP

readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments.

Systolic blood pressure (SBP) and HR data were recorded and transferred to a custom Matlab application (MATLAB R2024; The MathWorks Inc., Natick, MA, USA). Upon importing the data from LabChart into the Matlab application, a multi-step signal processing approach was applied to improve data quality. Initially, noise and motion artifacts were removed using a two-stage filtering process: a median filter was applied first, followed by a low-pass filter with a cutoff frequency of 0.05 rad/sample, as determined through scalogram analysis. A 5-second moving average filter was implemented to extract parameters of interest[96,120]. Following the signal processing steps, interpolation techniques were used to correct for resampling-induced delays at 1 Hz. The onset of active standing was set as time zero, with baseline represented as negative values and positive values indicating short-term compensatory responses.

Heart Rate Variability

Heart Rate Variability (HRV) was measured with continuous beat-by-beat recordings in the supine position using a three-lead electrocardiogram (ECG) module (Finometer, Finapres Medical System, Arnhem, The Netherlands) at a 1 kHz sampling rate, following the guidelines established by the *European Society of Cardiology and the North American Society of Pacing Electrophysiology*[149]. HRV data were processed using the HRV module in LabChart 8 (ADInstruments, Colorado Springs, USA), which automatically detects and extracts R-R intervals while differentiating between normal and ectopic beats. In the time domain, HRV parameters included the mean R-R interval, the standard deviation of R-R intervals (SDRR), and the root mean square of successive R-R interval differences (RMSSD). Spectral analysis of frequency domain variables was conducted using the Fast Fourier Transform method, with low-frequency (LF, 0.04–0.15 Hz) and high-frequency (HF, 0.15–0.45 Hz) spectral components reported as absolute power values (ms^2). Additionally, the low-frequency to high-frequency ratio (LF/HF) was computed based on the absolute power values of LF and HF.

Cardiac Parasympathetic Modulation

Cardiac parasympathetic modulation (CPM) was assessed using the Δ30:15 heart rate (HR) ratio, which is calculated as the ratio of the maximum and minimum HR occurring around the 15^{th} and 30^{th} heartbeats following standing[146]. Heartbeat data for this analysis were extracted from R-R intervals recorded via the ECG module (Finometer,

Finapres Medical System, Arnhem, The Netherlands). This measure is commonly used in clinical settings to evaluate autonomic cardiovascular reflex function and detect early signs of autonomic dysfunction[150,151]. It provides critical insight into the heart's adaptive response to physiological stressors, such as postural transitions, and aids in identifying conditions affecting cardiovascular stability, particularly in individuals with underlying health concerns[150,151].

Cardiac Baroreflex Gain

Cardiac baroreflex gain (CBG) was adapted from the method proposed by the Autonomic Disorders Consortium, calculated as the ratio of HR change to SBP drop (ΔHR/ΔSBP) at 30 s (phase 1), 60 s (phase 2), 180 s (phase 3), and 420 s (phase 4) following active standing orthostatic stress, expressed in bpm·mmHg^{-1} [152]. The selected time points were chosen to capture key phases of autonomic regulation following active standing. Phase 1 represents the immediate compensatory response to counteract the initial BP drop. Phase 2 reflects early stabilization through sustained sympathetic activation. Phases 3 and 4 assess autonomic dysregulation linked to late BP regulation[24,65]. HR data for this calculation were derived from R-R intervals recorded via the ECG module (Finometer, Finapres Medical System, Arnhem, The Netherlands). SBP was measured non-invasively using photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Calibration procedures, including return-to-flow adjustments, synchronization of finger and brachial arterial pressures, cuff size selection, and height correction, were conducted according to the previously described protocol. CBG assessment is widely used in clinical settings to evaluate blood pressure regulation during active standing and to detect autonomic dysfunction that may contribute to orthostatic intolerance, such as dizziness[153].

Sample Size

The sample size for this study was calculated using G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119], with the pilot study data (n = 15, 5 per group). The power analysis used the F-test ANOVA for fixed effects, omnibus, and one-way. The values were obtained from the differences in the Δ30:15 HR ratio across three groups (non-frail, pre-frail, and frail) for two conditions (sit-to-stand and lie-to-stand). The measurement was derived from the minimum and maximum HR observed around the 30th and 15th beats after standing. For experiment 1 (sit-to-stand), the analysis demonstrated an actual power of 0.8 and an effect size of 0.85, with a standard deviation (SD) σ within

groups (0.07) and each group mean: non-frail 0.82, pre-frail 0.98, and frail 0.89. Therefore, the estimated total sample for this experiment is 18 participants. For experiment 2 (lie-to-stand), the analysis showed an actual power of 0.81 and an effect size of 0.82, with an SD σ within groups (0.09) and each group mean, non-frail 0.82, pre-frail 0.89, and frail 1.00. The estimated total sample for this experiment is also 18 participants.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables following parametric distribution were reported as mean ± SD with 95% confidence interval (95% CI). The median, interquartile range, and minimum and maximum values were provided for non-parametric continuous variables. To describe the sample characteristics, continuous data were summarized using the mean, SD, 95% CI, and range (minimum and maximum). Categorical data were presented as absolute frequencies and percentages, and comparisons between groups were conducted using the Chi-square test.

For the comparisons between groups (non-frail, pre-frail, and frail), the one-way ANOVA was applied for parametric continuous data, and the Kruskal-Wallis test was used for non-parametric data with a Bonferroni *post-hoc*. To account for multiple hypothesis testing, particularly for CBG, the Benjamini-Hochberg procedure was applied, maintaining a false discovery rate (FDR) of 0.05 to minimize the risk of false-positive results[125]. Significant results were reported based on corrected *p*-values ($p < 0.05$).

The effect size was calculated for continuous variables and HRV measurements[126]. For effect size determination, Cohen's *d* was used for parametric data, while the *R* coefficient was applied for non-parametric data[127]. Effect size was classified as low (≤ 0.05), medium (0.06-0.25), high (0.26-0.50), and very high (> 0.50)[126]. All statistical analyses were conducted using R® (Version 4.1.1, Vienna, Austria), with a significance level of $\alpha < 0.05$.

Results

Figure 10.2 illustrates the recruitment process. Eligibility was assessed using a screening questionnaire developed by the research team to evaluate participants' health status and confirm adherence to the study's inclusion and exclusion criteria. Sixty participants were recruited. However, data from 11 participants were excluded from Experiment 1 and 10 from Experiment 2 due to poor signal quality (excessive motion

artifact during transition and noisy signals). Consequently, the final sample for Experiment 1 was 49 participants, consisting of 28 non-frail, 13 pre-frail, and 8 frail older adults, while Experiment 2 had 50 participants, including 28 non-frail, 14 pre-frail, and 8 frail participants.

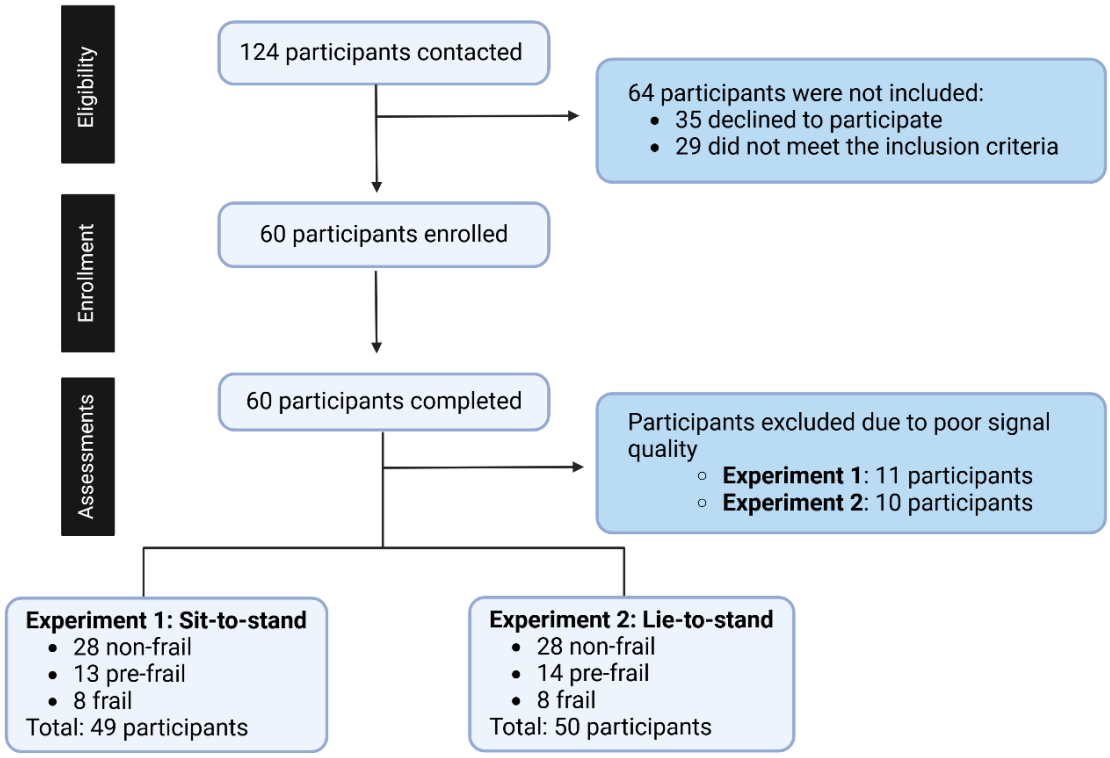

Figure 10.2 Study recruitment flowchart.

Anthropometric measurements, including height, body mass, and BMI, showed no statistically significant differences between the groups. Resting cardiovascular parameters showed no statistical differences in SBP and DBP, while resting HR was significantly higher in the frail group compared to the non-frail and pre-frail groups. The prevalence of OI self-reported symptoms did not differ significantly between groups (Table 10.1).

Table 10.1 Sample characteristics of participants by frailty status.

Variables	**Non-frail**		**Pre-frail**		**Frail**		***p***
Sit-to-stand	***n***	%	***n***	**%**	***n***	**%**	
Females	16	57	12	92	6	75	0.07
Males	12	43	1	8	2	25	
Lie-to-stand	***n***	%	***n***	**%**	***n***	**%**	
Females	16	57	13	93	6	75	0.056
Males	12	43	1	7	2	25	
Anthropometric	**Median |**	**Min; Max**	**Median |**	**Min; Max**	**Median |**	**Min; Max**	***p***
Age	70 | 6.7	63.0; 77.0	70.5|5.5	63.0; 78.0	73.5|3.7	68.0; 76.0	0.3
Height (m)	1.6 | 0.1	1.4; 1.8	1.5|0.1	1.5; 1.8	1.6|0.1	1.5; 1.7	0.2
Body mass (kg)	74.1 | 21.3	46.6; 110.0	73.6|19.6	50.8; 95.2	77.0|14.3	42.5; 109.0	0.4
BMI	26.7 | 5.6	17.1; 36.6	26.1|7.3	19.3; 37.7	29.0|2.8	17.9; 48.4	0.5
Hemodynamic	**Median |**	**Min; Max**	**Median |**	**Min; Max**	**Median |**	**Min; Max**	***p***
Rest SBP	126 | 20.0	108.0; 154.0	130 | 19.2	110.0; 150.0	140.0 | 12.7	118.0; 150.0	0.1
Rest DBP	78 | 7.5	56.0; 92.0	82 | 10.0	60.0; 92.0	84.0 | 11.0	66.0; 90.0	0.2
Rest HR	64 | 12.2	52.0; 84.0	74 | 7.2	62.0; 90.0	75.5 | 14.5↑	64.0; 92.0	**0.002***
OI symptoms[#]	***n***	**%**	***n***	**%**	***n***	**%**	***p***
No	25	89	11	78	7	87	0.3
Yes	3	11	3	22	1	13	

|: Interquartile range with Minimum (Min) and Maximum (Max); BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; ↑: higher than; [#]Orthostatic intolerance (OI) symptoms were assessed during the lie-to-stand transition, as this postural transition imposes higher orthostatic stress, resulting in a more pronounced cardiovascular adjustment due to the increased gravitational influence on blood volume distribution[7,42]. [*]Statistically significant differences.

Heart Rate Variability at Baseline in the Supine Position

In the time domain analysis, the non-frail group showed a higher RR peak interval than the pre-frail and frail groups, with no statistically significant differences between the pre-frail and frail groups. The three groups did not differ from each other regarding SDRR and RMSSD. In the frequency domain analysis, the groups showed similar responses in the HRV parameters (LF, HF and LF/HF) (Table 10.2).

Table 10.2 Heart Rate Variability (HRV) responses in time and frequency domains during supine position across frailty groups.

Time domain				
Frailty	NF	PF	F	*p* (ES)
RR	863.1|1.1↑ (980.3; 1.0)	780.5|903.2 (992.1; 1.0)	463.4|830.0 (999.7; 1.0)	**0.01 (0.18) ***
SDRR	36.6|18.9 (13.6; 73.0)	35.7|27.3 (15.4; 66.4)	21.4|28.6 (7.6; 59.6)	0.5 (0.02)
RMSSD	25.2|19.5 (8.4; 86.2)	24.5|12.0 (7.2; 81.4)	20.4|30.6 (9.1; 49.1)	0.7 (0.00)
Frequency domain				
LF	440.2|449.8 (44.3; 2226.0)	241.8|392.2 (41.4; 1188.0)	308.6|1122.5 (31.4; 2123.0)	0.5 (0.02)
HF	398.7|594.8 (22.4; 3186.0)	374.3|272.3 (22.4; 3186.0)	637.3|707.7 (13.1; 1169.0)	0.9 (0.00)
LF/HF	0.9|0.8 (0.3; 3.6)	0.5|0.5 (0.1;1.9)	0.6|0.7 (0.4; 2.4)	0.12 (0.09)

|: Interquartile range with Minimum and Maximum; ES: Effect size, HRV: heart rate variability; RR: Average interval between consecutive heartbeats (RR-intervals); SDRR: Standard Deviation of RR intervals; RMSSD: Root Mean Square of Successive differences between RR intervals; LF: Low-Frequency power; HF: High-Frequency power; LF/HF: Low Frequency to High-Frequency power ratio: HR: heart rate. *Statistically significant differences. ↑ higher than.

Cardiac Parasympathetic Modulation (CPM)

During the sit-to-stand transition, HR Δ 30:15 values were similar across all groups. During the lie-to-stand transition, HR Δ 30:15 values were significantly higher in the pre-frail group compared to the non-frail and frail groups ($p = 0.04$). The non-frail and frail groups had similar responses (Table 10.3).

Table 10.3 Cardiac parasympathetic modulation (HR Δ 30:15) during sit-to-stand and lie-to-stand transitions across frailty groups.

Cardiac parasympathetic modulation					
Sit-to-stand					
	Non-frail	Pre-frail	Frail	*p*	ES
HR Δ 30:15	1.09 | 0.07 (0.95; 1.29)	1.07 | 0.09 (1.02; 1.13)	1.06 | 0.03 (1.01; 1.12)	0.4	0.03
Lie-to-stand					
	Non-frail	Pre-frail	Frail	*p*	ES
HR Δ 30:15	1.10 | 0.09 (0.87; 1.37)	1.04 | 0.07↑ (0.91; 1.16)	1.03 | 0.06 (0.94; 1.12)	**0.04***	0.13

|: Interquartile range with (Minimum and Maximum); ES: Effect size; ↑ higher than. *Statistically significant differences.

Short-Term Cardiac Baroreflex Gain During Sit-to-Stand Orthostatic Stress Across Phases

In the sit-to-stand transition, no statistically significant differences were found in all phases between the groups. In the lie-to-stand transition, the frail group exhibited significantly higher CBG values compared to the non-frail and pre-frail groups in phase 1, but no differences were observed between the non-frail and pre-frail groups. From phases 2 to 4, no statistically significant differences were observed between these groups (Table 10.4).

Table 10.4 Cardiac baroreflex gain (CBG) responses during sit-to-stand and lie-to-stand transitions across frailty groups.

Sit-to-stand					
CBG ($bpm \cdot mmHg^{-1}$)	Non-frail	Pre-frail	Frail	*p*	ES
Phase 1 - 30 s	0.5|0.1 (0.3; 0.7)	0.5|0.1 (0.3; 0.9)	0.6|0.1 (0.4; 0.7)	0.13	0.01
Phase 2 - 60 s	0.5|0.1 (0.3; 0.7)	0.5|0.0 (0.3; 0.8)	0.6|0.1 (0.4; 0.7)	0.13	0.08
Phase 3 - 180 s	0.5|0.1 (0.3; 0.7)	0.5|0.1 (0.3; 0.8)	0.6|0.1 (0.4; 0.7)	0.13	0.09
Phase 4 - 420 s	0.5|0.1 (0.3; 0.8)	0.5|0.0 (0.4; 0.8)	0.6|0.1 (0.4; 0.8)	0.2	0.06
Lie-to-stand					
CBG ($bpm \cdot mmHg^{-1}$)	Non-frail	Pre-frail	Frail	*p*	ES
Phase 1 - 30 s	0.5|0.1 (0.3; 0.8)	0.6|0.1 (0.5; 0.9)	0.7|0.1↑ (0.4; 0.7)	**0.02***	0.22
Phase 2 - 60 s	0.5|0.1 (0.3; 0.9)	0.6|0.1 (0.5; 1.1)	0.6|0.1 (0.5; 0.8)	0.08	0.1
Phase 3 - 180 s	0.5|0.1 (0.3; 0.7)	0.5|0.1 (0.4; 0.9)	0.5|0.1 (0.4; 0.7)	0.2	0.06
Phase 4 - 420 s	0.5|0.1 (0.3; 0.7)	0.5|0.1 (0.4; 1.0)	0.5|0.1 (0.4; 0.7)	0.06	0.13

|: Interquartile range with (Minimum and Maximum); CBG: Cardiac baroreflex gain; ES: Effect size, ↑ higher than. *Statistically significant differences.

Discussion

This study is among the first to examine phase-specific short-term autonomic compensatory responses in frail community-dwelling older adults under two distinct active-standing orthostatic stress conditions. The study aimed to compare autonomic regulation during sit-to-stand and lie-to-stand transitions across non-frail, pre-frail, and frail individuals. Findings indicate that pre-frail and frail groups exhibited an imbalance between parasympathetic and sympathetic nervous system activity at baseline, as assessed by HRV indexes. The pre-frail group demonstrated higher cardiac parasympathetic modulation, while the frail group showed increased CBG. No statistically significant differences in self-reported OI symptoms were observed between these groups.

Heart Rate Variability Responses at Baseline

In the time domain analysis, the non-frail group showed a higher RR interval than pre-frail and frail groups, while no statistically significant differences were found in SDRR and RMSSD between these groups. In the frequency domain analysis, no statistical

differences between groups were identified in LF power, HF power, and LF/HF ratio. Katayama et al.[41] and Johnston et al.[194] did not find significant differences in RR, SDRR, and RMSSD in non-frail, pre-frail, and frail groups, which is consistent with our findings. However, Katayama et al.[41] reported that the frail group showed decreased HF power compared with the non-frail group, and increased LF power and LF/HF ratio compared with the non-frail and pre-frail groups. Johnston et al.[194] reported that the frail group showed a lower LF than non-frail and a higher LF/HF than pre-frail. These results do not align with our results.

These findings indicate distinct autonomic alterations across frailty stages. Lower RR intervals in pre-frail and frail individuals reflect reduced parasympathetic modulation[143], while similar SDRR and RMSSD values between groups suggest maintained vagal control[143]. The non-significant differences in frequency-domain parameters may indicate regulated autonomic functions among individuals, potentially influenced by compensatory mechanisms in autonomic control[24]. However, decreased LF power and LF/HF ratio were previously associated with increased frailty risk[18] and indicate impairments in baroreflex function and autonomic regulation[24]. Progressive reductions in HRV parameters contribute to hemodynamic instability, compromising vascular regulation and exacerbating cardiovascular dysregulation in frail individuals[41,96].

Cardiac Parasympathetic Modulation Responses During Active Standing Orthostatic Stress

This study brings a novel perspective by comparing the HR Δ30:15 ratio between non-frail, pre-frail, and frail community-dwelling older adults. CPM was lower in the pre-frail group compared to both the non-frail and frail groups. Given the novelty of this analysis, the discussion will focus on the physiological relevance of these findings.

The HR Δ30:15 ratio is a key marker of CPM, reflecting autonomic regulation during postural transitions. Reduced CPM indicates a higher parasympathetic activity[146], which may signal autonomic dysregulation. In a healthy autonomic response, parasympathetic withdrawal and sympathetic activation should occur in a coordinated manner to regulate BP and HR during standing[16]. However, higher CPM suggests an exaggerated autonomic response, which can interfere with the timely activation of the sympathetic nervous system[146]. This imbalance may lead to transient hemodynamic instability, which might increase susceptibility to OI symptoms such as dizziness, lightheadedness, and blurry vision[195]. Dysregulated parasympathetic dominance can

reflect an impaired baroreflex function, reduced autonomic adaptability, and a failure to appropriately modulate cardiovascular responses to postural challenges, highlighting its relevance as an indicator of autonomic dysfunction[16,24].

Short-term Cardiac Baroreflex Gain During Active Standing Orthostatic Stress

In the sit-to-stand transition, no statistically significant differences were found across all phases between groups. However, in the lie-to-stand transition, the frail group had a higher CBG in phase 1 than the non-frail and pre-frail groups, with no statistical differences in phases 2 to 4. Corroborating with our findings, Buto et al.[23] compared the CBG in non-frail, pre-frail, and frail groups in the lie-to-stand position using a cross-spectral analysis (bivariate autoregressive model), showing no differences between groups. Mol et al.[96] analyze the CBG through the increase in HR divided by SBP drop in a larger sample of older adults (n = 168), demonstrating no association between CBG and frailty using this approach.

The similarities in the CBG across the phases may be attributed to preserved baroreflex function despite frailty-related autonomic impairments[12]. CBG is influenced by multiple factors, including arterial compliance, autonomic nervous system integrity, and cardiovascular reflex adjustments[12,24]. In older adults, structural vascular changes, such as arterial stiffening, may reduce baroreflex effectiveness[24]. However, compensatory mechanisms, such as increased sympathetic drive, may sustain CBG within a similar response across frailty groups[23,96].

This finding could also be the result of baroreceptor resetting, where prolonged exposure to altered BP regulation shifts the operating point of the baroreflex, potentially normalizing CBG across phases despite underlying dysfunction[35]. Changes in afferent nerve firing due to age-related arterial stiffening might further contribute to a more uniform CBG response[35]. Central nervous system modulation, including adjustments in brainstem integration of baroreceptor input, may regulate compensatory responses, reducing phase-specific differences in CBG[35]. Additionally, the higher CBG observed in the frail group during phase 1 of the lie-to-stand transition may reflect an exaggerated initial HR response to compensate for impaired vascular regulation[24,65]. This transient CBG could result from increased reliance on cardiac autonomic modulation due to diminished peripheral vasoconstriction[24,65], a common characteristic in frailty.

Orthostatic Intolerance Symptoms

No statistically significant differences were found between non-frail, pre-frail, and frail regarding OI self-reported symptoms. In contrast with our results, Romero-Ortuno et al.[6] showed that the frail group had higher OI symptoms than the pre-frail and non-frail groups. O'Connell et al.[196] also reported that OI symptoms are highly related to frail populations.

The similar OI symptoms across frailty groups suggest that autonomic control during postural transitions may be maintained despite frailty progression. Also, central nervous system compensatory mechanisms, such as cortical influence on autonomic responses[15], could help maintain symptom stability across frailty groups. Furthermore, variability in symptom perception and reporting, particularly in frail individuals who may experience blunted sensory feedback or cognitive impairment[35] might contribute to the observed similarity in OI symptoms. The regulation of cerebral perfusion and BP during standing may remain adequate across groups, preventing significant differences in symptom occurrence. Additionally, factors such as arterial stiffness or neurovascular control could modulate symptom expression, potentially explaining the inconsistency with prior research[6,196]. These findings suggest that while frailty is linked to physiological impairments[197], its impact on OI symptoms may depend on cardiovascular regulation rather than frailty classification alone.

Limitations

While the study has several strengths, certain limitations should be considered when interpreting the findings. Medication use was documented but not controlled (Appendix 4), potentially influencing autonomic responses to orthostatic stress. A high number of older adults take antihypertensives, beta-blockers, or diuretics, which can affect HRV, CPM, and CBG[198–200]. Among non-frail individuals, 36% (n = 10) were prescribed calcium channel blockers, followed by beta-blockers (18%; n = 5), diuretics (9%; n = 3), and ACE inhibitors (36%; n = 10). In pre-frail individuals, calcium channel blockers accounted for 40% (n = 8) of prescriptions, with beta-blockers at 10% (n = 2), diuretics at 20% (n = 4), and angiotensin receptor blockers at 30% (n = 6). Frail individuals had the highest proportion of calcium channel blocker use (42%; n = 5), while beta-blockers were prescribed to 33% (n = 4), diuretics to 17% (n = 2), and angiotensin receptor blockers to 8% (n = 1). Although these medications may have influenced

compensatory responses, they also reflect real-world conditions, enhancing the findings' relevance to community-dwelling frail older adults.

Also, CBG was assessed at specific time points (30 s, 60 s, 180 s, and 420 s), potentially overlooking continuous changes in baroreflex function during active standing. While this approach provides short-term compensatory responses in key phases, it may miss transient fluctuations or phase-specific adaptations. Some analyses, like the sequence methods[153], which detects spontaneous SBP and RR interval changes, or transfer function analysis[153], which evaluates baroreflex function across frequency ranges, could provide a more comprehensive assessment. The frail group constituted a small proportion of the total sample (16%), which may have limited statistical power and reduced the ability to detect significant differences between groups. A smaller sample size increases the likelihood of type II errors, potentially obscuring physiologically relevant variations in BP regulation. Similarly, Romero-Ortuno et al.[6] reported a frail subgroup comprising only 7% of their total sample (n = 31). Despite this limitation, the consistency of our findings with prior research supports their reliability across studies[6] and validity (physiological differences associated with frailty)[23,41].

In addition, the uneven distribution of sexes across frailty groups may have impacted the outcome. Prior studies have shown that males and females differ in cardiovascular physiology, including vascular responsiveness and hormonal influences, which can affect hemodynamic responses to postural stress[1,63,190,191]. Therefore, some of the observed differences in cardiovascular regulation might be attributed to inherent sex-related physiological variation rather than frailty alone.

Conclusion

The findings of this study indicate differences in autonomic function, with the pre-frail and frail groups exhibiting greater variance between the parasympathetic and sympathetic nervous systems and the frail group showing increased CBG. However, no significant differences in OI self-reported symptoms were observed. These results provide insights into autonomic regulation across frailty stages and its potential role in autonomic responses during active standing orthostatic stress.

Brief Discussion of the Manuscript Written Exclusively by Dihogo de Matos

This study revealed distinct alterations in autonomic regulation across frailty levels during active standing. At baseline (supine position), pre-frail and frail individuals exhibited shorter RR intervals, indicating reduced parasympathetic tone, although no significant differences were observed in frequency-domain HRV indexes. During the lie-to-stand transition, the pre-frail group displayed lower CPM compared to both non-frail and frail groups, suggesting a exaggerated vagal withdrawal. Regarding CBG, the frail group exhibited a significantly higher BRG in phase 1 (0-30 s) of the lie-to-stand transition, possibly reflecting a transient compensatory HR response to an exaggerated BP drop. These findings suggest that frailty may affect the immediate autonomic response (phase 1), while later baroreflex adjustments appear preserved across groups. Despite physiological alterations, orthostatic intolerance symptoms did not differ significantly among groups. Together, these findings highlight the phase-specific autonomic dysregulation across the frailty spectrum and emphasize the importance of assessments when evaluating autonomic regulation in older adults.

11. Chapter 11

Progressive strength training counteracts frailty and improves the time of blood pressure regulation, but not autonomic modulation in older adults

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Preface to the Manuscript Written Exclusively by Dihogo De Matos

This chapter presents the effects of a 12-week progressive strength training intervention on cardiovascular and autonomic short-term compensatory responses to orthostatic stress in frail older adults. In addition, this study shows the incidence of orthostatic hypotension and orthostatic intolerance symptoms, as well as changes in physical activity levels, grip strength, and gait speed following 12 weeks of progressive strength training. The study was designed to assess the effects of exercise on cardiovascular and autonomic physiological variables, including systolic and diastolic blood pressure, heart rate, cardiac output, systemic vascular resistance, stroke volume, heart rate variability, cardiac parasympathetic modulation, and cardiac baroreflex gain. Dihogo, Dr. Rodrigo Villar, and Dr. Todd Duhamel were responsible for some aspects of the study, including conceptualization, design, and protocol development. I was responsible for data collection and processing, statistical analyses, and manuscript preparation. This chapter extends the earlier findings by evaluating whether the cardiovascular and autonomic impairments previously identified in frail individuals can be mitigated through a 12-week progressive strength training intervention. It offers translational evidence of the potential of progressive strength training to counteract frailty-related dysregulation in both cardiovascular and autonomic systems.

Publication Status

This study will be submitted to The Journal of Strength and Conditioning Research.

Abstract

This study examined whether a 12-week progressive strength training (PST) program could counteract frailty and improve cardiovascular and autonomic short-term compensatory responses during postural transitions in older adults living with pre-frailty or frailty. Eight pre-frail and frail participants (aged 60-79 years) completed active stand tests (up to 7 min) following 5 minutes of sitting or 10 minutes of lying. Cardiovascular variables, including systolic and diastolic blood pressure (SBP, DBP), mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), systemic vascular resistance (SVR), and heart rate (HR), were measured at baseline, immediately on standing, and across four specific phases (0-30s, 30-60s, 60-180s, and 300-420s) at pre-test, 8 weeks, and 12 weeks. Blood pressure (BP) regulation timing was determined using CO-SVR matching in each phase. Autonomic function was assessed via heart rate variability (HRV) indexes at baseline, cardiac parasympathetic modulation (CPM) immediately on standing (HR Δ30:15), and cardiac baroreflex gain (CBG: ΔHR/ΔSBP) across the same four phases. The incidence of orthostatic hypotension (OH) and orthostatic intolerance (OI) self-reported symptoms were also evaluated. Following 12 weeks of PST, frailty index scores decreased from 0.18 to 0.04, representing a 78% reduction. While the comparison between the pre-test, 8 and 12 weeks of PST did not significantly change the baseline, immediate, and short-term cardiovascular or autonomic responses, an improvement was observed in BP regulation. CO and SVR matching shifted from phase 2 (30-60s) in the pre-test to phase 1 (0-30s) at 12 weeks. OH classification was similar post-intervention. Although not statistically significant, the number of participants reporting OI symptoms decreased from three at pre-test to none at post-test. In summary, PST counteracted frailty and improved the timing of BP regulation during postural transitions, although it did not enhance short-term cardiovascular and autonomic compensatory responses. Despite the incidence of OH remaining similar after 12 weeks of PST, there were no complaints of OI symptoms after the PST.

Keywords: Orthostatic hypotension, frail, systolic blood pressure, systemic vascular resistance, cardiac output

Introduction

There is a consensus in the literature that frailty is a dynamic process and that individuals move between the statuses of non-frail, pre-frail, and frail[201]. However, this transition towards frailty can be counteracted by intervention strategies, such as exercise[202]. However, most studies focus only on the "frailty status" (classification)[203–205] rather than the underlying cardiovascular mechanisms that contribute to frailty. Frailty is way more complex than simply being a phenotype that is observed; rather, frailty is characterized by multi-system physiological decline, affecting people's lives profoundly[70,206].

Literature is limited regarding the effects of progressive strength training (PST) on improving short-term cardiovascular responses, and orthostatic hypotension (OH) and orthostatic intolerance symptoms (OI) in older adults living with frailty. To the best of our knowledge, only one study published by Brilla et al.[32] analyzed the effects of 8 weeks of ST on blood pressure and heart rate (HR) responses and OH in community-dwelling older adults. They concluded that 45% of the sample displayed at least one criterion for OH before training compared to 9% post-training. Although the results seemed quite promising, the population studied was not people living with frailty but rather community-dwelling older adults. Also, the authors only analyzed SBP and DBP responses measured manually, and HR was assessed by the radial palpation technique after active standing (10 minutes supine, 5 minutes sitting, and 2 minutes standing). Key variables in the cardiovascular system other than HR, such as mean arterial pressure (MAP), cardiac output (CO), stroke volume (SV), and systemic vascular resistance (SVR), should be analyzed due to their association with OH. Another relevant critique of the authors' analysis is that it focused on single measurements or specific time points due to equipment limitations (manual BP and pulse HR), not considering the continuous nature of cardiovascular adjustments that occur from the first seconds to the later minutes after postural transitions. To date, no study has analyzed the effects of PST on cardiovascular responses across specific phases after active standing orthostatic stress (phase 1: 0-30 s; phase 2: 30-60 s; phase 3: 60-180 s; phase 4: 300-420 s) in individuals living with frailty. A phase-specific approach is essential for identifying the time course of impairments, and providing information about when and how the cardiovascular system regulates or not BP.

In healthy individuals, standing causes gravitational blood pooling in the lower extremities, which reduces venous return and SV[49]. This leads to a transient drop in CO

and BP, as SVR does not initially compensate for the shift[49]. Within 15-20 seconds, baroreflex-mediated mechanisms trigger a compensatory response, involving an increase in heart rate and peripheral vasoconstriction, which together elevate CO and SVR to stabilize BP[49,109]. While this regulatory sequence is well-documented in younger adults, its occurrence in older adults living with frailty is limited. Therefore, examining the CO-SVR matching process in pre-frail and frail individuals, along with the effects of PST, is essential to understanding short-term compensatory responses in BP regulation and identifying potential strategies to mitigate frailty-related cardiovascular dysfunction.

The autonomic nervous system (ANS) is essential for regulating autonomic responses and ensuring rapid physiological adjustments during daily stressors such as postural transition (e.g., from lying to standing)[207]. If the ANS is not well-regulated, people could have orthostatic hypotension (OH), a condition characterized by a sudden drop in blood pressure upon standing[12]. OH is a key contributor to orthostatic intolerance (OI)[208] (e.g., dizziness, lightheadedness, blurry vision), increasing the risk of falls and instability in the first few seconds on standing[15] and has been linked with frailty[6].

One frequently used non-invasive measurement of autonomic function is heart rate variability (HRV)[143], which reflects the beat-to-beat fluctuations of the time intervals between successive heartbeats[209]. The literature remains inconsistent regarding the effects of PST on HRV. For example, Lin et al.[210] found significant changes in HRV indexes after traditional resistance training in older adults (females and males), showing that individual differences in baseline autonomic function, age-related physiological alterations, and health status may influence the autonomic adaptations after resistance training. In contrast, Gambassi et al.[211] reported no significant improvements in HRV indexes following a traditional resistance training program in older females, suggesting enhanced parasympathetic modulation.

Cardiac parasympathetic modulation (CPM) is another important factor for maintaining autonomic balance by regulating the interaction between the parasympathetic and sympathetic nervous systems on standing[146]. There is a lack of literature regarding the specific effects of PST on CPM in frail older adults, limiting our understanding of how exercise might improve autonomic regulation in this population. Another marker of autonomic function is cardiac baroreflex gain (CBG), which reflects the sensitivity of the baroreflex in modulating HR in response to BP fluctuations[153]. Despite its relevance, only a few studies have addressed how resistance training influences CBG[212,213]. However, no study has examined the effects of PST on CBG across multiple specific short-term

compensatory responses following postural transitions (e.g., 30 s, 60 s, 180 s, and 420 s) in frail individuals. Assessing the PST effects on CBG in this time-course framework could show novel insights into the temporal dynamics of autonomic adaptation to PST in frail older adults.

Therefore, this study aims to **(1)** determine whether frailty can be counteracted with 12 weeks of PST. Also, the study aims to describe and compare **(2)** baseline, **(3)** immediately on standing, **(4)** and SBP, DBP, MAP, CO, HR, SV, and SVR short-term compensatory responses in pre-frail and frail individuals when transitioning from (a) sit-to-stand (low orthostatic stress challenge) and (b) lie-to-stand (high orthostatic stress challenge) in subsequent time phases: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s) at pre-test, 8, and 12 weeks of PST. Additionally, it aims to analyze the effects of PST on **(5)** CO and SVR matching, as well as describe and compare **(6)** HRV indexes at baseline in the supine position, **(7)** CPM response immediately on standing, and **(8)** CBG responses at phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s) - after sit-to-stand and lie-to-stand between pre-test, 8 and 12 weeks of PST. Secondarily, the study seeks to describe and compare **(9)** the incidence of OH and OI symptoms, and **(10)** the level of physical activity, grip strength, and gait speed at pre-test, 8 and 12 weeks of a PST. To address these multiple objectives, this study has 10 hypotheses, as follows: **(i)** PST will counteract frailty by improving frailty status, as indicated by a lower frailty index score. **(ii)** At baseline, SBP, DBP, MAP, SVR, HR, CO, and SV will improve due to enhanced vascular function, such as increased arterial compliance and reduced stiffness, leading to improved BP regulation after PST. **(iii)** Immediately on standing, lower transient drop in SBP, DBP, MAP, and SVR and higher HR, CO, and SV peak following the postural transitions after PST due to reduced vascular stiffness and improved vasoconstriction response. **(iv)** Short-term cardiovascular compensatory responses, faster SBP, DBP, MAP, SVR, HR, CO, and SV responses in phase 1 (0-30 s) and 2 (30-60 s). PST might strengthen the heart muscle, increasing contractility, resulting in a higher HR and SV response, and increasing CO. **(v)** After PST, a faster match between CO and SVR occurring at phase 1 (0-30 seconds) instead of phase 2 (30-60 s) or 3 (60-180 s). The faster response will be due to improved vascular responsiveness and autonomic response. **(vi)** Improve HRV indexes at baseline due to improved sympathetic tone, reducing the parasympathetic activity after PST, resulting in faster adaptive responses to external stressors like postural transitions. **(vii)** PST will improve CPM, diminishing the reliance on parasympathetic modulation and

promoting a higher autonomic response. **(viii)** Higher CBG in phases 1 (0-30 s), 2 (30-60 s), 3 (60-180 s), and 4 (300-420 s) due to improvement in autonomic tone, which leads to faster baroreceptor activation. **(ix)** Lower incidence of OH and OI symptoms after PST. (**x**) Higher levels of physical activity, grip strength, and gait speed after PST.

Methods

Study design

This is a one-group time series quasi-experimental study design. The Transparent Reporting of Evaluations with Non-Randomized Designs (TREND)[214] (Appendix 16), the Sex and Gender Equity in Research[115] (SAGER) (Appendix 17), and the Consensus on Exercise Reporting Template (CERT)[215] (Appendix 18) were used as reporting guidelines.

Settings

This study was conducted at the Applied Research Centre, Faculty of Kinesiology and Recreation Management, University of Manitoba, between August 2022 and August 2023. Ethical approval was obtained from the University of Manitoba Health Research Ethics Board (Protocol # HE2022-0058).

Participants

A convenience sampling method was employed to recruit older adults with varying frailty levels from multiple sources. Dr. Todd Duhamel's database at the University of Manitoba, which includes approximately 1,000 female volunteers from the Women's Advanced Risk-Assessment in Manitoba (WARM) Hearts study, was the main source of recruitment. In addition, individuals who had previously participated in a related frailty study were invited to participate in the present investigation. Interested individuals contacted the research team via email or phone to express their interest in participating.

The study sample consisted of individuals aged 60 to 79 years who underwent a 12-week progressive strength training program and orthostatic stress assessments, including sit-to-stand and lie-to-stand transitions (Figure 11.1). Eligibility criteria specified that participants must be within this age range and have been assigned female or male at birth and classified as pre-frail or frail in the frailty index. Exclusion criteria included a history of cardiovascular diseases, such as ischemic heart disease, acute myocardial infarction, stroke, percutaneous coronary intervention, coronary artery bypass grafting, or congestive heart failure, as well as psychiatric disorders or severe cognitive

impairment. The participants reported that they were not on hormone replacement therapy, and the medication was recorded but not controlled (Appendix 4).

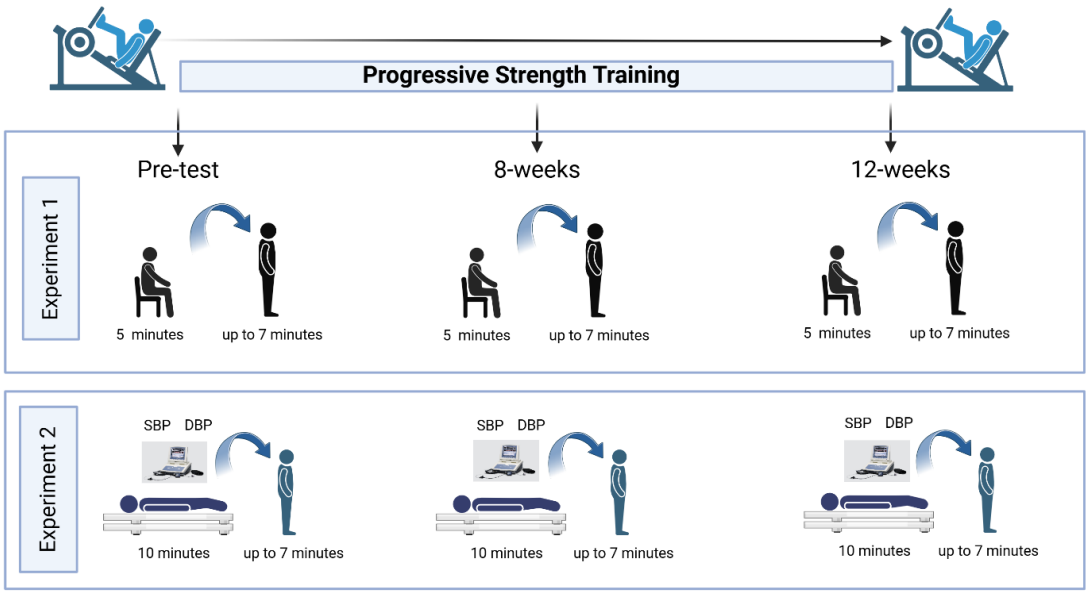


Figure 11.1 Progressive strength training program timeline.

Data Collection

Participants received pre-assessment instructions 48 hours before their scheduled laboratory visit. Upon arrival, they reviewed the informed consent document, and any questions or concerns were addressed by the research team before providing written consent. Before testing, a trained researcher assessed resting HR and BP to ensure participants met the safety criteria. All procedures were conducted following the guidelines set forth by the Canadian Society for Exercise Physiology (CSEP)[31].

Following the consent process and familiarization, participants underwent active standing orthostatic stress assessments with continuous beat-by-beat blood pressure monitoring using the Finometer^{TM} Pro device (Finapress Medical System BV, Amsterdam, The Netherlands). Resting systolic and diastolic blood pressures (SBP and DBP) were obtained using a digital BP monitor (ARSIMAI, BSX516, Munster, Germany). Immediately after completing the assessment, participants were queried regarding symptoms such as dizziness or light-headedness to evaluate potential OI-related symptoms. The study was conducted in a quiet, temperature-controlled room (22.0 ± 1.0ºC), with humidity and barometric pressure maintained at ambient levels. To mitigate

circadian influences, all orthostatic stress tests were performed on weekdays between 8:30 and 11:30 a.m.

Demographic, Anthropometric Measurements, and Frailty Index

Demographic data, including sex assigned at birth, age, and date of birth, were collected alongside anthropometric and body composition measurements to characterize the study sample. Body mass (kg) was assessed using the InBody 270 device (©2015 InBody CO., Ltd, Cerritos, CA, USA), while height (m) was measured with a SECA mobile stadiometer (SECA, Frankfurt, Germany). Body mass index (BMI) was calculated by dividing a participant's body mass in kilograms by the square of their height in meters (kg/m^2)[116]. Frailty classification was determined using the Frailty Index (FI), categorizing participants as non-frail (≤ 0.08), pre-frail (> 0.08 to 0.25), or frail (≥ 0.25), following established recommendations[187]. For example, if a person has 20 health deficits out of 30 possible variables, the FI would be 0.66, and this person will be classified as frail. The more health deficits a person has, the frailer they are.

Level of Physical activity, Hand grip, and Gait speed

Physical activity levels were assessed using the International Physical Activity Questionnaire - Short Form (IPAQ-SF)[216], a validated self-report instrument designed to estimate the time spent on physical activity across various intensities over the last seven days. The questionnaire includes seven items that capture the frequency and duration of vigorous-intensity activities, moderate-intensity activities, walking, and sedentary behavior. Total physical activity was calculated in MET-minutes per week by assigning standard MET values.

A Handful Hand Strength Dynamometer was used to measure the hand grip strength following CSEP guidelines[31]. Two repetitions were performed in the dominant hand with a 30-second interval between attempts. The highest value was used for the analyses. Gait speed was assessed by measuring the time it takes for a participant to walk a specified distance of 5 meters on a flat, straight pathway. Participants were instructed to walk at their normal pace while their time was recorded. This test was conducted three times, with a 60-second rest period between each trial. The time from all three attempts was recorded, and the average of these times was calculated to determine the participant's gait speed[31].

Definition of Short-Term Orthostatic Blood Pressure Recovery Responses

OH was classified into four categories based on SBP response during the active standing orthostatic stress test (lie-to-stand). A normal blood pressure (NBP) response was defined as SBP returning to baseline without a drop exceeding 20 mmHg within 30 seconds of standing. Initial orthostatic hypotension (IOH) was characterized by a transient SBP decline of more than 40 mmHg within the first 15 seconds post-stand, followed by full recovery within 30 seconds. Delayed blood pressure recovery (DBPR) was identified when SBP decreased by more than 20 mmHg and required more than 30 seconds to return to baseline, without meeting the criteria for sustained orthostatic hypotension (SOH). SOH was defined as a persistent SBP reduction of ≥ 20 mmHg occurring between 60 and 180 seconds after standing, in conjunction with supine hypertension (supine SBP ≥ 160 mmHg)[49].

Assessment of Cardiovascular Responses

HR was continuously recorded on a beat-by-beat basis using a 3-lead electrocardiogram (ECG) module (Finapres Medical System, Arnhem, The Netherlands) with a sampling frequency of 1 kHz, with HR derived from R-R intervals. Additionally, continuous non-invasive beat-by-beat measurements of SBP, DBP, and MAP were obtained via photoplethysmography at the middle finger of the left hand using the Finometer device (Finapres Medical System, Arnhem, The Netherlands)[117]. Prior to each procedure, the device was calibrated using the return-to-flow method to align finger pressure with brachial pressure approximately five minutes before data collection. Finger circumference was measured to select the appropriate cuff size, and a height correction system was used to reconstruct the BP readings from the hand (finger arterial pressure wave) to the heart level (brachial arterial pressure wave) throughout the assessments. CO was estimated using a model flow algorithm embedded in the Finometer device (Finapres Medical System, Arnhem, The Netherlands)[118]. Stroke volume (SV) was calculated using the formula SV = (CO/HR) × 1000, where CO was divided by HR and multiplied by 1000. SVR was determined by the ratio of MAP to CO (SVR = MAP/CO).

Assessment of Heart Rate Variability, Cardiac Parasympathetic Modulation, and Cardiac Baroreflex Gain

Heart rate variability (HRV), cardiac parasympathetic modulation (CPM), and cardiac baroreflex gain (CBG) were derived from the electrocardiogram (ECG) and Finometer (Finapres Medical System, Arnhem, The Netherlands)[117] and recorded using

LabChart 8.0 software (ADInstruments, Colorado Springs, USA) at a 1 kHz sampling rate. ECG signals were filtered using a 5-30 Hz bandpass filter to enhance R-peak detection, except during the 30 seconds before and 90 seconds following the postural transition, during which the raw ECG signal was preserved and Finometer calibration was manually disabled. Data from the sit-to-stand and lie-to-stand transitions were processed with a custom macro designed for R-R interval detection within LabChart 8. The resulting R-R intervals were used to compute HR through automated peak detection. In instances where ECG quality was compromised, peak detection was instead based on the pressure waveform.

Arterial pressure was assessed non-invasively using photoplethysmography at the middle finger of the left hand (Finometer - Finapres Medical System, Arnhem, The Netherlands)[117]. BP calibration was initially conducted following the manufacturer's standard procedure and subsequently refined using measurements from an automated BP monitor (ARSIMAI, BSX516, Münster, Germany). To align finger arterial pressure with brachial pressure, calibration was performed using the return-to-flow method approximately five minutes prior to each assessment. Finger circumference was measured to determine the appropriate cuff size, and a height correction system was employed to continuously adjust the finger arterial pressure waveform to reflect brachial-level values throughout the evaluation.

SBP and HR data were exported and analyzed using a custom-built application in Matlab (R2024; The MathWorks Inc., Natick, MA, USA). After importing the signals from LabChart, a multi-step signal processing protocol was applied to enhance data quality. This included an initial noise reduction phase using a two-stage filtering method: a median filter followed by a low-pass filter with a cutoff frequency of 0.05 rad/sample, based on insights from scalogram analysis. To smooth the data and extract key parameters, a 5-second moving average filter was subsequently applied[96,120]. After completing signal processing, interpolation techniques were applied to correct for resampling-induced delays at a frequency of 1 Hz. The onset of active standing was defined as time zero, with time points preceding the transition represented as negative values and those following it as positive values, reflecting the short-term compensatory responses.

Heart Rate Variability

Heart Rate Variability (HRV) was assessed through continuous beat-by-beat recordings in the supine position using a three-lead electrocardiogram (ECG) module integrated into the Finometer system (Finapres Medical System, Arnhem, The Netherlands), sampled at 1 kHz. The assessment followed established guidelines from the *European Society of Cardiology and the North American Society of Pacing Electrophysiology*[149]. HRV data were analyzed using the HRV module in LabChart 8 (ADInstruments, Colorado Springs, USA), which automatically detects and extracts R-R intervals while distinguishing normal beats from ectopic ones. In the time domain, key HRV metrics included the mean R-R interval, the standard deviation of R-R intervals (SDRR), and the root mean square of successive differences between R-R intervals (RMSSD). Frequency domain analysis was performed using the Fast Fourier Transform (FFT) method, with low-frequency (LF: 0.04–0.15 Hz) and high-frequency (HF: 0.15–0.45 Hz) components reported as absolute power values (ms^2). The LF/HF ratio was also calculated using these absolute power values to assess the balance between sympathetic and parasympathetic modulation.

Cardiac parasympathetic modulation

Cardiac parasympathetic modulation (CPM) was evaluated using the Δ30:15 heart rate (HR) ratio, defined as the ratio between the maximum and minimum HR at the 15^{th} beat and the 30^{th} beat following the transition to standing[146]. Heartbeat data used for this analysis were derived from R-R intervals obtained through the ECG module of the Finometer system (Finapres Medical System, Arnhem, The Netherlands). The Δ30:15 ratio is a widely recognized clinical marker for assessing autonomic cardiovascular reflexes and identifying early indicators of autonomic dysfunction[150,151]. This measure offers insight into the heart's ability to adapt to physiological stressors like postural changes and is useful for detecting conditions that may compromise cardiovascular regulation, especially in populations with underlying health issues[150,151].

Cardiac Baroreflex Gain

Cardiac baroreflex gain **(**CBG) was assessed using an adapted method from the Autonomic Disorders Consortium, calculated as the ratio of HR change to SBP reduction (ΔHR/ΔSBP) and expressed in $bpm \cdot mmHg^{-1}$. Measurements were taken at 30 seconds (phase 1), 60 seconds (phase 2), 180 seconds (phase 3), and 420 seconds (phase 4) following active standing to evaluate the dynamic baroreflex response to orthostatic

stress[152]. HR data for this calculation were derived from R-R intervals recorded via the ECG module (Finometer, Finapres Medical System, Arnhem, The Netherlands). SBP was measured non-invasively using photoplethysmography at the middle finger of the left hand (Finometer, Finapres Medical System, Arnhem, The Netherlands)[117]. Calibration procedures, including return-to-flow adjustments, synchronization of finger and brachial arterial pressures, appropriate cuff size selection, and application of the height correction system, were performed following the previously outlined protocol. CBG assessment is a commonly employed clinical tool for evaluating BP regulation in response to active standing and identifying signs of autonomic dysfunction that may underlie orthostatic intolerance symptoms, such as dizziness, blurred vision, and lightheadedness[153].

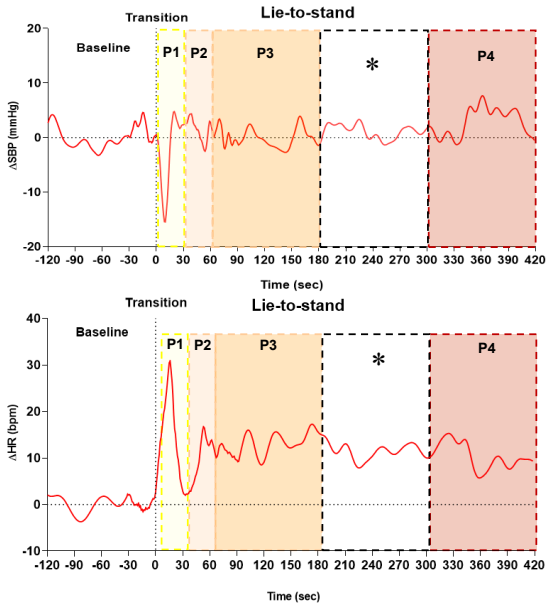
Data Analysis

Data from the Finometer were recorded and processed on a beat-by-beat basis using LabChart 8.0 (ADInstruments, Colorado Springs, CO, USA). Electrocardiogram (ECG) signals were filtered with a 5-30 Hz bandpass to detect R-peaks, except during the 30 seconds preceding and 90 seconds following the standing transition, where the raw signal was retained, and Finometer calibration was manually deactivated. Cardiovascular variables associated with the sit-to-stand and lie-to-stand transitions were analyzed using a custom macro developed for R-R interval detection. When the ECG signal quality was poor, analyses were performed using pressure waveform peaks. Blood pressure calibration adhered to the manufacturer's standard procedures and was further refined through manual calibration using an automated BP monitor (ARSIMAI, BSX516, Munster, Germany). All data were stored and subsequently transferred to a custom Matlab application for further processing and analysis (Matlab R2024; The MathWorks Inc, Natick, MA, USA).

Following data import from LabChart into the custom Matlab application (Matlab R2022b, MathWorks, Inc., USA), noise and motion artifacts were removed using a median filter, followed by a low-pass filter with a cutoff frequency of 0.05 rad/sample, as determined through scalogram analysis. To enhance signal quality, a 5-second moving average filter was applied, facilitating signal smoothing and the extraction of key parameters[96,120]. Data were interpolated and adjusted to correct for delays introduced by resampling at 1 Hz.

Variables Extracted and Analyzed During Active Standing Orthostatic Stress

Baseline measurements were established by averaging data from the last two minutes preceding the transition to standing. Within the first 30 seconds after standing up, the lowest values for SBP, DBP, MAP, and SVR (drop) were identified, along with the highest values for HR, CO, and SV (peak). Short-term cardiovascular compensatory responses were evaluated based on the peak values reached following the drop. These responses were categorized into four specific phases: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s), representing the progression of cardiovascular regulation after standing up. This classification aligns with established physiological response patterns in healthy adults and recognized OH criteria[121,122], enabling a comprehensive analysis of adaptive responses and frailty-related differences in cardiovascular regulation (Figure 11.2).



Phases	Time	Expected physiological responses
1	0-30 s	• Baroreceptor activation • Abruptly transient increase in HR • BP drops and then, overshooting over the baseline • Matching in CO and SVR • Slight decrease in SV
2	30-60 s	• Parasympathetic nervous system is activated • BP begins to drop • CO and HR decrease • Increase in SVR and SV
3	60-180 s	• BP, CO, SVR, and SV return to similar levels as baseline • HR remains elevated above the supine levels
4	300-420 s	• BP, CO, SVR, and SV remain close to the baseline measurement • HR stays above the baseline measurement

Figure 11.2 An illustration presents the systolic blood pressure (ΔSBP, top) and heart rate (ΔHR, bottom) responses during the lie-to-stand transition, divided into four specific phases: phase 1 (0–30 s), phase 2 (30–60 s), phase 3 (60–180 s), and phase 4 (300–420 s) post-transition. *The unshaded interval (180-300 s) represents a stabilization period similar to phase 3; therefore, it was excluded from the analysis. The analysis continues at phase 4 as it represents a higher incidence of DOH[124,217].

Progressive Strength Training

Participants performed a series of exercises recommended by the Canadian Society for Exercise Physiology (CSEP) for older adults[31]. These exercises included leg press, leg extension, seated leg curl, chest press, shoulder press, seated rowing, calf raises, and cat-camel exercise. Compliance and adherence were tracked through attendance

records and participant feedback, ensuring consistent engagement and adherence to the prescribed exercise program. The exercises sessions were performed in groups of 4-5 and supervised by Dihogo Gama de Matos.

Familiarization, 1 Repetition Maximum Test (1-RM), and Strength Training Intensity Control

All participants were familiarized with the test procedures, protocols, and exercise training. The first three weeks of resistance (load) were administered to ensure that participants could safely participate in the proposed PST. The 1 repetition maximum test (1-RM) was used for load determination. All participants performed familiarization test sessions with ~48 to 72 hours between each session. The first session consisted of familiarization with the procedures and protocol. The second session was to determine the specific workload to be used during the PST (Table 11.1). This 12-week training followed exercise prescription principles as recommended by the Canadian Society for Exercise Physiology[31] and the American College of Sports Medicine[218] guidelines. The intensity of the PST sessions was monitored using the OMNI-RES scale[219].

Table 11.1 Progressive strength training program progression.

Weeks	Frequency (days/week)	Loading (% RM)	Sets	Rest interval (sec)	Reps	Volume per session[#]	Volume per week[§]	Total Volume[$]
1-3*	2	40-50% of 1RM	1	120	15	40-50% of 1RM x 1 x 15	40-50% of 1RM x 1 x 2	40-50% of 1RM x 1 x 15
4-6	2	50-60% of 1RM	2	90	12	50-60% of 1RM x 2 x 12	50-60% of 1RM x 2 x 2	50-60% of 1RM x 2 x 12
7-9	3	60-70% of 1RM	3	60	10	60-70% of 1RM x 3 x 10	60-70% of 1RM x 3 x 3	60-70% of 1RM x 3 x 10
10-12	3	70-80% of 1RM	3	60	8	70-80% of 1RM x 3 x 8	70-80% of 1RM x 3 x 3	70-80% of 1RM x 3 x 8

* Indicates familiarization; # - %1RM x sets x reps (per exercise); § - Load x sets x reps x frequency (days/week); $ - Load (sum of all exercises) x sets x reps; 1 RM – 1 repetition maximum

Sample Size

The sample size was calculated using G*Power software (Heinrich Heine University, Dusseldorf, Germany)[119] based on an internal pilot study (n = 5). Power analysis was conducted using the F-test ANOVA repeated measures, within factors. For experiment 1 (sit-to-stand), an alpha of 0.05, with an actual power of 0.80, nonsphericity correction ε of 0.885, and an effect size of 0.57, based on a partial Eta-squared (η^2p) value of 0.250. The values were observed in the amplitude over and undershoot within 30 seconds after nadir during baseline, 8-week, and 12-week in the pre-frail/frail group. The total sample size required for this experiment is 7 participants. For experiment 2 (lie-to-stand), an alpha of 0.05, with an actual power of 0.92, nonsphericity correction ε of 0.597, and an effect size of 1.35, based on a partial Eta-squared (η^2p) value of 0.649. The values were observed in the amplitude over and undershoot within 30 seconds after nadir during baseline, 8-week, and 12-week in the pre-frail/frail group. The total sample size estimated for this experiment is 4 participants.

Statistical Analysis

The Shapiro-Wilk test was used to assess the normality of the data. Continuous variables following a parametric distribution were reported as mean ± standard deviation, along with the 95% confidence interval (95% CI). Non-parametric continuous variables were shown using the median, interquartile range, and minimum and maximum values. For sample description, continuous data were summarized using the mean, standard deviation, 95% CI, while categorical variables were described using absolute numbers and percentages. Categorical variables were analyzed using Cochran's Q test for repeated measures of categorical data over multiple time points.

The one-way repeated measures ANOVA assessed the difference over three-time points (pre-test, 8, and 12 weeks). The Friedman One-Way repeated measures analysis of variance by ranks test was used for non-parametric data. Bonferroni *post-hoc* was applied if significant differences were observed. To adjust for multiple hypothesis testing, the *p*-values were corrected using the Benjamini-Hochberg adjustment[125], with the false discovery rate set at 0.05. Correlations between CO and SVR were assessed at each of the three time points (pre-test, 8, and 12 weeks) across: phase 1 (0-30 s), phase 2 (30-60 s), phase 3 (60-180 s), and phase 4 (300-420 s) for each time point. Pearson or Spearman correlation was applied depending on the data distribution. Correlation magnitudes were

interpreted as small (r = 0.10-0.29), medium (r = 0.30-0.49), and large ($r \geq 0.50$)[126]. All statistical analyses were conducted using R® (Version 4.1.1, Vienna, Austria).

Results

The recruitment process is depicted in Figure 11.3. Participant eligibility was assessed using a screening questionnaire developed by the research team to evaluate health status and confirm adherence to the study's inclusion and exclusion criteria. A total of nine participants were initially recruited and completed assessments at pre-test, 8, and 12 weeks. However, one participant was excluded from the 12-week analysis due to poor signal quality. To avoid missing data and keep the assumptions of within-subject comparisons in repeated-measures analysis, only eight participants with complete data across all time points were included in the final analysis.

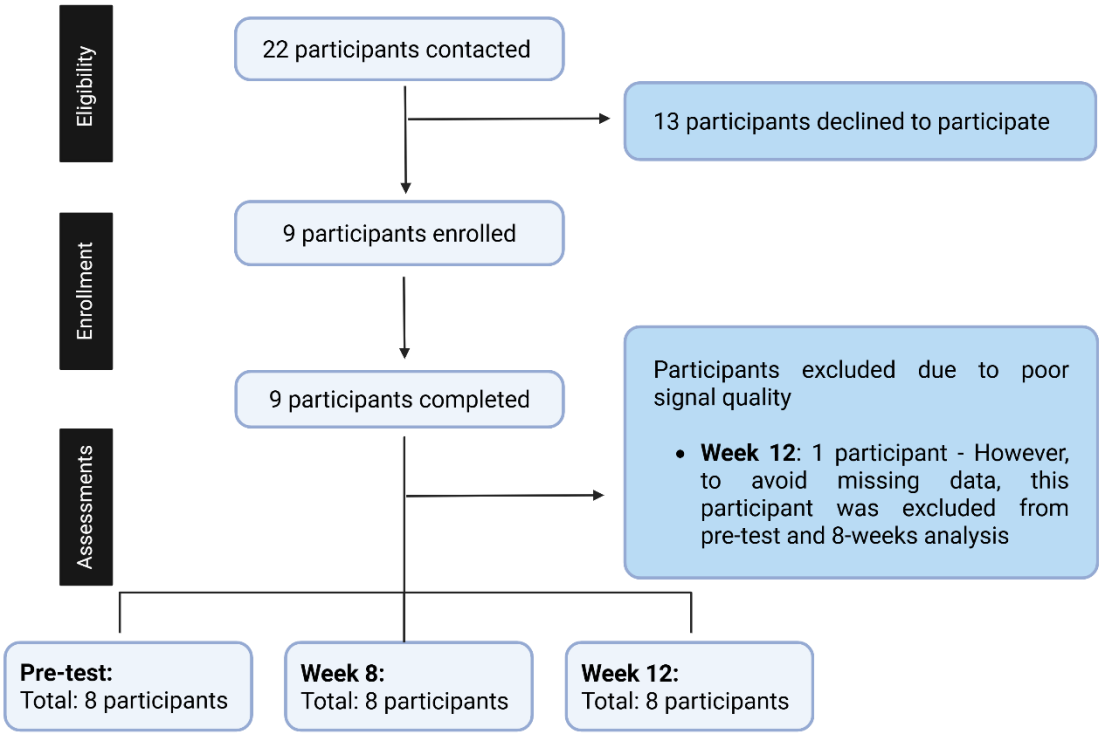


Figure 11.3 Flow chart of the recruitment participants.

Anthropometric measurements, including height, body mass, BMI, and cardiovascular resting data (SBP, DBP, and HR) were similar at pre-test, 8 and 12 weeks. Cochran's Q test for OH classification and OI self-reported symptoms showed no significant differences across the three analyzed points (Table 11.2).

Table 11.2 Sample characterization.

Variables	Pre-test		8 Weeks		12 Weeks		*p*
	n	%	***n***	**%**	***n***	**%**	
Females	7	87.5	7	87.5	7	87.5	**<0.001***
Males	1	12.5	1	12.5	1	12.5	
Anthropometric	**Mean±SD**	**Min; Max**	**Mean±SD**	**Min; Max**	**Mean±SD**	**Min; Max**	***p***
Age	70.3 ± 4.7	63; 78	70.3 ± 4.7	63; 78	70.3 ± 4.7	63; 78	0.1
Height (m)	1.61 ± 5.6	1.56; 1.74	1.61 ± 5.6	1.56; 1.74	1.61 ± 5.6	1.56; 1.74	0.3
Body mass (kg)	75.3 ± 13.3	54.7; 91.8	75.4 ± 13.5	55.1; 92.6	77.4 ± 12.8	56.7; 92.1	0.5
BMI	28.8 ± 4.9	22.5, 36.3	28.9 ± 5.0	22.6, 36.6	29.0 ± 4.7	23.3, 36.4	0.5
Cardiovascular	**Mean±SD**	**Min; Max**	**Mean±SD**	**Min; Max**	**Mean±SD**	**Min; Max**	***p***
Rest SBP	132 ± 8.7	120; 141	128.0 ± 11.7	113; 149	128.5 ± 11.8	114; 148	0.1
Rest DBP	80 ± 11.0	60; 92	76 ± 11.7	61; 91	75 ± 7.4	64; 88	0.4
Rest HR	74 ± 8.2	64; 88	75 ± 8.1	62; 85	76 ± 4.0	68, 80	0.7
OH Classification*	***n***	%	***n***	**%**	***n***	**%**	
NBP	1	12.5	3	37.5	3	37.5	0.44
IOH	1	12.5	1	12.5	1	12.5	1
DOH	6	75	4	50	4	50	0.56
SOH	0	0	0	--	0	0	--
OI symptoms#	***N***	**%**	***n***	**%**	***n***	**%**	***p***
No	5	62.5	7	87.5	8	100	0.09
Yes	3	37.5	1	12.5	0	0	

Values are mean ± SD; |: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. ↓ lower than; ↑ higher than. *Statistically significant differences between older females and older males. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Frailty Index Changes Over Time

Figure 11.4 shows group-level and individual changes in the frailty index scores at baseline, 8 weeks, and 12 weeks of PST. On average, the FI dropped by 55.5% from the pre-test (0.18 ± 0.1) to week 8 (0.08 ± 0.04), and an additional 50% from week 8 (0.08 ± 0.04) to week 12 (0.04 ± 0.04). From the pre-test (0.18 ± 0.1) to week 12 (0.04 ± 0.04) there was 78% improvement in the frailty scores. Participant 1 had the highest pre-test FI (0.33) decreased by 30% in 8 weeks (to 0.23) and by 78% from weeks 8 to 12 (to 0.05). Participant 2 declined from 0.29 to 0.17 in 8 weeks (41%) and to 0.10 in 12 weeks (41%). Participant 3 dropped from 0.18 to 0.04 (78%) in 8 weeks, remaining stable thereafter. Participant 4 had an FI of 0.15 in the pre-test, which decreased to 0.04 (73%) and then to 0.01 (75%) from weeks 8 to 12. Participant 5 went from 0.13 to 0.08 (38.5%) and then to 0.07 (12.5%). Participant 6 improved from 0.10 to 0.04 (60%) and reached 0.00 in 12 weeks. Participant 7 had a reduction from 0.09 to 0.00, which occurred by week 8, with no further change. Participant 8 had 0.08 in the pre-test, dropped to 0.02 (75%) and remained unchanged from week 8 to week 12. At baseline, two participants were classified as frail and six as pre-frail. By week 8, three participants were classified as pre-frail and five as non-frail. By week 12, one participant was classified as pre-frail and seven as non-frail.

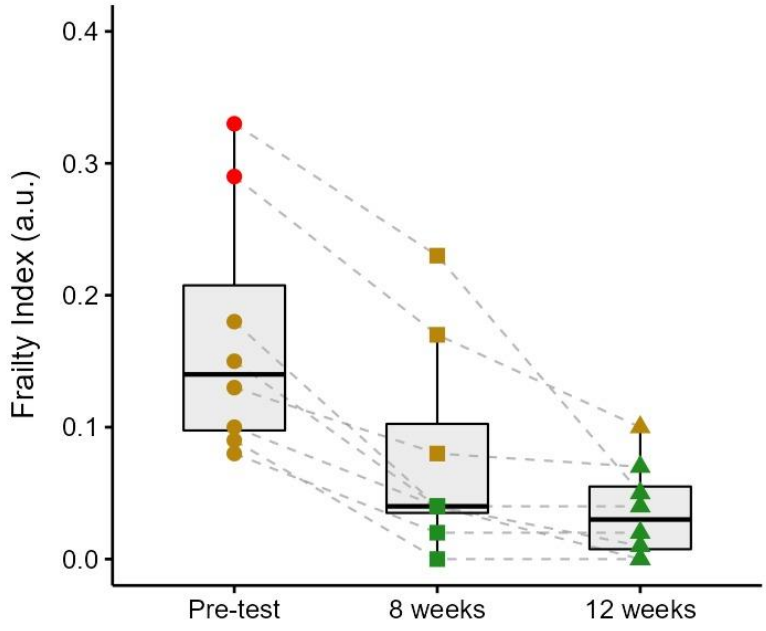


Figure 11.4 Frailty index scores at pre-test, 8 weeks and 12 weeks after progressive strength training. Red = frail; yellow = pre-frail; green = non-frail.

Level of Physical Activity, Hand Grip, and Gait Speed

Figure 11.5 shows the effects of PST on the level of physical activity, hand grip and gait speed. Participants demonstrated a progressive and statistically significant increase in physical activity levels across the 12 weeks of PST. The mean energy expenditure rose from 1695.34 ± 754.53 kcal/week at pre-test to 3310.39 ± 649.14 kcal/week at 8 weeks (95%; $p = 0.002$), and further to 4284.11 ± 675.48 kcal/week at 12 weeks (29%, $p = 0.001$). From pre-test to 12 weeks, there was a 153% increase in physical activity levels ($p < 0.001$). Hand grip strength significantly increased from pre-test to both 8 and 12 weeks. The was an increase from 23.61 ± 6.25 kg at pre-test to 25.76 ± 5.75 kg at 8 weeks ($p = 0.008$), and to 26.75 ± 5.82 kg at 12 weeks ($p = 0.046$), representing a 9% and 13% improvement, respectively. However, no significant differences were observed between the 8 and 12 weeks of PST. From pre-test to 12 weeks, there was a 13% increase in handgrip strength ($p = 0.046$). Gait speed improved significantly after 12 weeks of PST. Pre-test gait speed was 1.11 ± 0.20 m/s, increasing to 1.23 ± 0.16 m/s at 8 weeks (11%, $p = 0.018$), and further to 1.32 ± 0.18 m/s at 12 weeks (7%, $p = 0.017$). No statistical differences were identified between 8 and 12 weeks ($p = 0.1$). From pre-test to 12 weeks, there was an 18.9% increase in gait speed ($p = 0.01$).

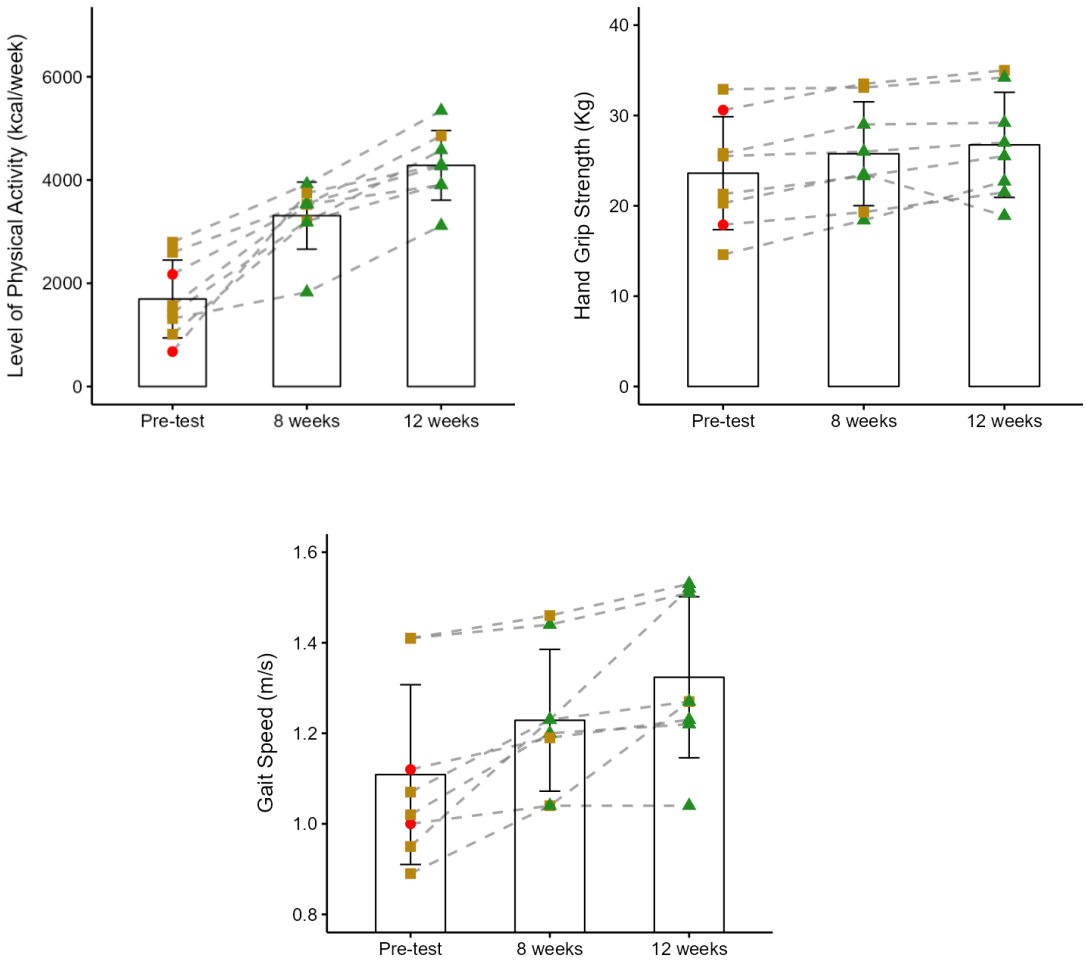


Figure 11.5 Level of physical activity, hand grip, and gait speed at pre-test, 8 weeks, and 12 weeks of progressive strength training. Red = frail, yellow = pre-frail, and green = non-frail.

Responses During Active Standing Orthostatic Stress After Progressive Strength Training

At baseline, immediately on standing, and during the short-term cardiovascular compensatory responses across specific phases, there were no statistically significant differences in any variables in the sit-to-stand and lie-to-stand transitions (Tables 11.3 and 11.4).

Table 11.3 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses across phases during sit-to-stand between pre-test, 8 weeks, and 12 weeks of progressive strength training.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Pre-test	127.5|13.5 (103.0; 140.0)	15.9|7.79 (8.7; 24.7)	1.5|7.35 (-15.7; 12.7)	3.0|5.3 (-10.2; 6.4)	7.9|13.2 (-7.9; 20.0)	8.8|14.9 (-13.0; 14.9)
	8 weeks	129.5|22.5 (109.0; 143.0)	13.4|3.1 (8.6; 30.7)	12.2|8.1 (-0.2; 18.0)	10.7|8.5 (-2.2; 15.1)	13.1|6.1 (5.1; 23.7)	7.3|6.7 (-1.6; 13.0)
	12 weeks	136.5|21.7 (109.0; 143.0)	15.4|15.8 (5.3; 34.4)	13.5|7.8 (0.5; 49.2)	16.0|12.3 (3.3; 53.1)	16.7|12.3 (3.4; 53.8)	10.4|7.3 (0.4; 40.9)
	Adj *p*	0.37	0.9	0.28	0.28	0.28	0.33
	ES	0.15	0.01	0.33	0.23	0.24	0.18
DBP (mmHg)	Pre-test	72.5|17.7 (57.0; 88.0)	9.8|7.2 (5.5; 22.3)	1.7|9.4 (-11.8; 4.8)	0.9|6.6 (-9.9; 3.7)	5.7|8.8 (-9.3; 12.4)	4.1|11.1 (-11.6; 11.2)
	8 weeks	77.5|21.0 (61.0; 92.0)	11.6|2.7 (4.6; 15.7)	8.0|5.7 (-4.5; 15.4)	6.6|6.6 (-0.1; 17.6)	7.4|9.7 (4.9; 19.7)	5.3|7.7 (-1.0; 17.6)
	12 weeks	81.0|14.7 (63.0; 91.0)	11.3|8.2 (2.8; 15.5)	7.2|7.9 (-0.4; 45.3)	9.5|14.2 (-0.2; 43.1)	9.1|11.2 (1.9; 43.8)	6.0|7.7 (0.5; 35.4)
	Adj *p*	0.14	0.78	0.19	0.14	0.26	0.32
	ES	0.37	0.03	0.27	0.36	0.21	0.17
MAP (mmHg)	Pre-test	91.5|15.2 (76.0;104.0)	12.3|4.5 (8.4; 23.7)	1.5|11.2 (-12.0; 6.0)	1.2|8.7 (-12.2; 5.3)	7.3|9.1 (-8.1; 16.1)	6.2|12.1 (-12.6; 10.7)
	8 weeks	93.5|19.5 (80.0; 108.0)	12.5|3.2 (4.4; 21.5)	9.9|4.1 (-3.5; 12.3)	8.1|7.2 (0.5; 15.4)	8.8|8.5 (5.6; 17.1)	6.1|5.5 (-1.9; 15.5)
	12 weeks	100.0|19.5 (81.0; 106.0)	12.5|8.3 (3.7; 21.1)	6.6|8.2 (2.3; 43.5)	10.6|14.3 (1.6; 44.5)	10.7|12.9 (2.1; 46.4)	7.2|6.4 (0.3; 34.7)
	Adj *p*	0.17	0.76	0.17	0.17	0.22	0.28
	ES	0.32	0.04	0.3	0.38	0.23	0.18

SVR ($mmHg.min^{-1}.L^{-1}$)	Pre-test	21.6|6.2 (15.1; 37.5)	8.8|7.1 (4.8; 13.6)	-0.7|3.5 (-9.7; 2.0)	-0.5|4.0 (-7.4; 3.5)	1.5|7.9 (-6.1; 9.5)	1.6|9.4 (-7.8; 8.2)
	8 weeks	24.6|11.2 (14.0; 43.0)	8.4|2.4 (6.3; 17.1)	2.8|8.3 (-4.2; 17.9)	2.0|6.2 (-2.6; 17.1)	4.4|9.7 (-0.1; 16.4)	2.0|10.0 (-1.6; 16.0)
	12 weeks	25.7|8.1 (18.1; 46.0)	10.2|1.9 (3.6; 12.7)	4.4|8.0 (-4.8; 26.6)	5.8|11.1 (-6.0; 22.7)	5.5|8.8 (-2.0; 22.1)	3.3|7.4 (-2.4; 16.2)
	Adj *p*	0.33	0.9	0.28	0.28	0.37	0.45
	ES	0.21	0.01	0.26	0.27	0.17	0.12
HR (bpm)	Pre-test	71.5|10.2 (56.0; 82.0)	11.9|6.6 (3.7; 18.4)	11.9|6.6 (3.7; 18.4)	7.6|3.3 (2.0; 14.2)	9.6|4.3 (5.9; 17.0)	8.8|4.5 (3.0; 13.4)
	8 weeks	67.5|7.7 (58.0; 78.0)	12.5|5.7 (5.9; 16.8)	12.5|5.7 (5.9; 16.8)	9.6|4.1 (5.3; 15.1)	10.6|4.3 (7.7; 16.3)	10.2|3.1 (5.7; 11.5)
	12 weeks	66.5|8.5 (58.0; 82.0)	10.5|1.7 (7.7; 13.6)	10.5|1.7 (7.7; 13.6)	7.9|4.1 (4.7; 12.5)	10.3|3.7 (6.6; 15.0)	7.2|2.4 (3.4; 14.6)
	Adj *p*	0.72	0.7	0.7	0.7	0.82	0.7
	ES	0.06	0.11	0.11	0.15	0.03	0.09
CO ($L.min^{-1}$)	Pre-test	3.5|0.8 (2.7; 6.4)	1.7|0.6 (0.6; 2.3)	1.7|0.6 (0.6; 2.3)	0.5|0.8 (-0.2; 1.2)	0.6|0.4 (0.1; 1.3)	0.1|0.9 (-1.2; 0.8)
	8 weeks	3.6|1.3 (2.8; 6.3)	1.4|0.7 (0.3; 3.2)	1.4|0.7 (0.3; 3.2)	0.3|0.9 (-0.3; 1.5)	0.3|0.6 (-0.2; 0.8)	0.0|0.6 (-0.7; 0.4)
	12 weeks	3.3|0.8 (2.2; 5.6)	1.3|0.8 (0.5; 2.8)	1.3|0.8 (0.5; 2.8)	0.2|1.2 (-0.5; 1.8)	0.1|0.6 (-0.3; 1.9)	-0.1|0.4 (-0.7; 0.6)
	Adj *p*	0.98	0.99	0.99	0.99	0.98	0.99
	ES	0.12	0.01	0.01	0.01	0.15	0.01

SV (mL)	Pre-test	51.5|10.5 (37.0; 93.0)	13.0|10.5 (1.0; 46.9)	2.8|8.2 (-6.7; 21.2)	-3.0|10.5 (-11.0; 21.2)	-6.7|15.4 (-13.2; 21.5)	2.3|19.6 (-33.6; 21.1)
	8 weeks	53.5|23.0 (36.0; 98.0)	13.4|9.0 (2.4; 31.7)	2.1|7.7 (-8.4; 3.3)	-4.5|5.5 (-10.9; 5.1)	-7.6|6.9 (-18.1; 0.9)	-8.3|6.8 (-20.1; 3.2)
	12 weeks	50.5|9.7 (31.0; 78.2)	12.4|17.8 (2.7; 29.4)	6.1|15.5 (-18.4; 16.8)	-1.6|17.3 (-16.2; 13.7)	-5.7|8.0 (-17.3; 6.1)	-4.8|7.9 (-21.5; 12.1)
	Adj *p*	0.82	0.86	0.82	0.82	0.52	0.82
	ES	0.05	0.02	0.08	0.07	0.23	0.07

|: Interquartile range with Minimum and Maximum; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Table 11.4 Comparison of baseline, amplitude, and short-term cardiovascular compensatory responses across phases during lie-to-stand between pre-test, 8 weeks, and 12 weeks of progressive strength training.

Variable	Group	Baseline	Amplitude	Phase 1	Phase 2	Phase 3	Phase 4
SBP (mmHg)	Pre-test	134.7 ± 16.2 (109; 157)	32.6 ± 10.3 (18.2; 52.9)	-5.6 ± 8.5 (-21.3; 5.99)	-3.2 ± 11.9 (-20.6; 21.3)	4.4 ± 10.1 (-5.4; 27.1)	0.5 ± 10.7 (-12.6; 19.8)
	8-weeks	131.6 ± 16.4 (109; 157)	24.2 ± 12.0 (15.2; 32.6)	5.99 ± 9.8 (-7.8; 20.7)	8.0 ± 18.3 (-29.4; 30.3)	12.5 ± 16.8 (-17.7; 34.9)	8.0 ± 13.3 (-11.8; 23.4)
	12-weeks	132.7 ± 19.0 (116.8; 148.6)	25.8 ± 11.0 (11.2; 41.6)	5.8 ± 20.6 (-16.2; 43.7)	8.5 ± 27.5 (-25.0; 54.4)	18.9 ± 27.3 (-17.4; 59.0)	14.6 ± 30.5 (-24.3; 57.1)
	Adj *p*	0.9	0.3	0.3	0.3	0.3	0.3
	ES	0.03	0.25	0.28	0.19	0.26	0.20
DBP (mmHg)	Pre-test	76.5 ± 15.8 (53; 96)	19.8 ± 5.6 (11.9; 28)	-1.2 ± 9.9 (-9.3; 21.7)	0.0 ± 11.8 (-10.0; 27.1)	6.0 ± 11.7 (-6.1; 32.4)	3.3 ± 11.0 (-8.2; 28.2)
	8 weeks	75.6 ± 13.3 (57.9; 89.0)	14.5 ± 6.0 (6.26; 25.7)	7.7 ± 11.4 (-3.4; 28.1)	8.5 ± 13.8 (-10.6; 26.3)	13.2 ± 14.2 (-2.0; 35.0)	11.4 ± 13.0 (-0.51; 33.0)
	12 weeks	74.1 ± 13.2 (54.5; 92.8)	15.8 ± 6.0 (6.26; 25.8)	8.0 ± 14.3 (-8.9; 33.6)	12.8 ± 26.1 (-13.5; 67.0)	16.3 ± 18.9 (-5.5; 43.0)	14.4 ± 20.9 (-7.8; 41.0)
	Adj *p*	0.7	0.39	0.39	0.39	0.39	0.39
	ES	0.06	0.19	0.22	0.16	0.22	0.22
MAP (mmHg)	Pre-test	97.2 ± 16.5 (71.5; 118)	24.8 ± 7.6 (7.6; 32.3)	-5.3 ± 7.7 (-13.9; 11.8)	-3.3 ± 11.0 (-15.3; 20.9)	4.5 ± 10.4 (-4.4; 26.8)	1.5 ± 10.1 (-13.3; 22.0)
	8 weeks	95.3 ± 13.1 (75; 113)	17.5 ± 10.7 (5.1; 35.4)	2.9 ± 13.7 (-21.2; 20.8)	6.0 ± 14.9 (-21.3; 22.3)	11.8 ± 15.0 (-8.8; 31.4)	9.38 ± 12.6 (-5.3; 29.0)
	12 weeks	95.3 ± 14.2 (75.8; 119.3)	22.1 ± 8.2 (10.1; 31.4)	4.0 ± 15.6 (-13.0; 32.0)	5.8 ± 20.3 (-20.2; 38.5)	15.5 ± 20.4 (-10.3; 44.0)	12.4 ± 22.4 (-15.2; 41.4)
	Adj *p*	0.79	0.4	0.4	0.42	0.4	0.4
	ES	0.03	0.19	0.19	0.16	0.21	0.19

SVR ($mmHg.min^{-1}L^{-1}$)	Pre-test	25.1 ± 10.0 (14.5; 41)	11.8 ± 5.0 (6.5; 22.08)	-2.0 ± 9.7 (-13.1; 19.5)	-0.5 ± 11.1 (-11.9; 24.9)	2.7 ± 12.4 (-11.1; 29.7)	0.6 ± 10.5 (-13.3; 22.4)
	8 weeks	26.4 ± 10.7 (11.8; 38)	10.9 ± 5.0 (5.3; 20.8)	10.5 ± 16.4 (-2.2; 37.9)	9.62 ± 14.2 (-3.15; 32.2)	11.7 ± 14.3 (0.74; 35.8)	9.4 ± 12.5 (1.2; 35.6)
	12 weeks	24.7 ± 10.7 (11.8; 38)	11.5 ± 3.8 (7.6; 17.5)	5.2 ± 11.6 (-5.2; 28.6)	6.6 ± 13.5 (-7.0; 33.1)	10.7 ± 14.5 (-3.94; 33.14)	9.1 ± 11.5 (-2.4; 24.5)
	Adj *p*	0.82	0.87	0.29	0.29	0.29	0.29
	ES	0.05	0.02	0.27	0.22	0.22	0.22
HR (bpm)	Pre-test	66.6 ± 7.8 (53; 75)	16.9 ± 3.8 (12.1; 24.8)	16.9 ± 3.8 (12.1; 24.8)	16.1 ± 2.7 (10.3; 19.6)	16.4 ± 4.3 (8.6; 24.4)	12.3 ± 3.7 (6.6; 17.2)
	8 weeks	63.44 ± 5.8 (57; 72)	16.0 ± 4.4 (10.3; 23.0)	16.0 ± 4.4 (10.3; 23.0)	15.9 ± 3.4 (8.5; 20)	17.1 ± 5.0 (9.0; 23.8)	13.0 ± 4.3 (5.0; 19.1)
	12 weeks	64.2 ± 7.6 (55.6; 78.8)	17.7 ± 4.3 (10.0; 24.7)	17.7 ± 4.3 (10.0; 24.7)	18.5 ± 4.4 (12.6; 23.5)	18.5 ± 5.2 (11.1; 23.5)	12.7 ± 3.8 (7.9; 21.0)
	Adj *p*	0.56	0.56	0.56	0.56	0.85	0.89
	ES	0.15	0.13	0.13	0.16	0.04	0.02
CO ($L.min^{-1}$)	Pre-test	4.2 ± 1.1 (2.8; 5.8)	2.1 ± 1.0 (0.9; 4.4)	2.1 ± 1.0 (0.9; 4.4)	0.4 ± 1.1 (-0.7; 2.7)	0.6 ± 0.8 (-0.8; 1.5)	-0.1 ± 0.8 (-1.0; 1.1)
	8 weeks	4.3 ± 1.8 (2.0; 7.2)	2.0 ± 0.8 (1.1; 3.5)	2.0 ± 0.8 (1.1; 3.5)	0.3 ± 1.0 (-0.7; 2.7)	0.1 ± 0.5 (-0.8; 0.7)	-0.5 ± 0.4 (-1.1; 0.0)
	12 weeks	4.4 ± 1.6 (2.4; 6.6)	2.5 ± 1.3 (1.2; 5.0)	2.5 ± 1.3 (1.2; 5.0)	0.6 ± 1.5 (-0.4; 4.1)	0.7 ± 1.8 (-0.7; 4.8)	-0.3 ± 1.0 (-0.9; 2.5)
	Adj *p*	0.82	0.51	0.51	0.51	0.51	0.51
	ES	0.03	0.18	0.18	0.15	0.13	0.17

SV (mL)	Pre-test	64.2 ± 19.9 (43.0; 92.5)	17.6 ± 18.6 (0.3; 61.4)	-3.3 ± 13.3 (-21.0; 10.5)	-7.3 ± 11.2 (-24.6; 11.0)	-9.6 ± 12.1 (-31.2; 9.2)	-10.0 ± 12.6 (-27.1; 9.9)
	8 weeks	69.7 ± 31.6 (30.4; 125.0)	12.9 ± 8.1 (4.5; 30.8)	2.6 ± 14.0 (-22.3; 17.7)	-13.2 ± 9.4 (-24.8; 5.9)	-16.7 ± 7.8 (-26.5; -6.0)	-17.8 ± 7.7 (-26.1; -5.8)
	12 weeks	70.1 ± 28.5 (38.6; 119.0)	17.7 ± 13.2 (4.2; 44.8)	-5.3 ± 11.6 (-19.4; 15.3)	-11.0 ± 13.7 (-27.4; 15.5)	-10.8 ± 13.8 (-27.9; 15.4)	-17.0 ± 9.4 (-35.4; -8.3)
	Adj *p*	0.46	0.46	0.46	0.46	0.46	0.46
	ES	0.14	0.14	0.14	0.12	0.17	0.28

±: Mean and SD; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; SVR: systemic vascular resistance; HR: heart rate; CO: cardiac output; SV: stroke volume; Adj *p*: adjusted *p*-value; ES: effect size. The variable values are expressed as absolute numbers at baseline and Δ from amplitude to phases 1-4, where negative numbers represent below baseline values and positive numbers above baseline values.

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress

Figure 11.6 illustrates the correlation coefficients (*r*), 95% confidence interval (CI 95%), and *p*-values for CO and SVR responses across four specific phases at pre-test, 8 weeks, and 12 weeks of PST. In the sit-to-stand transition, the pre-test analysis showed no significant correlation between CO and SVR in phase 1 (r = -0.333, 95% CI -0.841; 0.485, p = 0.42). However, a large and significant negative correlation was found in the following phases: phase 2 (r = -0.917, 95% CI -0.985; -0.601, p = 0.001), phase 3 (r = -0.854, 95% CI -0.973; -0.376, p = 0.007), and phase 4 (r = -0.904, 95% CI -0.983; -0.548, p = 0.002). At week 8, a large and significant negative correlation was observed in all phases: phase 1 (r = -0.763, 95% CI -0.955; -0.127, p = 0.028), phase 2 (r = -0.804, 95% CI -0.963; -0.229, p = 0.016), phase 3 (r = -0.977, 95% CI -0.996; -0.876, p < 0.001), and phase 4 (r = -0.846, 95% CI -0.972; -0.351, p = 0.008). At week 12, there were large and significant negative correlations in phase 1 (r = -0.719, 95% CI -0.945; -0.030, p = 0.044), phase 2 (r = -0.752, 95% CI -0.952; -0.101, p = 0.031), and phase 3 (r = -0.707, 95% CI -0.942; -0.004, p = 0.05). However, no significant negative correlation was observed in phase 4 (r = -0.664, 95% CI -0.933; 0.076, p = 0.07).

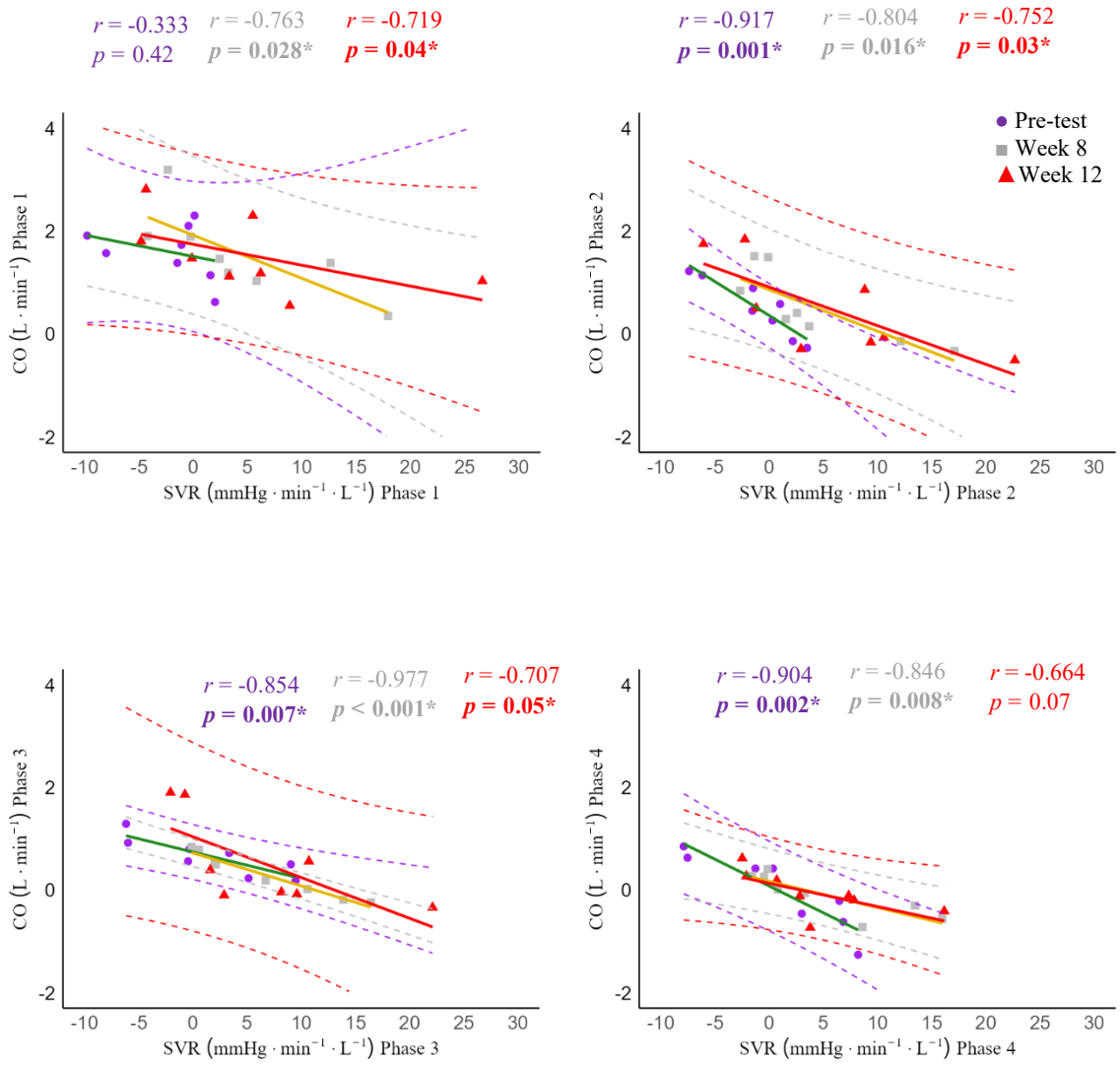


Figure 11.6 Correlation between cardiac output and systemic vascular resistance during the sit-to-stand transition across phases at pre-test, 8 weeks, and 12 weeks of progressive strength training.

Figure 11.7 illustrates the correlation coefficients (*r*), 95% confidence interval (CI 95%), and *p*-values for CO and SVR responses across four specific phases at pre-test, 8 weeks, and 12 weeks of PST. In the lie-to-stand transition, no significant correlation between CO and SVR was

observed in phase 1 (r = -0.352, 95% CI -0.847; 0.469, p = 0.3), and phase 2 (r = -0.656, 95% CI -0.931; 0.090, p = 0.07) at pre-test. However, at phase 3 (r = -0.795, 95% CI -0.690; 0.018, p = 0.018) and phase 4 (r = -0.824, 95% CI -0.967; -0.284, p = 0.012), a large and significant negative correlation was observed. At week 8, a large and significant negative correlation was observed in phase 1 (r = -0.717, 95% CI -0.944; -0.025, p = 0.04), and phase 3 (r = -0.808, 95% CI -0.964; -0.239, p = 0.015). While phase 2 (r = -0.597, 95% CI -0.916; 0.186, p = 0.1) and phase 4 (r = -0.199, 95% CI -0.588; 0.637, p = 0.6) showed no significant correlation. At week 12, a large and significant negative correlation was observed in phase 1 (r = -0.738, 95% CI -0.917; 0.184, p = 0.04), phase 2 (r = -0.833, 95% CI -0.886; 0.337, p = 0.01), and phase 3 (r = -0.833, 95% CI -0.939; 0.025, p = 0.01), but no significant correlation in phase 4 (r = -0.643, 95% CI -0.929; 0.098, p = 0.09).

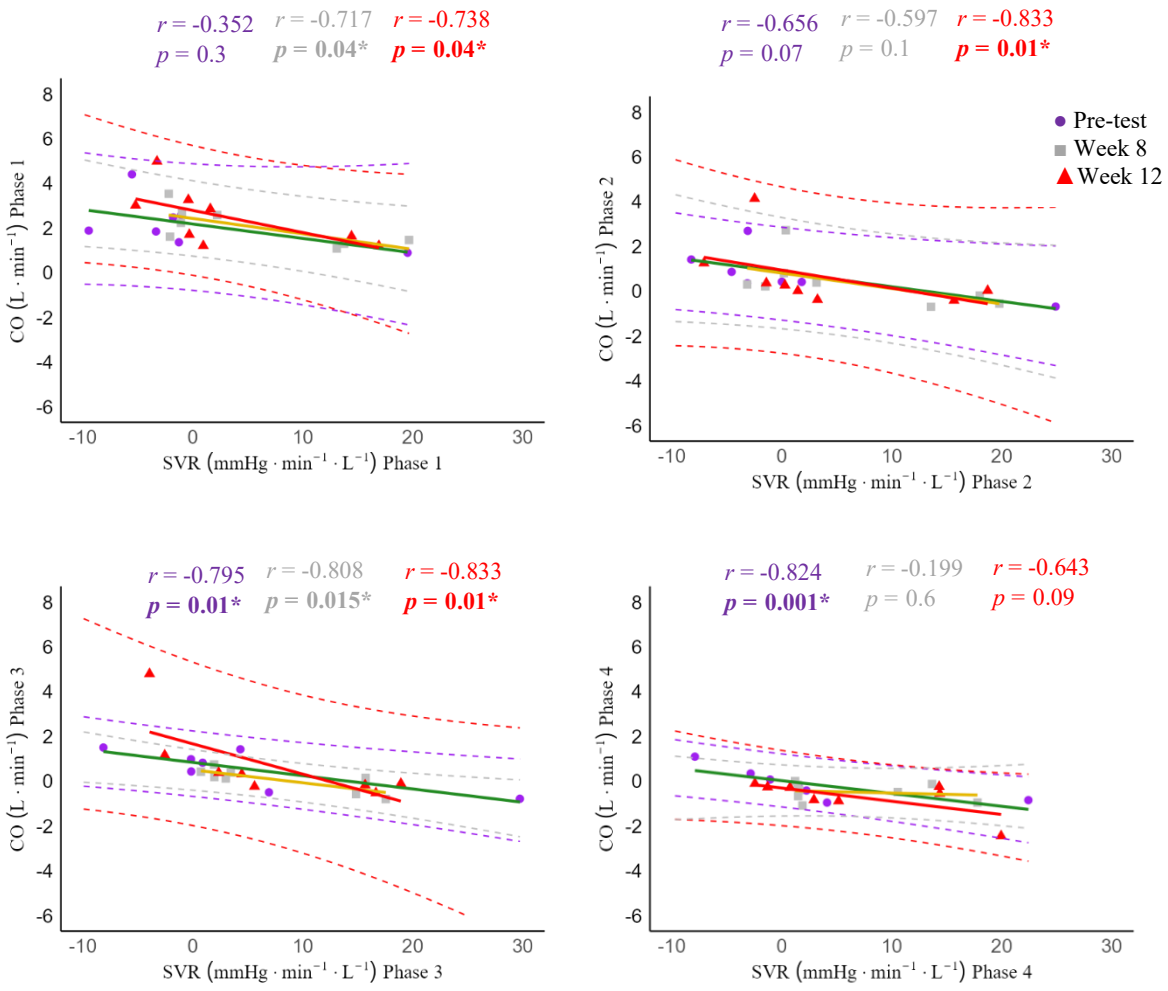


Figure 11.7 Correlation between cardiac output and systemic vascular resistance during the lie-to-stand transition across phases at pre-test, 8 weeks, and 12 weeks of progressive strength training.

Heart Rate Variability at Baseline in the Supine Position Over the Progressive Strength Training

In the time and frequency domain analysis, no statistically significant differences were observed between pre-test, 8 weeks and 12 weeks of PST (Table 11.5).**Table 11.5** Heart Rate variability (HRV) responses in time and frequency domains during supine position across frailty groups at pre-test, 8 weeks, and 12 weeks.

Time domain				
	Pre-test	8 weeks	12 weeks	*p* (ES)
RR	788.2 ± 300.7 (557.0; 1019.3)	814.2 ± 336.2 (533.2; 1095.2)	816.4 ± 365.0 (478.8; 1153.9)	0.9 (0.1)
SDRR	32.3 ± 15.5 (20.4; 44.1)	27.6 ± 8.7 (20.4; 34.9)	27.7 ± 5.1 (23.0; 32.4)	0.6 (0.04)
RMSSD	22.0 ± 7.3 (16.3; 27.6)	19.7 ± 4.0 (16.3; 23.0)	21.1 ± 6.3 (15.3; 26.9)	0.7 (0.03)
Frequency domain				
LF	438.3 ± 650.7 (−61.8; 938.5)	207.9 ± 264.5 (−13.2; 429.0)	100.0 ± 59.1 (45.4; 154.7)	0.2 (0.11)
HF	915.0 ± 1818.0 (−482.4; 2312.4)	426.4 ± 711.1 (−168.2; 1020.9)	194.1 ± 114.2 (88.5; 299.8)	0.4 (0.07)
LF/HF	0.7 ± 0.4 (0.4; 0.9)	0.7 ± 0.3 (0.4; 1.0)	0.7 ± 0.4 (0.3; 1.0)	0.9 (0.1)

ES: Effect size, HRV: heart rate variability; RR: Average interval between consecutive heartbeats (RR-intervals); SDRR: Standard Deviation of RR intervals; RMSSD: Root Mean Square of Successive differences between RR intervals; LF: Low-Frequency power; HF: High-Frequency power; LF/HF: Low Frequency to High-Frequency power ratio: HR: heart rate.

Cardiac Parasympathetic Modulation Over the Progressive Strength Training

There were no statistically significant differences in CPM responses between the pre-test, 8 weeks, and 12 weeks of PST (Table 11.6).

Table 11.6 Cardiac parasympathetic modulation (HR Δ 30:15) during sit-to-stand and lie-to-stand transitions across frailty groups at pre-test, 8 weeks, and 12 weeks.

Cardiac parasympathetic modulation					
Sit-to-stand					
	Pre-test	8 weeks	12 weeks	*p*	ES
HR Δ 30:15	1.05 | 0.04 (1.02; 1.18)	1.04 | 0.05 (0.93; 1.12)	1.02 | 0.04 (1.00; 1.17)	0.2	0.1
Lie-to-stand					
	Pre-test	8 weeks	12 weeks	*p*	ES
HR Δ 30:15	1.01 ± 0.06 (0.91; 1.10)	1.04 ± 0.05 (0.94; 1.12)	1.04 ± 0.04 (1.00; 1.12)	0.9	0.1

|: Interquartile range with (Minimum and Maximum). ES: effect size.

Short-Term Cardiac Baroreflex Gain During Active Stand Orthostatic Stress Across Phases Over the Progressive Strength Training

In the sit-to-stand and lie-to-stand transitions, no statistically significant differences were found in CBG for all phases between pre-test, 8 weeks and 12 weeks of PST (Table 11.7).

Table 11.7 Cardiac baroreflex gain (CBG) responses during sit-to-stand and lie-to-stand transitions across frailty groups at pre-test, 8 weeks, and 12 weeks.

Sit-to-stand					
CBG ($bpm \cdot mmHg^{-1}$)	Pre-test	8 weeks	12 weeks	*p*	ES
Phase 1: 30 s	0.6|0.1 (0.4; 0.8)	0.5|0.1 (0.4; 0.7)	0.5|0.1 (0.4; 0.6)	0.4	0.07
Phase 2: 60 s	0.6|0.1 (0.4; 0.8)	0.5|0.1 (0.4; 0.6)	0.5|0.1 (0.4; 0.7)	0.4	0.1
Phase 3: 180 s	0.5|0.1 (0.4; 0.8)	0.5|0.1 (0.4;0.7)	0.5|0.1 (0.3; 0.6)	0.6	0.03
Phase 4: 420 s	0.6|0.1 (0.4; 0.8)	0.5|0.1 (0.4; 0.7)	0.5|0.1 (0.4; 0.6)	0.4	0.1
Lie-to-stand					
	Pre-test	8 weeks	12 weeks	*p*	ES
Phase 1: 30 s	0.6 ± 0.1 (0.5; 0.7)	0.6 ± 0.1 (0.5; 0.6)	0.6 ± 0.1 (0.5; 0.7)	0.8	0.07
Phase 2: 60 s	0.6 ± 0.1 (0.5; 0.7)	0.6 ± 0.1 (0.5; 0.7)	0.6 ± 0.1 (0.5; 0.7)	0.8	0.03
Phase 3: 180 s	0.6 ± 0.1 (0.5; 0.6)	0.6 ± 0.1 (0.5; 0.6)	0.6 ± 0.1 (0.5; 0.6)	0.8	0.01
Phase 4: 420 s	0.6 ± 0.1 (0.5; 0.6)	0.5 ± 0.1 (0.5; 0.6)	0.6 ± 0.1 (0.5; 0.7)	0.8	0.05

|: Interquartile range with (Minimum and Maximum). CBG: Cardiac baroreflex gain; ES: Effect size.

Discussion

This study examined the effect of a 12-week progressive strength training (PST) program to counteract frailty and improve cardiovascular and autonomic short-term compensatory responses during postural transitions in older adults living with frailty. This is the first study that analyzes the effects of 12 weeks of PST on the short-term cardiovascular compensatory responses across specific phases in community-dwelling pre-frail and frail older adults under two different

active standing orthostatic stress (sit-to-stand; lie-to-stand). The PST counteracted frailty as demonstrated by the lower FI scores and improved physical activity levels, grip strength and gait speed as well as CO and SVR matching, indicating improved functional capacity and a faster BP regulation shifting from phase 3 (60-180 s) at pre-test to phase 1 (0-30 s) after 12 weeks in both postural transitions (sit-to-stand and lie-to-stand). However, PST did not improve the autonomic short-term compensatory responses.

Frailty Dynamics in Responses to 12 Weeks of Progressive Strength Training

Over the 12 weeks of PST, participants demonstrated a reduction in their FI scores. On average, the FI dropped by 55.5% from the pre-test to 8 weeks, 50% from week 8 to week 12, and 78% from the pre-test to week 12. The participant who was the frailest at the pre-test (FI = 0.33) exhibited the greatest overall improvement, with a 30% reduction after 8 weeks (FI = 0.23) and a total reduction of 85% by 12 weeks (FI = 0.05). This change far exceeds the minimal clinically important difference (MCID) for the FI, which has been suggested to be approximately 0.03 points in previous literature[220,221]. A reduction of 0.14 points in our sample not only represents a clinically meaningful improvement but also a shift from frailty toward a non-frail status. Such a significant change is likely to translate into meaningful improvements in physical function, independence, and overall quality of life. Also, corroborating our findings, Kehler et al.[222] found that individuals with higher baseline frailty (FI > 0.30) benefited the most from cardiac rehabilitation, with average FI reductions ranging from 0.08 to 0.11. Similarly, in our study, the frailest participants experienced the largest improvements, supporting prior findings that those with greater initial frailty show the most significant and clinically meaningful gains[222]. Also, aligned with our results, Perez-Zepeda et al.[202] showed that, from admission until discharge following a multi-component exercise program that included supervised progressive resistance training, balance, and walking exercise, hospitalized frail older adults had an improvement of 23% in the FI score (0.26 ± 0.1 to 0.20 ± 0.1).

The observed reduction in frailty index following 12 weeks of PST can be attributed to adaptations across the musculoskeletal and cardiovascular systems, as evidenced by our data that

showed a significant increase in physical activity levels, walking speed, and grip strength. Regular resistance exercise enhances skeletal muscle strength and power by increasing motor unit recruitment, improving neuromuscular coordination, and promoting hypertrophy of type II muscle fibers[223]. These neuromuscular improvements likely contributed to better performance in strength-dependent functional tasks[80]. Additionally, the repeated postural and muscular demands of training may have improved baroref

lex sensitivity and venous return, supporting more effective blood pressure regulation during orthostatic challenges[80,223]. Improved peripheral circulation and capillary density may also facilitate oxygen delivery and nutrient exchange during movement[223]. Altogether, these adaptations help to improve functional capacity, as shown in our study by the improvements in grip strength and gait speed, and reduce physiological impairments associated with frailty.

Level of Physical Activity, Hand Grip Strength, and Gait Speed After 12 Weeks of Progressive Strength Training

Over the 12-week intervention, participants demonstrated significant improvements in physical activity levels, hand grip strength, and gait speed, indicating enhanced functional capacity and muscular performance. Physical activity levels increased by 95% from pre-test to 8 weeks, followed by an additional 29% increase between 8 and 12 weeks, and 153% from pre-test to 12 weeks of PST. Hand grip strength increased by 9% from pre-test to 8 weeks and by 13% from pre-test to 12 weeks, with no significant changes between 8 and 12 weeks. It is worth mentioning that a participant showed a reduction in hand grip strength from 8 to 12 weeks. Gait speed improved by 11% from pre-test to 8 weeks and by 19% from pre-test to 12 weeks, with no statistically significant changes between 8 and 12 weeks.

The improvements observed in hand grip strength and gait speed are consistent with early-phase adaptations to resistance training, particularly those occurring during the neural phase[223]. This phase, which predominates in the initial weeks of training, involves increased motor unit recruitment, firing frequency, and reduced neural inhibition, all of which contribute to enhanced

force production[223]. Increases in gait speed may also reflect improved neuromuscular function, supporting more effective stride and postural control[223]. Over the 12 weeks of PST, repeated exposure to strength-based activity may have also initiated morphological adaptations, such as increased muscle cross-sectional area and tendon stiffness, which further support the observed functional improvements[223,224]. Moreover, the progressive increase in physical activity levels (153% from pre-test to 12 weeks) likely contributed to a higher overall mechanical stimulus, reinforcing the neuromuscular and structural changes associated with improved motor performance in older adults[223,225]. These improvements are clinically meaningful, as greater grip strength and faster gait speed are associated with better functional independence[223], lower risk of falls, and reduced all-cause mortality[223,224]. Similarly, increased physical activity levels are linked to enhanced cardiovascular health, cognitive function, and quality of life in aging populations[223,225].

Baseline Responses During Active Standing Orthostatic Stress After 12 weeks of Progressive Strength Training

No statistically significant differences were found at baseline after 12 weeks of PST in any of the variables in both postural transitions. Supporting our results, Coelho-Junior et al.[29] did not find statistical differences in SBP, DBP, and HR in frail older adults after 16 weeks of strength training. Brilla et al.[32] partially support our findings, reporting no statistical differences after 8 weeks of strength training in older adults in SBP and HR. However, they observed significant differences in DBP. Fecchio et al.[212] results also partially align with our results, reporting no statistically significant differences in SVR and CO. However, in contrast with our results, significant changes in SBP, DBP, HR, and SV were observed in older adults following 10 weeks of strength training[226].

Baseline values of SBP, DBP, HR, SV, CO, and SVR remained unchanged after 12 weeks of PST. These similarities may be attributed to the resting conditions during assessment, where cardiovascular demands are minimal[16]. Under these conditions (sitting or lying), adaptations such as improved venous return, enhanced muscle pump activity, and faster autonomic regulation are

not heavily engaged, and thus, their effects may not be reflected in resting measurements[16,132]. Our findings are consistent with previous studies that reported either no changes[29] or only minor changes[32,212] in resting cardiovascular parameters following resistance training, suggesting that resting measurements may not adequately capture the physiological adaptations resulting from PST.

Immediately on Active Standing Orthostatic Stress Responses After 12 Weeks of Progressive Strength Training

No statistically significant differences were observed in the immediate responses to active standing orthostatic stress across any variable during either sit-to-stand and lie-to-stand. This phase primarily involves rapid neural adjustments mediated by arterial baroreceptors located in the carotid sinus and aortic arch, which detect the transient drop in central blood volume and arterial pressure following a gravitational shift[16,24]. In response, there is an increase in sympathetic activity and withdrawal of parasympathetic tone, leading to changes in HR, vascular resistance, and CO to regulate BP and ensure adequate cerebral perfusion[16,24]. The similarity in responses across the intervention period may suggest that these compensatory mechanisms were not improved, potentially due to the limited duration of the intervention for detecting physiological adaptations. It is also possible that the community-dwelling older adults analyzed did not exhibit marked cardiovascular dysfunction, and the active standing protocol tests may not have been demanding enough to expose impairments in cardiovascular regulation.

Short-Term Cardiovascular Compensatory Responses During Active Standing Orthostatic Stress After 12 Weeks of Progressive Strength Training

No significant differences were found in any of the variables analyzed across phases (1-4) in either postural transition after 12 weeks of PST. Partially consistent with our findings, Brilla et al.[32] reported that after 8 weeks of training in older adults, DBP and HR remained unchanged, while SBP showed significant changes, showing lower amplitude drop during the transition from supine to sitting. During the sit-to-stand transition, SBP and DBP did not differ significantly, whereas HR increased significantly.

The comparable cardiovascular responses observed across phases and transitions may reflect the complexity of short-term cardiovascular regulation. The similarities in SBP, DBP, and MAP may be attributed to impairments in peripheral vasoconstriction[16]. In pre-frail and frail older adults, age-related reductions in arterial compliance and vascular smooth muscle responsiveness can limit the rapid response of arterial pressure following orthostatic stress[33,196]. Also, HR, CO, and SV compensatory responses in remained unchanged, suggesting that the cardiac adjustments required during the early postural challenge were not substantially modified by the PST training[80,204]. These outcomes may reflect a limited chronotropic response and reduced capacity to increase SV under acute gravitational load, possibly due to ongoing impairments in ventricular filling and central hemodynamic control despite improvements in muscular strength[80,204].

Cardiac Output and Systemic Vascular Resistance Matching Responses During Active Standing Orthostatic Stress After 12 Weeks of Progressive Strength Training

This is the first study to investigate the correlation between CO and SVR across specific temporal phases after 12 weeks of PST following postural transitions in older adults living with frailty. This phase-specific analysis provides novel insights into the potential timing of BP regulation relative to baseline values. The matching between CO and SVR plays a central role in BP regulation and the maintenance of cerebral perfusion[16,24] during active standing orthostatic stress. The results showed that in the sit-to-stand transition, at pre-test, no significant correlation between CO and SVR was observed during phase 1 (0-30 s), suggesting a delayed regulation of BP on standing. In contrast, significant negative correlations were found in phases 2 (30-60 s), 3 (60-180 s), and 4 (300-420 s), suggesting a late regulation of BP. By week 8, a significant negative correlation was observed across all four phases, reflecting an improved matching between CO and SVR. At week 12, significant negative correlations were found in phases 1, 2, and 4, while phase 3 was approaching statistical significance ($p < 0.06$). In the lie-to-stand transition, no significant correlation between CO and SVR was observed at pre-test during phase 1 (0-30 s) and phase 2 (30-60 s), indicating impaired cardiovascular responses in the first 60 seconds of active standing of orthostatic stress. In contrast, significant negative correlations were observed in phases 3 (60-

180 s) and 4 (300-420 s), indicating that BP regulation occurred later during the postural transition. At week 8, a significant negative correlation was present in phases 1 and 3. However, no significant correlation was found in phases 2 and 4 at this time point. By week 12, a significant correlation between CO and SVR was observed in phases 1 to 3, but no significant correlation in phase 4.

The significant improvements seen across all phases in the second assessment indicate that 8 weeks of PST were adequate to improve the timing of BP regulation during orthostatic stress. Such improvements may be attributed to increased muscle pump, improved venous return, and higher responsive vascular control, facilitating a faster regulation of arterial pressure following postural transitions[16,223]. The earlier phase-specific regulation observed post-training reflects a more integrated cardiovascular response, critical for maintaining cardiovascular stability in older adults with frailty.

Heart Rate Variability Responses at Baseline After Progressive Strength Training

No statistically significant differences were observed in HRV indexes in either the time or frequency domains at any of the points analyzed. Supporting our results, Gambassi et al.[211] reported no significant changes in HRV indexes after 10 weeks of resistance training when comparing older adults in the experimental groups *vs* the control group. However, they observed within-group improvements in HRV indexes among trained participants. The authors attributed these changes to reductions in body fat and increases in fat-free mass and muscular strength, suggesting that improvements in body composition might mediate autonomic adaptations. Similarly, Gerage et al.[226] found no statistical differences in HRV indexes following 12 weeks of resistance training in untrained older females compared to controls. They proposed that the protocol, short training duration and low-to-moderate volume may not have provided sufficient stimulus to promote autonomic changes. In contrast to our results, Lin et al.[210] observed improvements in HRV indexes in older females and males after 24 weeks of resistance training compared to the control group. However, the training duration in that study was twice as long as in our study. The authors suggested that the longer duration and higher intensity of training were

key factors for improving vagal tone and orthostatic tolerance, indicating that training load and duration are critical for inducing autonomic modulation.

There was no difference in HRV in both time and frequency domains, suggesting that autonomic cardiac modulation remained similar throughout the intervention. In pre-frail and frail older adults, autonomic regulation is often characterized by a reduction in parasympathetic activity and impaired reflex control of HR[35]. These alterations are frequently linked to structural and functional changes in the autonomic system[143], including diminished baroreceptor sensitivity and altered central autonomic integration[143]. Such alterations may limit the influence of resistance training on vagal modulation and autonomic balance over 12 weeks of PST.

Cardiac Parasympathetic Modulation Responses During Active Standing Orthostatic Stress After Progressive Strength Training

The CPM was similar across the pre-test, 8 weeks, and 12 weeks, with no statistically significant differences. The similarities in CPM throughout the 12-week intervention indicate that the PST did not influence the vagal regulation of HR in this sample of community-dwelling pre-frail and frail older adults. Aging and frailty are commonly associated with a decline in parasympathetic activity[35], which reflects changes at both central and peripheral levels of autonomic control[143]. These include altered neurotransmission in brainstem nuclei involved in cardiovagal regulation, reduced acetylcholine availability at the sinoatrial node, and structural changes in afferent and efferent pathways that mediate parasympathetic output[35,227]. Such impairments may limit the ability of short-term interventions to modify cardiovagal function. The present findings suggest that, in this population, PST may not alter vagally mediated HR control, at least within the timeframe assessed in the current study.

Short-term Cardiac Baroreflex Gain During Active Standing Orthostatic Stress After Progressive Strength Training

CBG remained similar across the pre-test, 8-week, and 12-week assessments, indicating no statistically significant adaptation in baroreflex sensitivity over the course of the intervention. Our findings are aligned with Fecchio et al.[212] who also observed no significant changes in CBG after

10 weeks of dynamic resistance training in hypertensive males. They proposed that despite improvements in vascular function and reductions in resting blood pressure, the short training duration may not have been sufficient to affect CBG. Similarly to our results, Bellavere et al.[228] did not find statistical differences in CBG after 16 weeks of resistance training in older females and males. They suggested that the similar response across the intervention may reflect either the limited sample size (n = 9) or potentially lower responsiveness of baroreflex components to resistance training.

In pre-frail and frail older adults, blunted baroreflex function is commonly observed and may reflect age-related alterations in arterial compliance, afferent baroreceptor signaling, and central autonomic integration[24,65]. These changes impair the regulation of HR in response to fluctuations in blood pressure, compromising short-term autonomic regulation[24]. Similar responses in the present study may suggest that PST over 12 weeks does not influence the components of the baroreflex arc among pre-frail and frail individuals.

Prevalence of Orthostatic Hypotension and Orthostatic Intolerance Symptoms After 12 Weeks of Progressive Strength Training

Over the 12-week PST intervention, the prevalence of OH showed no statistically significant differences. The lack of statistically significant prevalence of OH and OI self-reported symptoms over the 12 weeks of PST may suggest that some mechanisms involved in acute short-term blood pressure regulation, such as vascular responsiveness and muscle pump activation[141], remained with limited improvement to the intervention. In older adults with frailty, structural and functional alterations in the cardiovascular system may limit the capacity for short-term cardiovascular compensatory adjustments[6], thereby maintaining susceptibility to orthostatic disturbances despite gains in physical function. Despite that, descriptive trends suggest a potential shift toward a reduction in OH prevalence and OI self-reported symptoms. The number of participants with NBP increased from 1 at pre-test (12.5%) to 3 in weeks 8 and 12 (37.5%). IOH remained unchanged across all time points, with 1 participant (12.5%) meeting the criteria for this

category. For DOH, the number of participants declined from 6 at pre-test (75%) to 4 at week 8 and 12 (50%). There were no participants who met the criteria of SOH at any time point.

OI self-reported symptoms demonstrated no statistically significant differences in the 12 weeks of PST. However, it is worth mentioning that at pre-test, 37.5% of participants (3/8) reported OI-related symptoms. By week 8, this number dropped to 12.5% (1/8 participants). By week 12, no participants had reported OI-related symptoms, representing a 100% relative reduction from the pre-test. While the statistical analysis did not reach significance ($p = 0.09$), this trend may have clinical relevance, especially given the potential impact of OI symptoms on daily function and fall risk in frail older adults. With this context of clinically meaningful responses in mind, it is possible that improvements in neuromuscular coordination and postural control resulting from PST contributed to reduced OI symptoms by enhancing the body's ability to regulate BP during orthostatic challenges.

Limitations

The study had several relevant strengths; however, some limitations need to be considered. First, this study employed a quasi-experimental time-series design without a randomized control group, which limits the ability to establish causality[229]. The lack of randomization increases susceptibility to reduce internal validity compared to randomized controlled trials (RCT)[229]. The RCT's are designed to isolate the effect of the intervention through group equivalence at the baseline[229]. However, the use of a quasi-experimental design in a real-world setting enhances ecological validity[229], allowing the intervention to be implemented and assessed under conditions that closely reflect clinical practice. This design also facilitated the monitoring of individual responses over time, which is particularly relevant in complex populations such as older adults living with frailty. Also, this quasi-experimental design provided valuable preliminary insights. However, future randomized controlled trials (RCTs) should build upon these findings by incorporating larger, more balanced samples across sex and frailty status. The physiological data collected here could serve as a foundation for hypothesis generation and sample size estimation in

future RCTs aimed at isolating the effects of PST on cardiovascular and autonomic regulation across different subgroups.

Although the sample size was determined a priori based on power calculations, requiring seven participants, the final sample of eight older adults may still be considered small for generalizability and inter-individual variability. A smaller sample size increases the risk of type II error and limits the exploration of subgroup effects (e.g., by frailty level)[229]. On the other hand, small, well-characterized samples can offer relevant physiological insights, particularly in populations that are underrepresented or difficult to recruit, such as older adults living with frailty.

The study sample was composed predominantly of females (7 out of 8 participants), which limits the ability to draw conclusions about sex differences in response to PST. Furthermore, the distribution of frailty levels was uneven, with only two participants classified as frail and six as pre-frail. This imbalance may have limited the ability to explore differential effects of the intervention based on frailty severity. Lastly, as discussed in earlier chapters, factors such as age-related comorbidities, sex, and medication use may act as potential confounders that were not fully controlled in the present study. These variables should be carefully considered in the design and interpretation of future studies to strengthen causal inference and clarify the specific mechanisms underlying the observed adaptations.

Conclusion

The 12-week PST counteracted frailty status, as indicated by a 78% decrease in the FI from the pre-test to the post-test (0.18 to 0.04), representing a clinically meaningful improvement in frailty severity. Also, PST led to progressive improvements in physical activity levels, handgrip strength, and gait speed over 12 weeks. Despite these functional improvements, no significant changes were observed in the short-term cardiovascular and autonomic compensatory responses during both postural transitions. However, the timing of BP regulation improved, as demonstrated by the earlier (0-30 s) significant negative correlations between CO and SVR. This phase-specific shift indicates faster cardiovascular adjustments during orthostatic stress. Finally, although no statistical differences were observed in the prevalence of OH and OI self-reported symptoms,

improvements in the proportion of participants with NBP and a reduction in the number of individuals reporting OI symptoms after 12 weeks of PST suggest a potentially meaningful clinical benefit in orthostatic responses.

Brief Discussion of the Manuscript Written Exclusively By Dihogo De Matos

This study showed that a 12-week PST intervention significantly reduced frailty index scores in pre-frail and frail older adults. Also, PST resulted in progressive improvements in physical activity levels, handgrip strength, and gait speed over 12 weeks. However, PST did not have statistically significant changes in short-term cardiovascular or autonomic compensatory responses across any phases during either the sit-to-stand or lie-to-stand transitions. Despite this, there was a phase-specific improvement in CO-SVR matching, representing the timing of BP regulation. These findings suggest that PST improved the timing of BP regulation, shifting from delayed responses in phase 3 (60-180 s) at pre-test to earlier responses in phase 1 (0-30 s) after 12 weeks of PST. Taken together, this study highlights the functional and temporal cardiovascular benefits of PST in frail populations and underscores the need for longer or more intensive interventions to improve cardiovascular and autonomic short-term compensatory responses. Lastly, despite no statistically significant differences being observed in the prevalence of OH and OI self-reported symptoms, improvements in the proportion of participants with normal blood pressure response and decreased number of participants reporting OI-related symptoms suggest a potentially meaningful clinical benefit in orthostatic responses after 12 weeks of PST.

12. Chapter 12

General Discussion

The regulation of the cardiovascular and autonomic nervous systems is essential to maintain homeostasis in response to external stressors[3]. Postural transitions, such as standing up from a chair or bed, impose an abrupt gravitational challenge that requires rapid adjustments to preserve blood pressure (BP) and cerebral perfusion[3,132]. These adjustments include increased sympathetic activity, vasoconstriction, heart rate (HR), and baroreflex response[24,132] (Figure 12.1).

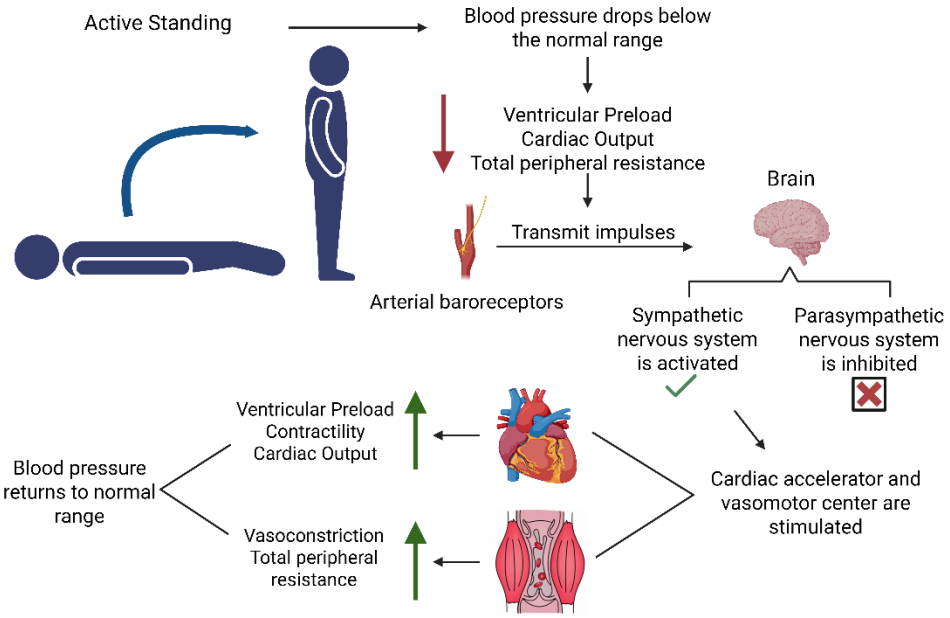


Figure 12.1 Cardiovascular and Autonomic regulation to orthostatic stress.

When this regulatory system is impaired, due to reduced baroreflex sensitivity[24], diminished vascular responsiveness[132], or altered autonomic tone[35], it leads to physiological dysregulation. As a result, individuals are more likely to experience a sudden drop in blood pressure upon standing, a condition known as orthostatic hypotension (OH), which significantly elevates the risk of falls[3]. OH can be accompanied by orthostatic intolerance (OI), characterized by symptoms such as dizziness, lightheadedness, blurred vision, and, in severe cases, syncope[42].

Older adults, females, and frail individuals appear to be more affected by OH and its underlying regulatory impairments. Older adults experience age-related structural and functional changes in the heart, vasculature, and autonomic pathways that hinder rapid compensatory responses to orthostatic stress[230]. Similarly, females may exhibit distinct cardiovascular and autonomic regulation patterns that make them more susceptible to inadequate BP regulation following standing[231]. Individuals living with frailty represent another group, often exhibiting attenuated cardiovascular response and autonomic dysregulation[6,18] (Figure 12.2).

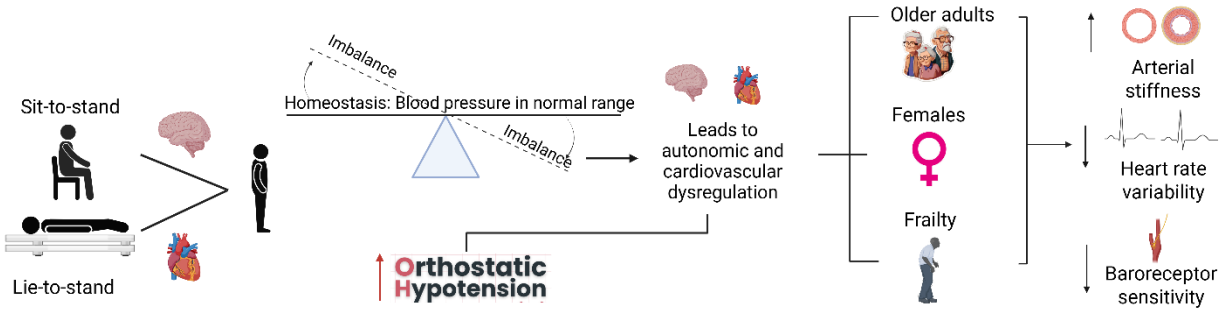


Figure 12.2 Factors influencing cardiovascular and autonomic responses after active standing orthostatic stress.

Among these factors, individuals with frailty are particularly vulnerable due to the cumulative impact of multisystem physiological decline, including reduced cardiovascular and autonomic dysfunction[70]. As such, frailty has emerged as a modifiable risk factor and a priority target for intervention. Progressive strength training (PST) has gained attention for its potential to counteract frailty status and improve vascular function and circulatory control[79,80]. Although evidence remains limited[32], it is hypothesized that PST may promote faster cardiovascular and autonomic short-term compensatory responses during postural transitions by improving vascular compliance, increasing muscle pump effectiveness, and modulating autonomic control mechanisms.

Overview of findings

This thesis was designed to examine cardiovascular and autonomic responses to orthostatic stress by integrating evidence from a systematic review and a series of experimental studies

addressing the influence of age, sex, frailty, and PST. The work integrates results (Figure 12.3) across these domains to offer a comprehensive and temporal understanding of short-term cardiovascular and autonomic regulation in older adults. This synthesis is centered on two methodological innovations: phase-specific analysis and the evaluation of cardiac output–systemic vascular resistance (CO-SVR) matching. The overarching goal was to confirm and expand upon existing physiological models while generating clinically meaningful insights that inform future research and practice.

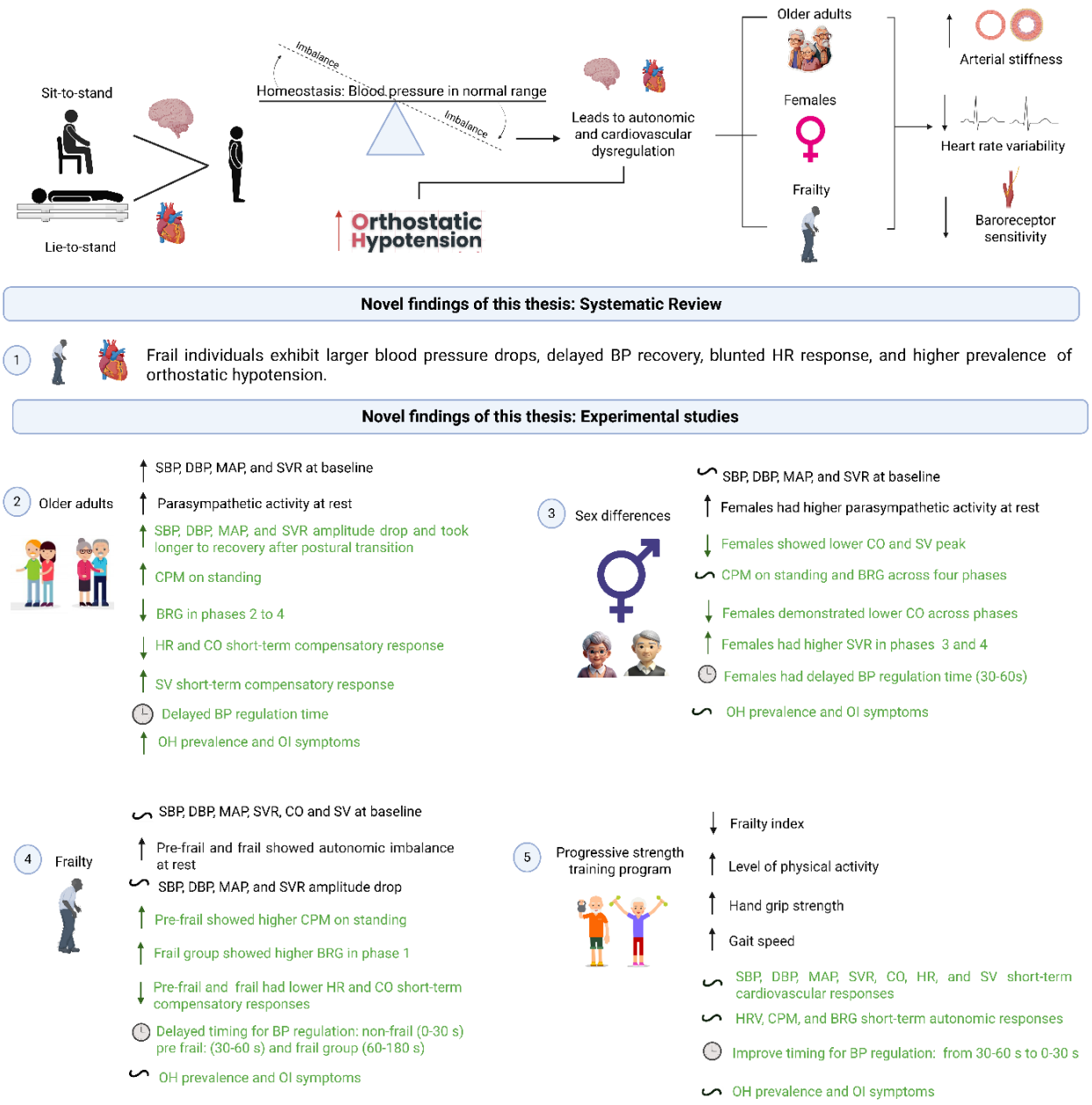


Figure 12.3 Thesis framework with a summary of the novel findings. Black words represent the summary of already known findings from the literature. Green words represent the summary of the novel findings of this thesis.

The initial systematic review in Chapter 4 identified significant limitations in the current literature[6,53,96,98,99], particularly a reliance on static time points and a lack of detail in the evaluation of frailty-related responses to orthostatic stress. Most prior studies reported exaggerated BP drops and attenuated HR responses in frail individuals[6,53,96,98,99] but rarely explored the timing of recovery or the dynamic interplay between cardiac and vascular factors. This thesis addressed those gaps by analyzing responses across specific recovery phases and introducing CO-SVR mismatch as a novel, mechanistically grounded marker of dysregulation.

The experimental data of this research confirmed previous findings that age is associated with delayed BP stabilization and reduced cardiovascular responsiveness. These impairments were accompanied by lower heart rate variability (HRV) indexes and diminished cardiac baroreflex gain (CBG), consistent with attenuated autonomic regulation. It is well-established that the prevalence of OH increases with age[7], affecting approximately 20% of community-dwelling older adults, and OI symptoms such as dizziness and light-headedness are common even in the absence of diagnostic OH thresholds[7]. Also, a novel contribution of this thesis is the characterization of how older females and males utilize different compensatory mechanisms in response to orthostatic stress. Specifically, older females relied more heavily on increasing SVR, while older males primarily increased CO. Although both groups achieved similar BP stabilization outcomes, these findings reveal that sex influences the underlying mechanisms of cardiovascular regulation. These sex-specific differences in compensatory strategy have not been consistently highlighted in previous literature[2,62] and provides new insight into how orthostatic adaptation may differ physiologically across sexes.

Frailty is well recognized in the literature as a clinical condition associated with impaired cardiovascular regulation[98], increased susceptibility to orthostatic hypotension[6], and a higher prevalence of delayed recovery following postural transitions[6,96]. Previous studies have shown that frail individuals often exhibit larger BP drops and attenuated heart rate responses[6,53,96]. However, most prior research has relied on single-time-point measurements, limiting the ability to characterize the dynamic regulation of BP over time. This thesis introduced phase-specific analysis to identify delays in BP stabilization that hold clinical relevance. Such regulatory delays would

remain undetected using conventional single-point or static evaluation methods[53]. Among frail individuals, delayed stabilization beyond phases 1 and 2 was observed, and the presence of a CO-SVR mismatch during these early recovery phases emerged as a physiological indicator of impaired integrative function. These novel approaches provide an applicable framework for identifying early dysfunction and suggest promising information for diagnostic and prognostic purposes in older adults, particularly those living with frailty. Furthermore, the use of phase-specific analysis in this work allowed for the detection of regulatory delays and CO-SVR mismatches more frequently in frail individuals, suggesting that frailty may intensify the effects of age on short-term hemodynamic BP regulation. The findings reinforce that both chronological age and frailty contribute to impairments in cardiovascular and autonomic regulation and show frailty as a more robust indicator of physiological vulnerability than age itself.

Previous research has established that strength training is effective in improving musculoskeletal function and reducing frailty in older adults[232,233]. However, limited evidence has addressed its impact on short-term cardiovascular adaptation to orthostatic stress[32]. A novel contribution of this thesis is the demonstration that PST led to earlier BP stabilization, shifting recovery from phase 2 to phase 1, despite the absence of significant changes in short-term cardiovascular responses, HRV indexes, CPM, or CBG. This suggests that PST enhanced hemodynamic control through peripheral mechanisms such as improved muscle pump activity and vascular responsiveness, rather than through autonomic modulation. Notably, although there were no statistically significant group-level reductions in OI-related symptoms, potentially due to the small sample size or the low pre-test prevalence, none of the participants reported experiencing OI symptoms by the end of the intervention. Clinically, the absence of OI symptoms is relevant, as these symptoms include dizziness, light-headedness, and instability upon standing[15,33,42]. These symptoms are associated with impaired cerebral perfusion and increased risk of falls, syncope, and functional decline in older adults[15,140]. The lack of self-reported OI symptoms, even in the absence of significant changes in autonomic indices, suggests a significant meaning in real-world functional capacity. This outcome reinforces the clinical value of improved recovery timing, as

timely BP stabilization can mitigate symptomatic consequences and reduce the burden of activity limitations and healthcare utilization associated with OI[15].

From a clinical implementation standpoint, the findings support the integration of phase-based BP analysis into routine orthostatic assessments. Clinicians could adopt non-invasive continuous BP monitoring, such as the Finapres NOVA system, to evaluate BP recovery during active stand tests beyond 3 minutes. Stabilization occurring beyond 30-60 seconds (phases 1-2) may serve as an early warning of impaired regulation, particularly when combined with evidence of CO-SVR mismatch and time to reach BP stabilization. These indicators could complement existing frailty assessments (e.g., frailty index[93]) by providing physiologically grounded metrics of the cardiovascular reserve.

This approach has practical implications. For example, a frail individual with delayed BP stabilization and CO-SVR mismatch may benefit from tailored interventions such as PST to improve functional capacity, even in the absence of autonomic improvement. Conversely, those with autonomic dysfunction may require other strategies, including, for example, longer PST (e.g., >12 weeks). Moving beyond categorical diagnostic thresholds for OH enables a more individualized and physiologically informed approach to patient management, based on the dynamic evaluation of short-term hemodynamic regulation.

Taken together, the findings of this thesis advance the understanding of orthostatic regulation, identifying ***when*** BP recovery occurs, through phase-specific analysis, yielding novel insights into the timing of short-term cardiovascular and autonomic regulation. In parallel, the CO-SVR mismatch analysis highlights the importance of ***how*** the system responds, reinforcing that ***"TIME MATTERS"*** in the evaluation of dynamic compensatory responses. Together, these approaches shed more light on how age, sex, frailty, and progressive strength training influence orthostatic cardiovascular and autonomic responses and support a more precise interpretation of hemodynamic adaptation.

This thesis contributes three main advancements to the field of human cardiovascular regulation. First, it introduces phase-specific analysis as a central framework for evaluating short-term compensation during postural transitions. Shifting the focus from static BP thresholds to the

timing of regulatory processes, the work enhances diagnostic resolution and enables earlier identification of dysfunction. Second, it establishes CO-SVR mismatch as a novel marker of physiological dysfunction, particularly frailty-related impairment. This metric quantifies the balance or imbalance between cardiac and vascular compensatory responses. Third, it shows that PST can improve recovery timing without improving autonomic tone, suggesting that peripheral mechanisms alone can yield meaningful functional gains.

These insights contribute to a more precise and clinically relevant framework for understanding orthostatic regulation in aging populations. Emphasizing the diagnostic value of recovery timing and the occurrence of CO-SVR mismatch strengthens the rationale for adopting dynamic hemodynamic responses as indicators of physiological dysregulation. The findings provide evidence that frailty, more than chronological age, reflects the true complexity of cardiovascular maladjustments during postural transitions. Moreover, the targeted analysis of early recovery phases emerges as a critical tool for clinical decision-making and risk stratification, as it can help identify individuals with delayed or impaired compensatory responses who may be at higher risk for falls, syncope, or cardiovascular and autonomic dysregulation. The thesis thus establishes a foundation for future investigations, translational applications, and methodological innovation in cardiovascular and autonomic assessment.

Limitations

Despite the strengths of the studies presented in this thesis, some limitations must be acknowledged, particularly regarding medication control and sample size. One limitation across studies is the lack of control over medication use (Appendix 4). A significant proportion of participants were taking antihypertensive agents, including β-blockers, calcium channel blockers, angiotensin receptor blockers, and diuretics. These medications can directly influence cardiovascular and autonomic variables such as HR, BP, and baroreflex sensitivity, potentially confounding the interpretation of physiological responses to postural transitions[3]. However, including medicated participants also reflects real-world clinical conditions, enhancing the external validity and applicability of the findings to community-dwelling older adults. To

minimize this limitation in future work, stratified analysis by medication type or inclusion of medication use as a covariate could improve the physiological interpretation and help distinguish intervention effects from pharmacological influences.

Another limitation concerns the relatively small sample sizes, particularly in the PST study. Although sample size calculations were conducted a priori and effect sizes were used to guide recruitment, the final numbers may have reduced statistical power and increased the risk of type II errors[229]. This limitation is common in frailty research, where recruitment challenges are exacerbated by health status, comorbidities, and willingness to participate. Still, the small but well-characterized samples allowed for in-depth physiological analysis, which provides valuable insight into this underrepresented population. Future studies should prioritize multicenter collaborations or extended recruitment periods to increase sample and statistical power. Additionally, it is possible that a longer duration of PST would lead to more pronounced improvements in cardiovascular and autonomic responses, which were not observed within the 12-week timeframe. These limitations do not undermine the overall findings but highlight important areas that need improvement, paving the way for future research in this field. Addressing these issues in future research could enhance the reliability, generalizability, and mechanistic interpretation of cardiovascular and autonomic outcomes in older adults undergoing active orthostatic stress tests or exercise interventions.

Specific methodological limitations must also be noted. Heart rate variability (HRV), although widely used to assess autonomic modulation, has interpretive challenges[234,235]. Frequency and time-domain indices are often simplistically linked to sympathetic and parasympathetic activity, yet they are influenced by overlapping factors such as respiration, baroreflexes, thermoregulation, and hormonal status[38,234–236]. This makes it problematic to treat HRV indices as direct markers of autonomic balance. HRV outcomes are also highly sensitive to recording length, analysis method, body position, circadian rhythms, and signal quality, which reduces reproducibility across studies[38,155,235,237]. Moreover, while reduced HRV indexes are associated with adverse outcomes (e.g., sudden cardiac death), elevated HRV indexes are not always

protective, as arrhythmias and conduction disorders can generate spuriously high variability[38,209,238]. Finally, interindividual variability, device differences, and the reliance on static rather than dynamic metrics further limit the specificity and clinical utility of HRV in isolation[38,155].

Similarly, Windkessel-based models used to estimate stroke volume (SV) and cardiac output (C)o) carry inherent limitations. The simplification of the arterial tree into only a few resistive, compliant, and inertial elements prevents these models from capturing wave propagation, reflection, or regional vascular heterogeneity[239]. As a result, they approximate global load but miss important features of the pressure waveform and left ventricular afterload[239]. Parameter estimation poses another challenge: compliance, resistance, and inertance are typically derived from population averages or peripheral signals and do not fully account for individual arterial mechanics, leading to systematic bias[117,240,241]. Even after calibration, Windkessel-derived measures often deviate from reference methods during orthostatic stress, exercise, or changes in vascular tone, reflecting the model's assumption of linear, time-invariant dynamics[117,240,241]. In addition, the accuracy of derived SV and CO is highly dependent on input signal quality, which can be compromised by peripheral vasoconstriction, motion, or arrhythmias[117,240,241]. These constraints mean that Windkessel-derived measures are most reliable for tracking trends rather than absolute values and should ideally be interpreted in conjunction with direct imaging or invasive reference methods[117,240,241].

Taken together, these limitations do not undermine the overall findings but highlight important areas for improvement. Addressing medication confounding, increasing sample size, and advancing the methodological rigor of HRV and Windkessel-derived measures would enhance the reliability, generalizability, and mechanistic interpretation of cardiovascular and autonomic outcomes in older adults undergoing active orthostatic stress tests or exercise interventions.

Conclusion

This thesis offers a comprehensive framework for understanding cardiovascular and autonomic responses to orthostatic stress in older adults. The systematic review revealed that older

adults living with frailty experience pronounced BP drops, delayed BP recovery, and blunted HR response following orthostatic stress. Phase-specific analysis clarified the timing of regulatory processes, showing that older adults have attenuated and delayed cardiovascular adjustments during the first 60 seconds of postural transitions, especially under greater orthostatic stress. Sex-based differences revealed that older females primarily relied on increases in SVR to regulate BP, whereas males depended more on CO. Additionally, females exhibited slower BP recovery compared to males during the early compensatory phases. Frail participants demonstrated a reduced CO peak, higher CPM, and delayed timing for BP regulation. These findings demonstrate that frailty is a more reliable indicator of delayed BP regulation than chronological age, as evidenced by prolonged recovery observed in phase 3 (60-180 s) among frail individuals. PST was shown to advance BP recovery timing through peripheral adjustments, even in the absence of autonomic improvements. Although the incidence of OH remained unchanged, the number of participants reporting OI symptoms decreased, and meaningful gains in grip strength, gait speed, and physical activity levels were observed. Therefore, these contributions expand the interpretation of orthostatic regulation and support more tailored assessment strategies for clinical and research applications in aging populations, particularly those individuals living with frailty.

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Appendices

Appendix 1 - Preferred Reporting Items for Systematic Reviews (PRISMA)

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	21
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	24
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	25-26
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	26
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	26-27
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	26
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	26
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	26-27
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	26-27
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	26-28
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	26-28
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	28
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	

Section and Topic	Item #	Checklist item	Location where item is reported
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	28
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	28
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	28
Study characteristics	17	Cite each included study and present its characteristics.	29-30
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	29
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	30-32
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	39
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	32-33
	23b	Discuss any limitations of the evidence included in the review.	35
	23c	Discuss any limitations of the review processes used.	35
	23d	Discuss implications of the results for practice, policy, and future research.	34
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	46

Section and Topic	Item #	Checklist item	Location where item is reported
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	46
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	
Competing interests	26	Declare any competing interests of review authors.	
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	