Cardiopulmonary Manifestations in Chronic Obstructive Pulmonary Disease (COPD)

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Abstract

Rationale

Chronic obstructive pulmonary disease (COPD) is a progressive lung condition with extrapulmonary manifestations- cardiovascular diseases (CVD), impaired physical function, activity and increased frailty. Integrating measures of function into community assessments is hindered by the space and time required. The association of function, activity and CVD has not been extensively investigated in COPD.

Objectives

- Explore the potential utility of Time Up and Go (TUG) as a measure of physical function in COPD
- Assess association of non-invasive measures of haemodynamics to physical function and self-reported activity
- Explore ambulatory haemodynamics in COPD and controls

Methods

Subjects with COPD (n=119) and controls (n=58) were recruited. Ethical and governance approvals were obtained. A medical history including falls, spirometry, peripheral and central haemodynamics, self-reported physical activity questionnaires and functional assessments (TUG and six-minute walk distance (6MWD)) were obtained from all subjects. Ambulatory 24-hour

haemodynamics including aortic pulse wave velocity (aPWV) and blood pressure were measured in patients (n=20) and controls (n=19).

Results

TUG mean(SD) was increased in patients 11.9(3.7)s compared to controls 9.5(1.8)s, $p<0.001$. In patients, fallers had longer TUG than non-fallers ($p=0.02$) and a cut-off time of 12s had the highest sensitivity and specificity to detect fallers and non-fallers. Aortic stiffness was not associated to physical function or physical activity, $p>0.05$. In the pilot study, significant nocturnal dip in aPWV was seen in controls, $p<0.01$, but not in patients, $p=0.07$.

Conclusion

TUG could be a useful measure of function and possibly be incorporated into COPD assessment, particularly where time and space are limited. Finally, ambulatory haemodynamic machine, the Mobil-O-Graph, is feasible and offers opportunity to assess 24-hour haemodynamics profile including aPWV as opposed to a one-off measurement.

Author's publications

Abstracts

Alhaddad, M. John, M. Hussain, S. Bolton, C.E The Time-Up and Go (TUG) Test in Chronic Obstructive Pulmonary Disease (Oral presentation). 2014 Annual ILH Respiratory Research day Loughborough, UK.

John, M. Hussain, S. Al Haddad, M. and Bolton, C.E Do Standard Cardiovascular Risk Scores Identify Risk in Patients with COPD? British Thoracic Society, London. Thorax 2014; 69:A212.

John, M. Alhaddad, M. Hussain, S. and Bolton, C.E. Advanced Glycation Endproducts and Lung Function in COPD. 2014 European Respiratory Society conference, Munich. ERJ 2014 vol. 44 no. Suppl 58 P3675.

Alhaddad, M. John, M. Hussain, S. Bolton, C.E Ambulatory Haemodynamics in Patients with COPD (Poster discussion). 2014 European Respiratory Society (ERS), Munich, Germany. ERJ 2014 vol. 44 no. Suppl 58 P4483.

Publications

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Personal contribution to the research

This research was part of a larger study "The association of lung function and cardiovascular risk" where the study documents such as Patients Information Sheets and Case Report Files and power calculation for the TUG test were in place prior to the start of my PhD. I adapted the previous Case Report File to suit data collection for this project. I performed the majority of work (with some help from colleagues in recruiting from the respiratory consultants from outpatients clinic) in recruitment, introducing and discussing the study with potential participants, posting study information and arranging appointments, clinical visits, informing of the subject's participation and sending results to the subject's general practitioner. I did the entire work of the literature review, data input, data analysis, interpretation of results and discussion. I was also able to present my work in national and international conferences in addition to submitting a paper entitled "The Role of the Time Up and Go in Patients with COPD" which was accepted in May 2015.

Abbreviations

6MWT/D	Six-minute walk test/distance
A	
α1AT	Alpha-1 antitrypsin
ABPM	Ambulatory blood pressure machines
ADO	Age, Dyspnoea and airway Obstruction index
AIDS	Acquired immune deficiency syndrome
AIx	Augmentation index
ANOVA	Analysis of variance
aPWV	Aortic pulse wave velocity
ATS	American Thoracic Society
AUC	Area under the curve
B	
BHS	British Hypertension Society
BIA	Bioelectrical Impedance
BMD	Bone mineral density
BMI	Body mass index
BODE	Body mass index, airway Obstruction, Dyspnoea and Exercise capacity index
BP	Blood pressure
C	
cABP	Central ambulatory blood pressure
CHF	Chronic heart failure
CI	Confidence interval
CO	Carbon monoxide
COPD	Chronic obstructive pulmonary disease
CRF	Chronic Renal Failure
CV	Cardiovascular
CVD	Cardiovascular Diseases
D	
DBP	Diastolic blood pressure
E	
ERS	European Respiratory Society
ESWT	Endurance shuttle walking test
F	

FEV_1	Forced expiratory volume in one second
FFM	Fat free mass
FFMI	Fat free mass index
FVC	Forced vital capacity

G

GOLD	Global Initiative for Chronic Obstructive Lung Disease
GP	General Practitioner

H

HDL	High density lipoproteins
HF	Heart failure
HR	Hazard ratio

I

ICC	Inter-class correlation coefficient
IHD	Ischemic heart disease
IQR	Interquartile range
ISWT	Incremental shuttle walking test

L

L	Litre
LDL	low density lipoproteins

M

m	metre
MAP	Mean arterial pressure
MCID	minimal clinically important difference
MID	Minimal important difference
Min	Minute
MMP	Matrix metalloproteinase
mmHg	Millimetre of mercury
MRC	Medical Research Council

N

NICE	National Institute for Health and Clinical Excellence
NRES	National Research Ethics Service
NRRU	Nottingham Respiratory Research Unit

O

OR	Odd ratio

P

pABP	Ambulatory blood pressure
PP	pulse pressure

R

r	Correlation
R&D	Research and Development
ROC	Receiver operating characteristic
RR	Relative risk

S

SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaires
SOP	Standard Operating Procedures
SpO2	Peripheral oxygen saturation
SPPB	Short physical performance battery
SPSS	Statistical Package of the Social Sciences
SV	Stroke volume

T

TT	Transit time
TUG	Time Up and Go

U

USA	United States of America

V

$\dot{V}O_{2peak}$	Maximum oxygen uptake

W

WHAS	Women's Health and Aging Study
WHO	World Health Organisation

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Chapter 1

Introduction

1.1 Definition

Chronic Obstructive Pulmonary Disease (COPD) is a descriptive term that encompasses both chronic bronchitis and emphysema. As the name of the condition implies, there is chronic obstruction and narrowing of the airways in the lungs: chronic bronchitis, and elasticity loss and alveolar wall destruction: emphysema. Chronic bronchitis is defined clinically as a productive cough for more than three months for two consecutive years; whereas emphysema is defined pathologically as permanent enlargement of the air space and alveolar wall destruction distal to terminal bronchioles (ATS-ERS, 2004). Such changes progress over time and cannot be completely reversed once the remodelling occurs (WHO, 2012). The American Thoracic Society (ATS) and the European Respiratory Society (ERS) state that these chronic airway limitations are "usually progressive and are associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking" (ATS-ERS, 2004).

1.2 Prevalence

The prevalence of COPD is increasing and it is considered a leading cause of mortality and morbidity worldwide (Murray and Lopez, 1997, CDC, 1997). A recently published study looking at the global burden of diseases showed that COPD became the third leading cause of death after ischemic heart disease (IHD) and stroke in the year of 2010 (Lozano et al., 2012). Still, population-

based studies show that the true prevalence of COPD is underestimated and underdiagnosed (Lindberg et al., 2006, Tinkelman et al., 2007).

Mannino et al., investigated the prevalence of obstructive lung disease in over 16,000 individuals (aged ≥ 25 years old) using data from the Third National Health and Nutrition Examination Survey (Mannino et al, 2000). Subjects in the study were considered having obstructive lung disease if they report current diagnoses of either asthma or bronchitis, or had ever been diagnosed with emphysema. Airflow limitation was defined by forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.7 and FEV_1 of <80% predicted. The study showed that the majority of subjects (63%) had undiagnosed obstructive lung disease (Mannino et al, 2000). Although the true prevalence of COPD remains underestimated around the world, reportedly its death rate in the year of 2000 was 2.7 million people (Lopez A., 2006, Mannino et al, 2000). In the UK alone, three million people have been estimated to have COPD, from whom two million remain undiagnosed (NICE, 2011a).

1.3 Risk factors

COPD has many risk factors where smoking is considered the primary risk factor for developing such disease especially in developed countries (NCQA, 2009). Other risk factors such as gender, genetic, socioeconomic, and environmental exposure should not be ignored as COPD can be found in those

who never smoked. The risk factors for COPD can be classified as modifiable and non-modifiable factors.

1.3.1 Modifiable risk factors

- ***Smoking***

Smoking – direct tobacco usage or second-hand smokers - is the leading cause of COPD (WHO, 2008). All types of smoking including cigarettes, cheroots, cigars and pipe are associated with COPD in different intensity (Godtfredsen et al., 2002). In a population-based study comparing smokers to never-smoked elderly in Sweden, cigarette smoking was a major and independent cause of COPD (Lindberg et al., 2006). They showed that all men with severe COPD were smokers or ex-smokers and 90% with mild COPD were smokers or ex-smokers. For smokers, the smoke, nicotine and other irritants in the cigarette all contribute to developing chronic airway obstruction (Bohadana et al., 2004). Therefore, the World Health Organization (WHO) identifies smoking cessation as the most effective approach to reduce the development of COPD and slow its progression (WHO, 2015). Furthermore, the latest BTS guideline on pulmonary rehabilitation in adults emphasises the need to identify smoking history in referrals and to provide opportunity to smoking cessations (Bolton et al., 2013).

- ***Socioeconomic status***

Socioeconomic status as defined by the American Psychological Association is "the social standing class of an individual or group. It is often measured as a

combination of education, income and occupation" (APA, 2014). The socioeconomic status was found to be directly associated with COPD independent of smoking history (Prescott et al., 1999). People with lower socioeconomic status and those with lower level of education tend to have more smoking habits (Hart et al., 2010). Even after adjusting for confounders, for example, smoking, body mass index (BMI) and physical activity, socioeconomic position is inversely associated with lung functions (Ramsay et al., 2011). Further, both social class and environmental factors are associated with lung function. People with lower social class are more likely to live in more polluted areas than those with higher social class (Wheeler and Ben-Shlomo, 2005).

- ***Environmental exposure***

Environmental factors such as long-term exposures to air-pollution (nitrogen dioxide, particular matters, sulphur dioxide and benzene) and living nearby busy roads have direct effect on lung functions and might increase the risk of developing COPD (Schikowski et al, 2005, Wheeler and Ben-Shlomo, 2005). Further, COPD is associated with the nature of work and/or the environment of the workplace especially in industries associated with prolonged exposure to chemicals, for example, rubber, plastics, and leather manufacturing, food products manufacturing, agriculture, construction and transportation (Hnizdo et al., 2002).

1.3.2 Non-modifiable risk factors

- ***Gender***

COPD has been associated with the male gender because males were notoriously known for smoking, until recently in the past four decades where the number of female smokers has dramatically increased, COPD is no longer predominantly recognised as a male disease (Tinkelman and Corsello, 2003, Mannino et al., 2002). Recent studies showed that females who were diagnosed with COPD had higher mortality rate and more susceptibility to the adverse effects of smoking than males with the same diagnosis (Maria-Christina L. Machado, 2006, Gold et al., 1996). This could be due to physiological and non-physiological differences.

Recent literature shows that COPD has autoimmune components which might play part in the onset and/or development of the disease (van der Strate et al., 2006). This might give rise to the prevalence of the disease in females as they are "physiologically" more susceptible to develop autoimmune disease (DeLisa Fairweather, 2008). In addition, females have relatively smaller lung size, hence smaller capacity, than males (Camp et al., 2009); therefore, they are more prone to shortness of breath (The Lung Association, 2006).

Non-physiological differences may include physician and public awareness of COPD amongst females, which may lead to delayed or misdiagnosis of COPD.

- ***Genetic***

Genetic susceptibility in COPD is an important area. One of the most common heredity disorders is a deficiency of Alpha-1 antitrypsin (α1AT) protein, encoded by SERPINA1, leading to early onset of emphysema (Mark Wewers, 1989). This protease inhibitor has a protective role over lung parenchyma from proteases (neutrophil elastase); thus, a deficiency in the α1AT leads to protease-antiprotease imbalance and destruction of the lung parenchyma, therefore, causing emphysematous lung (Hersh et al., 2004). Only 1-2% of all COPD cases have been related to a severe form of α1AT deficiency suggesting other genetic factors are involved in the predisposition of COPD (Hall and Lomas, 2010). Other genetic factors that have been linked to COPD include, but are not limited to, matrix metalloproteinase (MMP)-9 and 12 (Demedts et al., 2006, Lee et al., 2010).

1.4 Chronic obstructive pulmonary disease and patients' characteristics

COPD is a slow progressive disease that develops over long period of time. An international survey in North America and Europe of over 3000 individuals investigating the impact of COPD has stated that people with COPD experience limitations in their physical and social activity, and also have increased hospital admissions (Rennard et al., 2002). Although the disease progresses over many years and, hence, mainly affect the older adults, working age people with COPD also suffer from this condition. The same

survey found that 45% of patients under the age of 65 years lost their jobs in the past year due to COPD.

Classical symptoms of COPD include, but are not limited to, breathlessness and exercise limitation. Therefore, physical activity and social participation are limited in patients with COPD, in part, due to their breathing discomfort (ATS, 1999). This can be partially explained by the dyspnoea-function model which summarises the association between dyspnoea and functional limitation in people with airway obstruction (Sassi-Dambron et al., 1995). Briefly, this model states that people with dyspnoea, gradually, tend to limit their activities due to the discomfort and frustration caused by their shortness of breath which, with time, leads to physical deconditioning which is, again, responsible for increasing dyspnoea. In patients with COPD, inactivity is associated with faster disease progression, increased health care utilization, and higher mortality rate (ZuWallack and Hedges, 2008). More recent studies highlighted the importance of establishing personal level of physical activity at an early stage of COPD and work to maintain it at that level as the decline in physical activity is highly associated with mortality (Vaes et al., 2014).

Unlike healthy individuals, small changes in the physical function of patients with COPD significantly affect their activity of daily life and, hence, quality of life (Steele et al., 2000). Therefore, it is important to have a valid functional test in the assessment of COPD (Introduction, p 21). Other symptoms often described by patients with COPD include sputum production, wheeze and increased risk of exacerbations.

1.5 Systemic effect of chronic obstructive pulmonary disease

COPD is traditionally defined as a lung condition; however the latest definition also includes comorbidities (NICE, 2010). COPD is associated with systemic complications including, but not limited to, loss of weight and muscle, loss of bone mineral density (BMD) leading to osteoporosis, as well as increased cardiovascular (CV) diseases and psychological consequences including anxiety and depression (Pauwels et al., 2001, Bolton et al., 2004). It is important to mention that COPD and other co-morbid diseases share common risk factors such as cigarette smoking, increased age, and inactivity (Agusti et al., 2003, Wasswa-Kintu et al., 2005). Although the latter was highlighted by the ATS and the ERS COPD guidelines (ATS-ERS, 2004), still, a method for a routine assessments for such co-morbidities is not yet established.

Alterations in body composition are important with focus previously on weight and muscle loss (Landbo et al., 1999, Schols et al., 1998, Schols et al., 2005). Indeed, being underweight is related to having an increased risk of mortality (Landbo et al., 1999, Schols et al., 1998). Such studies have included relatively few obese patients but suggested a relatively protective mechanism of obesity in COPD. With a number of factors likely to account for weight and muscle loss including increased energy expenditure, reduced energy intake, physical inactivity and the interplay of systemic inflammation and hormonal influences. Patients with COPD experience nutritional depletion as a result of

imbalance between energy intake and energy expenditure; where the former is associated with loss of appetite, fatigue and postprandial dyspnoea (Cheol Kim et al., 2008) and the latter is believed to be cause by hypermetabolism (Ezzell and Jensen, 2000).

1.6 Cardiovascular risk in patients with chronic obstructive pulmonary disease

Patients with COPD are at a greater risk of developing CV diseases and literature shows that the mortality rate of patients with COPD is in a large proportion due to CV diseases (McGarvey et al., 2007, Camilli, 1991, Curkendall et al., 2006). This greater risk of CV diseases in patients with COPD has been highlighted in literature to be over and above the effects of smoking (Sin and Man, 2003). Therefore, the awareness of the association between CV risks and COPD as well as the recommendation to treat COPD as an independent risk factor for CV diseases has recently been highlighted (Hunninghake, 2005). Also to note that the association between COPD and CV risks is not well understood; however, it might be a contribution of several factors including smoking, age, systemic inflammation (Sin and Man, 2003) and lung function.

Arterial stiffness is a non-invasive measure and has been associated with future CV risks and deaths (discussed in Introduction, p 11).

1.6.1 Association of Lung function to cardiovascular risk

Lung function is an independent predictor of CV risks and mortality. This was shown in previous literature including a population-based study of 1,861 participants recruited from the first National Health and Nutrition Examination Survey (Sin et al., 2005). After adjusting for age, gender and smoking history, the study results showed that subjects in the lowest FEV_1 quantile had the highest relative risk (RR) of CV mortality, 3.36 (95% CI: 1.54-7.34). Another population-based study of 402 men born in 1914 found an inverse association between FEV_1% predicted and CV mortality rate even after adjusting for confounders such as cigarette smoking, angina pectoris, physical activity, alcohol consumption, and diabetes (Engström et al., 2001). The prevalence and outcome of diabetes, hypertension and CV diseases were investigated in over 20,200 participants (≥45 years old) recruited from Atherosclerosis Risk in Communities and the Cardiovascular Health Study. An inverse association was found between airways obstruction and CV diseases with high prevalence of CV diseases in patients with COPD (OR 2.4 95% CI 1.3-1.9) (Mannino et al., 2008). These findings, collectively, emphasise the association between airflow limitation and CV events, however, the mechanisms explaining how COPD increases the CV risks is still unclear.

1.6.2 Association of arterial stiffness to cardiovascular risk

Generally, aging is associated with physiologic and functional changes in the characteristics of blood vessels including their *distensibility*, *compliance* and

stiffness. These changes, in turn, make older people more susceptible to developing CV events (Rodney A. Rhoades, 2012, Kelly et al., 1989). The more distal (peripheral) the vasculature from the heart, the more musculature and stiffer (less elastic) they become; partly, due to the increased rigidity of the arterial walls as vessels reach the distal end of the arterial tree (Blacher, 2005). Arterial stiffness leads to an in increase in systolic blood pressure (SBP) and little or no change in diastolic blood pressure (DBP) which, eventually, leads to increase in pulse pressure (PP) – the difference between SBP and DBP (Mackenzie et al., 2002). There is a continuous rise in the DPB until middle-age which is related to increasing resistance of the peripheral arteries; whereas, SBP is affected by arterial stiffness and continue to increase as arterial stiffness increases with aging (Franklin et al., 1997). An increase in PP may lead to adverse cardiac events, for example, ventricular hypertrophy which is caused by increase in the left ventricular afterload and the myocardial oxygen demand (Nichols, 2005). Furthermore, another study found that aortic stiffness as opposed to peripheral arterial stiffness was related to aging (>50 years) in healthy subjects with minimal burden of CV diseases (Mitchell et al., 2004).

The pulse wave velocity (PWV) - a measure of the speed of the pulse wave as it travels between two regions within the arterial tree - is a non-invasive reproducible method to measure arterial stiffness (Laurent et al., 2006). Whereas, augmentation index (AIx), a measure of arterial stiffness and wave reflection, and pulse pressure are surrogate methods (Nichols, 2005, Laurent

et al., 2006). The gold standard measure of aortic stiffness is the aortic PWV (aPWV) (Laurent et al., 2006). Aortic PWV is an independent predictor of CV events and may help in identifying high-risk population (Ben-Shlomo et al., 2014).

The relationship between arterial stiffness (measured by PWV) and CV events, CV mortality and all-cause mortality was highlighted in a systematic review and meta-analysis of 17 longitudinal studies following 15,877 subjects for an average of 7.7 years (Vlachopoulos et al., 2010). The results show that an increase of 1 m/s in aPWV is associated with an increased RR of 1.14 (95%CI: 1.09-1.20), which equates to a 14% increase in total CV events. Both CV mortality and all-cause mortality increased by 15% with a 1m/s increase in PWV, with the same RR of 1.15 (95%CI: 1.09-1.21) for both.

In a population-based study, The Rotterdam Study, (n= 2835 healthy subjects, mean (SD) age of 72 (7)years) explored the association between arterial stiffness (measured by aPWV) and coronary heart disease and stroke (Mattace-Raso et al., 2006). The study results showed positive associations of arterial stiffness to coronary heart disease (mean follow-up period 4years), and stroke (mean follow-up period 3years), which were attenuated slightly after adjusting for CV risk factors. Increased aPWV was associated with approximately 1.7 to 2.5 increased risks of developing coronary heart disease and approximately 1.2 to 2.3 risks of developing stroke. Increased arterial stiffness has been found to be associated with greater CV risks in a number of

conditions including renal disease (Blacher et al., 1999), and diabetes (Cruickshank et al., 2002, Salomaa et al., 1995).

In a community-based study following over 2000 older subjects for a median of 7.8 (range, 0.2 to 8.9)years, aPWV was the only measure found to be associated with increased major CV risks when compared to other haemodynamic measures including central blood pressure, AIx, carotid-brachial pressure and carotid-radial PWV (Mitchell et al., 2010). Association between aPWV and CV event remained significant even after adjusting for brachial or central pulse pressure or carotid-brachial pulse pressure amplification.

1.6.2.1 Association of arterial stiffness to cardiovascular risk in patients with COPD

In COPD studies, there is a growing interest of investigating the association of arterial stiffness to COPD. Sabit et al., explored the association in clinically stable patients with COPD (n=75) and age- and sex-matched controls with smoking history (n=42) (Sabit et al., 2007). Both groups were similar in BP measurements and CV risks and results showed that arterial stiffness was increased in patients compared to controls and – in patients – it was related to severity of airflow obstruction. In a small study of male subjects (18 patients with COPD and 17 healthy subjects matched for age and smoking history), Maclay et al., found that the association of COPD to increased arterial stiffness was independent of smoking, characterised by elevated

augmentation index and reduced time to wave reflection (Maclay et al., 2009). McAllister et al., investigated the association of arterial stiffness to the severity of emphysema using brachial PWV (less prognostic measure of arterial stiffness) in 157 patients with COPD (McAllister et al., 2007). After adjusting for age, smoking history, sex, lung function, and other potential confounders, the study concluded that brachial arterial stiffness is independently associated with the severity of emphysema on HRCT scanning of the chest ($r= 0.47$, $P<0.001$).

Patients with COPD have increased markers of systemic inflammation (Sin and Man, 2003), which was discussed in later studies to be a potential reason for increased arterial stiffness in this population (Sabit et al., 2007, Mills et al., 2008). Other studies raised the possibility that the contribution of increased arterial stiffness in patients with COPD was linked to aortic calcification (Bolton et al., 2011) and microvascular damage (John et al., 2013).

1.7 Lung function, arterial stiffness, and physical functional limitation

Lung function, arterial stiffness, and physical limitation are all altered by the aging process independent of co-morbidity (Janssens et al., 1999, Mitchell et al., 2004, Freedman and Martin, 1998). However, Bolton et al., found that lung function in is an independent predictor of arterial stiffness over and above age in adult males (Bolton et al., 2009). They found that mid-life lung function was a stronger predictor of arterial stiffness than later-life where a

reduced volume of 500ml in FEV_1 and FVC was associated with an increase of PWV of 0.52m/s and 0.42m/s; respectively. Recently, there has been an interest in literature in exploring the association between arterial stiffness and functional limitation in the general population and in patients with chronic conditions including COPD.

In a population-based study, the Whitehall II, the association of arterial stiffness to physical function, functional limitation, and lung function was investigated using 5,392 relatively-healthy older subjects (Brunner et al., 2011). Gait speed was used to assess physical function over 8-ft track. The results of this study (adjusted for confounders such as age, gender and ethnicity) showed that arterial stiffness, using applanation tonometry (SphygmoCor), was inversely related to physical function (-0.96, 95% CI: -1.29 - -0.64 m/s) and to spirometry lung function (-1.23, 95% CI: -1.53 - -0.92 L). Similarly, inverse association between arterial stiffness, using doppler-recorded carotid and femoral pulse waveforms, and 20m gait speed in patients with peripheral arterial disease (PAD) but not in subjects without PAD (Watson et al., 2011). The authors summarised that therapeutic intervention in patients with PAD could be directed to arterial stiffness in order to improve peripheral perfusion and, hence, walking performance.

A previous study by Castagna et al., looked at PAD, primarily PAD contribution to arterial stiffness, and exercise capacity in patients with COPD (Castagna et al., 2008). The authors found that exercise capacity was inversely related to

arterial stiffness – measured by the carotid-femoral PWV (Comlior, France) - and, therefore, screening for CV risk in patients with COPD is important.

Given that patients with COPD are more susceptible to developing physical disability than healthy adults, the addition of physical functional assessment to spirometric measurements in the management of COPD may add valuable information that may guide therapeutic intervention (Celli et al., 2004, Geijer et al., 2007).

1.8 Determinants and potential benefits of aortic pulse wave velocity measurements in the assessment of COPD

Determinants of increased aortic stiffness differ from determinants of other conventional predictors of CV risk, for example hypertension. It was shown in previous studies that aortic stiffness predicts future incidents of hypertension; hence, aortic stiffness is not caused by hypertension (Kaess et al., 2012). It is important to mention that smoking (Mahmud and Freely., 2003) as well as some medical conditions like hypertension, diabetes mellitus and hypercholesterolemia are associated with increased aortic stiffness (Laurent et al., 2006). Early life determinants of increased arterial stiffness in adulthood have been highlighted in literature. Examples of these determinants are increased blood pressure and central fatness which are associated with poorer levels of blood lipids, cardiorespiratory fitness and heart rate (Ferreira et al., 2012).

As we age there is a linear increase of central haemodynamic measures, for example pulse pressure, but not aPWV which follows different pattern with a remarkable increase after the age of 50 years (McEniery et al., 2005). This suggests that using aPWV for people after the age of 50 years would give better prediction of future CV events. Comparison of age-matched groups of males and females showed different characteristics of increased aortic stiffness that appeared to be mainly affected by post-menopausal period (Nethononda et al., 2015). For example, females during pre-menopause have lower aortic stiffness than males and it is increased remarkably post-menopause, which was suggested to be a result of hormonal changes and/or fat distribution patters in females following menopause (Nethononda et al., 2015).

Drug therapy also has an effect on lowering arterial stiffness but in a different manner from drugs affecting peripheral or central haemodynamic measurements. Mackenzie et al. 2009 investigated the effect of four antihypertensive drugs (perindopril, atenolol, lercanidipine or bendrofluazide) on 59 patients with untreated isolated systolic hypertension (Mackenzie et al., 2009). They showed that each of these drugs has different effect on peripheral and central blood pressures, but no effect was found on aPWV. A double-blinded randomised study comparing the effects of combined drugs (perindopril and indapamide) and atenolol in hypertensive subjects over 12 months showed greater reductions of PWV in subjects treated with the combined drugs than those treated with the atenolol only (de Luca et al.,

2004). These findings suggest that assessment of aortic stiffness would provide better guidance to drug therapy.

In summary, it is apparent that measurements of peripheral BP, central BP and aPWV are not exchangeable and that assessment of aPWV provides additional information, which may lead to the advancement of clinical practice. Since CV events are common in patients with COPD, aPWV measurements could be used as a target for treatment as well as to detect improvement post drug and/or rehabilitation intervention to prevent or reduce the risks of CV events. Previous studies showed that patients with COPD have increased aortic stiffness (Sabit et al., 2007, Maclay et al., 2009) and it can be improved with rehabilitation through the improvement of BP (Gale et al., 2011, Vivodtzev et al., 2010). A direct measurement of the association of aortic stiffness to physical performance tests and self-reported physical activity is yet to be explored. The current research was to explore these associations in a wide range of patients with COPD and compared results to age- and gender-matched controls.

1.9 Assessment of physical performance

The concept of physical function has been used in literature to account for a wide range of assessment including, but not limited to, physical performance and psychological aspects (Podsiadlo and Richardson, 1991, Beauchamp et al., 2009, Schieman and Plickert, 2007). The current research focuses on the TUG test as a determinant of the physical limitation by based on performance

between patients and controls. Therefore, in this thesis the term physical performance is used when referring to the physical assessment tests.

There are two distinct methods used for the measurements of the physical performance: subjective and objective assessments. This thesis focuses on objective methods relevant to COPD.

1.9.1 Types of physical performance assessment

1.9.1.1 Subjective method

This approach includes self-reports and can be obtained by either questionnaire or telephone interview. Some of the advantages of this method are: relatively inexpensive and can be directed to address a specific area of problem (Reuben et al., 2004), and it is patient friendly (patients do not need to perform an activity in order to be assessed). Nevertheless, results obtained using these methods are more likely to be over or underestimated dependent on the person's judgment and ability to accurately recall information. Moreover, the longer the recall, the less accurate and reliable the information becomes (Sallis, 1993).

1.9.1.2 Objective method

Objective measures are performance-based tests. Objective methods may have less confounding variables in comparison to subjective methods (Ostir et al., 2002, Linn et al., 1980).

1.9.2 Physical performance tests

Assessment of physical performance in the general population is very important owing to its ability to provide a dimensional summary of the individual's physical environment, social participation and his/her daily life activity. Additionally, studies have proven repeatedly the ability of exercise tests to predict mortality, nursing home admissions, hospitalization, future incidence of disability (even for healthy individuals) (Chang et al, 2004, Eisner et al., 2007, Guralnik et al., 1994, Landi, 2007, Ostir et al., 2002, Rantanen et al., 1999, Studenski et al., 2003). Similarly, there is increasing interest in the use of exercise tests in patients with COPD because of its objectivity in evaluating exercise capacity and detecting changes pre/post intervention (Palange et al., 2007)

This section of the literature review critically discusses some of the up-to-date performance tests, which may be applicable to subjects with COPD. These tests include: the Six-Minute-Walk Test (6MWT), the Incremental Shuttle Walk Test (ISWT), the Short Physical Performance Battery (SPPB) and the Time Up and Go (TUG) test. The literature review addresses the advantages and disadvantages, nature of the test, validity, reliability and the sensitivity to change of each of these tests.

1.9.2.1 Six-Minute-Walk Test (6MWT)

Six minute walk test is a commonly used test in the assessment and evaluation of physical performance in pulmonary rehabilitation assessments

(Bromboszcz J, 2010). Over the past years, the measurements of physical performance using self-paced timed walking tests have become the scope of interest for many researchers. Self-paced walking tests were not restricted to six minutes only; investigators were interested in examining the different variations of timed-walk tests such as 12, 4, and 2-minute walking tests. However, the 6MWT, amongst all tests, was most favourable and thought of as a compromise between the 2 and the 12 minutes walking tests (Butland RJ, 1982).

1.9.2.1.1 Nature of the 6MWT

Six-minute walk is a timed submaximal test where individuals are instructed to walk as far as they can at their regular speed for 6 minutes. By the end of the 6min, the walked distance (6MWD) is recorded and used in the analysis as the primary outcome measure. It is a self-paced test that is performed on a marked walkway with two chairs – one at each end of the walkway - allowing the individuals to rest if needed. The ATS has published general guidelines with recommendations to follow for the 6MWT (ATS, 2002). The guidelines recommend that the test should be performed indoors on a straight, flat, and hard surface (30 metres) long.

Dyspnoea is an important part of the 6MWT and it can be measured subjectively using the Borg Scale (Galiè et al., 2004). The familiarity and simplicity of the test are plausible since walking is a simple activity of daily life and subjects are allowed to stop and rest if needed, within the allotted time. In addition, the 6MWT is an economic tool and only requires a stopwatch, a

pair of cones, a pair of chairs to be placed at each end of the walkway, and an oximeter device to measure the heart rate and oxygen saturation.

Furthermore, the 6MWT can detect certain walking behaviours such as the pace of the walk and the frequency of stops during the walk (Pitta et al., 2005a).

1.9.2.1.2 Validity

Examining the validity of a particular machine or questionnaire means investigating whether the machine or the questionnaire is actually measuring what it is supposed to measure. Harada et al., investigated the 6MWT on individuals from retirement homes and community centres and found a constructive validity of the 6MWT with five other physical performance tests (Harada et al., 1999). The correlation of the 6MWT was found in the chair stands (r= 0.70), tandem balance (r= 0.59), 8 feet walk (r= 0.68), but to a less extent to self-assessment measures. The associations between the 6MWT and other performance-based measurements were well established and similar results were found in other studies (Bean et al., 2002, Flansbjer et al., 2005).

1.9.2.1.3 Reliability and reproducibility

Reliability can be defined as the ability of a measure – e.g. a questionnaire or a device – to produce same results over different time. The test-retest reliability and reproducibility of the 6MWT have been shown in literature to be of a high standard, regardless of the different methodologies used in

different studies. For example, an observational study investigating the mobility-related function in healthy individuals (n=86) recruited from retirement homes and community centres (Harada et al., 1999). The authors reported that the 6MWT had a very high (r= 0.95) one week test-retest reliability. Other studies showed high one day test re-test reliability in elderly adults (61-89 years) and in patients with advanced heart failure (HF), interclass correlation coefficient (ICC)= 0.95 and ICC= 0.96; respectively (Cahalin et al., 1996, Steffen et al., 2002). Other studies presented similar findings in cardiac patients (O'Keeffe et al., 1998).

In COPD, Poulain et al., investigated the ability of the 6MWT to detect oxygen desaturation in 80 patients with COPD: FEV_1= 62.4 ± 2% predicted by comparing it to the cardiopulmonary exercise test (Poulain et al., 2003). The results obtained from the 6MWD (mean (SD) 495 (4)m) were similar to the results from the reference 6MWD (499 (18)m) confirmed by the low variation coefficient (5.4 ± 2%). The authors recommended the 6MWT to be used not only as a measurement tool of functional status and effectiveness of therapeutic intervention, but also as a diagnostic tool, for example, investigate the exercise-induce desaturation (Poulain et al., 2003). High reproducibility (ICC=0.93) was also found between the first and second 6MWD in a large retrospective observational study of 1,514 COPD patients with COPD (Hernandes et al., 2011).

1.9.2.1.4 Minimal Clinical Important Difference

The main outcome of the 6MWT is the distance covered by the end of the test. Therefore, clinicians need to determine the minimal clinical important difference of the distance covered, from which clinicians can determine the individuals' improvements of physical performance. With an intervention, the minimal clinical difference for patients with COPD was demonstrated in a study of 112 patients with COPD (mean age 67 years) who were already participating in a rehabilitation program strictly for their COPD conditions (Redelmeier et al., 1997). Patients were asked to perform 3 6MWTs on separate days and the third test was used in the analysis. To calculate the minimal clinical important difference, the authors compared the subjective (patients' rating: about the same/ a little bit better/ a little bit worse) and the objective (the 3rd 6MWT) methods after the rehabilitation. In the subjective method, patients were asked to rate performance against their peers. The results of the study showed that patients would recognise a difference in their physical performance when there is a 54 m difference in the distance they covered during the 6MWT. This cut-off value of 54m for the MCID has accepted and used in clinical practice. The method used in the study, where participants were asked to evaluate performance in comparison with each other, might be a useful to eliminate recall bias; however, this method might create an environmental bias where decisions on improvements might depend on the social interactions between subjects (Singh S. et al., 2008).

Two more recent studies, Puhan et al., and Holland et al., have re-evaluated the minimal important difference (35m and 25m, respectively) in people with COPD (Puhan et al., 2008, Holland et al., 2010). The main difference between these two studies and the Redelmeier et al., study was the methodological approach used for the patients' assessments of their improvements. The two studies used anchor-based and distribution-based methodologies and patients were asked to evaluate their improvement overtime. The small MID difference might be due to the self-report strategy used in each study. For example, Holland et al., asked patients to rate themselves using a "patient anchor specific to functional walking capacity" instead of health-related quality of life questionnaire, which was used in the other study. The strategy used by Holland et al., is considered more specific to walking capacity since health-related quality of life has been shown not to have good correlation with the 6MWT (de Torres et al., 2002).

1.9.2.1.5 6MWT in patients with COPD

Tests of exercise capacity (for example the 6MWT and the ISWT) are useful in the assessment of COPD and can detect significant improvement post rehabilitation intervention; however the long term benefits of these test are not know (Bolton et al., 2013, Rejbi et al., 2010). The 6MWT can detect improvements of functional status post rehabilitation as well as pharmacological intervention and reflect on the nature of improvements (Rejbi et al., 2010, Singh et al., 2014). The frequency and duration of the resting periods are believed to be an important part in the 6MWT. In a

retrospective chart review of 211 COPD patients, participants were grouped as Resters and Nonresters and measurements were taken pre and post 4-week rehabilitation (Wong et al., 2010). The results showed that *Resters* improved their 6MWD by reducing the frequency and duration of resting time (increasing the walking time); whereas, *Nonresters* improved their distance by increasing the average walking speed. It was suggested that the improvement in speed for the *Nonresters* group might reflect on the cardiovascular or peripheral muscle improvements during the rehabilitation program; whilst, the reduction in the frequency and the duration of the resting periods may be a reflection on the pacing technique which, in-turn, improves endurance.

A longitudinal three year study following 576 patients with COPD, reported the 6MWT as an independent predictor of respiratory-related mortality (Casanova et al., 2008). In the study, relative risk of 1.007 (95% CI: 1.005-1.009) was associated with every one metre decrease in the 6MWD. Similarly, 6MWT was found to be better predictor of mortality than FEV_1 in a 2-year longitudinal study of 198 COPD patients and 41 healthy participants (controls) (Pinto-Plata et al., 2004). The risk ratio of mortality found in the study was 0.82 (0.72-0.94, 95% CI) for each 50m increase in the 6MWD.

The size of learning effect in patients with COPD varies from 2.6% - or 15m - (Troosters et al., 2002) to approximately 9% - or 108m - difference between the first and second, same day, 6MWT (Stevens D. et al., 1999). The relatively small size effect (2.6%) was most likely due to the inclusion criteria where the

authors recruited individuals who had already experienced the 6MWT prior to the conduction of the study. Based on literature, it is most probable that the size effect would be higher if the participants had never experienced the 6MWT before. This size effect may vary among studies depending on numerous factors, for example, the condition of the subjects, the methodology used in research studies (including/exclusion criteria), frequency and intensity of encouragements, and other psychological factors such as depression (Spruit et al., 2010, Enright et al., 2003, de Torres et al., 2002). The 6MWT, unlike the shuttle walking test, is not responsive to medication. In a randomised double-blind study of 14 patients with COPD asked to perform two 6MWT and two endurance shuttle walk test post either 500mcg of ipratropium bromide of a placebo (Pepin et al., 2006). The study results showed that the endurance shuttle walk test was responsive to medications but not the 6MWD. A recently published systematic review of field walking tests in patients with chronic respiratory disease showed that the effect of medications (bronchodilators) on the 6MWD is minimal, not clinically significant (Singh et al., 2014). These findings strongly emphasise the importance of understanding and assessing both the pulmonary and the non-pulmonary aspects of COPD. Such findings led some researchers to imply that patients with mild COPD and poor 6MWD might indicate that health providers should look at extra-pulmonary rather than intra-pulmonary causes (Spruit et al., 2010).

According to the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines, a pulmonary rehabilitation programme has to be patient-centred because improvement in performance capacity is exercise specific and improvement in the general fitness doesn't necessarily reflect improvement in everyday activities (Nici et al., 2006). The 6MWT lacks the ability to reflect certain important characteristics of patients with COPD such as the ability to stand from a seated position and to sit back again; patients' coordination ability in changing direction while walking, which in turn reflects on risks of falling in COPD patients. However, the 6MWT was the preferred walking test over other walking tests owing to its simplicity, tolerability and safety - no reports of any injuries were found even in studies including patients with moderate to very severe cases of COPD (de Torres et al., 2002, Spruit et al., 2010, Enright et al., 2003).

1.9.2.2 Incremental shuttle walking test

This test was first introduced in patients with COPD as an objective measure of functional capacity. The incremental shuttle walking test (ISWT) was modified from the downgraded 10 level protocol to a modified 12 level protocol as the levels in the former might not be enough to stress patients with mild form of COPD to reveal their maximum functional capacity (Singh S. et al., 1992). Unlike self-paced test, ISWT can detect symptoms related limitation at maximal performance, which allows direct measurements of performance in patients with COPD (Singh S. et al., 1992).

1.9.2.2.1 The nature of the incremental shuttle walking test

ISWT requires patients to walk between two cones – placed on a ten metres course - within a set time that is indicated by pre-set beeps played on a recorded audiotape. The number of laps is recorded and the time starts very slow and progresses with each minute. The test ends when the subject is too breathlessness or cannot maintain the required speed (Singh S. et al., 1992). Learning effect is present in the ISWT and one practice test is recommended with a minimum of 30 minutes in between each performance (Singh S. et al., 1992, Vagaggini et al., 2003, Fowler et al., 2005).

ISWT has been used in number of conditions including COPD, cardiac patients, following coronary artery bypass surgery, evaluation of lung resection candidate, advanced cancer, and pulmonary rehabilitation (Lewis et al., 2001, Singh S. et al., 1992, Roberto P. Benzoa, 2010, Booth and Adams, 2001, Griffiths et al., 2000, Fowler et al., 2005).

1.9.2.2.2 Validity

When Singh et al., developed the ISWT, they investigated the test-retest reliability of the ISWT and the validity of the test against the 6MWT in COPD population (Singh S. et al., 1992). The results showed moderate correlation (r= 0.68) in the distance covered in both tests and graded cardiovascular response was obtained by the ISWT and not the 6MWT.

Singh et al., investigated the association of ISWT to the maximum oxygen uptake ($\dot{V}O_{2\,peak}$) – which is an index of cardiorespiratory capacity - during

treadmill test in 19 patients with chronic airflow limitation (Singh et al., 1994). The study demonstrated a strong correlation between the distance covered during the ISWT and $\dot{V}O_{2\ peak}$ during treadmill test (r=0.88) determined by the following regression equation:

$\dot{V}o_2max = 4.19 + 0.025$ (distance)

Fowler et al., have used similar methods to investigate the validity of the ISWT against standard measurements of $\dot{V}O_{2\ peak}$ - measured by gas analysis during incremental treadmill test - in 39 patients 6-8 weeks after coronary artery bypass surgery and prior to rehabilitation (Fowler et al., 2005). They showed strong associations between the ISWTs (distance covered) and $\dot{V}O_{2\ peak}$ measured by gas analysis during incremental treadmill test (r = 0.79, r = 0.86 and r = 0.87 for Tests 1–3, respectively). The maximum oxygen uptake obtained from the ISWT can be used to adjust the walking pace of the Endurance Shuttle Walk Test (ESWT), which is an externally paced field test developed to assess endurance capacity in patients with COPD *(Revill et al., 1999)*.

1.9.2.2.3 Reliability

The study conducted by Singh et al., (mentioned in p 29) 10 patients were examined for the test-retest reliability by performing three ISWT trials (Singh S. et al., 1992). All patients in their study completed the ISWT reaching level three to eight and no one finished the test at level 12. The study results showed significant differences when the first trial was compared to the second and third trials; whilst no difference was found between the second

and third trials (345m, 376m, and 378m; respectively), which emphasise the learning effect in the ISWT. Similarly, high reliability of the ISWT was found in number of conditions other than COPD, for example, patients with pacemakers (Payne and Skehan, 1996) and patients with advanced cancer (Booth and Adams, 2001).

1.9.2.2.4 Minimal Clinically Important Difference

In COPD, the minimal clinical important difference for the ISWT was, recently, established by investigating patients attending a seven week pulmonary rehabilitation programme (Singh S. et al., 2008). In the study, 372 patients with confirmed COPD (mean (SD) FEV_1= 1.06 (0.53)L FEV_1/FVC ratio 50.8 (18.1)% and a mean (SD) age of 69(4)years underwent ISWTs before and after the programme. Exercise tolerance was assessed after the ISWT using a 5-point Likert scale (range from "better" to "worse"). Patients who reported "better" showed improvement in their exercise tolerance after the rehabilitation programme with a mean distance of 78.7m (95% CI, 70.5 to 86.9) and those who reported "slightly better" they improved by 47.5m (95%CI, 38.6 to 56.5). Therefore, a change of 47.5m in the ISWT is recognised as a MCID where an improvement of 78.7m is suggested to be an indication of additional benefits.

1.9.2.2.5 Conclusion

The ISWT is a well-tolerated test of maximal exercise capacity in different chronic conditions. It is considered to be less expensive than other conventional tests – for example the ergometers – as the ISWT only requires

minimal equipment. Although it is standardised to perform one practice test, the use of audio-recorded external pace minimise in the ISWT minimises the degree of learning effect.

1.9.2.3 Short Physical Performance Battery (SPPB)

The ability of the exercise test to evaluate real life functional activities urged researchers to develop an accurate, reliable, sensitive, easier to perform, and less time and space consuming test which can relate to different dimensions of physical performance, for example the short physical performance battery (SPPB).

1.9.2.3.1 Nature of the short physical performance battery test

SPPB was first introduced by Guralnik et al., using data from the Established Populations for Epidemiologic Studies of the Elderly study (Guralnik et al., 1994). It is a simple and short test that was designed to measure three different types of manoeuvres: balance, gait speed and chair stand test. Each physical manoeuvre of the test is timed and scaled separately starting with standing balance test and ending with chair stand test. The entire test should not take more than 10 minutes to complete. Moreover, the SPPB is an inexpensive test; it only requires a standard chair and a stopwatch for timing. The short-distance walk (8-feet) in the SPPB test makes the test feasible to perform in a small space.

The SPPB consists of 5 points scale ranging from 0, not being able to perform the task, to 4 which is the highest performance score (Guralnik et al., 1994).

The full summed score ranges from 0 to 12 with 12 being the SPPB summary test of the highest possible performance score.

1.9.2.3.2 Validity

Guralnik et al., tested the validity of the SPPB test by investigating the following: its association to self-report measurements, its ability to measure performance along the entire functional spectrum (not only at the disabled end), and its ability to predict mortality and nursing home admissions (Guralnik et al., 1994). In a study of over 5000 participants (aged ≥71 years) who were recruited from the general population, showed that SPPB was positively related to self-reported measurements and inversely related to aging. In COPD, the Functional, Living, Outcome, and Work (FLOW) cohort study investigated the impact of COPD on physical performance limitations by comparing 1202 patients with COPD to 302 healthy controls, both groups were matched for age, gender and race (Eisner et al., 2008). The study showed that the SPPB score was 1.0 point less (9% decrease in the SPPB score) in the COPD group compared to the controls group, which was similar to the 6MWT where the COPD group walked 334 feet (20%) less than the controls group. Another study by Kon et al., showed that slow 4m gait speed component of the SPPB was strongly associated with reduced ISWT and higher MRC score and SGRQ in >500 patients with COPD; this was independence of the degree of airway obstruction (FEV_1% predicted (Kon et al., 2013).

1.9.2.3.3 Reliability

To investigate the reliability of the SPPB test, it was necessary to examine the three components of the test as well as the SPPB summary test.

- Reliability of the SPPB summary test:

Ostir et al., investigated the test-retest reliability in a 3-year prospective cohort study of over 1,000 moderately to severely disable older women in three different occasions - 5-6, 12-13, and 19-20 weeks – showing high Intra-class Correlation Coefficient (ICC) = 0.92, 0.88, and 0.91, respectively (Ostir et al., 2002). Another study of 52 African American older adults showed SPPB test-retest repeatability (ICC= 0.81) over one week (Mangione et al., 2010).

- Reliability of the gait speed test:

High reliability of the 4m gait test with ICC of 0.86, 0.80, and 0.89, respectively, was presented in the Women's Health and Aging Study (WHAS) study investigating disabled older women (Ostir et al., 2002). In another study, the 4m gait speed was also found to have high test-retest (r= 0.97, within 24hr and 48hr periods) and inter-observer (r= 0.99) reliability in patients with COPD (Kon et al., 2014).

- Reliability of the chair stand test:

Again, high reliability of the chair stand test was shown in the WHAS study; ICC 0.76, 0.86, and 0.90, respectively. Similar results of high reliability were shown in another population (age 35-71 years) with significant physical limitation; ICC= 0.80 (Curb et al., 2006).

- Reliability of the balance test:

The WHAS study showed ICC of 0.71 (5-6 weeks), 0.82 (12-13 weeks), and 0.70 (19-20 weeks) for the balance test (Ostir et al., 2002). The study by Curb et al., showed no reliability for the side-by-side and semi-tandem standing positions and only low reliability of the full tandem test with ICC of 0.22 (Curb et al., 2006). The main difference between the two studies was that the average age in the WHAS study was higher than the oldest participant in the Curb et al., 2006 study. Moreover, not only did Curb et al., recruit younger adults, but they also included only a high functioning Japanese American population who have an active life expectancy higher than any other ethnic groups (Tsuji et al., 1995). Therefore, the full tandem, which is the most difficult standing position among the three (Freeman et al., 2008), was the only challenging task for balance in this group of people.

1.9.2.3.4 Minimal Clinical Important Difference

Perera et al., have adopted the anchor-based approach trying to measure the minimal clinical important difference in the SPPB on community dwelling older adults and sub-acute stroke survivors (Perera et al., 2006). They showed small meaningful and substantial changes of 0.54 and 1.34, respectively, for the SPPB. Furthermore, in a longitudinal study following 542 community-dwelling adults (aged ≥65 years old) for three years using SPPB as a tool to predict the ability to walk 400m (Vasunilashorn et al., 2009). The results showed that SPPB score of ≤10 points was a significant indicator of future disability, SPPB score of ≤7 points was associated with increased risk

(26.9 times) of developing disability when compared to SPPB score of 12 points and SPPB score of ≤10 was with increased risk (3.4 times) to develop mobility disability when compared to SPPB score of 12 points.

1.9.2.3.5 SPPB in Patients with COPD

The FLOW study, mentioned earlier, is the largest cohort study investigating broad range of physical limitations in COPD patients (Eisner et al., 2008). The study shows consistency of the SPPB test with the 6MWT and self-reports. Although SPPB test and the 6MWT were used for the assessment of the lower extremity limitations and the submaximal exercise performance, respectively, the study population was only limited to younger adults (40-65 year-old) and; therefore, findings cannot be applied to older adults where the impact of COPD on the physical limitation might be underestimated.

One of the disadvantages of the SPPB test is that it has a ceiling effect for high functioning individuals. This was discussed in the earlier section when different findings were obtained from the WHAS and Curb et al., studies. This ceiling effect might be misleading specially when trying to detect early and more subtle impairments in patients with COPD (Curb et al., 2006).

1.9.2.4 Timed Up and Go (TUG) test

TUG is one of the tests that have been developed to measure basic physical performance in the elderly.

1.9.2.4.1 The Nature of the TUG Test

TUG test is adapted from the "Get-up and Go" test which was developed in 1986 by Mathias et al., on balance function (Mathias et al., 1986). It wasn't until 1991 when a modified, timed (seconds) version was introduced to overcome the subjectivity of "Get-up and Go" test (Podsiadlo and Richardson, 1991). The American College of Rheumatology recommended the use of a standard arm chair for the TUG test - seat height of 46cm and arm height of 64cm (Rheumatology., 2014), as the chair height might have an influence on the subjects performing the TUG test (Heung and Shamay, 2009). Meta-analysis of 21 studies showed that the mean time to complete the test for participants (60 year-old or above) was 9.4s (95% CI, 8.9-9.9) (Bohannon, 2006).

1.9.2.4.2 Validity

Since falls and balance impairments are common in patients with COPD (Beauchamp et al., 2009), it is necessary to validate a test which can discriminate between those who are at risk of falls and those who are not. In a study of 60 community-dwelling patients (mean age 79.5 years), Podsialdo and Richardson presented a good correlation between the TUG test and Berg balance scale, r= -0.81 (Podsiadlo and Richardson, 1991). Moreover, the validity of the TUG test and stair climbing power test was examined in a small cross sectional study of 21 patients with COPD (moderate-severe stage) and 21 healthy controls (Roig et al., 2010). The study showed moderate association (r= -0.46) between stair climbing power test and the TUG test in

this group of patients. In addition, validity was found between gait time (10m) and the TUG tests in an observational study of 79 orthopaedic patients (61-84 years old) entering rehabilitation program (r=0.75 on admission and r=0.82 on discharge) (Freter and Fruchter, 2000).

1.9.2.4.3 Reliability

Same day test-retest reliability of the TUG test was found to be high, ICC > 0.90, in older adults across several studies including those with balance deficits, patients with neurological disorder, patients with COPD, and community-dwelling healthy individuals (Bennie S, 2003, Salarian A et al., 2010, Roig et al., 2010, Steffen et al., 2002, Podsiadlo and Richardson, 1991, Mesquita et al., 2013). Recently, Mesquita et al., showed high same day test-retest reliability of the TUG test in patients with advanced COPD (ICC= 0.85, 95%CI: 0.76-0.91), chronic heart failure (CHR) (ICC= 0.94, 95% CI: 0.87-0.97) and chronic renal failure (CRF) (ICC= 0.91, 95% CI: 0.78-0.96) (Mesquita et al., 2013).

1.9.2.4.4 Sensitivity and specificity

Researchers have altered the TUG test either by measuring the time required by patients to perform each subcomponent of the test separately (Salarian A et al., 2010, Wall C., 2000) or by adding an extra task (dual-task) to the test ($TUG_{cognitive}$, and TUG_{manual}), for example, holding a glass of water while performing the TUG test (Shumway-Cook et al., 2000). Regardless of the different approaches used, the sensitivity and specificity of the single-task version of TUG test have been evidenced in these studies without the need to

make any modification which might interfere with the simplicity and objectivity of the test (Nordin et al., 2008, Gyrd Thrane, 2007, Kristensen et al., 2007). In a study to compare the sensitivity and specificity of the single-task TUG test and dual-task $TUG_{cognitive}$, and TUG_{manual} in community-dwelling elderly persons who are susceptible to falling, 15 older adults (mean (SD) age 78 (6)years) with no history of falls, and 15 older adults (age 86 (6) years) with history of two or more falls within six months prior to the study were examined (Shumway-Cook et al., 2000). The study used a cut-off time of ≥13.5s which gave 87% sensitivity and 87% specificity for the single-task TUG test to identify community-dwelling elderly people who are prone to fall without any significant difference when compared to results obtained from the other dual-task tests.

1.9.2.4.5 Minimal Clinical Important Difference

The minimal clinical important difference for the TUG test was investigated in a prospective study of patients with hip osteoarthritis undergoing physiotherapy treatment (9-weeks) (Wright A, 2011). Using three different methods (sensitivity and specificity based approach, within-patients score change approach and between patients score approach), the results showed TUG minimal clinical important difference of equal or less than 0.8s, 1.4s and 1.2s, respectively. To our knowledge the minimal clinical important difference for the TUG test in patients with COPD has not been established yet.

1.9.2.4.6 TUG cut-off values looking at mobility and falls

Literature shows different cut-off times of the TUG test when investigating different conditions, for example, TUG of ≤12 second in community-dwelling elderly women was established to identify normal mobility (Bischoff et al., 2003), TUG of ≥13.5 second in community-dwelling elderly who were susceptible of falling using assistive devices, 18 second for those using a cane, and 34 seconds for those using wheeled-walker (Shumway-Cook et al., 2000).

Gender might have a role in the mentioned cut-off values as in Bischoff et al., study only female participants were included; whereas, the Shumway-Cook et al., study included both genders (Bischoff et al., 2003, Shumway-Cook et al., 2000). Similarly, a two second difference was also found in a longitudinal population-based study (The Tromso study) investigating the association between the TUG test and history of falls in 974 participants (42.7% males) with the mean (SD) age of all participants was 78 (2) years (Gyrd Thrane, 2007). The results of the study support the gender differences where the mean (SD) time for men and women to complete the TUG test were 12 (5.4)s and 13.3 (7.1)s, respectively. Moreover, there is evidence in literature shows an association between the TUG test and age. Steffen et al., have shown an age-related trend of the TUG test in their study: 60-69 years = 8s (95% CI= 7-9), 70-79 years = 9s (95% CI= 7-11), and 80-89 years = 10s (95% CI= 9-12) (Steffen et al., 2002).

1.9.2.4.7 TUG in patients with COPD

In literature, the studies investigating the TUG test in patients with COPD are limited (Table 1.1). Roig et al., showed that muscle strength (assessed by stair climb power test) and mobility (assessed by 6MWD and TUG tests) were impaired in patients with COPD in comparison to healthy controls (Roig et al., 2010). However, their finding are not generalisable to the general COPD population as they used small (n=21) and convenient sample of patients with COPD - Global Initiative for Obstructive Lung Disease (GOLD) stage II and III.

Beauchamp et al., found that TUG is a useful test to differentiate between fallers and non-fallers in patients with COPD (Beauchamp et al., 2009). However, the authors did not use healthy comparators and did not investigate TUG association to the frequency of fall amongst COPD fallers. In comparison to non-fallers, fallers in their study also had greater functional limitations defined by a higher Medical Research Council (MRC) dyspnoea score, and lower walked distance in the 6MWT.

Janssen et al., investigated patients with advanced COPD and Chronic heart failure (CHF) and showed that TUG was inversely related to the general health status (Janssen et al., 2011)

Table 1.1: Studies Investigating TUG in Patients with COPD

n	Author	Year	Type	Size	Group I	Group II	Main Finding	Notes
1	Menard-Rothe et al.	1997	Cross-sectional	59	End-stage emphysema	-	- TUG was the same with 6MWD - Men walked farther and faster but rested more	- TUG instruction was to walk as quickly as possible
2	Butcher et al.	2004	Cross-sectional	51	COPD N=30	Healthy N=21	- TUG was increased in COPD - TUG associated with COPD severity and activity but not O_2 suppliment	- COPD during PR training (3wks minimum) prior to study - All controls were active or on regular exercise
3	Beauchamp et al.	2009	Cross-sectional	39	COPD	-	- Cut-off of 16s is accepted (50%sensitivity and specificity)	- TUG differentiate between fallers and non-fallers - FEV_1% predicted= 42%, 46% on O_2 supplement
4	Beauchamp et al.	2010	Intervention - 6wk cardiopulmonary rehabilitation	29	COPD	-	- Cardiopulmonary rehabilitation improves TUG	- patients recruited after minimum of 3wk of cardiopulmonary rehabilitation
5	Roig et al.	2010	Cross-sectional	42	COPD N=21	Healthy N=21	- TUG & 6MWD were impaired in COPD - Same day test re-test for TUG was ICC [2,1]= 0.95	-
6	Mesquita et al.	2013	Cross-sectional	235	Advance COPD	Advance CHF and CRF	- Improvement from 1st to 2nd TUG trials but not 3rd trial - TUG is reliable to be used in daily clinical practice	-

Abbreviation: Time-Up and Go (**TUG**), six-minute walk distance (**6MWD**), pulmonary rehabilitation (**PR**), chronic heart failure (**CHF**) and chronic renal failure (**CRF**)
References: (Menard-Rothe, 1997), (Butcher et al., 2004), (Beauchamp et al., 2009), (Beauchamp et al., 2010), (Roig et al., 2010), (Mesquita et al., 2013)

1.9.2.4.8 TUG test in research and clinical practice

The TUG is a valid and reliable test that has been shown to be a useful tool to detect limitations of physical performance and balance, risks of fall and improvement post-rehabilitation intervention in healthy subjects as well as number of medical conditions including, but not limited to patients with Parkinson's disease, osteoporosis and COPD (Podsiadlo and Richardson, 1991, Beauchamp et al., 2009, Madureira et al., 2007, Shumway-Cook et al., 2000). Currently, the most commonly used field walking tests have a number of limitations, mainly in the required time and space, which limit their use in research or clinical practice. For example, the 6MWD and ISW tests require certain space (walking track of 30m and 10m, respectively) and time to perform one practice and one actual test (Singh et al., 2014). The SPPB is a multi-task test of physical performance which requires small space, but is limited by ceiling effect (Curb et al., 2006). The TUG test, on the other hand, is a continuous multi-task test of physical performance that requires small space and short time to perform. It can also be used as an objective measure of risk of falls as well as balance impairment along with Borg Balance Scale. Moreover, literature showed that the TUG test has better prognostic power to predict future incidence of falls in community-dwelling older adults than other fall assessment tests such as muscle strength assessment and balance assessment tests including Borg Balance Scale (Bhatt et al., 2011).

These advantages of the TUG test make it superior over other physical performance tests to be used in the research unit environment, clinical

practice and in the community, for example, detecting improvement in tele-rehabilitation programme. Although the TUG test does not reflect exercise capacity or maximum oxygen uptake as the 6MWD and ISWT do, health care providers might, potentially, use the TUG test as streaming tool of physical performance prior to referring to these field walking tests.

Future studies may show that the TUG test adds value in the assessment of patients with COPD to detect reduced physical performance, improvement over time (for example post-rehabilitation intervention) and risks of fall. Furthermore, the TUG test might be used as an initial assessment of physical performance by which a decision of further investigation using other field walking test can be made. The multi-task components associated with the TUG test, for example standing from a seated position, turning and sitting down on the chair, may also be beneficial to assess strength, balance and coordination in patients with COPD as it requires more cognitive involvement. This research may help reveal the potential benefits of the TUG test in the assessment of patients with COPD and fulfil the gap in literature which highlights the need for a physical performance test which requires small space and time in the assessment of patients with COPD.

1.9.2.4.9 Conclusion

The TUG is a simple test of functional mobility that can be used in clinical settings as well as the community for functional assessments of patients with COPD. It is a continuous multi-task test measured in seconds with no ceiling effects. The studies investigating the TUG ability to detect functional

impairments and self-reported previous falls used small sample and convenient sample of patients with COPD. The reliability of the TUG in patients with COPD has been established using same day test-retest reliability. Same day inter-observer and different day intra-observer reliability of the TUG test have not been investigated.

1.10 Hypothesis

- The Time Up and Go (TUG) test is increased in patients with COPD compared to age- and gender-matched controls reflecting impaired physical performance in patients
- The TUG test is inversely related to the six minute walking distance (6MWD) in patients with COPD
- The TUG test is a simple test with high inter- and intra-observer reliability in patients with COPD
- The TUG is a useful test to differentiate between fallers and non-fallers in patients with COPD
- Impaired physical performance, as measured by TUG and/or 6MWT is a significant determinant of the increased aortic stiffness in patients with COPD, independent of age, gender and lung function
- Aortic stiffness is inversely related to self-reported physical activity in patients with COPD
- Patients with COPD have abnormal profile of 24-hour aortic pulse wave velocity when compared to age- and gender-matched controls

Chapter 2

Methods

2.1 Setting

This was a single centre, cross-sectional study that was undertaken at the Nottingham Respiratory Research Unit (NRRU) at Nottingham City Hospital. Each participant was invited to attend one study visit, which lasted approximately 120 minutes.

2.2 Sample size

To test the main hypothesis, the target recruitment number was 180 subjects with a smoking history of greater than 10 pack years: 120 patients with clinically stable COPD and 60 controls without COPD matched for age and gender. Dr Charlotte Bolton performed the statistical power calculation to determine sample size using *G power software* during the designing stage of the study. The calculation was based on mean (SD) TUG time of 15 (4.3) seconds for patients with COPD with no control arm group (Beauchamp et al., 2010). A two-tailed t-test was then used with an effect size of 0.52 and alpha of 0.05. This yielded a power of 90.8% to detect a 15% (2.25 second) difference between patients with COPD and control groups.

2.3 Recruitment

Three sources of recruitment were used for this study:

- **Out-Patients:** Patients attending Respiratory Out-Patient clinic at Nottingham University Hospitals (NHS) Trust were introduced to the study by one of the respiratory consultants. If patients were willing to consider the study, study information sheets (Appendix 1) were sent out and further discussion ensued.
- **Databases:** Potential patients were identified using the Nottingham Respiratory Research Database. This is a database of volunteers with and without respiratory diseases that have consented to have their details stored and to be contacted for future studies. Subjects are entered onto the database from clinics, rehabilitation and additionally from poster, web page (www.nrru.org) and formerly a Facebook link. These volunteers were contacted to be giver brief overview of the study followed by information sheets.
- **Advertisements:** Ethics allowed study specific posters to be placed across both the University of Nottingham and NUH NHS Trust as well as in local newspapers and on websites. Further, COPD posters regarding research in general at the NRRU permit a further source.

2.4 Ethics

This study was approved by the Nottingham Research Ethics Service (NRES): "*The association of lung function and cardiovascular risk*" 10/H0406/65. This ethical permission allows a large population of people with smoking history with and without COPD to be studied. An ethical amendment to permit the further specifics of this project was approved in January 2012. The studies and patients recruited for this study form a specific group for the purposes of this thesis and body of work.

2.5 Inclusion/exclusion criteria

The inclusion criteria for this study include

- Male and female subjects
- 40-85 years old
- >10 pack years history smoking (ex-smokers or current smokers)
- European ancestry. This latter inclusion was set because of the likely genetic, body composition, lung function and CV differences/ influences between subjects of different ethnic origin.

The exclusion criteria include:

- Terminal disease where mortality is expected within a 6-week period.
- Malignancy whether active or suspected,
- Known α1 antitrypsin deficiency
- Pregnancy for female participants.

Subjects were studied at clinical stability defined as ≥4 weeks free from a course of antibiotics for an exacerbation of COPD or change in symptoms suggesting an exacerbation. This was not an exclusion criterion as appointments could be rearranged and deferred. Subjects presenting with previously diagnosed CV disease or diabetes were not excluded in either group.

2.6 Process

All subjects received the study information sheet and given sufficient time (up to two weeks) to read through the information sheet and ask questions regarding their participation in the study. They were then contacted to assess whether they were willing to participate. A suitable date was arranged and an appointment letter, a map of the City Hospital and directions to the NRRU were sent. A taxi was offered to the subjects or alternatively the cost of travel and parking was reimbursed.

2.6.1 Informed consent

Upon arrival, the objectives of the study and the required tests to be performed during the study visit were discussed.

Consent allowed the opportunity for the subject to ask questions, the researcher to outline the nature of participation and specify the use of the obtained samples and confirmed the agreement to take part in the study. The consent also included optional points, which the participants may choose whether to agree on including consent for 24 hour ambulatory BP monitor in the subgroup (Appendix 2).

2.6.2 Patients' details and questionnaires

Detailed information regarding the patient's physical activity, smoking history and occupational exposure, history of falls, detailed lung related conditions, and other general medical conditions were recorded.

Further, subjects were asked to complete three respiratory related questionnaires during the study visit:

2.6.2.1 St George's Respiratory Questionnaire (SGRQ)

The SGRQ assesses how patients' view their illness (Jones et al., 1992). The SGRQ consists of three parts – symptoms, activity, and impacts of COPD (Appendix 3). Each part is calculated separately and the total score is calculated where higher scores indicate worse health status.

In a quiet clinical setting, subjects were given sufficient time to complete the questionnaire independently. Subjects were allowed to ask clarification questions as needed regarding the questionnaire. Once completed, the questionnaire was checked for missing or uncompleted answers and the scores calculated.

2.6.2.2 Medical Research Council (MRC) dyspnoea scale

The MRC dyspnoea scale is a graded scale to assess patient's breathlessness (Appendix 4). It consists of five sentences – numbered 1 to 5 - where the

patient is asked to tick the sentence which best describes his/her dyspnoea (Fletcher, 1960).

2.6.3 Height and weight measurements

Measurements of height (metres) and weight (kilograms) were obtained using Seca scales device (Seca, Germany). Subjects were asked to stand on the weight scale barefoot and without outdoor clothing on. From this, the body mass index (BMI) was calculated: weight/square of height (in metres). BMI is a widely accepted index to classify underweight, overweight, and obesity in adults (WHO, 2006).

2.6.4 Body composition

Bioelectrical Impedance Analysis (BIA) body (Tanita BC-418, UK) was used to measure the body composition including, but not limited to, fat and fat-free mass (Appendix 5). The participant's age, height and gender were inputted in the BIA before he/she was asked to stand on the device to obtain the measurements. Subjects were asked to empty their bladder and be bare foot so removing all socks/stockings. Contradictions to BIA include pacemakers and implantable cardiac defibrillator. Other contraindications for BIA such as pregnancy were excluded as part of the exclusion criteria for the main study.

2.6.5 Haemodynamic profile

Haemodynamic measurements preceded many investigations in order to avoid the effect of beta2-agonist drugs - used during the lung function test - or exhaustion after the 6MWT. Subjects were also asked to refrain from caffeine substances and other respiratory medications prior to their visit.

2.6.5.1 Peripheral blood pressure (BP) measurements

Subjects were asked to sit and resting time was allowed for a period of >10 minutes. The appropriate sized cuff was placed on the upper part of the right arm with the bladder placed over the brachial artery. The BP was measured on three occasions following detailed Standard Operating Procedures (SOP) using a British Hypertension Society (BHS) validated BP monitor (Omron 705IT, UK). The average of the three systolic and diastolic measures was used to determine seated BP. From these, the peripheral pulse pressure (PPP) and peripheral mean arterial pressure (MAP) were calculated

The subject was asked to lay down supine with one pillow in a comfortable position for >10 minutes allowing haemodynamic stability before taking further BP measurements for supine assessment. The same method to determine supine peripheral BP was undertaken.

2.6.5.2 Central haemodynamics

Central haemodynamics were taken with the subject both seated and supine using the Vicorder apparatus (Skidmore Medical, UK). The Vicorder cuff was

placed on the right brachial artery and systolic, diastolic, MAP, augmentation index (Aix), and heart rate were measured on three occasions and the average recorded following >10 minutes rest in the seated and then supine position.

2.6.5.3 Pulse wave velocity (PWV)

The aPWV was performed using Vicorder apparatus (Skidmore Medical, UK) which is non-invasive and a simple device that has been validated for measuring the PWV (Hickson et al., 2009) (although further methodological amendments have been made following discussion with the authors of this paper and the company).

In a supine position and after a period of rest - >10 minutes - in a quiet room, aPWV was performed by placing a standard vascular cuff around the right upper femoral artery and a bladder over the subject's carotid artery on the site of the carotid artery (Appendix 6).

Path length was measured starting from the suprasternal notch to the top of the femoral cuff and adding five centimetres (to represent the distance to the middle of the cuff where the maximum inflation point is and provide more accurate measurements of the length path. Transit time (TT) – the time in which the pulse wave travels between two arterial sites - was calculated by the Vicorder. The aPWV was calculated as path length/TT (m/s) (Appendix 7). Measurement of aPWV of <4.7m/s is considered inaccurate and any such values were excluded from analysis.

2.6.6 Spirometry measurements

A three-litre syringe was used to calibrate the Micro-medical spirometer (MicroLab MK6) on the day of each visit. All subjects were asked to refrain from respiratory inhalers six hours prior to their visit. Before performing the test, subjects were checked for any contraindications such as abdominal/thoracic/eye surgery or myocardial infarction within the past three months, unstable angina, uncontrolled hypertension, glaucoma, perforated eardrum, aneurysm, haemoptysis, and steroids/antibiotics for the chest within the past four weeks.

Pre and post bronchodilator measurements were determined while subjects were seated upright on a chair with arms. Subject's details were inputted in the spirometer including the age, gender and height and the procedure of how to perform the test was explained. Subjects were instructed to take a deep breath in and blow it out as fast and as long as possible while making a good seal with his/her mouth around the mouth piece of the spirometer.

With each blow, subjects received continuous encouragements by saying "keep going" until subjects could not blow anymore.

Three repeatable pre-bronchodilator attempts were taken according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) criteria (Miller et al., 2005).

Reversibility testing was performed by administering 400mcg Salbutamol via an MDI and spacer. Fifteen to twenty minutes were allowed before the

postbronchodilator test was performed. For pre and post bronchodilator spirometry , measurements of actual value of FEV_1, FEV_1% predicted, actual value of forced vital capacity (FVC), FVC% predicted, and the FEV_1/FVC ratio were measured against the predicted values based on gender, age and height. Only Post-bronchodilator measurements were used in the analysis.

Severity of airflow obstruction (FEV_1/FVC <0.7) in subjects with COPD was classified using the NICE criteria (Table 2.1) (NICE, 2010).

Table 2.1 NICE Classification of the Severity of COPD (NICE, 2010)

Abbreviation: Forced expiratory volume in one second (**FEV_1**)

Stage	**Post-bronchodilator Predicted value of FEV_1%**
Mild	$FEV_1 \geq 80\%$ (and symptoms)
Moderate	FEV_1 50-79%
Severe	FEV_1 30-49%
Very severe	FEV_1 <30%

2.6.7 Carbon monoxide measurement

The level of exhaled carbon monoxide (CO) was determined using Clement Clarke Smokerlyzer CO monitor. The obstacle some patients might encounter during this test is the 15 seconds breath hold. The recommended technique for using CO test is to ask the patients to hold their breath for few seconds and not to use the exact number 15 seconds (Covita., 2013). Thus, each subject was instructed to take a deep breath in and hold it for few seconds then breathe it out normally through the mouthpiece of the CO monitor. On a scale of 1-80 showing on the monitor, current smokers would likely exceed 10.

2.6.8 Venepuncture

Subjects' eligibility for blood sample was assessed and procedures were explained. Following the aseptic non-touch technique, up to two attempts (maximum) were performed on each subject; if both attempts failed, subject was taken to phlebotomy for venepuncture. For each subject, plasma (EDTA and Lithium Heparin) and serum was taken. Serum was sent for immediate biochemistry analysis (lipid profile) and further aliquots centrifuged and stored at -80 degrees Celsius for later research analysis (not covered in this Ph.D).

2.6.9 Field walking and physical performance tests

This was assessed objectively by asking the subject to perform two tests - the 6 minute-walk test (6MWT) and the Time Up and Go (TUG) test.

2.6.9.1 Six minute walk test (6MWT)

Oxygen saturation and heart rate (Konica Minolta Pulsox-300) were monitored before, during and immediately after the test. Self-reported level of breathlessness - measured by Borg scale (Burdon et al., 1982) (Appendix 8) – was recorded before and immediately after the test (ATS, 2002).

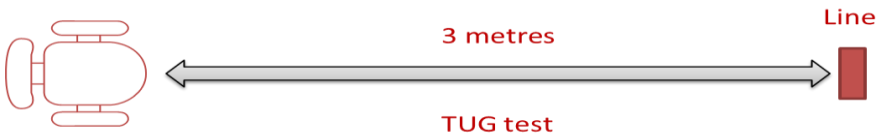
In a quiet enclosed corridor, subjects were asked to walk for six minutes on a 10-metre marked course with one cone placed at each end where the subject should turn around and continue his/her walk. One cone was placed at 0.5 and 9.5 to allow turning being 10 metres. Subjects were allowed to rest - if needed (chairs at either end of walking course) - and continue walking during the allocated time. Subjects were allowed to use any gait aid throughout the test.

2.6.9.2 Time Up and Go

Following the original procedures of the test, subjects were instructed to stand up from a seated position on a standard armed chair (46cm), walk for three metres, turn, return, and sit down (Figure 1.1) (Podsiadlo and Richardson, 1991).

Using one phrase, each subjects was instructed as follow: on the word go, I want you to stand up, walk at a regular pace to the line on the floor, turn, walk back to the chair and sit down, The timing of the test starts on the word "GO" while subjects in sitting position and ends when returning to initial sitting position. Usage of gait aids were allowed as needed and subjects were instructed to walk at their comfortable pace during the test.

Figure 1.1: Diagram of the Time Up and Go Test



2.6.10 Ambulatory 24 hour blood pressure and arterial stiffness

The Mobil-O-Graph 24-hour ambulatory BP monitor was used to measure haemodynamics during daytime and overnight via a pre-set protocol (Appendix 9).

The diurnal and nocturnal systolic BP measurements were used to detect nocturnal dip; by which, subjects can be classified into inverse dippers: systolic nocturnal dip of <0%; non-dippers: systolic nocturnal dip of <10%; dippers: systolic nocturnal dip <20%; and extreme dippers: systolic nocturnal dip of ≥20% (Kario et al., 2001a). Due to our small sample size, we grouped

inverse and non-dippers together, and then grouped dippers and extreme dippers together.

This was an exploratory study where an arbitrary 40 subjects (20 patients and 20 controls) were initially planned to recruit; however, 46 were invited to undertake this test. Subjects were taught how to use the device and initial reading was taken during the visit by placing the cuff on the upper arm. The cuff was pre-set to inflate intermittently - twice per hour during the daytime and once per hour during nighttime - to record the BP and other haemodynamic measures. On the return day, stored readings in the machine were transferred to a software programs in a password protected laptop provided by the University of Nottingham (Appendix 10).

2.6.11 Oxygen saturations

Oxygen saturation was measured by pulse oximeter with the patients breathing room air and rested for >20min (Konica Minolta Pulsox-300).

2.6.12 Composite COPD measures

The BMI, airway obstruction, dyspnoea and exercise capacity (BODE) index is a multidimensional grading system which helps to predict disease outcome in patients with COPD (Celli et al., 2004). In this index, systemic components of the disease such as exercise capacity and BMI are accounted for. BODE scale ranges from a minimum score of 0 to a maximum score of 10. Each of the four components of the BODE index is given a score range 0-3 except for the

BMI score which can only be 0-1 depends on the degree of impairment of each component (Appendix 11).

The ADO index on the other hand was developed to predict 3-year mortality and prognosis of COPD (Puhan et al., 2009). Each component of the ADO index is scored differently, for example, a score range of 0-5 is used for the age component, a score of 0-3 is used for MRC dyspnoea scale and a score of 0-2 is used for the airway obstruction (Appendix 12).

2.6.13 Assessment of self-reported physical activity

Self-reported physical activity questionnaires were divided into three parts: first is the frequency of doing mild, moderate and vigorous activity per week (≥3 times/wk, 1-2 times/ wk, 1-3 times/ month or almost never), second is the time (hrs/wk) each subject spends doing mild, moderate and vigorous activity, and finally is the time each subject spent walking outside home/workplace in the past week by reporting an average walking time (minutes) for each weekday as well as each weekend day.

Mild activity includes, but not limited to, walking, gardening, playing darts and housework. Moderate activity includes, but not limited to, scrubbing, polishing car, dancing, golf, cycling, decorating, lawn mowing and leisure swimming. Finally the vigorous activity includes, but not limited to, running, tennis, squash, digging and hard swimming.

2.6.14 Self-reported co-morbidity score

Co-morbidities were recorded in all subjects. From this, one point was given to each self-reported co-morbid condition listed in Charlson Co-morbidity Index which includes myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, COPD, connective tissue disease, peptic ulcer disease, diabetes mellitus, hemiplegia, malignant lymphoma, solid tumor, liver disease and acquired immune deficiency syndrome (AIDS) (Charlson et al., 1987). The nature of co-morbidity history taking in the design of our study did not allow for the accurate use of Charlson Co-morbidity Index. Also to note some of the comorbidities used in Charlson Co-morbidity Index were exclusion criteria for this study.

2.6.15 Post visit

After each visit, a thank you letter was sent showing appreciation to the participant for taking part in the study. A travel expenses form was completed if required and a letter of the patient's participation was sent to the general practitioner (GP) along with clinically relevant results (spirometry, carbon monoxide, pulse oximetry, MRC dyspnoea scale, BP, and blood results). Any abnormalities in the results were highlighted and assessed by the chief investigator prior to posting the letter to the GP.

2.7 Confidentiality

Subject's full name, date of birth, contact details, study code number, date of the visit, and the GP address were documented separately from the Case Report File. The Case Report File included limited personal information such as the subject initials, date of birth and a study code number thus anonymising the data, but allowing tracking of for example biochemistry results. All Case Report Files were stored in a locked office at the Clinical Sciences Building at the City Hospital and only the chief investigator, research team and authorised personnel from relevant regulatory authorities had access to these files. Anonymised electronic data was saved on a password-protected laptop, which was provided by the University of Nottingham

2.8 Statistics

Statistical package of the Social Sciences (SPSS) version 21 was used for data analysis. For normally distributed data parametric tests were used: Chi squire test was used to statistically compare two categorical variables. Independent t-test was used to look for differences of a continuous variable between groups and one way ANOVA (Post Hoc, Tukey) for a categorical variable with more than two groups). Pearson's test was used to analyse the correlation between two continuous variables. Inter-class correlation coefficient (ICC) with 95% confident interval (CI) was used to test for reliability of a measure. Bland-Altman plot was used to investigate the level of agreement between two measurements. A stepwise linear regression was used to examine

independent confounders for a specific variable where the variable of interest was the dependent variable and the potential confounders were the independent variables. For non-normally distributed data non-parametric tests were used: Mann-Whitney and Kruskal-Wallis tests were used to look for differences of a continuous variable between two groups (Mann-Whitney) or more than two groups (Kruskal-Wallis). Spearman's test was used to look for correlation between two continuous variables.

Area under the receiver operating characteristic (ROC) curve (AUC) was used to assess the sensitivity and specificity of the TUG time and look for the optimal absolute time (seconds) of the TUG test that is related to self-reported fallers and non-fallers in the past year. In all analyses, a $p<0.05$ was considered statistically significant.

Chapter 3

The Time Up and Go in Patients with COPD

3.1 Introduction

There is increasing evidence in literature relating impaired physical function to the burden of chronic obstructive pulmonary disease (COPD) (Pinto-Plata et al., 2004, Pitta et al., 2005a, Herman et al., 2011, Peruzza S, 2003). The standard and most commonly used measure of physical performance in patients with COPD is the Six-Minute Walk Test (6MWT) (Kario et al., 2001b). However, in the real world of clinical practice, the 6MWT takes time to perform, needs space (at least 10m and 30 metres recommended), and requires a practice walk followed by a resting period (ATS, 2002). Therefore, simple measures of physical performance that require less time and space to perform are required and that could be implemented into COPD assessments.

The Timed-Up and Go (TUG) is a physical performance test that was developed by Podsialdo and Richardson, to assess mobility and balance in frail elderly (Podsiadlo and Richardson, 1991). Owing to its simplicity, validity, and high reliability, TUG has become widespread in different research areas of interest and in different health conditions (van Hedel et al., 2005, Podsiadlo and Richardson, 1991, Mesquita et al., 2013, Kristensen et al., 2007, Bischoff et al., 2003).

There are studies investigating TUG in patients with COPD but they were limited by either small sample size or not having control comparators. These studies showed that the TUG test was inversely related to general health (Janssen et al., 2011), was useful test to detect limitation of physical

performance in patients with COPD in comparison to healthy controls (Roig et al., 2010) and to differentiate between patient fallers and non-fallers (Beauchamp et al., 2009). There were some studies investigating performance and balance in patients with COPD using TUG and 6MWT, but the relationship between these two tests was not assessed (Butcher et al., 2004, Beauchamp et al., 2009, Roig et al., 2010).

Recently, same day test-retest reliability and practice effects of the TUG test in patients with advanced COPD, CHF, and chronic renal failure (CRF) was explored (Mesquita et al., 2013). Each patient was asked to perform three consecutive TUG trials on the same day. Their results showed good correlations between the tests in all subjects as well as in each group defined by their medical condition (COPD, CHF or CRF). High reliability was found between the first two TUG trials, and no additional information found from the third trial. Same day inter-observer as well as different day intra-observer reliability test of TUG in patients with COPD was not available. In all of these studies, detailed comparison with healthy subjects has not been reported (Mesquita et al., 2013, Beauchamp et al., 2009, Menard-Rothe, 1997). Exploring the relationship of TUG to the established measure of physical performance in COPD – the 6MWT – is important.

Taken together, there is opportunity to further explore the potential role of TUG in patients with COPD in relation to controls, explore parameters affecting the TUG and assess its validity.

3.2 Hypothesis

- The Time Up and Go (TUG) test is increased in patients with COPD compared to age- and gender-matched controls reflecting impaired physical performance in patients
- The TUG test is inversely related to the six minute walking distance (6MWD) in patients with COPD
- The TUG test is a simple test with high inter- and intra-observer reliability in patients with COPD
- The TUG is a useful test to differentiate between fallers and non-fallers in patients with COPD

3.3 Methods

This was a single centre cross-sectional study to investigate the potential application of the TUG test in COPD physical performance assessment and with a comparator group of controls.

3.3.1 Study objectives

To:

- Compare TUG in patients with COPD and controls
- Investigate the association of baseline factors
- Explore the relationship between TUG and Six-Minute Walk Distance

- Investigate ability for TUG to differentiate between fallers and non-fallers in patients with COPD
- Investigate practice effect of TUG in patients and controls
- Assess the relationship of TUG to quality of life questionnaires
- Assess the relationship of TUG to self-reported physical activity
- Explore inter- and intra-observer reliability of the TUG test

3.3.2 Ethics

The study was approved by the National Research Ethics Service (NRES) (Methods, p 51)

3.3.3 Sample size

Subjects (n=181) were consented and included in the analysis of this study (Methods, P 49).

3.3.4 Inclusion and exclusion criteria

Details of inclusion and exclusion criteria are mentioned in the Methods, p 51. Subjects were allowed to use walking aids and oxygen supplement as needed. In order to have a representative sample of the general COPD group, a wide range of patients with different GOLD stages and with/without co-morbidities were included.

3.3.5 Procedure

3.3.5.1 Informed consent

Informed consent was obtained (Methods, p 53).

3.3.5.2 Timed-Up and Go (TUG) test

Each subject was instructed to stand up from a regular armed chair (46cm), walk for three metres indicated on the floor, turn around, go back to the chair, and sit down (Podsiadlo and Richardson, 1991). Using a regular stop watch, time was taken starting from the word "Go" and stopped when the subject returned and sat down on the chair like the starting position. As per protocol, two TUG trials were performed at each study visit with opportunity to recover in between the two trials. The time for the first practice TUG was only recorded in 141 subjects.

3.3.5.3 Six-Minute Walk Distance (6MWD)

After a minimum period of 60 minutes rest post the TUG test, subjects were asked to perform the six-minute walk distance (6MWD) (Methods, p 61)

3.3.5.4 Fall Assessment

All subjects were asked to report any experience of fall in the past year. Fall was defined as "when you find yourself suddenly on the ground, without intending to get there, after you were in either a lying, sitting or standing

position" (Cwikel et al., 1998). This was recorded as (0,1,2,3,4, ≥5 falls in the last year) and for analysis purposes grouped as 0,1,2,≥3 falls.

3.3.5.5 Self-Reported Physical Activity

Physical activity was classified based on intensity into mild, moderate, and vigorous energetic activity. Each activity level was described in Methods, p 64. Subjects were asked to report their activity level (mild, moderate, and vigorous), frequency of engaging in each activity level per week (never, 1/3 time/wk, 1/2 time/wk, ≥3 time/wk) and the average hours they spend in such activity per week.

3.3.5.6 Quality of life and respiratory questionnaires

St. George's Respiratory Questionnaires (SGRQ) and MRC dyspnoea scale were assessed (Methods, p 54).

3.3.5.7 Inter- and Intra-observer reliability tests

TUG reliability was assessed using two methods: inter- and intra-observer reliability tests. In the inter-observer reliability, two observers were assigned to take measurements of the TUG test at the same time. The intra-observer repeatability test was performed by a single observer taking two TUG readings on different days (two to seven days between each test).

3.3.5.8 Other baseline variables

Other variables, body composition (Body Mass Index (BMI), and Fat Free Mass Index (FFMI)), oxygen saturation, and spirometry were assessed (Methods, p 55). Baseline variables also included smoking history and co-morbidities - the co-morbidity score was calculated for each subject based on the reported conditions by assigning one point for each medical condition referred to in the Charlson Co-morbidity Index (Charlson et al., 1987) (Methods, p 65).

3.3.6 Statistics

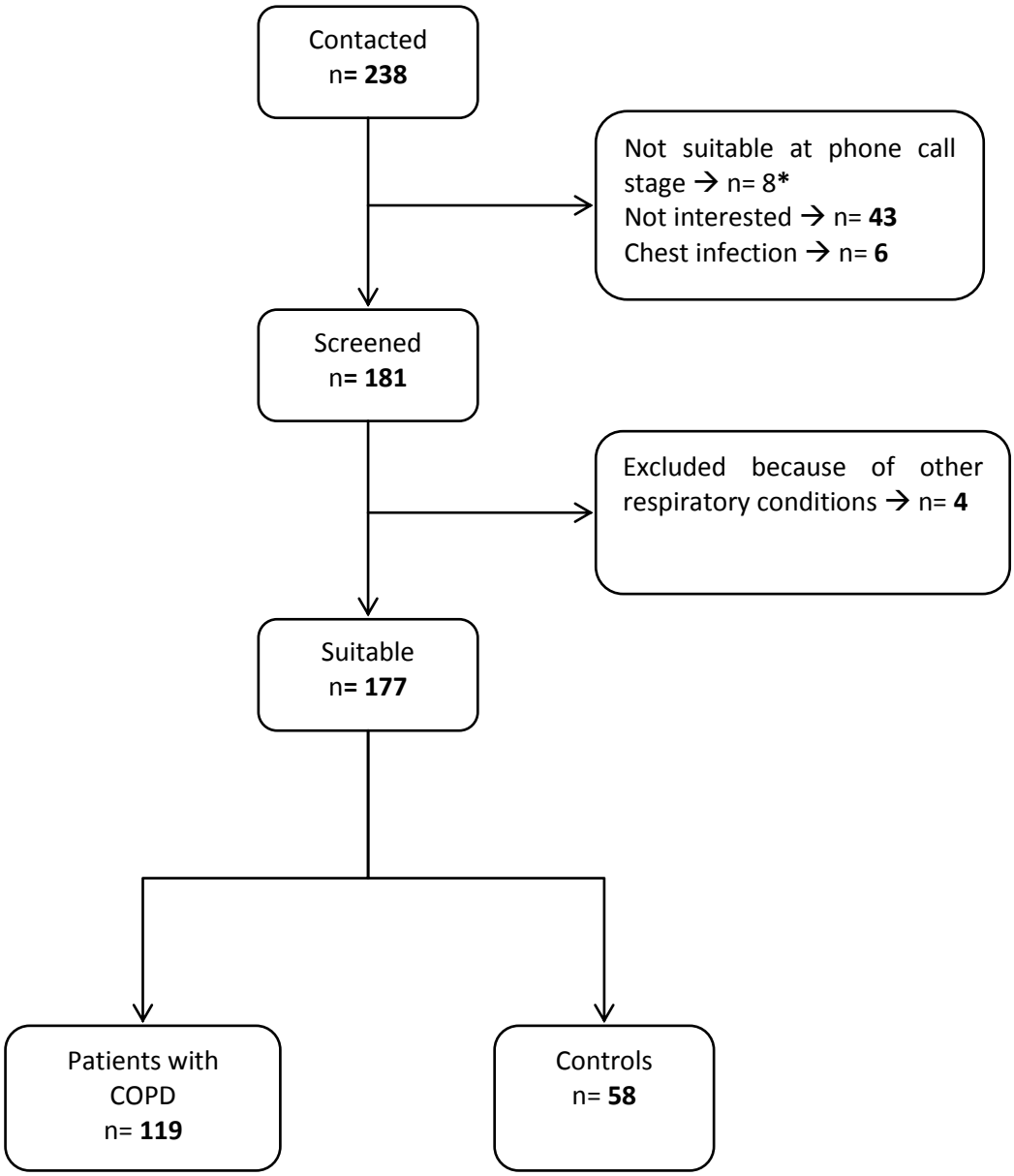
Statistical Package of the Social Science (SPSS) version 21 was used for data analysis. Any difference was considered statistically significant if p-value ≤0.05. Chi squire test was used for analysis of categorical variables. Independent t-test was used for comparison between the two groups where data was continuous and normally distributed. One way ANOVA was used when more than two groups and a continuous variable. Pearson (r) was used to assess correlations for continuous variables where normally distributed. Inter-class correlation coefficient (ICC) and Bland-Altman plot were used to demonstrate the level of agreement between two measurements when analysing different day 'intra-observer' reliability and same test 'inter-observer' reliability of the TUG test. A stepwise linear regression analysis was performed to detect factors influencing TUG and fall. Receiver operating characteristic (ROC) curve was used for sensitivity and specificity analysis of TUG test and self-reported fall incidence.

3.4 Results

From April 2012 to September 2013, 181 of the 238 subjects who were contacted by telephone calls and email messages attended a study visit. The main reasons for those who did not participate are listed in Figure 3.1. Out of the 181, four subjects who attended the clinic study had respiratory conditions other than COPD; therefore, study analysis included 177 subjects (Figure 3.1).

Patients and controls were matched for age, gender, and body mass index (BMI); however, both groups differed significantly in resting oxygen saturation and spirometric parameters (Table 3.1).

Figure 3.1: Flowchart of Study Recruitment



*Reasons for exclusion: smoking history <10 pack/year, and prior participation in the study

Table 3.1: Demographics of Study Groups - Patients and Controls

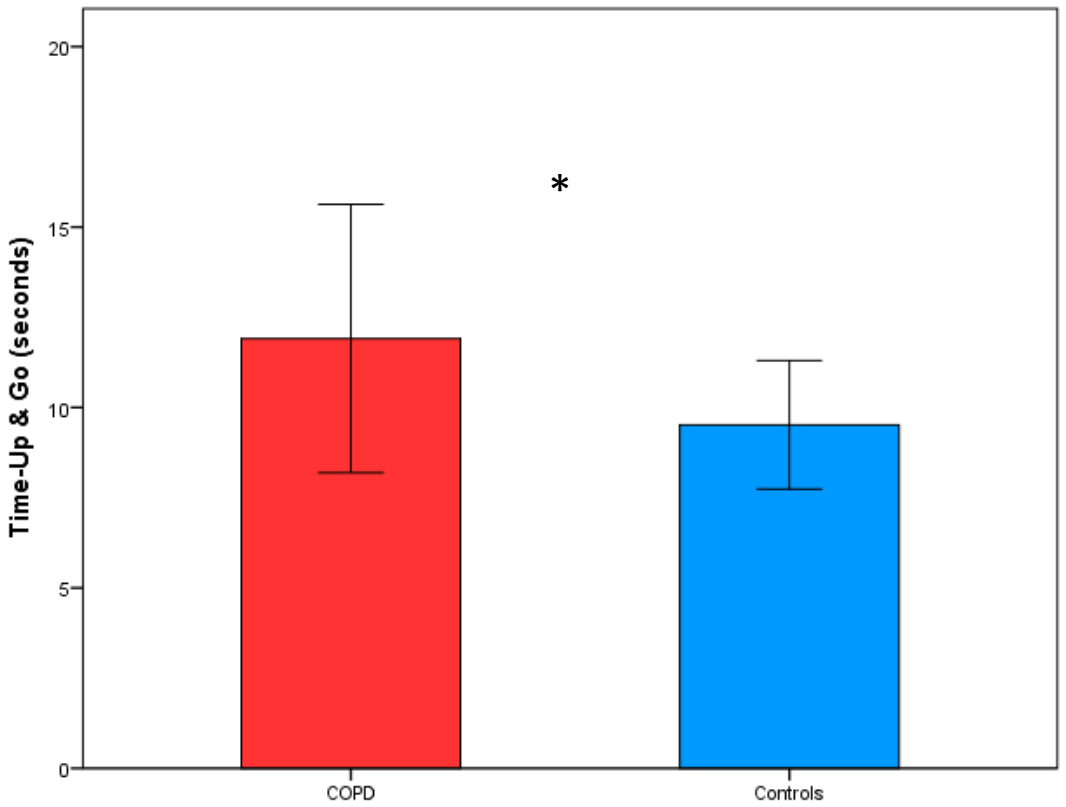
Mean (SD) unless otherwise indicated	**COPD n=119**	**Controls n=58**	**p-value**
Male n (%)	74 (62)	38 (66)	0.67
Age (years)	68 (8)	66 (9)	0.15
BMI (kg/m^2)	27.3 (6.0)	28.6 (5.2)	0.15
FFMI (kg/m^2) – Patients n= 114 / Controls n=58	18.4 (3.0)	19.2 (2.4)	0.12
Smoking history (pack years)	46 (26)	31 (20)	**<0.001**
Smoking status – n (current/ex-smoker)	39/80	8/50	**<0.01**
FEV_1 (L)	1.60 (0.57)	2.80 (0.61)	**<0.001**
FEV_1% predicted	59 (18)	100 (15)	**<0.001**
FVC (L)	3.25 (0.84)	3.79 (0.89)	**<0.001**
FVC% predicted	96 (19)	108 (19)	**<0.001**
FEV_1/FVC ratio	49 (13)	74 (7)	**<0.001**
SpO_2 (%)	95 (2)	96 (1)	**<0.001**
TUG time (seconds)	11.9 (3.7)	9.5 (1.8)	**<0.001**
6MWD (m) – Patients n=117 / Controls n=58	291 (97)	380 (76)	**<0.001**

Abbreviations: Body mass index (**BMI**), fat free mass index (**FFMI**), forced expiratory volume in 1 second (**FEV_1**), forced vital capacity (**FVC**), oxygen saturation (**SpO2**), Timed-Up and Go (**TUG**), six-minute walk distance (**6MWD**).

3.4.1 Time Up and Go in patients and controls

Patients had significantly increased mean (SD) TUG time of 11.9 (3.7)s compared to controls 9.5 (1.8)s; p<0.001 (Figure 3.2). The difference remained significant when adjusting for age and gender.

Figure 3.2: TUG Time in Patients and Controls



*significance at p<0.001
Error bars show ±1 standard deviation

3.4.2 Potential confounders of Time Up and Go test

3.4.2.1 3.4.2.1 Age

Pearson's correlation test did not show any significant association between TUG and age in all subjects; r= 0.11, p= 0.16. However, within groups' analysis showed significant association between TUG and age in controls (r= 0.33, p= 0.01) but not in patients (r= 0.01, p= 0.89).

3.4.2.2 Gender

Independent t-test analysis for the association between TUG and gender in all subjects as well as within - patients and controls - showed no significant difference; p= 0.74, and p=0.76, and p= 0.12; respectively.

3.4.2.3 Body composition

3.4.2.3.1 Body Mass Index

Analysis showed no significant correlation between TUG and BMI in all subjects (r= 0.14, p= 0.06) and controls (r= 0.21, p= 0.12); however, the correlation just reached significance in patients; r= 0.19, p= 0.04.

3.4.2.3.2 Fat Free Mass Index

Pearson's correlation showed no association between TUG and FFMI in all subjects, in patients alone, or in controls alone; p=0.30, p= 0.12, and p=0.82, respectively.

3.4.2.4 Smoking history (pack year)

The association between TUG and smoking history (pack years) did not reach significance; r= 0.15, p= 0.05 in all subjects, nor patients and controls separately; r= 0.03, p= 0.72, and r= 0.22, p= 0.09; respectively.

3.4.2.5 Oxygen saturation (at rest)

The TUG test was inversely associated with resting oxygen saturation (SpO_2) in all subjects (r= -0.28, p< 0.001) as well as in patients (r= -0.20, p= 0.03); but not in controls (r= -0.10, p= 0.44). All subjects performed the TUG test on room air. Resting SpO_2 measurements of all subjects were taken after 20 minutes on room air.

3.4.2.6 Self-reported co-morbidity score

A co-morbidity score was increased in patients with COPD compared to controls: median (IQR): 1 (1-2), and 0 (0-1), respectively; p<0.001. When not accounting for "COPD" in the score, both groups were similar in self-reported co-morbidity score: median (IQR) for patients 0 (0-1) and for controls 0 (0-1), p= 0.38.

Male patients (n= 74) reported significantly more co-morbidities 1 (1-2) compared to female patients (n= 45) median (IQR) 1 (1-2), p= 0.03; but no gender difference was found in self-reported co-morbidities in controls, p= 0.52. There was no association between age and self-reported co-morbidity score in patients, p= 0.11, or controls, p= 0.30. Correlation of the TUG test to self-reported co-

morbidity score was significant in patients (r= 0.26, p=0.004), and in controls (r=0.28, p=0.031).

3.4.2.7 Spirometry

Within group analysis showed no correlation between TUG time and any spirometer parameters with exception to FEV_1/FVC ratio in the control, but not in patients (Table 3.2).

Table 3.2: Correlations between TUG and Spirometric Lung Function

	COPD		**Controls**	
	Correlation (r)	**P-value**	**Correlation (r)**	**P-value**
FEV_1 (L)	0.04	0.64	-0.19	0.15
FEV_1% predicted	0.004	0.96	0.26	0.05
FVC (L)	-0.09	0.32	-0.26	0.05
FVC% predicted	-0.05	0.62	0.06	0.64
FEV_1/FVC	0.06	0.55	0.27	**0.04**

Abbreviations: Forced expiratory volume in one second (**FEV_1**), forced vital capacity (**FVC**).

3.4.2.7.1Time Up and Go test and GOLD stages of COPD

According to GOLD classification of COPD, only three patients were classified as GOLD IV stage and; therefore, GOLD III and GOLD IV were combined for analysis purposes. The mean time to complete TUG in each GOLD stage of COPD is shown in Table 3.3. One way ANOVA did not show significant difference between TUG test and different GOLD stages (GOLD I, GOLD II, and GOLD III/IV combined).

Table 3.3: Mean TUG test in Different Stages of COPD Based on GOLD

-	n	TUG time (seconds)
GOLD I	13	13.0 (3.6)
GOLD II	68	11.7 (4.0)
GOLD III/IV	38	12.0 (3.3)

Abbreviations: Time Up and Go (**TUG**), Global Initiative for Chronic Obstructive Lung Disease (**GOLD**)
Results are mean ±SD.

3.4.2.8 Regression analysis of the potential factors affecting TUG

A step-wise linear regression was performed where TUG was the dependent variable and the independent variables entered into the model were: age, gender, self-reported co-morbidity and resting oxygen saturation; only self-reported co-morbidity and resting oxygen saturations was found to be a significant variable, accounting for 9.3% of the variation between them.

3.4.3 Six-Minute Walk Distance

Two out of the 119 patients were not able to perform the 6MWD; therefore, 117 patients and 58 controls were included in the analysis. The mean (SD) 6MWD was decreased in patients, 291 (97)m, compared to control, 380 (76)m, $p<0.001$.

An inverse correlation was found between TUG and 6MWD in all subjects; $r= -0.76$, $p<0.001$ (Figure 3.3a). Similar associations were found for TUG and 6MWD when patients and controls were analysed separately; $r= -0.74$, $p< 0.001$, and $r= -0.71$, $p< 0.001$, respectively (Figure 3.3b, c).

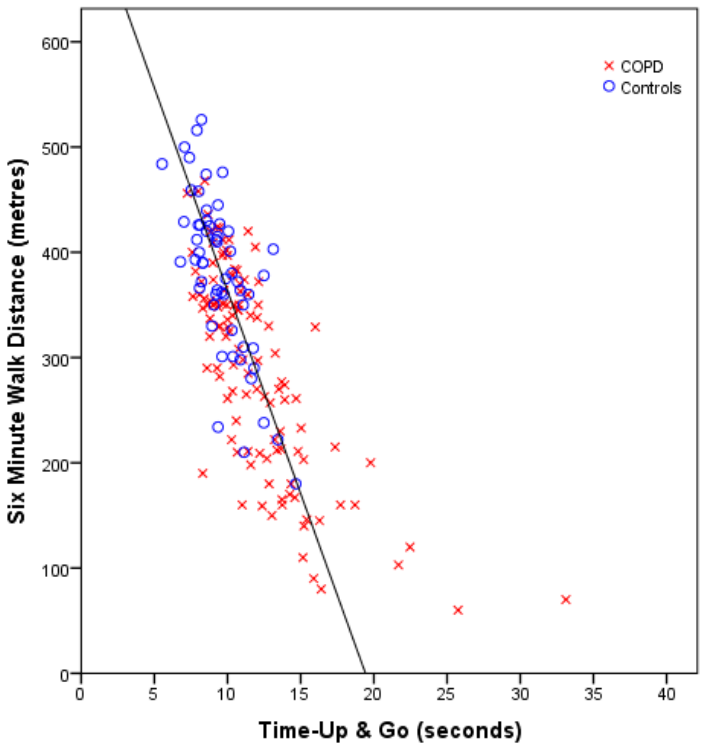
3.4.4 Time Up and Go and BODE in Patients

Of the 119 patients, two did not complete the 6MWD and, therefore, BODE was calculated in 117 patients. The mean (SD) BODE score was 4 (2). Correlation analysis showed significant association between TUG and the BODE score, $r= 0.53$, $p<0.001$.

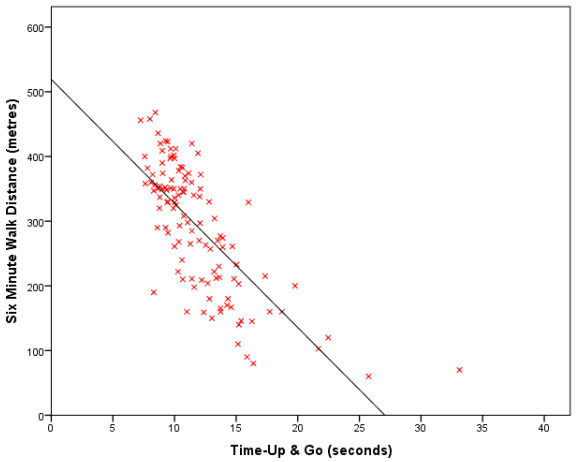
For the BODE index patients were classified as follows: BODE 0-2 (n=33), BODE 3-4 (n=28), BODE 5-6 (n=37) and BODE 7-10 (n=19). One way ANOVA (post HOC, Tukey) showed that TUG was significantly associated to the BODE index (Figure 3.4).

Figure 3.3: Inverse Association between TUG and 6MWD

a. All Subjects



b. **COPD**



c. Controls

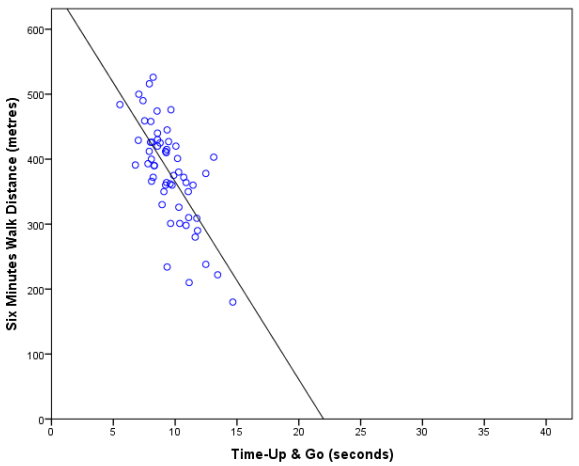
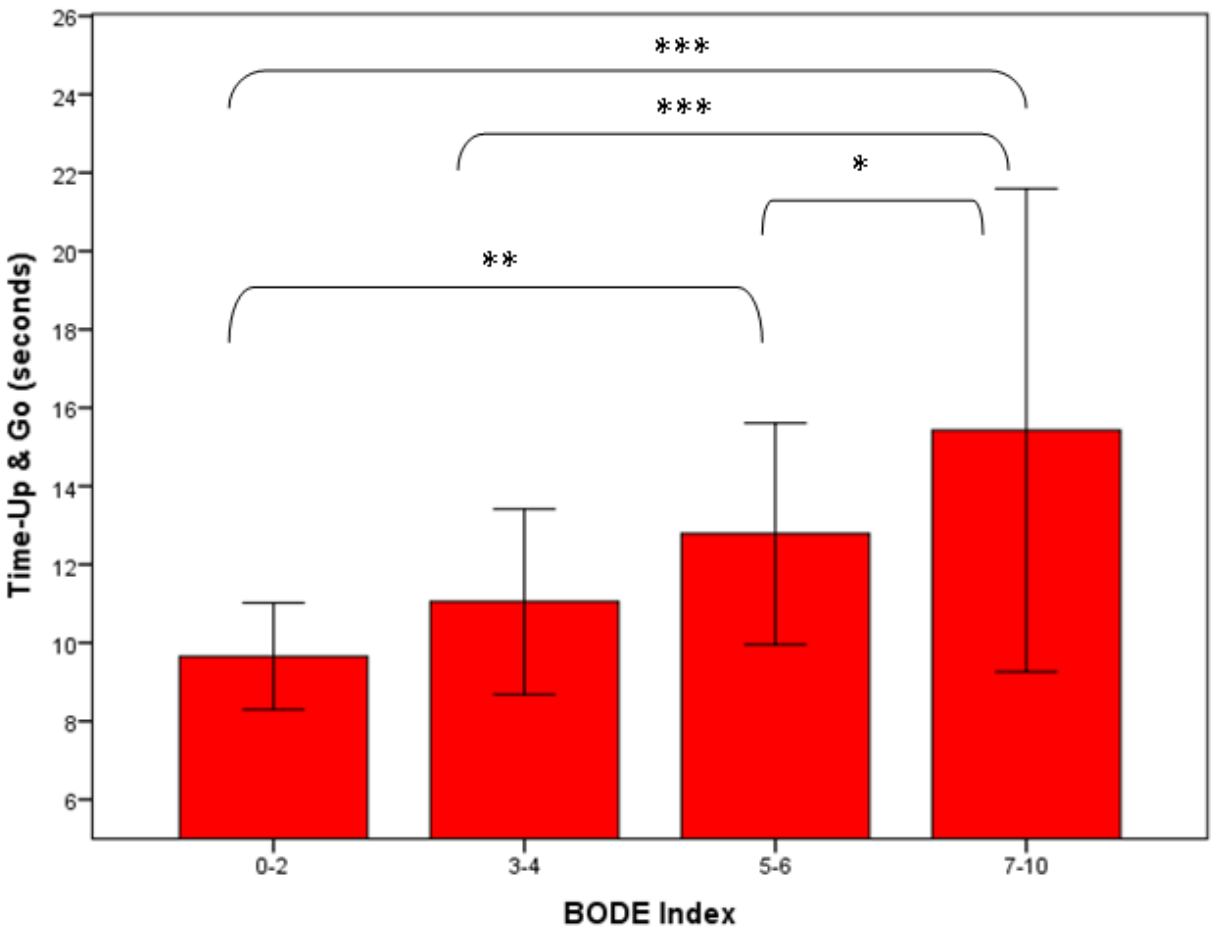


Figure 3.4: Association of Time Up and Go to the BODE Index in Patients



Error bars represent ±1 standard deviation
*Significance at p< 0.05
**Significance at p< 0.01
***Significance at p<0.001
Abbreviation: BODE - Body mass index, airway Obstruction, Dyspnoea and Exercise capacity

3.4.5 Physical performance tests and self-reported falls

3.4.5.1 Physical performance tests associations to fallers and non-fallers

Fall assessment was missing in eight patients; therefore, 111 patients and 58 controls were included. In addition, two other patients did not perform the 6MWT; thus, 109 patients were included in the 6MWT analysis of this section.

Patient fallers in the past year (n= 27) took significantly longer time to complete the TUG than patient non-fallers (n= 84), p= 0.02 (Table 3.4). In the control group, there was no significant difference between fallers and non-fallers, p= 0.07; however, there were few subjects reported ≥ one fall in the past year (n= 11).

Similarly, patient fallers in the past year covered significantly less distance in the 6MWT (233 (95)m) than patient non-fallers (311 (91)m), p< 0.001. Whereas, the 6MWT showed no significant difference in the controls group between fallers (372 (102)m) and non-fallers (382 (70)m), p= 0.71.

Table 3.4: Within Groups Analysis of Fallers and Non-fallers to Physical Performance Tests

Mean (SD) unless otherwise indicated	**COPD** (n=111)			**Controls** (n=58)		
	Fallers	**Non-Fallers**	**P**	**Fallers**	**Non-Fallers**	**P**
n	27	84	-	11	47	-
Age (years)	66 (8)	69 (6)	0.11	65 (6)	66 (9)	0.63
Male – n (%)	16 (59)	53 (63)	0.72	4 (36)	34 (71)	0.02
TUG (seconds)	14.5 (5.2)	11.0 (2.7)	0.02	10.4 (2.3)	9.3 (1.6)	0.07
6MWD (m) Patients= 109 Controls= 58	233 (95)	311 (91) (n=82)	0.001	372 (102)	382 (70)	0.71

Abbreviations: Six-Minute Walk Distance (**6MWD**), Time Up and Go (**TUG**)

3.4.5.2 Time Up and Go and fall frequency

In the 111 patients and 58 controls included in this section, there were more patients reported ≥3 falls than controls (Table 3.5).

There was a trend of direct relationship between TUG and fall frequency in patients with COPD. This relationship was not seen in controls, which might be because only three subjects reported more than one fall in the past year. In Patients, one way ANOVA (Post Hoc, Tukey) test showed a significant increase of TUG time in those who reported ≥3 falls compared to those who reported no fall in the past year, $p<0.001$.

Table 3.5: Self-Reported Fall Frequency in the past year and TUG Test in Patients and Controls

Mean (SD) unless otherwise indicated	**No fall**	**1 Fall**	**2 Falls**	**≥3 Falls**
COPD - n (%) **TUG (seconds)**	84 (76) 11.0 (2.7)	12 (11) 13.4 (2.9)	9 (8) 14.0 (4.7)	6 (5) 17.4 (8.6)
Controls – n (%) **TUG (seconds)**	47 (81) 9.3 (1.6)	8 (14) 10.4 (2.3)	1 (2) 13.4	2 (3) 8.9 (1.1)

Abbreviation: Time Up and Go (**TUG**)

3.4.6 Sensitivity and specificity of the Time Up and Go test in patients with COPD

Of the 111 patients ROC curve showed that TUG test was a good predictor of self-reported falls giving area under the ROC curve (AUC) for TUG time and reported falls in the past year of 0.77. An absolute cut-off time of 12 seconds provided 74% sensitivity and specificity to detect patients who reported one or more falls in the past year. 74% of patient fallers completed the TUG test in ≥12 seconds and 74% of patient non-faller completed the TUG test in <12 second. Dividing patients into two groups based on this cut-off time of 12 seconds showed no age or gender differences. Patients who completed the TUG test in <12 seconds had lower values of BMI, MRC dyspnoea score, self-reported co-morbidity score and higher resting oxygen saturation and longer 6MWD than patients who completed the TUG test in ≥ 12 seconds (**Table** 3.6).

Table 3.6: **TUG Cut-off Time of 12 seconds and Risk of Falls in Patients with COPD**

Mean (SD) unless otherwise indicated	**Time Up and Go**		
	<12 seconds	**≥12 seconds**	**P**
n	68	43	-
Male n (%)	43 (63)	26 (60)	0.772
Age (years)	68 (6)	68 (8)	0.998
BMI (kg/m^2)	25.9 (5.0)	29.1 (6.5)	**0.005**
Resting SpO_2 (%)	95 (2)	94 (2)	**0.002**
MRC dyspnoea scale – median (IQR)	2 (2-4)	4 (3-4)	**0.011**
Self-reported co-morbidity score - median (IQR)	1 (1-2)	2 (1-2)	**0.001**
6MWD (m)	346 (64)	208 (80)	**<0.001**

Abbreviations: Body mass index (**BMI**), oxygen saturation (**SpO_2**) and Medical Research Council (**MRC**).

3.4.7 Time Up and Go practice effect

A TUG practice was performed in all subjects but the time was recorded in 87 patients and 54 controls. There was a correlation between the first and second TUG trials in all subjects, in patients and in controls (Figure 3.5 and Table 3.7). Patients and controls spent less time to complete the second trial than the first trial (Table 3.7). The mean (SD) difference between the TUG trials (2^{nd} trial – 1^{st} trial) was -0.6 (0.9)s in all subjects and patient group and it was -0.5 (0.8)s in controls.

The difference between TUG trials was not significantly different between patients and controls, although marginally greater practice effect was seen in patients compared controls (Table 3.7).

Figure 3.5: Association of First (Practice) and Second (measured) TUG Trials

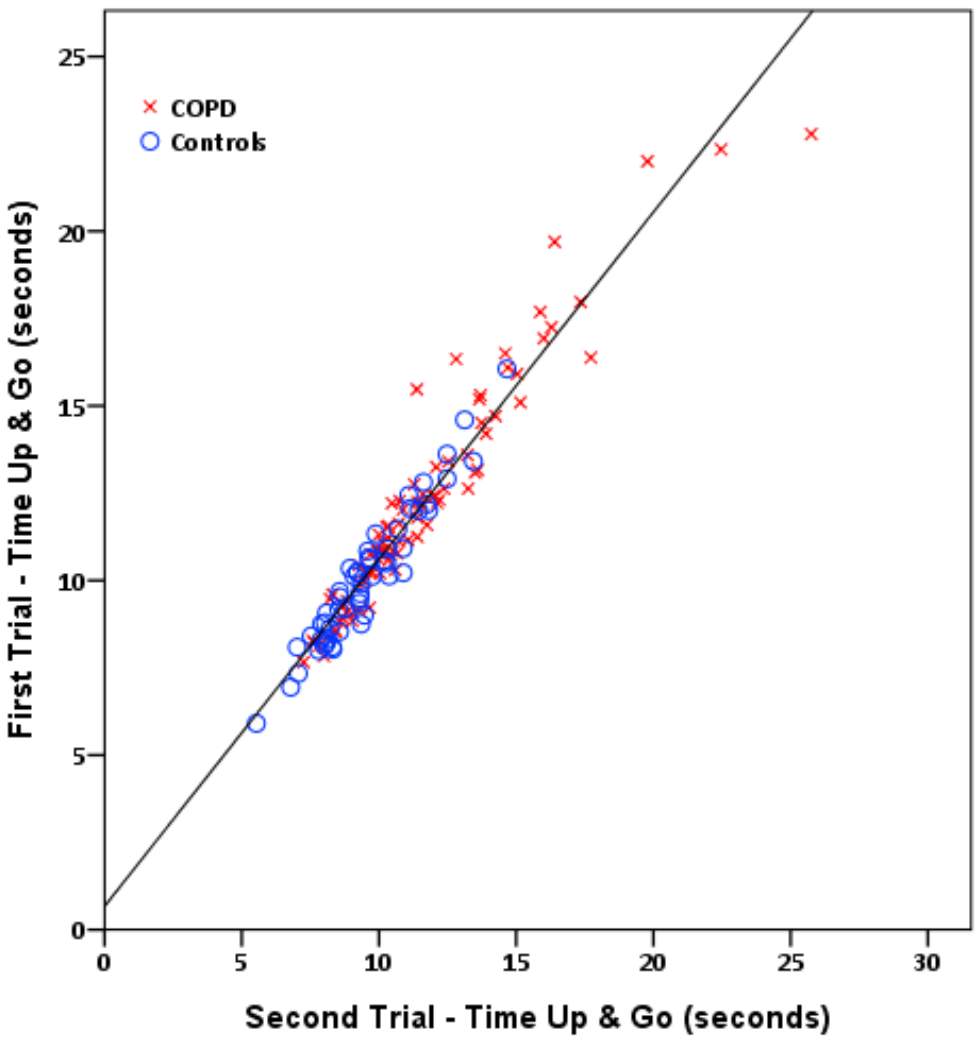


Table 3.7: First (practice) and Second (measured) TUG Trials

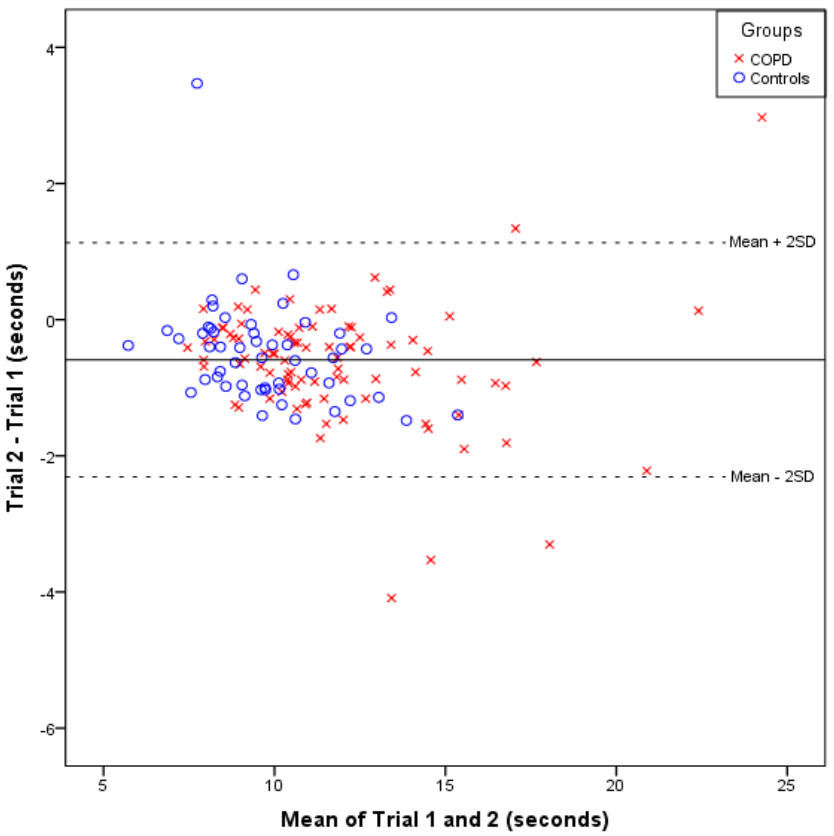
Mean (SD)	**First Trial (seconds)**	**Second Trial (seconds)**	**Correlation 1^{st} and 2^{nd} TUG trials (p-value)**	**Difference between the TUG trials (2^{nd}-1^{st}) (seconds)**
COPD – n= 87	12.2 (3.2)	11.6 (3.2)	0.96 (**<0.001**)	-0.6 (0.9)
Controls – n= 54	10.0 (2.1)	9.5 (1.8)	0.93 (**<0.001**)	-0.5 (0.8)
Total – n= 141	11.4 (3.0)	10.8 (2.9)	0.96 (**<0.001**)	-0.6(0.9)

Abbreviation: Time Up and Go (**TUG**)

Bland-Altman plot was constructed to assess the degree of agreement between both TUG trials within 2SD of the mean difference (Figure 3.6).

The mean difference of both TUG trials (2nd TUG measured trial – 1st TUG practice trial) in all subjects of -0.6s was used to construct the Bland-Altman plot. The majority of subjects fall within 2SD of the difference of TUG trial. Values falling outside the ±2SD limits in the Bland-Altman plot consist of five patients and one control, which appeared more disparate at higher TUG.

Figure 3.6: Bland-Altman Plot Showing the Agreement between the Two TUG Trials



3.4.8 Time Up and Go test and self-reported dyspnoea/Quality of Life

3.4.8.1 Medical Research Council dyspnoea scale in patients with COPD

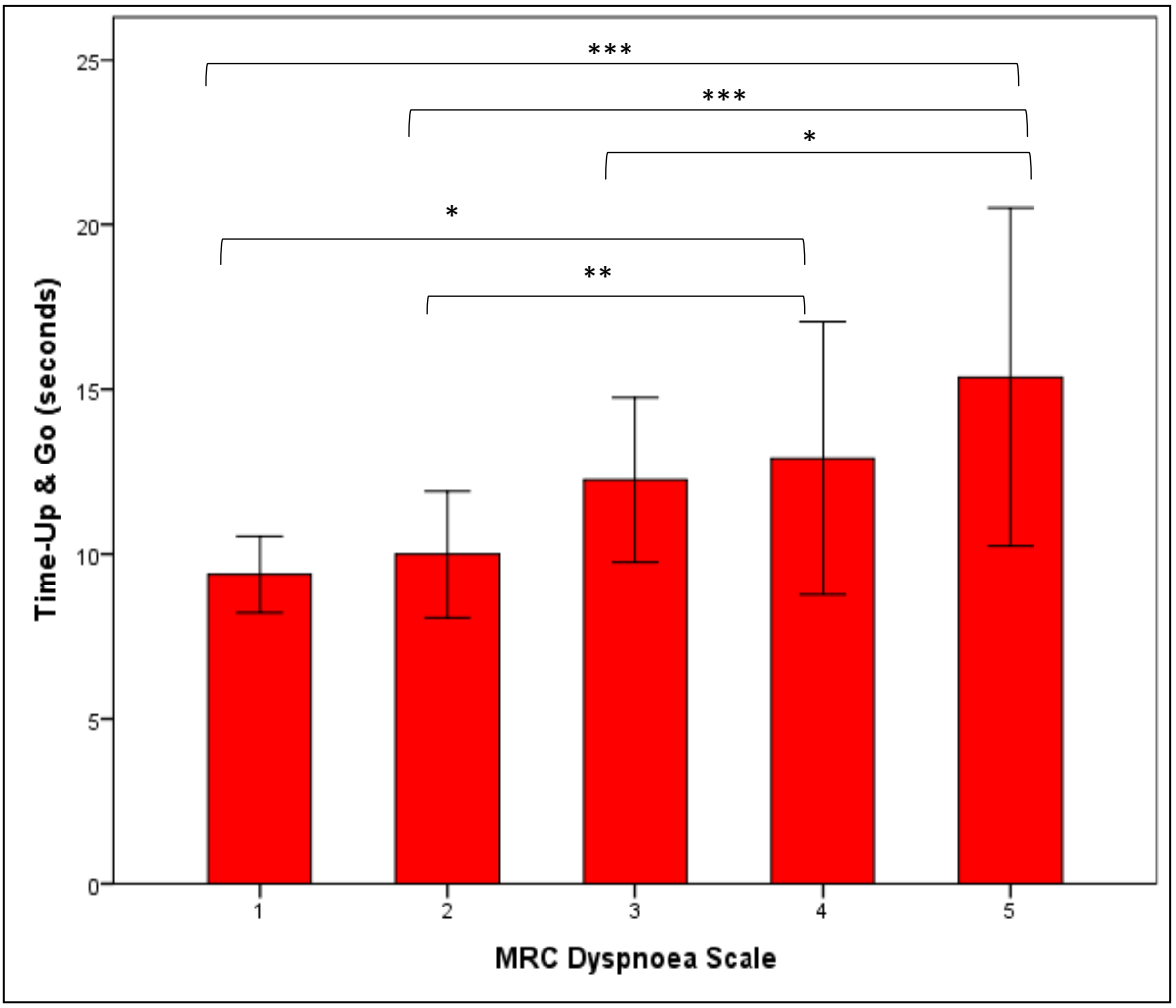
There was a good distribution of patients along the spectrum of MRC dyspnoea scale (Table 3.8). One way ANOVA (Post Hoc, Tukey) showed statistically significant correlation between TUG and MRC dyspnoea scale in patients with COPD. The higher the score in the MRC dyspnoea scale, the longer the time required to complete the TUG test (Figure 3.7).

Table 3.8: Number of Patients with COPD based on MRC Dyspnoea Scale

-	**MRC 1**	**MRC 2**	**MRC 3**	**MRC 4**	**MRC 5**
COPD (n)	11	36	24	34	15

Abbreviation: Medical Research Council (**MRC**)

Figure 3.7: TUG Test and MRC Dyspnoea Scale in Patients with COPD



Abbreviation: Medical Respiratory Council (**MRC**)
Error bars show ±1 standard deviation
*Significant at p<0.05
**Significant at p<0.01
***Significant at p<0.001

3.4.8.2 St. George's Respiratory Questionnaire (SGRQ)

All patients completed the SGRQ with a mean (SD) of the total SGRQ score= 57(28), activity domain= 41 (20), impact domain= 31 (20), and symptoms domain= 45 (21). Correlation analysis showed significantly positive association between TUG and total SGRQ score, and all SGRQ domains (Table 3.9).

Table 3.9: TUG Test and SGRQ Score in Patients with COPD

	Correlation (r)	**p-value**
SGRQ – Total score	0.43	**<0.001**
SGRQ – Activity	0.49	**<0.001**
SGRQ - Symptoms	0.20	**0.03**
SGRQ - Impact	0.38	**<0.001**

Abbreviation: St. George's Respiratory Questionnaires (**SGRQ**)

3.4.9 Time Up and Go and self-reported physical activity

The majority of patients and controls reported good engagement in mild and moderate activities but not to vigorous activity (Table 3.10). There were few subjects reporting vigorous activity so statistical analysis was not possible and was therefore only performed on mild and moderate activities. There was no association between age and self-reported physical activity (including the frequency and the amount of time (hrs/wk), and time of reported walk (hrs/wk) outside the home during weekdays or weekend) in patients and controls; $p>0.05$.

3.4.9.1 Mild physical activity in patients and controls

- **Frequency per week**

  The majority of patients reported doing mild activity ≥3 time/wk and only three reported 1-3 times/month or less (Table 3.10). The majority of controls (n=56) reported doing mild activity ≥3 times/wk and only two controls reported a frequency of 1-2 times/wk. There was no significant difference between male and female participants in the reported frequency of doing mild activity in patients group ($p= 0.7$) and in controls group ($p= 0.6$)

- **Duration (hours/week)**

  The median (IQR) time of mild activity reported by patients was 8 (4-18)hrs/wk compared to 14 (6-19)hrs/wk for controls. Although it was

marginally higher in controls, it did not reach significance, p= 0.6. The median (IQR) of self-reported time doing mild activity in males was 7 (4-14)hrs/wk and in females was 14 (4-21)hrs/wk, p= 0.03. In controls, there was no significant difference in self-reported time doing mild activity between males (14 (7-20)hrs/wk) and females (12 (6-15)hrs/wk), p=0.6.

- **Time Up and Go and self-reported mild activity**

  There were few (n= 3) patients who reported a frequency of doing mild activity 1-3 times/month or less (not included in this analysis); therefore, TUG was compared between subjects who reported a frequency of 1-2 times/wk and ≥3 times/wk. In patients, independent t-test showed that TUG was significantly increased (worse) in those who reported a frequency of 1-2 times/wk (TUG time= 14s) compared to ≥3 times/wk (TUG time= 11s), p=0.03.

  There was a significant correlation between TUG and the time (hrs/wk) spent doing mild activity in patients, r= -0.21, p<0.01, but not in controls, r= -0.06, p= 0.9.

Table 3.10: Frequency of Self-Reported Physical Activity in Patients with COPD and Controls

Activity level	Frequency	COPD n= 119	Controls n= 58
Mild activity	≥3/week	96	56
	1-2/week	20	2
	1-3/month	1	0
	Almost never	2	0
Moderate activity	≥3/week	16	15
	1-2/week	29	22
	1-3/month	21	12
	Almost never	53	9
Vigorous activity	≥3/week	2	9
	1-2/week	4	2
	1-3/month	6	5
	Almost never	107	42

Values represent the number of subjects reporting the frequency of doing mild, moderate and vigorous activity in each group.

oderate activity in patients and controls

- **Frequency per week**

  The majority of patients (n=53) reported "almost never" for moderate activity and the majority of controls (n=22) reported doing moderate activity 1-2 times/wk. Patients did moderate activity on less occasions compared to controls, p<0.001 (Table 3.11). There was no significant gender differences in patients and in controls when analysing the frequency of moderate activity; p= 0.30 and p= 0.06, respectively.

- **Duration (hours/week)**

  The median (IQR) time spent on moderate activity was significantly less in patients 0(0-2)hrs/wk compared to controls 2(1-4)hrs/wk, p<0.001. The median (IRQ) for self-reported moderate activity was 1(0-4)hrs/wk in patient males and 0(0-2)hrs/wk in females, p=0.11. In controls, males reported more time doing moderate activity, 4(2-5)hrs/wk, compared to females, 1(0-2)hrs/wk, p<0.001.

- **Time Up and Go and self-reported moderate activity**

  In all subjects, the results showed that TUG time increased as self-reported moderate activity declined; however, this was not significant, r= -0.23, p= 0.9 (Table 3.11).

  There was an inverse association between TUG and reported moderate activity duration (hrs/wk) in patients (r= -0.27, p= 0.003), but not in controls (r= -0.26, p= 0.5).

Table 3.11: TUG and Self-Reported Moderate Activity

Median (IQR)	COPD		Controls	
	n	TUG (Second)	n	TUG (seconds)
≥3 times/week	16	10.2 (2.0)	15	8.6 (1.6)
1-2 times/week	29	11.0 (2.4)	22	9.7 (1.9)
1-3 times/month	21	11.8 (3.7)	12	9.6 (1.8)
Almost never	53	13.0 (3.7)	9	10.5 (1.4)

3.4.9.2 Time Up and Go and self-reported weekdays/weekend walking

- **Weekdays walking**

The median (IQR) for the time spent in self-reported walk during each weekday in patients was 30(20-60)min/day, and in controls was 60(30-90)min/day, p= 0.04. There was no significant difference in the time spent walking during each weekday between male patients, 38(20-90)min/day, and female patients, 30(15-60)min/day, p= 0.11. Similarly, in controls there were no gender differences found for the reported walking time - males: 60 (15-60)min/day and females: 50(20-142)min/day, p= 0.72. With regards to the TUG, there was association between TUG and self-reported weekdays walking in patients (r=-0.13, p<0.01, but not in controls, r= -0.13, p=0.31.

- **Weekend days walking**

The median (IQR) self-reported walking time in each weekend day in patients was 30(10-90)min/day and in controls was 60(30-60)min/day, p= 0.22. There was borderline significant gender differences in self-reported walking time during each weekend days in patients, males: 30 (19-98)min/day and females: 30 (5-60)min/day, p= 0.049 but not in controls, males: 52(30-60)min/day and females: 60(13-90)min/day, p= 0.72. The time to complete the TUG test was significantly association with self-reported weekend days walking in patients (r= -0.20, p=0.03) but not in controls (r=-0.13, p= 0.34).

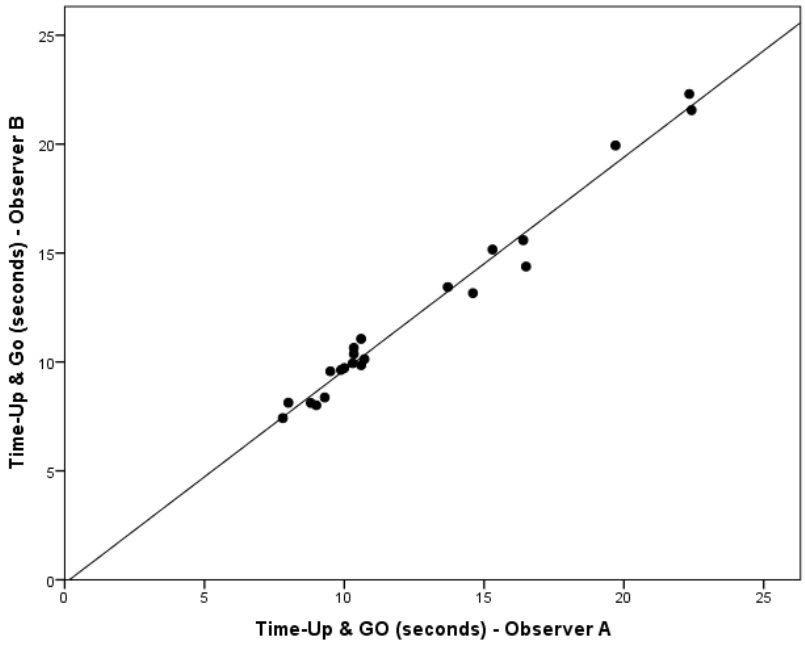
3.4.10 Time Up and Go intra-observer and Inter-observer reliability

3.4.10.1 Same 'test' inter-observer reliability

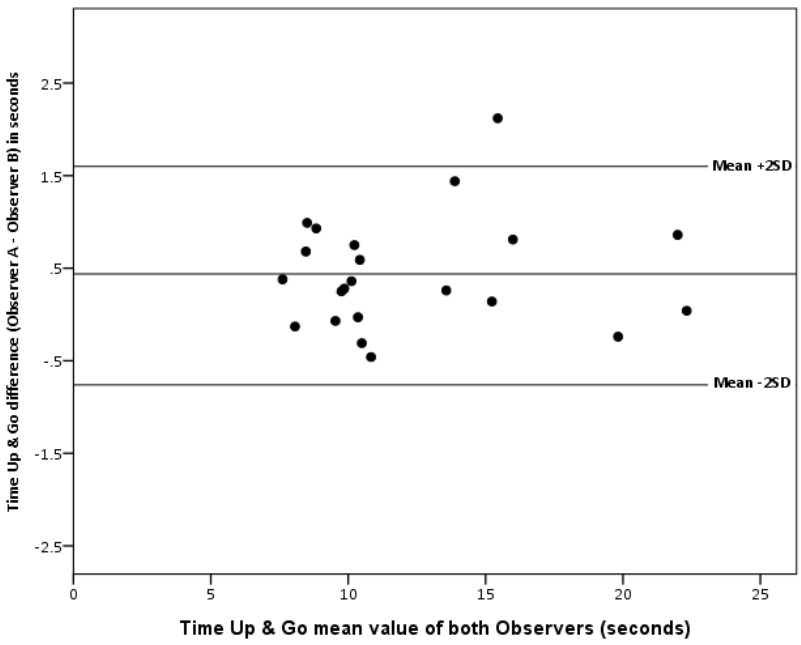
The mean (SD) difference between measurements obtained by the two observers in the same time was 0.4 (0.6)s and the duration to complete the test was 12.3 (4.4)s. Reliability analysis of ICC revealed strong correlation between both observers ICC= 0.990, 95% CI: 0.977 - 0.996 (Figure 3.8A). Bland-Altman plot showed good agreement of the measurements of both observers where the majority of values, except for one subject, fall within 2SD of the mean difference (Figure 3.8B).

Figure 3.8: TUG Inter-observer Reliability

A: Two Observers at the Same Time



B: Inter-observer Bland-Altman plot

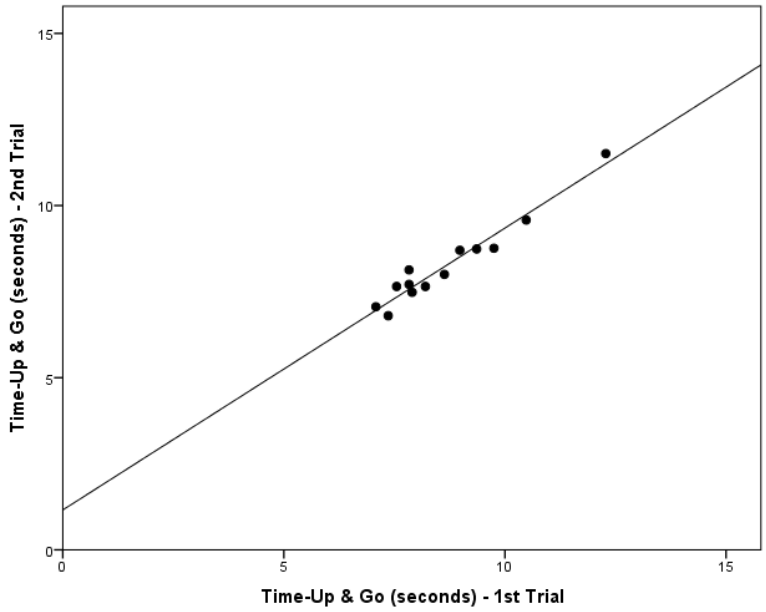


3.4.10.2 Different day intra-observer repeatability

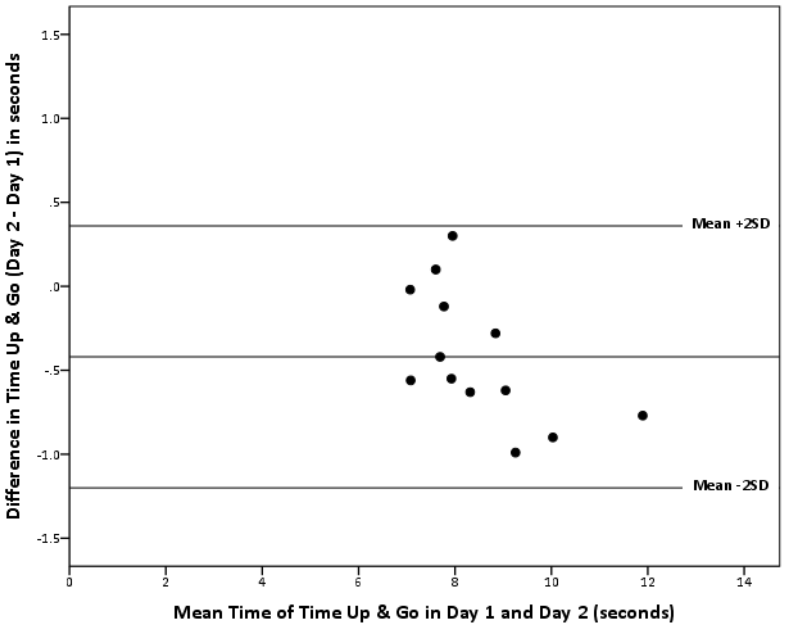
Thirteen healthy volunteers completed two TUG tests on different days within one week (two to seven days apart) preceded a practice test on each test day which was assessed by one observer. The mean difference of TUG measurements between the two days (day 2 – day 1) was -0.4 (0.4)s with time of 8.5 (1.3)s indicating better TUG performance on day two. There was a strong correlation between the two TUG tests, ICC = 0.958 with 95%CI: 0.868-0.987 (Figure 3.9A). Bland-Altman plot showed good agreement in TUG measurements taken on different days where all values fall within 2SD of the mean difference (Figure 3.9B).

Figure 3.9: TUG Intra-Observer Repeatability

A: Two TUG Trials on Different Days



B: Intra-observer (different days) Bland-Altman Plot



3.5 Discussion

We reported that the Time Up and Go test was increased in clinically stable patients with COPD in comparison to age- and gender-matched controls and was inversely related to 6MWD reflecting impaired physical performance in patients with COPD. The TUG was also increased in patients categorised as fallers in the past year compared to non-fallers and was directly associated with fall frequency, MRC dyspnoea scale, self-reported co-morbidity score, and worse SGRQ score. On the other hand, in patients TUG was inversely related to the time spent in self-reported moderate activity (hrs/wk) and to the self-reported walking time (each weekday and each weekend day). Finally, TUG was found to have high same day inter- and different days intra-observer reliability.

There were two small studies reporting that TUG was increased in patients with COPD compared to controls (Butcher et al., 2004, Roig et al., 2010); however, the novelty of this current work was including a wide range of disease severity of patients with COPD, thus making it a representative sample of the general population of patients with COPD in the clinical practice.

Generally, the findings of the earlier mentioned studies investigating TUG in patients with COPD and controls support our findings. Roig et al, 2010 conducted a relatively small study of patients with COPD (n=21) and controls (n=21) free from CV, neurological, and musculoskeletal problems; it was

reported that patients with COPD had increased TUG time and lower 6MWD compared to controls – mean (SD) for the TUG test was 9.5 (2.3)s in patients and 7.7 (1.1)s in controls (Roig et al., 2010). Similarly, we reported a two second increase of TUG time in patients with COPD compared to controls; however, the baseline values of TUG in the two studies vary. Given Roig et al., excluded patients with co-morbid conditions could explain the lower TUG time in their study as we showed that co-morbidities were inversely related to the TUG test. Moreover, they included healthy subjects but only those who reported no more than light activities in their daily lives, for example, slow walking. This selection of a clinically convenient sample of patients (without co-morbidity) and controls (with limited activity) would minimize the actual difference between these populations.

Butcher et al., explored TUG in a small population of patients (n=30) with active COPD with and without oxygen supplement during pulmonary rehabilitation programme (after a minimum enrolment of three weeks of pulmonary rehabilitation prior to the study) in comparison to healthy subjects (n=21) who used to exercise regularly (Butcher et al., 2004). After adjusting for age, they reported increased mean (SD) TUG time in patients - 7.2 (0.4)s with oxygen supplement and 5.9 (0.4)s without oxygen supplement - compared to controls 5.4 (0.3)s. These values again are lower than those demonstrated in our study. One plausible reason might be because of the effect of exercise on performance as cardiopulmonary rehabilitation improves TUG in patients with COPD (Beauchamp et al., 2010, Bellet et al., 2013). In

addition, they instructed patients to perform two trials and to walk as quick and safe as possible and the fastest attempt was recorded; in comparison, we followed the test protocol described by Podsialdo and Richardson, where subjects were instructed to walk at a regular pace and performed a practice followed by a second recorded trial (Podsiadlo and Richardson, 1991).

Age has been associated with TUG and normative cut-off time was established for specific population, for example community dwelling elderly people (Steffen et al., 2002). Similarly, we presented positive correlation between age and TUG in controls, but not in patients with COPD. Unlike in healthy subjects, some studies found that TUG was not associated with age in patients with COPD (Khandelwal et al., 2013). One explanation for this may be because of the muscle loss or possibly other factors caused by COPD, which in turn overrides physical mobility (Agusti et al., 2002). There is an evidence in literature shows that the accelerated decline in muscle strength in healthy subjects (aged ≥55years) has negative affect on mobility, suggesting that the muscle loss might be the reason of impaired physical performance rather than the age (Samson et al., 2000). Celli et al. argued that the severity of COPD should not be driven by age; rather, it should be driven by the influential factors associated with COPD such as physical mobility and BMI (Celli et al., 2009). We provided evidence to show positive association between TUG and BODE index and BODE score as well as with the 6MWD alone.

Other factors such as breathlessness, comorbidities, quality of life and oxygen saturation were more related to physical performance limitation in patients with COPD than age and gender. Of these factors, breathlessness (measured by MRC dyspnoea scale) itself was shown to have the greatest contribution for poor quality of life caused by inactivity and to be inversely related to physical performance (Reardon et al., 2006). This adds to the advantages of the TUG test in the COPD assessment as we have reported its direct association with dyspnoea and quality of life questionnaires. Similar results were published in earlier studies looking at the association of physical performance – using TUG - and balance to quality of life in elderly people (Hirano et al., 2013, Ozcan et al., 2005).

Comorbidities such as CV diseases, hypertension, osteoporosis, diabetes, musculoskeletal dysfunction, and psychological disorders have been documented to be associated with COPD (Chatila et al., 2008, Sabit et al., 2007, Sin et al., 2006). We demonstrated positive association between TUG and self-reported co-morbidity suggesting that co-morbidity somehow has a negative effect on physical mobility in patients with COPD.

We reported that TUG was highly related to 6MWD and both were associated with poor performance in patients with COPD compared to controls. In patients with Parkinson's Disease (PD), the TUG test was found to have the greatest influence on the 6MWT and this was independent of other variables, for example gender, balance and instability measures (Earhart, 2009). The studies investigated TUG in patients with hypertension, cardiac rehabilitation,

and PD showed moderate correlation with the 6MWD (Pedrosa R, 2009, Bellet et al., Earhart, 2009). Considering this high association between TUG and 6MWT, it might be useful to establish a cut-off time for TUG in patients with COPD to identify those patients who need further assessment of physical performance from those who do not. Other studies used different cut-off time for different populations or different age-group including, but not limited to, risk of falls, frail elderly and patients with PD (Shumway-Cook et al., 2000, Thomas and Lane, 2005, Nocera et al., 2013, Steffen et al., 2002). The cut-off time of 12s used in our study to distinguish between fallers and non-fallers, gave a difference of 138m in the 6MWT in patients with COPD; which is greater than double the minimal clinically important difference (MCID) of the 6MWD in patients with COPD (Cote et al., 2008, Wise and Brown, 2005). Other simple physical performance tests, for example the SPPB, have also been reported to be associated with the 6MWD in patients with COPD (Eisner et al., 2008); however, the SPPB has ceiling effects that limit the test to measure performance in active patients (Curb et al., 2006). On the other hand, the TUG test is a continuous, measured in seconds, and has no ceiling effect.

It is important to note that we intended to recruit control comparators with smoking history who were free from any respiratory condition, but not from other health conditions; therefore, were not considered healthy controls. This, in part, could explain the difference of the physical performance we presented for our control group compared to the healthy group reported in

literature. For example, the mean (SD) walking distance of our controls was 380 (76)m, which was below the average walking distance (>500m) found in literature for healthy subjects (Casanova et al., 2011, Steffen et al., 2002). In one of these studies, Casanova et al., included healthy subjects who were active; with no co-morbid condition that might influence their exercise capacity, and who was not on medications that affect the heart rate, and only 3% of their subjects were smokers (Casanova et al., 2011). In the other study, Steffen et al., excluded smokers, subjects with assistive devices and those who feel shortness of breath or leg, neck or back pain while walking (Steffen et al., 2002). Whilst our aim was to include a control group who were representative of the general public and free from respiratory conditions only. Therefore, we included controls with smoking history (≥10 pack year) regardless of their activity level, co-morbid condition (other than malignancy and alpha 1 antitrypsin deficiency) and use of medications. Secondly, unlike the previous studies, we used a 10m course for the 6MWD rather than the recommended 30m walking course. This might be another reason for our controls to cover less distance compared to the average walking distance presented in the previous studies as the 6MWD is positively related to the length of the walking course, which might be related to increased number of turns on the shorter walking track (ATS, 2002, Singh et al., 2014).

Recently, increasing number of studies showed that patients with COPD are more prone to balance impairment and fall than healthy controls (Butcher et al., 2004, Chang et al., 2008, Lawlor et al., 2003). The American Geriatric

Society and British Geriatric Society have listed balance as a risk factor of falls (AGS/BGS, 2010). The U.S Preventative Service Task Force Clinical Guidelines recommends the use of TUG as a risk assessment tool in older adults, ≥65years (Moyer, 2012). Therefore, investigating the risk of falls in patients with COPD in comparison to healthy controls became an important area of interest in research (Roig et al., 2009).

Previous work by Beauchamp et al., looked at the association of fall to TUG and balance related questionnaires in patients with COPD (Beauchamp et al., 2009). The authors used a cut-off time of 16s or more to discriminate patients' fallers from non-fallers. They showed that TUG was a useful measure to discriminate between patients' fallers from non-fallers and a cut-off time of 16s could identify 50% of the total number of fallers. Although our results were consistent with those presented in Beauchamp et al., study regarding the relationship between TUG and falls, the absolute time to complete the TUG test for patients' fallers and non-fallers was lower in our study and using a cut-off time of 12s could identify 74% of the total number of fallers and non-fallers in patients with COPD, respectively. The difference in the TUG results is expected because of the difference in patients' characteristics between the two studies. In comparison to our patients' group, patients in Beauchamp et al., study were in more severe stage of COPD (FEV_1% predicted = 42%), relatively older, and 46% were on oxygen supplement. Perhaps the severity of the disease and age, as mentioned

earlier, might not have an effect on TUG in patients with COPD; however, we demonstrated that oxygen saturation was inversely related to TUG.

Recently, a large cross-sectional study of 16 National Foundation Centers of Excellence where over 2000 patients with PD were included to investigate the ability of the TUG test to identify fallers and non-fallers (Nocera et al., 2013). The researchers showed that TUG was able to detect accurately 70% of the patient fallers and non-fallers and a one second increase in TUG was associated with 5.4% increase in the risk of falls. Currently, health care professionals rely on subjective methods for the assessment of falls; TUG as an objective to distinguish fallers from non-fallers was shown to be useful especially when space and time are limited. These findings encourage further research to investigate a potential predictive ability of the TUG test to identify future risk of falls in patients with COPD.

Physical activity was reduced in the patient group compared to the controls group of the present study. This was expected as inactivity is one of the main characteristics of COPD patients (Troosters et al., 2010b, Pitta et al., 2005b). Few patients reported doing vigorous activity; therefore, analysis included the association of TUG to self-reported mild and moderate activity only. TUG confirmed the association of physical performance to self-reported physical activity in patients with COPD. Although there was a weak (borderline) association found between TUG and self-reported mild activity (hrs/wk), TUG was strongly associated to self-reported moderate activity (hrs/wk), self-reported walking time. The associated between physical performance and

physical activity is expected as it has been shown in previous literature using different functional tests in patients with COPD (Pitta et al., 2005b, DePew et al., 2013, Garcia-Aymerich et al., 2009). This is consistent with previous findings of inverse correlation between TUG and physical energy expenditure/week in community-dwelling elderly people (Ewing et al., 2010).

Previous literature showed high reliability of TUG ranging from ICC 0.85 to 0.99 in the older people with and without co-morbid conditions (Bellet et al., van Hedel et al., 2005, Steffen et al., 2002, Mesquita et al., Podsiadlo and Richardson, 1991, Roig et al., 2010). In COPD studies, Roig et al., and a recently published study by Mesquita et al., showed high same-day test-retest reliability of the TUG test using same assessors. We reported similar TUG results in our patients with COPD to that published by Mesquita et al., however they had a more severe COPD population (Mesquita et al.). It is imperative to note that the present study showed that TUG was not related to the severity of the disease. Further, the majority of our controls (n=38) completed the TUG test in ≤10 seconds. Therefore, our mean TUG time of controls was similar to the normal values (≤10 seconds) of healthy elderly people that was reported by Podsialdo and Richardson, and by a meta-analysis of 21 studies of healthy subjects <80 years old (Podsiadlo and Richardson, 1991, Bohannon, 2006). Our study showed that the reliability of the TUG test remains high even when using two assessors and when using one assessor on different days.

3.5.1 Limitation

The study was a cross-sectional study, which made findings limited to correlations amongst variables, and not the cause and effect. Although the study was designed to include a wide range of disease severity of patients with COPD, few patients with GOLD stage IV were recruited. Furthermore, using a 10m track for the 6MWD reduced the actual walking distance of our subjects, however it must be noted that establishing normal values of the 6MWD was not the aim of our study. The results of the 6MWD were collected to investigate the potential use of another test that requires shorter time and smaller space - TUG - in patients with COPD. In the analysis of physical activity, there were few patients who reported vigorous activity, which made it difficult to compare this group with healthy volunteers with vigorous activity. Further, physical activity was obtained using a subjective approach and the scope of this approach is limited to recall bias. Furthermore, the design of our study did not allow precise use of Charlson Co-morbidity Index as some of the diseases in the index were exclusion criteria in this study. Finally, data was collected retrospectively; therefore, the ability of the TUG test to predict future falls in patients with COPD still needs to be investigated in a prospective study.

3.5.2 Conclusion

The TUG test is a simple and reliable test used to detect physical mobility and risk of falls in patients with COPD. Owing to the multiple components of the

TUG, it is a multi-physical performance as opposed to pure exercise test. TUG is a continuous test where performance is measured over time and, therefore; it is not limited by a ceiling effect. There was good correlation between TUG and 6MWT, with the advantage of TUG of being simple, tolerated, and consumed less time and space. A cut-off time of 12s in the TUG test was a useful measure to detect self-reported falls in the past year and gave a difference of more than double the minimal clinical important difference of the 6MWD (138m) in patients with COPD. This study does not suggest TUG as a replacement for 6MWT; rather, it has potential to be used as an initial evaluation of physical performance especially where time and space are of concerns.

Chapter 4

Physical Performance and Arterial Stiffness

4.1 Introduction

Chronic obstructive pulmonary disease (COPD) is strongly associated to cardiovascular (CV) morbidity and exercise limitation (Mannino et al., 2008, Agusti et al., 2003). The rate of decline in physical performance in patients with COPD increases as the severity of disease progresses (Casanova et al., 2007). Some studies have investigated the relationship between haemodynamic measures and exercise intervention in patients with COPD (Vivodtzev et al., 2010, Gale et al., 2011); however, association of the same haemodynamic measures to physical performance, the nature of this relationship and the factors influencing this association still needs to be explored in patients with COPD.

Arterial stiffness is a non-invasive haemodynamic measure which independently predicts CV events and it can be used to stratify high risk patients in general population (Boutouyrie et al., 2002, Ben-Shlomo et al., 2014). The gold-standard method of measuring arterial stiffness is the carotid-femoral (aortic) pulse wave velocity (aPWV) (Laurent et al., 2006) and it has been shown to be increased in patients with COPD (Sabit et al., 2007, Maclay et al., 2009). However, impaired physical performance in patients with COPD in relation to aPWV was not investigated in these studies.

In healthy subjects, a large longitudinal study investigating the relationship of arterial stiffness to age and both subjective and objective measures of physical performance by following more than 5000 healthy subjects for more

than 20 years, Bunner et al. showed that physical performance was inversly related to arterial stiffness; however, the mechanism of this association was not determined (Brunner et al., 2011). Ageing, in healthy subjects (20-90 years), is directly related to arterial stiffness; however, regular exercise can slow down the progression of arterial stiffness as we age (Vaitkevicius et al., 1993). Watson et al. reported that in older adults the association of arterial stiffness to physical performance was evidenced in people with pre-existing CV problems and peipheral arterial disease, but was not demonestrated in healthy subjects (Watson et al., 2011).

Indeed, it is important to further investigate the relationships between arterial stiffness and physical performance in patients with COPD especially when impaired physical performance and additionally inactivity are commonly found in this group of patients (Pitta et al., 2005a, Pinto-Plata et al., 2004).

In a small interventional study of patients with COPD (n=17) Vivodtezev et al. explored the association of exercise intervention to arterial stiffness where seven patients underwent four weeks exersice training and compared to the other 10 untrained patients (Vivodtzev et al., 2010). The authors showed a 10% improvement of aPWV as a result of a reduction in systolic BP in the trained group, and this improvement was proportional to their improvement in the exercise tests performance. This was similarly shown in post-rehabilitation improvement in aPWV in patients with COPD that was attributed to changes in blood pressure (Gale et al., 2011). These studies

showed an indirect improvement of arterial stiffness post exercise intervention.

This chapter aims to explore the relationship of aortic stiffness to physical performance in a large group of patients with COPD and controls. It will also consider aortic stiffness in relation to composite scores that include performance and self-reported co-morbidities.

4.2 Hypothesis

Impaired physical performance, as measured by TUG and/or 6MWT is a significant determinant of the increased aortic stiffness in patients with COPD, independent of age, gender and lung function

4.3 Methods

This was a cross-sectional study inviting patients with COPD and controls for a single clinical visit at the Respiratory Clinical Trial Unit, City Hospital, Nottingham.

4.3.1 Study objective

- Explore the relationship of physical performance and aortic stiffness in patients with COPD compared to controls
- Determining potential baseline factors affecting the relationship of aortic stiffness to physical performance

- Explore associations between aPWV and composite measures of COPD severity and self-reported co-morbidities

4.3.2 Ethics

The study was approved by the National Research Ethics Service (NRES) (Methods, p 51).

4.3.3 Sample size

Study sample size was based on the TUG calculation which included 181 subjects (Methods, p 49).

4.3.4 Inclusion and exclusion criteria

The inclusion and exclusion criteria were mentioned earlier in Chapter 2 (Methods, p 51). Subjects were excluded from analysis if measurements of aPWV were <4.7m/s.

4.3.5 Procedure

4.3.5.1 Informed consent

Informed written consent was obtained in all subjects (Methods, p 53).

4.3.5.2 Haemodynamics

- *Aortic stiffness*

The Vicorder was used to measure arterial stiffness while subjects were in a supine position (Laurent et al., 2006), see Methods, p 57. An aPWV >10m/s cut-off was used to identify those who were at higher risk of cardiovascular events (Mancia et al., 2013, Van Bortel et al., 2012).

- *Perpheral Blood Pressure*

Peripheral blood pressure (BP) was measured using Omron (705IT, UK) while subjects were seated (Methods, p 56). Mean arterial pressure (MAP) and pulse pressure (PP) were calculated (Methods, p 56).

- *Central Blood pressure*

Central BP was performed using the Vicorder (Skidmore Medical, UK) while subjected were seated (Methods, p 56).

4.3.5.3 Time Up and Go (TUG)

The TUG was performed following a practice trial, (Podsiadlo and Richardson, 1991) (Methods, p 61).

4.3.5.4 Six-Minute Walk Test

The Six-Minute Walk Test (6MWT) was performed at the end of each visit after subjects rested for at least 60min prior to the test in order to assess the distance (6MWD) (Methods, p 61).

A cut-off of 350m in the 6MWD was used in the analysis (Casanova et al., 2008, Torres et al., 2011).

4.3.5.5 MRC Dyspnoea Scale

All subjects completed the validated Medical Research Council (MRC) dysnpoea scale (Fletcher, 1960) (Methods, p 54).

4.3.5.6 Self-reported co-morbidity score

To assess measure self-reported co-morbidites, co-morbidity score was calculated for each subject based on the reported conditions by assigning one point for each medical condition referred to in the Charlson Co-morbidity Index (Charlson et al., 1987) (Methods, p 65).

4.3.5.7 Body composition

Height and weight were measure using Seca Scales (Hamburg, Germany). From this BMI was calculated. The fat free mass (FFM) was recorded using Tanita scale (Illinois, USA) and from this, the height squared index: FFMI was calculated (Methods, p 55).

4.3.5.8 Oxygen saturation at rest

Resting oxygen saturation (SpO_2) using Konica Minota Pulsox-300 (Tokyo, Japan) for each subject was measured (Methods, p 63).

4.3.5.9 Spirometric measurements

Post-bronchodilator spirometric measurements of lung function were obtained using micro-medical spirometer (MicroLab MK6). The severity of

airflow obstruction was used to classify patients into different Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages following the GOLD and the 2010 updated NICE classification of the COPD severity (Global Initiative for Chronic Obstructive Lung Disease GOLD, 2011, NICE, 2010) (Methods, p 58).

4.3.5.10 Composite COPD severity measures - BODE and ADO indices

Both indices were assessed in patients with COPD only:

*- BODE index: **B**MI, airway **O**bstruction, **D**yspnoea and **E**xercise capacity*

The BODE Index was calculated using scoring system which includes the four domains of BMI, FEV_1, MRC dyspnoea scale and the 6MWD (Celli et al., 2004) (Appendix 11).

- *ADO index: **A**ge, **D**yspnoea and airway **O**bstruction*

The ADO index was calculated using the scoring table of each of its component: age, dyspnoea and airway obstruction (Puhan et al., 2009) (Appendix 12).

4.3.6 Statistics

Statistical Package of the Social Science (SPSS) version 21 was used for data analysis. Independent t-test was used for comparison between the two groups where data was continuous and normally distributed. Mann-Whitney test was used for statistical difference in non-normally distributed variable. Chi-squire test was used when analysing two categorical data. One way ANOVA was used to look for significant differences between more than two

groups. Pearson (r) was used to assess correlations for continuous variables where normally distributed. Spearman's test was performed to assess correlation of non-parametric distributed variable. Stepwise linear regression analysis was performed to detect independent association of physical performance tests to aPWV. A p-value of <0.05 was considered significant.

4.4 Results

A total number of 181 subjects attended a study visit between April 2013 and September 2014. Four out of the 181 subjects had respiratory conditions other than COPD giving 119 COPD and 58 controls. Five patients were excluded because they had low aPWV (<4.7m/s). Therefore, analysis was performed on 114 patients and 58 controls (Figure 4.1). There were two patients did not complete the 6MWT, therefore, 112 patients were included in the analysis of the 6MWT and the BODE index. Body composition assessment were missing in four of the 114 patients because of machine technical issues; therefore, measurements of FFMI were obtained from 110 patients.

Patients with COPD and controls were matched for age and gender and also had similar BMI and FFMI (Table 4.1). The mean (SD) aPWV was significantly higher in patients 10.0 (2.1)m/s than controls 9.2 (1.8)m/s, p=0.01. As anticipated, patients had significantly lower spirometric and oxygen saturation measurements than controls. Further, smoking pack years was greater in patients than controls, p <0.001. Patients had significantly greater score in self-reported comorbidities compared to controls, p< 0.001 (Table 4.1). However, when analysing co-morbidity score without accounting for the COPD (co-morbidities - 1 in patients with COPD), patients and controls were not statistically different, p= 0.43. Patients reported significantly more CV

morbidity than controls, p=0.03, but both were similar in self-reported diabetes mellitus, p=0.19 (Table 4.2).

There was a significant difference between patients and controls in total cholestrol level, p= 0.04; but not in other serum concentration of high density lipoproteins (HDL), low density lipoproteins (LDL) and triglycerides, p >0.5 (Table 4.2).

There was no statistically significant difference in peripheral and central haemodynamic measurements between patients and controls, all p>0.05 (Table 4.3).

According to the severity of COPD, patients were divided into GOLD I (n=11), GOLD II (n=65), GOLD III (n=35) and GOLD IV (n=3). For analysis patients were divided into two groups: GOLD I and II and GOLD III and IV. Both groups were similar in age (p= 0.61) and gender (p= 0.50) but differed significantly in BMI (GOLD I&II: 34.4 (5.2)kg/m^2 and GOLD III&IV: 29.0 (5.8)kg/m^2, p< 0.001). The aPWV in GOLD I&II group was 9.9 (2.0)m/s and GOLD III&IV group was 10.4 (2.2)m/s, p= 0.23.

Figure 4.1: Recruitment Flowchart

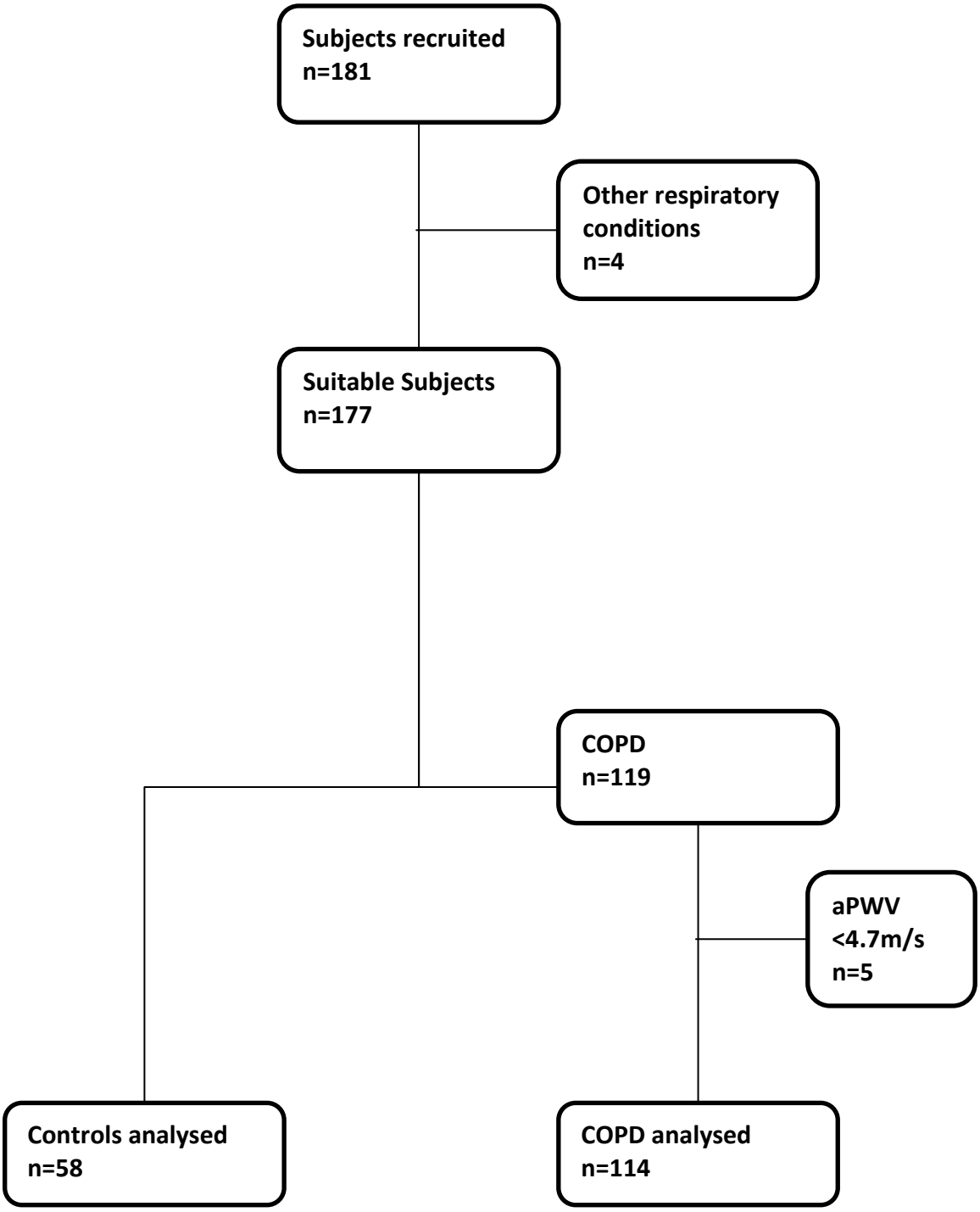


Table 4.1: Demographics of Study Groups

Mean (SD) unless otherwise indicated	**COPD**	**Controls**	**p-value**
n	114	58	
Male n (%)	71 (62)	38 (66)	0.68
Age (years)	68 (8)	66 (9)	0.15
BMI (kg/m^2)	27.5 (6.0)	28.6 (5.2)	0.21
FFMI (kg/m^2) - patients n= 110, controls n = 58	18.5 (3.0)	19.2 (2.4)	0.17
Smoking status – (current / ex-smokers)	39 / 80	8 / 50	**0.007**
Smoking history (pack year)	46 (26)	31 (20)	**<0.001**
FEV_1 (L)	1.60 (0.57)	2.80 (0.61)	**<0.001**
FEV_1% predicted	59 (18)	100 (15)	**<0.001**
FVC (L)	3.22 (0.84)	3.79 (0.89)	**<0.001**
FVC% predicted	95 (18)	108 (19)	**<0.001**
FEV_1/FVC ratio	49 (13)	74 (7)	**<0.001**
Co-morbidities – median (IQR)	1 (1-2)	0 (0-1)	**<0.001**
Resting SpO_2 (%)	95 (2)	96 (1)	**<0.001**
TUG time (seconds)	12.0 (3.7)	9.5 (1.8)	**<0.001**
6MWD (m) – patients n =112, controls n=58	287 (97)	380 (76)	**<0.001**

Abbreviations: Body mass index (**BMI**), fat free mass index (**FFMI**), forced expiratory volume in 1 second (**FEV_1**), forced vital capacity (**FVC**), oxygen saturation (**SpO_2**), Time Up and Go (**TUG**), Six-Minute Walk Distance (**6MWD**).

Table 4.2: Self-Reported Conditions, Medications, and Lipid Profile

Mean (SD) unless otherwise indicated		COPD n=114	Controls n=58	p-value
Self reported Cardiovascular disease n(%)*		30 (26)	7 (12)	**0.03**
Self reported diabetes mellitus n(%)		18 (16)	5 (9)	0.19
Cardiovascular Medications	**Angiotensin-converting-enzyme inhibitor n(%)**	26 (23)	9 (16)	0.26
	Angiotensin receptor blockers n(%)	5 (4)	3 (5)	0.82
	Beta blockers n(%)	11 (10)	9 (16)	0.26
	Statin n(%)	44 (39)	14 (24)	0.06
Total Cholesterol (mmol/L)		5.1 (1.3)	5.5 (1.0)	**0.04**
Triglycerides (mmol/L)		1.5 (0.8)	1.6 (0.8)	0.63
HDL Cholesterol (mmol/L)		1.6 (0.5)	1.7 (0.4)	0.38
LDL Cholesterol (mmol/L)		2.7 (1.1)	3.1 (1.0)	0.07
Cholesterol:HDL ratio		3.3 (1.0)	3.4 (0.9)	0.37

Abbreviations: High density lipoproteins (**HDL**), low density lipoproteins (**LDL**).
*Self-reported cardiovascular problems include: myocardial infarction, heart failure, arrhythmia, angina, bypass surgery and pacemaker.

Table 4.3: Peripheral and Central Haemodynamics

Mean (SD)	**COPD**	**Controls**	**p-value**
Peripheral systolic BP (mm Hg)	147 (23)	144 (15)	0.27
Peripheral diastolic BP (mm Hg)	84 (12)	83 (10)	0.56
Peripheral mean arterial pressure (mm Hg)	105 (14)	103 (10)	0.34
Peripheral pulse pressure (mm Hg)	63 (17)	61 (13)	0.42
aPWV (m/s)	10.0 (2.1)	9.2 (1.8)	**0.01**
Central systolic BP (mm Hg)	143 (23)	141 (14)	0.31
Central diastolic BP (mm Hg)	84 (12)	83 (10)	0.54
Central mean arterial pressure (mm Hg)	110 (15)	109 (11)	0.41
Central pulse pressure (mm Hg)	59 (17)	57 (13)	0.50
Heart rate (beat/min)	74 (14)	70 (14)	0.09

Abbreviations: Aortic pulse wave velocity (**aPWV**), blood pressure (**BP**)

4.4.1 Aortic PWV association to baseline variables:

- **Age, gender, BMI and FFMI**

Age was significantly associated to aPWV in patients (r= 0.47, p<0.001), controls (r= 0.45, p<0.001). The mean (SD) aPWV was greater in male patients 10.6 (2.0)m/s compared to female patients 9.1 (1.9)m/s, p<0.001; but no difference found between gender in controls, p= 0.17. There was no significant association of aPWV to either BMI or FFMI in patients or controls, p>0.05.

- **Spirometric measurements, smoking history, oxygen saturation and MRC dyspnoea scale**

In patients aPWV was inversely correlated with forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio; r= -0.20, p=0.04, but not in controls and not with other spirometric parameters (Table 4.4). There were no significant associations of aPWV to smoking pack years or to resting oxygen saturation in patients or control, p>0.05 In patients, there was no association between aPWV and MRC dyspnoea score, p= 0.51.

Table 4.4: Arterial Stiffness and Lung Function Correlations

Pearson correlation (p-value)	**aPWV (m/s)**	
	COPD	**Controls**
FEV_1 (L)	-0.08 (0.42)	-0.11 (0.43)
FEV_1 (%) predicted	-0.09 (0.35)	-0.09 (0.49)
FVC (L)	0.14 (0.14)	-0.06 (0.67)
FVC (%) Predicted	0.05 (0.62)	-0.15 (0.28)
FEV_1/FVC ratio	-0.20 (**0.04**)	-0.01 (0.97)

Abbreviations: Aortic pulse wave velocity (**aPWV**), forced expiratory volume in one second (**FEV_1**), forced vital capacity (**FVC**).

Peripheral (sitting) haemodynamic measurements

The association of aPWV to heart rate was significant in patients: r=0.20, p= 0.03, but not in controls: r= 0.14, p= 0.29.

In patients, there was a significant association of aPWV to pulse pressure (PP) (r=0.26, p<0.01) and to mean arterial pressure (MAP) (r=0.41, p<0.001). As expected, aPWV was associated to systolic BP (r=0.38) and diastolic BP (r=0.38), all with p<0.001.

In controls, aPWV was significantly associated to PP (r=0.28, p=0.04), but not to MAP (r=0.19, p=0.16). Again, aPWV was significantly associated to systolic BP (r=0.30, p=0.02), but not to diastolic BP (r=0.06, p=0.65).

- **Central (sitting) haemodynamic measurements**

In patients, there was a significant association of aPWV to PP (r=0.22, p=0.02) and to MAP (r=0.41, p<0.001). Similar to peripheral measurements, aPWV was signification associated to systolic BP (r=0.36) and diastolic BP (r=0.37), all with p<0.001.

In controls, aPWV was not significantly associated to PP (r=0.23, p=0.09) or to MAP (r=0.12, p=0.37). There was no association of aPWV to either systolic BP (r=0.23, p=0.08) or to diastolic BP (r=0.04, p=0.78).

- **Self-reported medical conditions, co-morbidity score and self-reported medications**

The aPWV for patients with and without self-reported CV problems was not significant (10.1 (2.7)m/s and 10.0 (1.8)m/s, respectively, p=0.93). Similarly, aPWV for patients with and without self-reported diabetes mellitus was not significantly different (10.8 (2.5)m/s and 9.9 (2.0)m/s, respectively, p= 0.11).

There was no difference in aPWV between controls with and without self-reported CV problems (9.4 (1.4)m/s and 9.2 (1.8)m/s, respectively, p=0.80. Again, aPWV was not significantly different in controls with and without self-reported diabetes mellitus (9.8(2.6)m/s and 9.2 (1.7)m/s, resprectively, p=0.44.

Spearman's test showed no correlation between aPWV and self-reported comorbidity score in patients (r= 0.14, p= 0.14) or in controls (r= 0.04, p=0.77).

4.4.2 Aortic PWV and physical performance tests

As reported in previous literature, patients covered less distance in the 6MWT and took longer time in TUG test than controls, p< 0.001 (Table 4.1). In all subjects, there was an inverse relationship between aPWV and 6MWD, r= -0.19, p= 0.01. Correlation of aPWV to 6MWD was not found in patients alone (r= -0.09, p= 0.34) or controls alone (r= -0.22, p= 0.10), (Figure 4.2). There was no association between aPWV and TUG in all subjects (r= 0.08, p= 0.27), in patients (r= -0.01, p= 0.93) or in controls (r= 0.16, p= 0.22). A stepwise

linear regression analysis was performed where aPWV was the dependent variable and age, gender, MAP and 6MWD or TUG were the independent variables, only age and MAP were independent predictors of aPWV, 27% change attributed to age and 8% attributed to MAP.

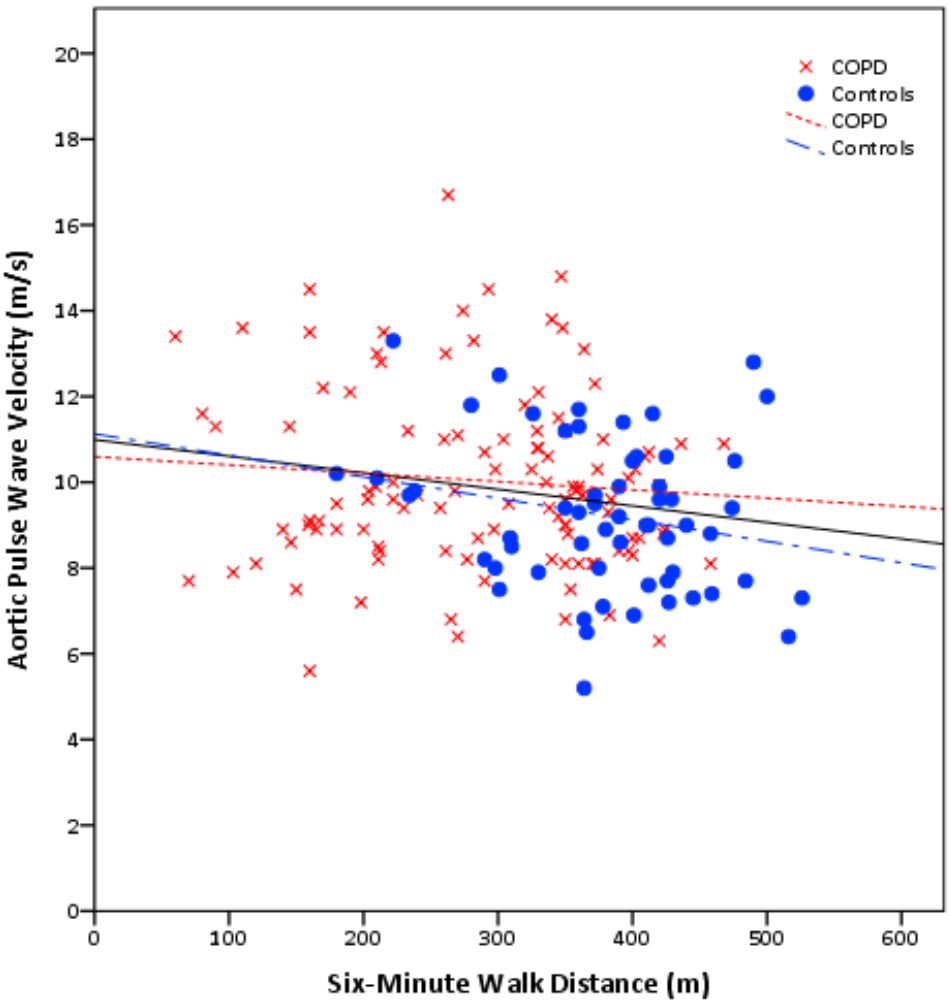
4.4.2.1 Aortic PWV cut-off point of 10m/s

Dividing subjects according to aPWV cut-off point of 10m/s showed no significant difference in the number of patients (n=47 (41%)) and controls (n= 17 (29%)) who had aPWV> 10m/s, p=0.13.

There was no significant difference in the 6MWD based on aPWV cut-off point of 10m/s: patients with aPWV ≤10m/s covered a distance of 286 (97)m and patients with aPWV >10m/s covered a distance of 287 (98)m, p= 0.94, remaining insignificant after adjustment for age, gender and MAP. Controls with aPWV ≤10m/s covered a distance of 389 (66)m and controls with aPWV >10m/s covered a distance of 358 (96)m, p= 0.17.

Similarly, the aPWV cut-off point of 10m/s did not show a significant difference in completing the TUG test in either patients or controls: Patients (n=47) with aPWV>10m/s completed the TUG test in 11.8 (3.4)s; whilst, patients (n=67) with aPWV≤10m/s completed the TUG test in 12.2(4)s, p=0.61. Similarly, controls (n=17) with aPWV>10m/s completed the TUG test in 10.2 (2.2)s; whilst, controls (n=41) with aPWV≤10m/s completed the TUG test in 9.2 (1.5)s, p=0.07.

Figure 4.2: Aortic Stiffness and Six-Minute Walk Distance in Patients and Controls

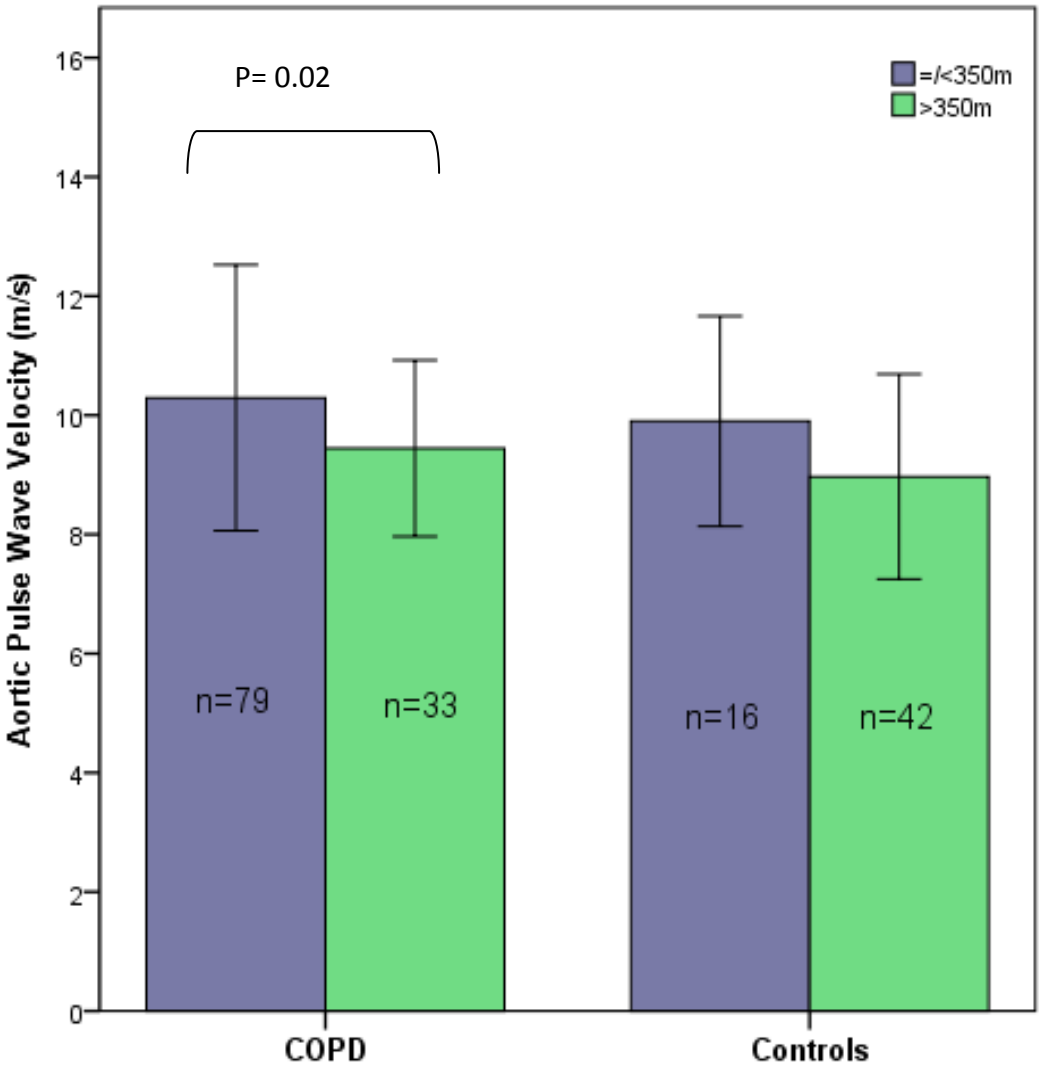


Solid line shows and inverse relationship between aPWV and 6MWD in all subjects

4.4.2.2 Aortic stiffness according to 6MWD of more or less than 350m

According to 6MWD cut-off distance of 350m there were 33 patients and 42 controls who covered >350m and 79 patients and 16 controls who covered ≤350m (Figure 4.3). The aPWV of patients who covered >350m was 9.4 (1.5)m/s compared to 10.3 (2.2)m/s in those who covered ≤350m, p= 0.02; and remained significant when adjusted for age, gender and MAP. In controls, those who covered >350m had aPWV of 9.0 (1.7)m/s compared to 9.9 (1.8)m/s for those who covered ≤350m in the 6MWD, p= 0.07.

Figure 4.3: Aortic Stiffness according to 6MWD group in Patients and Controls



Error bars represent ± 1 standard deviation

4.4.3 Aortic PWV and BODE index in patients

The median (IQR) for the BODE in patients was 4 (2-6). There was no significant associated between aPWV and BODE, p= 0.67. Similarly, one way ANOVA (post Hoc) test showed no significant association between aPWV and BODE categories (Table 4.5).

Table 4.5: Aortic PWV and BODE Index in Patients

Mean (SD)		**n**	**aPWV (m/s)**
BODE Index classification	**0-2**	31	9.8 (1.9)
	3-4	27	10.2 (2.5)
	5-6	35	10.3 (1.7)
	7-10	19	9.7 (2.4)

Abbreviations: Aortic pulse wave velocty (**aPWV**), BMI, airway obstruction, dyspnoea, exercise capacity (**BODE**).

4.4.3 Aortic PWV and ADO index

The median (IQR) score in patients was 4 (4-5). There was a significant association between aPWV and ADO index (r= 0.27, p=0.004)

4.5 Discussion

This study showed that aortic stiffness was increased in patients with COPD compared to age- and gender matched controls; whilst, it was inversely associated to physical performance measures in all subjects, it was not in patients with COPD alone. However, the 6MWD of 350m could significantly distinguish between patients with normal and increased arterial stiffness. Finally, we showed that arterial stiffness was positively related to age and ADO index, but not the BODE index.

Arterial stiffness has been repeatedly shown to be increased in patients with COPD compared to age matched controls (Sabit et al., 2007, Mills et al., 2008). Arterial stiffness has also been positively related to disease severity based on GOLD classification system (Sabit et al., 2007, McAllister et al., 2007). Our results confirmed previous findings where arterial stiffness was increased in patients compared to controls; yet, we did not find any association to disease severity in modified GOLD groups or when using single parameter of FEV_1% predicted. There were some characteristics differences where in Sabit et al, subjects with CV and metabolic or inflammatory conditions were excluded, unlike our study. Furthermore, the majority of our patients were GOLD II and only three were GOLD stage IV compared to Sabit et al. where nine out of 75 patients were in GOLD IV (Sabit et al., 2007). Bhatt et al., presented similar to our finding when investigating determinants of arterial stiffness by comparing patients with moderate (GOLD II) COPD to

patients with severe (GOLD III) and very severe (GOLD IV) COPD (Bhatt et al., 2014). The authors showed no difference in aPWV when comparing patients in GOLD stage II to patients in GOLD stage III and IV - both groups were similar in CV and cerebrovascular diseases.

It is important to note that our controls were not necessarily healthy subjects as they were similar to our patients in self-reported co-morbidities as described by Charlson index. Moreover, both groups were similar in self-reported use of CV medications. This could due to the fact that COPD is associated with increased arterial stiffness. This could play a part in explaining the similarity in other haemodynamics such as BP, PP and MAP readings in both groups, although the readings were marginally greater in patients, but not significant. Nevertheless, the measurement of aPWV was the only haemodynamic measure that was significantly increased in patients compared to controls. MAP is a contributing factor of aPWV (McEniery et al., 2005), therefore showing increased aPWV in patients compared to controls despite similar MAP is of heightened importance.

A previous study has demonstrated that exercise capacity as measured by 6MWT was inversely related to arterial stiffness in patients with COPD; therefore, suggesting that patients with COPD could benefit from CV risk screening in pulmonary rehabilitation programme (Castagna et al., 2008). The main aim of Castagna et al., study was looking at peripheral artery disease in patients with COPD rather than specific markers of arterial stiffness. Adjustment analysis was not reported so it is not known which confounding

variables account for the association. Compared to our study, patients in Castagna et al. study were in more severe stage of COPD, mean (standard error (SE)) FEV_1% predicted was 37 (6), with mean (SE) 6MWD (291 (41)m); which is similar to the distance presented in our study. There is evidence in literature showing that the prognostic power of 6MWD to predict mortality in patients with COPD is dependable on the severity of the disease and it becomes strongest in patients in the severe stages of COPD (Casanova et al., 2008). It is possible that the severity of COPD, also, has an influence on the strength of the association between the physical performance and arterial stiffness and, hence, having only few patients in the severe stages of COPD in our study might have obscured this association. If this is the case, it supports our findings that patients at high risk group of mortality according to their physical performance have significantly increased arterial stiffness compared to patients in the low risk group.

We reported no associations of arterial stiffness to the BODE or to any of its components unlike the apparent association with the ADO index. The association of age to arterial stiffness in patients with COPD and in general population has been repeatedly shown in literature (Sabit et al., 2007, Bhatt et al., 2014) as well as in the present study; therefore, the presence of age as one of the components of the ADO index might be the primary factor of such significance. It is important to note that age is not a disease specific but a common risk factor of mortality in the general public (Celli et al., 2009, Vaitkevicius et al., 1993); however, ADO has been validated to accurately

predicts 3-year mortality and a useful index for the assessment of medical intervention in patients with COPD (Puhan et al., 2012). Both BODE and ADO are individually useful indices and are important in the management of COPD. As both indices include an exercise component, better understanding of the effect of exercise on arterial stiffness in patients with COPD will increase the beneficial values of these indices.

In general, the relationship between physical performance and arterial stiffness in patients with COPD is still not clear and needs more investigations. Only two recently published studies by Vivodtzev et al. and Gale et al., showed that physical exercise improved BP which in turn improved aPWV (Vivodtzev et al., 2010, Gale et al., 2011). Given that the determinants of arterial stiffness differ from those for BP, more studies investigating in details the nature of the relationship between physical performance and arterial stiffness are warranted.

4.5.1 Limitation

The nature of this cross-sectional study did not allow detecting the cause and effect of arterial stiffness and physical performance in our population. The majority of the patients were in mild-moderate stage of the COPD, this might be a reason for the insignificant relationship between arterial stiffness and the severity of the disease. Second, because of the lack of space we used a 10m track for the 6MWD rather than the recommended 30m track (ATS, 2002). This, most likely, influenced the distance covered by our subjects and,

therefore, might have an effect on the lack of association between arterial stiffness and physical performance.

4.5.2 Conclusion and future plan

In a representative sample of patients with COPD and controls, we showed that COPD is an independent predictor of arterial stiffness and it was significantly increased in patients compared to age- and gender-matched controls and there was no difference in the self-reported co-morbidities in both groups. Although no association between arterial stiffness and physical performance in COPD was found in our study, we showed that there is a potential benefit of expanding the use of the 6MWD cut-off in identifying patients with high arterial stiffness.

Chapter 5

Physical Activity and Arterial Stiffness

5.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a respiratory condition with systemic complications including, but not limited to, muscle wasting and inactivity (Mannino et al., 2008, Schols et al., 2005, Pitta et al., 2005a). Muscle wasting and dysfunction in patients with COPD was shown to be affected by airway obstruction, hypoxemia and inactivity (Degens, 2007). Understanding the relationship between COPD and physical inactivity is important as inactivity is independently associated with hospitalisation and increased mortality rate in patients with COPD (Waschki et al., 2011, Garcia-Rio et al., 2012, Watz et al., 2014).

In general population physical inactivity is related to increased risk of developing serious conditions like cardiovascular (CV) diseases and hypertension (Kesaniemi YK, 2001). In the general population, one estimation of disease-specific death showed that physical inactivity was responsible for approximately 1 in 10 deaths due to coronary heart disease, similar to that of high blood cholesterol, high blood pressure and cigarette smoking (Lloyd-Jones et al., 2010). Whilst, reduction of physical activity in the USA alone was responsible for the increass of mortality rate of over 17,000 deaths from the year of 1980 to 2000 (Lloyd-Jones et al., 2010). Similarly, sedentary life-style even in healthy subjects is a leading cause of mortality, disability and serious conditions, for example, cardiovascular diseases and diabetes (Prakash, 2014). Therefore, the World Health Organisation (WHO) (WHO, 2010) as well as the

American college of Sports and Medicine and the American Heart Association (AHA) recommended 30min of moderate activity for 5 days/wk or 75min/wk of vigorous activity to reduce CV risks (Nelson et al., 2007).

When compared to healthy subjects, patients with COPD are less physically active (Pitta et al., 2005a, Vorrink et al., 2011) and have an accelerated decline of activity level over time (Vaes et al., 2014). Furthermore, patients with COPD spend more time lying down during the day, cover less walking distance and walk a slower pace in comparison to healthy controls (Pitta et al., 2005a). Even when compared to patients with other chronic conditions such as rheumatoid arthritis and diabetes, patients with COPD were found to be significantly less physically active (Arne et al., 2009). Therefore, better understanding of the determinants and consequences of physical inactivity in patients with COPD is necessary especially when the prevalence of inactivity is high amongst COPD patients.

Aortic stiffness is an independent predictor of CV diseases (Boutouyrie et al., 2002, Ben-Shlomo et al., 2014). Currently, the optimal non-invasive method of measuring arterial stiffness is the carotid-femoral pulse wave velocity (aPWV) (Laurent et al., 2006), and it has been found to be increased in patients with COPD when compared to healthy controls (Sabit et al., 2007).

In healthy population, literature shows that physical inactivity is related to increased arterial stiffness (Tanaka et al., 2000, Boreham et al., 2004). There is one small study by Stickland et al. exploring the association of physical activity – assessed by SenseWear® Pro3 Armband - to arterial stiffness –

assessed by carotid-radial PWV – in patients with COPD (n=33) and age-matched healthy controls (n=10) (Stickland, 2013). They found that arterial stiffness was significantly lower in controls in comparison to inactive COPD patients, but not to active COPD patients. In COPD alone, they demonstrated that physical activity and exercise tolerance were inversely related to arterial stiffness and that was independent of lung function; therefore, the authors concluded that increased stiffness in patients with COPD was related to the substantial decrease of physical activity rather than the impaired lung function.

The aim of our study was to investigate whether self-reported physical activity was a determinant of aortic stiffness in a large, representative sample of patients with COPD.

5.2 Hypothesis

Aortic stiffness is inversely related to self-reported physical activity in patients with COPD

5.3 Objectives

- To determine self-reported physical activity in patients with COPD
- To explore the association of self-reported physical activity to haemodynamic measurements in patients with COPD and contribution of confounding variables

5.4 Methods

This cross-sectional study invited patients with COPD during their stability to attend a single study visit at the Clinical Trial Unit, City Hospital, Nottingham. The study includes two groups of patients with COPD: patients with confirmed diagnoses of COPD – I presented in previous chapters - and patients with COPD recruited previously by a colleague using the same physical activity questionnaire and arterial stiffness measurements with the same inclusion and exclusion criteria. There was no overlap in subjects.

5.4.1 Ethics

The study was approved by the National Research Ethics Service (NRES) (Chapter 2, p 51).

5.4.2 Sample Size

The sample size of this study included the patients recruited and analysed in previous chapters as well as patients recruited by colleagues in the department using the same inclusion and exclusion criteria. We therefore used this large pragmatic size (n=167) of patients with COPD.

5.4.3 Procedure

5.4.3.1 Informed consent

Written informed consent was obtained in subjects (Methods, p 53).

5.4.3.2 Tests

5.4.3.2.1 Spirometric measurements

Subjects performed post-bronchodilator spirometry (MicroLab MK6) (Methods, p 58) (Miller et al., 2005). Patients were categorised according to GOLD stages (Methods, P 58) (Decramer et al., 2014).

5.4.3.2.2 Self-reported physical activity

Subjects were asked to report the time (hrs/wk) they spent doing mild, moderate and vigorous activity (Methods, P 64).

Based on the WHO guidelines (WHO, 2010), patients who reported doing ≥150min/wk (for example 30 minutes for five days per week) of combined moderate and vigorous (*active*) activities were compared to those who reported <150min/wk of the same activity levels (*inactive*); then, patients who reported doing ≥75min/wk of vigorous activity only were compared to those who reported <75min/wk of the same activity level.

5.4.3.2.3 Self-reported walking time

Patients were asked to report the average time (min/day) spent in walking outside the house/workplace for each weekday and weekend day in the past week (Methods, p 64). In the statistical analysis of this section, the average walking time per week was calculated as (5 x weekday) + (2 x weekend) using the self-reported walk time in each weekday and the average of self-reported walk time in each weekend day.

5.4.3.2.4 Haemodynamic measurements

Sitting peripheral (Omron) and central (Vicorder) blood pressure (BP), mean arterial pressure (MAP), pulse pressure (PP) and heart rate were obtained (Methods, p 56).

Arterial stiffness measurements were taken using the Vicorder according to the gold-standard method aPWV while subjects were in a supine position (Laurent et al., 2006). Aortic PWV measurement of ≤4.7m/s was considered invalid and subjects were excluded (Methods, p 57).

5.4.3.2.5 Body composition

Height (metres) and weight (kilograms) were obtained (Seca, Germany). From this, body mass index (BMI) was calculated. The fat free mass (FFM) and the height squared index of fat free mass index (FFMI) were calculated using bioelectrical impedance (Tanita, USA) (Methods, p 55).

5.4.3.2.6 Resting oxygen saturation

Oxygen saturation was taken while subjects at rest (Konica Minolta pulsox-300, Japan).

5.4.3.2.7 Medical Research Council (MRC) dyspnoea scale

All subjects were asked to complete the MRC dyspnoea scale (Methods, p 54). Detailed medical history including self-reported use of CV medications and smoking history were recorded.

5.4.4 Statistics

Statistical Package for Social Sciences (SPSS) version 21 was used for data analysis (Chicago, IL). Where variables were normally distributed: Chi squire test was used for comparison between two categorical variables; independent t-test to investigate if a continuous variable is statistically different between two groups. For non-parametric variables the median (interquartile range (IQR)) was used to describe variables. Spearman's test was used to assess the correlation of two continuous variables. If non-normally distributed, Mann-Whitney U test was used to investigate if a continuous variable is significantly different between two groups, where Kruskal-Wallis was used when comparing a continuous variable across more than two groups. A stepwise regression analysis was used to determine factors affecting aortic stiffness in patients with COPD. A p-value <0.05 was considered significant.

5.5 Results

Of the 172 patients, five patients were excluded because of aPWV ≤4.7m/s, therefore 167 patients included. The demographics and lung physiology parameters is presented in Table 5.1**.** Central and peripheral haemodynamics including aPWV are presented in Table 5.2. Both genders had similar FEV_1% predicted and MRC score, all with $p>0.05$. In all subjects, aPWV was positively related to age ($r=0.43$, $p<0.001$), heart rate ($r=0.22$, $p<0.01$) and central MAP ($r=0.32$, $p<0.001$), but not to FEV_1% predicted, MRC dyspnoea scale and FFMI, all with $p>0.05$.

According to GOLD stages, only seven patients were classified as GOLD IV and, therefore, an adapted GOLD stages of GOLD I (n=17), GOLD II (98) and GOLD III and IV (n=52) was used for statistical analysis. Out of the 167 patients, 31 patients reported having ischemic heart disease (IHD) and 23 patients reported having diabetes mellitus. Patients self-reports of CV medications include angiotensin-converting enzyme inhibitor (n= 32), angiotensin receptor inhibitor (n= 15), beta blockers (n= 14) and statin (n= 100).

Table 5.1: Demographics of Patients with COPD

Mean (SD) unless otherwise indicated	
n	167
Age (years)	68 (8)
BMI (kg/m^2)	27.1 (5.6)
FFMI (kg/m^2) - n=158	18.4 (2.8)
Smoking history (pack years)	44 (25)
Smoking status - n (current/ex-smoker)	50/117
FEV_1 (L)	1.6 (0.6)
FEV_1% predicted	59 (19)
FVC (L)	3.2 (0.9)
FVC% predicted	95 (19)
FEV_1/FVC ratio	49 (13)
Resting SpO_2 (%)	95 (2)
MRC dyspnoea scale – median (IQR)	3 (2-4)

Abbreviations: Body mass index (**BMI**), fat free mass index (**FFMI**), forced expiratory volume in 1 second (**FEV_1**), forced vital capacity (**FVC**), oxygen saturation (**SpO_2**), Medical Research Council (**MRC**)

Table 5.2: Haemodynamic Measurements in Patients with COPD

Mean (SD)	
Peripheral systolic BP (mmHg)	141 (21)
Peripheral diastolic BP (mmHg)	80 (11)
Peripheral MAP (mmHg)	101 (13)
Peripheral PP (mmHg)	61 (16)
Heart rate (beat/min)	75 (15)
aPWV (m/s)	10.3 (2.1)
Central systolic BP (mmHg)	141 (21)
Central diastolic BP (mmHg)	84 (13)
Central MAP (mmHg)	110 (15)
Central PP (mmHg)	58 (17)

Abbreviations: Blood pressure (**BP**), mean arterial pressure (**MAP**), pulse pressure (**PP**) and aortic pulse wave velocity (**aPWV**)

5.5.1 Self-reported physical activity and haemodynamic measurements

5.5.1.1 Self-reported physical activity (hrs/wk)

Spearman's test showed no significant association of aPWV to a combined mild, moderate and vigorous activity (hrs/wk) (r=0.10, p=0.21) or to a combined moderate and vigorous activity (hrs/wk) (r=0.02, p=0.84).

Both the combined mild, moderate and vigorous activity (hrs/wk) and the combined moderate and vigorous activity (hrs/wk) were inversely related to peripheral pulse pressure (r=0.15 and r=0.16, respectively, p<0.05), but they were not related to other haemodynamic measurements including central and peripheral systolic BP, diastolic BP, MAP, heart rate and central pulse pressure, all with p>0.05.

5.5.1.2 Self-reported physical activity based on WHO guidelines

The vast majority of patients (n=125) do ≥150min/wk of combined moderate and vigorous activity had mean (SD) aPWV of 10.3 (1.8)m/s compared to those who do <150min/wk (n= 42), 10.2 (2.1)m/s, p=0.79. Similarly, patients (n=8) who reported vigorous activity ≥75min/wk had mean aPWV of 11.3 (1.0)m/s compared to 10.2 (2.1)m/s for those (n=159) who reported vigorous activity <75min/wk, p=0.14.

There was no statistical difference in peripheral and central haemodynamic measurements including heart rate, based on the cut-off of the 150min/wk (combined moderate and vigorous) or the 75min/wk (vigorous activity only), all with p>0.05.

5.5.1.3 Self-reported physical activity based on frequency of ≥3 times/week

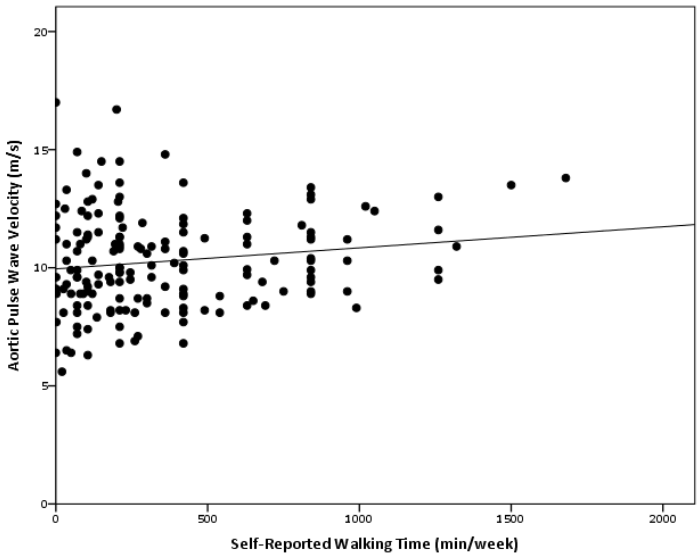
Patients who reported ≥3 times/wk of physical activity had mean (SD) aPWV of 10.2 (2.1)m/s and those with <3 times/wk had aPWV of 10.7 (2.0)m/s, p=0.24. There was no statistical difference in peripheral and central haemodynamic measurements when patients where compared based on self-reported >3times/wk of physical activity.

5.5.1.4 Self-reported walking time (minute/week)

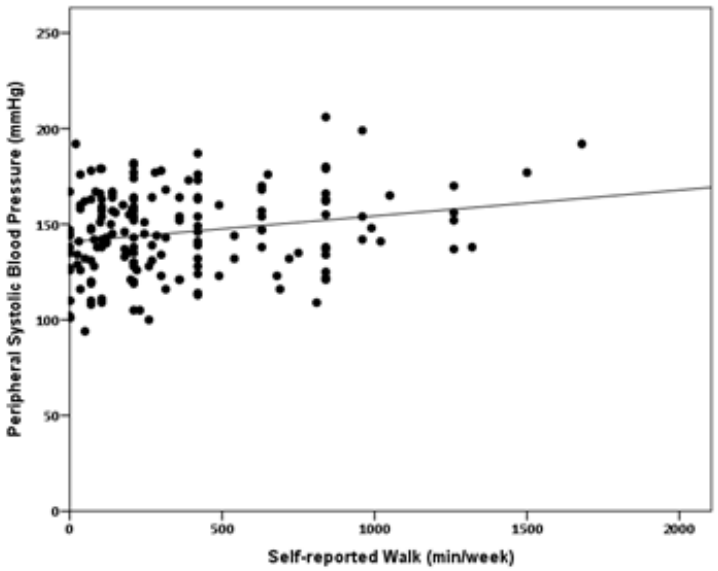
Spearman's test showed weak but significant association between self-reported walk time and both peripheral and central systolic BP (r= 0.16, p=0.04 and r= 0.18, p=0.02, respectively), but not between self-reported walk time and aPWV (r=0.11, p=0.14) (Figure 5.1). Analysis of other haemodynamic measures showed that self-reported walking time was associated with peripheral MAP (r=0.16, p=0.04), but not with other peripheral or central haemodynamic measures, p>0.05.

Figure 5.1: Association of Haemodynamic Measurements to Self-reported Walking Time

A: Aortic Stiffness and Self-Reported Walking Time



B: Peripheral Systolic Blood Pressure and Self-Reported Walking Time



5.5.2 Self-reported mild, moderate and vigorous activity (minute/week)

The median (IQR) time (min/wk) of self-reported combined mild, moderate and vigorous activity was 720 (300-1260)min/wk; and for the combined moderate and vigorous activity alone was 30 (0-150)min/wk.

5.5.2.1 Self-reported physical activity and GOLD stages of airflow obstruction and MRC dyspnoea scale

Kruskal-Wallis test showed significant difference between GOLD stages and the combined self-reported mild, moderate and vigorous activity (mins/wk) (p=0.02) (Figure 5.2), as well as between GOLD stages and the combined moderate and vigorous activity only, median (IQR) GOLD I: 30 (0-120)min/wk, GOLD II: 60 (0-240)min/wk, GOLD III and IV: 0 (0-60)min/wk, p= 0.02.

Likewise, Kruskal-Wallis test showed significant difference between MRC dyspnoea scale and the combined mild, moderate and vigorous self-reported physical activity (min/wk), p<0.001 (Figure 5.3), as well as the combined moderate and vigorous activities alone, median (IQR) MRC 1: 120 (0-720)min/wk, MRC 2: 90 (0-240)min/wk, MRC 3: 0 (0-60)min/wk, MRC 4: 0 (0-120)min/wk and MRC 5: 0 (0-18)min/wk, p<0.001.

5.5.2.2 Self-reported physical activity and other potential confounders

Other potential factors influencing self-reported physical activity to explore were age, gender, FEV_1% predicted, resting oxygen saturation and FFMI.

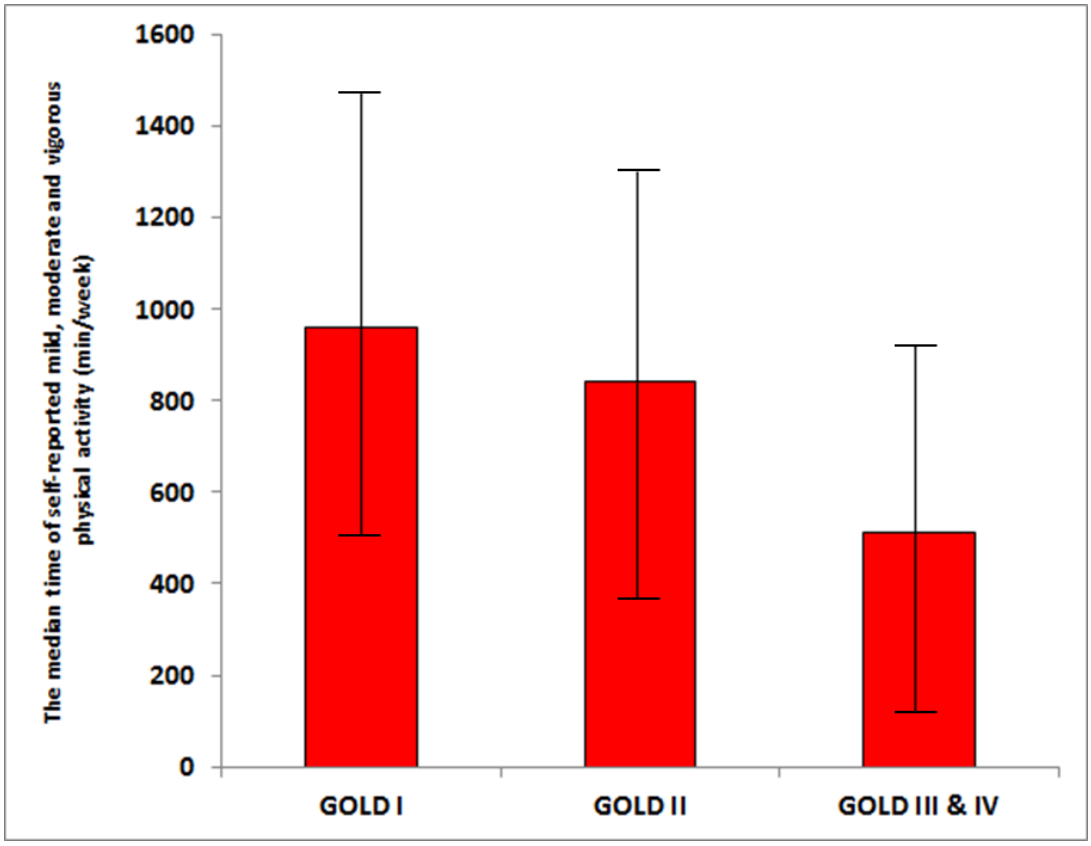
Spearman's test showed no significant association between age and neither a combined self-reported mild, moderate and vigorous activity (min/wk) (r= 0.14) or the combined moderate and vigorous activity only (r= 0.14), both p>0.05.

Mann-Whitney U tests showed no gender differences in self-reported combined mild, moderate and vigorous activity (min/wk), p>0.05; however, males reported significantly more time with a median (IQR), 60 (0-240)min/wk, doing combined moderate and vigorous activity than females, 0 (0-120)min/wk, p=0.001.

The combined mild, moderate and vigorous activity (min/wk) was associated to FEV_1% predicted (r= 0.32, p<0.001); but it was not associated to resting oxygen saturation, smoking history (pack year) or FFMI, all with p>0.05.

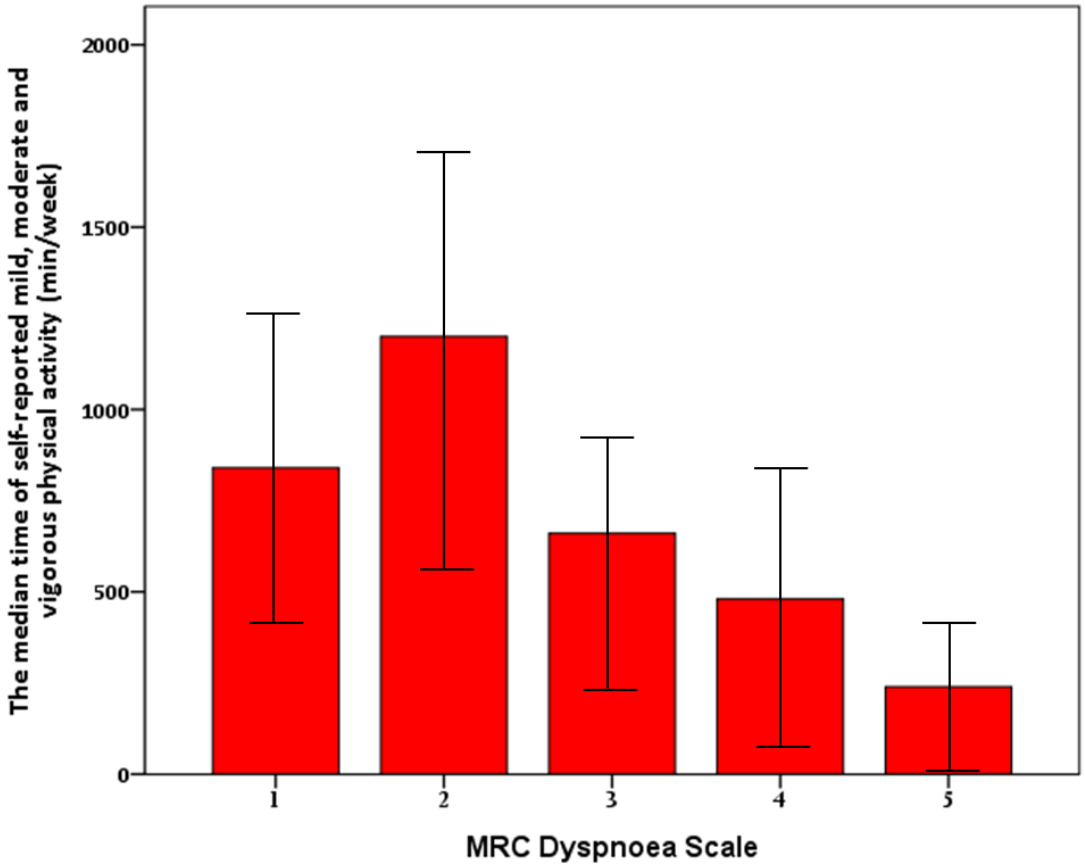
Comparable results were found when analysing the combined self-reported moderate and vigorous activity as it was associated to FEV_1% predicted (r=0.19, p=0.01), but it was also associated to FFMI (r=0.24, p=0.003). There was no significant association between the combined self-reported moderate and vigorous activity and the measurements of resting oxygen saturation or smoking history (pack year), all with p>0.05.

Figure 5.2: Self-reported Mild, Moderate and Vigorous Physical Activity Time and GOLD Stages



Error bars represent IQR
Abbreviation: Global Initiative for Chronic Obstructive Lung Disease (**GOLD**)

Figure 5.3: Self-reported Mild, Moderate and Vigorous Physical Activity Time and MRC Scale



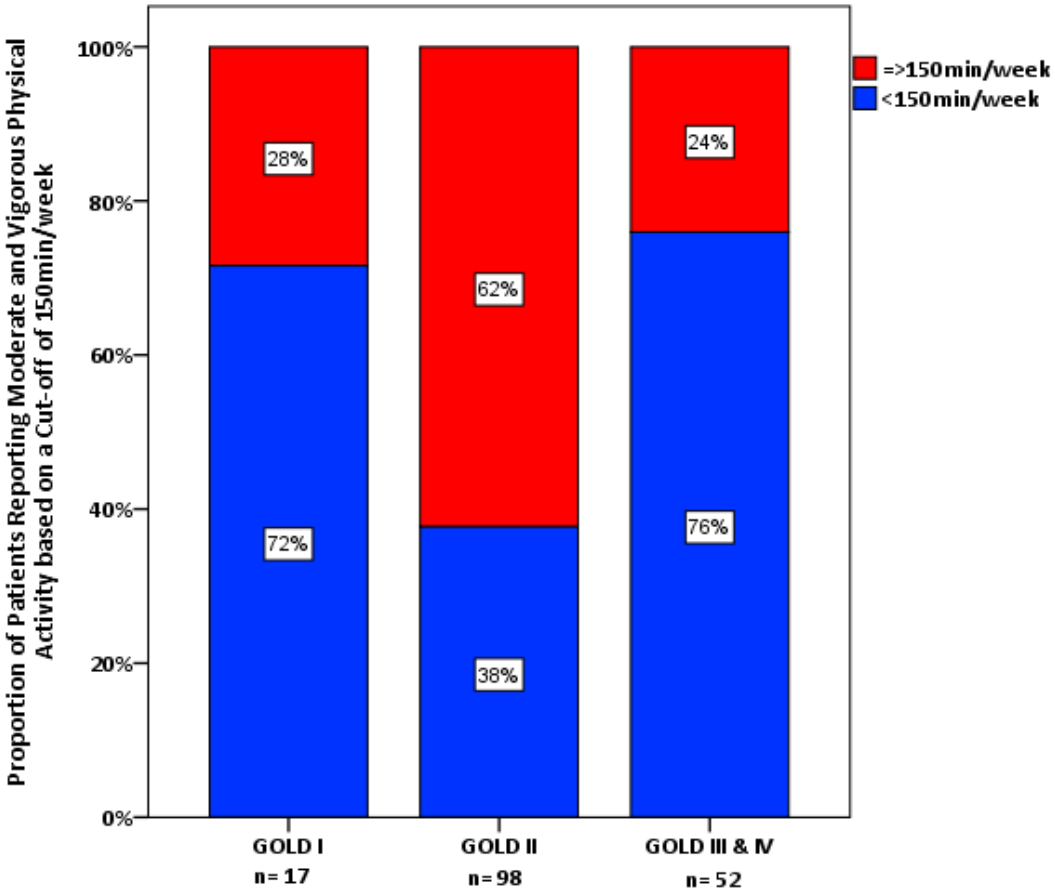
Error bars represent IQR
Abbreviation Medical research council (**MRC**)
MRC 1: n=13, MRC 2: n=65, MRC 3: n=35, MRC 4: n=39 and MRC 5: n=15

5.5.3 Comparison between active and inactive patients based on WHO guidelines for physical activity

Chi squared test showed that the proportion of patients who reported moderate and vigorous physical activity of ≥150min/wk (active patients) decreases as the severity of COPD – according to GOLD stages – increases, p=0.001 (Figure 5.4) (WHO, 2010).

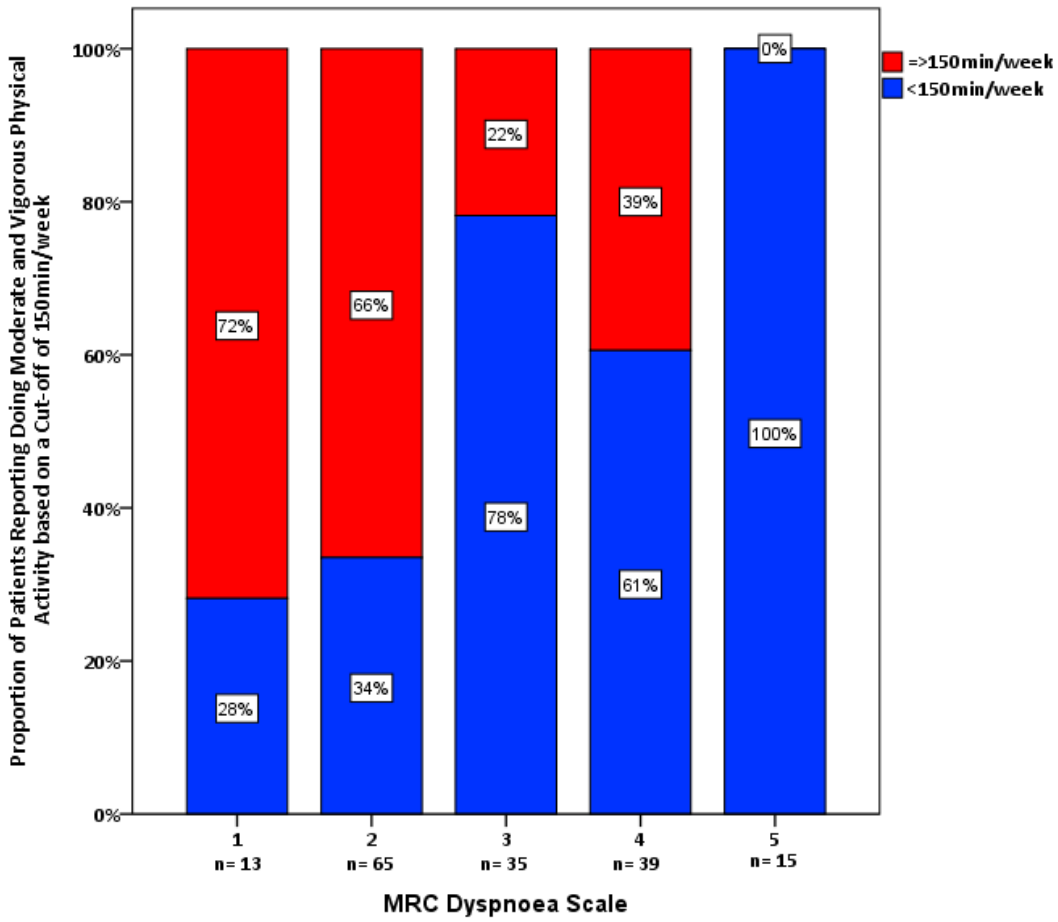
Similarly, as the MRC worsened the percentages of the inactive patients (<150min/wk of moderate and vigorous activity) became higher than the percentages of the active patients (150min/wk of moderate and vigorous activity), p<0.001 (Figure 5.5).

Figure 5.4: Proportion of Patients Classified as Inactive according to GOLD stages



Abbreviation Global Initiative for Chronic Obstructive Lung Disease (**GOLD**)
Active group: ≥150min/week
Inactive group: <150min/week

Figure 5.5: Proportion of Patients Classified as Inacitve according to MRC Dyspnoea Scale



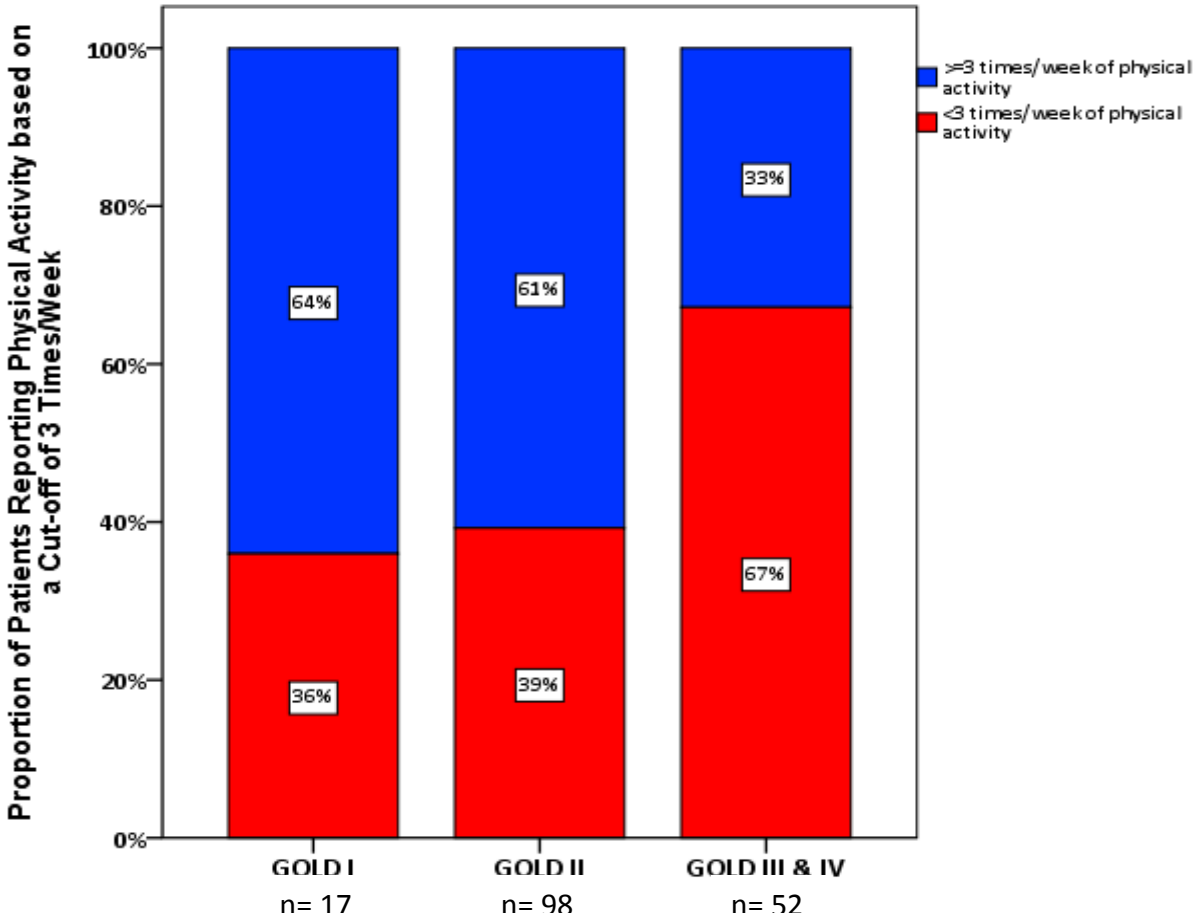
Abbreviation: Medical Research Council (**MRC**)
Active group: ≥150min/week
Inactive group: <150min/week

5.5.4 Self-reported physical activity based on a cut-off of 3 times/week

135 patients reported ≥3 times/wk whilst 32 patients reported <3 times/wk of mild, moderate or vigorous physical activity. Both groups were similar in age and gender, $p>0.05$. Chi squire test showed that the proportion of patients reporting doing physical activity ≥3 times/wk decreases as the severity of COPD based on GOLD stages increased, $p=0.01$ (Figure 5.6).

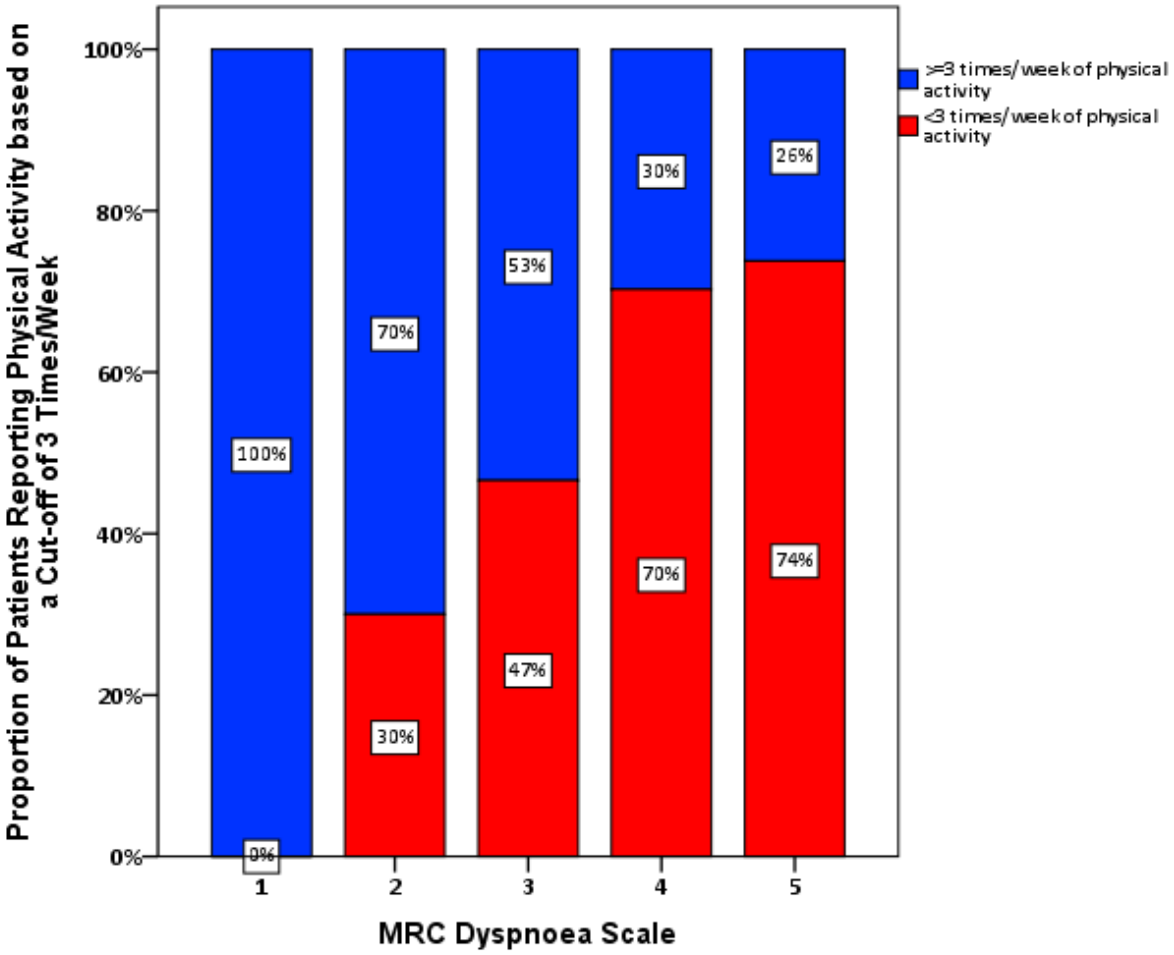
Similarly, Chi squire test showed that the proportion of patients who reported ≥3 times/wk decreases as the MRC score increased, $p=0.001$ (Figure 5.7).

Figure 5.6: GOLD Stages and Self-reported Frequency of Mild, Moderate and Vigorous Physical Activity



Abbreviation: Global Initiative for Chronic Obstructive Lung Disease (**GOLD**)

Figure 5.7: MRC Dyspnoea Scale and Self-reported Mild, Moderate and Vigorous Physical Activity

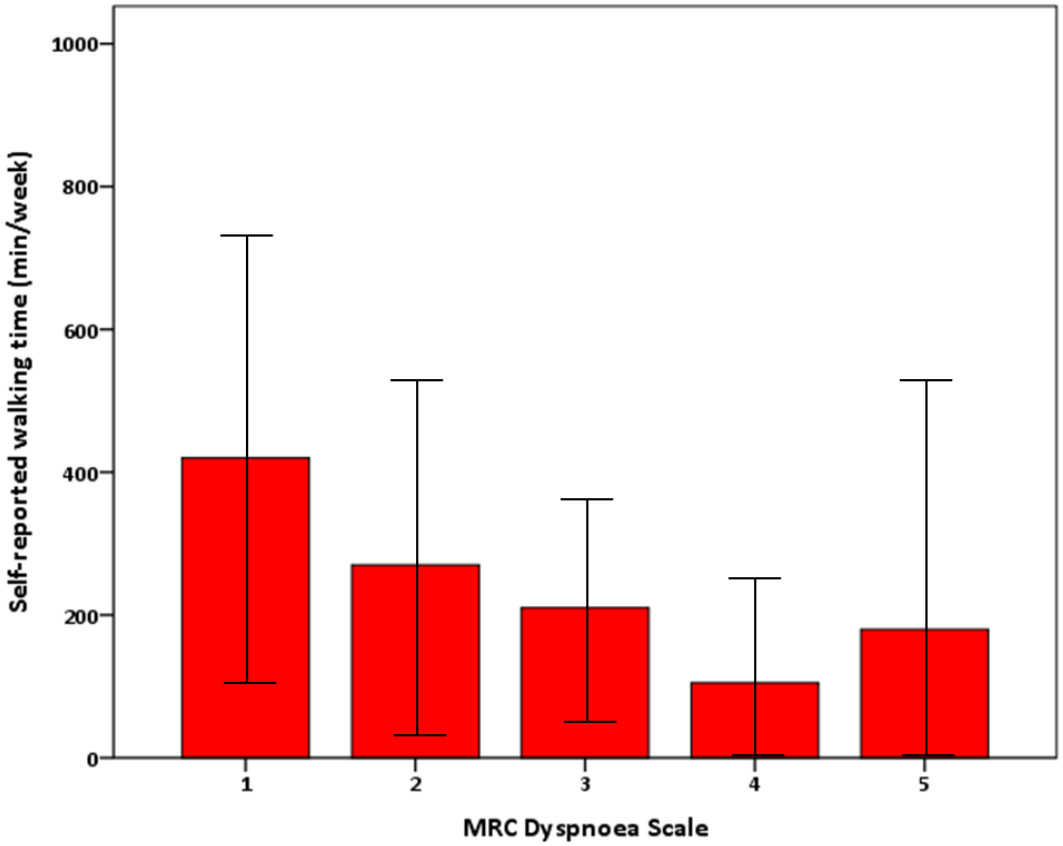


Abbreviation: Medical research council (**MRC**)
MRC 1: n= 13, MRC 2: n= 65, MRC 3: n= 35, MRC 4: n=39 and MRC 5: n= 15

5.5.5 Self-reported walking time

The median (IQR) of self-reported walking time was 210 (105-490)min/wk. Kruskal-Wallis test showed that self-reported walking time per week was not significantly different amongst the GOLD stages, p=0.15; but it was significantly different amongst the MRC dyspnoea scale, p=0.01 (Figure 5.8). In Figure 5.8 the unexpectedly high walking time in MRC score 5 could be explained by 2/15 of the patients reporting unexpectedly high walking time and their results being outliers.

Figure 5.8: Self-reported Walking Time (minute/week) across the MRC Dyspnoea Scale



Bars represent the median time (min/week) of self-reported walking time
Error bars represent the IQR
Abbreviation: Medical research council (**MRC**)
MRC 1: n= 13, MRC 2: n= 65, MRC 3: n= 35, MRC 4: n= 39 and MRC 5: n= 15

5.6 Discussion

The current study did not find an association between self-reported physical activity and aortic stiffness. Assessing patients during disease stability showed that the severity of COPD – assessed by GOLD stages – and dyspnoea – assessed by the MRC dyspnoea scale – were inversely related to the physical activity.

Expanding our understanding of the potential effects of daily life physical activity on arterial stiffness is important and might play crucial role in the future medical intervention to reduce death of cardiovascular diseases and reduce functional decline (Lloyd-Jones et al., 2010) in general public as well as in patients with COPD. Furthermore, previous studies showed that physical activity is an independent predictor of mortality in healthy subjects (Vaes et al., 2014) and in patients with COPD (Troosters et al., 2013, Garcia-Rio et al., 2012, Waschki et al., 2011, Vaes et al., 2014). Physical activity is a modifiable factor which can be improved and, therefore, provides long term benefits regarding patients' health (Troosters et al., 2013).

Stickland et al., looked at the relationship of physical activity to arterial stiffness in patients with COPD (20 inactive and 13 active) in comparison to 10 age-matched controls (Stickland, 2013). They showed an inverse association of time spent in moderate activity as well as the step counts to arterial stiffness when the total subjects were analysed and the authors suggested that physical activity may play a bigger role as a determinant of arterial

stiffness than does the lung function. The association of physical activity to arterial stiffness, undoubtedly, needs further investigation given that the sample of patients included in Stickland et al., study was not representative of the COPD population as the authors included patients with mild and moderate stage of COPD and without co-morbidities, for example diabetes, CV- and connective tissue diseases. Moreover, the authors relied on the brachial PWV - carotid-radial method of measuring PWV - instead of the carotid-femoral (aortic), where the latter is recognised to be an independent predicted of CV events (Laurent et al., 2006). This might be one explanation of the lack of association between arterial stiffness and age in their study; whereas, we reported with consistency to previous literature a positive association between age and aortic stiffness (Sabit et al., 2007). However, there is increasing interest in exploring the relationship between physical activity and arterial stiffness and some recent articles and abstracts concerning overweight and obese sedentary young adults (Hawkins et al., 2014) and community-dwelling older adult (Tanaka et al., 2014), support Stickland et al regarding the association of physical activity on arterial stiffness (Stickland, 2013). Compared to these studies, we did not find an association between aPWV and either self-reported physical activity or self-reported walking time. It should be noted that Stickland et al., study was published after we had conducted our work. Using subjective approach of quantifying physical activity in our study is a less accurate measurement of physical activity and walking time; however, it is inexpensive and permits assessment of more patients with less time when compared to objective

measures. Furthermore, the present study showed weak, but significant, association between physical activity and systolic blood pressure. This is consistent with a previous literature showing vigorous physical activity has positive effect on body metabolism and lowers the change of having high blood pressure in the general population (Janssen and Ross, 2012).

Physical activity has been shown repeatedly to be related to airway obstruction, dyspnoea and disease severity in COPD (Gimeno-Santos et al., 2014, Katajisto M, 2012, Troosters et al., 2010a, S. Barriga, 2014). Our study supports these findings using a simple subjective measure of self-reported physical activity questionnaires. A recently published study by Zogg et al., using physical activity monitor (SenseWear®) for 7 days showed that airway obstruction was positively related to daily steps count but not the level of physical activity (Zogg et al., 2014). In the previously mentioned study by Stickland et al., the authors did not find an association between physical activity and airways obstruction in patients with COPD (Stickland, 2013), for the sample size (33 patients with COPD) and, as we highlighted earlier, using limited population of patients with COPD were probably the key factors for the lack of significance.

Literature has highlighted some of the determinants of physical activity like age and gender in healthy subjects (Vern Seefeldt, 2002). In our patients we did not find an association between age and physical activity; however, there were gender differences in self-reported moderate- and vigorous- but not in mild-activity. Although both genders were similar in the degree of airway

obstruction and dyspnoea score male patients reported spending more time in moderate and vigorous activity than female patients. This likely corresponds to the greater muscular mass found in male patients in relation to their measurements of the FFMI.

5.6.1 Limitations

Although we included large representative patients with COPD, only a few of them were in very severe stage of the disease which might be one of the factors to conceal the potential association between physical activity and arterial stiffness specially if we take into account the inverse association of the severity of COPD to physical activity as well as severity of COPD to arterial stiffness. Although self-reported questionnaires is an accepted useful measure to assess physical activity (Troosters et al., 2013), it still can be underestimated or overestimated as a results of a recall bias or subjects' interpretation in particularly in reporting physical activities which require higher level of energy, for example "vigorous" activity (Prince et al., 2008).

5.6.2 Conclusion

Physical activity is, indeed, a modifiable risk factor and when properly managed can provide a long-term health benefits to patients with COPD. In the present study, the association of physical activity - assessed by a subjective approach – to arterial stiffness in patients with COPD did not reach significance. To our knowledge, there is only one published study looking at

the relationship between physical activity and arterial stiffness – using brachial PWV - in patients with COPD. However, Further studies are needed using more accurate measures of arterial stiffness – aPWV – in a wide range of a representative patients with COPD.

5.6.3 Future direction

There is a growing literature exploring the effect of COPD on physical activity using objective measures, for example the SenseWear®. Using a validated objective measure to explore the effects of daily life physical activity on arterial stiffness in representative patients with COPD is warranted; however expensive. This new area could potentially enhance our understanding of COPD and may add beneficial values to COPD management.

Chapter 6

Ambulatory Haemodynamics in Patients with COPD

6.1 Introduction

Chronic obstructive pulmonary disease (COPD) and its association to cardiovascular (CV) events has been extensively investigated in the past decade (Huiart et al., 2005, Sin and Man, 2003, Sabit et al., 2007, Curkendall et al., 2006). Studies investigating the extent of hemodynamic changes in patients with COPD are largely limited to resting measurements taken in a clinical setting. Depending on resting measurements alone may confine our understanding of the actual dynamic changes during daily life activities, where patients with COPD suffer exertion from seemingly simple tasks, for example walking down a corridor. Ambulatory blood pressure machines (ABPM) are useful, effective, and an easy way to obtain an overview of blood pressure (BP) and aortic stiffness profile over 24-hours period. Although ABPM measurements differ from those obtained from conventional BP monitors and might provide underestimated readings of some haemodynamics (Kallem et al., 2013, Luzardo et al., 2012), ABPM has been found to be superior to conventional BP monitors in predicting cerebrovascular and CV risks (Clement et al., 2003, Kario et al., 2001b, Verdecchia et al., 1994, Staessen et al., 1999, Shimada et al., 1990). It is noteworthy to mention that ABPM provides a more accurate haemodynamic profile over 24-hour period and helps to overcome limitations of in-clinic BP measurements, for example while coat and masked hypertension (NICE, 2011b, Pickering et al., 2002, Pickering et al., 2005). Therefore, implementing ABPM in research and clinical practice may help to better understand the

similarities and differences of 24hr haemodynamic profile in patients with COPD as compared to controls.

To our knowledge there is only one study investigating haemodynamic changes during 24-hour time period in patients with COPD with sleep desaturation using peripheral ambulatory BP (pABP) measurements (Aidar et al., 2009). This study showed that COPD alone was associated with increased peripheral BP measurements during the awake, night, and total 24-hr period compared to age- and BMI matched controls. Further, patients with COPD had significantly less overnight blood pressure dip compared to controls.

In addition to peripheral haemodynamic measurements, there has been interest in measurements of central haemodynamics such as central BP (cBP) and arterial, specifically aortic stiffness. These predict vascular hypertrophy, atherosclerosis, and CV events better than peripheral BP measurements (Laurent et al., 2006, Roman et al., 2007). Aortic stiffness, as measured by aortic pulse wave velocity is a gold standard, is increased in patients with COPD (Sabit et al., 2007) compared to smoker controls using tonometric (Sphygmocor®) and oscillometric (Vicorder®) devices (Sabit et al., 2007, John et al., 2013).

Exploring 24-hour central ambulatory haemodynamics in patients with COPD is of interest in light of above in order to provide important information regarding dynamic changes during daily life activities and sleep. The non-invasive automated oscillometric device (Mobil-O-Graph) has been validated according to the British Hypertension Society (BHS) (Jones et al., 2000) and

permits central ambulatory BP (cABP) using a brachial-cuff with transfer function-like algorithm (Weber et al., 2011) and it has been confirmed against the Sphygmocor® tonometric device (Weiss et al., 2012).

6.2 Hypothesis

Patients with COPD have abnormal profile of 24-hour aortic pulse wave velocity when compared to age- and gender-matched controls

6.3 Methods

6.3.1 Study objectives

- Assess the feasibility and acceptability of 24-hour BP monitor
- Measure the peripheral, cABP and aortic stiffness profile of patients with COPD and controls over a 24-hour period using the Mobil-O-Graph in a pilot study
- Compare the recorded aortic pulse wave velocity (aPWV) using the gold standard carotid-femoral PWV (Vicorder) and the derived at rest (in-clinic) measurements of aPWV using 24-hour cABP machine (Mobil-O-Graph)

6.3.2 Ethics

This sub-study was approved as an amendment to "The association of lung function and cardiovascular risk" 10/H0406/65, by the National Research Ethics Service (NRES), Nottingham committee.

6.3.3 Sample size and setting

This pilot sub-study encompassed patients with COPD and controls. As such a power calculation could not be performed but will inform for future studies. A pragmatic number of 20 patients and 20 controls with viable data were selected.

6.3.4 Inclusion and exclusion criteria

Detailed inclusion and exclusion criteria can be found in Methods, p 51.

6.3.5 Procedure

6.3.5.1 Informed Consent

In addition to the standard consent for the main study (Methods, p 53), subjects were asked to sign consent for this section and affirmation of responsibility and return of the machine.

Subjects were, consecutively, consented and asked for possible next day return of the cABP machine. Subjects were not consented if the ambulatory 24-hour machine was not available; e.g. had not yet returned from previous subject.

6.3.5.2 Tests

6.3.5.2.1 Ambulatory blood pressure

Following detailed discussion with each subject as to how to use and wear the device, a manual recording at rest by the cABP machine was performed and followed by another automatic recording during the visit to ensure that the device was prepared. These were performed seated after a period of rest.

Subjects were asked to press the day/night "marker" button when they went to bed and early morning when they first woke up. Moreover, a small card was attached to the device as a reminder where the subject could write the "bed" time and the "awake" time manually if he/she forgot to press the day/night button. Recordings of cABP were obtained following a Mobil-O-Graph pre-set protocol, programmed to take two diurnal recordings/hour and one nocturnal recording/hour. The subject was asked to return the device the following day and data downloaded.

Measurements of peripheral and central mean arterial pressure that were taken by the ABPM – in-clinic and over 24-hour period – were calculated as (1/3systolic + 2/3diastolic). Although the Mobil-O-Graph 24-hour PWV monitor provides measured recordings of peripheral MAP, we relied on

calculated measurements in our analysis for comparison purposes with measurements obtained from the Vicorder®. This was essential for consistency as calculated and measured MAP readings are not interchangeable (Kiers et al., 2008).

To investigate nocturnal haemodynamic differences between patients and controls, subjects in each group were classified as dippers (systolic nocturnal dip ≥10%) and non-dippers (systolic nocturnal dip <10%) adapted from systolic nocturnal dip classification: inverse dippers <0%, non-dippers - <10%, dippers <20%, and extreme dippers ≥20% (Kario et al., 2001a); for example, dippers (dippers and extreme dippers) and non-dippers (inverse dippers and non-dippers).

6.3.5.2.2 In-clinic haemodynamic measurements

As part of the main study, all subjects underwent detailed resting haemodynamic measurements including peripheral and central haemodynamic/ arterial stiffness measurements.

- *Peripheral blood pressure*

Peripheral resting BP was performed, Methods, p 56.

- *Pulse wave analysis and aortic stiffness*

Following the peripheral measurements, cBP and aPWV were attained at rest in a sitting position using the Vicorder (Method, p 57)

6.3.5.2.3 Spirometry

All subjects performed spirometry to determine forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC) and the ratio. Post bronchodilator readings in patients with COPD were recorded (Methods, p 58)

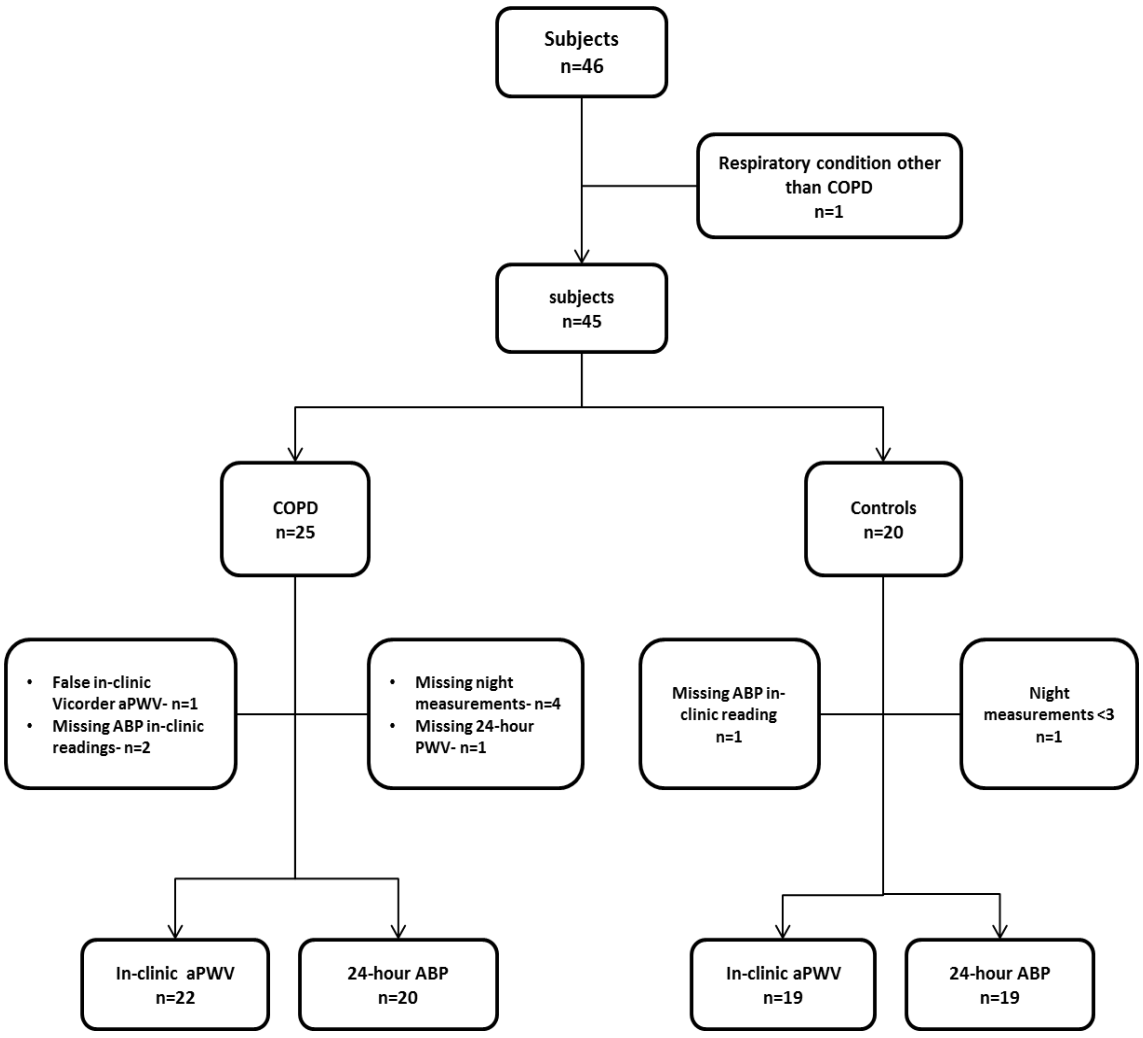
6.3.6 Statistics

Statistical package of the Social Sciences (SPSS) version 21 was used for data analysis. Comparison between the two groups was applied where data was continuous and normally distributed by parametric statistics e.g. independent t-test. Chi-squire test was used for categorical data. Pearson (or Spearman's rank for non-parametric) was used to analyse relationship between two variables and $p < 0.05$ was defined as significant. Paired sample t-test was used to detect haemodynamic differences during diurnal and nocturnal measurements. Bland-Altman plot was used for comparison between two different methods of measuring aPWV – Vicorder and Mobil-O-Graph.

6.4 Results

Study recruitment included 46 subjects - patients with COPD and smoker controls. Out of the 46 participants, one was excluded because of respiratory condition other than COPD. Thus, 25 COPD and 20 smoker controls were included in the demographics of this study. However not all subjects were suitable for all the analyses (Figure 6.1).

Figure 6.1: 24-hour Ambulatory blood pressure/aortic stiffness Study flowchart



Subjects were well-matched for age, gender and BMI (Table 6.1). There were significantly greater "current" smokers and smoking pack years in COPD group than controls. As expected, patients with COPD had lower FEV_1% and FEV_1/FVC ratio. A chi square analysis showed no significant difference in self-reported co-morbidities, although the values were low and analysis in results interpreted with caution (Table 6.1).

Table 6.1: Study Demographics of All Subjects Recruited

Mean (SD) unless otherwise stated		COPD N= 25	Controls N= 20	P-value
Gender (m/f) - n		16/9	10/10	0.35
Age (years)		68 (8)	64 (9)	.0.13
Smoking pack years		42 (19)	29 (11)	**<0.01**
Smoking status (current/ex) - n		11/14	3/17	**0.04**
Carbon monoxide		8 (9)	4 (5)	**0.03**
BMI (kg/m^2)		28.6 (7.6)	30.4 (6.3)	0.4
FEV_1 (L)		1.68 (0.58)	2.62 (0.63)	**<0.001**
FEV_1% predicted		62 (17)	100 (16)	**<0.001**
FEV_1/FVC ratio		52 (15)	75 (7)	**<0.001**
Resting Oxygen saturation %		95 (2)	96 (2)	**0.03**
Self-reported	**Cardiovascular diseases (n)**	7	2	0.13
	Hypertension (n)	7	4	0.54
	Diabetes mellitus (n)	4	2	0.56
	Osteoporosis (n)	1	2	0.42
	Hypercholesterolemia (n)	13	7	0.32
	Renal diseases (n)	0	1	0.26
	Cerebrovascular diseases (n)	1	0	0.37
	Rheumatoid arthritis (n)	2	3	0.46

Abbreviations: Body mass index (**BMI**), forced expiratory volume in one second (**FEV_1**), and forced expiratory volume (**FVC**).

6.4.1 Feasibility and acceptability of the Mobil-O-Graph 24-hour PWV monitor

Feasibility was assessed objectively by evaluating the number of recordings over 24-hour period, which can be determined by the number of registered recordings and feedback. Six out of the 45 participants: five out of 25 patients with COPD and one out of 20 controls did not have valid recording (minimum of three nocturnal and three diurnal measurements).

Reasons for invalid recordings included subject intolerability: measurement aborted or machine switched off by user (n=1), pressure increased during deflation "movement" (n=4), and pressure decrease during inflation (n=1); and machine faults: movement artefact (n=20), heart rate increase beyond range (n=2), leakage (n=3) and/or exceeded time of measurement (n=3). There was no feedback report of skin irritation or bruises from cABP machine wearers.

Movement artefact was the foremost reason accounting for 44% of all invalid measurements. Nevertheless, the overall "valid" measurements obtained from the machine were deemed acceptable. The maximum possible pre-set recordings per patient over a 24 hour period was 38; however manual recordings could be performed over and above this. The mean (SD) number recorded was 32 (12).

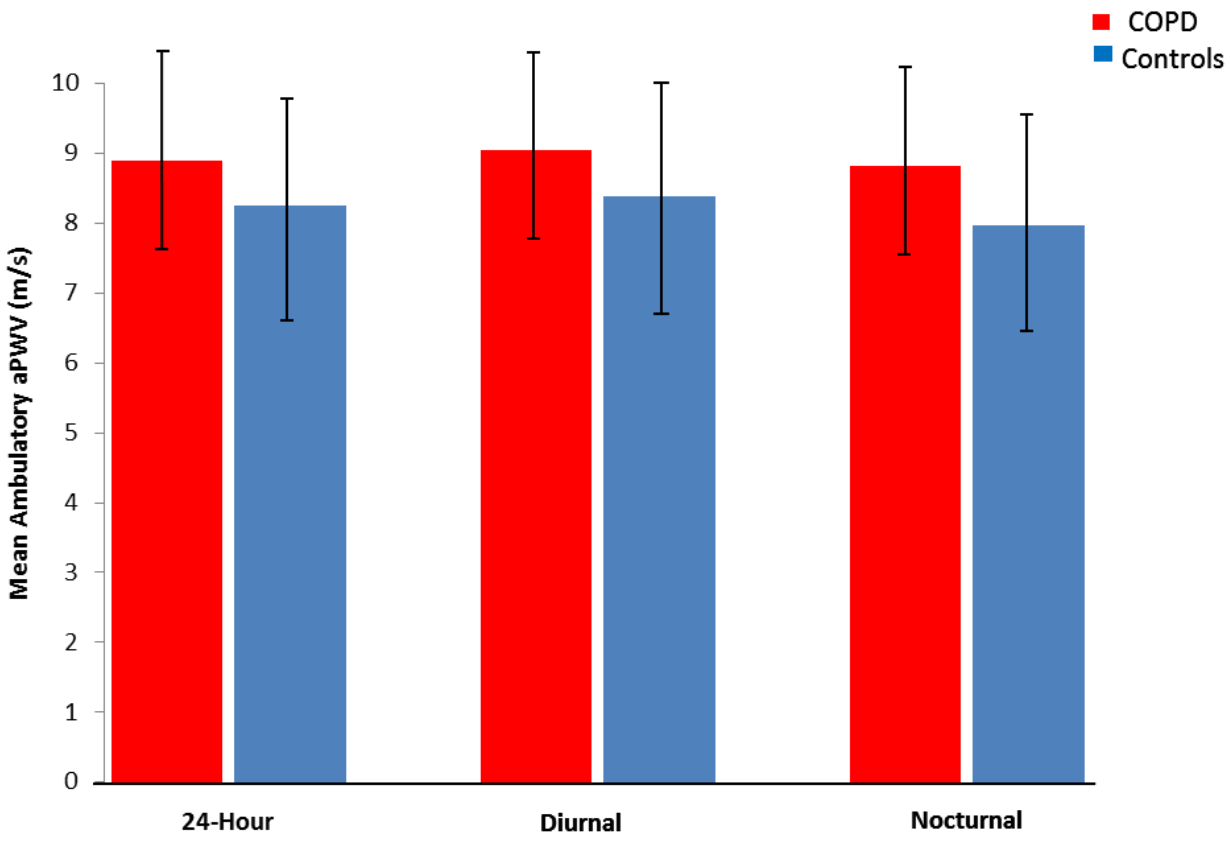
6.4.2 24-hour blood pressure and aortic stiffness profile in patients and controls

Subjects with valid measurements obtained by 24-hour cABP machine were included in this part of the analysis. Out of the 25 COPD subjects five were excluded: one did not have any 24-hour aPWV measurement and four others did not have nocturnal ambulatory aPWV measurements. In controls, one subject was excluded due to missing nocturnal measurements. Thus, 20 patients with COPD and 19 controls where included in this analysis (Figure 6.1).

The mean values for the total 24-hour, diurnal, and nocturnal aPWV were constantly greater in patients with COPD than controls, but did not reach statistical significance (Figure 6.2 and Table 6.2).

Other 24-hour, diurnal, and nocturnal haemodynamic measurements of patients and controls were demonstrated in Table 6.2**.** Peripheral measurements of PP and MAP were similar between patients and controls, all with $p>0.05$. Heart rate was consistently increased in patients compared to controls but was significant during the 24-hour and diurnal periods only, both with $p<0.05$.

Figure 6.2: Mean Ambulatory aPWV profile in Patients with COPD and Controls using 24-hour cABP machine



Abbreviation: Aortic pulse wave velocity (**aPWV**) and central ambulatory blood pressure monitor (**cABP**)
Error bars represent ±1SD

Table 6.2: 24-Hour, Diurnal, and Nocturnal Peripheral and Central Ambulatory Blood Pressure Measurements in Patients and Controls

Mean value unless otherwise indicated	24-hour		p	Diurnal		p	Nocturnal		P
	COPD n= 20	CONTROLS n= 19		COPD N= 20	CONTROLS n= 19		COPD n= 20	CONTROLS n= 19	
pSBP (mmHg)	133 (15)	127 (12)	0.19	137 (16)	130 (13)	0.19	119 (29)	119 (12)	0.99
pDBP (mmHg)	79 (8)	78 (7)	0.55	82 (8)	81 (8)	0.59	72 (8)	72 (8)	0.68
MAP (mmHg)	97 (9)	94 (7)	0.27	100 (10)	97 (8)	0.29	88 (13)	87 (8)	0.84
PPP (mmHg)	54 (12)	49 (12)	0.26	54 (13)	50 (13)	0.25	46 (25)	47 (13)	0.87
Heart rate (bpm)	75 (10)	68 (10)	**0.04**	77 (11)	70 (10)	**0.04**	70 (10)	65 (11)	0.12
cSBP (mmHg)	120 (12)	120 (13)	0.99	124 (14)	124 (15)	0.94	118 (22)	112 (13)	0.30
cDBP (mmHg)	80 (8)	79 (7)	0.76	85 (9)	83 (8)	0.60	77 (18)	73 (10)	0.41
cMAP (mmHg)	93 (9)	93 (7)	0.84	98 (10)	97 (9)	0.72	90 (19)	86 (9)	0.34
cPP (mmHg)	40 (9)	40 (12)	0.84	39 (10)	41 (13)	0.76	42 (9)	39 (12)	0.50
aPWV (m/s) – using the cABP machine	8.9 (1.3)	8.3 (1.6)	0.63	9.0 (1.2)	8.4 (1.6)	0.65	8.8 (1.3)	8.0 (1.5)	0.07

Abbreviations: Peripheral systolic blood pressure (**pSBP**), peripheral diastolic blood pressure (**pDBP**), mean arterial pressure (**MAP**), peripheral pulse pressure (**PPP**), central systolic blood pressure (**cSBP**), central diastolic blood pressure (**cDBP**), central mean arterial pressure (**cMAP**), central pulse pressure (**cPP**), aortic pulse wave velocity (**aPWV**) and central ambulatory blood pressure (**cABP**). The p-values represent the comparison between patients and controls

The relationship of 24-hour, diurnal and nocturnal ambulatory aPWV to other haemodynamic measurements in patients and controls were presented in Table 6.3. In patients, there were direct moderate correlations between ambulatory aPWV and cPP over the 24-hour and nocturnal measurements only. In controls, there were direct moderate association between mean aPWV (24-hour and diurnal) and diurnal cSBP and between aPWV and cPP measurements over the 24-hour, diurnal- and nocturnal periods.

Table 6.3: Association of aPWV and Haemodynamic Measurements During 24-hour, Diurnal and Nocturnal time

r (p-value)		COPD			Controls		
		24-hr aPWV	Diurnal aPWV	Nocturnal aPWV	24-hr aPWV	Diurnal aPWV	Nocturnal aPWV
cSBP (mmHg)	24-hr	0.33 (0.16)	0.35 (0.14)	**0.44 (0.05)**	0.42 (0.08)	0.45 (0.06)	0.36 (0.13)
	Diurnal	0.22 (0.36)	0.31 (0.19)	0.26 (0.27)	**0.47 (0.04)**	**0.52 (0.02)**	0.39 (0.1)
	Nocturnal	0.18 (0.44)	0.15 (0.54)	0.42 (0.07)	0.22 (0.37)	0.2 (0.41)	0.3 (0.21)
cDBP (mmHg)	24-hr	0.07 (0.78)	0.1 (0.69)	0.1 (0.68)	-0.21 (0.4)	-0.18 (0.47)	-0.27 (0.26)
	Diurnal	0.06 (0.79)	0.15 (0.53)	0.01 (0.97)	0.06 (0.8)	0.11 (0.65)	-0.04 (0.88)
	Nocturnal	-0.001 (0.99)	-0.02 (0.92)	0.21 (0.38)	-0.42 (0.08)	-0.44 (0.06)	-0.3 (0.21)
cMAP (mmHg)	24-hr	0.19 (0.41)	0.22 (0.35)	0.27 (0.26)	0.11 (0.64)	0.15 (0.54)	0.04 (0.87)
	Diurnal	0.14 (0.55)	0.34 (0.32)	0.13 (0.59)	0.29 (0.22)	0.35 (0.14)	0.19 (0.44)
	Nocturnal	0.07 (0.77)	0.04 (0.86)	0.29 (0.21)	-0.19 (0.45)	-0.21 (0.38)	-0.07 (0.79)
cPP (mmHg)	24-hr	0.39 (0.09)	0.39 (0.09)	**0.52 (0.02)**	**0.55 (0.02)**	**0.56 (0.01)**	**0.53 (0.02)**
	Diurnal	0.24 (0.31)	0.28 (0.23)	0.35 (0.13)	**0.53 (0.02)**	**0.56 (01)**	**0.5 (0.03)**
	Nocturnal	**0.45 (0.047)**	0.4 (0.08)	**0.61 (0.004)**	**0.58 (0.01)**	**0.58 (0.009)**	**0.58 (0.009)**
Heart rate (beat/min)	24-hr	-0.05 (0.84)	-0.13 (0.58)	-0.05 (0.84)	-0.17 (0.5)	-0.12 (0.61)	-0.22 (0.36)
	Diurnal	-0.06 (0.8)	-0.13 (0.58)	-0.08 (0.74)	-0.12 (0.66)	-0.07 (0.79)	-0.17 (0.5)
	Nocturnal	0.03 (0.9)	-0.06 (0.82)	0.04 (0.87)	-0.26 (0.29)	-0.23 (0.34)	-0.27 (0.26)

Abbreviations: Central systolic blood pressure (**cSBP**), central diastolic blood pressure (**cDBP**), central pulse pressure (**cPP**), central mean arterial pressure (**cMAP**) and aortic pulse wave velocity (**aPWV**).

6.4.3 Aortic stiffness: comparison between Vicorder and cABP machine - In-clinic measurements

Subjects with valid aPWV measurements obtained by the Vicorder® and the (in-clinic) 24-hour cABP machine while at rest were included. Of the 46 subjects, eligible readings in both devices were determined in 41 subjects: 22 patients and 19 controls (Figure 6.1). The Vicorder® gave higher central readings of SBP, PP, MAP and lower readings of central DBP and heart rate than the cABP machine. Both devices gave same measurements of aPWV, 9.2m/s. (Table 6.4).

To assess the level of agreement between the two devices in all subjects in measuring at rest aPWV, Bland-Altman plot was constructed. The mean (SD) difference of the aPWV measurements obtained from the two devices (Vicorder aPWV – cABP machine aPWV) was 0.1 (2.0)m/s. Values for aPWV were within 2SD except for one subject (Figure 6.3a). Vicorder measurements repeatedly showed increased cMAP compared to in-clinic cABP machine measurements, mean (SD) difference of MAP: Vicorder MAP – cABP machine MAP = 6 (12)mm Hg. Bland-Altman plot showed that values of MAP obtained from Vicorder and cABP machine fall were within 2SD except for one subject (Figure 6.3b).

Table 6.4: The mean values of central haemodynamic measurements taken using Vicorder and at rest measurement using (in-clinic) 24-hr Ambulatory Blood Pressure

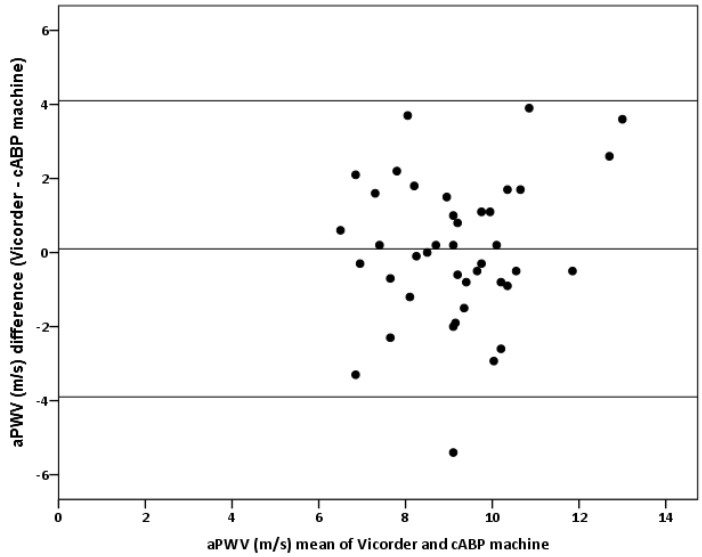
Mean (SD)	Vicorder n=41	24-hr ABPM (in-clinic) n=41
SBP (mmHg)	146 (17)	133 (26)
DBP (mmHg)	85 (11)	88 (14)
PP (mmHg)	61 (16)	46 (23)
MAP (mmHg)	112 (11)	103 (16)
Heart rate (bpm)	69 (13)	73 (14)
aPWV (m/s)	9.2 (1.9)	9.2 (1.6)

Abbreviations: Ambulatory blood pressure monitor (**ABPM**), systolic blood pressure (**SBP**), diastolic blood pressure (**DBP**), pulse pressure (**PP**), mean arterial pressure (**MAP**), aortic pulse wave velocity (**aPWV**).

Figure 6.3: Bland-Altman plot of Main Haemodynamic Measures

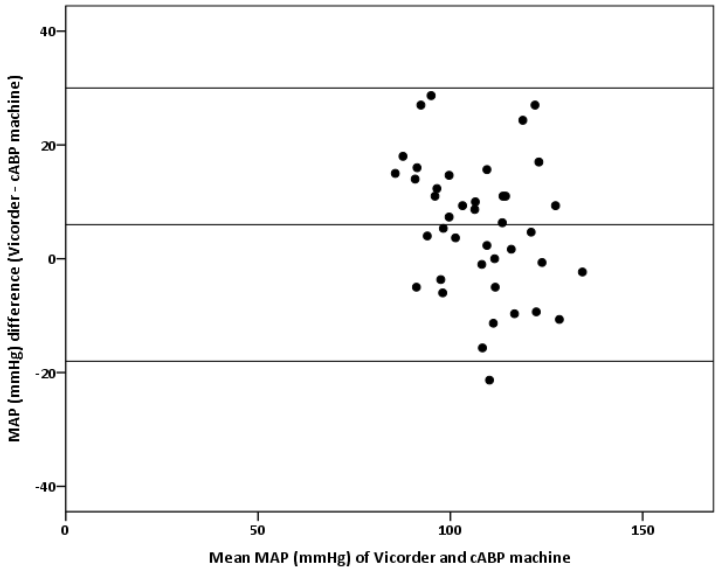
6.3a: Aortic Pulse Wave Velocity

Mean = 0.1m/s
2SD = 4.0m/s
aPWV (Vicorder) =9.2 (1.9)m/s
aPWV (cABP machine) =9.2 (1.6)m/s



6.3b: Mean arterial pressure

Mean = 6mmHg
2SD = 24mmHg
MAP (Vicorder) =112 (12)mmHg
MAP (cABP machine) =103 (16)mmHg



6.4.1 Systolic nocturnal dip and nocturnal aPWV

In our study there was a similar amount of systolic dippers in both the COPD (n=9) and control (n=10) groups, p=0.63. Measurements of 24-hour-, diurnal and nocturnal aPWV were increased in patients compared to control; however this trend did not reach significance. See Table 6.5. The greatest nocturnal-diurnal difference in 24-hour ambulatory aPWV of 0.9m/s was in patients when the non-dippers were compared to dippers. See Table 6.5.

The greatest differences between patients and controls based on dipping status was nocturnal aPWV measurements, however differences were not statistically significant (Table 6.5). In dippers, patients had an increase in the nocturnal aPWV by 0.7m/s compared to controls, p=0.30. In non-dippers, patients had an increase nocturnal aPWV of 1.1m/s compared to controls, p=0.10.

6.4.1.1 Diurnal and nocturnal cSBP and aPWV difference in patients with COPD and in controls

Paired Sample Test showed significant difference of diurnal and nocturnal cSBP in controls: mean (SD): 124 (15)mmHg and 112 (13)mmHg, respectively, p=0.001, but not in patients: mean (SD): 124 (14)mmHg and 118 (22)mmHg, respectively, p=0.14. Similarly, there was no significant difference between mean (SD) diurnal and nocturnal aPWV in patients, 9 (1.2)m/s, and 8.8 (1.3)m/s, respectively; p=0.67. In controls, there was an increased diurnal

aPWV measurements compared to nocturnal aPWV, mean (SD) = 8.4m/s (1.6), and 8.0m/s (1.5), respectively; p=0.001.

Table 6.5: The 24-Hour, Diurnal, and Nocturnal Aortic Pulse Wave Velocity according to Systolic Dippers or Non-dippers

Mean (SD) unless otherwise indicated	COPD			Controls		
	Non-dippers n= 11	Dippers n= 9	P	Non-dippers n= 9	Dippers n= 10	P
24-hour aPWV (m/s)	9.2 (1.4)	8.6 (1.2)	0.33	8.3 (1.6)	8.2 (1.7)	0.92
Diurnal aPWV (m/s)	9.2 (1.4)	8.9 (1.2)	0.60	8.4 (1.7)	8.4 (1.7)	0.95
Nocturnal aPWV (m/s)	9.3 (1.4)	8.4 (1.1)	0.12	8.2 (1.4)	7.7 (1.7)	0.51

Abbreviation: Aortic pulse wave velocity (**aPWV**)

6.5 Discussion

In this pilot study, the dynamic peripheral and central haemodynamics were assessed in patients with COPD compared to controls using the Mobil-O-Graph 24-hour PWV/cABP machine. The device was feasible to be used in this study in the vast majority of subjects and it provided acceptable number of recordings over 24-hour time. Bland Altman plot showed good agreements of resting (in-clinic) cABP machine and the Vicorder® haemodynamic measurements. As expected the cABP machine detected consistently higher values of 24-hour, diurnal, and nocturnal ambulatory aPWV in patients with COPD than controls as well as in patients and controls non-dippers compared to dippers, the differences were not statistically significant in this pilot study. Controls had significantly increased diurnal aPWV compared to nocturnal aPWV measurements. Patients, on the other hand, did not have significant nocturnal aPWV drop compared to diurnal aPWV.

The feasibility and the users' tolerability of a device can be assessed using subjective and/or objective approach. Although subjective measurements sometimes demonstrate inconvenience use of the ABPM, objective measurements demonstrate good tolerability and acceptability of the device (Tropeano, 2006). Viera et al., used the model 'Oscar 2' ABPM on people with borderline clinic BP and reported that ambulatory BP wearers mostly complain of sleep disturbance (Viera et al., 2011). Although our subjects did not complain of sleep disturbance, the majority of exclusion (13%) was

because of missing actual nocturnal haemodynamic measurements. Using Subjective approach, Elliot and Iqbal., showed good tolerability of the 24-hour peripheral ABPM - Mobil-O-Graph - in patients who were referred for CV investigations (Elliot and Iqbal, 2003). They reported that 95% of patients were willing to have a repeat of the ABPM.

Previous work using static one-off aPWV measurements as a marker of CV risks reported increased aPWV in patients with COPD compared to healthy controls (Sabit et al., 2007). Further, an improvement or a change of 1m/s in (at rest) measurement was shown to be associated with 14% higher risk of CV mortality and 15% higher risk of all-cause mortality (Vlachopoulos et al., 2010). With regards to ambulatory aPWV measurements, there is no established minimal threshold to rely on when interpreting an improvement or change in ambulatory aPWV. Nevertheless, our findings of a trend of increased aPWV over the 24-hour, diurnal and nocturnal periods in patients with COPD compared to controls is consistent with previously established work where in-clinic static measurement of aPWV was increased in COPD compared to controls (Sabit et al., 2007).

Only one study by Aidar et al., who looked at 24-hour peripheral haemodynamics in patients with COPD (n= 13) and age-matched controls (n= 14), but not PWV (Aidar et al., 2009). They showed significant increase of peripheral 24-hour, diurnal and nocturnal haemodynamic measurements in patients with COPD compared to controls. In our pilot study we showed increased peripheral and central haemodynamic measurements over the 24-

hour, diurnal and nocturnal periods in patients with COPD compared to controls, although the differences were not statistically significant. The lack of significance in our study might be because of subjects baseline characteristics as the patients in Aidar el at., study were in more severe stages of the disease (GOLD III) and relatively older with a mean age of 70 years. This could justify the lack of significance in our study as the severity of COPD and age are factors influencing haemodynamic/aortic stiffness changes (Sabit et al., 2007, Franklin et al., 1997).

Comparing in-clinic cABP measurements to a standardize measure of central haemodynamic/arterial stiffness – Vicorder® - is an important part of our work as investigating of the potential application of dynamic central BP/aortic stiffness measurements in COPD population has not been explored.

Luzardo et al., compared central haemodynamic/aortic stiffness measurements of Mobil-O-Graph 24-hour PWV monitor – at rest and under ambulatory conditions - to measurements obtained by SphygmoCor at rest (Luzardo et al., 2012). They showed good agreements of results obtained from both devices regardless of the study condition – at rest or ambulatory. Our Bland Altman plot showed similar findings, although we used oscillometric device - Vicorder® - instead of the tonometric SphygmoCor.

Superiority of ABPM over clinic or home BP monitoring has been well establish in previous literature, particular in the areas of diagnoses and drug intervention of hypertensive patients (Giles et al., 2011, Hodgkinson J, 2011). However, recently established work by Kallem et al., comparing two ABPMs

(Mobil-O-Graph [I.E.M., Stolberg, Germany] and Spacelabs 90207 [Spacelabs Medical, Issequal, WA]) found that both devices gave different haemodynamic measurements regardless of the side (dominant or non-dominant hand) of measurements (Kallem et al., 2013). They highlighted the importance of careful interpretations of the results and the necessity of references values for each device.

Nocturnal systolic dip has been found to be associated with CV risks and non-dippers are at higher CV risks than dippers regardless of in-clinic BP measurements (Huiart et al., 2005, Lekakis et al., 2005, Sin and Man, 2005, Sin and Man, 2003). As a pilot study using small sample size, we did not expect to find significant differences between dippers and non-dippers in patients or in controls; however, the trend we showed of consistently increased aPWV over 24-hour, diurnal and nocturnal periods in patients compared to controls encourages further investigation in this area. Moreover, this is the first study to show that the nocturnal aPWV seen in controls was not evidenced in patients with COPD. Although there was no difference in nocturnal cSBP between patients and controls, within group analysis showed that controls had significantly lower nocturnal cSBP compared to diurnal cSBP measurements, but this was not seen in patients.

6.5.1 Limitation

As a piloted study we used a small sample size and the majority of our patients with COPD were classified as moderate (GOLD II) stage which might

have an effect on minimizing some of haemodynamic/arterial stiffness differences between patients and controls. This could also be a good reason for future work with bigger sample size and more severe cases to potentially find greater and significant differences between patients and controls and probably among different GOLD stages of the disease. Another limitation was the difficulty of measuring subjects' tolerability of the cABP machine as we depended on objective measures (the number of actually recordings over 24-hour) and subjects' verbal instead of written feedback to use as a subjective measure.

6.5.2 Conclusion

This work objectively demonstrated that cABP machine is a feasible device to be used in patients with COPD and it provides useful and additional information over conventional BP. Central haemodynamic/aortic stiffness measurements using cABP machine showed good agreement with the standardize method - the Vicorder® - for static aPWV. Further, we showed that patients with COPD did not have nocturnal aPWV dip as it was observed in control comparators.

Taking into account that aPWV is a better predictor of CV events and COPD is a systemic disease with high CV risks, all suggest the need for further investigation in this area looking at aortic stiffness over 24-hour, diurnal, and nocturnal time instead of at rest one-off measurements. This puts the device in more favourable place for future work investigating this area.

Chapter 7

Conclusions

7.1 Introduction

Patients with COPD have compromised physical performance, physical activity and haemodynamics; therefore, the aim of this research was to explore the determinants and the potential use of a simple physical performance assessment test that requires small space and time (the TUG test) in patients with COPD as well as to explore the nature of haemodynamics profile in patients with COPD as compared to age and gender matched controls.

7.2 Time Up and Go (TUG) in patients with COPD

The study was designed to investigate the TUG test in a large representative population of patients with COPD. The baseline parameters for patients and controls were similar in age, gender and self-reported co-morbidity - if not accounting for COPD). This was important to minimise the potential effect of other confounders of physical performance and arterial stiffness, for example CV diseases, in our results.

First, TUG was able to detect impairment of physical performance in patients with COPD when compared to controls. Second, as a simple test with no ceiling effect, TUG was shown to be beneficial to be used as an initial assessment tool of physical performance and by which a decision might be decided of whether a further walking test is required. Third, TUG was shown to have high sensitivity and specificity to differentiate between faller and non-fallers in the past year in patients. We presented a TUG cut-off time of 12s

which was more accurate with higher sensitivity and specificity to detect self-reported previous falls. Finally, TUG was found to have good same day inter- and different days intra-observer reliability.

7.3 Physical performance and arterial stiffness

We looked at the association of arterial stiffness to measurements of physical performance in all subjects (patients with COPD and controls) and in patients alone. Aortic stiffness was assessed by the carotid-femoral pulse wave velocity (aPWV).

Aortic stiffness was increased in patients compared to age-, gender-matched controls. The association of physical performance and arterial stiffness did not reach significance in patients. Distance of >350m in the 6MWT was associated with high measurements of arterial stiffness in patients with COPD.

We should be careful when interpreting these results as the association of arterial stiffness to physical performance in our study could be concealed by the uneven distribution of patients across the spectrum of the GOLD stages of COPD.

7.4 Physical activity and arterial stiffness

We looked at the potential relationship between self-reported physical activity and aortic stiffness in a large population of patients with COPD. A subjective measure (questionnaires) was used for the self-reported physical

activity. Although increased arterial stiffness and declined physical activity independently are well established in patients with COPD, our results showed that self-reported physical activity was significantly associated to COPD airflow obstruction and dyspnoea, but not aortic stiffness.

7.5 Ambulatory haemodynamic/arterial stiffness profile in patients with COPD

This was a pilot study to explore the peripheral and central haemodynamic differences between patients with COPD and controls during 24-hour period. The Mobil-O-Graph machine was used to assess ambulatory haemodynamic/arterial stiffness measurements with the first measurements taken in-clinic while subjects at rest. The results of the ABPM in-clinic measurements were compared to the Vicorder® measurements for validation analysis.

Analysis of peripheral and central in-clinic haemodynamic measurements showed that results from the Mobil-O-Graph were in agreement with the results obtained from the Vicorder®.

When ambulatory haemodynamic measurements were analysed, the differences of diurnal, nocturnal and 24-hour arterial stiffness measurements showed a trend of increased arterial stiffness measurements in patients; despite low numbers in each group. Nocturnal aPWV dip was seen only in controls, but not in patients.

Chapter 8

Future Direction

8.1 Physical performance assessment of patients with COPD

This research presented TUG as a simple and a reliable test to detect self-reported falls and impairment of physical performance in patients with COPD. A prospectively designed study is needed to evaluate the ability of the TUG test to detect future falls and whether it can be used as an objective measure of falls. Further work looking at the potential of TUG to determine the effects of interventions is also needed.

8.2 Association of physical performance to arterial stiffness

This study showed that reduced physical performance and arterial stiffness were increased in patients with COPD compared to controls. The association between the two was not statistically significant which could be due to the several factors. One factor could be the lack of space which allowed 10m track to be used for the 6MWT instead of the recommended 30m track. This could influence the actual walked distance and, therefore, affected its association to arterial stiffness. Furthermore, a prospective cohort study looking at the direction of this association in terms of cause and effect is importance.

8.3 Self-reported physical activity and arterial stiffness

Given that there was no association between self-reported physical activity and arterial stiffness; future studies to reassess this relationship using objective measures of physical activity alongside the aPWV in a wide range of patients with COPD are needed; as well as additional studies looking at pre and post interventions such as pulmonary rehabilitation.

8.4 Ambulatory haemodynamics in patients with COPD

Ambulatory haemodynamics profile including arterial stiffness is feasible and reveals important information over 24-hour period as opposed to in-clinic one-off measurements. Future studies with a larger sample size are warranted. The results of this study could be used in power calculations to determine a sample size for such future work. Taking into consideration this finding could improve the assessment and management of COPD in terms of time, choice of medications and, possibly in the prediction of CV risks.

Chapter 9

Appendices

Appendix 1: Patient Information Sheet

PATIENT INFORMATION SHEET

Title: The association of lung function and cardiovascular risk

Chief Investigator: Dr Charlotte Bolton

Introduction

You are being invited to take part in a research study. Before you decide, it is important for you to understand why this research study is being conducted and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish. Please feel free to ask us if there is anything that is not clear or if you require any further information. You may keep this information for future reference.

Purpose of the Study

Previous studies have shown that people with poor lung function (who often have chronic lung disease) have an increased risk of cardiovascular disease (problems with the blood vessels) over and above the effects of smoking. However, at the moment we have a limited understanding of the reasons behind this.

Researchers wish to study people with and without lung disease who currently smoke or have smoked in the past, to explore people's risk of developing cardiovascular disease. Researchers will measure the stiffness of people's blood vessels and also look at levels of inflammation in the blood and compare this with people's lung function. Finally, researchers wish to see if people's kidneys are affected by the stiffening of the hearts main artery; the aorta. It is hoped that by studying people's blood vessels and lung function, it will lead to a greater understanding of why people with poor lung function (who often have chronic lung disease) have an increased risk of cardiovascular disease.

Why have I been chosen?

You have been chosen because you:-

- Have been diagnosed with COPD and are attending one of the researchers Respiratory Out-Patient Clinics.
- Have previously consented to be included on the Nottingham Respiratory Research Database or Professor Ian Halls Volunteer Database and to contacted regarding future research studies.
- Are replying to a poster or advertisement seeking volunteers.

Please note; this study is only available to people of European Ancestry, as the tests used in this study are not valid in any other skin type at present.

Do I have to take part?

It is entirely up to you whether or not you decide to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form (you will be given a copy of this as well). If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you already receive.

What will happen to me if I take part?

You will be asked to attend for one study visit at the Respiratory Biomedical Unit at Nottingham City Hospital. During this time (approximately 120 minutes) you will need to have various tests/procedures.

Visit 1

If after reading this information sheet and talking to a member of the research team, you would like to take part in this study, we would ask you to sign a consent form.

In addition we would like to conduct the following tests/procedures:-

- **Blood Sample**: we would like to take a small amount of blood (25mls or the equivalent of 5 teaspoons) from your arm for further analysis.
- **Urine Analysis**: we would like to take a sample of urine (10mls or the equivalent of 2 teaspoons), to analyse certain molecules.

- **Questionnaires**: You will be asked to fill out 3 short questionnaires about how your health affects your daily life.
- **Spirometry Test** (blowing test); which is used to measure your lung function (the size of your lungs and how quickly you can empty them). You will be asked to breathe in and then blow out very fast into a mouth piece.
- **Carbon Monoxide Test**: we would like to measure the level of a gas called carbon monoxide exhaled in your breath. This involves blowing into a machine which is a bit like an alcohol breathalyser to record the concentration of carbon monoxide.
- **Pulse Oximetry**; a simple non-invasive test which measures oxygen saturation in your blood.
- **Blood Pressure (BP)**
- **Arterial Stiffness Measurements:** A non-invasive test which involves placing a blood pressure cuff around the participant's upper leg and arm to measure the speed of pulsation down the participant's body, which is related to the stiffness of the arteries. In addition, a small probe is placed on the side of the neck over the pulse. Please be aware that all of the tests listed above will be performed by competent staff following standard operating procedures. Before starting any of the tests we will ensure that there are no reasons for the test not to be performed.
- **Skin Elasticity Measurements**: A non-invasive test used to measure the mechanical properties of people's skin (skin elasticity). Skin elasticity will be measured by applying a small suction force to the skin and measuring how the skin responds to this force.
- **Skin AGE Measurements:** A non-invasive test used to measure peoples skin metabolism. This involves participants placing their arm onto the device, which then shines light onto the skin. The reflected light is then measured and analysed.
- **Walking tests:** One test will measure how far you walk in a 6 minute period. The other will assess how long it takes you to stand up from a chair, walk 3 metres, return to chair and sit. We will allow time for you to recover in between.
- **24 hour blood pressure (BP) (optional).** We are seeking a few subjects to have their BP recorded over a 24 hour period with a device that can be worn at home. You will be taught how to use the device and it will be fitted on the upper arm before you go home. Over the 24 hour period, the cuff inflates on the arm intermittently and records your BP. On return of the machine, we download the information which gives information of your BP then when you are walking or doing other activities and whilst you are asleep.

Please be aware that all of the tests listed above will be performed by competent staff following standard operating procedures. Before starting any of the tests we will ensure that there are no reasons for the tests not to be performed.

Finally, we would like to record your past medical history; including your current medication and smoking history.

Follow-Up (Optional)

With your consent we would like to contact you in the future to follow you up and perform some of these tests again, in order to create a longitudinal study (a study over a longer period of time) of cardiovascular risk in patients with and without lung disease, dependent on funding. Please be aware that a member of the study team will contact your GP to check your ongoing health status before contacting you.

What do I have to do?

You should continue to carry on with your normal daily activities and take your usual medication. We also ask that you attend the scheduled study visit (although there is some flexibility in terms of the days and times when this can occur) and complete the study paperwork. You may be asked to refrain from eating or drinking for six hours prior to your appointment, although your study doctor will advise you before you attend for your visit. If you agree to the 24 hour BP test, we will need to arrange for a second visit to return the machine and review the data.

Will any genetic tests be carried out? (Optional)

Yes; it is hoped that the genetics part of the study (looking for differences in people's genes) will lead to a greater understanding of the relationship between lung function and the blood vessels. Please be aware that the results of any genetic testing will be kept strictly confidential and will NOT be sent out to you as they do not have any clinical relevance and will not affect any private medical or life insurance policies you may have. Please note; this part of the study is **optional** and if you agree to take part in the genetics part of the study you will be asked to sign an optional clause on the consent form.

What are the possible benefits of taking part?

You will not benefit directly from taking part in this study, however, it is hoped that the results of this study will lead to a greater understanding of the relationship between lung function and cardiovascular disease.

What are the possible disadvantages/risks of taking part?

As with all tests/procedures some people experience side effects, some of which are detailed below:-

Blood Tests: Occasionally, some people feel faint during a blood test. If this occurs, please tell the person doing the test, as you should immediately lie down to prevent fainting. Sometimes after donating blood, a bruise develops where the needle was inserted.

Will travel expenses be reimbursed?

Participants will not be paid an inconvenience allowance to participate in the study. However, we will cover the cost of travelling to the hospital (maximum £10 allowance per visit).

What will happen if I don't want to carry on with the study?

You are free to withdraw from this study at any time and without giving a reason. A decision to withdraw, will not affect the standard of care you already receive. However, please be aware, that should you wish to withdraw, the information collected so far cannot be erased and may still be used in the final project analysis. Any stored tissue samples that can still be identified as yours will be destroyed if you wish.

Where will my data be stored and will my details be kept confidential?

All data collected during the period of the study will be stored securely (password protected) on a dedicated trial database. Only the minimum required information for the purposes of the study shall be collected and this information will be subject to the same degree of confidentiality as your NHS notes. Access to the information will be limited to the research team and relevant regulatory authorities.

Information on the storage and use of tissue samples for research

Any tissue/blood sample you donate will be stored in a secure research facility at the University of Nottingham (Respiratory Biomedical Research Unit), for as long as is required for the purposes of this study. Your sample will have your code which is unique to yourself, a barcode and date of study. By using these numbers, we can trace which sample belongs to you. The analysis of samples will take place within the Respiratory Biomedical Research Unit at Nottingham

City Hospital. Please note; your sample will not be sold for profit or used in any animal research.

Your tissue/blood sample will be retained for 7 years in accordance with the University's Code of Research Conduct and then destroyed should you wish to do so. However, with your permission we would like to retain any remaining tissue/blood in a link-anonymised form for future laboratory research into respiratory disease (as yet unspecified). If you agree, the remaining tissue/blood will be stored on University premises under our Human Tissue Authority License.

Involvement of the General Practitioner/Family Doctor (GP)

With your permission we will write to your GP to notify them that you are going to take part in this study, and also inform them of any abnormal test results (if any) for appropriate action.

Who is organising and funding this study?

The research has been organised and funded by the University of Nottingham. Please be aware that the research team involved in this study are not being paid for including you in this study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable ethical opinion for conduct in the NHS by the Leicestershire, Northamptonshire & Rutland Research Ethics Committee 1 and will be subject to the Data Protection Act.

What will happen to the results of this study?

We intend to publish the results of this study in a medical respiratory journal. A summary of these results will also be made available on the Nottingham Respiratory Biomedical Research Unit's website (www.nrbru.org.uk). If you wish, you will be informed of the study results in clinic by the research nurse or doctor. Furthermore, a copy of any published material regarding the study will be made freely available to you.

What if there is a problem?

If you wish to complain or have any concerns about the way in which you have been treated, please get in touch with the research team (see below), who will do their best to answer any problems you might have. In addition, the normal NHS complaints procedures are also available to you (e.g. Patient Advice and Liaison Service – PALS). Details can be obtained from the hospital.

Contact for Further Information

Research Officers

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Appendix 2: Study Consent Form

CONSENT FORM

Title: The association of lung function and cardiovascular risk REC Ref: 10/H0406/65

Chief Investigator: **Dr Charlotte Bolton**

Name of Participant:

Please initial the box

1. I confirm that I have read and understand the information sheet (Version 1.4 dated 20/11/2011) for the above study and have had the opportunity to ask any questions. ☐

2. I understand that my participation in this study is entirely voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used for analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in the study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I understand and agree that samples of urine and blood will be taken for analysis of specific markers. ☐

5. I agree to my GP being informed of my participation in the study. I also agree for any abnormal results to be passed onto my GP for appropriate action. ☐

Title: The association of lung function and cardiovascular risk REC Ref: 10/H0406/65

Chief Investigator: Dr Charlotte Bolton

Name of Participant: **Please initial the box**

6. Consent for Follow-Up (Optional)
   I agree to be contacted in the future and followed up in order to create a longitudinal study (a study over a longer period of time) of cardiovascular risk in patients with and without lung disease, dependent on funding. ☐

☐

7. Consent for genetic research (Optional)
   I understand and agree that the samples I give may be used for genetic research in this the study and in future research aimed at understanding the relationship between lung function and the blood vessels.

☐

8. Consent for storage and use in possible future research (Optional)
   I agree that the samples I have given and the information gathered about me can be stored by Dr Charlotte Bolton at the Respiratory Biomedical Research Unit at Nottingham City Hospital, for possible use in future studies (as yet unspecified). I understand that some of these studies may be carried out by researchers other than current team of Dr Charlotte Bolton, who ran the first study, including researchers working for commercial companies. Please note; these samples will not be sold for profit or used in any animal research.

9. Consent for 24 hour BP recording (Optional) ☐
   I agree to have recorded my blood pressure (BP) over a 24 hour period. The cuff will inflate time-to-time over a 24 hour period and record my BP.

10. I agree to take part in the above study. ☐

Name of Participant	date	signature
signature	date	signature

3 copies: 1 for participant, 1 for the trial master file, 1 for medical notes Version 1.4 (20/11/2011)

Appendix 3: St. George's Respiratory Questionnaire

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE ORIGINAL ENGLISH VERSION

ST. GEORGE'S RESPIRATORY QUESTIONNAIRE (SGRQ)

This questionnaire is designed to help us learn much more about how your breathing is troubling you and how it affects your life. We are using it to find out which aspects of your illness cause you most problems, rather than what the doctors and nurses think your problems are.

Please read the instructions carefully and ask if you do not understand anything. Do not spend too long deciding about your answers.

Before completing the rest of the questionnaire:

Please tick in one box to show how you describe your current health:

Very good	Good	Fair	Poor	Very poor
☐	☐	☐	☐	☐

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St. George's Respiratory Questionnaire
PART 1

Questions about how much chest trouble you have had over the past 4 weeks.

Please tick (✓) *one box for each question*:

	most days a week	several days a week	a few days a month	only with chest infections	not at all
1. Over the past 4 weeks, I have coughed:	☐	☐	☐	☐	☐
2. Over the past 4 weeks, I have brought up phlegm (sputum):	☐	☐	☐	☐	☐
3. Over the past 4 weeks, I have had shortness of breath:	☐	☐	☐	☐	☐
4. Over the past 4 weeks, I have had attacks of wheezing:	☐	☐	☐	☐	☐

5. During the past 4 weeks, how many severe or very unpleasant attacks of chest trouble have you had?

Please tick (✓) *one*:

- more than 3 attacks ☐
- 3 attacks ☐
- 2 attacks ☐
- 1 attack ☐
- no attacks ☐

6. How long did the worst attack of chest trouble last?
(Go to question 7 if you had no severe attacks)

Please tick (✓) *one*:

- a week or more ☐
- 3 or more days ☐
- 1 or 2 days ☐
- less than a day ☐

7. Over the past 4 weeks, in an average week, how many good days (with little chest trouble) have you had?

Please tick (✓) *one*:

- No good days ☐
- 1 or 2 good days ☐
- 3 or 4 good days ☐
- nearly every day is good ☐
- every day is good ☐

8. If you have a wheeze, is it worse in the morning?

Please tick (✓) *one:*

- No ☐
- Yes ☐

St. George's Respiratory Questionnaire
PART 2

Section 1

How would you describe your chest condition?

Please tick (✓) *one*:

- The most important problem I have ☐
- Causes me quite a lot of problems ☐
- Causes me a few problems ☐
- Causes no problem ☐

If you have ever had paid employment.

Please tick (✓) *one*:

- My chest trouble made me stop work altogether ☐
- My chest trouble interferes with my work or made me change my work ☐
- My chest trouble does not affect my work ☐

Section 2

Questions about what activities usually make you feel breathless <u>these days</u>.

Please tick (✓) in ***each box*** that applies to you ***these days***:	True	False
Sitting or lying still	☐	☐
Getting washed or dressed	☐	☐
Walking around the home	☐	☐
Walking outside on the level	☐	☐
Walking up a flight of stairs	☐	☐
Walking up hills	☐	☐
Playing sports or games	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 3

Some more questions about your cough and breathlessness <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough hurts	☐	☐
My cough makes me tired	☐	☐
I am breathless when I talk	☐	☐
I am breathless when I bend over	☐	☐
My cough or breathing disturbs my sleep	☐	☐
I get exhausted easily	☐	☐

Section 4

Questions about other effects that your chest trouble may have on you <u>these days</u>.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My cough or breathing is embarrassing in public	☐	☐
My chest trouble is a nuisance to my family, friends or neighbours	☐	☐
I get afraid or panic when I cannot get my breath	☐	☐
I feel that I am not in control of my chest problem	☐	☐
I do not expect my chest to get any better	☐	☐
I have become frail or an invalid because of my chest	☐	☐
Exercise is not safe for me	☐	☐
Everything seems too much of an effort	☐	☐

Section 5

Questions about your medication, if you are receiving no medication go straight to section 6.

	Please tick (✓) in ***each box*** that applies to you ***these days***: True	False
My medication does not help me very much	☐	☐
I get embarrassed using my medication in public	☐	☐
I have unpleasant side effects from my medication	☐	☐
My medication interferes with my life a lot	☐	☐

St. George's Respiratory Questionnaire
PART 2

Section 6

These are questions about how your activities might be affected by your breathing.

Please tick (✓) in ***each box*** that applies to you ***because of your breathing***:

	True	False
I take a long time to get washed or dressed	☐	☐
I cannot take a bath or shower, or I take a long time	☐	☐
I walk slower than other people, or I stop for rests	☐	☐
Jobs such as housework take a long time, or I have to stop for rests	☐	☐
If I walk up one flight of stairs, I have to go slowly or stop	☐	☐
If I hurry or walk fast, I have to stop or slow down	☐	☐
My breathing makes it difficult to do things such as walk up hills, carrying things up stairs, light gardening such as weeding, dance, play bowls or play golf	☐	☐
My breathing makes it difficult to do things such as carry heavy loads, dig the garden or shovel snow, jog or walk at 5 miles per hour, play tennis or swim	☐	☐
My breathing makes it difficult to do things such as very heavy manual work, run, cycle, swim fast or play competitive sports	☐	☐

Section 7

We would like to know how your chest <u>usually</u> affects your daily life.

Please tick (✓) in ***each box*** that applies to you ***because of your chest trouble***:

	True	False
I cannot play sports or games	☐	☐
I cannot go out for entertainment or recreation	☐	☐
I cannot go out of the house to do the shopping	☐	☐
I cannot do housework	☐	☐
I cannot move far from my bed or chair	☐	☐

St. George's Respiratory Questionnaire

Here is a list of other activities that your chest trouble may prevent you doing. (You do not have to tick these, they are just to remind you of ways in which your breathlessness may affect you):

Going for walks or walking the dog

Doing things at home or in the garden

Sexual intercourse

Going out to church, pub, club or place of entertainment

Going out in bad weather or into smoky rooms

Visiting family or friends or playing with children

Please write in any other important activities that your chest trouble may stop you doing:

. . . . . .

. . . . . .

. . . . . .

. . . . . .

Now would you tick in the box (one only) which you think best describes how your chest affects you:

It does not stop me doing anything I would like to do ☐

It stops me doing one or two things I would like to do ☐

It stops me doing most of the things I would like to do ☐

It stops me doing everything I would like to do ☐

Thank you for filling in this questionnaire. Before you finish would you please check to see that you have answered all the questions.

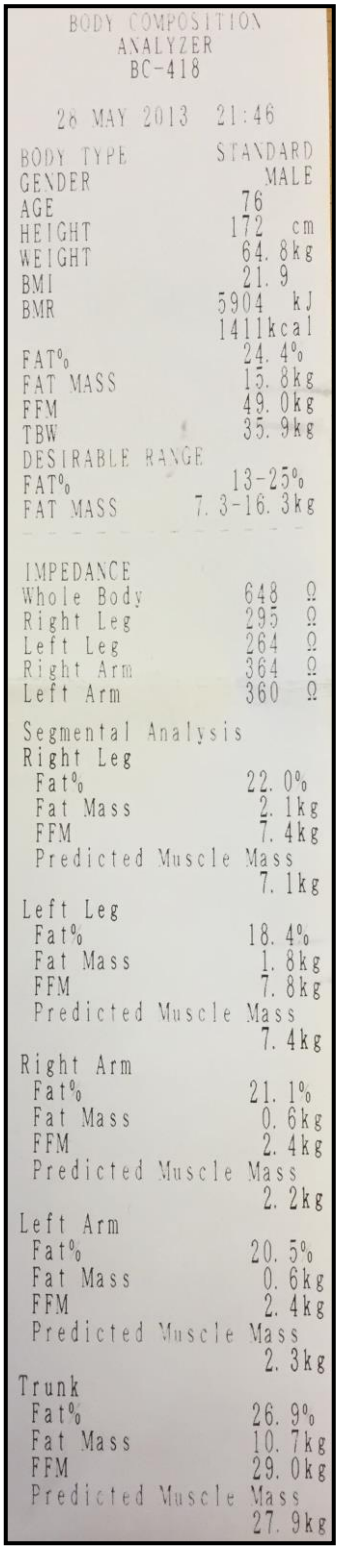
Appendix 4: Medical Research Council (MRC) Dyspnoea Scale

(Fletcher, 1960)

The MRC Breathlessness Scale

Grade	Degree of breathlessness related to activities
1	Not troubled by breathlessness except on strenuous exercise
2	Short of breath when hurrying on the level or walking up a slight hill
3	Walks slower than most people on the level, stops after a mile or so, or stops after 15 minutes walking at own pace
4	Stops for breath after walking about 100 yds or after a few minutes on level ground
5	Too breathless to leave the house, or breathless when undressing

Appendix 5: Body Composition - Bioelectrical Impedance (BIA)



BODY COMPOSITION
ANALYZER
BC-418

28 MAY 2013 21:46

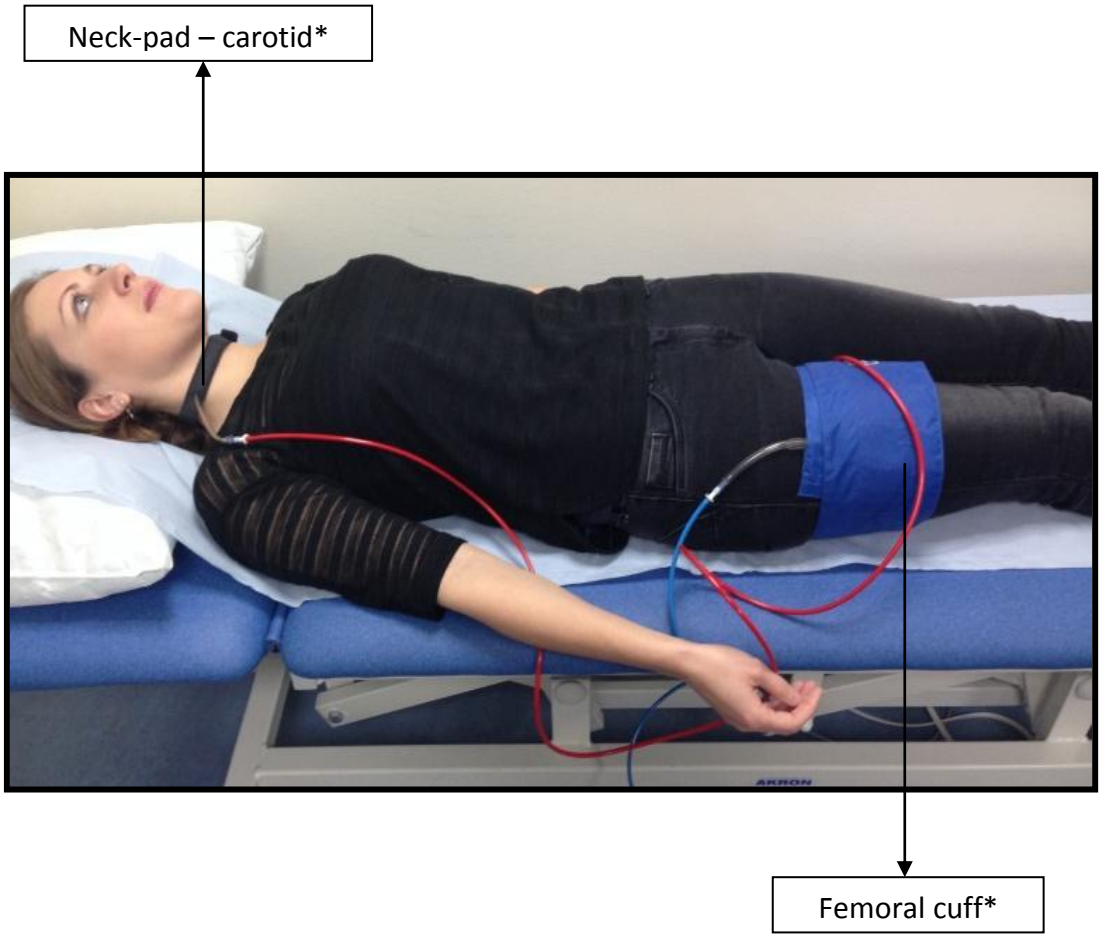
BODY TYPE	STANDARD
GENDER	MALE
AGE	76
HEIGHT	172 cm
WEIGHT	64.8kg
BMI	21.9
BMR	5904 kJ
	1411kcal
FAT%	24.4%
FAT MASS	15.8kg
FFM	49.0kg
TBW	35.9kg
DESIRABLE RANGE	
FAT%	13-25%
FAT MASS	7.3-16.3kg

IMPEDANCE	
Whole Body	648 Ω
Right Leg	295 Ω
Left Leg	264 Ω
Right Arm	364 Ω
Left Arm	360 Ω

Segmental Analysis

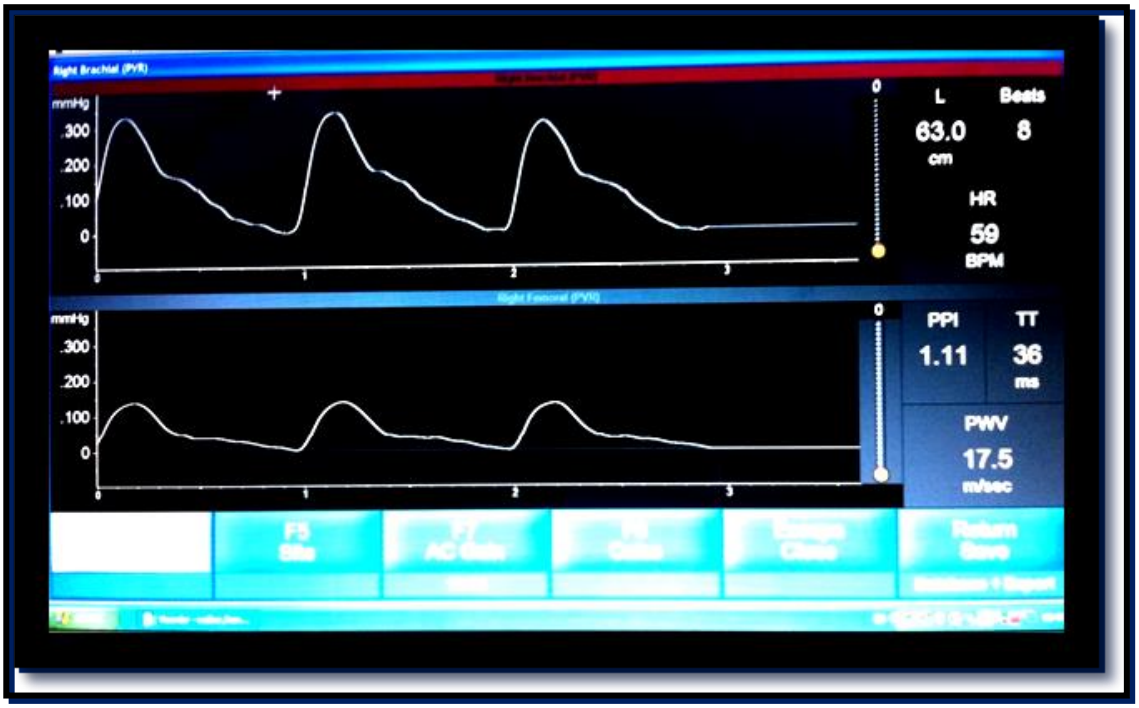
Right Leg	
Fat%	22.0%
Fat Mass	2.1kg
FFM	7.4kg
Predicted Muscle Mass	7.1kg
Left Leg	
Fat%	18.4%
Fat Mass	1.8kg
FFM	7.8kg
Predicted Muscle Mass	7.4kg
Right Arm	
Fat%	21.1%
Fat Mass	0.6kg
FFM	2.4kg
Predicted Muscle Mass	2.2kg
Left Arm	
Fat%	20.5%
Fat Mass	0.6kg
FFM	2.4kg
Predicted Muscle Mass	2.3kg
Trunk	
Fat%	26.9%
Fat Mass	10.7kg
FFM	29.0kg
Predicted Muscle Mass	27.9kg

Appendix 6: Carotid-Femoral Pulse Wave Velocity using the Vicorder



*Whole cuff inflates over the femoral artery whilst the neck-pad is just a small section – balloon only.

Appendix 7: Carotid-Femoral Pulse Wave Velocity - Screen Shot



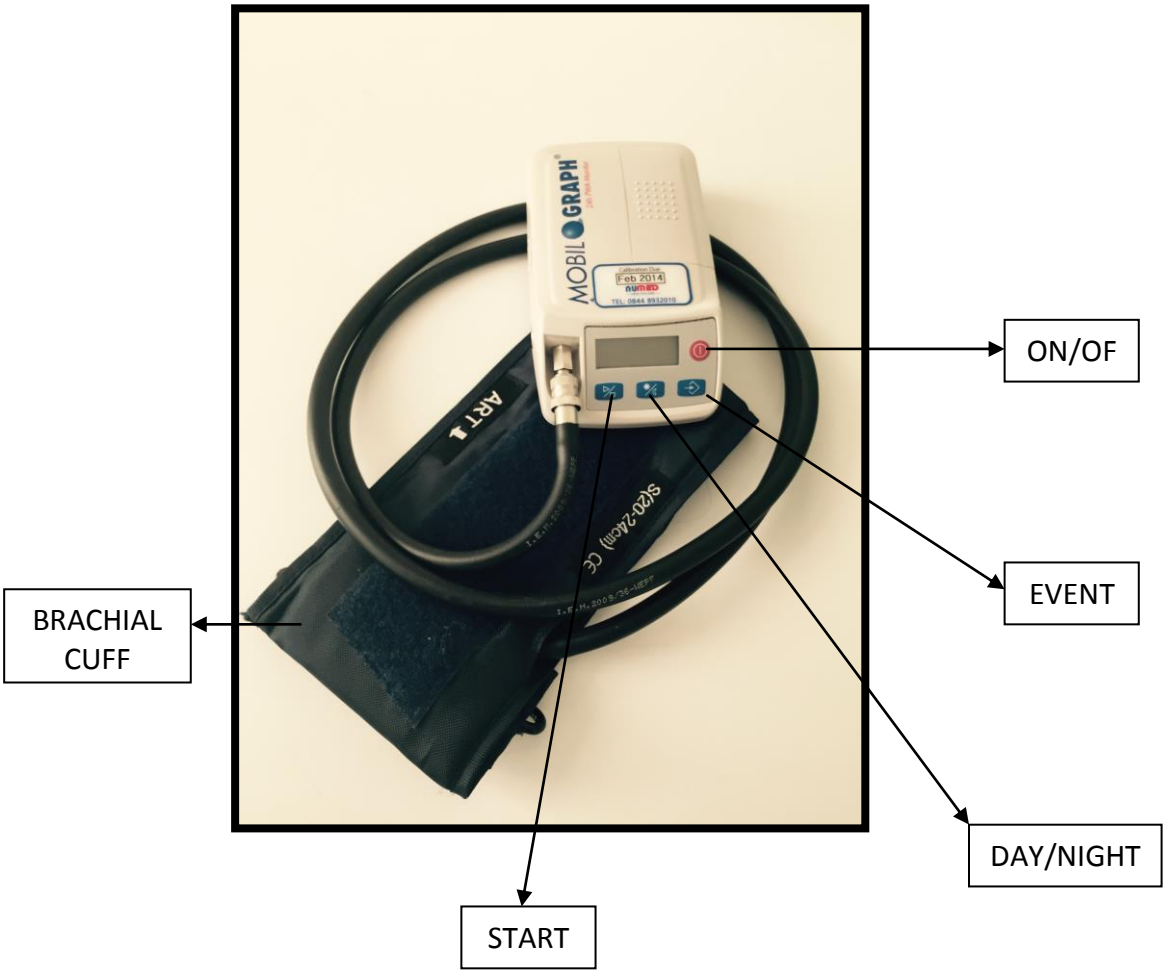
This is a screen shot of simultaneous carotid and femoral pulse wave forms obtained when performing pulse wave velocity measurements using the foot to foot method on the Vicorder machine.

Appendix 8: Borg Breathlessness Scale

(Burdon et al., 1982)

0	Nothing at all
0.5	Very, very slight
1	Very slight
2	Slight (light)
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very Severe
8	
9	Very, very severe (almost maximal)
10	Maximal

Appendix 9: Ambulatory Blood Pressure Device Mobil-o-graph

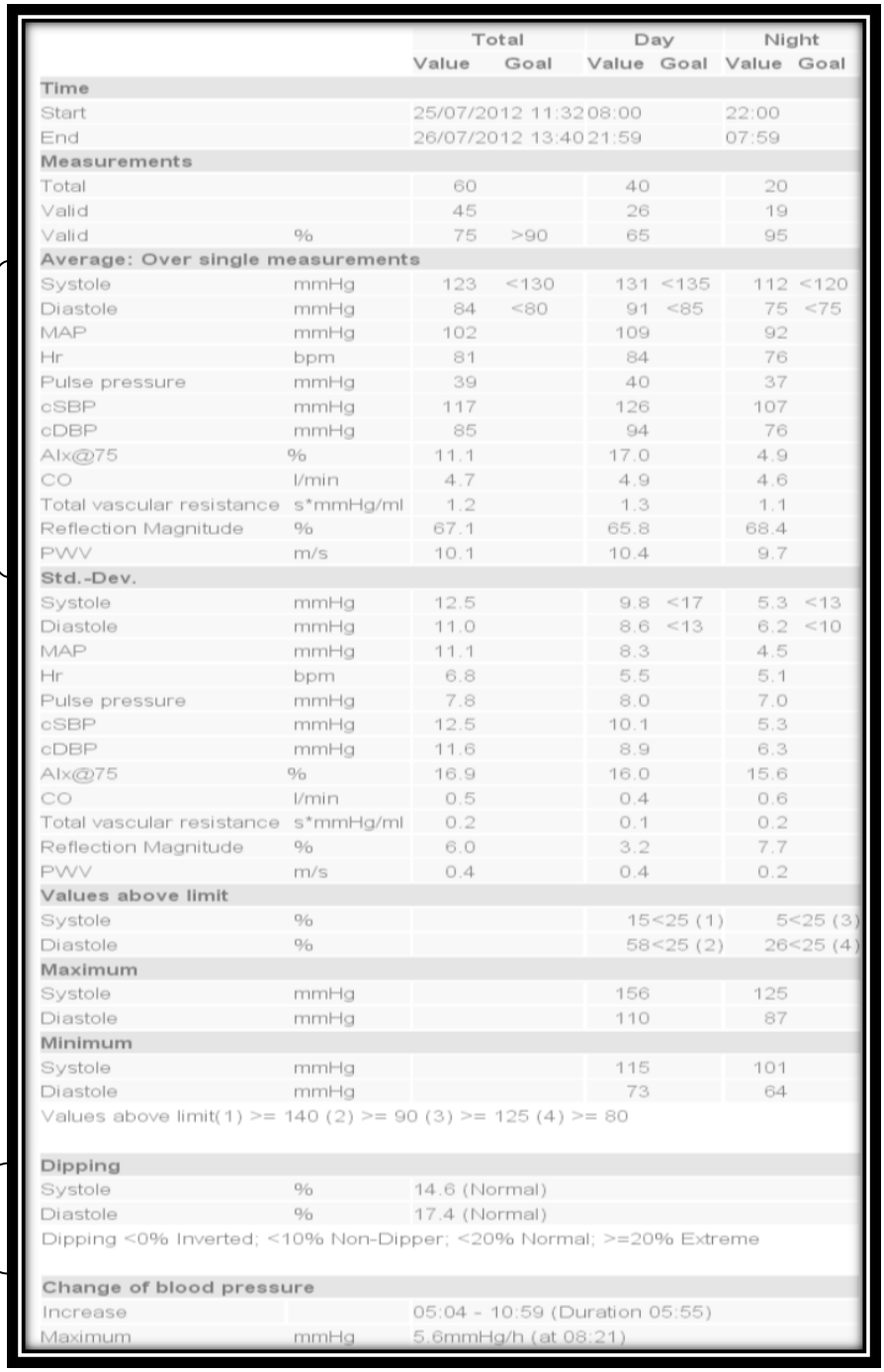


Appendix 10: Ambulatory Blood Pressure – Summary Report

Example of ambulatory BP summary report obtained from the Mobil-O-Graph device software

Haemodynamic measurements

Nocturnal dip



		Total		Day		Night	
		Value	Goal	Value	Goal	Value	Goal
Time							
Start		25/07/2012 11:32		08:00		22:00	
End		26/07/2012 13:40		21:59		07:59	
Measurements							
Total		60		40		20	
Valid		45		26		19	
Valid	%	75	>90	65		95	
Average: Over single measurements							
Systole	mmHg	123	<130	131	<135	112	<120
Diastole	mmHg	84	<80	91	<85	75	<75
MAP	mmHg	102		109		92	
Hr	bpm	81		84		76	
Pulse pressure	mmHg	39		40		37	
cSBP	mmHg	117		126		107	
cDBP	mmHg	85		94		76	
AIx@75	%	11.1		17.0		4.9	
CO	l/min	4.7		4.9		4.6	
Total vascular resistance	s*mmHg/ml	1.2		1.3		1.1	
Reflection Magnitude	%	67.1		65.8		68.4	
PWV	m/s	10.1		10.4		9.7	
Std.-Dev.							
Systole	mmHg	12.5		9.8	<17	5.3	<13
Diastole	mmHg	11.0		8.6	<13	6.2	<10
MAP	mmHg	11.1		8.3		4.5	
Hr	bpm	6.8		5.5		5.1	
Pulse pressure	mmHg	7.8		8.0		7.0	
cSBP	mmHg	12.5		10.1		5.3	
cDBP	mmHg	11.6		8.9		6.3	
AIx@75	%	16.9		16.0		15.6	
CO	l/min	0.5		0.4		0.6	
Total vascular resistance	s*mmHg/ml	0.2		0.1		0.2	
Reflection Magnitude	%	6.0		3.2		7.7	
PWV	m/s	0.4		0.4		0.2	
Values above limit							
Systole	%			15<25 (1)		5<25 (3)	
Diastole	%			58<25 (2)		26<25 (4)	
Maximum							
Systole	mmHg			156		125	
Diastole	mmHg			110		87	
Minimum							
Systole	mmHg			115		101	
Diastole	mmHg			73		64	
Values above limit(1) >= 140 (2) >= 90 (3) >= 125 (4) >= 80							
Dipping							
Systole	%	14.6 (Normal)					
Diastole	%	17.4 (Normal)					
Dipping <0% Inverted; <10% Non-Dipper; <20% Normal; >=20% Extreme							
Change of blood pressure							
Increase		05:04 - 10:59 (Duration 05:55)					
Maximum	mmHg	5.6mmHg/h (at 08:21)					

Appendix 11: BODE Index - Body Mass Index, Airway **O**bstruction, **D**yspnoea and **E**xercise Capacity

(Adopted from (Celli et al., 2004))

	0	**1**	**2**	**3**
FEV_1% predicted	≥65	50-64	36-49	≤34
6MWD (m)	≥350	250-349	150-249	≤149
MRC	1-2	3	4	5
BMI (kg/m2)	>21	≤21	…	…

Abbreviations: Forced expiratory volume in one second (**FEV_1**), six minute walk distance (**6MWD**), medical research council (**MRC**), body mass index (**BMI**)

Appendix 12: ADO Index - Age, **D**yspnoea and Airway **O**bstruction

(Adopted from (Puhan et al., 2009))

	0 points	**1 point**	**2 points**	**3 points**	**4 points**	**5 points**
FEV_1 (% predicted)	≥65%	≥36–64%	≤35%	…	...	...
Dyspnoea (MRC scale)	0–1	2	3	4	...	...
Age (years)	40–49	50–59	60–69	70–79	80–89	≥90

Abbreviations: Forced expiratory volume in one second (**$FEV_{1)}$** and medical research council (**MRC**)

Chapter 10

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