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Falls in the older adult population are a critical public health concern, resulting in significant personal and societal financial burden, and reduced independence and quality of life. Early identification of elevated fall risk is vital for implementation of effective fall prevention strategies. However, the unidimensional nature of traditional fall risk assessments fails to accurately determine fall risk (incidence of falls) in older adults. Additionally, fall risk assessments are most often measured in the clinical setting, and consequently many injurious falls occur prior to the identification of elevated risk by a healthcare provider. Assessment of heart rate variability (HRV) in the free-living environment provides a robust solution to the limitations of traditional fall risk assessments. HRV or the fluctuations in the time intervals between adjacent heartbeats, has emerged as a valuable assessment reflecting the dynamic, non-linear autonomic nervous systems (ANS) influence on cardiac rhythm. In alignment with dynamic systems theory, previous work supports system-based overlaps of the ANS and other fall risk related physiological systems. Thus, measurement of HRV presents an opportunity to assess the interaction of multiple physiological systems that influence falls. However, the efficacy of HRV to determine fall risk in healthy, community dwelling older adults is unknown. Therefore, the purpose of this dissertation is threefold: 1) to determine if HRV indices observed over a 24-hour monitoring period differ in community dwelling older adults with a history of falls and those who have not sustained a fall, 2) to determine the discriminative validity of HRV indices observed over a 24-hour monitoring period for classifying fall risk in older adults compared to traditional fall risk assessment tools, including the Timed Up and Go (TUG), the Functional Gait Assessment (FGA), and the Activities-specific Balance Confidence Scale

(ABC), 3) to examine associations between intrinsic fall risk factors [e.g., postural control, vestibular function, lower extremity muscular strength, executive function, and depression] and HRV indices observed over a 24-hour monitoring period and whether the relationships differ for those with a history of falls versus non-fallers**.** Forty-two healthy, community dwelling older adults (age 74.40 ± 5.46 years) participated in this study and were assigned to either the fallers group (n = 15) or non-fallers group (n = 27) based on self-reported fall history. Participants in the fallers group reported ≥1 fall during the 12 months prior to testing. All participants completed a demographics and health history survey, three traditional fall risk assessments (TUG, FGA, and ABC), and five measures to assess intrinsic fall risk. To measure HRV, participants wore a heart rate monitor for 24-hours in their free-living environment. Mann Whitney U tests were run to determine if HRV metrics differed between groups, and Wilcoxon effect size calculations were executed to determine the magnitude of the effect. The results reported in Manuscript I show that HRV metrics did not significantly differ between fallers and non-fallers; however, a medium effect of fall risk on the standard deviation of the normal-to-normal intervals was observed (SDNN). This suggests that SDNN may provide clinically relevant information regarding fall risk. Receiver operator characteristics (ROC) curves were run to determine the discriminative validity of HRV indices in comparison to traditional fall risk assessments. The results of Manuscript II suggest that SDNN had the greatest accuracy to differentiate fallers from non-fallers but was not significantly better than traditional fall risk assessments. Multiple regressions were completed to determine the extent to which intrinsic fall risk factors are associated with HRV indices, and whether the relationships differ for those with a history of falls versus non-fallers. The results reported in Manuscript III show that declines in postural control and vestibular function were associated with alterations in HRV non-linear parameters. These data suggest that HRV may be an effective measure of fall risk in community dwelling older adults. It is recommended that future work expand to include older adults with diagnoses of age-related diseases known to increase fall risk.

HEART RATE VARIABILITY AS AN ASSESSMENT OF FALL RISK IN OLDER ADULTS

by

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DEDICATION

Dedicated to my husband and son. Thank you for your love and constant encouragement.

APPROVAL PAGE

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CHAPTER I: INTRODUCTION

Approximately 25% of adults aged 65 and older fall annually (Bergen et al., 2016). These falls are often severe and result in significant injury and consequently restricted activity and decreased independence and quality of life (Bergen et al., 2016). In 2015, the estimated annual cost of fatal and non-fatal falls in older adults totaled approximately $50.0 billion dollars, with 99% of the cost attributed to healthcare treatment associated with non-fatal falls (Florence et al., 2018). The older adult population is expected to increase dramatically over the next decade (Ortman et al., 2014); thus, without pressing attention, the large economic burden of falls and fall-related injuries on the U.S. healthcare system is projected to increase significantly (CDC, 2017b).

Early detection of fall risk (e.g., likelihood of sustaining a fall) is an essential component for reducing falls and fall related injuries. However, current clinical methods for assessing fall risk in older adults are primarily unidimensional (e.g., balance, gait, cognitive function), negating the fact that fall risk is multifactorial. As a result, current assessments have demonstrated a wide range of variability in diagnostic accuracy for correctly identifying individuals with elevated fall risk (Perell et al., 2001). Additionally, these assessments are typically measured in a controlled setting (e.g. doctors office or physical therapy clinic), nullifying the dynamic nature of fall risk and demanding time and effort from an already taxed medical staff (Perell et al., 2001). Due to these barriers, many older adults fall prior to identification of elevated risk. To reduce falls and fall-related disability, there is a need for accurate, cost effective, and time efficient tools to assess fall risk in the free-living environment.

Advances in wearable sensor technology provide opportunity to fill these gaps through the assessment of underlying physiological factors that may predict elevated fall risk, such as heart rate variability (HRV). HRV, or the fluctuations in time between adjacent heartbeats, has emerged as a valuable parameter reflecting the dynamic, non-linear autonomic nervous system (ANS). It is well established that a healthy heart, as well as other biological systems (e.g., ANS) have oscillations that are complex and non-linear (Shaffer & Ginsberg, 2017; Stergiou & Decker, 2011). Moreover, the human system as a whole is dynamic and represents a collection of non-linear systems that interact (Cavanaugh et al., 2017). The complexity of non-linear systems provides individuals with the flexibility to rapidly cope with an ever-changing environment, which is a vital component of fall prevention. However, injury, disease, and aging, involve either a loss or increase in complexity in one or more physiological systems, as well as changes in the coupling between systems, thus hindering system flexibility and adaptability (Lipsitz & Goldberger, 1992).

Importantly, research has established an interaction of several intrinsic (e.g. person level) fall risk related factors/systems with the ANS to produce the complex heart rate signal, including: cognition (Thayer & Friedman, 2004; Thayer et al., 2009, 2012), cardiovascular dysregulation (e,g, postural hypotension, and orthostatic hypertension) (Li et al., 2020), and emotional regulation (e.g. depression) (Lane et al., 2009; Vasudev et al., 2011). When alterations to one of these contributing systems occurs as a result of injury, disease, or aging, it is likely that the coupling between said system and the ANS is altered resulting in loss of complexity of the heart rate signal. Thus, HRV presents an opportunity to assess the interaction of multiple physiologic systems associated with fall risk. HRV measured via a holter monitor has been shown to classify fallers and non-fallers in hypertensive individuals, a population known to have

ANS dysfunction (Melillo, Jovic, De Luca, et al., 2015), as well as patients in an acute care setting (Razjouyan et al., 2017). However, the efficacy of HRV to predict fall risk in healthy, community dwelling older adults remains unknown. To establish HRV as a fall risk assessment, it is also important to compare this new methodology to the current gold standard measures. Additionally, previous work has failed to explore the relationship between exposure to independent, intrinsic risk factors and HRV, an important component for confirming the relation between HRV and fall risk. Moreover, evaluating the interplay between HRV indices and intrinsic fall risk factors in fallers and non-fallers is vital for identifying the most important, primary targets (i.e., variables with the greatest influence on ANS alterations) for preventive interventions.

To close these gaps, a series of experiments are presented in three manuscripts. The aims and associated hypotheses for each manuscript are presented below:

Manuscript I

Aim: Determine if HRV indices observed over a 24-hour monitoring period differ in community dwelling older adults with a history of falls and those who have not sustained a fall.

Hypothesis: The HRV indices standard deviation of the normal-to-normal intervals (SDNN), low frequency (LF) power, high frequency (HF) power, and detrended fluctuation analysis (DFA) α_1 and α_2 will be significantly reduced in older adult fallers compared to non-fallers.

Manuscript II

Aim: Determine the discriminative validity of HRV indices (SDNN, LF Power, and DFA α_1) observed over a 24-hour monitoring period for classifying fall risk in older adults compared to traditional fall risk assessment tools, including the Timed Up and Go (TUG), the Functional Gait Assessment (FGA), and the Activities-specific Balance Confidence Scale (ABC).

Hypothesis: The HRV metrics SDNN, LF power, and DFA α_1 will correctly identify a greater percentage of fallers compared to the TUG, FGA, and ABC.

Manuscript III

Aim: Examine the associations between intrinsic fall risk factors [e.g., postural control (center of pressure displacement), vestibular function (Sensory Organization Tests 5-6), lower extremity muscular strength (30s Chair Stands), executive function (Trail Making Test), and depression (Beck Depression Index II)] and HRV indices (SDNN, LF Power, HF Power and DFA α_1 and α_2) observed over a 24-hour monitoring period and whether the relationships differ for those with a history of falls versus non-fallers.

Hypothesis: For fallers, a stronger negative relationship will be observed between the independent variables for postural control, executive function, and depression, and the HRV outcome variables. Additionally, for fallers, a stronger positive relationship will be observed between the independent variables for vestibular function and lower extremity strength and the HRV outcome variables.

CHAPTER II: REVIEW OF LITERATURE

Overview

This literature review will first discuss prevalence and risk factors associated with falling in older adults, proceeded by information on how fall risk has traditionally been assessed, with specific focus on limitations of current metrics. Next, this literature review will provide an overview of the proposed novel fall risk assessment, HRV, including a review of measurement standards and metrics, with important considerations for 24-hour monitoring. The discussion will proceed with how dynamical systems theory gives insights into the utility of HRV for assessing fall risk as well as the impact of aging on HRV and falls. Subsequently, evidence supporting the utility of HRV to tack physiological system changes will be discussed. Finally, a discussion of the previous research examining the relationship between HRV and fall risk and gaps in the literature with regards to this dissertation will be presented.

Falls in Older Adults

Prevalence

An estimated 29.0 million fall occur annually in the older adult population. It is projected that each year 27,000 of these falls result in death and 7.0 million in injury (e.g., a fall that required medical treatment or restricted activity for ≥1 day), making falls the leading cause of fatal an nonfatal injuries for older adults (Bergen et al., 2016). Individuals who fall are significantly more likely to be female, Caucasian, older (65-74 years of age = 26.7%, 75-84 years of age = 29.8%, ≥85 years of age = 36.5%), and lower income (Bergen et al., 2016; Florence et al., 2018). As a result of the high prevalence of fall related injuries, a substantial portion of the annual healthcare expenditure for older adults is attributed to falls. Florence et al.

(2018) found that based on fall reporting records from 2012, approximately 6.0% of Medicare and 8.0% of Medicaid expenditures and 5.0% of other source payments (e.g., private insurance and out-of-pocket spending) were attributable to falls. These percentages suggest fall-attributable expenses topping more than $49.5 billion annually. Furthermore, females account for 71% of the total medical costs of falls, with females aged 85 and older responsible for one-third of total medical costs (Burns et al., 2016). By 2030, more than 20 percent of U.S. residents are projected to be aged 65 and over, compared to 13 percent in 2010 (Ortman et al., 2014). To this end, falls and fall related injuries are expected to increase over the next decade and without prioritized attention will escalate the burden on an already taxed healthcare system.

Risk Factors

Fall risk is multi-factorial, and the combined result of person specific (intrinsic) and environmental (extrinsic) risk factors. In a 2013 systematic review, Ambrose and colleagues (2013) identified a number of fall risk factors in both categories. Identified intrinsic risk factors include age, sex (female), race, changes in gait dynamics, reduced postural control, reduced lower extremity strength, vestibular dysfunction, changes in vision, declines in cognitive function, neurodegenerative diseases, cardiovascular disease, depression, and certain medications. Identified extrinsic fall risk factors include slippery walking surfaces, ill-fitting footwear, loose rugs, or lack of handrails. While extrinsic risk factors certainly play a significant role in fall risk, improvement of intrinsic factors allow an individual to more safely and confidently navigate and respond to the extrinsic environment; thus, the remainder of this discussion will focus on intrinsic fall risk factors.

The normal aging process is associated with declines in several physiological systems associated with elevated fall risk including the musculoskeletal system (Kamel, 2003), vestibular system (Anson & Jeka, 2016), and cognition (Hoogendam et al., 2014). With regard to the musculoskeletal system, sarcopenia or the loss of muscle mass that occurs with aging is characterized as a decline in the number of muscle fibers (mainly type II myosin heavy chain isoforms) and a reduction in muscle fiber size (Kamel, 2003). Sarcopenia is also accompanied by concomitant declines in muscle strength and power (dynapenia), which occur more rapidly than the loss of muscle mass. Dynapenia is the combined result of sarcopenia and a complex interplay of neurologic and muscular mechanisms (Manini & Clark, 2012), the most prominent of which include: a reduction in central activation, denervation of type II muscle fibers, alterations in intrinsic force-generating capacity of muscle, changes in dihydropyridine and ryanodine receptors impacting excitation-contraction coupling, and increased inflammatory cytokine production (Clark & Manini, 2012; Manini & Clark, 2012). In a systematic review examining muscle weakness as a potential risk factor for falls, Moreland et al. (2004) observed that for lower extremity weakness, the combined odds ratio was 1.76 for any fall and 3.06 for recurrent falls. Since then, other studies have confirmed the important contribution of muscle weakness to the fall risk (Hasselgren et al., 2011; Horlings et al., 2008; Perry et al., 2007; Tiedemann et al., 2008; Yau et al., 2013). Additionally, the disproportionate reduction in muscle strength and power (1 to 3.5 % per year in older adults) relative to muscle mass (6% per decade after 50 years), suggests a decrease in muscle quality (Lynch et al., 1999; Skelton et al., 1994). Muscle quality or force per unit of muscle cross-sectional area is associated increased susceptibility to functional limitation and physical disability (Straight et al., 2015), both of which are associated with increased fall risk in the older adult population.

Aging is also accompanied by significant changes in the vestibular system with aging which contributes to elevated fall risk. It has been established that independent of vestibular disease, vestibular hair cells decline with age, with approximately 25% reduction in the saccule and utricle and 40% reduction in semi-circular canal hair cells in individuals over the age of 70 years (Matheson et al., 1999). Additionally, the size and number of neurons in the vestibular nucleus decrease by 3% each decade after age 40 (Lopez et al., 1997), and the number of vestibular nerve fibers consistently decline with age (Park et al., 2001). The consequence of reduction in vestibular sensory cells and neural pathways is diminished afferent signals to the central nervous system which manifests as functional impairments. Fewer sensory cells in the otolith organs (saccule and utricle) results in reduced sensitivity to gravity and linear acceleration (Igarashi et al., 1993; Walther & Westhofen, 2007). Additionally, age related declines in the sensitivity of the saccule results in smaller amplitudes of ocular and cervical vestibular-evoked myogenic potential (Piker et al., 2013). Moreover, in older adults, cervical vestibular-evoked myogenic potentials response latencies are longer and require a greater stimulus volume to generate an effective response (Welgampola & Colebatch, 2001). The aforementioned reduced capabilities in the aging vestibular system impair the ability of older adults to rapidly detect and respond to changes in head acceleration which contributes slower walking speeds and may be a potential protective strategy to prevent falls (Agrawal et al., 2013). Additionally, reduced sensitivity in the utricle has been associated with increased medial-lateral postural sway in older adults (Serrador et al., 2009), which has been linked to increased risk of falling.

Age related declines in cognitive function, particularly the domains of attention and executive function, have also demonstrated to increase fall risk. With regard to attention, much work in the dual task paradigm has established that the attentional demand to maintain upright posture increases with age. To this end, a systematic review conducted by Boisgontier et al. (2013) observed that older adults were able to perform a postural dual task (e.g. postural control task + concurrent task) as well as younger adults in a stable (stationary) task condition. However, when the complexity of the postural task increased (e.g., unstable surface), performance on the postural control task, concurrent task (cognitive or motor), or both tasks were more detrimentally affected in older compared to younger adults (Boisgontier et al., 2013). Similar findings have been observed in the dual task gait literature, with deterioration in gait (e.g., increased step width, step time, and step length) during dual task compared with single task performance associated with increased fall risk in community dwelling older adults (Muir-Hunter & Wittwer, 2016). Moreover, with regard to both attention and executive function, in a 5-year prospective study examining fall risk, Mirelman et al. (2012) evaluated executive function and attention using a computerized test battery (MindStreams, Neuro Trax Corp., TX) and assessed balance as well as single and dual task gait performance. They found that both the executive function and attention indices as well as dual task gait performance predicted the risk of future falls, with poorer performers at baseline more likely to report falling (Mirelman et al., 2012). These findings robustly support the importance of attention and executive function for maintaining upright posture.

The aforementioned age-related declines in the sensory system, motor systems, and cognitive function collectively contribute to changes in balance and gait dynamics, which have been consistently identified as the strongest predictors of falls (Deandrea et al., 2010; Woollacott & Shumway-Cook, 2002). With regard to changes in static balance with aging, increased postural sway (center of pressure displacement and velocity) during quiet standing has been consistently observed in older adults compared to young adults (Laughton et al., 2003) and in elderly fallers compared to non-fallers (Melzer et al., 2004). Additionally, changes in postural sway complexity (e.g., sample entropy and approximate entropy) have been observed in older adults compared to young adults (Borg & Laxåback, 2010), elderly individuals with a history of fall compared to non-fallers (Costa et al., 2007), and in frail individuals compared to healthy adults (Kang et al., 2009). Moreover, alterations in response to balance perturbations have been observed as a function of aging. Jensen et al. (2001) found that compared to young adults, older adults were more likely to employ a compensatory stepping mechanism when balance was perturbed as a result of a moving platform. Additionally, it was also found that older adults tend to take several smaller steps as opposed to one smooth step following a balance perturbation (McIlroy & Maki, 1996) and have difficulty initiating compensatory arm action to help maintain an upright stance (Maki & McIlroy, 2006). These responses may contribute to increased risk of falling when balance is perturbed.

Alterations in gait with aging have also been associated with falls. Verghese et al. (2009) found that older adults with a slow gait speed (≤70 cm/s) had a 1.5-fold increased risk of falls compared to those with normal speed. The researchers also observed that increased stride length and swing time variability were robust predictors of falls, as well as important predictors of injurious falls (Verghese et al., 2009). In a more recent review of the literature, Aboutaorabi (2016) and colleagues observed that in addition to slower walking, older adults tend to take shorter steps, demonstrate increased step width, and prolonged double support. These changes in gait with aging are likely compensatory strategies to overcome sensory (e.g., vision and vestibular) and motor (e.g., muscle strength and power) deficits and avoid falls.

Traditional Fall Risk Assessment Tools

A number of assessments (e.g., self-report and performance based measures) have been developed for and tested with community dwelling older adults to identify fall risk (Perell et al., 2001; Wrisley & Kumar, 2010). Majority of these assessments measure a single fall risk factor.

However, fall risk is multifactorial, and as a result no one measure has demonstrated to be an accurate diagnostic tool, with specificity and sensitivity of current measures broadly varying (Lusardi et al., 2017; Perell et al., 2001; Shumway-Cook et al., 1997). In a systematic review and meta-analysis, Lusardi and colleagues (2017) investigated the predictive ability of fall history questionnaires, self-report measures (e.g., ABC), and performance-based measures (e.g., TUG) for assessing fall risk in community dwelling older adults. Five history questions (fall history, difficulty with activities of daily living, use of an ambulatory device, concern about falling, and use of psychoactive medication) and two self-report measures (Geriatric Depression Scale-15 and the Falls Efficacy Scale International) were suggested to have clinical relevance in identifying individuals at risk of future falls. Moreover, three performance-based measures: BBS score of ≤50 points, TUG time ≥12 seconds, and 5 time sit-to-stand time ≥12 seconds were found to be the most evidence-supported measures for determining individual risk of future falls. Their findings suggest that a multi-dimensional assessment approach is needed to effectively identify individuals at increased risk of falling. However, because fall risk assessments most often takes place in a clinical setting (doctor's office or physical therapy clinic), administration of multiple assessments is unrealistic given the time and resource constraints of an already strained medical system. In an effort to advance fall risk assessment methods and reduce healthcare burden, researchers have investigated the ability of several technologies to identify and alert individuals to elevated fall risk, including: posturographs, sock pressure sensors, bed or chair alarms, as well as other indoor ambient sensors (Kosse et al., 2013). To date, majority of this work has been done in a nursing home setting, a relatively controlled environment compared to that of community dwelling individuals. In addition, the technologies listed above are costly and have demonstrated high occurrence of false alarms (Kosse et al., 2013). Thus, there is a need for accurate, cost-effective fall risk assessment tool with the ability to assess multiple dimensions (e.g., input from multiple physiological systems) of fall risk in a free-living environment. Using wearable sensor technology to measure physiological variables, such as HRV, provides a potential solution.

HRV Measurement

HRV is the fluctuation in time intervals between adjacent heart beats, or the time between R peaks (R-R intervals) on an ECG recording (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). It is an index of neurocardiac function and is generated by heart-brain interactions and the autonomic nervous system (Billman et al., 2015; Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). Further discussion regarding the emergent properties of HRV and its utility as an assessment of fall risk will be discussed in the subsequent section, here, the text will provide an overview of HRV indices and measurement standards for 24-hr recordings.

24-hr HRV recordings represent the "gold standard" for clinical HRV assessment (Shaffer et al., 2014). In comparison to short-term measurements, these recording achieve greater predictive power to differentiate between healthy and diseased states, as well as to predict a health related event (Fei et al., 1996; Moss, 2016; Nolan et al., 1998). While the same indices (time domain, frequency domain, and non-linear analyses) are used to analyze short-term and 24-hr recordings, they cannot substitute for one another and their physiological meaning can vary greatly (Kamath et al., 2012). Circadian rhythms, core body temperature, metabolism, sleep, and the renin-angiotensin system contribute to 24-hr recordings, while their contributions are less significant for short-term recordings (Shaffer et al., 2014).

Three domains of measurements are used to assess HRV, including time-domain, frequency domain, and non-linear measures. The simplest to perform are time-domain indices which quantify the amount of variability in the heartbeat observed during monitoring periods. Standard deviation of the normal-to-normal interval (SDNN) is one of the most commonly calculated time-domain variables and reflects all the cyclic components responsible for variability in the time series recording (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). It is important to note that “normal” when referring to the “normal to normal” intervals means that abnormal beats (e.g., ectopic beats) have been removed from the time series. For 24-hour recordings, SDNN can index the heart’s response to varying workloads as well as circadian rhythm processes, and is the “gold standard” for medical stratification of cardiac risk (Grant et al., 2011; Shaffer & Ginsberg, 2017).

To calculate frequency-domain outcomes, Fast Fourier Transformation or autoregressive modeling is used to separate the heartbeat time series into its component rhythms ultra-low frequency (ULF), very-low frequency (VLF), low frequency (LF), and high frequency (HF) that operate in different frequency ranges. The most commonly reported frequency components are the LF (0.04-0.15 Hz) and HF (0.15-0.40 Hz) bands. While the exact pathogenesis of the LF component is not yet known, it is believed to reflect both sympathetic and vagal (parasympathetic) influence on the heart rhythm and is also correlated with baroreflex sensitivity (La Rovere et al., 1998; Moak et al., 2007). With regard to the LF band as an outcome measure for this dissertation, blunted baroreflex sensitivity is associated with risk of falling in older adults (Isik et al., 2012). Additionally, two previous studies examining HRV and fall risk in clinical populations (Melillo, Jovic, De Luca, et al., 2015; Razjouyan et al., 2017), observed significant relationships between LF power measured over a 24-hour period and fall risk. With regard to the

HF band, it has been suggested that the HF band reflects vagal modulation of heart rate (Shaffer et al., 2014), and it is also called the respiratory band because it corresponds to the heart rate variations related to the respiratory cycle (e.g., heart rate accelerates during inspiration and slows during expiration) (Shaffer & Ginsberg, 2017). Deficient vagal inhibition reflected in the HF band is associated with increased morbidity (Thayer et al., 2010); thus, it is an important measure to consider regarding fall risk in older adults.

The theory and application of the third domain of HRV measures, non-linear metrics, will be discussed in detail in the subsequent section.

The Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology ("Heart Rate Variability," 1996) has established guidelines for the assessment of long-term (24-hr) HRV recordings. First, long-term recording must contain at least 18 hours of analyzable R-R data, including the whole night. Second, time domain (e.g., SDNN) and non-linear measures (DFA α_1 and DFA α_2), should be calculated for the entire 24-hr time series, while frequency domain measures (e.g., LF and HF power) should be obtained from averages of 5-minute segments over the 24-hour period. Third, visual inspection of the raw ECG signal should be used to detect artifact (missed or spurious beats). This is important as segments with substantial can significantly distort time- and frequency- domain measures (Peltola, 2012).

Dynamic Systems Theory and HRV

The human body is comprised of many systems with unique rhythms, some intrinsic (e.g., heartbeat, respiration, reproduction, etc.) and others under conscious control (e.g., chewing, walking gait) (Glass & Mackey, 1988). These rhythms can change over the course of one's life as a result of interaction with one another as well as the external environment, or in response to disease (Glass & Mackey, 1988; Lipsitz, 2002). Dynamic systems theory provides a framework to understanding the mechanisms underlying physiological rhythms through the integration of mathematics and physiology.

Stergiou and Decker (Stergiou & Decker, 2011, p. 870) described dynamic system theory as “biological systems [that] self-organize according to environmental, biochemical, and morphological constraints to find the most stable solution”. As such, heart rate is known to change in response to environmental, biochemical, and physical perturbations; yet it is generally thought to remain relatively stable during steady state. However, even during steady state, the heartbeat contains underlying dynamic fluctuations reflecting the interactions between multiple neural, hormonal, and mechanical control systems at both the local and central levels that interact to find the most stable solution (Shaffer et al., 2014). The nonlinear behavior of the heartbeat is overlooked when a mean value over time is calculated but is observable when heart rate is examined on a beat-to-beat basis (e.g., R-R intervals).

It is important to understand the term ‘nonlinear’ with regard to dynamic systems theory and physiological systems. ‘Nonlinear’ applies to systems whose components interact in a non-additive way (Goldberger, 2002). This occurs in physiological system because physiological processes operate with different mechanisms interacting over a variety of time scales (Lipsitz, 2002). As a result of this organization, the time-series outputs of physiological systems are complex and marked by a degree of non-random (or self-similar) fluctuations over multiple time scales (Goldberger, 2002). Regarding the nonlinear nature of the heartbeat, the cardiovascular systems organization is characterized by interacting subsystems, self-sustained oscillators, and feedback loops that consistently react to internal and external inputs including central commands, reflexive mechanisms, and humoral factors (Malliani Alberto & Montano Nicola, 2002; Porta et al., 2007), culminating in the complex heart rhythm. The nonlinear nature of physiological systems has led to the development of nonlinear analyses in order to distinguish healthy function from disease states and to predict the onset of a health-related event (Golberger, 1996). Such measures have been derived from dynamic systems theory and nonlinear dynamics and are based on the concept of fractals, which is a geometric object or temporal feature with self-similar patterns over multiple time scales (Golberger, 1996). While additional domains of analyses (time domain and frequency domain) are used to assess HRV, their utility of nonlinear metrics has become prominent in recent years.

One common nonlinear metric for assessing HRV is detrended fluctuation analysis (DFA). DFA quantifies the correlation between successive heart beats or R-R intervals over different time scales (Shaffer & Ginsberg, 2017). Like many biological signals, R-R intervals are highly nonstationary. Applying DFA to such signals detrends the time series, permitting the detection of intrinsic self-similarity embedded in a non-stationary time series, while also avoiding the spurious detection of self-similarity (Acharya et al., 2002). In this approach, the fractal scaling exponents α_1 and α_2 are calculated using short-term and longer frequency ranges respectively. α values equating to ≤ 0.5 correspond to white noise or uncorrelated data, values between 0.5-1 correspond to persistent long-range correlations, and values of ≥ 1.5 corresponds to Brownian noise (e.g., presence of a random walk) (Acharya et al., 2002). Importantly, the DFA method of HRV analysis has demonstrated clinical relevance to discriminate between heathy and diseased states. Yeh et al. (2006) investigated HRV in patients undergoing various types of neurosurgery operations. They found that the α_1 value of neurosurgery patients was significantly ($p < 0.05$) lower than healthy individuals and significantly ($p < 0.05$) higher than a white noise signal (Yeh et al., 2006). Additionally, Gospodinov et al. (2016) examined HRV in healthy subjects and diabetic patients and found that the α_1 value was significantly lower ($p <$

0.001) in Diabetic patients compared to healthy controls. While diseased states can depress some non-linear measurements, elevated values do not always indicate health. For example, increased DFA α_1 in post-myocardial infarction patients is an independent risk factor for mortality (Stein & Reddy, 2005)

Dynamic Systems Theory, Aging, and HRV

Decrements in the structure of physiological variability may be observed as individuals age or in the presence of disease. Lipsitz and Goldberger first proposed that aging can be defined by a progressive loss of complexity in physiologic system outputs (Lipsitz & Goldberger, 1992) which is believed to stem from deterioration of the underlying structural components of the physiological system, as well as changes to the coupling between systems (Lipsitz, 2002; Lipsitz, 2004). This phenomenon is known as the loss of complexity hypothesis. In alignment with this hypothesis, a reduction in overall HRV as well as changes in complexity of its physiologic dynamics are observed with aging. To this end, Umetani and colleagues (1998) observed that SDNN and the SDNN index decreased gradually, reaching 60% and 46% of second-decade values by the tenth decade, respectively. Additionally, the proportion of pairs of successive R-R intervals that differ by more than 50ms (pNN50) and RMSSD decreased most rapidly, reaching 24% and 47% of baseline, respectively, by the sixth decade (Utemani et al., 1998). With regard to HRV non-linear measures, in a cross-sectional study examining HRV across the lifespan (age range, 1 to 82 years), a progressive loss of complexity (decreased approximate entropy) and alterations of long-term fractal-like heart rhythm behavior (increased DFA$_{\alpha2}$) were observed beginning in middle age (40 to 60 years) and continuing thereafter (>60 years) (Pikkujämsä Sirkku et al., 1999). Similarly, in a more recent investigation, Takahashi et al. (2012) also found that aging was marked by a more regular, repetitive pattern in the heart rate signal, characterized by a decrease in both the Complexity Index and the Normalized Complexity Index. It has been suggested that these significant alterations in HRV with aging reflect loss of complexity of the autonomic regulation of heart rate and propose the utility of HRV to track changes in system inputs (e.g., autonomic nervous system) (Takahashi et al., 2012).

The ANS is essential for rapid adaptation or modulation of bodily functions during changes or perturbation in the external or internal environments. In elderly individuals, autonomic functions are relatively well maintained at rest, but the ability to adapt to internal and external changes are often severely impaired (Hotta & Uchida, 2010). With regard to age-related changes in sympathetic nerve activity, compared to adults, older adults have a higher amount of tissue norepinephrine spillover, an indirect index of sympathetic nerve activity, in the heart at rest (Seals & Esler, 2000). It has been hypothesized that this is a result of decreased baroreflex sensitivity that occurs with aging, which manifests as a diminished heart rate response to sympathetic nerve activity (Vasudev et al., 2011). Other explanations have also been suggested, including a chemoreceptor reflex-based increase (Sato et al., 1991). This may occur because oxygen exchange in the lungs declines with age and consequently a decrease in the partial pressure of arterial oxygen stimulating increased sympathetic nerve outflow. Additionally, a close relationship has been observed between age related increases in visceral fat and increased resting sympathetic nerve activity (Seals & Bell, 2004). It has been suggested that increases in adiposity-sensitive humoral signals (e.g., leptin and insulin) that cross the blood brain barrier, activate subcortical areas involved in the regulation of energy balance (e.g., hypothalamus), and stimulate sympathetic outflow to peripheral tissues (e.g., heart) (Seals & Bell, 2004).

In comparison to the sympathetic division of the ANS, less is known regarding age related changes in the parasympathetic division. However, it has been observed that heart rate changes in response to muscarinic acetylcholine receptor blocking agent are blunted in older adults (Brodde et al., 1998). Moreover, in animal studies, there is a reported reduction in the maximum conduction velocity of the myelinated vagal nerve fibers in ages rats (Sato et al., 1985). Due to the observed reduction in parasympathetic tone, less cardio acceleration occurs during vagal withdrawal with transition from a seated to standing position and in many instances results in orthostatic hypotension (Vasudev et al., 2011). Orthostatic hypotension, or declines in blood pressure when changing postures is a common problem in the elderly and is associated with increased fall risk (Mol et al., 2019). Moreover, among older adults, the HRV indices SDNN, VLF power, and the low frequency / high frequency ratio were significant negatively correlated with orthostatic hypotension (Li et al., 2020). In addition, alterations in the ANS as measured by HRV (decreased SDNN values) have been associated with increased risk of decline in functional status (e.g., basic and instrumental activities of daily living as measured by the Barthel and Lawton scales) (Ogliari et al., 2015). This is important with regard to falls risk as difficulty performing various tasks of normal daily functioning has been associated with future falls (Mamikonian-Zarpas & Laganá, 2015). These findings present evidence for the utility of HRV to track changes in the ANS that occur with aging, as well as the relationship between ANS alterations as measured by HRV and fall risk.

Utility of HRV to Track Systematic Changes in Other Systems Associated with Fall Risk

In addition to the suggestion that HRV can track changes in autonomic regulation that occur with aging, the Neurovisceral Integration model proposed by Thayer and colleagues suggests that vagally mediated HRV may serve as a measure of the functional capacity of brain structures, specifically those that support performance of executive function tasks (e.g., frontal cortex) and emotion regulation (Thayer & Lane, 2000). Importantly, both executive function (Mirelman et al., 2012) and emotion [e.g., fear of falling (Jung, 2008) and depression (Kamińska et al., 2015)] have been associated with fall risk in older adults. To this end, functional units within the central nervous system related to goal-directed behaviors and adaptability have been identified with output directly linked to the heart via the stellate ganglia (sympathetic nerves) and the Vagus nerve. These functional units have been termed the central autonomic network (CAN) (Benarroch, 1993) which consists of a number of brain structures including: the anterior cingulate, insular, and ventromedial prefrontal cortices, the central nucleus of the amygdala, the paraventricular nuclei of the hypothalamus, the periaqueductal gray matter, the parabrachial nucleus, the nucleus of the solitary tract, the nucleus ambiguus, the ventrolateral and ventromedial medulla, and the medullary tegmental tract. Both direct and indirect pathways have been identified connecting the frontal cortex to ANS circuits responsible for both excitatory (sympathetic) and inhibitory (parasympathetic) effects on the heart (Thayer & Lane, 2000). In addition, sensory information from peripheral organs, such as baroreceptors, are fed back to the CAN. These complex interactions between the heart, brain, and periphery suggest HRV as an index of the central nervous system through ANS integration as well as central-peripheral neural feedback (Thayer & Lane, 2000). Thus, it is likely that HRV provides utility to track changes in these integrated systems.

It is important to note that like heart rate, the CAN has many features of a nonlinear dynamic system, which is an important distinction with regard to its ability to track changes in other systems. First, the CAN consists of both positive and negative feedback interactions with autonomic responses. For example, at any given moment the CAN may integrate excitatory input from the frontal cortex while receiving inhibitory input from the baroreceptors. Second, the CAN output is comprised of many parallel pathways, allowing for many avenues by which a response (change in HRV) can occur. For example, an increase in heart rate may be the result of vagal withdrawal, increased sympathetic activity, or a combination of both. Additionally, in a third layer of control and complexity, the direct and indirect pathways of the CAN modify the output of parasympathetic and sympathetic neurons. These features represent vast control mechanisms within the CAN and demonstrate the influence of many factors and pathways on CAN output (e.g., HRV).

In support of the Neurovisceral Integration model, Thayer and colleagues have performed a series of studies examining correlations between neural activity and HRV in response to emotional arousal and executive function (goal directed) tasks. Regarding emotional arousal, using positron emission tomography, they observed significant correlations between high frequency HRV and blood flow in the right superior prefrontal cortex, the left rostral anterior cingulate cortex, the right dorsolateral prefrontal cortex, and the right parietal cortex during emotion evoking conditions (film clips and recall of personal experiences related to happiness, sadness, and disgust). Specifically, emotional arousal was associated with a decrease in HRV and a concomitant increase in brain activation in the aforementioned regions (Lane et al., 2009). Prior to this research, it had been suggested that the prefrontal cortex played a general inhibitory role on HRV via the Vagus nerve. It was proposed that decreased activation of the prefrontal cortex would lead to disinhibition of the tonically inhibited amygdala (Thayer et al., 2009). This, in turn, would lead to a simultaneous disinhibition of the sympathetic neurons in the rostral ventrolateral medulla and an inhibition of parasympathetic neurons in a second pathway (Thayer et al., 2009). Subsequently, both would lead to an increase in heart rate and an associated decrease of vagally mediated HRV. Importantly, these findings support the inhibitory role of the prefrontal cortex and link emotional arousal to changes in HRV.

Additionally, in a study examining working memory, nonexecutive, and executive function in military personnel (Hansen et al., 2003), participants were allocated to high or low HRV groups based on a median split of HRV (based on RMSSD values). Working memory was assessed using a modified version of a WMT developed by Hugdahl et al. (2000), and executive and nonexecutive function were assessed via subscales of the California Computerized Assessment Package Abbreviated Version (CALCAP; Norland Software, Los Angeles, CA). Results demonstrated that the high HRV group had superior performance on executive function and working memory tasks. In a follow-up study (Hansen et al., 2003), participants completed the same tasks but were presented with a stressful situation (e.g., threat of shock). Findings demonstrated that during the threat of shock, the low-HRV group had faster reaction times on nonexecutive function tasks compared to the high-HRV group. Moreover, in the working memory task, the low-HRV group showed improved performance under the threat of shock, while the high-HRV group demonstrated stable performance. These results suggest individual variability in the ability to cope with stressful situations. Importantly, the low-HRV group may be more reliant on outside stimulation to perform successfully (Thayer et al., 2009). Increased outside stimulation may allow for optimal cortical arousal, which would in turn increase HRV. Whereas, performance of the high HRV-group suggests a more adaptable system with the ability to self-regulate (Thayer et al., 2009). This work proposes that HRV may serve as a measure of changes in central nervous system networks involved in goal directed behavior, an essential component of fall risk.

Previous Findings of HRV and Fall Risk

To date, two studies have examined the utility of HRV indices to detect changes in fall risk in older adults. In a prospective study, Melillo et al. (2015) acquired 24-hour ECG Holter recordings from 168 hypertensive patients (age 72 ± 8 years, 60 females) and asked if they had experienced a fall during the 3-months prior to or following collection of ECG recordings. Forty-seven participants reported falling during the 6-month period. The researchers used a data mining algorithm integrating HRV indices extracted based on principle components analysis (LF power, Shannon entropy, and recurrence plots features) to create a classifier of fall risk. The classifier achieved high specificity (80%) but low sensitivity (51%) (Melillo, Jovic, DeLuca, et al., 2015). However, the low sensitivity observed is likely due to the fact that hypertension alters ANS function; thus, these individuals could have alterations in HRV that may not result in elevated fall risk. Additionally, Razjouyan and colleagues (2017) examined HRV as an indicator of fall risk in an acute care setting. Participants (n = 31, age 55.4 ± 15.5 years) receiving treatment in an oncology wing were stratified to low and high risk fall groups based on the Hendrich II fall risk assessment (≥5 = high fall risk, <5 = low fall risk). Significant negative correlations (r = -0.59, p = 0.001) were observed between fall risk and SDNN (Razjouyan et al., 2017).

Current Gaps in the Literature with Regard to this Dissertation

While previous studies (Melillo, Jovic, DeLuca, et al., 2015; Razjouyan et al., 2017) observed significant relationships between HRV indices and fall risk, the subjects were clinical populations (hypertensive patients and patients in an acute care setting); thus, these findings are not generalizable to the community dwelling population. Additionally, previous work has not examined the discriminative ability of HRV compared to traditional fall risk metrics for identifying individuals with elevated risk. It is important to compare HRV to these current “gold” standard measures. Exploration is also needed regarding the relationship between exposure to independent, intrinsic risk factors and HRV, which is important for confirming the relationship between HRV and fall risk. Finally, the sensors used for data collection in previous studies are bulky and costly, and thus do not translate well to use on a large scale with the general population. Advances in wearable sensor technology provide opportunity to overcome these shortcomings. with newer devices demonstrating high validity and reliability (Gilgen-Ammann et al., 2019), whilst being inconspicuous and cost effective.

CHAPTER III: OUTLINE OF PROCEDURES

Participants

We recruited 60 participants (60 intended – 42 collected) aged 65-90 years from the local community. All potential participants were screened for eligibility and were excluded due to any of the following criteria: 1) Not between the ages of 65-90 years; 2) Any diagnosed neurological condition that impacts postural control (e.g., Multiple Sclerosis, Parkinson's Disease, Peripheral Neuropathy); 3) Vision that was not normal or corrected-to-normal; 4) Inability to stand for at least 5 minutes without the use of an assistive device; 5) A Mini-Mental State Examination (MMSE) score <25; 6) Current smoker; 6) History of cardiovascular disease including: heart attack, stroke, bypass surgery, stent, or pacemaker implantation, 7) Diabetes (Type 1 or Type 2) diagnosis; 8) Hypo / hyperthyroidism diagnosis; 8) Change to medications during the previous two months. Participants were assigned to groups (fallers vs. non-fallers) based on self-reported fall history. Individuals were asked whether or not they had fallen at least once during the previous 12 months. A fall was defined as an event resulting in a person coming to rest on the ground or other lower level (CDC, 2017b). Participants who report sustaining a ≥ 1 fall in the were classified as a faller, and those who report no falls in the last 12 months were classified as a non-faller.

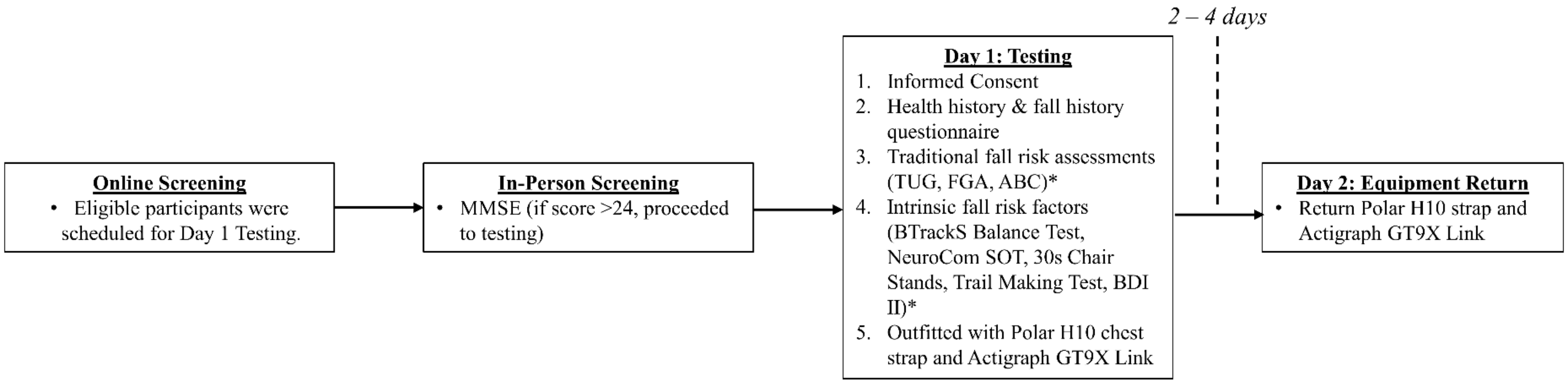
Procedure

The experimental design is shown in Figure 1. All data collection was completed in the Balance and Training Laboratory at the University of North Carolina Greensboro's (UNCG) main campus. The procedures for this study were approved by UNCG's institutional review board prior to collection. Interested individuals completed an online screening survey (via

Qualtrics). Eligible individuals were contacted via phone to confirm eligibility and schedule a laboratory testing session. When participants arrived at the lab, the Mini Mental State Examination (MMSE) (Tombaugh et al., 1996) was administered. If a score of >24 was achieved, informed consent was obtained and a general intake questionnaire including health history, fall history, and demographic information was completed. Next, participants completed three traditional fall risk assessments (e.g., TUG, FGA, and ABC) in a randomized order. Subsequently, participants completed five intrinsic fall risk factor assessment, including: the BTrackS Balance Test (postural control), the Equitest Sensory Organization Test (SOT) (vestibular function), 30s Chair Stands (lower extremity muscular strength), the Trail Making Test (executive function), and the second edition of the Beck Depression Inventory (BDI-II) (depression). Similar to administration of traditional fall risk assessments, the order of these measurements was randomized for each participant.

Following completion of the lab-based testing assessments, participants were outfitted with a Polar H10 chest strap integrated with an Actigraph GT9X Link (Actigraph, Pensacola, FL) wrist worn accelerometer to collect HRV. Accelerometers were initialized to start collecting R-R interval data 2-hours following visit completion, assuring participants had returned to their normal, free-living activity. Data collection continued for the subsequent 30-hour period guaranteeing collection of 24 hours of data, whilst accounting for any non-wear periods (e.g. showering). Participants were instructed to go about their normal daily activities (including sleeping) while wearing the sensor for the duration of the 30-hour period. Participants were asked to record the time they went to sleep, the time they woke up, and times the monitor was removed for showering/bathing. Prior to testing visit completion, a time was scheduled to return the Polar H10 and the Actigraph GT9X Link to the researchers.

Figure 1. Study Timeline



Note. Traditional fall risk assessments and fall risk factor measures (Day 1 Testing) denoted with * were administered in a randomized order.

Traditional Fall Risk Assessments

Participants completed three traditional fall risk assessments, including the Timed Up and Go (TUG), the Functional Gait Assessment (FGA), and the Activities Specific Balance Confidence Questionnaire. To account for potential fatigue, the administration order of the three assessments was randomized for each participant.

TUG

The TUG assesses the ability to initiate/terminate gait as well as change of directions. To complete the test, participants were timed as they stood up from a chair, walked 3 meters, turned around, and then walked back to the chair and sat down (Barry et al., 2014). Scores ranging from 10 to 30 seconds have been suggested to classify fall risk in community dwelling populations (Podsiadlo & Richardson, 1991; Shumway-Cook et al., 1997; Trueblood et al., 2001); however, participant's in a study by Trueblood et al. (2001) closely resembled participants in the current study and a cutoff score of $\geq$11 seconds indicated increased fall risk.

FGA

The FGA is a series of dynamic balance tasks designed to mimic real-world challenges (Wrisley & Kumar, 2010). The 10-item tests asked participants to perform the following gait activities: walk at normal speeds, at fast and slow speed, with vertical and horizontal head turns, with eyes closed, over obstacles, in tandem, backwards, and while ascending and descending stairs (Wrisley et al., 2004). In community dwelling older adults, a cutoff score of 22/30 on the FGA indicates increased risk of falls (Wrisley & Kumar, 2010).

ABC

The ABC is a 16-item self-efficacy scale that is scored on a 10-point ordinal scale (Powell & Myers, 1995). Participants were asked to rate their confidence in maintaining their balance while performing 16 activities of daily living. Scores on the ABC range from 0, indicating no confidence in participant's ability to maintain balance while completing the activity, to 100, indicating complete confidence. ABC scores of ≤ 67 indicate increased risk of falls (Lajoie & Gallagher, 2004).

Intrinsic Fall Risk Factor Measures

Participants completed five intrinsic fall risk factor assessment, including: the BTrackS Balance Test (postural control), the Equitest Sensory Organization Test (SOT) (vestibular function), 30s Chair Stands (lower extremity muscular strength), the Trail Making Test (executive function), and the second edition of the Beck Depression Inventory (BDI-II) (depression). To account for potential fatigue, the order of these measurements was randomized for each participant.

BTrackS Balance Test

The BTrackS Balance Tracking System with Sport Balance Software (BTrackS; Balance Tracking Systems, Inc, San Diego, California) quantifies postural sway via force plate center of pressure (COP) during quiet standing (Goble & Baweja, 2018). For three, 20-second trials, participants stood on the BTrackS force plate with feet shoulder-width apart, hands on hips, and eyes closed. The Sport Balance Software calculates the average total COP path length in centimeters across trials. Poor postural control and consequently increased fall risk is defined as greater CoP displacement (increased path length) and greater CoP velocity (Quijoux et al., 2020).

Sensory Organization Test

Computerized dynamic posturography, such as the SOT, allows researchers and clinicians to objectively measure the postural components of balance (Chaudhry et al., 2011). The SOT protocol was administered using the NeuroCom Smart Balance Master System (NeuroCom, Clackamas, OR). Participants stood with a standardized foot placement on a force platform that measured horizontal and vertical forces, and wore a harness secured to the platform frame to prevent injury in the event of a fall. The protocol consisted of 3, 20 second trials for each of the six SOT test conditions. SOT's 1-3 use a fixed platform, while SOTs 4-6 use a sway-referenced platform. There are also 3 visual conditions: eyes open and fixed on a stable visual surround (SOT's 1 and 4), eyes closed (SOT's 2 and 5), and eyes fixed on a sway-referenced visual surround (SOT's 3 and 6). The best of the 3 trails for each test was used to calculate the equilibrium score. The score is determined by calculating the angular difference between a participant's calculated maximum anterior-posterior center of gravity displacement and the theoretical maximum (angular difference without a fall occurring) of 12.5 degrees. Equilibrium scores are expressed as a percentage, with scores near 100 indicating no anterior-posterior excursion, and scores approaching 0 indicating an increase in anterior-posterior excursion (Evans & Kers, 1999). Importantly, SOT 5 and 6 have demonstrated to be moderately correlated ($r \leq .72$) with traditional vestibular-ocular test results (Evans & Kers, 1999) and were used as outcome measures in this study.

30 Second Chair Stands

The 30 second Chair Stand test is an assessment of lower extremity muscular strength, (Jones et al., 1999). The test was administered using a chair without arms, with a seat height of 17 inches, and began with participants seated in the middle of the chair, back straight, feet shoulder width apart, and arms crossed against the chest. Participants were instructed to stand and return to a seated position as many times as possible during a 30 second period. The total number of stands executed correctly during the time period were recorded (more than halfway up at the end of the 30 seconds was count as a full stand).

Trail Making Test

Executive function and in particular executive control was measured using the Trail Making Test (Arbuthnott & Frank, 2000; Bowie & Harvey, 2006). The test was given in two parts: Part A involved drawing a line connecting numbers from 1 to 25 in ascending order, Part B involved drawing a line connecting alternating numbers and letters in a sequence (e.g., 1-A-2-B, etc.). The time in seconds to complete each 'trail' was recorded. During test administration, the researcher pointed out errors as they occurred, and error-correction was included in the time to complete the trail (Lezak, 1995). A maximum time of 300 seconds was allotted for trail completion. If participants were still working at 300 seconds, the test was discontinued. As is commonly used in clinical practice, the ratio of time to complete B/A was used as the outcome measure in this study (Lamberty et al., 1994).

Beck Depression Scale-II

The BDI-II, a 21-item questionnaire measuring 21 depressive symptoms (Beck et al., 1996). Participants were asked to "think about how they have been feeling during the "past two weeks, including today" and then rate symptoms on a 4-point scale ranging from 0 to 3. The ratings of each symptom were summed for a total score ranging from 0 to 63, with higher scores indicating more depressive symptoms. Scores of 0-9 correlate to no or minimal depression, 10-18 correlates to mild to moderate depression, 19-29 correlates to moderate to severe depression, and scores of 30 or greater correlate to severe depression (Beck et al., 1996). Increased risk of falling has been correlated with greater depressive symptoms (Kamińska et al., 2015).

HRV Measurement

To collect HRV participants wore a Polar H10 chest strap (Polar Elector, Bethpage, NY) integrated with an Actigraph GT9X Link (Actigraph, Pensacola, FL) wrist worn accelerometer for

30 hours in their free-living environment. The Polar H10 chest strap collects R-R interval data that can be stored on the GT9X Link and downloaded in the ActiLife software (Actigraph, Pensacola, FL). The Polar H-10 monitor collects R-R interval data at a rate of 1000 Hz and has demonstrated to be valid measurement of R-R intervals across a wide range of activities (Gilgen-Ammann et al., 2019).

To obtain HRV indices, R-R interval data was extracted from the Actigraph software and uploaded to the Kubios Premium software (Kubios Premium 3.4.1, Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) for analysis. HRV analysis was conducted according to international guidelines by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology ("Heart Rate Variability," 1996). As is suggested for 24-hr analyses, recordings had to contain at least 18 hours of analyzable R-R data that include the whole night. Data was then visually inspected, and excessively noisy segments were removed from the time series. Time domain (SDNN) and non-linear measures (DFA α_1 and α_2), were calculated for the entire 24-hour time series, while frequency domain measures (LF, and HF power) were obtained from averages of 5-minute segments over the 24-hour period. Within the Kubios software, an automatic artefact correction algorithm was applied, in which artefacts were detected from a time series consisting of differences between successive R-R intervals. If an inter-beat-interval differed from the local average more than 0.25 seconds, defined as a 'medium' threshold, the interval was identified as an artefact and corrected by replacing it with an interpolated value using a cubic spline interpolation.

Statistical Analyses

Purpose 1: Determine if HRV indices observed over a 24-hour monitoring period differ in community dwelling older adults with a history of falls and those who have not sustained a fall.

Hypothesis 1: The HRV indices SDNN, LF and HF power, and DFA α_1 and α_2 will be significantly reduced in older adult fallers compared to non-fallers.

To answer Hypothesis 1, a MANCOVA was used to examine whether each of the dependent variables (SDNN, LF and HF power, and DFA α_1 and α_2) differs in fallers versus non-fallers, while controlling for the variable medications. Prior to analysis, correlations were performed between each of the dependent variables. If a correlation between two dependent variables was greater than .70, then one of the variables was removed from the analysis. Under such circumstances, one dependent variable becomes a near-linear combination of the other dependent variable, and thus it becomes statistically redundant to include both variables.

Purpose 2: Determine the discriminative validity of HRV indices (SDNN, LF Power, and DFA α_1) observed over a 24-hour monitoring period for classifying fall risk in older adults compared to traditional fall risk assessment tools, including the Timed Up and Go (TUG), the Functional Gait Assessment (FGA), and the Activities-specific Balance Confidence Scale (ABC).

Hypothesis 2: The HRV indices SDNN, LF power, and DFA α_1 will correctly identify a greater percentage of fallers compared to the TUG, FGA, and ABC.

Receiver operator characteristics (ROC) curves were used to determine the discriminative validity of HRV indices (SDNN, LF power, and DFA α_1) and traditional fall risk assessments (TUG, FGA, and ABC) in identifying fall risk. A series of pairwise comparisons (Hanley &

McNeil, 1983) were run of each HRV indices area under the curve (AUC) with every traditional fall risk assessments AUC to determine which measure is best in discriminating fallers from non-fallers.

Purpose 3: Examine the associations between intrinsic fall risk factors [e.g., postural control (center of pressure displacement), vestibular function (Sensory Organization Tests 5-6), lower extremity muscular strength (30s Chair Stands), executive function (Trail Making Test), and depression (Beck Depression Index II)] and HRV indices (SDNN, LF Power, HF Power and DFA α_1 and α_2) observed over a 24-hour monitoring period and whether the relationships differ for those with a history of falls versus non-fallers.

Hypothesis 3: For fallers, a stronger negative relationship will be observed between the independent variables for postural control, executive function, and depression, and the HRV outcome variables. Additionally, for fallers, a stronger positive relationship will be observed between the independent variables for vestibular function and lower extremity strength and the HRV outcome variables.

Associations between intrinsic fall risk factors and HRV indices were assessed using multivariable linear regressions. Models included main and interaction effects for fall risk factors (postural control, vestibular function, lower extremity muscular strength, executive function, and depression) and group (fallers vs. non-fallers). To assess multicollinearity amongst the independent variables, prior to analysis, the variance inflation factor (VIF) was calculated for each predictor by conducting a linear regression with one predictor on all other predictors to obtain the R^2 value for each regression. The VIF was then be calculated as $1/(1-R^2)$. If the VIF of two factors was greater than 5 (Johnston et al., 2018), one was removed from the models because they supply redundant information.

Adjustment Due to Reduced Sample Size

With the approval of my advisor, the following changes were made to the statistical analysis for Manuscript 1 (Purpose 1) due to the reduced sample size and non-parametric data. The, the Mann-Whitney U test was used to compare the HRV indices between fall risk groups (faller vs. non-faller). Wilcoxon Q effect size calculations (Wilcox, 2019) for non-parametric data were also calculated to test the effect of fall risk group on HRV indices.

CHAPTER IV: 24-HOUR HEART RATE VARIABILITY IN OLDER ADULT FALLERS AND NON-FALLERS

Introduction

Each year, approximately one in three adults age 65 and older will fall (Bergen et al., 2016). Many of these falls result in significant injury, including fractures and head trauma, with subsequent hospitalization, increased chance of morbidity, and decreased functional mobility (Bergen et al., 2016; Sterling et al., 2001; Tinetti et al., 1988, 1995). Fall related injuries also account for approximately $50 billion in annual US healthcare expenditures (Florence et al., 2018). As the older adult population of the United States rapidly increases, with projected growth from 16% to ~20% by 2030, fall rates are expected to increase in conjunction (Ortman et al., 2014). Thus, addressing fall risk is critical for reducing societal financial burden and improving quality of life for older adults.

Several assessments have been developed to identify elevated fall risk in community-dwelling older adults, including static and dynamic balance tests, gait assessments, and questionnaires (Perell et al., 2001b). However, fall risk is multifactorial (Tinetti et al., 1988) and such assessments are primarily designed to measure a single dimension of fall risk (e.g., static balance, dynamic balance, fear of falling). As a result, elevated fall risk often goes unidentified, negating opportunities to intervene prior to a fall with preventative interventions. Measuring physiological variables, such as heart rate variability (HRV), that reflect multiple fall risk dimensions, presents prospect for a more holistic assessment.

HRV is the fluctuation in time between adjacent heart beats (R-R intervals) and is an index of neurocardiac function resulting from heart-brain interactions and the autonomic nervous system (ANS) (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). It is assessed using three domains of measurement: time-domain, frequency domain, and non-linear analysis. Time-domain indices quantify the amount of variability in the heartbeat observed during a monitoring period. Of the time-domain measures, standard deviation of the normal to normal intervals (SDNN) is one of the most commonly calculated and reflects all the cyclic components responsible for variability in the time series recording (Electrophysiology Task Force of the European Society of Cardiology the North American Society of Pacing, 1996). Frequency domain indices are calculated using Fast Fourier Transformation or autoregressive modeling to separate a heartbeat time series into its component rhythms that operate in different frequency ranges. The most typically reported frequency components are the LF (0.04-0.15 Hz) and HF (0.15-0.40 Hz) bands. Detrended fluctuation analysis (DFA) is a common non-linear measure used to assess HRV. DFA quantifies the correlation between R-R intervals over different time scales (Shaffer & Ginsberg, 2017). R-R intervals as well as other physiological signals are highly nonstationary. Applying DFA to these signals detrends the time series, permitting the detection of intrinsic self-similarity embedded in a non-stationary time series, while avoiding spurious detection of self-similarity (Acharya et al., 2002). The outcome of DFA is the fractal scaling exponents α_1 and α_2 which are calculated by examining self-similarity over short-term and longer frequency ranges, respectively. α values equating to ≤ 0.5 correspond to white noise or uncorrelated data, values between 0.5-1 correspond to persistent long-range correlations, and values of ≥ 1.5 corresponds to Brownian noise (Acharya et al., 2002).

Importantly, dynamic system theory provides a theoretical framework for HRV as an assessment of fall risk. The theory suggests that physiological systems, such as the cardiovascular system, self-organize according to constraints (environmental, biochemical and morphological) in order to find the most stable solution (Stergiou & Decker, 2011). The dynamic interactions between the environment, other physiological systems (e.g., autonomic nervous system), and the cardiovascular system to find this "stable solution" are reflected in the underlying fluctuations of the heartbeat (e.g., HRV) that are overlooked when only mean heart rate value is observed (Shaffer et al., 2014). As stated previously, fall risk is multifactorial, and the result of both internal (physiological) and external (environmental) factors. In alignment with dynamic systems theory, HRV provides opportunity to assess internal (physiological) factors associated with fall risk, as well as physiological systems abilities to react to external (environmental) perturbations.

To illustrate the relationship between HRV and fall risk, consider the impact of aging, a primary fall risk factor (Tinetti et al., 1988), on the ANS. Compared to younger adults, older adults have a greater amount of sympathetic nerve activity (Seals & Bell, 2004). It has been suggested that this may be the result of decreased baroreflex sensitivity that occurs with aging, and thus decreased heart rate response to norepinephrine released from the sympathetic nerves (Vasudev et al., 2011). Alternatively, others have observed a close relationship between visceral fat and increased resting sympathetic nerve activity (Seals & Bell, 2004; Seals & Esler, 2000). Importantly, visceral adipose tissue accretion is associated with aging (Huffman & Barzilai, 2009). The increase in leptin and insulin that occurs as a result of excess visceral adiposity sends humoral signals across the blood brain barrier to the hypothalamus stimulating outflow of the sympathetic nervous system to the heart (Seals & Bell, 2004; Seals & Esler, 2000). Regarding age related changes to the parasympathetic division of the ANS, a reduction in parasympathetic (vagal) tone with aging has been observed (Brodde et al., 1998), resulting in less cardioaccelerator during vagal withdraw when transitioning positions (e.g., seated to standing) (Vasudev et al., 2011). In many instances, this leads to orthostatic hypotension or a drop in blood pressure when changing postures. These age-related changes in the ANS impair older adults' ability to adapt to alterations in the internal (physiological) and external environment, and are associated with increased risk of decline in functional mobility and falls (Hotta & Uchida, 2010; Mol et al., 2019; Ogliari et al., 2015). Moreover, alterations in ANS function have been associated with changes in HRV. Li and colleagues (2020) found that the HRV indices [standard deviation of the normal-to-normal intervals (SDNN), very low frequency power, and the low frequency power / high frequency power ratio] were significantly negatively correlated with orthostatic hypotension in a sample of older adults. Additionally, Ogliari et al.(2015) observed that decreased SDNN values were associated with decrements in the ability to perform activities of daily living.

Previous research examining the relationship between HRV and fall risk has demonstrated promise for identifying individuals with elevated risk. To classify fall risk in a sample of 168 patients with hypertension, Melillo and colleagues applied a data mining algorithm that included three HRV indices [low frequency (LF) power, Shannon entropy, and recurrence plots features] extracted from a principle components analysis (Melillo, Jovic, DeLuca, et al., 2015). Their classifier achieved high specificity (80%) but low sensitivity (51%) (Melillo, Jovic, DeLuca, et al., 2015) to differentiate fallers from non-fallers. In a second study, Razjouyan and colleagues (Razjouyan et al., 2017) examined HRV as a fall risk indicator for 31 patients in an acute care setting. They observed significant negative correlations (r = -0.59, p = 0.001) between fall risk and the time-domain metric, SDNN. However, both studies investigated clinical populations; and thus, their findings are not generalizable to community dwelling older adults. To this end, the purpose of this study was to determine if HRV indices differ in community dwelling older adults with a history of falls and those who have not sustained a fall. We hypothesized that the time-domain metric, SDNN, the frequency domain metrics, LF and high frequency (HF) power, and the non-linear metrics, detrended fluctuation analysis (DFA) α_1 and α_2 would be significantly reduced in older adult fallers compared to non-fallers. To test our hypothesis, healthy, community dwelling older adults (age 65-90 years) were recruited, and HRV was collected for 24-hours while participants continued their normal daily activities. A 24 hour wear period was chosen to align with previous HRV and fall risk research (Melillo, Jovic, DeLuca, et al., 2015; Razjouyan et al., 2017) and because it is considered the gold standard of clinical HRV assessment (Shaffer et al., 2014).

Methods

Participants

A total of 42 participants were recruited for this study. Participants were between the ages of 65-90 years; had never been diagnosed with a neurological condition known to impact balance (e.g., Parkinson's Disease, Peripheral Neuropathy, Multiple Sclerosis); had normal or corrected-to-normal vision; achieved a Mini-Mental State Examination (MMSE) score >24; were not current smoker; had the ability to stand for ≥ 5 minutes without the use of an assistive device; did not have a history of cardiovascular event or surgery including: heart attack, stroke, bypass surgery, stent, or pacemaker implantation, had never been diagnosed with Diabetes (Type 1 or Type 2); had never been diagnosed with Hypo / hyperthyroidism diagnosis; and their medications had been stable for the previous two months. With the exception of the MMSE, individuals were screened for the above criteria via an online survey (Qualtrics, Provo, Utah). Subsequently, inclusion criteria were reviewed via phone when individuals were contacted to schedule a laboratory visit. Participants were assigned to one of two group based on self-reported fall history. A fall was defined to participants as "an event resulting in you coming to rest on the ground or other lower level". Those who reported falling ≥ 1 fall during the previous 12 months were identified as a "faller", and participants who reported no falls during the same time frame were identified as "non-fallers". Participant demographics are presented in Table 1.

Procedure

All procedures were approved by the University's Institutional Review Board. Upon arrival to the lab, participants were screened for cognitive function via the MMSE. If a score of >24 was achieved, participants gave informed consent. Participants then completed a demographic and health history survey, and height and weight were measured. Participants were then equipped with a Polar H10 chest strap (Polar Elector, Bethpage, NY) and Actigraph GT9X Link accelerometer (Actigraph, Pensacola, FL). When integrated, the Polar H10 chest strap collects R-R interval data that can be stored on the GT9X Link accelerometer. R-R intervals are collected by the Polar H10 at a rate of of 1000 Hz, and prior research has established it as a valid measurement of R-R intervals across a broad range of activities (Gilgen-Ammann et al., 2019). Monitors were initialized to begin collecting data two hours after participants left the lab, ensuring they had returned to their free-living environment. Collection of R-R intervals continued for the subsequent 28-hour period. The Task Force of European Society of Cardiology and the North American Society of Pacing and Electrophysiology ("Heart Rate Variability," 1996) has recommended that long-term (24-hour) recordings include a minimum of 18 hours of succussive R-R intervals, including the whole period of nighttime sleep; thus, our methodology assured sufficient data collection. Participants were instructed to wear the monitors for the entirety of the 30-hour period, with the exception of when bathing, and to continue their normal daily activities. Periods of non-wear due to bathing and sleep time were recorded by participants and returned to researchers when monitors were retrieved.

HRV Data Reduction

In order to calculate HRV indices, R-R interval data was downloaded from the GT9X Link via the ActiLife software (Actigraph, Pensacola, FL). R-R intervals were then uploaded to the Kubios Premium software (Kubios Premium 3.4.1, Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) for HRV analysis. First, data was visually inspected to confirm R-R intervals for the entirety of nighttime sleep. *n* =1 participant was removed from analyses as a result of missing nighttime data. Next, data was visually inspected for excessively noisy segments, and identified segments were removed from the time series. An automatic artefact correction algorithm was then applied with a 'medium' threshold (inter-beat-interval differing from the local average more than 0.25 seconds were corrected). The time-domain metric, SDNN (ms), and the non-linear metrics, DFA α_1 and α_2, were calculated for the entire 24-hour time series. Frequency-domain metrics, LF and HF Power [(measured as normalized units (nu)], were calculated as averages of 5-minute segments.

Analysis

All data analyses were performed using R (R, Version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria). Independent samples t-tests were used to compare group demographics. The Shapiro-Wilks test was used to assess the distribution of each outcome variable [e.g., SDNN, LF Power, HF Power, DFA α_1, and DFA α_2), with some variables exhibiting a non-normal distribution. Therefore, non-parametric Mann Whitney U tests were performed to compare HRV indices (SDNN, LF Power, HF Power, DFA α_1, and DFA α_2) between fallers and non-fallers. Alpha level was set a priori at 0.05 for all analyses. To assess the strength of the association between fall risk and HRV indices, Wilcoxon Q effect size calculation (Wilcox, 2019) were conducted. The interpretation values for the Wilcoxon Q effect size are as follows: $r < 0.30$ = small effect, $r = 0.30 – 0.49$ = medium effect, and $r \geq 0.50$ = large effect (Wilcox, 2019).

Results

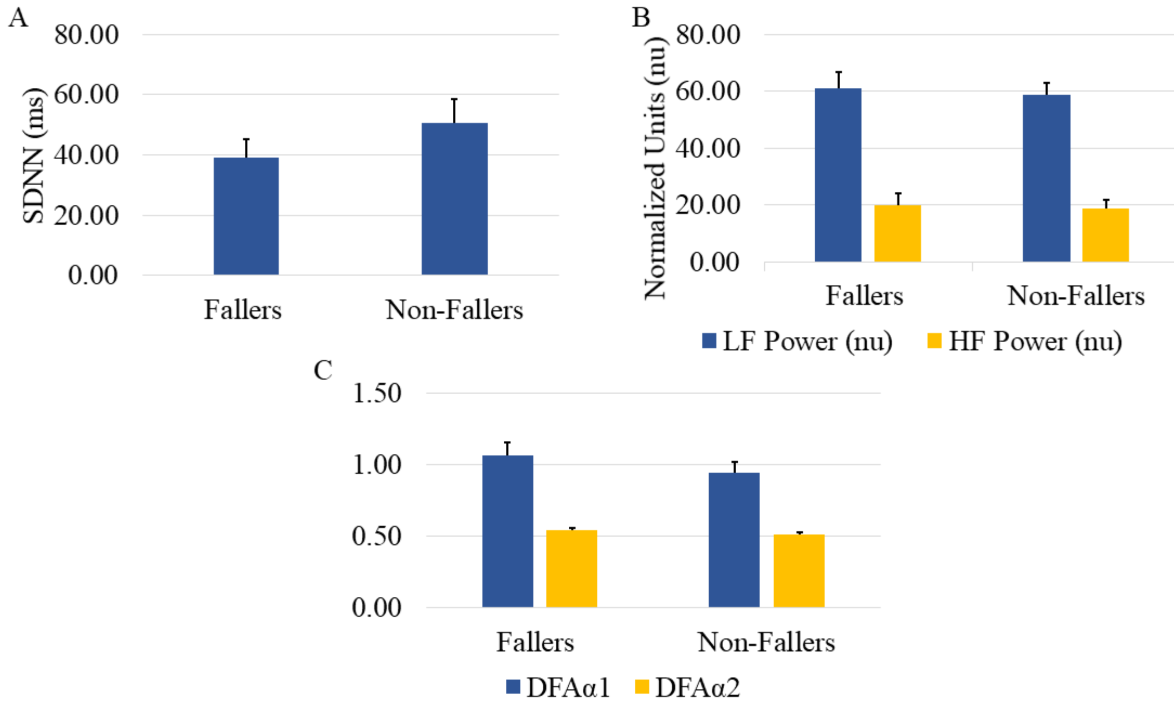
Independent samples t tests revealed a significant difference of age between groups (p = 0.026), with fallers having an older average age compared to non-fallers (Table 1). No other significant differences for demographic variables were observed. Mann Whitney U tests revealed that only the time-domain HRV metric, SDNN, approached significance $U = 257$, $p = 0.063$ CI [-0.46, 18.03]. No other HRV indices significantly differed between fallers and non-fallers: (LF Power: $U = 171$, $p = 0.634$, CI [-10.37, 5.51]; HF Power: $U = 207$, $p = 0.630$, CI [-5.49, 10.35], DFA α_1: $U = 178$, $p = 0.777$, CI [-0.14, 0.10]; DFA α_2: $U = 182$, $p = 0.858$, CI [-0.08, 0.05]) (Table 2). Figure 2 includes a visual representation of the mean and standard deviation values for each HRV indices by group. Finally, a medium effect size ($r = 0.30$, CI [0.02, 0.56]) for the effect of fall risk on SDNN was observed (Table 2). All other effect sizes were negligible ($r \leq$ 0.11).

Table 1. Participant Demographics

		Fallers (*n*=14)	Non-Fallers (*n*=27)	*p*
Sex	Male (*n*)	4	11	
	Female (*n*)	10	16	
Age (years)		77 ± 6.18	73 ± 4.70	0.026
Height (cm)		163.89 ± 11.01	167.38 ± 9.72	0.303
Weight (kg)		66.94 ± 14.32	74.58 ± 13.44	0.099
MMSE		29.07 ± 0.73	29.37 ± 0.93	0.301
Household Income (*n*)	$15,000 - $29,999	1	1	
	$30,000 - $44,999	1	3	
	$45,000 - $59,999	0	3	
	$60,000 - $74,999	0	4	
	$75,000 - $89,999	4	3	
	$90.000 or above	5	10	
	Chose not to answer	3	3	
Highest Level of Education (*n*)	Technical School	0	1	
	2 Year College	3	6	
	4 Year College	3	8	
	Graduate School	7	10	
	Professional School	1	2	

Note. Values are reported as mean ± SD, MMSE = Mini Mental State Examination, Household Income = based on annual income for the three years prior to retirement.

Figure 2. Mean and Standard Error of HRV Parameters



Note. SDNN = Standard Deviation of the Normal-to-Normal Intervals, LF Power = Low Frequency Power, HF Power = High Frequency Power, DFA = Detrended Fluctuation Analysis.

Table 2. Mean, Standard Error, and Mann Whitney U Test Results for HRV Parameters

					CI_{95}			CI_{95}	
	Fallers	Non-Fallers	*U*	*p*	LL	UL	*r*	LL	UL
SDNN (ms)	38.99 ± 6.24	50.67 ± 7.90	257	0.063	-0.46	18.03	0.30	0.02	0.56
LF Power (nu)	60.91 ± 5.76	58.87 ± 4.17	171	0.634	-10.37	5.51	0.05	-0.22	0.16
HF Power (nu)	19.96 ± 4.10	18.67 ± 3.33	207	0.63	-5.49	10.35	0.05	-0.22	0.16
DFAα_1	1.06 ± 0.09	0.94 ± 0.08	178	0.777	-0.14	0.10	0.11	-0.14	0.3
DFAα_2	0.54 ± 0.02	0.51 ± 0.02	182	0.858	-0.08	0.05	0.03	-0.27	0.13

Note. Values are reported as mean ± SE, SDNN = Standard Deviation of the Normal-to-Normal Intervals, LF Power = Low Frequency Power, HF Power = High Frequency Power, DFA = Detrended Fluctuation Analysis, CI_{95} = 95% Confidence Intervals.

Table 3. Medication Types by Group

	Fallers (*n*=14)		Non-Fallers (*n*=27)	
	n	%	*n*	%
No Meds	4	28.57	12	44.44
Cardiac Meds	7	50	10	37.04
Anti-Meds	1	7.14	1	3.7
Both	2	14.29	4	14.81

Note. Cardiac Meds = statins and ACE-inhibitors, Anti-Meds = anti-anxiety and anti-depression medications, Both = Cardiac and Anti-Meds.

Discussion

The aim of this study was to investigate if HRV indices, measured over a 24-hour period, differ in older adults who fell and those who did not during the 12 months prior to assessment. As fall rates in the older adult population are projected to increase, it is essential to identify holistic assessments that can characterize individuals with elevated risk, providing opportunity for implementation of preventative interventions. In the present study, older adults (age: 74.30 ± 5.56 years) were assigned to two groups based on self-reported fall history (N = 14 fallers, N = 27 non-fallers) and wore a heart rate monitor for 24 hours in their free-living environment. R-R interval data collected via the heart rate monitors was analyzed to obtain time-domain (SDNN), frequency-domain (LF and HF power), and non-linear (DFA α_1 and α_2) HRV indices. Based on previous literature, it was hypothesized that HRV metrics would be significantly reduced in older adult fallers compared to non-fallers.

Our results suggest that HRV metrics (SDNN, LF and HF Power, and DFA α_1 and α_2) did not significantly ($p > 0.05$) differ between healthy, community dwelling, older adult fallers, and non-fallers. However, a medium effect size was observed for the effect of fall risk on SDNN, with fallers demonstrating lower SDNN compared to non-fallers. Importantly, in contrast to null hypothesis testing, which provides information regarding the probability that the null hypothesis is true (e.g., no difference between in HRV between fallers and non-fallers), effect size calculations evidences the strength of the relationship between variables (e.g., strength of the relationship between fall risk and SDNN) and is an indication of whether findings are meaningful for clinicians and patients (Maher et al., 2013). The magnitude of the observed effect of fall risk on SDNN, suggests that the metric may provide clinically relevant information regarding fall risk in community dwelling older adults.

Importantly, SDNN has demonstrated clinical importance for differentiating between healthy and diseased states. For 24-hour recordings, it is regarded as the “gold standard” for stratifying cardiac risk (e.g., likelihood of a cardiac event) because it can index the heart’s response to circadian rhythm processes as well as varying workloads (Grant et al., 2011; Shaffer & Ginsberg, 2017). Additionally, SDNN has also been shown to differentiate between individuals with major depression and healthy controls (van der Kooy et al., 2006), as well as patients with Type II Diabetes and healthy controls (Benichou et al., 2018). With regard to fall risk, for patients in an acute care setting, Razjouyan and colleagues (2017a) observed a strong, negative correlation between fall risk and SDNN (p = 0.001, r = -0.59, d_s = 1.68), with high risk fallers demonstrating lower SDNN compared to low-risk fallers. While our finding of a medium effect size of fall risk on SDNN is not as strong as the aforementioned study, there are a few key differences of note. First, the sample of the current study was a healthy community dwelling population, while patients in Razjouyan et al.’s study were hospitalized in a hematology/oncology unit, and thus were likely already experiencing alteration to ANS as a result of illness (Kloter et al., 2018). Additionally, Razjouyan and colleagues used the Hendrich II fall risk assessment scale to classify individuals as low or high fall risk. Despite being a well-established and validated method of assessment for the hospital setting, the subjective assessment presents possibility for false positives/negatives. In contrast, participants in the current study reported whether or not they had fallen during the 12 months prior to HRV monitoring. While it is possible that mis-reporting can occur with fall recall, previous work has suggested no difference in recall accuracy once intervals extend beyond one month (Ganz et al., 2005). Razjoyan et al.’s study was similarly powered to ours, with N = 31 patients (N = 10 fallers and N = 21 non-fallers), and while their observed effect size was large, the aforementioned sample and methodological differences suggest that our observed moderate effect for SDNN may be clinically relevant to differentiate between community-dwelling fallers and non-fallers.

In contrast to our findings of no differences between fall risk and frequency and non-linear HRV indices, Melillo et al. (2015) observed differences in LF Power and Shannon Entropy between hypertensive patients (age: 72 ± 8 years) who fell within 3 months of HRV monitoring and those who did not. Yet, it is difficult to compare findings in hypertensive patients to healthy, community dwelling adults because hypertension is known to alter ANS function and consequently HRV (Carthy, 2014). Furthermore, hypertension related changes in ANS function also contribute to elevated fall risk (Chu et al., 2015); thus, it is likely that a greater percentage of hypertensive patients would fall compared to community dwelling adults. Indeed, of the 168 patients in Melillo et al. study, $n = 47$ reported a fall during the 3 months prior to or following HRV monitoring, equating to 28% of the sample. In comparison, current population fall rates project that approximately 25% of adults aged 65 and older fall annually. However, it remains important to consider hypertension in the community dwelling population. Currently, 74.5% of US adults over the age of 60 have hypertension (blood pressure above 130/80 mmHg) (Ostchega et al., 2020). Thus, to optimally infer study findings to the general population, it is important that a sample mirror these statistics. In the current study, $n = 23$ (55%) participants [$n = 14$ (50%) non-fallers and $n = 9$ (64%) fallers] reported use of prescription medications to manage hypertension (Table 3). Therefore, while hypertensive medication use was higher in the fallers group, the overall sample is below national hypertension rates for older adults. Such differences may have contributed to our null findings as our sample was generally healthy and may have better ANS function.

The current study was not without limitations. First, there was a significant difference in age between faller (77 ± 6.18 years) and non-faller (73 ± 4.70 years) groups. However, fall risk is known to increase with age, and thus one would suspect that individuals with a history of falls would likely have an older mean age compared to those with no history of falls (Bergen et al., 2016). Differences between groups in medication use was another limitation (Table 3), with a larger proportion of the fallers group (64% vs. 55%) reporting use of cardiac altering (statins and ACE-inhibitors) medications (Menezes & Melo, 2000; Pehlivanidis et al., 2001). While both classifications of drugs have demonstrated beneficial improvements in HRV (Menezes & Melo, 2000; Pehlivanidis et al., 2001), caution must be taken when interpreting these data. Finally, the small sample and strict inclusion criteria are limitations which may constrain the generalizability of these findings. A strict inclusion criterion was used to maintain internal validity as the following diseases are known to alter autonomic control: Diabetes, Hyper/hypothyroidism, cognitive decline, and dementia. Yet, in the US older adult population, an estimated 33% have diabetes (CDC, 2017a), 7-14% have hypothyroidism (Kim, 2000), 40-60% have mild cognitive impairment (Gillis et al., 2019), and 5 million have dementia (*What Is Dementia?*, 2019). Therefore, to improve generalizability, it is recommended that future studies consider broadening inclusion criteria to include diseases that impact older adults. Finally, due to the small sample, additional studies are warranted to confirm the observed results in a larger population.

In conclusion, this study examined the difference in HRV indices in older adult fallers and non-fallers. Although, no significant differences in HRV indices were observed between fallers and non-fallers, a medium effect of fall risk on the time-domain metric, SDNN, was found. This suggests that SDNN may provide clinically relevant information regarding fall risk.

Importantly, such an assessment presents a more holistic measure for identifying community dwelling older adults at high risk for falls.

CHAPTER V: A COMPARISON OF HEART RATE VARIABILITY INDICES AND TRADITIONAL FALL RISK MEASURES TO CLASSIFY FALL RISK

Introduction

Falls and fall related injuries in the older adult population can be reduced through the implementation of preventative interventions (Sherrington et al., 2011), secondary to the identification of elevated risk through the application of screening tools. A considerable number of screening tools are available with cutoff values for stratification of risk of falling (Chu et al., 2015; Perell et al., 2001a; Shumway-Cook et al., 1997). However, the comparison of sensitivity and specificity between methods indicates that no method is significantly better than another (da Costa et al., 2012; Gates et al., 2008), and most have demonstrated poor predictive power to classify the risk of falling in older adults (Balasubramanian et al., 2015; Gates et al., 2008).

One reason for the lack of effective fall risk measures is that fall risk is multifactorial, while majority of traditional assessments are unidimensional. Regarding the multifactorial nature of falls, fall risk is the result of both physiological and environmental factors. Intrinsic factors include age-related changes in the sensory, cognitive, neural, and muscular systems that impact postural control, as well as and psychoactive drugs (Ambrose et al., 2013a; Tinetti et al., 1995). Extrinsic factors include alterations in the environment or activities that perturb postural stability (Ambrose et al., 2013a; Deandrea et al., 2010; Tinetti et al., 1995). Research has suggested improved predictive ability when a battery functional assessments are performed together (Lusardi et al., 2017). However, this takes a significant amount of time and many of the functional measures require administration by a trained practitioner; thus, increasing the burden on an already taxed healthcare system (Casey et al., 2017). Therefore, there is a need for fall risk assessment tools that is time efficient and encompasses the multidimensional nature of fall risk.

Mobile, sensor-based technologies provide an opportunity to fill the current gaps in fall risk assessments by measuring physiological variables, such as heart rate variability (HRV), in the free-living environment. HRV or the interval in time between successive heart beats is an has demonstrated utility for tracking changes in intrinsic fall risk factors (Shaffer et al., 2014). For example, HRV has also demonstrated the ability to measure functional capacity of brain structures, and in particular those related to executive function, emotion, and depression (Kamińska et al., 2015; Thayer & Lane, 2000). Importantly, declines in executive function, changes in emotion, and depression are all associated with increased fall risk (Kamińska et al., 2015). The association between brain structures and HRV is supported by the Neurovisceral Integration Model. The model has identified functional units, known as the central autonomic network, within the central nervous system that are linked to the heart through the stellate ganglia and the Vagus nerve and responsible for excitatory and inhibitory effects on the heart (Benarroch, 1993; Thayer & Lane, 2000). In alignment with this model, Lane et al. (2009) observed that emotional arousal was associated with a decrease in the HRV parameter high frequency (HF) power, with a simultaneous increase of blood flow in the right superior prefrontal cortex, the left rostral anterior cingulate cortex, the right dorsolateral prefrontal cortex, and the right parietal cortex. Additionally, Hansen et al. (2003) examined working memory, nonexecutive, and executive function in military personnel. Participants were assigned to a high or low HRV group based on a median split of the HRV parameter root mean squared standard deviations (RMSSD). The high HRV group demonstrated superior performance on executive function and working memory tasks (Hansen et al., 2003). Furthermore, depression has also been linked to alterations in autonomic control and is characterized by reduced HRV (Sgoifo et al., 2015; Udupa et al., 2007). This previous work provides theoretical reasoning for HRV as a holistic measure of fall risk.

To establish the utility of HRV as a fall risk assessment tool, it must be compared against the current gold standard measures. Therefore, the goal of this study was to determine the discriminative validity of HRV indices standard deviation of the normal-to-normal intervals (SDNN), low frequency (LF) Power, and DFA α_1 observed over a 24-hour monitoring period for classifying fall risk in older adults compared to traditional fall risk assessment tools, including the Timed Up and Go (TUG), the Functional Gait Assessment (FGA), and the Activities-specific Balance Confidence Scale (ABC). The HRV metric SDNN reflects the cyclic components responsible for the variability of the heartbeat time series. It was chosen as an outcome measure in the current study because it has previously demonstrated the ability to differentiate high and low risk fallers in a sample of oncology patients residing in an acute care facility (Razjouyan et al., 2017). Additionally, SDNN is the "gold standard" for medical stratification when recorded over a 24-hour period (Shaffer & Ginsberg, 2017). LF power was chosen as an outcome measure because it has been correlated with baroreflex sensitivity (La Rovere et al., 1998; Moak et al., 2007), which is associated with risk of falling in older adults (Isik et al., 2012). Moreover, a previous study by Melillo et al. (2015) observed a significant relationship between LF power measured over a 24-hour period and fall risk in hypertensive patients. The non-linear metric DFA α_1 was chosen because it also reflects the baroreceptor reflex (Shaffer & Ginsberg, 2017) and has demonstrated the ability to differentiate between healthy and diseased states (Gospodinova et al., 2016; Yeh et al., 2006). The traditional fall risk measures (TUG, FGA, ABC) were selected as they are commonly used in the clinical setting and have been shown to be valid measures in the community dwelling population (Barry et al., 2014; Powell & Myers, 1995; Wrisley et al., 2004). We hypothesized that HRV indices will correctly identify a greater percentage of fallers compared to the TUG, FGA, and ABC. To test this hypothesis, traditional fall risk assessments and 24-hour HRV measures were collected on community dwelling older adults and compared using receiver operator characteristics (ROC) curves.

Methods

Participants

Participants were recruited from the surrounding community through email listservs, flyers, social media posts, and presentations at community events. Interested individuals completed an online survey (Qualtrics, Provo, Utah) that screened for the following inclusion criteria: 1) be between the ages of 65-90 years; 2) never been diagnosed with a neurological condition; 3) normal or corrected-to-normal vision; 4) not currently a smoker; 5) possess the ability to stand for ≥ 5 minutes without the use of an assistive device; 6) no history of cardiovascular event or surgery including: heart attack, stroke, bypass surgery, stent, or pacemaker implantation, 7) never been diagnosed with Diabetes (Type 1 or Type 2); 8) never been diagnosed with Hypo / hyperthyroidism diagnosis; and 9) no change in medication during the previous two months. Individuals who met the above criteria were contacted to confirm the inclusion criteria and schedule a lab testing visit. When participants arrived at the lab, the Mini-Mental State Examination (MMSE) was administered to screen for cognitive function. If participants, achieved an MMSE score >24, study procedures continued. A total of 42 participants (74.37 ± 5.52 years, 166.19 ± 10.18cm, 71.97 ±14.06kg) met the inclusion criteria and were enrolled in the study.

Procedure

The following procedures were approved by the University's Institutional Review Board. Following completion of the MMSE, participants gave informed consent. A demographics and healthy history survey was then completed, and anthropometrics were measured. The health history survey asked participants to indicate whether or not they had fallen at least once during the previous 12 months. A fall was defined as "an event resulting in you coming to rest on the ground or other lower level". Participants who reported falling during the previous 12 months were classified as a "faller", and participants who reported no falls were classified as a "non-faller". 15 participants were identified as fallers, and 27 participants were identified as non-fallers.

Participants then completed three traditional fall risk assessments (TUG, FGA, and ABC) in a randomized order. These assessments were chosen because they are commonly used in the clinical setting. Participants performed the TUG and FGA without shoes. To complete the TUG, participants were timed as they stood from a chair, walked 3 meters, turned around, walked back the chair and sat down (Barry et al., 2014). The total time required for participants to complete the TUG was used for analysis. The FGA consists of 10 dynamic gait tasks that are scored from 0 to 3, with higher scores indicating better functional gait (Wrisley & Kumar, 2010). To create an overall score, individual task scores were summed with a maximum value of 30. Overall FGA scores were used for analysis. The ABC consists of 16 items that assess balance self-efficacy during activities of daily living. Each item is scored on a 10-point ordinal scale (0 = no confidence to 100 = complete confidence to maintain balance while completing the activity) (Powell & Myers, 1995). Item scores were averaged to achieve an overall score. The overall ABC scores were used in analysis.

Following completion of the traditional fall risk assessments, participants were outfitted with a Polar H10 chest strap (Polar Elector, Bethpage, NY) and Actigraph GT9X Link accelerometer (Actigraph, Pensacola, FL). The Polar H10 sensor collected R-R intervals at a rate of 1000 Hz and stored them on the GT9X Link accelerometer. The literature has established the Polar H10 as a valid measurement of R-R intervals across a range of activities (Gilgen-Ammann et al., 2019). To ensure participants had returned to their normal daily activities following the testing visit, monitors were initialized to begin collecting data two hours after participants left the lab. R-R intervals were collected for the successive 28-hour period. With the exception of when bathing, participants were instructed to wear monitors for the entire 30-hour period, including while sleeping, and to continue their normal daily activities. It is recommended that long-term HRV recordings (e.g., 24-hour) include a minimum of 18 hours of successive R-R intervals, including the entire period of nighttime sleep ("Heart Rate Variability," 1996). For the current study, 30 hours of monitor wear time insured sufficient data for long-term recordings. Following completion of the 30-hour wear period, monitors were returned to the study team.

HRV Data Reduction

First, R-R intervals were downloaded from the GT9X Link to the ActiLife software (Actigraph, Pensacola, FL). Next, R-R intervals were uploaded to the Kubios Premium software (Kubios Premium 3.4.1, Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) to conduct HRV analysis. Data were then visually inspected to confirm inclusion of R-R intervals for the entire of nighttime sleep period. Nighttime sleep data was missing for $N = 1$ participant; therefore, they were removed from analyses. Subsequently, noisy segments were identified via visual inspection and removed from the time series. An automatic artefact correction algorithm within the Kubios Premium software was then applied with a 'medium' threshold (R-R intervals differing from the local average more than 0.25 seconds were corrected). The time-domain [SDNN (ms)] and the non-linear (DFA α_1) metrics were calculated for the entire 24-hour time series. The frequency-domain metric [LF Power (nu)] was calculated as average of 5-minute segments for the time-series.

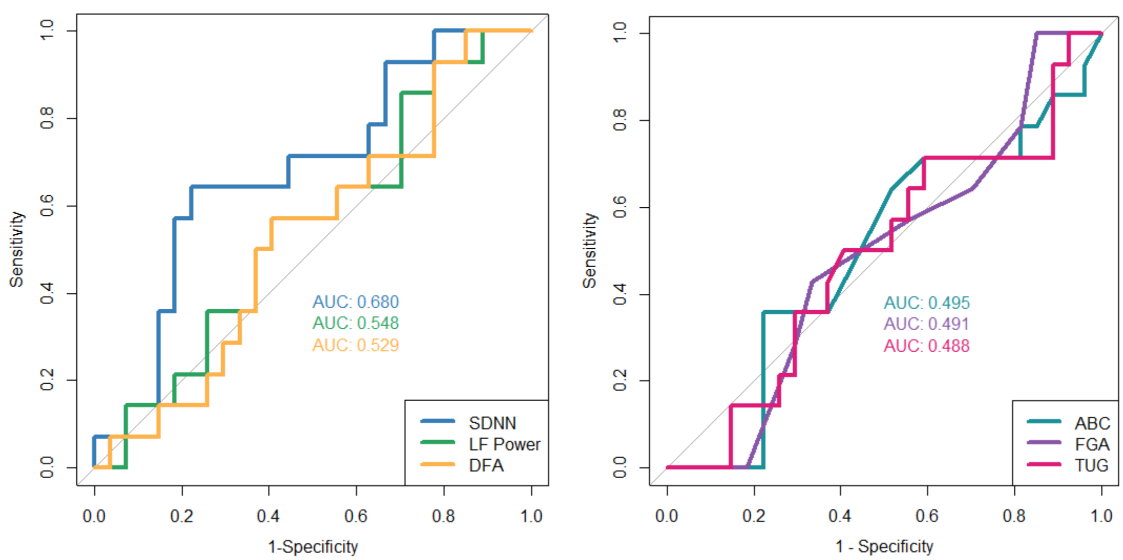
Analysis

41 participants were included in data analyses (*n*= 14 fallers: 77 ± 6.18 years, 163.89 ± 11.01 cm, 66.94 ± 14.32 kg, *n* = 27 non-fallers: 73 ± 4.70 years, 167.38 ± 9.72 cm, 74.58 ± 13.44 kg). All data analyses were performed using R (R, Version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria). Demographic and anthropometric characteristics broken down by group assignment (fallers vs. non-fallers) are presented in Table 1. Receiver operator characteristics (ROC) curves as executed in the "pROC" package (Robin et al., 2011) were used to assess the effectiveness of HRV indices (SDNN, LF power, and DFA α_1) and traditional fall risk assessments (TUG, FGA, and ABC) to identifying fall risk in community dwelling older adults. Using the roc.test function in pROC, a series of bootstrapped pairwise comparisons were performed for each HRV indices area under the curve (AUC) with each traditional fall risk assessment's AUC to determine which measure best discriminates fallers from non-fallers. Sensitivity and specificity were determined based on the highest threshold value with the highest sensitivity and specificity.

Results

The ROC curves for the ability of HRV (SDNN, LF power, and DFA α_1) and traditional fall risk assessments (TUG, FGA, and ABC) to identify fallers versus non-fallers in community dwelling older adults are depicted in Figure 4. The estimated AUC was 0.68 for SDNN, 0.55 for LF Power, 0.53 for DFAα_1, 0.49 for FGA, 0.49 for TUG, and 0.50 for ABC. The AUC corresponds to the ability of the test to correctly classify those with and without fall risk. A test with an AUC of 1 has perfect accuracy and an AUC of 0.50 suggests the test is no better than random chance (Fawcett, 2006). Pairwise comparisons of the AUC's for SDNN and the traditional fall risk assessments suggested that SDNN was not a superior test for discriminating fallers from non-fallers (FGA: $p = 0.17$, TUG: $p = 0.17$, ABC: $p = 0.10$). The AUCs for the remaining HRV indices and traditional fall risk assessments were near or below 0.50 suggesting that for the given sample these metrics were no better than random chance for detecting fall risk; therefore, no other pairwise comparisons were executed.

Figure 3. ROC Curves for HRV Metrics and Traditional Fall Risk Assessments



Note. SDNN = Standard Deviation of the Normal-to-Normal Intervals, LF Power = Low Frequency Power, DFA = Detrended Fluctuation Analysis α_1, ABC = Activities Balance Confidence Scale, FGA = Functional Gait Assessment, TUG = Timed Up and Go.

Table 4. AUC, Sensitivity, and Specificity for HRV Metrics and Traditional Fall Risk Assessments

	Fallers			Non-Fallers			AUC	Sn	Sp
SDNN (ms)	38.99	±	6.24	50.67	±	7.90	0.68	64.29	22.22
LF Power (nu)	60.91	±	5.76	58.87	±	4.17	0.55	50.00	37.04
DFAα_1	1.06	±	0.09	0.94	±	0.08	0.53	50.00	37.04
TUG	9.82	±	0.41	9.92	±	0.36	0.49	50.00	40.74
FGA	22.50	±	0.63	22.26	±	0.67	0.49	42.86	33.34
ABC	91.57	±	0.02	92.15	±	0.01	0.50	57.14	48.15

Note. Values are reported as mean ± SE, Sn = Sensitivity, Sp = Specificity, SDNN = Standard Deviation of the Normal-to-Normal Intervals, LF Power = Low Frequency Power, DFA = Detrended Fluctuation Analysis, TUG = Timed Up and Go, FGA = Functional Gait Assessment, ABC = Activities Balance Confidence Scale.

Discussion

This study compared the ability of HRV indices measured over a 24-hour period to traditional fall risk assessment tools for classifying fall risk in community dwelling older adults. Traditional fall risk assessments are primarily unidimensional and have demonstrated a range of variability to accurately detect falls (Lusardi et al., 2017; Perell et al., 2001a; Shumway-Cook et al., 1997). The multidimensional nature of falls risk requires a more holistic assessment tool. HRV presents opportunity to fill this gap due to its evidenced ability to track changes in multiple intrinsic fall risk factors (Sgoifo et al., 2015; Thayer & Lane, 2000). In this study, older adults (age: 74.30 ± 5.56 years) were assigned to one of two groups based on self-reported fall history (*n* = 14 fallers, *n* = 27 non-fallers), and completed three traditional fall risk assessments (FGA, TUG, and ABC) in a randomized order. Next, participants were equipped with a heart rate monitor chest strap and wore it for 24 hours in their free-living environment. To compare test's ability to differentiate fallers from non-fallers, ROC curves were generated for FGA, TUG, and ABC scores, as well as the HRV parameters SDNN, LF power, and DFA α_1.

Our results suggest that in a healthy, community dwelling, older adult population, SDNN was the best measure to correctly differentiate fallers from non-fallers. However, pairwise comparisons of the AUC's for SDNN and each traditional fall risk assessment, showed that performance of SDNN did not significantly differ from the clinical measures ($p > 0.10$). Thus, while SDNN performed best in this sample and is trending towards significance, as a result of reduced statistical power associated with the small sample it did not perform significantly (based on $p < 0.05$) better than the traditional fall risk measures.

However, SDNN was the only assessment that demonstrated to be "better than chance" (AUC = 0.68) at discriminating fall risk, with moderate sensitivity (64.29%) but low specificity (22.22%). Importantly, an AUC of 0.70 is a commonly used clinical cutoff to determine the utility of a test to diagnose patients with and without a disease or condition (Fawcett, 2006). The low specificity suggests that as a measure of fall risk, SDNN comes with a fairly high rate of false positives. These findings are similar to what has been observed in the application of other sensor-based (wearable and non-wearable) technologies for assessing fall risk. In a systematic review, Kosse and colleagues (2013) investigated the effects of sensor technologies to reduce falls and fall related injuries in patients residing in a nursing home setting. With the use of sensor systems (e.g., sock pressure sensors, movement sensors, bed and chair alarms), they observed up to a 77% reduction in falls and fall-related injuries but a high rate of false alarms (16%) (Kosse et al., 2013). They noted that the high rate of false alarms desensitized caregivers and medical staff against alarms, and thus reduced timely intervention. To improve measurement specificity of HRV, a time threshold could be used, where an alert is triggered after a certain time period when a parameter (e.g., SDNN) is above or below a threshold point. However, developing a predictive time threshold model for SDNN would require a larger dataset and measurement of HRV for days to weeks as well as fall occurrence for several months following assessment. Such time threshold models have been used to predict stressful episodes with a high level of specificity (94.8% for episodes of 13.5 minutes) (Sarker et al., 2016). Sarker et al. (2016) used physiological (HRV & respiration), GPS, and activity data collected from 38 users in their free-living environment to discover patterns of stress and develop a time threshold model to predict stressful episodes. The work of Sarker and colleagues highlights the importance of including activity data in a predictive time threshold model for HRV and fall risk as HRV is impacted by physical activity. Future research should consider examining the predictive ability of HRV for fall risk using a time threshold method.

It is important to note that the sample in the current study may not be representative of fall risk in the community dwelling population. Both the non-faller and faller groups achieved similar scores (Table 4) that were above cut-off values for fall risk on the traditional fall risk assessments. Various cut-off scores ranging from 10-20 seconds have been proposed for the TUG (Shumway-Cook et al., 1997; Trueblood et al., 2001), with a score of >12 seconds suggested as a cut-off for fall risk in community dwelling populations (Lusardi et al., 2017). In our sample, both fallers and non-fallers mean TUG scores were well below 12 seconds. For the FGA, a score of ≤ 22 has been suggested to provide both discriminative and predictive validity for falls (Wrisley et al., 2004). Again, in the current sample, mean scores of both the faller and non-faller groups were above 22. Regarding the ABC, scores of ≤ 67 have shown to indicate increased risk of falls (Lajoie & Gallagher, 2004). In our sample, both groups had mean ABC scores above 90. In addition to high performance on functional tests, to be included in the study, participants had to pass the Mini Mental State Examination with a score of > 24. Thus, the sample also had high cognitive ability. This suggests that our sample may have been more homogenous regarding fall risk. Future research should consider investigating HRV and fall risk in a broader range of community dwelling older adults, including individuals with age-related diseases known to increase fall risk.

The benefit of HRV as opposed to traditional functional and other sensor-based measurements is that it is cost effective and provides a multivariate approach for assessing fall risk factors and underlying mechanisms (McCraty & Shaffer, 2015). Other fall prevention sensor systems and traditional clinical measures are often based on a single fall risk factor (Kosse et al., 2013; Perell et al., 2001b), but fall risk is complex and multifactorial. Our findings suggest that while SDNN performed better than the clinical measures, but there is no evidence that HRV is a superior to traditional assessments for discriminating fall risk. These findings may have been influenced by the health of our sample. Both fallers and non-fallers performed better than the proposed cut-offs for TUG, FGA, and ABC, and thus may not be representative of the general population. Further research with an expanded sample is needed to confirm these findings. Additionally, future studies should consider prospective as opposed to retrospective design and use time threshold to improve accuracy and reduce bias (Peel, 2000).

CHAPTER VI: ASSOCIATIONS BETWEEN INTRINSIC FALL RISK FACTORS AND HEART RATE VARIABILITY

Introduction

Heart rate variability (HRV) has been investigated as an assessment of fall risk in clinical populations, including hypertensive patients and patients receiving oncology treatment in an acute care setting (Melillo, Jovic, DeLuca, et al., 2015; Razjouyan et al., 2017). In these populations, HRV metrics have demonstrated to be effective at identifying individuals with elevated fall risk (Melillo, Jovic, DeLuca, et al., 2015; Razjouyan et al., 2017). However, hypertension and cancer are known to cause autonomic dysfunction resulting in altered HRV, and prior work did not confirm findings of HRV and fall risk by examining additional intrinsic fall risk factors. To validate this novel measure of fall risk, it is important to explore the relationship between exposure to independent, intrinsic risk factors and HRV. Such information is also important for identifying variables with the greatest influence on HRV to be primary targets for preventative interventions.

While falls are most often reported as ‘accidental’ or environment-related, many of these falls really stem from the interaction between identifiable environmental hazards and individual susceptibility to hazards as a result of intrinsic risk factors (Rubenstein, 2006). Identified intrinsic fall risk factors including reduced lower extremity strength, changes in vision, vestibular dysfunction, and declines in cognitive function are associated with aging and result in alterations in postural control and gait dynamics (Ambrose et al., 2013b). Additionally, many age-related diseases and the medications used to treat them also impact fall risk such as cardiovascular disease, neurodegenerative disease, and depression (Ambrose et al., 2013b). Importantly, the most cited causes for falls by the elderly are decrements in gait and balance, lower extremity weakness, dizziness/vertigo, cognitive impairment, postural hypotension, emotional dysregulation, and visual disorders (Rubenstein, 2006). To assess these risk factors, several functional and survey-based measures have been developed and validated (Gates et al., 2008; Lusardi et al., 2017).

To this end, this study investigated associations between intrinsic fall risk factors, including postural control, vestibular function, lower extremity muscular strength, executive function, and depression, and the HRV parameters standard deviation of the normal-to-normal intervals (SDNN), low frequency (LF) power, high frequency (HF) power, and the non-linear measures DFA α_1 and α_2 in healthy, community dwelling older adult fallers and non-fallers. Postural control was measured as center of pressure (CoP) displacement, vestibular function was assessed using tests 5 & 6 of the Equitest Sensory Organization Test (SOT), lower extremity strength was measured using the 30s Chair Stand test, executive function was measured using the Trail Making test, and depression was assessed using the Beck Depression Inventory II (BDI II). HRV parameters were also assessed over a 24-hour period using wearable sensors. Previous research on HRV and fall risk has included patient populations with diseases known to impact autonomic control and consequently HRV; thus, to improve internal validity a healthy population was investigated. We hypothesized that for fallers a stronger negative relationship would be observed between the independent variables for postural control, executive function, and depression, and the HRV outcome variables. Furthermore, we hypothesized that for fallers, a stronger positive relationship would be observed between the independent variables vestibular function and lower extremity strength and the HRV parameters. Both hypotheses represent reduction in HRV parameters with an associated decline in each of the independent variables.

Methods

Participants

Forty-two healthy, community dwelling older adults (74.37 ± 5.52 years, 166.19 ± 10.18cm, 71.97 ±14.06kg) were enrolled in this study. Participants were between the age of 65-90 years, had normal or corrected-to-normal vision, did not currently smoke, had the ability to stand for ≥ 5 minutes without the use of an assistive device, and their medications had been stable for the prior two months. They had no history of cardiovascular event or surgery, and were free of any neurological disorders, Diabetes (Type I and II), and Hypo/hyperthyroidism. Individuals expressed interest by completing an online survey (Qualtrics, Provo, Utah) that screened for the above criteria. Qualifying individuals were contacted to schedule a lab testing visit. Upon arrival to the lab, participants were screened for cognitive function via the Mini-Mental State Examination (MMSE). To proceed with testing, participants had to achieve an MMSE score >24.

Procedure

Following completion of the MMSE and prior to initiation of testing measures, participants gave informed consent. Participants then completed a basic demographics and healthy history survey, and height and weight were measured. Within the health history survey, participants indicated if they had fallen during the prior 12 months. A fall was defined as “an event resulting in you coming to rest on the ground or other lower level”. Participants were assigned to one of two groups based on their fall history. Those who reported at least one fall during the prior 12 months were assigned to the “faller” group (n = 15), while those who reported no falls were assigned to the “non-faller” group (n = 27).

Participants then completed five tests used to assess intrinsic fall risk factors, including the BTrackS balance test, the EquiTest Sensory Organization Test (SOT), 30s Chair Stands, the Trail Making Test, and the second edition of the Beck Depression Inventory (BDI-II). To account for potential physical and mental fatigue, assessments were performed in a randomized order. Participants completed the BTrackS balance test, the EquiTest SOT, and 30s Chair Stands without shoes.

The BTrackS balance test was used to assess postural control and consists of a lightweight, portable force plate used to track the center of pressure (CoP) during quiet standing (Goble et al., 2016). Importantly the test has demonstrated to be a reliable and valid measure of postural control in older adults (Goble et al., 2017; Goble & Baweja, 2018; Levy et al., 2018). The test consists of three 20 second trials where participants stand on the force plate with feet hip width apart, hands on hips, and eyes closed. The test score is calculated by the BTrackS software and is equivalent to the average total CoP path length in centimeters across the three trials. Poor balance control is defined as a greater test score (increased CoP path length).

To assess vestibular function, the SOT was administered using the EquiTest (NeuroCom International) dynamic postural testing system. The device includes dual-force plates, which can be translated in the anterior-posterior direction or pitched up and down to provoke dorsiflexion / plantar flexion rotations about the ankles, and a visual surround that can be stationary or sway-referenced. During the test, participants stand upright on the force plates, and foot placement is standardized with the medial malleoli of the ankles centered over the axis of rotation of the force plates. A safety harness is worn throughout the test to provide support in the event of a fall. The SOT consists of six conditions, each with three 20-second trials, in which visual, somatosensory, and vestibular stimuli are manipulated. The six SOT conditions have been described in greater detail elsewhere (Pletcher et al., 2017), only conditions 5 and 6 will be described here as they have demonstrated to be moderately correlated ($r \leq .72$) with traditional vestibulo-ocular test results (Evans & Kers, 1999). During condition 5, participants stand on a sway-referenced platform with their eyes closed, and for condition 6, participants stand on a sway-referenced platform with their eyes open and fixed on a sway-referenced visual surround. The best of the 3 trials for each condition is used to calculate an equilibrium score. The equilibrium score is expressed as a percentage and calculated as the angular difference between the maximum anterior-posterior center of gravity displacement and the theoretical maximum of 12.5 degrees. A score of 100 indicates no anterior-posterior excursion, and scores approaching 0 indicate increased excursion (Evans & Kers, 1999). If participants fall during a trial, a score of 0 is given, and foot placement is reset for the subsequent trial.

The 30s Chair Stand test was used as an assessment of lower extremity strength (Cho et al., 2012; Jones et al., 1999). To complete the test, participants begin seated in a chair with no arms and a seat height of 17 inches. With arms across the chest, participants stand and return to a seated position as many times as possible in 30 seconds. The score of the test is recorded as the total number of stands executed properly.

As a measure of executive function, participants completed parts A and B of the Trail Making Test (Arbuthnott & Frank, 2000; Bowie & Harvey, 2006). Part A involves drawing a line connecting numbers from 1 to 25 in ascending order, and part B involves drawing a line connecting numbers (1 to 25) and letters (A to L) in a sequence (e.g., 1-A-2-B, etc.). The outcome measure of the test is the ratio of the time required to complete B/A (Lamberty et al., 1994).

Depression was measured using the BDI-II. A 21-item questionnaire that asks participants to describe how they have felt for the "past two weeks, including today" by rating each symptom on a 4-point scale ranging from 0 to 3 (Beck et al., 1996). Symptom ratings are summed to create a total score ranging from 0 to 63. Higher scores suggest more depressive symptoms.

After participants completed laboratory-based assessments, they were equipped with a heart rate monitor and accelerometer, Polar H10 chest strap (Polar Elector, Bethpage, NY) and Actigraph GT9X Link (Actigraph, Pensacola, FL) respectively. R-R intervals were collected at a rate of 1000 Hz by the Polar H10 sensor and stored on the GT9X Link accelerometer. Collection of R-R intervals began two hours after participants left the lab. The gap in time, allowed participants to return to their normal daily activities prior to collection. Participants were instructed to wear the monitions for 30 hours, including during nighttime sleep, and with exception of when bathing. They were also instructed to continue their normal daily activities inR-R intervals were collected for 28 hours of the 30-hour wear period. To be included in analyses, HRV recordings had to include a minimum of 18 hours of successive R-R intervals, and the entire period of nighttime sleep ("Heart Rate Variability," 1996). When monitors were collected, participants also returned a wear time log that included times monitors were removed for bathing as well as the time participants went to sleep at night and woke up the next morning.

HRV Data Reduction

The Kubios Premium software (Kubios Premium 3.4.1, Biosignal Analysis and Medical Imaging Group, Kuopio, Finland) was used to conduct HRV analysis. R-R intervals were uploaded to the Kubios software following extraction from the GT9X Link accelerometer using the ActiLife software (Actigraph, Pensacola, FL). The time series of R-R intervals was first visually inspected for inclusion of the entire nighttime sleep period. One participant in the fallers group was missing data for a portion of the nighttime sleep period and was therefore removed from analyses. Data was then visually inspected for excessively noisy segments, and identified segments were manually removed. To correct for ectopic beats, an automatic artefact correction algorithm with a 'medium' threshold (0.25 seconds) was employed. Finally, the entire 24-hour time series was used to calculate the time-domain (SDNN) and the non-linear (DFA α_1 and α_2) parameters, and the average of 5-minute segments was used to calculate the frequency-domain parameters (LF and HF Power).

Analysis

Statistical analysis was performed using R (R, Version 4.2.0; R Foundation for Statistical Computing, Vienna, Austria). Models were screened for normality of t residuals using visual inspection of Q-Q plots, and outliers were screened for using Cook's distance. *n* = 2 were identified as outliers in three of the models and were removed from the analysis. Following removal of *n* = 1 participant due to incomplete nighttime HRV data and *n* = 2 identified as outliers, 39 participants were included in data analyses (Table 6). Multicollinearity amongst the independent variables was also assessed by calculating the variance inflation factor (VIF) for each predictor. This was executed by conducting a linear regression with one predictor on all other predictors to obtain the R^2 value and then computing $1/(1-R^2)$. No VIF's greater than 5 were observed (Johnston et al., 2018); thus, all predictor variables were retained in the models. Multivariate linear regressions quantified the associations of the independent variables BTrackS test score (CoP path length), equilibrium scores for SOT conditions 5 and 6, 30s Chair Stand test score (number of sit to stands completed in 30s), Trail Making Test score (ratio of time to complete part B/A), and BDI II score with the dependent variables of HRV indices (SDNN, LF and HF Power, and DFA α_1 and α_2. Models included main and interaction effects for the above independent variables and group (fallers vs. non-fallers). When significant interactions were observed, simple slopes were performed to probe the interaction. When interactions were non-significant ($p > 0.05$), models were refit without interactions. Model fit was assessed using the adjusted R^2 statistic, comparing the full model with all possible interaction terms to the reduced model. Additionally, full and reduced models were compared using Akaike's information criterion (AIC). The statistical model with the lowest AIC reflects the most parsimonious model explained by the fewest variables.

Table 6. Participant Demographics

		Fallers (n=14)			Non-Fallers (n=25)			p
Sex	Male (n)	4			9			
	Female (n)	10			16			
Age (years)		77	±	6.18	72.48	±	4.46	0.012
Height (cm)		163.89	±	11.01	166.33	±	8.95	0.456
Weight (kg)		66.94	±	14.32	74.51	±	12.97	0.100
MMSE		29.07	±	0.73	29.36	±	0.95	0.333
BTrackS		40.50	±	29.70	36.60	±	18.03	0.660
TUG		9.82	±	1.53	9.99	±	1.86	0.771
FGA		22.57	±	2.41	22.04	±	3.55	0.583
Chair Stands		15.71	±	3.24	13.68	±	4.05	0.096
SOT 5		54.93	±	16.77	55.36	±	13.96	0.936
SOT6		44.55	±	19.12	48.94	±	21.19	0.513
Trail Making Ratio		2.53	±	0.91	2.34	±	0.83	0.534
BDI-II		5.57	±	4.70	2.52	±	2.96	0.041
Household Income (n)	\$15,000 - \$29,999	1			1			
	\$30,000 - \$44,999	1			3			
	\$45,000 - \$59,999	0			3			
	\$60,000 - \$74,999	0			4			
	\$75,000 - \$89,999	4			2			
	\$90.000 or above	5			9			
	Chose not to answer	3			3			
Highest Level of Education (n)	Technical School	0			1			
	2 Year College	3			6			
	4 Year College	3			8			
	Graduate School	7			8			
	Professional School	1			2			

Note. Values are reported as mean ± SD, MMSE = Mini Mental State Examination, BTrackS = BTrackS Balance Test score, TUG = Timed Up and Go, FGA, Functional Gait Assessment, Chair Stands = 30s Chair Stand test score, SOT5 = Sensory Organization Test 5, SOT6 = Sensory Organization Test 6, BDI-II = Beck Depression Index II, Household Income = based on annual income for the three years prior to retirement.

Results

SDNN

Full model results are presented in Table 7a. All simple effects ($p > 0.26$) and tests of group interactions ($p > 0.14$) failed to reach significance. Therefore, the model was refit without interactions. In the reduced model (Table 7b), no significant effects of intrinsic fall risk factors on SDNN were observed ($p > 0.27$). The full model explained 36.2% of the variation in SDNN (AIC = 373.06). Removing the interaction terms did not significantly change the proportion of variation explained by the model (adjusted $R^2 = 0.389$, AIC = 352.41, $p = 0.486$).

LF Power

Full model results are presented in Table 8a. All main ($p > 0.10$) and group interaction ($p > 0.15$) effects failed to reach significance; therefore, the model was refit without interactions. In the reduced model (Table 8b), no significant effects of intrinsic fall risk factors on LF Power were observed ($p > 0.31$). The full model explained 52.2% of the variation in LF Power (AIC = 359.21). Removing the interaction terms did not significantly change the proportion of variation explained by the model (adjusted $R^2 = 0.499$, AIC = 340.84, $p = 0.323$).

HF Power

Full model results are presented in Table 9a. All main ($p > 0.18$) and group interaction ($p > 0.39$) effects failed to reach significance; therefore, the model was refit without interactions. In the reduced model (Table 9b), equilibrium score for SOT condition 6 was significantly, negatively associated with HF Power ($\beta = -0.22$, $p = 0.04$). This suggests that as the equilibrium score for SOT condition 6 increases, the HF Power decreases. No other significant effects of intrinsic fall risk factors on HF Power were observed ($p > 0.16$). The full model explained 58.6% of the variation in HF Power (AIC = 324.54). Removing the interaction terms did not significantly change the proportion of variation explained by the model (R^2 = 0.641, AIC = 298.81, p = 0.912).

DFA α_1

Full model results are presented in Table 10a. A significant, negative effect of BTracks score on DFA α_1 was observed (β = -0.01, p = 0.03), and the interaction effect of group and SOT condition 6 approached significance (β = -0.010, p = 0.06), All other simple (p > 0.12) and group interaction (p > 0.06) effects failed to reach significance; therefore, the model was refit without interactions. In the reduced model (Table 10b), the equilibrium score for SOT condition 6 was significantly, negatively associated with DFA α_1 (β = -0.005 p = 0.05), suggesting that as equilibrium score for SOT condition 6 increases, the value of DFA α_1 decreases. Additionally, simple effect of SOT condition 5 trended towards significance (β = 0.004 p = 0.06). No other significant effects of intrinsic fall risk factors on DFA α_1 were observed (p > 0.16). The full model explained 72.8% of the variation in HF Power (AIC = 23.07). Removing the interaction terms did not significantly change the proportion of variation explained by the model (adjusted R^2 = 0.709, AIC = 5.58, p = 0.272).

DFA α_2

Full model results are presented in Table 11a. A significant interaction effects was observed for group × BTrackS test score (β = 0.005, p = 0.05). Simple slopes suggested a negative association in non-fallers (β = -0.01, p = 0.03) but not in fallers (β = -0.002, p = 0.62). All other main effects (p > 0.09) and tests of group interactions (p > 0.06) failed to reach significance. The full model explained only 13.0% of the variation in DFA α_2 (AIC = -42.73).

Table 7. SDNN Model Results

Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	68.91	51.00	0.189	0.362	373.06
Fall	-15.12	35.53	0.674		
Age	-0.43	0.75	0.570		
30s Chair Stands	-0.42	0.65	0.529		
Trail Making	-4.88	8.89	0.588		
BTrackS	0.49	0.43	0.263		
BDI II	0.75	0.81	0.360		
SOT 5	-0.08	0.24	0.742		
SOT 6	-0.16	0.39	0.678		
Fall*30s Chair Stands	1.55	1.00	0.136		
Fall*Trail Making	4.30	11.53	0.713		
Fall*BTrackS	-0.37	0.51	0.470		
Fall*BDI II	-1.28	1.44	0.383		
Fall*SOT 5	-0.34	0.43	0.439		
Fall*SOT 6	0.40	0.47	0.397		
Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	43.37	42.77	0.319	0.389	352.41
Fall	4.14	6.52	0.530		
Age	-0.18	0.66	0.789		
30s Chair Stands	0.07	0.44	0.882		
Trail Making	-6.85	6.11	0.271		
BTrackS	0.05	0.23	0.815		
BDI II	0.43	0.61	0.486		
SOT 5	-0.06	0.18	0.748		
SOT 6	0.22	0.20	0.266		

Note. Fall = group assignment, Trail Making = Part B / Part A, BTrackS = CoP path length, BDI II = Beck Depression Index II, SOT 5 = Sensory Organization Test condition 5, SOT 6 = Sensory Organization Test condition 6.

Table 8. LF Power Model Results

Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	44.24	42.70	0.311	0.522	359.21
Fall	-3.41	29.74	0.910		
Age	0.68	0.63	0.293		
30s Chair Stands	-0.23	0.55	0.683		
Trail Making	-2.16	7.44	0.774		
BTrackS	-0.62	0.36	0.100		
BDI II	-0.80	0.67	0.250		
SOT 5	-0.07	0.20	0.744		
SOT 6	0.30	0.33	0.374		
Fall*30s Chair Stands	-0.87	0.84	0.308		
Fall*Trail Making	-2.07	9.65	0.832		
Fall*BTrackS	0.45	0.43	0.301		
Fall*BDI II	0.92	1.21	0.455		
Fall*SOT 5	0.52	0.36	0.158		
Fall*SOT 6	-0.56	0.39	0.162		
Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	57.31	36.88	0.131	0.499	340.84
Fall	-5.09	5.62	0.373		
Age	0.47	0.57	0.416		
30s Chair Stands	-0.37	0.38	0.332		
Trail Making	1.27	5.27	0.811		
BTrackS	-0.17	0.20	0.391		
BDI II	-0.52	0.52	0.329		
SOT 5	0.01	0.15	0.929		
SOT 6	-0.17	0.17	0.311		

Note. Fall = group assignment, Trail Making = Part B / Part A, BTrackS = CoP path length, BDI II = Beck Depression Index II, SOT 5 = Sensory Organization Test condition 5, SOT 6 = Sensory Organization Test condition 6.

Table 9. HF Power Model Results

Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	27.89	27.38	0.319	0.586	324.54
Fall	20.89	19.07	0.284		
Age	-0.09	0.40	0.829		
30s Chair Stands	0.16	0.35	0.652		
Trail Making	6.63	4.77	0.178		
BTrackS	0.02	0.23	0.929		
BDI II	-0.37	0.43	0.400		
SOT 5	0.06	0.13	0.628		
SOT 6	-0.29	0.21	0.183		
Fall*30s Chair Stands	-0.16	0.54	0.770		
Fall*Trail Making	-3.66	6.19	0.560		
Fall*BTrackS	-0.24	0.27	0.387		
Fall*BDI II	0.47	0.78	0.550		
Fall*SOT 5	-0.16	0.23	0.493		
Fall*SOT 6	0.10	0.25	0.705		
Variable	**Coeff**	**Std.Err.**	***p***	**Adjusted R^2**	**AIC**
Intercept	40.25	21.51	0.072	0.641	298.81
Fall	0.42	3.28	0.899		
Age	-0.14	0.33	0.673		
30s Chair Stands	0.07	0.22	0.764		
Trail Making	4.37	3.07	0.165		
BTrackS	-0.09	0.11	0.454		
BDI II	-0.25	0.31	0.412		
SOT 5	0.01	0.09	0.928		
SOT 6	-0.22	0.10	0.037		

Note. Fall = group assignment, Trail Making = Part B / Part A, BTrackS = CoP path length, BDI II = Beck Depression Index II, SOT 5 = Sensory Organization Test condition 5, SOT 6 = Sensory Organization Test condition 6.

Table 10. DFAα_1 Model Results

Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	1.606	0.574	0.010	0.728	23.07
Fall	-0.294	0.400	0.469		
Age	-0.001	0.008	0.933		
30s Chair Stands	-0.007	0.007	0.341		
Trail Making	-0.059	0.100	0.560		
BTrackS	-0.011	0.005	0.027		
BDI II	-0.015	0.009	0.121		
SOT 5	0.003	0.002	0.209		
SOT 6	0.004	0.004	0.401		
Fall*30s Chair Stands	0.003	0.011	0.761		
Fall*Trail Making	0.042	0.130	0.750		
Fall*BTrackS	0.100	0.006	0.107		
Fall*BDI II	0.014	0.016	0.382		
Fall*SOT 5	0.005	0.005	0.297		
Fall*SOT 6	-0.010	0.005	0.056		
Variable	Coeff	Std.Err.	*p*	Adjusted R^2	AIC
Intercept	1.397	0.501	0.009	0.709	5.58
Fall	0.024	0.076	0.756		
Age	0.001	0.008	0.936		
30s Chair Stands	-0.005	0.005	0.311		
Trail Making	0.009	0.072	0.898		
BTrackS	-0.004	0.003	0.160		
BDI II	-0.005	0.007	0.531		
SOT 5	0.004	0.002	0.056		
SOT 6	-0.005	0.002	0.049		

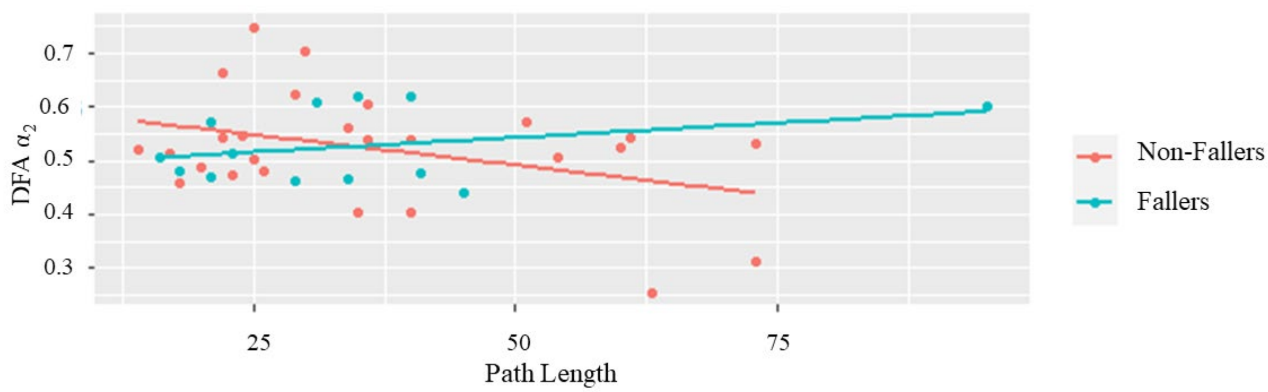
Note. Fall = group assignment, Trail Making = Part B / Part A, BTrackS = CoP path length, BDI II = Beck Depression Index II, SOT 5 = Sensory Organization Test condition 5, SOT 6 = Sensory Organization Test condition 6.

Table 11. DFAα_2 Model Results

Variable	Coeff	Std.Err.	P	Adjusted R^2	AIC
Intercept	0.914	0.247	0.001	0.130	-42.73
Fall	-0.156	0.172	0.373		
Age	-0.007	0.004	0.085		
30s Chair Stands	0.000	0.003	0.904		
Trail Making	0.003	0.043	0.947		
BTrackS	-0.003	0.002	0.110		
BDI II	-0.001	0.004	0.805		
SOT 5	0.001	0.001	0.321		
SOT 6	0.004	0.002	0.070		
Fall*30s Chair Stands	0.005	0.005	0.278		
Fall*Trail Making	0.020	0.056	0.721		
Fall*BTrackS	-0.005	0.002	0.048		
Fall*BDI II	0.002	0.007	0.777		
Fall*SOT 5	0.001	0.002	0.694		
Fall*SOT 6	-0.004	0.002	0.064		

Note. Fall = group assignment, Trail Making = Part B / Part A, BTrackS = CoP path length, BDI II = Beck Depression Index II, SOT 5 = Sensory Organization Test condition 5, SOT 6 = Sensory Organization Test condition 6.

Figure 4. Simple Slopes for the Interaction of BTrackS Score and DFA α_2



Discussion

To confirm the relationship between HRV and fall risk, this study examined associations between intrinsic fall risk factors and HRV parameters in healthy, community dwelling older adult fallers and non-fallers. Participants self-reported whether they had experienced a fall during the 12 months prior to testing (n = 14 fallers, 77 ± 6.18 years, and n = 25 non-fallers, 72.48 ± 4.46 years) and completed five assessments of intrinsic fall risk (BTrackS, SOT, 30s Chair Stands, Trail Making Test, and BDI-II) in a randomized order. Following lab-based assessments, HRV was assessed for 24 hours via a heart rate monitor chest strap in the free-living environment. Multiple regressions were used to examine associations between fall risk factors and HRV.

For the dependent variable DFA α_2, a significant interaction effect ($p = 0.05$) was observed for fall risk group and BTrackS test score (CoP displacement). Post hoc analysis demonstrated a significant negative association in non-fallers ($p = 0.03$) but not in fallers, suggesting that as non-faller's CoP displacement increased (decrements in balance control), the value of DFA α_2 decreased. Figure 4 depicts this interaction and demonstrates that there is a point at which path length and DFA α_2 values begin to look similar for fallers and non-fallers. This interaction point may provide clinically important information regarding the point at which path length and DFA α_2 may indicate increased fall risk. It is important to note that the BTrackS path length score was chosen above other CoP outcomes (e.g., velocity) because it is the outcome measure provided by the BTracks software and represents a clinical accessible measure. Additional CoP outcomes can be derived by performing computations on the raw data collected by the BTrackS force plate; however, this takes time and computational knowledge. Additionally, a normative data set for the BTrackS path length metric has been established with

16,357 community-dwelling individuals ranging from 5 to 100 years old (Goble & Baweja, 2018) and can assist in determining abnormalities in postural sway.

With regard to simple effects, a significant, negative effect of BTracks score on DFA α_1 was also observed ($p = 0.03$), with the simple effect of SOT condition 6 approaching significance ($p = 0.06$). In reduced models without interaction terms, SOT condition 6 was significantly, negatively associated with HF power ($p = 0.04$) and DFA α_1 ($p = 0.05$). This suggests that as SOT condition 6 scores increased (better vestibular function) HF power and DFA α_1 values decreased. Together, these findings demonstrate that alterations in postural control and vestibular function are represented in HRV parameters.

Non-linear measures such as DFA α_1 and α_2 index the unpredictability of a time series, which results from the complex mechanisms that regulate a physiological system, such as the cardiovascular system. In alignment with our hypothesis, poor postural control was associated with depressed non-linear values. However, contrary to what was hypothesized, superior vestibular function was associated with depressed DFA α_1 values. While stressors and disease can depress non-linear measurements, elevated values do not always represent 'health' (Shaffer & Ginsberg, 2017). For example, increased values of non-linear HRV metrics is an independent risk factor for mortality in post myocardial infarction patients (Stein & Reddy, 2005). Thus, with non-linear measures it is best to interpret the magnitude as opposed to the direction of the effect.

In the current study, no effects for the intrinsic fall risk factors lower extremity strength (30s Chair Stands), executive function (Trail Making Test), or depression (BDI-II) on HRV were observed. These findings were surprising as previous work has demonstrated alterations in HRV in response to executive functions tasks and emotion regulation (Lane et al., 2009; Thayer & Lane, 2000). However, based on the BDI-II, no participants were categorized as having greater than mild to moderate depression (score of 10-18 out of a possible 63). Thus, in the current sample, depression may not have impacted fall risk. Furthermore, while the ratio score of Trail B / Trail A was chosen for its utility to assess executive function in older adults (Arbuthnott & Frank, 2000; Drane et al., 2002), the range of scores created may be too narrow to detect an effect. Future research should consider using Trail Making Test Part B as others have suggested that it is a more sensitive measure of cognitive flexibility (Kortte et al., 2002). Finally, regarding the 30s Chair Stand test, to identify fall risk research has suggested a cutoff score of <9.75 chair stands in 30s (Roongbenjawan & Siriphorn, 2020). All participants in both groups completed ≥ 10 chair stands in the allotted 30s; therefore, this assessment may not have been sensitive enough to detect a difference between groups. Future research should consider using a more sensitive measure, such as isokinetic dynamometry, to assess lower extremity strength.

In conclusion, this study observed significant associations between postural control and non-linear HRV indices, as well as vestibular function and non-linear HRV indices. These findings suggest that HRV may be a useful measure of fall risk as it is associated with prominent intrinsic fall risk factors. Additionally, in alignment with previous literature (Rubenstein, 2006), these findings support postural control and vestibular function as primary targets for fall prevention interventions. Caution should be taken when interpreting these results as corrections for multiple comparisons were not applied, increasing the risk for Type I error. Future research should consider assessing the utility of HRV to track changes in intrinsic fall risk factors following preventative interventions as this would further confirm HRV as a valuable fall risk assessment. Furthermore, future studies should examine association between intrinsic fall risk factors and HRV in depressed elderly and in older adults with impaired cognitive function to examine the influence of these factors on HRV and fall risk.

CHAPTER VII: SUMMARY

Fall risk in the older adult population is identifiable and falls are preventable (Ambrose et al., 2013a; Sherrington et al., 2017), yet fall rates continue to increase. One potential reason for lack of attenuation in fall rate may be that traditional fall risk assessments fail to address the multidimensional nature of fall risk. Additionally, majority are the traditional measures are assessed in a controlled environment, negating the dynamic nature of falls. Advances in sensor-based technologies provide opportunity to address these disparities by assessing physiological variables, such as HRV, in the free-living environment. To this end, the purpose of this dissertation was to investigate HRV as an assessment of fall risk in community dwelling older adults. To do so, three separate studies were conducted. The first study examined differences in HRV indices recorded over a 24-hour period in older adults with a history of falls and those with no history of falls. The second study compared the discriminative ability of HRV metrics and traditional fall risk assessments to correctly identify older adults with a history of falls and those with no history of falls. Finally, to confirm HRV as a measure of fall risk, association between intrinsic fall risk factors and HRV were examined.

The findings of study one suggest that the HRV time-domain metric SDNN may provide clinically relevant information to differentiate older adults with a history of falls and non-fallers. In alignment with these findings, the results of study two suggest that in community dwelling older adults, SDNN may be a more accurate measure of fall risk compared to traditional fall risk assessments. However, SDNN did exhibit a high rate of false positives. Finally, results of manuscript three demonstrated that the HRV metrics DFA α_1 and α_2 may be associated with postural control and vestibular function. The association of HRV with prominent intrinsic fall risk factors advocates for HRV as a useful measure of fall risk.

The current study is not without limitations. First, caution must be taken when interpretating findings due to the small sample, and thus reduced statistical power to detect an effect. Second, the current sample was a healthy, community-dwelling population and many of the reported falls occurred during high intensity activities (e.g., playing pickle ball, while dismounting a bike, when hiking). As a result, both groups (fallers and non-fallers) appeared similar regarding fall risk (e.g., scores on traditional fall risk assessments and intrinsic fall risk factors) and may not accurately represent fall risk in the general population.

Future studies examining HRV and fall risk should consider including a more diverse older adult population, including individuals with diagnosis of age-related diseases known to impact fall risk. To improve the specificity of HRV assessment, future studies should also consider employing a time-threshold method, where an alert is triggered after a certain period when a parameter (e.g., SDNN) is above or below a threshold point. Additionally, the accuracy of HRV measures to assess fall risk may be improved by investigating prospective as opposed to retrospective falls. Finally, to further confirm HRV as a valuable fall risk assessment, future research should consider assessing the utility of HRV to track changes in intrinsic fall risk factors following preventative interventions.

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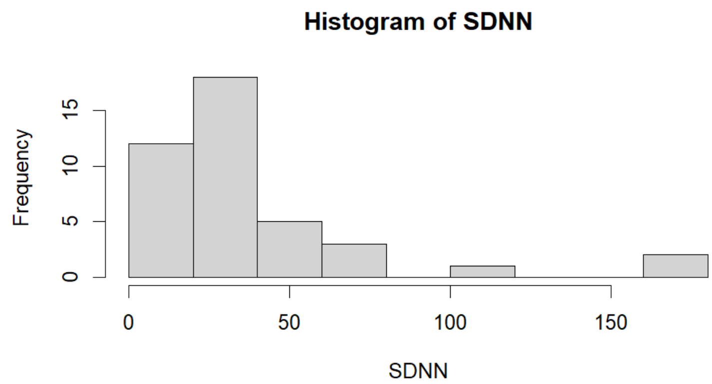
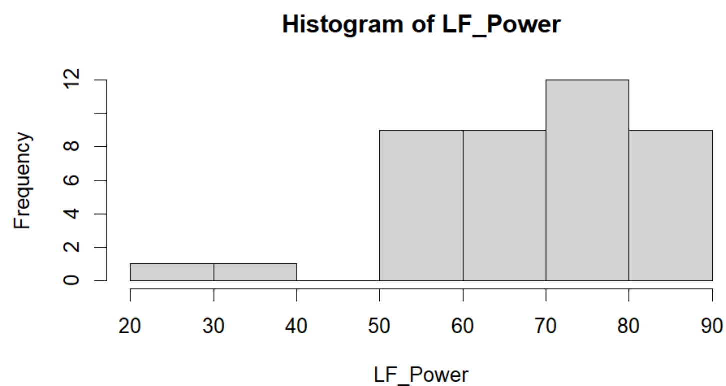
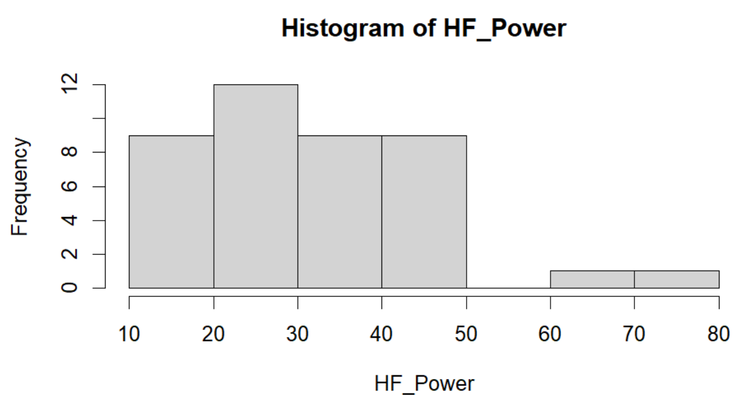
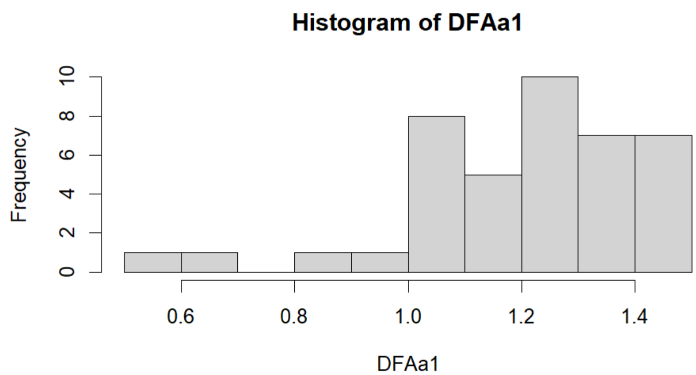
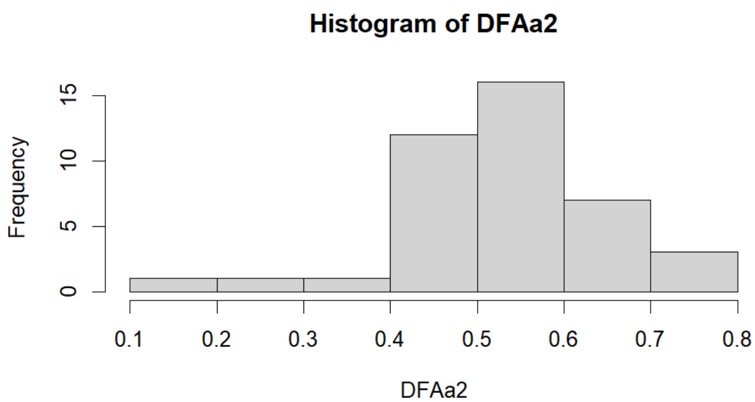
APPENDIX A: RAW DATA DISTRIBUTIONS FOR THE INDEPENDENT VARIABLES IN MANUSCRIPT 1








Histogram of DFAa1
Frequency
0
2
4
6
8
10
0.6
0.8
1.0
1.2
1.4
DFAa1


Histogram of DFAa2
Frequency
0
5
10
15
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
DFAa2