PHYSICAL ACTIVITY MEASUREMENT STRATEGIES IN ADVANCED CHRONIC LUNG DISEASE

by

Satvir Singh Dhillon

B.Sc., Simon Fraser University, 2011

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate and Postdoctoral Studies

(Rehabilitation Sciences)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

October 2014

Abstract

Background: Physical activity may reduce mortality risk in advanced chronic lung disease by optimizing functional capacity, which is a major prognostic indicator in lung transplantation candidates. There is uncertainty as to the optimal method to measure physical activity in this patient population. We assessed different commercially-available physical activity measurement techniques (flex heart rate monitoring (FHR); pedometry; tri-axial accelerometry; and multi-sensor technology) by investigating their agreement with indirect calorimetry (IC) in adult lung disease patients (chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), and cystic fibrosis (CF)) with advanced pulmonary impairment.

Methods: This is a cross-sectional method comparison study conducted on two separate days. We recruited consecutive COPD, ILD, and CF patients with physician diagnosis of advanced pulmonary impairment. On day one, participants performed cardiopulmonary exercise testing until exhaustion with measurements of oxygen uptake (VO_2) and heart rate (HR) collected. On day two, subjects had their VO_2 and HR measured during standardized resting and sub-maximal activity. SimultaneousVO_2 and HR measures from both days were used to develop individual regressions for FHR-derived energy expenditure (EE). We then simultaneously measured each subject's EE using a variety of index measures of physical activity and IC during standardized "free-living" type activities and varying intensities of sub-maximal cycle exercise.

Results: In a sample of eight participants (CF, n=5; COPD, n=2; ILD, n=1), Flex HR methods using submaximal (FMSUB) and CPET-derived (FMCPX) calibrations showed the best agreement and interchangeability with IC during free-living and cycling activities compared to the SenseWear (SW) and ActiCal (AC) devices as evidenced by lower mean differences with IC

and widths of limit of agreement (LOA) + 95% confidence interval (CI). For the secondary index methods assessed, the Tractivity and DigiWalker devices significantly over and underestimated IC EE respectively ($p<0.05$), whereas the Dynaport device did not differ from IC ($p>0.05$) over the entire protocol.

Conclusion: Our study found that the Flex HR method for EE estimation had the lowest bias and variability during free-living activities and exercise. EE estimation using Flex HR methods may be potentially useful clinical tools to ensure metabolic energy balance and activity monitoring in advanced lung disease groups.

Preface

This thesis is original work by the author, S. Dhillon. The UBC Pulmonary Rehabilitation Research Laboratory and Pacific Lung Health Centre assisted with data collection. Provision of patients for study recruitment; analysis and interpretation of data; critical revisions of the article for important intellectual content was done by the members of the author's supervisory committee, P. Camp, R. Levy, and P. Wilcox.

Providence Health Research Institute Ethics Boards approval was obtained for this research. The certificate number of the ethics certificate of approval to conduct research is H13-01117.

Table of Contents

Abstract ii
Preface iv
Table of Contents v
List of Tables vii
List of Figures viii
List of Abbreviations x
Acknowledgments xiii
Chapter 1: Introduction 1
1.1 Lung transplantation in advanced lung disease 1
1.2 Epidemiology, etiology, symptoms, and severity of the highest indications for adult lung transplantation 1
1.2.1 Chronic obstructive pulmonary disease 1
1.2.2 Interstitial lung disease 3
1.2.3 Cystic fibrosis 4
1.3 Growing healthcare burden of advanced lung disease 6
1.3.1 Increasing population of adults living with advanced lung disease 6
1.3.2 Lung transplantation waiting list trends showing increasing mortality 7
1.3.3 Mortality risk factors advanced lung disease 8
1.3.4 How can mortality risk be reduced in advanced lung disease? 9
1.4 Improving physical activity through pulmonary rehabilitation 10
1.5 Daily physical activity—how can we measure this outcome? 11
1.5.1 Physical activity conceptual framework 11
1.5.2 Physical activity quantification methodologies 12
1.6 Physical activity measurement validity in chronic lung disease 16
1.6.1 Inefficiencies of movement 16
1.6.2 Elevated resting metabolism 16
1.6.3 Interpretations of the literature 17
1.7 Rationale for this study 18
1.8 Study objectives and hypothesis 20

Chapter 2: Methods **22**
2.1 Statement of ethical adherence 22
2.2 Study design 22
2.3 Participants 22
2.4 Experimental procedures 25
2.5 Measurements 27
2.6 Data management and statistical analysis 35
2.6.1 Analyses 35
2.6.2 Prospective sample size calculation 37
Chapter 3: Results **40**
3.1 Study enrollment 40
3.2 Participant characteristics 40
3.3 Trends in Bland-Altman agreement plots 41
3.3.1 Bias estimates and limits of agreement during flat walking (Figure 12) 41
3.3.2 Bias estimates and limits of agreement during incline walking (Figure 13) 42
3.3.3 Bias estimates and limits of agreement during sit-to-stand activity (Figure 14) 42
3.3.4 Bias estimates and limits of agreement during lift-bend activity (Figure 15) 42
3.3.5 Bias estimates and limits of agreement during cycling (Figure 16 to 19) 43
3.3.6 Interchangeability between primary index and IC methods 43
3.4 Nonparametric significance testing 44
3.5 Graphical representations of validity 45
Chapter 4: Discussion **46**
4.1 Key findings 46
4.2 Clinical implications 48
4.3 Study limitations and future research 50
4.4 Conclusion 52
References **84**
Appendices **105**
Appendix A. Step-by-step cardiopulmonary exercise testing protocol 105
Appendix B. Calculations of standard deviation of difference from previous validation literature 106

List of Tables

Table 1. Participant Selection Criteria. 53

Table 2. Features of the Physical Activity Monitors Including Type, Location of Attachment, Units of Energy Expenditure Estimation, and Cost. 54

Table 3. Participant Characteristics for All Participants. 55

Table 4. Exacerbation History and Comorbidities. 56

Table 5. Cardiopulmonary Exercise Test Performance. 57

Table 6. Assessment of Interchangeability for Primary Index Methods using Limits of Agreement with Precision Estimates. 58

Table 7. Comparison of Average Energy Expenditure (kcal/min) Measured by Each Index Method During Free-Living Activities, Cycling, and the Entire Protocol. 60

List of Figures

Figure 1. Lung Transplantation Waiting List Trends in Canada. 61

Figure 2. Theoretical Model of Physical Fitness and Mortality Risk. 62

Figure 3. Conceptual Framework of Physical Activity Measurement. 63

Figure 4. Conceptual Framework of Indirect Calorimetry. 64

Figure 5. Conceptual Framework of Doubly Labeled Water Technique. 65

Figure 6. Step-By-Step Flow Diagram of Study Procedures. 66

Figure 7. Flex Heart Rate Calibration Protocol. 67

Figure 8. Location of Attachment of the Activity Monitors and Indirect Calorimeter. 68

Figure 9. Low Intensity Free-Living Activities Protocol. 69

Figure 10. Submaximal Steady-State Cycling Protocol 70

Figure 11. Participant Enrollment Flow Diagram. 71

Figure 12. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Flat Walk. 72

Figure 13. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Incline Walk. 73

Figure 14. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Sit-to-Stand Activity. 74

Figure 15. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Lift-Bend Activity. 75

Figure 16. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 10% Peak Workload..... 76

Figure 17. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 25% Peak Workload..... 77

Figure 18. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 50% Peak Workload..... 78

Figure 19. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 60% Peak Workload..... 79

Figure 20. Scatter Plots of Energy Expenditure During Free-Living Activities..... 80

Figure 21. Scatter Plots of Energy Expenditure During Cycling Activities. 81

Figure 22. Scatter Plots of Overall Energy Expenditure for Primary Index Methods. 82

Figure 23. Scatter Plots of Overall Energy Expenditure for Secondary Index Methods. 83

List of Abbreviations

6MWT	Six minute walk test
AC	ActiCal™
ATS	American Thoracic Society
BCC	Burkholderia cepacia complex
BMD	Bone mineral density
BMI	Body mass index
CF	Cystic fibrosis
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPDR	Canadian Cystic Fibrosis Patient Data Registry
CPET	Cardiopulmonary exercise testing
DLCO	Diffusing capacity of the lungs for carbon monoxide
DLW	Doubly labeled water
DP	Dynaport™
DW	DigiWalker™
ECA	Energy cost of activities

EE	Energy expenditure
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in one second
FMCPX	Flex heart rate method with peak exercise calibration profile
FMSUB	Flex heart rate method using submaximal exercise calibration profile
FVC	Forced vital capacity
HR	Heart rate
IC	Indirect calorimetry
I_{cap}	Inspiratory capacity
ILD	Interstitial lung disease
LAS	Lung allocation score
LOA	Limit of agreement
LTx	Lung transplantation
REE	Resting energy expenditure
SD	Standard deviation
SE	Standard error
SW	SenseWear™

TR	Tractivity^{TM}
VC	Vital capacity
VCO_2	Carbon dioxide production
VO_2	Oxygen uptake

Acknowledgments

I would first like to express my deepest appreciation to my supervisor Dr. Pat Camp for her mentorship, friendship, and encouragement, and patience with me throughout this graduate experience. I would also like to express my gratitude to the members of my supervisory committee, Dr. Robert Levy for your advice and guidance, and Dr. Pearce Wilcox for your support during data collection, advice, and guidance. I am grateful to have had the opportunity to work with such exceptional and influential mentors.

Thank you to my lab mates in the UBC Pulmonary Rehabilitation Research Laboratory and the UBC Cardiopulmonary Exercise Physiology Laboratory who have worked with me on this project for your contributions.

Last, but certainly not the least, thank you to my amazing family and friends for supporting me in so many ways throughout my studies. I feel so blessed to have been surrounding by such wonderful people who encouraged me to pursue my goals.

Chapter 1: Introduction

1.1 Lung transplantation in advanced lung disease

In the face of advanced lung disease, lung transplantation (LTx) may be the ultimate treatment option for those patients at a high risk of mortality who have exhausted all other conventional medical treatment options. The main goals of this procedure are to confer a survival benefit in patients as well as to improve health related quality of life[1, 2].

The annual number of all single and bilateral lung transplants performed in Canada has steadily risen from 116 in 2003 to 188 in 2012, with an overwhelming majority over 90% of first graft patients in Canada being of adult age[3]. The three most common indications for all single and bilateral adult LTx procedures performed worldwide between 1995 and 2012 (n=37,581) were chronic obstructive pulmonary disease (COPD, 39%), interstitial lung disease (ILD, 24%), and cystic fibrosis (CF, 17%)[4].

1.2 Epidemiology, etiology, symptoms, and severity of the highest indications for adult lung transplantation

1.2.1 Chronic obstructive pulmonary disease

COPD is a progressive pulmonary disorder mainly caused by smoking, and primarily characterized by irreversible airflow limitation[5, 6]. According to data from the *Canadian Health Measures Survey*, approximately 13% of Canadians aged 35-79 had spirometric evidence consistent with a diagnosis of COPD between 2009 and 2011[7]. Prevalence estimates of COPD have been quite variable in the literature[8], possibly due to different methods used to establish a COPD diagnosis.

The hallmark of COPD is chronic airflow limitation, which is due to a combination of obstructive bronchiolitis and emphysema[9]. The chronic inflammatory state of the respiratory tract results in airway remodeling and parenchymal destruction due to exposure to cigarette smoke[6]. These pathological changes characteristic of COPD also lead to a reduction in lung elastic recoil, thereby furthering airflow limitation[5]. In addition to the airflow limitation, COPD patients may also suffer from lung hyperinflation, systemic complications, and exacerbations[5].

The diagnosis and severity of COPD may be determined by assessing lung function using spirometry testing[10]. The ratio of the forced expiratory volume in one second and forced vital capacity (FEV_1/FVC) less than 0.7 is recommended to establish a diagnosis of COPD[6]. Further to confirming COPD diagnosis based on FEV_1/FVC, measurement of FEV_1 % predicted is used to grade the severity of pulmonary impairment according to guidelines developed by the *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease*[6]: mild ($FEV_1 \geq 80\%$ predicted), moderate ($50\% \leq FEV_1 < 80\%$ predicted), severe ($30\% \leq FEV_1 < 50\%$), and very severe ($FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ with chronic respiratory failure).

COPD patients suffer from skeletal muscle dysfunction in the peripheral locomotor muscles as a result of the disease progression[5]. Peripheral muscle wasting occurs in approximately 30% of patients and increases as disease severity advances[11]. In advanced stages of COPD, peripheral muscle force has been shown to be reduced to 60±15, 85±25, and 81±18 % of predicted values in the quadriceps, triceps, and biceps respectively[12]. These muscular abnormalities, which result from a combination of impaired mobility, poor nutrition, chronic hypoxia, and inflammatory state[13, 14], lead to a reduction in exercise capacity[15]. Abnormal

breathing mechanics, impaired ventilation, and dynamic hyperinflation of the lungs are other factors limiting exercise capacity in COPD[16, 17].

1.2.2 Interstitial lung disease

ILD is an umbrella term referring to a large number of distinct acute and chronic disorders known as diffuse parenchymal lung diseases which may be of known or unknown (idiopathic) etiologies[18]. Although heterogeneous in etiology and clinical manifestations, these conditions are characterized by the development of pulmonary fibrosis and diffuse pulmonary inflammation affecting the lung parenchyma[19]. Epidemiological data in ILD has been scarcely reported in Canada and globally. Registry data out of New Mexico, USA has been frequently cited in the literature to highlight ILD annual prevalence rates of 80.9 per 100,000 population in males and 67.2 per 100,000 population in females[20]. From the same registry study, ILD incidence is estimated at approximately 30 per 100,000 population annually with higher incidence estimates for males compared to females[20].

ILD primarily affects the interstitium of the lung parenchyma in the regions between capillary endothelial cells and alveolar epithelial cells[21]. Derangement of the alveolar walls is caused by the development of pulmonary fibrosis resulting from long-term pneumonitis, or diffuse pulmonary inflammation[22]. For the ILD subsets with known causes intrinsic or extrinsic to the body, environmental/occupational toxins, immunological factors, drugs, and radiation may be responsible for the pathogenesis[23]. Advanced fibrosis of the lung parenchyma is characterized by 'honeycombing' observed through high resolution CT scanning of the lungs[22]. Clinicians may suspect ILD by the presence of inspiratory crackles on auscultation, which result from the opening of alveolar airspaces encapsulated by a fibrotic interstitial wall[21]. Respiratory

manifestations common to all forms of ILD include shortness of breath and shadowing on chest imaging investigations[18]. Dyspnea and dry cough that worsens over time regardless of smoking history may also indicate ILD[21]. In advanced stages of the disease, ILD patients may also have resting tachypnoea, cyanosis, and cor pulmonale[18].

ILD patients commonly present a restrictive pattern of pulmonary dysfunction, characterized by abnormally reduced lung volumes despite preserved or elevated FEV_1/FVC ratios in addition to reduced diffusing capacity of the lungs for carbon monoxide (DLCO)[18]. Standard criteria for stratifying the severity of lung disease abnormality in ILD are nonexistent. Restrictive lung abnormality may be graded as followed based on % predicted vital capacity (VC) measurements[24]: mild severity (70% predicted ≤VC< Lower limit of normal), moderate severity (60%≤VC<70% predicted), moderate severe severity (50%≤VC<60%), severe severity (34%≤VC<50%), and very severe severity (VC<34% predicted). A DLCO ≤ 40% predicted may also indicate severe impairment[25].

Activity limitation and maximal oxygen uptake impairment is frequently seen in patients with restrictive lung diseases[26]. Gas exchange abnormality and circulatory limitations are the main factors reducing exercise capacity in ILD[27]. During exercise, venous return is reduced in ILD patients due to an increased pulmonary vascular resistance caused by a reduction in lung compliance and elevated work of breathing[27]. As a result, cardiac output increase is insufficient to meet the oxygen requirement of the muscles during exercise[27].

1.2.3 Cystic fibrosis

CF is a lethal autosomal recessively inherited disease most commonly seen in Caucasian populations[22]. The birth prevalence of CF is 1 in 3600 live births in Canada[28], with a total of

3849 individuals registered in one of the 42 CF clinics nationwide in 2010[29], up from 2191 registered CF patients in 1984[30]. With therapeutic advances, the prognosis for people born with CF has changed dramatically over the past few decades. The median survival age in Canada has steadily increased from 25 years in 1984[30] to nearly 50 years in 2010[29].

The hallmark of CF lung disease is the development of massive airway infection and inflammation[31] and airway obstruction by viscous mucus accumulation and aggregation of degraded cellular components, which is related to the failure of the epithelial ion transport system[32]. Chronic pulmonary dysfunction will eventually lead to respiratory failure and on occasion pulmonary hypertension as the disease severity worsens[33]. Although CF affects the epithelial cells of many systems in the body, pulmonary and gastrointestinal manifestations of the disease are the main concern. Multiple complications beyond the respiratory and GI systems associated with the disease process have been documented in CF patients including reduced bone mineral density (BMD)[34-37], malabsorption and undernutrition[34, 35, 37-39], pancreatic disease[40], and CF-related bone disease, diabetes, arthropathy, and liver disease[41]. Pulmonary dysfunction is the most common cause of death in people with CF[40].

The degree of CF lung disease impairment may be stratified using FEV_1 % predicted according to recently published recommendations[42]: normal lung function ($FEV_1 \geq 90$ % predicted), mild severity ($70\% \leq FEV_1 < 89\%$ predicted), moderate severity ($40\% \leq FEV_1 < 69\%$ predicted), and severe severity ($FEV_1 < 40$ % predicted).

Muscle weakness is a comorbidity commonly reported in CF[43-45]. In advanced stages of CF, peripheral muscle force has been shown to be reduced to 49±18, 60±20, and 71±22 % predicted in the quadriceps, triceps, and biceps respectively[12]. Despite controlling for lean body

mass there is reduced peripheral skeletal muscle mass in CF, suggesting the occurrence of muscle wasting with disease progression[46]. In addition to peripheral skeletal muscle abnormalities, increased work of breathing, respiratory muscle inefficiency and weakness, and arterial hypoxemia also contribute to exercise limitation in CF[47]. In advanced stages, the prolonged hypoxemic state can contribute to cardiac limitations to exercise as well such as the development of right ventricular dysfunction[47].

1.3 Growing healthcare burden of advanced lung disease

1.3.1 Increasing population of adults living with advanced lung disease

Population ageing is a global phenomenon, with projections of the population over 60 years of age expected to increase from 841 million people in the year 2013 to 3 billion in the year 2100[48]. The population of advanced COPD increases with age[49]. As the population ages and smoking frequencies increase, COPD prevalence is projected to increase in most countries around the world[49, 50]. Similarly to the COPD population, ILD incidence rises with advancing age[51]. Idiopathic pulmonary fibrosis is the most common and lethal form of ILD[52], comprising the majority of advanced ILD subgroups indicated for LTx[4]. Estimates of the prevalence of idiopathic pulmonary fibrosis have shown to drastically increase in older age, ranging from 4 per 100, 000 population in those aged 18-34 years to approximately 230 per 100, 000 population in those aged 75 years and older[53].

In addition, the proportion of CF patients reaching adulthood is continuing to rise. Of the 3849 patients with CF in the Canadian Cystic Fibrosis Patient Data Registry (CPDR) 2010 Report, 2201 (57.2%) were adults[29]. This represents a dramatic rise in the number of adults with CF over almost three decades, up from approximately 646 (29.5% of all CF patients) in 1984[30].

These changes may be largely attributed to significant improvements in survival as a result of advances in CF therapy. Although these successes have transformed the prognosis of CF for patients, this demographic shift into the adult CF population presents a growing healthcare burden as the longterm complications of the disease process associated with the increased patient lifespan are now more prevalent[54]. Adults have a higher risk for serious CF-related complications related to the longterm effects of ion transport abnormality, including more advanced lung function impairment as assessed by % predicted forced expiratory volume in 1 second (FEV_1)[29], CF-related diabetes[29], and low BMD with increased fracture risk[36, 54]. Additional CF-related complications seen more frequently in adults than children have been described in detail elsewhere[55].

1.3.2 Lung transplantation waiting list trends showing increasing mortality

As the population of advanced lung disease grows we can expect the number of lung transplant candidates to continue to increase as well. Recent registry data indicates a trend towards a concordant rise in the number of candidates and deaths on the lung transplant waiting list[3]. Figure 1 shows that the number of deaths in all patients waiting for LTx has risen steadily in Canada, from 29 (17% of 172 total LTx candidates) in 2003 to 69 (21% of 329 total LTx candidates) in 2012[3]. The rise in number of deaths on the waiting list may be attributed to the growing disparity between the increasing number of transplant candidates and the available organ donor pool, which has remained constant[56]. As a result, more patients will die in the pre-transplant stage while on the waiting list than from transplantation-related mortality[56]. Mortality of advanced lung disease patients awaiting lung transplantation represents an important public health concern and therefore there is a need to reduce mortality risk in lung transplant candidates.

1.3.3 Mortality risk factors advanced lung disease

With the recent adoption of the Lung Allocation (LAS) Score system in the United States[57], determination of waiting list survival probability has become an important allocation criterion in stratifying patients based on medical urgency. The LAS score is determined by waitlist urgency during pre-transplant stage and predicted survival post-transplant. The *International Society for Heart and Lung Transplantation* candidate selection guidelines suggest that patients be referred for LTx assessment if they have a less than 50% predicted chance of survival within the next 2 to 3 years or have a III or IV level of function according to the New York Heart Association classification, or both[58]. The decision to refer a patient for LTx is dependent on a thorough physiological and psychological evaluation of specific baseline prognostic indicators to determine the pulmonary disease severity and suitability of the patient for LTx.

Several models have been developed to assess mortality risk in advanced lung disease groups[59-61]. FEV_1 has been suggested as the best prognostic indicator in people with COPD[62] and CF[63]. FEV_1 % predicted measures of less than 20% in COPD and 30% for CF are suggested thresholds for listing advanced patients for LTx[58]. Other risk factors associated with poor prognosis in COPD which must be taken into consideration include arterial hypoxemia, hypercapnia, emaciation indicated by low BMI, and elevated dyspnea[64]. In ILD, measurement of DLCO and radiographic evidence of fibrosis are often used predictors of survival[60]. DLCO % predicted of less than 40% is a suggested threshold for listing ILD patients for LTx[58]. Exacerbation history is also a factor which must be considered when determining the optimal timing for listing[58].

Poor performance on physical fitness assessments such as the 6 minute walk test (6MWT) has been shown to be a significant mortality risk factor in LTx candidates[65-68]. The 6MWT is a submaximal field test of functional capacity that measures the distance walked by the subject on a hard flat surface in a 6 minute time period[69]. In a sample of 163 lung transplant candidates (46.6% COPD; 29.4% CF; 23.9% ILD) distance walked during 6MWT was a significant predictor of mortality ($p<0.001$) showing a relative risk of 0.994 (95% confidence interval, 0.990 to 0.997) with each meter increase in 6MWT performance[68]. Prognosis may also be ascertained by measures of peak aerobic fitness, or peak oxygen uptake (VO_2), during maximal exercise testing. Peak VO_2 is not associated with mortality in COPD (Hazard Ratio, 0.971; 95% confidence interval, 0.959 to 1.000; $p = 0.050$); however, non-survivors have a significantly lower mean peak VO_2 ($p<0.0001$) than survivors[70]. Peak VO_2 is significantly associated with mortality in ILD (Hazard Ratio, 0.88; 95% confidence interval, 0.79 to 0.99; $p = 0.039$)[71], and in CF showing a relative risk of 3.2 (95% confidence interval, 1.2 to 8.6; $p = 0.024$) with lower aerobic fitness[72].

1.3.4 How can mortality risk be reduced in advanced lung disease?

Unlike the other mortality risk factors discussed previously, physical fitness represents a modifiable risk factor which may be improved or maintained by exercise training, or physical activity conducted in a structured and repetitive manner designed to optimize fitness[73]. An individual's physical fitness level may be assessed by evaluating the health-related components of functional status, which include musculoskeletal fitness, cardiovascular fitness, body composition, and metabolism[74, 75]. In fact, physical activity has been reported as the strongest prognostic indicator for mortality in COPD[76]. Reputable guidelines have recognised physical activity as a non-pharmacological treatment option in COPD[9]. In candidates for LTx, exercise

training has been shown to lead to improvements in physical fitness as measured by 6MWT distance[77]. LTx candidates with higher exercise capacity have also been shown to have a shorter length of hospital stay post-transplant[78]. Therefore, optimization of the patient's physical fitness with tailored exercise intervention and overall maintenance of physical activity could theoretically improve the patient's chances of surviving while waiting for an organ to become available for LTx and improve post-transplant outcomes. Figure 2 presents a theoretical model linking physical fitness to mortality in advanced lung disease.

1.4 Improving physical activity through pulmonary rehabilitation

Exercise is a component of pulmonary rehabilitation, "...a multidisciplinary program of care for patients with chronic respiratory impairment that is individually tailored and designed to optimize physical and social performance and autonomy..."[79], which is considered an integral part of the clinical management of people with chronic lung disease[80, 81]. Pulmonary rehabilitation is implemented by lung transplant programs to improve the health of patients during both the pre- and post- transplant stage[82, 83]. It is comprised of exercise training, education, and nutritional and psychosocial support[80]. According to the American Thoracic Society, pulmonary rehabilitation is designed to "…(1) reduce symptoms, (2) optimize functional status, (3) increase participation, (4) and reduce healthcare costs through stabilizing or reversing systemic manifestations of the disease…"[80]. An additional goal of rehabilitation specifically for advanced lung disease patients awaiting surgery is to "...optimize physical and emotional health [prior to surgical intervention]..."[84] The primary purpose of a rehabilitation program is to improve the ability of the patients to perform their activities of daily living and improve habitual physical activity levels[85].

Physical activity level is an important outcome to consider in advanced lung disease patients in or close to the pre-transplant stage of their disease progression to determine whether or not patients are maintaining the effects of rehabilitation by continuing to be physically active in their home, or "free-living" environment. Langer and colleagues concluded that COPD and ILD LTx candidates are largely inactive (69% of waking hours measured as sedentary)[86]. Accurate and objective measurement of physical activity level would enable the monitoring of habitual physical activity levels and in the appropriate titration of exercise training prescriptions for these advanced lung disease patients. There are no evidence-based exercise training guidelines designed specifically for advanced lung disease patients[87].

1.5 Daily physical activity—how can we measure this outcome?

1.5.1 Physical activity conceptual framework

Physical activity is a bioenergetic process involving the conversion of the chemical energy obtained from dietary intake to the mechanical energy used to perform body movements. It has been defined as "any bodily movement produced by skeletal muscles that results in energy expenditure [above resting metabolism]."[73]Additionally, it has been defined as "… the totality of voluntary movement produced by skeletal muscles during everyday functioning…"[88]. Therefore, the measurement of physical activity may be assessed conceptually in relation to either energy expenditure or bodily movement dimensions. Metabolic energy expenditure (EE), has three components: resting energy expenditure (REE) for maintaining homeostasis at rest, dietary thermogenesis for the acquisition and storage of energy from caloric intake, and energy cost of activity (ECA)[89, 90]. ECA is the mechanical energy used by skeletal muscles to perform body movements, or physical activity. ECA may be exercise-related or incidental non-exercise activity

thermogenesis. Additionally, the dimensions of physical activity may be characterized by their frequency, intensity, duration, and mode of activity components[91, 92]. Figure 3 presents a conceptual framework of physical activity based on our understanding from the literature.

1.5.2 Physical activity quantification methodologies

Measurement of daily habitual or "free-living" EE or movement patterns throughout the day may be used to evaluate a patient's physical activity behavior at home or in a rehabilitation setting. The globally accepted "gold-standards" or criterion methods for quantifying EE are indirect calorimetry (IC) and doubly labeled water (DLW)[92]. Movement dimensions of physical activity can be measured by direct observation[4]. Other approaches for estimating daily physical activity are questionnaires and motion and/or physiological sensor devices. Although questionnaires are affordable and simple to use, they are subjective[93] and may be inaccurate due to recall bias[94] and unreliable due to memory limitations[95]. In general, there are three main types of field devices used most often in chronic disease populations: pedometry, accelerometry, and integrated multi-sensor technology[96]. Heart rate monitoring devices may also be utilized in the field setting to estimate physical activity levels[97]. An overview of the aforementioned objective methodologies, including their specific strengths and drawbacks, is presented in the proceeding sections.

1.5.2.1 Indirect calorimetry (Figure 4)

IC involves the measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) to calculate EE. The assumption underlying this methodology is that all consumed oxygen is utilized to metabolize chemical fuels from food intake and all carbon dioxide output is recovered[98]. Using known standard formulae[89], EE can be calculated from

measured VO_2 and VCO_2. Portable IC systems have been developed which have been shown to provide accurate and reliable pulmonary gas exchange measurements during rest and activity[99, 100]. Although IC techniques are highly valid, the instrumentation is prohibitively expensive, cumbersome for the patients to wear, and requires specialized expertise to interpret the recordings and set up the equipment. As a result, IC techniques are not appropriate for regular clinical use and are often used to validate other, more practical methods of physical activity measurement in controlled lab settings[101].

1.5.2.2 Doubly labeled water (Figure 5)

DLW involves the measurement of the differential clearance rates of previously ingested amounts of oxygen and hydrogen isotopes from the body over multiple days to calculate carbon dioxide production[102]. VCO_2 is then used in conjunction with measurements or estimations of the respiratory quotient to determine VO_2 and ultimately EE[103]. Although DLW provides valid measure of overall free-living EE during the measurement period (usually 4 to 21 days)[104], it does not describe day-to-day EE levels and the isotopes are prohibitively expensive[103]. Specialized expertise is also required to analyze the recordings and to operate the required equipment. As a result, DLW techniques are not appropriate for regular clinical use and are often used to validate other, more practical methods of physical activity measurement in free-living field settings[101].

1.5.2.3 Behavioural observation

Behavioural (direct) observation involves a designated observer, or group of observers, to meticulously quantify movements of subjects by watching their activities in real-time or videotaped recordings from previous activities[105]. This technique of physical activity assessment

requires a large time-commitment, is intrusive for the subjects being evaluated, and would be inappropriate for studying larger populations[93]. Similar to IC and DLW, it would be inappropriate for regular clinical use; however, may be employed to validate other more practical methods of physical activity measurement[106].

1.5.2.4 Pedometry

Pedometers are affordable, lightweight, small-sized monitors worn attached to the waist that provide motion counts, or steps, when its internal spring lever is deflected with each vertical deflection at the hip[93]. In addition to steps, pedometers may also be able to detect the vertical motions encountered when getting up from a seated position[107]. Given its ease of use for the general population, large-scale public health campaigns have suggested pedometer output thresholds (10 000 steps per day) to achieve health benefits[108]. Although simple and inexpensive, studies have shown a tendency for pedometers to underestimate steps during slower speeds of walking[109]. Additionally, improper positioning may also result in an underestimation of activity output from the pedometer[110]. Moreover, pedometers are incapable of providing information regarding the duration and intensity of physical activities[93, 110].

1.5.2.5 Accelerometry

Accelerometers, which may be uni-, bi-, or tri-axial, measure accelerations of body segments in one, two, or three dimensions respectively[96]. Accelerometers are capable of capturing the quantity and intensities of body movements[111]. These devices may be more expensive than pedometers and require additional software and expertise to analyze the recordings[93]. Additionally, waist and lower limb worn accelerometers are limited in their ability

to distinguish arm movements[93]. Some accelerometers may also be unable to measure activity during static exercises[112] or may underestimate activity during incline walking[113].

1.5.2.6 Multisensor Technology

Devices that integrate accelerometry data with physiological sensor data that records body responses (ie skin temperature or heart rate) have been shown to improve validity compared to accelerometry-only devices[114]. Multisensors have also been show to be valid in quantifying cycling exercise[115], compared to standard accelerometers which have largely underestimated activity level during cycling[116]. One of the major drawbacks of multisensors is their high costs relative to accelerometers and pedometers, which may increase depending on the type of additional software required for the data analysis[93].

1.5.2.7 Heart rate monitoring

Heart rate (HR) measurement has been widely used to assess physical activity. Flex-heart rate (HR) techniques assume a relationship between HR and physical activity, and that HR is closely associated with VO_2 above resting levels[117]. This technique involves recording minute-by-minute HR in the field and extrapolating EE data from individual HR-VO_2 regressions developed in the lab during invasive exercise testing[118]. After the invasive exercise testing required to construct the individual calibrations is complete, physical activity measurement by HR monitoring is relatively convenient, cheap, and noninvasive. Another strength of this technique is the individualized, subject-specific nature underlying the measurement of physical activity. One of the limitations of this technique is the requirement of IC instrumentation in developing their HR-VO_2 regression profiles in a lab setting which can be costly and time-consuming as discussed previously.

1.6 Physical activity measurement validity in chronic lung disease

1.6.1 Inefficiencies of movement

Skeletal muscles utilize a small portion of available EE output to perform external work, with the remaining EE lost to the environment as heat. Higher ratio of external work to EE indicates better muscular efficiency[119]. Evidence suggests that there may be reduced mechanical efficiency in COPD and CF, resulting in elevated costs of activity. Studies have reported up to 10% increases in energetic costs in COPD patients relative to healthy people when performing strenuous activities[120]. The energy cost of performing physical activities has been shown to be higher than normal in CF patients as well during walking and cycling[121]. As a result, patients may be expending greater amounts of energy than normal to carry out a given movement of activity and tiring sooner. In theory, movements or durations of certain activities suggested in the guidelines as of moderate or light intensities[122] may actually approach vigorous intensity levels in advanced lung disease patients. Therefore, devices used to monitor movements or durations in particular postures and compared to standard guidelines of the quantity of required activities required to elicit health benefits in healthy people may actually not be appropriate for advanced lung disease patients and require titrations of guidelines to accommodate their elevated energy demands.

1.6.2 Elevated resting metabolism

An elevated REE relative to healthy controls or predicted values has been shown in COPD patients (>10% above predicted)[123], ILD patients (>20% above predicted)[124], and CF patients (10% above predicted)[125]. REE 10% above predicted indicates a hypermetabolic state[90]. The elevated oxygen cost of breathing or oxygen consumption by the respiratory muscles, in

chronic lung disease patients with their abnormal pulmonary mechanics and structure may contribute to the increased REE[126-128]. A phenomenon reported in COPD and CF which may be the largest contributor to the hypermetabolic characteristics of advanced lung disease is dynamic hyperinflation. Lung hyperinflation is defined as the elevation of end expiratory lung volume above normal levels during rest and/or exercise[129]. Dynamic hyperinflation has been shown to occur in COPD[16] and CF[130]. As a result, using activity measurement techniques calibrated from healthy populations with normal metabolism may not accurately reflect the daily EE of hypermetabolic patient who require increased energy demands from breathing during rest and exercise.

Typically, field devices such as pedometers and accelerometry-based devices estimate energy expenditure using equations developed in relatively healthy populations[131]. Therefore, the elevated resting and activity EE resulting from abnormal body functioning may not be accurately measured by these physical activity monitors relying on EE estimations from standard equations developed in other non-disease populations.

1.6.3 Interpretations of the literature

In summary, many of the field devices discussed previously measure different components of physical activity (i.e. steps, acceleration, position changes, duration of movements, heart rate, etc). In addition, many of these devices provide an estimation of EE. Therefore, EE measurement is an outcome that can be compared across physical activity monitors. Most of these devices have been validated in young, healthy populations[96] and their applicability to a chronic lung disease population is not well established. Specifically, differences in efficiency of movement and resting metabolism, and the use of algorithms for estimating EE

derived likely from relatively healthy populations may result in an inaccurate measure of physical activity in chronic lung disease populations.

Our review of the literature identified a small number of validity studies of physical activity measures conducted in COPD[132-136] and CF patients[137, 138]. No validation studies in ILD were found. In general, the mean differences (standard deviation of differences) between estimated EE from actual EE measured by IC or DLW have been quite variable across validated monitors and disease. Pedometers underestimated EE in COPD by 2.4 ± 3.4 kcal/min difference with IC[132]. Multisensor accuracies ranged from underestimation in COPD of 1.3 ± 4.1 kcal/min difference with IC[132] to overestimation in CF of 1.8 ± 1.3 kcal/min difference with IC[137]. Flex HR was found to underestimate EE measured by DLW by 454.1 ± 406.3 kcal/day in CF[138]. Although all of these studies concluded the devices were valid for measuring EE, they did not provide any information on whether or not the magnitude of the EE differences was clinically acceptable. As a result, the accuracy and precision of the monitors still remains questionable. These studies were also conducted in samples with wide ranges of disease severity. No study was found that validated the monitors specifically in advanced lung disease patients or in a sample combining multiple disease groups.

1.7 Rationale for this study

It is challenging for clinicians and researchers to determine the appropriate tool for objectively measuring physical activity due to the vast selection of currently available measurement techniques. Although issues of practicality and feasibility come into play when judging which tool would be appropriate for a given patient population, the accuracy of the tool in measurement of a physical activity parameter is an important consideration as well.

Since participation in physical activity has the potential to reduce waiting list mortality in advanced chronic lung disease patients during the pre-transplant stage, valid physical activity monitors are needed to accurately monitor physical activity in this patient population. Tudor-Locke and colleagues suggest that motion sensing monitors (pedometers or accelerometers) are 'good enough' for monitoring activities in sedentary individuals[139]. To our knowledge, these devices would be unable to capture the true activity level of advanced lung disease patients who are prescribed activities more strenuous and complex than walking to maintain training effects of pulmonary rehabilitation programs at home. Accurate measurement of EE would provide a more appropriate evaluation of their activity level, assuming that the EE estimation of the particular monitor is accurate. Whether the standard EE estimation equations developed in commercially available monitors are superior to the EE estimation from an individually calibrated equation such as one developed using the Flex HR method remains to be determined.

Therefore, we undertook this study to investigate and compare the accuracy of a variety of physical activity monitoring techniques (pedometry, accelerometry, multi-sensor technology, HR monitoring techniques) simultaneously against a gold standard of indirect calorimetry-derived measurements from a portable metabolic system in a population of adults with advanced lung disease in a controlled lab setting. We also investigated how their accuracy changed with varying types and intensity levels of activity during standardized "lifestyle" activities and cycling exercise.

All of these techniques have been validated previously in chronic lung disease populations[132-136]; however, this is the first study to compare the validity of these objective energy expenditure measurement tools specifically in advanced lung disease populations. To our knowledge, no previous study has attempted to compare the validity of all of these specific

physical activity monitoring techniques simultaneously in their ability to estimate EE in any chronic lung disease population.

1.8 Study objectives and hypothesis

The objective of this study is to investigate and compare the accuracy of various commercially-available energy expenditure (EE) measurement techniques (index test methods) including flex heart rate (HR) technique, multi-sensor activity monitoring, 3 accelerometry devices, and pedometry against indirect calorimetry (gold standard method) during a battery of standardized free-living (lifestyle) - type activities and exercise of varying intensity in patients with advanced lung diseases. In addition, we will explore how the accuracy of the devices differs across different types of activities.

To achieve our objective, we addressed the following aims:

(1) To develop individualized HR-oxygen uptake (VO_2) regression profiles for each subject during standardized resting and submaximal cycling exercise of varying intensities for estimating EE using the Flex HR technique.

(2) To obtain simultaneous EE estimations from each of the index test methodologies using a HR monitor, a multi-sensor activity monitor, a pedometer, and three tri-axial accelerometers concurrently with a gold standard derived measurement of EE from a portable indirect calorimeter during a battery of standardized activities and during a standardized exercise protocol.

(3) To explore the criterion-related and concurrent validity of each index test method for EE estimation against indirect calorimetry-derived measurements of EE across monitors.

We proposed the following primary hypothesis based on our understanding of the literature:

Unlike pedometers, accelerometers, and multi-sensor methods, which estimate EE by transforming signals using proprietary prediction equations or equations calibrated in healthy people, an individually calibrated technique such as the Flex HR method may be more accurate for assessing EE in advanced lung disease patients as it takes their REE into account. Therefore, we hypothesized that the Flex HR methods would be more accurate than the other index measurements of EE evaluated in this study due to it being a more individualized approach compared to the other methods, which may not be as capable of quantifying the metabolic abnormalities associated with the disease.

Chapter 2: Methods

2.1 Statement of ethical adherence

All participants provided written informed consent and were given medical clearance to participate from the study physician prior to commencing any exercise testing conducted as part of this study. Our study protocol was approved by the Providence Health Research Institute Ethics Board (H13-01117).

2.2 Study design

This was a cross-sectional method comparison study to investigate and compare the accuracy of various measures of EE (index methods) against indirect calorimetry-derived criterion measures of EE during standardized activities and exercise in patients with COPD, ILD, and CF with advanced pulmonary impairment. We recruited consecutive patients meeting our selection criteria (Table 1) from the outpatient clinics (Pulmonary Rehabilitation Clinic, ILD Clinic, COPD Clinic, and Adult CF Clinic) at St. Paul's Hospital (Vancouver, BC, Canada). Additionally, CF inpatients staying at St. Paul's Hospital were also invited to participate in the study.

2.3 Participants

Inclusion criteria: Table 1 lists the participant selection criteria for this study. The criteria were chosen to be representative of patients who had "advanced lung disease" and may warrant referral for lung transplantation assessment to our provincial lung transplantation program (Solid Organ Transplant Clinic, Vancouver, BC, Canada) at BC Transplant Society. All selection criteria were unanimously agreed upon by our study physicians, one of whom is the Medical

Director of our provincial lung transplant program. We recruited adult patients (between 35 and 65 years of age) with a primary diagnosis of COPD or ILD and CF patients aged 19 years and older, as adults comprise the overwhelming majority of first graft LTx procedures in Canada and COPD and ILD are much rarer in younger populations. Participants had previous clinical diagnosis of advanced lung disease as judged by the study physician. COPD patients had a FEV_1/FVC ratio < 0.7 and FEV_1 less than 50% of predicted. CF patients had a FEV_1 less than 50% of predicted. ILD patients had a FVC less than 60% predicted or DLCO less than 40% predicted. These patients were identified from clinic chart data using pulmonary function tests performed within 6 months prior to recruitment. Pulmonary function inclusion criteria were based on routine clinical post-bronchodilator test results. All patients were nonsmokers. All patients were clinically stable at recruitment and maintained clinical stability on and between study days. For COPD and ILD outpatients recruited, clinical stability was defined as no increase in respiratory symptoms requiring hospital stay and no change in usual medications. Additionally for COPD and ILD patients, they had not been on antibiotic therapy or prednisone for 4 weeks prior to recruitment. For CF inpatients recruited, patients within the last week of a hospital stay were considered clinically stable. CF patients (inpatient or outpatient) were considered eligible for study participation even if they were on antibiotic therapy or prednisone because these medications are considered "usual medications" in advanced CF[42]. Patients also had to be able to speak English to be eligible so that they would have been able to understand the testing instructions given to them by the research staff. If an English-speaking translator was available for the patient, he or she was still eligible for inclusion.

Exclusion criteria: We excluded patients referred for LTx assessment who had any previously transplanted organs as metabolic imbalance in this group may have been largely attributed to

factors other than impaired pulmonary function, such as post-transplant medications required to prevent organ rejection[140]. Additionally, we excluded patients referred for heart+lung (combined) transplantation assessment as they may have been at a higher risk for cardiac events during exercise testing. Additionally, patients with any significant right or left heart disease absolutely contraindicated for cardiopulmonary exercise testing (CPET) according to the *American Thoracic Society* (ATS) guidelines[141] were also excluded. Patients with any non-cardiac related contraindications and other relative contraindications for exercise testing according to the ATS guidelines[141] were only included after approval from the study physician. Patients using any type of walker, cane, or wheelchair mobility aids were excluded from this study as these assistive devices would have interfered with the exercise testing and standardized activities protocol. Following the recommendations of recent infection control guidelines[142], CF patients with Burkholderia cepacia *complex* (BCC), *Myobacterium abscessus*, and/or *Burkholderia dolosa* (non-BCC) and closely related organisms (*Apista, Ralstonia*) were excluded from participation in this study as these organisms are easily transmissible between patients. Patients requiring supplemental oxygen during activity were also excluded because the face masks used on the subjects are not designed to fit the nasal prongs. Finally, those patients judged by the study physicians as having poor adherence to medications, uncontrolled diabetes, profound emaciation (body mass index<16), or indices of pulmonary hypertension (mean pulmonary artery pressure > 25 mmHg from right heart catheterization test; systolic pulmonary artery pressure > 35 mmHg from echocardiography test) were excluded.

Subject recruitment: Staff from the Adult CF clinic, ILD clinic, COPD clinic, and Pulmonary Rehabilitation clinic at St. Paul's Hospital identified outpatients eligible for study participation based on the data collected during their most recent clinical assessment. CF inpatients were

identified by additional methods including scanning daily admission rosters. On Day Zero of the study, eligible subjects were hand delivered a letter of initial contact which explained the purpose of the study, contained the informed consent form, and invited patients to participate in the study by contacting the research staff. Subjects agreed to perform a CPET on study Day One, followed by submaximal exercise testing on Day Two, preferably within a one month period. Patients who did not routinely attend the clinics were recruited by letter of initial contact sent by the clinic staff. The study nurse contacted any eligible patients in approximately 10 days after the letter of initial contact had been mailed out or hand delivered to the patient.

2.4 Experimental procedures

The following procedures were conducted in the University of British Columbia Pulmonary Rehabilitation Research Laboratory and Pacific Lung Health Centre at St. Paul's Hospital (Figure 6):

Day Zero: Patients regularly visiting the clinic who were eligible for participation in the study were given a letter of initial contact along with a consent form by the clinic staff. Patients who did not regularly attend the clinic were recruited by letter of initial contact sent by mail. The study nurse contacted the patient eligible for participation in approximately 10 days after the letter of initial contact had been mailed out or hand delivered to the patient to determine interest in study participation. Eligible subjects and patients interested in participating were asked to contact the research staff by phone or email and be scheduled for two study days conducted within a one month period. All eligible patients consented to allow us to review the clinic charts from their most recent clinical assessment to be enrolled in the study.

Day One: Demographic and anthropometric data were collected for each subject on entry. Subjects then performed a standardized research pulmonary function test (forced vital capacity manoeuvre only) on entry following standard testing guidelines[143]. Following pulmonary function testing, subjects performed a standardized symptom-limited CPET. A physician was in the proximity of the testing environment to respond immediately in case of an emergency as required according to ATS guidelines[141].

Day Two: Each subject performed a standardized calibration protocol comprised of resting and a submaximal cycle exercise protocol at two different relative work rates (25% and 50% of the peak VO_2) to develop their individual Flex HR physical activity measurement profile. Development of the Flex HR profile involved a multi-stage process where the subject's VO_2 and HR were measured simultaneously at rest and at increasing intensity levels of exercise. Following the calibration protocol, subjects rested in a quiet sitting position until he or she was ready to perform a battery of standardized "free-living" type physical activities and submaximal exercise. During these standardized physical activities and exercise, EE was simultaneously measured using each index method (Table 2) and a portable indirect calorimeter gold standard method.

Testing was conducted in the same controlled lab setting on both study days to minimize or eliminate the impact of differential temperature and humidity in multiple environments on our data. All measurement equipment used in this study were thoroughly cleaned and sanitized in accordance with the Providence Health Infection Control policies at St. Paul's Hospital. Disposable equipment were immediately discarded in appropriate containers after usage. Each subject was instructed to avoid strenuous activity for at least 24 hours and food or caffeine drinks for 2 hours prior to Day One CPET testing. They were also instructed to take all of their usual

medications including β_2-agonist inhalers for at least 2 hours prior to testing on both days. If applicable, patients were also instructed to perform airway clearance therapy at home prior to commencing testing on both study days. The purpose of the aforementioned pre-test instruction was to ensure that subjects were able to perform to their optimal ability on both study days.

2.5 Measurements

Basic Subject Information: Information abstracted from the patient's medical chart by the research staff included previously available pulmonary function test results (FEV_1 % predicted, FVC % predicted, FEV_1/FVC ratio, and DLCO % predicted if it was reported), exacerbation frequency within the last year, list of comorbidities, and list of current medications. Age, gender, city of residence, and ethnicity information were obtained by asking the subject. Height in meters (m) and weight in kilograms (kg) were measured with standard stadiometer and weight scale respectively. Body Mass Index (BMI) for each subject was calculated by dividing their weight in kilograms (kg) by height in meters (m) squared. Stride length was determined by asking the patient to walk 10 steps on a flat surface and measuring the distance walked (distance walked in meters divided by 10 equals stride length).

Spirometry on Entry: FVC manoeuvres were performed according to guidelines developed by the American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force[143]. Participants performed the pulmonary function test until three acceptable blows (largest and next largest FVC and FEV_1 within 0.150 litres) were made or until participant was no longer able to continue as required according to the ATS/ERS guidlines[143]. Testing was performed using the "Pulmonary Function" spirometry mode of the SensorMedics Vmax Encore^{TM} metabolic system (Viasys; Loma Linda, CA, USA). Absolute FEV_1 (liters) and Forced Vital Capacity (FVC)

(liters) as well as % predicted values were calculated from the highest values of the three acceptable trials. Predicted normal reference values were taken from Hankinson and colleagues [144]. The mass flow sensor of the SensorMedics Vmax Encore™ was calibrated prior to each pulmonary function test.

Cardiopulmonary Exercise Testing: Prior to the commencement of exercise, participants were instructed to perform three inspiratory capacity (I_{cap}) maneuvers following the ATS/ERS guidelines[143]. The average of the three I_{cap} maneuvers was recorded as the resting I_{cap}[143]. Each subject then performed a standardized symptom-limited CPET on an electronically-braked cycle ergometer (Ergoline; Bitz, Germany) using a stepwise protocol (Appendix A). Starting at 0 watts (W), the workload was increased by either 10 or 15 W every 2 minutes. The 2 minute protocol was chosen to ensure a physiological steady state at each incremental stage of exercise. Subject exercised until exhaustion. All gas exchange values (VO_2, VCO_2) and ventilations were measured using the SensorMedics Vmax™ metabolic system while the subject breathed room air. Cardiac rhythms and HR were continuously recorded by standard 12-lead electrocardiogram. Blood pressure, HR, oxygen saturation, and perceived dyspnea and muscular leg discomfort using scales based on standard 10-point schemes[145, 146] were continuously monitored during CPET for safety purposes. VO_2 and HR data were averaged into 30 second bins where the 60-90 second segment of each incremental exercise stage was sampled. Research staff recorded the VO_2, HR, and workload at peak exercise as well the peak VO_2 % predicted using reference values taken from Jones and colleagues[147]. The internal gas analyzers of the SensorMedics Vmax Encore™ and the workload of the cycle ergometer were calibrated prior to each test.

Portable Indirect Calorimetry: The K4b2™ breath by breath metabolic system (Cosmed; Rome, Italy) has been previously tested and well validated to provide accurate and reliable

measurements of respiratory gas exchange during resting and exercise[100]. The system provides measurements of EE (in units of kcal/min) by indirect calorimetry, using the formula by Elia and Livesey (EE = 3.781 * VO_2 + 1.237 * VCO_2) [89]. The lightweight (0.8kg) system consists of a battery pack-operated (1 to 5 hour data collection time before recharge is required) portable unit connected to a Hans Rudolph™ facemask (Hans Rudolph Inc, Kansas City, MO, USA). In addition to gas exchange measures, the K4b2™ stores simultaneous breath-by-breath measurements of HR collected from the Polar™ heart rate monitor belt (Polar Electro; Kempele, Finland) The internal gas analyzers and turbine were calibrated prior to each test.

Individual HR-VO_2 Calibration Protocol for Flex HR Measurement Technique: Subjects underwent a multi-step procedure to determine their individual HR-VO_2 regression equations for use in estimating physical activity from the Flex HR method. This method relies on the assumption that above a critical heart rate threshold known as the flex HR, VO_2 (and subsequently energy expenditure) and HR levels are linearly related[97, 117, 148]. Although there have is no standard Flex HR procedure, a variety of calibration protocols for deriving Flex HR and individual HR-VO_2 regression equations have been discussed in the literature[148-151].

In general, calibration testing involves simultaneous measurement of VO_2 and HR while the subject rests in various positions (lying, sitting, and/or standing) and exercises at different intensities. Measurements of HR and VO_2 are then taken over a given time period during steady state following an equilibration period. Flex HR is calculated as the average of the lowest HR during exercise and the highest HR during resting positions obtained during calibration testing conducted in a laboratory setting[97, 149]. Resting metabolic rate is calculated as the mean energy expenditure during the resting stages of the calibration test[150]. We conducted a resting and exercise Flex HR calibration procedure adapted from protocols used recently in CF patients[138,

[152]; however instead of using treadmill exercise at absolute workloads as done in these previous protocols, we chose to conduct cycling exercise at relative workloads for the exercise stages of the calibration protocol to allow for precise workload selections (Figure 7).

Step 1 - After arriving in the lab on Day Two, participants rested for 10-15 minutes. Each participant was then fitted with the K4b2^{TM} portable indirect calorimeter and Polar^{TM} heart rate monitor belt.

Step 2 – Gas exchange (VO_2 and VCO_2) measured by the K4b2^{TM} and HR measured by the Polar^{TM} were simultaneously sampled on a breath-by-breath basis during resting and cycling activities: (1) sitting quietly in a sitting position for 6 minutes, (2) standing quietly for 6 minutes, (3) cycling at 25% of their previously determined peak workload for 6 minutes (following a 1 minute warm-up period), (4) cycling at 50% of their peak workload for 6 minutes (followed by a self-selected cool-down period). Blood pressure, HR, and perceived dyspnea and leg discomfort were continuously monitored during exercise stages for safety purposes.

Step 3 – Using Microsoft Excel (2007) we constructed each subject's HR-VO_2 regression equation and calculated their Flex HR. Breath-by-breath HR and VO_2 levels were averaged into 1 minute bins where we sampled the last three minutes of each stage. We calculated the average HR and VO_2 values over the last 3 minutes of each of the 6 minute stages discussed in step 2. We then determined a regression profile using these averaged "calibration points" with the sum of least squares method[153].

Flex HR was determined as the mean of the lowest HR attained during the 3 minute sampling period of the cycle exercise and the highest HR attained during the 3 minute sampling period in sitting or standing obtained during calibration testing. We also calculated the subject's

resting metabolic rate, or "sedentary EE" as it has been referred to in previous flex HR studies, as the average EE attained by IC during the 3 minute measurement periods of the sitting and standing positions.

Additionally, we constructed separate HR-VO_2 regression profiles for each subject using the 30 second averaged HR and VO_2 measurements during the exercise stages from the CPET conducted on Day One. As a result, each participant had two separate flex HR calibration profiles: (1) flex HR curve calibrated during a submaximal exercise protocol and (2) flex HR curve calibrated during a peak exercise protocol. The flex HR and sedentary EE calculated on Day Two was assumed to be the same as on Day One.

Physical activity monitoring instruments: Following the flex HR calibration protocol patients were fitted with several physical activity monitors, all of which simultaneously measured EE in different ways (Figure 8):

The Digi-Walker CW 701^{TM} pedometer (Yamax; Tokyo, Japan) was attached to each subject's waist at the front on the right side. It uses weight and step length data input as well as vertical hip movement counts (steps) detected by an internal spring levered mechanism to estimate EE (in units of kcals) accumulated over a given period of time. Although the algorithm for calculating EE is not commercially available, we assume it is most likely developed using the motion counts and wearer characteristics in a non-disease standard population. Although the device does not come equipped with a timestamp or "marking" feature, it does allow the wearer to reset the display EE. We reset the display before the start of each activity.

The SenseWear Armband^{TM} multisensor (BodyMedia; Pittsburgh, PA, USA) was worn by each participant on the upper left arm (triceps). This device uses demographic, triaxial

accelerometry, and various other physiological sensor data input (galvanic skin receptor, skin temperature, and heat flux) to estimate minute-by-minute EE through proprietary manufacturer algorithms. The computer software (SenseWear Professional 7.0) used to analyze the data provided minute-by-minute EE in units of kilojoules. We converted the kilojoules per minute into units of kcal per minute using standard conversion factors.

The ActiCal™ triaxial accelerometer (Philips; Eindhoven, Netherlands) was worn on the wrist of each participant on the dominant side. EE was estimated using proprietary manufacturer algorithms incorporating age, height, and weight input from the wearer as well as triaxial accelerometry signals during physical activities. EE was collected in units of METs, which we converted to kcal/min using standard conversion factors. The monitors also had timestamp features allowing us the mark the start and end of each activity.

The DynaPort MiniMod™ triaxial accelerometer (McRoberts BV; The Hague, Netherlands) was worn by each participant on their waist at the lower back. This device consists of a piezoelectric triaxial accelerometer to measure the body's accelerations in three axes. It measures the amount of time spent in various activities and positions (walking, cycling, sitting, standing, and lying down) as well as walking intensity. EE in units of absolute kcals is accumulated from the start of data collection until the end of data collection. As a result, it provided us with EE accumulated over the entire activity protocol.

The Tractivity Sensor™ (Kineteks Corporation; Vancouver, BC, Canada), was worn on the right ankle of each participant. The sensor uses measures motion intensity from the triaxial accelerometer during walking or running along with height and weight input from the wearer to calculate EE using proprietary manufacturer algorithms. The online Tractivity web application

provided measurements of EE in absolute kcals in one hour bins throughout the day. Using recorded start and end times we calculated the total EE in kcals measured over the entire activity protocol.

The Polar^{TM} heart rate monitor belt (Polar Electro; Kempele, Finland) was attached around the subject's chest. This device transmits minute-by-minute HR recordings through telemetry to a computer software program for data storage and analysis. As discussed earlier, each subject's Flex HR was determined as the average of the highest HR during resting activities (during sitting and standing) and lowest HR during steady state submaximal cycle exercising at the two relative workloads during the calibration period. Also, sedentary EE for each participants was calculated as the average EE attained by IC during the 3 minute measurement periods of the sitting and standing positions. We also constructed two separate HR-VO_2 regression equations for each participant using: (1) HR-VO_2 calibration points collected during a submaximal exercise protocol and (2) HR-VO_2 calibration points collected during a peak exercise protocol. During activities, if minute-by-minute HR was below Flex HR, EE was recorded as sedentary EE for that minute. If HR was above or equal to Flex HR, EE were determined by applying HR-VO_2 regression equations developed earlier to first calculate the VO_2 estimated then converting to EE in kcals by multiplying it by a standard conversion factor of 4.9[154].

After being fitted with the aforementioned activity monitors and the portable indirect calorimeter, subjects were instructed to perform a sequence of free-living type activities followed by submaximal steady state cycle exercising at four separate relative workloads.

Free-living activities: Subjects perform a sequence of activities adapted and modified from the Glittre ADL-test of functional status in COPD patients[155] (Figure 9). Similar activity protocols

were used to validate activity monitors during standardized tasks in chronic lung disease patients[136]. Subjects were asked to perform the following activities in sequence at a normal pace: walking on flat treadmill, walking on incline treadmill, rising from a chair and sitting in another chair space 1 meter apart (Sit-to-stand), and moving a 1kg object in and out of two shelves positioned at shoulder level and waist level and the ground (Lifting-bending). Participants self-selected their treadmill walking speed such that they walked at a speed that elicited a perceived dyspnea of 'mild' to 'moderate' intensity[146]. Selected incline grade was between 2 to 4 % depending on the perceived dyspnea response. Participants rested in a quiet sitting position between each of the aforementioned tasks until their HR returned to with 10 beats per min of baseline levels. Each task was performed for 2 minute durations. The start and end times of each activity were synchronized on the SenseWear and ActiCal monitors as well as the portable unit of the indirect calorimeter and Polar HR monitor. The DigiWalker EE counter was reset to zero before the start of each activity. Blood pressure and perceived dyspnea and leg discomfort were measured at rest stages between free-living activities and at the first minute of each cycling stage for safety purposes. Additionally HR was continuously monitored during free-living activities and cycling to ensure that the HR did not exceed 80% HR max determined on Day One during CPET.

Submaximal cycling exercise: Following the free-living activities protocol, participants performed exercise on a cycle ergometer. Each subject performed cycle exercise at four relative intensities (at 10%, 25%, 50%, and 60% of peak workload) (Figure 10). Participants cycled for a period of 2 minutes at each workload. The start and end times of each exercise intensity stage were synchronized on the SenseWear and Actical monitors as well as the portable unit of the indirect calorimeter and Polar HR monitor. The DigiWalker EE counter was reset to zero before

the start of cycling, but not reset between intensity stages as it would have required to participant to stop cycling. During the cool-down stage we removed all measurement equipment from the participant. Blood pressure, HR, and perceived dyspnea and leg discomfort were continuously monitored during exercise stages for safety purposes.

2.6 Data management and statistical analysis

Analyses were performed using R 3.1.0[156] and SAS version 9.2 (SAS Institute; Cary, NC, USA). Our significance level was set as $p<0.05$. Data are presented as mean ± SD unless otherwise stated.

2.6.1 Analyses

Since only the SenseWear multisensor, ActiCal accelerometer, and Flex HR method had the capability for precisely marking the start and end times of activities, we chose these measurements techniques as our primary index methods for comparison. The DigiWalker pedometer, Dynaport, and Tractivity monitors had no marking feature, thus they were considered secondary index methods for comparison as we could not be confident in the exact synchronization of EE measured from these methods with concurrent IC EE values. Minute-by-minute EE in kcal/min from each primary index method had simultaneous minute-by-minute IC EE measurements in kcal/min data collected for comparison with the criterion method. Markers were used to synchronize the time (start and stop) on each primary index method and IC. Since actual EE is best approximated by IC during physiological steady state conditions[115], we sampled the last minute of each 2 minute activity for analysis of our primary index methods measuring in units of kcal/min. EE values were analyzed separately for each activity (free-living and cycling stages) as well as averaged over free-living (flat walking, incline walking, sit-to-stand, and lift-

bend), cycling (all stages; 10% peak, 25% peak, 50% peak, and 60% peak workloads), and overall (free-living and cycling combined). EE in units of absolute kcal from each secondary index method accumulated overall (free-living and cycling combined) were recorded for comparison with breath-by-breath IC EE in units of absolute kcal accumulated overall (start of free-living activities to end of cycling).

Descriptive analyses: Means and standard deviations were reported to describe continuous variables including age, height, weight, pulmonary function test results, clinical chart audit data, and cardiopulmonary exercise test results. Frequency data were reported for categorical variables including, primary diagnosis, sex, and comorbidities.

Primary analyses: Bland-Altman analyses were performed to investigate the agreement between EE estimated by the primary index methods and EE calculated by IC from the K4b2^{TM} portable indirect calorimeter. According to Bland and Altman[157], the analysis involves plotting the difference between the index method and criterion method against their average value for each participant. The mean of the differences represents the bias, which is assumed to be zero. The limit of agreement (LOA) between the index method and criterion method is calculated using the variability of the mean difference, or standard deviation (SD) of the differences (LOA = 1.96*SD). Additionally, Wilcoxon signed rank tests were used to assess significant differences between primary index method estimates of EE and IC EE.

Secondary analyses: Spearman correlational analyses were performed on data sampled during free-living activities, cycling (all stages), and overall to measure degree of association between the primary index methods and IC. Additional analyses performed strictly for descriptive purposes include construction of (1) scatter plots between each primary index method

measurement of EE and concurrent IC EE measurement with respect to the line of identity, and (2) scatter plot between each secondary index method measurement of EE and concurrent IC EE measurement with respect to the line of identity.

2.6.2 Prospective sample size calculation

We were interested in the interchangeability of the primary index methods with the criterion method of EE measurement (i.e. the appropriateness of using the index method in place of IC). Accurate measures of EE were deemed to be those that would measure EE (in kcal/min) within a clinically acceptable difference from IC. To our knowledge, there is no standard for an acceptable difference in EE measurement with gold standard techniques in chronic lung disease or healthy people. We stated *a priori* that the EE difference cannot be greater than the estimated energy required to maintain equilibrium between total daily EE and dietary intake. Differences greater than this threshold may inaccurately show the patient in an imbalanced metabolic state, which may be interpreted as a wasting or weight gaining condition depending on the direction of inaccuracy. Recent guidelines by *Health Canada* show that approximately 2000 kcal/day is the estimated energy requirement for sedentary Canadian adults, which ranges from 1550 to 2500 kcal/day for sedentary adults[158]. The actual estimated energy requirement will depend on age, gender, weight, height, and physical activity level[159]. The 2000 kcal/day estimated requirement equates to 1.39 kcal/min, which we assumed to be a clinically meaningful threshold for our primary index methods.

Step-by-step calculation of required sample size: Limits of agreement (LOA) have confidence intervals (CI) that can be wide or narrow depending on the required precision. Precision of the LOA required will impact the sample size. For an index method and criterion method to be

deemed interchangeable, LOA including the CI should not exceed a predetermined clinically meaningful threshold. Therefore, if the LOA is closer to the mean difference (assumed to be zero) relative to the chosen threshold, it may have a lower precision (width of the 95% CI of LOA) and require a lower sample size. To determine the sample size necessary for the 95% LOA of the mean difference including the 95% CI of the LOA not to exceed our predetermined clinically meaningful threshold, we referred to the equation described by Bland and Altman[157]. To use this equation we assumed a standard deviation (SD) of differences for each index method measuring EE in units of kcal/min (SenseWear, ActiCal, and Flex HR method) based on the EE measurement validation literature in chronic lung disease populations. A previous study validating SenseWear multisensor against IC in COPD patients found a SD of difference of 0.3 kcal/min[133]. Unfortunately, there was no study which had validated the ActiCal method for measuring EE in lung disease patients. Since the SenseWear method and Actical methods are both accelerometry based approaches, we assumed the same SD of differences for both of these measurement methods. Another previous study validating the Flex HR method against DLW in CF patients found a SD of differences of 0.3 kcal/min[138]. Our calculations of the aforementioned SDs are described in Appendix B. In interpreting the results from this study, we made the *apriori* assumption that the measurements from DLW method and IC may be interchangeable as they are both accepted gold standards for measuring energy expenditure.

Using our assumed SD of differences (=0.3 kcal/min for both SenseWear, ActiCal, and Flex HR method) and clinically important threshold (=1.39 kcal/min), we calculated our required sample size as follows:

LOA = 0.3 *1.96 = 0.588 (equation 1)

95%CI of LOA = 1.96*Standard Error (SE) of difference (equation 2)

SE of difference = 1.96 * √(3/n) * SD of difference (equation 3)

Since the threshold is 1.39 and the LOA is 0.588, the LOA can have a 95%CI of ± 0.802 that will not exceed the threshold; this scenario required a sample size of at least 6 for minimal precision required to determine interchangeability of the index methods.

Chapter 3: Results

3.1 Study enrollment

Participants were recruited from September 2013 to July 2014. A total of 108 patients identified by clinic staff were screened for potential inclusion (60% COPD; 20% CF; 20% ILD). After more thorough screening and initial contact with potentially eligible participants, a total of 13 participants were enrolled in the study. Primary reasons for excluding potentially eligible participants included supplemental O2 use, currently smoking, non-compliant with medications, required mobility aids, cardiac contraindications, missing recent pulmonary function test, upper age limit exceeded, upper lung function criteria exceeded, agreed to participate in future. Due to various reasons, data from 5 participants were disqualified following enrolment (unable to return for Day Two within one month, n=2; unable to complete Day Two activity protocols, n=2; technical difficulty with IC, n=1). A total of 8 participants had complete datasets that qualified for analysis. Figure 11 describes the enrolment process and reasons for exclusion/disqualification at each stage of the study.

3.2 Participant characteristics

The characteristics of 8 participants with complete datasets are summarized in Table 3. The sample was equally distributed in sex (male to female ratio=50/50). CF participants composed a majority of the sample (n=5; 63%). The mean age of the participants was 42.1±17.1 years. On entry, participants ranged from moderate to severe obstruction as assessed by FEV_1% predicted (26 to 65% predicted) and severe to non-existent restriction as assessed by FVC% predicted (45 to 117% predicted). There was a wide range in both age and BMI, from 23 years to 65 years and 18 to 31 kg/m^2, respectively. Table 4 presents the exacerbation history and

comorbidity information obtained from most recent clinical chart data. Approximately 63% of the participants had a known history of exacerbations that required hospital stay. Half of the participants were pancreatic insufficient, all with CF. Bone disease and asthma were other common comorbidities (approximately in 38% of the participants for both conditions). Other less common comorbidities seen in the participants included distal intestinal obstructive syndrome (n=1), arthropathy (n=2), dermatitis (n=1), impaired glucose tolerance (n=1), MRSA infection (n=1), liver disease (n=2), IgA deficiency (n=1), kidney disease (n=1), iron deficiency anemia (n=1), Barrett's esophagus (n=1), hiatus hernia (n=1), and splenomegaly (n=1). Heterogeneity in physical fitness levels was evidenced by the wide range in peak CPET parameters including VO_2 (52.29 to 93.96% predicted), HR (70 to 104 % predicted), and workload (33 to 136 W) (Table 5). On average, perceived muscular leg fatigue (7.25±2.82 rating on Borg scale) was slightly higher than perceived dyspnea (6.63±2.56 rating on Borg scale) at peak exercise. Participants also had a tendency towards dynamic hyperinflation showing a reduced I_{cap} at peak exercise compared to rest (mean ΔI_{cap} = -0.32±0.54).

3.3 Trends in Bland-Altman agreement plots

We present our findings of the agreement between each primary index and IC methods in the proceeding sections. The bias estimates and limits of agreement are represented as the mean difference (EE measured by primary index method – EE measured by IC) ± LOA.

3.3.1 Bias estimates and limits of agreement during flat walking (Figure 12)

The Flex HR methods (FM), both submaximal exercise- (SUB) and CPET- (CPX) derived methods underestimated by 0.48±1.13 and 0.25±1.60 kcal/min respectively. ActiCal had the highest underestimation at 1.26±1.40 kcal/min. SenseWear (SW) overestimated by 0.36±2.72

kcal/min. Therefore, FMCPX provided the closest approximation of EE (lowest bias) during flat walking.

3.3.2 Bias estimates and limits of agreement during incline walking (Figure 13)

FMSUB and FMCPX underestimated by 0.37±1.29 and 0.17±1.79 kcal/min respectively; however, the magnitude of the bias was lower than it was during flat walking. The magnitude of the bias for AC and SW increased with the increased walking intensity resulting from increased grade, with an underestimation of 1.80±2.36 and overestimation of 0.56±2.24 kcal/min respectively. Therefore, FMCPX provided the closest approximation of EE during incline walking.

3.3.3 Bias estimates and limits of agreement during sit-to-stand activity (Figure 14)

AC and SW underestimated to a higher degree than FM methods at 1.05±1.67 and 0.38±1.54 kcal/min respectively. FMSUB underestimated by just 0.06±0.91 kcal/min and FMCPX overestimated by 0.29±1.41 kcal/min. Therefore, FMSUB provided the closest approximation of EE during sit-to-stand activity.

3.3.4 Bias estimates and limits of agreement during lift-bend activity (Figure 15)

The same trend was seen during lift-bend activity as in sit-stand where AC and SW underestimated to a higher degree than FM methods at 0.78±0.82 and 0.39±2.86 kcal/min respectively. FMSUB underestimated by just 0.01±0.90 kcal/min and FMCPX overestimated by 0.28±1.57 kcal/min. Therefore, FMSUB provided the closest approximation of EE during lift-bend activity.

3.3.5 Bias estimates and limits of agreement during cycling (Figure 16 to 19)

As cycling intensity increased from 10 to 60% peak workload the magnitude of underestimation by AC also increased from 1.01±1.26 kcal/min (10% peak workload) to 3.36±3.00 kcal/min (60% peak workload). SW underestimated to a lower degree than AC at a given cycling intensity, ranging from 0.86±1.30 kcal/min (10% peak workload) to 1.26±3.45 kcal/min (60% peak workload). The Flex HR methods both provided closer approximations of EE than AC and SW. Both FMSUB and FMCPX underestimated during 10% peak workload, by 0.11±1.46 and 0.03±1.49 kcal/min respectively. Both FMSUB and FMCPX overestimated during higher intensity cycling (25 to 60% peak workload), with FMSUB providing closer approximations of EE than FMCPX (0.21±1.08 to 0.42±0.74 kcal/min by FMSUB; 0.36±1.09 to 0.59±1.46 kcal/min by FMCPX).

3.3.6 Interchangeability between primary index and IC methods

For the primary index method to be deemed interchangeable at a clinically acceptable level, the limit of agreement combined with its 95% CI (LOA + 95%CI) must be within the meaningful threshold fixed *a priori*. We considered that a reasonable threshold could be within 1.39 kcal/min of an assumed mean difference of zero between the primary index method and IC. Table 6 presents the limits of agreement and associated precision (95% CI) between each primary index method and IC during free-living activities and cycling stages. During free-living activities, the most interchangeable index method (lowest sum of LOA + 95%CI) was FMSUB during flat walk, incline walk, sit-to-stand, and lift-bend activities with interchangeability factors of 2.48, 2.83, 2.01, and 1.99 respectively. During cycling, AC was the most interchangeable during cycling at 10% peak with an interchangeability factor of 2.77; however, FMSUB was

most interchangeable during increasing cycling intensities with interchangeability factors of 2.38, 1.61, and 1.62 during cycling at 25%, 50%, and 60% peak respectively. Since none of the limits (including 95% CI) were within the clinically meaningful threshold of 1.39kcal/min, none of the primary index methods were sufficiently interchangeable at a clinically acceptable level; however, due to the small sample size, these results must be interpreted with caution. Indeed, a larger sample size is required for better precision of the limits as our assumed SD of 0.3 prior to the start of this study may have been too small. Our study found SD of differences higher than our *a prior* assumption, ranging from 0.46 to 0.92 for the Flex methods, 0.79 to 1.76 for SW, and 0.63 to 1.53 for AC. As a result, the aforementioned interchangeability assessment is intended to show the trend rather than actual level of interchangeability, which will require a larger sample size for better precision around the limits.

3.4 Nonparametric significance testing

Table 7 presents the EE measurements (expressed as median and inter-quartile range) by each primary index method and IC averaged over free-living activities, cycling (all stages), and overall (free-living and cycling). We observed significant differences between EE measured by AC and by IC during free-living activities, cycling, and overall as well as between EE measured by FMCPX and by IC during cycling only ($p<0.05$). The EE measurements from SW and FMSUB were not found to be different from IC. For the secondary index methods (Dynaport, Tractivity, and Digiwalker), the Dynaport estimation of accumulated EE (median = 82.5 kcals) was not significantly different from the accumulated EE measured by IC (median =85.8 kcals) over the entire protocol ($p>0.05$). Whereas accumulated EE was significantly overestimated by Tractivity (median = 144 kcals) and significantly underestimated by DigiWalker (median = 12.7 kcals) ($p<0.05$).

3.5 Graphical representations of validity

X-Y scatter plots with line of identity: To visually observe whether or not there may be a fixed bias, we compared the index methods (ordinates) to the criterion method (abscissa) for the primary index methods (Figure 20, 21, and 22) and secondary index methods (Figure 23). The line of identity was shown on each plot, representing the ideal scenario where both methods give the same EE measurements. According to Figure 20, we noticed FMSUB to most closely approximate EE and suspected a negative bias to exist by nature for AC during free-living activities. From Figure 21, we noticed FMSUB and FMCPX to most closely approximate EE and suspected a negative bias to exist by nature for AC during cycling activities. Overall, the correlations between the EE measured by SW, AC, and FMSUB and by IC were very high (r= 0.90, 0.79, 0.90 respectively; $p<0.05$) (Figure 22). The mean correlation between FMCPX EE and IC EE only reached significance during cycling (r=0.90; p,0.05). According to Figure 23, we suspected a positive bias to exist by nature for Tractivity monitor, and negative bias to exist by nature for both the Dynaport monitor and to a greater magnitude for the DigiWalker pedometer during the entire protocol. The Dynaport most closely approximated EE over the entire protocol. The mean correlations between the secondary index methods and IC were low and non significant.

Chapter 4: Discussion

4.1 Key findings

This cross-sectional study investigated the validity of three primary index methods and three secondary index methods commonly used to estimate energy expenditure (EE) by comparing their outputs with simultaneous gold standard EE measurements from indirect calorimetry (IC) in a population of advanced lung disease groups. We found that the Flex HR methods (FM) provided a closer approximation of measured EE (lower bias magnitude) than the multisensor and accelerometry methods over the entire free-living and cycling activities. During walking of increasing intensity (flat to incline), the bias was reduced for the Flex HR methods, but increased for the SenseWear and Actical. During cycling of increasing intensity (10% peak workload to 60% peak workload), the bias was increased for all devices; however, the magnitude of bias was lower for the Flex HR methods.

Few studies have validated several physical activity monitors head-to-head with gold standard EE in chronic lung disease populations[160, 161]. No previous studies have included an individually calibrated approach, such as the Flex HR method, in these head-to-head comparisons. Only one other study validated the Flex HR method by itself in a chronic lung disease population[138] In CF patients with moderately severe lung function (FEV_1 %predicted mean±SD = 52±12%), the mean % difference ± SD between Flex HR estimation of EE and DLW gold standard EE measurements was 8.8± 7.9% (Flex method underestimated)[138]. Our findings were in agreement with the aforementioned study, showing a trend towards underestimation of EE compared to the gold standard measurement of EE from IC. Additionally, validation studies of physical activity monitoring devices specifically in advanced lung disease

populations are scarce. To our knowledge, only one other study has validated a commercially available physical activity monitor for estimating EE against an accepted gold standard method specifically in an advanced lung disease population[135].

Another interesting finding of our study was that the accuracy of the Actical declined with increasing intensities of activities (walking from flat to incline; cycling from lower to higher workloads). Overall, the Actical significantly underestimated EE. As a result, motion counts alone were insufficient in being able to accurately estimate the elevated metabolism in participants due to increased activity intensity. The additional physiological sensory input incorporated into the EE estimation algorithms of the SenseWear allowed this instrument to capture the additional EE required during increasing intensities resulting in a lower bias during a given activity or intensity relative to the Actical; however, it still had a higher bias relative to the Flex HR methods. As a result, the individually calibrated nature of the models used to estimate EE in the Flex HR methods may provide a more accurate representation of true EE in advanced lung disease groups. A physical activity monitoring technique known as the ActiReg^{TM} that uses individually measured resting EE, and incorporates body positioning as well as motion (with an option to use additional HR measurement) has been validated by Arvidsson and colleagues in severe COPD patients (FEV_1% predicted between 20 and 49%)[135]. The ActiReg^{TM} estimation of EE and DLW gold standard EE measurements were not found to be significantly different[135]. As a result, EE estimation based on an individually calibrated approach to physical activity measurement may be superior to devices using manufacturer-developed algorithms relying mainly of body motion and subject demographic input. Additionally, out of the secondary index methods evaluated in this study, the Dynaport monitor which was not significantly different from accumulated EE measured by IC, was shown to be more valid than the Tractivity (significantly

overestimated EE) and Digiwalker (significantly underestimated EE). In agreement with our findings, the Digiwalker has been previously shown to significantly underestimate EE compared to EE measured by IC[136]. In accordance with our findings, Dynaport monitor has been shown to be valid for estimating EE as evidenced by mean correlation coefficient of 0.45 ($p<0.05$) during a standard 59 minute activity protocol reported by Van Remoortel and colleagues[160]. The Tractivity has not been previously validated for estimating EE in chronic lung disease.

4.2 Clinical implications

Although previous validation studies of EE estimation in chronic lung disease have employed Bland-Altman plots to evaluate validity[132, 133, 135, 137, 162, 163], none of these studies defined a threshold for how far apart the EE estimation can be from measured EE without causing difficulties in clinical interpretation. The interchangeability factor, or appropriateness of replacing the gold standard with index method depends on how much the method is likely to differ from the gold standard. According to Bland and Altman, this difference is calculated as the width of the combined LOA and 95% CI for the LOA[157]. If the width of the LOA and 95%CI is within an acceptable threshold determined a priori, the index method may replace the gold standard.

Wasting diseases are conditions that results in an imbalance in the metabolic energy expenditure/intake dynamics in humans. The main reason for this imbalance may be hypermetabolism resulting from an elevated REE[164]. Evidence suggests that COPD, ILD, and CF patients are in this hypermetabolic state[125, 165, 166], hence may be prone to having a mismatch between their energy expenditure and intake leading a catabolic or wasting state. Knowledge of the true EE of the patient at home would be important for clinicians to help optimize this

metabolic balance by appropriately titrating exercise prescriptions in addition to monitoring their physical activity level outside of the rehabilitation setting. Although there are no standard cutoffs for determining whether or not a physical activity monitor may be considered to have acceptable validity for estimating EE at home, previous investigators have set *a priori* thresholds of greater than 0.7 correlation with gold standard measurements as constituting acceptable validity[161]. Based on this correlation threshold, we found that all primary index methods were valid over the entire protocol, except for FMCPX which was only valid during cycling activities. According to Bland and Altman, correlation alone is not sufficient to determine device validity[157]. Acceptable correlations may actually conceal poor agreement. Index methods require a certain level of agreement before they can be deemed interchangeable with the gold standard method for routine clinical practice. Based on our a prior selected threshold for determining interchangeability, FMSUB was the most interchangeable, having the lowest LOA+95%CI interval width; however, since it was higher than our chosen clinically meaningful threshold of 1.39 kcal/min, it may not be interchangeable with IC at a clinically acceptable level. Evidence suggests that patients with chronic lung disease may require a higher dietary intake to maintain body mass relative to standard norms[167, 168]. As a result, our arbitrarily selected threshold based on available standard dietary intake data from the general population[158] may be too low for advanced chronic lung disease populations. Therefore, consensus on an acceptable clinically important threshold of difference for EE estimation is still needed. Although further study is required to determine clinical acceptance, our findings show that the Flex method has great potential as a useful physical activity measurement technique. The development of the individual Flex HR calibration equations for each patient may be constructed during a clinically routine CPET or submaximal exercise test in patients unable to perform a maximal exercise test and have comparable EE

estimation validity as implicated by our findings. Due to time commitments and portable metabolic instrumentation required to calibrate submaximal Flex HR profiles, it may be more feasible for some clinical programs to calibrate Flex HR profiles during routine clinical CPET.

4.3 Study limitations and future research

One of the major limitations of this study is our sample size. Our proposed sample size calculation was based on assumed SD of mean differences and arbitrary cutoffs for acceptable interchangeability based on the literature. The results of our study show that a slightly higher SD than the assumed SD would have been more appropriate. Future studies may use our calculated SDs of the differences as pilot data to determine the appropriate sample size required to ensure adequate precisions around the LOAs of the index method estimations of EE relative to IC EE. Additionally, future research may focus on determining an appropriate daily caloric intake requirement for advanced lung disease groups rather than relying on an arbitrarily chosen value based on healthy norms. If a higher threshold is shown to be more applicable for our patient population, more of the index methods evaluated in this study could possibly deemed to have acceptable interchangeability at a clinically meaningful level.

Although the primary index methods were synchronously time-stamped to the best of our ability, it is unrealistic to be able to mark the start and stop of each activity at exactly the same time on each device. The marking of the HR data was more in sync with the marking of the IC measurements than the SenseWear and Actical markings as the Polar monitor signals were incorporated into the Cosmed K4b2 software to allow for HR data to be assigned to each breath of the participant. As a result, this may have introduced potential bias towards the HR input for the Flex methods being more accurate and precise than the SenseWear and Actical estimates of

EE. A future study validating a third party HR monitor with data storage capability which is not linked to the breath-by-breath acquisition software of the IC may be required to confirm our findings.

When measuring energy expenditure (EE), determination of whether the subject has reached a physiological 'steady state' is important. Steady state is the stage during physical activity when oxygen consumption matches oxygen requirement. If steady state is not attained, the measured energy expenditure will be less than the actual energy expenditure in the body. Since the approximate time required to reach this steady in patients with severe lung disease is unknown, we assumed a 1 minute equilibration period to allow ventilations to stabilize before all measurements of gas exchange during the standardized activities and exercise (including calibration during CPET). This *a prior* selected length of time for reaching a steady or stable ventilatory state has been used by previous investigators[16]. More research needs to be conducted to determine appropriate conditions and approximate time to reach physiological steady state in advanced lung disease conditions.

Due to issues of practicality, we were also limited in the number of activity monitors we were able to simultaneously compare in this study. For each type of activity monitoring device (ie pedometry, accelerometry, multisensor technology, and HR monitoring), a variety of device manufacturers are available. The objective of our study was to evaluate the validity of the most commonly used methods to estimate EE. Based on the results of a systematic review of the literature, we chose to validate these particular activity monitor manufactures as they have been used extensively in chronic lung disease patients. We excluded surveys and questionnaires for assessing EE as these methods were deemed too subjective to include in our study.

Finally, in order to evaluate the true "accuracy" of a measurement tool, all clinimetric properties of the tool (ie reliability, responsiveness, and validity) should be evaluated. However, due to the burden that would have been placed on these severely debilitated advanced lung disease patients from measuring all these components of accuracy, we chose not to investigate the reliability or responsiveness. Future studies may look to elucidate these understudied, yet important requirements for measurement accuracy.

4.4 Conclusion

Physical inactivity is common in lung transplant candidates and can worsen their prognosis. As a result, physical activity is a key outcome for pulmonary rehabilitation programs in advanced chronic lung disease. Future interventions aimed at modifying behaviour and exercise training to improve physical activity may use Flex HR methods to accurately evaluate responses in energy expenditure. For pulmonary rehabilitation programs with access to indirect calorimetry instrumentation or routine cardiopulmonary exercise testing, FMSUB or FMCPX may be more feasible physical activity monitoring techniques to employ compared to the costly SenseWear and Actical devices.

Tables

Table 1. Participant Selection Criteria.

Inclusion Criteria	**Exclusion Criteria**
Adult patients (between 35 and 65 years) with a primary diagnosis of COPD or ILD	Require mobility aids to ambulate
Adult patients (19 years and older) with a primary diagnosis of CF	Qualified for supplemental oxygen during exercise
Ability to speak English or availability of English-speaking translator	Referred for Heart+Lung (combined) transplant assessment
Clinically stable at time of recruitment and maintained clinical stability during testing	Poor adherence to medication, uncontrolled diabetes, profound emaciation (BMI(16), or indices of pulmonary hypertension
Previous clinical diagnosis of advanced pulmonary impairment: • For COPD: FEV_1/FVC ratio < 0.7 and FEV_1 % predicted < 50 • For ILD: FVC % predicted < 60 or DLCO % predicted < 40 • For CF: FEV_1 % predicted < 50	For CF only: Colonized with Burkholderia cepacia *complex* (BCC), *Myobacterium abscessus*, and/or *Burkholderia dolosa* (non BCC) and closely related organisms (*Apista, Ralstonia*)
Medically cleared for exercise by study physician	Significant right or left heart disease contraindicated for exercise testing

Table 2. Features of the Physical Activity Monitors Including Type, Location of Attachment, Units of Energy Expenditure Estimation, and Cost.

Activity Monitor Features				
Name (Manufacturer)	**Type**	**Location**	**EE Units**	**Approx. Cost (Cdn)**
Digi-Walker CW 701™ pedometer (Yamax; Tokyo, Japan)	Pedometry	Waist (Right)	kcal	$51.99 (no additional software costs)
ActiCal™ triaxial accelerometer (Philips; Eindhoven, Netherlands)	Triaxial Accelerometry	Wrist (Right)	Kcal/min/kg	$968.30 (Incl. Software)
DynaPort MiniMod™ triaxial accelerometer (McRoberts BV; The Hague, Netherlands)	Triaxial Accelerometry	Waist (Lower Back)	kcal	$2142.30 (+Software and yearly subscription)
Tractivity Sensor™ (Kineteks Corporation; Vancouver, BC, Canada)	Triaxial Accelerometry	Ankle (Right)	kcal	$39.95
Polar™ heart rate monitor belt (Polar Electro; Kempele, Finland)	Flex Heart Rate	Chest	kcal/min	$50 for HR belt (+ data storage device approx. $100 to $150
SenseWear Armband™ multisensor (BodyMedia; Pittsburgh, PA, USA)	Multisensor Technology (in combination with accelerometry)	Upper Left Arm (Triceps)	kJ/min	$700 (+ Software)

Table 3. Participant Characteristics for All Participants.

Participant Characteristics n total=8; %female=50; COPD (n=2), ILD (n=1), and CF (n=5)				
Variable	**Mean**	**SD**	**Minimum**	**Maximum**
Age (years)	42.10	17.10	23.00	65.00
Height (cm)	164.6	6.20	157.0	174.50
BMI (kg/m^2)	23.40	4.10	18.20	30.80
FVC (L)	2.68	0.90	1.79	4.13
FVC % predicted	67.38	22.39	45.00	117.00
FEV_1 (L)	1.28	0.32	0.83	1.61
FEV_1 % predicted	41.25	14.02	26.00	65.00
FEV_1/FVC %	49.89	12.09	37.77	76.65

SD = standard deviation; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second

Table 4. Exacerbation History and Comorbidities.

Comorbidities		
Diagnosis	**N**	**%**
Participants with known recent exacerbation history	5	62.50
Diabetes	2	25.00
Pancreatic Insufficiency	4	50.00
Bone Disease	3	37.50
Asthma	3	37.50
Gastro Esophageal Reflux Disease	2	25.00
Mental Illness	1	12.50
Chronic Sinusitis	3	37.50

Table 5. Cardiopulmonary Exercise Test Performance.

Cardiopulmonary Exercise Test Performance				
Variable	**Mean**	**SD**	**Minimum**	**Maximum**
VO_2 peak (L/min)	1.43	0.50	0.87	2.40
VO_2 peak (mL/kg/min)	23.15	8.20	13.40	36.50
VO_2 peak % predicted	76.47	18.01	52.29	93.96
Workload peak (watts)	71.63	34.02	33.00	136.00
Inspiratory Capacity (L) at Rest	2.03	0.82	1.12	3.23
Inspiratory Capacity (L) at Peak	1.71	0.46	1.06	2.39
Δ Inspiratory Capacity (L)	-0.32	0.54	-1.39	0.34
HR peak (Beats/min)	145.50	22.54	109.00	181.00
HR peak % predicted	84.63	10.91	70.23	103.64
Borg Dyspnea score at peak	6.63	2.56	2.00	10.00
Borg Leg Fatigue score at peak	7.25	2.82	2.00	10.00

VO_2 = oxygen consumption; HR = heart rate; Δ = change between peak and rest (peak-rest)

Table 6. Assessment of Interchangeability for Primary Index Methods using Limits of Agreement with Precision Estimates.

Activity	Device	Bias	LOA	SD	95%CI of LOA	Interchangeability
Flat Walking	FMSUB	-0.48	1.13	0.58	1.35	2.48
	FMCPX	-0.25	1.59	0.81	1.91	3.51
	SW	0.36	2.72	1.39	3.26	5.98
	AC	-1.26	1.40	0.72	1.69	3.09
Incline Walking	FMSUB	-0.37	1.29	0.66	1.54	2.83
	FMCPX	-0.17	1.79	0.92	2.15	3.95
	SW	0.56	2.24	1.14	2.68	4.92
	AC	-1.80	2.36	1.20	2.83	5.19
Sit-to-Stand	FMSUB	-0.06	0.91	0.47	1.10	2.01
	FMCPX	0.29	1.41	0.72	1.70	3.11
	SW	-0.38	1.54	0.79	1.85	3.40
	AC	-1.05	1.67	0.85	2.00	3.67
Lift-Bend	FMSUB	-0.01	0.90	0.46	1.08	1.99
	FMCPX	0.28	1.57	0.80	1.88	3.45
	SW	-0.39	2.86	1.46	3.43	6.29
	AC	-0.78	1.26	0.64	1.51	2.77

Activity	Device	Bias	LOA	SD	95%CI of LOA	Interchangeability
Cycling at 10% peak work rate	FMSUB	-0.11	1.46	0.74	1.75	3.21
	FMCPX	-0.03	1.49	0.76	1.79	3.29
	SW	-0.86	1.30	0.66	1.56	2.86
	AC	-1.01	1.26	0.64	1.51	2.77
Cycling at 25% peak work rate	FMSUB	0.21	1.08	0.55	1.30	2.38
	FMCPX	0.36	1.09	0.56	1.31	2.40
	SW	-0.70	2.05	1.04	2.46	4.50
	AC	-1.59	1.24	0.63	1.49	2.73
Cycling at 50% peak work rate	FMSUB	0.39	0.73	0.37	0.88	1.61
	FMCPX	0.67	1.40	0.71	1.68	3.08
	SW	-0.69	3.32	1.70	3.99	7.31
	AC	-2.51	2.03	1.03	2.42	4.45
Cycling at 60% peak work rate	FMSUB	0.42	0.74	0.38	0.89	1.62
	FMCPX	0.59	1.46	0.74	1.75	3.20
	SW	-1.26	3.45	1.76	4.14	7.58
	AC	-3.36	3.00	1.53	3.60	6.60

SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; Interchangeability is the sum of the limit of agreement (LOA) and the 95% confidence interval (CI) of LOA associated with the mean difference (bias) between index method and indirect calorimetry. Lower interchangeability value suggests the device is more interchangeable.

Table 7. Comparison of Average Energy Expenditure (kcal/min) Measured by Each Index Method During Free-Living Activities, Cycling, and the Entire Protocol.

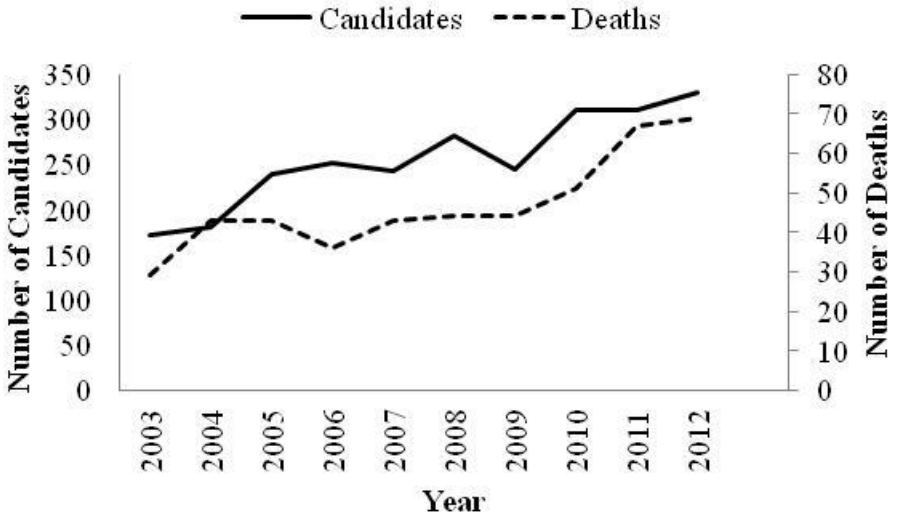
	IC	**SW**	**AC**	**FMSUB**	**FMCPX**
Free-Living	3.43 [0.85]	3.76 [2.33]	*2.24 [1.07]	3.61 [0.96]	3.52 [1.03]
Cycling (All Stages)	3.35 [1.33]	2.51 [3.27]	*1.30 [0.41]	3.63 [1.56]	*3.69 [1.33]
Averaged Overall	3.43 [1.04]	2.82 [2.21]	*1.83 [0.69]	3.62 [1.36]	3.61 [0.94]

All values are expressed as median [inter-quartile range] as data were not normally distributed

*Significantly different vs IC at $p<0.05$ level of acceptance according to Wilcoxon Signed Rank Test

Figures

Figure 1. Lung Transplantation Waiting List Trends in Canada.



Adapted from the Canadian Organ Replacement Register at the Canadian Institute for Health Information[3].

Figure 2. Theoretical Model of Physical Fitness and Mortality Risk.

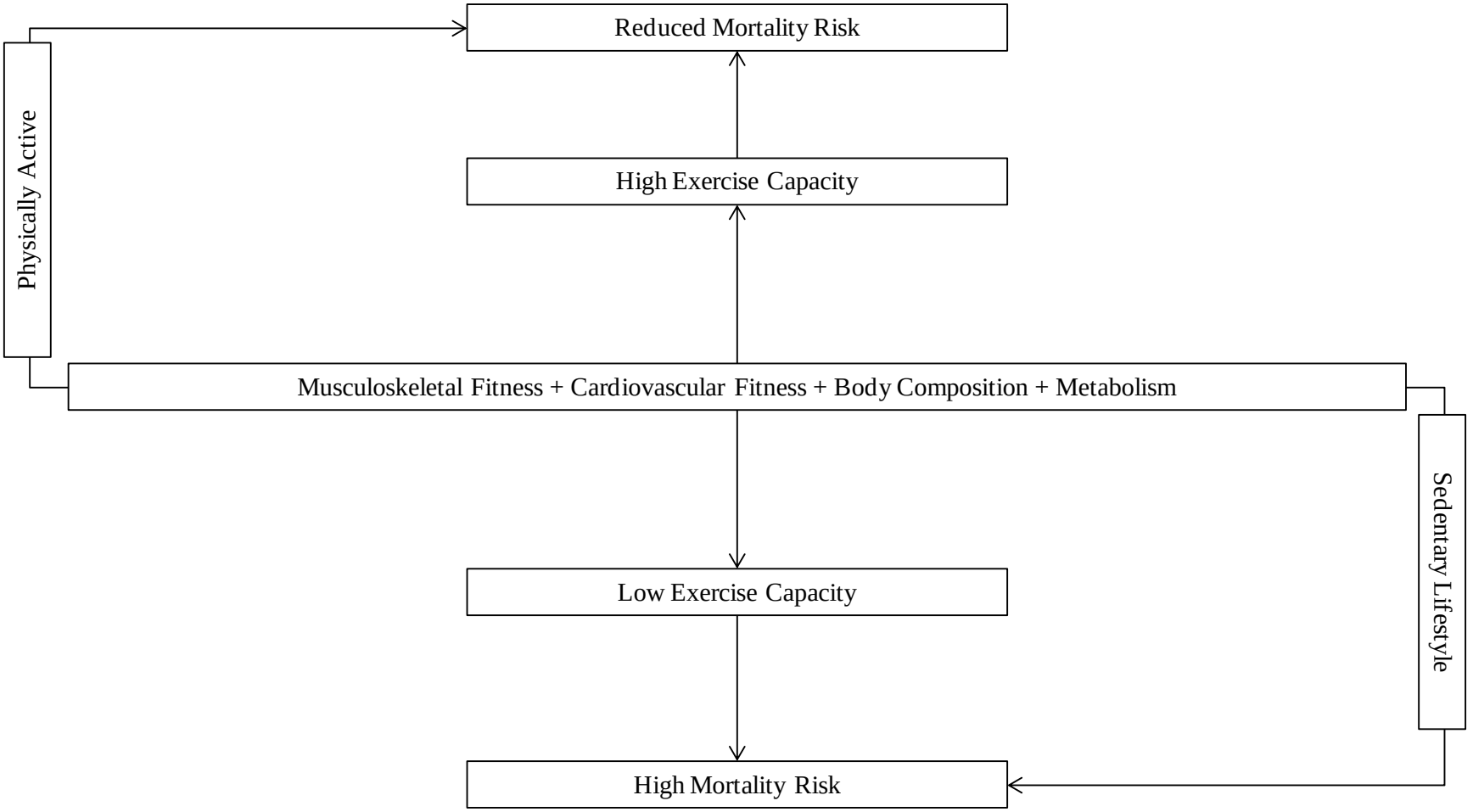


Figure 3. Conceptual Framework of Physical Activity Measurement.

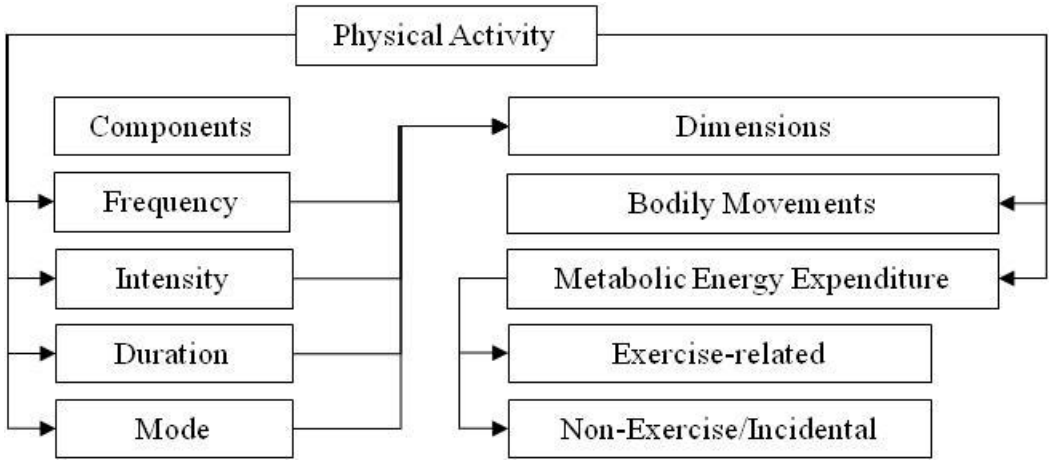


Figure 4. Conceptual Framework of Indirect Calorimetry.

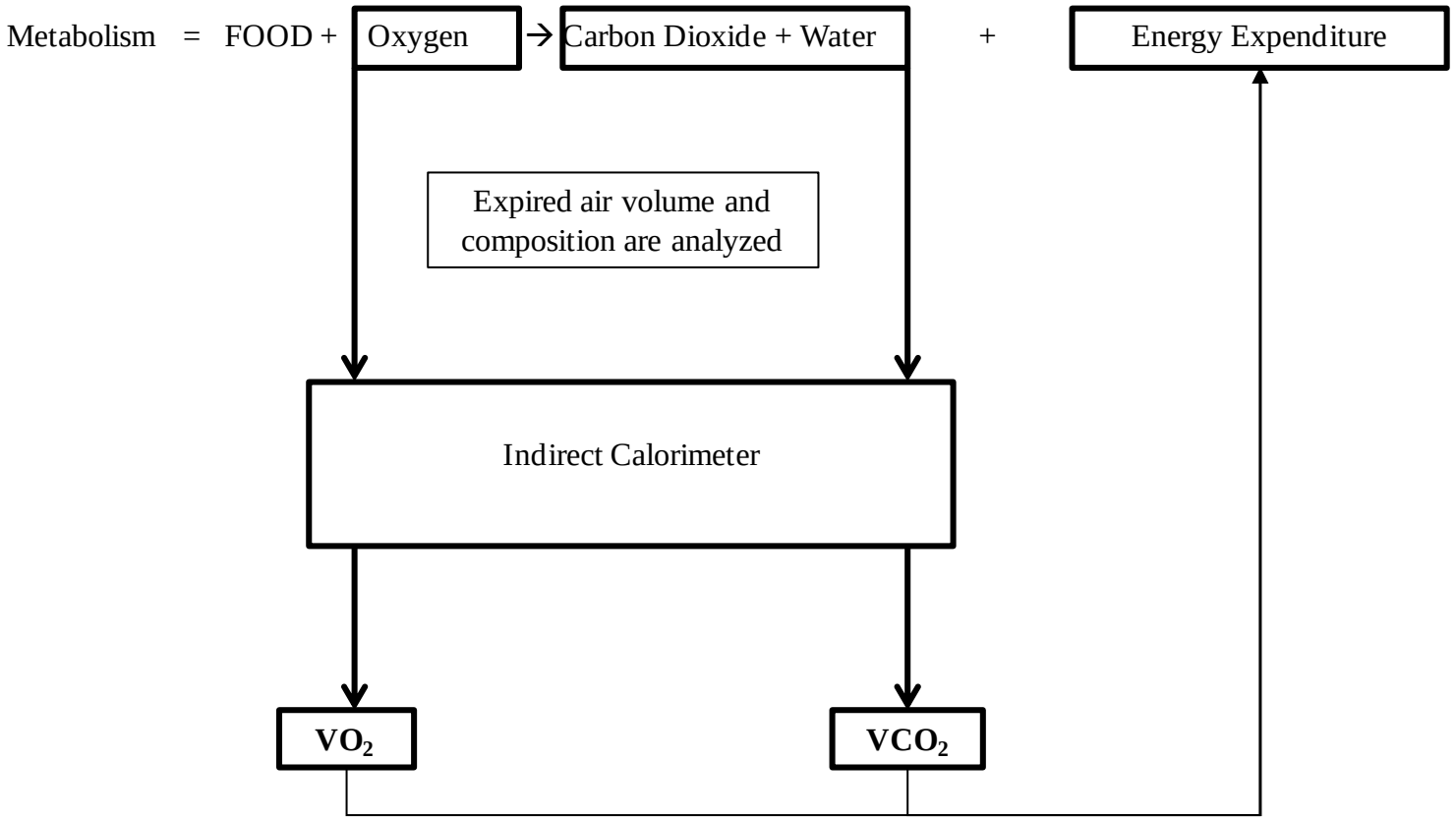


Figure 5. Conceptual Framework of Doubly Labeled Water Technique.

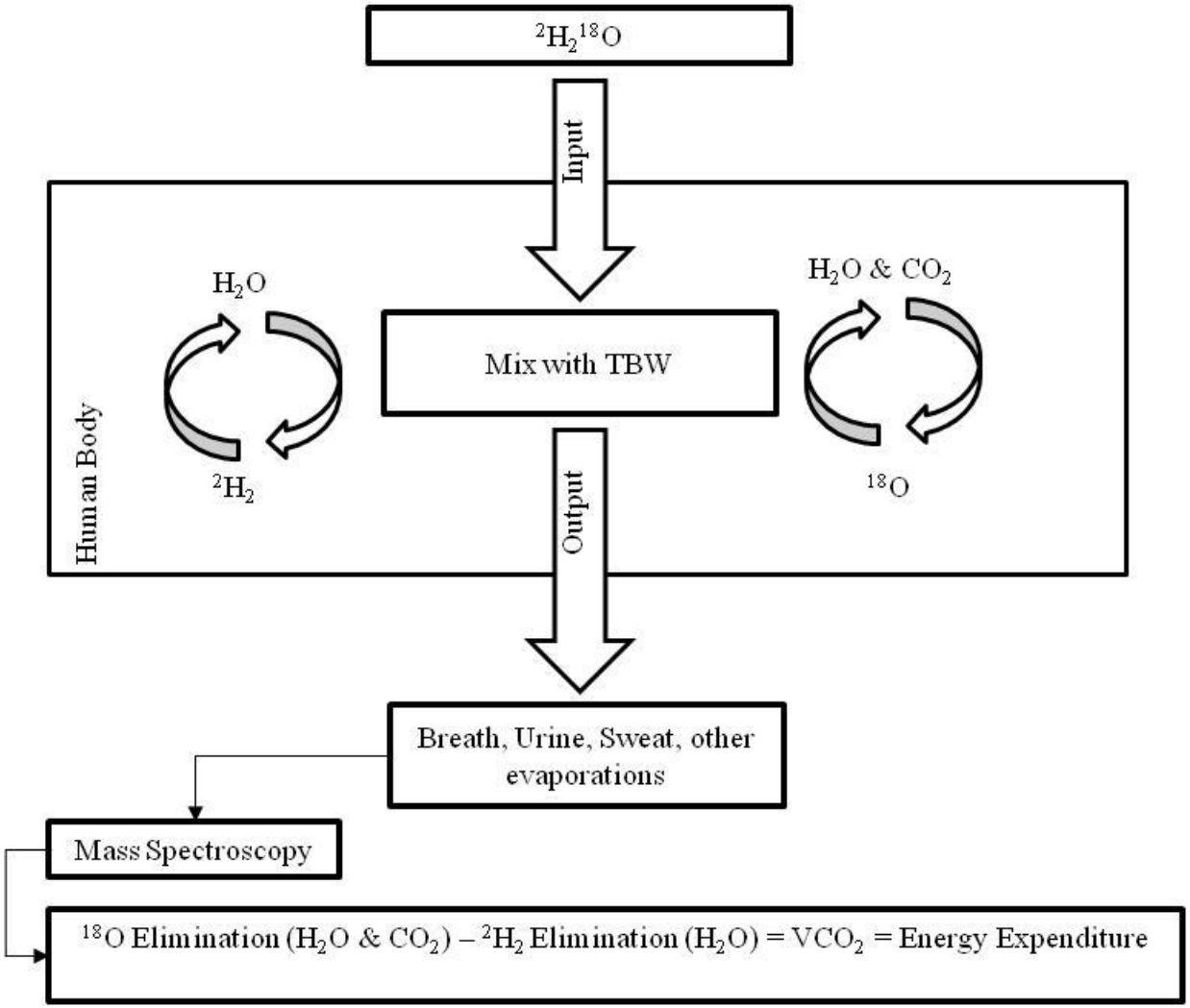


Figure 6. Step-By-Step Flow Diagram of Study Procedures.

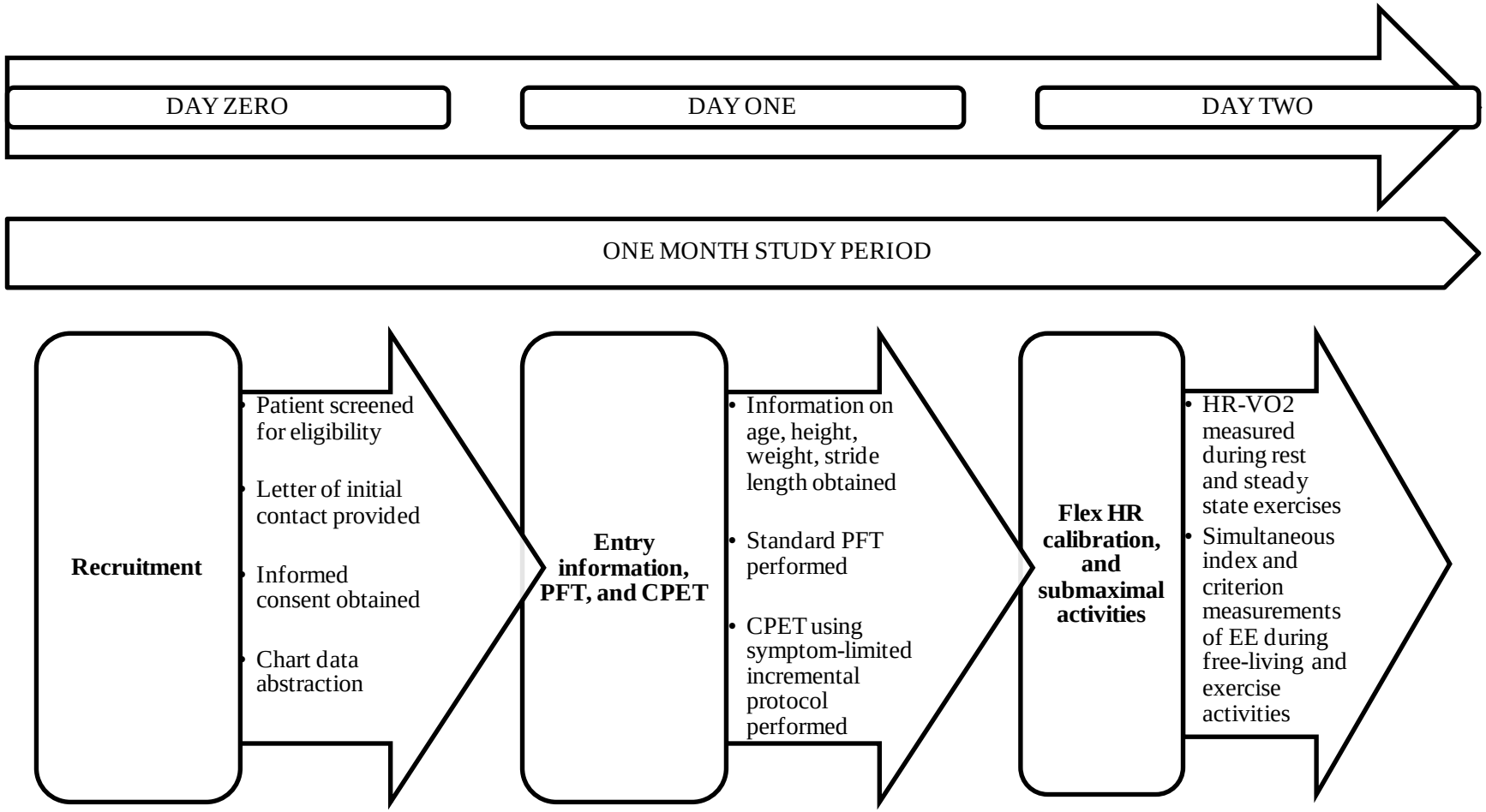


Figure 7. Flex Heart Rate Calibration Protocol.

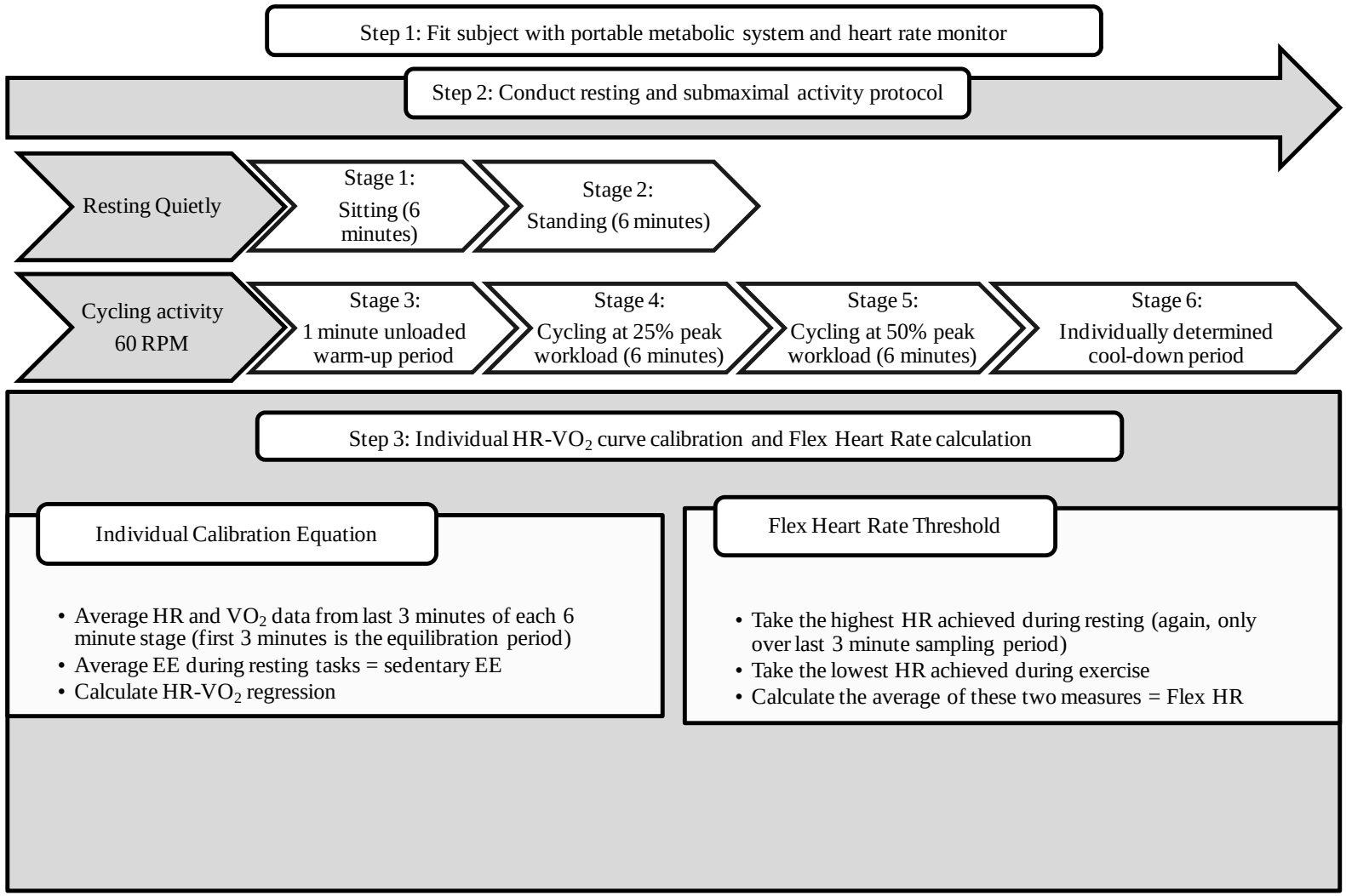


Figure 8. Location of Attachment of the Activity Monitors and Indirect Calorimeter.

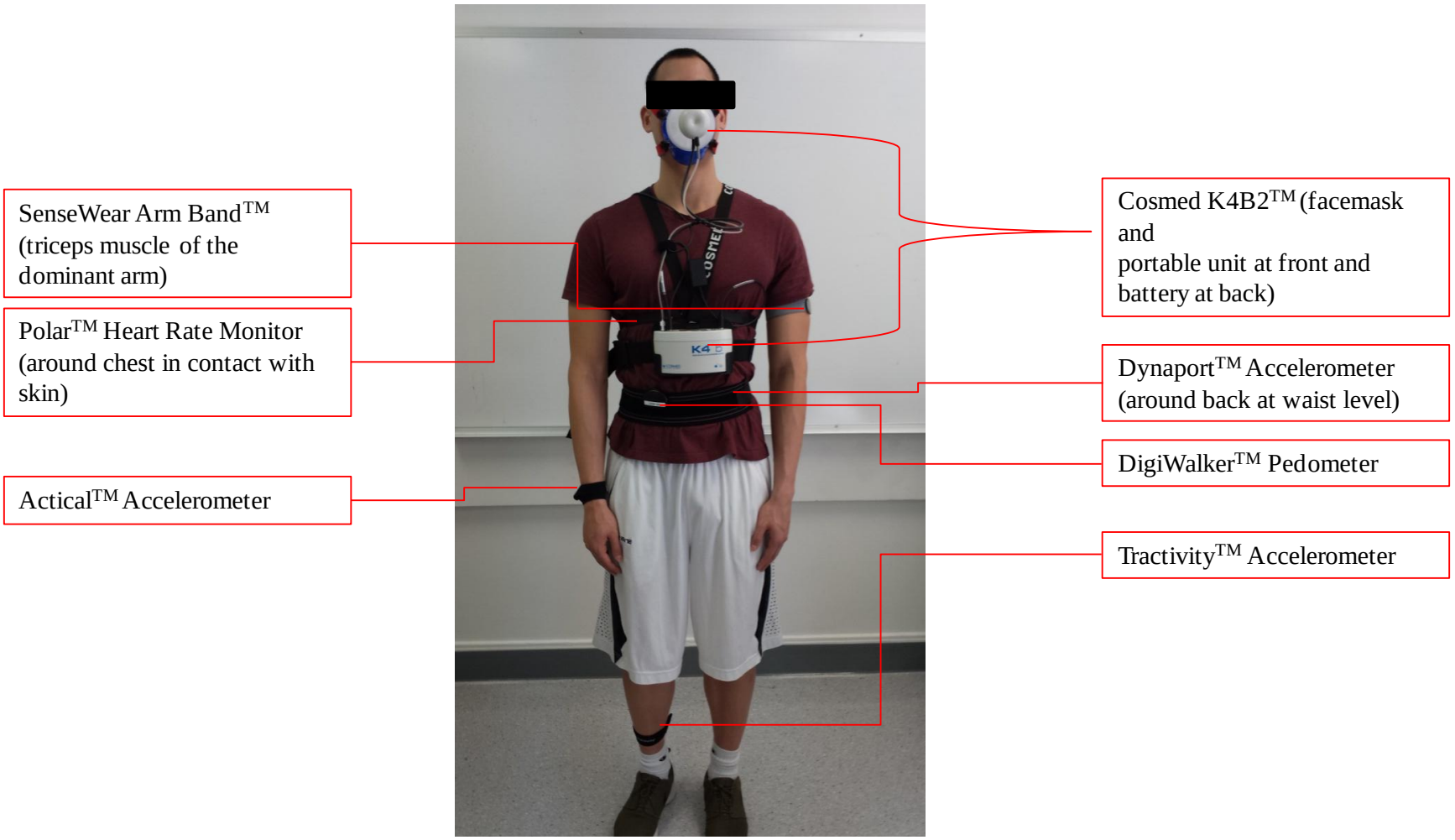


Figure 9. Low Intensity Free-Living Activities Protocol.

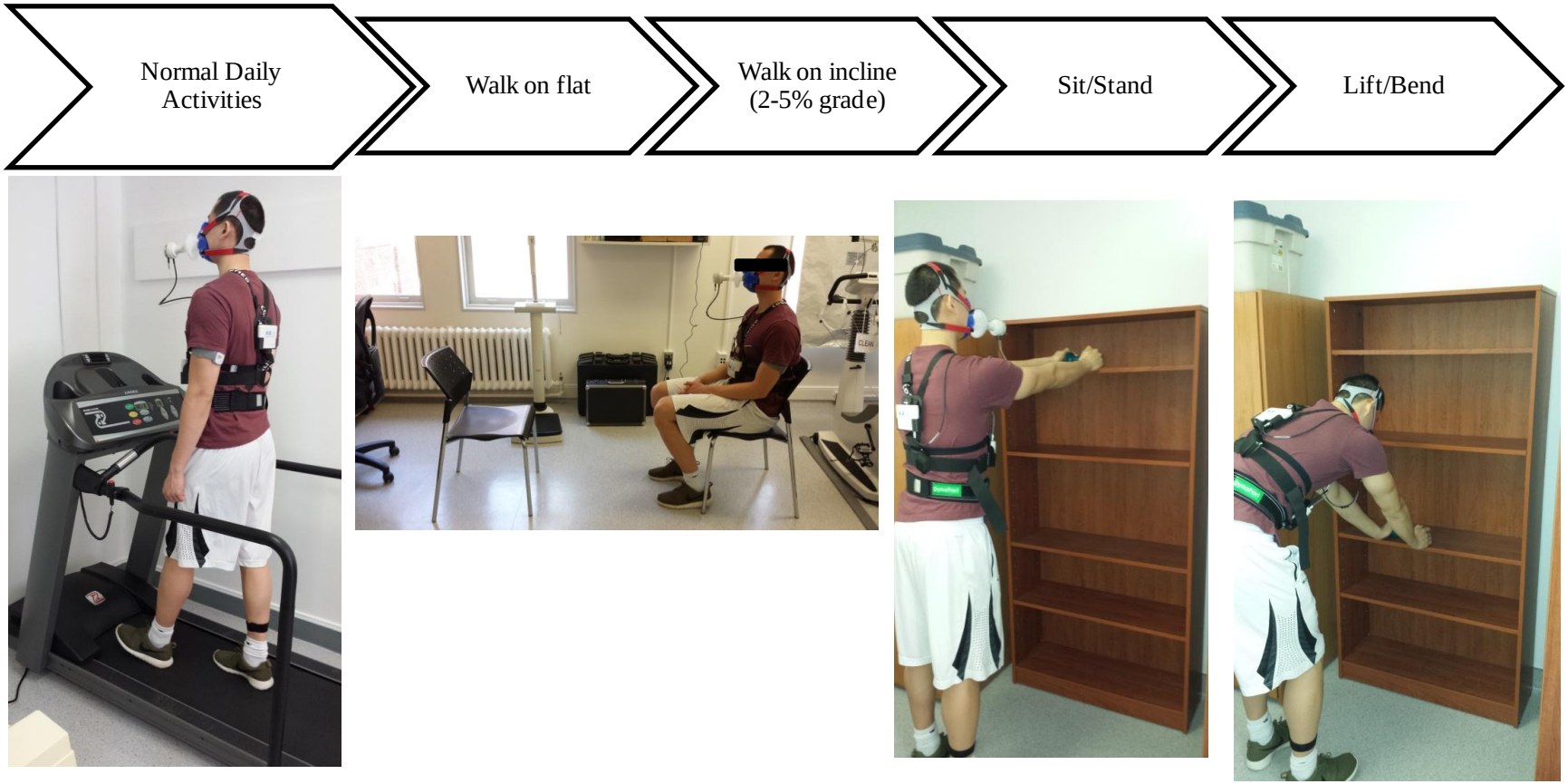


Figure 10. Submaximal Steady-State Cycling Protocol

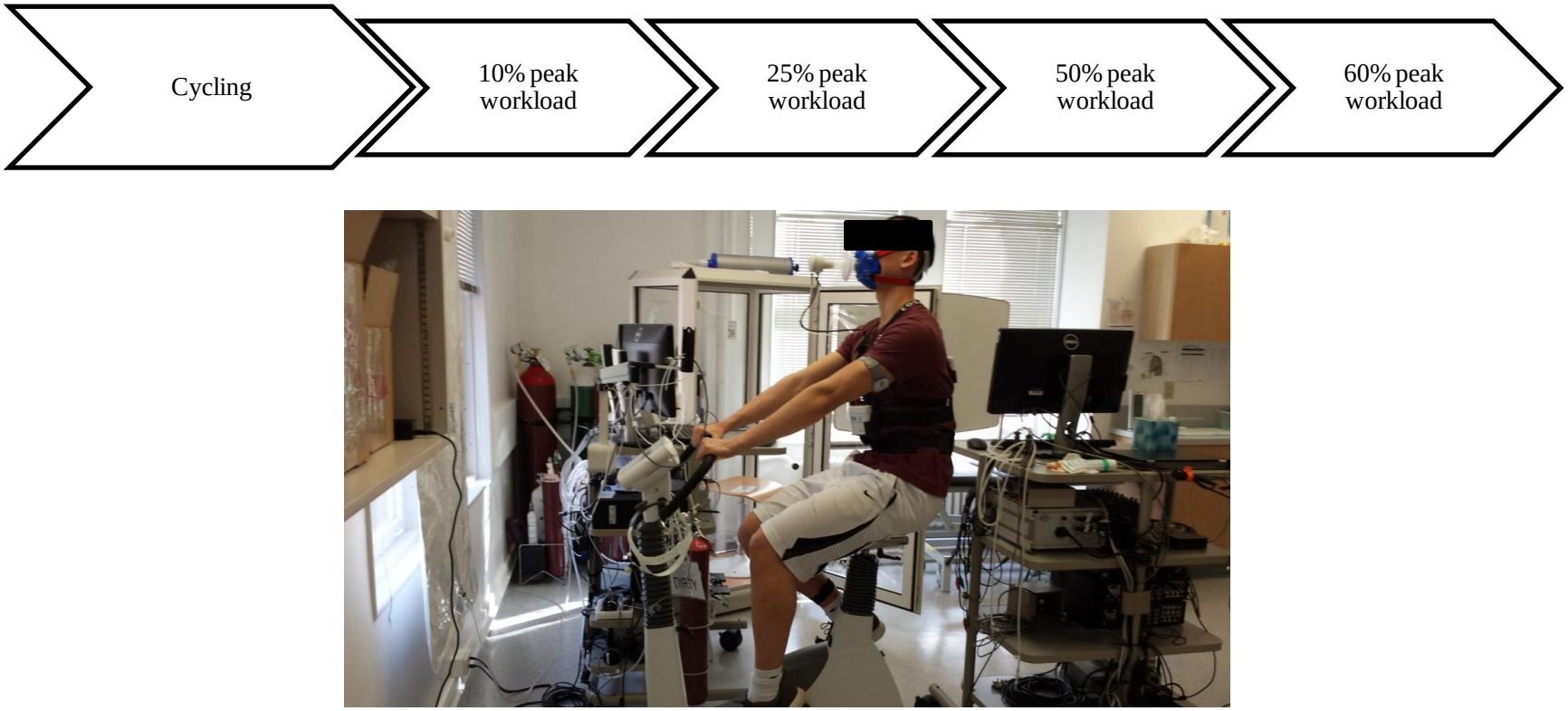


Figure 11. Participant Enrollment Flow Diagram

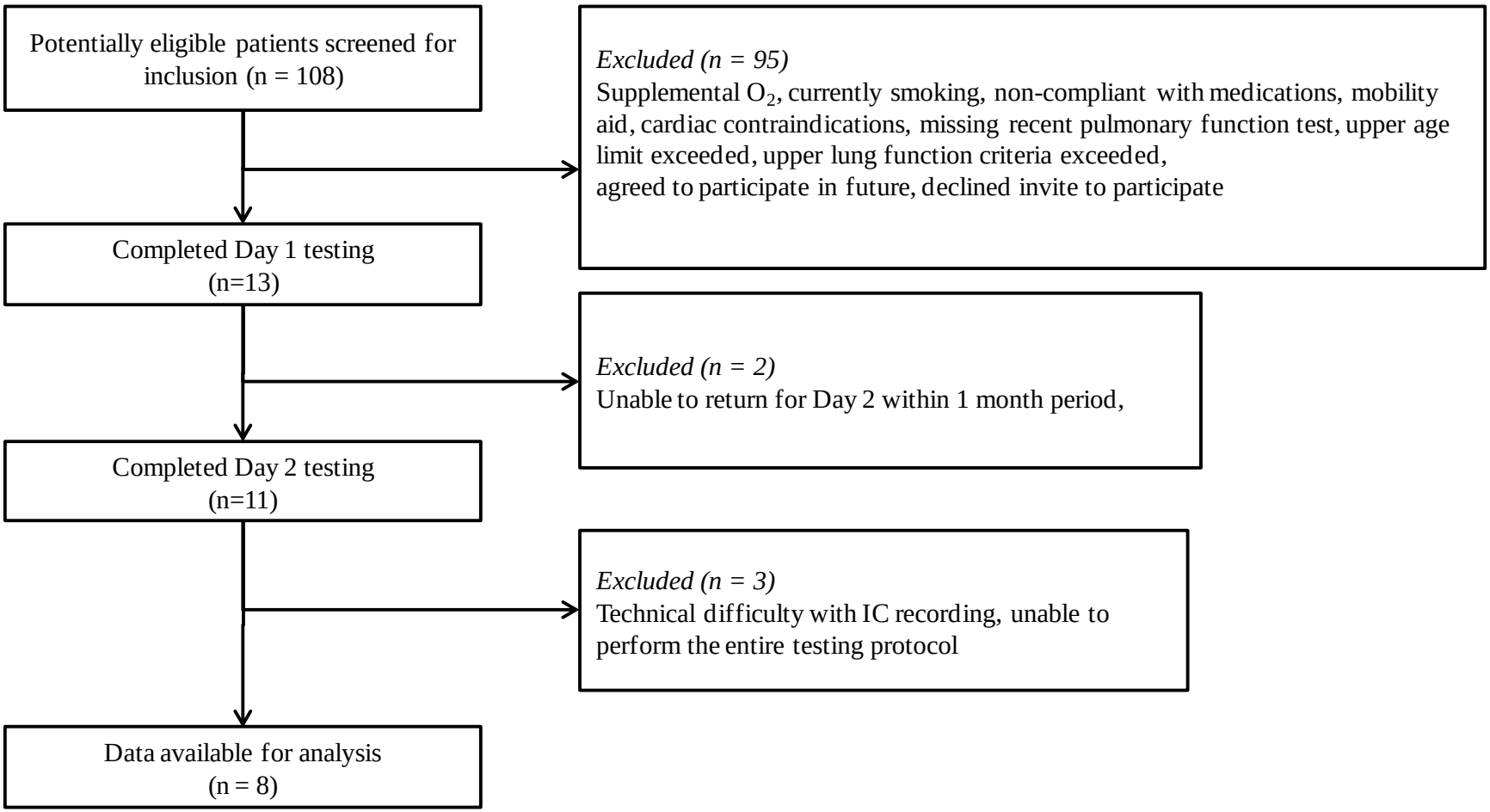
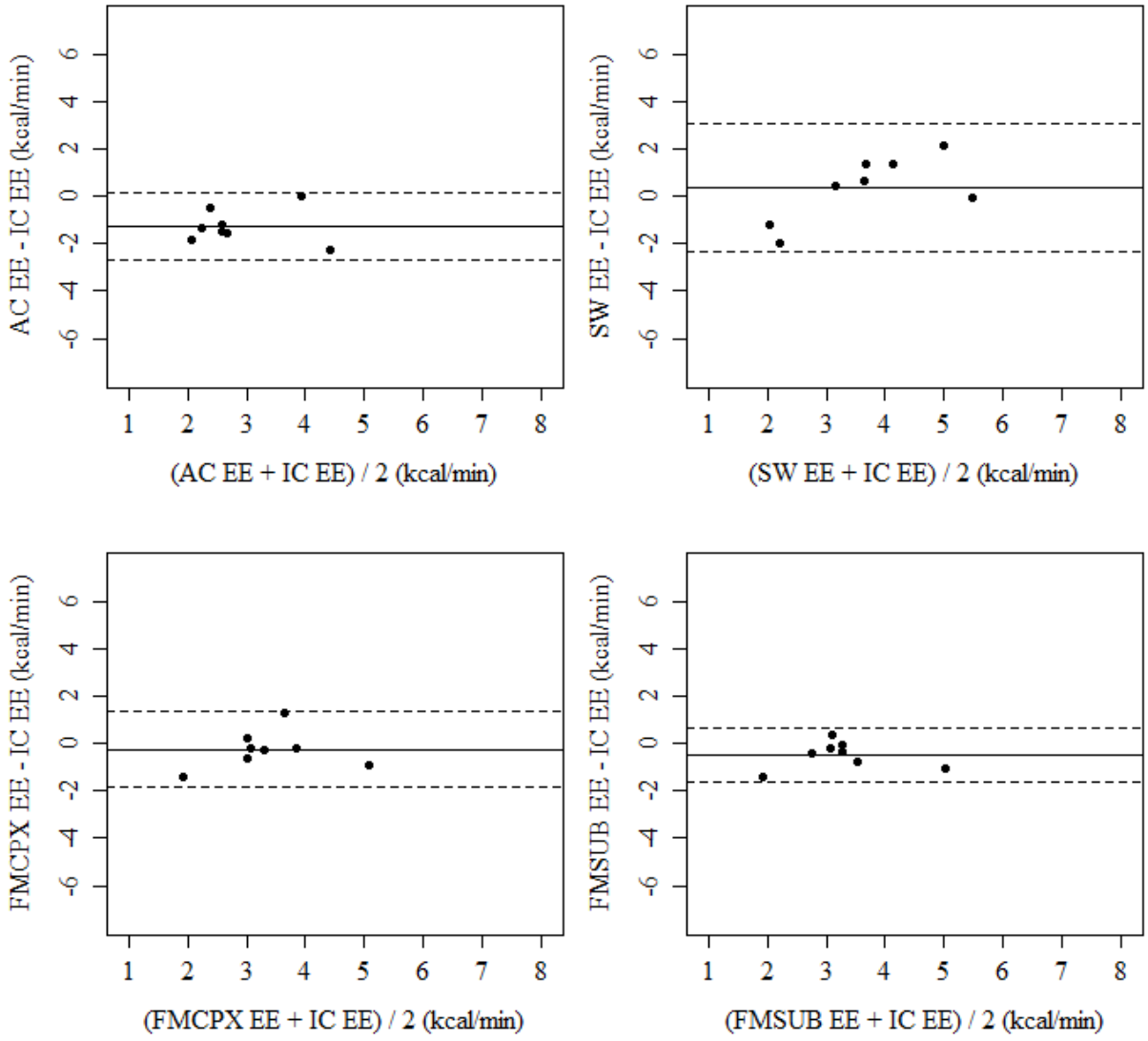
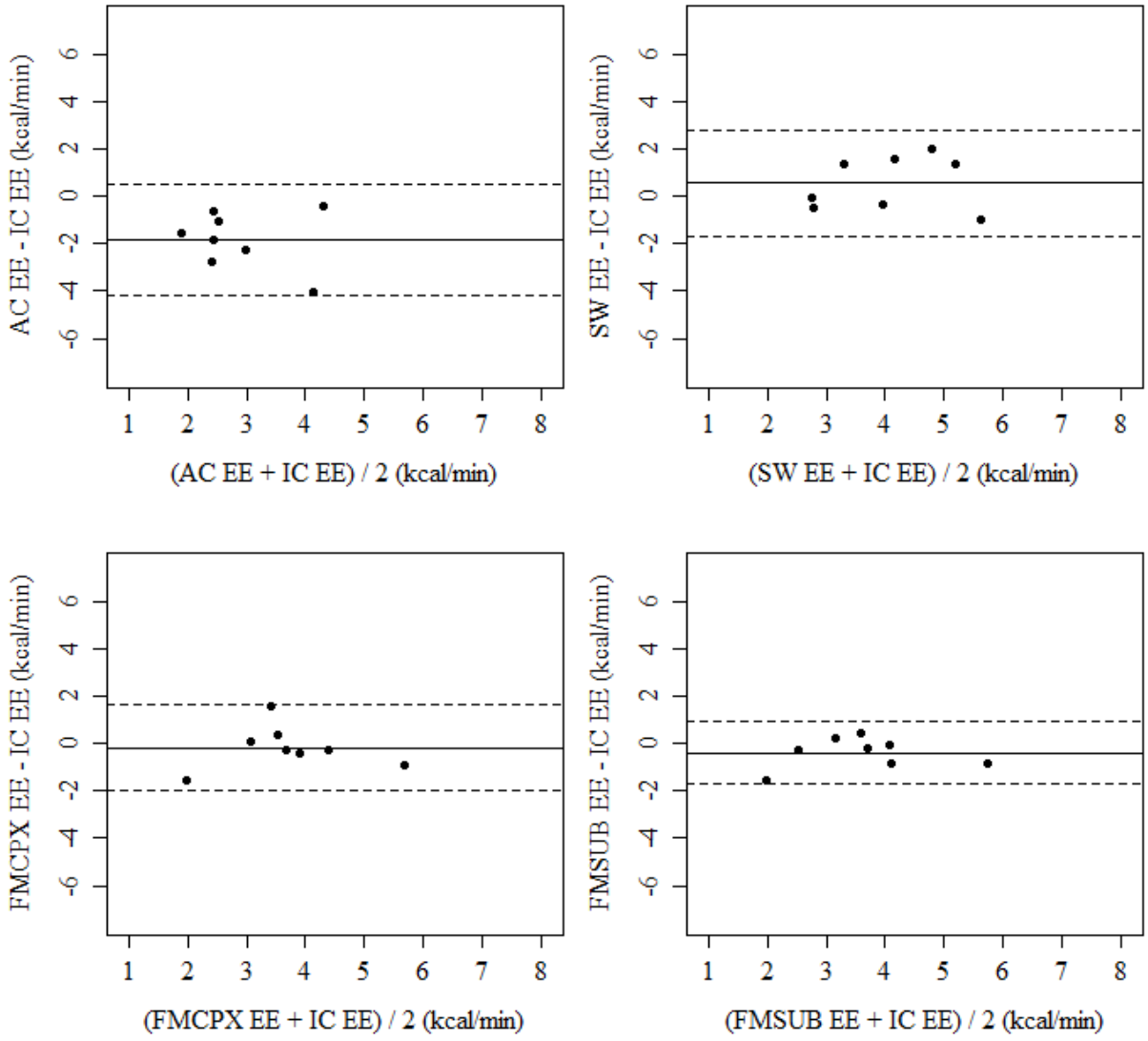


Figure 12. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Flat Walk.



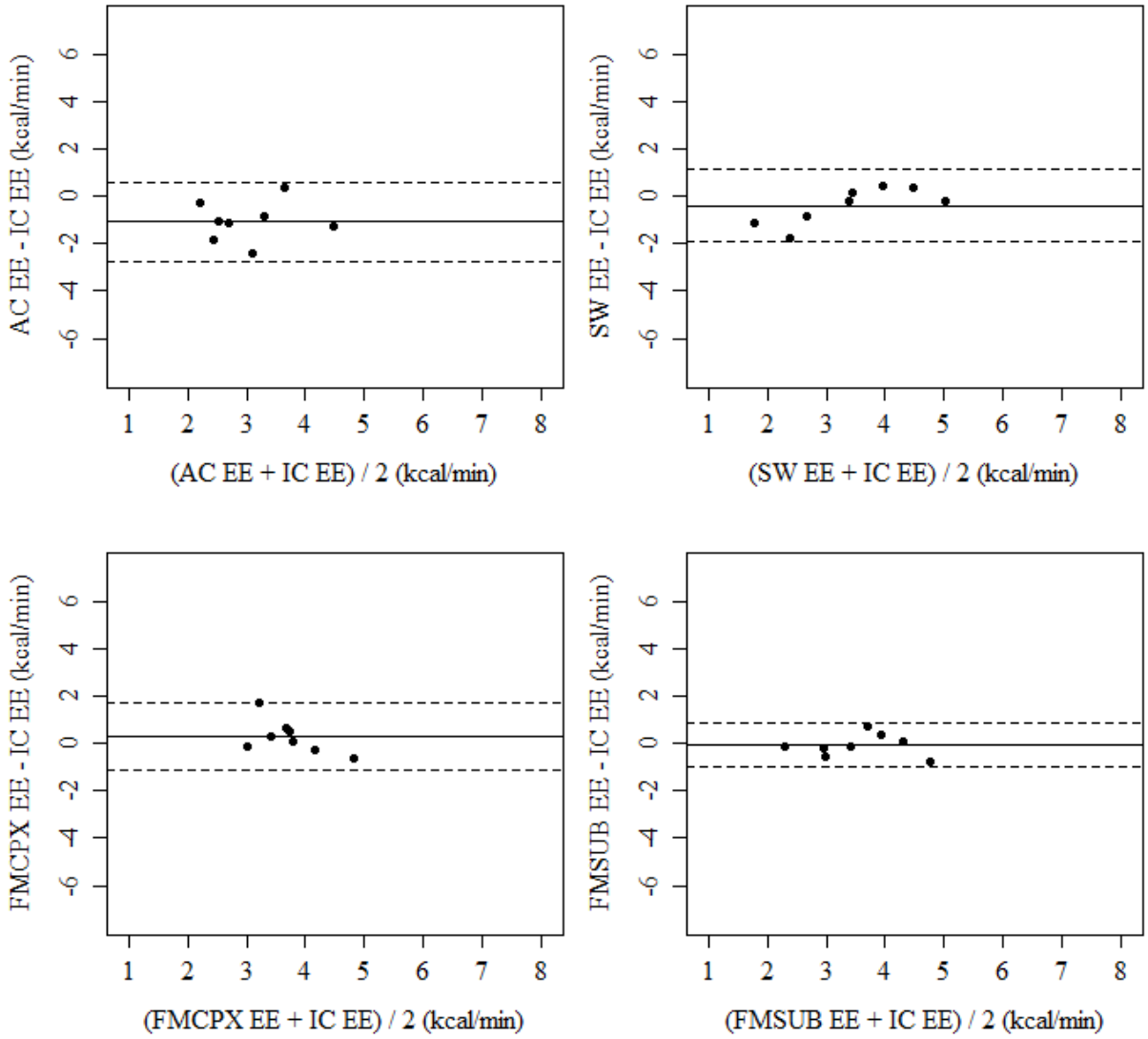
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 13. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Incline Walk.



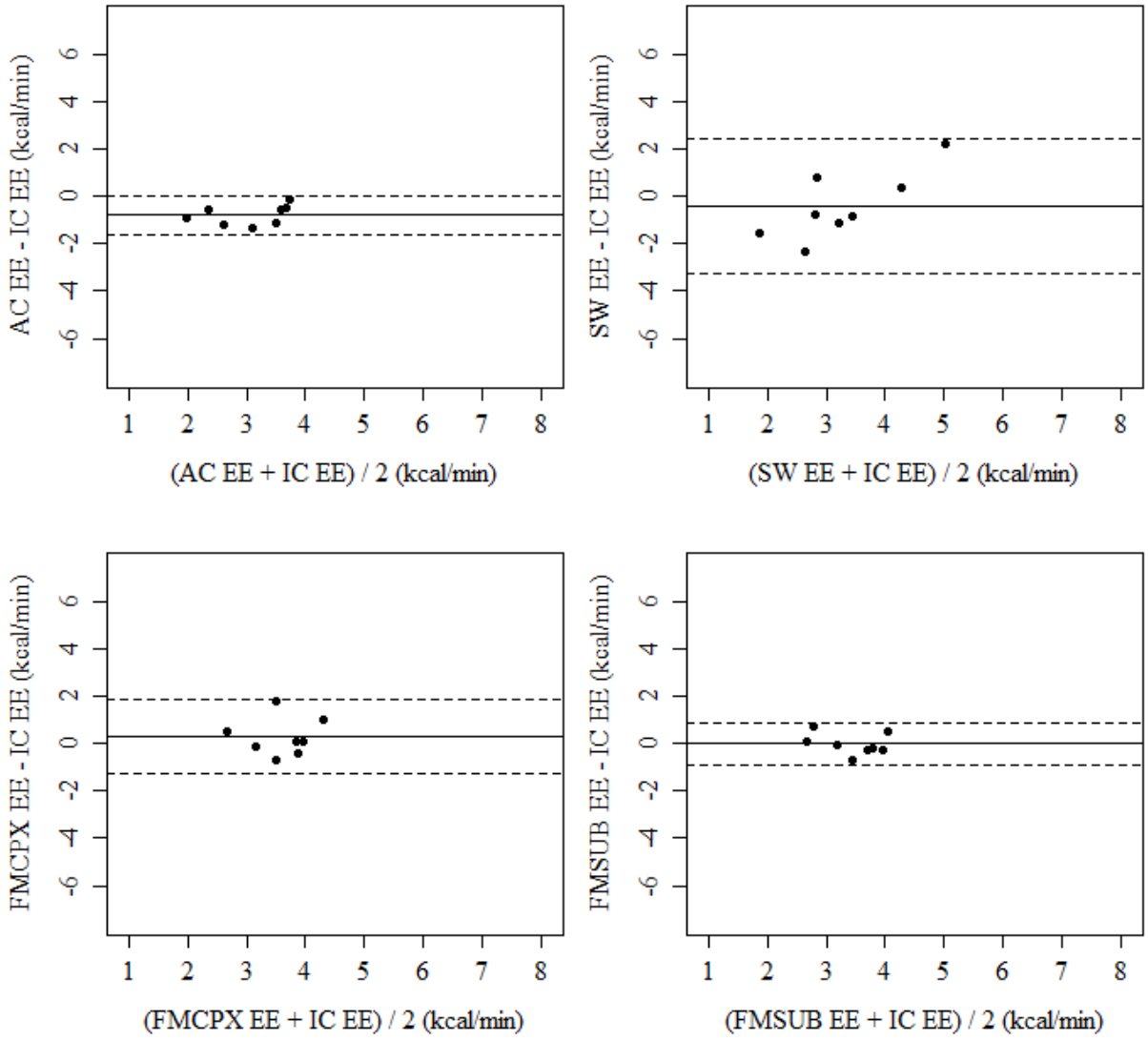
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 14. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Sit-to-Stand Activity.



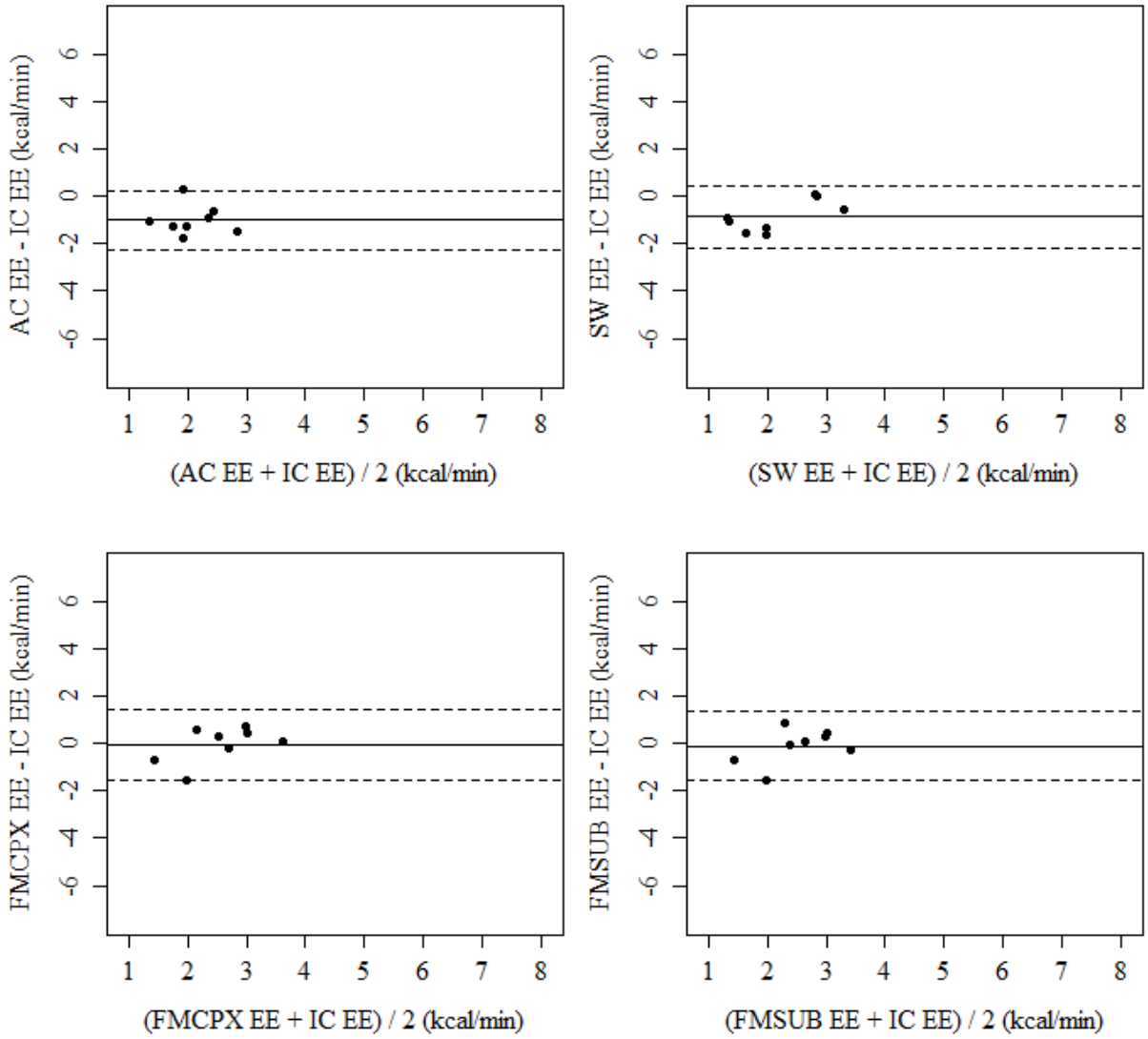
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 15. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Lift-Bend Activity.



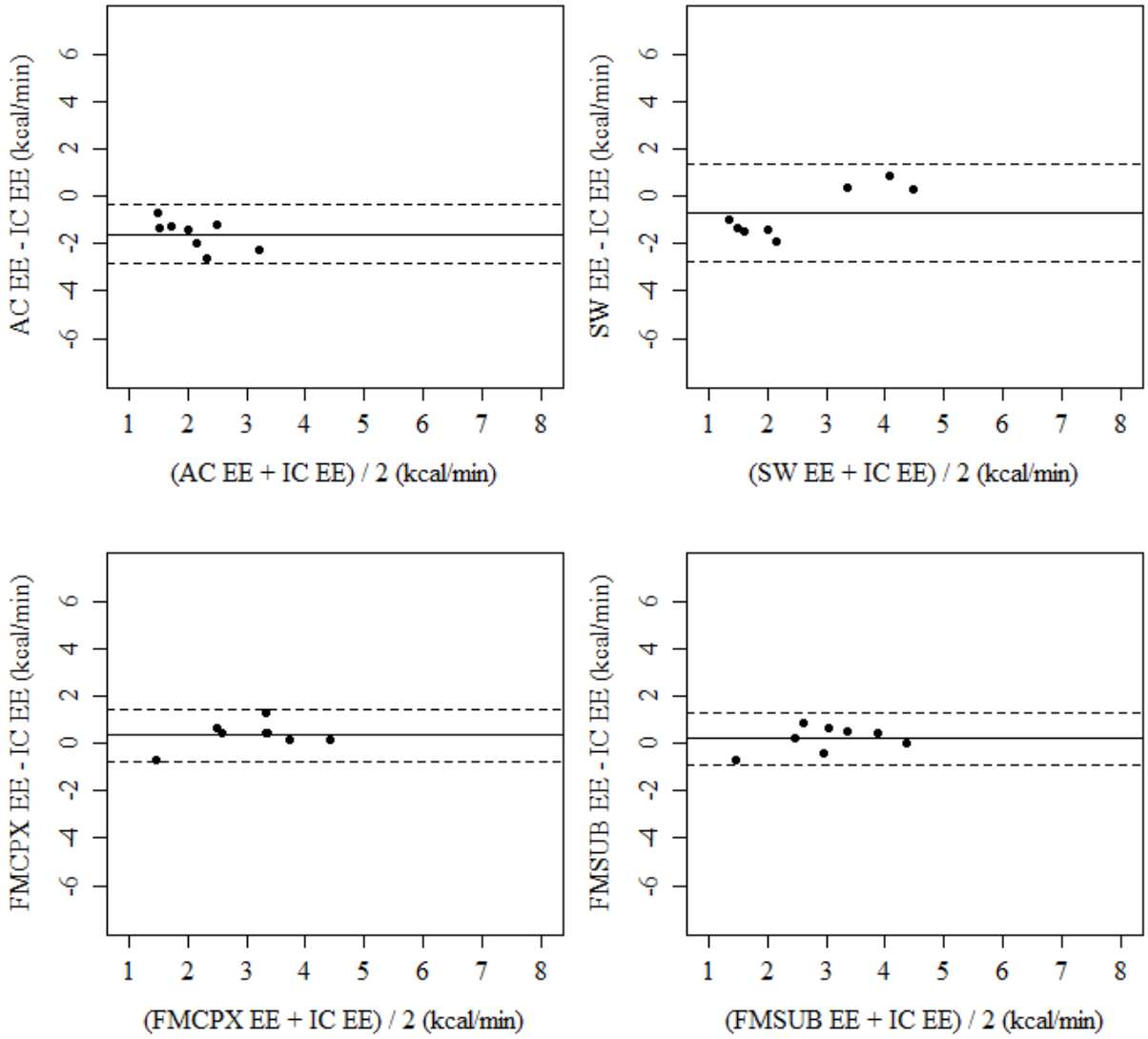
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 16. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 10% Peak Workload.



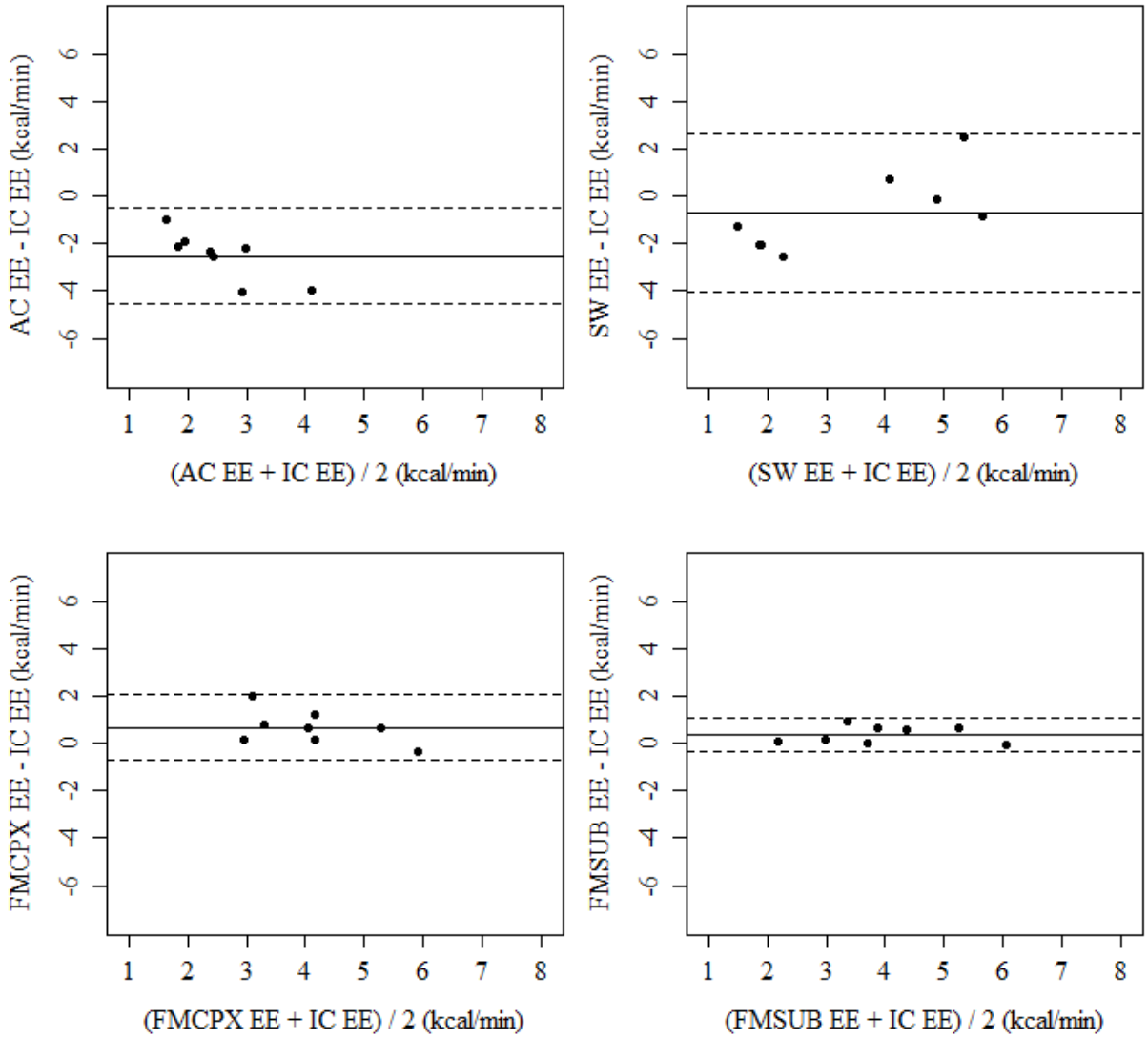
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 17. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 25% Peak Workload.



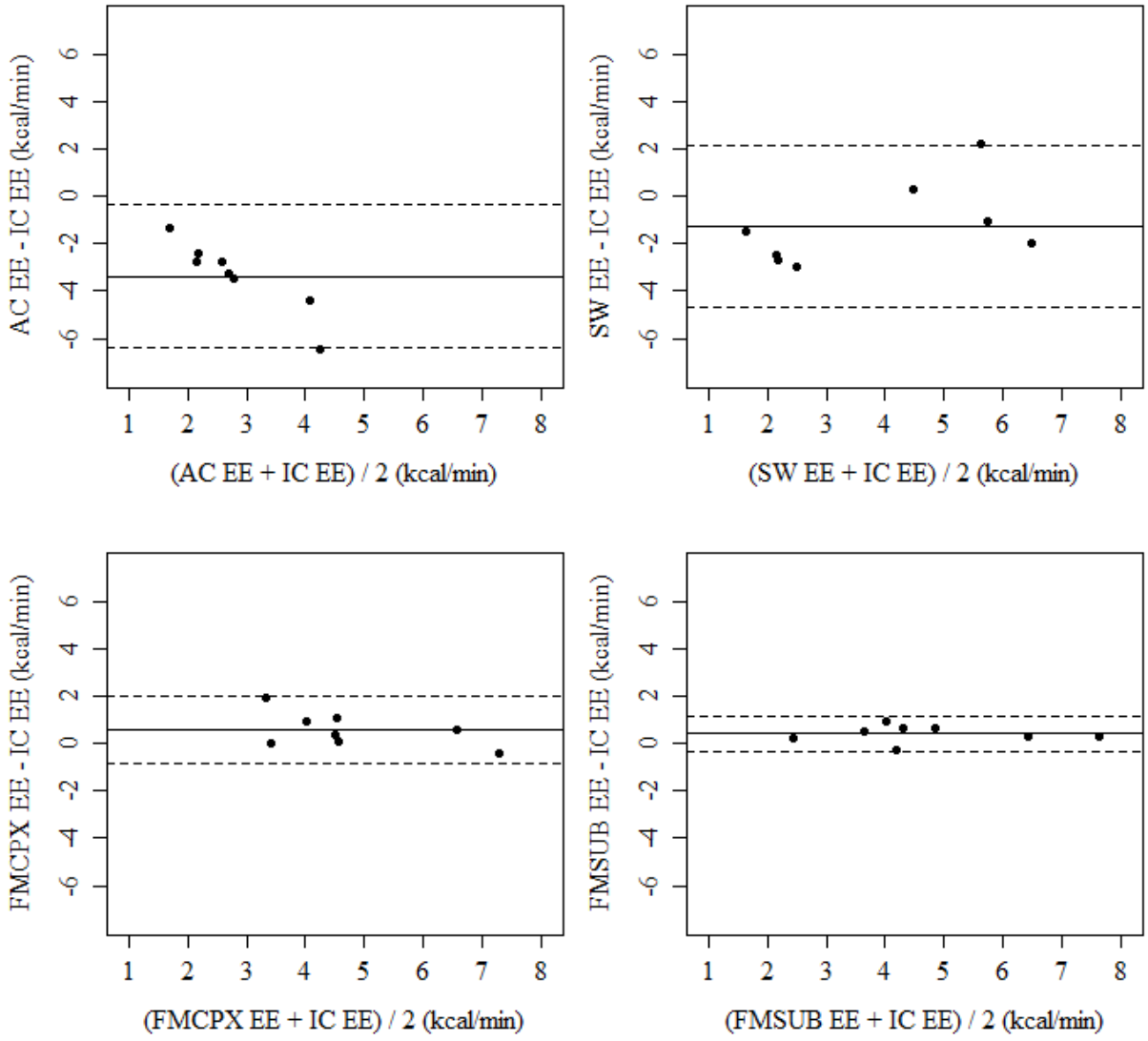
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 18. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 50% Peak Workload.



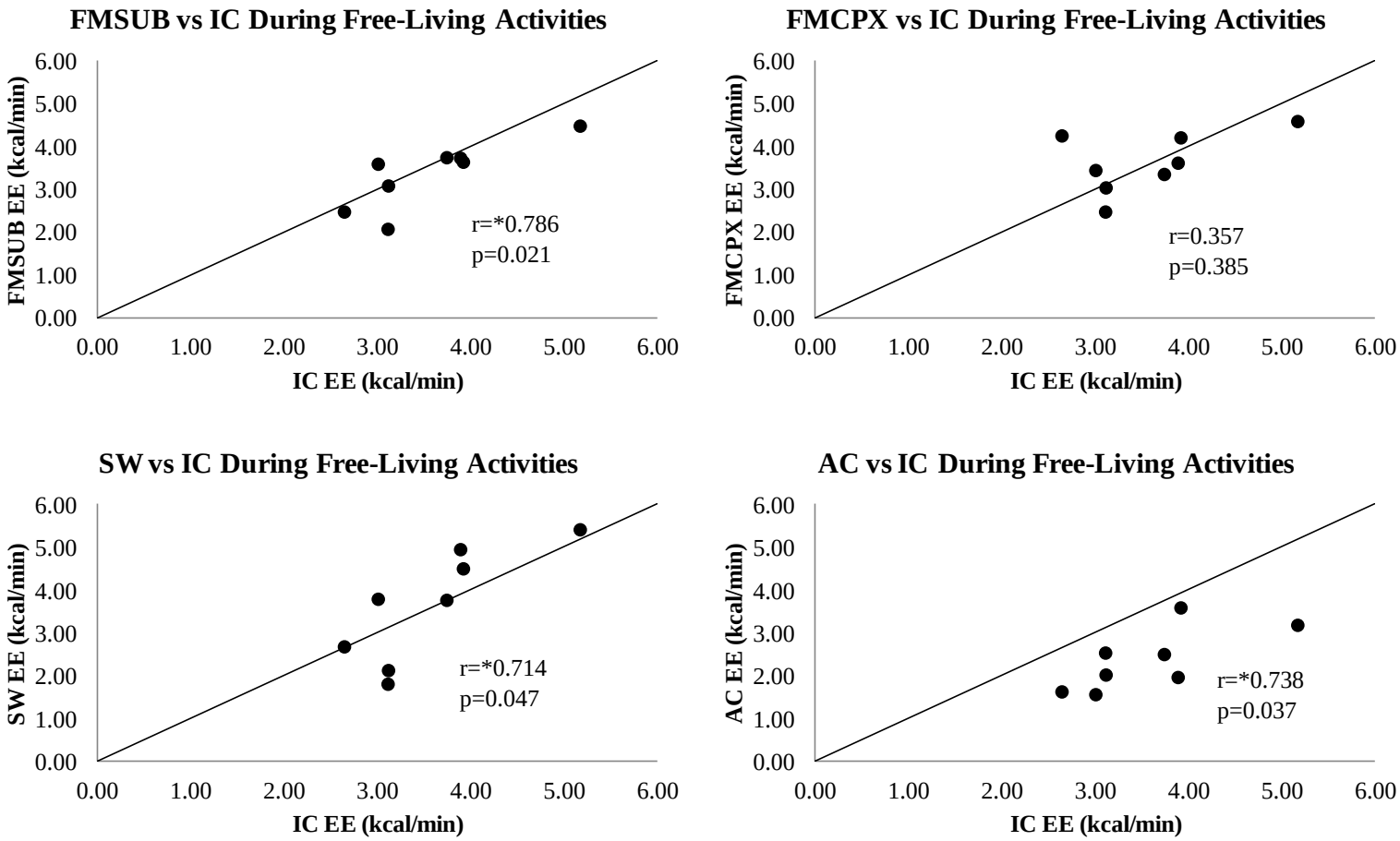
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 19. Bland-Altman Plot of Agreement Between Indirect Calorimetry and Primary Index Methods During Cycling at 60% Peak Workload.



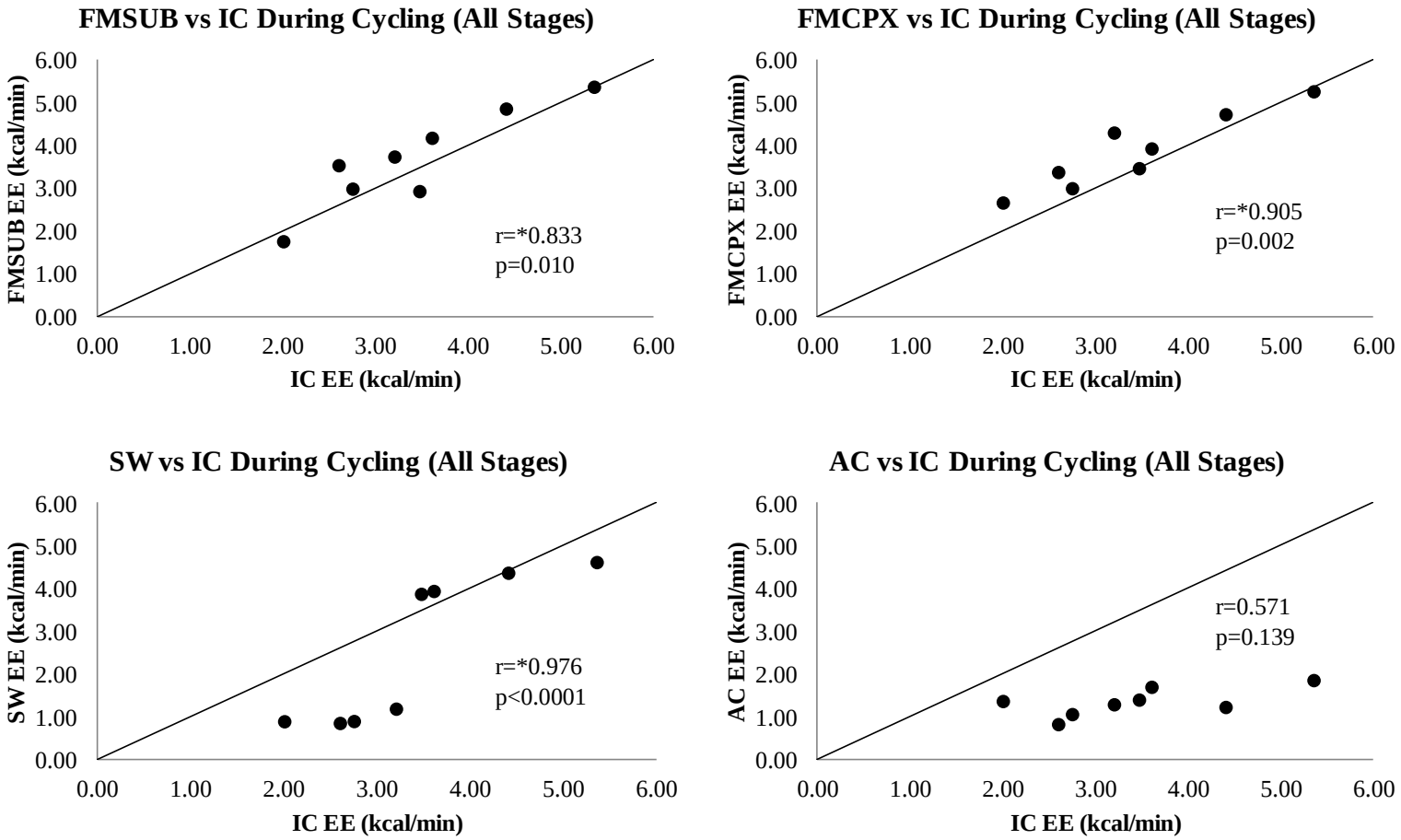
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; Solid horizontal line is the mean difference (index-IC). Dotted lines are the limits of agreement.

Figure 20. Scatter Plots of Energy Expenditure During Free-Living Activities.



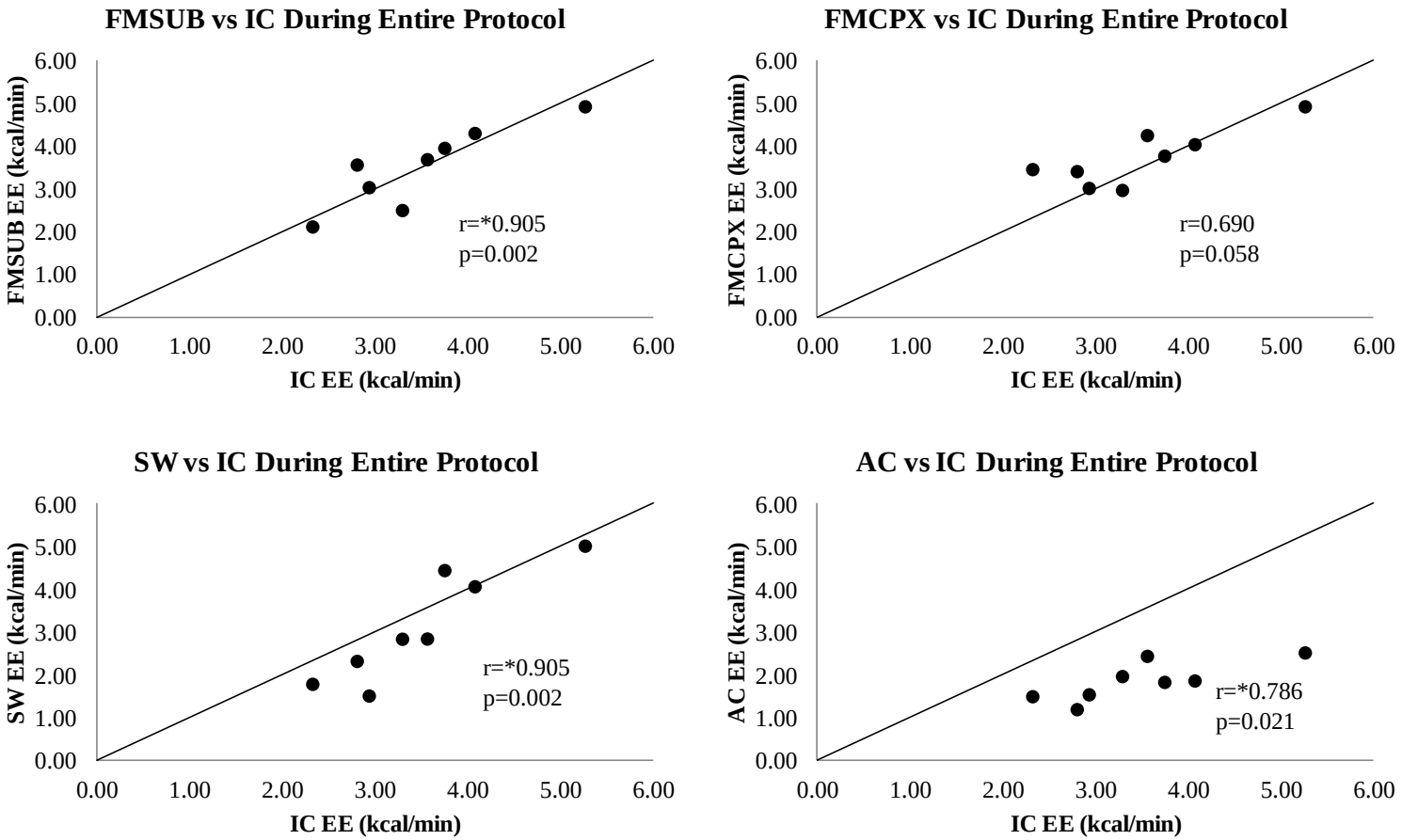
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; r = Spearman correlation coefficient; *significant at $p<0.05$; Solid diagonal line across from XY intersect represents the line of identity.

Figure 21. Scatter Plots of Energy Expenditure During Cycling Activities.



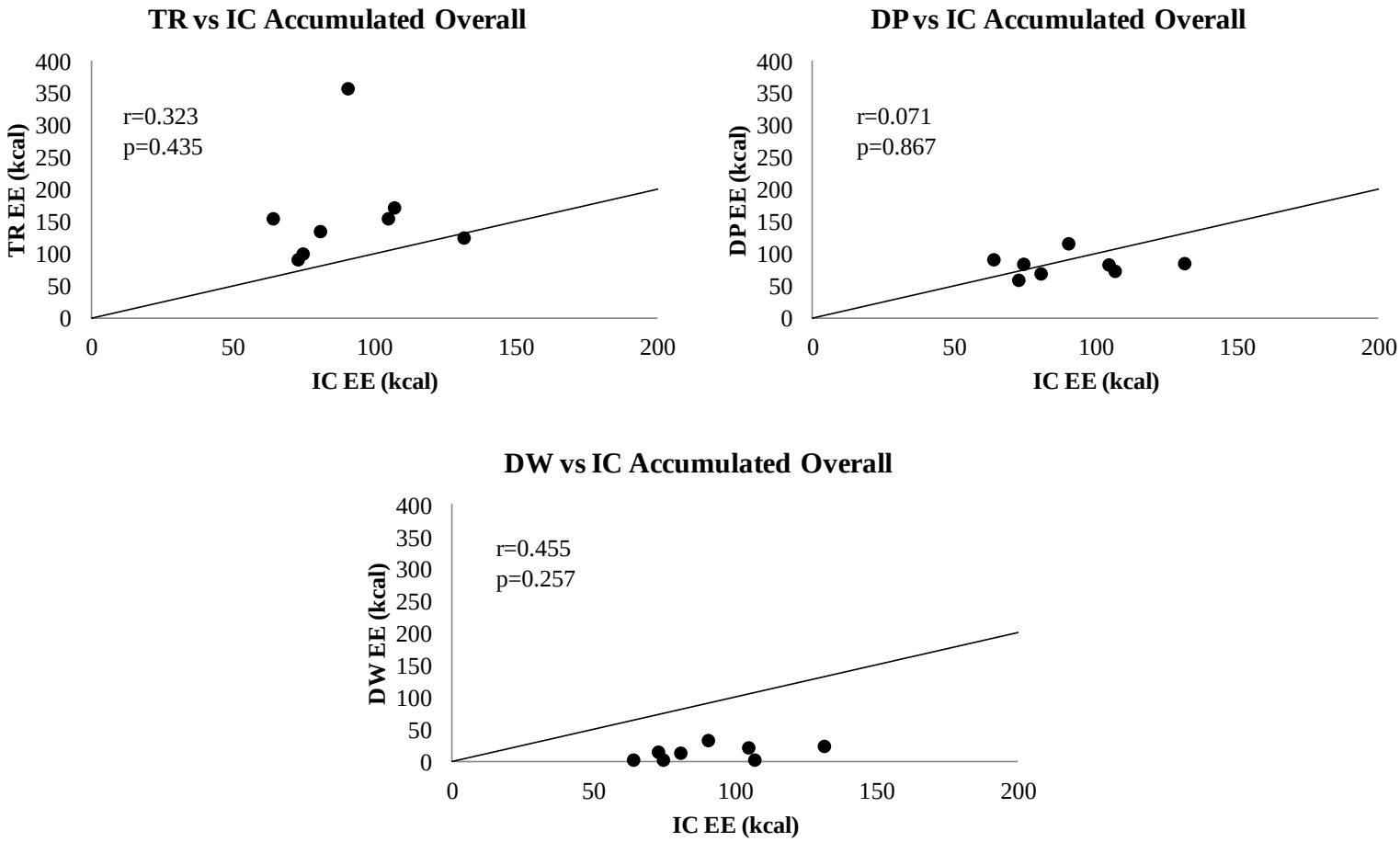
SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; r = Spearman correlation coefficient; *significant at $p<0.05$; Solid diagonal line across from XY intersect represents the line of identity

Figure 22. Scatter Plots of Overall Energy Expenditure for Primary Index Methods.



SW = SenseWear; AC = ActiCal; FMSUB = Flex heart rate method using submaximal exercise protocol calibration; FMCPX = Flex heart rate method using peak exercise protocol calibration; IC = indirect calorimetry; EE = energy expenditure; r = Spearman correlation coefficient; *significant at $p<0.05$; Solid diagonal line across from XY intersect represents the line of identity

Figure 23. Scatter Plots of Overall Energy Expenditure for Secondary Index Methods.



DW = DigiWalker pedometer; DP = Dynaport monitor; TR = Tractivity monitor; IC = indirect calorimetry; EE = energy expenditure; r = Spearman correlation coefficient; *significant at $p<0.05$; Solid diagonal line across from XY intersect represents the line of identity

References

1. Studer SM, Levy RD, McNeil K, Orens JB. Lung transplant outcomes: a review of survival, graft function, physiology, health-related quality of life and cost-effectiveness. *Eur Respir J*. 2004;24:674-685.

2. Gross CR, Savik K, Bolman RM, Hertz MI. Long-term health status and quality of life outcomes of lung transplant recipients. *CHEST*. 1995;108:1587-1593.

3. Canadian Institute for Health Information. *Canadian Organ Replacement Register Annual Report: Treatment of End-Stage Organ Failure in Canada, 2003-2012.* Ottawa, ON: CIHI; 2014.

4. Yusen RD, Christie JD, Edwards LB, et al. The Registry of the International Society for Heart and Lung Transplantation: thirtieth adult lung and heart-lung transplant report—2013; focus theme: age. *J Heart Lung Transplant*. 2013;32:965-978.

5. O'Donnell DE, Aaron S, Bourbeau J, et al. Canadian Thoracic Society recommendations for management of chronic obstructive pulmonary disease - 2007 update. *Can Respir J*. 2007;14 Suppl B:5B-32B.

6. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176:532-555.

7. Statistics Canada, Health Statistics Division. *Health Fact Sheet (Catalogue no. 82-625-X): Chronic Obstructive Pulmonary Disease in Canadians, 2009 to 2011*. Minister of Industry;

2012. Available at http://www.statcan.gc.ca/pub/82-625-x/2012001/article/11709-eng.htm, Accessed September 08 2014.

8. Halbert RJ, Natoli JL, Gano A, Badamgarav E, Buist AS, Mannino DM. Global burden of COPD: systematic review and meta-analysis. *Eur Respir J*. 2006;28:523-532.

9. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2013;187:347-365.

10. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. 2005;26:948-968.

11. Jagoe RT, Engelen MP. Muscle wasting and changes in muscle protein metabolism in chronic obstructive pulmonary disease. *Eur Respir J Suppl*. 2003;46:52s-63s.

12. Van Der Woude BT, Kropmans TJ, Douma KW, et al. Peripheral muscle force and exercise capacity in lung transplant candidates. *Int J Rehabil Res*. 2002;25:351-355.

13. Satta A, Migliori GB, Spanevello A, et al. Fibre types in skeletal muscles of chronic obstructive pulmonary disease patients related to respiratory function and exercise tolerance. *Eur Respir J*. 1997;10:2853-2860.

14. Hughes R, Katz H, Sahgal V, Campbell J, Hartz R, Shields T. Fiber size and energy metabolites in five separate muscles from patients with chronic obstructive lung disease. *Respiration*. 1983;44:321-328.

15. Schols AM, Mostert R, Soeters PB, Wouters EF. Body composition and exercise performance in patients with chronic obstructive pulmonary disease. *Thorax*. 1991;46:695-699.

16. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;164:770-777.

17. Montes de Oca M, Rassulo J, Celli BR. Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. *Am J Respir Crit Care Med*. 1996;154:1284-1289.

18. Cushley M, Davison A, du Bois R, et al. The Diagnosis, Assessment and Treatment of Diffuse Parenchymal Lung Disease in Adults. *Thorax*. 1999;54:S1-S30.

19. Demedts M, Costabel U. ATS/ERS international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Eur Respir J*. 2002;19:794-796.

20. Coultas DB, Zumwalt RE, Black WC, Sobonya RE. The epidemiology of interstitial lung diseases. *Am J Respir Crit Care Med*. 1994;150:967-972.

21. Gulati M. Diagnostic assessment of patients with interstitial lung disease. *Prim Care Respir J*. 2011;20:120-127.

22. Lumb AB. *Nunn's Applied Respiratory Physiology.* Elsevier Butterworth Heinemann Philadelphia; 2005.

23. Raghu G, Nyberg F, Morgan G. The epidemiology of interstitial lung disease and its association with lung cancer. *Br J Cancer*. 2004;91:S3-S10.

24. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144:1202-1218.

25. American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. *Am Rev Respir Dis*. 1986;133:1205-1209.

26. Hsia CC. Cardiopulmonary limitations to exercise in restrictive lung disease. *Med Sci Sports Exerc*. 1999;31:S28-32.

27. Hansen JE, Wasserman K. Pathophysiology of activity limitation in patients with interstitial lung disease. *CHEST*. 1996;109:1566-1576.

28. Dupuis A, Hamilton D, Cole DE, Corey M. Cystic fibrosis birth rates in Canada: a decreasing trend since the onset of genetic testing. *J Pediatr*. 2005;147:312-315.

29. Stephenson A, Chilvers M, Durie P, et al. *Canadian cystic fibrosis patient data registry*. Toronto, ON. Cystic Fibrosis Canada; 2010.

30. Stephenson A, Chilvers M, Durie P, et al. *Canadian cystic fibrosis patient data registry.* Toronto, ON: Cystic Fibrosis Canada; 2009.

31. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Am J Respir Crit Care Med.* 1996;154:1229-1256.

32. Flume PA, Mogayzel PJ, Robinson KA, et al. Cystic Fibrosis Pulmonary Guidelines. *Am J Respir Crit Care Med*. 2009;180:802-808.

33. Fraser KL, Tullis DE, Sasson Z, Hyland RH, Thornley KS, Hanly PJ. Pulmonary Hypertension and Cardiac Function in Adult Cystic FibrosisRole of Hypoxemia. *CHEST*. 1999;115:1321-1328.

34. Haworth C, Selby P, Webb A, et al. Low bone mineral density in adults with cystic fibrosis. *Thorax*. 1999;54:961-967.

35. Conway S, Morton A, Oldroyd B, et al. Osteoporosis and osteopenia in adults and adolescents with cystic fibrosis: prevalence and associated factors. *Thorax*. 2000;55:798-804.

36. Buntain H, Greer R, Schluter P, et al. Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. *Thorax*. 2004;59:149-155.

37. Hanly J, McKenna M, Quigley C, Freaney R, Muldowney F, FitzGerald M. Hypovitaminosis D and response to supplementation in older patients with cystic fibrosis. *QJM*. 1985;56:377-385.

38. Frangolias DD, Pare PD, Kendler DL, et al. Role of exercise and nutrition status on bone mineral density in cystic fibrosis. *J Cyst Fibros*. 2003;2:163-170.

39. Donovan DS, Papadopoulos A, Staron RB, et al. Bone mass and vitamin D deficiency in adults with advanced cystic fibrosis lung disease. *Am J Respir Crit Care Med*. 1998;157:1892-1899.

40. Bush A. *Cystic Fibrosis in the 21st Century*. Vol 34. Karger Medical Scientific; 2006.

41. Elborn JS. How can we prevent multisystem complications of cystic fibrosis? Copyright© 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA.; 2007;28:303-311.

42. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176:957-969.

43. Sahlberg ME, Svantesson U, Thomas EMM, Strandvik B. Muscular strength and function in patients with cystic fibrosis. *CHEST*. 2005;127:1587-1592.

44. Barry SC, Gallagher CG. Corticosteroids and skeletal muscle function in cystic fibrosis. *J Appl Physiol*. 2003;95:1379-1384.

45. Elkin SL, Williams L, Moore M, Hodson ME, Rutherford OM. Relationship of skeletal muscle mass, muscle strength and bone mineral density in adults with cystic fibrosis. *Clin Sci*. 2000;99:309-314.

46. Pinet C, Scillia P, Cassart M, et al. Preferential reduction of quadriceps over respiratory muscle strength and bulk after lung transplantation for cystic fibrosis. *Thorax*. 2004;59:783-789.

47. Almajed A, Lands LC. The evolution of exercise capacity and its limiting factors in Cystic Fibrosis. *Paediatr Respir Rev*. 2012;13:195-199.

48. DESA U. World Population Prospects, The 2012 Revision. *New York: Department for Economic and Social Affairs*. 2013.

49. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet*. 2007;370:765-773.

50. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. *JAMA*. 2005;294:1255-1259.

51. Kornum JB, Christensen S, Grijota M, et al. The incidence of interstitial lung disease 1995-2005: a Danish nationwide population-based study. *BMC Pulm Med*. 2008;8:24-2466-8-24.

52. Pérez ERF, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *CHEST*. 2010;137:129-137.

53. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174:810-816.

54. Frangolias DD, Paré PD, Kendler DL, et al. Role of exercise and nutrition status on bone mineral density in cystic fibrosis. *J Cyst Fibros*. 2003;2:163-170.

55. Yankaskas JR, Marshall BC, Sufian B, Simon RH, Rodman D. Cystic fibrosis adult care consensus conference report. *CHEST*. 2004;125:1S-39S.

56. Wilkes DS, Egan TM, Reynolds HY. Lung transplantation opportunities for research and clinical advancement. *Am J Respir Crit Care Med*. 2005;172:944-955.

57. Egan TM, Murray S, Bustami R, et al. Development of the new lung allocation system in the United States. *Am J Transplant*. 2006;6:1212-1227.

58. Orens JB, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update – a consensus report from the pulmonary scientific council of the international society for heart and lung transplantation. *J Heart Lung Transplant*. 2006;25:745-755.

59. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350:1005-1012.

60. Mogulkoc N, Brutsche MH, Bishop PW, Greaves SM, Horrocks AW, Egan JJ. Pulmonary function in idiopathic pulmonary fibrosis and referral for lung transplantation. *Am J Respir Crit Care Med*. 2001;164:103-108.

61. Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med*. 1992;326:1187-1191.

62. Traver GA, Cline MG, Burrows B. Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. *Am Rev Respir Dis*. 1979;119:895-902.

63. Kerem B, Rommens JM, Buchanan JA, et al. Identification of the cystic fibrosis gene: genetic analysis. *Science*. 1989;245:1073-1080.

64. Martinez FJ, Kotloff R. Prognostication in chronic obstructive pulmonary disease: implications for lung transplantation. Copyright© 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: 1 (212) 584-4662; 2001;22:489-498.

65. Vizza CD, Yusen RD, Lynch JP, Fedele F, Patterson GA, Trulock EP. Outcome of patients with cystic fibrosis awaiting lung transplantation. *Am J Respir Crit Care Med*. 2000;162:819-825.

66. Lederer DJ, Arcasoy SM, Wilt JS, D'Ovidio F, Sonett JR, Kawut SM. Six-minute-walk distance predicts waiting list survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2006;174:659-664.

67. Martinu T, Babyak M, O'Connell C, et al. Baseline 6- min walk distance predicts survival in lung transplant candidates. *Am J Transplant*. 2008;8:1498-1505.

68. Tuppin MP, Paratz JD, Chang AT, et al. Predictive utility of the 6-minute walk distance on survival in patients awaiting lung transplantation. *J Heart Lung Transplant*. 2008;27:729-734.

69. Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166:111-117.

70. Cote CG, Pinto-Plata V, Kasprzyk K, Dordelly LJ, Celli BR. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. *CHEST*. 2007;132:1778-1785.

71. Kawut SM, O'Shea MK, Bartels MN, Wilt JS, Sonett JR, Arcasoy SM. Exercise testing determines survival in patients with diffuse parenchymal lung disease evaluated for lung transplantation. *Respir Med*. 2005;99:1431-1439.

72. Nixon PA, Orenstein DM, Kelsey SF, Doershuk CF. The prognostic value of exercise testing in patients with cystic fibrosis. *N Engl J Med*. 1992;327:1785-1788.

73. Haskell WL, Montoye HJ, Orenstein D. Physical activity and exercise to achieve health-related physical fitness components. *Public Health Rep*. 1985;100:202.

74. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep*. 1985;100:126.

75. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. *Can Med Assoc J*. 2006;174:801-809.

76. Waschki B, Kirsten A, Holz O, et al. Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study. *CHEST*. 2011;140:331-342.

77. Manzetti JD, Hoffman LA, Sereika SM, Sciurba FC, Griffith BP. Exercise, education, and quality of life in lung transplant candidates. *J Heart Lung Transplant*. 1994;13:297-305.

78. Li M, Mathur S, Chowdhury NA, Helm D, Singer LG. Pulmonary rehabilitation in lung transplant candidates. *J Heart Lung Transplant*. 2013;32:626-632.

79. American Thoracic Society Official Statement. Pulmonary rehabilitation - 1999. *Am J Respir Crit Care Med*. 1999;159:1666-1682.

80. Nici L, Donner C, Wouters E, et al. American thoracic society/European respiratory society statement on pulmonary rehabilitation. *Am J Respir Crit Care Med*. 2006;173:1390-1413.

81. Ries AL, Bauldoff GS, Carlin BW, et al. Pulmonary Rehabilitation Executive Summary, Joint American College of Chest Physicians/American Association of Cardiovascular and

Pulmonary Rehabilitation Evidence-Based Clinical Practice Guidelines. *CHEST*. 2007;131:1S-3S.

82. Munro P, Holland A, Bailey M, Button B, Snell G. Pulmonary rehabilitation following lung transplantation. *Transplant Proc*; 2009;41:292-295.

83. Rochester CL. Pulmonary rehabilitation for patients who undergo lung-volume-reduction surgery or lung transplantation. *Respir Care*. 2008;53:1196-1202.

84. Kesten S. Pulmonary rehabilitation and surgery for end-stage lung disease. *Clin Chest Med*. 1997;18:173-181.

85. Decramer M, Gosselink R. Physical activity in patients with cystic fibrosis: a new variable in the health-status equation unravelled? *Eur Respir J*. 2006;28:678-679.

86. Langer D, Cebrià i Iranzo M, Burtin C, et al. Determinants of physical activity in daily life in candidates for lung transplantation. *Respir Med*. 2012;106:747-754.

87. Mathur S, Hornblower E, Levy RD. Exercise training before and after lung transplantation. *Phys Sportsmed*. 2009;37:78-87.

88. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. *Public Health Rep*. 1985;100:126.

89. Elia M, Livesey G. Energy expenditure and fuel selection in biological systems: the theory and practice of calculations based on indirect calorimetry and tracer methods. *World Rev Nutr Diet*. 1992;70:68-131.

90. Kulstad R, Schoeller DA. The energetics of wasting diseases. *Curr Opin Clin Nutr Metab Care*. 2007;10:488-493.

91. Montoye HJ. Introduction: evaluation of some measurements of physical activity and energy expenditure. *Med Sci Sports Exerc*. 2000;32:S439-S441.

92. Vanhees L, Lefevre J, Philippaerts R, et al. How to assess physical activity? How to assess physical fitness? *Eur J Cardiovasc Prev Rehabil*. 2005;12:102-114.

93. Pitta F, Troosters T, Probst VS, Spruit MA, Decramer M, Gosselink R. Quantifying physical activity in daily life with questionnaires and motion sensors in COPD. *Eur Respir J*. 2006;27:1040-1055.

94. Washburn RA, Heath GW, Jackson AW. Reliability and validity issues concerning large-scale surveillance of physical activity. *Res Q Exerc Sport.* 2000; 71(2 Suppl):S104-13.

95. Bonnefoy M, Normand S, Pachiaudi C, Lacour JR, Laville M, Kostka T. Simultaneous validation of ten physical activity questionnaires in older men: a doubly labeled water study. *J Am Geriatr Soc*. 2001;49:28-35.

96. Van Remoortel H, Giavedoni S, Raste Y, et al. Validity of activity monitors in health and chronic disease: a systematic review. *Int J Behav Nutr Phys Act*. 2012;9:84.

97. Christensen CC, Frey H, Foenstelien E, Aadland E, Refsum HE. A critical evaluation of energy expenditure estimates based on individual O2 consumption/heart rate curves and average daily heart rate. *Am J Clin Nutr*. 1983;37:468-472.

98. Garrow JS, Halliday D, Clinical Reasearch Centre (Harrow, Lodon,England).Symposium (3rd. Substrate and energy metabolism in man. London: Libbey; 1985.

99. Schulz H, Helle S, Heck H. The validity of the telemetric system CORTEX X1 in the ventilatory and gas exchange measurement during exercise. *Int J Sports Med*. 1997;28:454-457.

100. Meyer T, Georg T, Becker C, Kindermann W. Reliability of gas exchange measurements from two different spiroergometry systems. *Int J Sports Med*. 2001;22:593-597.

101. Laporte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Rep*. 1985;100:131.

102. DeLany JP, Lovejoy JC. Energy expenditure. *Endocrinol Metab Clin North Am*. 1996;25:831-846.

103. Ainslie PN, Reilly T, Westerterp KR. Estimating human energy expenditure. *Sports Medicine*. 2003;33:683-698.

104. Schoeller DA, Hnilicka JM. Reliability of the doubly labeled water method for the measurement of total daily energy expenditure in free-living subjects. *J Nutr*. 1996;126:348S-354S.

105. Welk G. *Physical Activity Assessments for Health-Related Research.* Champaign, IL: Human Kinetics; 2002.

106. Laporte RE, Montoye HJ, Caspersen CJ. Assessment of physical activity in epidemiologic research: problems and prospects. *Public Health Rep*. 1985;100:131.

107. Schonhofer B, Ardes P, Geibel M, Kohler D, Jones PW. Evaluation of a movement detector to measure daily activity in patients with chronic lung disease. *Eur Respir J*. 1997;10:2814-2819.

108. Chan CB, Ryan DA, Tudor-Locke C. Health benefits of a pedometer-based physical activity intervention in sedentary workers. *Prev Med*. 2004;39:1215-1222.

109. Cyarto EV, Myers A, Tudor-Locke C. Pedometer accuracy in nursing home and community-dwelling older adults. *Med Sci Sports Exerc*. 2004;36:205-209.

110. Steele BG, Belza B, Cain K, Warms C, Coppersmith J, Howard J. Bodies in motion: monitoring daily activity and exercise with motion sensors in people with chronic pulmonary disease. *JRRD*. 2003;40:45-58.

111. Plasqui G, Westerterp KR. Physical activity assessment with accelerometers: an evaluation against doubly labeled water. *Obesity*. 2007;15:2371-2379.

112. Freedson PS, Miller K. Objective monitoring of physical activity using motion sensors and heart rate. *Res Q Exerc Sport*. 2000;71:S21-9.

113. Levine JA, Baukol PA, Westerterp KR. Validation of the Tracmor triaxial accelerometer system for walking. *Med Sci Sports Exerc*. 2001;33:1593-1597.

114. Cole PJ, LeMura LM, Klinger TA, Strohecker K, McConnell TR. Measuring energy expenditure in cardiac patients using the Body Media Armband versus indirect calorimetry. A validation study. *J Sports Med Phys Fitness*. 2004;44:262-271.

115. Fruin ML, Rankin JW. Validity of a multi-sensor armband in estimating rest and exercise energy expenditure. *Med Sci Sports Exerc*. 2004;36:1063-1069.

116. Jakicic JM, Winters C, Lagally K, Ho J, Robertson RJ, Wing RR. The accuracy of the TriTrac-R3D accelerometer to estimate energy expenditure. *Med Sci Sports Exerc*. 1999;31:747-754.

117. Livingstone M, Prentice AM, Coward WA, et al. Simultaneous measurement of free-living energy expenditure by the doubly labeled water method and heart-rate monitoring. *Am J Clin Nutr*. 1990;52:59-65.

118. Johnson MR, Ferkol TW, Shepherd RW. Energy cost of activity and exercise in children and adolescents with cystic fibrosis. *J Cyst Fibros*. 2006;5:53-58.

119. Perrault H. Efficiency of movement in health and chronic disease. *Clin Invest Med*. 2006;29:117-121.

120. Baarends EM, Schols AM, Akkermans MA, Wouters EF. Decreased mechanical efficiency in clinically stable patients with COPD. *Thorax*. 1997;52:981-986.

121. Richards ML, Davies P, Bell S. Energy cost of physical activity in cystic fibrosis. *Eur J Clin Nutr*. 2001;55:690-697.

122. Ainsworth BE, Haskell WL, Whitt MC, et al. Compendium of physical activities: an update of activity codes and MET intensities. *Med Sci Sports Exerc*. 2000;32:S498-S504.

123. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC, Wouters EF. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr*. 1998;52:396-401.

124. Fitting J, Frascarolo P, Jéquier E, Leuenberger P. Resting energy expenditure in interstitial lung disease. *Am J Respir Crit Care Med*. 1990;142:631-635.

125. Buchdahl R, Cox M, Fulleylove C, et al. Increased resting energy expenditure in cystic fibrosis. *J Appl Physiol*. 1988;64:1810-1816.

126. Bell S, Saunders M, Elborn J, Shale D. Resting energy expenditure and oxygen cost of breathing in patients with cystic fibrosis. *Thorax*. 1996;51:126-131.

127. Donahoe M, Rogers RM, Wilson DO, Pennock BE. Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1989;140:385-391.

128. Mannix ET, Manfredi F, Farber MO. Elevated O2 cost of ventilation contributes to tissue wasting in COPD*. *Chest*. 1999;115:708-713.

129. O'Donnell DE. Dynamic lung hyperinflation and its clinical implication in COPD. *Rev Mal Respir*. 2009;26:e19-29.

130. Alison JA, Regnis JA, Donnelly PM, Adams RD, Sullivan CE, Bye PT. End-expiratory lung volume during arm and leg exercise in normal subjects and patients with cystic fibrosis. *Am J Respir Crit Care Med*. 1998;158:1450-1458.

131. Troiano RP. Translating accelerometer counts into energy expenditure: advancing the quest. *J Appl Physiol (1985)*. 2006;100:1107-1108.

132. Furlanetto KC, Bisca GW, Oldemberg N, et al. Step counting and energy expenditure estimation in patients with chronic obstructive pulmonary disease and healthy elderly: accuracy of 2 motion sensors. *Arch Phys Med Rehabil*. 2010;91:261-267.

133. Patel SA, Benzo RP, Slivka WA, Sciurba FC. Activity monitoring and energy expenditure in COPD patients: a validation study. *COPD*. 2007;4:107-112.

134. Hill K, Dolmage TE, Woon L, Goldstein R, Brooks D. Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease. *Thorax*. 2010;65:486-491.

135. Arvidsson D, Slinde F, Nordenson A, Larsson S, Hulthén L. Validity of the ActiReg system in assessing energy requirement in chronic obstructive pulmonary disease patients. *Clin Nutr*. 2006;25:68-74.

136. Cavalheri V, Donária L, Ferreira T, et al. Energy expenditure during daily activities as measured by two motion sensors in patients with COPD. *Respir Med*. 2011;105:922-929.

137. Dwyer TJ, Alison JA, McKeough ZJ, Elkins MR, Bye PTP. Evaluation of the SenseWear activity monitor during exercise in cystic fibrosis and in health. *Respir Med*. 2009;103:1511-1517.

138. McCloskey M, Redmond A, Pyper S, McCabe C, Westerterp K, Elborn J. Total energy expenditure in stable patients with cystic fibrosis. *Clin Nutri*. 2001;20:235-241.

139. Tudor-Locke CE, Myers AM. Challenges and opportunities for measuring physical activity in sedentary adults. *Sports Medicine*. 2001;31:91-100.

140. Trulock E. Management of lung transplant rejection. *CHEST Journal*. 1993;103:1566-1576.

141. American Thoracic Society, American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*. 2003;167:211-277.

142. Campbell P, Saiman L, Marshall B, Hazle L. *Infection prevention and control policy*. 2013. Available at http://www.cff.org/aboutCFFoundation/InfectionPreventionControlPolicy/, Accessed September 11 2014.

143. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

144. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general US population. *Am J Respir Crit Care Med*. 1999;159:179-187.

145. Mahler DA, Mejia-Alfaro R, Ward J, Baird JC. Continuous measurement of breathlessness during exercise: validity, reliability, and responsiveness. *J Appl Physiol (1985)*. 2001;90:2188-2196.

146. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc*. 1982;14:377-381.

147. Jones NL, Makrides L, Hitchcock C, Chypchar T, McCartney N. Normal standards for an incremental progressive cycle ergometer test. *Am Rev Respir Dis*. 1985;131:700-708.

148. Livingstone M, Coward WA, Prentice AM, et al. Daily energy expenditure in free-living children: comparison of heart-rate monitoring with the doubly labeled water (2H2 (18) O) method. *Am J Clin Nutr*. 1992;56:343-352.

149. Spurr G, Prentice A, Murgatroyd P, Goldberg G, Reina J, Christman N. Energy expenditure from minute-by-minute heart-rate recording: comparison with indirect calorimetry. *Am J Clin Nutr*. 1988;48:552-559.

150. Ceesay SM, Prentice AM, Day KC, et al. The use of heart rate monitoring in the estimation of energy expenditure: a validation study using indirect whole-body calorimetry. *Br J Nutr*. 1989;61:175-186.

151. Spicher V, Roulet M, Schutz Y. Assessment of total energy expenditure in free-living patients with cystic fibrosis. *J Pediatr*. 1991;118:865-872.

152. Mc Closkey M, Redmond AO, Mc Cabe C, Pyper S, Westerterp KR, Elborn SJ. Energy balance in cystic fibrosis when stable and during a respiratory exacerbation. *Clin Nutr*. 2004;23:1405-1412.

153. Charnes A, Frome E, Yu P. The equivalence of generalized least squares and maximum likelihood estimates in the exponential family. *JASA*. 1976;71:169-171.

154. Weir JB. New methods for calculating metabolic rate with special reference to protein metabolism. 1949. *Nutrition*. 1990;6:213-221.

155. Skumlien S, Hagelund T, Bjørtuft Ø, Ryg MS. A field test of functional status as performance of activities of daily living in COPD patients. *Respir Med*. 2006;100:316-323.

156. R Core Team. A language and environment for statistical computing. R foundation for statistical computing; 2014. Available at www.R-project.org, Accessed September 11 2014.

157. Martin Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet*. 1986;327:307-310.

158. Health Canada. Canada's food guide: estimated energy requirements. Available at http://www.hc-sc.gc.ca/fn-an/food-guide-aliment/basics-base/1_1_1-eng.php, Accessed August 29 2014.

159. Trumbo P, Schlicker S, Yates AA, Poos M. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids. *J Am Diet Assoc*. 2002;102:1621-1630.

160. Van Remoortel H, Raste Y, Louvaris Z, et al. Validity of six activity monitors in chronic obstructive pulmonary disease: a comparison with indirect calorimetry. *PLoS One*. 2012;7:e39198.

161. Rabinovich RA, Louvaris Z, Raste Y, et al. Validity of physical activity monitors during daily life in patients with COPD. *Eur Respir J*. 2013;42:1205-1215.

162. Cox NS, Alison JA, Button BM, et al. Validation of a multi-sensor armband during free-living activity in adults with cystic fibrosis. *J Cyst Fibros*. 2014;13:347-350.

163. Hill K, Dolmage TE, Woon L, Goldstein R, Brooks D. Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease. *Thorax*. 2010;65:486-491.

164. Kulstad R, Schoeller DA. The energetics of wasting diseases. *Curr Opin Clin Nutr Metab Care*. 2007;10:488.

165. Creutzberg EC, Schols AM, Bothmer-Quaedvlieg FC, Wouters EF. Prevalence of an elevated resting energy expenditure in patients with chronic obstructive pulmonary disease in relation to body composition and lung function. *Eur J Clin Nutr*. 1998;52:396-401.

166. Fitting JW, Frascarolo P, Jéquier E, Leuenberger P. Resting energy expenditure in interstitial lung disease. *Am J Respir Crit Care Med.*1990;142:631-635.

167. Wouters EF. Nutrition and metabolism in COPD. *CHEST*. 2000;117:274S-280S.

168. Donahoe M. Nutritional support in advanced lung disease: the pulmonary cachexia syndrome. *Clin Chest Med*. 1997;18:547-561.

Appendices

Appendix A. Step-by-step cardiopulmonary exercise testing protocol

***Step 1(No Stage)* –** Patients were fitted with a headset, nose clip, mouthpiece attached to an antibacterial filter, automated blood pressure monitor, pulse oximeter, and a multi-lead ECG monitor and then seated on an electronically braked SensorMedics cycle ergometer properly adjusted for each patient. All required patient demographic and anthropometric data were input into the Vmax metabolic computer program which controls the intensity stages of the exercise.

***Step 2(Baseline)* –** After at least 3 minutes of resting comfortably on the cycle, we measured and recorded the subject's resting HR, blood pressure, oxygen saturation, and sense of dyspnea and perceived leg discomfort using the modified 10-point Borg scales at baseline. These Borg scores were recorded at each incremental stage of the CPET exercise stage (step 4) as well. Subjects were also instructed to perform three resting inspiratory capacity (IC) maneuvers.

***Step 3(Warmup)* –** To acclimatize patients to the cycling exercise they were instructed to warm-up for 1 minute by pedaling between 60-70 revolutions per minute (rpm) at a 0 watt (W) workload.

***Step 4(Exercise)* –** Following the brief 1 minute warm-up period patients continued pedaling at the same cadence as we conducted a progressive incremental exercise (every 2 minutes) protocol for each subject where the power increased electro-magnetically by 15 W every 2 minutes in a stepwise fashion for CF, COPD and ILD patients. If needed, an adapted protocol were implemented where the intensity increased by 10 W every 2 minutes instead of 15 W.. Appropriate protocol selection was determined by communication with treating physician and/or physical therapist. During this step, we continuously monitored the patient's blood pressure, HR, VO_2, RQ, and Borg scores at each incremental stage. Inspiratory capacity was measured during the last 30 seconds of each incremental stage. Exercise was terminated when the patient requested to stop.

***Step 5(Recovery)* –** Following exercise termination patients continued cycling at a self-selected comfortable work rate for a self-determined time period and continue resting until HR returned to baseline levels. The duration of this cool-down stage varied from subject to subject. During this time, all measurement equipment except for ECG monitoring equipment was removed from the patients.

Appendix B. Calculations of standard deviation of difference from previous validation literature

Study 1: Flex Method versus gold standard

Lead Author:	McCloskey, M
Study Title:	Total energy expenditure in stable patients with cystic fibrosis
Journal Name:	Clinical Nutrition
Year:	2001
Study ID (j)	**Calculations for imputing missing parameters**
1	**Given in article:** Polar Sports Tester (Flex Heart Rate Method) vs Doubly Labeled Water • For free-living activities averaged over a 14 day time period**: o Xi = 9.14 o Si = 1.62 o Xr = 11.07 o Sr =2.44 o Xd = Not reported: 9.14-11.07 = -1.93 MJ/day o **Sd = Not reported –calculated below using calculated Rir** o **Rir = 0.73** ****recalculated all data from individual patient data reported in this study for patients with complete flex heart rate and doubly labeled water data.** $\mathbf{Sd^2_j = var(Xr_j - Xi_j) = var(Xr_j) + var(Xi_j) – 2Rir_j * Si_j * Sr_j}$ $\mathbf{Sd^2 = 2.44^2 + 1.62^2 – 2* 0.73 * 1.62 * 2.44}$ **= 2.81 MJ/day** **Sd = 1.68MJ/day** **Units in Kcal/day:** **1kcal = 0.004184 MJ** Xd = -1.9MJ/day / 0.004184MJ/Kcal = -454.1 kcal/day Sd = (1/0.004184) * 1.7 = 406.3 kcal/day Sd = 406.3kcal/day /1440min/day = 0.3 kcal/min

Study 2 : SenseWear versus gold standard

Lead Author:	Patel, SA
Study Title:	Activity monitoring and energy expenditure in COPD patients: A validation study
Journal Name:	COPD: Journal of chronic obstructive pulmonary disease
Year:	2007
Study ID (j)	**Calculations for imputing missing parameters**
2	**Given in article:** SenseWear Pro Armband (Multi Sensor Activity Monitor) vs Indirect Calorimetry (Vmax ST, Sensormedics) • For 2 walk tests (six minute walk and incremental shuttle walk), cumulated over both tests (will need to confirm with author that the total time of these two walks was 14 minutes [6 plus 8 minutes]): o Xi = NOT GIVEN (request from author) o Si = NOT GIVEN (request from author) o Xr = NOT GIVEN (request from author) o Sr = NOT GIVEN (request from author) o Xd = **-2.8 kcal***** o **Sd = 4.3 kcal** o **Rir =0.93 (P<0.001)*** reported as the correlation between the devices during cumulative kcals from both of the 2nd walks.** **Units in Kcal/min:** Assuming 14 minutes of sampling time over which the energy expenditure was accumulated: Xd = 2.8 kcal / 14 min = 0.2 kcal/min Sd =sqroot($(1/14)^2$ * $(4.3\text{kcals})^2$) Sd = 0.31 = 0.3 kcal/min