ASSOCIATIONS OF CARDIAC AUTONOMIC FUNCTION AND PHYSICAL FUNCTIONAL CAPACITY WITH SELF-RATED HEALTH IN AGING POPULATION

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Sorola, S. 2021. Sydämen autonomisen toiminnan ja fyysisen toimintakyvyn yhteydet koettuun terveyteen ikääntyvässä väestössä. Liikuntatieteellinen tiedekunta, Jyväskylän yliopisto, Liikuntafysiologian pro gradu -tutkielma, 93 s.

Kuinka yksilö arvioi omaa terveyttään riippuu monimutkaisista psykologisista ja fysiologisista mekanismeista, joita ei hyvin tunneta. Koettu terveys on subjektiivinen, kliininen kyselytyökalu, jonka on havaittu olevan yhteydessä terveystuloksiin ja biomarkkereiden määrään. Fyysinen toimintakyky mitattuna kuuden minuutin kävelytestin kävelyetäisyytenä on havaittu olevan yhteydessä terveystuloksiin iäkkäillä henkilöillä. Samoin sydämen autonominen toiminta mitattuna sykevasteena liikunnan aikana ja sykkeen palautuminen sen jälkeen liittyvät terveyteen. Kuitenkaan kävelyetäisyyden, sykevasteen tai syke palautumisen yhteyksiä koettuun terveyteen ei ole tutkittu. Tämän tutkimuksen tarkoituksena on siis tutkia, että ovatko sykevaste, syke palautuminen ja kävelyetäisyys yhteydessä koettuun terveyteen samalla tavalla. Hypoteesina oli, että koetun terveyden positiivinen yhteys kävelyetäisyyden kanssa olisi vahvempi kuin sykevasteen tai syke palautumisen kanssa.

518 yksilöä 75-, 80- ja 85-vuotiaiden ikäryhmissä osallistui tähän kohorttitutkimukseen. Osallistujat arvioivat terveyttään viiden pisteen koettu terveys asteikolla. Koetun terveyden tulokset koodattiin binäärisesti arvoihin erinomainen/hyvä ja tyydyttävä/huono. Kukaan ei arvioinut terveyttään "erittäin huonoksi". Kävelyetäisyys ja syke mitattiin kuuden minuutin kohdalla. Kävelytestin jälkeinen syke mitattiin 30 ja 60 sekunnin istumisen jälkeen. Sykevaste laskettiin kävelytestin sykearvosta miinus leposyke. Syke palautuminen laskettiin kävelytestin sykkeestä miinus kävelytestin jälkeisestä leposykkeestä, 30 ja 60 sekunnin jälkeen. Chi-neliötesti ja t-testi valittiin analysoimaan merkittäviä eroja luokkien ja keskiarvojen välillä. Pearsonin korrelaatio tutki korrelaatioiden suuntaa ja vahvuutta. Logistinen regressioanalyysi analysoi itsenäisiä yhteyksiä ja mallien ennustavaa tarkkuutta suhteessa koettuun terveyteen.

Koetun terveyden ja sykevasteen yhteys ei ollut huomattava ($p = 0.183$), mutta 30 sekunnin syke palautumisen yhteys oli positiivinen ($r = 0,088$; $p = 0,043$), 60 sekunnin syke palautuminen positiivinen ($r = 0,117$; $p = 0,007$), kävelyetäisyys positiivinen ($r = 0,410$; $p = <0,001$) ja iän kanssa negatiivinen ($r = -0,251$; $p = <0,001$). Syke palautuminen ja sykevaste menettivät yhteytensä koettuun terveyteen, kun adjustoitiin kävelyetäisyyden kanssa. Vain malli 1 (kävelyetäisyys) ja malli 2 (kävelyetäisyys ja ikä) olivat huomattavasti yhteydessä koettuun terveyteen. Mallit ennustivat tarkemmin parempaa koettua terveyttä kuin huonompaa (malli 2: 73,9% vs. 56,3%). Täten vain kävelyetäisyys on itsenäisesti yhteydessä koettuun terveyteen. Tosin tutkimukset osoittavat, että sykevaste ja syke palautus ovat tärkeitä sydän- ja verisuoniterveyden ennustajia ja syke vaikuttaa huomattavasti fyysiseen toimintakykyyn. Epätarkka huonon koetun terveyden ennustaminen johtuu luultavasti ikääntymiseen liittyvistä sairauksista, jotka aiheuttavat vaihtelua kävelyetäisyydessä, joten sairauksien, iän ja fyysisen kunnon kontrollointi on kriittistä. Sydämen autonomisen toiminnan tutkiminen saattaa vaatia kliinisen stressitestin, jotta sekoittavia muuttujia voidaan minimoida.

Asiasanat: Koettu terveys, fyysinen toimintakyky, sydämen autonominen toiminta

ABSTRACT

Sorola, S. 2021. Associations of cardiac autonomic function and physical functional capacity with self-rated health in aging population. Faculty of Sport and Health Sciences, University of Jyväskylä, Master's Thesis in Exercise Physiology, 93 pp.

How an individual rates her or his own health is an outcome of complex psychological and physiological mechanisms not well known. Self-rated health (SRH) is a subjective clinical survey tool, which associates with health outcomes and number of biomarkers. Physical functional capacity (PFC) measured as 6-minute walk test (6MWT) walking distance (6MWD) is associated with health outcomes in aging population. Similarly, cardiac autonomic function (CAF) measured as heart rate response to exercise (HRRTE) and heart rate recovery (HRR) associate with health. However, 6MWD, HRRTE or HRR associations with SRH has not been studied. Thus, the aim of this study is to investigate if CAF measured as HRRTE and HRR and PFC measured as 6MWD associate similarly with SRH. It was hypothesized that SRH positive association with 6MWD would be stronger than with HRRTE or HRR.

518 individuals, in age groups of 75-, 80- and 85-year-olds, participated in this observational cohort study. Participants rated their health based on SRH 5-point scale. SRH results were binarily encoded into excellent/good and satisfactory/poor. No one rated their health as "very poor". 6MWD and heart rate (HR) was recorded at the 6-minute mark. Post-exercise HR was recorded after sitting for 30 and 60 seconds. HRRTE was calculated from exercise HR minus resting HR. HRR was calculated from exercise HR minus post exercise HR after 30 and 60 seconds. Chi-square test and t-test were run to investigate significant differences between categories and means, respectively. Pearson correlations explored the direction and strength of correlations (r). Logistic regression analysis examined independent associations and the predictive accuracy of models in relation to SRH.

SRH association with HRRTE was non-significant ($p = 0.183$), with 30-second HRR positive ($r = 0.088$; $p = 0.043$), 60-second HRR positive ($r = 0.117$; $p = 0.007$), 6MWD positive ($r = 0.410$; $p = <0.001$), and with age negative ($r = -0.251$; $p = <0.001$). HRR variables lost association with SRH when adjusted for 6MWD. Only model 1 (6MWD) and model 2 (6MWD and age) associated with SRH. Model 2 had slightly higher accuracy, but only 6MWD independently associated with SRH. Models were weaker at accurately predicting poorer SRH than better SRH (model 2: 56.3% vs. 73.9%). Thus, 6MWD independently associates with SRH, however, studies show that HRRTE and HRR are important predictors of cardiovascular health, and HR is a critical contributor to PFC. Inaccurate predictions of poorer SRH are likely due to aging-related diseases causing variance in 6MWD, thus control of diseases, age and physical fitness is critical. For future research, study of CAF variables may require graded exercise stress test to minimize confounding factors.

Key words: Self-rated health, physical functional capacity, cardiac autonomic function

ABBREVIATIONS

ANS	Autonomic nervous system
Bpm	Beats per minute
CAF	Cardiac autonomic function
CO	Cardiac output
CVS	Cardiovascular system
ECG	Electrocardiography
HR	Heart rate
HRR	Heart rate recovery
HRRTE	Heart rate response to exercise
PFC	Physical functional capacity
PNS	Parasympathetic nervous system
SNS	Sympathetic nervous system
SRH	Self-rated health
SV	Stroke volume
VO_{2max}	Maximal oxygen consumption
6MWD	6-minute walking distance
6MWT	6-minute walk test

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1 INTRODUCTION

Finnish population is aging rapidly, increasing health-care service demands (Finnish Institute for Health and Welfare 2021). Aging population health status strongly predicts health and social service expenditure, therefore feasible and cost-effective clinical assessment methods are critical. In this regard, the National Research Council (2001) suggests development of research methods that are multidisciplinary, including both psychological and physiological aspects to guide public health policy making.

Health consists of physiological and psychological factors (Card 2017). Further, both factors influence how individuals define their own health (Jylhä 2009). Self-rated health (SRH) is a subjective clinical survey tool used in assessing health. SRH predicts all-cause mortality regardless of age and associates with biomarkers and physical function, however, the exact physiological mechanisms leading to a person assessing their state of health remains unknown (Kananen et al. 2021). Physical functional capacity (PFC) measures the ability to undertake physically demanding activities of daily living and its attenuation associates with declined mental and physical wellbeing in aging population (Guyatt et al. 1985; Oliveira et al. 2019). PFC can be measured by assessing muscle performance, cardiorespiratory fitness, mobility, neuromuscular control, and balance (Kisner & Colby 2012, 2). The 6-minute walk test (6MWT) has been shown to be a valid choice for assessing PFC in aging individuals, to which maximal exercise testing might be too challenging (Troosters et al. 1999). Physiologically, heart rate (HR) strongly contributes to exercise tolerance in healthy humans (Brubaker & Katzman 2011), and subsequently cardiac autonomic function (CAF) has been found to predict cardiovascular health through assessment of heart rate variability, heart rate response to exercise (HRRTE) and heart rate recovery (HRR) (Jarczok et al. 2015; Peçanha et al. 2013; Lauer et al. 1999). Thus, SRH, PFC and CAF associate with health outcomes.

However, 6MWT HRRTE, HRR and walking distance associations with SRH has not been previously studied. This investigation may provide an insight to how objective physiological measures are connected to subjective perception of self-health in aging population.

2 SELF-RATED HEALTH

SRH is widely recommended as a health survey tool (Robine et al. 2003) in terms of disease screening (May et al. 2006) and clinical assessments (Fayers & Sprangers 2002). SRH utilizes a four- or five-point scale system. The wording utilized to describe SRH in the scaling system may vary between studies and researchers, but specifically the World Health Organization (WHO) suggests a five-point scaling of "very good", "good", "fair", "bad", and "very bad" (WHO 1996). A recent study by Kananen et al. (2021) utilized two different kinds of rating methods: (1) "excellent", "very good", "good", "fair" and "poor", and (2) "good", "rather good", "moderate", "rather poor" and "poor". In clinical terms, the patient's selected rating is then compared to normative data of the particular age group to gain knowledge on the patient's health status. SRH has been in frequent use in social health science since the 1950s (Garrity et al. 1978; Maddox 1962; Suchman et al. 1989). However, its beginnings in medical research started from the 1970s, when SRH was discovered to associate with mortality (Mossey & Saphiro 1982; Kaplan & Camacho 1983; Singer et al. 1976).

Unfortunately, the mechanisms behind why SRH associates with mortality or health are poorly understood (Jylhä 2009; Kananen et al. 2021). Further, SRH is a subjective measurement tool, relying on the individual's sensations and feelings of self, therefore the mechanisms prove difficult to measure objectively (Suchman et al. 1958). In this regard, more than hundred studies have been trying to understand the mechanisms through environmental factors and inter-individual variability (Kananen et al. 2021; Jylhä 2009). Despite not knowing the mechanisms behind SRH, studies still show a consistent and strong association between subjective perception of self-health and the objective biomarkers and all-cause mortality (Jylhä 2009; Kananen et al. 2021).

2.1 Defining self-rated health

SRH is different than most health assessment tools because it is based on perception of self without definitions or agreed rules, consequently used in combination with objective measures to assess health (Jylhä 2009). In other words, the process of assessing one's health does not

always follow logical reasoning but may be based on intuition and feeling. However, the selected words to describe health are based on social and cultural norms, therefore, the concepts are defined by the environment and rooted into agreed rules. Below is a framework of the SRH assessment process.

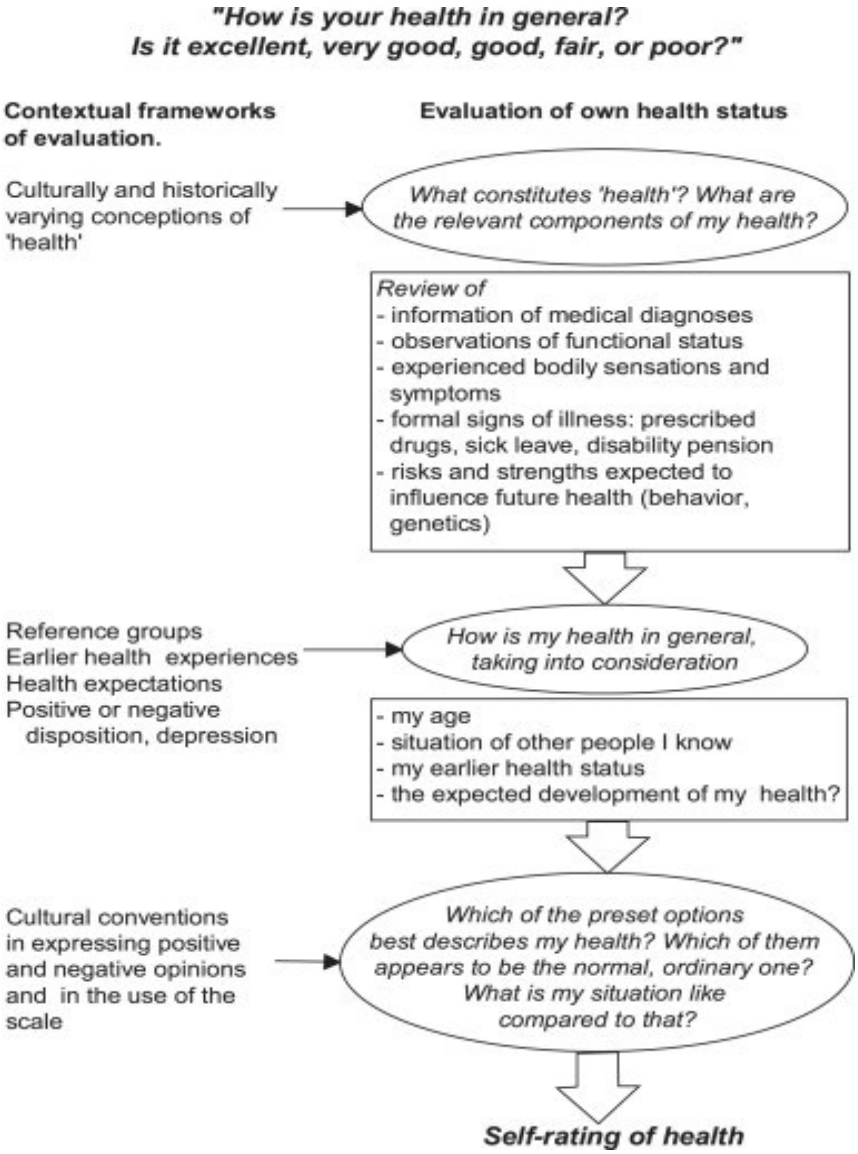


FIGURE 1: The different stages of self-assessment in terms of health (Jylhä 2009). Copyright (2009), with permission from Elsevier

The issue is there is no universal agreement on what "health" specifically means (Jylhä 2009). In other words, it is used generally, but not specifically. From clinical perspective, health is assessed through a process that includes symptoms, laboratory values and functionality. However, how health is quantified does not follow any specific rules (Jylhä 2009). The model (figure 1) suggests how individual perceives health is affected by external influencers such as the environment and culture (Mansyur et al. 2008). Furthermore, although health outcomes can be quantified objectively through assessing physiological changes in the human body, the diagnostic process may still require information from the patient about how they feel, which is subjective and cannot be measured externally (Campbell et al. 2008; Idler et al. 2004). For example, fatigue, pain, ache, and dizziness are about mind-to-body connection, therefore subjective in nature, but may still give information as a sensation to possible underlying health conditions (Knäuper & Turner 2003).

Twin studies show that genetics explain approximately 60% of the SRH variability, whereas the rest is possibly influenced by externally gained knowledge about the state of one's health (Leinonen et al. 2005; Silventoinen et al. 2007). Therefore, in the process of rating self-health, an individual still requires external knowledge about symptoms and diseases, which the person is unable to understand by just feeling a sensation (Jylhä 2009). Moreover, a person who has had a serious injury or disease and has recovered may have more accurate and in-depth understanding on one's health from scale of "very poor" to "very good" (Heller et al. 2008). On the other hand, a person who has never been seriously ill or injured may have a different way to apply the rating scale because lack of dynamic experience about the limits of health (Heller et al. 2008). However, it has been found that older people with chronic diseases are less likely to rate their health lower than younger individuals, who are more sensitive to responding to changes in health (Heller et al. 2008). Therefore, it seems that older people rate their health higher due to being used to having chronic illnesses versus younger individuals. In addition to different experiences about body health, different age groups have age-related social stereotypes, i.e., young are supposed to be healthy whereas older people are likely to have chronic illnesses. Thus, the rating scale should always be referred to standards of the age group to be valid (Tornstam 1975).

2.2 Validity of self-rated health

Several reviews show consistently that SRH is a strong independent predictor of mortality (Benyamini & Idler 1999; DeSalvo et al. 2006; Idler & Benyamini 1997). The relationship has been studied and confirmed in young (Larsson et al. 2002) and old people (Nybo et al. 2003) in European and Asian populations (Jylhä 2009), in patient groups including coronary artery disease (Bosworth et al. 1999), emergency department patients (Wong et al. 2007) and in cognitive decline patients (Walker et al. 2004). However, as previously discussed, the ratings must be compared to allocated age groups, as different age groups perceive health differently (Jylhä 2009). For example, Benyamini et al. (2003) suggests that self-rating of health might be easier for younger individuals, as for them health is commonly perceived as either "good" or "bad", which is mostly based on being either seriously ill or completely healthy. Conversely, older individuals are mostly somewhere in between due to chronic diseases and decline in health and physical function. Thus, the rating process might be more complex for the aging population due to complex health-illness dimensions (Benyamini et al. 2003).

The self-rating of health process is similar for men and women, as shown in figure 1. However, it seems that middle aged and older men value physical functioning more than women, thus physical functioning for men weights more in the rating process. On average, women rate their health worse than men, but this rating is reversed at older ages possibly due to attenuation in physical capacity, which men perceive more negatively. (Zajacova et al. 2017).

SRH is not directly measuring the biological processes leading to death but is a summary of a person's biological status (Jylhä, 2009). Therefore, the perception about one's health in terms of SRH correlates with mortality but is not causative. In other words, a person does not have omniscience about the state of their health, but the accuracy of predicting it can be increased with accumulated internal and external knowledge incorporated into the SRH assessment process. SRH is difficult to quantify, thus, objectively has no gold standard or criterion to confirm validity (Jylhä, 2009). Although death is the strongest biological indicator of health, mortality might not be the best reflection of health because health is more than just either being alive or dead (Lee et al. 2007).

SRH is recommended to be used in clinical trials, health risk assessments, clinical evaluations, and in comparing health status of different age groups (Jylhä 2009). Regarding strengths and limitations, SRH is comprehensively including many variables into the process of health assessment (figure 1), but consequently is non-specific. Therefore, the different aspects of health cannot be separately evaluated through SRH. Concerning feasibility, SRH is powerful and can be applied inclusively in health-care sectors with varied cultures. However, similarly to the age groups, different cultures cannot be directly compared in terms of SRH as an independent variable because cultural groups may perceive health differently (Bardage et al. 2005). Therefore, comparing SRH objectively between countries is not valid, instead, should be utilized within the context of the culture and what it is used to measure (Jylhä 2009).

Adjusting for diseases have been found to significantly attenuate SRH association with mortality if age is not controlled (Jylhä 2009). Vuorisalmi et al. (2005) suggests that this might be because older individuals rate consistently their health as "good" regardless of having number of chronic diseases. Consequently, with older age SRH may not decline as health issues increase. Thus, comparative research questions between age groups would not be directly comparable because the question is dependable on the age of a person (Vuorisalmi et al. 2005). However, when within the context of age and culture, the outcome is sensitive to the subjective perception of an individual, thus SRH can significantly complement a specific diagnosis process (Bjorner et al. 2005, 309-323). Interestingly, in cancer patients, SRH associates stronger with mortality than with symptoms, clinical indicators, or functional performance (Shadbolt et al. 2002). Moreover, functional performance associates with mortality and with SRH in cancer and AIDS patients (Fleishman & Crystal 1998; Shadbolt et al. 2002). In summary, the amount of science-based evidence indicates that SRH is a valid tool as a complementary outcome measure when age and culture are controlled, however, is unable to replace any specific measurement tools.

2.3 Self-rated health associations with physical fitness and biomarkers

A body of research shows significant association between biomarkers and SRH (Christian et al. 2011; Jarczok et al. 2015; Kananen et al. 2021; Saudny et al. 2012; Undén et al. 2007). For example, biomarkers such as hemoglobin, albumin, HDL-cholesterol, white cell count, creatine (Jylhä et al. 2006), triglyceride levels, waist circumference and CRP (inflammatory marker) (Saudny et al. 2012) associate with SRH. On the other hand, a study conducted by Jarczok et al. (2015) did not find associations with SRH and blood pressure, blood lipids or inflammatory markers.

A more recent study conducted by Kananen et al. (2021) found that out of 150 biomarkers 57 had significant association with SRH in almost 15,000 participants. Further, 26 biomarkers retained association after adjusting for physical functioning and number of chronic diseases. However, association between mortality and SRH weakened but did not disappear after adjusting for the biomarkers. Specifically, the biomarkers with significant association with SRH describe the physiological functioning of the human body, such as glucose metabolism, tissue damage, inflammation, and oxidative stress. Interestingly, many of these biomarkers have been reported to be biomarkers of aging (Justice et al. 2018). A number of these biomarkers have been found to associate with cardiovascular diseases as well, such as apolipoprotein B (i.e., LDL carrier protein) (Feng et al. 2018) and circulating cell-free DNA (Jylhävä et al. 2014). However, it is not that an individual is aware of these biomarkers, but they may play a role in the health assessment process, as the biomarkers can change physical sensations and thus transform into feeling of fatigue, influencing the self-rating of health (Kananen et al. 2021). Specifically, perceiving fatigue in aging population has been related to inflammation biomarker C-reactive protein (CRP) (Hughes & Kumari 2018), indicating that humans have a physiological mechanism sensing fatigue and health status, although it is not known how these connections exactly work (Jylhä 2009; Kananen et al. 2021).

Physical functional capacity (PFC), regardless of age, has been shown to associate with SRH in number of studies (Gander et al. 2011; Herman et al. 2014; Kantomaa et al. 2015; Ramírez-Vélez et al. 2017). PFC can be measured in number of ways, including stability, muscle

performance, cardiorespiratory fitness, mobility/flexibility, neuromuscular control, and balance/postural equilibrium (Kisner & Colby 2012, 2). Therefore, PFC association with SRH indicates that individual's rate their health partly based on their ability to undertake physical challenges. In addition, waist circumference and obesity has been found to strongly associate with SRH (Chaparro et al. 2019). Interestingly, it is possible that present information and promotion of the dangers related to obesity have affected the perception of how people relate these visible biomarkers to health (Altman et al. 2016) and consequently affecting how individuals rate their health (Medic et al. 2016). Similarly, the strong presence of fitness lifestyle in the media may influence how individuals perceive fitness and body image (e.g., weight, muscle mass and fat mass). In other words, an individual may rate self-health based on what is socially acceptable. Therefore, social behaviors may influence how health is perceived (Chaparro et al. 2019). These findings indicate that although objective markers indeed associate with SRH, social and psychological aspects, subjective in nature, affect the rating process overall.

Some research has been done on the relationship between cardiac autonomic function (CAF) and perception of self-health. Namely, Jarczok et al. (2015) found that SRH associates stronger with heart rate variability, than with inflammatory biomarkers such as C-reactive protein and white blood cell count. Further, a body of research has been done on the relationship between health-related quality of life and heart rate recovery (HRR) (Li et al. 2019; Öte Karaca et al. 2017; Tsarouhas et al. 2011; Känel et al. 2009). Similarly to SRH, health-related quality of life is used by researchers and clinical practitioners to assess individual's health and disease status (Till et al. 1994). The mechanisms for both systems in predicting cardiovascular-related mortality are unknown but work similarly as strong independent predictors for cardiovascular health (Osibogun et al. 2018; Ko et al. 2015). Therefore, SRH does not imply causation, but correlation with health outcomes. Regardless, only heart rate variability association with SRH has been previously studied, thus investigation of heart rate response to exercise (HRRTE) and HRR association with SRH could further explain the connection between CAF and SRH.

3 AGING CARDIOVACULAR SYSTEM AND EXERCISE

The cardiovascular system (CVS) consists of the heart, blood vessels and blood. The purpose of CVS is to meet the metabolic needs of working muscles and maintain homeostasis in the body (Smith & Fernhall 2011, 1 as cited in Sorola 2020). Cardiovascular fitness or cardiorespiratory fitness describes the performance of the lungs, heart, and vascular system to deliver oxygen and nutrition to muscles (Zeiher et al. 2019). Maximal oxygen consumption (VO_{2max}) is considered as the "gold standard" to measure cardiorespiratory fitness (Zeiher et al. 2019). As a contributor to cardiorespiratory fitness, the working capacity of the heart is studied as an interplay between the amount of blood volume pumped by the left ventricle (i.e., stroke volume (SV)) and heart rate (HR), summating as the cardiac output (CO) (Lavie et al. 2015).

3.1 Heart's response to exercise

The heart has a conductive system that propagates rhythmical impulses from the sinoatrial node to atriums and ventricles to excite chamber contractions. Specifically, the frequency of these electrochemical impulses dictates HR, whereas the intensity of propagation dictates SV (Hill et al. 2012, 57-66). The maximal HR is mainly determined by the cardiac depolarization frequency of the sinoatrial node (Bassett & Howley 2000), whereas the maximal SV is determined by the velocity and force of cardiac muscle contraction (Hill et al. 2012, 57-66). Further, the stretching of cardiac muscle fibers during diastole (i.e., ventricles filling with blood) lengthens the fibers, increasing time to produce force during systole (i.e., blood is pumped out of the heart) (Hill et al. 2012, 57-66). Specifically, SV is the blood volume exiting left ventricle during systolic contraction. However, left ventricle is never fully empty, thus the blood staying in the left ventricle after systole is called end-systolic volume, whereas end-diastolic volume depicts the total volume before contraction. Therefore SV = end-diastolic volume – end-systolic volume (Bruss & Raja 2020).

When exercise intensity increases followed by increased blood flow and pressure, the blood returning to the heart (i.e., venous return) causes additional stretching of the left ventricle. This Frank-Starling mechanism causes stretching and passive tension in the cardiac muscle,

increasing the contraction force and chamber blood volume – leading to higher SV (Han et al. 2019). However, the structure of the left ventricle limits the SV responses to exercise, as a systematic review by Vieira et al. (2016) found untrained and trained individuals are able to increase SV at submaximal, but would plateau at maximal intensities, while HR would increase linearly with exercise intensity. Further, some studies in the review found that untrained individuals experience decreased SV at maximal intensities, which the HR compensates to meet the oxygen demands. Therefore, it seems that HR functions as a compensatory mechanism to decreased or plateaued SV. However, Zhou et al. (2001) found that elite level runner's SV does not plateau (figure 2), indicating that heart's response to exercise may be dependable on both genetics and training status. Excluding elite level athletes, SV plateauing before HR indicates that HR seems to be stronger contributor to maximal exercise tolerance, as suggested by Brubaker et al. (2011). Truly, SV and HR dynamics are highly variable between individuals, depending on age (Paneni et al. 2017), sex (Miller 2020), genetics (van de Vegte et al. 2019) and exercise background (Brubaker et al. 2011).

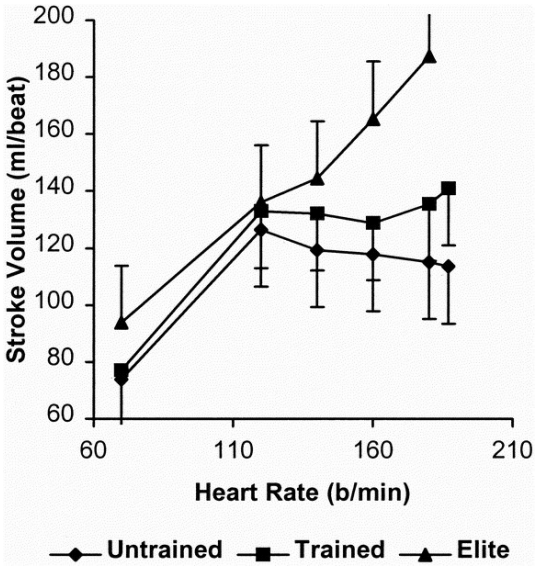


FIGURE 2: SV and HR response from rest to maximal exertion in untrained, trained, and elite runners (Zhou et al. 2001). Copyright (2001), with permission from Wolters Kluwer Health, Inc.

In addition to internal factors, external factors such as weather humidity, environmental temperature and fluid balance cause changes in vascular resistances and blood volume and pressure, leading to changes in HR and SV (Delp & O'Leary 2004; Holowatz 2010). Further, skeletal muscle number and recruitment patterns significantly influence SV and HR dynamics. To elaborate, HR is significantly higher at same intensities in running than in cycling due to running requiring upper body muscles, and both exercise types have different neural patterns and mechanical work (Millet et al. 2009).

3.2 Cardiovascular aging

The underlying mechanisms of cardiovascular aging include mitochondrial oxidative stress, epigenetic changes, genomic instability, and endothelial senescence – leading to collagen accumulation and elastin depletion in tissues (Paneni et al. 2017 as cited in Sorola 2020). Specifically, collagen types I and III, which increase with aging, provide high tensile strength in the heart and blood vessels, causing tissue stiffness (de Souza 2002). Moreover, the elasticity of elastin protects against tissue scarring and high-pressures in the heart and arteries, but its content reduces with age (Protti et al. 2015; Cocciolone et al. 2018). Due to collagen accumulation and reduction of elastin content, the arteries become stiffer, affecting their properties to vasodilate (Shirwany & Zou 2010 as cited in Sorola 2020). Therefore, arterial pressure remains elevated, increasing vascular resistance and cardiac work against blood pressure (Coates et al. 2018 as cited in Sorola 2020). Furthermore, vasodilation has an important role in directing blood flow to working muscles, therefore inhibited vasodilation reduces the oxygen supply and response time to exercise. Further, inhibited vasodilation reduces regulation of body temperature (Holowatz 2010 as cited in Sorola 2020).

The venous valves become thicker and less elastic with aging due to collagen accumulation and therefore restrict venous return (van Langevelde et al. 2010 as cited in Sorola 2020). A study shows that 64-year-olds have 45% reduction in venous compliance in the calves versus 22-year-olds (Olsen & Länne 1998 as cited in Sorola 2020). Thus, venous return can be considerably lower in older adults due to the stiffer valves. Thus, the muscle pump mechanism helping blood to return the heart is attenuated during exercise in older individuals, causing reductions in CO.

As a compensatory mechanism, stiffening of arteries causes a relative increase of SV at peak exercise intensities in older individuals. SV is lower during resting conditions but relatively higher during peak exercise in older versus younger adults because of the age-related delayed diastole and systolic contraction (Houghton et al. 2016 as cited in Sorola 2020). Specifically, SV seems to be higher at peak exercise intensities to function as a compensatory mechanism against diminished ability to empty the left ventricle at contraction due to reduced cardiac elasticity (Fleg et al. 1995; Lakatta & Levy 2003 as cited in Sorola 2020). Fleg et al. (2005) found that HR longitudinally decreases by 4% to 6% per decade, and minimally accelerates with age. This was observed with a longitudinal decline of VO_{2max} by 3% to 6% per decade, which also accelerated with age. Moreover, Strait and Lakatta (2012) found that VO_{2max} is 50% lower in 80-year-olds vs. 20-year-olds. Thus, molecular composition changes in terms of collagen and elastin cause weaker heart function and higher blood pressure gradients, both affectively attenuating CO, elevating SV at peak intensities and significantly reducing maximal HR. Therefore, maximal HR and cardiorespiratory fitness are expected to be attenuated in aging population.

However, cardiovascular aging can be slowed down by exercising (Paneni et al. 2017). Specifically, exercising may cause cardiorespiratory adaptations by increasing particularly SV capacity (Weeks & McMullen 2011). This can be seen especially in those with lengthy exercise backgrounds. The high CO of endurance athletes can be explained with high blood volume, cardiac muscle contractility, cardiac chamber and muscle size and elasticity (Calbet & Joyner 2010). Interestingly, although age-related decrease in cardiorespiratory fitness is inevitable, number of studies in a review conducted by Borges et al. (2016) shows that aging related CVS changes influencing endurance performance are less so affected in master's level older athletes due to higher cardiorespiratory fitness and vigorous exercising. However, it is of worth to note that elite level athlete hormone profile differs from usual reference ranges, and therefore the physiology of an elite athlete should not be used to explain the cardiovascular aging in general population (Healy et al. 2014). Regardless, it has been suggested that aging-related cardiovascular changes are more affected by physical inactivity than by actual biological decrements (Breuer et al. 2010). Therefore, aging individual who is physically active may have significantly different cardiorespiratory fitness and HR values than their sedentary counterpart.

4 CARDIAC AUTONOMIC FUNCTION AND HEART RATE

The sinoatrial node in right atrium, also called the pacemaker, controls CO. The sinoatrial node is unique because it can maintain HR and SV without external neural stimulation from the autonomic nervous system (ANS) (Monfredi et al. 2010 as cited in Sorola 2020). However, ANS has a critical role in optimizing blood circulation to meet metabolic demands of working muscles during exercise (Grotle et al. 2020). ANS is commonly divided into sympathetic nervous system (SNS) and parasympathetic nervous system (PNS). SNS activity increases with exercise intensity, which is also known as the "flight or fight" response. In contrast when exercise intensity decreases, PNS reactivates, also known as the "rest & digest" response. It has been reported that dynamical activity of both SNS and PNS is required for healthy functioning of the cardiovascular system (Parashar 2016 as cited in Sorola 2020). SNS and PNS activation dynamics are based on feed-forward and feed-back mechanisms (Grotle et al. 2020).

4.1 Autonomic nervous system physiology

4.1.1 Feed-forward mechanism

The feed-forward mechanism is primarily controlled by central command consisting of motor cortex, mesencephalic and hypothalamic regions that activate cardiovascular, ventilatory and locomotor functions (Fu & Levine 2013 as cited in Sorola 2020). In terms of feed-forward connection to cardiac function, the sympathetic nerves originate from the thoracic and lumbar regions of the spinal cord (figure 3) (Alshak & Das 2020), whereas vagus (parasympathetic) nerves originate from the medulla of the brain stem (figure 3) (Karemaker 2017). Sympathetic and vagus nerves do not have a direct nerve cell connection from the central nervous system (i.e., the brain and spinal cord) to the heart, but through a ganglion, which works as a relay station for nerves, hence both have pre- and postganglionic nerves (Karemaker 2017). The sympathetic postganglionic nerve terminals release noradrenaline which binds with sinoatrial node, atrioventricular (AV) node, atrial and ventricular cardiomyocyte β adrenergic receptors (figure 3), causing HR acceleration and increased SV (Freeman et al. 2006; Gordan et al. 2015; Mason 1968). On the other hand, the vagal postganglionic nerve terminals release

acetylcholine, binding with SA and AV nodes, left atrial and ventricular cardiomyocyte M2 muscarinic receptors (figure 3), causing HR deceleration and to a lesser extent reduces SV (Gordan et al. 2015). Opposite to SNS, it is important to note that PNS has no nerve terminal connection to the left ventricle, thus has smaller impact on its contraction force – leading to smaller influence over SV, which is indirectly influenced by reducing the contractility of atrial cardiomyocytes (Gordan et al. 2015).

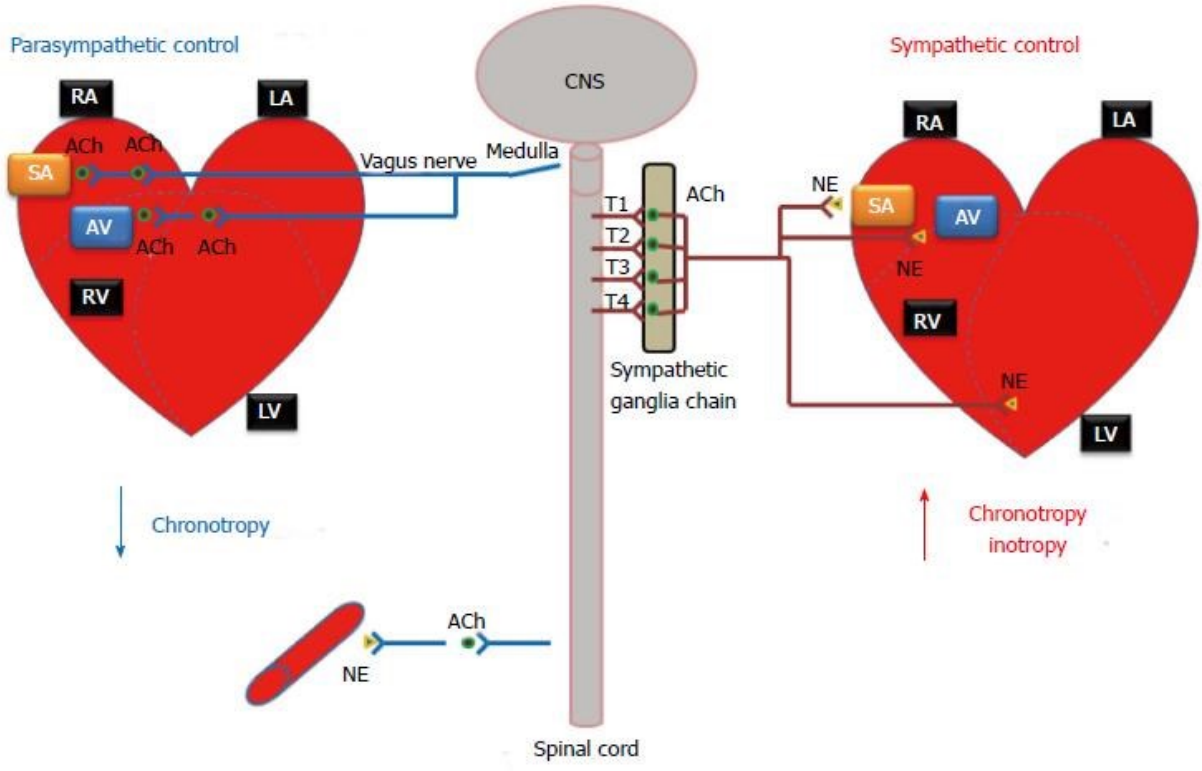


FIGURE 3: Autonomic nervous system regulation of the heart function (Gordan, Gwathmey & Xie 2015). Published by Baishideng Publishing Group Inc. An open-access article.

4.1.2 Feed-back mechanisms

The feed-back mechanisms: exercise pressor reflex and arterial baroreflexes, send information via afferent (sensory) neurons to the cardiovascular control areas in the brain stem (Mitchell 2017). The exercise pressor reflex, consisting of metaboreflexes and mechanoreflexes, originating from working skeletal muscles, affects the sympathetic outflow by the central

command (McCloskey & Mitchell 1972; Michelini & Stern 2009). Specifically, the skeletal muscles can sense metabolites, such as lactate through metaboreceptors, which are connected to afferent neurons (Gujic et al. 2007; Rotto & Kaufman 1988). For example, accumulation of lactate causes the metaboreflex to excite the central command, activating sympathetic outflow to the heart and increasing HR and SV. In addition, mechanoreceptors are sensitive to motor unit recruitment rate in muscles, causing mechanoreflex to excite sympathetic outflow for CVS to meet the metabolic demands in similar fashion (Raven et al. 2006; Gladwell & Coote 2002; Mitchell 2017).

Conversely to the exercise pressor reflex, the arterial baroreflexes excite the parasympathetic outflow. Through baroreceptors located in the aortic arch and carotid arteries, the mechanism senses blood pressure and stretching of arteries, promoting parasympathetic outflow (i.e., reduced HR) into the heart to limit excessive blood pressures (Kaye & Esler 2008). However, it has been found that during exercising the baroreflex sensitivity to blood pressure and HR resets to higher threshold to allow higher exercise intensities without inhibition (Fadel & Raven 2012). In the heart, when PNS activity is mostly dominating, the effects of SNS on heartbeat acceleration are minimal due to PNS acetylcholine secretion inhibiting the secretion of noradrenaline from SNS (Mendelowitz 1999). In terms of response to exercise, PNS affects cardiac function quickly; its response time to stimulus is less than a second whereas SNS response time is from 10 to 15 seconds (Rowell 1997 as cited in Sorola 2020).

4.2 Resting heart rate

PNS dominates HR regulation in resting state (Weissman & Mendes 2021). Interestingly, both PNS and SNS remain active even at rested state, and the dominance between the systems change based on stimulus (Cohen-Solal 1999). In resting condition, SNS still activates nerves to uphold consistent but partial vasoconstriction of the blood vessels. The purpose of the partial vasoconstriction is to maintain a state in the circulatory system that can respond quickly to changes in exercise intensity or body position. This tonic vasoconstriction is partially maintained during skeletal muscle workloads as well, to protect the stability of arterial pressure (Rowell 1997).

The normal resting HR varies greatly between individuals, a typical value ranging from 50 to 90 beats per minute (bpm), and determination of what is considered normal is very difficult due to lifestyle choices and genetics (Nanchen 2018 as cited in Sorola 2020). Resting HR may become slower due to physiological adaptations to aerobic training but may increase because of illness or weakened physical fitness. Further, age does not seem to change resting HR in a healthy person significantly (Stessman et al. 2013 as cited in Sorola 2020). However, a study followed changes in resting HR for 20 years and found that 50 to 60-year-old men with chronic increase in HR were associated with 44% higher risk for all-cause mortality and cardiovascular disease (Chen et al. 2019 as cited in Sorola 2020). Therefore, elevated resting HR may associate with ANS dysfunction and cardiovascular diseases.

4.3 Heart rate response to exercise

The feedback mechanisms signal the central command of sensed physical exertion, causing the feed-forward mechanism to activate sympathetic outflow and reduce vagal outflow, increasing HR and SV. At lower exercise intensities PNS activity on sinoatrial node decreases, increasing HR (Kannankeril et al. 2004). Consequently, SNS becomes dominant in regulating HR and PNS activity almost completely disappears at 50 – 60% VO_{2max} intensity range (Tulppo et al. 1998). Further, it has been found that the vagal tone regulated by PNS withdraws at approximately 120 bpm in healthy young adults (Ogoh et al. 2005). In terms of older population, similar findings have been found as PNS activity seems to be significant still at 100-110 bpm in 59 ± 18-year-olds (Kannankeril & Goldberger 2002).

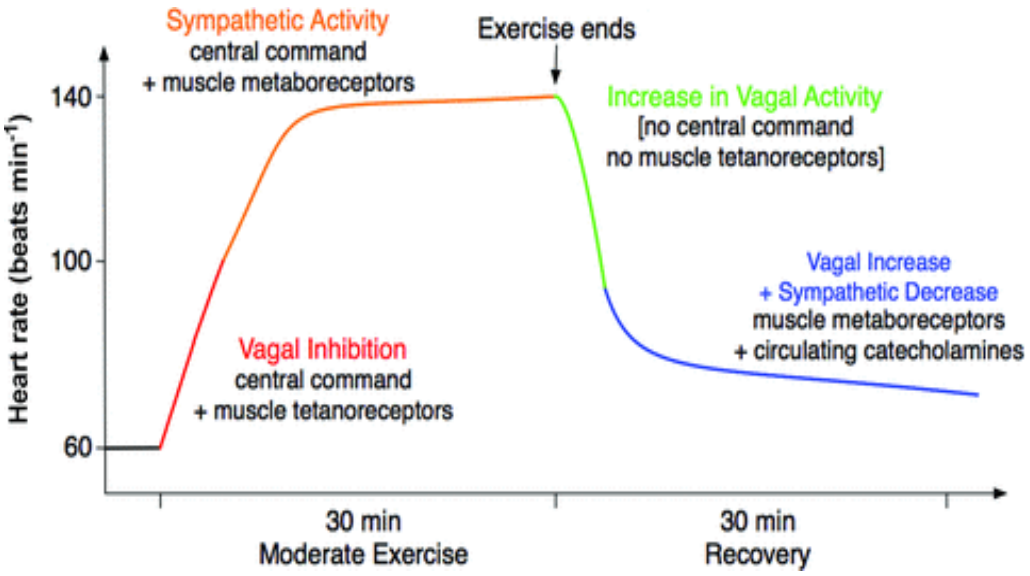


FIGURE 4: Sympathetic and vagal responses to exercise intensity and recovery (Coote 2010). Copyright (2010), with permission from John Wiley and Sons.

As exercise intensity approaches maximal capacity, it is possible that the metaboreflex activates to secure vital organ oxygen demands by stimulating CO, and vasoconstricting blood vessels at non-vital organs and tissues (Ichinose et al. 2010). In addition, SNS vasoconstricts skin and digestive organ blood vessels, whereas working skeletal muscles produce vasodilatory metabolites such as nitric oxide, which promotes vasodilation in local muscles (Fu et al. 2013 as cited in Sorola 2020). Thus, blood flow is directed to working skeletal muscles, which have the least vascular resistance (Guynet 2006 as cited in Sorola 2020). This effectively eases HR and SV work to meet the metabolic needs of working skeletal muscles. However, PNS does not remain passive, as the baroreflex adjusts to higher blood pressure and HR to provide a negative feedback loop in case the blood pressure increases excessively. If excessive pressure triggers baroreflex, PNS activity increases, causing negative chronotropic effect, i.e., reduces HR. Therefore, PNS can still be detected at higher exercise intensities (Rowell 1997).

In terms of response time, the entire CVS takes time to meet the metabolic demands. Specifically, at the beginning of an exercise bout, if exercise intensity remains the same, it takes approximately 2 to 3 minutes for the respiratory and cardiovascular systems to meet the oxygen demands. When the demand is met, HR and SV reach a steady state (Bassett et al. 2000 as cited

in Sorola 2020). However, in exercising lasting more than 10 to 20 minutes, cardiovascular drift (i.e., progressive decline in SV) causes increases in HR although exercise intensity would remain the same (Coyle & González-Alonso 2001; Wingo et al. 2019).

4.3.1 Measurement of heart rate response to exercise

Commonly, heart rate response to exercise (HRRTE) is calculated from peak exercise HR minus resting HR (Bunc et al. 1988; Gulati et al. 2010; Kawasaki et al. 2010; Savonen et al. 2006; Scheidt et al. 2019). However, measuring exercise HR at the end of exercising has been reported, specifically in sub-maximal exercise tests like 6MWT (Girotra et al. 2012). Regarding what is the correct method of measuring HRRTE, HR has been shown to plateau after 30 seconds into 6MWT (Someya et al. 2015) or peak at 6 minutes (Deboeck et al. 2005). Therefore, it seems peak HR and HR at the end of 6 minutes are likely to be at same values in 6MWT. However, significant amount of research shows peak HR does not equal HR at the end of an exercise session, as HRRTE may fluctuate significantly within the same exercise session due to external (i.e., nutrition, water balance, environmental conditions) and internal (i.e., genetics, physiology, age, sex, training status) factors (Achten & Jeukendrup 2003; Bunc et al. 1988; Boushel et al. 2001; Ewing et al. 1991).

To measure HRRTE reliably, exercise test duration, intensity, type, and environment needs to be controlled. The duration of exercise with environmental temperature and humidity cause changes in blood circulation dynamics in terms of body temperature cooling and dehydration, both requiring increased vasodilation of arteries, influencing blood flow and pressure (Delp et al. 2004). Furthermore, cardiac drift increases with exercise duration and environmental temperature (Heaps et al. 1994). Therefore, exercise duration and temperature may influence HRRTE. Further, HRRTE is subjected to exercise type and intensity and can be categorized into (1) delayed heart response to changes in training speed or load (Bunc et al. 1988), (2) S-curved HRRTE to incremental training protocols (Brooke & Hamley 1972), and (3) exhaustion of glycogen supplies as the main source of energy (Stevinson & Biddle 1998).

Due to HRRTE being subjected to type and intensity of exercise, exercise HR is mostly controlled by increasing workload in stages, such as in Bruce protocol. This effectively forces HR to increase with the workload to meet the oxygen demands (Kharabsheh et al. 2006). Therefore, the purpose of reaching peak HR in exercise testing is to maximally elicit sympathetic activation and parasympathetic withdrawal to investigate the maximal difference between resting HR and exercise HR, which equals to HRRTE. Lastly, the type of exercise has a considerable impact on HRRTE. It has been found that at resting state, CO is approximately 5 L/min and may increase up to 8 times if all the large muscle groups are active (Perrey et al. 2010, 148 as cited in Sorola 2020). Thus, how many muscles activate in exercising affects HRRTE.

In addition to how exercise HR is measured, there seems to be disagreement on how to measure resting HR before the exercise test. Studies measure resting HR at different body positions such as in upright standing (Scheidt et al. 2019) and sitting (Kawasaki et al. 2010). In addition, how long a participant stays at the rested state before recording resting HR may vary as well, for example from 2-minutes (Scheidt et al. 2019), 3-minutes (Bunc et al. 1988) to 5-minutes (Kawasaki et al. 2010). Therefore, standard protocols measuring resting HR does not exist, and it has been known for a long time that body position changes HR significantly, although inter-individual variations exist (Macwilliam 1933). Further, the different body position may require different resting durations to achieve homeostasis in terms of HR to record reliable resting values (Hnatkova et al. 2019). Thus, neither resting HR nor exercise HR measurement standards exist, making comparison of HRRTE study results debatable.

4.3.2 Aging-related changes in heart rate response to exercise

Although mechanisms are not fully understood, β-adrenergic receptors have been reported to lose responsiveness to noradrenaline due to aging and it is a plausible cause for decreased HR acceleration and maximal HR (Ferrara et al. 2014 as cited in Sorola 2020). In addition to β-adrenergic receptors, intrinsic HR has been identified influencing HR (Christou & Seals 2008 as cited in Sorola 2020). Intrinsic HR (i.e., HR observed in the absence of ANS influences, done by blocking its function with drugs) is decreased possibly because of collagen

accumulation in sinoatrial node, reducing its electrical signal conductivity (Christou et al. 2008 as cited in Sorola 2020). Moreover, intrinsic HR has been reported to strongly correlate with maximal HR, which both decrease linearly with age (Jose & Collison 1970 as cited in Sorola 2020). Regarding influence of age on HRRTE, Birnbaumer et al. (2020) found that healthy females and males (13–87 years) have been found to have a mean decrease of 8.2 ± 1.9 bpm per decade in graded ergometer testing, in which workload was increased by 20 watts after every minute until volitional failure. Further, individual variability based on aerobic fitness exists as vagal tone of PNS has been observed at higher intensities in aerobically trained, conversely to individuals with poor aerobic capacity (Tulppo et al. 1998). Therefore, SNS and PNS dynamics concerning HRRTE are dependable on age and exercise background.

4.3.3 Heart rate response to exercise as a health and fitness indicator

Attenuated HRRTE or maximal HR, that is considered below normal reference values, is defined as chronotropic incompetence, and has been found to be an independent predictor of cardiovascular mortality (Lauer et al. 1999). Specifically, according to a position statement by Lauer et al. (2005), chronotropic incompetence in defined as failure to reach 85% of age predicted maximal HR (220 – age), or failure to use 80% of age predicted HR reserve (Peak HR−resting HR)/ (220−age−resting HR). According to this statement for professionals, people with chronotropic incompetence have higher rates of mortality and serious cardiac events. This is further agreed as chronotropic incompetence in graded Bruce or modified Bruce treadmill protocol is a risk for clinical outcomes (Girotra et al. 2009), a severity predictor of artery occlusion in coronary artery disease (Brener et al. 1995), independent predictor of all-cause mortality for coronary artery patients (Lauer et al. 1999) and strong independent predictor of all-cause mortality (Dresing et al. 2000). It has been studied that chronotropic incompetence is due to β1 adrenergic receptors of sinoatrial node desensitizing to noradrenaline, released by postganglionic sympathetic nerves (Colucci et al. 1989). Thus, the sympathetic drive to increase HR has been weakened.

Similar predictions in terms of risk of mortality and coronary artery disease have been found in sub-maximal tests like in 6MWT in aging population when HR fails to increase more than 20

bpm (Girotra et al. 2012). However, these associations became non-significant after adjusting for 6MWT walking distance (6MWD). Therefore, HRRTE was not found to be independently predictive of mortality, on the contrary, 6MWD was an independent predictor of mortality and had stronger predictive power than HRRTE (Girotra et al. 2012). It is discussed that chronotropic incompetence is one of the causes for reduced ability to perform physical activities, i.e., termed as reduced physical functional capacity (PFC), hence share the same causal pathway with walking distance leading to risk of mortality and coronary artery disease (Brubaker et al. 2011). This relation has been further confirmed in aging population with cardiovascular diseases, as HRRTE positively associates with PFC in incremental bicycle exercise test (Domínguez et al. 2018). Thus, higher HRRTE contributes to better oxygen delivery to working skeletal muscles, improving PFC (Amann & Calbet 2008).

There seems to be differences between pathological and physiological adaptations to HRRTE in terms of CAF. To elaborate, as previously mentioned, the pathological chronotropic incompetence is due to sinoatrial node receptor desensitization to noradrenaline, indicating sympathetic outflow as the limiting factor. Conversely, physiological adaptations would suggest fast acceleration of HR in healthy individuals is mainly due to quick parasympathetic withdrawal, sympathetic outflow having a lower effect on HR at increasing exercise intensities (Robinson et al. 1966; Rowell & O'Leary 1990; Victor et al. 1987).

4.4 Heart rate recovery

In contrast to HRRTE, heart rate recovery (HRR) is effectively helping cardiovascular function to return to resting homeostasis. Specifically, when exercise intensity and muscle oxygen demand decreases, acetylcholine is secreted by PNS and bound with cardiac M2 muscarinic receptors to slow HR (Kaye et al. 2008 as cited in Sorola 2020) and to a lesser extent cardiac muscle contractility (i.e., reduction in SV), which is mostly controlled by direct SNS nerve innervation to the left ventricle. Therefore, reduction in SV is mostly caused by sympathetic withdrawal, not by parasympathetic reactivation (Gordan et al. 2015). In addition, because acetylcholine inhibits the secretion of noradrenaline (Mendelowitz 1999), the reactivation of PNS inhibits the effects of SNS on the heart. Furthermore, PNS reactivation causes increased

activation of the digestive system, reduced activation of skeletal muscles, reduced bronchodilation in the lungs, increased secretion of insulin by the pancreas and decreased secretion of renin by the kidneys to reduce intravascular blood volume (Alshak et al. 2020).

HRR can be separated into phases based on time. Imai et al. (1994) explored mechanisms of vagal reactivation (i.e., HRR) in healthy adults, cardiovascular disease patients and athletes after a maximal intensity exercise and found that the first 30 seconds after exercising are mostly influenced by the vagal reactivation by PNS (Imai et al. 1994 as cited in Sorola 2020). Another study found a strong correlation with deceleration of HR and noradrenaline reduction after two minutes of exercising and shows HRR is influenced by the SNS withdrawal (Perini et al. 1989 as cited in Sorola 2020). Therefore, HRR can be separated into fast and slow recovery phases, when specified, the fast recovery phase happens during the first 60 seconds post-exercise and is depicted as a rapid decline in HR, and mostly influenced by the vagal reactivation (Coote 2010; Peçanha et al. 2013 as cited in Sorola 2020). The slow recovery phase on the other hand, happens after the 60 seconds in which the recovery speed declines significantly, controlled by both vagal reactivation and sympathetic withdrawal (Coote 2010; Peçanha et al. 2013 as cited in Sorola 2020).

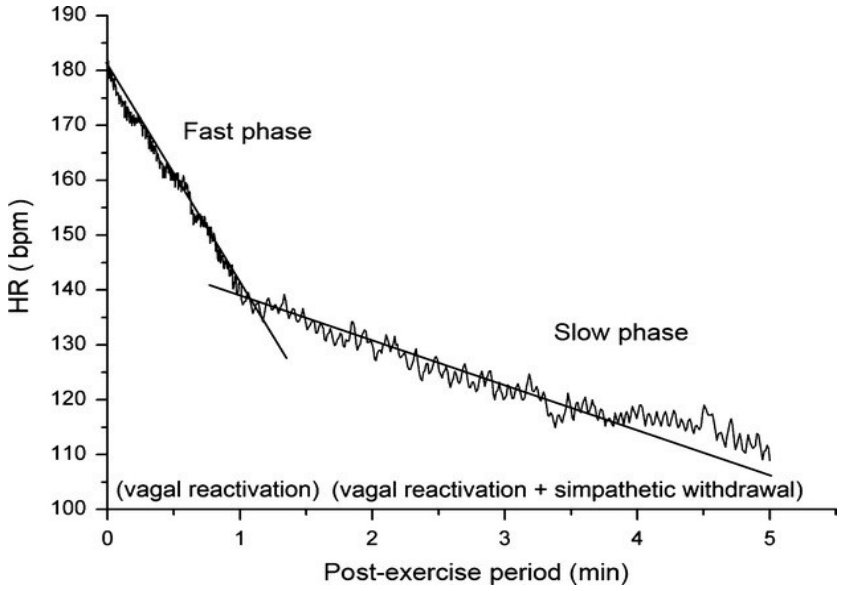


FIGURE 5: Fast and slow phases of HRR (Peçanha et al. 2013). Copyright (2013), with permission from John Wiley and Sons.

4.4.1 Measurement of heart rate recovery

HRR is a simple and relatively inexpensive way to assess CAF with exercise testing (Lauer 2011), and commonly calculated from peak exercise HR minus HR after cessation of maximal exercise (Cole et al. 1999; Buchheit & Gindre 2006). HRR has been assessed in sub-maximal tests as well, like in 6MWT (Lindemberg et al. 2014). However, maximal exercise testing may elicit stronger metabolic accumulation, which causes significant changes in HRR versus sub-maximal testing (Bosquet et al. 2008), thus it is debatable whether HRR of different intensity exercise tests can be reliably compared, and which one might be the most accurate and precise.

There are no internationally accepted HRR protocols, which admittedly affects the reliability of comparing studies or patient recovery results especially in clinical setting (Lauer 2011). For example, HRR has been recorded for 10 seconds (van de Vegte et al. 2018), 30 seconds (Imai et al. 1994), 60 seconds, (Peçanha et al. 2013) and 5 minutes after cessation of exercise (Carter et al. 2001). However, the 60-second HRR has been considered as the standard (van de Vegte et al. 2018). Regardless, comparison of studies with different recording times is questionable since PNS and SNS dynamics are highly dependable on fast and slow recovery phases which are based on time.

Furthermore, the slow phase of HRR after the 60-seconds has been shown to be dependent of exercise intensity (Lamberts et al. 2009 as cited in Sorola 2020). Lamberts et al. (2009) found that HRR in moderately trained healthy young males after supramaximal and sub-maximal test had significantly different reliability values. It is suggested that supramaximal testing elicits stronger metabolic accumulation, which causes significant changes in HRR versus sub-maximal testing (Bosquet et al. 2008). In other words, supramaximal test causes greater PNS suppression and stronger SNS activation, thus HRR is slower (Goulopoulou et al. 2006). At the time of this literature review, it was unclear if similar results and mechanisms can be seen in older adults, but it is reasonable to suggest that HRR might be even slower after maximal exercise in aging population due to the desensitized baroreflex slowly reactivates parasympathetic outflow in older adults (Kaye et al. 2008).

In addition, body position and number of muscles exerted in exercising influences HRR. For example, the first minute of HRR has been suggested to be significantly different after cycle ergometer and treadmill testing protocols (Maeder et al. 2009). Further, sitting and standing recovery or passive and active recovery protocols are not comparable in terms of HR (Barak et al. 2011), and Buchheit et al. (2009) states that sitting, standing and supine HRR protocols may elicit different results.

The absence of standardized HRR testing protocols is a major limitation in clinical and research setting (Lauer 2011). Therefore, it is suggested by Peçanha et al. (2013) that the Bruce treadmill protocol should be selected because it is already widely used. Moreover, as a recovery protocol either a passive recovery with a complete stop to supine position after exercising or an active recovery lasting 2 minutes at set walking speed of 2.4 km/h is recommended. This recovery speed should be achievable by aging population, as Busch et al. (2015) found that a community-dwelling older adult average walking speed is between 2.808 to 3.096 km/h.

4.4.2 Aging and other influencers of heart rate recovery

Aging is linked to decrease in PNS and increase in SNS activity (Kaye et al. 2008 as cited in Sorola 2020), thus HRR has been reported to become slower with aging (Gagné et al. 2014 as cited in Sorola 2020). In addition, number of studies show that HRR abnormalities increase with age (Cole et al. 1999; Vivekananthan et al. 2003; Watanabe et al. 2001 as cited in Sorola 2020). It seems some debate exists: HRR has been shown to be similar between young (20-30) and middle aged (40-50) individuals (Trevizani et al. 2012 as cited in Sorola 2020). However, Watanabe et al (2001) suggests that abnormal changes in HRR happen at 65±10-year-olds, indicating that participants in Trevizani et al. (2012) study were not old enough (40-50 years old) to see significant differences in HRR. In broader sense, age does play a factor, as children have considerably faster HRR than adults (Buchheit et al. 2010 as cited in Sorola 2020).

It is not very well studied what is considered as normal HRR in healthy aging population (Jouven et al. 2005). Regardless, it is suggested that PNS reactivation declines with aging and may result in constant elevated HR and blood pressure, causing increased sympathetic and

suppressed parasympathetic outflow (Masi et al. 2007). The mechanisms behind aging and PNS are not well understood because of indirect measurement methods used such as HR variability (Kaye et al. 2008 as cited in Sorola 2020). It has been suggested that reduced density of M2 muscarinic receptors occurs with aging and might be one of the reasons for declined PNS reactivation (Brodde et al. 1998 as cited in Sorola 2020). A more widely studied association is with the baroreceptor reflex and weakened PNS activation (Kaye et al. 2008). It is believed stiffened arteries inhibit the baroreflex receptors from sensing the changes in blood pressure and therefore PNS reactivation is weaker, thus blood pressure and HR remain elevated (Holowatz 2010; Monahan et al. 2000 as cited in Sorola 2020).

The studies have been inconsistent in finding differences between males and females in terms of HRR. For example, a study conducted by Carter et al. (2001) found no significant differences between men and women, whereas Kligfield et al. (2003) found women had faster HRR. However, participants in the first study were healthy and the latter had cardiovascular disease patients. Therefore, the studies cannot be directly compared.

4.4.3 Heart rate recovery, health and exercise performance

HRR has not just been proven to be an index in evaluating CAF, but relationships with cardiovascular risk factors and diseases have been identified, including risk for heart failure, diabetes mellitus, coronary artery disease and hypertension (Racine et al. 2003; Sacre et al. 2012; Lipinski et al. 2004; Erdogan et al. 2011 as cited in Sorola 2020). Therefore, HRR works as a powerful tool for predicting mortality and health (Peçanha et al. 2013 as cited in Sorola 2020). It has been reported that weaker PNS and stronger SNS activation may become a chronic autonomic dysfunction, which has been related to cardiovascular disease due to chronic elevation of blood pressure and HR (Buch et al. 2002; Gerritsen et al. 2001; Thayer & Lane 2007 as cited in Sorola 2020).

Normal HRR reference values are not well-studied in healthy population, but it has been suggested that HRR of 25 bpm in the first passive recovery minute is a cut-off point for increased mortality risk for healthy persons after maximal exercise (Jouven et al. 2005 as cited

in Sorola 2020). In addition, slower HRR than 12 bpm within the first recovery minute is considered abnormal for people with chronic illnesses and weak physical fitness (Cole et al. 1999; Peçanha et al. 2013 as cited in Sorola 2020). The standard of HRR <12 bpm threshold is a finding from a study conducted by Cole et al. (1999), that included 2428 adult participants (mean age 57 ± 12 years; 63 % men) with cardiovascular disease history. The participants performed a maximum effort treadmill exercise test followed by an active recovery on a treadmill for 2 minutes. It was found that lower than 12 bpm HRR value within the first recovery minute was strongly predictive of death (relative risk, 4.0; 95% confidence interval, 3.0 to 5.2; P<0.001). Specifically, 639 of the participants had abnormally low HRR of whom 213 died from all causes. It was discussed that the underlying mechanism is the slow vagal reactivation of PNS in response to cessation of exercise, regardless of age range (45-69) or peak exercise intensity present in the study (Cole et al. 1999 as cited in Sorola 2020). Therefore, HR should recover more than 12 bpm within the first 60 seconds after cessation of exercise in middle aged to older adult cardiovascular patients to be considered normal, whereas 25bpm HRR is expected from healthy adults Jouven et al. (2005). Further, a review conducted by Okutucu et al. (2011) found that what is considered abnormal HRR varies greatly between studies; after ramp or Bruce protocol the threshold varied from 47 bpm to 6.5 bpm at first minute of rest (passive recovery). The thresholds were based on the power of predicting all-cause mortality. Such variance in HRR threshold seems to be due to participants having different testing methods, cardiovascular diseases, and diseases at different stages.

The exact mechanisms of how HRR is connected to health remains unclear (Qiu et al. 2017). However, evidence suggests there is a direct relationship between cardiorespiratory fitness and HRR (Cole at al. 1999 as cited in Sorola 2020). Moreover, HRR is closely associated with all-cause mortality and risk for cardiovascular events (Campos 2012 as cited in Sorola 2020). Furthermore, ANS is in a major role of maintaining glycemic homeostasis, therefore, connected to diabetes mellitus. Specifically, PNS stimulates the release of insulin, whereas SNS inhibits its secretion (Kiba 2004 as cited in Sorola 2020). Therefore, slow HRR indicates weak PNS reactivation and more active SNS, which promotes glucose toxicity (Campos 2012 as cited in Sorola 2020).

PNS activity has been related to heart antiarrhythmic events. In other words, PNS stimulates the stability of heart rhythm, and therefore a slow HRR – connected to slow PNS reactivation, is a predictor of cardiac arrhythmia (Lauer 2009 as cited in Sorola 2020). Interestingly, a 20-year follow-up study by Mora et al. (2003) discovered that low HRR and exercise capacity in exercise testing (Bruce treadmill protocol) are independently associated with risk of all-cause and cardiovascular mortality in symptomless women, whereas electrocardiography ST-segment depression of at least 2 mm during exercise testing had no significant relationship with mortality risk.

Poor VO_{2max} values have been reported to strongly associate with abnormal HRR (HRR < 12bpm) (Cole et al. 1999 as cited in Sorola 2020). However, abnormal HRR seems to be reversable: improved physical fitness in rehabilitation programs has been found to increase HRR in cardiovascular disease, overweight and coronary artery patients (Myers et al. 2007a; Kline et al. 2013; Legramante et al. 2007 as cited in Sorola 2020). It is believed HRR association to exercise performance is due to ANS adaptations to repetitive physical stress, which allows faster switching between sympathetic and parasympathetic outflows (Al Haddad et al. 2011; Lamberts & Lambert 2009). This relationship has been further confirmed in aging population, as a review conducted by Wichi et al. (2009) suggests that chronic exercising increases the sensitivity of baroreflex to reactivate parasympathetic outflow and decreases the sympathetic outflow, thus prevents aging related negative ANS changes in older adults.

5 SIX-MINUTE WALK TEST AND PHYSICAL FUNCTIONAL CAPACITY

Physical functional capacity (PFC) measures individual's ability to undertake physically demanding activities in daily living, and associates with mental and physical wellbeing in aging population (Guyatt et al. 1985; Oliveira et al. 2019). Specifically, PFC is a summation of stability, muscle performance, cardiorespiratory fitness, mobility/flexibility, neuromuscular control, and balance/postural equilibrium (Kisner & Colby 2012, 2). 6MWT is commonly used to assess PFC in terms of distance walked (Cahalin et al. 2013). In addition, 6MWT has been used in studies to assess both HRRTE (Girotra et al. 2012) and HRR (Lindemberg et al. 2014), especially in aging population and cardiovascular disease patients. However, 6MWD has been the traditional outcome variable (Duncan et al. 2015), instead of HRRTE or HRR. This indicates that 6MWT is used for assessing PFC of an individual instead of CAF. Further, PFC association with SRH has been found at different age ranges (Gander et al. 2011; Ramírez-Vélez et al. 2017; Herman et al. 2014; Kantomaa et al. 2015), but specifically 6MWD association with SRH remains unclear.

5.1 Protocol

6MWT is recommended to be conducted on a flat surface, preferably indoors, in a space of at least 30 meters long (Holland et al. 2014). Pre-testing baseline measurements of HR, blood pressure, oxygen saturation and Borg scale rating should be taken. Subsequently, the patient is familiarized with the testing process. The testing field should be marked every three meters and an indication of a turnaround should be at 30 meters at each end. The participant is allowed to select the walking speed but is encouraged by a supervisor to walk at the best of her/his abilities, furthermore, she/he is allowed to stop and rest periodically (ATS Statement, 2002). The encouragement should be a standard procedure since it has been shown to affect results (Morales Mestre et al. 2018). After the 6 minutes, Borg scale, HR, blood pressure and oxygen saturation are taken. Lastly, the distance covered, and number of laps are recorded (Holland et al. 2014). It has been suggested that the test should be done twice due to learning effect may influence the results (Spencer et al., 2018). It is of worth to mention that 6MWT is modifiable and it is common to see variations, especially in the distance between the turnaround points.

Although 6MWT is safe, it still has contraindications including uncontrolled arrythmia, myocardial infraction, acute myocarditis, uncontrolled acutely decompensated heart failure, suspected dissecting aneurysm, acute pulmonary embolism, acute noncardiopulmonary disorder, acute respiratory failure and cognitive impairment impacting inability to cooperate. Further, relative contraindications are systolic blood pressure >180 mm Hg or diastolic pressure >100 mm Hg and resting HR >120 bpm. The test should be immediately stopped if the participant has excessive sweating, chest pain, leg cramps, excessive shortness of breath or not feeling well (Holland et al. 2014).

5.2 Validity, reliability and feasibility

Although the 6MWT protocol guidelines have been updated quite recently (Holland et al. 2014), several protocol variations are still being used, limiting the validity of comparing the results (Giannitsi et al. 2019). Some studies use 15- (Mänttäri er al. 2018), 20- (Lipkin et al. 1986), 30- (Guyatt et al. 1985) and 50-meter corridors (Troosters et al. 1999), raising a concern in terms of reliability. To elaborate, the frequency of turning might impact the total walking distance. However, a study conducted by Sciurba et al. (2003) suggests that straight courses from 15 to 50 meters have no significant differences in walking distance travelled, but oval shaped courses produced significantly longer walking distances in patients with emphysema. Regarding the normative values of walking distance, a range from 400 to 700m has been reported in healthy adults (Enright 2003). Walking distance of less than 300m is associated with increased mortality rate in post heart failure patients (Cahalin et al. 2014). However, standardized reference values have not been developed due to the aforementioned issues concerning lack of 6MWT standard protocol utilization.

Moreover, cognitive impairment and depression have been shown to decline the accuracy of 6MWT by reducing the distance walked during the test (Reybrouck 2003) and has been reported to unreliably show changes in walking distance in cardiac transplant patients (Cheetham et al. 2005). Further, as the purpose of 6MWT is to generally assess PFC of a person, it fails to consider specific areas of exercise limitations included in many clinical maximal exercise test protocols, such as musculoskeletal, pulmonary, or vascular, which may have different

physiological mechanisms that confound with each other (Garin, et al. 2009). Regardless, the reliability of 6MWT is very good when standard protocols are followed by an experienced healthcare or clinical exercise physiology professional (Beriault et al. 2009). The reliability of 6MWT has been shown to be high (Intra class correlation = 0.93) in the aging population and patients to assess PFC (Wright et al. 2001).

6MWT has been shown to be a valid test to estimate VO_{2max} (Mänttäri et al. 2018). Mänttäri et al. (2018) compared maximal graded exercise testing VO_{2max} and 6MWT VO_{2max} with utilization of portable gas analyzer and found that prediction of VO_{2max} is similar with an accuracy of 1 MET (metabolic equivalent, i.e., oxygen consumption of 3·5 ml min−1kg−1) in healthy adults (19- to 75-year-olds). However, Guyatt et al. (1985) found that 6MWT correlates with the quality-of-life measure (i.e., a person's perception about their position in life) better than with VO_{2max}. Further, Venkatesh et al. (2011) reported 6MWT might be more valid for cardiovascular patients than for healthy adults to estimate $VO2_{max}$. It is further agreed, that 6MWT strongest indicators in clinical setting are the medical intervention effects on patients with moderate to severe lung or heart disease (ATS Statement 2002). Regardless, the findings by Mänttäri et al. (2018) are reliable, as the new technological advancements in terms of portable gas analysis equipment has opened new testing options that have not been available for the older studies.

Maximal exercise testing has been the default for assessing physical fitness, diagnosis, risk assessment and exercise tolerance for rehabilitation purposes and is commonly performed on a bicycle ergometer or treadmill Venkatesh et al. (2011). However, testing equipment is laboratory based with limited portability, requiring specialized expertise on health and diseases and therefore expensive to conduct. On the other hand, submaximal testing can be more feasible, portable, and safer especially for the frail aging population and cardiovascular disease patients who are unable to perform maximal exertion tests (Venkatesh et al. 2011). 6MWT has been used for assessing response to treatment, as functional walking performance changes in patients with lung (Butland et al. 1982) or heart disease (Faggiano et al. 2004). In addition, walking speed in 6MWT has been associated with mortality and morbidity (Harada et al. 2002). Furthermore, 6MWT has been validated to work as an alternative method to maximal exercise testing for cardiovascular patients in terms of risk stratification (Alahdab et al. 2009; Guazzi,

Dickstein et al. 2009). Lastly, regarding the aging population, a study conducted by Peeters and Mets (1996) found that one out of five is unable to perform maximal exertion tests due to cognitive and physical performance decline.

Although 6MWT is commonly used to assess PFC in terms of distance walked within 6 minutes (Cahalin et al. 2013), it has been used to assess both HRRTE (Girotra et al. 2012) and HRR (Lindemberg et al. 2014), especially with aging population and cardiovascular disease patients. In clinical setting, the validity of HRR seems not to be dependent on maximal exercise intensity in patients with cardiovascular conditions as two studies found terminating exercise test at 85-90% of age-predicted HR max did not significantly influence the study prognosis index (Cole et al. 2000; Morshedi-Meibodi et al. 2002). Moreover, a study conducted by Cahalin et al. (2013) discovered that HRR measured after 6MWT in participants with past heart failure was stronger predictor of cardiac related deaths than distance walked and behaves similarly to HRR measured after a maximal exercise test. In the same study, maximal exercise testing and 6MWT were compared with HRRTE. Interestingly, the cardiac responses were reported to be similar regardless of testing intensity; mean maximum HR in 6MWT was 122 ± 16 bpm, whereas in maximal testing 129 ± 17 bpm. However, the study did not investigate if the mean maximum HR was statistically different between the tests in terms of p-value.

Regarding ANS response to 6MWT, the balance between SNS and PNS might be better during sub maximal testing in heart failure patients, consequently promoting stronger PNS reactivation, therefore positively affecting how quickly HR recovers (Chua et al. 1997). Besides to validity of 6MWT HRR as a predictor of mortality, in addition to previously mentioned applicability and feasibility advances over maximal exercise tests, the aging population seems to poorly tolerate the maximal testing protocols that require a nose clip and mouthpiece (Cahalin et al. 2013).

5.3 Independent contributors to six-minute walking distance

A study with sample size of 51 found that sex, age, height, and weight constitute 66% of the distance walked in 6MWT by healthy individuals aged from 50 to 85 years (Troosters et al.

1999). Another study with sample size of 290 including healthy 40- to 80-year-olds reported that the same variables constituted 40% of the distance walked (Enright & Sherrill 1998). In addition, it was noted that age and weight were significant influencers in both men and women. Moreover, a cross-sectional study with a sample size of 1187 men and 2721 women who were functionally independent found that 5-year difference in age significantly declines the distance walked, which impacted men less (Rikli & Jones 1999). Further, 6MWD in the aging population is mostly studied in terms of obesity (Hulens et al. 2003), diseases impacting musculoskeletal function (Bean et al. 2002) and aerobic capacity decline due to cardiovascular and pulmonary disease (Miyamoto et al. 2000; Opasich 2001; Solway et al. 2001). It is not exactly known how a specific disease affects the distance walked since in clinical practice patients commonly have more than one disease or symptom. Lastly, HR has been shown to be strongest contributor to aerobic fitness (Higginbotham et al. 1986), and HR and 6MWD have an important link leading to health outcomes Brubaker et al. (2011).

6 PURPOSE OF THE STUDY AND RESEARCH QUESTIONS

The purpose of this study is to investigate the associations of HRR, HRRTE and 6MWD with SRH in aging population.

Question 1: What is the strength of association and direction of HRRTE and HRR with SRH?

Hypothesis 1: Attenuated HRR and HRRTE have been shown to be independent predictors of mortality (Cole et al. 1999; Lauer et al. 1999). Similarly, SRH is a strong independent predictor of mortality (DeSalvo et al. 2006; Benyamini et al. 1999; Idler et al. 1997). Thus, it is hypothesized HRR and HRRTE would have positive association with SRH.

Question 2: What is the strength of association and direction of SRH with 6MWD?

Hypothesis 2: Number of studies show PFC associates with SRH (Gander et al. 2011; Ramírez-Vélez et al. 2017; Herman et al. 2014; Kantomaa et al. 2015). The main function of 6MWD is to assess a person's PFC (Enright et al. 2003). Thus, it is hypothesized 6MWD would have positive association with SRH.

Question 3: Does HRR or HRRTE independently associate with SRH when adjusted for 6MWD?

Hypothesis 3: Girotra et al. (2012) found 6MWT HRRTE association with mortality disappeared after adjusting for walking distance. Interestingly, Cahalin et al. (2013) suggests HRR is stronger predictor of mortality than 6MWD in heart failure survival patients. However, this might be due to severely impaired CAF related to heart failure. Thus, it is hypothesized HRR or HRRTE do not independently predict SRH when adjusted for 6MWD.

7 METHODS

This Master's Thesis uses data from the observational 'Active aging – resilience and external support as modifiers of the disablement outcome' (AGNES) study. The AGNES study participants were selected from the population register, using three age groups (75, 80 and 85 years) as a criterion. The residential area had to be within a 10-kilometer radius of the center of Jyväskylä or local public transport within reach. Other inclusion criteria for study participants were independent living and ability to communicate (Rantanen et al. 2018). The study protocol followed phases of: (1) initial information letter and phone contact (n = 2348), (2) phone interview (n = 1887), (3) postal questionnaire and face-to-face at-home interview (n = 1021), and (4) assessments in the research center of Faculty of Sport and Health Sciences of the University of Jyvaskylä, Finland (n = 910). Finnish language was used throughout the phases and the data was collected between 2017 and 2018 (Portegijs et al. 2019; Rantanen et al. 2018).

7.1 Participants

To answer the research questions of this observational master's thesis study, SRH, age, sex, and cardiovascular medication information were collected from the postal questionnaires and face-to-face at-home interviews. The medication use was collected from the postal questionnaires, in which the participants were asked to report all physician prescribed medications. In addition, 6MWT, orthostatic test results and HR recordings from the research center assessments needed to be collected. Therefore, the inclusion criteria required that the participant had SRH questionnaire and 6MWT test completed, in addition, HR recorded in resting, walking and recovery phases. Consequently, out of the 910 participants who participated in the research center assessment phase of the AGNES study, 45 were excluded due to no 6MWT data, 1 had no resting HR data, 278 did not have HR recordings, and lastly 58 were excluded because of ECG (electrocardiography) artifacts including physiological reasons (e.g., irregular heartbeats) and noise, both causing unreliable interpretation of HR. Therefore, 528 were selected for this Master's Thesis study, of which 209 were males and 319 females. Similarly to the AGNES study, this study had three age cohorts of 75 (n=283), 80 (n=152) and 85 (n=93) years.

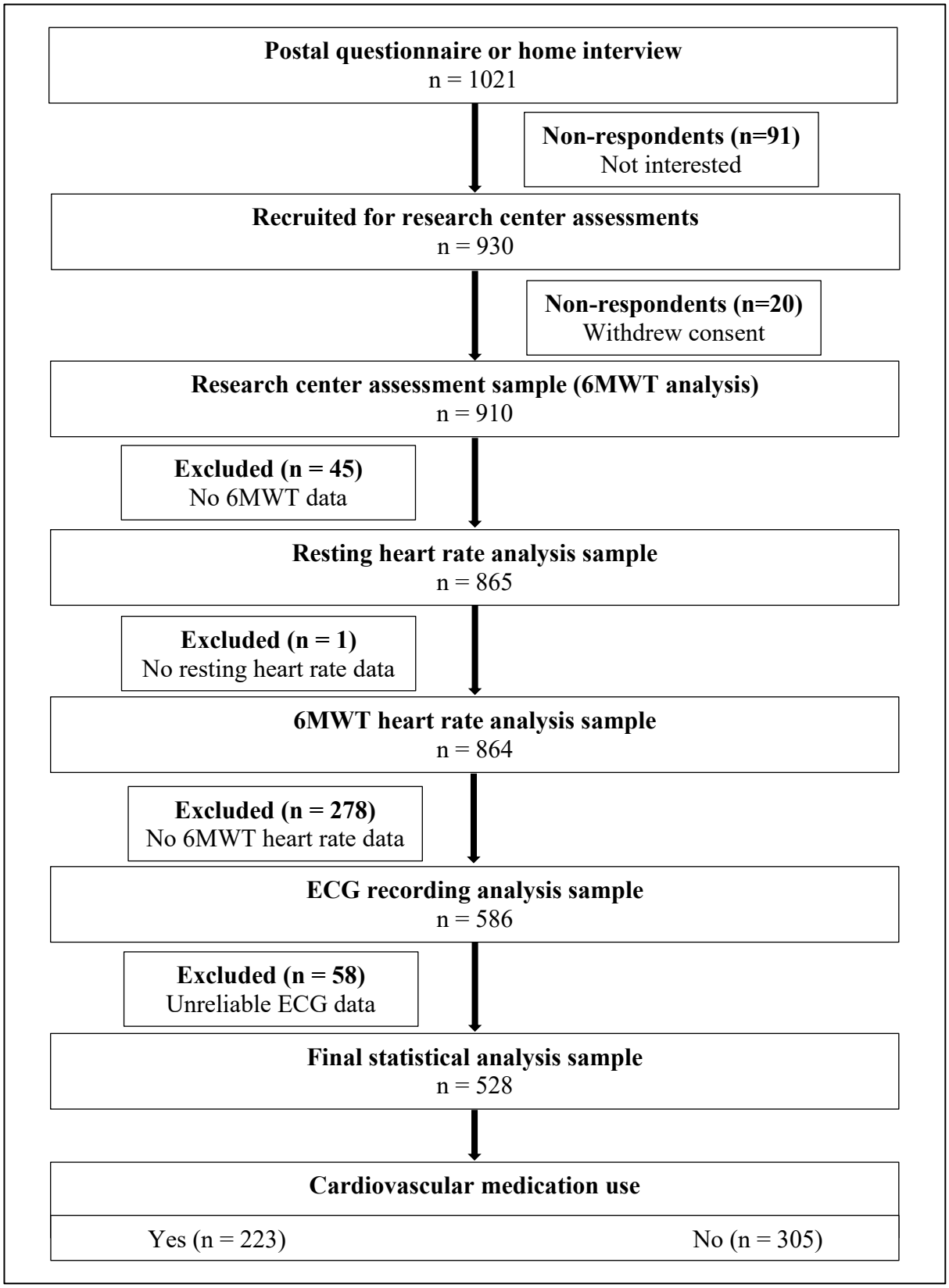


FIGURE 2. Exclusion flow chart and cardiovascular medication use (i.e., beta blockers, calcium channel blockers, antiarrhythmics).

During the home interview, the participants were given verbal and written instructions for preparation of the assessments in the research center. On the day before the assessments, the participants were not to stay up late, drink alcohol or do extremely exhaustive physical activities, in addition, for 2 hours before the assessments, not to drink caffeinated drinks or smoke. Further, on the day of the assessments, it was advised to eat light meals and no less than 2 hours before the assessments. At the assessments, the participants were provided with caffeine-free drinks and a light meal (Rantanen et al. 2018).

Ethics. The AGNES study received an approval from the ethical committee of the Central Finland Health Care District on August 23, 2017 and complies with the Declaration of Helsinki principles and ethical guidelines (Rantanen et al. 2018). The study does not include invasive (intrusive) or potentially physical or psychological detrimental factors more than what subjects may experience in their daily lives. At the beginning of the home interview, study participants signed a written consent form. Throughout the study, participants had the opportunity to request information about the study and its procedures. The participant had the right to withdraw their consent at any time during the study or at any individual stage of the study.

7.2 Measurements

7.2.1 Self-rated health

SRH was assessed in the home interview. The participant was presented a simple question in Finnish without any additional cues by asking: "Millaiseksi arvioisitte nykyisen terveydentilanne yleisesti? 1=erittäin hyvä, 2=hyvä, 3=keskinkertainen, 4=huono, 5=erittäin huono" or in English" How would you rate your current health situation in general? 1 = excellent, 2=good, 3=fair, 4=poor, 5=very poor". As discussed in the literature review, it is important to present the question in its original language, as wording and culture has been found to influence how SRH is perceived (Jylhä 2009). However, after the interviews the numbering of the self-rating of health was flipped and set to descend from excellent = 5 to very poor = 1, because this would make understanding the direction of associations easier in the correlation analyses and results.

7.2.2 Six-minute walk test

A modified 6-minute walking test (6MWT) was conducted, in which the participant could select a preferred walking pace while wearing a portable ECG device (Gremeaux et al. 2008). Moreover, the participant could use a cane if required. The testing was conducted in an indoor corridor, in which traffic cones were placed at the ends 19.66 m apart, and a tape indicating a bend of a 0.30 m radius around cones totaling a 40-m walk distance per lap. The number of laps and distance a participant was able to perform within 6 minutes were recorded manually. The results were presented as distance walked in meters.

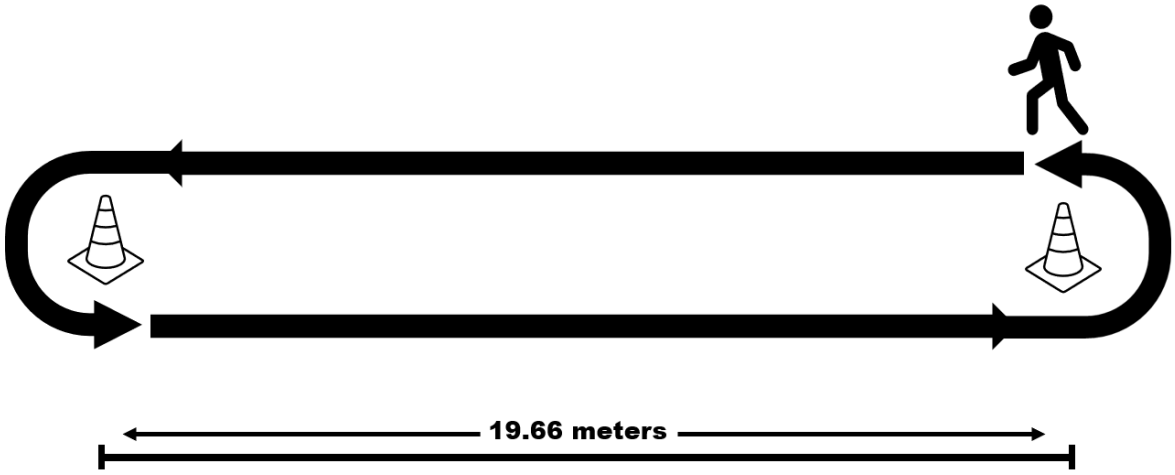


FIGURE 6: Depiction of 6MWT path of walk.

7.2.3 Heart rate

During 6MWT and recovery period, the participants wore a portable ECG device (eMotion Faros 180, Bittium Corporation, Oulu, Finland). The ECG device included two electrodes 12 cm apart, attached with a strip to the left side under the chest diagonally, or alternatively vertically to the sternum. The selection of the attachment style was based on what is anatomically most suitable for the participant (Rantanen et al. 2018).

The ECG recordings were analyzed with Kubios HRV – Heart rate variability analysis software (Kubios HRV, version 3.2.0., Kubios Oy, Kuopio, Finland). The software provides an automatic QRS detection algorithm, from which beat-to-beat RR interval data can be calculated. The process required a manual analysis to confirm the software has correctly identified the R-waves from the QRS complexes, and that the ECG data is reliable. ECG data would be deemed unreliable if (1) excessive amount of irregular heart rhythms is detected (i.e., causes inaccurate calculations of HRR), (2) signal strength was weak (i.e., QRS complexes are not visible), and (3) skeletal muscle contractions have masked the QRS complexes.

The resting HR was collected from a supine orthostatic test conducted approximately 2 hours prior to the 6MWT. In the orthostatic test, the participant laid on her or his back for 10 minutes after which the participant stood up and stood without speaking or moving for 6 minutes. The resting HR was measured with a digital blood pressure monitor 1 minute prior to standing up, at 9-minute mark (Rantanen et al. 2018) and was recorded as bpm.

The 6MWT HR was recorded at 6-minute mark and calculated as the mean of 5 RR intervals (i.e., time between two heart beats) in seconds, which was converted to bpm. In this study, the HRRTE was measured by calculating the change from resting HR to the 6MWT HR (i.e., 6MWT mean end HR – resting HR = HRRTE).

After the 6MWT, the participant stopped moving and was brought a chair to sit on quietly for 2 minutes to measure changes in HR. The HR was calculated from ECG beat-by-beat RR interval data over 90 seconds and was regressed (quadratic) (Brage et al. 2007). From this, HR at 30 seconds and 60 seconds after 6MWT were calculated as bpm. Subsequently, the 30-second and 60-second HR values were then subtracted from the 6MWT mean end HR to calculate HRR (e.g., mean end HR - HR after 60-seconds = 60-second HRR).

7.3 Statistical analysis

As summary descriptive statistics, the means and percentages of the categorical variables of age groups (i.e., 75, 80 and 85), sex and self-rated health were calculated. In addition, the continuous variables of walking distance, HRRTE, 30-second-, and 60-second HRR were calculated as means and standard deviations. To explore selection bias, the difference between included and excluded group was assessed with chi-squared test for categorized variables (i.e., age, sex and SRH) and independent samples t-test for 6MWD. SRH was binarily encoded into excellent/good (n = 283) and fair/poor/very poor (n = 245). Because most of the participants (89.9%) rated their health either "good" (46%) or "fair" (43.9%), the binarily encoded groups were named as good SRH and fair SRH, respectively. Before the binary comparison of means in independent t-test, the Levene's test for equality of variances was run. For the walking distance variable, the variances were not equal ($p = 0.025$). Therefore, unequal variances t-test was selected. For the rest of the continuous variances were equal, and equal variance t-test was run.

Before calculating strength and direction of association and statistical differences between SRH 5-point scale, age, walking distance, HRRTE and HRR, test of normality was run. Shapiro-Wilk test was selected as it has good power in asymmetric distributions at wide range of sample sizes (Yap & Sim 2011). Only walking distance was found to be normally distributed ($p = 0.132$). Yet, Pearson correlation method was selected for correlation analysis, as it has been suggested to be accurate with non-parametric data when the sample size is large and has no significant outliers (Norman 2010). In terms of strength of associations, the effect sizes were set as small: $r = \pm 0.1 – 0.3$, medium: $r = \pm 0.3 – 0.5$ and large: $r = \pm 0.5 – 1.0$ (Cohen 1992).

Binary logistics regression analysis, a forward selection (likelihood ratio) method, was run to determine which variables (i.e., age, walking distance, HRRTE and 60-second HRR) increase the prediction accuracy of SRH and independently associate with SRH. Firstly, the variables were added simultaneously into the forward selection model. Model fit test was run: Omnibus chi-square model tests if the selected variables in the model are of significant fit over the null model (i.e., null model being no variables added). Results showed significant fit ($p = <.001$).

The model starts with zero variables, then adding variables with best improvements to the model one by one in steps. The forward selection model excluded HRRTE and 60-second HRR as being not statistically significant and therefore not contributing to the prediction accuracies.

Lastly, an independent t-test and Pearson correlation test were run to investigate whether cardiovascular medication user and non-user results significantly differ from one another in terms of research questions.

All statistical analyses were conducted with the Statistical Package for the Social Sciences (IBM SPSS, version 21, Chicago, IL, USA). Because the direction of significance is uncertain, 2-tailed test of significance was selected (Tenenbaum et al. 2005), and statistical significance was set to less than 0.05.

8 RESULTS

Table 1 below shows 528 individuals were included in this study, whereas 337 individuals were excluded due to no existing HR data or unreliable ECG data. The included group was female-dominant (60.4%), whereas comparatively the excluded group was more equal (51.3% female). The inclusion favored younger individuals, whereas the exclusion group had more older individuals. Most of the included participants (89.9%) rated their health as either "good" or "fair" almost evenly. Further, inclusion favored those who rated health as "excellent" more than those who rated health as "fair" or "poor". No one rated their health as "very poor". Lastly, the included participants walked longer distances in 6MWT than the excluded counterparts.

TABLE 1: Characteristics of included and excluded participants.

	Included	Excluded	
Heart rate recordings	Yes	No	
6MWT walk distance	Yes	Yes	
Self-rated health	Yes	Yes	
Characteristics	% (n)	% (n)	*P*
Participants (n)	(528)	(337)	
Sex: Male	39.6 (209)	48.7 (164)	0.009[a]
Female	60.4 (319)	51.3 (173)	
Age: 75 years	53.6 (283)	40.7 (137)	0.001[a]
80 Years	28.8 (152)	37.7 (127)	
85 Years	17.6 (93)	21.7 (73)	
Self-rated health	% (n)	% (n)	*P*
Excellent	7.6 (40)	2.7 (9)	<0.001[a]
Good	46 (243)	38.6 (130)	
Fair	43.9 (232)	54 (182)	
Poor	2.5 (13)	4.7 (16)	
Very poor	0	0	
6-minute walk	Mean ± SD	Mean ± SD	*P*
Walk distance (m)	428 ± 79	389 ± 89	<0.001[b]

[a] Chi-square test, [b] independent t-test

8.1 Self-rated health groups' heart rate, walking distance and age differences

In table 2, good SRH group (excellent/good) walked significantly longer distance in 6MWT than fair SRH group (fair/poor). However, HRRTE was not significantly different between the groups. 30s HRR was not significantly different, whereas 60s HRR was. Lastly, age was significantly different between the groups.

TABLE 2. 6MWD, HRRTE, 30s HRR, 60s HRR and age differences between SRH groups.

Self-rated health	Excellent, good	Fair, poor	
	n=283	n=245	
	Mean ± SD	Mean ± SD	p-value
Walking distance (m)	455 ± 69	397 ± 78	**<0.001**
Heart rate response to exercise (bpm)	41 ± 12	40 ± 14	0.376
30s heart rate recovery (bpm)	11 ± 6	10 ± 6	0.100
60s heart rate recovery (bpm)	19 ± 7	18 ± 8	**0.025**
Age	77 ± 3	79 ± 4	**<0.001**

m, meters; bpm, beats per minute

8.2 Associations between self-rated health, heart rate, walking distance and age

Table 3 shows that SRH had moderate positive correlation with 6MWD, whereas age had negative small correlation and 60s HRR had small positive correlation with SRH. HRRTE correlation with SRH was non-significant and 30s HRR correlation strength with SRH was trivial.

TABLE 3. Associations between SRH, age, walking distance, HRRTE, 30-second HRR and 60-second HRR.

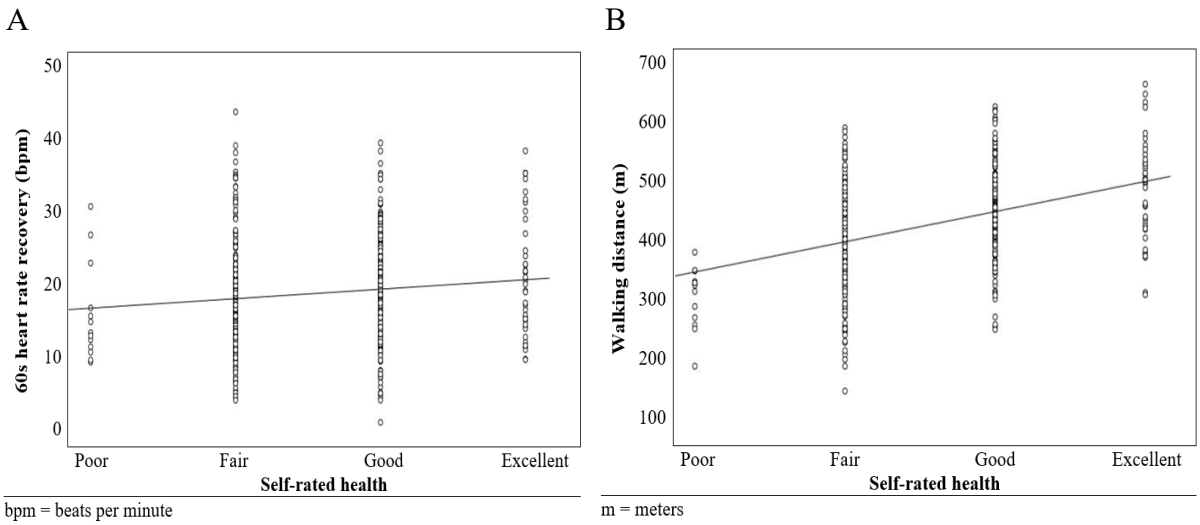
	Self-rated health	Age	Walking distance	Heart rate response to exercise	30s heart rate recovery
Age	-0.251[a] **<0.001[b]**				
Walking distance	0.410[a] **<0.001[b]**	-0.359[a] **<0.001[b]**			
Heart rate response to exercise	0.058[a] 0.183[b]	-0.041[a] 0.352[b]	0.323[a] **<0.0001[b]**		
30s heart rate recovery	0.088[a] **0.043[b]**	-0.096[a] **0.027[b]**	0.309[a] **<0.001[b]**	0.477[a] **<0.001[b]**	
60s heart rate recovery	0.117[a] **0.007[b]**	-0.097[a] **0.026[b]**	0.331[a] **<0.001[b]**	0.624[a] **<0.001[b]**	0.934[a] **<0.001[b]**

[a] Correlation coefficient (r); [b] p-value; strength of correlations (r), small = ±0.1 – 0.3, medium = ±0.3 – 0.5 and large = ±0.5 – 1.0

In addition, table 3 shows SRH and age correlate with other variables similarly. Although HRRTE did not correlate with SRH, HRRTE had moderate correlation with 6MWD, 30s HRR

and 60s HRR variables. Furthermore, higher HRRTE was associated with faster HRR. In terms of HRR time, 30s and 60s HRR correlation was large positive. Figure 3 illustrates the direction of associations: higher SRH was associated with faster HRR and longer 6MWD.

FIGURE 3. Direction of associations of SRH with 60s HRR (A) and 6MWD (B).



bpm = beats per minute

m = meters

8.3 Independent associations with self-rated health and prediction accuracy

Table 4 below shows all the variables added into the binary logistic regression likelihood equation. SRH was binarily encoded into group 1 (excellent/good) and 0 (fair/poor). The equation excluded 60s HRR variable from the analysis as being non-significant contributor to the models. Table 5 indicates that 6WD (i.e., model 1) independently associates with SRH. One unit of walking distance was encoded to 10 meters instead of 1 meter. Thus, OR (odds ratio) shows every additional 10 meters in walking distance equals to 11.5% more likelihood to belong to excellent/good SRH group. This likelihood drops to 10.2% in Model 2 when age is added into the equation. In Model 2, age was shown to be the second strongest variable that associates with SRH. Age as units was grouped into 75-, 80- and 85-year-olds. Thus, OR shows one increase in age group equals to 31% increase in likelihood to belong to fair/poor SRH group. In other words, age and SRH have negative relationship whereas walking distance and SRH have positive relationship.

TABLE 4. All variables added into the SRH binary logistic regression model

		p-value
Variables		
	60s heart rate recovery	**0.025**
	Heart rate response to exercise	0.375
	Age	**<0.001**
	Walking distance	**<0.001**

TABLE 5. Input variables within models recognized to significantly associate with SRH

			CI 95%	
	OR	p-value	Lower	Upper
Model 1				
Walking Distance	1.115	**<0.001**	1.008	1.014
Model 2				
Walking Distance	1.102	**<0.001**	1.007	1.013
Age	0.690	**0.005**	0.533	0.892

OR, odds ratio; CI, confidence interval.
OR per variable unit; walking distance 10m, age in groups 75, 80 and 85.

Table 6 shows that model 1 (i.e., walking distance only) correctly predicted 132 (true positives) but failed in 113 (false positives) participants with "fair" to "poor" SRH (accuracy 52.9%). In terms of "excellent" to "good" SRH, model 1 correctly predicted 202 (true negatives) and failed in 81 (false negatives) participants (accuracy 71.4%). Therefore, the overall accuracy of model 1 in predicting SRH is 63.3%. In model 2 (i.e., walking distance and age) the accuracies slightly increased: 138 were correctly predicted whereas 107 were false in participants with "fair" to "poor" SRH (accuracy 56.3%). Further, model 2 predicted 202 correctly and failed in 81 participants with "excellent" to "good" SRH (accuracy 73.9%). Thus, the overall accuracy of model 2 is 65.7%.

TABLE 6. Comparison of the number of participants with lower and higher SRH, and prediction of model accuracies

		Fair, poor	Excellent, good	Accuracy
Model 1	Fair, poor	132	113	53.9%
	Excellent, good	81	202	71.4%
	Overall accuracy			63.3%
Model 2	Fair, poor	138	107	56.3%
	Excellent, good	74	209	73.9%
	Overall accuracy			65.7%

8.4 Cardiovascular medication user and non-user differences

Investigation of the possible influence of cardiovascular medication on the studied variables shows that in average non-users walked significantly longer distance in 6MWT, had higher HRRTE, and faster 30s HRR and 60s HRR than those who were medicated (table 7). Further, table 8 shows that SRH correlated with 6MWD, HRRTE, 30s HRR and 60s HRR similarly in both groups. SRH correlation with 30s HRR and 60s HRR became non-significant in both groups, conversely to what was observed with the whole sample size correlation analysis (table 3). However, the non-user group strength of association with the above-mentioned variables remained similar to the whole sample size analysis.

TABLE 7. 6MWD, HRRTE, 30s HRR and 60s HRR mean differences between cardiovascular medication users and non-users

Cardiovascular medication	Yes	No	
	n=223	n=305	
	Mean ± SD	Mean ± SD	p-value
Walking distance (m)	413 ± 78	439 ± 78	**<0.001**
Heart rate response to exercise (bpm)	37 ± 12	43 ± 14	**<0.001**
30s heart rate recovery (bpm)	9 ± 5	11 ± 6	**0.001**
60s heart rate recovery (bpm)	17 ± 7	20 ± 8	**<0.001**

m, meters; bpm, beats per minute; cardiovascular medication, beta blockers, calcium channel blockers, antiarrhythmics.

TABLE 8. SRH correlation to walking distance, HRRTE, 30s HRR and 60s HRR in cardiovascular medication users and non-users

Cardiovascular medication		Walking distance	Heart rate response to exercise	30s heart rate recovery	60s heart rate recovery
No (n=305)	Self-rated health	0.413[a] **<0.001**[b]	0.022[a] 0.696[b]	0.086[a] 0.132[b]	0.111[a] 0.053[b]
Yes (n=223)	Self-rated health	0.354[a] **<0.001**[b]	0.002[a] 0.973[b]	0.019[a] 0.782[b]	0.031[a] 0.641[b]

[a] Correlation coefficient (r), [b] p-value; cardiovascular medication, beta blockers, calcium channel blockers, antiarrhythmics

9 DISCUSSION

SRH had a moderate positive correlation with 6MWD, meaning that individuals with better SRH tend to walk longer distance in 6MWT. HRRTE correlation was non-significant and trivial, thus did not correlate with SRH. 30s HRR had positive trivial correlation with SRH, whereas 60s HRR correlation with SRH was small positive, meaning individuals with better SRH had faster 60s HRR after 6MWT. In addition, good SRH (excellent/good) group, in average, walked significantly longer distance, had faster 60s HRR and were younger versus fair SRH (fair/poor) group. However, regression analysis showed that association of CAF variables (i.e., HRRTE and 60s HRR) with SRH disappeared after adjusting for 6MWD. Thus, indicating that PFC explains SRH more than CAF in this study, and that 6MWD independently associates with SRH. Lastly, the cardiovascular medication results showed that although non-users walked longer distance, had higher HRRTE and faster HRR, the correlation results show cardiovascular medication does not seem to have a significant influence on HRRTE or HRR association with SRH.

9.1 Associations of self-rated health with heart rate

The hypothesized significant relationship between HRRTE and SRH was not found in this study. In addition, HRRTE was not significantly different between good SRH group and fair SRH group, and mean HRRTE was >40 bpm in both groups. According to Girotra et al. (2012), failure to increase HR more than 20 bpm in 6MWT is an indication of health issues. Since HRRTE was >40 bpm in both groups and correlations were non-significant, poorer SRH cannot be associated with poor or abnormal HRRTE in this study. It is surprising that 60s HRR significantly correlated with SRH, whereas HRRTE did not. However, the relationship with SRH and HRRTE and HRR disappeared when adjusted for 6MWD, indicating that PFC explains relationship with SRH more than CAF does.

Regardless, it was expected that both HRRTE and HRR would have similar relationships with SRH, because both are independent predictors of health outcomes (Cole et al. 1999; Lauer et al. 1999), and the accuracy of predicting cardiovascular mortality significantly increases when

both HRRTE and HRR are measured (Myers et al. 2007b). Further, research shows that health-related quality of life has a relationship with HRR (Li et al. 2019; Öte Karaca et al. 2017; Tsarouhas et al. 2011; Känel et al. 2009). Health-related quality of life is a clinical survey tool similar to SRH (Till et al. 1994). In addition, HR variability, a variation in the time interval between consecutive heartbeats, is a measure of CAF and associates with SRH (Jarczok et al. 2015). Specifically, SRH has been shown to have a stronger association with HR variability than with inflammatory biomarkers C-reactive protein or white blood cell count (Jarczok et al. 2015). The cause for no associations in this study might be due to several factors, namely, different physiological mechanisms, nature of the exercise test and participants' physiological and mental state.

It is possible that 6MWT was not physically challenging enough for those with better SRH, thus HR did not increase. HRRTE is dependable on exercise intensity and physical fitness, as HR has been shown to linearly increase with intensity in sub-maximal tests (Vieira et al. 2016). Greater muscle work requires higher oxygen demands, which triggers feedback mechanisms, signalling feedforward mechanisms in turn to increase sympathetic outflow and decrease vagal outflow, consequently elevating HR (Kannankeril et al. 2004). However, results show that individuals with better SRH walked significantly longer distances in 6MWT than those with poorer SRH, although mean HRRTE was similar between good SRH group and fair SRH group. This might be an indication that those with better SRH are more physically fit and the sub-maximal nature of the 6MWT is not eliciting additional oxygen demands in individuals with better physical condition, thus higher HR is not required. This might explain as well why 60s HRR was significantly faster in good SRH group versus fair SRH group, as faster HRR has been associated with better cardiorespiratory fitness (Cole et al. 1999). Therefore, HRRTE and HRR might not always be comparable, but dependable on person's physical fitness and the absolute intensity of the exercise. However, it could be that HRRTE has simply plateaued in both good SRH group and fair SRH group. Specifically, aging related desensitization of β-adrenergic receptors to adrenaline inhibits HR from increasing, which has been suggested to be the reason for gradual maximal HR attenuation with age (Ferrara et al. 2014). Further, resting HR has a large inter-individual variance in terms of what is considered normal (i.e., 50-90 bpm) in healthy adults (Nanchen 2018). Therefore, determining what HRRTE value is "good" or "poor" has been difficult to establish clinically since HR can be significantly different between

individuals and still be “normal”, reflecting large variance in resting and exercise HR, both equating as HRRTE.

As to other possible reasons for HRRTE non-significant association with SRH, biological aging of the body and number of diseases might hinder a person from achieving exercise intensities that CVS would be able to reach. For example, arthritis has been shown to be associated with poor physical function (Singh & Strand 2009), and sarcopenia causes muscle atrophy (Tanimoto et al. 2021), which are both common in aging population. Thus, although a person might be in good cardiovascular and respiratory condition, is unable to reach its full potential in terms of HRRTE. However, reductions caused by these diseases in terms of PFC would be observed in 6MWD, which seems not to be the case, as the walking distance was significantly different between good SRH group and fair SRH group, and the correlation between SRH and walking distance was moderate. Therefore, it is unlikely that the cause for non-significant relationship between SRH and HRRTE is because of reduced capability to reach higher physical exertion. Conversely, it can be argued that cardiovascular diseases impacting HR are more of a limiting factor in terms of PFC than arthritis and sarcopenia, as cardiovascular diseases are the leading causes of death in European countries (Nichols et al. 2014). Unfortunately, how cardiovascular diseases influence PFC is difficult to assess because individuals tend to have not one, but several diseases related to both cardiovascular function and PFC (Metsios et al. 2008).

Psychological aspects and inter-individual variability might have played a role affecting HRRTE results. Specifically, the “white-coat” effect might have influenced the resting HR measurements done at the research center. “White-coat” effect takes place when HR is measured in an unusual or new environment, which causes anxiety, increased sympathetic outflow and elevated HR. Lequeux et al. (2018) found that HR measured by a physician in clinical setting is significantly different to HR measured at home (i.e., true resting HR). Further, the magnitude of “white-coat” effect significantly varies between individuals (Terracciano et al. 2014). It is speculated that both factors could potentially cause inaccuracy in HRRTE results and confounding the association between HRRTE and SRH.

Other reasons for HRRTE non-significant association with SRH might be in the HR recording and testing methods. HRRTE is commonly calculated from peak exercise HR minus resting HR (Bunc et al. 1988; Gulati et al. 2010; Kawasaki et al. 2010; Savonen et al. 2006; Scheidt et al. 2019), however measuring exercise HR at the end of exercising has been reported, specifically in sub-maximal exercise tests like in 6MWT (Girotra et al. 2012). In the present study, the exercise HR was recorded at the end of 6 minutes as mean end HR from last 5 heart beats. In terms of peak exercise HR, Lindemberg et al. (2014) found in 6MWT with healthy middle aged and aging population and post heart failure patients that the mean peak HR is not at the end of 6MTW, but at beginning or middle stages of the test. This might indicate that the participants have started walking slower close to the 6-minute mark. Conversely, Someya et al. (2015) suggests that in average HR plateaus at 2 minutes and peaks at the 6-minute mark during 6MWT in healthy aging population. In addition, Deboeck et al. (2005) found HR to plateau at 2 to 3 minutes in pulmonary arterial hypertension patients and mean values show peaking at the 6-minute mark. However, it can be argued that the fluctuation of HR during 6MWT is unlikely to be significant enough to change HRRTE results considerably in the present study. For example, Lindemberg et al. (2014) found that the mean HR during 6MWT varies approximately from 104 bpm to 108 bpm in healthy adults. Similar HR variance can be observed in studies conducted by Someya et al. (2015) and Lindemberg et al. (2014). Thus, it seems that peak HR may or may not be at the 6-minute mark in 6MWT, regardless the HR variance seems not be significant enough to affect HRRTE association with SRH in the present study.

As it was hypothesized, significant relationship between HRR and SRH was found in the present study. However, SRH correlation strength with 60s HRR and 30s HRR was small and trivial, respectively. In addition, 30s HRR was not significantly different between good SRH group and fair SRH group, whereas 60s HRR was. Interestingly, van de Vegte et al. (2018) suggests that 10-second HRR predicts health outcomes stronger than 60s HRR. The physiological reasoning is that parasympathetic reactivation, pronounced at the beginning of recovery period, is associated with health outcomes more than sympathetic withdrawal is, which activates around 60 seconds after cessation of exercise (Coote 2010; Peçanha et al. 2013). Imai et al. (1994) suggests that after 30 seconds of exercising HRR is almost completely influenced by vagal reactivation, however, Peçanha et al. (2013) suggest that 60 seconds after exercise is still mostly influenced by vagal reactivation, which is dominantly used in clinical

testing as a cut-off point. Regardless, research indicates that vagal reactivation closer to the cessation of exercise time is linked to health and may lose associations as recovery time increase due to diminished vagal reactivation and initiation of sympathetic withdrawal.

There are number of possible reasons to why SRH did not correlate significantly stronger with 30s HRR than with 60s HRR. Firstly, it is possible that 6MWT might have been exhaustive to less physically fit and older participants. It has been suggested that maximal exercise may cause excessive accumulation of metabolites, such as lactate and carbon dioxide, causing the metaboreflex to excite the central command, activating sympathetic outflow to the heart and inhibiting parasympathetic reactivation (Gujic et al. 2007; Rotto et al. 1988). Secondly, parasympathetic reactivation might be delayed in older individuals, as M2 muscarinic receptor density has been shown to reduce in aging population (Brodde et al. 1998). To elaborate, the postganglionic parasympathetic nerve terminals release acetylcholine neurotransmitters into the synaptic cleft, which are unable to bind due to the sparsity of receptors available, thus parasympathetic reactivation in the heart is slower (Brodde et al. 1998). Thirdly, age related stiffening of arteries may inhibit the baroreflex receptors from sensing drop in blood pressure, thus delaying the parasympathetic reactivation (Holowatz 2010; Monahan et al. 2000).

Further reasons might be in participant adherence to the testing protocol. HRR was calculated from the mean end HR minus HR after 30-, and 60-seconds of exercising. Further, although the absolute values were similar, the standard deviation of 30s HRR was relatively larger than that of 60s HRR. It is possible that some of the participants in this study might have still been moving for 5-10 seconds after the 6 minutes, which causes attenuation in parasympathetic reactivation, adversely affecting the accuracy of results. Thus, moving for 5-10 seconds at the beginning of the resting period means 16-33% out of the 30 seconds was spent inhibiting parasympathetic reactivation, whereas from the 60-seconds the inhibition is effectively halved, therefore relatively not affecting as much. In the ECG analysis, it was observed (skeletal muscle noise) that some participants kept moving at the beginning of the resting period. Why the participants kept moving might be due to miscommunication, cognitive impairment or misunderstanding the importance of not to move after the 6 minutes. All the above-mentioned factors may play a role in why HRR has larger variability in 30s HRR than in 60s HRR.

The validity of utilizing HRR to investigate how CAF might be connected to SRH should be considered, as the correlation between HRR and SRH was small. It is difficult to confirm these findings as no previous studies has been done on the relationship between SRH and HRR. Compared to HRRTE, controlling HRR seems to be easier, which might have influenced the accuracy of results and partly explain differences in correlations with SRH. This is due to the simpler HRR protocol, in which a participant is only asked to sit and not to move or talk for one minute after cessation of exercise. In addition, the resting HR used to calculate HRRTE was measured at supine position, whereas the HRR was measured at sitting position. This might have caused additional disparities between the variables, as it has been known for a longer time that body positions significantly influence HR (Macwilliam 1933).

In terms of what is considered "normal" or "poor" HRR, 60s HRR was significantly different between good SRH group and fair SRH group. However, neither group reached 25 bpm HRR within the first minute, which is considered as a threshold reference value for normal HRR in healthy population after a maximal exercise test (Jouven et al. 2005). However, it is important to note that the participants in the present study were older and many had cardiovascular diseases, both negatively influencing vagal and sympathetic activity (Gagné et al. 2014 Cole et al. 1999; Vivekananthan et al. 2003; Watanabe et al. 2001), and that the exercise test was sub-maximal, suggesting that the nature of the test might not be exhaustive enough for eliciting larger changes in HRR. Thus, it is not surprising that the 25bpm 60s HRR threshold was not reached. In addition, what is considered "poor" HRR seems to be highly dependable of which study is referred, as an expert review conducted by Okutucu et al. (2011) found that "abnormal" HRR threshold value connected to higher all-cause mortality risk varies from <47 bpm to <6.5bpm. The studies reviewed used test protocols with different intensities and increments (i.e., ramp, Bruce, sub-maximal protocols) and participants had different diseases at different stages, different age groups and different fitness levels. Thus, comparisons in terms of what is an abnormal HRR is debatable.

60s HRR results in the present study can be compared to a study which has similarly aged participants. For example, healthy middle aged and aging population participants in 6MWT study conducted by Lindemberg et al. (2014) had 21 ± 13 bpm HRR, whereas post heart failure patients had 18 ± 16 bpm HRR. In the present study, good SRH group and fair SRH group had

19 ± 7 bpm HRR and 18 ± 8 bpm HRR, respectively. Thus, the means are quite similar although the standard deviation is twice as wide in the compared study. Regardless, it is difficult to connect does poor SRH relate to poor HRR in a way that is clinically meaningful and predicts health, because agreement on reference values does not exist. These issues further reflect on why association between CAF variables and SRH might be difficult to investigate in 6MWT observational study, in which diseases (especially cardiovascular), medication or physical fitness are not controlled.

SRH has been shown to associate with cardiorespiratory fitness, that is, individuals tend to rate their health lower if their physical fitness is low as well (Mota et al. 2012). Furthermore, cardiorespiratory fitness and HRR have been shown to predict cardiac health outcomes similarly (Hernesniemi et al. 2019; Kiviniemi et al. 2015). Therefore, previous studies would suggest that SRH as a subjective measure correlates with the objective measures of HRR and cardiorespiratory fitness. Based on these previous studies, HRR could be added into the substantial list of health and disease related biomarkers associating with SRH (Kananen et al. 2021). However, the physiological mechanisms how the body senses health and its causal connection to SRH is still unknown, and individuals might rate their health differently although objective biomarkers would be similar between them. This might be due to individuals having different experiences about health and fitness, as suggested by Jylhä (2009). Therefore, it is not suspiring that the findings in this study only show small to trivial correlations at best between SRH and HRR, and not causations. Thus, although 60s HRR was significantly different between the SRH groups and had a small correlation with SRH, poor SRH does not seem to be an indication of poor 60s HRR or HRRTE, suggesting that SRH does not have a relationship with CAF in the present study.

9.2 Association of self-rated health with walking distance

In the present study, 6MWD had a positive moderate correlation with SRH. Although no studies have compared 6MWD and SRH, PFC has been shown to associate with SRH (Gander et al. 2011; Herman et al. 2014; Kantomaa et al. 2015; Ramírez-Vélez et al. 2017). 6MWD has been used to assess PFC in many clinical studies and shown to be stronger independent predictor of

health outcomes than for example HRRTE (Girotra et al. 2012). In addition, several studies show 6MWT to be comparable to maximal graded testing especially in aging population and cardiovascular patients, who might be unable to perform maximal testing (Alahdab et al. 2009; Guazzi et al. 2009). However, graded exercise tests are clinically more informative about wide range of physiological conditions including heart function through ECG interpretation and respiratory function with gas analysis, minimizing the possibility of confounding factors within the test (Garin et al. 2009).

Unfortunately, 6MWD normative values follow a similar trend as the CAF variables, that is, there are no agreed values on what is "good" or "poor". However, Enright (2003) suggests that 400m to 700m 6MWD being "normal" for healthy adults. Further, Cahalin et al. (2013) found that less than 300m is associated with increased mortality rate in post heart failure patients. The issue seems to be in lack of standardizing 6MWT protocol. In the present study, good SRH group and fair SRH group mean walking distances were 455 ± 69 and 397 ± 78, respectively. Although there is a significant difference between the groups, the values do not cross any reference values that could be used in relating "poor" SRH with "poor" 6MWD. On the other hand, it could be argued that the lower SRH group is at the lower end of the 400m to 700m range, as suggested by Enright (2003). However, the most important finding is that the mean distance travelled between the groups is larger than 45m, which is considered as a significant change in physical condition by Resnik and Borgia (2011). Therefore, SRH and 6MWD in the present study seem to have a clinical connection that is evidence based.

9.3 Independent associations with SRH

As hypothesized, SRH correlated stronger with 6MWD than with HRRTE or HRR, thus suggesting that SRH has stronger association with PFC than with CAF. It seems that PFC as a measure of health might be more accurate than CAF, as Girotra et al. (2012) found that when 6MWD is added into a prediction model HRRTE loses its association to cardiovascular health outcomes, while 6MWD retains its strong predictive power. In the present study, HRR or HRRTE did not independently associate with SRH, as the associations were eliminated after

adjustment for 6MWD. Interestingly, 6MWD had a moderate positive correlation with HRRTE and HRR, indicating that PFC and CAF have a significant relationship.

Truly, it can be argued that walking distance itself is an outcome to which HR contributes. To elaborate, human movement is an outcome of complex physiological mechanisms comprising of respiratory, vascular, cardiac, neural, and muscular functions (Ezati et al. 2019; Stickford & Stickford 2014). Specifically, the components of PFC are stability, muscle performance, cardiorespiratory fitness, mobility/flexibility, neuromuscular control, and balance/postural equilibrium (Kisner & Colby 2012, 2). Under the umbrella of cardiorespiratory fitness, HR and SV have a dynamical relationship summating as CO (Strait et al. 2012). Further, 6MWD seems to depend on the ability to increase CO based on HR after plateau of SV in healthy adults and aging participants (Someya et al. 2015). Higginbotham et al. (1986) agrees that HR is the strongest contributor to sustaining aerobic exercising. Moreover, Brubaker et al. (2011) hypothesizes that HR and walking distance share the same causal pathway to health outcomes. Thus, the evidence is indicating that PFC independently associates with SRH, and that CAF is a contributor to PFC.

However, HR may significantly vary between individuals based on physical fitness, age, and cardiovascular diseases and medication. For example, even when two individuals would walk significantly different distances in 6MWT, the present data suggests that HRRTE can still be similar. Further, similar HRR can be observed between individuals with different 6MWD due to differences in cardiorespiratory fitness and/or cardiovascular health. It is plausible that HRR and HRRTE as measures of CAF and their association to other health-related variables is valid under a more controlled setting. For example, Garin et al. (2009) suggests that 6MWD fails to explain some of the physiological factors that could be examined in clinical graded testing such as cardiac function with ECG and respiratory function with gas analysis. In addition, in graded testing the intensity is controlled, consequently, cardiac and respiratory responses can be evaluated and referenced to intensity standards. Thus, studying CAF needs more specific tools and controlled setting, whereas 6MWD as a measure of PFC and its association with SRH is more valid in an observational study.

Therefore, PFC is similar to SRH, which is non-specific but all inclusive (Jylhä 2009). However, how individuals perceive SRH may vary. The determinants of how health is perceived are commonly nested in individual experiences, culture, education, lifestyle, socioeconomic status and genetics (Kananen et al. 2021; Jylhä 2009). Therefore, although walk distance between two individuals would be the same does not mean that they would rate their own health similarly. For example, an individual with extensive sports background might not rate health similarly versus a sedentary individual who was able to walk the same distance.

Both model 1 (6MWD) and model 2 (6MWD and age) were significantly worse in predicting lower SRH accurately versus higher SRH. There can be number of reasons to why low SRH values are harder to predict. Based on the findings in this study, it seems participants who rated their health lower are more likely to be older, have lower 6MD and suffer from number of diseases. Due to this it is hypothesized that the number of confounding factors may increase in less healthier participants, for example, Guazzi et al. (2009) found left ventricle dysfunction declines the prognostic accuracy of 6MWD. Moreover, sarcopenia and arthritis significantly influence PFC (Tanimoto et al. 2021; Singh & Strand 2009). However, it is difficult to assess which factors influence 6MWD in an observational study without control of diseases. In summary, all these factors causing variances in CAF variables might explain some of the weak correlations and prediction inaccuracies.

9.4 Influence of age

Although 6MWT is evidently valid for assessing PFC in aging population, older age may create significant variance in HRRTE and HRR in 6MWT. To elaborate, attenuated age-related maximal HR can be compensated due to Frank-Starling mechanism which increases SV leading to higher CO (Houghton et al. 2016). Thus, lower HRRTE or lower maximal HR do not always translate into significantly different PFC. Consequently, HRR would be affected by this as well since it is calculated from exercise HR – HR after one minute of rest. This could provide further explanation to why 6MWD associates with SRH stronger than HRRTE or HRR in the present study.

Age had a negative association with SRH, thus older age was related to poorer SRH. Being the only variables directly compared in previous research, age and its connection to SRH has been widely studied and has been shown to be an independent predictor of health outcomes (Jylhä 2009). As suggested by Jylhä (2009), age significantly influences how SRH is rated, thus indicating the validity of SRH in this study as the target population was 75- to 85-year-olds. Further, age works in this study to confirm what has been found in previous studies. In addition, age can be used with SRH to triangulate 6MWD, HRRTE and HRR associations. In other words, the correlations of SRH and age are similar with 6MWD, HRR and HRRTE. In this regard, it is surprising that the correlation between age and SRH was only small. It is possible selection bias has weakened the strength of relationship between SRH and age, that is, those with poor SRH results and older age were significantly more excluded from the final analysis sample, as over 50% being in the youngest group (75 years), thus the range is narrow. In addition, no one rated their health as "very poor".

Within model 2 (6MWD and age), increase in age group by one increased the likelihood of belonging to lower SRH group by 31%. Finnish Institute for Health and Welfare (2021) indicates that mortality rates in Finnish population exponentially increase from 75- to 85-year-olds. Thus, being in line with findings in this study, suggesting that older age at this range is associated with lower SRH and shorter 6MWD. Thus, age negatively associated with 6MWD, which was expected because PFC has been shown decrease with age. Further, aging has been shown to associate with additional diseases (Heller et al. 2008) and weakened cardiorespiratory fitness (Strait et al. 2012). Specifically, sarcopenia and arthritis has been shown to significantly reduce PFC (Tanimoto et al. 2021; Singh & Strand 2009). Moreover, both HRRTE (Ferrara et al. 2014) and HRR (Vivekananthan et al. 2003; Watanabe et al. 2001; Cole et al. 1999) attenuate due to biological aging and diseases, which all consequently reduce 6MWD (Rikli et al. 1999).

9.5 Influence of cardiovascular medication

The results showed that the medication non-users walked significantly longer, had higher HRRTE and faster HRR than users. However, the mean differences did not cross any health-related reference values. The speculation for this difference between users and non-users is that the medicated individuals have more sever diseases adversely impacting physical condition. SRH had moderate positive correlation with 6MWD and non-significant correlations with all CAF variables in both groups. This means that HRRTE and HRR variables lost association to SRH after the study sample was split based on medication use. The reason of the investigation was to confirm if cardiovascular medication has significant influence on the study results. It was expected that HRR association with SRH would disappear in the medication user group, interestingly, the association was lost in both non-users and users.

The reasoning for the expected change in association especially with the users is that calcium channel blockers are known to decrease exercise HR although CO would remain the same (Kinderman 1987). Further, beta blockers are known to blunt the sympathetic outflow into the heart by blocking the β-adrenergic receptors from binding with noradrenaline (Stoschitzky et al., 2003). Thus, beta blockers inhibit HRRTE and should not influence HRR as it is almost completely controlled by the PNS within the first minute after exercising (Karnik et al. 2008). However, Desai et al. (2001) argues that if beta blockers influence HRRTE, they should influence HRR as well since both are calculated from peak or end exercise HR. Lindermberg et al. (2014) agrees as their study shows beta blocker use significantly influences HRR after 6MWT.

Therefore, there seems to be some debate over what the effects of cardiovascular medication on HHRTE and HRR are. In addition, there seems to be a large variance in how individuals respond to medication: it has been known for a longer time that beta blocker use may improve PFC (Tesch, 1985). In other words, some users may have had longer 6MWD than non-users in the present study. Further, a study by Stoschitzky et al. (2003) found that some beta blockers decrease HR and some do not. Thus, assuming that the participants in the present study are using different kinds of beta blockers - could potentially be a cause for variance in HR as well.

However, this notion would expect non-users and users having similar cardiovascular diseases, age and fitness for validation. As it seems, the factors influencing HR are numerous and complex without control, and a simple splitting of participants into non-users and users might not be accurate enough for the purpose of investigating medication effects on the correlations.

The real reason for losing significant association between SRH and HRR might be due to the statistical calculations. Namely, p-value is known to show significance between any variable when the sample size is large enough (Sullivan & Feinn 2012). In the present study, the sample size of 528 was split into users (n=223) and non-users (n=305). Such a large change in sample size may have caused disappearance of the significance. Therefore, the investigation shows that the association between HRR and SRH in the full sample size as well could be false positive and observed only when the sample size is large enough. However, it is of worth to note that the strength of association was small to begin with, consequently HRRTE and HRR variables were excluded in the logistic regression equation, therefore the disappearance of significance does not change the results of this study.

9.6 Selection bias

Results show that there is a significant difference between included and excluded participants in terms of walking distance, age, SRH and biological sex. In addition, some of the participants were excluded due to arrhythmia, as it influences HRRTE significantly. Further, participation numbers show that younger individuals (i.e., 75-year-olds) were significantly more likely to participate than older ones (80- or 85-years olds). This might be due to considerably higher mortality rates in 85-year-olds than in 75-year-olds (Finnish Institute for Health and Welfare 2021). Ultimately the withdrawal rates and exclusions led to no one rating SRH as “very poor”.

Those with weaker physical condition might be subjected to physical attrition from travelling to the research centre (Hardy et al. 2009). As shown by Rijk et al. (2016), study participation for the aging population may require additional physical stress in addition to daily challenges and therefore individuals with cognitive or functional decline may withdraw. These findings are in line with studies suggesting that individuals with better health and PFC are more likely

to participate in studies (Kelfve et al. 2013; Hardy et al. 2009; Mody et al. 2008). This raises a concern in terms of accurate representation of the population sample, which is a weakness in cohort studies, as suggested by Jager et al. (2020). The study sample should include individuals regardless of health, physical or cognitive impairments (Kelfve et al. 2013). In summary, it is difficult to determine the magnitude of misrepresentation of the population and how much the selection bias has affected the accuracy of the statistical analysis.

9.7 Limitations and future research

Walking distance, age and HR are all objective measures. However, SRH is subjective and unquantifiable. In other words, what does SRH measure? Jylhä (2009) suggests that SRH measures health, but health is a very broad term and has not been defined in clinical sciences. It can be said that health is a sum of wide variety of factors and may even have a different meaning depending on culture, age or simply individuality (Jylhä, 2009). Thus, the dilemma is that the validity of SRH is studied through mortality predictions, but as noted by Lee et al. (2007), health is more than just being alive or dead. In this regard, one should exercise caution when producing conclusions about correlations between the subjective and objective associations in this study. However, further mapping of biomarkers which associate with SRH is important for investigations about the physiological mechanisms connected to SRH (Kananen et al. 2021).

The nature of a cohort study is to observe a target population. Therefore, it is all inclusive but non-specific. This raises a limitation to explain connection between variables if confounders are not controlled. A common limitation in cohort study is confusion bias; other unmeasured variables called confounders may distort the association between walking distance, HR and SRH (Gamble 2014). This especially applies to HRRTE and HRR variables, which are significantly influenced by physical fitness, age, cardiovascular health, medication, and genetics. Thus, future research that controls these factors might reveal more accurate associations with SRH.

6MWT may not be the most accurate to measure HRRTE since exercise intensity is not controlled. Further, sub-maximal test might not elicit significant changes in HRRTE with more physically conditioned individuals. Small change in HRRTE may also translate to blunted changes in HRR. It could be better to assess HRRTE with a graded testing, which controls intensities. Further, in clinical setting it is possible to observe cardiac function with ECG and respiratory function with gas analysis to minimize confounding factors. In terms of reaching more accurate representation of aging populations, it could be better to provide field testing options at home or in close vicinity to encourage participation and limit participant attrition. However, this might raise new issues in terms reliability and reproducibility if testing methods are used at different locations by different personnel, as suggested by Ritchie et al. (2005). In this regard, it is important to pay attention to validity and reliability of exercise test selection.

9.8 Conclusions

Associations of SRH with CAF and PFC in aging population may provide additional insight to the physiological mechanisms leading to self-health rating process. Specifically, investigation of 6MWD, HRRTE and HRR association with SRH may further lead to better understanding of human health. This study showed that 6MWD and HRRTE positively associated with SRH. However, HRR association with SRH disappeared after adjusting for 6MWD. 6MWD was found to independently associate with SRH in aging population, and 6MWD and SRH reference values show connections that are clinically evident. However, HRRTE and HRR are measures of fitness and health, and HR is an important contributor to 6MWD. In other words, CAF significantly contributes to PFC. Interestingly, 6MWD associations with poorer SRH were significantly less accurate versus better SRH. In addition, individuals with poorer SRH were significantly older. It is likely that individuals with poorer SRH, shorter 6MWD and older age have more confounding factors, namely cardiovascular diseases, and musculoskeletal disorders. Moreover, especially cardiovascular diseases, medication, physical fitness, and age may cause variance in HRRTE and HRR. Future studies should investigate HRRTE and HRR association with SRH in a study setting that controls these factors causing possible variance. Although 6MWT is valid for assessing PFC, it may not be accurate to measure CAF, thus graded exercise stress test with electrocardiograph assessment might be better option to control physiological confounders.

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