Physical Activity in COPD

Dr Yogini Raste

The National Heart & Lung Institute, Imperial College

Submitted for the degree of Doctor of Philosophy (PhD)

Imperial College London, January 2016

Copyright declaration

The copyright of this thesis rests with the author and is made available under a Creative Commons Attribution Non-Commercial No Derivatives licence. Researchers are free to copy, distribute or transmit the thesis on the condition that they attribute it, that they do not use it for commercial purposes and that they do not alter, transform or build upon it. For any reuse or redistribution, researchers must make clear to others the licence terms of this work.

Declaration of originality

The data arising from this thesis is entirely a result of my own work. The work of others is appropriately referenced.

Acknowledgements

I spent the last 5 years only imagining writing these words, so it is with some relief, as well as a sense of achievement that I am finally able to do so. My journey on this PhD has certainly been nothing I expected it to be, but I have learnt a great deal about my chosen subject, as well as about myself, for which I am grateful.

To this end I must thank the people who enabled me to complete my PhD. First and foremost, I must thank my supervisors Dr Nick Hopkinson and Professor Mike Polkey, who appointed me to my research fellow post in the Muscle Lab at the Royal Brompton Hospital, and from whom I have learnt an enormous amount about COPD, respiratory physiology and research as a whole. I must also thank Professor Mary Morrell for mentoring me and providing much appreciated sensible advice.

None of this work could have taken place without the Muscle Lab, whose members past and present I must also thank: Sam Clark, Katrina Curtis, Claire Davey, Anna Donaldson, Davide Elia, Julia Kelly, Dario Martolini, Patrick Murphy, Mehul Patel, Helen Purcell, Divya Sharma, Dinesh Shrikrishna, Cayley Smith and Zaid Zoumot. Special thanks must go to Becky Tanner, who worked with me throughout, not only on the PROactive project but also on all things 'Muscle Lab'; and also to Afroditi Boutou for statistical help and general PhD advice. The wider London Respiratory Muscle Group also needs a mention, specifically, Eui-Sik Suh, Vicky MacBean and Bronwen Connolly. Integral to our research is the work of the Respiratory Physiology Department at the Royal Brompton Hospital, whose physiologists are a font of knowledge and always willing to help in our studies. Also thanks to the Respiratory BRU staff for their support.

My thesis could not have taken shape without the work of the PROactive project and I must thank Professor Thierry Troosters from Leuven, Belgium, along with Hans Van Remoortel, Chris Burtin, Daniel Langer, who all helped me whilst I was in Leuven, first learning how to do the study for Chapter 3 and then later, when analysing the (tons of) data, which subsequently led to a successful publication. Also thanks to Professor Judith Garcia-Aymerich for her guidance throughout WP4 which led to the work in Chapter 5.

Last but not least, I must thank my family for their unwavering support throughout the last 5 years – my husband Amol, with whom I am blessed to have our three wonderful children Anusha, Omkar and Manisha, all of whom were born throughout this PhD; my sisters Devayani and especially Shalini, who always provided a sympathetic ear; and finally my inspirational parents, Udaya and Mukund, to whom this thesis is dedicated.

15th January 2016

Abstract

Reduced physical activity is an important feature of Chronic Obstructive Pulmonary Disease (COPD). This thesis explores the importance of technical, environmental and patient factors in physical activity in COPD.

Activity monitors are integral in accurately measuring physical activity in COPD but, to date, commercially available monitors had not been satisfactorily validated in this patient group. The first study (Chapter 3) was a multicentre validation study of 6 different physical activity monitors in a laboratory setting in 40 COPD patients, against a gold standard of indirect calorimetry from a portable metabolic kit. Validity was assessed by correlation of each monitor output with indirect calorimetry during a standardised activity protocol (including slow and fast walking, sitting, standing, lifting and stair climbing). From this method, three triaxial accelerometers were found to be the most accurate activity monitors (SenseWear Armband, Actigraph GT3X and Dynaport MiniMod). The Dynaport MiniMod and Actigraph GT3X were best able to discriminate between different walking speeds.

Chapter 4 describes a further validation study of 3 of the activity monitors used in Chapter 3, as well as a novel activity monitor (the Imperial eAR monitor) in a domestic setting in 20 UK-based patients. Monitor outputs were assessed against a gold standard of indirect calorimetry from the doubly labelled water method.

Chapter 5 describes a multicentre longitudinal study of 236 COPD patients. Physical activity was measured at 3 different time points over 12 months with 2 triaxial monitors (Actigraph GT3X and Dynaport MiniMod) previously validated in the laboratory study (Chapter 3) with the aim to assess the effect of time, geographic location and climatic conditions on physical activity. There was a significant effect of time with a decline in physical activity over time. There was no effect of centre on activity despite differences in baseline characteristics. These changes were demonstrated with both activity monitors. There was also a significant effect of temperature and day length with lower levels of activity associated with lower temperatures and shorter day length, although the effect of day length was only demonstrated with the Actigraph device. This has implications for future studies in COPD using physical activity as an outcome measure, in terms of adjusting for climatic conditions in multicentre trials. In addition, a decline in physical activity over time across several European centres supports the importance of physical activity in the course of COPD and early intervention to attenuate its decline.

The breathing response to the initiation of exercise in COPD and its association with daily physical activity levels was investigated (Chapter 6). A rapid shallow pattern of breathing on exertion is commonly found in COPD, which worsens with disease severity. Dyspnoea is arguably the most important symptom that limits patients during exertion and behavioural adoption of this maladaptive breathing pattern early in exercise was hypothesised to be associated with lower levels of daily physical activity; however, this link was not found. Tackling the perception of dyspnoea during physical activity successfully may enable patients to be less symptomatic and therefore increase their daily activity levels, which could attenuate disease progression. This represents an important therapeutic target.

Further work assessing a semi-automated coaching tool with a smart phone and pedometer in an interventional study to increase physical activity in COPD is ongoing, The use of devices in both research and clinical settings in both COPD as well as other patient groups to increase physical activity levels remains an exciting opportunity for future work.

Publications arising from this thesis

Raste Y, Langer D, Burtin C, Louvaris Z, Giavedoni S, Costa F, Wilson F, Rabinovich R, Hopkinson N, Vogiatzis I, Peterson B, Troosters T. *Validity of 6 activity monitors during standard physical activities in COPD – Comparison with indirect calorimetry* Presented as a spoken session at the annual ERS Congress, Amsterdam 2011.

Van Remoortel H & **Raste Y**, Louvaris Z, Giavedoni S, Burtin C, Langer D, Wilson F, Rabinovich R, Vogiatzis I, Hopkinson NS, Troosters T on behalf of the PROactive consortium. *Validity of Six Activity Monitors in Chronic Obstructive Pulmonary Disease: A Comparison with Indirect Calorimetry*. PLoS One. 7(6): p. e39198

Rabinovich RA, Louvaris Z, **Raste Y**, Langer D, Van Remoortel D, Giavedoni, S, Burtin C, Regueiro E, Vogiatzis I, Hopkinson NS, Polkey MI, Wilson FJ, MacNee W, Westerterp KR, Troosters T on behalf of the PROactive consortium. *Validity of physical activity monitors during daily life in patients with COPD.* Eur Respir J, 2013. 42(5): p. 1205-15.

Gimeno-Santos E, **Raste Y**, Demeyer H, Louvaris Z, de Jong C, Rabinovich RA, Hopkinson NS, Polkey MI, Vogiatzis I, Tabberer M, Dobbels, Ivanoff N, de Boer W, van der Molen T, Kulich K, Serra I, Basagana X, Troosters T, Karlsson & Garcia-Aymerich G on behalf of the PROactive consortium. *The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease.* Eur Respir J, 2015. 46(4): p. 988-1000.

Table of contents

1 Introduction 19

1.1 Physical activity and COPD: summary 19

1.2 Physical activity 21

1.2.1 Patterns of physical activity 21
1.2.2 Physical activity: historical perspective 22
1.2.3 Physical activity: the evidence 24
1.2.4 Physical activity: the benefits 26

1.3 Physical activity in COPD 28

1.3.1 Pulmonary rehabilitation and the relationship with physical activity 29

1.4 COPD pathophysiology 31

1.4.1 Main pathological features of COPD 31
1.4.2 Disease mechanisms 32
1.4.3 COPD as a systemic disease 34

1.5 Mechanisms of exercise limitation in COPD 38

1.5.1 Ventilatory factors 38
1.5.2 Other factors 40

1.6 Measuring physical activity 41

1.6.1 Physical activity questionnaires 41
1.6.2 Physical activity monitors 44
1.6.3 Energy expenditure and physical activity 45

1.7 Physical activity and exercise capacity 47

1.7.1 The Borg scale of perceived exertion 48
1.7.2 Cardiopulmonary exercise testing 48
1.7.3 Field exercise capacity tests 51

1.8 Physical activity: behaviour versus physiology? 54

1.8.1 Barriers to physical activity 54

1.8.2 The effect of weather on physical activity…… 55

1.9 The PROactive project..... 56

1.10 Thesis aims 58

2 Methods 59

2.1 Ethical approval 59

2.2 Statistical analysis..... 59

2.3 Study subjects 59

2.4 Pulmonary Function Testing 60

2.5 Exercise testing 60

2.5.1 The Borg scale of perceived exertion…….. 60
2.5.2 Six minute walking test (6MWT)……61
2.5.3 Cardiopulmonary exercise testing…… 62

2.6 Indirect calorimetry..... 64

2.6.1 Indirect calorimetry: doubly labelled water (DLW) method……64.
2.6.2 Indirect calorimetry: ventilated hood method…….. .64

2.7 Measurement of muscle strength..... 65

2.8 Body composition analysis 65

2.8.1 Bioelectrical impedence analysis (BIA)…… 65
2.8.2 Dual energy x-ray absorptiometry (DEXA) scanning ……..66

2.9 Health-related quality of life questionnaires 66

2.9.1 The Medical Research Council Dyspnoea Scale……66
2.9.2 The Chronic Respiratory Diseases Questionnaire (CRQ)…… 67
2.9.3 The St. George's Respiratory Questionnaire (SGRQ)…….. 67
2.9.4 The COPD Assessment Test (CAT)…….. 67
2.9.5 The Clinical COPD Questionnaire (CCQ)……68

3 Laboratory validation of six activity monitors in COPD: a comparison with indirect calorimetry 69

3.1 Introduction 69

3.2 Materials and Methods 69

3.2.1 Study subjects 69
3.2.2 Study design 70
3.2.3 Expired gases method of indirect calorimetry 72

3.3 Statistical analysis 75

3.3.1 Primary outcomes 76
3.3.2 Secondary outcomes 76

3.4 Results 76

3.5 Discussion 83

3.5.1 Significance of the findings 83
3.5.2 Critique of the method 84

4 Domestic validation study of physical activity monitors in COPD in daily life 86

4.1 Introduction 86

4.1.1 The Imperial College eAR monitor 88

4.2 Materials and methods 90

4.2.1 Study subjects 90
4.2.2 Study design 90
4.2.3 Doubly labelled water method of indirect calorimetry 91
4.2.4 Measurement of resting energy expenditure 91

4.3 Statistical analysis 92

4.3.1 Primary outcomes 92
4.3.2 Secondary outcomes 92

4.4 Results 93

4.5 Discussion 100

4.5.1 Significance of the findings 100
4.5.2 Critique of the method 101

5 Change in physical activity with time and climate in COPD 104

5.1 Introduction 104

5.2 Materials and methods 106

5.2.1 Study subjects 106
5.2.2 Physical activity monitoring 108
5.2.3 Weather data 108

5.3 Data handling and statistical analysis 108

5.4 Results 110

5.5 Discussion 121

5.5.1 Significance of findings 121
5.5.2 Limitations 123

5.6 Conclusion 124

6 Changes in early exercise in patients with COPD and their association with daily physical activity 126

6.1 Introduction 126

6.2 Methods 129

6.2.1 Cardiopulmonary exercise testing 129
6.2.2 Six minute walk tests 130
6.2.3 Physical activity monitoring 131

6.3 Data analysis 131

6.3.1 Exercise data 131
6.3.2 Six minute walks 132
6.3.3 Physical activity data 132

6.4 Results 132

6.4.1 Cardiopulmonary exercise testing 132
6.4.2 Six minute walk tests 135

6.5 Discussion 137

6.5.1 Significance of findings…… 137
6.5.2 Critique of the method…… 138
6.5.3 Conclusions…… 140

7 Conclusions and future work 141

7.1 Laboratory validation of six activity monitors in COPD: a comparison with indirect calorimetry. 141

7.1.1 Summary of findings……141
7.1.2 Limitations……..143
7.1.3 Future work……... 143

7.2 Domestic validation study of physical activity monitors in COPD in daily life 145

7.2.1 Summary of findings……145
7.2.2 Limitations……..146
7.2.3 Future work……...148

7.3 Change in physical activity with time and climate in COPD 148

7.3.1 Summary of findings……149
7.3.2 Limitations……..150
7.3.3 Future work……...151

7.4 Changes in early exercise in patients with COPD and their association with daily physical activity 152

7.4.1 Summary of findings……152
7.4.2 Limitations……..152

7.5 Future research..... 154

7.5.1 Change in PRO over time…….. 154
7.5.2 Physical activity as an interventional therapy…….. 154
7.5.3 Wider use of activity monitors – implications in public health……....155
7.5.4 Further study of the ventilator response to exercise in COPD…….. 156

8 References 158

List of figures

Figure 3.1 Position of the activity monitors and metabolic kit 71

Figure 1.1 Example of one patient's experiment, showing indirect calorimetry data from the Oxycon Mobile (METs) plotted against the different activity monitor outputs……77

Figure 1.2 Minute-by-minute correlations (R) between activity monitor outputs and metabolic equivalents of task (METs) per patient……78

Figure 3.4 Bland-Altman plot showing comparisons of manual step counts with Sensewear, Dynaport Minimod and Video step counts. 79

Figure 3.5 Bland Altman plot showing comparison of manual step count with Sensewear an Dynaport Minimod monitors for slow and fast paced walking 80

Figure 3.6 Mean correlations of each activity monitor output with indirect calorimetry (METs). 81

Figure 3.7 Bland regression analysis for each activity monitor output versus indirect calorimetry (IC). 82

Figure 4.1 Imperial eAR monitor 88

Figure 4.2 Example of data from eAR monitor. 89

Figure 4.3 Coefficient of variation for each patient for each activity monitor. 94

Figure 4.4 Percentage difference in mean activity between weekday and weekend for activity monitor output (with maximum and minimum difference plotted on error bars) 94

Figure 4.5 Correlations between activity monitor outputs and 6 minute walk distance. 96

Figure 4.6 Correlations between activity monitor outputs and active energy expenditure measured with doubly labelled water (AEE..... 97

Figure 4.7 Correlations between monitor outputs and AEE as calculated by the Weir method using measured REE values from the ventilated hood.. 98

Figure 4.8 Bland-Altman plot of Sensewear (SW) and RT3 energy expenditure (EE) versus total energy expenditure (TEE) as measured by the doubly labelled water method. 99

Figure 4.9 Correlations between eAR activity index and other activity monitor outputs (significant correlations shown). 100

Figure 5.1 WP4 study design 107

Figure 6.1 Lung compliance as a function of respiratory rate in an emphysema patient 129

Figure 6.2 Relationship of steps per day with FEV_1, RV/TLC ratio, six minute walk distance and TLco 133

Figure 6.3 Example from one patient: Area under curve for tidal volume (VT) and respiratory rate (RR) for first minute of loaded cycling. 134

Figure 6.4 Graphs showing linear regression for area under curve for VT, RR and VT/RR 134

Figure 6.5 Linear regression of K values for all patients plotted against time periods of 1 minute for rest, unloaded cycling, 10W, 20W and at peak exercise. 135

Figure 6.6 Area under curve for VT and RR against steps per day for slow and fast walks. 136

Figure 6.7 AUC VT to AUC RR for slow and fast walks during the first minute of exercise. 136

Figure 6.8 Linear regression of k values against steps per day for slow and fast walks. 137

List of tables

Table 3.1 Patient characteristics 73

Table 3.2 Details of type, location and output of the six activity monitors 74

Table 3.3 Schedule of physical activities in the standardised protocol. 75

Table 4.1 Patient characteristics 92

Table 1.1 Baseline characteristics of all patients at Visit 1……...111

Table 5.2 Baseline characteristics by centre & ANOVA 113

Table 5.3 Results of repeated measures ANOVA 115

Table 5.4 AG mvpa ln……116

Table 5.5 AG VMU ln 117

Table 5.6 AG steps ln……117

Table 5.7 MMwalktime ln 118

Table 5.8 MMintensity ln 118

Table 5.9 MMsteps ln 118

Table 5.10 MM VMU ln 119

Table 5.11 Baseline characteristics in dropout subjects vs non-dropout subjects. 120

Table 6.1 Patient characteristics – cardiopulmonary exercise testing……..130

Table 6.2 Patient characteristics – six minute walk distance 130

Abbreviations

AC	activity count
AEE	active energy expenditure
AG	Actigraph activity monitor
ANOVA	analysis of variance
AP-1	activator protein-1
AU	arbitrary unit
AUC	area under the curve
BIA	bioelectrical impedence analysis
BMI	body mass index
BP	blood pressure
bpm	beats per minute
CaO_2	oxygen concentration of arterial blood
CAT	COPD assessment test
CCQ	Clinical COPD Questionnaire
CD	compact disc
$CD8^+$	cluster of differentiation
CF	cystic fibrosis
CHAMPS	Community Healthy Activities Model Program for Seniors
COPD	chronic obstructive pulmonary disease
CPET	cardiopulmonary exercise test
CRP	c-reactive protein
CRQ	Chronic Respiratory Questionnaire
CSA	cross-sectional area
CvO_2	oxygen concentration of venous blood
DEXA	dual energy x-ray absorptiometry

DLW	doubly labelled water
Δt	sampling interval
ECG	electrocardiogram
EE	energy expenditure
EELV	end expiratory lung volume
EFL	expiratory flow limitation
EILV	end inspiratory lung volume
EU	European Union
FFM	fat free mass
FFMI	fat free mass index
$FECO_2$	fractional instantaneous concentration of expired CO_2
FEO_2	fractional instantaneous concentration of expired O_2
FEV_1	forced expiratory volume in 1 second
FIO_2	fractional instantaneous concentration of inspired O_2
FVC	forced vital capacity
GP	general practitioner
GOLD	Global initiative for chronic Obstructive Lung Disease
HAD A	Hospital anxiety and depression scale – anxiety score
HAD D	Hospital anxiety and depression scale – depression score
HDL	high density lipoprotein
hs-CRP	high sensitivity c-reactive protein
IGF-1	insulin-like growth factor-1
IL-6	interleukin-6
ILD	interstitial lung disease
IPAQ	International Physical Activity Questionnaire
ISWT	incremental shuttle walk test
K2	rate of elimination of deuterium

K18	rate of elimination of 18-oxygen
kCal	kilocalories
kDa	kilo Dalton
LC3B	light chain 3B
Ln	natural logarithm
MET	metabolic equivalent of task
MM	Minimod activity monitor
mmHg	millimetres of mercury
MMP-2	metalloproteinase-2
MMP-9	metalloproteinase-9
Mol	moles
MRC	Medical Research Council
6MWD	six minute walk distance
NF-κB	nuclear factor kappa B
NT-BNP	N-terminal pro-B-type natriuretic peptide
OEP	opto-electronic plethysmography
PaO2	partial pressure of arterial oxygen
PEEPi	intrinsic positive end expiratory pressure
PF	pulmonary fibrosis
PM10	particulate matter 10
ppm	parts per million
PR	pulmonary rehabilitation
PRO	patient reported outcome
Q	cardiac output
QMVC	quadriceps maximal voluntary contraction
rco_2	rate of co_2 production
REE	resting energy expenditure

rpm	revolutions per minute
ROC	receiver operator curve
ROS	reactive oxygen species
RR	respiratory rate
RV	residual volume
SGRQ	St George's Respiratory Questionnaire
SMP-30	senescence marker protein-30
Te	expiratory time
TEE	total energy expenditure
Ti	inspiratory time
TLC	total lung capacity
TLCOc	corrected transfer factor of lung for carbon monoxide
TNF-α	tumour necrosis factor-α
TORCH	Towards a Revolution in COPD Health
TwQ	twitch quadriceps force
VC	vital capacity
VCO_2	carbon dioxide output
VE	minute ventilation
VMU	vector magnitude units
$VO_{2\ max}$	maximal oxygen uptake
VO_{2peak}	peak oxygen uptake
VQ	ventilation perfusion
W	watts
WHO	World Health Organisation
WR	work rate

1 Introduction

1.1 Physical activity and COPD: summary

Physical activity is defined as any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level [1], thus encompassing both formal exercise as well as many activities of daily living. Adequate levels of physical activity are vital for health and well-being in all populations; physical inactivity is one of the most prevalent modifiable risk factor in a number of non-communicable diseases including chronic obstructive pulmonary disease, COPD [2-6].

COPD is a chronic progressive condition caused by inhalation of noxious particles, such as cigarette smoke or biomass fumes. It is a major worldwide health problem, with global prevalence estimated at around 10% of the adult population [7]. Prevalence continues to increase, particularly in the developing world, largely due to the increase in tobacco use and it is now the third largest cause of death globally [8]. COPD is characterised by poorly reversible airflow limitation and destruction of lung parenchyma. Loss of lung elastic recoil leads to gas trapping, resulting in hyperinflation. Ventilatory capacity is reduced and patients experience breathlessness and exercise limitation.

The significance of physical inactivity in COPD is well established, not only as a consequence of exercise limitation and dyspnoea which has a direct effect on patients' quality of life, but as an important factor in disease progression at an early stage, even perhaps before onset of other symptoms [9]. In fact, recent worldwide epidemiological studies have highlighted physical inactivity as a leading contributor to morbidity and mortality in non-communicable diseases, estimated to have caused 9% of worldwide mortality in 2008 alone [10].

Increasing physical activity in COPD should therefore be a cornerstone of treatment in COPD. Pulmonary rehabilitation has been proven to be the most cost effective intervention in COPD, over and above any pharmacological therapy including inhaled bronchodilators [11]. Exercise training forms an integral part of pulmonary rehabilitation, with the aim of increasing participants' exercise capacity. This, along with the education provided to patients to enable them to be more autonomous in managing their condition, should promote increased daily physical activity. Those patients who are able to complete pulmonary rehabilitation do show improvements in exercise capacity, dyspnoea and quality of life measures. There is also good evidence to show it is a safe and effective intervention to reduce hospital admission, morbidity and mortality in patients who have recently suffered an exacerbation of COPD [12].However, the effects on daily physical activity are less clear; a recent

review by Spruit et al have highlighted the difficulties with translating the benefits experienced from pulmonary rehabilitation, in terms of exercise capacity and quality of life, to 'real life' improvements in daily physical activity [13], with only some studies showing an increase in levels of physical activity after completion of a pulmonary rehabilitation programme. [14-16]. For example, Walker et al evaluated the effect of a standard 8 week programme in 24 patients with moderate to very severe COPD using an accelerometer and found an increase in time spent mobile, mean activity score and mean activity intensity, as well as improvements in exercise capacity, health related quality of life measures and lower limb function. Conversely, other studies have found no increase in physical activity following pulmonary rehabilitation [17-19]. For example, Saunders et al looked at the effect of 7 pulmonary rehabilitation programmes, both community and hospital based, on daily physical activity in 294 COPD patients, as measured by a pedometer. There was no change in daily steps after completion of rehabilitation [19].

Despite the clear benefits, only around a third of patients referred for pulmonary rehabilitation actually complete a course with a third never actually even starting [20]. In addition, the beneficial effects of pulmonary rehabilitation are short-lived, lasting approximately 6 months for a typical programme of 8 to 12 weeks [21]. This, along with the mixed outcomes from studies looking at levels of daily physical activity following pulmonary rehabilitation, suggests that COPD patients find it difficult to make lifestyle changes necessary to increase daily physical activity and thus sustain the benefits that are gained in the short term through pulmonary rehabilitation.

Being able to measure daily physical activity levels in COPD accurately could make it easier for clinicians to facilitate patients to increase their daily physical activity, either following a course of pulmonary rehabilitation, or as an alternative if patients were unable to access a course. This could potentially improve both effectiveness and cost-effectiveness of COPD management, as well as encouraging patient autonomy. A number of sophisticated physical activity monitors are now available and this has made objective measurement of physical activity in COPD patients possible in a number of circumstances, such as in the community, during rehabilitation programmes [18], during exacerbation and hospital admission [22], and in response to pharmacotherapy [23]. Most of the monitors currently available have been validated in healthy subjects, but not necessarily in patients with chronic diseases. As such patients, including those with COPD, are less physically active and move more slowly than healthy subjects [24], the validity of these monitors to detect movement in these patients needs to be evaluated.

In addition, other factors which determine patients' ability to be physically active need to be clearly understood, if they are to be influenced in a positive manner by clinicians. These include environmental factors such as weather and climate, geographical location and accessibility to

rehabilitation programmes; and personal factors such as other co-morbidities, personal motivation and disease factors which may be specific to that individual such as perception of breathlessness. A comprehensive understanding of all determinants of physical activity in COPD will enable more effective interventions to be delivered in this population.

1.2 Physical activity

Physical activity is defined as '*any bodily movement produced by the contraction of skeletal muscle that increases energy expenditure above a basal level'* [1]; thus it incorporates not only formal exercise but also movements a patient must undertake whilst performing many activities of daily living. In contrast, exercise[1] is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective of the improvement or maintenance of physical fitness [25].The World Health Organisation recommends that healthy adults aged 18 to 64 years should do at least 150 minutes of moderate to vigorous intensity aerobic physical activity, in at least 10 minute bouts, (which roughly equates to 30 minutes five times a week), as well as muscle strengthening exercise at least twice a week [26]. The importance of physical activity in healthy populations is well established; it is one of the most prevalent modifiable risk factors for a number of chronic diseases such as cardiovascular disease, diabetes, osteoporosis, cancer, obesity and depression [2-6].

1.2.1 Patterns of physical activity

1.2.1.1 Aerobic or endurance activity

This involves movement of the large muscle groups, such as walking, running or cycling, and increases oxygen consumption from resting levels. Repeated aerobic activity improves cardiovascular fitness, that is, the ability of the heart to deliver oxygen to the muscles for use, and how efficiently that process occurs.

1.2.1.2 Resistance activity

Resistance training is any exercise that causes the muscles to contract against an external resistance, such as weight training, sprinting or resistance cycling. This improves muscle condition as well as bone strength.

[1] Exercise and physical activity as terms are often used interchangeably but are not synonymous; exercise is a subset of physical activity.

1.2.1.3 Flexibility activity

Stretching improves joint flexibility and stretches muscles, improving range of motion, thereby reducing risk of injury.

1.2.1.4 Frequency and amount of activity

Frequency refers to the number of times per week the activity is carried out. As mentioned above, WHO recommendations are for a total of 150 minutes per week, but ideally at least 30 minutes 5 times per week.

Amount can be described in terms of duration i.e. the number of minutes the activity is performed; and intensity, that is, the energy expended per minute as compared to resting energy expenditure levels. A common expression of intensity is the MET, or Metabolic equivalent of Task, defined as 3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$, or 1 MET. This value is typically considered to be resting metabolic rate. Light intensity is classified as less than 3 METS (such as slow walking), moderate 3 to 6 METS (such as light cycling or fast walking) and vigorous above 6 METS (such as jogging).

1.2.2 Physical activity: historical perspective

"Lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it." – Plato (427-347 BC)

The benefits of physical activity in the general population have long been established; there are records of exercise being prescribed for health and well-being in the ancient civilisations of China, Greece and India [27, 28].

Over two thousand years ago, in 600 BC, Susruta, an ancient Indian physician, was the first recorded physician to prescribe exercise for health, stating that "*it should be taken every day*" but "*only to half extent of his capacity*" as otherwise "*may prove fatal*" and was *"absolutely conducive to a better preservation of health"*. He advised consideration of the age and strength of the patient beforehand. He prescribed diet and exercise to cure diabetes, and also observed that exercise '*made the body stout, strong, firm, compact, and light, enhanced the growth of limbs and muscles, improved digestion and complexion, prevented laziness, and reduced senility*' [29].

Hippocrates, widely considered to be the father of modern medicine, wrote on the importance of diet and exercise: '*eating alone will not keep a man well; he must also take exercise. For food and exercise work together to produce health'*. In his work 'Regimen in Acute Diseases', he gives a detailed account of the personalisation of exercise, gymnastics and diet according to that person's individual nature. He suggested modification to diet and exercise that should be made according to season. He recognised that exercise should not be excessive as that would also have detrimental effects, for example regarding horseriding: *''Horse riding causes chronic arthritis because the legs are always suspended. In serious cases, the cohesion of the tissues on the ischium totally loosens up and the horsemen are lamed...'* He also advised on how exercise should take place, for example '*walks after gymnastics..., running with the clothes on ….*' and *'….the holding of the breath...'[30]*

500 years after Hippocrates, Galen emerged as one of the most influential physicians of the ancient period. He began studying medicine at the age of 16 and was physician to the gladiators. His theories were heavily influenced by Hippocrates' humoral theory which taught that an imbalance of the humors caused disease. He developed his own medical theory based on the 'natural' or physiological factors, 'non-natural' or external factors such as exercise and diet and the pathological or disease factors. Exercise was prescribed for several illnesses such as gout, dyspepsia, arthritis and depression. He specified that the activity had to be vigorous enough to cause laboured breathing [31].

After Galen, during the Renaissance period and further, integral to the historical development of medicine as a discipline was the study of anatomy and physiology of exercise as well as of health and illness. For example, Andreas Vesalius (1541-64) was a Dutch physician and anatomist who produced high quality anatomical drawings. He tried to connect form to functions, that is, that nerves controlled muscle movement. This was an important development in the evolution of medicine as a modern science. Lavoisier (1743-94) was the first person to conduct experiments on human respiration and supervised the first physiology experiment during which the subject breathed through a copper pipe and oxygen consumption and heart rate were measured in response to increasing the work of depressing a foot pedal. William Prout (1785-1850), the English chemist and physician, measured expired CO_2 when exercising to exhaustion and found it to increase in fatiguing exercise.

The first formal exercise physiology laboratory was established in Harvard University in 1891. This was followed by the Harvard Fatigue Laboratory in 1927 which specialised in experimental physiology. Its importance emerged with the outbreak of the Second World War as it had the only experimental altitude chamber, valuable to the US Air Force, as well as hot and cold chambers, which were valuable in assessing the physiological effects of extreme climates on soldiers.

1.2.3 Physical activity: the evidence

Despite the historical roots of exercise prescription for health and treatment of disease in the ancient civilisations of Greece and India, as far back as ancient Greece, the importance of physical activity in the primary prevention of disease has come to prominence in modern medicine only more recently, since the work of Jerry Morris in the 1950s.

Morris and his colleagues were the first to describe the link between physical activity and coronary artery disease, specifically the protective effects of physical activity in cardiovascular disease, through large epidemiological studies. It had long been observed that, for example, bus drivers seemed to have a higher incidence of cardiovascular disease than bus conductors, raising the possibility that those in physically demanding jobs were more protected from cardiovascular disease than their sedentary peers; this was formally demonstrated in Morris' landmark 1953 study [32]. It was the first large scale study showing the long term health benefits associated with physical activity. In a subsequent study looking at post mortem data on cause of death in nearly 4000 patients, they found an almost threefold increase in incidence of large healed myocardial infarcts in those occupied in light work [33].

Similar work from a US group led by Paffenbarger in over 6000 Californian longshoreman followed and supported these findings, that is, the more physically active longshoreman had lower all-cause mortality rates [34]. Over 30 years after Morris' original study, similar results were reported in Pafferbarger's Harvard alumini study. Nearly 20000 Harvard alumini were followed over 16 years; again, all-cause mortality was better for those individuals who were more physically active. In this particular study physical activity was self-reported via questionnaire [35].

Another landmark study, the Whitehall study, was initiated by Professor DD Reid in 1967, and was so dubbed because its subjects were male civil servants based in London. It was ground-breaking in terms of the scale of the study, and its analysis of the implications of the social gradient on health. Confining the study to the London civil service minimised the number of confounding variables, thus strengthening its findings. Of the 18403 participants recruited from 1967 to 1969, 17530 were included in the final analysis of mortality and morbidity by Professor Sir Michael Marmot in 1978 [36]. As well as measuring parameters such as pulse, blood pressure and BMI, questionnaires were used to gather information on leisure activities including physical activity. The main findings were that workers in higher grades had lower mortality compared to those in lower grades. They also had lower blood pressure and smoking rates, as well as higher physical activity levels, albeit self-reported.

The Whitehall II study was set up in 1985 by Marmot and investigated the effects of the work and home environment on long term health outcomes in over 10000 civil servants[37], this time in both male (6900) and female subjects (3414) aged between 33 and 55 years. The findings were similar, in that moderate or vigorous exercise was less common in those in lower grade jobs.

In a follow up phase of Whitehall II, physical activity (self-reported via a questionnaire) and inflammatory markers (high sensitivity C-reactive protein, hs-CRP; and interleukin-6, IL-6) were measured in 4289 men and women (mean age 49.2 years). 49% were found to adhere to the guideline of 2.5 hours of moderate or vigorous physical activity per week. Those who were more physically active had lower levels of inflammatory markers at baseline and these remained stable over 10 years. This suggests that physical activity may be important in preventing the pro-inflammatory state which accompanies ageing and that may lie behind the development of chronic diseases [38]. Logically the counter hypothesis would of course be that an inflammatory condition (of whatever cause) reduced patients' physical activity.

Several subsequent large meta-analyses have found a lower relative risk of death for those men and women who reported increased levels of physical activity and fitness. Nocon *et al* performed a systematic review and meta-analysis of 33 studies with 883,372 subjects [39]. The studies were prospective in nature and had to have a minimum of 5000 participants from a general, healthy population. Follow up ranged from 4 to 20 years. They found reductions in cardiovascular and all-cause mortality of 35% and 33% respectively between the least active and most active subjects. However there was great heterogeneity in the risk reductions found, from 16 to 57%, which they attributed to the method of recording activity. Larger risk reductions were found where fitness tests were used. Participants may have tended to overestimate their activity in a self-reported questionnaire, thereby reducing the beneficial effect of activity. Interestingly, in the subgroup analysis, lower reductions of mortality were found where questionnaires rather than objective measures (e.g. fitness test) were used to assess physical activity levels. However the authors acknowledge that there may be publication bias in favour of positive studies. Samitz *et al* conducted a similar analysis of 80 studies with 1338143 participants, but studies with at least 2 years follow up were included [40]. They classified outcomes according to intensity (low, moderate and vigorous) and domain of activity (sports and exercise, occupational and daily living). They found both the domain and intensity to be important; risk reduction was greatest for vigorous activity and for occupational and sports activity. They also found that studies which used complex questionnaires showed a lower risk reduction, perhaps due to difficulties administering the questionnaires, as did those studies with longer follow up (greater than 11 years), which could be explained by under-powering from loss of subjects to follow up.

The difficulty with any such analysis is that it is observational and therefore prone to bias. There is great heterogeneity when analysing such a large number of studies, which may cause confounding. It is also unclear whether it is the intensity rather than duration of activity or total energy expended that is important in mortality reduction. This can only be established in a prospective randomised interventional study.

However, the evidence supporting physical activity in overall health is such that the World Health Organisation has recognised physical inactivity as one of the most important risk factors threatening global health [26]. In fact, it could be argued that there is now a pandemic of physical inactivity, with an estimated 31% of the world's population not meeting minimum recommendations for physical activity [41]. 6-10% of all non-communicable diseases are attributable to physical inactivity; this rises to around 30% in ischaemic heart disease [7]. The economic cost of morbidity due to physical inactivity is a substantial burden on health systems and society as a whole. Reduced physical activity is associated with urbanisation and modernisation; there has been a definitive shift in morbidity from communicable diseases to non-communicable diseases in countries which have undergone recent rapid modernisation and industrialisation, such as China and India [42]. With improved survival rates due to improved medical care, as well as falling birth rates, in both the developed world and the newly industrialised countries, the health burden of an ageing population is a more prescient concern. People over the age of 65 years make up one of the fastest growing population segments in industrialised countries; they carry the greatest proportion of the chronic disease burden, disability and health utilisation. They are also the most sedentary and physically inactive [43]. However, of growing concern is the lack of physical activity in adult populations as a whole, resulting in these diseases, traditionally associated with advanced age, manifesting at an earlier age [44].

1.2.4 Physical activity: the benefits

The benefits of physical activity have been demonstrated in a number of chronic diseases.

1.2.4.1 Cardiovascular disease

Cardiovascular disease, including coronary artery disease and cerebrovascular disease, is the most prevalent chronic disease accounting for approximately 50% of deaths worldwide [45]. Physical inactivity is one of several modifiable risk factors, as well as hypertension, hyperlipidaemia, smoking, obesity and elevated blood glucose levels. With regard to exercise based interventions, several studies have shown a reduction in cardiovascular mortality in myocardial infarction patients who have

participated in cardiac rehabilitation which includes physical activity and exercise [46].A meta-analysis by O'Connor et al of 22 randomised controlled trials of cardiac rehabilitation with over 4000 patients demonstrated a 20% mortality reduction at 1 year [47]. However, a similar problem to that of pulmonary rehabilitation exists, in that it is difficult to sustain the benefits gained from an initial course of cardiac rehabilitation. A subanalysis of two randomised controlled trials of exercise based cardiac rehabilitation by Ribeiro et al in 50 patients following myocardial infarction showed that physical activity levels measured with an accelerometer were increased immediately after rehabilitation [48]. However, Ayabe et al showed that physical activity levels in patients on days that they were not attending cardiac rehabilitation were significantly lower than on rehabilitation days [49]. Butler et al showed that physical activity levels were only sustained at 6 months following rehabilitation if patients were given a pedometer based intervention [50]. Nevertheless, other benefits of exercise based cardiac rehabilitation also include improved muscle strength and aerobic capacity; and reduced blood pressure, submaximal heart rate, inflammatory markers, and HDL cholesterol [51].

1.2.4.2 Type 2 diabetes

The worldwide incidence of type 2 diabetes is increasing with UK prevalence approximately 7.4% or 3.2 million adults [52]. There is also an increased incidence of impaired glucose tolerance which confers a 10% risk of subsequently developing type 2 diabetes [53]. Type 2 diabetes is strongly associated with physical inactivity, so increasing physical activity is a key intervention in both primary and secondary prevention [54]. Aerobic exercise has been shown to improve insulin sensitivity [55]. A review of several exercise programmes targeted at diabetic patients has shown that one week of at least moderate intensity exercise can improve insulin sensitivity [56]. Other benefits include weight loss, lowering of systolic blood pressure and improved lipid profile which in turn has positive effects on the known associated increased cardiovascular risk [57].

1.2.4.3 Cancer

Cancer is the second leading cause of death worldwide, causing around 15% of all deaths. There is evidence to support the association of physical inactivity with certain malignancies such as breast, prostate and colon cancer [58]. Moreover, studies have demonstrated improved survival in patients previously diagnosed with cancer who are more physically active. For example, Holmes et al followed approximately 3000 women diagnosed with breast cancer between 1984 and 1998 until 2002 or death. They categorised their physical activity levels according to MET-hours per week and found that survival rates were better in those women who had an average of the equivalent of walking 3 to 5 hours a day have an adjusted relative risk of 0.5 of mortality during follow up compared to those who were less active [59]. Whilst this evidence is compelling, it is difficult to know whether this is

confounded by disease severity rather than a true effect of physical activity. However it may be beneficial to incorporate exercise into the management plans of patients with diagnosed with cancer.

1.2.4.4 Osteoporosis

Osteoporosis is a chronic degenerative multifactorial metabolic disease of bone. It results in reduced bone density and increased propensity to fractures and associated pain. Physical activity stimulates bone formation through weightbearing and improved associated muscle strength, and is important in disease prevention [60]. In patients with established osteoporosis, exercise is still a valuable therapy once pain is controlled, as it can improve balance and muscle strength and reduce falls risk [61].

1.3 Physical activity in COPD

Given the significance of physical activity in the general population, it would come as no surprise that it is also an important factor is COPD and there is a growing body of work to support this. In one of the first studies to confirm the finding that had only been previously demonstrable from questionnaire data - that patients with chronic respiratory disease are less physically active in day to day life than healthy controls - Schonhofer *et al* [62] used simple pedometers to quantify physical activity objectively in COPD patients compared to controls. This was, in the main, a feasibility study to show that it was possible to carry out this kind of measurement in this patient group. A later study by Pitta *et al* used a more sophisticated monitor to show that indeed COPD patients are less physically active than aged-matched healthy subjects; they spend less time walking or standing and more time lying or sitting, and when they are moving, they are doing so at a much lower intensity compared to healthy subjects [24, 62]. Time spent walking also correlates strongly with measures of functional exercise capacity such as six minute walking distance.

However, it is in day-to-day life that COPD has its greatest impact; patients report being unable to complete activities of daily living (such as dressing, shopping, household tasks), due to physical limitation [63, 64]. Exercise capacity and quality of life measures are often impaired disproportionately to lung function [65]. There is increasing evidence, mainly epidemiological, that reduced physical activity is not only a manifestation of disease severity in COPD, but is intrinsic to disease progression. A large population based cohort study by Garcia-Aymerich *et al* 2007 assessed a random population sample of nearly 7000 adults that had been previously recruited into the Copenhagen City Heart Study and followed up over a ten year period. Physical activity was assessed by questionnaires on occupational and spare time work originally devised by Saltin and Grimby in 1968, and then

categorised into low, medium and high activity levels. They found that healthy smokers with increased levels of physical activity show a slower decline in lung function compared to healthy but less active smokers, as well as a lower risk of developing COPD [9]. There also seems to be a dose-response relationship – the higher the levels of activity amongst smokers, the lower the decline in lung function and therefore incidence of COPD.

In another study, a subset of the same cohort (2386 subjects) who had been diagnosed with COPD, were followed over a mean 12 year period. Using similar physical activity data, it was found that those who reported some regular physical activity (low, moderate or high levels) had a reduced risk of both hospital admission and mortality compared to those who reported very low levels of physical activity [66]. The importance of physical activity in hospital admission is further supported by the finding that patients with COPD and low reported physical activity levels also have an increased risk of readmission after a severe exacerbation [67].

The results of these large cohort studies are compelling, but could be criticised for the way the activity data was collected – questionnaires as opposed to objective measurement – as there is scope for recall bias and inaccuracy of self-reporting in terms of under or overestimating amount of activity undertaken. There is also the potential problem of survival bias; those surviving being more physically active, causing an underestimation of the effect of physical activity. These drawbacks seem to necessitate a more reliable method of measuring physical activity in not only this group of patients, but in the general population.

1.3.1 Pulmonary rehabilitation and the relationship with physical activity

This is a multidisciplinary programme of care for patients with chronic respiratory impairment, including COPD, that is individually tailored and designed to optimise physical and social performance and autonomy [68]. The fundamental components are a structured and regular exercise programme and an education programme, giving advice on nutrition, medication, and social aspects of the disease (e.g. available financial support) [69]. The aim of pulmonary rehabilitation is not to reverse the disease process, but to reduce the symptoms experienced, and therefore the distress caused; and also to encourage patients to be more independent and able to self-manage their disease as far as possible. Exercise is essential to this process; the patients are supervised during the classes and taught how to manage their dyspnoea to eventually enable them to increase their exercise capacity, and therefore their daily physically activity once they have finished the programme.

Notwithstanding the heterogeneity of rehabilitation programmes, specifically with respect to exercising training intensity, a Cochrane meta-analysis of numerous studies involving pulmonary rehabilitation in COPD has found both short and long term benefits. Pulmonary rehabilitation improves exercise capacity, muscle endurance, dyspnoea and quality of life-related outcome measures. There is also evidence to show that pulmonary rehabilitation is highly effective and safe intervention to reduce hospital admission, mortality and health-related quality of life in patients who have recently suffered an exacerbation of COPD [70, 71].

Despite the clear benefits of pulmonary rehabilitation, one of the main shortcomings is that the effects are short-lived, and this seems to be inherent to the way that most programmes are delivered. The majority are between 8 to 12 weeks in duration; the beneficial effects in terms of improved exercise capacity and quality of life measures tend to decline after 6 months. However, these effects are greater and more sustained if programmes are longer. For example, a study comparing 3 months versus 18 months rehabilitation showed a greater increase in six minute walk distance and health-related quality of life after the longer programme. Another study showed the effects of 6 months of rehabilitation were sustained up to 18 months after completion [72]. However, even with these longer programmes, effects do seem to eventually wane [21]. Long term maintenance strategies that have been tried include prescribed structured home exercise programmes, or monthly maintenance classes with weekly telephone contact. These have been shown to maintain the benefits gained from rehabilitation compared to those who did not have such input [73].

Thus it follows that if pulmonary rehabilitation were truly successful in effecting behaviour change in COPD, then one would expect to find increased levels of physical activity well after completion. Although there is improvement in measures of exercise capacity such as six minute walk distance, when it comes to daily physical activity levels as an outcome measure, the results are less convincing. A meta-analysis by Cindy Ng et al [74] looked at studies which investigated the effect of exercise training, of at least 4 weeks, on physical activity levels measured with an activity monitor. Only 7 studies (with a total number of 472 subjects) met their criteria, none of which were randomised controlled trials. There was great heterogeneity amongst the studies; some included pulmonary rehabilitation as the intervention, while others just used a general exercise programme with or without counselling; sample size also varied greatly. Overall only a very small positive effect on physical activity levels was found as a result of pulmonary rehabilitation of formal exercise training. A more recent review by Spruit et al [13] echoes the previous systematic review; they cite 12 studies (including 6 studies not reviewed by Cindy Ng et al) which evaluated the effect of pulmonary rehabilitation on physical activity in COPD. Results were inconsistent: 3 studies showed increased activity levels (measured with an activity monitor) immediately after a standard 8 week programme in both inpatient and outpatient settings [14-16]; 5 studies had negative findings with no increase in physical activity immediately after pulmonary rehabilitation [17-19, 75, 76]; the remaining 3 studies

showed mixed results with some measures improving (such as daily step count) and others not (such as movement intensity [77-79]. However whether any positive effect is maintained over a longer period of time is unknown.

Currently, pulmonary rehabilitation is the best 'weapon' in the clinician's armoury in terms of dealing with physical deconditioning and exertional dyspnoea in COPD, but it is far from perfect in dealing with physical inactivity in the long term. The benefits of physical activity on morbidity and mortality are undisputed. However, the evidence so far illustrates that it is much more difficult for patients to make lifestyle changes in order to sustain the physical benefits that are undoubtedly achievable in the short term. Therein lies the key to not only the long term success of pulmonary rehabilitation, but also the management of COPD as a whole.

1.4 COPD pathophysiology

COPD is essentially a chronic inflammatory disorder triggered by inhalation of noxious particles. How the cellular and molecular mechanisms link to the pathological findings, abnormal physiology and symptoms is still not fully understood. This is compounded by the considerable heterogeneity of the disease; patients with similar smoking backgrounds can have vastly differing disease phenotypes, ranging from widespread emphysema, to predominant airways disease with chronic bronchitis, to a mixture of both to a varying degree. Indeed, only around a quarter of all smokers will go on to develop COPD (although up to half may have abnormal spirometry without symptoms) [80], and of these, some will have a more rapid progression in disease than others, emphasising the importance of genetic susceptibility and other host factors in its pathogenesis.

1.4.1 Main pathological features of COPD

1.4.1.1 Chronic bronchitis

Cigarette smoke triggers infiltration of the bronchial wall with inflammatory cells, predominantly macrophages and $CD8^+$ lymphocytes, with increased number of fibroblasts [81]. Damage to the bronchial wall endothelium impairs the mucociliary response, which causes mucous secretions to accumulate in the airway, resulting in obstruction. Chronic inflammation leads to goblet cell metaplasia, smooth muscle hyperplasia and peribronchial fibrosis. The airway is deformed with luminal narrowing, causing further airway obstruction [82].

1.4.1.2 Emphysema

This is defined as permanent enlargement of the airspaces distal to the terminal bronchioles. The pattern of emphysema typically seen in COPD is centriacinar (focal destruction limited to the respiratory bronchioles and the central portions of the acini), and is usually most severe in the upper lobes [83]. The result is a marked decline in alveolar surface area available for gas exchange. Loss of alveoli and supporting structures leads to reduced elastic recoil of the lung; airways collapse more easily, resulting in airflow limitation.

1.4.1.3 Hyperinflation

Reduced lung recoil means that equilibrium with the pressure exerted by the chest wall occurs at higher lung volumes, causing static hyperinflation. Dynamic hyperinflation can also occur, independent of or in addition to static hyperinflation. It results from air being trapped within the lungs after each breath due to a disequilibrium between the volumes inhaled and exhaled. The ability to fully exhale depends on the degree of airflow limitation and the time available for exhalation. Each of these can vary, causing greater hyperinflation for example during exacerbations or exercise. Both static and dynamic hyperinflation contribute significantly to the degree of breathlessness perceived by patients with COPD [84, 85].

1.4.2 Disease mechanisms

1.4.2.1 Abnormal inflammation

Cigarette smoke and other noxious substances trigger an abnormal and exaggerated inflammatory response in the lungs. The macrophage (which is activated by cigarette smoking) is perhaps the most important inflammatory cell in this response. In patients with COPD compared to normal smokers, macrophages seem to be more pro-inflammatory and this is further increased by exposure to cigarette smoke. There are increased numbers (5-10 times) of macrophages in the airways, sputum, bronchoalveolar lavage and parenchyma of patients with COPD [86]. They release inflammatory mediators such as TNFα, IL-8 and other chemokines, secrete elastases including matrix metalloproteinases 2 and 9 (MMP-2, MMP-9) and neutrophils elastases, and generate reactive oxygen species (ROS) [87].There are also increased numbers of other inflammatory cells, such as neutrophils and CD8+ T lymphocytes [88], but their role in the development of COPD is not as clear.

1.4.2.2 Oxidative stress

Oxidative stress is the cellular and molecular damage that occurs as a result of cumulative exposure to reactive oxidative species (ROS). Oxidative changes affect protein conformation, trafficking and DNA interaction. Cigarette smoke is an important exogenous source of ROS. Chronic smoking exposes the respiratory tree to ROS, either directly, or by stimulating their production, causing oxidative stress and injury [89, 90]. ROS activate NF-κB and AP-1, which switch on multiple inflammatory genes resulting in amplification of the inflammatory response [91]. Population studies have shown that genetic polymorphisms in antioxidant genes (e.g. superoxide dismutase 3), with the resulting reduced antioxidant levels, are associated with an increased susceptibility to emphysema in smokers [92]. It is therefore possible that smokers who go on to develop COPD are less able to deal with oxidative stress than normal smokers, providing a possible link between smoking and cellular mechanisms.

1.4.2.3 COPD: a disease of the ageing lung

Ageing is a natural process consisting of a progressive functional impairment and reduced capacity to respond appropriately to environmental stimuli and injury. For example, lung function declines with age in normal subjects; however, this decline is accelerated in COPD [93]. As the incidence of COPD increases with age, it is possible that abnormalities in the normal ageing process could contribute to the pathogenesis of COPD. Mechanisms of ageing are as follows:

Increased oxidative stress

As already discussed, oxidative stress has a role in the pathogenesis of COPD, and this may represent accelerated or abnormal ageing. Neutrophils, monocytes and macrophages show enhanced ROS production in mice models of ageing [94]. Telomere shortening (see below) has been shown to be enhanced by ROS in vitro and in vivo there is a strong correlation between telomere length and vascular dementia, typically a disease of ageing [95].

Changes in regulation of telomere length

Telomeres are the regions at each end of the chromosome containing a 1 to 5 kDa sequence of specific base pair repeats which protect the chromosome during cell division. Telomere shortening is a natural consequence of ageing, but length is also affected by cumulative oxidative stress and chronic inflammation. The telomeres of alveolar type II cells and endothelial cells of COPD patients have been found to be significantly shorter than those in age matched asymptomatic non smokers [96] and there is a dose-dependent relationship between smoking history and telomere length [97].

Cellular senescence

Cell death or senescence occurs once telomere shortening reaches a critical level, and is part of the normal ageing process. However increased senescence has been found in COPD. Exposure of lung fibroblasts and human alveolar epithelial cells to cigarette smoke in vitro results in senescence [98]. Patients with emphysema have increased expression of senescence markers in type II alveolar cells, [96, 99]. There is also a strong relationship between senescence and proinflammatory mediators such as NFkB. Telomerase deficient mice were found to have shorter telomeres in lung cells as well as higher levels of inflammatory markers in the lungs, which could result in protease release and therefore progression of emphysema [100].

Changes in anti-ageing molecules

Anti-ageing molecules may also have a role in the pathogenesis of COPD. Senescence marker protein-30 (SMP-30) levels increase in early life and decline with age. SMP-30 knockout mice develop changes in the lung consistent with emphysema and if these mice are exposed to cigarette smoke, they develop a greater degree of emphysema than wild type mice [101, 102]. Klotho is an important protein in cell senescence. It is a transmembrane protein that, amongst other effects, modulates insulin sensitivity, although its mechanism of action is not completely understood. Genetic variants in klotho are associated with human ageing and circulating serum klotho levels have been found to decline with age [103]. Klotho deficient mice have a shortened life span and display features of ageing such as thinned skin, accelerated atherosclerosis, osteoporosis and emphysema [104-107].

Apoptosis

Apoptosis is programmed cell death and serves to eliminate damaged or infected cells. There is evidence for a disruption in the balance between apoptosis and cell proliferation in COPD. Various studies have found increased apoptosis in alveolar and airway epithelial cells and interstitial cells of patients with COPD [99, 108]. There is also increased expression of autophagic proteins in emphysematous lungs [109]; autophagy is an important part of cell apoptosis. Ryter *et al* found increased autophagy in COPD lung specimens, both morphologically and with increased levels of autophagic regulator proteins such as beclin-1 and LC3B [110].

1.4.3 COPD as a systemic disease

COPD is no longer regarded exclusively as a disease of the lungs, but as a systemic disease with several extrapulmonary sequelae: skeletal muscle wasting, cachexia, low-grade systemic

inflammation, increased cardiovascular risk and metabolic disturbance (e.g. insulin resistance) [111, 112]. In fact, indices of airflow limitation, such as decline in FEV_1, correlate poorly with survival [113]. Other factors, such as exercise intolerance, dyspnoea, skeletal muscle wasting and weakness, and physical inactivity are better predictors of mortality [114, 115]. The pathophysiological mechanisms have not yet been fully elucidated, but many factors, including genetic susceptibility and local and systemic inflammation are involved.

1.4.3.1 Skeletal muscle in COPD

Peripheral skeletal muscle dysfunction, with loss of both strength and endurance, is a well recognised feature of COPD, with the lower limbs affected to a greater degree than the upper limbs, and has a significant role in exercise limitation and thus, reduced quality of life [116, 117].

The quadriceps muscle group is a major muscle of locomotion and dysfunction is common in COPD. Killian *et al* first described COPD patients reporting leg fatigue to be as limiting as breathlessness during a cycle cardiopulmonary exercise test [118]. Gosselink *et al* showed quadriceps strength (measured by maximal volitional contraction) correlated strongly with exercise capacity as measured by distance achieved in the six minute walk test [116]. Bernard *et al* found that COPD patients were around 30% weaker than controls [119]. They also found that although the cross-sectional area (CSA) of the quadriceps muscle group was smaller in COPD patients (on computed tomography), the ratio of strength to CSA was similar to that in controls, suggesting weakness was due to atrophy. In addition, the quadriceps muscles were proportionally weaker than the shoulder girdle muscles in COPD. Previous work in this group by Man *et al* has shown the type of activity to be important in terms of symptoms reported, with more patients reporting leg fatigue during cycling than whilst walking [120].

Endurance is defined as the capacity of the muscle to maintain a certain force over time; quadriceps endurance is also attenuated in COPD. Studies of quadriceps endurance have shown a reduction in endurance time compared to healthy controls, and also increased fatigue at equivalent workloads [121, 122]. Work in our lab by Swallow *et al* demonstrated increased quadriceps fatigue in COPD using repetitive magnetic stimulation of the femoral nerve [121].

It should be noted that quadriceps dysfunction in COPD is independent of airflow limitation; quadriceps weakness can be found in COPD patients with mild disease and yet be absent in those with severe airflow limitation [123, 124]. Analysis of the quadriceps muscle at the microscopic level is most commonly done through biopsies of the vastus lateralis which is the most easily accessible. A hallmark feature in COPD patients is a change in muscle fibre composition. In healthy elderly

subjects, muscle biopsy shows approximately 50% type I fibres (oxidative) and 50% type II fibres (type IIx glycolytic and type IIa intermediate oxidative/glyolytic fibres) and a minimal number of hybrid fibres. In contrast, COPD patients show an increase in type II fibres with more hybrid fibres, i.e. fibre shift [125]. Fibre atrophy has also been reported in some studies [126]. However, this morphology has recently been shown to be heterogeneous amongst COPD patients. Again, through work done in our lab, Natanek et al.analysed the quadriceps biopsies of 114 COPD patients and 30 controls with a range of findings in the patients compared to controls: isolated fibre shift in 31%, fibre atrophy alone in 20%, both fibre shift and atrophy in 25% and normal morphology in 24%. The findings correlated poorly to clinical parameters including lung function.

In contrast, there seems to be relative preservation of other muscle groups, such as the adductor pollicis and elbow flexors [127, 128]. The diaphragm is also preserved, perhaps even augmented; although transdiaphragmatic pressure is reduced in COPD, this is a result of hyperinflation which puts the diaphragm at a mechanical disadvantage, and is mitigated by correcting for lung volume [129, 130]. Biopsies of the diaphragm have shown a shift to fatigue resistant type I fibres, which is probably due to training of the muscle from increased work of breathing [131], Indeed, the accessory muscles of breathing have also shown a similar pattern in COPD [132].

Skeletal muscle dysfunction in COPD is clinically significant, both prognostically and from a treatment perspective. Quadriceps weakness is a better predictor of mortality in COPD than FEV_1. In fact, once FEV_1 has dropped below 50% predicted, it has no further influence on mortality [114]. Despite double lung transplantation restoring lung function, peak exercise capacity does not improve to the same degree and remains at 50% predicted at up to 2 years follow-up after surgery [133]. Furthermore, pulmonary rehabilitation, which improves exercise capacity, muscle function and quality of life, does not improve lung function [134]. Thus, muscle dysfunction represents an important treatment target in COPD.

1.4.3.2 Cachexia

Related to muscle dysfunction is cachexia, which encompasses weight loss, muscle atrophy, weakness, fatigue and loss of appetite. As loss of fat free mass is important, a definition for cachexia of fat free mass less than 16 kg/m^2 (men) and 15 kg/m^2 (women) has been proposed [135]. 20 to 40% of COPD patients will develop cachexia [136, 137], and it is associated with a 50% reduction in median survival [135].

1.4.3.3 Cardiovascular disease

There is a significant burden of cardiovascular disease amongst COPD patients; in fact, it is the cause of mortality in the majority of these patients, rather than lung failure [138]. In the TORCH study (Towards a Revolution in COPD Health), a multicentre randomised controlled study looking at all cause mortality in around 6000 COPD patients treated with either salmeterol/fluticasone propionate, salmeterol alone, fluticasone proprionate alone or placebo for 3 years [139], 25% of patients died from cardiovascular events [140]. The risk of cardiovascular events seems to be highest after exacerbations of COPD; Donaldson *et al* reported a 2.3 fold increase in myocardial infarction 1 to 5 days after an exacerbation [141], and exacerbation is also associated with an increase in biochemical markers such as NT-proBNP and troponin T [142]. Again, systemic inflammation is likely to play a significant role; its role in the development of atherosclerosis is well characterised [143]. Compared to age-matched controls, patients with stable COPD have increased levels of circulating platelet-monocyte aggregates, which are a sensitive marker of platelet activation, and are also raised in patients with acute coronary syndrome. These levels increase after an exacerbation [144], proving a potential pathological link between COPD exacerbations and cardiovascular events. Fibrinogen, an acute phase protein, has also been shown to be a useful biomarker in COPD, since fibrinogen levels are not only increased in COPD patients as compared to controls, but also because fibrinogen levels also correspond with frequency and severity of exacerbations [145]. Fibrinogen is also associated with cardiovascular mortality [146]. Pulse wave velocity, a measure of arterial stiffness, and thus cardiovascular disease has been shown to be increased in patients with COPD.[147]. In addition, it has been recently demonstrated that COPD patients who exacerbate frequently have increased arterial stiffness as measured by pulse wave velocity. These increases are slow to recover and are related to airway inflammation, which again lends weight to the argument that inflammation contributes significantly to cardiovascular disease in COPD [148].

There is also a significant incidence of cardiac dysfunction, both left and right sided, in patients with COPD. Cor pulmonale can develop in any chronic respiratory disease, including COPD and ILD, and is associated with increased pulmonary vascular resistance and right heart failure. CT scanning studies have shown a linear relationship between the extent of emphysema and airflow obstruction and degree of left ventricular filling impairment, whilst ejection fraction remains relatively preserved, indicating that subclinical haemodynamic changes do occur even in mild disease [149, 150].

1.4.3.4 Metabolic disease

Metabolic syndrome is characterised clinically by abdominal obesity, elevated triglycerides, dyslipidaemia, insulin resistance and/or high blood glucose and hypertension. It is associated with a pro-inflammatory and pro-thrombotic state [151, 152]. Bolton *et al* found an increased incidence of

insulin resistance and circulating inflammatory mediators in COPD patients, in the absence of diabetes [153].

1.4.3.5 Osteoporosis

Osteoporosis is characterised by a decrease in bone density and deterioration in bone microarchitecture, and is defined by the World Health Organisation as bone mineral density 2 standard deviations or more below the mean peak bone mass (average of young, healthy adults) as measured by dual-energy X-ray absorptiometry (DEXA) [154]. Patients with COPD have an increased risk of developing osteoporosis and the proportion increases with disease severity. Causative factors include smoking, low BMI, immobility and skeletal muscle dysfunction, glucocorticoid use and vitamin D deficiency. It is a significant cause of morbidity in these patients, with vertebral fractures affecting lung function and hip fractures resulting in decreased mobility [155].

1.5 Mechanisms of exercise limitation in COPD

As explained earlier, exertional dyspnoea is one of the cardinal features of COPD and is responsible for exercise limitation in the majority of patients of all disease severities, compared to their healthy counterparts [156]. Exercise limitation itself is a measure of poor health status in COPD [157]; measures of exercise performance, such as six minute walk distance or maximal oxygen uptake ($VO_{2\,max}$) on cardiopulmonary exercise testing, predict poor prognosis [158, 159]. Ventilatory limitation is the most common factor in these patients because of an inability to increase ventilation in response to the increased metabolic demands of exercise, although other factors such as cardiac and metabolic dysfunction also contribute to a greater or lesser extent [160, 161].

1.5.1 Ventilatory factors

1.5.1.1 Expiratory flow limitation and dynamic hyperinflation

Expiratory flow limitation is defined as the attainment of the maximal expiratory flow during tidal expiration and occurs when a further increase in transpulmonary pressure does not result in a further increase in expiratory flow [162]. It results from the pathological changes seen in COPD, namely airway narrowing from chronic inflammation and airway wall thickening, and parenchymal destruction leading to reduced elastic recoil and static hyperinflation, which causes early airway closure [163]. Expiratory flow limitation can be present during exercise alone, or in more advanced disease at rest

as well [164]. Patients with severe COPD often exhale along the same flow-volume curve during quiet breathing as during a forced expiratory vital capacity manoeuvre. Others may only reach this during exercise, in contrast to healthy individuals who do not reach this threshold on the flow volume curve even at maximal exercise [165, 166].

One of the consequences of EFL is dynamic hyperinflation; there is no way for flow limited patients to increase ventilation with the increasing metabolic demands of exercise other than to increase lung volumes. However, as respiratory rate increases, expiratory time falls, resulting in gas trapping, an increase in end expiratory lung volume (EELV) and a consequent reduction in inspiratory capacity. This means that end inspiratory lung volume (EILV) becomes positioned close to total lung capacity (TLC), and a further increase in tidal volume is not possible. Conversely in healthy individuals, there is often a fall in EELV and tidal volume never reaches TLC, even at maximum exercise [167].

1.5.1.2 Diaphragm and inspiratory muscle dysfunction

Both static and dynamic hyperinflation lead to inspiratory muscle impairment in some COPD patients through a number of mechanisms. Static hyperinflation causes diaphragm flattening and shortening of its fibres, reducing its force generating potential [168]. It is also unable to produce as much lateral expansion of the rib cage during inspiration. In severe dynamic hyperinflation, diaphragm contraction causes indrawing of the lateral rib cage as its fibres are orientated radially rather than axially. In addition, inward lateral recoil of chest wall means the inspiratory muscles need to work against this as well as lung elastic recoil and therefore need to generate more force to overcome PEEPi and increased elastic load.

1.5.1.3 VQ mismatch

Emphysema results in increased ventilation of poorly perfused areas due to parenchymal destruction of alveolar capillaries i.e. increased dead space. Conversely, chronic bronchitis leads to alveolar hypoperfusion and perfusion of underventilated areas i.e. physiological shunt. Both are measurable in even mild COPD, but become more prominent with increasing disease severity. On exercise, hypoxaemia may actually improve in milder COPD patients due to improved VQ matching [169].

However in severe disease, there is increased peripheral oxygen extraction and VQ mismatch [170]; dynamic hyperinflation, alveolar hypoventilation and worsening hypoxia [171]. Alveolar hypoxia and hypoxaemia increase respiratory neural drive with a subsequent increase in tidal volume and respiratory rate. However, an increased respiratory rate increases both dynamic elastance of the lung as well as dynamic hyperinflation, contributing to increased work of breathing [172].

1.5.1.4 Increased work of breathing

The work of breathing is that required from the respiratory muscles to overcome elastic forces (lung elastic recoil, thoracic cage displacement) and frictional forces (airway resistance). This is increased in COPD, as explained above, and in fact, during exercise, up to 50% of the metabolic cost of exercise can be due to this increased workload.

1.5.2 Other factors

1.5.2.1 Cardiac dysfunction

Hypoxia contributes to the development of pulmonary hypertension in COPD [173], although there is some evidence for pulmonary vascular remodelling in normoxic patients, perhaps as a result of low grade systemic inflammation [174]. In addition, evidence of right ventricular dysfunction has been found in both mildly hypoxic and normoxic COPD [175]. This right ventricular dysfunction can be exacerbated on exercise, resulting in a lower stroke volume and cardiac output [176].

Hyperinflation itself causes cardiac dysfunction due to intrathoracic pressure changes. MRI analysis of ventricular size in severe emphysema patients has shown reduced end diastolic volumes and stroke volume compared to healthy controls. In addition, decreased biventricular preload and relative intrathoracic hypovolaemia was attributed to hyperinflation [177]. On exercise, dynamic hyperinflation have been shown to be negatively correlated with the oxygen pulse ($r=0.48$), a surrogate for cardiac output [160]. Intrathoracic pressure swings limit stroke volume; the high intrathoracic pressures generated in severe airflow limitation impede venous return, so cardiac output falls.

COPD patients are also known to have excess risk for cardiovascular disease [178], which in itself could contribute to exercise limitation, for example as a result of ischaemia or heart failure.

1.5.2.2 Skeletal muscle dysfunction

As discussed earlier, skeletal muscle dysfunction is well recognised in COPD as a cause of exercise limitation [116]; patients are often equally limited by leg fatigue as by dyspnoea [118]. In particular, the muscles of the lower extremities seem to be more susceptible to changes associated with muscle dysfunction, namely reduced strength and endurance, and fatigability.

1.5.2.3 Deconditioning

Deconditioning is defined as a loss of physiological function as a result of reduction of training intensity and affects healthy subjects as well as those with chronic disease. COPD patients are much less physically active than their healthy counterparts, leading to the theory that deconditioning causes muscle dysfunction; However deconditioning affects all systems. Cardiovascular effects include reduction in maximal oxygen uptake capacity, an increase in resting heart rate and increased heart rate recovery time and a reduction in stroke volume [179]. Other metabolic effects include change in lipid profile towards less high density lipoproteins, reduction in muscle oxidative capacity and muscle fibre atrophy [180]. However, it is difficult to distinguish changes due to deconditioning and general lack of fitness from other changes in the muscle thought to be specific to COPD itself and not seen in other patient populations.

1.6 Measuring physical activity

1.6.1 Physical activity questionnaires

In order to change behaviour with a view to increasing patients' physical activity in day to day life, it is necessary to establish baseline levels of activity, but accurately measuring this remains challenging. When studying small numbers of subjects, direct methods of recording physical activity such as motion detectors or heart rate monitors can be used. However, this is simply not feasible when studying physical activity patterns at the population level. Where occupation had originally been used to classify levels of activity (such as in the Morris and Paffenberger studies), the changing and varied patterns of modern working life make this unreliable. Questionnaires are therefore the only practical alternative. Numerous questionnaires or surveys on physical activity (e.g. IPAQ [181], Yale physical activity questionnaire [182], CHAMPS [183], Harvard alumni questionnaire [184], Minnesota leisure time physical activity questionnaire [185]), have been used over the last few decadesin epidemiological studies, all measuring different factors over time periods of day to years. Whilst they are cheap, usually easy to administer and often the only feasible way to measure physical activity at a population level, there are several problems associated with their use.

1.6.1.1 Type of physical activity

Physical activity as an entity is not uniform or one-dimensional (such as measuring blood pressure or heart rate for example), which makes it challenging to be assessed accurately by questionnaires.

Activity itself can mean several things, as discussed earlier; anything from formal exercise to housework. Intensity, frequency, duration, aerobic and resistance activity are all different facets of physical activity, and questionnaires must be able capture all these aspects to truly reflect an individual's activity. For example, a common classification of intensity is to use METs with light exercise anything below 3 METs, to vigorous exercise above 6 METs. However, this classification is mainly based on values in young adults; thus what may be classed as light intensity for a 20 year old may actually constitute vigorous activity for a 50 year old, but a questionnaire may not be able to make this distinction if simply asking patients to list their activities.

1.6.1.2 Reliability

This is the ability of a questionnaire to give the same result on re-testing the same factor. (Measures of reliability include Chi squared statistics, the coefficient of repeatability and test/retest intraclass - correlation coefficients). Any changes on re-testing either represent true change from the subject or errors of subject reporting. In addition, if the test in administered by an observer, inter- and intra-observer errors can add to the inaccuracy.

Reliability is also compromised due to differing perceptions between individuals regarding perception of intensity or duration of exercise. As already mentioned, an activity which may constitute light exercise to one person may be vigorous to another and a questionnaire may not be able to assess this.

Reliability of response deteriorates the greater the interval between test and retest. For example, test/retest correlation coefficient on the college alumnus questionnaire found r values of 0.72 at one month, but only 0.3 to 0.4 at 12 months[186]. Similar findings were observed with other questionnaires, such as the CHAMPS questionnaire (r=0.58-0.67 at 6 months)[183].

Another reason for poor reliability is recall bias. This is a systematic error that occurs due to inaccuracies in the recollections retrieved. This is a particular problem in retrospective studies, particularly if the questionnaire is administered after a long time period after the activity to be measured.

Other sources of error include cultural or social pressures to respond in a certain, e.g. over-reporting amount of activity; or lack of awareness about what constitutes activity (such as under-reporting housework).

1.6.1.3 Validity

This is an important aspect of questionnaire design and refers to how well the questionnaire measures what it says it is measuring i.e. physical activity. Although there are many components of validity, criterion validity is the most relevant; that is, assessing the questionnaire against another related measure, such as energy expenditure as recorded by an activity monitor. For example, the Minnesota leisure time physical activity questionnaire was validated with a waist mounted activity monitor, resulting in a correlation coefficient of 0.69, although this fell to 0.43 when the monitor was to the leg [187]. The doubly labelled water method of measuring energy expenditure, although expensive and technically challenging, has also been used to validate questionnaires (this method is discussed later), for example, to assess the Baecke total activity index, giving a correlation coefficient of 0.68 [188].

1.6.1.4 Sensitivity

This refers to the ability of a questionnaire to detect change in the factor being measured, such as amount of activity. In one study, activity was measured with monitors and questionnaires in patients with peripheral arterial disease compared to controls. Activity monitor data suggested the patients' energy expenditure was only 46% of the controls, whereas the Stanford 7 day activity recall suggested it was much higher at 98% [189].

Floor effects are common and occur when the questionnaire is not sensitive to discriminate activity at lower levels. This is a major weakness in severe COPD patients who typically have low levels of activity and have poor repeatability and sensitivity [190].

The number of physical activity questionnaires is vast, all measuring physical activity in a different way, but very few have been tested for reliability, validity or sensitivity. For example, a systematic review by van Poppel et al [191] tested the measurement properties of 85 different physical activity questionnaires. Properties such as validity, responsiveness (i.e. does the questionnaire score change to reflect changes in the factor being measured?) and reliability were investigated. Validity was also assessed in 76 of these questionnaires using accelerometer or metabolic data. 51 were tested for reliability. Overall, few questionnaires had sufficient reliability and validity. They also found lack of standardisation of questionnaires, leading to many variations in questionnaires. They didn't find any questionnaire to be better than others and suggested more care when assessing the measurement properties of questionnaires in order to develop more reliable tools.

These problems have predicated the need for more accurate ways to measure physical activity, in order to not only study its effects, but also to implement changes to improve health.

1.6.2 Physical activity monitors

Physical activity monitors are devices which are increasingly used to provide objective measures of daily physical activity levels in both healthy subjects and patients. A wide variety of activity monitors are currently available, and they continue to grow in number, but they all have the common feature of piezoelectric accelerometers. The piezo[2]electric effect was first demonstrated in 1880 by the Curie brothers Pierre and Jacques, and is the property of certain crystals to exhibit electrical change under mechanical loading. (Examples include quartz, topaz and lead zirconate titanate).

Accelerometers are able to use the piezoelectric effect to transduce forces of movement, usually in two or three axes, into an electrical signal. Accelerations of the human body are usually less than 10Hz and between -6 to 6g (although higher forces occur during impacts and landings). Therefore the raw accelerometer signals require filtering to accurately reflect human movement. High pass filters remove low frequency signals such as normal gravitational force; this allows monitors to record zero acceleration when a person is stationary. Conversely, low pass filters remove high frequency accelerations and electrical interference (typically at around 20Hz in order to capture the full range of human movement).

These signals can then be transformed into a measure of energy expenditure using one of a number of algorithms, or summarised as activity counts or vector magnitude units (reflecting acceleration of the body in different planes). With the information obtained in the vertical plane or through pattern recognition, steps or walking time can also be derived by some monitors.

Due to their very nature, accelerometers are not perfect in their measurement of movement. Sources of error include detection of gravitational acceleration, external vibration or jolting of the sensor due to incorrect fastening, all of which are not attributable to actual physical activity. Positioning of activity monitors is important to consider. The manufacturers of several monitors indicate their preference of position to be at the hip, as this position will capture walking but is perhaps less obtrusive than a thigh or ankle worn device. However, wrist and arm worn devices are also available. Lower limb-positioned

[2] Piezo from the Greek *piezin,* meaning to press or squeeze

monitors may capture walking and running activities more accurately than arm or wrist worn monitors, but upper limb devices may better capture activities such as lifting. However, Bouten *et al* have found very little difference in prediction of energy expenditure during physical activity from monitors placed in different positions on the body, despite positional differences in absolute movement detected; change in movement, and therefore acceleration, from baseline was more important [192].

A well-known limitation of activity monitors is their inability to accurately detect incline walking, which requires more effort but with relatively unchanged accelerometry compared to walking on the flat [193]. There is on the whole an underestimation of energy expenditure for activities with a large force:displacement ratio (such as stair climbing or knee bends), versus an overestimation with activities such as running or jumping with a low force:displacement ratio [194].

1.6.3 Energy expenditure and physical activity

As previously discussed, energy expenditure has long been accepted as the reference measure of physical activity. Early studies have shown a linear relationship between body acceleration and energy expenditure during physical activity [195, 196]. Most of the validation studies of contemporary physical activity monitors have been done against some form of energy expenditure measurement, known as calorimetry.

1.6.3.1 Whole body direct calorimetry

Energy released from metabolism results in heat production, which can be measured directly in a human calorimetry chamber. This is a well-insulated, adequately ventilated chamber, above which are a series of coils through which water flows, absorbing the heat released from the room. The difference in temperature of the water at the start and end of the circuit can be used to calculate energy expenditure. Air circulation is also carefully controlled to avoid heat loss from expired gases. Although highly accurate, this method is expensive and not widely available, requires a great deal of technical expertise, and is not suitable for field studies.

1.6.3.2 Indirect calorimetry

Indirect calorimetry uses the principle that, in order to produce energy from food, the body must use oxygen and produces carbon dioxide as a waste product. There are a number of accepted methods, depending on the time scale over which measurements are to be made, described below. Resting

energy expenditure, REE, that is, the amount of energy required by the body during a 24 hour period in resting conditions, can thus be estimated according to the abbreviated Weir equation:

$$\text{REE per day (kcal)} = [3.9\ (VO_{2\ ml/min}) + 1.1(VCO_{2\ ml/min})] \times 1.44$$

This takes into account certain assumptions about the composition of the 'fuel' or dietary intake of carbohydrates, fat and protein; all are metabolised using oxygen to produce energy, water and carbon dioxide, although protein is usually only metabolised during periods of negative energy balance e.g. starvation. The respiratory quotient (RQ) is the ratio of carbon dioxide produced to oxygen consumed. The RQ for carbohydrate metabolism is 1; for fat it is 0.7; for an equal mixture it is 0.85.

Indirect calorimetry: expired gases method

This can be measured directly, using the ventilated hood method [197]. Patients are instructed to lie still under a canopy after an overnight fast. The canopy is connected to an analyser and the changes in oxygen and carbon dioxide concentrations are measured over a 30 minute period. Resting energy expenditure can be calculated using the Weir equation as described above. Similarly, expired gases analysis during cardiopulmonary exercise testing can also be used to calculate energy expenditure at rest and during exercise. Both methods are useful when making measurements over minutes or hours.

Indirect calorimetry: doubly labelled water method

This method can be used for measurements over longer time periods. The technique is based on the administration of water containing a known quantity of two stable isotopes of water, $^{2}H_2O$ and $H_2{}^{18}O$. The water equilibrates throughout the body. Labelled hydrogen will leave the body as water (urine, sweat), whereas labelled oxygen will leave as both water and carbon dioxide. The difference between the levels of the two isotopes can be measured in the urine, indicating the amount of carbon dioxide produced. This represents the amount of energy expended since carbon dioxide is a waste product of metabolism. Urine samples are typically collected over a two week period, so the end result is total energy expenditure (TEE) over that time period, i.e. the total amount of energy (in calories or joules) expended at rest and during physical activity per day. Active energy expenditure can be calculated by subtracting resting energy expenditure from this total. Again, energy expenditure is calculated using the abbreviated Weir equation [198].

Estimating energy expenditure

Predicted resting energy expenditure (REE) can also be estimated using the Harris Benedict equations [199], which predict values for individuals based on age, sex, weight (in kilograms) and height (in metres).

Male: (66.5 + 13.8 x weight) + (5.0 x height) - (6.8 x age)

Female: (665.1 + 9.6 x weight) + (1.8 x height) - (4.7 x age)

Active energy expenditure (AEE) is calculated as $(0.9 \times TEE) - REE$, assuming diet-induced thermogenesis to be 10% of total energy expenditure (TEE).

It is important to note that these predicted values apply to healthy subjects, and are not necessarily accurate for all COPD patients. It is known that COPD patients have higher resting energy requirements, reportedly around 10% higher than demographically matched healthy subjects [200]. Fat free mass is the main determinant of resting energy expenditure, but when cachectic COPD patients are compared to non-COPD patients with cachexia, they have higher resting energy expenditure levels [201]. A number of mechanisms have been postulated. Hypoxia itself causes sympathetic activation, which leads to up-regulation of the mitochondrial enzyme, cytochrome oxidase, and increased oxygen consumption [202, 203]. Increased work of breathing is more 'energy expensive', as is poor mechanical efficiency [204, 205]. Muscle fibre shift itself may be responsible, as type II fibres consume more oxygen per unit than type I fibres [206]. The role of systemic inflammation as a driver for increased energy expenditure is less clear; some studies have found an association with TNFα, a marker of inflammation; others have not [207, 208]. Medications such as theophyllines and beta agonists have also been shown to increase resting energy expenditure in COPD [209, 210]. Regardless of the mechanism, this phenomenon needs to be taken into account when estimating active energy expenditure values for COPD patients, particularly when validating physical activity monitors against this so-called 'gold standard'.

1.7 Physical activity and exercise capacity

Exercise capacity and physical activity are two distinct concepts but are often erroneously used interchangeably. Exercise capacity is a measure of an individual's maximum ability to do work and

can be measured in a number of ways, including walking or cycling tests, whereas physical activity is the amount of activity of any type that a person actually does that raises energy expenditure above a basal level, as explained earlier.

Exercise testing is useful to assess functional capacity, degree of disability, prognosis for survival, limitations such as exercise-induced hypoxaemia and response to interventions. Exercise testing can be divided into field tests, such as the six-minute walk test and incremental and endurance shuttle tests; and cardiopulmonary exercise testing which is carried out on either a treadmill or braked bicycle, with measurement of metabolic data via expired gases analysis, cardiac monitoring via ECG and perceived exertion with the Borg scale.

1.7.1 The Borg scale of perceived exertion

Gunnar Borg first described the perception of exertion as a 'gestalt' of numerous stimuli from the heart, lungs, muscles, joints, as well as perceptions of pain, anxiety, heat and resistance to movement (e.g. whilst pedalling, or walking uphill) [211]. Thus, the Borg scale was developed in order to better understand an individual's perceived exertion whilst undertaking physical activity. The 15 point scale from 6 (none) to 20 (maximum) was originally designed in this way to be directly scalable to heart rate (by a factor of 10); there are good correlations between Borg score and heart rate during exercise [177]. A modified 11 point version (0 to 10) with ratio properties (see p 55) was subsequently developed to be easier to use (i.e. if 4 is 'light', then 2 will be half as much exertion etc.) The scale can be applied to both breathlessness and leg fatigue, and scores for both factors are recorded before and immediately after any exercise test.

1.7.2 Cardiopulmonary exercise testing

The gold standard of assessment of exercise capacity is cardiopulmonary exercise testing, during which several cardiovascular, respiratory and metabolic variables can be collected for a dynamic, global assessment of the integrated physiological response to exercise which cannot be assessed by measuring the function of individual organ systems alone. Usually this test is carried out on either a treadmill or a static bike. Both submaximal and peak exercise responses can be assessed, and well as giving information on functional exercise capacity and impairment, CPET aids evaluation of undiagnosed exercise-induced dyspnoea, and preoperative assessment of patients with cardiopulmonary disease [212].

1.7.2.1 Principles of CPET testing

The metabolic response to exercise is determined through measurement of a number of variables. The subject wears either a tightly fitting mask or mouthpiece with a nose clip to prevent air leaks. Airflow is measured either with a pneumotachograph or a turbine flow transducer. Expired oxygen and carbon dioxide are measured during the test with a gas analyser. Breath by breath analysis was used in these studies to calculate the rate of oxygen uptake, VO_2, and carbon dioxide output, VCO_2 per minute:

$$VO_2 = \Sigma (FIO_2 – FEO_2) \times VE \times \Delta t$$

$$VCO_2 = \Sigma (FECO_2 \times VE \times \Delta t)$$

VE = Expired airflow rate

FIO_2, FEO_2, and $FECO_2$ are the fractional concentrations of expired O_2, and expired CO_2, respectively.

Δt – sampling interval

Oxygen uptake, VO_2, is determined by cellular oxygen demand and can be calculated from blood flow as expressed by the Fick equation:

$$VO_2 = Q (CaO_2 - CvO_2)$$

Q = cardiac output

CaO_2 = oxygen concentration of arterial blood

CvO_2 = oxygen concentration of venous blood

Heart rate is monitored continuously with a 12 lead ECG which gives information regarding arrhythmias and ischaemic changes during exercise. Heart rate response to exercise is important to record; the normal response to exercise is an immediate increase in heart rate due to decreased vagal tone and increased sympathetic drive. Heart rate increases linearly with increasing workload but the rate of increase and the maximum heart rate achieved is determined by several factors including age and comorbidities. Medications are also important; beta-blockers will blunt the chronotropic response whereas beta agonist treatment has been shown to cause a significant increase in heart rate during exercise in healthy subjects compared to placebo, [213] so must be considered in patients

with COPD who are usually prescribed long acting beta agonist inhaled therapy. Cardiac output monitoring is rarely done in the clinical setting as it is an invasive procedure. Oxygen saturation is also monitored with an oximeter. In these studies, patients' blood pressure was measured at the start and end of exercise.

Factors affecting oxygen availability include haemoglobin concentration, oxygen saturation, cardiac function (stroke volume and heart rate), peripheral blood flow to tissues and tissue extraction of oxygen (mitochondrial density and function, capillary density and tissue diffusion).

VO_2 increases in proportion to work rate until one of its determinants reaches its limit, when the VO_2/WR slope begins to plateau, giving a good indication of $VO_{2max.}$ However a clear plateau may not be reached if increased symptoms (breathlessness, leg fatigue) cause termination of the test before this point; the result is measurement of VO_{2peak}, which is used as an approximation of VO_{2max}.

Ventilation increases in response to exercise to meet metabolic oxygen demand, but also serves to modulate acid-base changes that occur due to increased muscle activity. Minute ventilation, VE, tidal breathing and breathing frequency are all measured during CPET. Breathing depth and frequency increase in exercise and in healthy subjects at higher work rates, there is both a decrease in end expiratory lung volume (EELV) and an increase in end inspiratory lung volume (EILV). Ventilation increases linearly with VO_2 until anaerobic threshold, where VCO_2 and VE increase more than VO_2. The point at which this happens is a good indicator of the anaerobic threshold, i.e the onset of lactic acidosis in the exercising muscles. In healthy subjects, this usually occurs at around 50 to 60% of VO_{2max}. A lower value may indicate a problem with oxygen delivery to the muscles, be it cardiac, pulmonary or metabolic in the muscle itself.

The ventilatory response to exercise is particularly important in COPD, as it is this factor that most limits patients during exercise. CPET has demonstrated the problems these patients encounter with dynamic hyperinflation. As ventilatory demands increase during exercise, there is progressive gas trapping due to airflow obstruction. This results in a paradoxical increase in EELV and reduction in inspiratory capacity, which limits the degree to which tidal volume can increase. There is a greater mechanical load on the respiratory system causing increased work of breathing, dyspnoea at lower workloads and a lower peak VO_2 [84]. CPET has proved to be more sensitive in detecting improvements in exercise performance due to medication than the 6MWT [214]. CPET has also demonstrated that COPD patients experience an early-onset metabolic acidosis, which is associated with skeletal muscle dysfunction [215].

1.7.2.2 Incremental CPET

A CPET protocol in which the work rate increases at a constant rate enables rapid acquisition of data. Cycle ergometry permits increments of 5 to 20 watts per minute by increasing resistance to pedaling and subjects are encouraged to continue to exhaustion. Such an approach enables assessment of the integrated response of cardiovascular, respiratory and metabolic systems at peak exercise, through parameters such as VO2, lactate threshold, O2 pulse, CO2 production and minute ventilation. This can also be used as a diagnostic tool to detect pathology within one or more of these systems as the cause for exercise limitation or dyspnoea.

1.7.2.3 Endurance CPET

An endurance or steady state test is usually based upon the results of a maximal test, by taking a percentage of the maximum work load achieved (e.g.75%) and applying this as a constant work rate. During a steady state test, the period of dynamic adjustment to the constant work rate provides information regarding the dynamic behaviour of lung function, haemodynamics and tissue O2 utilisation. Such a protocol may be more useful in establishing response to an intervention such as bronchodilator therapy or lung volume reduction surgery.

1.7.3 Field exercise capacity tests

Clearly, cardiopulmonary exercise testing requires complex equipment in the form of either a stationary bike or treadmill, together with a 'metabolic cart' which includes expired gas analysis, ECG monitoring and even blood gas analysis, as well as specialist training to both carry out the test and analyse the results. Hence, other measures of exercise capacity have been developed which are simpler to perform and require much less equipment and training. These include the six minute walk (6MWT) and incremental shuttle walk tests.

1.7.3.1 Incremental shuttle walk test (ISWT)

This test was developed by Professor Sally Singh to simulate a cardiopulmonary exercise test using a field walking test [216]. The patient is asked to walk between two cones, 10 metres apart, in time to a set of auditory beeps played on a CD. The speed of the beeps gradually increases each minute and patients walk as long as they are able to keep up with the beeps or until symptoms (dyspnoea, leg fatigue) no longer allow. Borg scores are recorded before and immediately afterwards. The number of shuttles (distance between the cones represents one shuttle) is recorded. Standardisation of the test is important; the ISWT should be performed twice to account for a learning effect.

The result of the ISWT can be used to prescribe exercise, as well as to evaluate efficacy of this exercise as in a pulmonary rehabilitation programme. According to Singh *et al*, an improvement of 47.5 metres in ISWT distance indicates that patients with COPD are 'slightly better'; an improvement of 78.7 metres represents 'better' [217].

1.7.3.2 Six minute walk test

This is a simple exercise test which only requires a minimum 30 metre flat straight walking course with markings every 3 metres to aid measurement. The strongest indication for the 6MWT is to measure the response to medical interventions in patients with moderate to severe heart or lung disease. It has also been used as a measure of functional status of patients, as well as a predictor of morbidity and mortality [218, 219].

There several sources of variation which influence the distance walked, including height, age, sex, and comorbidities (presence of musculoskeletal disorders such as arthritis, cognitive impairment), as well as technical factors such as using a shorter corridor necessitating more turning or degree of encouragement given during the test. However, it has been shown that while distance walked increases with practice indicating a training effect, performance plateaus after two tests [220], so patients should perform the test twice, with at least 30 minutes rest in between if on the same day but no more than a week apart, if they have never performed the test before.

However, rather than absolute values, change with time or after a particular intervention is a more useful measure. Polkey et al have recently showed in a cohort of over 2000 patients with COPD that a mean decline in six minute walk distance over 1 year of at least 30m confers an increased risk of mortality (hazard ratio 1.93, 95% confidence interval, 1.29–2.90; p = 0.001) [221], establishing a minimal clinically important difference in this population.

As the test is self paced and patients can stop and rest when they feel they need to, the test is submaximal in nature, when compared to cardiopulmonary exercise testing with subjects reaching around 80% of peak VO2 during a six minute walk test compared to an incremental CPET [222]. However it is for this reason that the six minute walk test is perhaps a more useful indicator of functional capacity and symptoms experienced, as patients will tend to perform their normal daily activities also at a submaximal level.

These field exercise tests do not give any information regarding oxygen uptake during exercise, and it is suggested that they should complementary to CPET, rather than a substitute. However, the VO2

obtained on the ISWT has been shown to have a strong correlation (r=0.88) with VO2 obtained on a CPET on a treadmill [223].

Good correlations have been reported between the outcome of the 6MWT and CPET VO_{2max} (r=0.73). Although both tests are effort dependent to an extent, the 6MWT is perhaps more so as patients pace themselves rather than having to meet an external pacing requirement, such as revolutions per minute on a stationary bike. It is perhaps why the 6MWT has been shown to correlate better than VO_{2max} with patients' ability to perform daily activities. Pitta *et al* 2005 studied 50 patients with COPD and found a weak correlation between daily physical activity levels as recorded with a physical activity monitor and VO_{2max} achieved on an incremental CPET (r=0.33), compared to 6 minute walk distance (r=0.76).

But how good is the 6MWT? Eliason *et al* [224] found positive associations of mean physical activity and time spent in moderate to vigorous physical activity, MVPA (as measured with the Actigraph a triaxial accelerometer) with 6MWD in 44 COPD patients. There was no association between exercise capacity and time spent sedentary, suggesting a role for at least moderate physical activity in contributing to exercise capacity.

However, a recent study looked at the power of the 6MWT, as well as other functional measures (sit to stand test, hand grip strength) and a physical activity questionnaire, to predict daily physical activity in 70 COPD patients, as measured by a multisensor accelerometer [225]. They found that whilst there was a good correlation between the 6MWD and the steps per day measured by the activity monitor (r=0.69), the area under the curve on a subsequent receiver-operator curve was only 0.68, indicating moderate predictive power only, with a distance of 425m having positive and negative predictive value of 0.46 and 0.65 respectively. Interestingly, there were only weak correlations within variables of the activity monitor itself, namely both energy expenditure and average METs with steps/per day, which perhaps illustrates further the difficulties of accurately representing physical activity in this largely inactive patient group. However the ROC analysis with 6MWD was not done with either METs or EE. Nevertheless, the results of this study do suggest a significant behavioural component to physical activity levels in this population which are difficult to capture with objective measures such as activity monitoring or exercise capacity.

1.8 Physical activity: behaviour versus physiology?

Despite the well-established benefits of physical activity in adults and children alike, nearly a third of the adult population worldwide are inactive. In order to improve this statistic, not only is it important to be able to accurately measure physical activity, as described earlier, but to also identify the barriers to increasing physical activity, particularly those which are potentially modifiable.

1.8.1 Barriers to physical activity

It is well recognised that the determinants of physical activity interact in a complex way, in that there may be several pathways to change in behaviour [226]; interventions may have different effects according to individual, cultural and social influences; and may also differ at initiation, maintenance and cessation of activity [227]. Broadly speaking, these determinants can be divided into personal and environmental factors [228].

Personal factors include health, motivation level, time constraints and previous exercise experience. Older adults often cite poor health as a barrier to being active [229]. Gender differences have also been found, with women more likely to be inactive than men, and this gap widens with age [230]. Previous experience of activity in childhood may have a carry over into adulthood in a positive way if it was enjoyed, but could also be a negative influence, for example if forced to do sports by parents. Socio-economic factors also influence barriers; for example, lack of time has been found to correlate positively with socio-economic status, whereas lack of money or transport correlated negatively [231].

Environmental factors cited include weather, transportation, access to resources, safety concerns about the locality or suitability of the local area, for example, availability of parks and pavements for walking, and social factors such as lack of social support or other people to exercise with [232].

Adults over 65 have the highest prevalence of inactivity; 66% of those over 75 do not engage in any regular physical activity [233]. This is relevant to COPD as incidence of this disease increases with age [234]. Of those older adults who are active, adherence is poor, with only 30% of men and 15% of women participating in regular sustained activity. Physical activity is particularly important in this age group; as well as reducing risk factors associated with specific diseases such as cardiovascular disease it also improves overall quality of life, for example through promoting independence and preserving functional ability. In older adults, it is difficult to promote adherence to activity programmes – up to 50% drop out inside 6 months. It may be that changing attitudes to exercise in this group is

important – exercise should be seen not as a recreational activity, but a necessary medical treatment. In addition, older adults including those with chronic diseases such as COPD may need specific guidelines, rather than general advice to 'be more active', especially as they might perceive symptoms associated with exercise such as breathlessness, sweating and muscle fatigue as negative.

1.8.2 The effect of weather on physical activity

One potential environmental barrier to physical activity, weather, and seasonal differences in weather and climate, in the context of COPD will be discussed in this thesis in more detail in Chapter 5. The effect of weather and climate on physical activity levels in the general population has been recently examined in more depth. A systematic review by Tucker *et al* [235] looked at 37 studies published over a 26 year period, with nearly 30000 subjects across 8 countries. Physical activity was measured either through questionnaires or with activity monitors. They found that in most studies, physical activity was found to peak in summer months and was significantly lower during winter. This decline was attributed to poor weather conditions and shorter day length [236]. However, one study carried out in Texas found physical activity to be lower in the summer [237]. This was attributed to extreme heat acting as a deterrent to outdoor activity – the average temperature for July was 29°C. Interestingly, an Australian study of 1754 healthy adults participating in a 5 year study on the effect of urban design on physical activity [238] found very little effect of weather on physical activity levels as measured with both a questionnaire and a pedometer. However the authors commented that weather conditions were fairly constant throughout the study and only explained up to 6% of the variance in physical activity.

There is little data looking at the effect of weather and season on physical activity in COPD. O'Shea *et al* [239] interviewed 22 patients with COPD who were enrolled in a 12 week progressive resistance exercise programme, with the aim of identifying factors that would affect adherence. They found several barriers, in keeping with the themes already discussed (environmental, personal). Weather was the most commonly stated major environmental barrier to activity, but nevertheless was only cited by 7 participants. This was a mainly qualitative study with no objective physical activity measurement or systematic recording of weather conditions, and largely supported what is already known – that there is a complex interaction between personal and environmental factors in both short and long-term adherence. Other studies in healthy populations have shown the weather to be less of a barrier in those who are more physically active and enjoyed being so [240]. However, a recent study in another disease population, adults with arthritis, did find an objective effect of weather on physical activity levels as measured with an accelerometer. 214 patients were monitored over 3 years throughout the year to capture activity data throughout the year. Temperature, daylight hours, rain

and snowfall data was also collected. They found heavy rain to be associated with a 12% fall in activity and shorter day length characteristic of winter associated with a 14% fall in activity. On average, patients had a 38% lower activity level in winter compared to summer.

A smaller study with direct measurement of physical activity in COPD by Sewell *et al* examined the effect of season in 95 patients participating in a pulmonary rehabilitation programme [241]. The patients were split into 4 groups according to when they enrolled in the programme. Physical activity was measured using a uniaxial accelerometer. They found that those starting pulmonary rehabilitation in the winter had lower physical activity levels at baseline but also improved the most. However, there was no effect of season on the other outcome measures before and after rehabilitation, namely incremental shuttle walk distance or quality of life measures. In addition, the number of patients in each group was relatively small (n=18 to 34) and the same patients were not followed up throughout the seasons.

If it could be shown that there is a significant difference in physical activity due to season within the same subject, this would have to be taken account in terms of choosing when to monitor patients as well as for how long, as this may influence outcomes in not only interventional studies in clinical settings such as pulmonary rehabilitation. Optimisation of clinical resources in a financially restrained environment is vital for all stakeholders. Geographical location becomes more pertinent in multicentre studies where patients are being recruited from different countries, and inter-centre differences in results would also have to be accounted for. These potential variations could act as confounders for any effect that was being investigated. This question is addressed in more detail in Chapter 5.

1.9 The PROactive project

Much of the work of this thesis was carried out as part of the PROactive initiative. This is an EU wide multicentre project spanning 6 years and funded by the Innovative Medicines Agency. As has already been discussed, the importance of physical activity in COPD is undisputed. Patients struggle with simple activities of daily living which involve physical exertion. However, to date, there is no measure of physical activity that accurately captures the patient's experience of physical activity and any difficulties associated with it as a result of COPD. This represents an important therapeutic target from the patient's perspective, over and above traditional outcome measures such as FEV_1. Thus, the main aim of this project is to develop a patient reported outcome tool, incorporating items from a questionnaire with data collected from a physical activity monitor (such as step count for an objective measure of amount of physical activity) to accurately record this experience of physical activity. Going

forward, this tool could then be used to measure physical activity as an outcome measure in randomised controlled trials, particularly for labelling purposes in pharmaceutical trials.

The PROactive project is guided by a consortium of 19 partners including academic institutions, 8 major pharmaceutical companies and patient organisations. The studies are implemented by research teams across Europe; in addition, there is an academic board which provide independent peer review of the work of the project.

The process of developing this tool has taken several steps, firstly with a systematic review of the literature regarding activity monitors that have been previously used and validated in chronic diseases [242]. This review enabled selection of the activity monitors that were used in the validation studies presented in this thesis. A further systematic review set out to look at the determinants of physical activity, to give a better understanding of this concept, which would help plan interventions, guide research and manage COPD more effectively [243]. The main findings were that the overall quality of evidence regarding determinants of physical activity in COPD is low, but consistent evidence for the effect of physical activity on COPD exacerbations and mortality. Very few interventions on determinants of physical activity have been tested, with inconsistent results.

As well as the findings of the systematic review, further information was gained from a study involving patient interviews and focus groups with COPD patients [244]. 116 patients from 4 different European countries participated in 3 consecutive qualitative studies; firstly, one to one interviews about how they experienced physical activity; secondly, focus groups where patients shared and compared their experiences; and thirdly, cognitive debriefings where patients were encouraged to think about the meanings of questions about physical activity initially derived from the first 2 studies. What patients actually said enabled the development of draft items for the patient reported outcome tool.

In addition, this study, as well as the systematic review, enabled the development of a conceptual model of physical activity in COPD, comprising sociodemographic, environmental, lifestyle, clinical and functional determinants; and outcomes such as FEV_1, dyspnoea and quality of life measures. . This is in accordance with guidelines set out by the US Food and Drugs Agency, which state that development of PROs must be based on a conceptual framework. The European Medicines Association defines a PRO as “any outcome directly evaluated by the patient and based on the patient’s perception of a disease and its treatment(s)”. Clearly, for pharmaceutical labelling purposes, adherence to these guidelines was a major consideration in the PROactive project as a whole.

Two versions of the draft questionnaire were developed – a daily PRO for use over a 1 to 2 week period; and a clinic PRO for use in an outpatient setting to reflect the previous 7 days' experience of physical activity. These were used in an item reduction study, which is discussed further in Chapter 5 [245], and provided data for the work presented in this chapter. The culmination of the project will be to use the final versions of the PROs in randomised controlled trials. These studies are ongoing at date of print.

1.10 Thesis aims

This thesis will explore the importance of technical, environmental and patient factors in physical activity in COPD. Much of the work of this thesis was carried out as part of the PROactive initiative. The first two studies are validation experiments of a number of physical activity monitors in COPD patients in laboratory and domestic settings for suitability as part of the PROactive tool.

The third study explores the changes in physical activity over time, and how this varies according to season and climate. Physical activity was measured with monitors validated for use in COPD patients from the first two studies. Again, these patients were studied under the PROactive project, but as an additional study to the project's primary objective, which was the formulation of the questionnaire part of the PRO tool. One of the aims of the PROactive tool is to use it as a secondary outcome measure in pharmacological and other interventional studies. As these studies are often multicentre and multinational in nature, how geographical location and climate might affect physical activity are factors which may require consideration in future studies, where physical activity is used as an outcome measure.

The fourth study examines the influence of behavioural over physiological factors on daily physical activity in COPD, the hypothesis being that physiological factors contributing to dyspnoea at the beginning of any physical activity may drive behaviour in COPD of all severities and deter patients from persisting with activity, thus causing inactivity. The relationship of measured daily physical activity in COPD with the early physiological response to exercise is tested. The aim is to validate the analysis of this response and to test the hypothesis that the early response is better related to and more representative of daily physical activity in COPD patients than other measures of maximal exercise capacity.

2 Methods

2.1 Ethical approval

For the studies in Chapters 3 and 4 (laboratory and field validation studies), ethical approval was given for the UK by the Lothian Ethical committee (ethics number 10/S1102/37). For the study comprising Chapter 5, approval for the UK was granted by the London Bloomsbury Ethical committee (ethics number 11/LO/07111). Further approval for all studies was given by the Research and Development department of the Royal Brompton & Harefield NHS Trust. All subjects gave their written informed consent.

2.2 Statistical analysis

Analyses were carried out using SPSS Statistics 19 (IBM Corporation, New York, USA) and GraphPad Prism 5.0 (GraphPad Software Inc., CA, USA). GraphPad Prism was also used to construct the graphs. Specific analyses used in each study are described in more detail in the relevant chapters. A p-value <0.05 was taken to be significant (this takes into account corrections for multiple comparisons).

2.3 Study subjects

Most of the patients used were recruited from the COPD database, which included patients who attended the outpatients department in the Royal Brompton Hospital, as well as those from other trusts who had volunteered to participate in research. Only patients with COPD were recruited. Diagnosis was confirmed according to the GOLD guidelines [246], i.e. patients with predominantly irreversible airflow limitation with FEV_1<80% predicted and/or an FEV_1/FVC ratio<70% and a clinical history consistent with the diagnosis (symptoms of exertional dyspnoea, chronic cough, wheeze and regular sputum production with a significant smoking history). Patients with other primary respiratory conditions (such as asthma, bronchiectasis or pulmonary fibrosis) were excluded. Patients were also excluded if they had significant co-morbidities, including active malignancy, chronic heart failure, dementia, physical disability and other neurological and rheumatological conditions (e.g. Parkinson's disease, severe arthritis) which prevented them being physically active for reasons other than COPD.

An exacerbation of COPD was defined as an episode of worsening in respiratory symptoms, which could be any of the following: increased breathlessness/wheeze, cough, increased sputum production/change in colour; requiring systemic glucocorticosteroids and/or antibiotics [247].

2.4 Pulmonary Function Testing

All pulmonary function measurements were performed with standardised equipment which was calibrated daily. Spirometry was obtained using a pneumotachograph and after administration of a bronchodilator. Diffusing capacity of the lung was determined by the single breath carbon monoxide gas transfer method. Lung volumes were measured using whole body plethysmography. Blood gas levels were measured using arterialised earlobe capillary samples. Patients who were on supplementary oxygen were asked to do the tests after a washout period of 30 minutes without oxygen, if symptoms allowed. All variables are given as absolute values expressed as percent predicted of reference values [248, 249]. In this thesis, these tests were carried out by respiratory physiologists in the Lung Function department of the Royal Brompton Hospital, according to American Thoracic Society and European Respiratory Society guidelines [250].

2.5 Exercise testing

Exercise tests were used to assess the patients' functional capacity; the six minute walk test and cardiopulmonary exercise test were used.

2.5.1 The Borg scale of perceived exertion

A Borg score was obtained before any exercise test, at rest, and immediately on cessation of exercise. A score for dyspnoea and leg fatigue were obtained using the scale below:

Borg score	
0	Nothing at all
0.5	Just noticeable
1	Very slight
2	Slight
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very severe
8	
9	Very very severe
10	Maximal

2.5.2 Six minute walking test (6MWT)

This test was used to assess patients' functional exercise capacity. As described earlier, two tests were performed to account for the learning effect, with at least 30 minutes rest in between if on the same day but no more than a week apart, if they had never performed the test before. The greater of the two results was used. This was performed in a marked 30 metre course.
In a subset of patients studied for the third study in this thesis, the mean difference between the two walks was 12.8m (standard deviation 25.8m), well below the minimal clinically important difference described in the previous chapter [221]. Most of these patients had previously performed six minute walk tests either in previous studies or for clinical reasons, thereby accounting for any training effect. Absolute contraindications were unstable angina or myocardial infarction one month prior to the test. Relative contraindications were resting heart rate > 120 bpm, systolic blood pressure > 180mmHg and diastolic BP >120mmHg. Prior to the test, patients' resting blood pressure, heart rate and oxygen saturation were recorded, as well as Borg scores for breathlessness and leg fatigue. Patients who required ambulatory oxygen were given supplementary oxygen (which was carried for them) during the test and the flow rate was noted. Patients were then instructed to walk as far as they can in six minutes and given standardised encouragement [218]. They were allowed to stop if they need to at

any time during the test and asked to resume walking as soon as they felt able to. If they did stop, the total length of time spent resting was noted. The clinician supervising the test did not walk with the patient to avoid pace setting. The test was stopped in the event of intolerable dyspnoea or leg fatigue, angina-like chest pain, light-headedness or any other appropriate clinical reason. Blood pressure, heart rate, oxygen saturation and Borg scores were recorded immediately at the end of the test.

2.5.3 Cardiopulmonary exercise testing

Cardiopulmonary exercise testing was carried out using a magnetically braked exercise bicycle. This was chosen over a treadmill as it provides a more stable platform than a moving treadmill which is better for some of the more severe and frailer COPD patients. (Although the peak VO_2 reached in healthy subjects on the bike is around 10% lower than that achieved on the treadmill in walking or running, this is not the case in COPD [251]). The resistance on the pedals was adjusted to give a stable workload regardless of speed of pedalling, although patients were instructed to pedal at around 60 rpm.

Absolute contraindications to exercise testing are:

Aortic Aneurysm

Current viral illness / acute infection

Unstable angina / acute ECG changes of ischaemia / acute cardiac event

Myocardial infarction within the last 4 weeks

Severe hypertension (systolic >240 mmHg; diastolic >120 mmHg)

Poorly controlled heart failure

Myocarditis / Endocarditis

Exacerbation of asthma

Severe aortic stenosis

Acute pulmonary embolus / thrombus / venous thromboembolic disorders

In the presence of relative contraindications, testing was carried out at my discretion:

Gross arrhythmias

Resting tachycardia >120 beats/min.

Electrolyte disturbance

Epilepsy / Cerebrovascular disease

Resting PaO2 < 7.0kPa.

Pulmonary hypertension.

Uncontrolled metabolic disorders

Advanced or complicated pregnancy

Subjects wore a mouthpiece within which was a turbine unit. An electronic sensor detects rotation of the vane inside the turbine; the number of pulses per unit time is equal to flow. It was important to get a good seal around the mouthpiece to avoid air leak and thus inaccurate airflow measurements. A gas analyser tube was attached to the mouthpiece and connected to the gas analyser unit, which comprised an O_2 fuel cell analyser and a CO_2 thermal conductivity analyser. Both volume and gas calibrations were carried out prior to testing.

Subjects were seated on the bike and saddle height was adjusted accordingly. They were asked to wear the mouthpiece ensuring a good seal and ECG leads were connected. They started with a 2 minute rest period to allow adjustment to the mouthpiece, followed by 1 minute of unloaded pedalling. This enabled patients to become accustomed to pedaling, whilst also allowing for the lag time between increment in workload and VE, VO_2 and VCO_2. They were given standardised encouragement throughout the test. Borg scores were recorded in rest and immediately on cessation of exercise. The test was terminated if the patient could not continue due to exhaustion, was unable to maintain a cadence of pedalling of 60 rpm despite verbal encouragement, exceeded 85% of their maximum predicted heart rate, desaturated significantly or if ECG abnormalities were seen.

2.5.3.1 Incremental CPET

After the 2 minute rest period followed by 1 minute unloaded cycling, loaded pedaling began with increments every minute. Work load increment was determined by disease severity; those with MRC dyspnoea scores of 4 or 5 did a 5W increment protocol, whereas less severe patients did a 10 or 20W increment protocol. Patients continued the test until exhaustion or unless the test was terminated for reasons listed above. The majority did not reach VO_{2max} so their peak VO_2 was used.

2.5.3.2 Endurance CPET

The patients performed a constant rate protocol based on 75% of the maximum workload achieved in the incremental CPET. Again, patients cycled until exhaustion after similar periods of rest and unloaded cycling, but were asked to perform inspiratory capacity manoeuvres at rest and every 2 minutes during the test. When instructed to, they were asked to inspire maximally from the end of expiration. This enabled the measurement of inspiratory capacity and EELV, and thus the degree of dynamic hyperinflation with progressive exertion.

2.6 Indirect calorimetry

2.6.1 Indirect calorimetry: doubly labelled water (DLW) method

As previously described, this technique is based on the administration water containing a known quantity of two stable isotopes of water, $^{2}H_2O$ and $H_2{}^{18}O$. Each patient was instructed to completely void his bladder and a sample from this was taken as a background sample. The patient's weight was measured. The patient then ingested a known volume of DLW and the time noted (this was usually done in the morning). A urine sample was taken from the second voiding after ingesting the DLW (usually at least 6 hours after) to enable the isotopes to equilibrate throughout the body. Samples were immediately stored in the fridge overnight and subsequently frozen at -20°C. Further urine samples were obtained on the mornings of days 2, 7 and 14 and the evening of days 6 and 13 and stored in a similar way, accurately noting the time each sample was obtained. The difference in elimination rates of ^{2}H and ^{18}O were calculated as a measure of carbon dioxide production and therefore total energy expenditure over the two week monitoring period. Active energy expenditure was calculated by subtracting resting energy expenditure from this total, as measured below.

2.6.2 Indirect calorimetry: ventilated hood method

This method was used to calculate resting energy expenditure in the second study. Patients were instructed to fast overnight and the measurements were taken first thing in the morning. Each patient was asked to lie in a supine position (as far as dyspnoea would allow) under a canopy which was connected to a gas analyser. They were asked to remain as still as possible to minimise energy expenditure through movement, but not to fall asleep, as this rate of energy expenditure would actually have been lower than whilst awake at rest. Once the readings of VCO_2 had stabilised (usually after around 10 minutes), the changes in O_2 and CO_2 concentrations were measured over about a 30

minute period. Resting energy expenditure was calculated using the Weir equation as described above.

The measurement was carried out on two separate occasions and the mean of the two measurements was taken. Measurements were not made if the patient was experiencing an exacerbation as this is known to increase resting energy expenditure [252].

2.7 Measurement of muscle strength

Isometric quadriceps maximal voluntary contraction (QMVC) in kg, defined as the highest mean force that could be sustained over 1 second, was measured in the right leg. Patients were seated on a couch at 90° and with the knee joint flexed at 90°. The ankle was placed in a strap attached to a strain gauge (Strainstall UK Ltd, Cowes, UK; range 0-100kg). Patients were instructed to make a maximal voluntary leg extension effort with standardised encouragement and asked to sustain this for 1 second. This force was converted to a digital signal with Labview software (National Instruments, USA). The highest value of 5 efforts was accepted [253]. Each value was expressed as %predicted according to prediction equations from our group, based on gender, age and fat-free mass[123].

2.8 Body composition analysis

Body weight (in kilograms) and height (in metres, measured with a stadiometer) were measured.

2.8.1 Bioelectrical impedence analysis (BIA)

This method of body composition measurement uses the principle that if a small electrical current is applied to the body, the extent to which it will be impede or resisted will depend upon the type and amount of tissues present. Fat almost completely blocks any current and is therefore an excellent resistor. Tissues with high water content (e.g. blood, extracellular fluid, muscle) have very low resistance. Other tissues merely impede, i.e., slow down the current. Cell membranes act as resistors at very low frequencies (<50Hz), but above this, act as capacitors, impeding the current. Using currents at different frequencies, it is possible to measure intracellular fluid, as well as fat mass, fat free mass and total body water content. Bioelectrical impedance as a measure of body composition [254] was assessed using the Bodystat Quadscan 4000 (Bodystat Ltd, Douglas, Isle of Man). This

uses four electrodes (two to pass the current and two to sense it). As factors such as hydration, distribution of body water and orientation of tissue affects the measurement, it was done after the patient had been lying for 5 to 10 minutes (and long longer to avoid 'settling' of water), and 2 hours after eating and 8 to 12 hours after exercise or drinking alcohol. Socks were removed, along with any metallic objects. Their legs were positioned so that the thighs were not touching and the ankles were about 20cm apart. The skin on the top of the right hand and foot was cleaned with alcohol to ensure the electrodes adhered properly. Electrodes were placed proximal to the metacarpophalangeal joints and just proximal to the lateral malleolus of the wrist on the right hand, and similarly on the right foot (metatarsal joints and lateral malleolus of the ankle). Fat free mass and total body water measurements were noted.

2.8.2 Dual energy x-ray absorptiometry (DEXA) scanning

This method uses a very low dose of radiation to measure body composition. Two x-ray beams of different energy levels are aimed at the patient's body. The differences in absorption occur due to differences in regional content of fat, muscle and bone. These differences are used to calculate trunk and limb fat and muscle content. Some patients also underwent this test as well as BIA to assess body composition.

2.9 Health-related quality of life questionnaires

2.9.1 The Medical Research Council Dyspnoea Scale

Breathlessness is a complex and subjective sensation, and perhaps the most important symptom experienced in COPD. Fletcher *et al* first developed a numerical scale of breathlessness when working with coal miners in the Medical Research Council (MRC) Pneumoconiosis unit in the 1940s [255]. The MRC dyspnoea scale rates the type and magnitude of dyspnoea according to five grades of increasing severity [256], encompassing the whole range of respiratory disability (from none to almost complete incapacity). It can be self-administered and the score is the number that best fits the patient's level of activity. All the questions relate to everyday activities and are generally easily understood by patients. A score can usually be obtained in a few seconds. The MRC scale doesn't quantify breathlessness itself, but the disability associated with physical activity.

2.9.2 The Chronic Respiratory Diseases Questionnaire (CRQ)

This is an investigator administered 20 item questionnaire which measures both the physical and emotional aspects of chronic respiratory disease. It takes 15 to 25 minutes to complete. There are 4 domains – dyspnoea, fatigue, emotional function and mastery. A higher total score indicates better quality of life. The minimal clinically important difference in score is 0.5, with a change of 1.5 indicating a major change [257]. Good internal consistency reliability has been shown for all domains apart from dyspnoea in COPD patients [68].

2.9.3 The St. George's Respiratory Questionnaire (SGRQ)

The SGRQ is a self-administered index designed to measure health status in patients with chronic airflow limitation. It comprises 2 parts with 3 components and a total of 50 items. Part 1 gathers information on 'Symptoms' (frequency and severity) with 1, 3 or 12 month recall. Part 2 focuses on 'Activities' that cause breathlessness or are limited by it. The third 'Impacts' component examines social functioning and psychological disturbances resulting from airways disease and refers to the current state as the recall. Scores range from 0 (no impairment) to 100 (worst possible) [258]. There is very good test-retest reliability with intra-class correlations reported from 0.795 to 0.900. Significant correlations have also been reported between total score and presence of cough, sputum, and wheeze; and between the activity and impact domains and other measures of disease activity (such as FEV_1, FVC, SaO_2 at rest, 6MWD, MRC dyspnoea grade and anxiety and depression scores) [258, 259].

2.9.4 The COPD Assessment Test (CAT)

This was developed as a shorter questionnaire tool which would be easier and quicker to complete and therefore more applicable in clinical settings. It is a self-administered questionnaire with eight items (cough, phlegm, chest tightness, breathlessness, going up hills/stairs, activity limitations at home, confidence leaving home, sleep and energy) and takes less than 5 minutes to complete. Each item is scored from 0 to 5 giving a total score range from 0 to 40, corresponding to the best and worst health status in patients with COPD, respectively [260].In terms of reliability, an intra-class correlation coefficient of 0.8 has been reported. A strong correlation with the SGRQ across 7 European countries has also been reported [261].

2.9.5 The Clinical COPD Questionnaire (CCQ)

This questionnaire was also developed as a shorter, easier to use tool in the clinical setting, which also reflected the patient's activity limitation and emotional response to the disease, as well as physical symptoms. There are 10 questions, reflecting symptoms, functional state and mental, with each item answered on a Likert scale (0 to 6) with a maximum score of 15, indicating severe disability. It takes around 10 minutes to complete. Good intra-class correlations with the SGRQ have been reported, regardless of COPD severity [262].

3 Laboratory validation of six activity monitors in COPD: a comparison with indirect calorimetry

3.1 Introduction

The importance of physical activity in COPD is clear, not only due to prognostic implications, but also as it may be intrinsic to disease progression itself. Therefore, accurately measuring physical activity in COPD enables stratification of patients at baseline prior to intervention, such as pulmonary rehabilitation, and monitoring for change in response to such interventions. Independent activity monitoring using physical activity monitors is desirable due to the objectivity of the measurements obtained, as compared to the information obtained from questionnaires or from patient reported diaries, which are both prone to inaccuracies. However, commercial devices are all developed in healthy subjects and need validation for use in COPD, in particular because these patients tend to move more slowly than healthy age-matched subjects. The aim of this study was to validate six physical activity monitors in COPD patients, against a gold standard of indirect calorimetry in the form of VO_2 data from a portable metabolic system under controlled laboratory conditions. Triaxial accelerometers have previously been reported as more accurately estimating energy expenditure and therefore physical activity levels than uniaxial accelerometers (transducing the body's acceleration in three axes and one axis respectively) [263].

Therefore, the hypothesis to be tested was that triaxial activity monitors would more faithfully reflect metabolic activity as assessed by indirect calorimetry than uniaxial activity monitors. Both the minute-by-minute correlations of the activity monitor outputs, as well as an overall correlation over the study period, with indirect calorimetry were used as measures to validate them. The ability of these various monitors to detect differences in walking speed was also investigated.

3.2 Materials and Methods

3.2.1 Study subjects

39 (25 male) patients from 4 centres across Europe were studied (London and Edinburgh in the UK, Athens in Greece and Leuven in Belgium). The number of patients was pre-determined by the PROactive consortium. 40 patients, that is, 10 from each participating study centre. A specific sample

size calculation was not undertaken as this was a validation study assessing the accuracy of monitors against a pre-set threshold (see analysis section below); the number was decided as being a workable number for each centre as the study protocol was complex. Unfortunately one patient's data had to be excluded due to technical difficulties (inaccurate metabolic data which was only picked up during the data analysis stage). All patients were diagnosed with COPD with a severity ranging from mild to very severe according to the Global Initiative for Chronic Obstructive Lung Disease (or GOLD) (stages I to IV) [246]. Patients were phenotyped as described in Chapter 2; their characteristics are shown in **Table 3.1** They were clinically stable and free of exacerbations for at least 4 weeks prior to the study. Patients were excluded if they had other co-morbidities which restricted their physical activity other than COPD (e.g. arthritis), or if they were on long term or ambulatory oxygen therapy, as they were unable to have supplemental oxygen whilst wearing the metabolic equipment. Patients provided written informed consent. In the UK, the study had ethical approval from the Lothian Regional Ethics Committee (Edinburgh, United Kingdom) and local site specific approval from the Research and Development department of the Royal Brompton Hospital. In Greece, ethical approval was given by University Hospital Ethics Committee "Sotiria" hospital Athens. In Belgium, approval was from the UZ Leuven Medical Ethics Committee.

3.2.2 Study design

Each patient wore 6 activity monitors simultaneously, which were selected as a result of a systematic review of the literature as having been previously validated in chronic disease [242, 264]. This set out to identify monitors which had been validated in both healthy adults and those with chronic disease in whom inactivity is an important therapeutic target, but where mobility is preserved (i.e. studies in patients with conditions such as arthritis had to be excluded). All studies that used any commercially available accelerometer, pedometer or multisensory device were included. In addition, the validity of the device had to be tested against a criterion method such as indirect calorimetry (either using a metabolic cart or doubly labelled water). Validity was measured using coefficients of correlation with the criterion method between total and active energy expenditure measured with the monitor compared to the same measured by the metabolic cart or doubly labelled water.

The following monitors were selected (i.e. those with good correlations with the criterion method): two uniaxial activity monitors; Kenz Lifecorder (Kenz), Actiwatch (Actiwatch), three triaxial activity monitors; RT3, Actigraph GT3X (Actigraph), Dynaport MiniMod (MiniMod) and one triaxial activity monitor combined with different sensors (multisensory); SenseWear Armband (SenseWear). More details about software, type, body location and outputs of these monitors can be found in **Table 3.2**.

Patients also wore a portable metabolic system (Jaeger Oxycon Mobile), an oxygen saturation finger probe and a Polar T31 (Polar) coded transmitter belt for heart rate monitoring. The portable metabolic system was attached to the upper chest with a harness and due to its low weight (950g), caused minimal discomfort. A face mask with a dead space of < 30mL (Hans Rudolph Inc, Kansas City MO/USA) was used. Location of attachment for the Oxycon Mobile together with the six activity monitors is shown in **Figure 3.1**. A two-point gas calibration was completed prior to each test. All monitors were time synchronised with each other and with the metabolic kit.

.

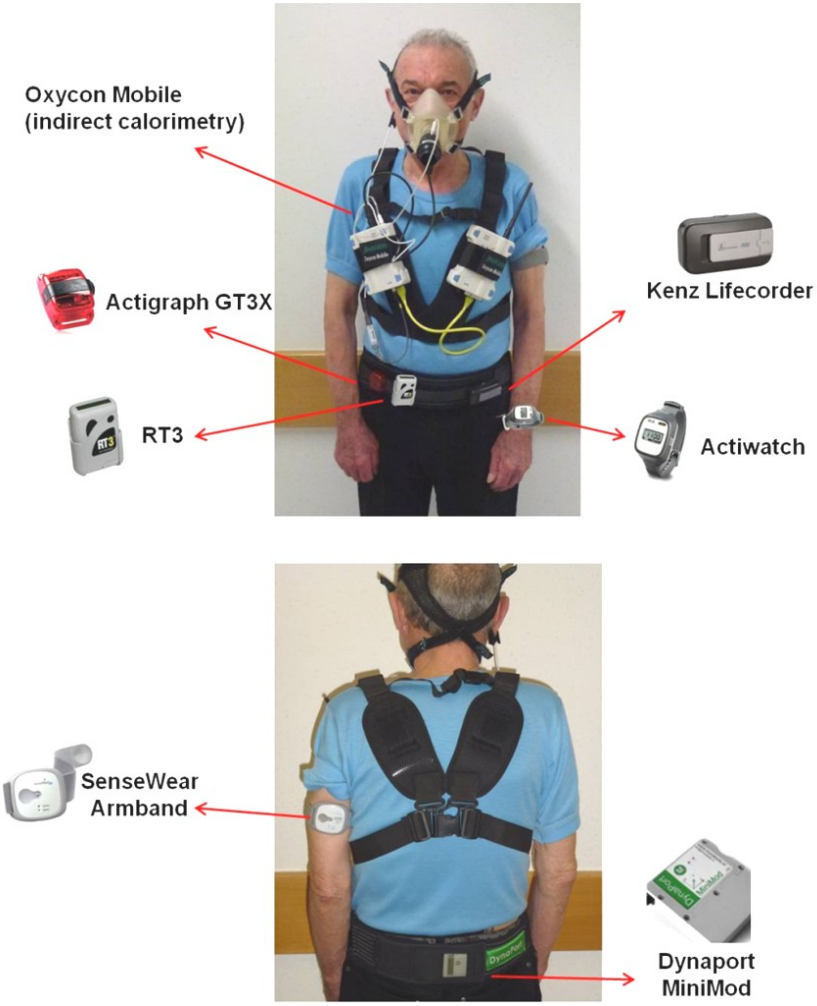


Figure 3.1 Position of the activity monitors and metabolic kit

3.2.3 Expired gases method of indirect calorimetry

Expired oxygen and carbon dioxide levels were measured from a tightly fitted mask, or mouthpiece and nose clip, minimising loss of these expired gases through leak. Room air was inspired (the equipment is calibrated to this prior to any test). The rate of oxygen consumption (VO_2) and carbon dioxide elimination (VCO_2) are therefore calculated as ml/min, VO_2 can be expressed as metabolic rate in ml/kg/min, or as METs (Metabolic Equivalent of Task[4]) [28], using the subject's body weight. 1 MET is equivalent to 3.5ml O_2/kg/min. Energy expenditure can be derived from these measurements using the Weir equation [198]

In this study, VO_2, VCO_2, heart rate, respiratory rate and tidal volume were measured continuously from the metabolic cart. Breath-by-breath measurements were averaged over one-minute intervals. After the experiment, stored data were downloaded from the portable metabolic device to a personal computer. Energy expenditure estimates from the portable metabolic system (METs) were used as a criterion measure for energy expenditure and were compared with the following activity monitor outputs: Kenz- arbitrary unit (AU); Actiwatch – activity count (AC); Actigraph and RT3 – vector magnitude unit (VMU); MiniMod and SenseWear – METs.

Patients were instructed to perform a strict schedule of activities lasting 59 minutes (**Table 3.3**) which were chosen to be representative of everyday tasks (such as walking, stair climbing and sweeping the floor [265]. Time was kept with both a stopwatch as well as a laptop computer clock so that activities were completed in whole minutes. During the activities, a manual step count was recorded with a clicker counter. The patient's feet were also filmed using a handheld camcorder in order to provide a videoed step count. This served to verify the manual step count. Oxygen saturations and heart rate readings as well as Borg scores for breathlessness and fatigue were recorded at regular intervals during the protocol. Although the duration of the protocol was 59 minutes, occasionally it took longer to complete (for example if the patient needed to rest for longer in between activities).

[4] The Metabolic Equivalent of Task (MET) is a physiological measure expressing the energy cost of physical activities. It is defined as the ratio of metabolic rate and therefore rate of energy expenditure. 1MET is the metabolic rate obtained when sitting resting. Activity intensity typically ranges from 0.9 MET (during sleep) to 23 during fast running at 22/5km/hr.

Variable	COPD patients (n=39)
Age (years)	67.9 ± 7.4
Gender (male/female, n)	25/14
FEV_1 (L)	1.43 ± 0.60
FEV_1 (%predicted)	54 ± 18
FVC (L)	2.97 ± 0.85
FVC (%predicted)	90 ± 16
GOLD stage I/II/III/IV (n)	4/18/14/3
TL_{co} (%predicted)	61.0 ± 25.9
BMI (kg/m^2)	26.2 ± 5.2
6 MWD (m)	438 ± 115
VO_{2peak} ($ml.min^{-1}.kg^{-1}$)	16.9 ± 5.5
VO_{2peak} (%predicted)	79 ± 31
MRC	2.6 ± 0.7
CAT	15 ± 8
SGRQ	
Total Score	42 ± 18
Activities	60 ± 24
Impacts	30 ± 17
Symptoms	44 ± 23

Table 3.1 Patient characteristics

Data are expressed as mean ± std. FEV_1- forced expiratory volume in 1s; FVC- forced vital capacity; 6 MWD - six-minute walking distance; MRC - Medical Research Council; CAT - COPD Assessment Test; SGRQ - St George's Respiratory Questionnaire.

Name, (*Manufacturer;* software)	**Type**	**Location**	**Measured output**	**Estimated output**
Kenz Lifecorder Plus (*Suzuken Co Ltd., Nagoya, Japan*; Physical Activity Analysis Software)	Uniaxial accelerometer	Waist (left)	Steps, activity score	EE[c], activity intensity level
Actiwatch (*MiniMitterCo,Sunriver, OR, USA;* Respironics Actiware 5)	Uniaxial accelerometer	Wrist (left)	AC[a]	
RT3 (*Stayhealthy Inc. Monrovia, CA, USA*; Stayhealthy RT3 Assist Version 1.0.7)	Triaxial accelerometer	Waist (right)	AC, VMU[b]	EE
Actigraph GT3X (Actigraph LLC Pensacola, FL ; Actilife 5)	Triaxial accelerometer	Waist (right)	Steps, AC	EE, activity intensity level
DynaPort® MiniMod (McRoberts BV, The Hague, The Netherlands; www.gaitweb.nl)	Triaxial accelerometer	Waist (lower back)	Steps, movement intensity, different body positions	EE
SenseWear Armband (*Bodymedia, Pittsburgh, PA, USA*; SenseWear Professional 6.0)	Multisensor device: triaxial accelerometer + sensors (heat flux, galvanic skin response and skin temperature)	Upper left arm at triceps	Steps, activity intensity level	EE

Table 3.2. Details of type, location and output of the six activity monitors

(a AC – activity counts; b VMU – vector magnitude units; c EE – energy expenditure).

Activity	Duration (minutes)
Standing	1
Lying	3
Sitting	2
Standing	2
Slow walk*	6
Sitting	2
Standing	2
Fast walk*	6
Sitting	2
Standing	2
Sweeping	2
Sitting	2
Standing	2
Lifting	2
Sitting	2
Walking/standing	1
Stairs	1
Sitting	5
Walking/standing	1
Walking on treadmill (flat)**	4
Standing	2
Walking on treadmill (4% incline)**	4
Walking/standing	1
Sitting	2

Table 3.3 Schedule of physical activities in the standardised protocol.

* These walking activities were performed in a 30m corridor. Speeds were self-selected. During fast walking, patients were instructed to walk as fast as possible. ** Participants walked at 85% of their fast walking speed, first on the flat and then at an incline of 4%. Participants were instructed not to support their arms during treadmill walking.

3.3 Statistical analysis

Minute-by-minute data were compiled for each patient in one database and synchronisation was verified by inspection of the curves to ensure the best fit on a patient-by-patient basis for each of the monitors. The analyses were carried out as follows:

3.3.1 Primary outcomes

First, a minute-by-minute correlation between METs from the portable metabolic system and each of the activity monitor outputs was calculated for every patient. Correlations between minute-by-minute VO_2 and activity monitor outputs were reported as median with inter-quartile range.

Second, mean METs level for the 59 minute protocol was calculated for each patient and correlated to the mean activity monitor output over this period. A statistically significant relationship was judged as indicative of validity.

3.3.2 Secondary outcomes

First, the response of monitors to slow and fast walking was assessed by evaluating the correlation between changes in METs and changes in activity monitor outputs at the different speeds. For this analysis the first minute of the walking bouts was excluded; stronger correlations were taken to indicate greater validity.

Second, for monitors which gave a stepcount as an output, the accuracy was compared to the verified manual stepcounts using Bland Altman analysis. This was also analysed at slow and fast walking speeds to test whether walking speed affected stepcount accuracy..

Third, Bland regression analyses [266] were performed to test the agreement between indirect calorimetry (METs) and the activity monitor outputs. The 95% predictions limits of the METs at the mean (of the different activity monitor outputs) were calculated.

3.4 Results

Due to technical difficulties with the RT3 monitor, only 29 patients used this monitor. An example of one patient's data is provided in **Figure 3.2**.

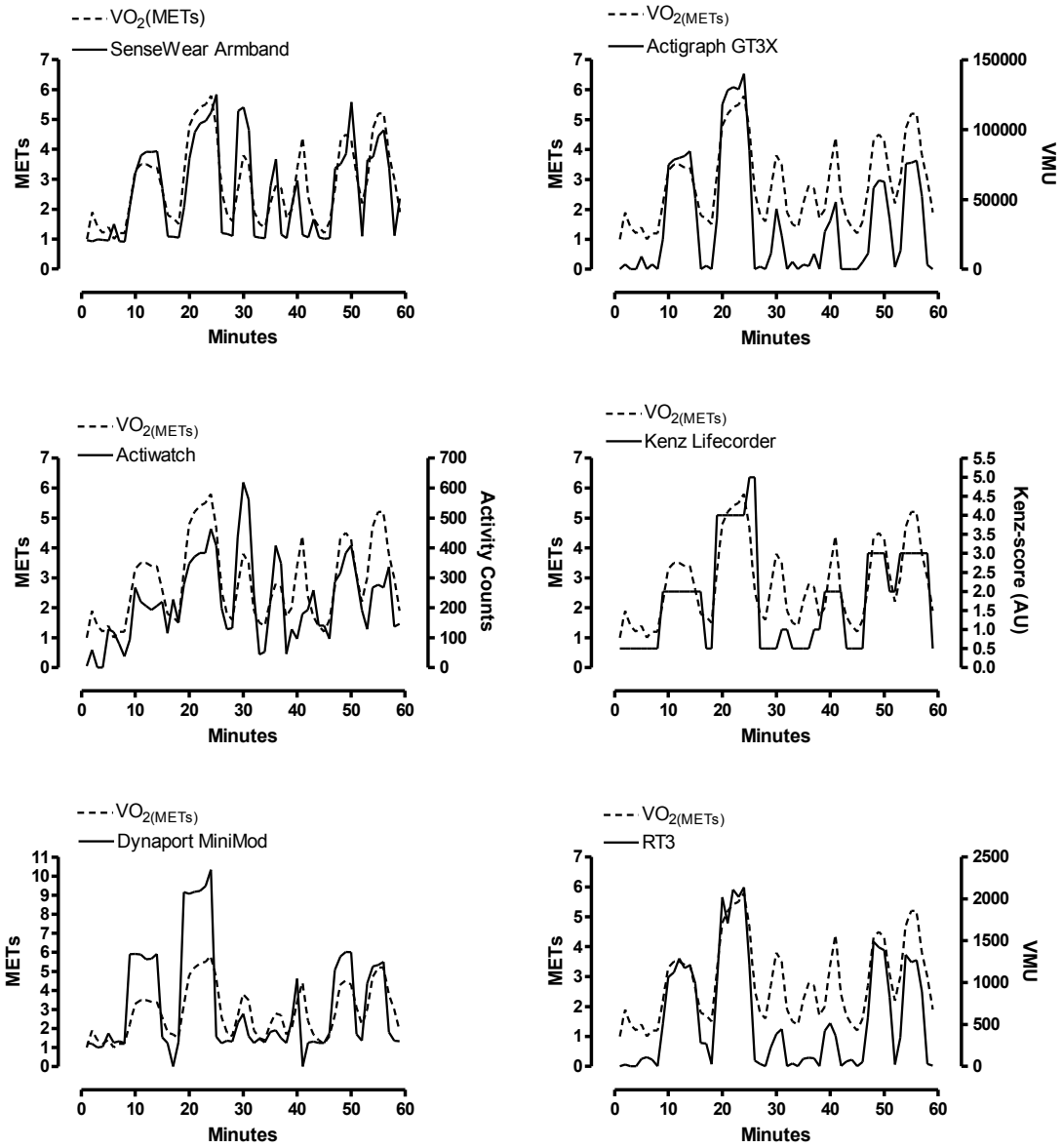


Figure 3.2 Example of one patient's experiment, showing indirect calorimetry data from the Oxycon Mobile (METs) plotted against the different activity monitor outputs.

Minute by minute correlations between metabolic cost and activity monitor output are shown in **Figure 3.3**. Strong correlations (R>0.7) were found with the MiniMod (0.82 (interquartile range (IQR) 0.13)), Actigraph (0.79 (IQR 0.11)), SenseWear (0.73 (IQR 0.18)) and RT3 (0.73 (IQR 0.15)) but not for the Actiwatch (0.53 (IQR 0.21)) and Kenz (0.57 (IQR 0.26)).

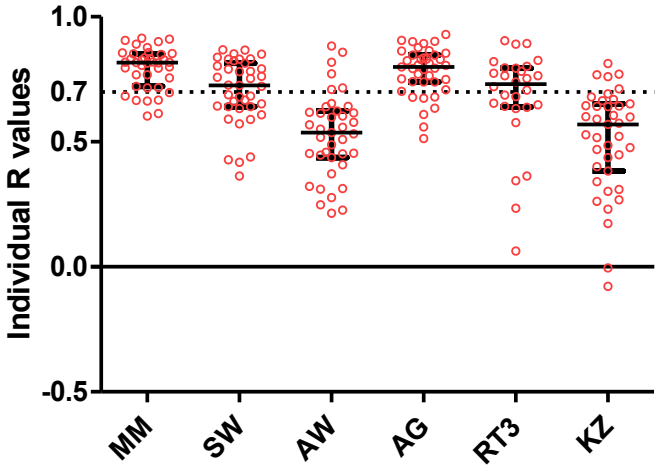


Figure 3.3. Minute-by-minute correlations (R) between activity monitor outputs and metabolic equivalents of task (METs) per patient (white dots).

MM; MiniMod, AG; Actigraph, SW; SenseWear, AW; Actiwatch, VMU; vector magnitude unit, AC, activity count, AU; arbitrary unit. Median (inter-quartile range) correlation for each activity monitor is reflected by cross bars, *p<0.05."

The mean correlation between metabolic cost (METs) and activity monitor outputs over the whole protocol was, from highest to lowest; SenseWear (r=0.76 [95% confidence interval (CI) 0.54-0.91]), Kenz (r=0.52 [95% CI 0.27-0.73]), Actigraph (r=0.49 [95% CI 0.28-0.64]), MiniMod (r=0.45 [95% CI 0.21-0.61]), Actiwatch (r=0.37 [95% CI 0.17-0.56]), all p<0.05 and RT3 (r=0.35 [95% CI -0.04-0.48], p=0.06) (**Figure 3.6**).

Patients changed their mean walking speed by 1.31km/h from the slow (3.27±0.47 km/h) to the fast (4.65±1.28 km/h) walking phase. As expected, the change in walking speed correlated with the change in VO_2 determined by the metabolic equipment (r=0.65) increasing from 3.11±0.74 METs to 3.93±1.23 METs. All monitors detected this increase in energy expenditure, via their outputs, during fast walking compared to slow walking. The highest correlations were reported for the MiniMod (r=0.94 [95% CI 0.89-0.97]) and Actigraph (r=0.88 [95% CI 0.77-0.93]) compared to the RT3 (r=0.69 [95% CI 0.42-0.85]), Actiwatch (r=0.59 [95% CI 0.34-0.76]), Kenz (r=0.57 [95% CI 0.31-0.76]) and SenseWear (r=0.52 [95% CI 0.25-0.72]), all p<0.0001. Both the Actigraph and Minimod are worn at the hip, whereas the Sensewear is worn on the upper arm.

The stepcount accuracy for the Sensewear and MiniMod was analysed against the verified stepcount where available, i.e. the manual stepcount verified by the video data. In some cases, a verified count

was not available, so only the manual count was used. However, there was a very good agreement between the manual and video stepcounts (as shown in the Bland Altman analysis in **Figure 3.4**).

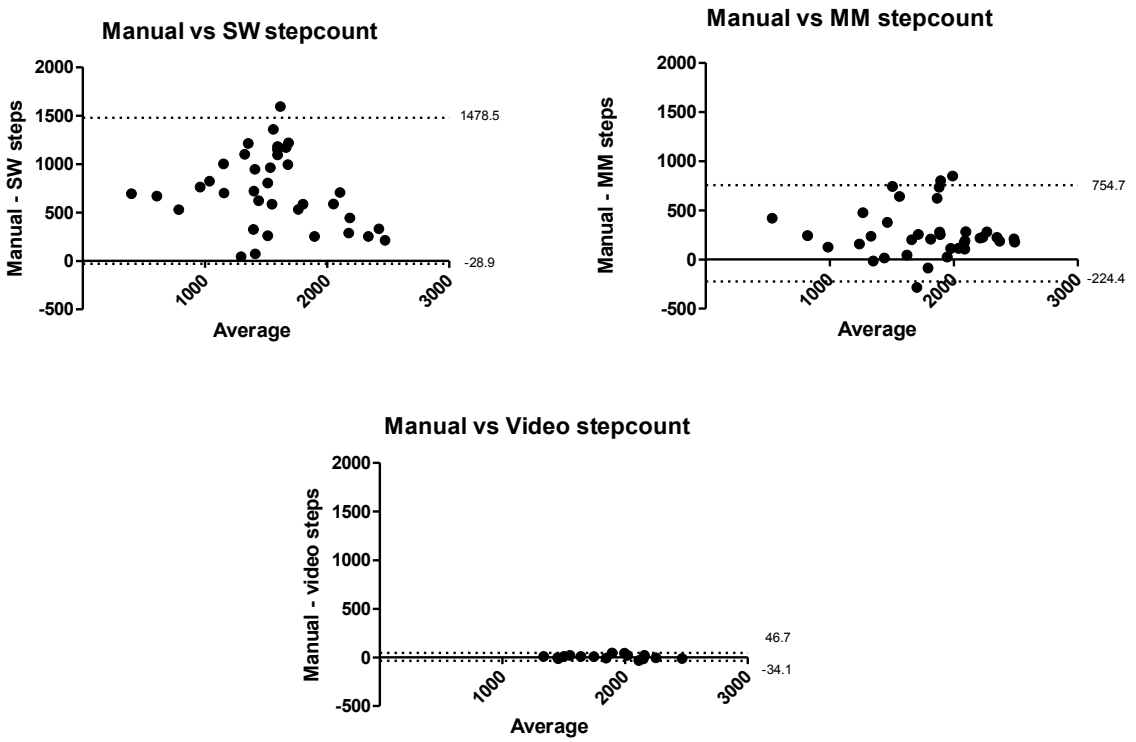


Figure 3.4 Bland-Altman plot showing comparisons of manual step counts with Sensewear, Dynaport Minimod and Video step counts.

The Sensewear tended to underestimate the stepcount more than the MiniMod, which actually had a slight tendency to overestimate the stepcount (95% confidence intervals 147.8 to -26.9 for Sensewear compared to 754.7 to -224.4 for Minimod)The Sensewear also underestimated at both walking speeds (see **Figure 3.5**), and more so at slow walking speeds (95% CI at slow walking 365.1 to -103.7 and 251.8 to -56.2 at fast walking). The MiniMod performed well at both speeds (95% CI at slow walking 140.5 to -80.6 and 53.9 to -13.3 at fast walking).

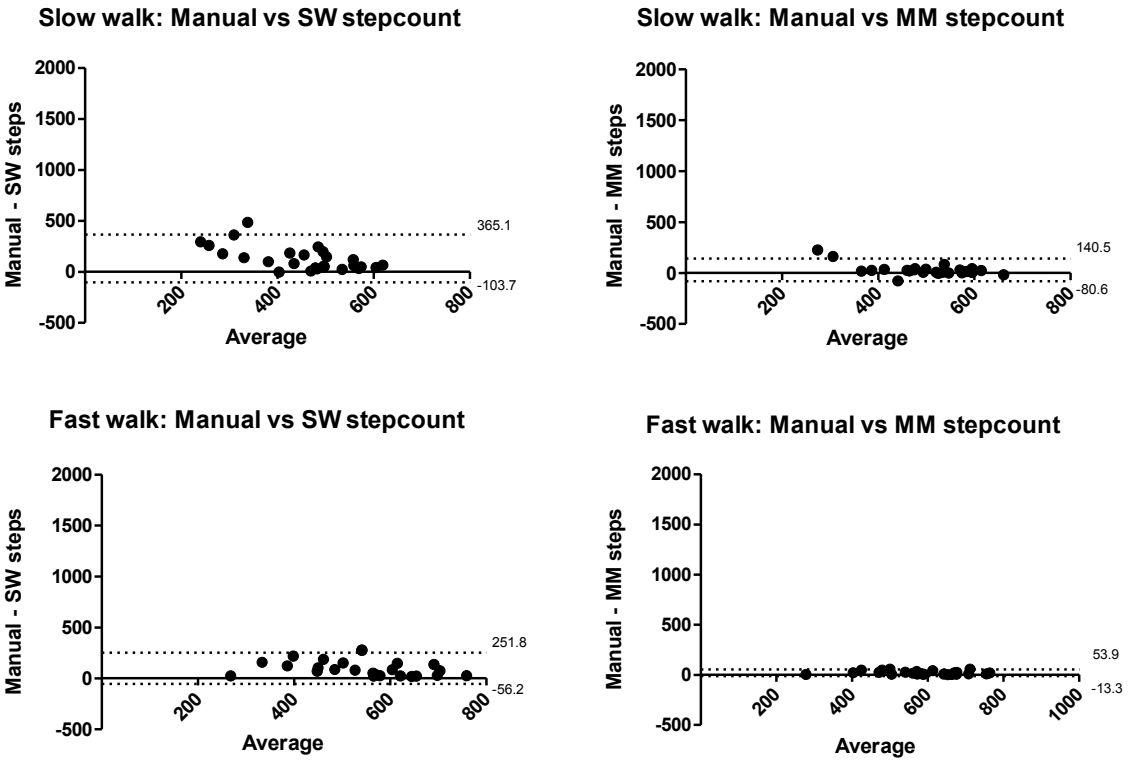


Figure 3.5. Bland Altman plot showing comparison of manual step count with Sensewear an Dynaport Minimod monitors for slow and fast paced walking

Bland regression analyses showed significant relationships ($p<0.05$) between METs derived from indirect calorimetry and the different activity monitor outputs, except for the RT3 ($p=0.06$) (**Figure 3.7**). The 95% limits of prediction for METs (derived from indirect calorimetry) at the mean (3.59 METs) were from lowest to highest: 1.13 METs with the SenseWear, 1.15 METs with the Actigraph, 1.17 METs with the MiniMod, 1.25 METs with the Actiwatch, 1.28 METs with the Kenz and 1.41 METs with the RT3.

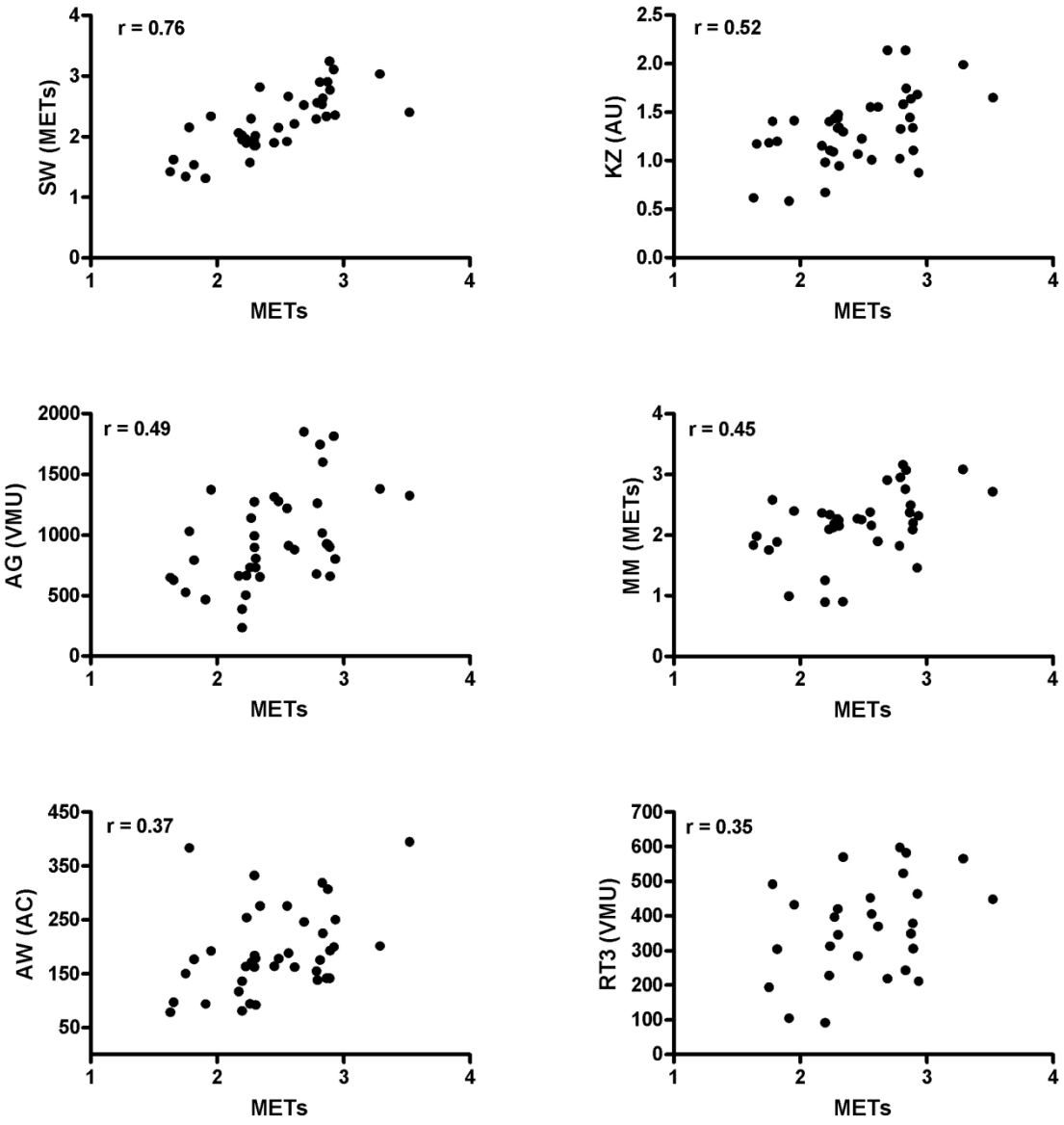


Figure 3.6. Mean correlations of each activity monitor output with indirect calorimetry (METs).

R Value shown for each monitor (all p<0.001)

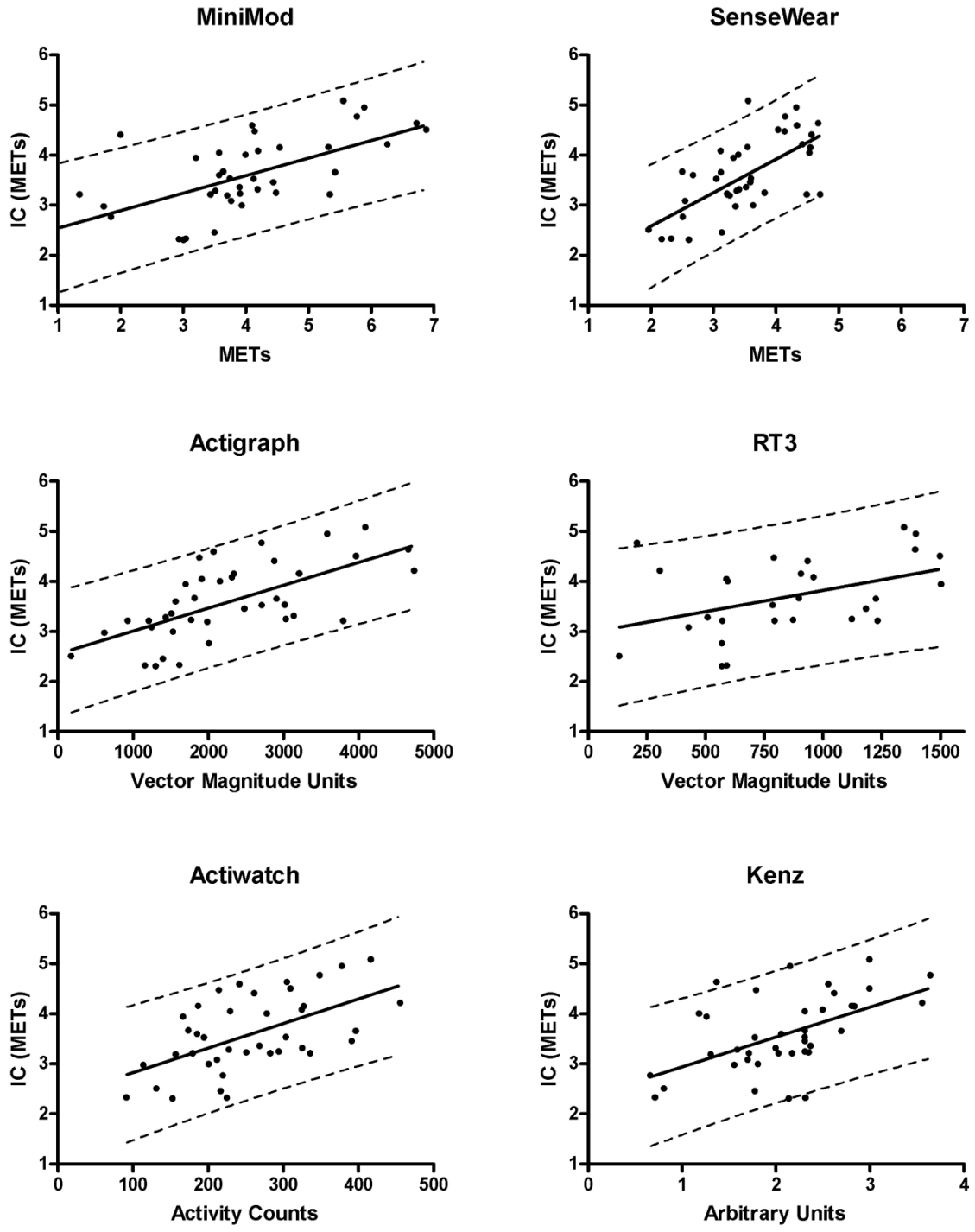


Figure 3.7. Bland regression analysis for each activity monitor output versus indirect calorimetry (IC).

95% confidence intervals are shown as dashed lines.

3.5 Discussion

3.5.1 Significance of the findings

The validity of six physical activity monitors was investigated by comparing activity monitor outputs for each monitor to actual VO_2 measured with indirect calorimetry from a portable metabolic kit in controlled laboratory conditions. Triaxial activity monitors were judged to be more valid compared to uniaxial activity monitors according to a number of criteria.

Correlations between minute-by-minute outputs and VO_2 were highest with the Dynaport MiniMod, Actigraph GT3X, SenseWear Armband and RT3, all exceeding an r value of 0.7. The best correlations of mean activity monitor output with mean VO_2 over the 59 minute activity protocol were again reported for the three triaxial activity monitors (SenseWear Armband (r=0.76), Actigraph GT3X (r=0.49) and Dynaport MiniMod (r=0.45)) and one uniaxial activity monitor (Kenz Lifecorder (r=0.52)).

All monitors were able to detect modest changes in walking speed, but two triaxial activity monitors had the strongest correlations with indirect calorimetry (MiniMod (r=0.94) and SenseWear (r=0.88)). The ability of an activity monitor to detect a difference in walking speed of 1.31 km/hr or 0.36 m/s is clinically relevant. Patients with COPD do walk more slowly than healthy subjects, and this is reflected, for example, by their reduced six minute walking distance [267, 268]. In this study, all monitors were responsive enough to detect these modest changes in walking speed.

Interestingly, step count accuracy varied with walking speed. Only the Sensewear and MiniMod were considered in this analysis. The Sensewear was much less accurate overall than the MiniMod, but was worse at slow walking speeds. This is probably because the Sensewear is positioned on the upper limb, so unless there was reasonable arm excursion during walking (part of a normal gait pattern), it may not always detect a step. The MiniMod's greater accuracy is probably due to the fact it is positioned around the waist and would give more information about hip movement during walking. All activity monitor outputs showed similar variability in predicting energy expenditure. The 95% prediction limits for mean METs (3.59 METs) varied between ±1.13 METs (SenseWear) and ±1.41 METs, (RT3). This implies that, from a clinical perspective, predicting oxygen consumption directly from different activity monitor outputs is not accurate. However, when patients engage in activity, monitors do indeed detect the increase in physical activity levels within a range of 1 to 1.5 METs.

This is the first multi-centre trial where several activity monitors have been validated against indirect calorimetry (VO_2) in different stages of COPD. Until now, only the Dynaport MiniMod and SenseWear Armband had been validated against VO_2 in patients with COPD. In these devices, similar correlation coefficients were previously reported between activity monitor outputs and total energy expenditure

(r=0.75 and r=0.93 for the SenseWear Armband [269, 270], r=0.7 for the Dynaport MiniMod) [269]. In a previous study, during a set of 5 daily activities, a high level of agreement between SenseWear Armband (22.7±7 kcal) and indirect calorimetry (21.0±7.9 kcal) was observed [271]. In a similar protocol, a moderate agreement between energy expenditure estimated from the SenseWear Armband and energy expenditure measured from indirect calorimetry was reported (mean difference of -0.2 METs with a limit of agreement of 1.3 METs) [272].

3.5.2 Critique of the method

In this study, validity was assessed using correlation analyses rather than a measure of agreement (e.g. Bland-Altman plot), as most of the outputs of the activity monitors are in different units (activity counts, vector magnitude units etc.) to each other, and to the VO_2 data. Although several prediction equations are available to convert some outcomes (e.g. VMU) to energy expenditure (which can also be derived from the VO_2 data for direct comparison), these are not available for all of the monitors used [273-276][6]. Moreover, the goal of the study was to assess the validity of the devices rather than their prediction equations. Therefore, comparing the raw data from the activity monitor with VO_2 data from the portable metabolic kit using correlation analysis was more appropriate than using a measure of agreement.

Although the monitors were able to detect modest changes in walking speed, which is important for use in the COPD population, overall, it could be argued that the patients who participated in this study were perhaps not as limited as some of the more severe patients encountered clinically. For example, the mean six minute walk distance was 438m, and there were only 3 GOLD stage IV patients. Therefore the findings of validity must be interpreted in this light. Therefore it may be more accurate to repeat the study protocol in patients who, for example, have a six minute walk distance less than 200m, giving a walking speed of 2km/hr, as compared to the 'slow walk' speed of 3.27km/hr in this study. In fact, Harrison et al [277] recently assessed the sensitivity of the Sensewear armband in 57 COPD patients during the incremental shuttle walk test. In 7 patients at level 1 of the test and at a speed of 1.8km/h, they found that the Senswear was not able to detect any steps at all. (These patitents were not significantly phenotypically different to the other patients in terms of baseline characteristics or distance walked). However, step count was a sensitive measure with significant differences between levels 1 and 2 if these 7 patients were excluded. In contrast, the measure of energy expenditure was only significantly different as patients progressed from level 1 to level 2. Step count was significantly sensitive at higher levels of the test.

[6] Publicly available for the Actigraph (7164 model and GT1M), Actiwatch, Kenz and RT3, but not for the SenseWear and MiniMod as these use proprietary algorithms developed by the device manufacturers.

It must be highlighted that the gold standard used, energy expenditure, is driven to a large extent by a number of other factors. Whilst specific factors such as body weight, age, and height can be incorporated into prediction equations, it is more difficult with non-specific factors such as mechanical efficiency, especially in patients with COPD. These patients have a higher active energy expenditure [278], even though it is well recognised that they are moving less. This is consistent with findings of reduced mechanical efficiency in these patients compared to healthy controls [279, 280]. An activity monitor cannot be expected to detect this complex variable accurately, and thus perhaps greater weight should be given to direct monitor outputs (steps, activity counts, vector magnitude units). Activity monitors are most appropriately used for the assessment of the activities of patients in terms of amount and/or intensity. The derivation of energy expenditure from activity monitors is imprecise so therefore not necessarily the ideal gold standard for assessing monitor performance, but the only one available for this currently.

A limitation of this study was that inter- and intra-device reliability of the different activity monitors were not evaluated. Inter-device reliability is essentially the accuracy or repeatability of two different devices (e.g. two identical Sensewear armbands) when measuring exactly the same activity (for example the same patient performing a particular activity wearing two identical activity monitors on the arm simultaneously). Ideally, there should be no differences at all between the two measures. Similarly, intra-device reliability is the repeatability of the measurement of the same device measuring exactly the same activity (e.g. monitoring a patient while walking a given distance at a given speed twice and comparing the two results). This is important when physical activity levels of patients are followed over time. Several studies have shown moderate to high inter-device reliability (intra-class correlation coefficient (r_{ICC}) = 0.99 for the Actigraph Model 7164 [281], r_{ICC} = 0.95 for Kenz Lifecorder [282] and r_{ICC} = 0.75 for the RT3 [283]) as well as intra-device reliability (r_{ICC} = 0.98 for the Actiwatch [284], r_{ICC} = 0.97 for the SenseWear Armband [285] and r_{ICC} = 0.86-0.99 for the Dynaport MiniMod [286]). Apart from the concepts of validity and reliability, other factors such as size and scope of the study, usability and cost of the activity monitor need to be taken into consideration when selecting an activity monitor for use in clinical trials. The validation of these activity monitors in a laboratory setting (validation against VO_2) can be considered as an important step in ascertaining their validity. An essential next step will be to confirm their validity in a field setting.

In conclusion, the present study found that three triaxial activity monitors (Dynaport MiniMod, Actigraph GT3X and SenseWear Armband) were the best of 6 monitors tested to assess standardised and common physical activities in the range of intensity conducted by patients with COPD. Changes in walking speed are most accurately registered by the Dynaport MiniMod and Actigraph, which are both worn on the hip. These results should serve as a useful guide for future choice of valid activity monitors for both research and clinical use in patients with chronic diseases including COPD.

4 Domestic validation study of physical activity monitors in COPD in daily life

4.1 Introduction

This study sought to validate a number of different physical activity monitors in COPD patients in a free living home environment, as opposed to the previous study, which took place under strict laboratory controlled conditions and which was limited to 1 hour. Whilst minute-by-minute performance of activity monitors is important in terms of their technical accuracy, from a practical perspective, patients would be required to wear activity monitors for a number of days in, for instance, clinical studies or as part of an exercise programme. Therefore, consistent performance over a period of time becomes more relevant. Another significant consideration is that monitors should be able to detect change or variability in physical activity; a COPD patient suffering an exacerbation is much less physically active, and a suitable activity monitor should be able to detect this change adequately, particularly if it is to be used in future interventional studies.

As discussed earlier, the accepted method of validation of physical activity monitors is via calorimetry to measure energy expenditure. In the domestic setting, clearly it is not practical to use the expired gases method of indirect calorimetry used in the previous study as the reference against which to validate any physical activity monitors. Whole body direct calorimetry would be theoretically possible in free living individuals who could wear activity monitors in a room calorimeter, but whilst very accurate, this method would be limiting in terms of cost and time, as it would only be possible to test subjects one at a time. Physical activity would also be confined to what was possible within the room, and would not be reflective of how most patients go about their daily lives, e.g. going out of the house for a walk, shopping etc., as well as probably being less acceptable as a method to potential study participants themselves.

This leaves the only other method of calorimetry which could be used for a long term validation of physical activity monitors; that of doubly labelled water (DLW). This has been used in several previous validation studies of activity monitors and is accepted as the gold standard criterion.
As already discussed, this method relies on the fact that labelled 18-oxygen is eliminated as both water and carbon dioxide, whereas labelled hydrogen (deuterium) is only eliminated as water. Thus the difference between the two rates of elimination is a measure of CO_2 flux, described by the following equation:

$$r_{CO2} = N/2\ (k_{18} - k_2)$$

where r_{CO2} is CO_2 production rate (mol/day), N is the total body water pool size (mol) and k_{18} and k_2 are the elimination rates of labelled 18-oxygen and deuterium respectively.

Sources of error include isotope measurement, variations in background levels of isotope (both deuterium and 18-oxygen are naturally occurring in small concentrations) and unanticipated changes in the body water pool (for example due to large insensible losses or diuretic therapy) or atypical diets or other metabolic disorders which would significantly alter the respiratory quotient (estimated to be around 0.85).

Carbon dioxide and water production and energy expenditure as measured with DLW was validated against room calorimetry by Schoeller *et al*, and shown to be accurate to 1 to 2% [287]. Reproducibility was assessed in a review by Schoeller and Hnilicka and shown to have a mean coefficient of variation of 8%, largely due to physiological variation of 7%, which seems to reflect variation in physical activity [288].

Whilst this method has been used widely in validation studies in healthy populations, there has been very little work in disease populations, including COPD. In fact, in a systematic review by Van Remoortel *et al* as part of the PROactive project, of the 48 studies that had used doubly labelled water as the criterion method, only 5 studied subjects with chronic disease. Most studies used a single monitor, with a few using 2 simultaneously. The review showed that studies in general had wide heterogeneity and as such, validation studies in chronic disease are lacking [264]. Disease specific studies are essential as these patients tend to move more slowly than healthy subjects. Therefore energy expenditure will be accounted for to a greater proportion by individual patient characteristics such as weight and age, rather than necessarily physical activity. Baarends *et al* showed that COPD patients have a higher active energy expenditure although they are less physically active according to physical monitor outputs, suggesting metabolic inefficiency, i.e. they require more energy to achieve the same level of movement compared to healthy subjects [279].

Patients in this study used 3 activity monitors simultaneously which enabled direct comparison as well as validation against doubly labelled water. A fourth, novel monitor, the Imperial eAR monitor was also added. The hypothesis tested was that the outputs of all monitors would show strong correlations with the total energy expenditure calculated using the doubly labelled water method over a 14 day period, but that energy expenditure outputs would have a better correlation, This relationship with the gold standard measurement of doubly labelled water would serve to validate the use of these activity monitors in COPD in a long term domestic setting.

4.1.1 The Imperial College eAR monitor

This ear-worn device consists of a miniaturised computer and triaxial accelerometer, allowing the measurement of activity (activity index), as well as mobility and gait pattern continuously whilst the patient is at home. The monitor is connected to a base unit which serves as both a charger as well as adata storage hub. This base unit can be connected to a PC via USB connection in order to download the data.



Figure 4.1 Imperial eAR monitor

The positioning of the monitor on the ear is critical in its ability to detect information regarding posture and balance in a similar way to the vestibular function of the human ear [289]. The output of the monitor appears as raw counts in each axis of movement with 20 measurements per second (corresponding to a frequency of 20Hz). To get an actual activity count, the variance of each second in each axis is calculated to produce the eAR activity index. The raw data from each axis can also be plotted in a graph to give characteristic waveforms with specific features depending on the activity being undertaken, such as running or jumping. In one study with healthy subjects, investigators were blinded to the activity performed (lying down, running, sitting, cycling etc.) when analysing the raw data and had a 80 to 99% accuracy level when predicting the type of activity [290]. It is also possible to determine gait pattern as the waveform patterns vary characteristically when weight is transferred from one foot to the other. This has been validated against the gold standard of foot force plates [289]. The accessibility to the raw data counts and graphs is far superior to the commercial devices which have been used, whose algorithms are not disclosed and whose data are filtered by the software provided.

The eAR monitor has been used in a number of different populations for example in sportsmen and women, to monitor posture during rowing or for swim stroke analysis [291, 292], thereby aiding training and performance, as well as rehabilitation after injury.

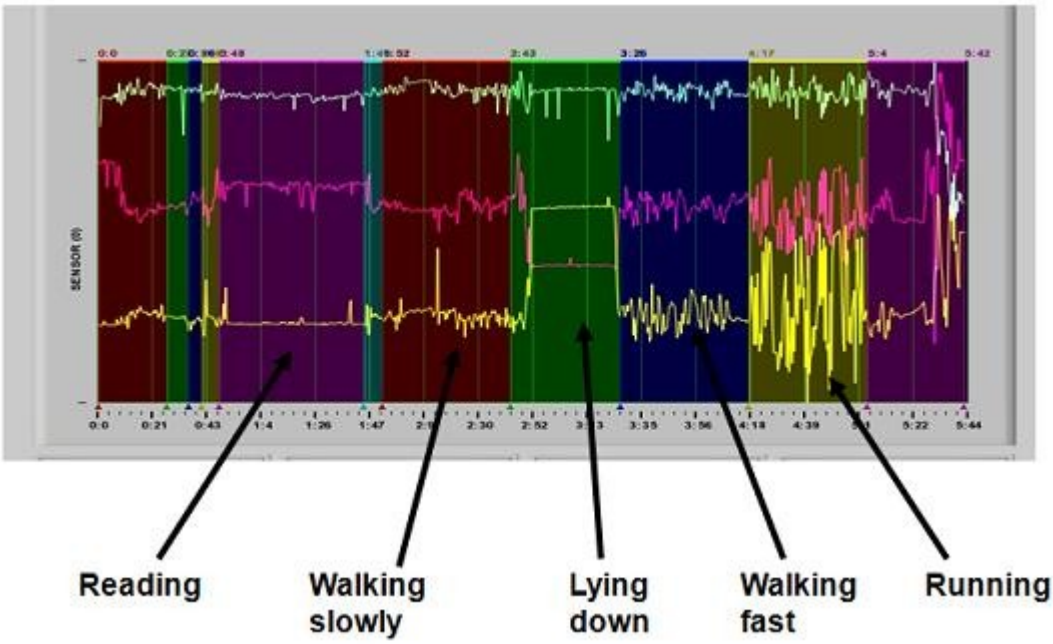


Figure 4.2. Example of data from eAR monitor.

Using the eAR monitor gave the opportunity to compare it with other relatively established commercial devices in terms of both accuracy as well as usability to both investigator and subject alike. The eAR has had good results in other populations, namely healthy subjects, and in elderly patients with knee osteoarthritis and abdominal surgery [293-295]. It has been previously used in cystic fibrosis patients to measure physical activity around the time of exacerbation by this group [296]. It therefore was an attractive choice to validate in the COPD population.

The rationale for using this device was primarily to validate it in a COPD population against doubly labelled water, which has not been done previously. The device has been previously validated in COPD patients against another device, the Sensewear armband (which was validated in the previous present studies) [297]. It has also been validated against indirect calorimetry using mobile metabolic data in a similar way to the previous study, albeit in healthy participants [290]. There was good agreement between predicted energy expenditure according to activity and measured energy expenditure from the metabolic data.

4.2 Materials and methods

4.2.1 Study subjects

20 patients with COPD were recruited. All had a clinical history compatible with COPD as well as evidence of chronic airflow limitation, and ranged in severity from GOLD stage II to IV [246]. They were all clinically stable and free from exacerbations for a minimum of 4 weeks prior to the study. Patients were excluded if they had other co-morbidities which would interfere with their movement, other than due to COPD (e.g. arthritis, neuromuscular disease) or respiratory diseases other than COPD (e.g. asthma), or cognitive impairment. Patients were also excluded if they were on variable doses of diuretics as this causes too great a fluctuation in the body water pool which would violate the assumptions made with the doubly labelled water method of indirect calorimetry. Patient characteristics are shown in **Table 4.1**. All patients gave written informed consent. The study had ethical approval from the Lothian Regional Ethics Committee (Edinburgh, United Kingdom) and local site specific approval from the Research and Development department of the Royal Brompton Hospital. The sample size was determined (as in Chapter 3) by the PROactive consortium in terms of what had been previously done in the literature and what was technically possible. A calculation to find a specific change was not undertaken due to the observational nature of the study and also the fact that there was a limited quantity of doubly labelled water that could be used in this study. Regarding the eAR monitor, essentially, this was a pilot study, so no sample size calculation was performed.

All patients underwent baseline testing as described above in the Methods section.

4.2.2 Study design

Three of the six monitors used in the laboratory validation study were also used in the field study (see **Table 3.2**), in addition to a novel device, the eAR monitor (Imperial; **Figure 4.1**). All six were not used as this would have been too uncomfortable for the patient. The AG and RT3 were chosen to compare two hip worn devices, along with the Sensewear as it was a multisensor device. Their outputs over 2 weeks were compared to a gold standard of indirect calorimetry as obtained from doubly labelled water. This method is described in detail below. Patients wore the activity monitors for 14 consecutive days, but were instructed not to wear them at night or while bathing or swimming. At the end of this period, they also completed a usability questionnaire for each monitor, which assessed factors such as ease of use, comfort and obtrusiveness.

4.2.3 Doubly labelled water method of indirect calorimetry

The total energy expenditure (TEE) over the 14 day period of monitoring was measured using doubly isotopically labelled water (DLW), according to the Maastricht protocol [298]. On the morning of day 0, body weight was recorded, and after the collection of a background urine sample, subjects drank a weighed amount of doubly labelled water (enriched with $^{2}H_2$ and ^{18}O such that baseline levels were increased by 100 ppm for ^{2}H and 200 ppm for ^{18}O). Urine samples were collected in the afternoon of day 0 approximately 6 hours post ingestion and from the second voiding. Further samples were collected on the mornings of day 1, day 7, and day 14, and in the evening of day 6, and day 13. Patients were asked to note carefully the exact time of each urine sample.

4.2.4 Measurement of resting energy expenditure

This was done using the ventilated hood method [197]. Patients were instructed to fast overnight and measurements were taken first thing in the morning of the first day of the study period. The calorimeter was calibrated before each patient measurement using a span gas (20% CO_2, 1% O_2), and to nitrogen for a zero calibration. Patients were asked to lie still under the canopy for 20-30 minutes until the readings of VO_2 and VCO_2 had reached equilibrium. The next 10 minutes of readings were taken to calculate resting energy expenditure. A second measurement was taken during the second week of the study and a mean of the two values was used. The Weir equation was used to calculate resting energy expenditure (REE) from the VO_2 and VCO_2 values obtained [198].

Predicted resting energy expenditure (REE) was also calculated using the Harris Benedict equation [199]. Active energy expenditure (AEE) was measured as (0.9 × TEE) − REE, assuming diet-induced thermogenesis to be 10% of TEE [299]. AEE was further normalized by body weight in kg and expressed as $AEE.kg^{-1}$. TBW was calculated as the ^{2}H dilution space from the ^{2}H enrichment of the second voiding minus the ^{2}H concentration of the sample before dose administration [300]. The ^{2}H dilution space was divided by 1.04 to correct for isotope exchange with non-aqueous hydrogen of body solids [301].

Variable	COPD patients (n=20)
Age (years)	68.5 ± 8.0
Gender (male/female, n)	16/4
FEV_1 (L)	1.27 ± 0.62
FEV_1 (%predicted)	48.3 ± 19.2
GOLD stage II/III/IV (n)	9/7/4
BMI (kg/m^2)	24.7 ± 4.8
6MWD (m)	435 ± 111
VO_{2peak} ($ml.min^{-1}.kg^{-1}$)	14.2 ± 6.4
MRC	2.8 ± 1.0
CAT	16.4 ± 7.7
SGRQ	
Total Score	43.0 ± 19.7
Activities	60.1 ± 29.7
Impacts	29.2 ± 16.7
Symptoms	50.8 ± 25.7

Table 4.1. Patient characteristics

Data are expressed as mean ± std. FEV_1- forced expiratory volume in 1s; 6MWD - six-minute walking distance; MRC - Medical Research Council; CAT - COPD Assessment Test; SGRQ - St George's Respiratory Questionnaire.

4.3 Statistical analysis

A priori criteria for validation of the monitors were established before any analyses were undertaken:

.

4.3.1 Primary outcomes

The ability to capture day-to-day variability of physical activity levels throughout the period of assessment, as expressed by the coefficient of variation for each activity monitor.

4.3.2 Secondary outcomes

First, the ability to capture the lower levels of activity levels during weekends characteristic of COPD patients [302], at least of GOLD I-III.

Second, the relationship with parameters of exercise capacity (6 minute walk distance and peak VO_2), as this comparison had been used in the previous laboratory based study.

Third, the relationship of each activity monitor output with active energy expenditure as assessed by DLW, demonstrated by Pearson's correlation; and Bland-Altman plot for those monitors giving an estimate of mean daily energy expenditure.

Fourth, the correlation of the eAR monitor with other monitor outputs.

Lastly, while not a test of monitor accuracy we took the opportunity to evaluate the patient user-friendliness from the results of the usability questionnaire.

4.4 Results

Patients had at least 2 weekends and 6 weekdays of data for each activity monitor. Although subjects wore the monitor for 14 days, in some cases, technical problems resulted in incomplete data collection. No patient had to be entirely excluded from the analyses. However, incomplete days of monitoring were excluded.

In some of the patients, the resting energy measurements (REE) from the ventilated hood method gave unexpectedly low readings, despite repeating the measurements on different days, which could have been due to technical problems such as from the canopy or errors in calibration, although these were not apparent at the time of the measurements. Therefore the analyses presented shows results using predicted resting energy expenditure using the Harris Benedict equation as well as those results obtained using the ventilated hood and the Weir method (see Methods section).

The ability to capture day-to-day variability was expressed as a coefficient of variation for each monitor output. This reflects the intra-patient variability. The mean (SEM) for each output is plotted in **Figure 4.3**.

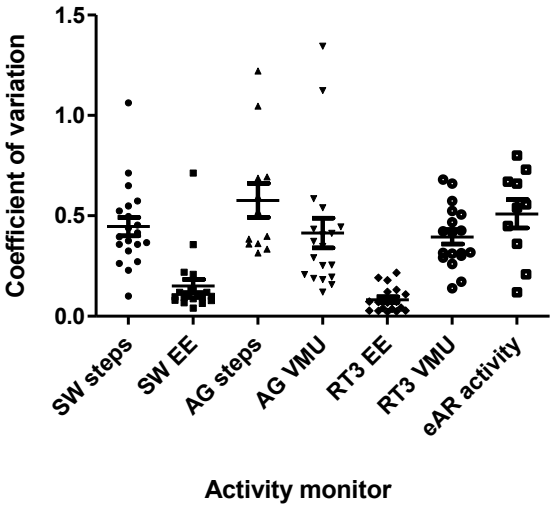


Figure 4.3. Coefficient of variation for each patient for each activity monitor.

SEM as follows: SW steps 0.35-0.54; SW EE 0.08-0.22; AG steps 0.39-0.76; AG VMU 0.26-0.57; RT3 EE 0.05-0.11; RT3 VMU 0.32-0.47; eAR activity 0.44-0.58)

A t-test was carried out to compare weekday with weekend activity for the various monitor outputs. The test was not significant for any output although a trend was noted for the Actigraph (AG) step count (p=0.08) and AG vector magnitude units (VMU) (p=0.06). This implied that these monitor outputs were different during the week versus the weekend. However some patients were actually more active at the weekend than during the week according to the activity monitor data in contrast to the hypothesis.

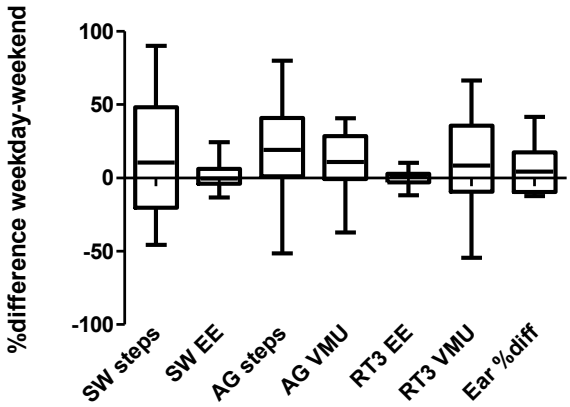


Figure 4.4. Percentage difference in mean activity between weekday and weekend for activity monitor output (with maximum and minimum difference plotted on error bars)

Pearson's correlations with 6 minute walking distance and mean activity output are shown in **Figure 4.5**. Significant correlations were obtained for all monitor outputs evaluated except for the eAR with Pearson's r as follows: AG steps 0.87 (p=0.0005), SW steps 0.84 (p<0.0001), RT3 VMU 0.77 (p=0.0003), AG VMU 0.58 (p=0.012), RT3 EE 0.54 (p=0.025) and SW EE 0.46 (p=0.05).

Correlations of the various monitor outputs with active energy expenditure (AEE) as measured with doubly labelled water are shown in **Figure 4.6**. AEE was calculated using the Harris Benedict prediction equations due to discrepancies with some of the REE values collected with the ventilated hood. Significant correlations were obtained for Sensewear step count (r=0.51) and RT3 energy expenditure (r=0.53) only. **Figure 4.7** shows the same analysis but using the AEE values obtained with the ventilated hood. The only significant correlation was with RT3 AEE (r=0.83). AEE was calculated by subtracting the REE values obtained from the hood from the TEE values obtained from the activity monitor to enable a more accurate comparison. The same was done for the Sensewear to obtain SW AEE; however this correlation was not significant (r=0.37).

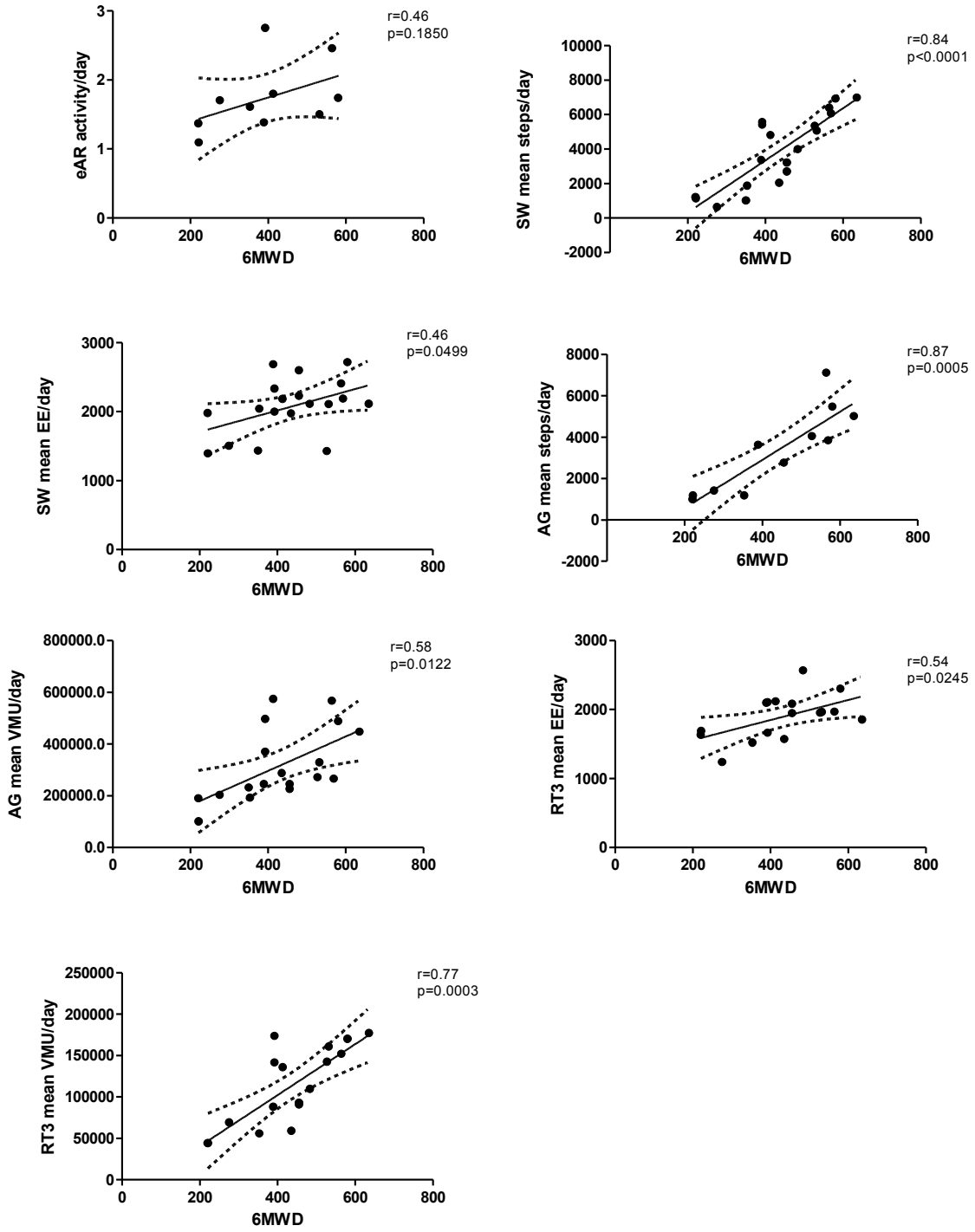


Figure 4.5. Correlations between activity monitor outputs and 6 minute walk distance.

r values are shown for each monitor. 95% confidence intervals of the line of best fit are indicated by the dashed lines.

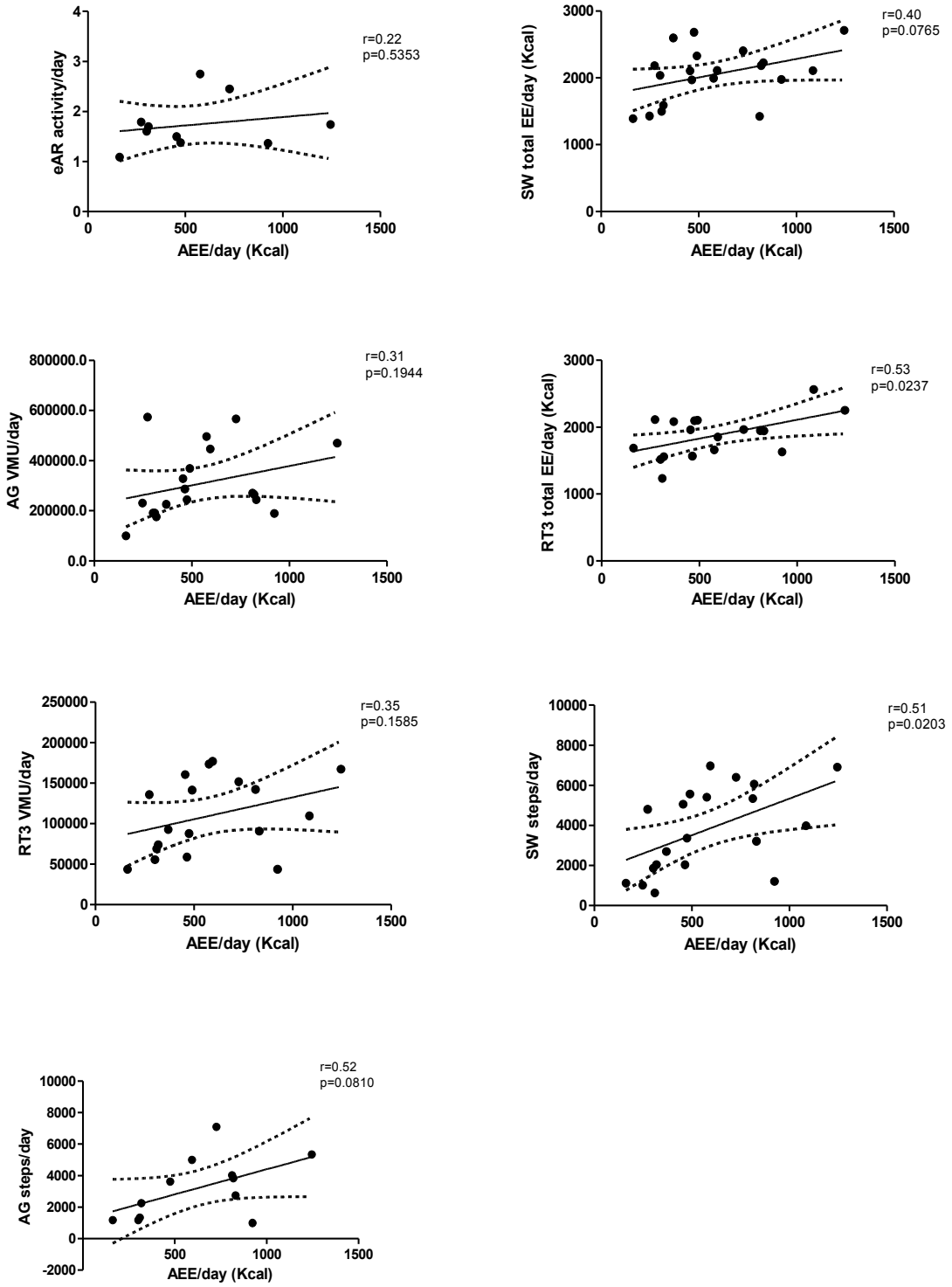


Figure 4.6. Correlations between activity monitor outputs and active energy expenditure measured with doubly labelled water (AEE); REE calculated using Harris-Benedict predicted values. SW – Sensewear; AG VMU – Actigraph vector magnitude units. r values are shown for each monitor. 95% confidence intervals of the line of best fit are indicated by the dashed lines.

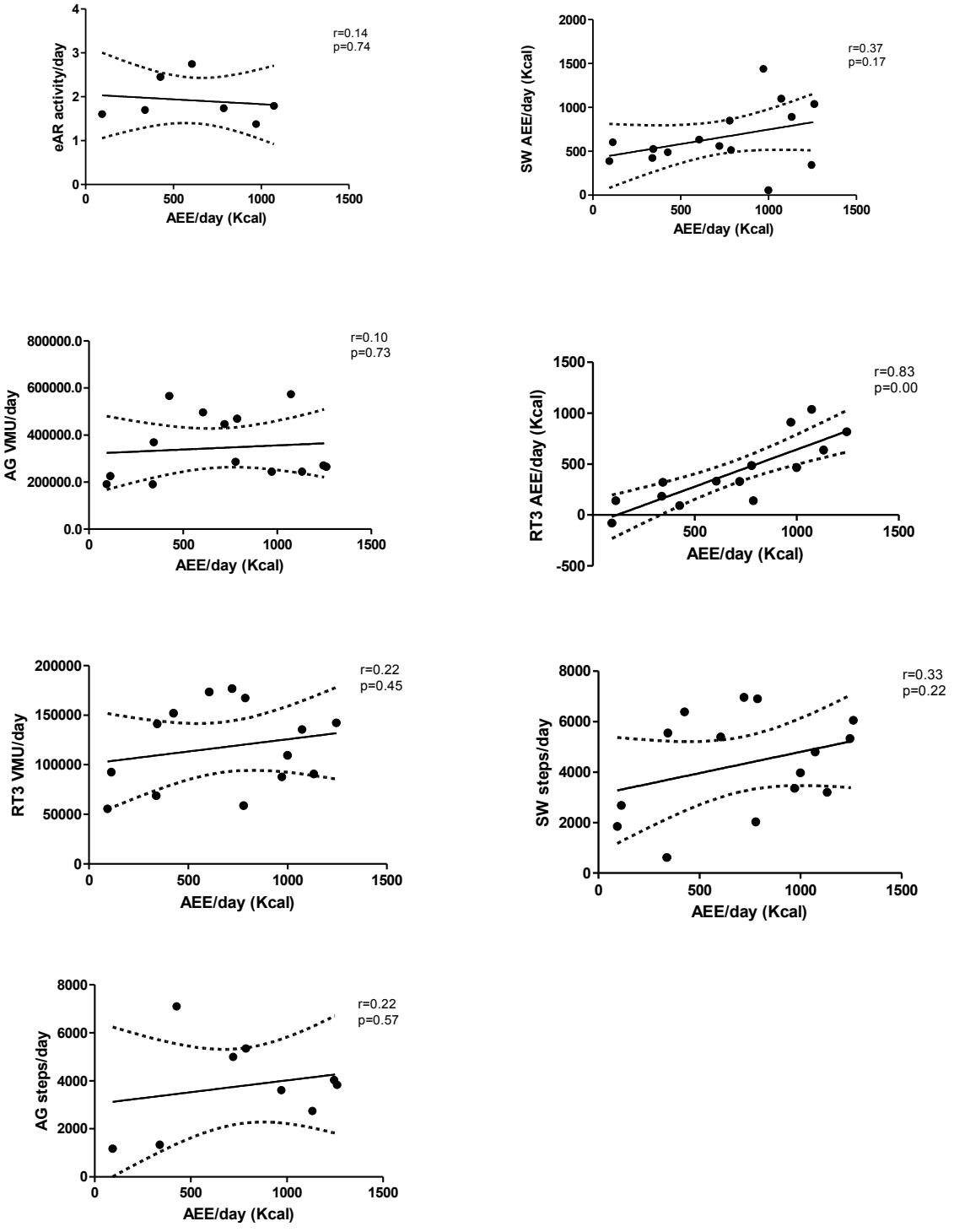


Figure 4.7. Correlations between monitor outputs and AEE as calculated by the Weir method using measured REE values from the ventilated hood. 95% confidence intervals of the line of best fit are indicated by the dashed lines.

The Sensewear and RT3 monitors gave a derived estimated energy output based on proprietary equations. Agreement with total energy expenditure as measured by doubly labelled water (TEE-DLW) is shown in **Figure 4.8** in a Bland-Altman plot.

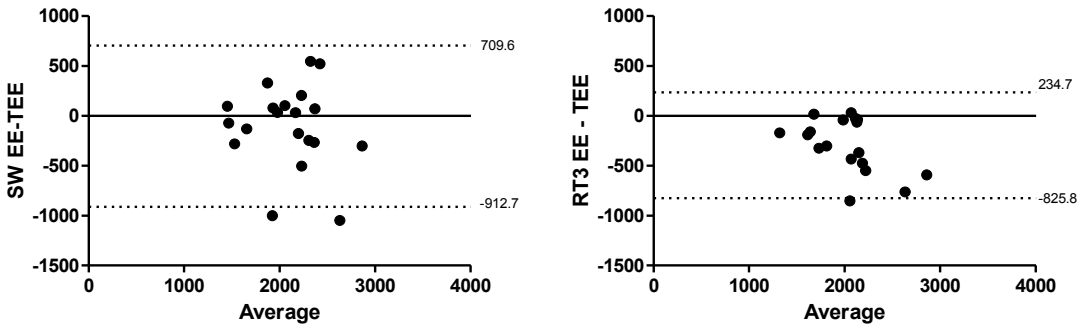


Figure 4.8. Bland-Altman plot of Sensewear (SW) and RT3 energy expenditure (EE) versus total energy expenditure (TEE) as measured by the doubly labelled water method.

The dashed lines indicate the 95% confidence intervals.

Correlation of the eAR monitor with other monitor outputs is shown in **Figure 4.9**. Significant correlations were seen with AG step count, AG VMU and RT3 VMU.

In terms of acceptability to patients as assessed by the usability questionnaire, the monitors scored out of a total score of 100 as follows: Sensewear 74.0, Actigraph 71.5, RT3 62.0 and eAR 56.7.

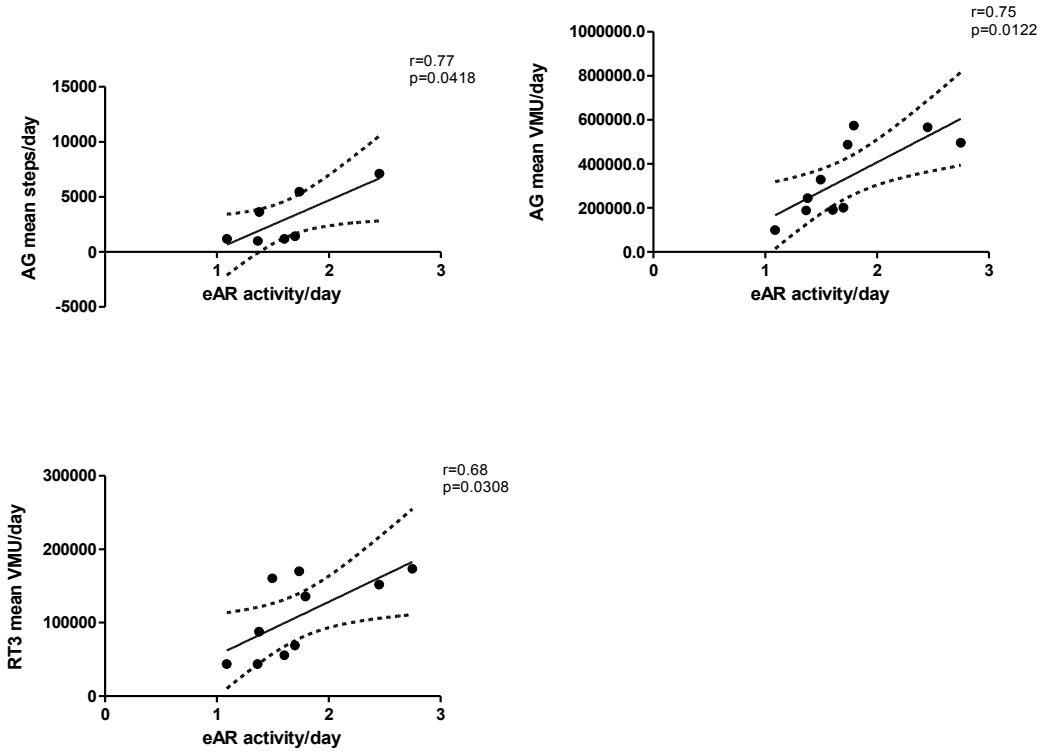


Figure 4.9. Correlations between eAR activity index and other activity monitor outputs (significant correlations shown).

Dashed lines indicate 95% confidence levels of line of best fit.

4.5 Discussion

4.5.1 Significance of the findings

The validity of three commercially available physical activity monitors and one novel device were evaluated against indirect calorimetry in 20 COPD patients in a home setting over a 14 day period. All monitor outputs evaluated had high coefficients of variation (all greater than 0.20) apart from SW-EE and RT3- EE (less than 0.1). A high coefficient of variation implies that the monitor is able to detect a great deal of variation in physical activity within a patient, which is over and above the margin of error of the device. However, intradevice reliability was not formally tested in this study. The monitors (apart from the eAR) used have previously been reported to have high interdevice [281-283] and intradevice

correlations [284-286]. In the laboratory validation study (Chapter 3), we have shown there to be strong correlations (all $r>0.7$, $p<0.05$) between activity monitor outputs and indirect calorimetry for all monitors used in this subsequent study, with 95% limits of prediction of energy expenditure to be between 1.13 METS (SW) and 1.41 (RT3). This implies that the margin of error of the monitors (apart from the eAR) is sufficiently low to consider that the variation in physical activity is likely to result from the patient.

All monitors apart from the eAR showed good correlations with 6MWD. This implies that they were able to capture the activity at the speed at which the patient moved during the six minute walk test and that the activity measured by that device parameter reflected that patient's exercise capacity. However, patients do not typically move at the speed at which they perform the six minute walk test, during which they are encouraged to walk as fast as they can for the duration of the test. Therefore it is merely assumed that all movements which expend energy are captured, including those performed very slowly.

The Sensewear step count and the RT3 energy expenditure demonstrated a statistically significant correlation with indirect calorimetry from doubly labelled water if predicted values for REE as calculated by the Harris Benedict equations were used. However, if actual measured values for REE from the ventilated hood were measured then only the RT3 energy expenditure output was significant. This could be due to fewer values as 5 subjects had to be excluded from the analysis using the measured REE values as data could not be obtained from them due to difficulties tolerating the test (unable to fast, undergoing a concurrent exacerbation, technical problems with canopy leak).

4.5.2 Critique of the method

The eAR monitor did not show any significant correlations with AEE or 6MWD, but this may be due to the small sample size – only 10 out of the 20 patients tested actually gave a full set of data. The eAR monitor has previously been shown to be a valid head-worn monitor for gait analysis [289], to predict energy expenditure [290] and has also been validated for use in COPD patients [297]. Good correlations were found between the eAR activity index and the AG step count and VMU and the RT3 VMU. This may be because they all generate the same raw data i.e. a vector in 3 different axes.

Reasons for lost data from the eAR monitor include technical problems with devices themselves either not recording accurately or losing data. One device suffered water damage and another was lost. Some patients also found the device uncomfortable to wear, particularly if they wore glasses or a hearing aid, due to its location behind the earlobe; it scored the lowest on the usability questionnaire (56.9%). Wearing glasses or hearing aids does become more common with age so is an issue which

needs due consideration in the design of this device going forwards. Overall, the most acceptable monitors were the Sensewear (74%), worn on the upper arm, and Actigraph (72%), worn on a belt over the right hip.

The other monitor to suffer significant technical problems was the RT3, mainly because it failed to record for a whole week (half of the testing period) in eight patients due to poor battery life, and totally failed in one patient. The Sensewear also suffered from lost data of 2 to 3 days in seven patients, again due to battery life. Only one patient's data was lost with the Actigraph. Technical reliability is crucial when considering a monitor for use in interventional studies or for long term home use. Moreover, if a monitor is too inconvenient or uncomfortable to wear, as seemed to be the case with the eAR, then it also cannot be used with any confidence in larger studies.

It was not possible to use a measure of agreement for all the monitors as only the Sensewear and RT3 gave estimated energy expenditure values as one of their outputs. A Bland-Altman analysis for these two monitors showed both monitors to be prone to error, but less so with the RT3 (see **Figure 4.6**).The overall trend for both monitors was to under-record energy expenditure; it is well known that COPD patients have higher resting energy expenditure levels, so the monitors were not able to estimate this accurately. However, a closer look at the individual data points seems to suggest that the tendency to under-record energy expenditure is greatest in the two patients with highest total energy expenditure as measured by DLW. This could be for one of 2 reasons – firstly, active energy expenditure during physical activity was under-recorded, or that resting energy expenditure was underestimated. In fact, in these two patients, REE as predicted by the Harris-Benedict equation was significantly lower than that measured by the Weir method using the ventilated hood (1468kCal vs 1926kCal and 1754kCal vs 1840kCal). Their respective mean stepcounts as recorded by the Sensewear were 6903 and 3204, which were not especially high, but doesn't exclude the possibility that this was inaccurate in these two patients. Such errors in a small sample size would influence the overall results more than in a larger cohort.

Some patients in this study were actually more active during weekends than on weekdays. This observation does not support previous findings of lower activity of COPD patients at weekends. This could be due to a number of factors, such as a chance distribution of poor weather during the two week study period during the week as opposed to the weekend. This data was not collected in this study, but was investigated in the study in the next chapter. Such confounding factors are likely mitigated by having a larger sample size. In fact, in the whole data set of 80 patients, weekend activity was found to be lower than weekday [303].

In terms of the gold standard of calorimetry itself, there was certainly the possibility of error in the measurements. The patients may have incorrectly recorded the time of their samples. A more accurate method of measuring total energy expenditure is to use a thermogenesis room for direct

calorimetry [304-306], but this method would not have been practical in this study, where the aim was to record patients' usual physical activity over a number of days in a free living environment.

The REE values measured with the ventilated hood were unexpectedly low for some patients (e.g. 50% of predicted values from Harris Benedict equations). Although these problems were not apparent at the time of making the measurements, these low results could represent incorrect data due leak from the canopy. This is why the analysis has been presented using both values. (In 5 patients, results were not at all available either due to having an exacerbation at the time of the measurement, being unable to fast or being unable to tolerate lying flat under the canopy).In fact, in the wider multicentre EU study [307], other European centres encountered similar problems, and it seemed to be generally when unexpectedly low measurements were obtained from the ventilated hood than the values predicted by the Harris-Benedict method (these patients were excluded from the final analysis in the published paper). If it is assumed that the patients for whom an actual resting energy expenditure measurement (via ventilated hood) was not available did in fact have a high higher REE that predicted due to having COPD, then active energy expenditure would in fact have been lower. In fact, previous work in COPD patients using doubly labelled water and the ventilated hood method to measure total and resting energy expenditure respectively have shown consistently that resting energy expenditure values are higher than healthy controls [278, 308]. This seems to be independent of disease severity and other factors such as fat free mass (i.e. metabolically active muscle tissue). In a study by Sergi et al comparing elderly COPD and healthy age matched controls, fat free mass index was similar in both groups but hypermetabolism (REE > 110% predicted REE) was found in 60% of the COPD patients compared to 13.7% of controls. However the hypermetabolic COPD patients did not have significantly worse spirometry than the other COPD patients [308]. Other possible reasons include medications (beta agonists, theophyllines), and the pro-inflammatory state known to exist in COPD [309].

In conclusion, the Sensewear and RT3 monitors were found to be the most accurate monitors in a field setting in this group of patients when validated against indirect calorimetry. All monitors apart from the novel eAR device showed good correlation with patients' exercise capacity in terms of 6 minute walk distance. However, the RT3 was far more prone to technical problems leading to lost data. All monitors, with the exception of the eAR, were reasonably well tolerated with the Sensewear and Actigraph being the most popular. These results, together with the results of the laboratory validation study, should help to guide researchers in selection of activity monitor in future research studies in similar patient groups.

5 Change in physical activity with time and climate in COPD

5.1 Introduction

The importance of physical activity in COPD is well established. The seminal studies from Garcia-Aymerich et al [9, 66, 67] have established the importance of physical activity in long term outcomes in COPD in terms of exacerbation rate, hospital admission and mortality. However, physical activity was assessed in these studies using questionnaire data, which have certain limitations, including recall bias. There have been few studies published showing longitudinal data from physical activity monitoring in COPD patients, showing the effect of time on lung function parameters or health related quality of life measures [310], [311], The most recent and comprehensive of these was published by Waschki et al [312], who followed up 163 patients with COPD and chronic bronchitis over a median of 2.8 years. Data regarding physical activity was collected prospectively over this time from the Sensewear armband. A decline in all measures of physical activity over the follow up period was found in all GOLD stages of COPD.

In addition, the variability of physical activity with season or climate (and therefore geographical location) is an important factor to consider; climate is a non-modifiable factor but a better understanding of how it influences physical activity would enable strategies to mitigate any negative effects or enhance any beneficial effects, for example, in how patients are advised medically or availability of resources such as pulmonary rehabilitation at different times of the year. There would also be implications in further studies using physical activity as an outcome measure in COPD, in particular with respect to interventional studies and trial design.

There is much evidence in healthy populations that physical activity is influenced by environmental conditions such as temperature, as already discussed earlier. For example, a large systematic review looking at over 30000 subjects over a 26 year period found that physical activity peaked in the summer months and was significantly lower in winter [235] . However, very high environmental temperatures can also be prohibitive; a Texan study found that high temperature (average 29°C) acted as a deterrent to physical activity [7]. It may be that the effect seen in healthy populations is more marked in COPD subjects.

It is known that falls in environmental temperatures are associated with falls in FEV_1 and FVC as well as an increase in exacerbation frequency [313], which would likely impact physical activity. Sewell *et al* [241] examined the effect of season on physical activity in 95 patients participating in a pulmonary rehabilitation programme. The patients were split into 4 groups according to when they enrolled in the programme. They found that those starting pulmonary rehabilitation in the winter had lower physical activity levels at baseline but also improved the most. However, there was no effect of season on the

other outcome measures before and after rehabilitation, namely incremental shuttle walk distance or quality of life measures. In addition, the number of patients in each group was relatively small (n=18 to 34) and the same patients were not followed up throughout the seasons. Importantly, the investigators did not explain how they defined the seasons, for example, stating differences in temperature with winter being cooler, so it seems that these were decided arbitrarily depending in the month of the year, rather by than climatic conditions such as temperature, rainfall, sunshine or day length.

Another study, published in 2012 by Moy et al [310], measured physical activity in a cohort of 102 COPD patients using the StepWatch activity monitor at two time points ranging from 3 to 9 months apart [310]. This US based group found a decline in physical activity over time with a mean of 645 fewer steps per day. There was also some evidence of seasonal variation with a greater decline in step count if patients were followed up in winter, over and above the mean decline over time for the cohort as a whole. However, the cohort was divided into 4 groups depending on which season they were monitored in, resulting in very small numbers in each group. This is a similar limitation to the Sewell study referenced above. Again, these investigators also do not state clearly how they defined each season as no information regarding temperature was given. In addition 98% of the patients were male, which is not truly representative of the COPD population.

A more recent study by Alahmari et al [314] involved a London-based cohort of 73 COPD patients who had daily physical activity monitoring by way of the Yamax DigiWalker pedometer, for a mean of 267 days, although the range was wide (29 to 658 days). They also recorded daily weather data in terms of temperature, rainfall, sunshine and wind speed, as well as pollution levels specified by levels of PM10. They found that step count increased with environmental temperature, but only up to 22.5 degrees C, after which there seemed to be a negative association between step count and temperature. They stated a 43 steps increase for every degree increase in temperature, but the range was again wide (95% CI 2.14 to 84.4 steps). They also found activity to be higher on sunny or dry days.

If it could be shown that there is a significant difference in physical activity within the same subject due to climatic conditions mentioned above, then this would have to be taken account in terms of choosing when to monitor patients as well as for how long, as this would influence outcomes in not only interventional studies but in clinical settings such as pulmonary rehabilitation.

Against this background, we conducted a study aiming to assess the effects of time, as well as climatic conditions, namely temperature, sunshine, rainfall and day length, on physical activity levels in COPD patients over a 12 month period. We hypothesised that:

1. Physical activity would decline with time, that is be lower at the end of the 12 month study period

2. Physical activity would be affected by climate, that is, would be lower in conditions of cooler temperature, increased rainfall and shorter day length (which acts as a surrogate for season with shorter day length during the winter months).

5.2 Materials and methods

5.2.1 Study subjects

236 patients were recruited from 5 European centres as part of the PROactive study (Royal Brompton Hospital, London UK: Elegi Colt Institute, Edinburgh, UK; KU Leuven, Belgium; Thorax Institute Athens, Greece; Department of General Practice, University Medical Center Groningen, Netherlands). All had a clinical history compatible with COPD as well as evidence of chronic airflow limitation, and ranged in severity from GOLD stage II to IV [246]. Other than a subset of exacerbation patients (n=11), all were clinically stable and free from exacerbations for a minimum of 4 weeks prior to the study. Patients were excluded if they had co-morbidities which would interfere with their movement, other than COPD (e.g. arthritis, neuromuscular disease) or respiratory diseases other than COPD (e.g. asthma), or cognitive impairment. Patient characteristics are shown in **Table 5.1**. All patients gave written informed consent. The study had ethical approval from the respective ethics committees (Lothian Regional Ethics Committee, UK; UZ Leuven Medical Ethics Committee, Belgium; University Hospital Ethics Committee "Sotiria" Hospital Athens, Greece, University Medical Center Ethics Committee University of Groningen, The Netherlands) as well as local site specific approval. All patients underwent baseline tests as described in the Methods section, apart from incremental cardiopulmonary exercise testing which was optional.

The patients were all recruited as part of Work Package 4 (WP4) of the PROactive project. The main purpose of the WP4 study was an item reduction exercise of two draft patient reported outcome tools to record physical activity in COPD (daily and clinic versions), in order to eliminate redundant questions and produce a final version of each tool, as previously published [245]. These were completed electronically on a personal digital assistant device (PDA). This was a multicentre study across the 5 European centres described. The initial phase of the study was 6 weeks, with a subsequent 6 and 12 month follow up visit. The study design is shown in **Figure 5.1**.

The first 6 weeks represent a cross-over study where the patients were randomised to either Arm 1 or 2 (to complete either the daily PRO or the Clinic PRO first), followed by a 2 week washout and then a

further 2 weeks with the other PRO. Each part was accompanied with 2 weeks of physical activity monitoring. Visit 1 (V1) occurred at the start of the study prior to randomisation, followed by Visit 2 (V2), 2 weeks later. Visit 3 (V3) took place after the 2 week washout period with Visit 4 (V4) a further 2 weeks later. Each of these initial 2 week blocks involved physical activity monitoring for 2 weeks, along with completion of one of the ePROs.



Figure 5.1. WP4 study design (adapted from Gimeno-Santos et al [245]).

Follow up was conducted at 6 and 12 months from Visit 1, but with only 1 week of activity monitoring at 6 and 12 months (Visits 5 and 6 and Visits 7 and 8 respectively). This shorter period of monitoring was decided as a result of work previously published by the PROactive consortium from the domestic validation study of activity monitors which showed that accuracy of monitoring was not significantly improved with 2 weeks of activity monitoring compared to 1 week[7] [307].

[7] Data was repeatable over 2 weeks; the second week of monitoring did not change variability necessitating a change in sample size.

Sample size was calculated according to the primary objective of the study, which was the item reduction exercise, and based on test-retest analysis of the draft clinic PRO. It was calculated as 200 (to give 90% power and taking into account the probability of answering to each response for each draft question administered. A further 50 exacerbated patients were also to be recruited to represent a full range of patients, to give a total of 250 subjects. The final number of 280 was agreed upon, to allow for approximately a 10% dropout rate.

5.2.2 Physical activity monitoring

As well as completing the draft questionnaires, patients were also required to wear 2 physical activity monitors, the Dynaport MiniMod and Actigraph GT3X simultaneously for two 2 week periods initially. These monitors had been previously validated in the first two studies described in previous chapters. Both monitors are trunk-worn triaxial accelerometers; the MiniMod is worn in the small of the back; the Actigraph is worn at the right hip. Patients wore the activity monitors for 14 consecutive days during the first part of the study, and for 7 consecutive days during follow up, but were instructed not to wear them at night when asleep or while bathing or swimming.

5.2.3 Weather data

Data specific to the time periods during which patients were studied, as well as to their location, were provided by the Met Office. The Met Office provided weather information for all European centres. These data comprised daily highest temperature and information on number of hours of sunlight and total rainfall per day (mm). Therefore daily weather data was available for every day of activity monitoring collected. Unfortunately, data on daily hours of sunshine was not available for two of the centres (Leuven and Groningen) so these centres could not be included in that particular analysis.

5.3 Data handling and statistical analysis

The following guidelines were used when processing the activity data:

1. Incomplete days of activity monitoring were excluded – at least 10 hours of activity data for a day were required for that day to be included in the analysis (patients were not asked to wear the monitors in bed at night).

2. Wherever possible, activity data was used from V1-2, but if not possible (for example, due to technical problems), data from V3-4 was used instead.

3. Patients who did not participate in all 3 time points (baseline, 6 and 12 months) were not included in the analysis.

Statistical analysis was carried out using IBM SPSS Version 19. Continuous variables are presented as mean value ±1 standard deviation (SD) or as median values (interquartile range) depending on the normality or not of their distribution, while categorical variables are presented as % predicted value. Normality distribution was assessed utilising Shapiro-Wilk normality test, while Q-Q plots[8] were used for visual confirmation of distribution of data. Comparisons of non-normally distributed physical activity measures across several groups and time points were conducted after they were transformed to natural logarithms. One-way ANOVA and Chi-square test were used to compare quantitative and qualitative variables across different sites at baseline. Further analysis of results, addressing 2 main objectives, was set out *a priori* as follows:

1. Assessment of changes in physical activity levels with time

Mixed repeated measures ANOVA was used to compare measurements of physical activity of the patients (steps, walking time etc) between baseline, 6 and 12 months (V1-2, V5-6 and V7-8) (within-subjects factor), with site being the grouping variable (between-subjects factor). Equality of the variances of differences was tested utilising the Mauchly's test of sphericity[9] and the Huyhn-Feldt correction[10] was used when assumption of sphericity was violated, because epsilon was>0.75 in all cases. Levene's test was used to investigate the equality of error variances. Bonferroni Post-Hoc test was used for pairwise comparisons between groups. The F statistic was reported to describe effect of time on PA measures.

[8] These are plots of quantiles of the first data set against the second data set to check visually for normality.

[9] Sphericity means that the variances of all possible pairs of groups are equal. If Mauchly's test is violated, variance calculations can be distorted, leading to inflated F ratios and increasing the chance of Type I errors, i.e incorrectly rejecting the null hypothesis.

[10] The Huyn-Feldt correction modifies the degrees of freedom to get a valid F ratio: the further the F ratio from 1, the worse the violation of sphericity.

2. Assessment of the effect of climate condition on physical activity changes over three time points (baseline, 6 months, 12 months)

Multivariate analysis was conducted using mixed linear models. Separate models were built with each measure of physical activity (steps, walking time etc) being the dependent variable. Repeated variable was time period (visit), while site, FEV_1, age, BMI, QMVC, RV/TLC and climate conditions (temperature, day length, rainfall and their interactions) entered the model as potential explanatory variables. The model fit was tested using the -2 Log Likelihood and the Akaike's information criterion, with the smallest value indicating the test with the best fit. The estimates of fixed effects with corresponding 95% confidence intervals were used to describe the effect of each of the explanatory variables (covariates) on each physical activity measure. A level of $p<0.05$ was considered significant.

5.4 Results

236 patients with COPD were recruited from 5 different European centres. Their baseline characteristics are detailed in **Table 5.1**. A breakdown by centre is also given in **Table 5.2** with results of ANOVA showing the differences between patients in each centre. However only 157 patients actually completed 12 month follow up successfully (i.e completing visits for baseline, 6 and 12 months with valid data from at least one activity monitor). This significant drop out rate is discussed later.

Variable	N	Mean	Std. Deviation
Age (years)	236	67.4	8.42
BMI (kg/m2)	236	27.0	5.50
FEV_1 % predicted	235	57.0	20.5
RV/TLC%	221	50.9	11.4
Male:Female~	236	160:76	-
6MWD (m)	229	430	129
QMVC (kg)	233	31.8	11.8
AG mvpa* (mins)	227	7.7	16.6
AG mvpa ln (mins)	227	1.84	1.53
AG steps*	227	3715	3400
AG steps ln	227	8.17	0.72
AG VMU*	227	368000	248000
AG VMU ln	227	12.7	0.54
AG temperature^ (°C)	227	17.3	6.35
AG daily sunshine (hrs)	139	4.94	2.60
AG daily rainfall (hrs)	227	0.75	0.97
MM walktime (mins)*	229	55.8	41.3
MM walktime ln (mins)	229	3.94	0.68
MM intensity* (g)	229	0.18	0.04
MM intensity ln (g)	229	-1.72	0.34
MM steps*	229	4290	3410
MM steps ln	229	8.30	0.74
MM VMU*	229	267000	239000
MM VMU ln	229	12.4	0.70
MM temperature^ (°C)	229	17.3	6.07
MM daily sunshine (hrs)	139	4.80	2.660
MM daily rainfall (mm)	229	0.74	0.96
Daylength AG (hrs)	234	649	125
Daylength MM (hrs)	234	648	122
HAD A score	235	5.63	4.16
HAD D score	235	4.98	3.44
CAT score	226	14.4	8.12
CCQ score	230	1.78	1.06

Table 5.1. Baseline characteristics of all patients at Visit 1

BMI – body mass index; FEV1% – forced expiratory volume in 1 second percentage predicted; RV/TLC% - ratio of residual volume to total lung volume percentage predicted; 6MWD –six minute walk distance; QMVC – quadriceps maximal voluntary contraction; AG – Actigraph GT3X monitor; MM – Dynaport MiniMod monitor; mvpa – moderate to vigorous physical activity; VMU – vector magnitude units; ln – natural logarithm; °C – degrees centigrade; HAD A – Hospital Anxiety and Depression Scale – Anxiety score; HAD D – Hospital Anxiety and Depression Scale – Depression score; CAT – COPD Assessment Tool; CCQ – Clinical COPD

Questionnaire. * These variables were non normally distributed so values shown are median an interquartile range. ~Male:Female presented as frequency.

^On some days, patients had activity data available from only one of the two activity monitors (largely due to technical problems such as failed recording or incomplete days of monitoring). This is the reason that the mean temperature for the days AG data was collected was slightly different to that for the days MM data was collected, although there was no significant difference between the two measures of temperature. The same applies to rainfall, sunshine hours and day length.

Baseline characteristics that were different between centres as demonstrated by ANOVA (see **table 5.2**) are as follows:

Age, FEV_1% predicted, resting HR, six minute walk distance, QMVC, AG steps, AG VMU, temperature, hours of sunshine per day, daily rainfall, MM steps, MM walktime, MM intensity, MM VMU, Daylength, HAD score (A and D) and CCQ score.

For example, the patients in Athens had on average a lower FEV_1 than the other centres, with lower six minute walk distance. The patients in Leuven had higher baseline step counts and other PA measures with both activity monitors compared to other centres. Day length was significantly longer and sunshine hours greater in Athens compared to the other centres. Rainfall in Athens was much lower. The HAD and CCQ scores were significantly lower in Groningen (which sees a larger proportion of patients in primary care).

Variable	Athens		Edinburgh		Leuven		London		Groningen		ANOVA p value
	N	Mean (sd)	n	Mean (sd)	n	Mean (sd)	N	Mean (sd)	N	Mean (sd)	
Age yrs	49	66.1 (8.01)	45	71.7 (7.38)	54	66.3 (6.50)	49	68.6 (9.06)	39	64.0 (9.59)	**0.00** [a]
Male:Female~	49	38:11	45	28:17	54	42:12	49	28:21	39	24:17	0.075
BMI kg/m^2	49	27.0 (6.22)	45	28.8 (5.80)	54	26.6 (5.13)	49	26.3 (5.97)	39	26.6 (3.56)	0.18
FEV_1 %	49	46.9 (15.3)	44	61.6 (20.3)	54	61.9 (21.9)	49	53.6 (23.2)	39	62.3 (15.6)	**0.00** [a, b, c]
RV/TLC%	47	51.8 (12.8)	32	48.9 (9.30)	54	51.9 (13.0)	49	53.0 (9.81)	39	47.3 (10.3)	0.13
6MWD m	49	356 (99.1)	43	404 (125)	54	501 (136)	44	412 (128)	39	472 (91.7)	**0.00**[b, c]
QMVC kg	49	27.7 (8.20)	44	37.6 (12.7)	52	34.1 (10.0)	49	27.5 (10.4)	39	32.5 (14.8)	**0.00**[a,d,e]
AG steps*	48	3437 (3225)	44	2979 (2792)	50	4736 (1905)	47	3980 (3825)	38	3784 (3496)	**0.02**[f]
AG steps ln	48	8.09 (0.82)	44	7.93 (0.65)	50	8.37 (0.65)	47	8.15 (0.80)	38	8.32 (0.57)	**0.03** [f]
AG mvpa (mins)*	48	17.53 (20.2)	44	4.61 (8.82)	50	10.1 (17.1)	47	9.38 (27.3)	38	6.77 (8.93)	0.06
AG mvpa ln	48	1.90 (1.64)	44	1.27 (1.56)	50	2.26 (1.26)	47	1.83 (1.75)	38	1.89 (1.23)	**0.04**[&]
AG VMU*	48	307457 (210000)	44	297143 (164000)	49	443000 (246000)	47	372927 (301000)	38	408210 (235000)	**0.02**[f]
AG VMU ln	48	12.6 (0.57)	44	12.6 (0.43)	49	12.9 (0.57)	47	12.7 (0.62)	38	12.8 (0.41)	0.09
AG temp (°C)	48	23.6 (7.05)	44	14.5 (3.19)	50	17.1 (4.63)	47	19.0 (4.10)	38	10.5 (3.29)	**0.00**[a,b,c,g,h,l,j]
AG sunshine (hrs)	48	7.07 (2.57)	44	3.22 (1.31)	n/a		47	4.36 (1.98)	n/a		**0.00**[a,d,g]
AG rainfall cm	48	0.32 (0.89)	44	1.19 (1.00)	50	0.97 (10.8)	47	0.76 (0.90)	38	0.47 (0.62)	**0.00**[a,h]
MM steps*	49	4045 (3452)	41	3463 (2651)	54	5476 (3870)	48	3732 (4301)	37	4895 (3605)	**0.00**[b,f]
MM steps ln	49	8.16 (0.83)	41	8.06 (0.63)	54	8.60 (0.56)	48	8.15 (0.92)	37	8.47 (0.49)	**0.00** [b,f]
MM walktime*	49	53.7 (42.0)	41	42.9 (27.7)	54	71.8 (40.4)	48	48.0 (47.7)	37	59.6 (37.9)	**0.00**[a,f,k]
MM walktime ln	49	3.82 (0.77)	41	3.73 (0.55)	54	4.23 (0.51)	48	3.79 (0.84)	37	4.11 (0.46)	**0.00** [a,f,k]
MMintensity (g)*	49	0.17 (0.04)	41	0.17 (0.02)	54	0.19 (0.03)	48	0.18 (0.05)	37	0.19 (0.04)	**0.02**[&]
MM intensity (g) ln	49	-1.50 (0.15)	41	-1.76 (0.14)	54	-1.70 (0.15)	48	-1.76 (0.70)	37	-1.66 (0.13)	0.63
MM VMU*	49	223569 (251000)	41	209730 (137000)	54	353717 (258000)	48	295948 (240000)	37	360802 (193000)	**0.02**[h]
MM VMU ln	49	12.3 (0.73)	41	12.2 (0.57)	54	12.7 (0.64)	48	12.4 (0.86)	37	12.7 (0.51)	**0.00** [h]
Daylength (mins)	49	978 (71.1)	44	599 (98.7)	54	682 (167)	48	698 (129)	39	563 (49.1)	**0.00**[a,c,f,k,l,j]
HAD A[$]	49	5.98 (4.25)	45	6.71 (4.01)	53	5.08 (4.00)	49	6.47 (4.72)	39	3.67 (2.88)	**0.00j**
HAD D[$]	49	5.35 (3.56)	45	5.11 (3.14)	53	5.53 (3.41)	49	5.25 (3.81)	39	3.28 (2.80)	**0.02**[c,l]
CAT[$]	49	14.5 (7.46)	44	15.9 (7.77)	54	14.1 (8.39)	45	15.2 (9.21)	34	11.8 (7.29)	0.25
CCQ[$]	49	1.87 (0.99)	45	1.96 (1.03)	54	1.59 (0.99)	46	2.00 (1.26)	36	1.43 (0.89)	**0.05**[&]

Table 5.2. Baseline characteristics by centre & ANOVA

BMI – body mass index; FEV1% – forced expiratory volume in 1 second percentage predicted; RV/TLC% - ratio of residual volume to total lung volume percentage predicted; 6MWD –six minute walk distance; QMVC – quadriceps maximal voluntary contraction; AG – Actigraph GT3X monitor; MM – Dynaport MiniMod monitor; mvpa – moderate to vigorous physical activity; VMU – vector magnitude units; ln – natural logarithm; °C – degrees centigrade; HAD A – Hospital Anxiety and Depression Scale – Anxiety score; HAD D – Hospital Anxiety and Depression Scale – Depression score; CAT – COPD Assessment Tool; CCQ – Clinical COPD Questionnaire. . * These variables were non-normally distributed so values shown are median and interquartile range. ~Male:Female represented as frequencies with result of Chi squared test presented.

Post-hoc analysis differences: a=Athens & Edinburgh; b=Athens & Leuven; c=Athens & Groningen; d=Edinburgh & London; e=Leuven & London; f=Edinburgh & Leuven; g=Athens & London, h= Edinburgh & Groningen; i=Leuven & Groningen; j=London & Groningen; k= Leuven & London; &=non-significant on post-hoc analysis

[$]Although these data are presented, there were several missing values so they were not used in the further analysis

1. Assessment of changes in physical activity levels with time

Repeated ANOVA analysis showed that physical activity declined with time. For all the measures of physical activity, pairwise comparison indicated that physical activity change with time was similar across centres ($p<0.05$), although there were differences between the patients in each centre at baseline (**Table 5.3**).

Variable	Baseline	6 months	12 months	ANOVA p value
FEV_1%	56.7 (1.69)	56.7 (1.75)	57.6 (1.76)	0.19
6MWD (m)	440(10.7)	437(10.4)	441 (10.7)	0.57
QMVC (kg)	32.9 (0.92)	31.9 (0.84)	32.3 (0.88)	, 0.11
RV/TLC%	50.2 (0.95)	56.7 (1.65)	57.5 (1.74)	<0.05
AG steps	4770 (2930)	4120 (2480)	4010 (2480)	<0.05
AG steps ln	8.27 (0.06)	8.13 (0.06)	8.10 (0.06)	<0.05
AG mvpa	18.5 (28.6)	16.3 (36.8)	12.0 (17.0)	0.08*
AG mvpa ln	2.07 (0.13)	1.83 (0.13)	1.67 (0.12)	<0.05
AG VMU	405000 (181000)	356000 (163000)	348000 (167000)	<0.05
AG VMU ln	12.7 (0.04)	12.6 (0.04)	5.49 (0.02)	<0.05
MM steps	5560 (3260)	5040 (3140)	5170 (3160)	<0.05
MM steps ln	8.41 (0.06)	8.29 (0.07)	8.33 (0.06)	<0.05
MM walktime (mins)	68.6 (36.2)	62.4 (34.8)	64.2 (35.8)	<0.05
MM walktime ln (mins)	3.94 (0.04)	3.89 (0.06)	3.95 (0.05)	<0.05
MM intensity (g)	0.19 (0.02)	0.18 (0.03)	0.18 (0.03)	0.05
MM intensity ln (g)	-1.68 (0.01)	-1.71 (0.01)	-1.71 (0.01)	<0.05
MM VMU	349000 (220000)	313000 (199000)	309000 (199000)	<0.05
MM VMU ln	12.6 (0.06)	12.4 (0.06)	12.4 (0.06)	<0.05

Table 5.3. Results of repeated measures ANOVA. FEV_1% – forced expiratory volume in 1 second percentage predicted; RV/TLC% - ratio of residual volume to total lung volume percentage predicted; 6MWD –six minute walk distance; QMVC – quadriceps maximal voluntary contraction; AG – Actigraph GT3X monitor; MM – Dynaport MiniMod monitor; mvpa – moderate to vigorous physical activity; VMU – vector magnitude units; ln – natural logarithm; °C – degrees centigrade; HAD A – Hospital Anxiety and Depression Scale – Anxiety score; HAD D – Hospital Anxiety and Depression Scale – Depression score; CAT – COPD Assessment Tool; CCQ – Clinical COPD Questionnaire. *Although p 0.08, significant difference between baseline and 12 months (p=0.03)

2. Assessment of the effect of climate condition on physical activity changes over three time points (baseline, 6 months, 12 months)

For each activity monitor, the following variables were tested in the mixed model method:

Actigraph: Centre, age, BMI, FEV_1%, RV/TLC%, QMVC, daylength, temperature, daylength x temperature (daylength-temperature interaction)

Minimod: Centre, age, BMI, FEV_1%, RV/TLC%, QMVC, temperature

The mixed model results tables show F and p values and upper and lower 95% confidence levels for each activity monitor output. Each activity monitor variable was tested in this analysis. 95% confidence intervals are not shown for centre number as this was non-significant (and on subsequent pairwise analysis, confidence intervals were calculated for each centre).

Variable	**F**	**P value**	**95% confidence interval**
Intercept	40.5	0.00	3.13 – 6.23
QMVC (kg)	14.5	0.00	0.01 – 0.04
FEV1%	39.9	0.00	0.02 – 0.03
BMI (kg/m2)	10.9	0.00	-0.08 - -0.02
Age (years)	36.8	0.00	-0.08 - -0.04
Temperature (°C)	0.90	0.35	-0.02 – 0.008
Centre no	5.02	0.01	na^

Table 5.4 AG mvpa ln

(^Although initially significant, this effect does not persist on pairwise comparison).

Variable	F	P value	95% confidence intervals
Intercept	1407	0.00	12.6 – 14.0
QMVC (kg)	6.77	0.01	0.001- 0.010
FEV_1%	54.1	0.00	0.007 – 0.012
BMI (kg/m^2)	13.9	0.00	-0.030 - -0.009
Age (years)	31.5	0.00	-0.026 - -0.001
Day length (mins)	5.44	0.02	0.0010 – 0.0011
Temperature (°C)	9.04	0.00	0.0146 – 0.070
RV/TLC%	1.27	0.28	-0.003 – 0.0009
Temperature x Day length	6.44	0.00	-8.23 - -1.04
Centre no	0.33	0.86	na

Table 5.5 AG VMU ln

Variable	F	P value	95% confidence interval
Intercept	1388	0.00	2.05-2.28
QMVC (kg)	14.7	0.00	0.0007 – 0.002
FEV_1%	52.1	0.00	0.001 - 0.002
BMI (kg/m^2)	4.92	0.03	-0.004 - -0.0002
Age (years)	29.2	0.00	-0.004 - -0.002
Day length	3.67	0.06	-2.10 – 0.0002
Temperature (°C)	6.12	0.01	0.001 – 0.010
Temperature x Day length	4.12	0.04	-1.12 - -1.17
Centre no	0.70	0.59	na
RV/TLC%	1.07	0.30	-0.0005 – 0.0002

Table 5.6 AG steps ln

Variable	F	P value	95% confidence interval
Intercept	121.1	0.00	3.67 – 5.20
Age (years)	8.70	0.00	-0.02 - -0.005
BMI (kg/m2)	7.48	0.01	-0.03 - -0.005
FEV1%	34.9	0.00	0.007 – 0.013
RV/TLC%	0.312	0.58	-0.003 – 0.016
Temperature (°C)	13.3	0.00	0.005 – 0.016
QMVC (kg)	13.7	0.00	0.005 – 0.015
Centre no	1.64	0.16	na

Table 5.7 MMwalktime ln

Variable	F	P value	95% confidence interval
Intercept	116.3	0.00	-1.81 - -1.25
Age (years)	10.0	0.00	-0.009 - -0.002
BMI (kg/m2)	4.58	0.03	-0.01 - -0.0004
FEV1%	19.4	0.00	0.002 – 0.
Temperature (°C)	4.62	0.03	0.0003 – 0.007
QMVC (kg)	7.79	0.01	0.001 – 0.006
Centre no	0.21	0.93	na

Table 5.8 MMintensity ln

Variable	F	P value	95% confidence interval
Intercept	414.9	0.00	8.01 – 9.98
Age (years)	9.80	0.00	-0.026 – -0.006
BMI (kg/m2)	5.87	0.00	-0.03 – -0.004
FEV1%	38.4	0.00	0.008 – 0.015
Temperature (°C)	11.5	0.00	0.004 – 0.016
QMVC (kg)	11.1	0.00	0.004 – 0.016
Centre no	1.20	0.31	na
RV/TLC%	0.39	0,53	-0.003 – 0.002

Table 5.9 MMsteps ln

Variable	F	P value	95% confidence interval
Intercept	1291	0.00	13.0 – 14.5
Age (years)	26.9	0.00	-0.032 - -0.014
BMI (kg/m2)	13.3	0.00	-0.039 - -0.011
FEV1%	52.8	0.00	0.009 – 0.016
Temperature (°C)	4.81	0.03	0.0007 – 0.012
QMVC (kg)	11.3	0.00	0.004 – 0.014
Centre no	0.21	0.94	na
RV/TLC%	3.26	0.07	-0.004 – 0.0002

Table 5.10 MM VMU ln

In summary, for both activity monitors, RV/TLC% and centre were never significant predictors of physical activity measures. For Actigraph measures, age, BMI, FEV_1%, temperature, day length and the interaction between temperature and daylength did have a significant effect.

For MiniMod measures, age, BMI, FEV_1%, temperature, day length and the interaction between temperature and daylength did have a significant effect.

3. Dropouts

Across all centres, dropouts were a problem (see **table 5.11**) ; 236 patients were initially recruited, but only 157 patients had data for at least one activity monitor for all visits, representing a 33% dropout rate over 1 year across the whole studies.

Overall, the subjects who dropped out of the study at some point throughout the 12 month follow up period had lower baseline physical activity levels as measured by either activity monitor. They also had a lower baseline six minute walk distance (mean difference 60m lower) and lower quadriceps strength. In addition, CCQ scores were also lower in the dropout group, suggesting lower quality of life, although CAT scores were not statistically significantly different at baseline. However, there was no difference in exacerbation frequency between the groups (Chi squared = 0.187, p=0.67) and the groups were well matched for age, BMI and FEV_1. Weather conditions at baseline were also similar, although temperature was statistically significantly different between the two groups, with the mean difference approximately 2 degrees.

Variable	Dropout	Non dropout	Difference	T test p value
Age (years)	67.8 (9.42)	67.2 (7.89)	0.63	0.626
BMI (kg/m2)	27.7 (6.52)	26.7 (4.90)	1.04	0.172
FEV_1%	55.7 (14.4)	57.7 (22.0)	2.04	0.475
RV/TLC%	52.4 (10.4)	50.2 (11.9)	2.17	0.193
6MWD (m)	389 (130)	449 (124)	60.0	**0.001**
QMVC (kg)	28.5 (12.2)	33.3 (11.3)	4.85	**0.003**
AG mvpa ln	1.42 (1.61)	2.05 (1.45)	0.63	**0.00**
AG steps ln	7.97 (0.78)	8.27 (0.67)	0.30	**0.00**
AG VMU ln	12.6 (0.58)	12.8 (0.51)	0.02	0.06
AG temp (°C)	16.0 (6.09)	17.9 (6.41)	1.85	**0.040**
AG sunshine (hrs)	4.60 (2.27)	5.11 (2.75)	0.51	0.277
AG rainfall (mm)	0.81 (0.96)	0.72 (0.97)	0.09	0.523
MM walktime ln (mins)	3.73 (0.79)	4.05 (0.59)	0.32	**0.00**
MM intensity ln	-1.79 (0.55)	-1.69 (0.15)	0.1	**0.03**
MM steps ln	8.07 (0.85)	8.41 (0.65)	0.34	**0.00**
MM VMU ln	12.3 (0.81)	12.5 (0.63)	0.02	**0.00**
MM temp(°C)	15.9 (5.86)	17.9 (6.10)	2.04	**0.016**
MM sunshine (hrs)	4.35 (2.24)	5.09 (2.71)	0.74	0.108
MM rainfall (mm)	0.80 (0.98)	0.70 (0.94)	0.10	0.457
Daylength (mins)	636 (113)	656 (130)	19.9	0.253
HAD A	6.28 (4.58)	5.31 (3.91)	0.971	0.091
HAD D	5.34 (3.58)	4.80 (3.37)	0.547	0.251
CAT	15.7 (8.03)	13.8 (8.12)	1.90	0.100
CCQ	2.00 (1.12)	1.67 (1.01)	0.318	**0.032**

Table 5.11: Baseline characteristics in dropout subjects vs non-dropout subjects.

FEV1% – forced expiratory volume in 1 second percentage predicted; RV/TLC% - ratio of residual volume to total lung volume percentage predicted; 6MWD –six minute walk distance; QMVC – quadriceps maximal voluntary contraction; AG – Actigraph GT3X monitor; MM – Dynaport MiniMod monitor; mvpa – moderate to vigorous physical activity; VMU – vector magnitude units; ln – natural logarithm; °C – degrees centigrade; HAD A – Hospital Anxiety and Depression Scale – Anxiety score; HAD D – Hospital Anxiety and Depression Scale – Depression score; CAT – COPD Assessment Tool; CCQ – Clinical COPD Questionnaire.

5.5 Discussion

The effect of time and seasonal factors, namely temperature, rainfall, sunshine and day length, on physical activity in COPD as measured by two validated, commercially available physical activity monitors, at baseline, 6 and 12 months, was investigated. There was a significant effect of time with a decline in all measures of PA over 12 months, as well as climate in the form of temperature. This study has many strengths: it involved a large cohort of patients across a range of disease severities and they were followed up over three time points during the year. In addition, this was a multicentre study covering different geographical areas, enabling investigation of the effect of different climates on physical activity in COPD.

5.5.1 Significance of findings

Decline in physical activity over time

There was a significant effect of time with a decline in all measures of physical activity over 12 months. This applied to all centres, despite the patients having significant differences in baseline characteristics, including FEV_1, six minute walk distance and baseline physical activity.

This is a significant finding, given the importance of physical activity as the strongest predictor of mortality in COPD [115] . Moreover, the finding that there was no effect of centre on this decline with time is a valuable one as it has positive implications for future multicentre studies in COPD patients, using physical activity as an outcome measure.

In this study 6MWD and FEV_1 did not decline significantly with time, albeit over a follow up period of 1 year. Although Waschki et al did find a decline in FEV_1 and 6MWD as well as physical activity, during a more long term follow up (over 3 years) and that this decline in physical activity was significantly associated with decline in FEV_1 over time, they did not find this in those subjects who had a sustained low physical activity level. They also did not find an association of decline in physical activity with 6MWD decline [312]. These findings support our conclusions that measures of physical activity in COPD are potentially much more sensitive measures of disease progression than FEV_1 and exercise capacity, commonly used outcome measures.[315]; as our follow up period was only a year, it may not have been long enough to see significant changes in FEV_1 and 6MWD. Physical activity therefore should be considered as a primary outcome measure in intervention studies as well as longitudinal prospective studies in COPD.

Effect of climate on physical activity

A significant effect of climate on physical activity, in the form of temperature was also found, with lower levels associated with cooler temperatures. This change was independent of centre; it was not the fact that the patients were recruited at different locations that explained the variation in activity levels, but the change in environmental temperature itself.

A persistent effect of temperature was seen for almost all measures of physical activity. However, other seasonal factors were less significant. Rainfall, where available, was not a significant determinant of physical activity for any measures. Unfortunately, the analysis of climate was limited by availability of data. For example, the number of hours of sunshine per day was not available for all centres, and other factors such as humidity or pollution levels were not available. The effect of the interaction between temperature and day length as a separate variable was tested and found to be significant for AG VMU ln, and approached significance for AG steps ln only (and not for any MM measures), but it seems that most of this effect is accounted for by temperature. One would expect temperature to be higher in the summer than the winter, so a seasonal effect can be inferred from this finding, which seems to be over and above the decline seen in physical activity over time, although we did not specifically test for this. This has implications in choosing when to conduct studies, particularly multi centre studies in different countries and temperature is one of the factors that would need to be controlled for. A practical solution would be to do all measures in the same season to try and match environmental temperature as best as possible, for baseline and follow up; or to at least to correct for this effect during any data analysis or to randomise as patients are recruited so that the effect of climate is negated.

Another interesting observation was that temperature was 2 degrees lower in the patients that dropped out of the study. Step count was approximately 1000 steps per day lower in these subjects compared to the non-dropouts. It is only possible to speculate as to the reason for this; lower environmental temperatures could be driving the lower physical activity levels and cause more drop outs due to increased frequency or severity of exacerbations, although we did not find a difference in exacerbation frequency between dropouts compared to non-dropouts.
There are few published studies looking at the effect of climate on physical activity in COPD, and as already alluded to, they are not without their limitations. Moy et al's cohort was small and made up mostly of male patients; there were no data regarding climatic conditions such as temperature or sunshine to define the seasons [310]. The recent study by Alahmari et al in 73 COPD patients measured physical activity daily for 12 months using pedometers, as well as daily weather data (temperature, rainfall, sunshine) and data for atmospheric PM10 and ozone [314]. They found step count to be lower on weekends and on colder and overcast days. There was also an impact on step count of environmental PM10 and ozone levels with higher levels of each correlating with decreased activity levels. However, a closer look at the data reveals quite large standard deviations of, for

example, the daily average step count and the step count increase that each degree in temperature rise produced. The physical activity data were linearly distributed in this study of only 73 patients, whereas in our multicentre study we had to log-transform much of the data in order to model it accurately. This could be explained by the multicentre nature of the study producing a wide spread of the data, or the fact that physical activity and other variables were only sampled at 6 month intervals, and not daily. However, the wide range of physical activity that is seen COPD patients needs to be considered carefully during data analysis in order to produce accurate results and draw valid conclusions.

In the wider context, lower environmental temperature and the association with lower physical activity levels, increased exacerbation rates and lung function decline in COPD could be driving mortality in COPD, but causality needs to be established. It is already well established that early pulmonary rehabilitation following exacerbation reduces the risk of re-exacerbation [316]. If physical activity levels during winter were increased through therapeutic interventions, would this act as a preventative measure to reduce exacerbation rates, lung function decline and therefore mortality?

5.5.2 Limitations

There were some limitations to this study. The primary objective was to perform the item reduction task for the PRO tool and so it was powered to this endpoint and not to detect the physical activity changes over time. However, decline of physical activity was significant, so it is improbable that a larger sample size would have altered the conclusions of the study.

The staggered start times of the patients proved problematic when analysing the data fro climate and seasonal differences. Ideally all patients should have been enrolled into the study within the summer in a short period to minimize the differences in climate; they would then have been followed up in winter at the first follow up visit at 6 months. However, in reality, patients were slowly recruited into the study with some entering during summer, and others in autumn with a handful in winter. Those who were enrolled in autumn were followed up at 6 months in spring, at which time there was not a great difference in temperature compared to the time of enrollment. Daylength was used as a surrogate for season, but again is only relevant when comparing winter and summer (as, again, daylength in autumn and spring is similar), and that too only in northern European countries (daylength did not vary as much in Athens as, for example, in Edinburgh). It could be possible to group patients according to the season in which they were recruited, but this would have to be done arbitrarily, as there is a gradual transition from one season to the next. It would also mean that patients recruited in autumn may end up being excluded from the analysis, which could skew results. Therefore, rather

than being able to look for a seasonal effect, the main variable of temperature had to be used, as this was deemed a more objective and robust variable.

Weather data was collected retrospectively, and although these were official data from the Met Office, and this technique has been previously used [314, 317], it would have been more accurate to keep real time records of weather conditions at the time of the study.

Dropouts were a problem as 33% of the initial patient population dropped out. The recent study by Waschki et al had a dropout rate of around 20% (single centre), which is lower than the present study, but still represents a significant number. In both studies, patients who dropped out had significantly lower physical activity levels at baseline. This seems to be a particular feature of COPD patients and mirrors the finding in pulmonary rehabilitation that those patients who do not complete have more to gain; those who drop out are more breathless, have poorer health related quality of life , lower FEV_1, weaker quadriceps strength and higher anxiety and depression scores [20, 318]. In this study, patients who dropped out had lower quadriceps strength, six minute walk distance and CCQ score, as well as physical activity levels, but not increased exacerbation rates. However, with respect pulmonary rehabilitation, other socioeconomic factors such as access to transport,, living alone and smoking status [319]. We did not necessarily allow for these factors in this study, but is something that could be targeted to reduce the dropout rate in future studies. As a whole, dropout rate represents an important factor that clearly needs to be accounted for in any future studies investigating physical activity in this population. This also needs to be accounted for in future studies in both patient selection and sample size calculations.

5.6 Conclusion

We have demonstrated a decline in physical activity in COPD over 1 year follow up, in the absence of significant decline in FEV_1 or 6MWD, commonly used outcome measures in this population group. We have also shown an effect of climate, namely that of temperature, with cooler temperatures associated with lower physical activity levels, independent of geographical location.

These findings have important implications regarding future research in this field, particularly regarding trial design. As already alluded to, as temperature has been found to have a significant effect on physical activify levels, this variable has to be controlled for when recruiting patients into studies where physical activity is to be used as an outcome measure, Either patients should be recruited during similar climatic conditions, or sample size calculations have to allow for the effect of temperature. When conducting follow up, an attempt should be made to control for climatic conditions such as temperature, such as following up patients in the same season, or adjusting for the effect of

temperature in subsequent statistical analysis. Effects of interventions must be ‘real effects’, not just the result of following patients up in better weather.

Reassuringly, we did not find an effect of centre on physical activity, and this bodes well for future European multicentre studies using physical activity as an outcome measure. Further research into how physical activity varies in COPD, as well as in other chronic diseases, in other parts of the world with very different climatic conditions (e.g. countries around the equator) is needed to provide a more comprehensive understanding of this area, in order to effectively design trials and develop new interventions for COPD.

These findings also have significant clinical relevance. It is already known that physical activity is the strongest predictor of mortality, and seems to decline earlier than other clinically important measures such as exercise capacity or lung function. If physical inactivity could be tackled earlier with intervention, then there could be real promise in attenuating decline in these patients. This could represent a new emphasis in therapy, over and above existing pulmonary rehabilitation programmes and could be tested in further randomised controlled studies. Our dropout rates and lower levels of physical activity in those who do drop out parallels the limitations of pulmonary rehabilitation, in that it is those who do not complete who are those who have most to gain. More innovative ways of reaching this target population need to be devised in order to make a real impact on this as yet incurable disease.

6 Changes in early exercise in patients with COPD and their association with daily physical activity

6.1 Introduction

As discussed in previous chapters, exertional dyspnoea is the predominant limiting symptom in COPD patients, with respect to physical activity, be it exercise or activities of daily living. A number of factors are responsible for early termination of physical activity due to dyspnoea, but the key phenomenon is widely agreed to be dynamic hyperinflation. In fact, Garcia-Rio *et al* found in 110 patients with moderate to severe COPD that daily physical activity as measured with a triaxial accelerometer (RT3) was mainly related to the presence of dynamic hyperinflation on CPET, (as well as 6MWD), with lower vector magnitude units recorded in those who did develop dynamic hyperinflation ($p<0.001$) [320]. This relationship was independent of disease severity as classified by FEV_1.

It may be reasonably postulated that in COPD, as in many biological systems, physiological phenomena are responsible for behavioural adaptation to potentially unpleasant stimuli [321] i.e. dyspnoea. It could be argued that in COPD, dynamic hyperinflation is a consequence of a maladaptive breathing response to increased load on the respiratory system during exercise. Compared to healthy controls, patients with COPD have been observed to have a faster, more superficial ventilatory response to exercise, i.e. a more rapid and shallow pattern of breathing, which contributes to the development of dynamic hyperinflation [322, 323]. It has also been observed that hypercapnic patients exhibit a more rapid and shallow breathing pattern than eucapnic patients [324]. In addition, there is some evidence to suggest that those COPD patients displaying this pattern of breathing are more likely to fail a trial of weaning from mechanical ventilation [325].

The usual response to breathing in healthy adults is dependent on the type of exercise and intensity. The response to exercise at a constant work load consists of 3 phases: an immediate abrupt increase in minute ventilation (VE i.e. the product of tidal volume and respiratory rate) within seconds of the onset of exercise, which is neurally mediated; a slower exponential rate of increase in VE; and a steady state (usually at around 4 minutes) where tidal volume and respiratory rate remain constant and VE is related to CO_2 production linearly. As exercise becomes heavier, respiratory rate increases. At peak exercise, tidal volume is 50 to 60% of vital capacity [326] [327].

Several studies have analysed the pattern of breathing in response to exercise in COPD. Casaburi *et al* studied 25 COPD patients in a pulmonary rehabilitation setting over 15 years ago [328]. The subjects went through an 8 week training programme consisting of 45 minute periods of cycling 3

times per week at 80% of peak work rate with CPETs before and after the training period. After training, there was a significant increase in the patients' tidal volume, VT (11%) with a reduction in respiratory rate, RR (15%) and a reduction in the ratio of dead space to tidal volume (V_D/V_T), i.e. more efficient breathing and an attenuation of the 'rapid shallow' pattern of breathing.

Gorini et al investigated the relationship between $PaCO_2$, breathing pattern and inspiratory muscle strength in COPD during normal breathing at rest [324]. Pleural pressure was measured using the oesophageal balloon technique[11]. They found an inverse relationship between inspiratory time and pleural pressure swing, i.e. the shorter the inspiratory time, the greater the pressure required for breathing relative to inspiratory muscle strength. They also found a significant association between dyspnoea score, reduced inspiratory time and increased pleural pressure swing. Hypercapnic patients were more likely to have a reduced tidal volume and increased respiratory rate than eucapnic patients. It could be that by reducing tidal volume, this allows patients to reduce the pressure changes required during breathing relative to inspiratory muscle strength, thereby reducing breathlessness and avoiding inspiratory muscle fatigue. The cost of this is hypercapnia due to reduced alveolar ventilation. However, Polkey et al showed that diaphragm fatigue is very difficult to elicit in COPD [329].

The results of Marin *et al*'s study suggest that abnormal resting pulmonary mechanics are responsible for the abnormal breathing pattern adopted during exercise [330]. They studied resting lung mechanics in 29 GOLD II to IV COPD patients using the oesophageal balloon technique to measure resting pleural pressure. Transpulmonary pressure was estimated as the difference between oesophageal and mouth pressure when flow was zero. All patients went on to have a symptom limited incremental CPET. At rest and at each workload, the VT/VC ratio and VT/VC over VE were calculated and formulated into a single exponential equation as described by Jones *et al* [331]:

VT = VC (1-e-kVE)

They found that patients who had the highest k values had worse lung function (r=0.55 for FEV_1% predicted), generated higher VT/VC ratios and had abnormal resting pulmonary mechanics with higher resting transpulmonary resistance.

Neural mechanisms may also be important. Loveridge et al measured normal rest breathing in COPD patients and age matched controls using a dual band respiratory inductance plethysmograph [332]. They found there was less variability in breathing in patients with COPD compared to the controls, in terms of Ti, T_I/T_{TOT} and ventilation, despite similar mean tidal volumes in both groups, and suggest that changes in the neural control of breathing due to the disease state are responsible. This

[11] This technique uses two catheters connected to pressure transducers. One is passed through the nose and placed in the oesophagus - position is indicated by negative sniff pressure on the pressure trace – and represents intrathoracic presure. The other is passed further down to the stomach and represents abdominal pressure. A difference between the two measures represents transdiaphragmatic pressure. Other measures such as compliance can also be made.

assertion is supported by the results of their subsequent study in patients ranging from moderate to severe, and with respiratory failure [333]. Despite the severe and respiratory failure groups' reduced tidal volumes and faster respiratory rates, there was no significant difference in the variability of breathing. This suggests that changes in the control of breathing are independent of disease severity and mechanical abnormalities.

The findings of Wilkens *et al* also warrant discussion [322]. They studied the lung compartment volumes of three groups of lung transplant candidate patients; COPD (n=21), pulmonary fibrosis (PF; n=9) and cystic fibrosis (CF; n=9), as well as 10 healthy controls and 16 transplanted patients, using opto-electronic plethysmography (OEP) at both rest and exercise. At rest, the PF and CF patients had higher respiratory rates than the COPD patients (who had a mean FEV_1 of 20.8% predicted) and healthy controls (35 and 24 breaths/minute compared to 16 and 14 breaths/minute respectively). The COPD patients had proportionally longer expiratory times (T_E) than the other groups, resulting in a lower duty cycle. They found that at maximal exercise, the patients with PF and CF developed a rapid shallow breathing pattern, with much shorter inspiratory (T_I) and expiratory times. However, the COPD patients actually had longer T_I and T_E than even the controls, with much longer T_E as well as increases in EELV (and therefore dynamic hyperinflation) compared to the other subjects. The changes in the disease groups were not seen in the transplant group who behaved similarly to the controls, suggesting that the lungs themselves are responsible for the exercise response, rather than systemic disease factors.

Nonetheless, rapid shallow breathing is less energy efficient in COPD (see **Figure 6.1**); due to loss of elastic recoil and airway obstruction, a slow deep pattern of breathing is optimal, taking advantage of low pressures needed to overcome the elastic recoil, while minimising the pressures required to produce airflow. This would result in less dyspnoea and better exercise tolerance. It may be that this is a dysfunctional pattern of breathing and it could be associated with reduced daily physical activity; individuals adapt their behaviour byavoiding physical exertion because of the unpleasant sensation of dyspnoea, resulting in reduced daily physical activity. It may also be much easier to detect this breathing pattern compared to dynamic hyperinflation, simply by measuring respiratory rate in clinical settings: dynamic hyperinflation measures must at least be done in laboratory conditions with either ventilatory flow meters and inspiratory capacity manoeuvres or with the use of optoelectroplethysmography. Both methods can be challenging to patients, so a simple method would be advantageous for both patient and clinician in terms of better understanding disease severity and limitations in daily life.

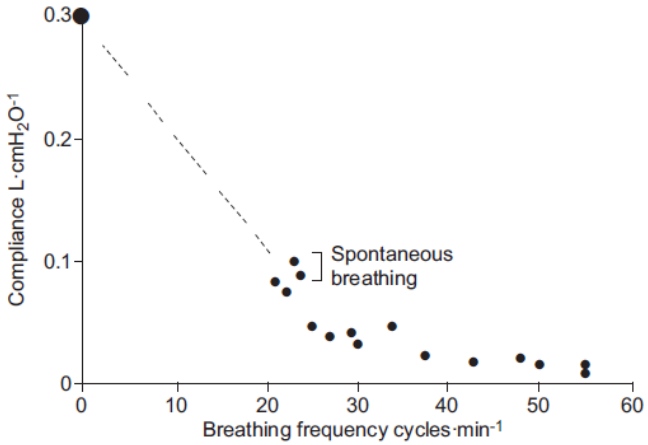


Figure 6.1. Lung compliance as a function of respiratory rate in an emphysema patient [334]

Thus in the present study, we hypothesised that patients who disproportionately increased their respiratory rate compared to tidal volume (i.e. who had a rapid shallow breathing pattern) would have lower daily physical activity levels. We also hypothesised that the correlation between rapid shallow breathing and daily physical activity would be stronger than that of peak performance (VO_{2max}) with daily physical activity.

Patients' responses to cardiopulmonary exercise testing were analysed. A subset of these patients' responses to walking during a six minute walk test was also analysed. Daily physical activity data in the form of step count collected from a triaxial accelerometer was used.

It was further hypothesised that there would be a stronger correlation between the breathing response during the early part of the six minute walk tests and daily physical activity levels than that during the cardiopulmonary exercise tests, as this measure of exercise capacity has been shown to correlate better with measures of physical activity than CPET VO_{2max} and is therefore more representative of what patients actually do.

6.2 Methods

6.2.1 Cardiopulmonary exercise testing

25 patients with COPD (GOLD I to IV) who were recruited at the Royal Brompton Hospital as part of the PROactive Work Package 4 Item Reduction study were studied. Their baseline characteristics are shown in **Table 6.1**. All patients underwent cardiopulmonary exercise testing on a stationary bike using a 10W incremental protocol preceded by a 2 minute rest period and a further minute of

unloaded pedalling. Patients were attached to expired gas analysers via a mouthpiece and wore a nose clip. They were instructed to pedal at 60 revolutions per minute until exhaustion or until they reached 85% of their maximum predicted heart rate.

Variable	Mean (sd)
N	25
Male: Female	14:11
Age (years)	69.3 (8.6)
FEV1%	60.1 (20.4)
QMVC (kg)	30.1 (11.0)
RV/TLV%	51.3 (7.2)
6MWD (m)	467 (102)
Mean daily step count	4396 (2730)
Peak VO2 (ml/min/kg)	15.2 (3.5)

Table 6.1. Patient characteristics – cardiopulmonary exercise testing

6.2.2 Six minute walk tests

A subset of the above patients (n=8) who had also participated in the laboratory validation study of Work Package 2 (described earlier in Chapter 3) were studied [335]. As part of the laboratory study protocol, they undertook a schedule of activities including two six minute walk tests at slow and fast pace whilst wearing a portable metabolic kit. Both tests were preceded by at least 2 minutes of rest with the patient sitting quietly prior to starting the walk. During the 'slow walk' the patients were instructed to go at comfortable pace, around 50% of their maximum walking pace. During the 'fast' walk, they were instructed to go as fast as was comfortably possible in order to cover the greatest distance during the six minutes. The same physical activity data was used as in the first analysis.

Variable	Mean (sd)
N	8
Male:Female	6:2
Age (years)	70.9 (9.9)
FEV_1 %predicted	48.8 (24.0)
TLco %predicted	45.9 (20.3)
RV/TLC ratio %	56.5 (11.8)
6MWD (m)	422 (124)
Peak VO_2 (ml/min/kg)	15.0 (3.5)
Mean daily steps	3161 (1541)

Table 6.2. Patient characteristics – six minute walk distance

6.2.3 Physical activity monitoring

Physical activity monitoring was carried out using the Actigraph, a triaxial accelerometer, which the patients were instructed to wear for 2 weeks during all waking hours (apart from bathing or swimming) at the right hip, in accordance with the manufacturer's guidelines. This was validated for use in COPD in the earlier chapters [303, 335]

Other baseline tests were carried out as previously described in the Methods chapter.

6.3 Data analysis

6.3.1 Exercise data

The CPET breath by breath raw data was analysed for all patients, focusing specifically at the initiation of exercise, which was defined as being at the onset of loaded pedalling (at 10W). For each parameter, a rolling 8 breath average was calculated. The changes in tidal volume and respiratory rate during the first minute of loaded pedalling were analysed in the following way:

Firstly, the area under the curve (AUC) for tidal volume (VT) and respiratory rate (RR) were calculated. VT and RR were expressed as a percentage of change from baseline. Baseline was calculated from an average of the tidal volume or respiratory rate during the 2 minute rest period of the CPET before the start of unloaded pedalling respectively. The ratio of change in AUC VT over change in AUC RR was calculated for each patient. The relationship between these values and physical activity levels were expressed using linear regression.

Secondly, the rate of change of VT, as a proportion of VC, with VE was calculated using the exponential relationship described by Jones et al [331]:

$$VT = VC\ (1-e^{-kVE})$$

So $$k = -\ [\ \ln\ (1-VT/VC)\ ]\ /VE$$

The relationship of these k values with physical activity was also expressed using linear regression.

6.3.2 Six minute walks

For each walk (slow and fast), the first minute of metabolic data was analysed using a similar method to above, i.e. the area under the curve for both VT and RR was calculated for the first minute of the walk. Baseline for each parameter was calculated from the period of rest earlier in the laboratory protocol. A ratio for AUC VT/AUC RR was calculated. A k value was also calculated for this minute for each walk as described above. Each value was related to average daily step count using linear regression.

6.3.3 Physical activity data

Physical activity data recorded with the Actigraph was available for at least 7 days for all patients. Incomplete days, where less than 10 hours of data were recorded, were excluded. Mean steps per day was calculated using all the complete days of activity data for each patient.

6.4 Results

6.4.1 Cardiopulmonary exercise testing

Figure 6.2 shows the relationship of physical activity (steps per day) with various lung function parameters as well as with 6 minute walk distance. In this cohort, there is only a moderately good correlation with 6MWD (r=0.51) and a relatively poor correlation with RV/TLC ratio, a measure of dynamic hyperinflation, which is contrary to what Garcio-Rio et al found [320].

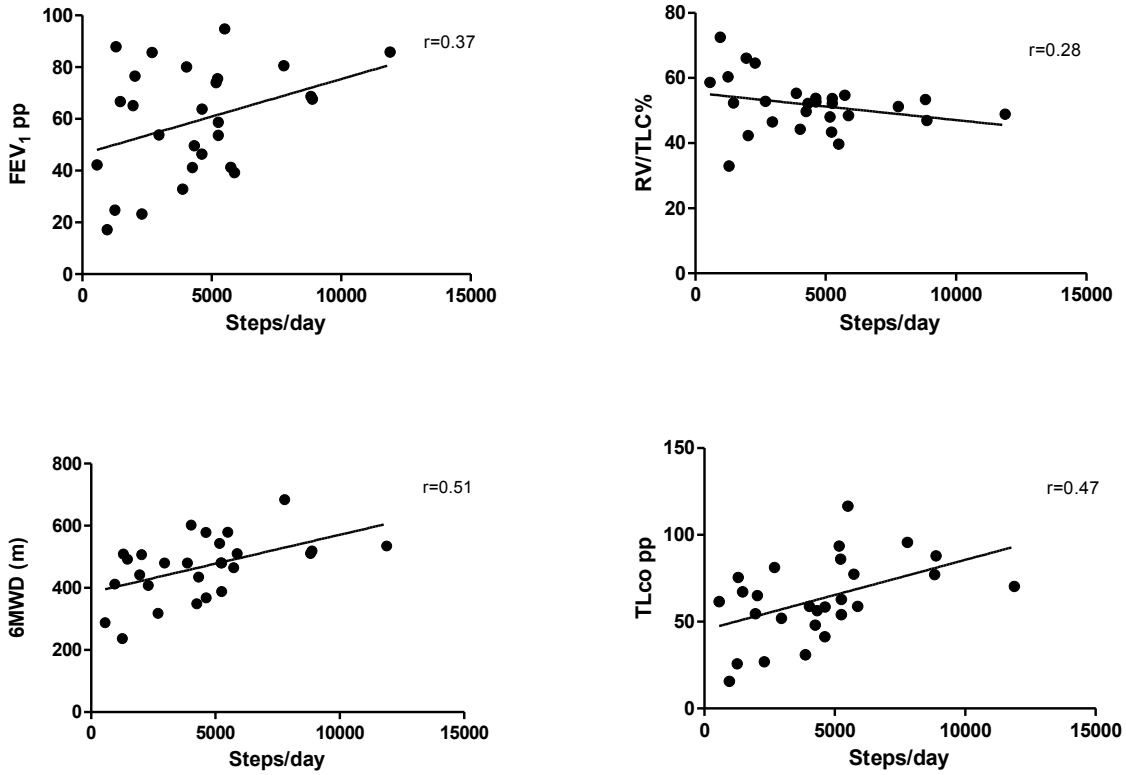


Figure 6.2. Relationship of steps per day with FEV_1, RV/TLC ratio, six minute walk distance and TLco

6.4.1.1 Area under the curve

Figure 6.3 shows an example of a patient's data. The area under the curve for the first minute after loaded pedalling (and following a period of rest and 1 minute of unloaded pedalling) was calculated as shown in the shaded area. Interestingly, this patient does seem to demonstrate an increase in respiratory rate with a concomitant reduction in tidal volume immediately on initiation of exercise.

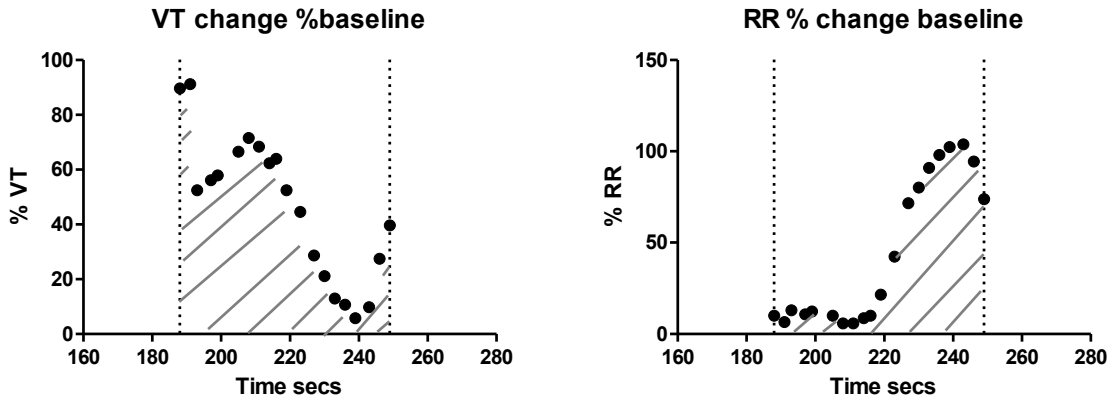


Figure 6.3. Example from one patient: Area under curve for tidal volume (VT) and respiratory rate (RR) for first minute of loaded cycling.

Figure 6.4 shows the results of linear regression for all the patients of area under the curve and steps per day. There was no significant relationship either with AUC VT or AUC RR or with the ratio of these and daily steps.

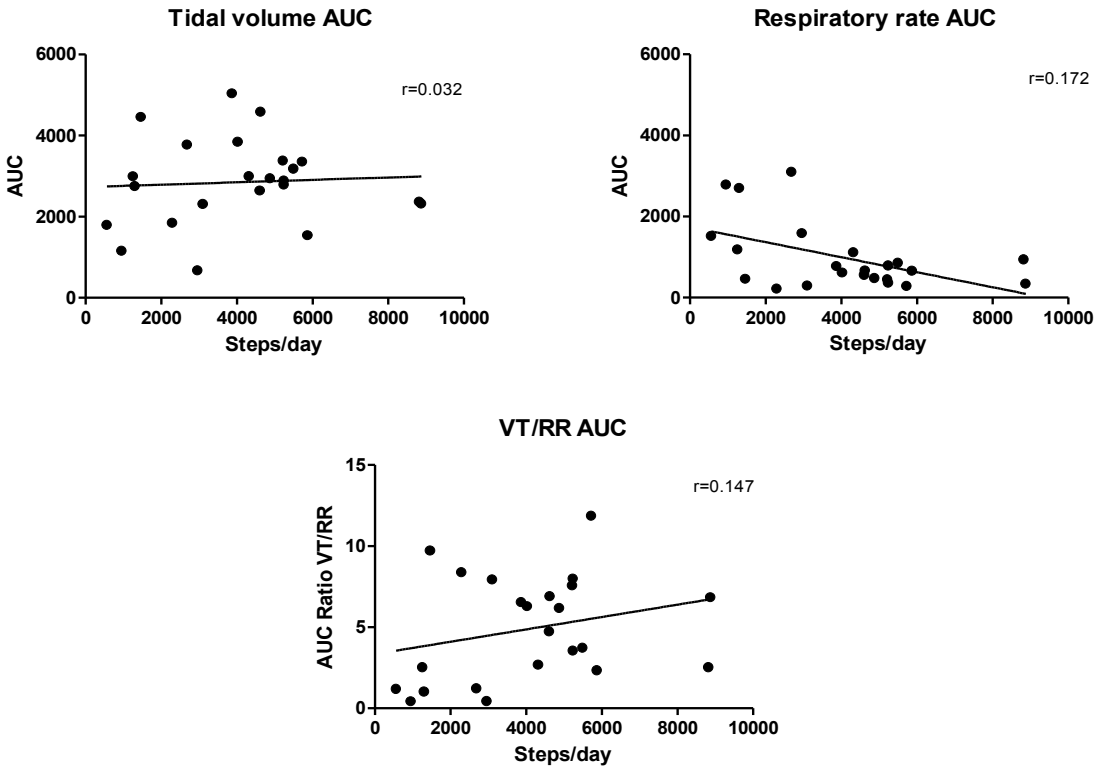


Figure 6.4. Graphs showing linear regression for area under curve for VT, RR and VT/RR

6.4.1.2 Change of VT/VC with VE

Figure 6.5 shows the k values obtained for each patient during the first minute of loaded pedalling plotted against steps per day. K values at different stages of the exercise test are also shown for comparison. There was a moderate correlation of k value with daily steps at 10W (r=0.49), and similarly at unloaded pedalling (r=0.48) compared to that obtained at peak exercise (r=0.33). This is against the hypothesis; Marin et al found that higher k values were associated with worse lung function, so a negative correlation between k value and physical activity would be expected.

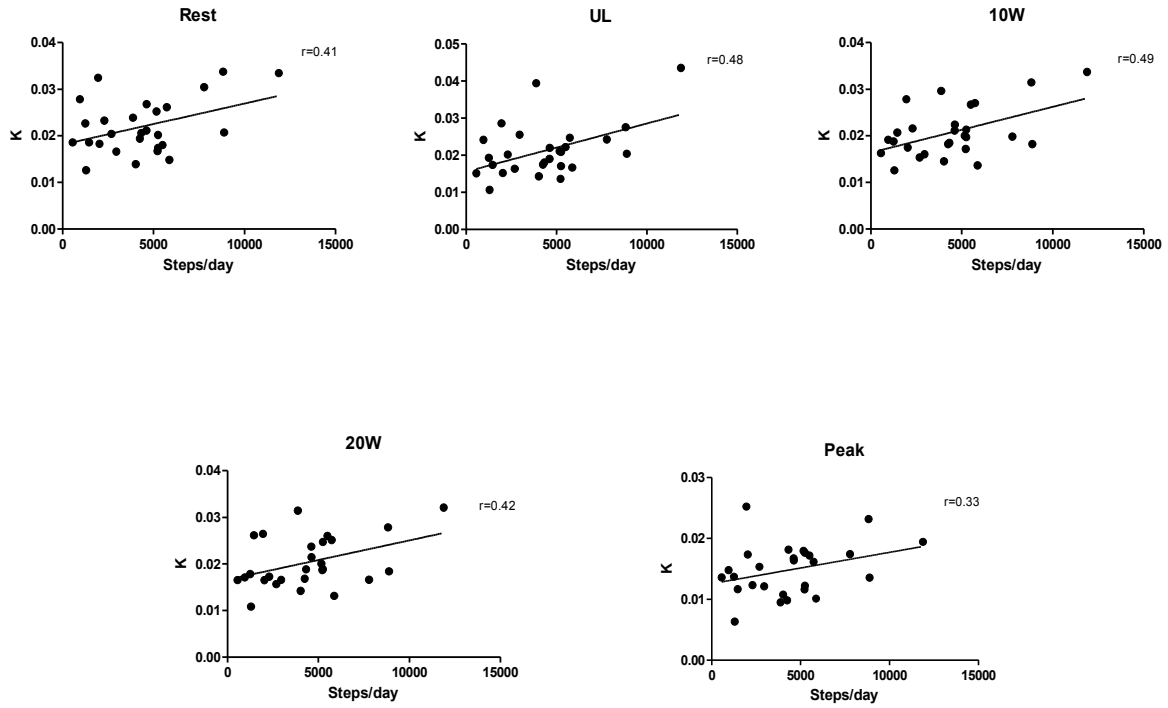


Figure 6.5. Linear regression of K values for all patients plotted against time periods of 1 minute for rest, unloaded cycling, 10W, 20W and at peak exercise.

6.4.2 Six minute walk tests

6.4.2.1 Area under the curve

Figure 6.6 shows the area under the curve for tidal volume and respiratory rate plotted against daily steps. There is only a positive correlation between respiratory rate and daily steps, i.e. as daily physical activity increases, the proportional increase in respiratory rate from baseline is greater.

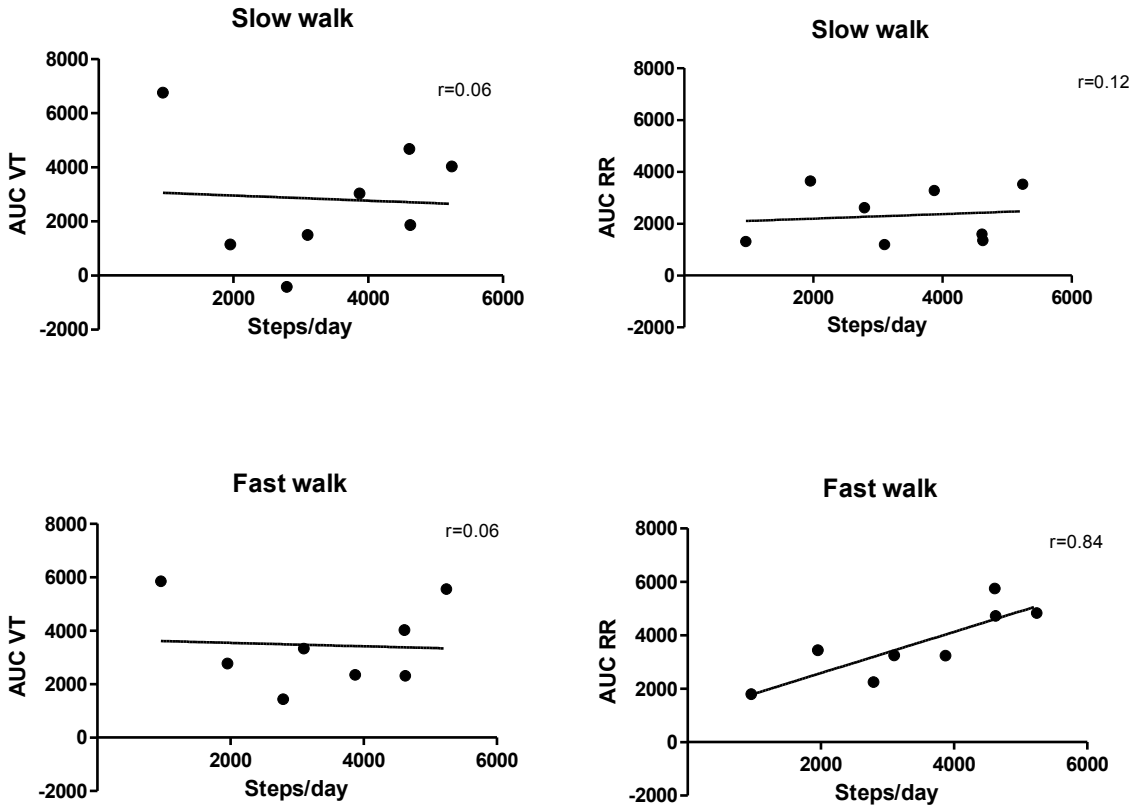


Figure 6.6. Area under curve for VT and RR against steps per day for slow and fast walks.

Figure 6.7 shows the ratio of AUC VT to AUC RR for both slow and fast walks during the first minute of exercise. There is a positive correlation between this ratio and daily steps at slow paced walking (r=0.63), i.e. as daily physical activity levels increase, the proportion to which tidal volume increases compared to respiratory rate is greater. In other words, the more physically active a person is, the more they increase their depth of breathing than their respiratory rate. However, no relationship is found at the faster walking pace.

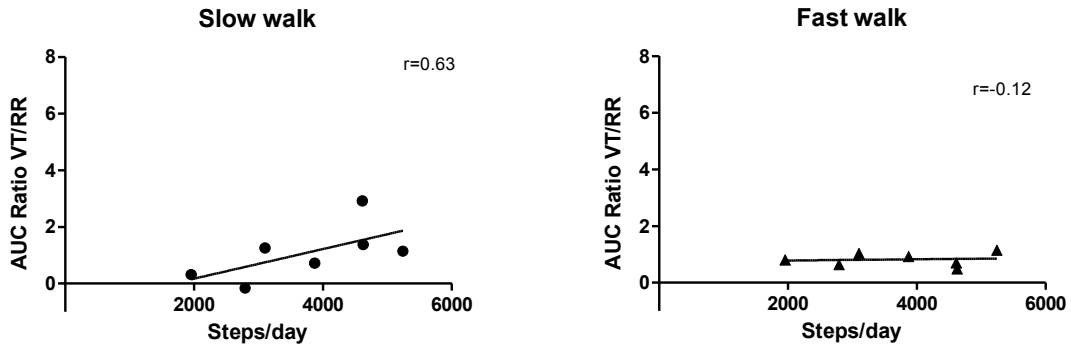


Figure 6.7. AUC VT to AUC RR for slow and fast walks during the first minute of exercise.

6.4.2.2 Change of VT/VC with VE

Figure 6.8 shows the k values for each patient plotted against physical activity for both slow and fast walks. There is no significant correlation between k value and daily steps for either walk speeds.

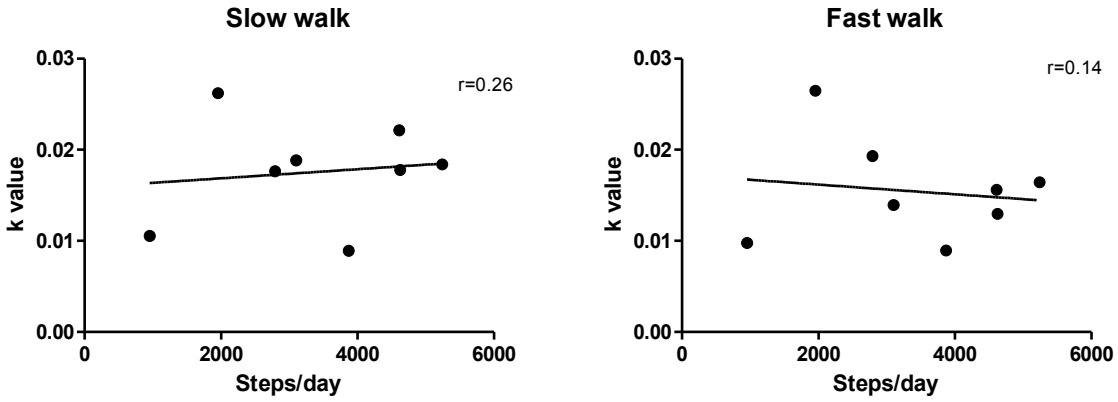


Figure 6.8. Linear regression of k values against steps per day for slow and fast walks.

6.5 Discussion

The early response to exercise in COPD was investigated. The hypothesis that a rapid shallow breathing pattern (i.e. a disproportionate increase in respiratory rate to tidal volume) at the onset of exercise would be associated with lower daily physical activity levels and would be better related than measures of peak performance was tested in two modalities of exercise, (during an incremental cycle CPET and during the first minute of slow and fast paced walking for 6 minutes) but was not proven.

6.5.1 Significance of findings

The area under the curve method was used to assess the rate of change of tidal volume in relation to respiratory rate at the onset of exercise. It was hypothesised that there would be a positive correlation between the ratio of AUC VT/AUC RR and daily steps, and that this relationship would be stronger for walking than during cycling as walking is more representative of what patients actually do on a daily basis. No significant correlation was found during for the CPET modality of exercise, or for fast walking, but was found for slow walking.

Using the exponential equation $VT = VC\ (1\text{-}e^{-kVE})$ describing the rate of change of VT/VC with time to calculate a constant, k, during the first minute of exercise, a moderately significant relationship with physical activity was found during cycling both during the first minute of loaded pedalling as well as during unloaded cycling, (r=0.49 and 0.48 respectively) and was stronger than that found at peak (r=0.33). However, this was not what was expected and was not in keeping with the findings of Marin et al who found a higher k value associated with poor lung function.

These findings could be explained because patients usually do things at their own pace throughout the day and not at maximal effort, hence the similarities between changes in breathing pattern during slow paced walking and physical activity levels. It may be that some patients have to consciously alter their breathing pattern to do so slowly and deeply, and may find this more difficult to do at higher intensities of exercise. It may explain the training effect found in Casaburi's pulmonary rehabilitation study where patients' breathing pattern during exercise was altered after 8 weeks of pulmonary rehabilitation. However, it may also be the case that the early response to exercise is not indicative of either exercise capacity or daily physical activity levels.

As previously discussed, several factors contribute to whether an individual is active on any given day. Disease factors have already been discussed, including exertional dyspnoea, dynamic hyperinflation and leg fatigue. Other factors include exacerbation frequency and severity and adherence to medication which could help to alleviate symptoms [22] [336].

Many other factors are involved. Personal factors such as motivation, cultural background, mood, previous experience of activity, along with environmental factors such as access to facilities and weather, also influence physical activity levels independent of pathophysiology, so analysing an aspect of one of the physiological parameters is likely overly reductive.

6.5.2 Critique of the method

There are several limitations with the current study. During the CPET, patients' breathing during rest was often erratic and therefore affected the initial baseline calculations of VT and RR. It may have been better to extend the period of rest so that patients were fully accustomed to the mouthpiece and breathing in a fully relaxed way prior to the start of cycling. The phenomenon of anticipation is well recognised and was not controlled for in this protocol, as patients knew when they were due to start exercising. Tobin et al [337] demonstrated this in healthy subjects who were given verbal warnings every 30 seconds for 5 minutes prior to the onset of exercise. Compared to the control group, they increased their tidal volume and hence minute ventilation on commencing exercise (during the first minute). The same effect was observed in subjects who were asked to perform mental arithmetic prior

to starting exercise. However, this result was not seen in all the subjects in the present study. Tobin et al state this response likely to be cortical in nature, although the absence of a fall in end tidal CO_2 suggests mechanisms other than stimulation of the respiratory centres. It could be that cardiac factors are responsible; they noted a concomitant increase in heart rate and O_2 pulse which could be catecholamine driven. This would be in keeping with the findings of Wasserman et al who demonstrated in anaesthetised dogs an increase in ventilation as a result of increased cardiac output, either with cardiac pacing or infusion of isoprenaline; the cardiogenic hyperpnea theory [338]. However, the patients in the present study did not seem to exhibit a similar O_2 pulse response at the onset of exercise.

Fukuba et al studied the effects of prior exercise, anticipation and breathing frequency on the breathing response to exercise on a static bike at workload of 75W [303]. When preceded by a period of rest, they found a rapid increase in tidal volume (phase 1 response) on initiation of cycling if exercise was anticipated by the subject. If exercise was not anticipated, this tidal volume response was slower if preceded by rest but not if by light exercise, i.e. there is no effect of anticipation on the VE response to exercise if preceded by light exercise.

In this study, rest was followed by a period of unloaded cycling, which could have had a similar effect to the light exercise in the Fukuba protocol, thereby altering the ventilator response. Similarly, during the walking protocol, patients did the fast walk around 4 to 5 minutes after the slow walk, which could again have mimicked the light exercise condition.

For some of the more severe patients, unloaded pedalling would cause greater exertion than the milder patients and so in these cases, the analysis of unloaded rather than loaded cycling would have been more accurate in terms of looking at the immediate breathing response to exercise. Overall, it would have been better to have asked the patients to go straight from rest to loaded pedalling to reduce the possibility of error here.

The number of patients studied for the walking modality was very small. More patients could be studied to generate more data. Each patient could also be studied several times to see if the breathing response is reproducible in each patient, or if other factors could influence it, such as a training effect, anticipation, length of rest period between walks, or the effect of walking on different days or walking outside. For instance it is known that in a standard six minute walk test, encouragement increases the distance walked [326], and so might also have an effect on breathing pattern. In this protocol, there was a short period between the slow and fast walks of around 5 minutes, but a longer period may be necessary in this patient group.

It should also be noted that the patients wore a mask during the walking tests, as opposed to a mouthpiece during the CPET. The experiment could be repeated with a mask during the CPET to see if this influenced breathing pattern, particularly during rest.

A much more standardised protocol where factors such as anticipation are controlled for should have been employed. In terms of physical activity monitoring, this should have been done as close to the time of exercise testing as possible in order to draw any valid conclusions about the relationship between daily physical activity and early breathing response on exertion. Both quantity (total steps, vector magnitude etc) as well as intensity (time spent in moderate or vigorous physical activity) should be measured to see which measure is most closely linked, if at all, with the early breathing response.

No data was collected about resting pulmonary mechanics, which would have been useful since this has been previously reported to be related to the ventilatory response to exercise, including by Marin et al. It would also be possible to measure intrathoracic pressure changes on exertion using the oesophageal balloon technique, and this would be valuable to do in future studies.

The area under the curve method of analysis is a novel one, and may itself need to be evaluated under stricter controlled conditions, for example, in a simpler exercise protocol and several times in the same patient for reproducibility, as it is particularly susceptible to error incurred if data acquired during rest, which is used as baseline for the AUC calculation, is not stable.

6.5.3 Conclusions

The results of this study illustrate the complexity and variability of the breathing response to exercise initiation in COPD, and that much more controlled conditions are required for a meaningful analysis in this population. However, to link this response to actual daily physical activity may merely serve to introduce yet more variables into an already complex phenomenon; preliminary data at least failed to show a link between respiratory pattern and daily PA. Nevertheless, a greater understanding of this response may help to better support patients during pulmonary rehabilitation which is known to influence morbidity significantly, over and above drug therapy. If patients could be taught to control their breathing in such a way as to improve exercise performance, this would serve not only to increase exercise capacity, but also could improve quality of life. They key would be if any such intervention did increase daily physical activity.

7 Conclusions and future work

The significance of physical activity in Chronic Obstructive Pulmonary Disease is undisputed. Physical inactivity is not only a consequence of disease, due to exertional dyspnoea and other factors such as muscle weakness and cardiovascular disease, which lead to exercise limitation, but also an emerging factor in the progression of COPD, even before symptoms have developed. This thesis has explored the importance of technical, environmental and patient factors in physical activity in COPD, to further our understanding in this important field. Much of the work in this thesis has its origins in the PROactive project, the EU wide 6 year initiative to develop a patient reported outcome tool to accurately reflect COPD patients' experience of physical activity, as such a tool did not previously exist. Alongside the development of this PRO, each of the chapters in this thesis has sought to further our understanding of technical aspects of physical activity monitoring, how physical activity is influenced by time, climate and geographical factors, as well as exploring the possible interaction of a dysfunctional breathing pattern with daily physical activity levels.

7.1 Laboratory validation of six activity monitors in COPD: a comparison with indirect calorimetry.

7.1.1 Summary of findings

The validity of six physical activity monitors was investigated by comparing activity monitor outputs for each monitor to the gold standard of indirect calorimetry from a portable metabolic kit in controlled laboratory conditions. The main rationale for conducting this study is that whilst several activity monitors are commercially available, very few have been validated in populations with chronic disease. COPD patients have been shown to move much more slowly than healthy subjects, so it was not known if the monitors in question would be sensitive enough to detect this slower pace of movement. In addition, some COPD patients have a higher rate of resting energy expenditure, and as such, the outputs of energy expenditure from some of the activity monitors, which have been previously validated in healthy subjects, could not be relied upon without first validating them in this population.

This study found triaxial activity monitors to be more valid compared to uniaxial activity monitors according to a number of predetermined criteria, namely correlation with energy expenditure derived from indirect calorimetry.

Firstly, correlations between minute-by-minute outputs and VO_2 (representing energy expenditure) were highest with the Dynaport MiniMod, Actigraph GT3X, SenseWear Armband and RT3, all triaxial monitors, and all exceeding an r value of 0.7. This shows that the monitors are sensitive and responsive to changes in physical activity, even at the small time epoch of minutes.

Secondly, using cumulative energy expenditure over the whole 59 minute protocol, the best correlations of mean activity monitor output were again found for three of the triaxial activity monitors (SenseWear Armband, Actigraph GT3X and Dynaport MiniMod, as well as one uniaxial activity monitor (Kenz Lifecorder). This demonstrates that monitors can accurately reflect a variety of activities that patients may realistically do in normal life over a sustained time period, such as housework or shopping.

Thirdly, with respect to detecting slower speeds of motion, step count accuracy was assessed and found to vary with walking speed, although only two monitors, the Sensewear and MiniMod, were considered in this analysis. The Sensewear was much less accurate overall than the MiniMod, particularly at slow walking speeds, likely due its positioning on the upper limb. In contrast, the MiniMod is positioned around the waist, giving more information about hip movement during walking and improving its sensitivity.

Fourthly, all monitors were able to detect a modest change in walking speed of 1.31km/hr, but two triaxial activity monitors had the strongest correlations with indirect calorimetry (MiniMod and SenseWear).

Fifthly, all activity monitor outputs showed similar variability in predicting energy expenditure. However there were fairly wide margins of error (95% prediction limits for mean METs (3.59 METs) varied between ±1.13 METs (SenseWear) and ±1.41 METs, (RT3)). Therefore, predicting oxygen consumption directly from different activity monitor outputs is not accurate but when patients engage in activity, monitors do detect the increase in physical activity levels within a range of 1 to 1.5 METs. This confirmed the assertion that the prediction equations for energy expenditure are only relevant for healthy subjects.

This study has many strengths. It is the first multi-centre multinational trial where several activity monitors were validated simultaneously against indirect calorimetry in different stages of COPD. A complex protocol of various activities was used, to include not only walking, but others such as lifting and sweeping, to mirror more closely activities of daily living that COPD patients actually perform. All

the monitors were sensitive to changes in activity at the minute by minute level, as well as being able to accurately record activity over a period of an hour. Some of the triaxial monitors' ability to detect slower speeds of walking was demonstrated.

The protocol used in this study provides a 'blueprint' which can be used in future to assess other activity monitors, including newer versions of those used here as well as novel devices. It is a valuable robust approach which has been shown to be technically feasible in this group of patients.

7.1.2 Limitations

There are however, limitations to this study. Although patients from all GOLD stages were tested, the mean six minute walk distance was 438m, with standard deviation 115m. These patients were therefore functionally not as severely limited as some of our more severe patients, who for example, cannot walk more than 100m in six minutes. Therefore, it could be argued that the activity monitors were not validated in the slowest moving COPD patients. In fact, as previously discussed, a recent study by Harrison et al showed the Sensewear step count to be less accurate at slower speeds of 1.8km/hr [277].

The gold standard of energy expenditure, which was used to validate the activity monitors, is driven to a large extent by a number of other factors, namely body weight, age and height. Whilst these specific factors such can be incorporated into prediction equations, it is more difficult with non-specific factors such as mechanical efficiency, especially in patients with COPD. These patients have a higher active energy expenditure [278], and reduced mechanical efficiency in these patients compared to healthy controls [279, 280]. An activity monitor cannot be expected to detect this complex variable accurately. Activity monitors are most appropriately used for the assessment of the activities of patients in terms of amount and/or intensity, so perhaps greater weight should be given to direct monitor outputs in future research (steps, activity counts, vector magnitude units). The derivation of energy expenditure from activity monitors is imprecise so therefore not necessarily the ideal gold standard for assessing monitor performance, but the only one available for this currently.

7.1.3 Future work

In light of the findings of Harrison et al regarding sensitivity of the Sensewear during very slow walking, it is important to validate all the monitors from this study at this slower speed and the protocol

should be adjusted accordingly if used to validate newer monitors in future research. It is equally, if not more important to measure physical activity accurately in these patients, in order to accurately capture the little activity they do engage in. Not only would it provide a greater understanding of disability, but also could be used to target interventions in this severe group.

In the wider context, it is unclear which aspect of physical activity is more beneficial: steps walked per day; amount of time spent in moderate or vigorous activity; level of intensity or frequency of intense periods; total energy expended in activity; activity targeting specific muscle groups to improve endurance; or activity to improve cardiovascular fitness. Further work is needed in this area, and future interventional studies should use various activity measures, such as those listed above to determine if improving overall activity amount is sufficient to improve prognosis, or whether a more specific targeted approach is beneficial (such as improved cardiovascular fitness, intensity training etc.).

A recent study by Demeyer et al found the minimal important difference in step count in COPD after completing pulmonary rehabilitation to be between 600 and 110 steps per day [339], but there are problems with using an absolute figure, rather than percentage improvement from baseline. Nonetheless, a 'How much is enough?' question needs to be asked, in terms of morbidity (such as exacerbation frequency, hospital admission rate) and the answer may be different in different GOLD stages of COPD.

Apart from the concepts of validity and reliability, other factors such as size and scope of the study, usability and cost of the activity monitor need to be taken into consideration when selecting an activity monitor for use in clinical trials. All the monitors used in this study require specialist software in order to read and download data, which adds to research expense and time. However, if a more simple intervention, such as increasing steps walked per day is required, then a simple pedometer will suffice, and be much more cost effective in the long term.

Overall, we concluded that triaxial monitors are superior to unaxial monitors when measuring physical activity in the COPD population, and specifically those worn on the hip as opposed to the upper limb (namely the Dynaport and Actigraph devices). They can detect slower movement in this population but further validation work is needed in the slowest moving and more severely affected patients. These results should serve as a useful guide for future choice of valid activity monitors for both research and clinical use in patients with chronic diseases including COPD.

7.2 Domestic validation study of physical activity monitors in COPD in daily life

This study built on the work from the previous chapter in terms of validating activity monitors in COPD, this time in a domestic environment, as ultimately, if these monitors are to be used in large scale trials, as is the aim of the PROactive project, then they must be suitable for home use in this patient group. The validity of four triaxial accelerometers, three of which had been studied in the previous chapter (RT3, Sensewear and Actigraph GT3X), as well as one novel device, the eAR, was evaluated against the gold standard of indirect calorimetry from the doubly labelled water (DLW) method in 20 COPD patients in a home setting over a 14 day period. This was the first study to validate a number of monitors simultaneously in this patient group using the DLW method.

7.2.1 Summary of findings

All monitor outputs evaluated had high coefficients of variation (all greater than 0.20) apart from Sensewear energy expenditure per day (SW-EE) and RT3 energy expenditure per day (RT3-EE) (less than 0.1). This implies that the monitor is able to detect a great deal of variation in physical activity within a patient, which is over and above the margin of error of the device. The lack of variability in SW-EE and RT3-EE could be because the majority of the energy expended is due to high levels of resting energy expenditure because the patients are very inactive; these outputs rely on prediction equations incorporating factors such as age and weight, and as previously discussed, may not be accurate in the COPD population. However, due to problems with the measurement of resting energy, it is not possible to be certain on this point (see below).

In the previous chapter, we have shown there to be strong correlations (all $r>0.7$, $p<0.05$) between activity monitor outputs and indirect calorimetry for all monitors used in the domestic study, with 95% limits of prediction of energy expenditure to be between 1.13 METS (SW) and 1.41 (RT3). This implies that the margin of error of the monitors (apart from the eAR) is sufficiently low to consider that the variation in physical activity is likely to result from the patient.

The Sensewear step count and the RT3 energy expenditure demonstrated a statistically significant correlation with indirect calorimetry from doubly labelled water if predicted values for REE as calculated by the Harris Benedict equations were used. However, if actual measured values for REE from the ventilated hood were measured then only the RT3 energy expenditure output was significant. This could be due to underpowering as 5 subjects had to be excluded from the analysis using the measured REE values as data could not be obtained from them due to difficulties tolerating the test (unable to fast, undergoing a concurrent exacerbation, technical problems with canopy leak). Equally,

it could be that the Sensewear prediction equations for energy expenditure are not as valid in this population as the RT3 equations.

Although the eAR monitor suffered technical issues (see below), good correlations were found between the eAR activity index and the AG step count and VMU and the RT3 VMU, perhaps because this was a direct comparison of the raw data i.e. a vector in 3 different axes.

All monitors apart from the eAR showed good correlations with 6MWD. This implies that they were able to capture the activity at the speed at which the patient moved during the six minute walk test and that the activity measured by that device parameter reflected that patient's exercise capacity. However, patients do not typically move at the speed at which they perform the six minute walk test, during which they are encouraged to walk as fast as they can for the duration of the test. Therefore, it is merely assumed that all movements which expend energy are captured, including those performed very slowly.

7.2.2 Limitations

A common theme with problems experienced during the study was technical failure. The eAR monitor did not show any significant correlations with AEE or 6MWD, but as only 10 out of the 20 patients tested actually gave a full set of data, the analysis could have been underpowered. (However, the eAR monitor has previously been shown to be a valid head-worn monitor for gait analysis [289], to predict energy expenditure [290] and has also been validated for use in COPD patients [297]).

Reasons for lost data from the eAR monitor were due to technical problems with devices themselves, either not recording accurately or losing data. Some patients also found the device uncomfortable to wear, particularly if they wore glasses or a hearing aid, due to its location behind the earlobe; it scored the lowest on the usability questionnaire (56.9%). This issue warrants further consideration regarding the design of this device going forwards, especially in this age group, where wearing hearing aids or glasses is common. Overall, the most acceptable monitors were the Sensewear (74%), worn on the upper arm, and Actigraph (72%), worn on a belt over the right hip.

The RT3 also encountered technical problems, mainly because it failed to record for a whole week (half of the testing period) in eight patients due to poor battery life. The Sensewear also suffered from lost data of 2 to 3 days in seven patients, again due to battery life. Technical reliability is crucial when considering a monitor for use in interventional studies or for long term home use. Moreover, if a monitor is too inconvenient or uncomfortable to wear, as seemed to be the case with the eAR, then it also cannot be used with any confidence in larger studies.

It was not possible to use a measure of agreement for all the monitors as only the Sensewear and RT3 gave estimated energy expenditure values as one of their outputs. A Bland-Altman analysis for these two monitors showed both monitors to be prone to error, but less so with the RT3 (see **Figure 4.6**).The overall trend for both monitors was to under-record energy expenditure; it is well known that COPD patients have higher resting energy expenditure levels, so the monitors were not able to estimate this accurately.

Some patients in this study were actually more active during weekends than on weekdays. This observation does not support previous findings of lower activity of COPD patients at weekends. This could be due to a number of factors, such as a chance distribution of poor weather during the two week study period during the week as opposed to the weekend. In fact, in the whole data set of 80 patients, weekend activity was found to be lower than weekday [303], so this error could be due to the small sample size.

Further significant technical problems were experienced with ventilated hood measurements for resting energy expenditure. The REE values measured with the ventilated hood were unexpectedly low for some patients (some as much as 50% of predicted values from Harris Benedict equations). Although these problems were not apparent at the time of making the measurements, these low results could represent incorrect data due leak from the canopy. In 5 patients, results were not at all available either due to having an exacerbation at the time of the measurement, being unable to fast or being unable to tolerate lying flat under the canopy. In fact, in the wider multicentre EU study [307], other European centres encountered similar problems, and it seemed to be generally when unexpectedly low measurements were obtained from the ventilated hood than the values predicted by the Harris-Benedict method (these patients were excluded from the final analysis in the published paper).

Previous work in COPD patients using doubly labelled water and the ventilated hood method to measure total and resting energy expenditure respectively have shown consistently that resting energy expenditure values are higher than healthy controls [278, 308]. This seems to be independent of disease severity and other factors such as fat free mass. Other possible reasons for this include medications (beta agonists, theophyllines), and the pro-inflammatory state known to exist in COPD [309].

Another potential source of error was the measurement of total energy expenditure from the doubly labelled water method, such as incorrect labelling of the timing of the urine samples, as they were given by the patients at home, rather than at the study centre,

7.2.3 Future work

Going forward, the eAR monitor should be validated again, using both this protocol as well as the laboratory validation protocol presented in Chapter 3. However, some design issues need to be addressed to make this device more acceptable to patients in the future. Technical difficulties with the other monitors should be fed back to the manufacturers so that improvements can be made.

The problems with measuring resting energy expenditure using the ventilated hood should be addressed. This is an important technical method with implications for further validation of activity monitors. It will also improve our understanding of the systemic effects of COPD. An interesting study would be to perform the ventilated hood measurements before and after a physical activity intervention, such as an 8 week exercise programme. A sub set analysis would look at how the patients with higher than predicted resting energy expenditure performed and whether the intervention succeeded in lowering their resting energy expenditure rate.

In conclusion, the Sensewear and RT3 monitors were found to be the most accurate monitors in a field setting in this group of patients when validated against indirect calorimetry. All monitors apart from the novel eAR device showed good correlation with patients' exercise capacity in terms of 6 minute walk distance. However, this was a technically difficult study to carry out; all monitors suffered technical problems in terms of lost data. Results were further compromised due major technical difficulties using the ventilated hood; moreover, it was not possible to quantifiy errors when collecting urine samples for the DLW analysis. However, all monitors, with the exception of the eAR, were reasonably well tolerated with the Sensewear and Actigraph being the most popular, and either of these could be used in larger studies in the COPD population. Preference would be for the Actigraph, as it is a hip worn device, which would make it more accurate in step counting than the Sensewear, given the findings of the previous chapter.

7.3 Change in physical activity with time and climate in COPD

This study was the first to measure physical activity in COPD longitudinally in different centres across different countries. The main aim of this study was item reduction of the draft PRO as part of the PROactive project, but we were also able to assess the effect of time and seasonal factors, that is, temperature, rainfall, sunshine and daylength, on physical activity as measured by two activity monitors at baseline, 6 and 12 months. These commercially available activity monitors had been previously validated in the home and laboratory settings (see Chapters 3 and 4) and selected as a result of this previous work.

7.3.1 Summary of findings

There was a significant effect of time on physical activity, with a decline in all measures of physical activity over 12 months. This applied to all centres, despite the patients having significant differences in baseline characteristics, including FEV_1, six minute walk distance and baseline physical activity. This is in keeping with the established concept of physical activity as the strongest predictor of mortality in COPD [115] . Moreover, the finding that there was no effect of centre on this decline with time is a valuable one as it has positive implications for future multicentre studies in COPD patients, using physical activity as an outcome measure.

In this study 6MWD and FEV_1 did not decline significantly with time, albeit over a follow up period of 1 year; although this has been shown in a more recent study by Waschki et al with a longer follow up period of 3 years[312]. They found decline in physical activity to be associated with decline in FEV_1 (although not with 6MWD). It is possible that measures of physical activity in COPD are much more sensitive measures of disease progression than FEV_1 and exercise capacity, commonly used outcome measures.[315]; as our follow up period was only a year, it may not have been long enough to see significant changes in FEV_1 and 6MWD. Physical activity therefore should be considered as a primary outcome measure in intervention studies as well as longitudinal prospective studies in COPD.

A significant effect of climate on physical activity, in the form of temperature was also found, with lower levels associated with cooler temperatures. This change was independent of centre; it was not the fact that the patients were recruited at different locations that explained the variation in activity levels, but the change in environmental temperature itself.

A persistent effect of temperature was seen for almost all measures of physical activity. However, other seasonal factors were less significant. Rainfall, where available, was not a significant determinant of physical activity for any measures. The effect of the interaction between temperature and day length as a separate variable was tested and found to be significant for some measures, but it seems that most of this effect is accounted for by temperature. One would expect temperature to be higher in the summer than the winter, so a seasonal effect can be inferred from this finding, which seems to be over and above the decline seen in physical activity over time, although we did not specifically test for this.

This has implications in choosing when to conduct studies, particularly multi centre studies in different countries and temperature is one of the factors that would need to be controlled for. A practical solution would be to do all measures in the same season to try and match environmental temperature

as best as possible, for baseline and follow up; or to at least to correct for this effect during any data analysis, or to randomise as patients are recruited so that the effect of climate is negated.

7.3.2 Limitations

There were some limitations to this study. The primary objective was to perform the item reduction task for the PRO tool and so it was powered to this endpoint and not to detect the physical activity changes over time. However, decline of physical activity was significant, so it is improbable that a larger sample size would have altered the conclusions of the study.

The staggered start times of the patients proved problematic when analysing the data for climate and seasonal differences. Ideally all patients should have been enrolled into the study within the summer in a short period to minimize the differences in climate; they would then have been followed up in winter at the first follow up visit at 6 months. However, in reality, patients were slowly recruited into the study with some entering during summer, and others in autumn with a handful in winter. Those who were enrolled in autumn were followed up at 6 months in spring, at which time there was not a great difference in temperature compared to the time of enrollment.

Daylength was used as a surrogate for season, but again is only relevant when comparing winter and summer (as, again, daylength in autumn and spring is similar), and that too only in northern European countries (daylength did not vary as much in Athens as, for example, in Edinburgh). It was not possible to group patients according to the season in which they were recruited, as this would have been done arbitrarily, as there is a gradual transition from one season to the next. Therefore, rather than being able to look for a seasonal effect, the main variable of temperature was used, as this was more objective.

Weather data were collected retrospectively, and although these were official data from the Met Office, and this technique has been previously used [314, 317], it would have been more accurate to keep real time records of weather conditions at the time of the study. Unfortunately, the analysis of climate was limited by availability of data. For example, the number of hours of sunshine per day was not available for all centres, and other factors such as humidity or pollution levels were not available.

Dropouts were a problem as 33% of the initial patient population dropped out. Those who dropped out had significantly lower physical activity levels at baseline as well as lower quadriceps strength, six minute walk distance and CCQ score, as well as physical activity levels, but not increased exacerbation rates. This seems to be a particular feature of COPD patients and mirrors the finding in pulmonary rehabilitation that those patients who do not complete have more to gain; those who drop

out are more breathless, have poorer health related quality of life , lower FEV_1, weaker quadriceps strength and higher anxiety and depression scores [20, 318]. However, with respect to pulmonary rehabilitation, other socioeconomic factors such as access to transport, living alone and smoking status are influential [319]. We did not necessarily allow for these factors in this study, but is something that could be targeted to reduce the dropout rate in future studies. As a whole, dropout rate represents an important factor that clearly needs to be accounted for in any future studies investigating physical activity in this population. This also needs to be accounted for in future studies in both patient selection and sample size calculations.

7.3.3 Future work

These findings have important implications regarding future research in this field, particularly regarding trial design. As already alluded to, as temperature has been found to have a significant effect on physical activity levels, this variable has to be controlled for when recruiting patients into studies where physical activity is to be used as an outcome measure, Either patients should be recruited during similar climatic conditions, or sample size calculations have to allow for the effect of temperature. When conducting follow up, an attempt should be made to control for climatic conditions such as temperature, such as following up patients in the same season, or adjusting for the effect of temperature in subsequent statistical analysis. Effects of interventions must be 'real effects', not just the result of following patients up in better weather.

Reassuringly, we did not find an effect of centre on physical activity, and this bodes well for future European multicentre studies using physical activity as an outcome measure. Further research into how physical activity varies in COPD, as well as in other chronic diseases, in other parts of the world with very different climatic conditions (e.g. countries around the equator) is needed to provide a more comprehensive understanding of this area, in order to effectively design trials and develop new interventions for COPD.

These findings also have significant clinical relevance. It is already known that physical activity is the strongest predictor of mortality, and seems to decline earlier than other clinically important measures such as exercise capacity or lung function. If physical inactivity could be tackled earlier with intervention, then there could be real promise in attenuating decline in these patients. This could represent a new emphasis in therapy, over and above existing pulmonary rehabilitation programmes and could be tested in further randomised controlled studies. Our dropout rates and lower levels of physical activity in those who do drop out parallels the limitations of pulmonary rehabilitation, in that it is those who do not complete who are those who have most to gain. More innovative ways of reaching this target population need to be devised in order to make a real impact on this as yet incurable disease.

7.4 Changes in early exercise in patients with COPD and their association with daily physical activity

This study was a largely exploratory study into the possible association between breathing pattern at the start of exercise with daily physical activity levels. However, the hypothesis that a rapid shallow breathing pattern (i.e. a disproportionate increase in respiratory rate to tidal volume) at the onset of exercise would be associated with lower daily physical activity levels and would be better related than measures of peak performance was tested in two modalities of exercise, (during an incremental cycle CPET and during the first minute of slow and fast paced walking for 6 minutes) but was not proven.

7.4.1 Summary of findings

Firstly, a novel method of analysis was used to assess the rate of change of tidal volume with respiratory rate at the onset of exercise by looking at the area under the curve during the first minute of exercise, and expressing this as the ratio AUC VT/AUC RR. Ventilation data from cycling (from a cardiopulmonary exercise test) and walking (during a six minute walk test) recorded with a metabolic cart, was used in this analysis. However there was no relationship between this measure and daily step count.

Secondly, an exponential equation previously used by Marin et al was used to describe the rate of change on VT/VC with time to calculate a constant k during the first minute of exercise for both cycling and walking. The hypothesis was that a lower k value would be associated with better daily physical activity levels as measured by step count, (as they had found higher k values to be associated with poorer lung function) but this was not found in either exercise modality.

7.4.2 Limitations

There were several limitations with this study, apart from it being a total novel and unproven method. During the CPET, patients' breathing during rest was often erratic and therefore affected the initial baseline calculations of VT and RR. It may have been better to extend the period of rest so that patients were fully accustomed to the mouthpiece and breathing in a fully relaxed way prior to the start of cycling. The phenomenon of anticipation is well recognised and was not controlled for in this protocol, as patients knew when they were due to start exercising.

In this study, rest was followed by a period of unloaded cycling, which could have had a similar effect to light exercise, thereby altering the ventilatory response. Similarly, during the walking protocol, patients did the fast walk around 4 to 5 minutes after the slow walk, which could again have mimicked the light exercise condition.

For some of the more severe patients, unloaded pedalling would cause greater exertion than the milder patients and so in these cases, the analysis of unloaded rather than loaded cycling would have been more accurate in terms of looking at the immediate breathing response to exercise. Overall, it would have been better to have asked the patients to go straight from rest to loaded pedalling to reduce the possibility of error here.

The number of patients studied for the walking modality was very small. More patients could be studied to generate more data. Each patient could also be studied several times to see if the breathing response is reproducible in each patient, or if other factors could influence it, such as a training effect, anticipation, length of rest period between walks, or the effect of walking on different days or walking outside. For instance it is known that in a standard six minute walk test, encouragement increases the distance walked [326], and so might also have an effect on breathing pattern. In this protocol, there was a short period between the slow and fast walks of around 5 minutes, but a longer period may be necessary in this patient group.

It should also be noted that the patients wore a mask during the walking tests, as opposed to a mouthpiece during the CPET. The experiment could be repeated with a mask during the CPET to see if this influenced breathing pattern, particularly during rest.

A much more standardised protocol where factors such as anticipation are controlled for should have been employed. In terms of physical activity monitoring, this should have been done as close to the time of exercise testing as possible in order to draw any valid conclusions about the relationship between daily physical activity and early breathing response on exertion. Both quantity (total steps, vector magnitude etc) as well as intensity (time spent in moderate or vigorous physical activity) should be measured to see which measure is most closely linked, if at all, with the early breathing response.

No data was collected about resting pulmonary mechanics, which would have been useful since this has been previously reported to be related to the ventilatory response to exercise, including by Marin et al. Employing the oesophageal balloon technique to measure intrathoracic pressure changes on exertion would be valuable to do in future studies, and again, to investige any link with daily physical activity levels.

The results of this study illustrate the complexity and variability of the breathing response to exercise initiation in COPD, and that much more controlled conditions are required for a meaningful analysis in

this population. However, to link this response to actual daily physical activity may merely serve to introduce yet more variables into an already complex phenomenon; preliminary data at least failed to show a link between respiratory pattern and daily PA. Nevertheless, a greater understanding of this response may help to better support patients during pulmonary rehabilitation which is known to influence morbidity significantly, over and above drug therapy. If patients could be taught to control their breathing in such a way as to improve exercise performance, this would serve not only to increase exercise capacity, but also could improve quality of life. They key would be if any such intervention did increase daily physical activity.

7.5 Future research

7.5.1 Change in PRO over time

The next major work that needs to be completed is analysis of how the scores of the final versions of both PROs change over the 1 year follow up period, and whether the results are similar to those obtained with the activity monitor data alone. If the PROs are responsive to change over time, this would strengthen them as a tool for further use in COPD in both research and clinical contexts.

7.5.2 Physical activity as an interventional therapy

There is now a comprehensive understanding of the importance of physical activity in the course of COPD, but interventions remain sparse. Although pulmonary rehabilitation is an effective intervention in COPD in terms of improving self-efficacy and symptoms, there is little evidence that it can produce sustained increases in daily physical activity levels. There is a need for an effective alternative which serves both to replace pulmonary rehabilitation for patients unable to access a local programme, and as an additional therapy which enables patients to increase their daily physical activity levels in the long term. Future research must therefore be targeted at novel interventional therapies aiming to do just this.

To that end, and building on the work already accomplished by the PROactive project with validation of physical activity monitors and formulation of draft patient reported outcome tools in COPD, the last study in the 6 year project is an interventional study (National Clinical Trials number NCT02158065). The intervention is a semi-automated home activity coaching tool delivered to patients via a tablet or smart phone in conjunction with a simple pedometer. Participants receive daily feedback regarding

the number of steps walked and whether they have achieved their daily goal. Physical activity before and after the intervention will be measured using two of the previously validated activity monitors (Actigraph and Dynaport); the daily PRO tool will also be validated during the study. If successful, the semi-automated activity intervention could be used as a therapeutic measure for patients following pulmonary rehabilitation (PR) as an adjunct to improve the duration of the beneficial effect of PR; or as an alternative to PR for those patients unable to easily access services, either due to resource issues or for clinical reasons, for example, following exacerbation, where a home based activity programme would be easier.

7.5.3 Wider use of activity monitors – implications in public health

Accuracy of measurement of physical activity in COPD is important as physical activity is a strong predictor of mortality [115]. However the devices used in the studies in this thesis cannot give real time feedback to patients regarding their daily physical activity. Feedback *is* important: several studies have shown that subjects receiving feedback from, for example, simple pedometers, are more successful in increasing their step counts and therefore physical activity, than those receiving only encouragement from investigators [340-342]. Therefore, when considering employing activity monitors on a larger scale, such as in public health initiatives to increase physical activity in certain target patient groups, including COPD, a more pragmatic approach may be needed. This would be to opt for a less complex device such as a simple pedometer which is easier to use and more cost effective on a larger scale. The more complex devices may be better suited to a research context.

In fact, consumer technology is far ahead of research in terms of developing devices which are pitched at an affordable price point, are user friendly, able to give real-time feedback in terms of step count or calories burnt, and can be paired with one's smartphone with free or cheap software. Examples include the Fitbit range of devices, the Microsoft Band activity tracker as well as numerous GPS-ready sports watches and other simple pedometers. Most current smartphones themselves now have integrated accelerometers and are able to track step counts and calories burnt, again through free or relatively cheap software. A future direction of research would be to validate one or more of these commercially available devices in COPD and to then use them either in intervention studies or as an alternative to pulmonary rehabilitation.

In a wider context, if validated, such technology could be used in other disease groups, and in public health initiatives to promote physical activity in the population as a whole. This would follow on from the findings of the recent WHO review which sites physical inactivity as a major modifiable risk factor in non-communicable disease throughout the developed world.

7.5.4 Further study of the ventilator response to exercise in COPD

As already alluded to, this area warrants further work. In the study in this thesis, no relationship was found between breathing pattern in early exercise and physical activity. However a recent paper has followed up breathing pattern in COPD over a 4 year period and found that a more rapid shallow pattern of breathing developed over this time. This was defined by a reduced tidal volume for a given minute ventilation and was related to an increase in hyperinflation, a fall in FEV_1 and persistent smoking over this period [343].

Breathlessness is well recognised to be multifactorial in aetiology, including not only physiological factors such as dynamic hyperinflation, but also psychological aspects and increased neural drive and may explain the differing results of these two studies.

The initial response to exercise must be studied during a stricter exercise protocol and should include measurement of intrapulmonary pressure. The kinetics of the VO_2 response could also be analysed if a slightly different cycle exercise protocol was used with a shorter warm-up or unloaded pedalling phase. This gives an estimation of the rate of oxygen delivery against utilisation when moving from rest to exercise. Our group has shown accelerated exercise oxygen kinetics in COPD patients who have successfully undergone bronchoscopic lung volume reduction surgery and was associated with improved cardiovascular response to exercise [344]. A similar analysis could be done before and after the above interventional study discussed above to test for improvements in the exercise response after the intervention, and how this relates to daily physical activity. This may help to explain the incongruity between patients' exercise capacity and actual physical activity levels.

Breathlessness is multifaceted and all aspects must be addressed, including physiological and psychological components. Effective treatment of breathlessness in COPD (as well as in other chronic conditions such as interstitial lung disease, cardiac failure) is important to well being and quality of life as it the single most reported symptom of patients who want to be able to do more and feel less breathless. Simple measures such as applying a hand held fan to the face during exercise have been shown to be effective in reducing dyspnoea scores and improving exercise performance [345]. More recently, an integrated breathlessness service has been shown to improve quality of life scores and have an impact on mortality [346]. If patients can feel less breathless when being physically active, this is a potential mechanism to moderating disease progression in terms of improved muscle strength, reduced exacerbation frequency and reduced systemic inflammation.

In conclusion, this thesis has explored several aspects of physical activity in COPD, from accurate measurement using various activity monitors, to changes in physical activity with time and climate, and an as yet unproven relationship between physical activity levels and changes in breathing in early

exercise. The importance of physical activity in the course of COPD is undisputed. They key issue of how to increase activity in COPD in sustained and meaningful way remains unresolved. Future research should be targeted at understanding how to overcome the barriers to physical activity, and at interventions which increase physical activity in patients with established COPD, as well as in the wider public as part of disease prevention.

8 References

1. Thompson, P.D., et al., *Exercise and Physical Activity in the Prevention and Treatment of Atherosclerotic Cardiovascular Disease.* Circulation, 2003. **107**(24): p. 3109-3116.

2. Bardia, A., et al., *Recreational physical activity and risk of postmenopausal breast cancer based on hormone receptor status.* Arch Intern Med, 2006. **166**(22): p. 2478-83.

3. Blair, S.N., et al., *Changes in physical fitness and all-cause mortality. A prospective study of healthy and unhealthy men.* JAMA, 1995. **273**(14): p. 1093-8.

4. Chien, M.Y., et al., *Efficacy of a 24-week aerobic exercise program for osteopenic postmenopausal women.* Calcif Tissue Int, 2000. **67**(6): p. 443-8.

5. Hambrecht R Fau - Fiehn, E., et al., *Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure.* 1998(0009-7322 (Print)).

6. Hsia, J., et al., *Physical activity and diabetes risk in postmenopausal women.* Am J Prev Med, 2005. **28**(1): p. 19-25.

7. *Global health risks: mortality and burden of disease attributable to selected major risks*, 2009, World Health Organisation: Geneva.

8. Lozano, R., et al., *Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010.* Lancet, 2012. **380**(9859): p. 2095-128.

9. Garcia-Aymerich, J., et al., *Regular Physical Activity Modifies Smoking-related Lung Function Decline and Reduces Risk of Chronic Obstructive Pulmonary Disease: A Population-based Cohort Study.* Am. J. Respir. Crit. Care Med., 2007. **175**(5): p. 458-463.

10. Lee, I.M., et al., *Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy.* Lancet, 2012. **380**(9838): p. 219-29.

11. Society, B.T., *IMPRESS Guide to the relative value of COPD interventions*, 2012.

12. Seymour, J.M., et al., *Outpatient pulmonary rehabilitation following acute exacerbations of COPD.* Thorax, 2010. **65**(5): p. 423-428.

13. Spruit, M.A., et al., *Pulmonary Rehabilitation and Physical Activity in Patients with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2015. **192**(8): p. 924-33.

14. Walker, P.P., et al., *Lower limb activity and its determinants in COPD.* Thorax, 2008. **63**(8): p. 683-689.

15. Mercken, E.M., et al., *Rehabilitation Decreases Exercise-induced Oxidative Stress in Chronic Obstructive Pulmonary Disease.* Am. J. Respir. Crit. Care Med., 2005. **172**(8): p. 994-1001.

16. Sewell, L., et al., *Can individualized rehabilitation improve functional independence in elderly patients with COPD?* Chest, 2005. **128**(3): p. 1194-200.

17. Steele, B.G., et al., *Monitoring daily activity during pulmonary rehabilitation using a triaxial accelerometer.* J Cardiopulm Rehabil, 2003. **23**: p. 139 - 142.

18. Coronado, M., et al., *Walking activity measured by accelerometry during respiratory rehabilitation.* J Cardiopulm Rehabil, 2003. **23**: p. 357 - 364.

19. Saunders, T.J., et al., *Distinct Trajectories of Physical Activity Among Patients with COPD During and After Pulmonary Rehabilitation.* COPD, 2015. **12**(5): p. 539-45.

20. Garrod, R., et al., *Predictors of success and failure in pulmonary rehabilitation.* Eur Respir J, 2006. **27**(4): p. 788-94.

21. Ries, A.L., et al., *Maintenance after Pulmonary Rehabilitation in Chronic Lung Disease.* American Journal of Respiratory and Critical Care Medicine, 2003. **167**(6): p. 880-888.

22. Pitta, F., et al., *Physical activity and hospitalization for exacerbation of COPD.* Chest, 2006. **129**(3): p. 536-544.

23. Troosters, T., et al., *Assessing the Impact of Tiotropium on Lung Function and Physical Activity in GOLD Stage II COPD Patients who are Naive to Maintenance Respiratory Therapy: A Study Protocol.* Open Respir Med J, 2011. **5**: p. 1-9.

24. Pitta, F., et al., *Characteristics of physical activities in daily life in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2005. **171**(9): p. 972-7.

25. Caspersen, C.J., K.E. Powell, and G.M. Christenson, *Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research.* Public Health Rep, 1985. **100**(2): p. 126-31.

26. *Global recommendations on physical activity for health*, 2010, World Health Organisation: Geneva.

27. Lee, T.H., et al., *Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery.* Circulation, 1999. **100**(10): p. 1043-9.

28. McArdle WD, K.F., Katch VL, editors, *Essentials of Exercise Physiology: Energy Expenditure During Rest and Physical Activity*. 3rd ed2005: Lippincott Williams & Wilkins. 262-288.

29. Tipton, C.M., *Susruta of India, an unrecognized contributor to the history of exercise physiology.* J Appl Physiol (1985), 2008. **104**(6): p. 1553-6.

30. Hippocrates, *On Regimen in Acute Diseases*.

31. Berryman, J.W., *Motion and rest: Galen on exercise and health.* Lancet, 2012. **380**(9838): p. 210-211.

32. Morris, J.N., et al., *Coronary heart-disease and physical activity of work.* Lancet, 1953. **265**(6796): p. 1111-20; concl.

33. Morris, J.N. and M.D. Crawford, *Coronary heart disease and physical activity of work; evidence of a national necropsy survey.* Br Med J, 1958. **2**(5111): p. 1485-96.

34. Paffenbarger, R.S., et al., *Characteristics of longshoremen related fatal coronary heart disease and stroke.* Am J Public Health, 1971. **61**(7): p. 1362-70.

35. Paffenbarger, R.S., Jr., et al., *Physical activity, all-cause mortality, and longevity of college alumni.* N Engl J Med, 1986. **314**(10): p. 605-13.

36. Donaldson, P.T., *TNF gene polymorphisms in primary biliary cirrhosis: a critical appraisal.* J Hepatol, 1999. **31**(2): p. 366-8.

37. Hudson, M.M. and S.S. Donaldson, *Treatment of pediatric Hodgkin's lymphoma.* Semin Hematol, 1999. **36**(3): p. 313-23.

38. Hamer, M., et al., *Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study.* Circulation. **126**(8): p. 928-33.

39. Nocon, M., et al., *Association of physical activity with all-cause and cardiovascular mortality: a systematic review and meta-analysis.* Eur J Cardiovasc Prev Rehabil, 2008. **15**(3): p. 239-46.

40. Christensen, V.L., W.E. Donaldson, and K.E. Nestor, *Length of the plateau and pipping stages of incubation affects the physiology and survival of turkeys.* Br Poult Sci, 1999. **40**(2): p. 297-303.

41. Kohl, H.W., 3rd, et al., *The pandemic of physical inactivity: global action for public health.* Lancet. **380**(9838): p. 294-305.

42. Ng, S.W., E.C. Norton, and B.M. Popkin, *Why have physical activity levels declined among Chinese adults? Findings from the 1991-2006 China Health and Nutrition Surveys.* Soc Sci Med, 2009. **68**(7): p. 1305-14.

43. *Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention.* JAMA, 1996. **276**(7): p. 522.

44. Flynn, M.A., et al., *Reducing obesity and related chronic disease risk in children and youth: a synthesis of evidence with 'best practice' recommendations.* Obes Rev, 2006. **7 Suppl 1**: p. 7-66.

45. Lloyd-Jones, D., et al., *Heart disease and stroke statistics--2010 update: a report from the American Heart Association.* Circulation, 2010. **121**(7): p. e46-e215.

46. Leon, A.S., et al., *Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation.* Circulation, 2005. **111**(3): p. 369-76.

47. O'Connor, G.T., et al., *An overview of randomized trials of rehabilitation with exercise after myocardial infarction.* Circulation, 1989. **80**(2): p. 234-44.

48. Ribeiro, F., et al., *Exercise-based cardiac rehabilitation increases daily physical activity of patients following myocardial infarction: Subanalysis of two randomised controlled trials.* Physiotherapy.

49. Ayabe, M., et al., *The physical activity patterns of cardiac rehabilitation program participants.* J Cardiopulm Rehabil, 2004. **24**(2): p. 80-6.

50. Butler, L., et al., *Effects of a pedometer-based intervention on physical activity levels after cardiac rehabilitation: a randomized controlled trial.* J Cardiopulm Rehabil Prev, 2009. **29**(2): p. 105-14.

51. Wenger, N.K., et al., *Cardiac rehabilitation as secondary prevention. Agency for Health Care Policy and Research and National Heart, Lung, and Blood Institute.* Clin Pract Guidel Quick Ref Guide Clin, 1995(17): p. 1-23.

52. UK, D., *Diabetes Facts and Stats*, 2014.

53. WHO/IDF, *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia* 2006.

54. Sigal, R.J., et al., *Physical activity/exercise and type 2 diabetes.* Diabetes Care, 2004. **27**(10): p. 2518-39.

55. Mourier, A., et al., *Mobilization of visceral adipose tissue related to the improvement in insulin sensitivity in response to physical training in NIDDM. Effects of branched-chain amino acid supplements.* Diabetes Care, 1997. **20**(3): p. 385-91.

56. Colberg, S.R., et al., *Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement executive summary.* Diabetes Care, 2010. **33**(12): p. 2692-6.

57. Cauza, E., et al., *The relative benefits of endurance and strength training on the metabolic factors and muscle function of people with type 2 diabetes mellitus.* Arch Phys Med Rehabil, 2005. **86**(8): p. 1527-33.

58. Friedenreich, C.M. and M.R. Orenstein, *Physical activity and cancer prevention: etiologic evidence and biological mechanisms.* J Nutr, 2002. **132**(11 Suppl): p. 3456S-3464S.

59. Holmes, M.D., et al., *PHysical activity and survival after breast cancer diagnosis.* JAMA, 2005. **293**(20): p. 2479-2486.

60. Borer, K.T., *Physical activity in the prevention and amelioration of osteoporosis in women : interaction of mechanical, hormonal and dietary factors.* Sports Med, 2005. **35**(9): p. 779-830.

61. Teoman, N., A. Ozcan, and B. Acar, *The effect of exercise on physical fitness and quality of life in postmenopausal women.* Maturitas, 2004. **47**(1): p. 71-7.

62. Schonhofer, B., et al., *Evaluation of a movement detector to measure daily activity in patients with chronic lung disease.* Eur Respir J, 1997. **10**(12): p. 2814-9.

63. Bestall, J.C., et al., *Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease.* Thorax, 1999. **54**(7): p. 581-586.

64. Restrick, L.J., et al., *Assessment and follow up of patients prescribed long term oxygen treatment.* Thorax, 1993. **48**(7): p. 708-713.

65. Wegner, R.E., et al., *Factor analysis of exercise capacity, dyspnoea ratings and lung function in patients with severe COPD.* Eur Respir J, 1994. **7**(4): p. 725-9.

66. Garcia-Aymerich, J., et al., *Regular physical activity reduces hospital admission and mortality in chronic obstructive pulmonary disease: a population based cohort study.* Thorax, 2006. **61**(9): p. 772-778.

67. Garcia-Aymerich, J., et al., *Risk factors of readmission to hospital for a COPD exacerbation: a prospective study.* Thorax, 2003. **58**(2): p. 100-5.

68. *Pulmonary rehabilitation-1999. American Thoracic Society.* Am J Respir Crit Care Med, 1999. **159**(5 Pt 1): p. 1666-82.

69. Nici, L., et al., *American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation.* American Journal of Respiratory and Critical Care Medicine, 2006. **173**(12): p. 1390-1413.

70. Lacasse, Y., et al., *Meta-analysis of respiratory rehabilitation in chronic obstructive pulmonary disease. A Cochrane systematic review.* Europa medicophysica, 2007. **43**(4): p. 475-485.

71. Puhan, M., et al., *Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease.* Cochrane Database Syst Rev, 2009(1): p. CD005305.

72. Troosters, T., R. Gosselink, and M. Decramer, *Short- and long-term effects of outpatient rehabilitation in patients with chronic obstructive pulmonary disease: a randomized trial.* The American journal of medicine, 2000. **109**(3): p. 207-212.

73. Wijkstra, P.J., et al., *Long term benefits of rehabilitation at home on quality of life and exercise tolerance in patients with chronic obstructive pulmonary disease.* Thorax, 1995. **50**(8): p. 824-828.

74. Cindy Ng, L.W., et al., *Does exercise training change physical activity in people with COPD? A systematic review and meta-analysis.* Chron Respir Dis, 2012. **9**(1): p. 17-26.

75. Dallas, M.I., et al., *Using pedometers to monitor walking activity in outcome assessment for pulmonary rehabilitation.* Chron Respir Dis, 2009. **6**(4): p. 217-24.

76. Mador, M.J., A.N. Patel, and J. Nadler, *Effects of pulmonary rehabilitation on activity levels in patients with chronic obstructive pulmonary disease.* J Cardiopulm Rehabil Prev, 2011. **31**(1): p. 52-9.

77. Pitta, F., et al., *Are Patients With COPD More Active After Pulmonary Rehabilitation?* Chest, 2008. **134**(2): p. 273-280.

78. Demeyer, H., et al., *Standardizing the analysis of physical activity in patients with COPD following a pulmonary rehabilitation program.* Chest, 2014. **146**(2): p. 318-27.

79. Egan, C., et al., *Short term and long term effects of pulmonary rehabilitation on physical activity in COPD.* Respir Med, 2012. **106**(12): p. 1671-9.

80. Lokke, A., et al., *Developing COPD: a 25 year follow up study of the general population.* Thorax, 2006. **61**(11): p. 935-939.

81. O'Shaughnessy, T.C., et al., *Inflammation in bronchial biopsies of subjects with chronic bronchitis: inverse relationship of CD8+ T lymphocytes with FEV1.* Am J Respir Crit Care Med, 1997. **155**(3): p. 852-7.

82. Hogg, J.C., et al., *The nature of small-airway obstruction in chronic obstructive pulmonary disease.* N Engl J Med, 2004. **350**(26): p. 2645-53.

83. Kim, W.D., et al., *Centrilobular and panlobular emphysema in smokers. Two distinct morphologic and functional entities.* Am Rev Respir Dis, 1991. **144**(6): p. 1385-90.

84. O'Donnell, D.E., S.M. Revill, and K.A. Webb, *Dynamic Hyperinflation and Exercise Intolerance in Chronic Obstructive Pulmonary Disease.* Am. J. Respir. Crit. Care Med., 2001. **164**(5): p. 770-777.

85. O'Donnell, D.E. and C.M. Parker, *COPD exacerbations . 3: Pathophysiology.* Thorax, 2006. **61**(4): p. 354-61.

86. Retamales, I., et al., *Amplification of inflammation in emphysema and its association with latent adenoviral infection.* Am J Respir Crit Care Med, 2001. **164**(3): p. 469-73.

87. Russell, R.E., et al., *Alveolar macrophage-mediated elastolysis: roles of matrix metalloproteinases, cysteine, and serine proteases.* Am J Physiol Lung Cell Mol Physiol, 2002. **283**(4): p. L867-73.

88. Lacoste, J.Y., et al., *Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease.* J Allergy Clin Immunol, 1993. **92**(4): p. 537-48.

89. Repine, J.E., A. Bast, and I. Lankhorst, *Oxidative stress in chronic obstructive pulmonary disease. Oxidative Stress Study Group.* Am J Respir Crit Care Med, 1997. **156**(2 Pt 1): p. 341-57.

90. MacNee, W., *Oxidative stress and lung inflammation in airways disease.* Eur J Pharmacol, 2001. **429**(1-3): p. 195-207.

91. Barnes, P.J. and M. Karin, *Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases.* N Engl J Med, 1997. **336**(15): p. 1066-71.

92. Young, R.P., et al., *Functional variants of antioxidant genes in smokers with COPD and in those with normal lung function.* Thorax, 2006. **61**(5): p. 394-9.

93. Fletcher, C. and R. Peto, *The natural history of chronic airflow obstruction.* British Medical Journal, 1977. **1**(6077): p. 1645-1648.

94. Beerman, I., et al., *Functionally distinct hematopoietic stem cells modulate hematopoietic lineage potential during aging by a mechanism of clonal expansion.* Proc Natl Acad Sci U S A, 2010. **107**(12): p. 5465-70.

95. Saretzki, G. and T. Von Zglinicki, *Replicative aging, telomeres, and oxidative stress.* Ann N Y Acad Sci, 2002. **959**: p. 24-9.

96. Tsuji, T., K. Aoshiba, and A. Nagai, *Alveolar cell senescence in patients with pulmonary emphysema.* Am J Respir Crit Care Med, 2006. **174**(8): p. 886-93.

97. Lee, J., et al., *The relationship between telomere length and mortality in chronic obstructive pulmonary disease (COPD).* PLoS One, 2012. **7**(4): p. e35567.

98. Nyunoya, T., et al., *Cigarette smoke induces cellular senescence.* Am J Respir Cell Mol Biol, 2006. **35**(6): p. 681-8.

99. Yokohori, N., K. Aoshiba, and A. Nagai, *Increased levels of cell death and proliferation in alveolar wall cells in patients with pulmonary emphysema.* Chest, 2004. **125**(2): p. 626-32.

100. Alder, J.K., et al., *Telomere length is a determinant of emphysema susceptibility.* Am J Respir Crit Care Med, 2011. **184**(8): p. 904-12.

101. Sato, T., et al., *Senescence marker protein-30 protects mice lungs from oxidative stress, aging, and smoking.* Am J Respir Crit Care Med, 2006. **174**(5): p. 530-7.

102. Mori, T., et al., *Senescence marker protein-30 knockout mouse as a novel murine model of senile lung.* Pathol Int, 2004. **54**(3): p. 167-73.

103. Xiao, N.M., et al., *Klotho is a serum factor related to human aging.* Chin Med J (Engl), 2004. **117**(5): p. 742-7.

104. Utsugi, T., et al., *Decreased insulin production and increased insulin sensitivity in the klotho mutant mouse, a novel animal model for human aging.* Metabolism, 2000. **49**(9): p. 1118-23.

105. Suga, T., et al., *Disruption of the klotho gene causes pulmonary emphysema in mice. Defect in maintenance of pulmonary integrity during postnatal life.* Am J Respir Cell Mol Biol, 2000. **22**(1): p. 26-33.

106. Nagai, R., et al., *Endothelial dysfunction in the klotho mouse and downregulation of klotho gene expression in various animal models of vascular and metabolic diseases.* Cell Mol Life Sci, 2000. **57**(5): p. 738-46.

107. Mori, K., et al., *Disruption of klotho gene causes an abnormal energy homeostasis in mice.* Biochem Biophys Res Commun, 2000. **278**(3): p. 665-70.

108. Imai, K., et al., *Correlation of lung surface area to apoptosis and proliferation in human emphysema.* Eur Respir J, 2005. **25**(2): p. 250-8.

109. Chen, Z.H., et al., *Egr-1 regulates autophagy in cigarette smoke-induced chronic obstructive pulmonary disease.* PLoS One, 2008. **3**(10): p. e3316.

110. Ryter, S.W., et al., *Deadly triplex: smoke, autophagy and apoptosis.* Autophagy, 2011. **7**(4): p. 436-7.

111. Fabbri, L.M. and K.F. Rabe, *From COPD to chronic systemic inflammatory syndrome?* Lancet, 2007. **370**(9589): p. 797-9.

112. Watz, H., et al., *Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study.* Am J Respir Crit Care Med, 2008. **177**(7): p. 743-51.

113. Celli, B.R., et al., *The Body-Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity Index in Chronic Obstructive Pulmonary Disease.* N Engl J Med, 2004. **350**(10): p. 1005-1012.

114. Swallow, E.B., et al., *Quadriceps strength predicts mortality in patients with moderate to severe chronic obstructive pulmonary disease.* Thorax, 2007. **62**(2): p. 115-20.

115. Waschki, B., et al., *Physical activity is the strongest predictor of all-cause mortality in patients with COPD: a prospective cohort study.* Chest, 2011. **140**(2): p. 331-42.

116. Gosselink, R., T. Troosters, and M. Decramer, *Peripheral muscle weakness contributes to exercise limitation in COPD.* Am J Respir Crit Care Med, 1996. **153**(3): p. 976-80.

117. Decramer, M., et al., *Muscle weakness is related to utilization of health care resources in COPD patients.* Eur Resp J, 1997. **10**: p. 417-23.

118. Killian, K.J., et al., *Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation.* Am Rev Respir Dis, 1992. **146**(4): p. 935-40.

119. Bernard, S., et al., *Peripheral muscle weakness in patients with chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1998. **158**(2): p. 629-34.

120. Man, W.D., et al., *Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2003. **168**(5): p. 562-7.

121. Swallow, E.B., et al., *A novel technique for nonvolitional assessment of quadriceps muscle endurance in humans.* J Appl Physiol, 2007. **103**(3): p. 739-46.

122. Van't Hul, A., et al., *Quadriceps muscle endurance in patients with chronic obstructive pulmonary disease.* Muscle Nerve, 2004. **29**(2): p. 267-74.

123. Seymour, J.M., et al., *The prevalence of quadriceps weakness in COPD and the relationship with disease severity.* Eur Respir J, 2010. **36**(1): p. 81-88.

124. Shrikrishna, D., et al., *Quadriceps wasting and physical inactivity in patients with COPD.* Eur Respir J, 2012. **40**(5): p. 1115-22.

125. Gosker, H.R., et al., *Muscle fibre type shifting in the vastus lateralis of patients with COPD is associated with disease severity: a systematic review and meta-analysis.* Thorax, 2007. **62**(11): p. 944-9.

126. Gosker, H.R., et al., *Muscle fiber type IIX atrophy is involved in the loss of fat-free mass in chronic obstructive pulmonary disease.* Am J Clin Nutr, 2002. **76**(1): p. 113-119.

127. Man, W.D.C., et al., *Non-volitional assessment of skeletal muscle strength in patients with chronic obstructive pulmonary disease.* Thorax, 2003. **58**(8): p. 665-669.

128. Man, W.D., et al., *Abdominal muscle and quadriceps strength in chronic obstructive pulmonary disease.* Thorax, 2005. **60**(9): p. 718-22.

129. Polkey, M.I., et al., *Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD.* Am J Respir Crit Care Med, 1995. **152**(3): p. 959-64.

130. Polkey, M.I., et al., *Influence of acute lung volume change on contractile properties of human diaphragm.* J Appl Physiol, 1998. **85**(4): p. 1322-8.

131. Stubbings, A.K., et al., *Physiological properties of human diaphragm muscle fibres and the effect of chronic obstructive pulmonary disease.* J Physiol, 2008. **586**(10): p. 2637-2650.

132. Donaldson, M.J., et al., *XR3054, structurally related to limonene, is a novel inhibitor of farnesyl protein transferase.* Eur J Cancer, 1999. **35**(6): p. 1014-9.

133. Williams, T.J., et al., *Maximal exercise testing in single and double lung transplant recipients.* Am Rev Respir Dis, 1992. **145**(1): p. 101-5.

134. Griffiths, T.L., et al., *Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial.* Lancet, 2000. **355**(9201): p. 362-8.

135. Schols, A.M., et al., *Body composition and mortality in chronic obstructive pulmonary disease.* Am J Clin Nutr, 2005. **82**(1): p. 53-59.

136. Schols, A.M., *Pulmonary cachexia.* Int J Cardiol, 2002. **85**(1): p. 101-10.

137. Congleton, J., *The pulmonary cachexia syndrome: aspects of energy balance.* Proc Nutr Soc, 1999. **58**(2): p. 321-8.

138. Anthonisen, N.R., et al., *Hospitalizations and mortality in the Lung Health Study.* Am J Respir Crit Care Med, 2002. **166**(3): p. 333-9.

139. Vestbo, J., *The TORCH (towards a revolution in COPD health) survival study protocol.* Eur Respir J, 2004. **24**(2): p. 206-10.

140. McGarvey, L.P., et al., *Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee.* Thorax, 2007. **62**(5): p. 411-415.

141. Donaldson, G.C., et al., *Increased Risk of Myocardial Infarction and Stroke Following Exacerbation of COPD.* Chest, 2010. **137**(5): p. 1091-1097.

142. Chang, C.L., et al., *Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD.* Thorax. **66**(9): p. 764-8.

143. Ross, R., *Atherosclerosis--an inflammatory disease.* N Engl J Med, 1999. **340**(2): p. 115-26.

144. Maclay, J.D., et al., *Increased platelet activation in patients with stable and acute exacerbation of COPD.* Thorax. **66**(9): p. 769-74.

145. Duvoix, A., et al., *Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease.* Thorax.

146. Stec, J.J., et al., *Association of fibrinogen with cardiovascular risk factors and cardiovascular disease in the Framingham Offspring Population.* Circulation, 2000. **102**(14): p. 1634-8.

147. Maclay, J.D., et al., *Vascular dysfunction in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2009. **180**(6): p. 513-20.

148. Patel, A.R., et al., *Cardiovascular risk, myocardial injury, and exacerbations of chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2013. **188**(9): p. 1091-9.

149. Barr, R.G., et al., *Percent Emphysema, Airflow Obstruction, and Impaired Left Ventricular Filling.* N Engl J Med, 2010. **362**(3): p. 217-227.

150. Watz, H., et al., *Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation.* Chest. **138**(1): p. 32-8.

151. Sutherland, J.P., B. McKinley, and R.H. Eckel, *The metabolic syndrome and inflammation.* Metab Syndr Relat Disord, 2004. **2**(2): p. 82-104.

152. Onat, A., et al., *Apolipoprotein C-III, a strong discriminant of coronary risk in men and a determinant of the metabolic syndrome in both genders.* Atherosclerosis, 2003. **168**(1): p. 81-9.

153. Bolton, C.E., et al., *Insulin Resistance and inflammation—A Further Systemic Complication of COPD.* COPD: Journal of Chronic Obstructive Pulmonary Disease, 2007. **4**(2): p. 121 - 126.

154. Genant, H.K., et al., *Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis.* Osteoporos Int, 1999. **10**(4): p. 259-64.

155. Ionescu, A.A. and E. Schoon, *Osteoporosis in chronic obstructive pulmonary disease.* Eur Respir J Suppl, 2003. **46**: p. 64s-75s.

156. O'Donnell, D.E., et al., *Reliability of ventilatory parameters during cycle ergometry in multicentre trials in COPD.* Eur Respir J, 2009. **34**(4): p. 866-74.

157. Jones, P.W., *Health status measurement in chronic obstructive pulmonary disease.* Thorax, 2001. **56**(11): p. 880-7.

158. Pinto-Plata, V.M., et al., *The 6-min walk distance: change over time and value as a predictor of survival in severe COPD.* Eur Respir J, 2004. **23**(1): p. 28-33.

159. Oga, T., et al., *Analysis of the Factors Related to Mortality in Chronic Obstructive Pulmonary Disease: Role of Exercise Capacity and Health Status.* Am. J. Respir. Crit. Care Med., 2003. **167**(4): p. 544-549.

160. Tzani, P., et al., *Dynamic hyperinflation is associated with a poor cardiovascular response to exercise in COPD patients.* Respir Res, 2011. **12**: p. 150.

161. Maltais, F., et al., *Metabolic and hemodynamic responses of lower limb during exercise in patients with COPD.* J Appl Physiol, 1998. **84**(5): p. 1573-80.

162. Potter, W.A., S. Olafsson, and R.E. Hyatt, *Ventilatory mechanics and expiratory flow limitation during exercise in patients with obstructive lung disease.* J Clin Invest, 1971. **50**(4): p. 910-9.

163. Hyatt, R.E., *Expiratory flow limitation.* J Appl Physiol, 1983. **55**(1 Pt 1): p. 1-7.

164. Koulouris, N.G., et al., *A simple method to detect expiratory flow limitation during spontaneous breathing.* Eur Respir J, 1995. **8**(2): p. 306-13.

165. Leaver, D.G. and N.B. Pride, *Flow-volume curves and expiratory pressures during exercise in patients with chronic airways obstruction.* Scand J Respir Dis Suppl, 1971. **77**: p. 23-7.

166. Diaz, O., et al., *Breathing pattern and gas exchange at peak exercise in COPD patients with and without tidal flow limitation at rest.* Eur Respir J, 2001. **17**(6): p. 1120-7.

167. O'Donnell, D.E., S.M. Revill, and K.A. Webb, *Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 2001. **164**(5): p. 770-7.

168. Polkey, M.I., et al., *Diaphragm strength in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1996. **154**(5): p. 1310-7.

169. Barbera, J.A., et al., *Gas exchange during exercise in mild chronic obstructive pulmonary disease. Correlation with lung structure.* Am Rev Respir Dis, 1991. **144**(3 Pt 1): p. 520-5.

170. Dantzker, D.R. and G.E. D'Alonzo, *The effect of exercise on pulmonary gas exchange in patients with severe chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1986. **134**(6): p. 1135-9.

171. O'Donnell, D.E., et al., *Exercise hypercapnia in advanced chronic obstructive pulmonary disease: the role of lung hyperinflation.* Am J Respir Crit Care Med, 2002. **166**(5): p. 663-8.

172. Loring, S.H., M. Garcia-Jacques, and A. Malhotra, *Pulmonary characteristics in COPD and mechanisms of increased work of breathing.* J Appl Physiol, 2009. **107**(1): p. 309-14.

173. Christensen, C.C., et al., *Relationship between exercise desaturation and pulmonary haemodynamics in COPD patients.* Eur Respir J, 2004. **24**(4): p. 580-6.

174. Agusti, A.G., et al., *Systemic effects of chronic obstructive pulmonary disease.* Eur Respir J, 2003. **21**(2): p. 347-60.

175. Vonk-Noordegraaf, A., et al., *Early changes of cardiac structure and function in COPD patients with mild hypoxemia.* Chest, 2005. **127**(6): p. 1898-903.

176. Morrison, D.A., et al., *Right ventricular dysfunction and the exercise limitation of chronic obstructive pulmonary disease.* J Am Coll Cardiol, 1987. **9**(6): p. 1219-29.

177. Jorgensen, K., et al., *Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study.* Chest, 2007. **131**(4): p. 1050-7.

178. Sin, D.D. and S.F. Man, *Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality.* Proc Am Thorac Soc, 2005. **2**(1): p. 8-11.

179. Alvarez, F., et al., *International Autoimmune Hepatitis Group Report: review of criteria for diagnosis of autoimmune hepatitis.* J Hepatol, 1999. **31**(5): p. 929-38.

180. Bloomfield, S.A., *Changes in musculoskeletal structure and function with prolonged bed rest.* Med Sci Sports Exerc, 1997. **29**(2): p. 197-206.

181. McGrother, C.W. and M.M. Donaldson, *Changing perceptions in osteoporosis. Several risk factors are important.* BMJ, 1999. **319**(7221): p. 1371; author reply 1372.

182. Dipietro, L., et al., *A survey for assessing physical activity among older adults.* Med Sci Sports Exerc, 1993. **25**(5): p. 628-42.

183. Stewart, A.L., et al., *CHAMPS physical activity questionnaire for older adults: outcomes for interventions.* Med Sci Sports Exerc, 2001. **33**(7): p. 1126-41.

184. Christensen, V.L., et al., *Supplemental oxygen affects plasma insulin-like growth factors in embryos from selected lines of turkeys.* Poult Sci, 1999. **78**(11): p. 1606-10.

185. Christensen, V.L., W.E. Donaldson, and K.E. Nestor, *Effect of supplemental oxygen on blood plasma organic acids within embryos from selected lines of turkeys.* Poult Sci, 1999. **78**(11): p. 1601-5.

186. Ainsworth, B.E., et al., *Accuracy of the College Alumnus Physical Activity Questionnaire.* J Clin Epidemiol, 1993. **46**(12): p. 1403-11.

187. LaPorte, R.E., et al., *An objective measure of physical activity for epidemiologic research.* Am J Epidemiol, 1979. **109**(2): p. 158-68.

188. Philippaerts, R.M., K.R. Westerterp, and J. Lefevre, *Doubly labelled water validation of three physical activity questionnaires.* Int J Sports Med, 1999. **20**(5): p. 284-9.

189. McDermott, M.M., et al., *Measuring physical activity in peripheral arterial disease: a comparison of two physical activity questionnaires with an accelerometer.* Angiology, 2000. **51**(2): p. 91-100.

190. Shephard, R.J., *Limits to the measurement of habitual physical activity by questionnaires.* Br J Sports Med, 2003. **37**(3): p. 197-206; discussion 206.

191. van Poppel, M.N., et al., *Physical activity questionnaires for adults: a systematic review of measurement properties.* Sports Med, 2010. **40**(7): p. 565-600.

192. Bouten, C.V., et al., *Effects of placement and orientation of body-fixed accelerometers on the assessment of energy expenditure during walking.* Med Biol Eng Comput, 1997. **35**(1): p. 50-6.

193. Fehling, P.C., et al., *Comparison of accelerometers with oxygen consumption in older adults during exercise.* Med Sci Sports Exerc, 1999. **31**(1): p. 171-5.

194. Jakicic, J.M., et al., *The accuracy of the TriTrac-R3D accelerometer to estimate energy expenditure.* Med Sci Sports Exerc, 1999. **31**(5): p. 747-54.

195. Brouha, L., *Evaluation of requirements of jobs*, in *Physiology in industry*1960, Pergamon Press: Oxford. p. pp. 94-108.

196. Reswick, J., *Preliminary evaluation of the vertical acceleratin gait analyzer' (VAGA).* , in *Prec. 6th Ann. Syrup. on External Control Extremities*1978: Dubrovnik, Yugoslavia. p. pp. 305-314.

197. Welle, S., *Metabolic responses to a meal during rest and low-intensity exercise.* Am J Clin Nutr, 1984. **40**(5): p. 990-4.

198. Weir, J.B., *New methods for calculating metabolic rate with special reference to protein metabolism.* J Physiol, 1949. **109**(1-2): p. 1-9.

199. Harris J, B.F., *A biometric study of basal metabolism in man*, 1919, Carnigie Institute of Washington: Washington DC.

200. Schols, A.M., et al., *Resting energy expenditure in patients with chronic obstructive pulmonary disease.* Am J Clin Nutr, 1991. **54**(6): p. 983-7.

201. Goldstein, S., et al., *Energy expenditure in patients with chronic obstructive pulmonary disease.* Chest, 1987. **91**(2): p. 222-4.

202. Andreas, S., et al., *Neurohumoral activation as a link to systemic manifestations of chronic lung disease.* Chest, 2005. **128**(5): p. 3618-24.

203. Sauleda, J., et al., *Cytochrome Oxidase Activity and Mitochondrial Gene Expression in Skeletal Muscle of Patients with Chronic Obstructive Pulmonary Disease.* Am. J. Respir. Crit. Care Med., 1998. **157**(5): p. 1413-1417.

204. Richardson, R.S., et al., *Reduced mechanical efficiency in chronic obstructive pulmonary disease but normal peak VO2 with small muscle mass exercise.* Am J Respir Crit Care Med, 2004. **169**(1): p. 89-96.

205. Donahoe, M., et al., *Oxygen consumption of the respiratory muscles in normal and in malnourished patients with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1989. **140**(2): p. 385-91.

206. Essen, B., et al., *Metabolic characteristics of fibre types in human skeletal muscle.* Acta Physiol Scand, 1975. **95**(2): p. 153-65.

207. Sridhar, M.K., *Why do patients with emphysema lose weight?* Lancet, 1995. **345**(8959): p. 1190-1.

208. Nguyen, L.T., et al., *Increased resting energy expenditure is related to plasma TNF-alpha concentration in stable COPD patients.* Clin Nutr, 1999. **18**(5): p. 269-74.

209. Dulloo, A.G. and D.S. Miller, *The thermogenic properties of ephedrine/methylxanthine mixtures: human studies.* Int J Obes, 1986. **10**(6): p. 467-81.

210. Vaisman, N., et al., *Effect of salbutamol on resting energy expenditure in patients with cystic fibrosis.* J Pediatr, 1987. **111**(1): p. 137-9.

211. Marrugat J, V.J., Pavesi M, Sanz F, *Estimación del tamaño de la muestra en la investigación clīnica y epidemiológica* Med Clin(Barc), 1998. **111**: p. 267-276.

212. *ATS/ACCP Statement on Cardiopulmonary Exercise Testing.* American Journal of Respiratory and Critical Care Medicine, 2003. **167**(2): p. 211-277.

213. Cekici, L., et al., *Short-term effects of inhaled salbutamol on autonomic cardiovascular control in healthy subjects: a placebo-controlled study.* Br J Clin Pharmacol, 2009. **67**(4): p. 394-402.

214. Donaldson, B., *Choosing the road less traveled. Interview by Marlene Jezierski.* J Emerg Nurs, 1999. **25**(3): p. 251-4.

215. Maltais, F., et al., *Oxidative capacity of the skeletal muscle and lactic acid kinetics during exercise in normal subjects and in patients with COPD.* Am J Respir Crit Care Med, 1996. **153**(1): p. 288-93.

216. Singh, S.J., et al., *Development of a shuttle walking test of disability in patients with chronic airways obstruction.* Thorax, 1992. **47**(12): p. 1019-24.

217. Singh, S.J., et al., *Minimum clinically important improvement for the incremental shuttle walking test.* Thorax, 2008. **63**(9): p. 775-777.

218. *ATS Statement: Guidelines for the Six-Minute Walk Test.* Am. J. Respir. Crit. Care Med., 2002. **166**(1): p. 111-117.

219. Meisel, J.A., et al., *Significance and management of computed tomography detected pulmonary nodules: a report from the National Wilms Tumor Study Group.* Int J Radiat Oncol Biol Phys, 1999. **44**(3): p. 579-85.

220. Guyatt, G.H., et al., *The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure.* Can Med Assoc J, 1985. **132**(8): p. 919-923.

221. Polkey, M.I., et al., *Six-Minute-Walk Test in Chronic Obstructive Pulmonary Disease.* American Journal of Respiratory and Critical Care Medicine, 2013. **187**(4): p. 382-386.

222. Sperandio, E.F., et al., *Intensity and physiological responses to the 6-minute walk test in middle-aged and older adults: a comparison with cardiopulmonary exercise testing.* Braz J Med Biol Res, 2015. **48**(4): p. 349-53.

223. Singh, S.J., et al., *Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation.* Eur Respir J, 1994. **7**(11): p. 2016-20.

224. Eliason, G., et al., *Physical activity patterns in patients in different stages of chronic obstructive pulmonary disease.* COPD. **8**(5): p. 369-74.

225. van Gestel, A.J., et al., *Predicting daily physical activity in patients with chronic obstructive pulmonary disease.* PLoS One. **7**(11): p. e48081.

226. Baranowski, T., C. Anderson, and C. Carmack, *Mediating variable framework in physical activity interventions. How are we doing? How might we do better?* Am J Prev Med, 1998. **15**(4): p. 266-97.

227. Marcus, B.H., et al., *Efficacy of an individualized, motivationally-tailored physical activity intervention.* Ann Behav Med, 1998. **20**(3): p. 174-80.

228. Sherwood, N.E. and R.W. Jeffery, *The behavioral determinants of exercise: implications for physical activity interventions.* Annu Rev Nutr, 2000. **20**: p. 21-44.

229. Pennington, M.W., et al., *Role of disulfide bonds in the structure and potassium channel blocking activity of ShK toxin.* Biochemistry, 1999. **38**(44): p. 14549-58.

230. Dasan, S., et al., *Treatment of persistent pruritus ani in a combined colorectal and dermatological clinic.* Br J Surg, 1999. **86**(10): p. 1337-40.

231. Chinn, D.J., et al., *Barriers to physical activity and socioeconomic position: implications for health promotion.* J Epidemiol Community Health, 1999. **53**(3): p. 191-2.

232. Seefeldt, V., R.M. Malina, and M.A. Clark, *Factors affecting levels of physical activity in adults.* Sports Med, 2002. **32**(3): p. 143-68.

233. Sun, F., I.J. Norman, and A.E. While, *Physical activity in older people: a systematic review.* BMC Public Health, 2013. **13**: p. 449.

234. McIntosh, E., C. Donaldson, and M. Ryan, *Recent advances in the methods of cost-benefit analysis in healthcare. Matching the art to the science.* Pharmacoeconomics, 1999. **15**(4): p. 357-67.

235. Tucker, P. and J. Gilliland, *The effect of season and weather on physical activity: a systematic review.* Public Health, 2007. **121**(12): p. 909-22.

236. Haggarty, P., et al., *The influence of exercise on the energy requirements of adult males in the UK.* Br J Nutr, 1994. **72**(6): p. 799-813.

237. Baranowski, T., et al., *Observations on physical activity in physical locations: age, gender, ethnicity, and month effects.* Res Q Exerc Sport, 1993. **64**(2): p. 127-33.

238. Badland, H.M., et al., *Seasonality in physical activity: should this be a concern in all settings?* Health Place, 2011. **17**(5): p. 1084-9.

239. O'Shea, S.D., N.F. Taylor, and J.D. Paratz, *. . . But watch out for the weather: factors affecting adherence to progressive resistance exercise for persons with COPD.* J Cardiopulm Rehabil Prev, 2007. **27**(3): p. 166-74; quiz 175-6.

240. Donaldson, L.F., *Unilateral arthritis: contralateral effects.* Trends Neurosci, 1999. **22**(11): p. 495-6.

241. Sewell, L., et al., *Seasonal variations affect physical activity and pulmonary rehabilitation outcomes.* J Cardiopulm Rehabil Prev. **30**(5): p. 329-33.

242. Van Remoortel, H., et al., *Validity of activity monitors in health and chronic disease: a systematic review.* Int J Behav Nutr Phys Act, 2012. **9**: p. 84.

243. Gimeno-Santos, E., et al., *Determinants and outcomes of physical activity in patients with COPD: a systematic review.* Thorax, 2014. **69**(8): p. 731-9.

244. Dobbels, F., et al., *The PROactive innovative conceptual framework on physical activity.* Eur Respir J, 2014. **44**(5): p. 1223-33.

245. Gimeno-Santos, E., et al., *The PROactive instruments to measure physical activity in patients with chronic obstructive pulmonary disease.* Eur Respir J, 2015. **46**(4): p. 988-1000.

246. Rabe, K.F., 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**(6): p. 532-555.

247. Newton, R.L., Jr., et al., *Pedometer determined physical activity tracks in African American adults: the Jackson Heart Study.* Int J Behav Nutr Phys Act. **9**: p. 44.

248. Cotes, J.E., et al., *Standardization of the measurement of transfer factor (diffusing capacity). Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society.* Eur Respir J Suppl, 1993. **16**: p. 41-52.

249. Quanjer, P.H., et al., *Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society.* Eur Respir J Suppl, 1993. **16**: p. 5-40.

250. Miller, M.R., et al., *Standardisation of spirometry.* Eur Respir J, 2005. **26**(2): p. 319-338.

251. Mathur, R.S., et al., *Comparison of peak oxygen consumption during cycle and treadmill exercise in severe chronic obstructive pulmonary disease.* Thorax, 1995. **50**(8): p. 829-33.

252. Vermeeren, M.A., A.M. Schols, and E.F. Wouters, *Effects of an acute exacerbation on nutritional and metabolic profile of patients with COPD.* Eur Respir J, 1997. **10**(10): p. 2264-9.

253. Edwards, R.H., et al., *Human skeletal muscle function: description of tests and normal values.* Clin Sci Mol Med, 1977. **52**(3): p. 283-90.

254. Lukaski, H.C., et al., *Assessment of fat-free mass using bioelectrical impedance measurements of the human body.* The American Journal of Clinical Nutrition, 1985. **41**(4): p. 810-817.

255. Troosters, T., R. Gosselink, and M. Decramer, *Pulmonary rehabilitation in patients with severe chronic obstructive pulmonary disease.* Monaldi Arch Chest Dis, 1999. **54**(6): p. 510-3.

256. Reinsmoen, N.L., et al., *Impact of transfusions and acute rejection on posttransplantation donor antigen-specific responses in two study populations. Cooperative Clinical Trial in Transplantation Research Group.* Transplantation, 1999. **67**(5): p. 697-702.

257. Schunemann, H.J., et al., *Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ).* COPD, 2005. **2**(1): p. 81-9.

258. Jones, P.W., et al., *A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire.* Am Rev Respir Dis, 1992. **145**(6): p. 1321-7.

259. Donaldson, V. and C. Donaldson, *EMS hero commits suicide.* JEMS, 1999. **24**(3): p. 94-100, 103, 105.

260. Jones, P.W., et al., *Development and first validation of the COPD Assessment Test.* Eur Respir J, 2009. **34**(3): p. 648-654.

261. Wren, C., S. Richmond, and L. Donaldson, *Presentation of congenital heart disease in infancy: implications for routine examination.* Arch Dis Child Fetal Neonatal Ed, 1999. **80**(1): p. F49-53.

262. Seifer, F.D., et al., *Pulmonary rehabilitation: Sisyphus or Odysseus?* Chest, 1999. **115**(2): p. 311-3.

263. Bouten, C.V., et al., *A triaxial accelerometer and portable data processing unit for the assessment of daily physical activity.* IEEE Trans Biomed Eng, 1997. **44**: p. 136 - 147.

264. Van Remoortel H & Giavedoni S, R.R., Raste Y, Louvaris Z, Langer D, Burtin C, Glendenning A, Hopkinson NS, Vogiatzis I, Peterson BT, Wilson F, Mann B, Gimeno E & Troosters T, *Validity of Activity Monitors in Health and Chronic Disease:A Systematic Review*, in *International Journal of Behavioural Nutrition and Physical Activity (submitted for publication)*2012.

265. Annegarn, J., et al., *Problematic activities of daily life are weakly associated with clinical characteristics in COPD.* J Am Med Dir Assoc. **13**(3): p. 284-90.

266. Bland JM, A.D., *Statistical methods for assessing agreement between two methods of clinical measurement.* Lancet, 1986. **327**: p. 307-10.

267. Behnke, M., et al., *Home-based exercise is capable of preserving hospital-based improvements in severe chronic obstructive pulmonary disease.* Respiratory Medicine, 2000. **94**(12): p. 1184-1191.

268. Hernandes, N.A., et al., *Profile of the level of physical activity in the daily lives of patients with COPD in Brazil.* J Bras Pneumol, 2009. **35**(10): p. 949-56.

269. Langer, D., et al., *Validation of two activity monitors in patients with COPD.* Thorax, 2009. **64**(7): p. 641-642.

270. Patel, S.A., et al., *Activity Monitoring and Energy Expenditure in COPD Patients: A Validation Study.* COPD: Journal of Chronic Obstructive Pulmonary Disease, 2007. **4**(2): p. 107-112.

271. Cavalheri V, D.L., Ferreira T, FInatti M, Camillo CA, et al, *Energy expenditure during daily activities as measured by two motion sensors in patients with COPD.* Respiratory Medicine 2011. **105**: p. 922-929.

272. Hill, K., et al., *Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease.* Thorax, 2010. **65**(6): p. 486-491.

273. Abel, M.G., et al., *Validation of the Kenz Lifecorder EX and ActiGraph GT1M accelerometers for walking and running in adults.* Appl Physiol Nutr Metab, 2008. **33**(6): p. 1155-64.

274. Chen, K.Y., et al., *Predicting energy expenditure of physical activity using hip- and wrist-worn accelerometers.* Diabetes Technol Ther, 2003. **5**(6): p. 1023-33.

275. Crouter, S.E., J.R. Churilla, and D.R. Bassett, Jr., *Estimating energy expenditure using accelerometers.* Eur J Appl Physiol, 2006. **98**(6): p. 601-12.

276. Rothney, M.P., et al., *Validity of physical activity intensity predictions by ActiGraph, Actical, and RT3 accelerometers.* Obesity (Silver Spring), 2008. **16**(8): p. 1946-52.

277. Harrison, S.L., et al., *Physical activity monitoring: addressing the difficulties of accurately detecting slow walking speeds.* Heart Lung, 2013. **42**(5): p. 361-4 e1.

278. Baarends, E.M., et al., *Total daily energy expenditure relative to resting energy expenditure in clinically stable patients with COPD.* Thorax, 1997. **52**(9): p. 780-5.

279. Baarends, E.M., et al., *Decreased mechanical efficiency in clinically stable patients with COPD.* Thorax, 1997. **52**(11): p. 981-6.

280. Hoydal, K.L., et al., *Patients with coronary artery- or chronic obstructive pulmonary disease walk with mechanical inefficiency.* Scand Cardiovasc J, 2007. **41**(6): p. 405-10.

281. McClain, J.J., S.B. Sisson, and C. Tudor-Locke, *Actigraph accelerometer interinstrument reliability during free-living in adults.* Med Sci Sports Exerc, 2007. **39**(9): p. 1509-14.

282. McClain, J.J., et al., *Comparison of Lifecorder EX and ActiGraph accelerometers under free-living conditions.* Appl Physiol Nutr Metab, 2007. **32**(4): p. 753-61.

283. Reneman, M. and M. Helmus, *Interinstrument reliability of the RT3 accelerometer.* Int J Rehabil Res, 2010. **33**(2): p. 178-9.

284. Gironda, R.J., et al., *Preliminary evaluation of reliability and criterion validity of Actiwatch-Score.* J Rehabil Res Dev, 2007. **44**(2): p. 223-30.

285. Brazeau, A.S., et al., *Test-retest reliability of a portable monitor to assess energy expenditure.* Appl Physiol Nutr Metab, 2011. **36**(3): p. 339-43.

286. Hartmann, A., et al., *Concurrent validity of a trunk tri-axial accelerometer system for gait analysis in older adults.* Gait Posture, 2009. **29**(3): p. 444-8.

287. Schoeller, D.A., *Measurement of energy expenditure in free-living humans by using doubly labeled water.* J Nutr, 1988. **118**(11): p. 1278-89.

288. Schoeller, D.A. and J.M. Hnilicka, *Reliability of the doubly labeled water method for the measurement of total daily energy expenditure in free-living subjects.* J Nutr, 1996. **126**(1): p. 348S-354S.

289. Atallah, L., et al., *Validation of an ear-worn sensor for gait monitoring using a force-plate instrumented treadmill.* Gait Posture, 2011. **35**(4): p. 674-6.

290. Atallah, L., et al., *Energy expenditure prediction using a miniaturized ear-worn sensor.* Med Sci Sports Exerc. **43**(7): p. 1369-77.

291. King, R.C. *Body Sensor Networks for Monitoring Rowing Technique*. in *Wearable and Implantable Body Sensor Networks, International Workshop on, Wearable and Implantable Body Sensor Networks, International Workshop on 2009*. 2009.

292. Julien Pansiot, B.L.a.G.-Z.Y. *Swimming Stroke Kinematic Analysis with BSN*. in *2010 International Conference on Body Sensor Networks (BSN 2010)*. June 2010. Singapore.

293. Atallah, L., et al., *Validation of an ear-worn sensor for gait monitoring using a force-plate instrumented treadmill.* Gait Posture, 2012. **35**(4): p. 674-6.

294. Atallah, L., et al., *An ear-worn sensor for the detection of gait impairment after abdominal surgery.* Surg Innov, 2013. **20**(1): p. 86-94.

295. Atallah, L., et al., *Gait asymmetry detection in older adults using a light ear-worn sensor.* Physiol Meas, 2014. **35**(5): p. N29-40.

296. Wieboldt, J., et al., *Effect of acute exacerbations on skeletal muscle strength and physical activity in cystic fibrosis.* J Cyst Fibros, 2012. **11**(3): p. 209-15.

297. Atallah, L., *Validation Of An Ear Worn Sensor For Activity Monitoring In COPD.* American journal of respiratory and critical care medicine, 2010. **181**: p. A1211.

298. Westerterp, K.R., L. Wouters, and W.D. van Marken Lichtenbelt, *The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water.* Obes Res, 1995. **3 Suppl 1**: p. 49-57.

299. Westerterp, K.R., *Diet induced thermogenesis.* Nutr Metab (Lond), 2004. **1**(1): p. 5.

300. van Marken Lichtenbelt, W.D., K.R. Westerterp, and L. Wouters, *Deuterium dilution as a method for determining total body water: effect of test protocol and sampling time.* Br J Nutr, 1994. **72**(4): p. 491-7.

301. Schoeller, D.A., et al., *Total body water measurement in humans with 18O and 2H labeled water.* Am J Clin Nutr, 1980. **33**(12): p. 2686-93.

302. Watz, H., et al., *Physical activity in patients with COPD.* Eur Respir J, 2009. **33**(2): p. 262-272.

303. Fukuba, Y., S. Usui, and H. Takahashi, *Effects of anticipation, prior-exercise, and breathing frequency to ventilatory response during step exercise: a preliminary study.* J Hum Ergol (Tokyo), 1992. **21**(2): p. 183-9.

304. Webster, J.D., et al., *Description of a human direct calorimeter, with a note on the energy cost of clerical work.* Br J Nutr, 1986. **55**(1): p. 1-6.

305. Snellen, J.W., *An improved estimation of mean body temperature using combined direct calorimetry and thermometry.* Eur J Appl Physiol, 2000. **82**(3): p. 188-96.

306. Snellen, J.W., K.S. Chang, and W. Smith, *Technical description and performance characteristics of a human whole-body calorimeter.* Med Biol Eng Comput, 1983. **21**(1): p. 9-20.

307. Rabinovich, R.A., et al., *Validity of physical activity monitors during daily life in patients with COPD.* Eur Respir J, 2013. **42**(5): p. 1205-15.

308. Sergi, G., et al., *Body composition and resting energy expenditure in elderly male patients with chronic obstructive pulmonary disease.* Respiratory Medicine, 2006. **100**(11): p. 1918-1924.

309. Engelen, M.P., et al., *Nutritional depletion in relation to respiratory and peripheral skeletal muscle function in out-patients with COPD.* Eur Respir J, 1994. **7**(10): p. 1793-7.

310. Moy, M.L., et al., *Daily step counts in a US cohort with COPD.* Respir Med, 2012. **106**(7): p. 962-9.

311. Agarwal, V., et al., *Longitudinal changes in directly measured physical activity in patients with chronic obstructive pulmonary disease: the trajectory of change.* J Cardiopulm Rehabil Prev, 2012. **32**(5): p. 292-5.

312. Waschki, B., et al., *Disease Progression and Changes in Physical Activity in Patients with Chronic Obstructive Pulmonary Disease.* Am J Respir Crit Care Med, 2015. **192**(3): p. 295-306.

313. Donaldson, G.C., et al., *Effect of temperature on lung function and symptoms in chronic obstructive pulmonary disease.* Eur Respir J, 1999. **13**(4): p. 844-9.

314. Alahmari, A.D., et al., *Influence of weather and atmospheric pollution on physical activity in patients with COPD.* Respir Res, 2015. **16**: p. 71.

315. Spruit, M.A., et al., *Determinants of poor 6-min walking distance in patients with COPD: the ECLIPSE cohort.* Respir Med, 2010. **104**(6): p. 849-57.

316. Man, W.D., et al., *Community pulmonary rehabilitation after hospitalisation for acute exacerbations of chronic obstructive pulmonary disease: randomised controlled study.* BMJ, 2004. **329**(7476): p. 1209.

317. Sumukadas, D., et al., *Day length and weather conditions profoundly affect physical activity levels in older functionally impaired people.* J Epidemiol Community Health, 2009. **63**(4): p. 305-9.

318. Boutou, A.K., et al., *An evaluation of factors associated with completion and benefit from pulmonary rehabilitation in COPD.* BMJ Open Respir Res, 2014. **1**(1): p. e000051.

319. Fischer, M.J., et al., *Drop-out and attendance in pulmonary rehabilitation: the role of clinical and psychosocial variables.* Respir Med, 2009. **103**(10): p. 1564-71.

320. Garcia-Rio, F., et al., *Daily physical activity in patients with chronic obstructive pulmonary disease is mainly associated with dynamic hyperinflation.* Am J Respir Crit Care Med, 2009. **180**(6): p. 506-12.

321. Pavlov, I., *Conditioned reflexes*1927, London: Oxford University Press.

322. Wilkens, H., et al., *Breathing pattern and chest wall volumes during exercise in patients with cystic fibrosis, pulmonary fibrosis and COPD before and after lung transplantation.* Thorax, 2010. **65**(9): p. 808-14.

323. Vaz Fragoso, C.A., T. Clark, and A. Kotch, *The tidal volume response to incremental exercise in COPD.* Chest, 1993. **103**(5): p. 1438-41.

324. Gorini, M., et al., *Breathing pattern and carbon dioxide retention in severe chronic obstructive pulmonary disease.* Thorax, 1996. **51**(7): p. 677-83.

325. Jubran, A. and M.J. Tobin, *Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation.* Am J Respir Crit Care Med, 1997. **155**(3): p. 906-15.

326. *The Control of Breathing in Man*. Physiological Society Study Guides. Vol. 3. 1987, Manchester, UK: Manchester University Press.

327. Whipp, B.J., et al., *Parameters of ventilatory and gas exchange dynamics during exercise.* J Appl Physiol Respir Environ Exerc Physiol, 1982. **52**(6): p. 1506-13.

328. Casaburi, R., et al., *Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **155**(5): p. 1541-51.

329. Polkey, M.I., et al., *Diaphragm performance during maximal voluntary ventilation in chronic obstructive pulmonary disease.* Am J Respir Crit Care Med, 1997. **155**(2): p. 642-8.

330. Marin, J.M., et al., *Relationship of resting lung mechanics and exercise pattern of breathing in patients with chronic obstructive lung disease.* Chest, 1993. **104**(3): p. 705-11.

331. Jones NL, K.K., Stubbing DG., *The thorax in exercise*, in *The thorax*, M.P. Boussos C, Editor 1985, Marcel Dekker mc: New York. p. 627-62.

332. Loveridge, B., et al., *Breathing patterns in patients with chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1984. **130**(5): p. 730-3.

333. Loveridge, B., et al., *Alteration in breathing pattern with progression of chronic obstructive pulmonary disease.* Am Rev Respir Dis, 1986. **134**(5): p. 930-4.

334. Scano, G., et al., *Carbon dioxide responsiveness in COPD patients with and without chronic hypercapnia.* Eur Respir J, 1995. **8**(1): p. 78-85.

335. Van Remoortel, H., et al., *Validity of Six Activity Monitors in Chronic Obstructive Pulmonary Disease: A Comparison with Indirect Calorimetry.* PLoS One. **7**(6): p. e39198.

336. Vestbo, J., et al., *Adherence to inhaled therapy, mortality and hospital admission in COPD.* Thorax, 2009. **64**(11): p. 939-43.

337. Tobin, M.J., et al., *Breathing pattern and metabolic behavior during anticipation of exercise.* J Appl Physiol (1985), 1986. **60**(4): p. 1306-12.

338. Wasserman, K., B.J. Whipp, and J. Castagna, *Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase.* J Appl Physiol, 1974. **36**(4): p. 457-64.

339. Demeyer, H., et al., *The Minimal Important Difference in Physical Activity in Patients with COPD.* PLoS One, 2016. **11**(4): p. e0154587.

340. Mendoza, L., et al., *Pedometers to enhance physical activity in COPD: a randomised controlled trial.* Eur Respir J, 2015. **45**(2): p. 347-54.

341. Bravata, D.M., et al., *Using Pedometers to Increase Physical Activity and Improve Health: A Systematic Review.* JAMA, 2007. **298**(19): p. 2296-2304.

342. Hospes, G., et al., *Enhancement of daily physical activity increases physical fitness of outclinic COPD patients: Results of an exercise counseling program.* Patient Education and Counseling, 2009. **75**(2): p. 274-278.

343. Frisk, B., et al., *Peak oxygen uptake and breathing pattern in COPD patients--a four-year longitudinal study.* BMC Pulm Med, 2015. **15**: p. 93.

344. Faisal, A., et al., *Effective Bronchoscopic Lung Volume Reduction Accelerates Exercise Oxygen Uptake Kinetics in Emphysema.* Chest, 2015.

345. Bausewein, C., et al., *Effectiveness of a hand-held fan for breathlessness: a randomised phase II trial.* BMC Palliat Care, 2010. **9**: p. 22.

346. Higginson, I.J., et al., *An integrated palliative and respiratory care service for patients with advanced disease and refractory breathlessness: a randomised controlled trial.* Lancet Respir Med, 2014. **2**(12): p. 979-87.