RESTING HEART RATE AND ARTERIAL STIFFNESS RELATIONSHIP IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

by

Carmen Aurelia Sima

B.Med. (Hons), The University of Medicine and Pharmacy of Craiova, 1995
M.Sc., The University of Victoria, 2010

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Abstract

Background: Patients with chronic obstructive pulmonary disease (COPD) are known to have an increased risk of ischemic heart disease. Persistently elevated resting heart rate and arterial stiffness, two common clinical manifestations in COPD, are known determinants of myocardial ischemia as well as predictors of cardiovascular events. Controversies exist on the effect of pulmonary rehabilitation on these ischemic heart disease risk factors. No study has explored the effect of pulmonary rehabilitation on the resting heart rate - arterial stiffness relationship in COPD.

Objectives and Methods: The overall objectives of this dissertation were to provide a comprehensive investigation of the resting heart rate and arterial stiffness in patients with COPD, and explore the impact of pulmonary rehabilitation on their relationship in this population. We describe the association between resting heart rate and prior myocardial infarction in patients with chronic lung disease attending pulmonary rehabilitation (Chapter 2). We test the reliability of resting heart rate and arterial stiffness measurements in COPD patients (Chapters 3 and 4). We determine the association between resting heart rate and arterial stiffness (Chapter 5), and explore the potential beneficial effects of standard pulmonary rehabilitation on resting heart rate and/or arterial stiffness in COPD (Chapter 6).

Summary of findings: We showed that an elevated resting heart rate is a potential indicator of prior myocardial infarction in patients with chronic lung disease (Chapter 2). Resting heart rate and arterial stiffness measurements have excellent and substantial reliability, respectively, under a standardized procedure in COPD patients (Chapters 3 and 4). The association between resting heart rate and arterial stiffness in control subjects is not present in patients with COPD (Chapter 5). Standard pulmonary rehabilitation in COPD

reduces arterial stiffness, but not resting heart rate, and does not impact the resting heart rate - arterial stiffness relationship (Chapter 6).

Conclusions: This dissertation provides new knowledge on resting heart rate and arterial stiffness, as well as on the potential beneficial effects of pulmonary rehabilitation on these two ischemic heart disease risk factors in COPD patients.

Preface

This statement is to certify that the research work presented in this dissertation was conceived, conducted, analyzed, and written by Carmen A. Sima. Ethical approval to conduct the studies described in this dissertation was obtained at various stages of the research process from the Research Ethics Boards of the Providence Health Research Institute, Vancouver Coastal Health Research Institute, Fraser Health Research Institute, and the University of British Columbia (H11-00984-A005 and H11-00984-A007). Dr. Pat G. Camp, the principal supervisor, as well as Dr. W. Darlene Reid, Dr. Andrew W. Sheel, and Dr. Stephan F. van Eeden, the supervisory committee members (names arranged in alphabetical order), provided valuable assistance and input during the entire research process.

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The journal articles resulting from this doctoral dissertation (published or submitted for publication) are presented below. The chapters of this dissertation related to these published or submitted publications may contain additional materials to increase the clarity and coherence of the research work and dissertation as a whole.

A version of Chapter 2 has been submitted for publication. **Sima CA**, Lau BC, Taylor CM, van Eeden SF, Reid WD, Sheel AW, Kirkham AR, Camp PG. *Myocardial infarction injury in chronic lung disease patients undergoing pulmonary rehabilitation: Frequency and association with heart rate parameters*.

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rate variability during spontaneous breathing in people with chronic obstructive pulmonary disease.

A version of Chapter 4 has been published. **Sima CA**, Sheel AW, van Eeden SF, Reid WD, Taylor CM, Camp PG. (2016). *Pulse wave velocity measurements in moderate to severe chronic obstructive pulmonary disease: A test-retest reliability study*. International Journal of Cardiology, 15; 203:301-2. doi: 10.1016/j.ijcard.2015.10.131.

A version of Chapter 5 is being prepared for submission. **Sima CA**, van Eeden SF, Reid WD, Sheel AW, Benari O, Kirkham AR, Camp PG. *The relationship between resting heart rate and arterial stiffness in patients with chronic obstructive pulmonary disease*.

A version of Chapter 6 is being prepared for submission. **Sima CA**, van Eeden SF, Reid WD, Sheel AW, Benari O, Kirkham AR, Camp PG. *The effect of pulmonary rehabilitation on the relationship between heart rate and arterial stiffness in patients with chronic obstructive pulmonary disease.*

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List of Abbreviations

%	percent
ΔP	pressure change
ΔV	volume change
6MWD	six-minute walk distance
ACOS	Asthma-COPD Overlap Syndrome
AS	arterial stiffness
ATS	American Thoracic Society
beats/min	beats per minute
BMI	body mass index
c	central
CIIS	cardiac infarction injury score
CLD	chronic lung disease
COPD	Chronic Obstructive Pulmonary Disease
CPET	cardiopulmonary exercise test
CRP	C-reactive protein
CTL	Control
CV	coefficient of variation
DBP	diastolic blood pressure
DM	diabetes mellitus
ECG	electrocardiogram
FEV_1	forced expiratory volume in one second

FVC	forced vital capacity
GEE	generalized estimating equations
GERD	gastroesophageal reflux disease
GMCSF	granulocyte-macrophage colony-stimulating factor
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HF	high frequency
HR	heart rate
HRV	heart rate variability
Hz	hertz
ICC	intraclass correlation
IHD	ischemic heart disease
IL	interleukin
LF	low frequency
ln	natural logarithm
m	meter
ms	millisecond
MBP	mean blood pressure
MCP-1	monocyte chemoattractant protein-1
MI	myocardial infarction
mmHg	millimetre of mercury
mmol/L	millimol per litre
mMRC	modified Medical Research Council scale

p	peripheral
PP	pulse pressure
PR	pulmonary rehabilitation
PRP	pulmonary rehabilitation program
PWV	pulse wave velocity
R^2	coefficient of determination R squared
RAS	renin-angiotensin system
RMSSD	square root of mean squared difference of successive R-R intervals
RR	interval between successive R waves of the ECG complex wave
s	second
SAN	sinoatrial node
SBP	systolic blood pressure
SD	standard deviation
SDNN	standard deviation of normal to normal R-R intervals
SEM	standard error of the mean
SpO_2	saturation of oxygen
SRD	smallest real difference
TNFα	tumor necrosis factor alpha
TP	total power
VO_2	oxygen consumption

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Dedication

To my beloved father

who is no longer with me,

but who taught me

to always follow the straight path

no matter what happens along the way.

Chapter 1: Introduction

Patients with chronic obstructive pulmonary disease (COPD) are known to have an increased risk of morbidity and mortality from ischemic heart disease (1,2). Persistent low-grade systemic inflammation and autonomic sympathetic dominance are proposed mechanisms to explain the pathogenesis of ischemic heart disease in COPD (3,4). An elevated resting heart rate, which is one main clinical manifestation of these two mechanisms, has not only been found in patients with COPD (5,6), but is also known to be a strong predictor of major cardiac ischemic events (7-9). Recent experimental and population-based epidemiological studies report heart rate dependency of arterial stiffness (10-13), which is itself a strong predictor of cardiovascular morbidity and mortality (14-16). Therefore, arterial stiffness may be a link between an elevated resting heart rate and increased cardiac ischemic risk. Given that aerobic exercise training, which is the core component of pulmonary rehabilitation, has the potential to modulate both resting heart rate and arterial stiffness (17,18) with beneficial effects for overall cardiovascular health (19,20), the resting heart rate-arterial stiffness relationship may be particularly relevant in COPD. If this relationship proves to be strong in COPD, it can serve as a basis for cardiac risk stratification and for gauging the efficacy of pulmonary rehabilitation in controlling the ischemic heart disease in this population. Based on these considerations, the overall objectives of this dissertation work are to comprehensively investigate the resting heart rate and arterial stiffness relationship in patients with COPD, as well as the effect of standard pulmonary rehabilitation on these two parameters taken individually and combined in this population. In the following general introduction, the key components of this topic will be

introduced, in order to facilitate the understanding of the reasoning behind conducting this research. Lastly, an overview of the dissertation will be provided along with an outline of the phases required to complete the present research work.

1.1 Chronic obstructive pulmonary disease (COPD)

COPD is one of the leading causes of morbidity, mortality, and health care utilization worldwide. The presence of associated comorbidities, such as cardiovascular diseases, substantially contributes to the overall health burden of COPD. In this section, COPD is discussed from an epidemiological point of view to explain the ongoing interest of the scientific community in this disease.

1.1.1 Pathophysiological and clinical features of COPD

COPD is a respiratory disorder characterized by a progressive obstruction of the lung airflow that is not fully reversible with bronchodilator therapy (21). The pathological changes in COPD develop insidiously, and are caused largely by an abnormal inflammatory response to various noxious particles or gases resulting from cigarette smoking and air pollutants (22). The inflammatory process primarily involves the airways, in particular those less than 2 mm in diameter (23), and subsequently includes the parenchyma and pulmonary vasculature (24). Thus, the progressive airflow limitation in COPD is produced by a combination of small airway remodeling (which occurs in chronic bronchitis) and alveoli destruction (which occurs in emphysema) that ultimately leads to disturbances in ventilatory and cardiovascular functions (24,25).

The clinical diagnosis of COPD normally follows the pathophysiological course, and relies on the patient's history, respiratory symptoms, and spirometric evidence of expiratory flow limitation. Current or former smokers are considered at greatest risk for developing COPD, as are people exposed to inhaled irritants (26). Respiratory symptoms such as cough, sputum production, and shortness of breath are present in COPD, and manifest clinically as more lung structures become involved (22). However, the measurement of airflow obstruction by spirometry is necessary to confirm the diagnosis of COPD and quantify the disease severity. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines (27), a post-bronchodilator ratio of forced expiratory volume in one second (FEV_1) to forced vital capacity (FVC) less than 70%, associated with a forced expiratory volume in one second (FEV_1) value less than 80% of the predicted normal values, are diagnostic of airflow limitation and COPD. It is worth mentioning that COPD often shares similar features with asthma and therefore, the existence of Asthma-COPD Overlap Syndrome (ACOS) can make diagnosis of COPD challenging (28,29).

1.1.2 Epidemiology and health burden of COPD

COPD is currently recognized as one of the leading causes of morbidity, mortality, and health care utilization worldwide. The prevalence of COPD in the general population has been estimated to be between 9% and 14% amongst adults over 40 years of age (30,31). However, epidemiological data indicate that COPD prevalence might be underestimated due to either the heterogeneity of terminology and definition criteria, or to the delay of patients in seeking medical attention (22).

Data on morbidity collected from physician visits, emergency department visits and/or hospitalization admissions shows that COPD places a substantial economic burden on both patients and society (32,33). In the USA alone, the 2010 annual economic costs arising from direct and indirect morbidity from COPD were estimated at approximately $50 billion (33). Further, the average annual cost per COPD patient has been calculated to be close to $4000 (33), with hospitalizations representing the largest component of this cost (34). These estimates were similar to those found in Canada, where COPD counted as the fourth and sixth most common cause of hospitalization among men and women, respectively (35).

In terms of mortality, the Global Burden of Disease Study (36) has shown that COPD is the fourth leading cause of death worldwide and is predicted to become the third leading cause of death by 2020. However, it has also been suggested that data on COPD mortality might also be underestimated, because of either the difficulty in identifying the precise cause of death, or the infrequent listing of COPD as a contributing factor to the cause of death (37). Notably, a change in the gender mortality pattern has recently been noticed, with an increased mortality from COPD among women compared to men (21). These epidemiological data highlight that COPD is a broad public health problem that needs to be addressed for the benefit of both patients and society.

1.1.3 Extra-pulmonary manifestations of COPD

Recent evidence shows that the health burden of COPD is represented not only by the disease itself, but also by its association with multiple comorbid conditions. This issue has been recognized by the GOLD guidelines, which have expanded the COPD definition beyond the physical boundaries of the lung, stating that “airflow limitation is associated with

an abnormal chronic inflammatory response," and "significant extra-pulmonary effects may contribute to the severity in individual patients" (38). Among various associated comorbidities, cardiovascular diseases and in particular ischemic heart disease, have recently received much attention because they are not only prevalent in patients with COPD, but also appear to worsen the prognosis in this population (37,39,40).

Several epidemiological studies have reported that the prevalence of cardiovascular diseases was consistently higher in COPD groups than in their matched control populations (41,42). This higher prevalence of cardiovascular diseases in the COPD population was associated with an increased risk of hospitalizations and deaths by cardiovascular events (41-43). For example, the Lung Health Study (43), which was conducted over a 5-year period in smokers with mild to moderate lung function impairment, showed that cardiovascular diseases accounted for 42% of first hospitalizations and 48% of second hospitalizations in this population. Even more interesting, hospitalizations for respiratory causes were approximately one-third less than those for cardiovascular diseases (43). Mortality data has shown a similar trend, with cardiovascular diseases accounting for either the primary (44) or secondary (45) cause of death in COPD. However, when the risk of death was taken into account in this population, the prevalence of mortality from ischemic heart disease exceeded the number of deaths attributed to any other pathological condition, including other cardiovascular disorders (1,46). Therefore, the increased risk of ischemic heart disease in people with COPD cannot be neglected, and specific risk factors must be identified in order to implement preventive measures and target intervention strategies in this population.

1.2 Ischemic heart disease in COPD

Ischemic heart disease accounts for a large proportion of morbidity and mortality in patients with COPD. Yet, our understanding of the pathogenic mechanisms underlying the ischemic heart disease - COPD association is still incomplete. In this section, the epidemiology and physiopathology of ischemic heart disease will be discussed in connection with COPD, in order to provide the necessary background for the forthcoming sections.

1.2.1 Pathophysiological and clinical features of ischemic heart disease

Ischemic heart disease (IHD), also known as coronary artery disease, is a cardiovascular disorder characterized by a reduced blood supply to the heart muscle (47). This condition is commonly a result of atherosclerosis defined by structural changes within the walls of the coronary arteries, which result from a complex interplay between lipoproteins accumulation (cholesterol), leukocyte infiltration, and vascular inflammation (48). In the evolution of this process, the build-up of fatty materials, known as plaque, can either narrow the coronary arteries leading to the reduction of the blood flow to the heart, or rupture leading to the formation of a blood clot that can completely block the blood flow through the coronary arteries. In the last case, a myocardial infarction (heart attack) can occur, which can be fatal in the absence of adequate treatment (49). Although this is a common scenario for myocardial ischemia, it is currently recognized that dysfunctions of the endothelium and wall distensibility within the coronary arteries occur in response to sustained hemodynamic disturbances at an early stage in the atherosclerotic process, playing a major role in ischemic heart disease progression (50). This hypothesis is supported by experimental studies, which show not only the predisposition of the atherosclerotic lesion formation at the arterial

bifurcations or curvatures, but also the increase in risk of cardiac ischemic events in the presence of disturbed pulsatile blood flow (51,52).

The diagnosis of IHD takes into account the progressive nature of this disorder and relies on a composite of family and medical history, atherogenic risk factors, symptoms, and cardiac laboratory and function tests (53). While being mostly asymptomatic in the early stages and resting conditions, the occurrence of specific ischemic symptoms, such as angina, shortness of breath, or fatigue, signal the transition to a more advanced disease stage and conveys warning signs of increased heart attack risk (53,54). Yet, the clinical presentation of IHD depends largely on the imbalance between coronary blood flow and myocardial oxygen consumption (55). In this context, myocardial ischemia can be viewed best not as an isolated disorder, but rather as a group of disorders, including angina, myocardial infarction, and heart failure (53). Despite various available tests, ranging from simple electrocardiogram and stress testing to sophisticated coronary angiography and cardiac catheterization, IHD continues to pose significant diagnostic and public health challenges (56,57).

1.2.2 Epidemiology and health burden of ischemic heart disease in COPD

Ischemic heart disease is recognized as a leading cause of disability, premature mortality, and health care utilization worldwide. The prevalence of IHD in the general population is approximately 7% among individuals aged 45-64 years and 20% among those aged ≥ 65 years (58). However, it has also been recognized that these prevalence figures may be underestimated due to the fact that most information is drawn from national surveys and therefore, respondents may not be fully aware of their pathology (59). The actual cost estimates of total and per patient annual ischemic heart disease healthcare in the USA are

$120 billion and $3000, respectively, but most importantly they are projected to triple by 2030 (60,61). Notably, one out of six deaths is caused by IHD despite advances in the diagnosis and treatment of this condition (62). Besides its progressive and silent nature, a possible explanation for this paradoxical evolution of IHD would be that as the population ages, the associated chronic conditions shift their profile from a localized disorder characterized by atherosclerotic obstructive lesions to a more generalized disorder characterized by aortic wall arteriosclerosis and stiffening (63).

COPD is a condition associated with an increased risk of ischemic heart disease. The prevalence of IHD in the COPD population has been reported to be two to three times higher than in the general population (42,64), with the mortality rate ranging from 10% to 30% depending on the person's age and the method used to confirm the diagnosis (65). However, it has also been recognized that IHD remains commonly undetected in a large number of COPD individuals and vice versa, and this aspect imposes important constraints in the management of both diseases. Reed et al. (66), in a retrospective cross-sectional study of patients with COPD evaluated for lung transplantation, found that occult coronary artery disease and severe occult coronary artery disease were present in 53% and 9% of the COPD patients, respectively. Berger et al. (67), by investigating the survival of 4,284 patients with coronary artery disease who underwent percutaneous coronary intervention, found at the end of a 3-year follow-up that the all-cause mortality of patients with COPD was 21%, compared to 9% in patients without COPD. These results were supported by other interventional studies, which indicated that patients with COPD had more adverse cardiac events, longer hospital stays, and more repeated revascularizations than their counterparts (68,69).

Therefore, in order to implement adequate preventive measures in this population, it is necessary to understand the underlying mechanisms of the IHD - COPD relationship.

1.2.3 Pathogenic mechanisms linking ischemic heart disease and COPD

Despite strong evidence of the association between ischemic heart disease and COPD, the underlying mechanism is still not completely understood due to the complex and intricate pathophysiological processes involved. Both diseases share common risk factors such as advanced age, smoking history, excess weight, physical inactivity, high blood pressure and/or metabolic syndromes (53,65). Impaired lung function *per se* has also been found to be a risk factor for myocardial ischemia in both the general population (70) and patients with COPD (2). Sin and Man (2) found that for every 10% decrease in FEV_1 in patients with COPD, nonfatal coronary events and cardiovascular mortality increased by approximately 20% and 28%, respectively. Lastly, a number of COPD biological markers, such as systemic inflammation, hypoxia, or neuro-hormonal activation, have also been shown to contribute to the induction of myocardial ischemia (71-74). Among all these mechanisms, persistent low-grade systemic inflammation and autonomic sympathetic dominance have gained acceptance in the scientific community as playing major roles in the pathogenesis of ischemic heart disease in COPD, as described below.

1.2.3.1 Low-grade systemic inflammation

The role of inflammation in the atherogenesis process has been extensively studied in both animals and human subjects. Briefly, it has been shown that once an atherogenic stimulus is initiated, the endothelial cells begin to express selective adhesion molecules that

bind blood borne leukocytes. Once they become adherent to the endothelium, the leukocytes migrate into the intima and activate blood-derived inflammatory cells and fibrinogenic mediators, which not only promote the formation of atheromatous plaque, but also contribute to plaque thrombosis (48,49).

Since the inflammatory component is central to the pathogenesis of COPD, a theoretical model has been proposed for the inflammation translocation (which is also referred to as "spill over") from lung to systemic circulation, and also for the contribution of systemic inflammation to atherosclerotic plaque formation in this population (3,75). Van Eeden et al. (75,76) suggested that, under the direct effect of cigarette smoke oxidants, the epithelial cells and alveolar macrophages in the lungs release pro-inflammatory cytokines, such as interleukins (IL 1β, 6, 8) and tumor necrosis factor (TNFα), as well as neutrophilic and monocyte mediators (MCP-1, GMCSF). When the balance between pro- and anti-inflammatory cytokines in the lungs is disrupted, the pro-inflammatory cytokines produced in the airways and lung tissue have the ability to translocate into the systemic circulation and to further promote a systemic inflammatory response. While some circulating pro-inflammatory mediators (e.g., GMCSF, IL6, IL8) stimulate the hematopoietic system and release granulocytes, monocytes, and platelets into the circulatory system, other circulating pro-inflammatory mediators (e.g., IL6, IL1β, TNFα) stimulate the liver and release acute-phase inflammatory proteins and coagulation factors (e.g., CRP, fibrinogen, factor VIII). Over time a positive feedback is initiated as more circulating leukocytes, platelets, and pro-inflammatory proteins are produced, and the resulting sustained lung and systemic inflammation lead to plaque deposition and rupture (75).

Findings from experimental and epidemiological studies are in agreement with this hypothesis. While the Gan et al. review (77) showed elevated serum levels of pro-inflammatory cytokines and acute-phase proteins (e.g., CRP, fibrinogen, leucocytes, and TNFα) associated with reduced lung function in COPD patients, the Torres et al. review (78) showed the contribution of inflammatory markers, namely CRP, to the destabilization of atherosclerotic plaque. Lastly, Sin et al. (79), using NHANES III data, found that the cardiac risk doubled in the presence of elevated CRP in patients with COPD, suggesting a link between systemic inflammation and cardiac ischemic injury in this population.

1.2.3.2 Autonomic nervous dysfunction with sympathetic dominance

Dysfunctions of the autonomic nervous system have also been related to the development and progression of atherosclerosis. Both direct and indirect evidence show that persistent activation of the sympathetic nervous system can promote atherogenesis and increase the risk of cardiovascular events. Lichtor et al. (80), in a morphometric study, found important reductions in the progression of atherosclerosis in the carotid arteries and thoracic aorta of rhesus monkeys that underwent bilateral surgical thoracic sympathectomy or treatment with beta adrenoceptors antagonist (e.g., propranolol) prior to being fed an atherogenic diet for 12 months. In a similar study, Beere et al. (51) also demonstrated a reduction of coronary atherosclerosis lesions by approximately 50% in adult male cynomolgus monkeys whose heart rates were lowered through surgical ablation of the sinoatrial node prior to being fed an atherogenic diet for 6 months. The findings of the above mentioned studies indirectly support the hypothesis that a persistently elevated heart rate, which is a marker of sympathetic overactivity, tends to accelerate the atherosclerotic lesion formation in coronary arteries.

These observations have been confirmed in human studies that have also explored various complex biological and pathophysiological pathways of this association (81-83).

Although autonomic nervous system dysfunction has been detected in the course of COPD (84-86), only recently has the role of sympathetic overactivity in the association between COPD and ischemic heart disease started to capture the attention of researchers. Van Gestel et al. (87), in a review of the current literature of the sympathetic overactivity in COPD, highlighted that multiple COPD characteristics (e.g., hypoxia, oxidative stress, intrathoracic pressure changes, or physical inactivity) can influence sympathetic nervous activity. However, one main clinical manifestation of a higher sympathetic-parasympathetic ratio, alone or in combination with systemic inflammation, is a persistently elevated resting heart rate (88,89). This is an important observation since an elevated resting heart rate has not only been commonly found in patients with COPD (5,90), but is also known as an important predictor for major cardiac ischemic events in many disease populations, including COPD (6,7,91-93). Taken altogether, these findings highlight the major role of systemic inflammation and sympathetic overactivity in the development of ischemic heart disease in patients with COPD, and also emphasize the potential clinical utility of the resting heart rate in assessing and controlling cardiac ischemic risk in this population.

1.3 Resting heart rate as a determinant of myocardial ischemia

Resting heart rate is a vital sign that reflects the autonomic nervous system balance as well as the body's metabolic rate. A persistently elevated resting heart rate has been shown to be both a determinant of myocardial ischemia and a risk factor for cardiovascular mortality.

This section presents evidence that supports the prognostic value of the resting heart rate, along with the pathogenic mechanisms thought to be involved in this association.

1.3.1 Pathophysiological and clinical features of resting heart rate

Human heartbeats are generated by rhythmic electrical discharges of the sinoatrial node (SAN) cells, which are located in the posterior wall of the right atrium, at a spontaneous firing rate of 80-100 beats/minute (94). However, at every moment this intrinsic heart rate is under the influence of the autonomic nervous and endocrine control mechanisms, which adjust the instantaneous heart rate to the body's metabolic needs. Under normal resting conditions, due to the dominant vagal influences over sympathetic influences, the heart operates at lower rates than the SAN intrinsic firing rate. In the presence of neuro-hormonal stimulation, which occurs under various physiological and pathophysiological conditions, the heart operates at rates that approach the intrinsic rate due to the dominant influence of sympathetic nerve activation and withdrawal of the vagal nerve (55). Therefore, the instantaneous value of the resting heart rate is largely the result of a complex interplay between the two branches of the autonomic nervous system, ranging commonly between 60-80 beats/min in an adult population (95). Yet, it is generally accepted that a lower resting heart rate implies more efficient heart functioning and better cardiovascular fitness, while a persistently elevated resting heart rate can signal the presence of serious underlying medical conditions (96,97). This latter aspect has been extensively investigated in patients with cardiovascular diseases (98-100), and is proven to have important implications for the prognosis and therapy of ischemic heart disease (101-103).

1.3.2 Prognostic value of resting heart rate for ischemic heart disease risk

The importance of the resting heart rate as a prognostic factor for survival was advanced for the first time in Levine's paper (104), which described an inverse relationship between heart rate and life expectancy in animals. He postulated that all animals have approximately the same number of heart beats during their lifetime, but individual life expectancy depends largely on the animal's resting heart rate. This cardinal theory was later supported by a large body of evidence that documented not only the association of elevated resting heart rate with an increased risk of all-cause and cardiovascular morbidity in both general (98,100) and disease populations (103,105), but also the beneficial effects of lowering the heart rate for better cardiovascular health (97,106,107). Some of these findings will be discussed next.

Saxena et al. (97) investigated in their Aerobics Center Longitudinal Study the relationship between resting heart rate and mortality risk in a large cohort of 53,322 individuals, with and without hypertension. They reported that patients with a resting heart rate over 80 beats/minute had a significantly higher risk for all-cause and cardiovascular mortality than those with a resting heart rate of less than 60 beats/min, even after adjusting for traditional cardiovascular risk factors and cardiorespiratory fitness [e.g., hazard ratio of 1.38 (95% CI, 1.21-1.58) and 1.51 (95% CI, 1.22-1.87), respectively]. When data was stratified by hypertension, those hypertensive individuals with a resting heart rate of over 80 beats/min were also found to be at risk of greater all-cause and cardiovascular mortality compared to those with hypertension and a resting heart rate of less than 60 beats/min [e.g., hazard ratio of 1.38 (95% CI, 1.10-1.72) and 1.52 (95% CI, 1.10-2.09), respectively]. The Coronary Artery Surgery Study (105), which involved a large cohort of 24,913 patients who underwent coronary arteriography for the presence of suspected or proven coronary artery

disease, and was followed-up for approximately 15 years, found similar results. After adjustment for various cardiovascular risk factors (e.g., age, sex, hypertension, diabetes mellitus, cigarette smoking, ejection fraction, type of recreational activity, and use of beta blockers), patients with a resting heart rate between 77 and 82 beats/min and over 83 beats/min had a significantly higher risk for total mortality and cardiovascular mortality than those with a resting heart rate of less than 62 beats/min [e.g., hazard ratio of 1.16 (99% CI, 1.04-1.28) and 1.32 (99% CI, 1.19-1.47), respectively]. Lastly, in the placebo arm of the BEAUTIFUL trial (morBidity-mortality EvAlUaTion of the If inhibitor Ivabradine in patients with coronary disease and left ventricular dysfunction study), the patients with baseline heart rates over 70 beats/min were found to have a 34% increased risk of cardiovascular death, a 46% increase in hospital admission for myocardial infarction, and a 38% increase in coronary revascularization, after adjustments for other predictors of outcomes (103). Even though different cut-off values of resting heart rate were used in the aforementioned studies, it is apparent that an elevation in resting heart rate progressively increased the cardiovascular risk.

Some of the studies that investigated the prognostic value of the resting heart rate in COPD populations found similar results. Jensen et al. (6), who examined the association between resting heart rate, pulmonary function, and prognosis in subjects with COPD from the Copenhagen City Heart Study, found that the resting heart rate not only increased with the severity of COPD, but was also associated with both cardiovascular and all-cause mortality across all stages of COPD. In a prospective cohort study conducted in 405 elderly patients with COPD, which were followed up for a median period of 7 years, Warnier et al. (108) found that for every 10 beats/min increase in resting heart rate, the relative risk for

all-cause mortality increased by 21% [e.g., crude hazard ratio: 1.28 (95% CI, 1.14-1.43); adjusted hazard ratio: 1.21 (95% CI, 1.07-1.36)] and the risk of cardiovascular mortality increased by 43% [e.g., crude hazard ratio: 1.44 (95% CI, 1.18-1.75); adjusted hazard ratio: 1.43 (95% CI, 1.17-1.76)]. Therefore, because ischemic heart disease is a major concern in COPD patients, the potential value of monitoring resting heart rate to improve risk stratification and prevent cardiovascular complications is worth considering in this population. However, these aspects could be better managed if we were able to target intervention to the pathways that lead to this detrimental association.

1.3.3 Mechanisms linking elevated resting heart rate to ischemic heart disease

Several hypotheses have been proposed to explain the mechanisms through which an elevated resting heart rate may lead to ischemic heart disease at different stages of atherogenesis (48,109,110), and a number of review papers have addressed the cardiovascular pathophysiological responses to an increased resting heart rate (111,112). Since the impact of elevated resting heart rate on myocardial ischemia depends largely on the myocardial oxygen supply-demand mismatch, two associated phenomena, namely decreased diastolic time (112) and altered mechanical properties of the vascular wall (111), will be discussed. The oxygen-rich blood delivery to the heart mainly occurs during diastole, which is responsible for approximately 80% of the coronary blood flow (113). As heart rate increases, the fraction of the cardiac cycle occupied by diastole decreases, and thus, diminishes the myocardial perfusion (111). Increases in mean arterial pressure may also occur as a compensatory physiological mechanism to elevated heart rate, favoring coronary contraction, increased tension on ventricular myocytes, and myocardial oxygen consumption

(114). A faster heart rate may also increase the fatigue of the elastic fibers by increasing the number of the stretching cycles and reducing the relaxation time of arteries between ventricular contractions (112). In the long-term, a prolonged oscillatory shear stress can trigger compensatory changes in the endothelial function and vascular smooth muscle cells of the arteries, which in turn leads to the development of atherosclerosis lesions (111). Lastly, persistent mechanical stress on the impaired endothelium results in decreases in the arterial dynamic compliance, leading to vascular remodeling and stiffening of the arterial wall (115).

1.4 Arterial stiffness

Arterial stiffness, which is a well-known predictor of cardiovascular risk, has been proposed as a link between elevated resting heart rate and ischemic heart disease. Yet, no study has explored this interdependence in patients with COPD, despite its potential importance for cardiac risk stratification. This section presents evidence on the prognostic value of the arterial stiffness, as well as factors influencing arterial stiffness in both the general population and patients with COPD.

1.4.1 Pathophysiological and clinical features of arterial stiffness

The primary function of the human circulatory system is to supply the body's cells with oxygen and nutrients, and remove their waste products (116). In order for oxygen-rich blood to be circulated throughout the body, the heart and blood vessels must exert specific functions (55). As the heart, through the cardiac muscle, acts as a pump that rhythmically propels blood into the pulmonary and systemic circulation, the blood vessels function as active channels that store, transport, and exchange blood in accordance with their

physiological function. In particular, the large arteries (namely the aorta and its branches), because of the large amount of elastic tissue in their walls, are able to store and dampen an important portion of the high-pressure blood ejected by the left ventricle during systole, as well as recoil and dispense the stored blood during ventricular diastole (113). Thus, the large arteries are considered to exert two major functions in the hemodynamic homeostasis: a conduit function, through which the blood is propelled from heart to organs, and a cushioning or smoothing function, through which intermittent or pulsatile blood flow resulting from ventricular ejection is delivered into a more continuous and steady stream within the peripheral arterial tree (117). These functions enable the small arteries and arterioles, which have extensively developed smooth muscle fibers, to regulate the blood flow at the level of microcirculation in accordance with the metabolic needs of specific tissues.

In the presence of arterial degeneration, which commonly occurs with aging and various disorders, the conduit and/or cushioning functions of the arteries can be disrupted (113,118). While the conduit function is believed to be primarily affected by the atherosclerosis process through the narrowing of the lumen within the arteries, the cushioning function is thought to be affected by the arteriosclerosis process through the stiffening and dilation of the large arteries (119). Overall, the presence of arterial stiffness is seen as an indicator of a more generalized arterial disease and also as a predictor of atherosclerosis severity (120).

1.4.2 Assessment of arterial stiffness

Arterial stiffness, also defined as a reduction in arterial distensibility, can be assessed non-invasively using various methods, such as arterial pulse waveform analysis, ultrasound, or magnetic resonance imaging (121,122). Depending on the method used, different

parameters can be quantified including, but not limited to, elastic modulus, pulse wave velocity, or augmentation index (122). Among these measurements, the aortic pulse wave velocity is considered the "gold-standard" measurement of arterial stiffness (123) due to its strong predictive value for all-cause and cardiovascular mortality in high-risk (14,16) and community-based populations (124).

The aortic pulse wave velocity (PWV) is determined through recording the arterial pressure waveforms at the carotid and femoral sites using applanation tonometry, calculating the carotid-to-femoral propagation time of the arterial pressure wave, and measuring the distance between these two sites (125). As such, the pulse wave velocity is commonly expressed as the ratio between the distance traveled by the arterial pulse wave and its propagation time ($\Delta_{distance}/\Delta_{time}$), and its value increases with age from approximately 5 m/s to 12 m/s (117). Although a PWV threshold value of 12 m/s has been initially suggested as an estimate of significant alterations in the aortic function of a hypertensive population (126), recent literature considers that a PWV threshold value of 10 m/s offers a better estimate of cardiovascular risk for both normal and hypertensive populations (127). Thus, pulse wave velocity, as a measure of arterial stiffness, can be a useful tool for studying the cardiovascular pathophysiology and predicting the cardiac risk.

1.4.3 Prognostic value of arterial stiffness for ischemic heart disease risk

The prognostic value of arterial stiffness for cardiovascular mortality has been well documented in multiple studies conducted in healthy and disease populations. For example, Mitchell et al. (124) investigated the relationship between various measures of arterial stiffness, including the PWV, and major cardiovascular events (e.g., myocardial infarction,

unstable angina, heart failure, or stroke) in 2232 participants during a median follow-up of approximately 8 years in the community-based Framingham Heart study. With multivariable models adjusted for traditional cardiovascular risk factors, they found that the aortic PWV was the best predictor of cardiovascular outcomes; a standard deviation (SD) increase in aortic PWV was associated with a 48% increase in cardiovascular disease risk (95% CI, 1.16-1.91 per SD). Laurent et al. (16) also found in a cohort of 1980 essential hypertensive patients followed for approximately 10 years that PWV was significantly associated with all-cause and cardiovascular mortality [odds ratios for 5 m/s increase in PWV were 2.14 (95% CI, 1.71-2.67) and 2.35 (95% CI, 1.76-3.14), respectively]. Mattace-Raso et al. (128), who evaluated in their Rotterdam Study the predictive value of arterial stiffness for coronary heart disease in 2835 apparently healthy subjects followed for a mean period of 4 years, also found that the risk of cardiovascular disease increased with increasing aortic PWV. After adjusting the statistical model for age, gender, mean arterial pressure, and heart rate, the hazard ratios and the corresponding 95% CIs of coronary heart disease for subjects in the second and third tertiles of the aortic PWV were 1.72 (95% CI, 0.91-3.24) and 2.45 (95% CI, 1.29-4.66), respectively, in comparison with the subjects in the reference category. Lastly, Vlachopoulos et al. (129), by performing a meta-analysis of 17 longitudinal studies that followed up 15,877 subjects for a mean of 7.7 years, indicated that the pooled relative risk of clinical events increased in a stepwise, linear-like fashion from the first to the third tertile of the aortic PWV. An increase in the aortic PWV by 1 m/s corresponded to an adjusted risk increase of 14%, 15%, and 15% in total cardiovascular events, cardiovascular mortality, and all-cause mortality, respectively. Also, an increase in the aortic PWV by 1 SD was associated with risk increases of 47%, 47%, and 42%, respectively. They concluded that aortic PWV is

a strong predictor of future cardiovascular events and all-cause mortality, and that the predictive ability of arterial stiffness is greater in subjects with a higher baseline cardiovascular risk.

Despite a large body of evidence showing that COPD is associated with increased arterial stiffness independently of comorbidities or cardiovascular risk factors (130-132), there is no study to date investigating the predictive value of PWV for cardiovascular events in these patients. Such an investigation will need to take into consideration the COPD characteristics, since PWV measurements are reported to have considerable variability in this population (133). Specific disease features may impact the reliability of PWV measurements, which in turn can also have confounding effects on the predictive ability of these measurements.

1.4.4 Factors influencing arterial stiffness

Age and blood pressure are the most accepted physiological factors influencing arterial compliance and thus, determining arterial stiffness (113,117). While the age-related increase in arterial stiffness is associated with structural changes in the arterial wall, the hypertension-related increase in arterial stiffness is mostly a result of functional changes in the arterial wall (134).

Structural changes associated with the arterial stiffening process are mainly determined by the dysregulation of the scaffolding proteins within the aortic media, which manifests by fracture and fragmentation of the elastic layer and excessive stimulation of collagen production (118,135). In contrast, the functional changes associated with an increased rigidity of the lumen of the large arteries are determined by persistent modifications in the cardiovascular hemodynamics, which are characterized by the rapid travel of the pressure

wave along the major arteries and the early return of the reflected wave from regions of discontinuity, such as arterioles. From the perspective of the heart, arterial stiffness influences the load encountered by the left ventricle, since the aorta becomes less able to accommodate the volume of blood ejected by the left ventricle; therefore, a higher ventricular end-systolic pressure is needed to overcome the increased outflow resistance. The greater pressure increment during systole results not only in a greater energy requirement for a given level of ejected flow, but also exposes the myocardium to a higher systolic pressure that leads to left ventricular hypertrophy and ischemia (119). From the perspective of the vasculature, the arterial stiffness reduces the cushioning function; thus, a greater proportion of stroke volume is forwarded during systole to the periphery in the form of a turbulent flow that induces endothelial dysfunction and promotes atherosclerosis (63). The reduced aortic elastic recoil also forces the reflected wave to return to the central aorta during systole, which not only increases systolic blood pressure, but also lowers diastolic blood pressure. The lower diastolic blood pressure further reduces the coronary artery perfusion, contributing to myocardial ischemia (63). As a result, it is largely accepted that the main hemodynamic consequences of arterial stiffness are represented by increases in systolic blood pressure, decreases in diastolic blood pressure, and augmentation of the pulse pressure, with the ultimate effect of isolated hypertension (117,136).

Besides age and blood pressure, several other factors have been described that influence the arterial stiffness, including body mass index, diabetes, hyperlipidemia, gender, and heart rate (137). Among these determinants, the heart rate dependency of arterial stiffness has recently received much attention, due to the assumption that arterial stiffness can add to the ischemic risk of a persistently elevated resting heart rate (128). Thus, understanding the

relationship between arterial stiffness and resting heart rate can have important clinical value in better prevention and control of ischemic heart disease.

1.4.5 The relationship between resting heart rate and arterial stiffness

One of the seminal studies on the heart rate - arterial stiffness relationship was conducted by Bergel et al. (138), who showed that arterial stiffness, as defined by the dynamic elastic modulus, increased linearly with the heart rate in both the elastic and muscular arteries of dogs. This observation was later confirmed by a number of experimental and clinical studies. Tan et al. (10) examined the effect of heart rate changes on the PWV in the aorta of adult male rats, over a range of mean arterial pressures raised with phenylephrine and lowered with sodium nitroprusside. They found that across the range of mean arterial pressures measured, PWV generally increased with an increasing heart rate. However, PWV changes with heart rate were statistically non-significant at a low mean arterial pressure (60-80 mmHg), and significant at a medium to high mean arterial pressure (110-130 mmHg). When PWV measurements were corrected for a reference mean arterial pressure of 100 mmHg, the heart rate was still shown to significantly affect PWV, indicating that the effect of heart rate was present even in the absence of a heart rate-mean arterial pressure interaction.

Studies conducted in human subjects implanted with cardiac pacemakers showed similar results, although the influence of arterial pressure on this relationship was not constant. Albaladejo et al. (139) showed a marked 20% increase in the PWV of elderly hypertensive patients, when their heart rate was accelerated by atrial pacing from 60 to 114 beats/min. Since the PWV increase was complemented by a 19% rise in the mean arterial pressure, the PWV changes that occurred with an elevated heart rate were attributed to changes in the

mean arterial pressure. In contrast, Lantelme et al. (140) showed, in patients referred for pacemaker implantation, an increase in the PWV as the heart rate increased, but without any significant changes in the mean arterial pressure. These last results were in line with Haesler et al. (141), who assessed the heart rate effect on PWV in adults implanted with a pacemaker, and having a relatively low arterial stiffness and a normal left ventricular ejection fraction. They found no significant changes in systolic blood pressure or mean arterial pressure at any heart rate level, but the PWV increased significantly (by 22%) as the heart rate increased from the baseline sinus rhythm (e.g., 62 beats/min) to 100 beats/min. All these results were achieved during atrial pacing and are thus considered acute changes in the heart rate.

A number of epidemiological studies examining the heart rate dependency of arterial stiffening have also found a significant positive association between the resting heart rate and various arterial stiffness indices in healthy individuals and patients with a high prevalence of cardiovascular disease or risk factors. Sa Cunha et al. (142) performed one of the first epidemiological studies on the heart rate-arterial stiffness relationship. They showed that PWV and casual heart rate at rest were positively correlated in 213 patients with untreated mild-to-moderate hypertension. Chen et al. (13) examined the influence of heart rate on arterial stiffness in a cohort of Black and White young adults in the Bogalusa Heart Study. In a multivariate regression model adjusted for traditional cardiovascular risk variables (e.g., age, gender, smoking, cholesterol, and blood pressure), they found that the resting heart rate was independently associated with the central pulse wave velocity. Park et al. (11) also determined the association between the resting heart rate and arterial stiffness, as measured by brachial-ankle PWV in Korean adults free of coronary artery disease. They found that the age-adjusted brachial-ankle PWV mean values increased gradually with the heart rate

quartile, even after adjusting for classic cardiovascular risk factors, including inflammatory biomarkers. Lastly, Whelton et al. (12) showed, in a population free of known cardiovascular disease, that aortic distensibility, as a measure of arterial elasticity, decreased monotonically with an increasing resting heart rate. In their study, the heart rate was divided into quintiles and progressively adjusted for cardiovascular risk factors, including physical activity and atrioventricular nodal blocking agents.

Despite a large amount of evidence supporting the association between resting heart rate and arterial stiffness in healthy and disease populations, questions remain related to the physiological basis of this relationship and methodological aspects of arterial stiffness measurement (143). Addressing some of these controversies in a population of COPD patients known to commonly experience both an elevated resting heart rate (5,6) and arterial stiffness (130,131) may reveal the cumulative effect of heart rate and arterial stiffness on increasing the ischemic risk in this population. Moreover, given the potential of pulmonary rehabilitation through aerobic exercise training to reduce hemodynamic parameters (17,18), the heart rate-arterial stiffness relationship may be used to improve the cardiac risk stratification and to gauge the efficacy of pulmonary rehabilitation in controlling ischemic heart disease in COPD patients.

1.5 Pulmonary rehabilitation program (PRP)

Pulmonary rehabilitation is an evidence-based intervention that has been proven to improve clinical outcomes such as respiratory symptoms, functional capacity, and quality of life in COPD patients. Despite the fact that pulmonary rehabilitation program includes an important aerobic component, which is known to generally improve cardiovascular health,

limited evidence exists about the potential of pulmonary rehabilitation to reduce cardiovascular risk in COPD patients. This section presents current evidence and issues concerning the impact of pulmonary rehabilitation in controlling two ischemic risk factors, namely, resting heart rate and arterial stiffness in patients with COPD.

1.5.1 General considerations on pulmonary rehabilitation

Pulmonary rehabilitation is an evidence-based, multidisciplinary, and comprehensive intervention designed for patients with chronic respiratory diseases, whose everyday life is affected by respiratory and functional symptoms despite adequate drug therapy (144,145). A pulmonary rehabilitation program normally includes a spectrum of long-term intervention strategies, such as exercise training, nutritional counselling, psychosocial support, and self-management education (144,146), which are designed to improve clinical outcomes and quality of life, as well as to reduce healthcare costs associated with these diseases (145-147). Exercise training, which is the core component of any pulmonary rehabilitation program, is integrated into an individualized treatment plan and commonly performed in an outpatient hospital setting under the direct supervision of a health care professional (148,149). It has proved to have the strongest evidence among the pulmonary rehabilitation components for increasing patients' functional capacity and reducing respiratory symptoms such as dyspnea (147,150). Yet, despite scientific evidence of physiological (151) and clinical benefits (152) from exercise training for patients with COPD, approximately one third of the patients referred to pulmonary rehabilitation are non-responders in terms of exercise capacity (e.g., quantified by six-minute walk distance) and/or health-related quality of life (e.g., assessed by St. George's Respiratory Questionnaire) (153,154). While the lack of response to

participation in a pulmonary rehabilitation program has been mainly attributed to ventilatory impairment (154), there is evidence that even those patients with very severe COPD are able to achieve clinically significant improvements in pulmonary rehabilitation outcomes (153). These findings reinforce the opinion that the ventilatory dysfunction alone cannot completely explain the variability in response to pulmonary rehabilitation (155,156), and the presence of the associated comorbidities, such as cardiovascular diseases, may represent limiting factors that work against a beneficial response to pulmonary rehabilitation in COPD (157,158). Therefore, in order to maximize the benefits of pulmonary rehabilitation in COPD patients, a change of focus from an evidence-based to an optimization-based approach has been proposed (159), with a particular focus on cardiovascular comorbidities.

1.5.2 Ischemic heart disease in COPD patients attending PRP

Ischemic heart disease is a common comorbidity in patients with COPD attending a pulmonary rehabilitation program. While the prevalence figures show that between 10% and 30% of COPD patients undergoing pulmonary rehabilitation present with ischemic heart disease (158,160), there are studies reporting that ischemic heart disease is often undetected or unreported in COPD patients (161,162). This can be due to similar COPD and ischemic heart disease symptoms, such as breathlessness, limited ability to exercise, and fatigue, which make a specific diagnosis difficult (156,163).

The presence of ischemic heart disease in COPD patients undergoing pulmonary rehabilitation has also been shown to negatively influence clinical outcomes (157,158,164). However, questions remain as to whether poor rehabilitation outcomes associated with ischemic heart disease in COPD are due to the difficulty in achieving the optimal training

intensity necessary to produce physiological adaptations (151,165), or to reaching a critical training intensity that leads to physiological dysfunctions (166). Equally important, poor adherence and/or compliance to pulmonary rehabilitation have also been associated with the presence of ischemic heart disease, due to the exacerbation of disease symptoms with exercise or the perception of an insufficient response to rehabilitation (39,167,168). Thus, the implementation of an effective pulmonary rehabilitation in COPD patients with ischemic heart disease poses important challenges for physiotherapists in providing optimal exercise prescriptions and recommendations in this population (159,169). New insights on specific cardiovascular risk factors, such as heart rate or arterial stiffness, can be useful in gauging the efficacy of pulmonary rehabilitation in controlling myocardial ischemia in this population.

1.5.3 Physiological benefits of exercise on cardiovascular health

Current recommendations for primary and secondary prevention of cardiovascular diseases in general, and ischemic heart disease in particular, promote lifestyle changes such as increasing physical activity (170). These recommendations are strengthened by the evidence that aerobic exercise training has beneficial effects on hemodynamic and metabolic factors (171), with a subsequent reduction in cardiovascular risks (172).

One of the first indicators of cardiovascular adaptation to aerobic exercise training, which occurs mainly due to increases in the vagal activity, is represented by a decrease in the resting heart rate (173,174). However, a low intrinsic heart rate has also been attributed to atrial enlargement, which occurs in response to training-induced increases in blood volume and pressure load. A higher plasma volume, together with an increased venous return to the left ventricle, normally increases diastolic filling and ventricular compliance, which

subsequently improves cardiac performance (175). Regular aerobic training also produces vascular adaptions arising from adjustments in the neuro-humoral control of vascular tone. Enhanced endothelium-dependent vasodilation links vascular resistance reduction with lower systolic and diastolic blood pressure (20,176). All these hemodynamic adaptations are complemented by significant improvements in exercise capacity following endurance training, and represent indirect evidence for improved myocardial oxygenation and cardiovascular health (177,178). Thus, a lower resting heart rate and increased vascular compliance are commonly seen as markers of cardiorespiratory fitness, and their control is essential in reducing the cardiovascular risk.

Although the resting indices of cardiac function can be modulated by exercise training, substantial differences in the hemodynamic responses to exercise training between healthy and disease populations have been reported. While most of the studies performed in healthy individuals indicated reductions of up to 10 beats/min in resting heart rate following exercise training (179,180), studies performed in disease populations found either no significant changes or small reductions in resting heart rate following aerobic exercise training (181,182). The effects of exercise training on vascular compliance or arterial stiffness followed a similar trend, with more evident improvements in the general population (18,20) than in disease populations (183,184). Differences in the maintenance of hemodynamic responses to exercise training have also been reported. For example, at a six-month follow-up, an attenuation of short-term improvements in both resting heart rate and arterial stiffness has been described in older adults with multiple cardiovascular risk factors (182), but not in community-dwelling healthy elderly subjects (185). Together, these findings suggest that

there are still many aspects related to exercise training-induced hemodynamic changes that need to be better understood in disease populations.

1.5.4 Exercise effects on resting heart rate and arterial stiffness in COPD

Although the effect of aerobic exercise training on hemodynamic factors, such as resting heart rate and arterial stiffness, is well established in healthy individuals, studies performed in COPD patients have reported contradictory findings. The Vivodtzev et al. (186) study was one of the first investigating the effect of endurance training on arterial stiffness in patients with COPD. Seventeen COPD patients included in a case-controlled study matched for age, disease severity, and walking distance were evaluated at baseline and after four weeks of training. Pulse wave velocity significantly decreased (10.3 ± 0.7 to 9.2 ± 0.8 m/s, $p = 0.001$) in the trained group (10 COPD patients) in comparison with the untrained group (7 COPD patients). The authors suggested a link between improvements in arterial stiffness following exercise training and decreases in blood pressure. Although the effect of exercise training on resting heart rate was not reported, the authors did mention that heart rate was reduced in 75% of the patients diagnosed as hypertensive. The Gale et al. study (181) found in 22 stable COPD patients, completing a pulmonary rehabilitation program, that aortic PWV was reduced significantly after two months of exercise training (9.8 ± 3.0 to 9.3 ± 2.7 m/s, $p < 0.05$), and those improvements were associated with significant reductions in systolic and diastolic blood pressure, but not the resting heart rate. Finally, Vanfleteren et al. (187) conducted a study investigating the effect of pulmonary rehabilitation on arterial stiffness in 129 stable COPD patients. They found that aortic PWV did not change following pulmonary rehabilitation (10.7 ± 2.7 versus 10.9 ± 2.5 m/s, $p = 0.339$), and stated that arterial stiffness in

COPD patients did not respond to state-of-the-art pulmonary rehabilitation. In contrast to previous studies, they found a significant reduction in the resting heart rate of 1 beat/min, but an increase in the systolic blood pressure that almost reached a statistically-significant level.

It is apparent that the overall results of these studies exhibit many inconsistencies that make it difficult to draw a conclusion about the effect of pulmonary rehabilitation on resting heart rate and arterial stiffness in the COPD population. Thus, there are a few comments that are worth making here. First, large variations in the aortic PWV in response to exercise training in COPD patients were reported within all studies. This observation raises concerns that there were either methodological limitations associated with the PWV measurement, variations in training protocols, or specific disease factors that might have increased the vascular response variability in this population. Second, no study took into account the potential effect of resting heart rate on arterial stiffness in response to exercise training, although the heart rate dependency of arterial stiffness in the general population is established (11,12). This dissertation was designed around determining if the heart rate is a possible determinant of arterial stiffness in patients with COPD, as well as the potential of pulmonary rehabilitation to modulate the heart rate - arterial stiffness relationship.

1.6 Dissertation overview

The overall objectives of this dissertation work are to provide a comprehensive investigation into the relationship between resting heart rate and arterial stiffness in patients with COPD, as well as into the modulatory effect of aerobic exercise training used in a standard pulmonary rehabilitation program on these two parameters. The research included in

this dissertation was developed as an original multi-phase project (Figure 1.1), in which each phase was designed to address a specific research objective as presented below.

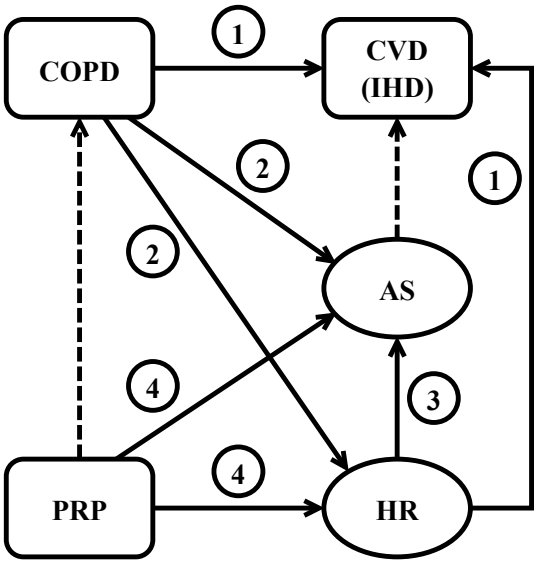

Figure 1.1. Organization of the dissertation research. Numerical labels and their solid arrows correspond to research objectives. (COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; IHD = ischemic heart disease; AS = arterial stiffness; HR = resting heart rate; PRP = pulmonary rehabilitation program)

1.6.1 Specific research objectives

The first objective of this research was to investigate the frequency of ischemic heart disease, as evidenced by prior myocardial infarction, in patients with chronic lung disease attending a standard pulmonary rehabilitation program. The resting heart rate, as a potential indicator of prior myocardial infarction injury, was also explored in this study. The working hypothesis was that in this chronic lung disease population the frequency of prior myocardial infarction quantified through a validated electrocardiographic (ECG) score would be higher than that reported in the medical records, and an elevated resting heart rate would be

associated with a higher risk of prior myocardial infarction. This project is presented in Chapter 2 of this dissertation.

The second objective of this research work was to investigate the test-retest reliability of resting heart rate and arterial stiffness measurements in a population of moderate-to-severe COPD patients, who would normally be referred to a pulmonary rehabilitation program. The working hypothesis was that both resting heart rate and pulse velocity measurements would have a good repeatability throughout different testing days, and could be used reliably for monitoring the cardiovascular risk of patients with COPD in a pulmonary rehabilitation setting. These projects are presented in Chapters 3 and 4 of this dissertation.

The third objective of this research work was to evaluate the relationship between resting heart rate and arterial stiffness in individuals with COPD, in comparison with that of control individuals. The working hypothesis was that PWV would be positively associated with resting heart rate in both COPD and control groups, and would persist independently of common cardiovascular risk factors. This project is presented in Chapter 5.

Finally, the fourth objective of this research was to investigate the effect of aerobic exercise training, used in a standard pulmonary rehabilitation program, on resting heart rate and arterial stiffness, as well as on the relationship between the two parameters in COPD. The working hypothesis was that a standard pulmonary rehabilitation program would decrease both resting heart rate and pulse wave velocity in COPD patients, and the changes in the resting heart rate would explain the changes in arterial stiffness with pulmonary rehabilitation program in this population. This project is presented in Chapter 6.

The last chapter of this dissertation, Chapter 7, provides a general discussion of the main findings of the dissertation, along with its limitations, future directions, and conclusions.

Chapter 2: Resting heart rate as an indicator of prior myocardial infarction in subjects with chronic lung disease attending pulmonary rehabilitation

2.1 Introduction

Ischemic heart disease is a major determinant of morbidity and mortality among individuals with chronic lung diseases (CLD) (188,189), particularly those with COPD (2,70). Moreover, prior myocardial infarction (MI), which is a serious manifestation of ischemic heart disease, remains commonly under-recognized in this population (161,162). Given that survivors of myocardial infarction are at increased risk of poor outcomes and future cardiac events (190), overlooking this condition in CLD patients can lead to inadequate treatment decisions. This aspect is particularly relevant in a pulmonary rehabilitation setting where health care professionals should be aware of prior myocardial infarction to determine appropriate training prescription and avoid adverse cardiac events associated with exercise such as arrhythmia, recurrent myocardial ischemia, or myocardial infarction (191,192).

Before starting a pulmonary rehabilitation program, patients with CLD undergo a health history to identify those at high risk for complications that may emerge during exercise training (144,169). However, the history of comorbidities often relies on patients' self-reporting rather than objective medical assessments. Exercise tests are also performed to evaluate patients' exercise tolerance and prescribe exercise intensity (193). Nevertheless, while symptom-limited incremental exercise tests, such as a cardiopulmonary exercise

test (CPET), are useful for identifying myocardial ischemic injury, they are not always available or routinely performed before pulmonary rehabilitation (194,195). Therefore, rehabilitation health professionals must rely on other accessible clinical measurements to estimate the presence of prior myocardial infarction.

A number of electrocardiographic (ECG) classification systems are currently available to estimate the presence and/or severity of prior myocardial ischemic injury. The Cardiac Infarction Injury Score (CIIS), which is a validated electrocardiographic score (196), has been shown to be highly accurate at detecting prior myocardial infarction. Whether used as a categorical or continuous variable, the CIIS can provide useful information on myocardial damage and cardiac events (197,198). Furthermore, a CIIS value equal to or greater than 20 is a significant predictor of cardiovascular mortality in apparently healthy, middle-aged individuals (199) and patients with COPD (162,200). Therefore, the CIIS is a convenient, non-invasive diagnostic tool to detect prior myocardial infarction.

Resting heart rate (HR) and heart rate response to exercise are two hemodynamic parameters regularly monitored in the rehabilitation setting, which also impart important prognostic information about cardiac ischemic risk (8,201). A persistently elevated resting heart rate has been shown to be involved in the pathophysiology of atherosclerosis (110), and to contribute to plaque disruption (202) and acute coronary events (203). In particular, a resting heart rate over 80 beats/minute has been reported to be associated with increased risk of all-cause and cardiovascular mortality in both general and high-risk populations (97,105). An inadequate heart rate increase in response to exercise (e.g., chronotropic incompetence) has also been correlated with the incidence of coronary disease and the risk of cardiovascular death (204,205). Despite patients with chronic lung diseases commonly displaying both an

elevated resting heart rate and chronotropic incompetence (5,206,207), there has been no study to date investigating the relationship between these two parameters and prior MI in this population.

We conducted this study to estimate the presence of prior myocardial infarction in chronic lung disease patients attending a pulmonary rehabilitation program based on their CIIS, and to determine if a myocardial infarction was reported in the medical records. Secondly, we evaluated whether resting heart rate and chronotropic response are associated with prior myocardial infarction, as assessed by the CIIS, in this chronic lung disease population. Our hypothesis was that the frequency of prior myocardial infarction quantified through the CIIS would be higher than that reported in the medical records, and a positive association between heart rate parameters and CIIS would be present in this population. Because chronic lung disease patients are a heterogeneous group, we also determined if the findings differed in patients diagnosed with COPD compared to patients diagnosed with other chronic lung diseases.

2.2 Methodology

2.2.1 Study design and setting

This study used a retrospective cohort design and was conducted in a pulmonary rehabilitation outpatient clinic at St. Paul's Hospital, a tertiary care university-affiliated hospital in Vancouver, British Columbia, Canada.

2.2.2 Study population

The medical records of CLD patients enrolled in a PRP between January 2010 and December 2014 were reviewed. Data was collected from the patients who met the following inclusion criteria: over 35 years of age; a physician diagnosis of CLD confirmed by clinical, radiological, and pulmonary function examinations; an available symptom-limited incremental exercise test (CPET) performed on a cycle ergometer before the start of the PRP; and twelve-lead ECG recordings obtained at rest before the CPET. Patients were excluded if they had: uninterpretable or irretrievable resting ECG; missing hemodynamic data at resting and peak exercise; or conditions altering CIIS calculation such as atrial fibrillation, ventricular paced rhythm, left bundle branch block, and left ventricular hypertrophy with repolarization abnormalities. For patients with more than one admission to the PRP during the inclusion period, data collected from the latest admission was used. Ethical approval to conduct the study was obtained from the Research Ethics Board at Providence Health Research Institute/University of British Columbia (H11–00984–A007).

2.2.3 Study procedure

Two sources of data consisting of the patients' medical records and the PRP database contributed to the retrospective data collection. First, each patient's medical records were electronically searched in order to retrieve information on the completion of a CPET prior to initiation of the PRP and standard 12-lead ECGs recorded at rest. Next, the PRP database and CPET electronic records were reviewed in order to collect patients' characteristics, medical history, and hemodynamic and functional measurements.

2.2.3.1 Electrocardiographic classification of prior myocardial infarction

To estimate the presence of prior myocardial events, the CIIS was calculated. A cardiologist and a trained health professional with expertise in electrocardiography, blind to any patient information, independently analyzed each ECG for recording accuracy. Twelve specific ECG features including R, S, and T wave amplitudes, Q wave duration, and Q/R amplitude ratios were measured, tabulated, and converted to a CIIS (196). In order to avoid any interpretation errors in this process, a calculation protocol was developed *a priori* and refined until the inter-rater reliability exceeded 0.90. Any disagreements between the two assessors were resolved through discussion. Patients were classified as having prior MI if their CIIS was equal to or greater than 20, as this value accurately classifies a "probable infarction" in an adult population (196,208).

2.2.3.2 Heart rate measurements

Resting and peak heart rate were collected as values measured at rest prior to CPET and during the last minute of CPET, respectively. Chronotropic response index (CRI), which represents the capacity to increase the heart rate in response to exercise, was calculated as the percentage of heart rate reserve that was used during exercise: [(peak heart rate – resting heart rate) x 100/(220-age) – (resting heart rate)] (93). A cut-off point of ≤ 80% was considered as chronotropic incompetence (205), except for subjects on beta-blockers where a cut-off point of ≤ 62% was applied (209). Failure to achieve 85% of the maximal age-predicted heart rate was also collected from the CPET results.

2.2.3.3 Additional clinical outcomes

Spirometric measurements [percent predicted forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio] were gathered from patient records along with age, height, weight, smoking status, and use of oxygen. Body mass index (BMI) was calculated as weight divided by height squared. Indices of submaximal [e.g., distance walked during a six minute walk test (6MWD)] and maximal/peak exercise capacity [e.g., oxygen uptake (VO_2), workload, and exercise time] were collected and information on medications and comorbidities was recorded. Cardiovascular comorbidities, including myocardial infarction, were defined on the basis of self-reports or physician reports.

2.2.4 Statistical analysis

For descriptive statistics, continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. Differences in patients' baseline characteristics according to the patient groups (COPD versus non-COPD) were compared using parametric (Student's t-test) or non-parametric (Wilcoxon Mann-Whitney) tests for continuous variables, and Chi-square or Fisher's tests for categorical variables. The Cohen's Kappa test was used to compare the agreement between CIIS and medical records of past myocardial events. Univariate correlations and multivariate regression analyses were performed to assess the relationship between CIIS and heart rate parameters in our CLD population, considering CIIS first as a continuous variable, then as a dichotomous variable (CIIS $\geq$ 20 versus CIIS $<$ 20). Stepwise regression was applied to select suitable variables for use in the regression model. All statistical analyses were

performed using the statistical software package SAS for Windows, version 9.4 (SAS Institute, Cary, North Carolina). A p value < 0.05 was considered statistically significant.

2.3 Results

2.3.1 Study population

One hundred and sixteen chronic lung disease patients with cardiopulmonary exercise testing were identified in the St. Paul's Hospital outpatient pulmonary rehabilitation program database. Of the 116 potential participants, 31 patients (27%) were excluded because they either had uninterpretable or missing ECG tests, pharmacological or treadmill stress testing, or conditions known to alter CIIS interpretation. Therefore, 85 CLD patients were included, in the final analysis of whom 54 patients had a physician diagnosis of COPD (COPD group) and 31 patients had a physician diagnosis of CLD other than COPD (non-COPD group) according to their lung function tests, clinical, and radiological examinations. Diagnoses in the non-COPD group included bronchiectasis (n = 1), chronic asthma (n = 2), cystic fibrosis (n = 2), combined obstructive-restrictive patterns ($FEV_1/FVC > 70$) (n = 10), and interstitial lung diseases such as sarcoidosis, nonspecific interstitial pneumonia, idiopathic pulmonary fibrosis, and hypersensitivity pneumonitis (n = 16). The study flow diagram is presented in Figure 2.1.

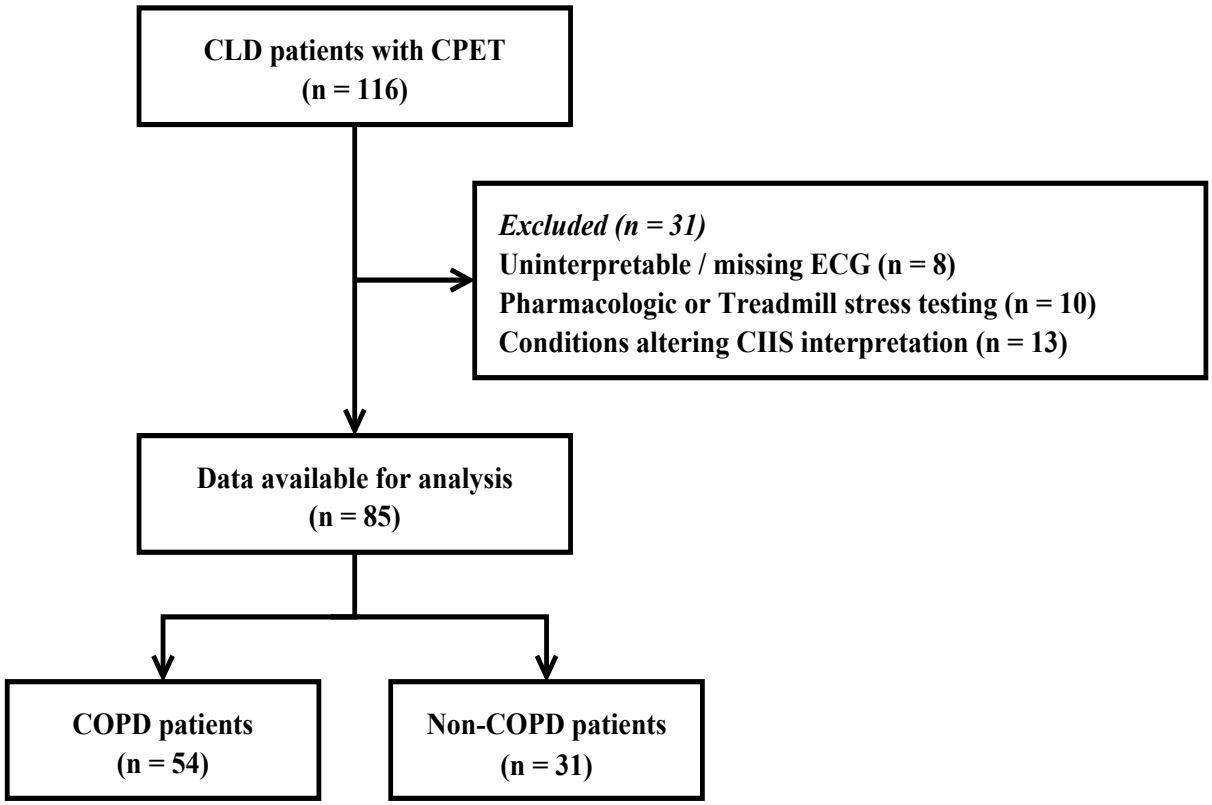

Figure 2.1. Study flow diagram

2.3.2 Participant characteristics

The study population had a mean age (± SD) of 64 ± 10 years and 52% were male. The COPD and non-COPD groups did not differ significantly in patient characteristics except for sex, smoking status, pulmonary function tests, and pulmonary medication prescription (Table 2.1). While the individuals in the COPD group were predominantly men (61%) with moderate-severe pulmonary obstruction (FEV_1 50 ± 17% predicted; FEV_1/FVC 48 ± 12), the individuals in the non-COPD group were predominantly women (65%) with mild-moderate pulmonary restriction (FVC 73 ± 14% predicted; FEV_1/FVC 77 ± 12), and fewer pack-years. The COPD patients used significantly more lung medications than those in the non-COPD

group, but no differences between the two groups were found in the use of cardiovascular medications. Renin-angiotensin system (RAS) antagonists were the most frequent, and beta-blockers the least frequent, cardiovascular medications prescribed in this population. Ischemic heart disease, hypertension, and dysrhythmias were the principal cardiovascular diseases found in the patients' medical records.

Table 2.1. Characteristics of the study population

Variables	**Total (n = 85)**	**COPD (n = 54)**	**Non-COPD (n = 31)**	*p value*
Age (years)	64 ± 10	65 ± 8	62 ± 13	*0.197*
Male/female (%)	52/48	61/39	35/65	***0.023***
BMI (kg/m^2)	27.3 ± 6.4	26.4 ± 6.4	28.7 ± 6.3	*0.087*
Smoking history (pack-year)	34 ± 26	44 ± 23	17 ± 22	***<0.0001***
Current smokers, n (%)	16 (19)	14 (26)	2 (6)	***0.042***
Pulmonary function				
FEV_1 (% predicted)	57 ± 19	50 ± 17	70 ± 15	***<0.0001***
FVC (% predicted)	77 ± 17	79 ± 18	73 ± 14	*0.072*
FEV_1/FVC	59 ± 19	48 ± 12	77 ± 12	***<0.0001***
Long-term oxygen therapy, n (%)	8 (9)	7 (13)	1 (3)	*0.248*
Lung medications				
Number of lung medications	3 ± 2	4 ± 2	2 ± 2	***0.002***
Short/long muscarinic antagonists, n (%)	43 (51)	34 (63)	9 (29)	***0.003***

Variables	Total (n = 85)	COPD (n = 54)	Non-COPD (n = 31)	*p* value
Short/long beta agonists, n (%)	61 (72)	46 (85)	15 (48)	***0.0003***
Inhaled/oral corticosteroids, n (%)	56 (66)	36 (67)	20 (65)	*0.841*
Cardiovascular medications				
Number of medications	1 ± 2	1 ± 2	1 ± 2	*0.981*
RAS antagonists, n (%)	29 (34)	18 (33)	11 (35)	*0.841*
Anticoagulants, n (%)	19 (22)	12 (22)	7 (23)	*0.970*
Diuretics, n (%)	17 (20)	11 (20)	6 (19)	*0.910*
Statins, n (%)	15 (18)	9 (17)	6 (19)	*0.754*
Calcium antagonists, n (%)	14 (16)	9 (17)	5 (16)	*0.949*
Beta-blockers, n (%)	9 (11)	6 (11)	3 (10)	*1.000*
Cardiovascular comorbidities				
Ischemic heart disease, n (%)	29 (34)	18 (33)	11 (35)	*0.841*
Hypertension, n (%)	27 (32)	14 (26)	13 (42)	*0.127*
Dysrhythmias, n (%)	24 (28)	18 (33)	6 (19)	*0.168*

Legend: BMI = body mass index, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, RAS = renin angiotensin system; Values are described as mean ± standard deviation, except for sex, smoking status, medication, and comorbidities, which are described as counts and percentage; p < 0.05 significantly different between COPD and non-COPD patients

2.3.3 Myocardial infarction history

Sixteen CLD patients (19%) were classified as having prior MI based on a CIIS ≥ 20, compared to only seven patients (8%) who had reported acute myocardial events according to their medical records (p = 0.036). The Cohen's Kappa test revealed poor level of agreement between CIIS and medical records (kappa = 0.165; 95% CI, -0.08, 0.41). This means that a significant percentage of patients with prior MI were detected only through CIIS, indicating that prior MI diagnosis was underreported in the medical records. The percentages of patients with prior MI evidenced by CIIS ≥ 20 and medical records were similar in the COPD group (17% versus 11%, p = 0.374), but differed significantly in the non-COPD group (23% versus 3%, p = 0.020), as illustrated in Figure 2.2.

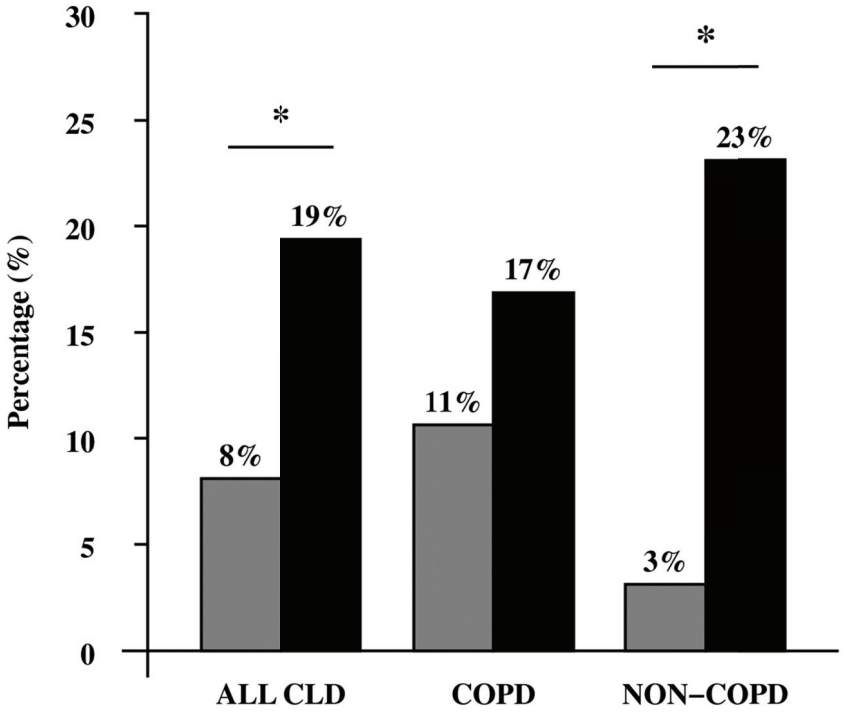

Figure 2.2. Percentage of patients with myocardial infarction based on the medical records (gray bars) and Cardiac Infarction Injury Score (black bars); Total chronic lung disease patients (ALL CLD), COPD, and Non-COPD; * p < 0.05

2.3.4 Relationship between CIIS and heart rate parameters

Hemodynamic and functional capacity data are presented in Table 2.2. On average, the study population had a CIIS of 13.0 ± 8.1 units with similar (non-significant differences) values in the non-COPD group (12.5 ± 10.1 units) and the COPD group (13.2 ± 6.8 units). While resting heart rate did not differ between the two groups, the COPD group manifested significantly lower peak heart rate and percent predicted heart rate (121 ± 18 beats/min and 78 ± 12%, respectively) on the CPET compared to the non-COPD group (138 ± 19 beats/min and 87 ± 11%, respectively). The COPD group also had significantly lower chronotropic response (CRI 53 ± 22% versus 74 ± 21%), submaximal (6MWD, 385 ± 106 meters versus 438 ± 92 meters) and maximal functional exercise capacity indices (relative peak VO_2 16.6 ± 4.9 mL/kg/min versus 19.1 ± 4.5 mL/kg/min) compared to the non-COPD group.

Table 2.2. Hemodynamic and functional capacity variables

Variables	**Total (n = 85)**	**COPD (n = 54)**	**Non-COPD (n = 31)**	*p value*
CIIS (units)	13.0 ± 8.1	13.2 ± 6.8	12.5 ± 10.1	*0.757*
Hemodynamic measures				
Resting HR (beats/min)	85 ± 13	85 ± 14	85 ± 11	*0.804*
Resting HR > 80, n (%)	55 (65)	33 (61)	22 (71)	*0.360*
Resting SBP (mmHg)	128 ± 20	127 ± 20	128 ± 22	*0.832*
Resting DBP (mmHg)	78 ± 12	78 ± 13	77 ± 12	*0.834*
Resting SpO_2 (%)	97 ± 2	96 ± 2	97 ± 3	***0.011***

Variables	Total (n = 85)	COPD (n = 54)	Non-COPD (n = 31)	*p* value
Maximal functional capacity				
Peak HR (beats/min)	127 ± 20	121 ± 18	138 ± 19	***<0.0001***
Peak HR (% predicted)	81 ± 12	78 ± 12	87 ± 11	***0.0007***
Peak SBP (mmHg)	176 ± 25	175 ± 26	179 ± 23	*0.451*
Peak DBP (mmHg)	85 ± 13	85 ± 14	84 ± 12	*0.699*
Relative Peak VO_2 (mL/kg/min)	17.5 ± 4.9	16.6 ± 4.9	19.1 ± 4.5	***0.026***
Peak workload (Watts)	71 ± 27	68 ± 29	78 ± 23	***0.048***
Exercise time (min)	6 ± 3	6 ± 3	7 ± 2	***0.032***
Target HR reached (%)	32 (38)	15 (28)	17 (55)	***0.013***
CRI (%)	60 ± 24	53 ± 22	74 ± 21	***<0.0001***
CRI < 80, n (%)	67 (79)	47 (87)	20 (65)	***0.014***
Submaximal functional capacity				
6 MWD (meters)	405 ± 104	385 ± 106	438 ± 92	***0.040***

Legend: HR = heart rate, SBP = systolic blood pressure, DBP = diastolic blood pressure, SpO2 = blood oxygen saturation, VO2 = oxygen uptake, CRI = chronotropic response index, 6MWD = six minute walk distance test; Values are described as mean ± standard deviation, except for resting HR > 80, target HR and CRI, which are described as counts and percentage; p < 0.05 significantly different between COPD and non-COPD patients

Univariate correlations, employed to determine heart rate parameters significantly associated with CIIS, considered as a continuous variable, showed that resting heart rate (r = 0.22, p = 0.045), but not chronotropic response index (r = 0.12, p = 0.276) was positively

associated with CIIS. Multivariate regression analyses also indicated that resting heart rate continued to be significantly associated with CIIS after adjusting for diastolic blood pressure, FVC, and the use of cardiovascular medication (particularly the absence of RAS antagonists prescription) ($R^2 = 0.29$, $p < 0.0001$). These results were similar ($R^2 = 0.27$, $p < 0.0001$) when resting heart rate was expressed as a dichotomous variable (Table 2.3).

Table 2.3. Multiple regression analysis for CIIS as continuous variable

Independent variables	**β**	**95% CI**	*p value*
Model 1 (HR as continuous variable)			
Resting HR (beats/min)	0.17	(0.05, 0.28)	***0.004***
Resting DBP (mmHg)	-0.17	(-0.29, -0.04)	***0.008***
FVC (% predicted)	0.13	(0.04, 0.22)	***0.005***
RAS antagonists (0)	4.64	(1.53, 7.75)	***0.003***
R-square	**0.29**		
Model 2 (HR as dichotomous variable)			
Resting HR > 80 (beats/min)	3.92	(0.59, 7.25)	***0.022***
Resting DBP (mmHg)	-0.16	(-0.29, -0.03)	***0.014***
FVC (% predicted)	0.14	(0.04, 0.23)	***0.006***
RAS antagonists (0)	4.44	(1.12, 7.76)	***0.009***
R-square	**0.27**		

Legend: HR = heart rate, DBP = diastolic blood pressure, FVC = forced vital capacity, RAS (0) = absence of RAS antagonist prescriptions

When CIIS was considered as a dichotomous variable (CIIS ≥ 20 versus CIIS < 20), the logistic regression indicated that the resting heart rate was a significant predictor of CIIS ($p = 0.048$) only when resting heart rate was a dichotomous variable; patients with a resting heart rate over 80 beats/min had approximately 5 times higher odds of having a CIIS ≥ 20. In the same analysis, the absence of RAS antagonist medications but not diastolic blood pressure, or FVC reached significance (Table 2.4). The inclusion of the diagnosis groups as an independent variable did not improve any of the regression models.

Table 2.4. Logistic regression analysis for CIIS as categorical variable

Independent variables	**β**	**Wald Chi-square**	**Point estimate**	**95% Wald confidence limits**	*p value*
Model 1 (HR as continuous variable)					
Resting HR (beats/min)	0.05	3.4	1.1	(0.99, 1.11)	*0.064*
Resting DBP (mmHg)	-0.05	3.6	0.9	(0.90, 1.00)	*0.057*
FVC (% predicted)	0.03	2.3	1.0	(0.99, 1.07)	*0.134*
RAS antagonists (0)	2.29	4.3	9.8	(1.14, 85.03)	***0.038***
Model 2 (HR as dichotomous variable)					
Resting HR > 80 (beats/min)	1.56	3.9	4.7	(1.01, 22.24)	***0.048***
Resting DBP (mmHg)	-0.06	3.7	0.9	(0.89, 1.00)	*0.054*
FVC (% predicted)	0.03	2.7	1.0	(0.99, 1.07)	*0.099*
RAS antagonists (0)	2.20	4.1	9.2	(1.06, 76.08)	***0.044***

Legend: HR = heart rate, DBP = diastolic blood pressure, FVC = forced vital capacity, RAS (0) = absence of RAS antagonist prescriptions

2.4 Discussion

We found that CLD patients entering pulmonary rehabilitation were at risk of unreported prior MI. Although the proportion of prior myocardial injury, as detected by the CIIS score, was similar in COPD and non-COPD patient groups, the COPD patients were more likely to have a reported MI in their medical history. In addition, resting heart rate, but not chronotropic response index, was significantly associated with CIIS, in this CLD population.

Previous studies that investigated MI history in patients with COPD using ECG classification schemes reported frequency values around 20%. Vanfleteren et al. (161), using the Minnesota scoring system, found that 21% of COPD patients entering a pulmonary rehabilitation program presented ECG changes suggestive of silent MI, and 14% of these patients did not have any medical records of ischemic heart disease. With a CIIS cut-off value of 20, Sillen et al. (198) showed that approximately 10% of the COPD patients in Global Initiative for Chronic Obstructive Lung Disease (GOLD)-D stage that were referred to a PRP had prior MI. Similarly, Karoli et al. (200) found that 12.1% and 5.6% of the COPD patients in their study had a prior MI according to the ECG and medical records, respectively. Moreover, they found that a CIIS above 20 represented a risk factor for death in this population. Although the prevalence values may vary with the population or the diagnosis method, our results are in line with these studies and show that 19% and 8% of the CLD patients enrolled in a PRP had a prior MI according to the ECG and medical records, respectively. However, to the best of our knowledge, this study is the first to show that the non-COPD patients were less likely to have a reported MI in their history compared to the COPD patients. Therefore, these results show the importance of screening for ischemic heart disease in all patients with CLD attending pulmonary rehabilitation.

We also found that CLD patients enrolled in our PRP displayed elevated resting and peak heart rate, with values being about 20 beats/min higher than those reported in the literature for apparently healthy individuals of the same age and exercising at the same workload (approximately 70 Watts) (210). Moreover, the resting heart rate in our CLD population was on average 85 beats/min, a value that has been associated with increased risk of all-cause and cardiovascular mortality in both general (97,105) and COPD (6) populations. These findings confirm that heart rate is a hemodynamic parameter that should be considered thoroughly in the pulmonary rehabilitation setting.

Despite similar resting heart rate values, we found that the COPD group displayed significantly lower heart rate values at peak exercise than the non-COPD group. This hemodynamic feature, paralleled by significantly lower submaximal and maximal functional capacities, can be explained by higher pulmonary function impairment in the COPD group compared to the non-COPD group. Nevertheless, both COPD and non-COPD patients in our study showed a limited capacity to increase their heart rate in response to exercise, as evidenced by the presence of impaired chronotropic response and a failure to achieve the target heart rate (85% of the maximal age-predicted heart rate) in more than three-quarters of all CLD patients. These results reinforce the opinion that in addition to ventilatory limitation, which is recognized as a primary determinant of exercise tolerance (25), the hemodynamic limitations, which have also been reported as exercise tolerance predictors (90), should be taken into consideration in this population. Cardiac medication such as beta-blocker therapy (211) also prevents patients from reaching their maximal aerobic capacity. However, this medication had a low prescription rate in our CLD population, and therefore is unlikely to be responsible for the low exercise capacity in our study.

Finally, our results indicated that higher resting heart rate, along with lower resting diastolic blood pressure, higher FVC, and absence of RAS antagonists medication were significantly associated with the CIIS in our CLD population. While the relationship between elevated resting heart rate and cardiovascular ischemic risk is clearly established (8,105), there are also studies that have reported a relationship between low diastolic blood pressure and increased risk of MI in elderly people (212,213). Our data also indicated that in the absence of RAS antagonists, CLD patients were more likely to have had a past myocardial event. These findings are in agreement with studies reporting that RAS antagonists (particularly, angiotensin-converting enzyme inhibitors) have an important role in the management of patients at increased cardiovascular risk by reducing MI, stroke, and new-onset congestive heart failure (214). Similar to other investigators (162), we were not able to confirm the association between FEV_1 and CIIS (162); however, we found that FVC was one of the parameters of the model.

In summary, the weak but statistically significant relationship between resting heart rate and CIIS found in this study cannot be excluded from consideration due to the magnitude of risk associated with MI history. Moreover, elevated resting heart rate (e.g., values over 80 beats/min) seems to be an indicator of prior MI in CLD patients, and therefore, may be useful in raising awareness for careful adjustments of training intensity such as intermittent training under these circumstances.

2.4.1 Strengths and limitations of the study

A number of limitations need to be considered in the interpretation of these data. First, the study had a retrospective design, which might have introduced bias related to accuracy

and completeness of data from the medical records. Moreover, we excluded patients with cardiac conditions, such as ventricular paced rhythm, left bundle branch block, and left ventricular hypertrophy with repolarization abnormalities, that are known to alter the CIIS interpretation. Since these conditions commonly co-exist with ischemic heart disease, our findings might actually underestimate the real proportion of myocardial injury or infarction in this population. Another limitation of our study could be related to the nature of the ECG recordings. Some resting ECG recordings may have been performed with the patients in a sitting position instead of supine, which could have introduced motion artifacts that could alter the CIIS calculation. However, our total CIIS (13.0 ± 8.1 units) was similar to Brekke's study (13.5 ± 11.6 units), which was performed supine in a population of patients with acute exacerbation of COPD (162), giving us confidence that the patients' position did not significantly alter the CIIS score.

2.5 Conclusions

The present study showed that patients with CLD undergoing pulmonary rehabilitation were at increased risk of unreported prior MI. Both COPD and non-COPD patients should receive the same attention regarding MI history. An elevated resting heart rate appears to be associated with a high risk of prior MI in CLD patients, and it raises awareness for careful adjustments of training intensity such as intermittent training under these circumstances. Further studies are needed to explore this relationship under rigorously controlled conditions along with the effect of pulmonary rehabilitation in lowering resting heart rate and cardiovascular risk in the CLD population.

Chapter 3: The reliability of short-term measurement of resting heart rate parameters in patients with COPD

3.1 Introduction

Cardiovascular disease is a common comorbidity in patients with chronic obstructive pulmonary disease (COPD) (2,41,189), yet our understanding of the complex pathogenic mechanisms underlying this association is still incomplete. Recent literature suggests that cardiac autonomic dysfunction, through sympathetic nervous system overactivity, may play an important role in the initiation and progression of cardiovascular disease in this population (4,87). Reduced heart rate variability (HRV), which is a marker of cardiovascular autonomic neuropathy (215,216) and a significant predictor of cardiac events in various clinical populations (217,218), has been reported in patients with COPD (85,219). Therefore, assessing HRV with various interventions in this population may be beneficial in monitoring their cardiovascular risk profile.

Aerobic exercise training such as during pulmonary rehabilitation has the potential to influence HRV in COPD patients (17,220). However, measuring HRV for cardiac risk stratification or evaluation of rehabilitation program effectiveness in improving cardiac autonomic function has not yet been implemented clinically. Possible explanations for this delay are related to the complexity of HRV analysis and the instability of this measurement under various physio-psychological conditions (221), which may limit its reliability.

The reliability of short-term HRV measurements can be particularly challenging and a review of existing literature shows that HRV reliability coefficients had a large dynamic

range across healthy and disease populations (222). In addition, clinical populations tend to display worse HRV reliability than healthy participants, suggesting that the extrapolation of reliability results from normal to clinical populations should be viewed with caution (222).

To our knowledge, there is only one study investigating HRV reliability in patients with COPD (223). Despite reporting good measurement reliability, the study employed too few HRV parameters and statistical analysis to be of use for clinical decision making. Moreover, the HRV measurement was performed under controlled respiratory rate – a procedure that requires prolonged training or is not always feasible in a more severe COPD population which would be referred for pulmonary rehabilitation (224).

Therefore, we conducted this study to examine the test-retest reliability of HRV measurements from short-term ECG recordings, performed during spontaneous breathing, in individuals with moderate-to-severe COPD.

3.2 Methodology

3.2.1 Study design and setting

This study used a within-subject repeated measure design, and was conducted in an outpatient Pulmonary Rehabilitation Clinic at St. Paul's Hospital, Vancouver, B.C., Canada.

3.2.2 Study population

The study population included seventeen COPD patients prospectively recruited from participants referred for admission to the PRP. All participants had a physician diagnosis of COPD confirmed by spirometry ($FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted) according to the GOLD guidelines (225). Participants were over 40 years of age, in stable lung and

cardiac condition at the time of the study (e.g., without respiratory infection or hospitalization during the preceding month). The exclusion criteria were cardiac dysrhythmia, cardiac pacemaker, valvular disease, and conditions that would preclude lying supine in a relaxed position (e.g., psychiatric disorders, drug and alcohol addiction). The study was approved by the Research Ethics Board at Providence Health Research Institute/University of British Columbia (H11–00984–A005) and all participants provided written informed consent.

3.2.3 Study procedure

Resting HRV data were collected on two visits separated by an average interval of four days. Testing sessions were conducted by a single investigator at the same time of day (~ 9:00 a.m.) with the participants lying supine in a quiet and temperature controlled room, and following a rigorous standardized protocol. All participants were instructed in advance to avoid heavy exertion for a minimum of 24 hours before testing, and to refrain from taking any medication, smoking, eating, drinking alcohol and beverages containing caffeine or other stimulants for at least 12 hours prior to testing. All medications were resumed the morning of the testing day, after the cardiovascular measurements were completed. Compliance with the study requirements was confirmed by all participants at the beginning of each testing session.

During the first visit, demographic data including age, sex, smoking history, current medication use, and medical history were collected. Body weight and height were recorded using a stadiometer and a stand-on scale, with the patient in socks and wearing a hospital gown. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Then, the experimental procedure was described and patients were

asked to relax, breathe normally, and refrain from moving, talking, or sleeping during the procedure.

Prior to the initiation of the HRV data collection, brachial blood pressure measurements were performed on the right arm using an automated oscillometric device (Model HEM 907XL, Omron Healthcare, USA) after at least five minutes of complete rest. The average of three consecutive blood pressure measurements, separated by one minute intervals, was calculated, and the mean blood pressure was expressed as diastolic pressure plus one third of the pulse pressure. A 3-lead ECG was attached to the participants' chest in the lead II configuration, and they were left to rest in the supine position for ten more minutes before the ECG recordings were performed.

3.2.3.1 Heart rate variability measurements

Time and frequency domain evaluations of HRV were obtained from short-term five-minute ECG recordings under spontaneous breathing using a SphygmoCor® CPV device (AtCor Medical, Inc. USA). One recording was obtained at each visit. The SphygmoCor system records continuous ECG waveforms, and computes temporal and spectral parameters related to the autonomic nervous system.

Three time domain HRV parameters were analyzed: mean heart rate, standard deviation of normal to normal R-R intervals (SDNN), and square root of the mean squared difference of successive normal to normal R-R intervals (RMSSD). Mean heart rate reflects autonomic balance, with higher heart rate values being associated with sympathetic predominance and reduced HRV (226). The SDNN is considered to be a measure of combined sympathetic and parasympathetic activity, while the RMSSD represents primarily the parasympathetic or

vagal influences. As a result, lower SDNN and RMSSD levels indicate reduced overall HRV and parasympathetic control, respectively (215).

The frequency domain HRV parameters included the following measurements: low frequency (LF, 0.04-0.15 Hz), high frequency (HF, 0.15-0.4 Hz), and total power (TP, 0-0.5 Hz). While the HF power reflects primarily vagal control and the mechanical effects of breathing on heart rate throughout the respiratory cycle, the LF power is modulated by both parasympathetic and sympathetic control of the heart (215). The ratio between LF and HF power (LF/HF) is also often used to assess the sympatho-parasympathetic balance; however, some caution is required due to the mixed sympathetic-parasympathetic nature of the LF power and the non-linear interactions between these two divisions (227). Ultimately, the total power is considered to be a global index of HRV (215).

Following visual examination of the ECG recordings, only stable and artifact free ECG recordings with normal sinus rhythm were included in the analysis. Any possible ectopic beats were automatically discarded and replaced by an interpolation of the non-ectopic R-R intervals by the SphygmoCor device. The calculation of the heart rate variability was deemed unacceptable in three patients due to extreme noise or large number of ectopic beats, as per SphygmoCor manufacturer's recommendations. One participant was excluded, as they were unable to complete the two testing sessions. A total of thirteen patients were included in the final analysis.

3.2.4 Statistical analysis

For descriptive statistics, continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. Since computation of reliability coefficients depends on the assumption of normal distribution (228,229), the data was examined for normality using the Kolmogorov-Smirnov test and HRV indices with skewed distribution were log-transformed using the natural logarithm (ln). A Student's paired t-test for normally distributed data, or Wilcoxon signed-rank test for non-normally distributed data was used to determine significant differences between the two testing days. Further, absolute and relative reliability of HRV measurement was evaluated by changes in the mean [mean difference, 95% confidence interval (CI) mean difference, and standard deviation (SD) of the difference between the testing days], measurement variability [standard error of measurement (SEM) and coefficient of variation (CV%)], and retest correlations [Pearson's and intraclass correlation coefficients (ICC)] (228,229). SEM was calculated as the square root of the within-subject mean square error from the analysis of variance test. CV% was calculated as the ratio of the method error to the mean of all HRV data from the two test occasions multiplied by 100 (229). $ICCs_{2,1}$ were estimated using two-way analysis of variance (229) and their values were interpreted as fair (0.21 - 0.40), moderate (0.41 - 0.60), substantial (0.61 - 0.80), and excellent or almost perfect (0.81 - 1.00) (230). The 95% CI for each ICC was also calculated. A two-tailed p value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

3.3 Results

3.3.1 Participant characteristics

Data were collected from thirteen participants with COPD, with a mean (± SD) age of 63 ± 6 years, and smoking history of 33 ± 19 pack-years. Over half of participants were in GOLD stage III (61%). All participants were on inhaled lung medication, but none of them were on oral corticosteroids. On average, participants had two comorbid conditions, including approximately 30% with a diagnosed cardiovascular disorder (Table 3.1).

Table 3.1. Characteristics of the study participants

Variables	**COPD (n = 13)**
Age (years)	63 ± 6
Male/Female, n (%)	8/5 (62/38)
BMI (kg/m^2)	27.4 ± 3.4
Smoking status	
Smoking history (pack-year)	33 ± 19
Current smoker, n (%)	2 (15%)
Pulmonary function test	
FEV_1 (% predicted)	46 ± 16
FVC (% predicted)	75 ± 22
FEV_1/FVC	49 ± 13
COPD stage	
Stage 2: moderate	4 (31%)

Variables	COPD (n = 13)
Stage 3: severe	8 (61%)
Stage 4: very severe	1 (8%)
Comorbidities	
Number of comorbidities	2 ± 1
Musculoskeletal (osteoporosis, osteoarthritis), n (%)	8 (62%)
Psychological (anxiety, depression), n (%)	6 (46%)
Endocrino-metabolic (hypothyroidism, DM), n (%)	5 (38%)
Hepato-digestive (hepatitis C, GERD), n (%)	5 (38%)
Cardiovascular (hypertension, ischemic heart disease), n (%)	4 (31%)

Legend: BMI = body mass index, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, DM = diabetes mellitus, GERD = gastroesophageal reflux disease. Values are described as mean ± standard deviation, except for sex, smoking status, medication, and comorbidities, which are described as counts and percentages

3.3.2 Reliability of heart rate variability measurements

Table 3.2 and Table 3.3 present the time and frequency domain HRV indices for the two testing days, and their absolute and relative reliability coefficients, respectively. None of the studied variables were statistically different between the testing days. All of the time and frequency domain variables, except mean heart rate, exhibited a non-normal distribution; therefore, these parameters were log-transformed before calculating their reliability coefficients.

Table 3.2. Heart rate variability indices and hemodynamic variables on testing sessions

Variables	Visit 1	Visit 2	*p value*
MBP (mmHg)	96 ± 11	98 ± 11	*0.157*
SpO_2 (%)	94 ± 2	94 ± 2	*0.632*
Time domain			
HR (beats/min)	77 ± 11	77 ± 12	*0.685*
SDNN (ms)	31 ± 24	30 ± 22	*0.766*
lnSDNN (ms)	3.2 ± 0.8	3.2 ± 0.7	*0.756*
RMSSD (ms)	32 ± 39	33 ± 36	*0.874*
lnRMSSD (ms)	2.9 ± 1.1	2.9 ± 1.2	*0.940*
Frequency domain			
LF power (ms^2)	386 ± 703	285 ± 519	*0.327*
lnLF (ms^2)	4.5 ± 1.9	4.3 ± 1.7	*0.756*
HF power (ms^2)	283 ± 612	275 ± 464	*0.951*
lnHF (ms^2)	3.9 ± 2.0	4.2 ± 2.0	*0.635*
LF/HF	3.7 ± 3.8	2.7 ± 3.8	*0.208*
lnLF/lnHF	0.6 ± 1.6	0.2 ± 1.5	*0.199*
TP (ms^2)	1137 ± 1775	805 ± 1178	*0.357*
lnTP (ms^2)	5.8 ± 1.7	5.7 ± 1.6	*0.746*

Legend: MBP = mean blood pressure; SpO2 = blood oxygen saturation; HR = heart rate; SDNN = standard deviation of all normal-to-normal RR intervals; RMSSD = root mean square of successive differences in normal-to-normal RR intervals; HF = high frequency; LF = low frequency; TP = total power; ms = milliseconds; ln = natural logarithm

Mean heart rate showed the smallest measurement variability with a CV% of 4.3%. The highest CV% value of 193.4% was found in the log-transformed LF/HF ratio. The other heart rate variability parameters displayed moderate measurement variabilities with time and frequency domain CVs ranging from 11% to 32% after log-transformation. No systematic changes in any of the time or frequency HRV measurements occurred, since 95% CI for the mean difference included zero. The ICC coefficient for mean heart rate showed excellent reliability with a value greater than 0.9 indicating that the random error accounted for approximately 10% of this measurement variability. The variables reflecting overall HRV (lnSDNN, lnLF, and lnTP) showed substantial reliability with ICC values over 0.7. In contrast, the HRV variables reflecting primarily vagal or parasympathetic activity (lnRMSSD and lnHF) showed only moderate reliability with ICC values around 0.5.

Table 3.3. Indices of measurement variability and reliability of HRV between the testing sessions

Variables	Mean diff.	SD diff.	95% CI Mean diff.	SEM	CV%	R	ICC (95%CI)
HR (beats/min)	-0.5	4.7	-3.1, 2.1	3.3	4.3	0.93#	0.93 (0.80, 0.98)
lnSDNN (ms)	0.01	0.5	-0.3, 0.3	0.4	10.9	0.78#	0.79 (0.48, 0.93)
lnRMSSD (ms)	-0.02	1.1	-0.6, 0.6	0.8	26.6	0.55	0.57 (0.09, 0.83)
lnLF (ms^2)	0.1	1.2	-0.6, 0.8	0.9	19.9	0.78#	0.79 (0.48, 0.93)
lnHF (ms^2)	-0.3	1.9	-1.3, 0.8	1.3	32.4	0.57#	0.59 (0.12, 0.84)
lnLF/lnHF	0.4	1.0	-0.2, 0.9	0.7	193.4	0.82#	0.77 (0.43, 0.92)
lnTP (ms^2)	0.1	1.3	-0.6, 0.8	0.9	15.8	0.71#	0.72 (0.34, 0.90)

Legend: HR = heart rate; SDNN = standard deviation of all normal-to-normal RR intervals; RMSSD = root mean square of successive differences in normal-to-normal RR intervals; HF = high frequency; LF = low frequency; TP = total power; ms = milliseconds; ln = natural logarithm; # $p < 0.05$

3.4 Discussion

The present study analyzes the test-retest reliability of standard indices of HRV from short-term recordings performed under spontaneous breathing conditions in moderate-to-severe COPD patients. We found that the time and frequency domain parameters related with the overall HRV showed substantial reliability. In contrast, the HRV parameters associated primarily with parasympathetic tone showed moderate reliability. The only parameter related to the HRV that showed excellent absolute and relative reliability was mean heart rate. Our findings support the use of HRV parameters for diagnosis and cardiac risk assessment, but only the mean heart rate can be used as a reliable clinical assessment tool for pre-post interventions related with autonomic dysfunction in COPD patients.

In our study, the measurement variability analysis revealed that patients with moderate-to-severe COPD displayed a moderate absolute HRV reliability in both time and frequency domains (e.g., as evidenced by CV values between 11% and 32%). These findings are similar to previous studies on HRV measurements performed under spontaneous breathing in healthy (231,232) and various clinical populations (233,234) (e.g., as evidenced by CV values between 6% and 33%). The intrinsic lability of the HRV parameters, sampling variability, and changes in the frequency and depth of respiration are a number of factors that are thought to be responsible for this measurement variability (231,233). The relative reliability showed a similar trend in our study. The ICCs in both time and frequency domain indicated substantial reliability for the parameters related to overall heart rate variability, and moderate reliability for the parameters reflecting the parasympathetic tone. However, the confidence intervals for these last parameters were very wide (e.g., lnHF exhibited a 95% CI of 0.12, 0.84) precluding any practical use. These results are in line with those performed under

spontaneous breathing in healthy individuals (232) and various disease populations (233,235,236), which showed substantial relative reliability of the LF component of HRV as indicated by ICC values exceeding 0.7. However, the reliability of the HF component of HRV in the above-mentioned studies showed inconsistent results. The reliability of the HF component of the HRV in healthy (ICC, lnHF = 0.79) (232), diabetes mellitus (ICC, lnHF = 0.78) (236), and previous MI (ICC, HF = 0.77) (233) populations remained substantial. However, in disease populations manifesting impairments of the respiratory system, such as individuals with spinal cord injury, the reliability of the HF component of heart rate variability was moderate (ICC, HF = 0.53) (235), and similar to the results we obtained in the COPD population. These findings highlight the remaining controversies in regard to the reproducibility of the HF measurements, particularly when they are performed under spontaneous breathing. While some studies showed that these measurements are more reproducible during controlled breathing (237,238), others have not found any improvement in the reliability of HF component using paced breathing (233,239). It is worth mentioning that most of these studies were performed in healthy individuals in whom respiratory interference on HRV is expected to be lower than in populations with respiratory impairments.

Although reduced HRV has been reported in COPD (85,219), and the respiratory frequency variation is known to influence the autonomic nervous activity (215,238), limited data exist on the repeatability of short-term HRV measures in patients with COPD. To our knowledge, only one study examined the HRV reliability in patients with COPD. Bartels et al. (223) investigated the reproducibility of two consecutive measurements of HRV, and found that the time-frequency analysis was reproducible and reliable under controlled

respiratory rate and oxygen hemoglobin saturation in this population. Their reported correlation coefficient of the LF domain parameter (lnLF, r = 0.89) was similar to ours, which was performed under spontaneous breathing. However, the use of paced breathing could mostly explain the better correlation coefficient of the HF domain parameters (lnHF, r = 0.89) that they reported. Since the Bartels et al. study did not report typical error or intraclass correlation coefficients, we could not make any further comparisons.

In the COPD population, we found that the mean resting heart rate displayed excellent measurement variability (CV% of 4.3%) and almost perfect reliability (ICC of 0.93, with a 95% CI of 0.80, 0.98). These figures indicate that for an average resting heart rate of 77 beats/min, as found in our population, a change of at least 3 beats/minute after an intervention may indicate a clinically important change (CV%*mean resting HR). Given the recognized inverse relationship between heart rate and HRV (226), these findings also indicate that the resting heart rate can be used as a reliable clinical assessment tool for obtaining information about the effectiveness of rehabilitation program (e.g., exercise) on cardiac autonomic function in a COPD population.

3.4.1 Strengths and limitations of the study

Our study enrolled a sample of moderate-to-severe COPD patients whose clinical features (e.g., high variations in respiratory frequency) can impact the reliability and accuracy of HRV measurement. We showed that, despite the recognized augmented respiratory sinus arrhythmia in this population, under a rigorously standardized procedure the HRV parameters derived from short-term stable ECG recordings can be used for cardiac screening. In addition, the mean resting heart rate can be used as a reliable clinical parameter

for monitoring the effectiveness of the rehabilitation program in improving cardiac autonomic function and physical fitness in this population.

The inclusion of comparisons of HRV reliability coefficients under both controlled and spontaneous breathing conditions, or between COPD and healthy controls, would have provided additional information about the impact of breathing on different HRV measurements; however, such an approach was beyond the scope of this study. We also recorded only a single 5-minute ECG dataset; performing longer recordings or several recordings could have further improved the reliability of our HRV measurements.

3.5 Conclusions

Heart rate variability measurements provide a simple and non-invasive assessment of autonomic nervous system function. Our findings show that in a population of moderate-to-severe COPD, the HRV measurements performed during spontaneous breathing have substantial reliability for the time and frequency domain parameters related with the overall HRV and moderate reliability for the time and frequency domain parameters related with the parasympathetic tone. Mean resting heart rate was the only parameter related with HRV that showed excellent absolute and relative reliability. The information provided by our study on the HRV reliability derived from short-term recordings should be of value to researchers planning future studies to evaluate the effectiveness of rehabilitation programs in improving cardiac autonomic function in the COPD population.

Chapter 4: The reliability of pulse wave velocity measurement in patients with COPD

4.1 Introduction

Current evidence indicates that the coexistence of COPD and ischemic heart disease occurs frequently and is associated with a poor prognosis (2,70). The prevalence of ischemic heart disease in the COPD population has been reported to be two to three times higher than in the general population (42,64), with the mortality ranging from 10% to 30% depending on the person's age and the method used to confirm the diagnosis (65). These estimates translate into elevated healthcare costs due mainly to the increased risk for hospitalization (64,68). Given the impact of ischemic heart disease on the health burden in the COPD population, it is important to identify COPD patients with increased cardiac risk and implement preventive strategies in this population.

Elastic artery stiffening has recently emerged as a marker for cardiovascular disease (16). Two meta-analyses (124,129) comprised of thousands of subjects have confirmed that the carotid-femoral pulse wave velocity (PWV), which is the gold standard method for assessing aortic stiffness (16), is an independent predictor of adverse coronary events and all-cause mortality in healthy and chronic disease populations. Based on these findings, arterial stiffness has been proposed as a target for cardiac risk assessment and therapy monitoring.

Elevated arterial stiffness has been consistently reported in patients with COPD (130,131,240). However, the clinical use of arterial stiffness measurements to assess cardiac risk and intervention impact has not yet been determined. This may be attributed to

substantial variation in the mean PWV values across COPD studies, which have ranged from approximately 7 m/s to 12 m/s (133). In addition, a number of studies, which investigated the impact of pharmacological (241,242) or non-pharmacological (181,186,187) interventions on arterial stiffness in patients with COPD, have not only shown contradictory results, but also a large variability in the PWV response with these interventions. All these studies investigating arterial stiffness have raised concerns on the poor repeatability of the PWV measurements in COPD patients.

Applanation tonometry, a common and well-accepted non-invasive technique (16) for measuring PWV has been shown to have good reliability and reproducibility in healthy (243,244) and various disease populations (245-247). However, a number of limitations have also been reported (248,249), including the ability to accurately record the PWV in the presence of pressure waveform changes. These limitations may be particularly relevant when measuring PWV in COPD, where the clinical features of this condition (e.g. respiratory limitations in the supine position, dysrhythmias, and often obesity) may impact the reliability of this measurement.

To our knowledge, only three studies investigated the repeatability of PWV measurements in patients with COPD using applanation tonometry (250-252). Despite that these studies found that the PWV measurements were reliable, they reported different mean PWV values in COPD populations with similar disease severity. They also suggested that unstable PWV measurements are expected in the presence of higher PWV values, a feature which also raised concerns regarding the challenges of obtaining quality PWV measurements in more severe COPD, where alterations in breathing pattern can induce changes in the

arterial pressure waveform. All these aspects need to be carefully addressed in order to use reliable arterial stiffness measurements in the clinical practice for patients with COPD.

Here we conducted a study to assess the test-retest reliability of aortic PWV measurement in individuals with COPD referred to a pulmonary rehabilitation program. Our aim was to characterize the clinical and methodological challenges of measuring PWV in a population of subjects with moderate-to-severe COPD, who may benefit from early evaluation of their cardiovascular risk and therapy monitoring.

4.2 Methodology

4.2.1 Study design and setting

This study used a within-subject repeated measure design, and was conducted in a rehabilitation outpatient clinic at St. Paul's Hospital, a tertiary care university-affiliated hospital in Vancouver, B.C., Canada.

4.2.2 Study population

Consecutive ambulatory COPD patients referred for pulmonary rehabilitation between September 2014 and April 2015 were invited to participate in this study. Participants were over 40 years of age, with a physician diagnosis of COPD confirmed by spirometry ($FEV_1/FVC < 0.70$ and $FEV_1 < 80\%$ predicted) according to the GOLD guidelines (225), and in stable lung and cardiac condition at the time of the study (e.g. without respiratory infection or hospitalization during the preceding month). Pulmonary function tests within one year prior to the enrollment in the rehabilitation program were used to confirm patient eligibility. Patients were excluded if they had cardiac dysrhythmias, cardiac pacemakers, valvular

diseases, and conditions that would preclude lying supine in a relaxed position (e.g., psychiatric disorders, drugs and alcohol addictions) as per SphygmoCor operator manual recommendations (253). Ethical approval to conduct the study was obtained from the Research Ethics Board at Providence Health Research Institute/University of British Columbia (H11–00984–A005). All participants provided written informed consent for study participation.

4.2.3 Study procedure

The participants were examined by the same investigator on three separate days (Visit 1, 2, and 3) within a 10-day period following a standardized procedure and the expert consensus documents on the measurement of aortic stiffness using carotid-femoral PWV (125,254). The testing sessions were conducted at the same time of day (~ 9:00 a.m.) in a quiet and temperature controlled room (~23^{o}C). The participants were instructed to avoid heavy exertion for a minimum of 24 hours, and to refrain from taking any medication, smoking, eating, drinking alcohol and beverages containing caffeine for at least 12 hours prior to each testing day. All medications were postponed the morning of the testing day, until after the cardiovascular measurements were completed. At baseline, the participants were interviewed about their current medications and comorbid medical conditions. Body height and weight measurements of each participant were recorded using a stadiometer and a stand-on scale, with the patient in socks and wearing a hospital gown. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. All participants confirmed their compliance to the study requirements at the beginning of each testing session.

4.2.3.1 Pulse wave velocity measurement

Following the baseline measurements, three electrocardiogram electrodes were placed on the participant's chest in a modified lead II configuration with the participant in the supine position. The carotid pulse was palpated between the larynx and the anterior border of the sternocleidomastoid muscle at the level of the cricoid cartilage (255). Similarly, the femoral pulse was palpated into the groin area, one third of the distance from the pubis to the anterior superior iliac spine (256). The strongest carotid and femoral pulse points were then marked with a felt pen, and the distance from the suprasternal notch to the carotid site as well as the distance from the suprasternal notch to the femoral site were measured along the surface of the body using a non-elastic measuring tape. Each distance was measured twice to reduce measurement error. Brachial blood pressure measurements were performed on the right arm using an automated oscillometric device (Model HEM 907XL, Omron Healthcare, USA) after at least 5 minutes of complete rest. The mean of three consecutive blood pressure measurements, performed at one minute intervals, was used to calibrate the hemodynamic variables derived from arterial pressure waveforms.

The carotid-femoral PWV was determined with a SphygmoCor® CPV device (AtCor Medical, Inc. USA) after a minimum period of 15 minutes supine rest, which is needed to achieve a stable hemodynamic condition (125). The pressure waves from the marked points at the carotid and femoral arterial sites were captured sequentially using an applanation tonometer (Millar Instruments Inc, Houston, Texas, USA), while ECG data was recorded concurrently. The recording was continuously checked on the data capture screen to achieve the recommended strength and quality of the arterial pulse signal. Ten seconds of consistent waveforms were captured for each site to cover at least one respiratory cycle. After each

carotid and femoral waveform pair was recorded, the device automatically calculated the aortic PWV as the distance between the measurements sites (meters) divided by the pulse transit time (seconds). The distance was obtained by subtracting the distance from the carotid site to the suprasternal notch from the distance between the suprasternal notch and the femoral site of measurements. The wave transit time (t) was calculated by the system software, using the R-waves of the ECG and the foot of the pressure waves at the site of measurement, employing the intersecting tangent algorithm method. Five carotid-femoral PWV measurements were performed during each visit, and their mean value was subsequently used for analysis. The time taken to perform five PWV measurements was on average 15 minutes (range 7-35 minutes), depending on the signal strength, stability of the pressure waveforms, and patient cooperation. The SphygmoCor device also recorded the resting heart rate during the carotid and femoral PWV measurements, and the average of these values was subsequently used for analysis.

4.2.3.2 Pulse wave velocity quality control indices

A number of quality criteria were considered during PWV measurements, as per SphygmoCor device recommendations (253): 1) signal strength larger than 360 raw digital units for achieving an adequate pulse height of 80 mV; 2) pulse waveforms consistent in size and shape across the screen; 3) standard deviation for carotid and femoral sites in the SphygmoCor statistical table below 6% of the mean wave propagation time; and 4) percent standard error of mean (SEM) of the PWV less than 10%. Readings with a percent SEM between 10 and 15%, which are considered borderline, were retained only if the repeated PWV measurements were consistently in this range. Readings with a percent SEM over 15%

were rejected. During data acquisition, the percent variations of the pulse height, length, and base line were also monitored, since values < 5% are recommended to ensure quality control.

4.2.4 Statistical analysis

For descriptive statistics, continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. Within-subject differences in the main outcomes among the three testing days were assessed using a repeated measures analysis of variance (ANOVA) test. Further, test-retest reliability of PWV measurements was evaluated through Pearson's and intraclass correlation coefficients, changes in the mean (mean difference and standard deviation of the mean difference), and measurement variability (coefficient of variation). Clinically important changes were evaluated by means of the smallest real difference. The intraclass correlation coefficients (ICC) were estimated using mixed two-way analysis of variance and their values were interpreted as poor (0.0 - 0.20), fair (0.21 - 0.40), moderate (0.41 - 0.60), substantial (0.61 - 0.80), and excellent or almost perfect (0.81 - 1.00) (230). In addition, Bland-Altman plots (257) were generated to assess the degree of agreement between PWV measurements in successive visits. The coefficient of variation (CV%) was calculated as the ratio of the method error to the mean of all PWV data from two test occasions multiplied by 100. The smallest real difference (SRD) and the percent SRD (SRD%) were calculated as 1.96 x standard error of measurement x $\sqrt{2}$, and the ratio of the SRD to the mean of all PWV data from two test occasions multiplied by 100, respectively (229).

Based on previous studies of PWV repeatability (245,250) we determined that a sample size of 11 patients was needed to achieve a test power of 80% and a 5% level of significance

in detecting an intraclass correlation coefficient of 0.7 with a confidence interval width of 0.4. Given that a sample size between 15 and 20 subjects is recommended in the literature for similar reliability studies (229), we aimed to recruit a minimum of 15 patients. All statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC).

4.3 Results

4.3.1 Participant characteristics

A total of 32 COPD patients referred for pulmonary rehabilitation between September 2014 and April 2015 were invited to participate in the study. Six patients declined to participate and 9 patients were excluded due to a history of cardiac or mental disorders. Two of the remaining seventeen patients were further excluded because they could not complete all the testing sessions. In total, 15 participants (10 men and 5 women) were included in the final analysis (Figure 4.1).

Characteristics of the study participants are shown in Table 4.1. The mean (± SD) age was 64 ± 6.0 years (range 52-73 years), and the mean smoking history was 34 ± 18 pack-years. Our study sample exhibited moderate to severe pulmonary obstruction (FEV_1 45 ± 16% predicted; FEV_1/FVC 48 ± 13). Half the participants were in GOLD stage III, and the other half were in stage II and IV. Most of the participants were using short acting beta2-agonists, long acting anticholinergics, and a combination of long acting beta2-agonist and inhaled corticosteroid. None of the participants were on oral corticosteroids. On average, participants had two comorbid conditions in which musculoskeletal and psychological disorders were the most common (53% and 47%, respectively). However, it is worth mentioning that, based on the SphygmoCor device

recommendation, we excluded seven participants with cardiac conditions such as dysrhythmia, pacemaker implantation, and aortic valvulopathy. Their inclusion would have ranked the cardiovascular comorbidity as frequent (50%) in this population.

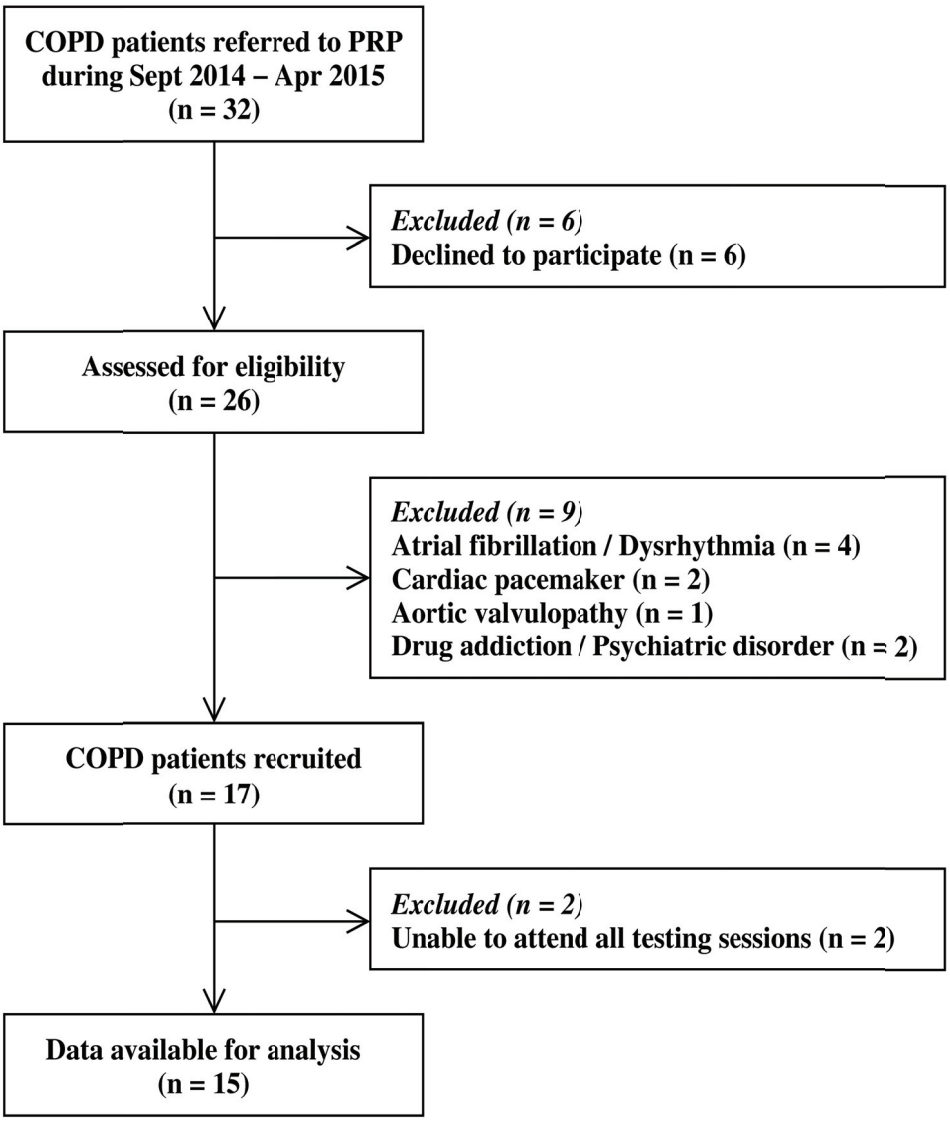

Figure 4.1. Study flow diagram

Table 4.1. Characteristics of the study participants

Variables	COPD (n = 15)
Age (years)	64 ± 6
Male/Female, n (%)	10/5 (67/33)
BMI (kg/m^2)	26.8 ± 3.5
Smoking status	
Smoking history (pack-year)	34 ± 18
Current smoker, n (%)	3 (20%)
Pulmonary function	
FEV_1 (% predicted)	45 ± 16
FVC (% predicted)	75 ± 21
FEV_1/FVC	48 ± 13
COPD stage	
Stage 2: moderate	5 (33%)
Stage 3: severe	8 (53%)
Stage 4: very severe	2 (13%)
Lung medication	
Number of lung medications	3 ± 1
Short acting β_2 agonists, n (%)	14 (93%)
Long acting β_2 agonists, n (%)	2 (13%)
Long acting anticholinergics, n (%)	12 (80%)

Variables	COPD (n = 15)
Corticosteroid/Long acting β_2 agonist combination, n (%)	12 (80%)
Medical conditions	
Number of comorbidities	2 ± 1
Musculoskeletal (osteoporosis, osteoarthritis), n (%)	8 (53%)
Psychological (anxiety, depression), n (%)	7 (47%)
Endocrine (hypothyroidism, adrenal insufficiency), n (%)	5 (33%)
Hepato-digestive (hepatitis C, Crohn's disease, GERD), n (%)	5 (33%)
Cardiovascular (hypertension, ischemic heart disease), n (%)	4 (27%)
Metabolic (gout, diabetes mellitus), n (%)	2 (13%)

Legend: BMI = body mass index, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, GERD = gastroesophageal reflux disease. Values are described as mean ± standard deviation, except for sex, smoking status, lung medication, and comorbidities that are described as counts and percentage

Table 4.2 presents the average PWV and hemodynamic measurements on the three days of testing. The average PWV values on Visit 1, 2, and 3 (10.2 ± 1.9 m/sec, 10.1 ± 1.6 m/sec, and 10.6 ± 1.7 m/sec, respectively) were not statistically different according to the within-subjects repeated measures ANOVA ($p = 0.248$). Furthermore, no significant differences were observed among the three testing days for any of hemodynamic measurements (blood pressure, heart rate, and saturation of oxygen values).

Table 4.2. Analysis of variance for comparing the pulse wave velocity and hemodynamic variables across the testing sessions

Variables	Visit 1	Visit 2	Visit 3	*p value*
PWV (m/s)	10.2 ± 1.9	10.1 ± 1.6	10.6 ± 1.7	*0.248*
Systolic blood pressure (mmHg)	127 ± 17	124 ± 15	130 ± 16	*0.088*
Diastolic blood pressure (mmHg)	80 ± 10	78 ± 9	80 ± 11	*0.383*
Heart rate (beats/min)	74 ± 12	72 ± 11	73 ± 12	*0.246*
SpO_2 (%)	93.9 ± 1.7	93.9 ± 2.0	94.3 ± 1.8	*0.502*

Legend: PWV = pulse wave velocity, SpO2 = blood oxygen saturation. Values are described as mean ± standard deviation; $p < 0.05$ significantly different among the three testing days

4.3.2 Reliability of pulse wave velocity measurement

To determine the test-retest correlation between PWV measurements performed on different visits, scatter plots were built for all three visit pairs: 1 versus 2, 2 versus 3, and 1 versus 3 (Figure 4.2). The Pearson's correlation coefficients showed a strong measurement correlation within each visit pair ($r_{V1\text{-}V2} = 0.76$ with $p_{V1\text{-}V2} = 0.0011$; $r_{V2\text{-}V3} = 0.73$ with $p_{V2\text{-}V3} = 0.0018$, and $r_{V3\text{-}V1} = 0.79$ with $p_{V3\text{-}V1} = 0.0005$). The intraclass correlation coefficient (ICC), which described the correlation among the measurements performed on the same individual during the three visits, also showed substantial reliability of 0.75 (95% CI, 0.53-0.89).

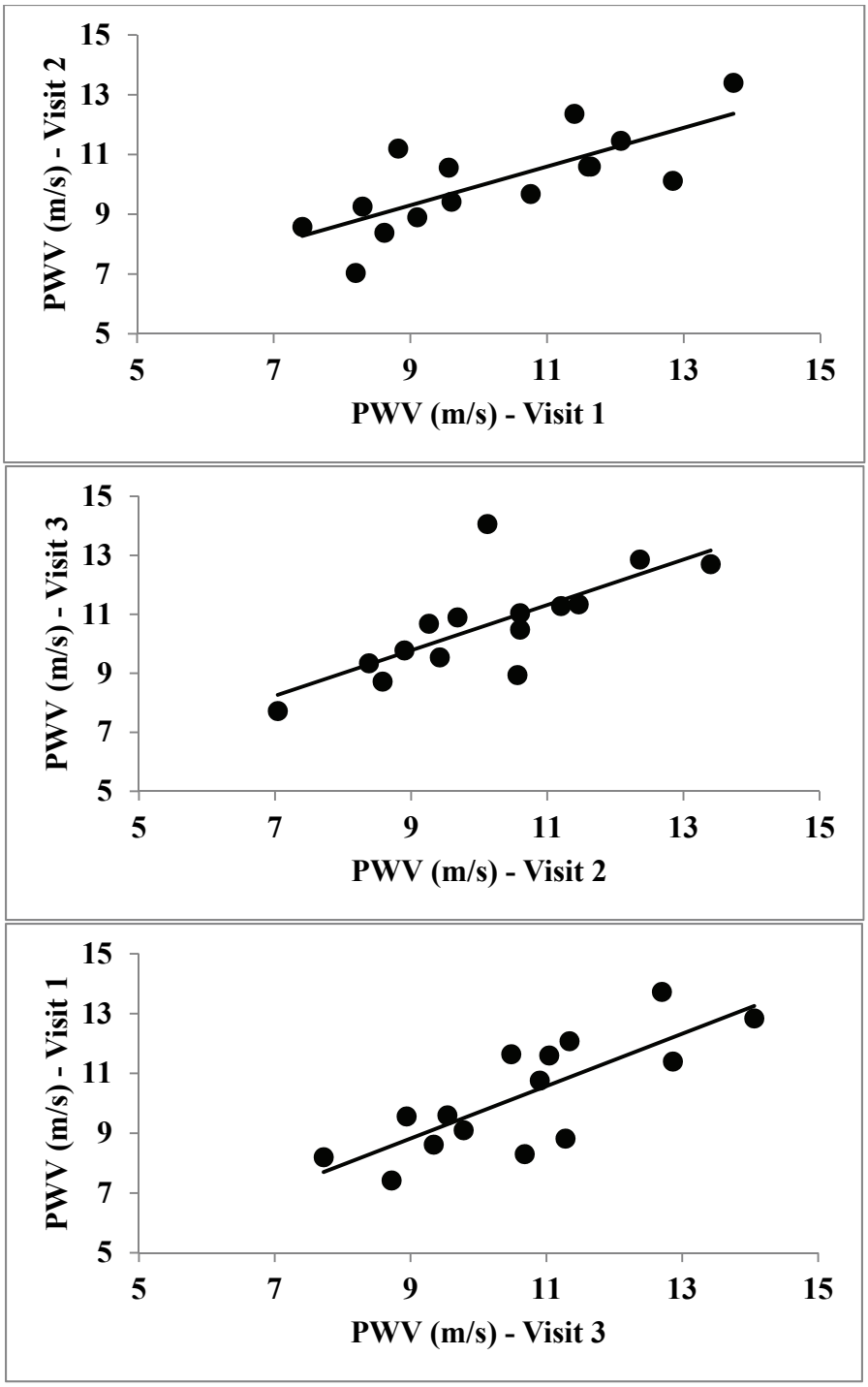

Figure 4.2. Scatter plots of average pulse wave velocity measurements performed on two different testing sessions: Visit 1 versus Visit 2 (r = 0.76; p= 0.0011), Visit 2 versus Visit 3 (r = 0.73; p = 0.0018), and Visit 1 versus Visit 3 (r = 0.79; p = 0.0005)

Bland-Altman plots (Figure 4.3) of the differences between PWV measurements in two successive visits showed a symmetrical distribution of points around the zero line, indicating the absence of a systematic change in these measurements. Although the mean differences between any-pair visits measurements were close to zero, the limits of agreement were found to be wide, reflecting great variation in the PWV measurements at each visit.

As shown in Table 4.3, the mean and standard deviation of differences (SD) in PWV between Visits 1-2, 2-3, and 3-1 were 0.14 (1.26) m/s, -0.52 (1.22) m/s, and 0.38 (1.19) m/s, respectively. No systematic changes in the mean PWV occurred within each of the visit pairs as the corresponding 95% CI for the mean difference included zero. The measurement variability was quantified in terms of within subject coefficient of variation (CV%). The CV% between Visits 1-2, 2-3, and 3-1 were 8.7%, 8.3%, and 8.0%, respectively. Given the fact that the average PWV and CV% on the three visits were slightly above 10 m/s and 8%, respectively (Table 4.2), the average variation of PWV from one visit to another was 0.8 m/s (10 m/s · 8%). The smallest real difference was used to determine the minimum detectable change in PWV. Our calculations showed that the percent smallest real difference ranged from 32% to 34%, which means that the PWV has to change by more than 3 m/s (10 m/s · 34%) to indicate a clinically important improvement in arterial stiffness during an intervention in the COPD population.

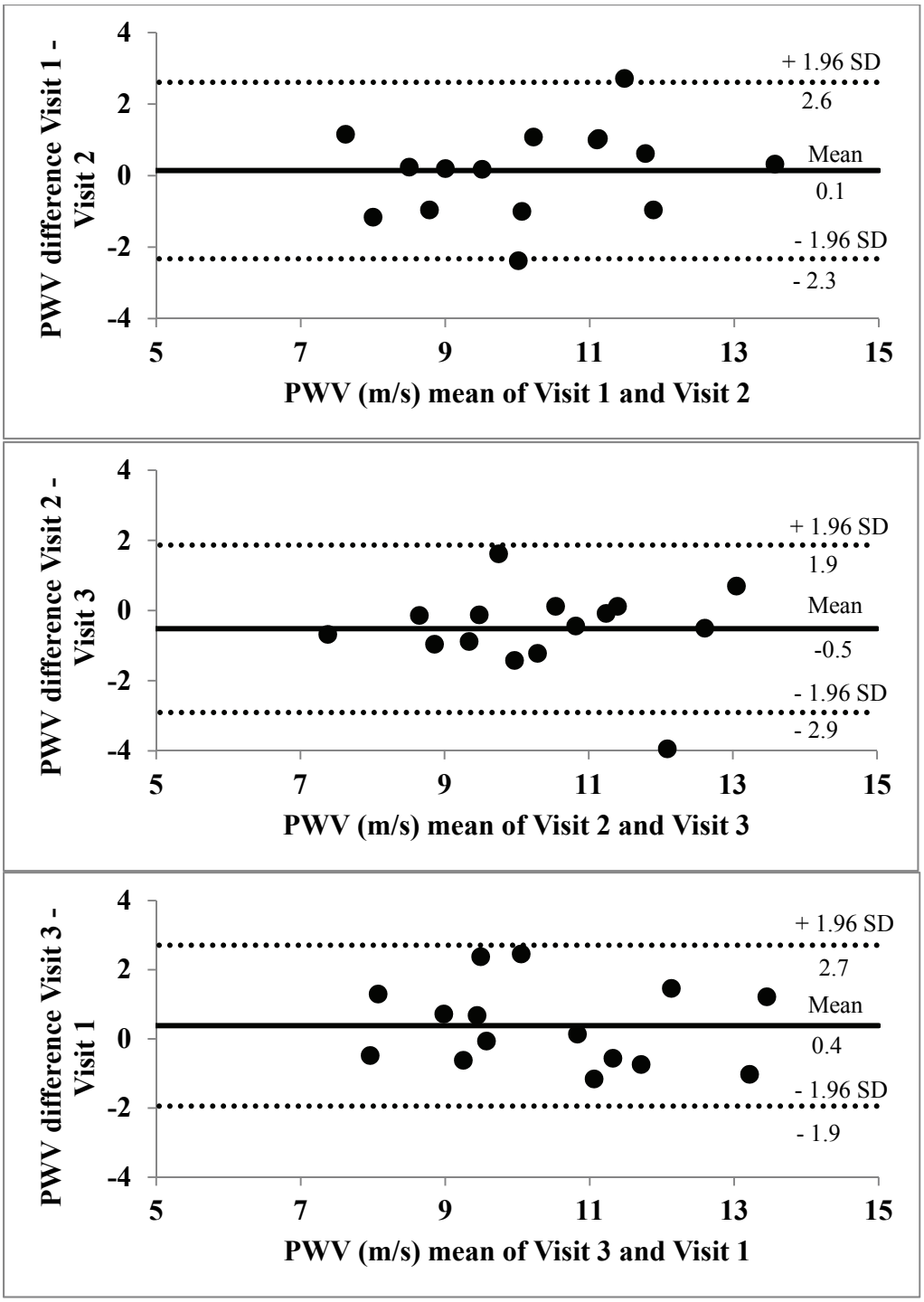

Figure 4.3. Bland-Altman plots of agreement between successive pulse wave velocity measurements. The solid lines represent the mean of the paired differences. The dotted lines represent the limits of agreement (mean ± 1.96 SD)

Table 4.3. Indices of measurement variability and clinically important changes in pulse wave velocity across the testing sessions

Variables	Visit 1 - 2	Visit 2 - 3	Visit 3 - 1
Mean Difference	0.14	-0.52	0.38
Standard deviation of difference	1.26	1.22	1.19
95% CI Mean Difference	-0.51 to 0.79	-1.15 to 0.11	-0.99 to 0.23
Coefficient of variation (CV %)	8.7	8.3	8.0
Smallest real difference (SRD)	3.5	3.4	3.3
Smallest real difference (95% CI)	-3.3 to 3.6	-3.9 to 2.9	-3.7 to 2.9
Smallest real difference (SRD %)	34	33	32

4.3.3 Methodological aspects of pulse wave velocity measurement

The standard deviation of the mean wave propagation time and percent standard error of mean (SEM) of the PWV, which are two commonly used quality criteria in applanation tonometry measurements (253), met the SphygmoCor recommendations for the entire population sample. In contrast, the strength and quality of the pulse signal recommendations were difficult to reach in some of the patients despite repeated measurements. In approximately half of the population sample (8 out of 15), the signal was not strong enough to obtain a pulse height above the 80 mV threshold. Also, the pulse height and baseline variation were both constantly large, exceeding 5% in most patients. However, the recommendation for a pulse length variation below 5% was met in all patients. As presented

in Figures 4.4, 4.5, and 4.6 the most frequent reasons for such inadequate quality control indices were a weak signal and beat-to-beat alterations in arterial pulse shape and amplitude (although the heart rhythm was regular).

The following figures show a series of study screens displaying carotid (top) and femoral (bottom) waveforms together with the associated ECG recordings. The first set of quality criteria (mean time SD < 6% and SEM < 15%) are presented at the bottom of the study screen and the second set of quality criteria (pulse height > 80 mV, variation in pulse height, length, and baseline < 5%) are presented at the end of the arterial and ECG waveforms on the right site.

The data capture in Figure 4.4 shows pulse signals that met both set of quality criteria.

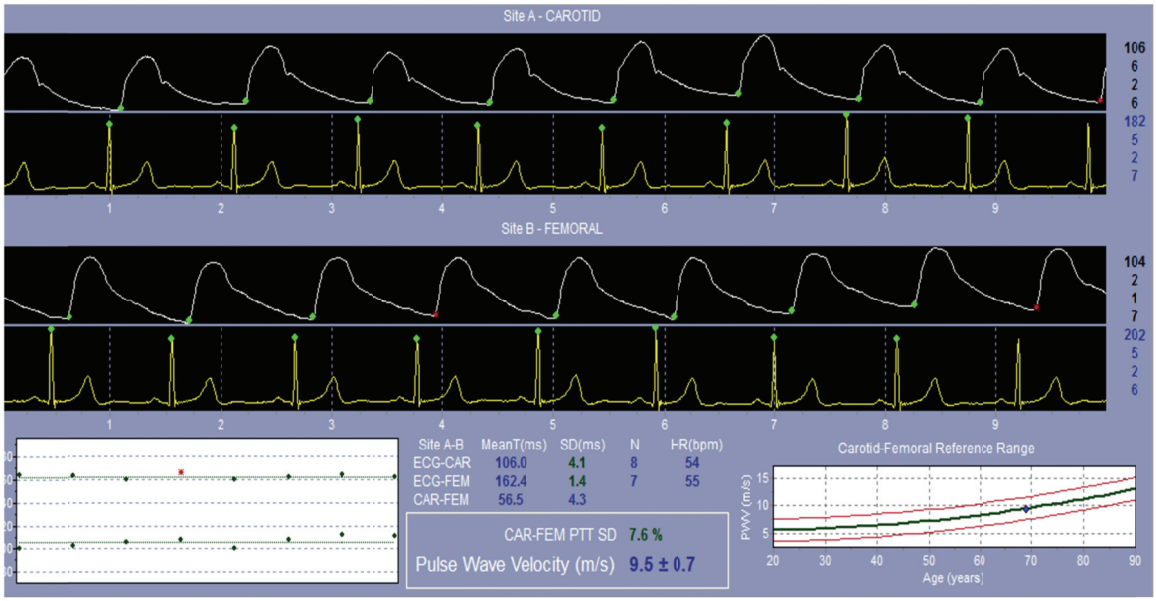

Figure 4.4. Pulse signals that met both sets of quality criteria

The data capture in the Figure 4.5 shows that the first but not the second quality criteria are met; a weak pulse signal that varied in amplitude, size, and shape was responsible for a large variation in pulse height and baseline signal particularly for the carotid site.

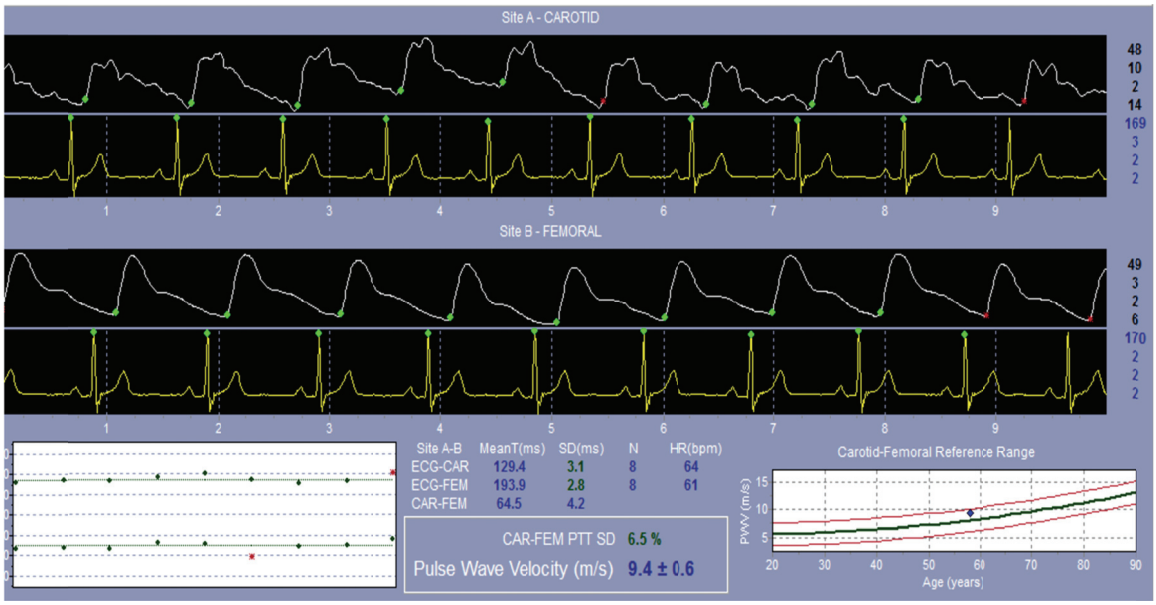

Figure 4.5. Pulse signals that partially met the quality criteria

The data capture in Figure 4.6 shows that while the first quality criteria is met at borderline, the second quality criteria are not completely met; a strong pulse signal that varied in amplitude, size, and shape was responsible for a large variation in pulse height.

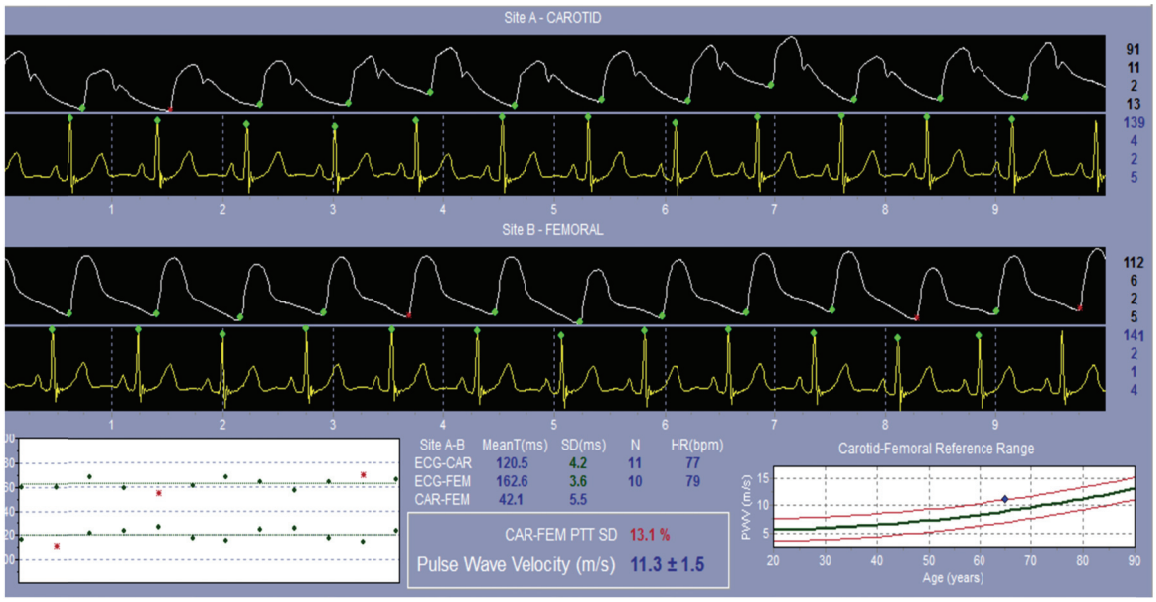

Figure 4.6. Pulse signals that did not meet the quality criteria

4.4 Discussion

We found that the aortic PWV measurements performed with a SphygmoCor device exhibited substantial test-retest reliability and acceptable variability in individuals with moderate-to-severe COPD. We also found that the measurement process suffered from suboptimal pulse signal strength and quality despite repeated PWV measurements. The difficulty encountered in obtaining optimal quality measurements in this population is likely due to clinical rather than methodological factors.

The values of the reliability coefficients found in our study were comparable to other studies that have examined the reliability and reproducibility of aortic PWV in healthy (243,244) and chronic disease populations (245-247). These studies, in spite of using different applanation tonometry devices, showed good correlation coefficients (ranging from 0.7 to 0.9) and relatively low PWV (intra- and inter-observer) mean differences between tests (ranging from -0.7 to 0.3 m/s). There are three previous studies that assessed the repeatability of PWV measurements in patients with COPD. Vivodtzev et al. (250) used a Complior device and reported the reliability of PWV measurements between baseline, day 15, and day 42 in stable COPD patients. At baseline (Day 0), the PWV mean (± SD) was 11.1 ± 1.9 m/s (range 7.0 to 14.9 m/s), with 79% of patients exhibiting abnormal PWV greater than 9.3 m/s (129). The Spearman's and ICC coefficients calculated on PWV measurements on Day 15 versus Day 0, which represents a time frame similar to our study, were 0.78 ($p < 0.001$) and 0.75 (95CI, 0.63-0.89), respectively. This indicates a good reliability of PWV measurements in stable COPD patients. They also reported a higher dispersion of PWV values in patients with an initially high value of PWV (> 11m/s), suggesting that a very good repeatability was expected at lower pulse wave velocity values.

This observation was confirmed by Stone et al. (251), who found excellent correlation ($r = 0.96$; $p < 0.001$) in the presence of low mean PWV values (~9 m/s) between two measurements performed with a Vicorder device within a two weeks period. However, we were not able to determine the reason for their low PWV values in a COPD population with a disease severity similar to Vivodtzev et al., since their methodology section (251) was insufficiently elaborated. However, Rodriguez-Miguelez et al. (252) reported near perfect reliability (ICC 0.98) in the presence of a reduced mean PWV (~8.5 m/s), which was obtained with a less representative COPD population sample (e.g., younger patients with less severe disease, no overt cardiovascular diseases, and a PWV percent SEM < 10%). Our data indicates substantial PWV measurement reliability with intraclass correlation coefficient of 0.75 (95% CI, 0.53-0.89), which is in line with the reliability reported by Vivodtzev et al. (250). This confirms the reliability of PWV measurements performed with a SphygmoCor device in a moderate-to-severe COPD population.

In a reliability analysis, it is also important to quantify the measurement variability between different test occasions, and estimate the threshold value beyond which a true change in an outcome has occurred (229,258). Information is scarce in the literature about the actual size of the PWV variability or the minimal detectable changes in the PWV measurement. This information is particularly important when the pre-post changes due to an intervention are to be assessed. Two studies that evaluated the test-retest reliability of aortic PWV in people with chronic spinal cord injury found an intra-observer coefficient of variation of 5.9% (259), and a smallest real difference of PWV value in the range of 1 m/s [0.9 m/s in (259), and 1.04 m/s in (245)]. To the best of our knowledge, our study is the first one that reports variability in aortic PWV measurements in a population of COPD patients.

Our three coefficients of variation of 8.7%, 8.3%, and 8.0% were each smaller than the 10% threshold considered as acceptable in the literature for PWV measurements (246,260). We also calculated that a PWV decrease of 3 m/s would indicate a clinical improvement following an intervention. Further research is needed to determine if such a large value can be achieved through a pulmonary rehabilitation program in a COPD population.

With respect to the aortic PWV measurement process in our moderate-to-severe COPD population sample, not all SphygmoCor quality settings were achieved in spite of repeated measurements. COPD patients commonly displayed weak signals and/or beat-to-beat alterations in their pulse shape and amplitude even if they had a regular heart rhythm. Given the fact that the applanation tonometry method is based on a geometric analysis of the waveform (261), the intersecting tangent algorithm used by the SphygmoCor device can affect parameter calculations. This algorithm uses the point formed by the intersection of a line tangent to the initial systolic upstroke of the pressure waveform and a horizontal line through the minimum point (262). Therefore, it has been suggested that the pulse wave fluctuations according to respiratory rhythm may affect the detection of the correct upstroke point (262,263).

The human operator can also have an impact on the pulse amplitude measurement through the amount of pressure applied on the artery site (249). We minimized the human measurement error by following a standardized procedure delivered by an experienced operator. We also observed that some of the acquired pressure waveforms exhibited abnormal patterns resembling the pulsus alternans (264) and pulsus paradoxus (265). These patterns of pathological waveforms are described in the medical literature as responses of the

blood pressure to a respiratory dysfunction, cardiac dysfunction, or both (266). Therefore, the human operator alone is not necessarily the source of poor quality signal acquisition.

The anatomical and physiological characteristics of COPD individuals can be responsible for other suboptimal quality control indices. Reduced signal strength at the carotid site may be due to a hypertrophied sternocleidomastoid muscle, which is an important accessory muscle of breathing (267). Further, pulse signal of insufficient strength at both the carotid and femoral sites can reflect either obesity or low blood perfusion (256). Overall, this suggests that clinical (patient-related) rather than methodological factors prevented the obtaining of optimal quality measurements in this population.

4.4.1 Strengths and limitations of the study

Various guidelines and expert consensus documents are available for measuring the aortic stiffness reliably and accurately by means of carotid-femoral PWV (123,125,127). These documents are commonly developed using data from relatively healthy individuals, and for this reason applying their recommendations in a clinical setting can be challenging. A good example is represented by the recommendation that a single PWV reading should be deemed acceptable, particularly for a SphygmoCor device, if the standard deviation of the calculated PWV is lower than 0.5 m/s (125). Such small standard deviation values can be easily achieved in healthy individuals, who do not present variations in pulse waveform due to an underlying disease condition. By using this recommendation only, we found that the mean PWV was 9 m/s, correlation coefficients increased to 0.90, coefficient of variation decreased to 6%, and smallest real difference decreased to 20% (data not shown). However, according to this recommendation more than half (53%) of the patients would have to be

excluded, which limits the use of PWV in a moderate-to-severe COPD population. It follows that the use of PWV as a clinical outcome measure requires stringent application of quality criteria to achieve optimal results in the COPD population.

Finally, a substantial number of individuals were excluded from our study due to underlying dysrhythmias or cardiac valvulopathy. These exclusion criteria represent common coexisting conditions in COPD, which not only impact the cardiovascular risk assessment, but also can be the subject of an intervention such as pulmonary rehabilitation. Excluding these conditions would probably increase the reliability and accuracy of the PWV measurements, but the results obtained from the remaining patient sample is no longer representative of the COPD population. Despite many contradictory results reported in the literature regarding PWV measurement in COPD, to the best of our knowledge no studies have addressed these concerns and limitations in this population.

4.5 Conclusions

Our findings show that PWV measurements performed with a SphygmoCor device are reliable in individuals with moderate-to-severe COPD. However, a subset of PWV measurement quality settings is difficult to achieve in all patients. Clinical (patient-related) rather methodological factors lead to these suboptimal quality measurements. Our findings open the avenue for the use of PWV measurements for quantifying the cardiac risk in COPD, although assessing the PWV response to intervention requires further investigation in this population.

Chapter 5: The relationship between resting heart rate and arterial stiffness in patients with COPD

5.1 Introduction

Chronic obstructive pulmonary disease is recognized as one of the leading causes of morbidity and mortality worldwide (30,268). Emerging evidence indicates that coexisting cardiovascular comorbidity, particularly ischemic heart disease, substantially contributes to the overall health burden of COPD (1,37). Therefore, identifying specific risk factors and intervention strategies to control ischemic heart disease in patients with COPD is currently of particular interest to researchers.

A persistently elevated resting heart rate has long been recognized as a determinant of myocardial ischemia (9,269), and numerous epidemiological studies have provided evidence on the predictive power of resting heart rate for cardiovascular mortality in both general (7,99) and disease populations (6,91,270). More importantly, recent experimental and clinical studies indicate that arterial stiffness, which alone is a strong predictor of cardiovascular events (14,124,129), is associated with resting heart rate (11,12,271) and thus may represent a link between persistently elevated heart rate and increased cardiac ischemic risk. Since questions concerning the physiological basis of the heart rate dependency of arterial stiffness still remain (143), it is essential to thoroughly investigate this relationship to be able to use it in clinical practice.

Patients with COPD commonly experience both elevated resting heart rate (5,6) and arterial stiffness (130,131), but to date there has been no indication of the strength of the

heart rate - arterial stiffness relationship in this population. Such knowledge would be valuable for the management of COPD patients, particularly in the pulmonary rehabilitation setting. Aerobic exercise training, which is the central component of any PRP (144), is known to reduce the resting heart rate (17,179), with subsequent benefits on cardiovascular health (272,273). If a relationship exists between resting heart rate and arterial stiffness in COPD, changes in resting heart rate may be able to influence arterial stiffness, with the ultimate goal of controlling ischemic risk in this population.

This study was conducted to examine the relationship between resting heart rate and arterial stiffness in individuals with COPD, in comparison with that of their control (CTL) counterparts. Our hypothesis was that PWV, which is a measure of arterial stiffness, would be positively associated with the resting heart rate in both COPD and control groups, and would persist independently of common cardiovascular risk factors.

5.2 Methodology

5.2.1 Study design and setting

This study used a cross-sectional, observational design and was conducted in three pulmonary rehabilitation outpatient clinics located in university-affiliated teaching hospitals (St. Paul's Hospital, Vancouver General Hospital, and Ridge Meadows Hospital) within the area of Vancouver, British Columbia, Canada.

5.2.2 Study population

Patients with COPD who were referred to a pulmonary rehabilitation program between January 2014 and April 2016 were invited to participate in the study. The inclusion criteria

were: 40 or more years of age, a physician diagnosis of COPD confirmed by spirometry (22), stable lung and cardiac condition at the time of the study (e.g., no change in usual medication, no respiratory infection or hospitalization in the preceding month), and normal sinus rhythm. Patients were excluded if they had cardiac dysrhythmias, cardiac pacemakers, valvular diseases, and conditions that would preclude lying supine in a relaxed position (e.g. psychiatric disorders, drug or alcohol addictions). During the same time period, control subjects were recruited from the hospital staff, family members of the COPD patients, or volunteers who responded to advertising posters. Except for impaired lung function, the same inclusion and exclusion criteria were applied for the control group.

A sample size of 37 participants per group was required to observe a moderate correlation of 0.45 at a 5% significance level and 80% power. The cases and controls were frequency matched for sex and age (within 10 years). To mitigate the established methodological limitations of the PWV measurement in COPD patients (133,274), additional participants were enrolled in both groups. Over the study duration, 70 COPD and 50 CTL subjects were recruited, out of which 55 COPD and 41 CTL subjects were eligible for the final analysis (Figure 5.1).

Ethical approval to conduct the study was obtained from the Research Ethics Board at Providence Health Research Institute, Vancouver Coastal Health Research Institute, Fraser Health Research Institute, and the University of British Columbia (H11–00984–A005). The subjects gave written informed consent before participating in this study.

5.2.3 Study procedure

All participants were evaluated by the same investigator, with two years of experience in measuring arterial stiffness. A standardized procedure based on expert consensus documents on the measurement of resting heart rate (275) and arterial stiffness using carotid-femoral PWV (125) was followed. The measurements were conducted in a quiet and temperature controlled room (~23^{o}C) at the same time of day (about 9:00 a.m.). The participants were instructed to avoid heavy exertion for a minimum of 24 hours, and to refrain from taking any medication, smoking, eating, drinking alcohol and beverages containing caffeine for at least 12 hours prior to their testing time. All medications were postponed the morning of the testing day, until after the cardiovascular measurements were completed in order to eliminate any major hemodynamic influences. Participants were asked to confirm their compliance to the study requirements at the beginning of their testing session. Non-compliant participants were identified and asked to repeat the measurements under the stated conditions the following day.

Self- and interviewer-administered questionnaires were used to obtain information on participants' medical history, current medications, and smoking habits. Pulmonary function tests were collected from the pulmonary rehabilitation database for the participants in the COPD group. To ensure that the control subjects were free of lung dysfunction, lung function tests were performed with a portable MicroLab spirometer (CareFusion, CA, USA) before starting their hemodynamic measurements. Normal spirometry was defined as FEV_1 and FVC > 80% predicted and FEV_1/FVC > 0.70. The body height and weight of each participant were measured using a stadiometer and a stand-on scale, with the participants in socks and

wearing a hospital gown. Body mass index was calculated as weight in kilograms divided by the square of the height in meters.

Following the baseline measurements, the participants were asked to lie down in the supine position, and each subject was instrumented with a blood pressure cuff adjusted to their arm circumference and three electrocardiogram electrodes placed on their chest in a modified lead II configuration. After at least five minutes of full rest, brachial systolic and diastolic blood pressure measurements were performed on the right arm using an automated oscillometric device (Model HEM 907XL, Omron Healthcare, USA). The mean of three consecutive peripheral blood pressure measurements, performed at one minute intervals, was used for the calibration of the central hemodynamic variables and subsequent analysis. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure, and mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure.

5.2.3.1 Resting heart rate and pulse wave velocity measurements

The carotid-femoral PWV was determined with a SphygmoCor® CPV device (AtCor Medical, Inc. USA) after a minimum period of 15 minutes rest in a supine position, which is recommended for the achievement of a stable hemodynamic condition (125). The pressure waves from the carotid and femoral arterial sites were captured sequentially using an applanation tonometer (Millar Instruments Inc, Houston, Texas, USA), while ECG data was recorded concurrently. After each carotid and femoral waveform pair was recorded, the device automatically calculated the aortic PWV as the distance between the measurements sites (meters) divided by the pulse transit time (seconds). The distance was obtained with a

measuring tape, by subtracting the carotid-suprasternal notch distance from the suprasternal notch-femoral distance (125). The wave transit time (t) was calculated by the system software using the R-waves of the ECG and the foot of the pressure waves at the site of the measurement, employing the intersecting tangent algorithm (262). Five carotid-femoral PWV measurements were performed and their mean value was used in the subsequent analysis. The quality criteria employed during the PWV measurements are described elsewhere (274). Briefly, readings of PWV with percent SEM less than 10% were selected for analysis. The borderline readings with a percent SEM between 10 and 15% were retained only if the repeated PWV measurements were consistently in this range. Readings with a percent SEM over 15% were rejected, as recommended by the manufacturer. Resting heart rate was automatically calculated from the RR intervals of the electrocardiogram, obtained during both carotid and femoral measurements. The average of these two values was used in the subsequent analysis. We determined that the coefficient of variation for repeated PWV and resting heart rate measurements in patients with moderate-to-severe COPD were 8% (274) and 4% (Chapter 3), respectively.

5.2.3.2 Additional clinical outcomes

The central blood pressures were assessed through pulse wave analysis, given their better predictive value for cardiovascular outcomes than peripheral blood pressures (276). Peripheral pressure waveforms were recorded from the radial artery of the right-hand wrist through applanation tonometry with the SphygmoCor device. After acquiring 20 stable radial pressure waveforms, the system software generated the corresponding central waveforms and calculated the values of central blood pressures using a validated mathematical transfer

function (277). The recordings were not retained if the systolic or diastolic variability of the pulse waveforms exceeded 5%, the amplitude of the pulse waveform was less than 80 mV, or the operator index was lower than 80% as per the manufacturer's instruction. The mean of at least three recordings was calculated, and the central blood pressure figures (systolic, diastolic, mean, and pulse pressure) were used for statistical analysis. In our study, the mean operator index was 95 ± 5%, which indicates that our measurements fully met the required quality recommendations. In order to confirm the individuals' hemodynamic stability during the study, values of resting heart rate acquired during pulse wave analysis were also recorded and subsequently compared with those obtained during the PWV measurements. The internal consistency of our resting heart rate measurements is indicated in the strong correlation between the values obtained during pulse wave analysis and PWV assessments ($r = 0.939$, $p < 0.0001$).

5.2.4 Statistical analysis

For descriptive statistics, the continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. Differences in the continuous variables between the COPD and CTL groups were compared using the two-tailed, Student's unpaired t-test for normally distributed data, and Mann-Whitney U-tests for non-normally distributed data. Differences in categorical variables between the COPD and CTL groups were compared with the Chi-square (χ^2) or Fisher test. The data was examined for normality of distribution using the Kolmogorov-Smirnov test. Univariate correlation analyses were first performed to describe the strength and direction of the association between the resting heart rate and pulse wave velocity in both the COPD and

CTL groups. Multivariate regression models were employed to examine the relationship between resting heart rate and pulse wave velocity in both the CTL and COPD groups in the presence of covariate factors. Stepwise regression analysis was performed to select suitable variables for use in the regression model. Resting heart rate was rescaled in units of 10 beats/minute (HR 10) to facilitate a meaningful clinical interpretation (e.g., what the PWV increase is, in response to a 10-unit increase in HR). Interaction terms (e.g., age and pulse pressure) were also incorporated into various regression models to better understand the heart rate – arterial stiffness relationship in our disease population. Given the exploratory nature of the present study and marginally normal distribution of the PWV data in the control individuals, a non-linear model based on the gamma distribution was tested in addition to the linear regression model. All statistical analyses were performed using SAS for Windows, version 9.4 (SAS Institute, Cary, NC). A p value of < 0.05 was considered statistically significant.

5.3 Results

5.3.1 Participant characteristics

The original cohort consisted of 70 patients with COPD and 50 CTL individuals. Of these, 15 (21%) COPD patients and 9 (18%) CTL individuals did not meet inclusion and exclusion criteria. Data of the remaining 55 COPD patients (33 females and 22 males, age 65 ± 8 years) and 41 CTL individuals (24 females and 17 males, age 62 ± 11 years) were used for the statistical analysis. Figure 5.1 provides the flow chart of the study design.

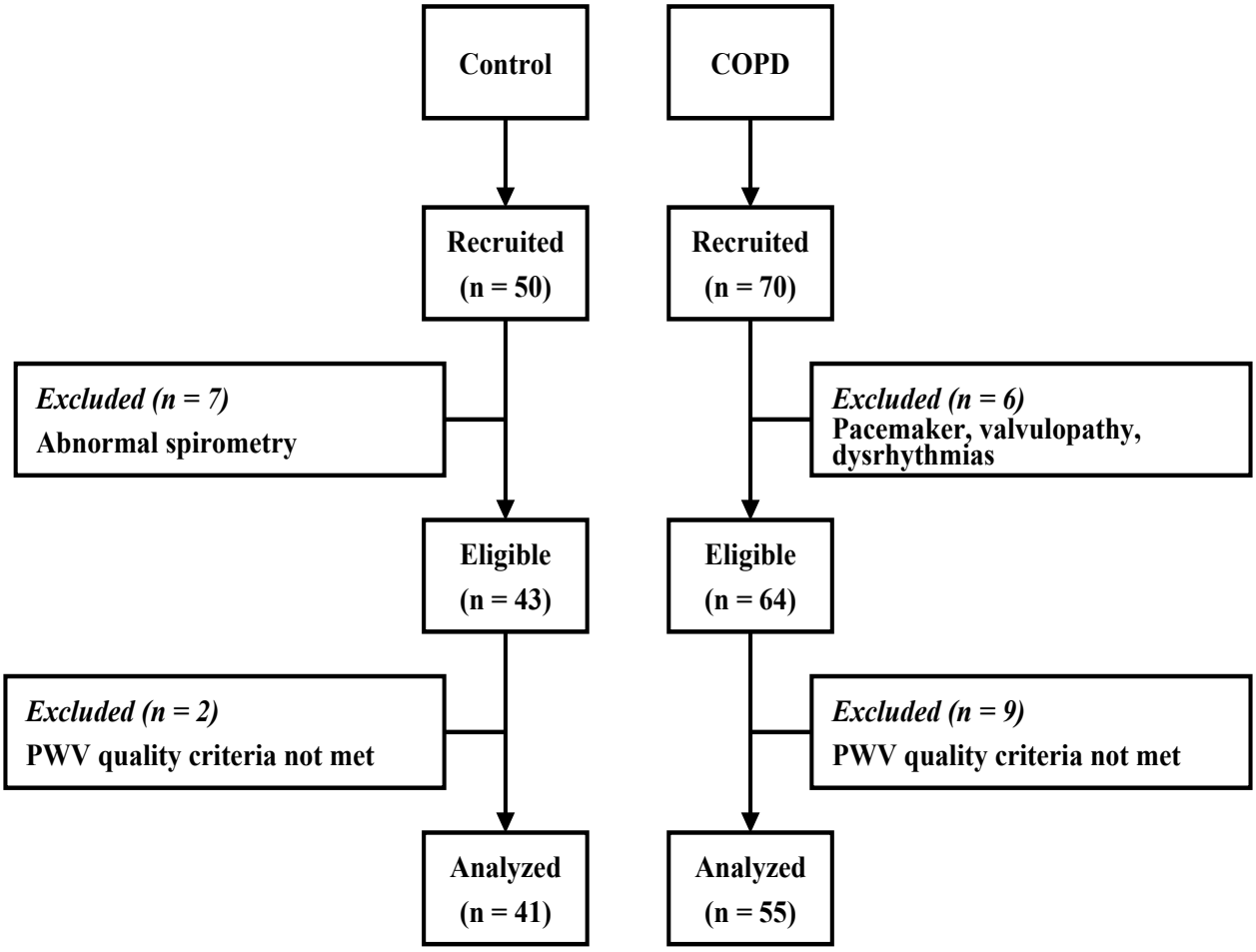

Figure 5.1. Study flow diagram

As shown in Table 5.1, the two groups did not differ in terms of anthropometric characteristics; however, the COPD patients displayed higher BMI values than the CTL subjects, which approached significance (p = 0.055). Patients with COPD had on average moderate-severe airflow limitation (FEV_1 of 54 ± 22% predicted and FEV_1/FVC 51 ± 14), in contrast with the CTL individuals, who had normal lung function tests (FEV_1 of 105 ± 11% predicted and FEV_1/FVC 80 ± 6). Except for cardiovascular morbidity, patients with COPD had a significantly higher percent of comorbid conditions than the individuals in the CTL

group. The hemodynamic parameters also differed significantly between the two groups. Patients with COPD had significantly higher values of resting heart rate (67 ± 11 beats/min versus 60 ± 9 beats/min, $p < 0.002$) and PWV (9.9 ± 1.9 m/s versus 8.7 ± 2.1 m/s, $p < 0.004$) compared to the controls. Despite significantly higher values of peripheral and central blood pressures (systolic, diastolic, and mean) in the COPD group compared to CTL group, no significant differences were found between the groups in terms of peripheral pulse pressure (54 ± 16 mmHg versus 51 ± 11 mmHg, $p = 0.545$) or central pulse pressure (44 ± 16 mmHg versus 41 ± 11 mmHg, $p = 0.461$).

Table 5.1. Characteristics of the study participants

Variables	**COPD (n = 55)**	**CTL (n = 41)**	*p value*
Age (years)	65 ± 8	62 ± 11	*0.110*
Gender: male/female, n (%)	22/33 (40/60)	17/24 (41/59)	*0.885*
BMI (kg/m^2)	27.1 ± 5.0	24.8 ± 3.6	*0.055*
Smoking status			
Smoking history (pack-year)	32 ± 22	10 ± 18	***0.0001***
Current smoker, n (%)	9 (16%)	4 (10%)	*0.386*
Pulmonary function			
FEV_1 (% predicted)	54 ± 22	105 ± 11	***< 0.0001***
FVC (% predicted)	82 ± 23	106 ± 12	***< 0.0001***
FEV_1/FVC	51 ± 14	80 ± 6	***< 0.0001***

Variables	COPD (n = 55)	CTL (n = 41)	*p* value
COPD stage			
Stage 1: mild	8 (15%)		
Stage 2: moderate	21 (38%)		
Stage 3: severe	18 (33%)		
Stage 4: very severe	8 (15%)		
Medical conditions			
Number of comorbidities	3 ± 2	2 ± 1	***< 0.0001***
Musculoskeletal, n (%)	35 (64%)	13 (32%)	***0.002***
Cardiovascular, n (%)	26 (47%)	16 (39%)	*0.420*
Hypertension, n (%)	19 (35%)	10 (24%)	*0.284*
Ischemic heart disease, n (%)	6 (11%)	3 (7%)	*0.550*
Hepato-digestive, n (%)	20 (36%)	6 (15%)	***0.018***
Neuropsychiatric, n (%)	19 (35%)	5 (12%)	***0.012***
Endocrino-metabolic, n (%)	16 (29%)	4 (10%)	***0.024***
Hemodynamics tests			
HR (beats/min)	67 ± 11	60 ± 9	***0.002***
PWV (m/s)	9.9 ± 1.9	8.7 ± 2.1	***0.004***
pSBP (mmHg)	132 ± 20	124 ± 15	***0.036***
pDBP (mmHg)	78 ± 10	73 ± 10	***0.021***
pMBP (mmHg)	97 ± 12	91 ± 11	***0.019***

Variables	COPD (n = 55)	CTL (n = 41)	*p* value
pPP (mmHg)	54 ± 16	51 ± 11	*0.545*
cSBP (mmHg)	123 ± 19	115 ± 15	***0.027***
cDBP (mmHg)	79 ± 10	74 ± 10	***0.021***
cMBP (mmHg)	97 ± 12	91 ± 11	***0.019***
cPP (mmHg)	44 ± 16	41 ± 11	*0.461*

Legend: BMI = body mass index, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, HR = resting heart rate, PWV = pulse wave velocity, p = peripheral, c = central, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, PP = pulse pressure. Values are described as mean ± standard deviation, except for sex, smoking status, COPD stage, and comorbidities that are described as counts and percentage; $p < 0.05$ statistically significant

5.3.2 Relationship between resting heart rate and pulse wave velocity

Univariate correlation analysis revealed a moderate positive association between the resting heart rate and PWV in the CTL group (r = 0.51, $p < 0.0005$), but not in the COPD group (r = 0.12, $p = 0.366$). The scatter plots for the relationship between resting heart rate and PWV in the COPD and CTL groups are displayed in Figure 5.2.

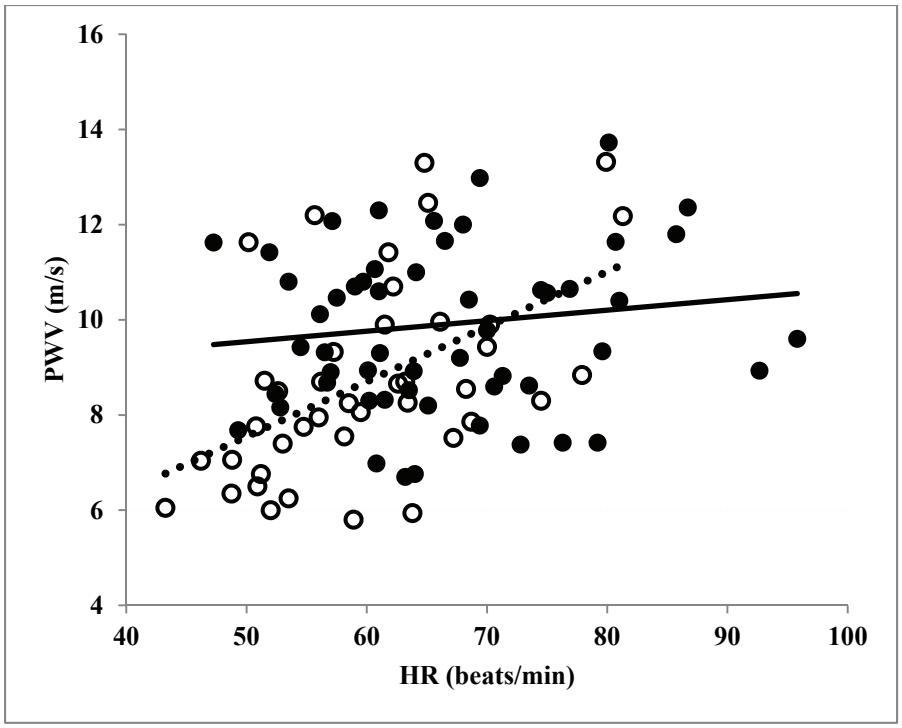

Figure 5.2. Correlation between pulse wave velocity and resting heart rate in COPD patients (r = 0.12, p = 0.366) and CTL subjects (r = 0.51, p < 0.0005). Filled circles represent COPD patient data and open circles represent CTL subject data. The continuous line represents the line of best fit through COPD patient data and the dashed line represents the line of best fit through CTL patient data

In the multiple regression analyses, when potential confounding factors were entered, the resting heart rate remained significantly associated with PWV in the CTL group and became significantly associated with PWV in the COPD group. 52% of the variance in the COPD group ($p < 0.001$) and 70% of the variance in the CTL group ($p < 0.001$) were explained by the linear regression model when age, sex, central pulse pressure, and FEV_1/FVC were included in the model as covariates. We further explored whether the effect of heart rate on PWV depended on the level of specific covariates, namely age and central pulse pressure in

patients with COPD. Using cut-off points represented by the medians of age and central pulse pressure, we found that in the COPD group the effect of heart rate on PWV was significant only for those of an older age (e.g., $\geq$ 65 years old) and high central pulse pressure (e.g., $\geq$ 40 mmHg) (Table 5.2).

A generalized non-linear model based on the gamma distribution was also tested; however, the statistical inferences were similar to those obtained with the linear model. According to the non-linear model, a 10-unit increase in heart rate was associated with a 14% increase in PWV in the CTL group [exp (0.1310) = 1.14, $p = 0.0004$], but only a 2% increase in PWV in the COPD group [exp (0.0222) = 1.02, $p = 0.351$].

Table 5.2. Linear regression analysis between pulse wave velocity and resting heart rate in the CTL and COPD groups

Groups		**COPD**			**CTL**	
Independent variables	**β**	**95% CI**	*p value*	**β**	**95% CI**	*p value*
Model 1 (unadjusted)						
HR 10 (units of 10 beats/min)	0.22	(-0.27, 0.71)	*0.366*	1.15	(0.53, 1.78)	***0.0006***
Model 2 (adjusted for covariates)						
HR 10 (units of 10 beats/min)	0.498	(0.08, 0.92)	***0.021***	0.788	(0.29, 1.29)	***0.003***
Age (years)	0.099	(0.05, 0.15)	***0.0008***	0.079	(0.03, 0.13)	***0.002***
Sex (F=1)	-0.781	(-0.04, 1.61)	*0.063*	-0.839	(-1.66, -0.02)	***0.045***
cPP (mmHg)	0.045	(0.01, 0.08)	***0.006***	0.056	(0.01, 0.10)	***0.020***
FEV_1/FVC	-0.028	(-0.06, 0.001)	*0.061*	0.033	(-0.04, 0.10)	*0.355*
Model 3 (including Age as interaction term)						
HR10*Age<65	0.032	(-0.01, 0.07)	*0.099*			
HR10*Age≥65	0.066	(0.03, 0.11)	***0.003***			

Groups		**COPD**			**CTL**	
Independent variables	**β**	**95% CI**	*p value*	**β**	**95% CI**	*p value*
Model 4 (including cPP as interaction term)						
HR10*cPP<40	0.031	(-0.01, 0.08)	*0.171*			
HR10*cPP≥40	0.051	(0.002, 0.10)	***0.048***			
Model 5 (including Age, and cPP as class variable)						
HR10/(Age<65,cPP≤40)	0.188	(-0.2, 0.6)	*0.347*	0.530	(0.1, 1.0)	***0.029***
HR10/(Age<65,cPP≥40)	0.220	(-0.2, 0.6)	*0.292*	0.693	(0.2, 1.2)	***0.015***
HR10/(Age≥65,cPP<40)	0.386	(0.0, 0.8)	*0.072*	0.750	(0.3, 1.2)	***0.003***
HR10/(Age≥65,cPP>40)	0.580	(0.2, 1.0)	***0.011***	1.028	(0.6, 1.5)	***<0.0001***
Sex (F=1)	-0.863	(-1.7, -0.1)	***0.040***	-0.930	(-1.7, -0.2)	***0.023***
FEV_1/FVC	-0.032	(-0.1, 0.0)	***0.037***	0.052	(0.0, 0.1)	*0.143*

Legend: HR = heart rate, F = female, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, cPP = central pulse pressure; p < 0.05 significantly different

5.4 Discussion

This study is the first to address the relationship between the resting heart rate and arterial stiffness, as assessed by PWV, in patients with COPD and their control counterparts. We showed that the resting heart rate was significantly associated with pulse wave velocity in both COPD and control groups, after adjusting for age, sex, and central pulse pressure. As this relationship was not seen in the COPD group in the univariate analysis, our findings suggest that the resting heart rate dependency of arterial stiffness in patients with COPD could be mediated by different physiological mechanisms.

Consistent with other studies (5,130), we found that the hemodynamic parameters differed between the COPD and control groups. Although we did not stratify our population for comorbidities, we were fortunate to have a similar prevalence of cardiovascular diseases in the COPD and control groups (likely due to the study advertising, which may have attracted control individuals with known cardiac history). This showed that even in the presence of a similar cardiovascular burden, patients with COPD displayed a significantly higher resting heart rate, peripheral and central blood pressures, and pulse wave velocity compared to the controls. Moreover, the average values of resting heart rate and pulse wave velocity measured in the COPD group were, according to the literature (103,129), at the levels that induce an increased risk of cardiovascular events. It is also important to observe the absence of statistically significant differences in the peripheral and central pulse pressure values between the two groups, whereas both the systolic and diastolic blood pressures were significantly higher in the COPD group. Given that the accepted physiological mechanism for arterial stiffness is represented by the pulse pressure amplification, which consists of the movement of the reflected wave from diastole to systole augmenting the systolic pressure

and diminishing the diastolic pressure (113), the tandem of higher systolic and diastolic blood pressures along with higher heart rate in COPD may represent physiological responses needed to maintain a suitable cardiac output in the presence of disease specific cardiac dysfunction (278).

Similar to other studies (11-13), we found a significant association between resting heart rate and arterial stiffness in the control individuals. The magnitude of the correlation in our study was 0.51, which is greater than those reported in other clinical studies (11,13). A possible explanation for our result could be the standardization of the examination and measurement procedure. We also found that the association between resting heart rate and arterial stiffness in the control group remained significant even after adjustment for known covariates factors (e.g., age, sex, and pulse pressure). In line with prior research in this field, our findings indicated increased age (279) and pulse pressure (280) as determinants of arterial stiffness. Our results also showed that females had significantly lower PWV than males. However, the literature is inconsistent in regard to the sex influences on arterial stiffness (281-283). Other potential confounding factors including atrioventricular nodal blocking agents (284) and beta-adrenergic agonists (242) were included in the regression analysis. Since we did not find a statistically significant association between these factors and PWV in our study, those variables were not included in the final analysis.

Since both a persistently elevated resting heart rate and arterial stiffness are well documented in COPD patients (130,131), we expected that the heart rate - arterial stiffness relationship would be maintained in the COPD patients. We did not find a statistically significant association between resting heart rate and arterial stiffness in univariate analysis.

However, this association became statistically significant after adjusting for a number of confounding factors. A few comments are worth making in respect to this issue.

Studies on the mechanical properties of the vascular arterial tree show that arteries manifest nonlinear viscoelastic properties (138,285). For example, Bergel et al. (138) found that the dynamic elastic modulus, which is defined as the ratio of stress to strain under vibratory conditions, increased linearly in both the elastic and muscular arteries of dogs for a heart rate below 120 beats/min. At higher heart rates, the dynamic modulus remained relatively constant. Studies on subjects free of known cardiovascular disease also showed (11,12,286) that aortic distensibility and aortic stiffness decreased and increased, respectively, monotonically with increasing resting heart rate. However, both the resting heart rate and arterial stiffness were largely within normal range. These observations suggest that the absence of a significant association between heart rate and arterial stiffness in COPD could be due to the increased resting heart rate and arterial stiffness, which place their values on the saturation region of the heart rate - pulse wave velocity curve. On the other hand, the significant association between the heart rate and arterial stiffness in COPD patients older than 65 years and with a pulse pressure over 40 mmHg may illustrate that the combination of the variation of the heart rate with systolic and diastolic blood pressures can play an important physiopathological role in the heart rate - pulse wave velocity relationship. However, additional studies are necessary to further investigate these aspects.

Given the exploratory nature of this study and the marginally normal distribution of the PWV data in the control individuals, we also used a nonlinear regression analysis to explore the association between heart rate and arterial stiffness. The results in the linear and nonlinear analyses were similar, improving our confidence in these results. Moreover, the

nonlinear analysis indicated that, in the control population, a heart rate increase of 10 beats/min translates into a 14% increase in the PWV. Since an increase in the aortic PWV by 1 m/s has been found to correspond to an adjusted risk increase of 15% in total cardiovascular mortality (129), we can infer that by reducing the resting heart rate in this population, it would be possible to obtain important reductions in the PWV and cardiac risk. Therefore, the early detection of an increased resting heart rate is important for the preservation of the arterial function and the assessment of the cardiovascular risk in this population. In contrast, a heart rate increase of 10 beats/min in the COPD group translates into a 2% increase in PWV. This suggests that there may be increased difficulty in managing a more advanced arterial disease in COPD, since these patients may be already at the plateau of the curve, and decreasing resting heart rate may bring little change to PWV. Overall, these findings open further avenues for exploring whether an intervention such as pulmonary rehabitation can influence the heart rate - arterial stiffness relationship, and reduce the myocardial ischemic risk in a COPD population.

5.4.1 Strengths and limitations of the study

There are several limitations to this study that should be noted. First, because of the cross-sectional nature, this study does not indicate causality, for which longitudinal studies will be needed. This study was comprised of a population of moderate-to-severe COPD patients referred for pulmonary rehabilitation. Therefore, our results may not be applicable to other COPD patients with less severe disease. Numerous physiopathological factors are known to influence heart rate and arterial stiffness. While we tried to match our populations by age and sex, we were not able to match them by blood pressure, which is known to

correlate positively with both heart rate and arterial stiffness. This is an important aspect that needs further investigation. Lastly, our study focused on the heart rate in a stable condition. While the resting heart rate is a good representation of basal metabolic rate and autonomic activity, temporal changes in heart rate, such as during exercise, could exhibit a higher dependency on pulse wave velocity.

5.5 Conclusions

The findings of the present study provide insight into the relationship between the resting heart rate and arterial stiffness in patients with COPD, in comparison with their controls. Our data indicate that COPD patients manifest elevated resting heart rate and vascular stiffness, which predispose them to increased cardiovascular risk. In addition, resting heart rate has been found to be a less powerful predictor of arterial stiffness in the COPD patients than their control counterparts. Age and pulse pressure play a mediating role in the resting heart rate - arterial stiffness relationship in COPD. Further studies are needed to explore the potential of specific interventions, such as pulmonary rehabilitation, to modulate the heart rate - arterial stiffness relationship and control the ischemic risk in this population.

Chapter 6: The effect of standard pulmonary rehabilitation on resting heart rate and arterial stiffness relationship in patients with COPD

6.1 Introduction

Cardiovascular comorbidities, in particular ischemic heart disease, are commonly reported in patients with COPD (287,288). Aerobic exercise training, which is the core component of any pulmonary rehabilitation program (144), has the potential to improve the cardiovascular health of these patients through controlling various hemodynamic risk factors including elevated resting heart rate (179) and arterial stiffness (18). However, limited data exists in the COPD literature on this topic, despite the fact that these two parameters are recognized to be independent predictors of cardiovascular events and mortality in both general (97,124) and disease (6,16,105,128) populations.

To date, only a few studies have evaluated the effect of pulmonary rehabilitation on arterial stiffness in patients with COPD, and they have reported contradictory results. While some of these studies found significant reductions in arterial stiffness as indicated by lower aortic PWV following exercise training (181,186), others did not confirm those results (187). In these studies, a reduction in arterial stiffness through exercise training was attributed mainly to a decrease in blood pressure. However, the effect of pulmonary rehabilitation on resting heart rate was not explicitly investigated, despite the well-established association of resting heart rate with both blood pressure (289,290) and arterial stiffness (10-12). In addition, there were large variations in the aortic PWV in response to exercise training, which were found consistently across all of these studies. This led us to question if resting heart rate might have played a role in this variability, due to its known intermediary role in

the relationship between cardiorespiratory fitness and arterial stiffness (291). Therefore, the clinical implications of the heart rate - arterial stiffness relationship is worth investigating in a pulmonary rehabilitation setting in the view of optimizing this intervention and potentially controlling the ischemic heart disease risk in patients with COPD.

The purpose of this study was to determine the effect of a standard 8-week pulmonary rehabilitation program on the resting heart rate and arterial stiffness, as well as on the relationship between these parameters in patients with COPD. Our hypothesis was that pulmonary rehabilitation through exercise training would reduce the resting heart rate and arterial stiffness of COPD patients, as well as modulate the relationship between these two parameters in this population. Secondly, the study aimed to provide an overall picture of the patient responses to pulmonary rehabilitation in terms of functional capacity, arterial stiffness, and resting heart rate in order to reveal their logical interrelations and implications for clinical practice.

6.2 Methodology

6.2.1 Study design and setting

This study used a prospective observational design and was conducted between January 2014 and April 2016 in three pulmonary rehabilitation outpatient clinics located in university-affiliated teaching hospitals (St. Paul's Hospital, Vancouver General Hospital, and Ridge Meadows Hospital) within the Vancouver area, British Columbia, Canada.

6.2.2 Study population

Convenience sampling was employed, in which COPD patients were recruited consecutively as they entered a pulmonary rehabilitation program. The subjects were eligible to be enrolled in the study according to the following criteria: 40 or more years of age, both sexes, a physician record of COPD diagnosis confirmed by spirometry (28,225), stable lung and cardiac conditions (defined as no change in usual medication, no respiratory infection and/or hospitalization in the month preceding the rehabilitation program, as well as during the period of the study), normal sinus rhythm, ability to walk independently with/without walking aid. The individuals with cardiac dysrhythmias, cardiac pacemakers, valvulopathy, and drug and alcohol addictions as well those attending less than 80% of the pulmonary rehabilitation sessions were excluded. A pulmonary rehabilitation health care provider at each clinic was responsible for the recruiting and screening process, and eligible participants were enrolled in the study. Ethical approval to conduct the study was obtained from the Research Ethics Board at the Providence Health Research Institute, Vancouver Coastal Health Research Institute, Fraser Health Research Institute, and the University of British Columbia (H11–00984–A005). Written informed consent was obtained from all participants before taking part in this study.

6.2.3 Study procedure

Each eligible subject underwent two evaluation sessions: a baseline assessment (Visit 1) performed within one week prior to starting the pulmonary rehabilitation program and a follow-up assessment (Visit 2) performed within one week of completion of the 8-week pulmonary rehabilitation training. Resting heart rate and PWV, as a measure of arterial

stiffness, were collected by the same investigator, who had more than two years of experience in vascular and hemodynamic assessments.

To minimize the effect of potential confounding factors on the parameters of interest, we followed a standardized procedure based on expert consensus documents on the measurement of resting heart rate (275) and aortic stiffness using carotid-femoral PWV (125). The measurements were conducted in a quiet and temperature controlled room (~23^{o}C) at the same time of day (approximately 9:00 a.m.). The participants were instructed to avoid heavy exertion for a minimum of 24 hours, and to refrain from taking any medication, smoking, eating, drinking alcohol and beverages containing caffeine for at least 12 hours prior to their testing time. All medications were resumed after the cardiovascular measurements were completed, in order to eliminate any major hemodynamic influences. Participants were asked to confirm their compliance with study requirements at the beginning of their testing sessions. Non-compliant participants were identified and asked to repeat the measurements under the stated conditions on the following day.

Self- and interviewer-administered questionnaires were used to obtain information on each participant's medical history, current medications, smoking habits, and respiratory symptoms. Each participant's body height and weight were measured using a stadiometer and a stand-on scale, with the participant in socks and wearing a hospital gown. Body mass index was calculated as weight in kilograms divided by the square of the height in meters. Each participant's pulmonary function test results, no older than one year, were collected from a pulmonary rehabilitation database.

Following baseline measurements, the participants were asked to lie down in the supine position, and each subject was fitted with a blood pressure cuff adjusted to their arm

circumference and three electrocardiogram electrodes placed on their chest in a modified lead II configuration. After at least five minutes of full rest, brachial systolic and diastolic blood pressure measurements were performed on the right arm using an automated oscillometric device (Model HEM 907XL, Omron Healthcare, USA). The mean of three consecutive peripheral blood pressure measurements, performed at one minute intervals, was used for the calibration of the central hemodynamic variables and subsequent analysis. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure, and mean arterial pressure was calculated as diastolic pressure plus one third of the pulse pressure. Oxygen saturation (SpO_2) was also recorded using a pulse oximeter (Nonin Medical Inc., MN, USA).

6.2.3.1 Primary outcome measurements

The resting heart rate and carotid-femoral PWV were determined with a SphygmoCor® CPV device (AtCor Medical, Inc., USA) with the subject in a supine position for at least 15 minutes before the assessment, which was needed to achieve a stable hemodynamic condition (125). The methodological procedure and quality criteria are described elsewhere in detail (274). Pressure waves from the carotid and femoral arterial sites were captured sequentially using an applanation tonometer (Millar Instruments Inc, Houston, Texas, USA), while ECG data was recorded concurrently. After each carotid and femoral waveform pair was recorded, the device automatically calculated the aortic PWV as the distance between the measurements sites (meters) divided by the pulse transit time (seconds). The distance was obtained with a measuring tape, by subtracting the carotid-suprasternal notch distance from the suprasternal notch-femoral distance (125). The wave transit time (t) was calculated by the system software using the R-waves of the ECG and the foot of the pressure waves at the site

of the measurement, employing the intersecting tangent algorithm (262). Five carotid-femoral PWV measurements were performed, and their mean value was used in the subsequent analysis. Readings of PWV with percent SEM less than 10% were selected for analysis. The borderline readings with a percent SEM between 10 and 15% were retained only if the repeated PWV measurements were consistently in this range. Resting heart rate was automatically calculated from the RR intervals of the electrocardiogram, obtained during both carotid and femoral measurements. The average of these two values was used in the subsequent analysis. We determined that the coefficient of variation for repeated PWV and resting heart rate measurements in patients with moderate-to-severe COPD were 8% (274) and 4% (Chapter 3), respectively.

6.2.3.2 Secondary outcome measurements

Central blood pressure was assessed by pulse wave analysis. Thus, peripheral pressure waveforms were recorded from the radial artery of the right-hand wrist through applanation tonometry with the SphygmoCor device. After acquiring 20 stable radial pressure waveforms, the system software generated the corresponding central waveforms and calculated the values of central blood pressures using a validated mathematical transfer function (277). The recordings were not retained if the systolic or diastolic variability of the pulse waveforms exceeded 5%, the amplitude of the pulse waveform was less than 80 mV, or the operator index was lower than 80% as per the manufacturer's instruction. The mean of at least three recordings was calculated, and the central blood pressure figures (systolic, diastolic, mean, and pulse pressure) were used in the statistical analysis. In our study, the average operator index was 95 ± 4%, which shows that our measurements fully met the

required quality recommendations. To confirm the individuals' hemodynamic stability during the study, values of resting heart rate acquired during pulse wave analysis were also compared with those obtained during PWV measurement. The internal consistency of the resting heart rate measurements is indicated by the strong correlation between the values obtained during pulse wave analysis and PWV assessments ($r = 0.968$, $p < 0.0001$).

Functional capacity was assessed by the means of the six-minute walk distance test (6MWD) performed in an enclosed flat corridor, 30-m in length, following the American Thoracic Society (ATS) standard guidelines (292). Patients were instructed to cover the longest distance possible in six minutes, with or without pause. During the test, standardized encouragement was given to the patients. The test was performed twice, once under researcher supervision and once under physiotherapist supervision. Since a time interval of approximately one week separated the two assessments, we considered that the average of those distance values was a better representation of the participant's functional capacity; thus, the average value was used in the subsequent analysis.

The modified Medical Research Council (mMRC) scale was used to assess patient disability associated with breathlessness (293). This scale is comprised of five statements that describe respiratory disability during daily activities from no (grade 0) to almost complete (grade 4) incapacity (294).

6.2.4 Pulmonary rehabilitation program

Following the baseline assessment (Visit 1), participants began an 8-week comprehensive pulmonary rehabilitation program, which was delivered 3 days per week, and included 1 hour of education and 1 hour of supervised exercise training per session, according to the current

recommendations (145,295). The education component focused on promoting self-management skills and behavioral improvements. The exercise component focused mainly on lower-limb endurance training. Each session consisted of 10 minutes warm-up, 40 minutes exercise training, and 10 minutes cool down and stretching. The warm-up component included active mobility exercises for the joints and muscles. Lower limb endurance training was based on a combination of cycle ergometry and walking (either treadmill or ground-based). The starting intensity for the cycle ergometry training was 60%-80% of the peak workload achieved during a prior cardiopulmonary exercise test. For treadmill walking, the training intensity was 60%-80% of the average walking speed achieved during the baseline 6MWD test. The duration of each mode of exercise was initially set at 15-20 minutes and increased up to 30 minutes. In order to achieve physiological benefits, the intensity and the duration of the training program were gradually increased to moderate-vigorous levels according to a dyspnea score of 3-5 (moderate-to-severe on the Borg rating of perceived exertion scale). For those patients unable to sustain 20-30 minutes of continuous exercise due to intolerable symptoms such as dyspnea on exertion or fatigue, regular breaks of either no load or reduced load were included in interval training. Supplemental oxygen was also provided to those participants whose oxygen saturation levels fell below 88% during exercise training. When needed, upper- and lower-limb strength training (e.g., hand weights, step-ups, or sit-to-stand) was included as an adjunct to lower limb training to reduce the age-related decline in muscle mass. During the cool-down period, participants used a variety of relaxation techniques, such as flexibility and static stretching exercises under controlled breathing.

All training sessions were led by a health care professional who monitored the training intensity and progression, and also provided motivation and encouragement. The training mode, intensity, and duration were recorded in each participant's exercise log at every class, along with their attendance. At the end of each class, the participants were encouraged to remain active and practice exercises that could be performed safely at home. The type and duration of the exercise training were similarly employed at the three pulmonary outpatient clinics, with one clinic using a block entry program and the other two clinics using a rolling entry program. The same study procedure and measurements were repeated after two months in those participants who completed the pulmonary rehabilitation programs (Visit 2).

Based on the clinically significant thresholds reported in the literature, COPD patients with an improvement in the six-minute walk distance test greater than 25 m (296) were considered responders to the rehabilitation program in terms of functional capacity. Based on our previous reliability studies, improvements greater than 4% beats/min and 8% m/s in the resting heart rate and PWV, respectively, were considered true (clinically meaningful) changes. The score changes were calculated by subtracting the post-rehabilitation values from pre-rehabilitation values.

6.2.5 Statistical analysis

For descriptive statistics, continuous variables were described using means and standard deviations, whereas categorical data were described using counts and percentages. The data was examined for normality of the distribution using the Kolmogorov-Smirnov test. The within-group differences in the variables of interest before and after the pulmonary rehabilitation intervention were compared by two tailed, Student's paired t-test for normally

distributed data, and Wilcoxon signed-rank test for non-normally distributed data. The individual changes in pulse wave velocity and resting heart rate, along with the mean percentage changes in the hemodynamic parameters (calculated as the difference between post- and pre-rehabilitation values divided by pre-rehabilitation values and multiplied by 100) were also presented to illustrate the variability and magnitude of the pulmonary rehabilitation effect. Univariate correlation analyses were first performed to assess the association between the resting heart rate and PWV in the pre and post-pulmonary rehabilitation groups, and scatter plots were created to illustrate these relationships. Then, multivariate analyses employing a generalized estimating equation (GEE) for longitudinal data analysis was used to determine the modulatory effect of pulmonary rehabilitation on the PWV in the presence of covariates including resting heart rate. An Euler-Venn diagram was constructed to describe the overlap in the responses to pulmonary rehabilitation in terms of functional capacity, arterial stiffness, and resting heart rate in our COPD population. All statistical analyses were performed using the SAS package for Windows, version 9.4 (SAS Institute, Cary, North Carolina). A p value < 0.05 was considered statistically significant.

6.3 Results

6.3.1 Participant characteristics

All patients with COPD starting a pulmonary rehabilitation program in the considered time frame were approached. Of those who agreed to participate in the study, 61 passed the first screening and thus attended the baseline study assessment. Following the baseline assessment, 12 participants were excluded from the study due to the fact that their PWV measurements did not meet the SphygmoCor device quality criteria. Of the 49 participants

who remained in the study, 22 individuals dropped out of the program. The main reasons for dropping-out were: medical conditions that required hospitalization [acute exacerbation of COPD (n = 3), cancer (n = 2), thrombophlebitis (n = 1), osteoarticular surgery repair (n = 1)], change in medication (n = 2), job related issues (n = 6), insufficient number of sessions attended (n = 3), and unknown causes (n = 4). In total, 27 COPD participants (7 men and 20 women) successfully completed the 8-week intervention and underwent both the pre- and post-PRP evaluations. Figure 6.1 presents the flow diagram of the described study.

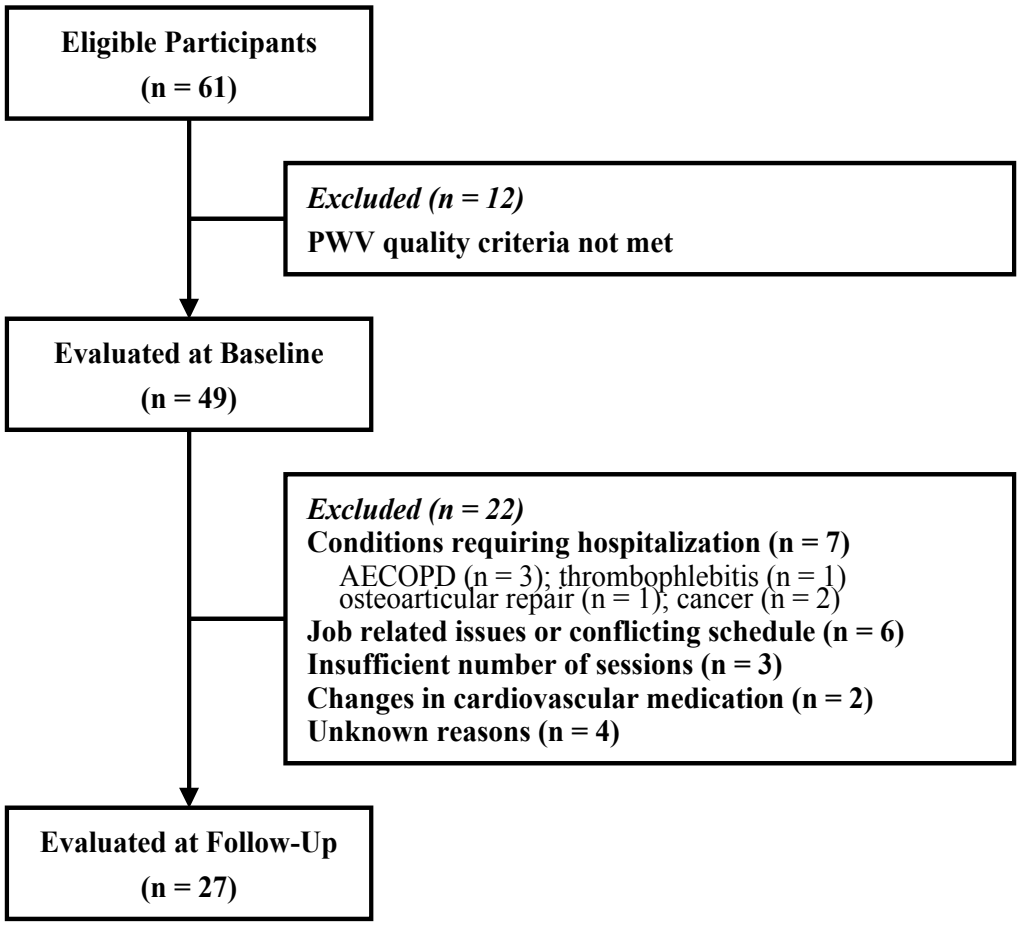

Figure 6.1. Study flow diagram

On average, the study population was aged 67 ± 8 years and had moderate-to-severe disease severity (FEV_1 59 ± 21% predicted, FEV_1/FVC 57 ± 13). Musculoskeletal and cardiovascular diseases were the most common comorbidities, with a frequency of 78% and 67%, respectively. Approximately 90% of patients were receiving short- and/or long-acting beta-agonists, and approximately 60% were receiving inhaled muscarinic antagonists and/or corticosteroids. Renin-angiotensin antagonists and statins were the most frequent, and beta-blockers and calcium channel blockers the least frequent, cardiovascular medications prescribed in this population. The baseline characteristics of COPD patients are presented in Table 6.1.

Table 6.1. Characteristics of the study participants

Variables	COPD (n = 27)
Age (years)	67 ± 8
Male/Female, n (%)	7/20 (26/74)
BMI (kg/m^2)	28.4 ± 5.5
Smoking history (pack-year)	25 ± 19
Current smoker, n (%)	3 (11 %)
SpO_2 (%)	94 ± 2
Pulmonary function	
FEV_1 (% predicted)	59 ± 21
FVC (% predicted)	82 ± 23
FEV_1/FVC	57 ± 13
COPD stage	
Stage 1: mild	4 (15%)
Stage 2: moderate	13 (48%)
Stage 3: severe	9 (33%)
Stage 4: very severe	1 (4%)
Medical conditions	
Musculoskeletal (osteoporosis, osteoarthritis), n (%)	21 (78 %)
Cardiovascular (hypertension, ischemic heart disease), n (%)	18 (67 %)
Hepato-digestive (hepatitis C, GERD), n (%)	10 (37 %)
Neuropsychiatric (anxiety, depression), n (%)	8 (30 %)

Variables	COPD (n = 27)
Endocrino-metabolic (DM, hypo/hyperthyroidism), n (%)	8 (30 %)
Lung medications	
Short/long muscarinic antagonists, n (%)	16 (59%)
Short/long beta agonists, n (%)	24 (89 %)
Inhaled corticosteroids, n (%)	18 (67 %)
Cardiovascular medications	
RAS antagonists, n (%)	11 (41)
Statins, n (%)	9 (33)
Anticoagulants, n (%)	8 (30)
Diuretics, n (%)	7 (26)
Beta-blockers, n (%)	5 (19)
Calcium antagonists, n (%)	3 (11)

Legend: BMI = body mass index, SpO2 = blood oxygen saturation, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, GERD = gastroesophageal reflux disease, DM = diabetes mellitus, RAS = renin-angiotensin system, Values are described as mean ± standard deviation, except for sex, smoking status, medication, and comorbidities that are described as counts and percentage

6.3.2 Hemodynamic and functional changes with pulmonary rehabilitation

Table 6.2 presents the baseline and post-pulmonary rehabilitation anthropometric, hemodynamic, and functional parameters. There were no significant changes in BMI or oxygen saturation after rehabilitation. Although there were no significant differences in resting heart rate (65 ± 10 beats/min versus 66 ± 9 beats/min, $p = 0.163$) after pulmonary

rehabilitation, PWV significantly decreased (10.3 ± 2.5 m/s versus 9.6 ± 2.0 m/s, $p = 0.004$) after 8 weeks of rehabilitation. Systolic blood pressure, mean arterial pressure, and central pulse pressure significantly improved with exercise training, while peripheral and central diastolic blood pressure, and peripheral pulse pressure did not. There were no significant changes in the MRC dyspnea score, but functional capacity assessed by 6MWD significantly improved after pulmonary rehabilitation (389 ± 125 m versus 446 ± 126 m, $p = 0.0001$).

Table 6.2. Hemodynamic and functional changes with pulmonary rehabilitation

Variables	**Pre PRP**	**Post PRP**	*Delta*	*p value*
BMI (kg/m^2)	28.4 ± 5.5	28.2 ± 5.2	-0.2 ± 0.7	*0.086*
SpO_2 (%)	94 ± 2	95 ± 2	0.4 ± 1.8	*0.442*
Hemodynamic parameters				
HR (beats/min)	65 ± 10	66 ± 9	1.3 ± 4.7	*0.163*
PWV (m/s)	10.3 ± 2.5	9.6 ± 2.0	-0.7 ± 1.2	***0.004***
pSBP (mmHg)	136 ± 21	130 ± 18	-5.2 ± 12.2	***0.035***
pDBP (mmHg)	77 ± 11	76 ± 11	-1.9 ± 6.5	*0.151*
pMBP (mmHg)	98 ± 13	95 ± 12	-3.3 ± 7.6	***0.033***
pPP (mmHg)	58 ± 17	55 ± 16	-3.4 ± 10.5	*0.108*
cSBP (mmHg)	127 ± 19	121 ± 18	-5.6 ± 11.1	***0.014***
cDBP (mmHg)	78 ± 11	76 ± 11	-2.0 ± 6.5	*0.128*
cMBP (mmHg)	98 ± 13	95 ± 12	-3.3 ± 7.6	***0.033***

Variables	**Pre PRP**	**Post PRP**	*Delta*	*p value*
cPP (mmHg)	48 ± 16	45 ± 17	-3.7 ± 8.2	***0.029***
Functional parameters				
6MWD (metres)	389 ± 125	446 ± 126	57 ± 38	***0.0001***
mMRC (unit)	1.9 ± 0.9	1.7 ± 0.9	-0.2 ± 0.6	*0.212*

Legend: BMI = body mass index, SpO2 = blood oxygen saturation, HR = resting heart rate, PWV = pulse wave velocity, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, PP = pulse pressure, p = peripheral, c = central, 6MWD = six minute walk distance, mMRC = modified Medical Research Council scale. Values are described as mean ± standard deviation. $p < 0.05$ significantly different

Figures 6.2 and 6.3 show the individual responses to pulmonary rehabilitation in terms of pulse wave velocity and resting heart rate, respectively. There was large variability in these responses with exercise training. The percent changes in the hemodynamic parameters of interest are represented in Figure 6.4 as box plots. Pulse wave velocity decreased on average by 6%, whereas the resting heart rate increased on average by 2%. Among the blood pressure parameters, central pulse pressure decreased by the largest percent change after exercise training (7%).

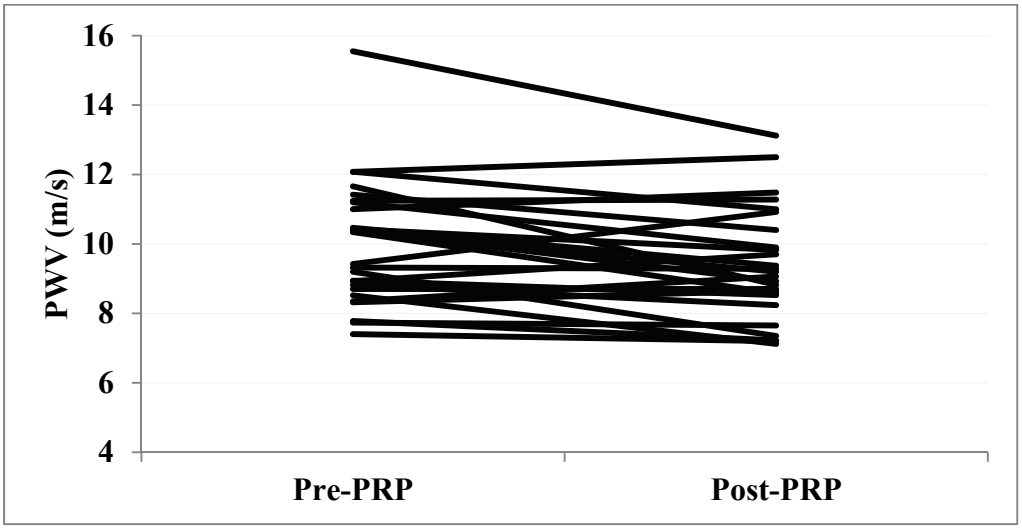

Figure 6.2. Graphical representation of individual responses in pulse wave velocity with pulmonary rehabilitation in patients with COPD

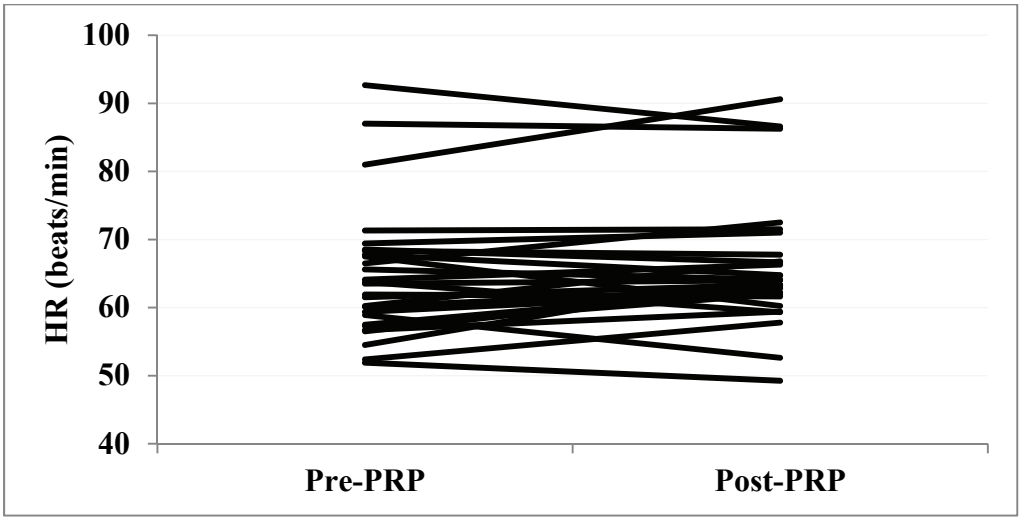

Figure 6.3. Graphical representation of individual responses in resting heart rate with pulmonary rehabilitation in patients with COPD

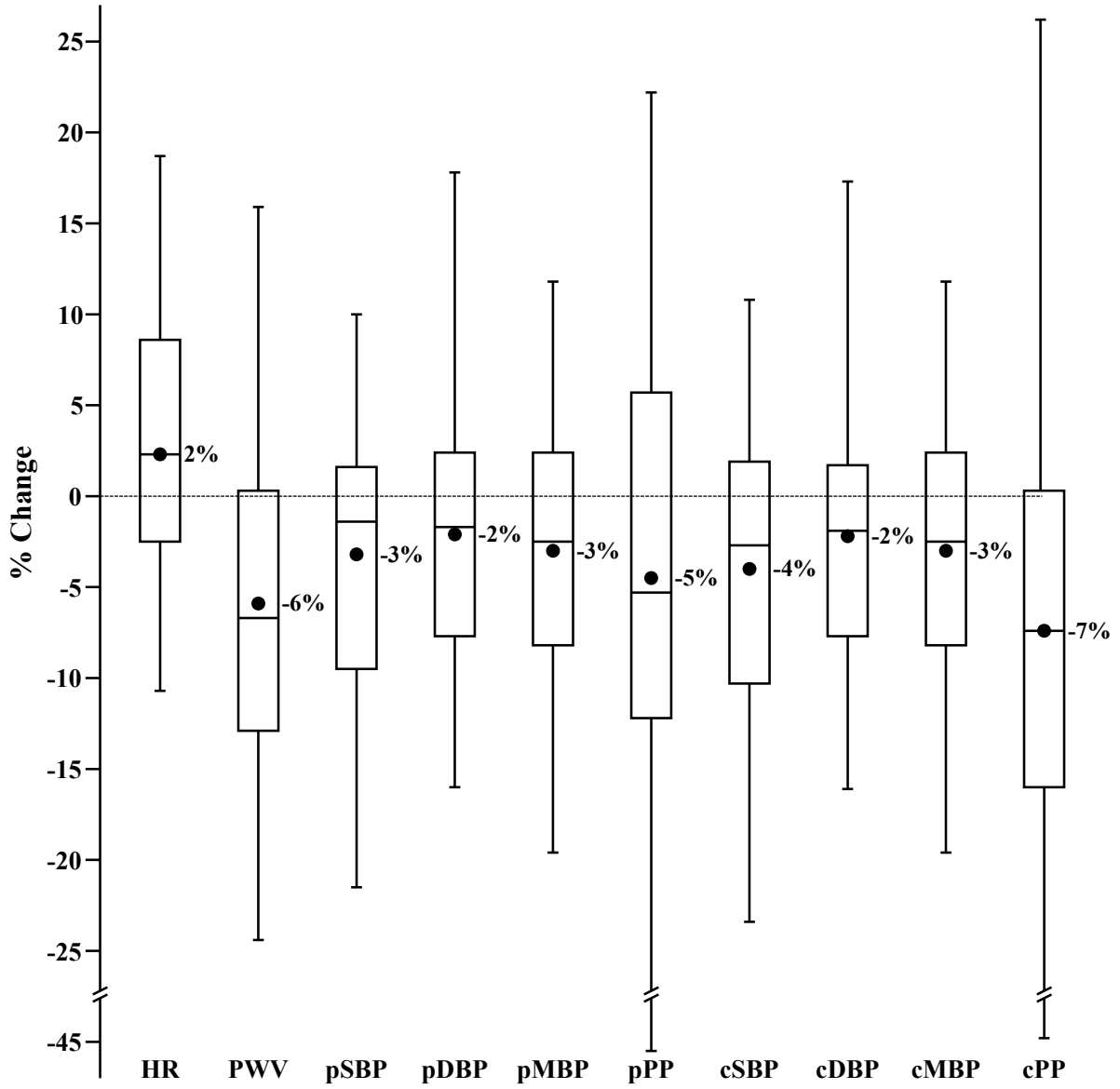

Figure 6.4. Box plots representing the percent changes in hemodynamic parameters with pulmonary rehabilitation. The median and mean values are represented as horizontal lines and dots, respectively. (HR = resting heart rate, PWV = pulse wave velocity, SBP = systolic blood pressure, DBP = diastolic blood pressure, MBP = mean blood pressure, PP = pulse pressure, p = peripheral, c = central)

6.3.3 Relationship between resting heart rate and pulse wave velocity

The univariate analyses showed no significant association between resting heart rate and PWV either pre or post-rehabilitation. The scatter plot representing the relationship between resting heart rate and PWV in the pre and post-pulmonary rehabilitation groups is displayed in Figure 6.5. The longitudinal analysis (Table 6.3) showed that pulmonary rehabilitation had a significant effect on PWV, which was maintained even when confounding factors (age, heart rate, and central pulse pressure) were taken into account. However, the heart rate was not a significant predictor in this model.

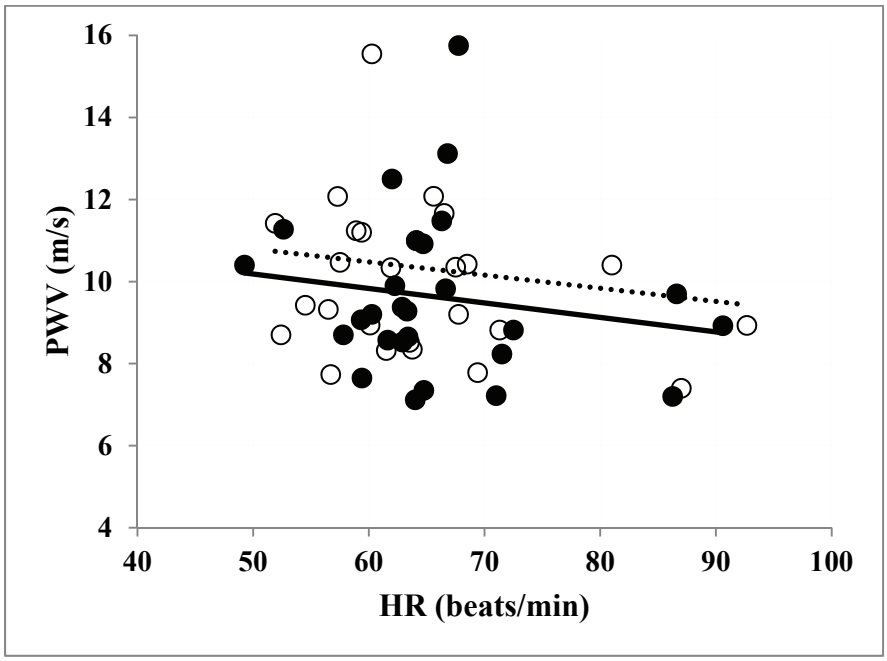

Figure 6.5. Correlation between heart rate and pulse wave velocity in COPD patients pre (r = - 0.12, *p* = 0.536) and post (r = - 0.17, *p* = 0.409) pulmonary rehabilitation. Open circles represent COPD patient data pre-rehabilitation and filled circles represent COPD patient data post-rehabilitation. The dashed line represents the line of best fit through COPD patient data pre-rehabilitation and the continuous line represents the line of best fit through COPD patient data post-rehabilitation

Table 6.3. Longitudinal analysis examining the effect of pulmonary rehabilitation on pulse wave velocity

Independent variables	**β**	**95% CI**	*p value*
Model 1			
PRP phase (post = 1)	-0.71	(-1.1, -0.28)	***0.0012***
Model 2			
PRP phase (post = 1)	-0.69	(-1.1, -0.27)	***0.0014***
HR (beats/min)	-0.02	(-0.09, 0.06)	*0.648*
Model 3			
PRP phase (post = 1)	-0.83	(-1.21, -0.44)	***< 0.0001***
HR (beats/min)	-0.03	(-0.12, 0.06)	*0.554*
Age (years)	0.17	(0.06, 0.28)	***0.002***
Sex (F = 1)	-1.76	(-4.18, 0.66)	*0.155*
cPP (mmHg)	-0.04	(-0.08, -0.003)	***0.036***
FEV_1/FVC	-0.03	(-0.08, -0.03)	*0.368*

Legend: PRP = pulmonary rehabilitation program, HR = heart rate, FEV1 = forced expiratory volume in one second, FVC = forced vital capacity, F = female; cPP = central pulse pressure.

Figure 6.6 is an Euler-Venn diagram that presents the patient response rates to rehabilitation in terms of functional capacity, arterial stiffness, and resting heart rate in our COPD population. In our sample, 81% of the patients increased their 6MWD beyond the clinically meaningful thresholds. In terms of PWV and heart rate, 45% and 22% of the patients, respectively, showed improvement. Overall, almost half (48%) of the patients showed improvements in at least two out of three parameters of interest. Only two patients showed no improvement.

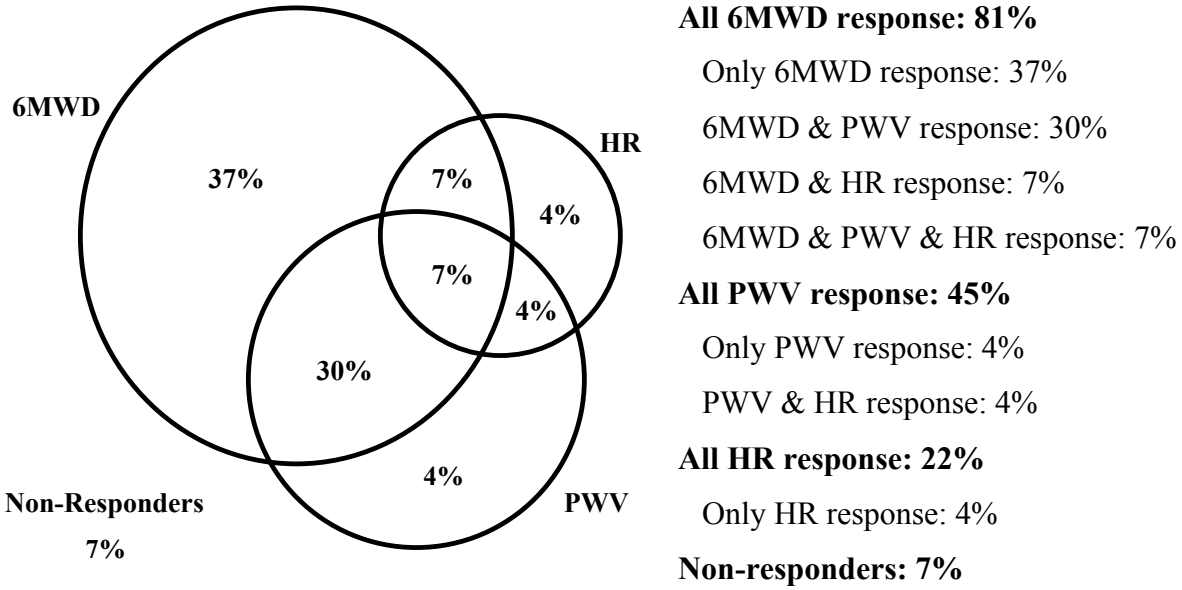

Figure 6.6. Patient response rates to pulmonary rehabilitation in terms of functional capacity (6MWD), pulse wave velocity (PWV), and resting heart rate (HR)

6.4 Discussion

This study investigated the effect of a standard 8-week pulmonary rehabilitation program on resting heart rate and arterial stiffness, as well as on the relationship between these two

parameters in patients with COPD. Additionally, the responses to pulmonary rehabilitation in terms of functional capacity, arterial stiffness, and resting heart rate were calculated in this population. We found that PWV (as a measure of arterial stiffness), but not resting heart rate decreased significantly after 8 weeks of standard pulmonary rehabilitation. Pulmonary rehabilitation did not modulate the relationship between resting heart rate and arterial stiffness in our population sample. The patient response rates in terms of functional capacity, arterial stiffness, and resting heart rate indicated that almost half of the COPD patients (48%) showed improvement in at least two of these parameters of interest; however, only 7% of the patients showed improvement in all three parameters.

Our main findings confirmed a number of previous research studies on the effect of exercise training on arterial stiffness (181,186), but contradicted others (187). Vivodtzev et al. (186) found that PWV significantly decreased (10.3 ± 0.7 m/s to 9.2 ± 0.8 m/s, $p = 0.001$) in patients with COPD after four weeks of exercise training. Similarly, Gale et al. study (181), reported a significant reduction in aortic PWV after exercise training (9.8 ± 3.0 m/s to 9.3 ± 2.7 m/s, $p < 0.05$) in a population of stable COPD patients completing an 8-week pulmonary rehabilitation program. However, Vanfleteren et al. (187) found that aortic PWV did not change following pulmonary rehabilitation (10.7 ± 2.7 m/s versus 10.9 ± 2.5 m/s, $p = 0.339$), and stated that the arterial stiffness in COPD patients did not respond to state-of-the-art pulmonary rehabilitation. In these studies, the changes in resting heart rate due to exercise training were also contradictory. Both the Vivodtzev et al. (186) and Gale et al. (181) studies found no significant change in resting heart rate through exercise training. In contrast, the Vanfleteren et al. (187) study found a significant reduction in the resting heart rate of 1 beat/min, which was associated with an increase in the systolic blood pressure that

almost reached the statistically-significant level. Such changes in resting heart rate with exercise training, which are opposite to changes in blood pressure and arterial stiffness in patients with COPD, were also observed in our study.

We found significant reductions in PWV between pre- and post-pulmonary rehabilitation (10.3 ± 2.5 m/s versus 9.6 ± 2.0 m/s, $p = 0.004$), but not in resting heart rate (65 ± 10 beats/min versus 66 ± 9 beats/min, $p = 0.163$). The percent reductions in PWV with pulmonary rehabilitation were on average approximately 6%, and were accompanied by reductions in blood pressure measures including central pulse pressure. The resting heart rate changed in the opposite direction, showing on average an increase of 2% following rehabilitation, although this was not significant. It is worth mentioning that the percent change in PWV with pulmonary rehabilitation was close to the 8% threshold, which represents a true change for our measurements (274). In contrast, the percent change in resting heart rate after pulmonary rehabilitation was within the intrinsic variability of the measurement (Chapter 3).

A number of factors could have contributed to the absence of significant changes in resting heart rate with pulmonary rehabilitation. First, we cannot exclude the possibility that exercise training intensity was not great enough to influence the autonomic nervous system. Given the nature of a standard pulmonary rehabilitation program, exercise training and progression were adapted to the effort that could be tolerated by the individual in order to achieve their best performance. However, the large number of participants who increased their functional capacity indicates that pulmonary rehabilitation was at an adequate level of intensity. Second, patients with COPD commonly manifest left ventricular diastolic dysfunction (297), which is known to increase the resting heart rate (298); therefore we can

hypothesize that the lack of changes in resting heart rate, which were also opposite to changes in blood pressure and arterial stiffness, may be due to the heart's adaptive response to maintain hemodynamic homeostasis during pulmonary rehabilitation. Such interpretation is supported by literature suggesting that patients with cardiovascular risk (182,299) in contrast to healthy elderly subjects (185) show no significant changes or only small reductions in resting heart rate following aerobic exercise training.

Despite the well-established relationship between resting heart rate and arterial stiffness in experimental (10) and population-based epidemiological studies (11-13), we did not find evidence of this relationship in the present study of participants with COPD. Moreover, pulmonary rehabilitation was not able to restore the resting heart rate - arterial stiffness relationship to that found in control individuals (Chapter 5). Given that systolic blood pressure and pulse pressure are main determinants of arterial stiffness, the positive association between resting heart rate and arterial stiffness described in the literature might be related to the interdependence between resting heart rate and these blood pressure variables. Due to the study sample size limitation, we could not make complex inferences between resting heart rate and blood pressure parameters in this population. However, a sub-analysis showed that in our population resting heart rate was negatively associated with central pulse pressure (pre-PRP, r = -0.37; $p = 0.049$ and post-PRP, r = -0.57; $p = 0.002$), and PWV was positively associated with central pulse pressure (pre-PRP, r = 0.46; $p = 0.016$ and post-PRP, r = 0.39; $p = 0.024$); these opposite associations may explain the absence of a resting heart rate - arterial stiffness relationship in our study.

Overall, these findings highlight that a standard 8-week pulmonary rehabilitation program has the potential to induce important physiological adaptations in the vasculature,

which can lead to reductions in blood pressure and arterial stiffness, subsequently improving oxygen delivery and utilization by peripheral tissues. However, large variability in the PWV and resting heart rate responses to pulmonary rehabilitation was also observed in our population, despite a rigorously controlled and standardized measurement procedure. This observation needs to be further investigated by considering methodological aspects, population specific characteristics, or differences in training intensity.

By investigating the effect of pulmonary rehabilitation on the heart rate and arterial stiffness in a population of COPD patients, we deepened our understanding in the hemodynamic characteristics of this population, and addressed concerns expressed in the literature that the heart rate dependency of arterial stiffness is frail and does not have a strong physiological basis (143). However, future research is needed to establish whether a simultaneous reduction in the resting heart rate and arterial stiffness rather than in arterial stiffness alone is beneficial in patients with COPD, and can be achieved through a longer exercise training duration.

We also found a dissociated response to pulmonary rehabilitation in terms of functional capacity, and hemodynamic parameters, such as resting heart rate and arterial stiffness. Despite the fact that increased physical activity has been found to be associated with a low resting heart rate in the general population (291), the large percentage of responders in functional capacity (81%) was accompanied by only 22% of responders in resting heart rate in our COPD population. However, a larger proportion of those individuals were responders in terms of PWV (45%). Even though these responder percentages show the potential of exercise training to improve both hemodynamic and pulmonary rehabilitation outcomes

(such as functional capacity), the development of composite measures, which would combine both pulmonary rehabilitation and hemodynamic outcomes, remains a topic for future work.

6.4.1 Strengths and limitations of the study

While the present findings shed light on the effects of an 8-week standard pulmonary rehabilitation program on resting heart rate and arterial stiffness, as well as on the relationship between these two parameters, there are limitations that indicate these results should be applied with caution. The main limitation is related to the sample size. As previously shown in Chapter 4, the large variation in the arterial pulse wave signal with breathing is one of the limiting factors in obtaining reliable PWV measurements in patients with COPD. This variability contributes to the difficulties in meeting the SphymoCor quality criteria, and leads to exclusion of a large proportion of patients (which reached approximately 20% in our study). Since drop-outs from a pulmonary rehabilitation program are expected, due to the necessity for a patient's long term commitment and the presence of multiple comorbidities, planning a study assessing arterial stiffness in patients with COPD proves to be challenging. These were major reasons for failing to achieve as large a number of participants as initially planned. Since female participants were in a higher proportion than male participants in our sample, extrapolating these results to the whole COPD population will require additional research. Resting heart rate is also a parameter that can easily change under various physio-pathological conditions. For example, pain or seasonal influences on the respiratory system could have impacted these results, given that pain may occur with exercise training and pulmonary rehabilitation attendance is usually higher in cold months. These aspects also require further investigation.

6.5 Conclusions

Elevated resting heart rate and arterial stiffness are well-established risk factors for cardiovascular events. We found that a standard 8-week pulmonary rehabilitation program may be an effective intervention for attenuating the cardiovascular risk in patients with COPD, mainly through reduction in arterial stiffness, but less through reduction in resting heart rate. Pulmonary rehabilitation did not modulate the relationship between resting heart rate and arterial stiffness in our COPD population. Further investigation would be needed to address the reduced sensitivity of the heart rate to pulmonary rehabilitation intervention and to establish whether simultaneous reduction in resting heart rate and arterial stiffness is achievable in patients with COPD.

Chapter 7: Conclusions

The main purpose of this dissertation was to investigate the relationship between the resting heart rate and arterial stiffness in patients with COPD, as well as the potential of exercise training, administered via a standard pulmonary rehabilitation program, to influence the heart rate - arterial stiffness relationship in this population.

Resting heart rate, which is a clinical parameter commonly monitored in the rehabilitation setting, has been shown to be a determinant of myocardial ischemia (110,269) and a risk factor for cardiovascular mortality (97,103,300). Despite recent experimental and epidemiological evidence of an association between resting heart rate and arterial stiffness (11,12), which is also a strong predictor of cardiovascular morbidity and mortality (129), there has been no investigation into this relationship in COPD. As aerobic exercise training is known to reduce the resting heart rate (179) and arterial stiffness (18), and as a result have a beneficial effect on overall cardiovascular health, understanding the heart rate - arterial stiffness relationship in COPD can serve as a basis for better cardiac risk stratification and higher efficacy of pulmonary rehabilitation in this population. The major findings presented in this dissertation are summarized below, along with the strengths and limitations of the research methodology. Lastly, the significance of this topic and possible future directions are presented along with the overall conclusions of this dissertation.

7.1 Overview of major findings

7.1.1 Resting heart rate as an indicator of prior myocardial infarction in subjects with chronic lung disease attending pulmonary rehabilitation (Chapter 2)

Before proceeding to the main studies of this dissertation, a few steps have been taken to define the boundaries of our research work. First, the presence of prior myocardial infarction injury, which can be regarded as a serious manifestation of ischemic heart disease, was investigated in a population of patients with chronic lung disease, including COPD, who were referred to our pulmonary rehabilitation program. The main goal was to determine the possibility of overlooking serious myocardial impairments, even in the presence of valuable tests, such as the cardiopulmonary exercise test (CPET), performed prior to pulmonary rehabilitation. In addition, by quantifying the relationship between heart rate parameters and prior myocardial infarction in these patients, we intended to provide convenient clinical parameters to assist in adapting exercise training to ensure COPD patients' safety and minimize possible cardiac risks.

The study presented in Chapter 2 estimated the frequency of prior myocardial infarction in a chronic lung disease population referred to pulmonary rehabilitation by assessing the discordance between an electrocardiographic score of past myocardial infarction injury (Cardiac Infarction Injury Score; CIIS) and medical records of past myocardial events. The CIIS was chosen because of its ease of use and high accuracy for detecting prior myocardial infarction. Further, the association between the electrocardiographic score and heart rate parameters, such as resting heart rate and chronotropic incompetence, was also evaluated in these patients. The main findings of this study were that approximately one out of five

patients entering the pulmonary rehabilitation program had evidence of prior myocardial infarction that were commonly unreported. However, COPD patients, most probably due to the recent awareness of their increased ischemic heart disease risk, were more likely to have a reported myocardial infarction in their history compared to patients with other chronic lung diseases. Thus, increased attention needs to be given not only to patients with COPD, but also to patients with other chronic lung diseases (e.g., restrictive lung diseases), who have a similar, but commonly undetected, myocardial ischemic injury even in the presence of milder pulmonary dysfunctions. Overall, these results show the importance of screening for ischemic heart disease in patients with chronic lung diseases attending pulmonary rehabilitation.

In our population, we found that elevated resting heart rate was associated with prior myocardial infarction injury, as expressed by the CIIS. Albeit significant, the association was weak and underlined the inherent limitations in assessing resting heart rate in clinical studies. Since the resting heart rates were measured before the cardiopulmonary exercise testing, one could infer that neural impulses from the central command in anticipation of the onset of exercise (301), use of inhaled bronchodilators (e.g., beta-adrenergic agonists) (302), and/or specific disease conditions (e.g., hypoxemia, dyspnea) (87) could have reduced the accuracy of the data. However, the strength of this study is represented by the fact that even in the presence of these potential influencing factors, we were able to detect a clinically relevant association between elevated resting heart rate and prior myocardial infarction in patients with chronic lung diseases, and provide physiotherapists with a resting heart rate threshold (e.g., 80 beats/min) that would enable them to make adequate clinical decisions.

Therefore, the overall conclusions of this study were that chronic lung disease patients undergoing pulmonary rehabilitation were at increased risk of an unreported prior myocardial infarction, and that an elevated resting heart rate could signal an increased risk of prior myocardial infarction injury. These findings represent a significant contribution because they: (i) indicate resting heart rate as a convenient clinical tool for estimating the presence of prior myocardial infarction in patients attending a pulmonary rehabilitation program; and (ii) raise awareness for carefully adjusting exercise prescription and recommendations (e.g., such as using intermittent training) after taking elevated resting heart rate into consideration. Moreover, this study justified our interest in further exploring the potential of resting heart rate for improving cardiac risk stratification and for gauging the efficacy of pulmonary rehabilitation in controlling ischemic heart disease in COPD patients.

7.1.2 The reliability of short-term measurement of resting heart rate parameters in patients with COPD (Chapter 3)

Given the potential instability of resting heart rate under various physio-psychological conditions (221), performing a test-retest reliability study was required to ensure the consistency of this measurement before investigating the relationship between resting heart rate and arterial stiffness, or the effect of standard pulmonary rehabilitation on this relationship in a COPD population. This analysis was performed by the means of a heart rate variability measurement for two reasons. First, heart rate variability was expected to provide more insights into autonomic nervous system function and cardiac risk in this population. Second, we wanted to explore the advantage of having state-of-the-art instruments in assessing complex heart rate parameters.

The work described in Chapter 3 investigated the test-retest reliability of standard indices of heart rate variability from short-term electrocardiogram recordings performed during spontaneous breathing condition and standardized procedure in moderate-to-severe COPD patients. The time and frequency domain representations of heart rate variability were analyzed through a within-subject repeated measure design over two testing sessions. In addition, this study quantified the measurement variability of the mean resting heart rate in patients with COPD, information which was useful not only in showing the consistency of the data, but also in assessing the clinically important change associated with standard pulmonary rehabilitation in our population. The main findings of this study were that the time and frequency domain parameters related to overall heart rate variability showed substantial reliability. In contrast, the heart rate variability parameters associated primarily with parasympathetic tone showed moderate reliability. The only parameter related to heart rate variability that showed excellent absolute and relative reliability was the mean resting heart rate. As a result, the findings of this study recommended the use of heart rate variability parameters for diagnosis and cardiac risk assessment, but only the mean resting heart rate would be a reliable clinical assessment tool for autonomic function changes with pulmonary rehabilitation in COPD patients.

Despite the clinical relevance of these results, we also encountered a few methodological limitations related to the assessment of heart rate variability in patients with COPD. First, heart rate variability is a measure of autonomic nervous function under preserved sinus rhythm. Thus, any rhythm disturbances, which often occur in COPD patients, can cause errors in the calculation of heart rate variability parameters (215). Second, we showed that, under spontaneous breathing, the heart rate variability indexes reflecting primarily vagal or

parasympathetic activity exhibited moderate reliability in patients with COPD. There is evidence that the heart rate variability indexes tend to improve under paced breathing (223). However, this maneuver is difficult to perform in severe COPD patients since it requires a high compliance to measurement instructions. These are methodological limitations which may determine sampling bias, and thus limit the use of heart rate variability in a clinical setting for accurate diagnosis of cardiac autonomic dysfunction in the COPD population.

We can conclude that this study, besides its clinical relevance, opened up a new avenue of research in the area of heart rate variability in patients with COPD. More complex studies are needed to investigate disease-specific factors that influence the accuracy and reliability of these measurements. These future research steps should be mandatory if heart rate variability measures are to be used for obtaining information about the effectiveness of a standard rehabilitation program on cardiac autonomic control in the COPD population. Nevertheless, this study emphasized that under a rigorously controlled and standardized procedure, the mean resting heart rate had an excellent reliability in patients with COPD, and recommends its use more often as a primary rather than a secondary outcome in the pulmonary rehabilitation setting.

7.1.3 The reliability of pulse wave velocity measurement in patients with COPD (Chapter 4)

A complementary reliability study involving pulse wave velocity was presented in Chapter 4. The reasoning behind this decision was not only the need to confirm the reliability of this measurement before investigating its response to pulmonary rehabilitation intervention, but also to assess the methodological limitations associated with the pulse wave

velocity measurement in patients with COPD. Substantial variations in the mean pulse wave velocity values across COPD studies (133), and also a large variability in the pulse wave velocity response with exercise intervention (181,186,187) have previously been described in the literature, but no study addressed these aspects comprehensively.

The study described in Chapter 4 investigated the test-retest reliability of pulse wave velocity as a measure of arterial stiffness, and in addition characterized the clinical and methodological challenges of pulse wave velocity measurement in a population of moderate-to-severe COPD patients who were commonly referred to a pulmonary rehabilitation program. The main findings of this study were that the aortic pulse wave velocity measurement performed with a SphygmoCor device exhibited substantial test-retest reliability and acceptable variability in individuals with moderate-to-severe COPD. However, we found that the measurement process suffered from suboptimal pulse signal strength and quality despite rigorously controlled and repeated pulse wave velocity measurements. COPD patients commonly displayed weak signals and/or beat-to-beat alterations in their pulse shape and amplitude, even if they had a regular heart rhythm. As a result, a subset of PWV measurement quality settings was difficult to achieve in those patients. By analyzing various anatomical and physiological specific disease factors that might have influenced these results, we concluded that clinical (patient-related) rather than methodological factors prevented us from obtaining optimal quality measurements in this population. Other contributions of this study were the estimation of the pulse wave velocity variability, as well as the threshold value beyond which a change in pulse wave velocity is clinically meaningful in the COPD population. These findings are of use for researchers planning intervention studies involving pulse wave velocity measure in patients with COPD. Since our coefficients

of variation were smaller than the 10% threshold considered as acceptable for pulse wave velocity (246,260), we also had a strong confidence in the consistency and stability of our data and measurements.

Based on our analysis of the practical and methodological challenges associated with measuring arterial stiffness in patients with COPD, we recommend that clinicians have a good understanding of the instrument's limitations. Without complete control of the operation of the medical device under various pathological conditions, misdiagnoses may occur, leading to inappropriate clinical decisions. We also highlighted that the set of quality criteria used in the measurement process of pulse wave velocity has a major influence on the inclusion / exclusion of subjects into a COPD population sample. Therefore, the use of pulse wave velocity as a clinical measure requires stringent application of quality criteria to achieve optimal results in COPD patients. This study also opened up future avenues of research on the reliability of pulse wave velocity measurement in patients with COPD. By simultaneous monitoring of the arterial pulse wave and breathing, it would be possible to better understand the physiopathological aspects of cardiopulmonary interaction in COPD. Overall, this study brought forward a large body of information related to the methodological aspects of aortic pulse wave velocity measurement in patients with COPD.

7.1.4 The relationship between resting heart rate and arterial stiffness in patients with COPD (Chapter 5)

After the reliability of resting heart rate and arterial stiffness measurements was established, we proceeded to study whether the positive association between resting heart rate and arterial stiffness described in the literature was confirmed in our COPD patients. The

study presented in Chapter 5 investigated the relationship between resting heart rate and arterial stiffness in individuals with COPD, in comparison with control individuals. A univariate analysis revealed a significant positive association between the resting heart rate and pulse wave velocity in control individuals, but not in COPD patients. However, a multivariate analysis, which considered age, sex, central pulse pressure, and pulmonary obstruction as covariate factors, showed that the resting heart rate was significantly associated with pulse wave velocity in both the COPD patients and the control group. These findings indicated that the relationship between resting heart rate and arterial stiffness in patients with COPD was influenced by mediating factors, in particular age and pulse pressure. Our results, together with other published results on this topic (11,138,286), led us to infer that the weaker association between resting heart rate and arterial stiffness found in COPD was a result of two factors. First, the elevated resting heart rate and arterial stiffness found in the COPD population might position the set point on the curve plateau rather than on its slope. Second, the influence of resting heart rate on arterial stiffness in COPD might occur in these patients only when paired with increased pulse pressure. While these assumptions require further validation, a few remarks are worth making with regards to the physiological role of age and pulse pressure in mediating the relationship between resting heart rate and arterial stiffness in patients with COPD.

Our data showed that despite significantly higher values of resting heart rate and pulse wave velocity in patients with COPD compared to controls, no significant differences were found between the two groups in terms of pulse pressure. Knowing that pulse pressure depends on the stroke volume and arterial stiffness, it follows that a similar pulse pressure in the presence of increased arterial stiffness leads to a reduced stroke volume, which was

confirmed by prior research in patients with pulmonary emphysema (303). Further, assuming a similar cardiac output for the two groups (COPD and CTL), the reduced stroke volume in patients with COPD is accompanied by an increase in resting heart rate and a narrow pulse pressure. Since the physiological mechanism for arterial stiffness is represented by the pulse pressure amplification, the heart rate - arterial stiffness relationship becomes evident in COPD only in the presence of age-related changes in arterial stiffness, evidenced by wide pulse pressure. Under these circumstances, the association between resting heart rate and arterial stiffness will largely depend on the dynamic cardiovascular interactions needed to maintain circulation homeostasis.

Given the rigor of our measurements, these observations represent evidence that supports the idea that elevated heart rate is likely an epiphenomenon of arterial stiffness, which results mainly from its interrelation with increased pulse pressure. Overall, this study not only provided insights into the characteristics of hemodynamics in patients with COPD, but also opened the door for a subsequent study focusing on the modulatory effect of pulmonary rehabilitation on the heart rate - arterial stiffness relationship through aerobic exercise training.

7.1.5 The effect of standard pulmonary rehabilitation on resting heart rate and arterial stiffness in patients with COPD (Chapter 6)

The study presented in Chapter 6 investigated the potential of a standard 8-week pulmonary rehabilitation program in reducing resting heart rate and arterial stiffness, as well as in influencing the relationship between these two parameters in patients with COPD. The main findings were that the pulse wave velocity, as a measure of arterial stiffness, but not

resting heart rate, significantly improved after 8 weeks of standard pulmonary rehabilitation. We also found that the association between resting heart rate and arterial stiffness was not statistically significant in COPD, and exercise training alone was not able to restore it to the level of a healthy population, due to the heart rate's reduced sensitivity to intervention.

Our results demonstrated that standard pulmonary rehabilitation increased exercise capacity and decreased arterial stiffness, but did not change the resting heart rate. These results extended prior findings on the dissociated responses in resting heart rate and arterial stiffness in sedentary, healthy individuals of middle-age and older. (20,304). Adaptations to exercise training were suggested to reflect a predominantly peripheral effect (by enhanced endothelium-dependent vasodilation) rather than a central effect (by increasing venous return and systolic volume with effect on sinoatrial node). Since there is evidence that COPD patients may manifest limited stroke volume response to exercise mainly due to an unaltered pulmonary vascular resistance and increased pulmonary arterial pressure (305), it becomes evident that the lack of change in resting heart rate with exercise can be part of the cardiovascular hemodynamics compensatory mechanism to exercise training.

This study's main contribution is that it sheds light on the controversies found in the literature with regards to the physiopathological mechanisms that underlie the heart rate dependency of arterial stiffness. The lack of an association between resting heart rate and arterial stiffness in COPD was mainly the result of an opposing association between resting heart rate and pulse pressure in this population. Based on these findings, we considered that the changes in the resting heart rate in opposition to blood pressure and arterial stiffness changes were mostly due to the heart's adaptive response to maintain hemodynamic homeostasis with exercise training in this population. Nevertheless, our study recommends

the use of pulmonary rehabilitation intervention to control ischemic risk factors in such patients, but with particular attention given to the degree of heart rate elevation.

By considering the responses to pulmonary rehabilitation in terms of resting heart rate, arterial stiffness, and functional capacity in our COPD population, we showed that from the large number of responders in functional capacity, almost half of them were also responders in terms of pulse wave velocity, and about one-fifth in terms of resting heart rate. These findings show the potential of exercise training to improve both hemodynamic and pulmonary rehabilitation outcomes in patients with COPD. However, further work is needed to clarify the large variability in hemodynamic responses with pulmonary rehabilitation in patients with COPD, and to determine whether or not reductions in both resting heart rate and arterial stiffness are achievable in this population to improve their cardiovascular health. Also, more research is needed to elucidate the COPD patient profile that would improve both hemodynamic and pulmonary rehabilitation outcomes. Overall, these results open new and exciting areas of research for the optimization of pulmonary rehabilitation intervention.

7.2 Strengths and limitations

The strengths of this research work lie in its clinical relevance and strong methodological component. Resting heart rate is a vital sign commonly monitored in clinical and pulmonary rehabilitation settings, but often not used to its full clinical potential. Exploring the relationship between resting heart rate and arterial stiffness, along with the potential for aerobic exercise training to influence this relationship, is a novel approach in the pulmonary rehabilitation field. In addition, our findings rely on a strong methodology, which reinforces the value of this research work. Lastly, the results of the projects included in the present

dissertation could be of use to physiotherapists in their clinical practice, for better prescription and monitoring of exercise training in the COPD population.

The main limitation of this study was the patient sample size, a direct result of the difficulty we experienced in recruiting a large number of participants. The SphygmoCor device eligibility criteria, low participation willingness, and significant time commitment associated with the pulmonary rehabilitation program were the major difficulties we faced when recruiting participants. An increased patient sample size would have increased the statistical power of our studies and allowed more complex statistical analyses. However, despite the recognized limitations of any research involving hemodynamic parameters and pulmonary rehabilitation, the generalization of our findings to a larger COPD population should be taken into account in future studies.

7.3 Significance and future directions

The major significance of this dissertation work is represented by the novel information brought to the field of pulmonary rehabilitation with regards to its potential to control or prevent cardiovascular risk in patients with COPD. By studying resting heart rate and arterial stiffness, which are two cardiovascular risk factors commonly present in patients with COPD, we increased our understanding of their methodological limitations in this population, as well as their susceptibility to be influenced by pulmonary rehabilitation. The results of our study will be of help to researchers planning future studies involving similar measures, and will assist them in making appropriate decisions related to sample size, controlling confounding factors, and posing new questions related to hemodynamic physiopathology in patients with COPD. Also, these findings raise awareness among

physiotherapists with regards to the beneficial effect of pulmonary rehabilitation in decreasing arterial stiffness, and also with regards to the need to adjust the training intensity when there is an elevated resting heart rate present.

An important future direction for this research work will include validating the algorithm used for calculation of pulse wave velocity and heart rate variability in populations manifesting respiratory disorders, and developing pulmonary rehabilitation strategies to produce both peripheral and central physiological effects on the cardiovascular system in COPD patients. Another possible future direction emerging from this research would consist of studying the resting heart rate and arterial stiffness parameters before and after pulmonary rehabilitation, along with non-invasive cardiac ischemic tests in a randomized controlled trial. Such a research design would be able to resolve the degree to which simultaneous reduction in both arterial stiffness and heart rate following pulmonary rehabilitation is necessary to reduce the cardiac ischemic risk in this population. Investigation of the dynamic changes in heart rate and arterial stiffness through aerobic exercise training would also bring important insights into exercise-induced or exercise-relief ischemia. Overall, both COPD patients and physiotherapists can benefit from information resulting from this dissertation work, which is aligned with the current trend of optimizing rehabilitation programs through better understanding of the potential of exercise training to reduce cardiovascular risk.

7.4 Overall conclusions

The research presented in this dissertation contributes to the field of pulmonary rehabilitation. Specifically, our findings extend the knowledge of resting heart rate and arterial stiffness in COPD, as well as of the potential of pulmonary rehabilitation to control

heart rate - arterial stiffness relationship, with the ultimate goal of reducing the cardiovascular risk in this population. We showed that pulmonary rehabilitation in COPD has a stronger effect on arterial stiffness than resting heart rate. The resting heart rate - arterial stiffness relationship alone cannot be used for cardiovascular risk stratification in COPD. However, it can provide information on the evolution of the hemodynamic cardiovascular risk in COPD patients undergoing pulmonary rehabilitation.

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