MONASH University
Medicine, Nursing and Health Sciences

PATHOPHYSIOLOGY OF PULMONARY HYPERTENSION IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Dr Jeremy Paul Wrobel

MBBS(hons), BCom, LLB, MPH, FRACP

A thesis submitted for the degree of Doctor of Philosophy

Department of Medicine, Nursing and Health Sciences

Monash University

Melbourne, Australia

2013

Errata

1. page 5, para 5, line 1: “patients” for “patient”
2. page 11, para 1, line 7: “Index).” for “Index.)”
3. page 31, para 1, line 6: “despite including no patients” for “despite no patients”
4. page 33, para 4, line 5: “LVRS with 27” for “LVRS compared with 27”
5. page 49, para 4, line 2: “Indeed” for In deed”
6. page 56, para 4, line 5: “medial” for “medal”
7. page 95, para 2, line 14: “Indeed” for In deed”
8. page 99, para 2, line 8: “leads’” for “lead”
9. page 125, para 1, line 7: “modelling” for “remodelling”
10. page 126, para 1, line 2: “mortality^{1,2}” for “mortality1,2”
11. page 184, para 2, line 2: “will occur secondary” for “will secondary”
12. page 187, point 6, line 1: “and there are” for “and that there are”
13. page 191, para 3, line 1: “has been diagnosed” for “have been diagnosed”
14. page 192, para 3, line 5: “2000).” for “2000)”

Addendum

1. page 120, Insert prior to para 1:

> “The present study demonstrates that RVSP is associated with worse intensive care outcomes following lung transplantation for COPD based on univariate analysis. In addition, multiple stepwise linear regression reveals (i) RVSP and recipient smoking history are independent risk factors for duration of mechanical ventilation, (ii) RVSP and functional residual capacity are independent risk factors for ICU length of stay, and (iii) early transplant era is an independent risk factor for inferior PaO_2/F_IO_2 at 24 hours. Nevertheless, this multivariate analysis is interpreted with caution due to the relatively small sample size and numerous variables assessed.
>
> The small sample size in this study was partly a result of our decision to exclude patients whose echocardiogram was performed at an external institution. As mentioned previously, echocardiography is not the gold standard for measurement of pulmonary arterial pressures. Furthermore, the quality of echocardiography can vary widely across institutions. As echocardiogram assessment was integral to the validity of this study, we aimed to minimise measurement error and ensure consistency by excluding patients if their echocardiogram was performed at an external institution. Importantly, there were no differences at baseline between the included and excluded patients. Furthermore, there was no difference in ICU length of stay, 12-month survival or long-term survival between the 46 included and 92 excluded patients.”

Table of Contents

Summary

Chronic obstructive pulmonary disease (COPD) is a major international health burden. Moderate and severe COPD is often complicated by the development of pulmonary hypertension (PHT) which is associated with a worse prognosis. As targeted therapies for PHT in COPD patients are lacking, there is renewed interest in understanding the underlying pathophysiology of this complication. An extensive literature review reveals that the aetiology of PHT in COPD is complex, multifaceted and due to both pre- and post capillary mechanisms. Furthermore, the strength of evidence implicating the various postulated mechanisms is highly variable. This thesis contributes to our understanding of PHT in COPD by investigating clinical, pathological and physiological aspects of this condition.

PHT in COPD is associated with a poor prognosis and there is evidence to suggest that it may also be associated with inferior outcomes following lung transplantation. We retrospectively studied a single institution's transplant experience over a 10 year period. Amongst 46 patients that underwent lung transplantation for COPD, patients with moderate-severe PHT on echocardiographic criteria, had inferior short-term outcomes following lung transplantation. The potential pathophysiological mechanisms underlying this are discussed with a focus on cardiopulmonary interactions.

Pulmonary arterial remodelling is a pathological hallmark of pulmonary arterial hypertension. Although pulmonary arterial remodelling has also been demonstrated in patients with COPD, the significance of this is unclear. We performed prospective pathological assessment on stored explanted lung specimens from 42 COPD lung transplant patients and demonstrated significant pulmonary arterial remodelling compared with non-smoking, age-matched controls. There was significant heterogeneity of remodelling in the COPD patients. Although remodelling was not significantly increased amongst COPD patients with moderate-severe PHT compared with no PHT or mild PHT, complex interactions were identified between pulmonary arterial pressure, lung lobe and pulmonary arterial size. Furthermore, there was a

positive relationship between pulmonary arterial remodelling and regional perfusion which suggests that cardiopulmonary interactions likely contribute to the remodelling process.

Functional factors have also been postulated to contribute to PHT in COPD. In particular, it has been suggested that dynamic hyperinflation is associated with increased pulmonary arterial pressures in patients with COPD. We prospectively investigated the haemodynamic effects of intermittent positive pressure ventilation on 22 subjects with severe, stable COPD. We demonstrate that increased airway pressure was associated with a small but consistent increase in the diastolic pulmonary arterial pressure. Whilst this study provides "in principle" support for the notion that dynamic hyperinflation is associated with increased pulmonary arterial pressures, the magnitude of change is of marginal clinical significance for patients during spontaneous ventilation. Nevertheless, the cardiovascular consequences of intermittent positive pressure ventilation demonstrated in this study suggest that cardiopulmonary interactions are clinically relevant in patients receiving positive pressure ventilation.

This thesis demonstrates that cardiopulmonary interactions contribute to the pathophysiology and clinical outcomes in COPD patients with PHT. Further research is required to better understand the full extent of these interactions and to explore avenues to translate this information into improved clinical outcomes.

General Declaration (Part A)

Monash University

Monash Research Graduate School

Declaration for thesis based or partially based on conjointly published or unpublished work

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes three original papers of which one is published, one has been accepted for publication (currently unpublished) and one is currently under review in peer reviewed journals. The core theme of the thesis is the pathophysiology of pulmonary hypertension in chronic obstructive pulmonary disease. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Department of Medicine under the supervision of Professor Trevor Williams.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 1, 2, 3 and 4, my contribution to the work involved the following:

Thesis Chapter	Publication title	Publication status	Nature and extent of candidate's contribution
2	Preoperative echocardiographic-defined moderate-severe pulmonary hypertension predicts prolonged duration of mechanical ventilation following lung transplantation for patients with COPD.	Published	- Study design - Ethics application - Data acquisition - Data analysis and interpretation - Manuscript preparation - Final approval of manuscript - Extent: 85%
3	Pulmonary arterial remodelling in COPD is lobe dependant. Pulmonary Circulation.	Accepted	- Study design - Ethics application - Data acquisition - Data analysis and interpretation - Manuscript preparation - Final approval of manuscript - Extent: 85%
4	Lung-heart interactions: Intermittent positive pressure ventilation increases diastolic pulmonary arterial pressure in COPD.	Submitted	- Study design - Ethics application - Data acquisition - Data analysis and interpretation - Manuscript preparation - Final approval of manuscript - Extent: 85%
Appendix 1	Mechanisms of pulmonary hypertension in COPD: A pathophysiologic review.	Published	- Literature search - Critical appraisal of literature - Manuscript preparation - Final approval of manuscript - Extent: 90%

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ……

Date: ……

Acknowledgements

I would like to express my gratitude to my primary supervisor, Professor Trevor Williams, whose commitment and guidance has been invaluable during my research. Trevor, you have strengthened the scientific process of my research at every step. I especially appreciate your commitment to my research during your sabbatical and I am grateful for your mentorship during the past three years.

I would also like to thank my co-supervisor, Associate Professor Bruce Thompson, for his direction and support. Bruce, you have helped me maintain my focus during both the research itself and during the preparation of each manuscript. You have consistently helped me keep my messages on track. I would also like to acknowledge Professor Greg Snell who has provided personal guidance and departmental support for each of my studies and the lung transplant co-ordinators for identifying potential study subjects.

I have been fortunate to have received a National Health and Medical Research Council Postgraduate Scholarship which has provided financial support during my PhD. I am extremely appreciative of this support.

A special thanks goes to Dr Christopher Stuart-Andrews who has provided fantastic instruction and encouragement. Chris, you willingness to provide support of every sort has been inspirational. Similarly, thank you to Professor Catriona McLean who has provided many hours of personal and departmental support of which I am extremely grateful.

Thank you to the cardiothoracic anaesthetists who supported the research in the operating theatre during the time critical pre-transplant period. Thank you also to the cardiothoracic surgical staff for enabling me to conduct my research in this challenging and often stressful environment. I also acknowledge the many hours provided by Biomedical Engineering in helping me to setup the data acquisition software that was integral to my research.

I pay special tribute to the lung transplant recipients that participated in my study on lung-heart interactions. Despite the severity of their illness, these patients were all very supportive and keen to participate in any way they could.

Finally, a very special thank you goes to my wife and children whose patience and encouragement has enable me to conduct this research. Amanda, each time I was awoken in the middle of the night for a potential study participant, you always encouraged me to go despite the added difficulty my absence would cause. You have encouraged me at every stage of my clinical and research journey and for that I am forever grateful.

List of Abbreviations

COPD	Chronic obstructive pulmonary disease
CT	Computed tomography
dBP	Diastolic systemic arterial pressure
dPAP	Diastolic pulmonary arterial pressure
FEV_1	Forced expiratory volume in one second
F_IO_2	Fraction of inspired oxygen
FRC	Functional residual capacity
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ITP	Intrathoracic pressure(s)
iPAH	Idiopathic pulmonary arterial hypertension
LV	Left ventricle
LVRS	Lung volume reduction surgery
mPAP	Mean pulmonary arterial pressure
$PaCO_2$	Partial pressure of arterial carbon dioxide
PaO_2	Partial pressure of arterial oxygen
PAH	Pulmonary arterial hypertension
$PEEP_E$	Extrinsic positive end-expiratory pressure
$PEEP_I$	Intrinsic positive end-expiratory pressure
PGD	Primary graft dysfunction
PHT	Pulmonary hypertension
PVH	Pulmonary venous hypertension
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RVSP	Right ventricular systolic pressure
sBP	Systolic systemic arterial pressure
sPAP	Systolic pulmonary arterial pressure
V_r	Relaxation volume
V_T	Tidal volume

Abstracts Presented at National Conferences

2013 Thoracic Society of Australia and New Zealand, Annual Scientific Meeting (Darwin, Australia), Oral:

Wrobel JP, McLean CA, Thompson BR, Stuart-Andrews CR, Paul E, Snell GI, Williams TJ. Increased pulmonary artery perfusion contributes to pulmonary arterial remodelling in COPD.

2013 Thoracic Society of Australia and New Zealand, Annual Scientific Meeting (Darwin, Australia), Oral:

Wrobel JP, Thompson BR, CR Stuart-Andrews, K Kee, Snell GI, Buckland M, Williams TJ. Positive pressure ventilation increases pulmonary vascular tone and reduces stroke volume in COPD.

2012 Pulmonary Hypertension Society of Australia and New Zealand, Annual Scientific Meeting (Sydney, Australia), Oral:

Wrobel JP, McLean CA, Thompson BR, Snell GI, Williams TJ. Increased pulmonary arterial perfusion measured by technetium-99m is associated with increased pulmonary arterial remodelling in COPD.

2012 Thoracic Society of Australia and New Zealand, Annual Scientific Meeting (Canberra, Australia), Oral:

Wrobel JP, McLean CA, Thompson BR, Snell GI, Williams TJ. The relationship between pulmonary hypertension and pulmonary arterial remodelling in COPD is lobe dependent.

2012 Thoracic Society of Australia and New Zealand, Annual Scientific Meeting (Canberra, Australia), Poster:

Wrobel JP, Thompson BR, Stuart-Andrews CR, Kee K, Snell GI, Buckland M, Williams TJ. Positive inspiratory pressure increases pulmonary vascular tone in subjects with COPD.

2011 Thoracic Society of Australia and New Zealand, Annual Scientific Meeting (Perth, Australia), Oral:

Wrobel JP, Thompson BR, Snell GI, Williams TJ. Pulmonary hypertension severity predicts short term lung transplantation outcomes in COPD subjects.

Abstracts Presented at International Conferences

2013 American College of Chest Physicians, Annual Scientific Meeting (Chicago, USA), Poster:

Wrobel JP, Thompson BR, Stuart-Andrews CR, Kee K, Snell GI, Buckland M, Williams TJ. Positive pressure ventilation reduces right ventricular stroke volume via alterations in both preload and afterload.

2013 5th World Symposium on Pulmonary Hypertension (Nice, France), Poster:

Wrobel JP, McLean CA, Thompson BR, Snell GI, Williams TJ. Increased pulmonary arterial perfusion measured by technetium-99m is associated with increased pulmonary arterial remodeling in COPD.

2012 American Thoracic Society, Annual Scientific Meeting (San Francisco, USA), Poster:

Wrobel JP, McLean CA, Thompson BR, Snell GI, Williams TJ. The relationship between pulmonary hypertension and pulmonary arterial remodelling in COPD is lobe dependent.

2012 American Thoracic Society, Annual Scientific Meeting (San Francisco, USA), Poster:

Wrobel JP, Thompson BR, Stuart-Andrews CR, Kee K, Snell GI, Buckland M, Williams TJ. Positive inspiratory pressure increases pulmonary vascular tone in subjects with COPD.

2011 American Thoracic Society, Annual Scientific Meeting (Denver, USA), Poster:

Wrobel JP, Thompson BR, Snell GI, Williams TJ. Pulmonary hypertension severity predicts short term lung transplantation outcomes in subjects with chronic obstructive pulmonary disease.

2011 International Society for Heart and Lung Transplantation, Annual Scientific Meeting (San Diego, USA), Poster:

Wrobel JP, Thompson BR, Snell GI, Williams TJ. Severity of pulmonary hypertension predicts short term lung transplantation outcomes in subjects with chronic obstructive pulmonary disease.

Published Papers

Wrobel JP, Thompson BR, Snell GI and Williams TJ (2012). Preoperative echocardiographic-defined moderate-severe pulmonary hypertension predicts prolonged duration of mechanical ventilation following lung transplantation for patients with COPD. Lung 190(6):635-643.

Erratum:
Wrobel JP, Thompson BR, Snell GI and Williams TJ (2012). Erratum to: Preoperative echocardiographic-defined moderate-severe pulmonary hypertension predicts prolonged duration of mechanical ventilation following lung transplantation for patients with COPD. Lung 191(2):227-228.

Wrobel JP, Thompson BR and Williams TJ (2012). Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. Journal of Heart and Lung Transplantation 31(6):557-564.

Accepted Papers

Wrobel JP, McLean CA, Thompson BR, Stuart-Andrews CR, Paul E, Snell GI and Williams TJ. Pulmonary arterial remodelling in COPD is lobe dependant. *Pulmonary Circulation*. Accepted 2013.

Submitted Papers

Wrobel JP, Thompson BR, Stuart-Andrews CR, Kee K, Snell GI, Buckland M, and Williams TJ. Intermittent positive pressure ventilation increases diastolic pulmonary arterial pressure in advanced COPD. *Heart & Lung*. Submitted 2013.

Awards

2013 Finalist, Ann Woolcock Young Investigator Award, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2013 Winner, best oral presentation for OLIV (incorporating orphan lung disease, lung transplantation, interstitial lung disease, pulmonary vascular disease) special interest group, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2012 Travel Award to attend the Annual Scientific Meeting, *Pulmonary Hypertension Society of Australia and New Zealand* Annual Scientific Meeting

2012 Winner, Janet Elder International Travel Award for the best abstract by an advanced trainee or junior respiratory physician, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2012 Winner, Boehringer Ingelheim & Pfizer American College of Chest Physicians Travel Award for the best COPD abstract by an advanced trainee or junior respiratory physician, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2012 Travel Award to attend the Annual Scientific Meeting, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2011 Winner, Best Presentation, Lung Physiology and Sleep Medicine, Victorian Branch, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2011 Winner, Actelion International Travel Award for the best oral presentation for OLIV special interest group, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2011 Winner, Actelion American College of Chest Physicians Travel Award for best abstract by an advanced trainee or junior respiratory physician, *Thoracic Society of Australia and New Zealand* Annual Scientific Meeting

2011 National Health and Medical Research Council (NHMRC) Postgraduate Research Scholarship (APP1017853)

Chapter 1: General Introduction and Review of the Literature

1.1 Chronic Obstructive Pulmonary Disease – A General Overview

1.1.1 Definition of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) refers to a condition of the lungs that is characterised by chronic airflow limitation that is not fully reversible and is generally a progressive disease. COPD is a broad term that encapsulates the pathological processes of emphysema and the clinical condition of chronic bronchitis (MacNee 2007, GOLD 2009).

In 1997, The United States National Heart, Lung and Blood Institute in conjunction with the World Health Organization established the Global Initiative for Chronic Obstructive Lung Disease (GOLD) in an attempt to increase the awareness of COPD and improve the prevention and management of this disease (Pauwels, Buist et al. 2001). The GOLD provides the following working definition of COPD:

> *"Chronic Obstructive Pulmonary Disease (COPD), a common preventable and treatable disease, is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients"* (GOLD 2011).

Confirmation of the diagnosis may be made by post-bronchodilator spirometry with a forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) ratio < 70%, however some laboratories use the lower limit of normal as the preferred reference

range (GOLD 2011). Spirometry can also be used to assess the severity of COPD (refer to Table 1).

Table 1 COPD Severity Classification

Adapted from (GOLD 2011).

Stage	Severity	Spirometry
I	Mild	$FEV_1/FVC < 70\%$ $FEV_1 \geq 80\%$ predicted
II	Moderate	$FEV_1/FVC < 70\%$ $50\% \leq FEV_1 < 80\%$ predicted
III	Severe	$FEV_1/FVC < 70\%$ $30\% \leq FEV_1 < 50\%$ predicted
IV	Very severe	$FEV_1/FVC < 70\%$ $FEV_1 < 30\%$ predicted, or $FEV_1 < 50\%$ predicted and $PaO_2 < 60$ mm Hg

1.1.2 Epidemiology of COPD

COPD is a major public health problem both internationally and in Australia. COPD is currently the fifth leading cause of death in Australia, contributing to 12,000-16,000 deaths in Australia per annum (Access Economics 2008, Australian Institute of Health and Welfare 2010). In addition, COPD is responsible for over 50,000 hospitalisations annually (Australian Institute of Health and Welfare 2010). Worldwide, COPD is the fourth leading cause of death and is expected to be ranked third by 2050 (World Health Organization 2008).

It is estimated that there are over 2 million Australians with COPD, of which 1.2 million are symptomatic and 150,000 have severe or very severe disease. The total financial costs attributable to COPD in Australia are immense at approximately $8.8 billion annually, comprising $0.9 billion in direct health system expenditure, $6.8 billion in lost productivity, $0.9 billion in deadweight losses and $0.3 billion in other indirect costs (Access Economics 2008).

1.1.3 Aetiology of COPD

A number of risk factors have been determined for the establishment of COPD however there is significant variability of disease expression amongst individuals exposed to risk factors. It is generally accepted that there is interplay between genetic and environmental factors that predispose some individuals to COPD. The most common risk factor for COPD is cigarette smoking, however air pollution and occupational dusts are significant contributors. Amongst the genetic factors, homozygous alpha-1 antitrypsin deficiency is the most recognised cause of COPD which causes early and accelerated panlobular emphysema, which is worsened further by cigarette smoke exposure. Risk factors are listed in Table 2 (GOLD 2009, Eisner, Anthonisen et al. 2010).

Table 2 Risk Factors for COPD

Adapted from (GOLD 2009).

Genes
Exposure to particles - Tobacco smoke - Occupational dusts, organic and inorganic - Indoor air pollution from heating and cooking with biomass in poorly ventilated dwellings - Outdoor air pollution
Reduced lung growth and development
Oxidate stress
Female gender
Increasing age
Respiratory infections
Previous tuberculosis
Lower socioeconomic status
Malnutrition
Comorbidities (eg. Asthma)

1.1.4 Pathology of COPD

A number of pathological processes occur in the lungs of patients with COPD that are mediated by an inflammatory response to inhaled noxious particles. The inflammation appears to be an amplification of the normal inflammatory response involving mostly neutrophils, macrophages and $CD8^+$ T lymphocytes. The exaggerated inflammatory response leads to changes in the proximal airways, peripheral airways, lung parenchyma and pulmonary vasculature as described in Table 3. These pathological processes are promoted by oxidative stress and protease enzymes within the lung (MacNee 2007, GOLD 2009).

Table 3 Pathological Changes in COPD

Adapted from (GOLD 2009).

Proximal airways: - Increased goblet cells - Enlarged submucosal glands - Mucous hypersecretion - Squamous metaplasia of epithelium - Reduced mucociliary clearance
Peripheral airways: - Airway wall thickening - Peribronchial fibrosis - Luminal inflammatory exudate - Airway narrowing (obstructive bronchiolitis)
Lung parenchyma: - Alveolar wall destruction - Apoptosis of epithelial and endothelial cells
Pulmonary vasculature - Thickening of intima - Endothelial cell dysfunction - Smooth muscle hypertrophy

The pathological processes that occur in COPD lead to a range of physiological pulmonary abnormalities including airflow limitation, pulmonary hyperinflation, impaired gas exchange and mucous hypersecretion (GOLD 2009). Some COPD patients also experience acute exacerbations of their pulmonary disease and recent work has focussed on determining COPD phenotypes that are more likely to suffer exacerbations (Hurst, Vestbo et al. 2010).

The destruction of lung tissue in COPD leads to an increase in lung compliance and reduced elastic recoil. In addition, the associated airway obstruction contributes to the process of pulmonary hyperinflation. Pulmonary hyperinflation may alter cardio-pulmonary physiology and is discussed in greater detail in Section 1.4.

1.1.5 Clinical Features of COPD

Patients with mild COPD may be asymptomatic but others may experience a variety of symptoms including dyspnoea, chronic cough, chronic sputum production, wheeze and chest tightness. Some patients may develop pulmonary hypertension (PHT), which may progress to right ventricular hypertrophy and cor pulmonale (right heart failure). In addition, systemic features of COPD include cachexia, skeletal muscle abnormalities, osteoporosis, depression, anaemia and cardiovascular disease (GOLD 2009).

Exertional dyspnoea is very common in COPD and is due to the combination of airflow limitation, impaired gas exchange and deranged pulmonary mechanics caused by pulmonary hyperinflation. Pulmonary hyperinflation leads to a reduction in inspiratory capacity and many authors feel that this is the single greatest contributor to exercise limitation in patients with COPD (O'Donnell and Webb 2008b).

There was early recognition of different presentations of patient with COPD (Dornhorst 1955). Subsequent descriptions included the terms “pink puffers and blue bloaters” and “Type A and Type B”. Type A patients tend to have radiographic evidence of emphysema with increased lung capacity, reduced diffusing capacity, minimal sputum and rarely have hypercapnia (Burrows, Niden et al. 1964, Burrows, Fletcher et al. 1966). In contrast, Type B patients did not have radiographic evidence of emphysema;

they produced large quantities of sputum, had frequent hypercapnia with recurrent cor pulmonale, smaller total lung capacities and preserved diffusing capacities. Type X patients were those with intermediate features. Over subsequent years, these terms have been intermittently used. It is noteworthy that the current and previous reports of the Global Initiative for Chronic Obstructive Lung Disease do not use "emphysema" or "chronic bronchitis" in the definition of COPD (GOLD 2011). Nor do they employ the terms *pink puffer*, *blue bloater*, *Type A* or *Type B*.

Ironically, despite this trend away from such descriptive terms, there has recently been an increased push towards identifying COPD sub-types or phenotypes in an attempt to better delineate COPD and its variety of clinical presentations and outcomes (Marsh, Travers et al. 2008, Agusti and Barnes 2010, Han, Agusti et al. 2010, Garcia-Aymerich, Gomez et al. 2011). A phenotype definition for the purposes of classifying COPD was recently advanced as "a single or combination of attributes that describe differences between individuals with COPD as they relate to clinically meaningful outcomes (symptoms, exacerbations, response to therapy, rate of disease progression, or death)" (Han, Agusti et al. 2010).

In 2008, Marsh et al (Marsh, Travers et al. 2008) published their proportional classifications of different COPD phenotypes across asthma, chronic bronchitis and emphysema. In 2011, Agusti and Vestbo (Agusti and Vestbo 2011) described their mechanistic view of how genetic and environmental factors interact with intermediate phenotypes (or endotypes) to produce a range of clinical phenotypes. They highlight the complexity of interactions that occur at an environmental level, clinical level, biological level and genetic level.

Increasing evidence suggests that the COPD "syndrome" is comprised of many smaller COPD phenotypes. Garcia-Aymerich et al (Garcia-Aymerich, Gomez et al. 2011) performed cluster analysis on 342 COPD patients presenting for their first admission due to an acute exacerbation of COPD and identified three distinct clinical phenotypes. Their group 1 patients had severe airflow limitation, group 2 patients had moderate airflow limitation and the group 3 patients also had moderate airflow limitation but had more systemic disease. Agusti et al (Agusti, Edwards et al. 2012) examined inflammatory markers from the Eclipse study cohort (a 3-year longitudinal study in

COPD patients (Vestbo, Anderson et al. 2008)) and were able to identify a systemic inflammatory COPD phenotype. Mejia et al (Mejia, Carrillo et al. 2009) compared pulmonary fibrosis patients with and without co-existing emphysema and demonstrated that those with co-existing emphysema had a higher mortality that was partly due to the development of severe PHT. Finally, some patients with COPD develop PHT that is "out of proportion" to their severity of airflow limitation and these patients also represent a different clinical phenotype (Chaouat, Bugnet et al. 2005, Thabut, Dauriat et al. 2005, Adir, Shachner et al. 2012).

1.1.6 COPD and Cardiovascular Disease

A number of comorbidities frequently occur in COPD including cardiovascular disease, lung cancer, disordered sleep, anxiety, depression, cognitive decline, skeletal muscle dysfunction, metabolic syndrome and osteoporosis (Stone and Nici 2007, GOLD 2011).

Cardiovascular disease in COPD warrants special attention due to its high prevalence and impact upon mortality. The increased prevalence of cardiovascular disease in COPD is partially due to shared risk factors (for example, increasing age, hypertension and cigarette exposure). However, the increased risk of a low FEV_1 persists after controlling for a host of confounders (Hole, Watt et al. 1996, Schunemann, Dorn et al. 2000). It is likely that the shared pathogenic role of inflammation in both COPD and cardiovascular disease may help explain the high cardiovascular risk associated with COPD (Sin and Man 2003, Sin, Anthonisen et al. 2006). Furthermore, heart-lung interactions due to the shared anatomical space of the heart and lungs likely contribute to an increased prevalence of cardiac failure in the setting of pulmonary hyperinflation (Jorgensen, Muller et al. 2007, Stone and Nici 2007).

Zielinski and colleagues (Zielinski, MacNee et al. 1997) examined the causes of death for 215 COPD patients with chronic respiratory failure treated with long-term oxygen therapy across 10 European centres. They identified the major causes of death as acute on chronic respiratory failure (accounting for 38%), heart failure (13%), pulmonary infection (11%), pulmonary embolism (10%), cardiac arrhythmia (8%) and lung cancer (7%).

Causes for mortality following acute exacerbations of COPD have been variably ascribed to respiratory and/or cardiovascular factors. Almagro and colleagues (Almagro, Calbo et al. 2002) prospectively followed 135 consecutive patients admitted for an acute exacerbation of COPD for a median of 838 days and reported an overall mortality of 47%. Respiratory disease accounted for 50% of fatalities and cardiovascular disease for 19%. In contrast, Zvezdin and colleagues (Zvezdin, Milutinov et al. 2009) evaluated 43 autopsy records from patients that had died in hospital following a hospital admission with a diagnosis of COPD exacerbation. They identified that all subjects had died within 24 hours of admission and that the primary cause of death was cardiac failure in 37% and pneumonia in 27%. More recently, Chang et al (Chang, Robinson et al. 2011) identified that elevated levels of N-terminal pro-BNP and/or troponin T were associated with increased 30 day all-cause mortality amongst 244 patients admitted to hospital with an acute exacerbation of COPD.

The range of cardiovascular disorders that more commonly occur in COPD includes PHT with right ventricular compromise, ischaemic heart disease, atrial fibrillation, hypertension, left ventricular systolic failure, and left ventricular diastolic dysfunction (Stone and Nici 2007, GOLD 2011). Pulmonary vascular resistance (PVR) is often elevated in COPD due to multiple factors including direct vascular injury, destruction of the pulmonary vascular bed and hypoxic pulmonary vasoconstriction (Stone and Nici 2007). The elevated PVR can lead to right ventricular hypertrophy and subsequent left heart compromise through ventricular interdependence. Other factors likely contribute to the development of PHT in COPD. This is discussed in further detail in Section 1.2.

COPD patients are at increased risk of ischaemic heart disease. Sin and Man identified increased risk of cardiovascular mortality and morbidity amongst subjects with reduced FEV_1, reduced FEV_1/FVC ratio and those with symptoms of chronic bronchitis (Sin and Man 2005). Anthonisen and colleagues (Anthonisen, Connett et al. 2002) similarly demonstrated that lower FEV_1 was associated with increased cardiovascular mortality and hospitalisations. Other studies have supported this association between FEV_1 and cardiovascular risk (Tockman, Pearson et al. 1995, Sin, Wu et al. 2005). Furthermore, amongst patients with coronary artery disease, patients with COPD have a greater 3 year all-cause mortality than patients without COPD (21% v 9%, log-rank $P < 0.001$) (Berger, Sanborn et al. 2004).

Buch and colleagues (Buch, Friberg et al. 2003) identified FEV_1 as an independent predictor of incident atrial fibrillation in the Copenhagen City Heart Study after adjusting for sex, age, smoking, blood pressure, diabetes and body mass index. Anderson and colleagues (Anderson, Lipworth et al. 2013) identified greater left ventricular hypertrophy amongst 93 normoxaemic patients with COPD compared with 34 controls, despite the absence of hypertension and normal left ventricular ejection fraction.

The prevalence of COPD in hospitalised patients for heart failure has been reported as 35% (Iversen, Kjaergaard et al. 2008). The same study demonstrated an association between COPD severity (on spirometry) and right ventricular function. A follow-up study by the same group identified FEV_1 as an independent predictor of all-cause mortality in this heart failure cohort (Iversen, Kjaergaard et al. 2010). Amongst patients with COPD, Watz and colleagues (Watz, Waschki et al. 2008) identified that markers of cardiac dysfunction (N-terminal B-type natriuretic peptide levels (NT-BNP), echocardiography-based measured left ventricular diastolic dysfunction and systemic inflammation) were independently associated with reduced physical activity (independent of GOLD stage or BODE index – discussed in Section 1.1.7 below).

Furthermore, there is increasing evidence that there is an increased risk of cardiac dysfunction amongst patients with reduced FEV_1 and/or evidence of pulmonary hyperinflation. In 2010, Watz et al (Watz, Waschki et al. 2010a) demonstrated that static hyperinflation, functional residual capacity (FRC) and residual volume were strongly associated with cardiac chamber size as measured by magnetic resonance imaging. They demonstrated that static hyperinflation was significantly correlated with left ventricular diastolic dysfunction ($r^2 = 0.44$, $P < 0.001$).

Similarly in 2010, Barr and colleagues (Barr, Bluemke et al. 2010) investigated 2,816 subjects in a population study and demonstrated that the severity of emphysema, regardless of whether measured by computed tomography (CT) or spirometry, was strongly associated with left ventricular diastolic dysfunction and reduced left ventricular stroke volume but not left ventricular ejection fraction. The reduced stroke volume with preserved ejection fraction indicates that the stroke volume impairment was due to impaired diastolic filling rather than impaired systolic function.

Mineo and colleagues (Mineo, Pompeo et al. 2002) demonstrated improved right ventricular ejection fraction following bilateral lung volume reduction surgery. More recently in 2012, Come and colleagues (Come, Divo et al. 2012) were able to demonstrate improvements in exercise-related left ventricular stroke volume amongst COPD patients from the National Emphysema Treatment Trial that had obtained improvements in static measures of hyperinflation.

In Chapter 4, heart-lung interactions are explored with a special emphasis on the effects of intermittent positive inspiratory pressure upon pulmonary haemodynamics.

1.1.7 Prognosis of COPD

Given the irreversible nature of COPD and the variability in clinical features, there has been considerable research exploring the predictors of prognosis. Despite a number of studies exploring various risk factors for mortality, it was recognised early that there is a significant variability in survival even amongst individuals with similar baseline physiologic parameters and demographics (Traver, Cline et al. 1979).

Nevertheless, frequent risk factors for mortality include age, FEV_1, PaO_2, $PaCO_2$, pulmonary arterial pressure and the presence of cor pulmonale (Traver, Cline et al. 1979, Weitzenblum, Hirth et al. 1981, Bishop and Cross 1984, Cooper, Waterhouse et al. 1987, Skwarski, MacNee et al. 1991, Oswald-Mammosser, Weitzenblum et al. 1995, Gorecka, Gorzelak et al. 1997, Incalzi, Fuso et al. 1999, Burgess, Mogulkoc et al. 2002, Doi, Nakano et al. 2003). In COPD patients with severe hypoxia, age and pulmonary arterial pressure appear to be the strongest independent predictors of mortality (Oswald-Mammosser, Weitzenblum et al. 1995). Similarly, Doi and colleagues (Doi, Nakano et al. 2003) identified pulmonary arterial pressure as the only independent prognostic marker for mortality on multivariate analysis in a group of COPD patients with variable severity and less severe hypoxia.

In 2004, the BODE index was constructed after a retrospective assessment of 207 patients across 12 domains identified that the strongest combination of risk factors for one-year mortality were body mass index, FEV_1 percent predicted, Modified Medical

Research Council (MMRC) Dyspnoea Score and six-minute walk distance (Celli, Cote et al. 2004). These parameters were used to construct a 10-point BODE index which was prospectively validated in 625 patients. Of note, pulmonary arterial pressure, SpO_2, PaO_2 and diffusing capacity for carbon monoxide were not assessed. (The parameters that were assessed but not included in the final BODE index were age, FVC, FEV_1 (Litres), inspiratory capacity, haematocrit, albumin, smoking history and the Charlson Index.)

The BODE index was subsequently updated, calibrated and then simplified to become the ADO Index (age, MMRC Dyspnoea Score and FEV_1 percent predicted) which improved the accuracy of the 3-year predicted mortality and was more easily applicable in a clinical setting (Puhan, Garcia-Aymerich et al. 2009). Neither the BODE or ADO indices have been compared against pulmonary arterial pressure for determining mortality risk.

In addition to being a strong predictor for mortality in COPD, pulmonary arterial pressure has also been shown to be an independent predictor of increased hospitalisation, along with $PaCO_2$ (Kessler, Faller et al. 1999). Similarly, Wells and colleagues (Wells, Washko et al. 2012) demonstrated that a pulmonary artery to aorta diameter ratio greater than 1 was associated with a history of severe exacerbations and predicted future severe exacerbations.

Furthermore, Sims and colleagues (Sims, Margolis et al. 2009) have shown that pulmonary arterial pressure is independently associated with reduced six-minute walk distance. In fact, many authors report that the severity of PHT is the single most important prognostic indicator in COPD subjects (Weitzenblum, Hirth et al. 1981, Oswald-Mammosser, Weitzenblum et al. 1995, Kessler, Faller et al. 1999). As COPD carries such a significant health and economic burden, and pulmonary arterial pressure is regarded as an important prognostic indicator in COPD subjects, a more comprehensive understanding of the COPD-associated PHT is essential. Section 1.2 explores COPD-associated PHT in further detail.

1.1.8 Treatment of COPD

As COPD is irreversible, much of the management is aimed at preventing deterioration of pulmonary pathology, optimisation of pulmonary function and managing exacerbations when they occur (McKenzie, Frith et al. 2008). Preventing deterioration of pulmonary pathology is achieved through avoidance of noxious stimuli, such as cigarette smoke, and appropriate utilisation of vaccines. Pulmonary function can be optimised through the use of bronchodilators and pulmonary rehabilitation, whereas exacerbations are usually managed with bronchodilators, antibiotics and corticosteroids.

Two studies simultaneously demonstrated survival benefit of long-term oxygen use in COPD patients with respiratory failure (Nocturnal Oxygen Therapy Trial Group 1980, Medical Research Council Working Party 1981). The Nocturnal Oxygen Therapy Trial (NOTT) assessed continuous versus nocturnal oxygen in 203 COPD patients with hypoxaemia and demonstrated a survival benefit in the continuous oxygen group. The benefit was most marked in patients with $PaCO_2 \geq 43$ mm Hg, pH < 7.4, FVC < 1.89 Litres, haematocrit < 47.4%, nocturnal mean arterial oxygen saturation < 85%, mPAP < 27 mm Hg, PVR < 279, greater mood disturbance and worse cognitive function.

The Medical Research Council (MRC) Working Party (Medical Research Council Working Party 1981) compared continuous oxygen (≥ 15 hours / day) versus no supplemental oxygen in 87 COPD patients with at least one clinical episode of heart failure. The oxygen group had improved survival that was not apparent until 500 days of treatment had elapsed.

Ambulatory, continuous or nocturnal oxygen supplementation is indicated for patients with exercise-induced, chronic or nocturnal hypoxia, respectively. Continuous oxygen is also indicated for patients with the complication of PHT (Weitzenblum, Sautegeau et al. 1985, Weitzenblum, Kessler et al. 1994). Lung volume reduction surgery is indicated for select patients in an attempt to manage dynamic hyperinflation and improve respiratory mechanics (Fishman, Martinez et al. 2003). Current research is also exploring the potential role for a variety of bronchoscopic lung volume reduction strategies as a less invasive method to reduce hyperinflation (Snell, Holsworth et al.

2003, Snell, Hopkins et al. 2009, Criner 2011). For patients with very severe disease and minimal comorbidities, lung transplantation may be indicated (Todd and Palmer 2010). Finally, screening and targeted therapy for the systemic features of COPD are required (McKenzie, Frith et al. 2008, GOLD 2009).

1.1.9 Lung Transplantation for COPD

Lung transplantation is offered to select patients with advanced lung disease with the purpose of improving survival and / or quality of life. COPD, exclusive of alpha-1 antitrypsin deficiency, has traditionally been the largest indication for lung transplantation both in Australia (Keogh, Williams et al. 2012) and internationally (Christie, Edwards et al. 2012). However, in recent years, there have been a similar number of lung transplants for idiopathic pulmonary fibrosis and COPD which is partly due to increased transplant activity for idiopathic pulmonary fibrosis in North America (Christie, Edwards et al. 2012).

Indications for Lung Transplantation for COPD

In select patients with very severe COPD and limited comorbidities, lung transplantation may be indicated (McKenzie, Frith et al. 2008, GOLD 2009). Whilst lung transplantation does offer a survival advantage to some COPD patients (Thabut, Ravaud et al. 2008), lung transplantation is generally performed to improve quality of life rather than survival (Hosenpud, Bennett et al. 1998).

For consideration of lung transplantation, patients must be deteriorating despite optimal medical and surgical therapy, including smoking cessation, bronchodilatation, pulmonary rehabilitation, oxygen therapy and endoscopic or surgical lung volume reduction if feasible. Indications for lung transplantation for COPD include (Orens, Estenne et al. 2006, GOLD 2009):

(i) BODE index of 7-10,

(ii) FEV_1 < 20-35 % predicted,

(iii) PaO_2 < 55-60 mm Hg,

(iv) Hospitalisation for acute hypercapnia ($PaCO_2$ > 50 mm Hg), or

(v) Pulmonary hypertension or cor pulmonale, despite oxygen therapy.

Whilst absolute contraindications vary across transplant centres, they generally include any of the following (Orens, Estenne et al. 2006):

(i) Malignancy in the previous 2-5 years,
(ii) Advanced dysfunction of another major organ not amenable to treatment,
(iii) Non-curable chronic extrapulmonary infections,
(iv) Significant chest wall or spinal deformity,
(v) Documented noncompliance with medical therapy,
(vi) Untreatable psychiatric or psychological conditions that will interfere with medical therapy,
(vii) Lack of adequate social supports, or
(viii) Substance addiction within the previous 6 months.

In addition, a number of relative contraindications exist including (Orens, Estenne et al. 2006):

(i) Age > 65 years,
(ii) Unstable clinical condition, such as mechanical ventilation or shock,
(iii) Poor rehabilitation potential,
(iv) Colonisation with highly resistant or virulent microorganisms,
(v) Severe osteoporosis, or
(vi) Body mass index > 30 kg / m^2.

Prevalence of Lung Transplantation for COPD

According to the registry of the International Society for Heart & Lung Transplantation, COPD (including alpha-1 antitrypsin deficiency) has consistently represented the largest indication for adult lung transplantation worldwide in the past 15 years, representing 43% of all adult lung transplants (Christie, Edwards et al. 2010). Similarly in Australia, COPD (including alpha-1 antitrypsin deficiency) was the indication for approximately 42% of all lung transplants for the past 18 years (Keogh and Pettersson 2009).

Whilst single lung transplant was initially the procedure of choice for COPD, in recent years there has been an increasing number of bilateral lung transplants performed

worldwide (Christie, Edwards et al. 2010). This trend towards increasing number of bilateral lung transplants has also occurred in Australia (Keogh and Pettersson 2009). Decisions regarding procedure type must take into account the allocation of scarce donor organs, resources available at the transplant institution(s) and recipient prognosis. In addition, recipient and/or donor specific factors may dictate a preference for either single or double lung transplant.

Outcomes of Lung Transplantation for COPD

Despite continued improvements in transplant outcomes, lung transplantation is still associated with considerable early morbidity and mortality. Lung transplant outcomes vary considerably according to transplant indication and length of follow-up. 12 month outcomes for COPD compare favourably with other lung transplant indications with a 1 year survival rate of 82% versus 82% for cystic fibrosis and only 69% for idiopathic pulmonary artery hypertension. However, 5 year survival for COPD is 51% compared with 58% for cystic fibrosis and 50% for idiopathic pulmonary artery hypertension. The 5 year survival conditional on survival to 1 year is relatively poor for COPD at 62% compared with 70% for cystic fibrosis and 72% for idiopathic pulmonary artery hypertension (Christie, Edwards et al. 2010). The overall lung transplantation survival by underlying diagnosis is presented in Figure 1.

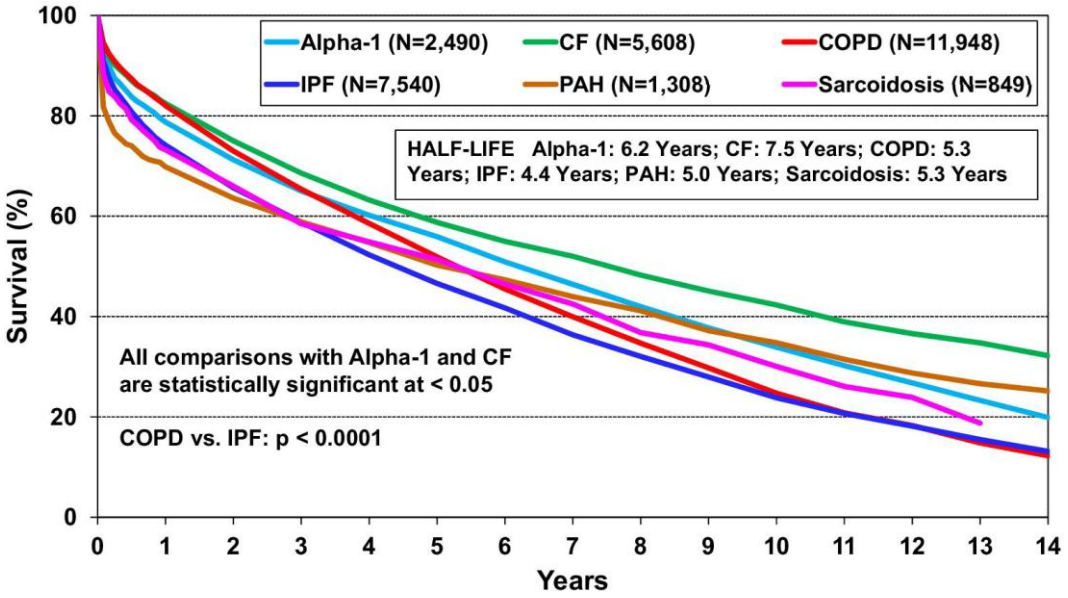

Figure 1
Lung transplantation survival (Kaplan-Meier) by diagnosis
Reprinted from (Christie, Edwards et al. 2012) with permission from Elselvier.
CF, cystic fibrosis; IPF, idiopathic pulmonary fibrosis.

For COPD, transplant recipient risk factors for one year mortality include hospitalisation, ventilator dependence, chronic corticosteroid use, age, greater than 2 L/min oxygen required at rest, and low cardiac output. In addition, donor-recipient CMV mismatch, donor-recipient sex, donor history of diabetes, and low volume transplant centre also confer additional risk (Christie, Edwards et al. 2010).

Several studies assessing outcomes of lung transplantation for COPD have focussed their analysis towards the issue of single versus bilateral lung transplantation (Pochettino, Kotloff et al. 2000, Meyer, Bennett et al. 2001, Cassivi, Meyers et al. 2002). Pochettino and colleagues (Pochettino, Kotloff et al. 2000) retrospectively assessed 84 bilateral lung transplant recipients versus 46 single lung transplant recipients, all with COPD. The bilateral lung transplant group was younger at baseline and had improved lung function and six-minute walk distance following transplant but there was no significant difference in survival or incidence of bronchiolitis obliterans syndrome.

Meyer and colleagues (Meyer, Bennett et al. 2001) assessed registry data from 1991 to 1997 of 2,260 COPD transplant recipients and demonstrated significant interactions

between transplant type (single versus bilateral) and recipient age. For COPD patients aged 40 to 57 years, there was improved survival of bilateral lung transplant compared with single lung transplant. However, beyond age 60 years, bilateral lung transplant was associated with increased mortality compared with single lung transplant.

More recently, Thabut and colleagues (Thabut, Christie et al. 2008) performed a larger registry analysis of 9,883 (6,358 bilateral and 3,525 single) lung transplant recipients for COPD between 1987 and 2006. Overall, there was improved survival following bilateral versus single lung transplantation using a variety of modelling techniques and there was no interaction between recipient age and transplant type. However, when the subjects were arranged by age quartile, the survival advantage of bilateral lung transplant was evident in patients less than 60 years but there was no significant survival difference in patients aged older than 60 years.

Consequently, bilateral lung transplant is the preferred option for COPD patients younger than 60 years but additional factors are important to consider when selecting the transplant procedure for patients aged older than 60 years. As mentioned above, such considerations may include optimisation of scarce donor lungs, operative risk, previous thoracic surgery and recipient comorbidities.

1.2 COPD-Associated Pulmonary Hypertension

1.2.1 Definition of Pulmonary Hypertension

PHT is by definition a mean pulmonary arterial pressure (mPAP) measured by right heart catheterisation at rest of greater than or equal to 25 mm Hg (Badesch, Champion et al. 2009). The mean pulmonary arterial pressure results from the product of pulmonary blood flow and total pulmonary resistance. Pulmonary blood flow is usually measured as right ventricular cardiac output, thus:

$$mPAP = CO \times TPR, \text{ where}$$

mPAP = mean pulmonary arterial pressure
CO = right ventricular cardiac output
TPR = total pulmonary resistance

The total pulmonary resistance represents the total resistance load on the right ventricle comprising the pulmonary vascular resistance and the resistance from the left side of the heart. Thus:

$$TPR = PVR + R_{(\text{left heart})},$$
$$mPAP = CO \times (PVR + R_{(\text{left heart})}),$$
$$= (CO \times PVR) + \text{left atrial pressure},$$
$$= (CO \times PVR) + PAWP, \text{ where}$$

$R_{(\text{left heart})}$ = resistance from the left side of the heart
PVR = pulmonary vascular resistance
PAWP = pulmonary arterial wedge pressure

Whilst the term ‘primary pulmonary hypertension’ (PPH) was employed in earlier classification schemes, ‘primary pulmonary hypertension’ was dropped in the 3rd World

Symposium on Pulmonary Arterial Hypertension and was replaced by 'idiopathic pulmonary arterial hypertension' (iPAH) (Simonneau, Galie et al. 2004).

In 2008, the 4th World Symposium on Pulmonary Hypertension presented an updated clinical classification of PHT as presented in Table 4 (Simonneau, Robbins et al. 2009).

Table 4 Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

Reprinted from (Simonneau, Robbins et al. 2009) with permission from Elselvier.

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. **Heritable**
1.2.1. **BMPR2**
1.2.2. **ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)**
1.2.3. **Unknown**
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. **Schistosomiasis**
1.4.6. **Chronic hemolytic anemia**
1.5 Persistent pulmonary hypertension of the newborn
1′. **Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)**
2. Pulmonary hypertension owing to left heart disease
2.1. **Systolic dysfunction**
2.2. **Diastolic dysfunction**
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. **Other pulmonary diseases with mixed restrictive and obstructive pattern**
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. **Chronic thromboembolic pulmonary hypertension (CTEPH)**
5. **Pulmonary hypertension with unclear multifactorial mechanisms**
5.1. **Hematologic disorders: myeloproliferative disorders, splenectomy**
5.2. **Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis**
5.3. **Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders**
5.4. **Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis**

Main modifications to the previous Venice classification are in **bold**.
ALK1 = activin receptor-like kinase type 1; BMPR2 = bone morphogenetic protein receptor type 2; HIV = human immunodeficiency virus.

In addition to the updated clinical classification, the 4th World Symposium eliminated the entity of exercise-induced PHT from the definition of PHT, acknowledging that the level, type and posture of exercise all affect pulmonary haemodynamics but have not been standardised (Badesch, Champion et al. 2009). In addition, it was acknowledged that amongst healthy subjects, pulmonary arterial pressure during exercise varies with age.

Pulmonary arterial hypertension (PAH) and pulmonary venous hypertension (PVH) refer to the pathophysiological mechanism of PHT as being due either to factors upstream or downstream of the pulmonary capillary, respectively. PVH may be due to "back pressure" effects from the left side of the heart or obstruction of the pulmonary veins and venules (for example, pulmonary veno-occlusive disease). Traditionally, a PAWP of greater than 15 mm Hg and a transpulmonary gradient (that is, mPAP less PAWP) of less than 10 to 12 mm Hg have been used as evidence of left heart disease, however, recently Halpern and Taichman (Halpern and Taichman 2009) questioned the accuracy of using PAWP to discriminate PVH from PAH.

The 2008 Symposium classified PHT associated with COPD into Group 3 'Pulmonary hypertension associated with lung disease and/or hypoxemia' but did not expressly distinguish between PAH and PVH in this group (Simonneau, Robbins et al. 2009). Furthermore, the literature addressing PHT in COPD is confounded as many studies have not distinguished PAH from PVH. Nevertheless, PHT associated with COPD is generally considered to be PAH resulting from an elevated PVR but when PAWP is greater than 15 mm Hg, such patients are regarded as having PHT owing to left heart disease (Group 2 PHT). The role of COPD-associated pulmonary hyperinflation upon PHT has not been thoroughly assessed and whether it primarily contributes to PAH or PVH is uncertain.

Whilst right heart catheterisation is the gold standard for the diagnosis of PHT (Weitzenblum and Chaouat 2009), due to the invasive nature of this test, echocardiography is often performed as a screening tool in the clinical and research setting. Fisher and colleagues (Fisher, Criner et al. 2007) have recently shown that in COPD patients, echocardiography has a diagnostic sensitivity and specificity for PHT of only 60% and 74%, respectively. This is supported by other studies highlighting the

limitations of echocardiography (Arcasoy, Christie et al. 2003, Fisher, Forfia et al. 2009, Rich, Shah et al. 2011). Another limitation of echocardiography is that although cardiac function can be assessed, PVH cannot be reliably distinguished from PAH.

1.2.2 Epidemiology of PHT in COPD

The prevalence of PHT in COPD is difficult to ascertain. This is primarily due to the absence of right heart catheter information from large cohorts of COPD patients due to the expense and potential risk of performing right heart catheterisation. Current literature determining prevalence is highly variable as it comes from heterogeneous populations of COPD subjects and uses non-uniform definitions of PHT. As a result, the reported prevalence of PHT in moderate-severe COPD ranges from 23-91% (Matthay, Schwarz et al. 1981, Keller, Shepard et al. 1986, Kessler, Faller et al. 1999, Scharf, Iqbal et al. 2002, Thabut, Dauriat et al. 2005, Sims, Margolis et al. 2009).

Only a few studies have sought to determine the natural history of pulmonary arterial pressures in COPD subjects with longitudinal follow up. Kessler and colleagues (Kessler, Faller et al. 2001) assessed 131 mild-moderate hypoxaemic COPD subjects without PHT at rest and not requiring long-term oxygen therapy for an average of 6.8 years and determined that the mPAP increased on average by 0.4 mm Hg per year. The authors also revealed that patients with exercise-induced PHT (mPAP > 30 mm Hg during exercise) at baseline were significantly more likely to develop PHT at rest (defined as mPAP $\geq$ 20 mm Hg) at follow up. These results are similar to an earlier report of 93 subjects which demonstrated an average increase in mPAP of 0.39 and 0.65 mm Hg per year for COPD subjects with PHT and without PHT, respectively (Weitzenblum, Sautegeau et al. 1984). In contrast, in a smaller cohort of sixteen subjects with more severe COPD, Weitzenblum and colleagues (Weitzenblum, Sautegeau et al. 1985) demonstrated a greater annual increase in mPAP of 1.47 mm Hg.

1.2.3 Pathogenesis of PHT in COPD

The pathogenesis of PHT in COPD remains unclear however several factors have been postulated with varying supporting evidence. Broadly speaking, PAH in COPD may be due to structural and/or functional factors. Structural changes tend to cause fixed elevations of pulmonary arterial pressures, whereby functional changes tend to be more dynamic. Structural changes include destruction of the pulmonary vascular bed, pulmonary vascular remodelling and thromboembolic lesions, whereas functional changes may result from hypoxia, hypercapnia, acidaemia, pulmonary hyperinflation, airway resistance, endothelial dysfunction, inflammation and polycythaemia. In addition, genetics and environmental exposures likely play a significant role (Minai, Chaouat et al. 2010). In contrast, PVH in COPD is either due to left heart disease and/or pulmonary hyperinflation. Figure 2 illustrates the putative mechanisms for PHT in COPD and Figure 3 illustrates the principal site of action for each mechanism.

The following sections will review the evidence supporting each of the postulated mechanisms in turn. These sections form the basis of the review paper that has been published and is attached in Appendix 1.

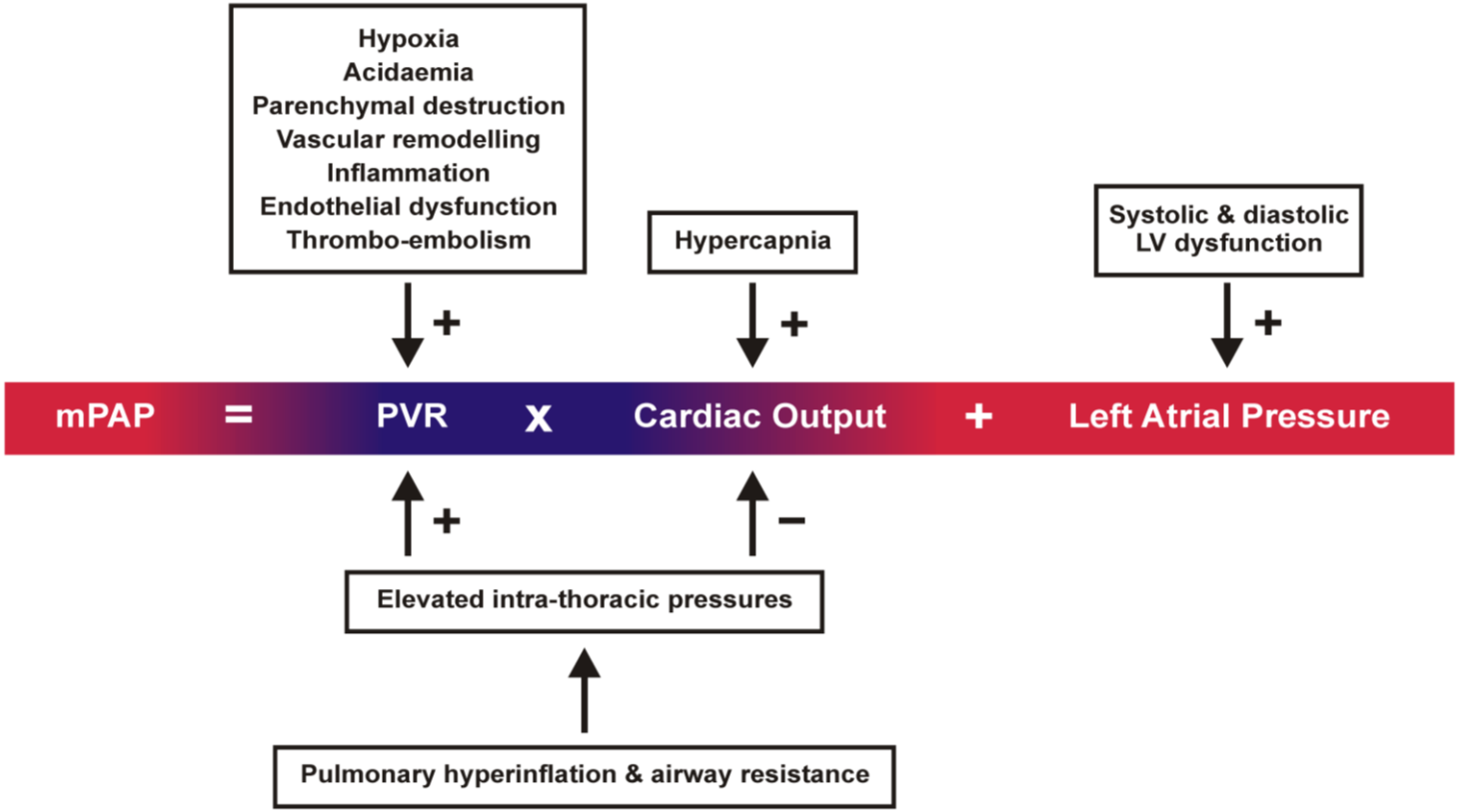

Figure 2
Putative mechanisms for pulmonary hypertension in COPD
LV, left ventricle; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance.

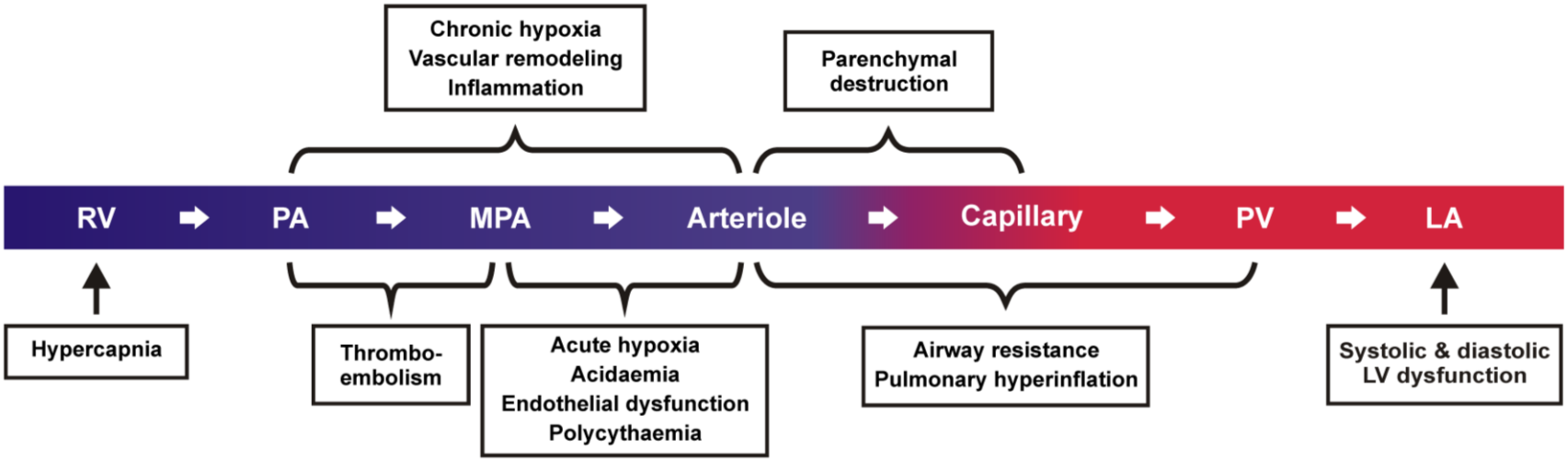

Figure 3
Site of action of pathogenic mechanisms for PHT in COPD
Reprinted from (Wrobel, Thompson et al. 2012b) with permission from Elselvier.
LA, left atrium; LV, left ventricle; MPA, muscular pulmonary artery; PA, pulmonary artery; PV, pulmonary vein; RV, right ventricle.

1.2.3.1 Hypoxia

At present, there is general agreement that hypoxia contributes to PHT via two mechanisms. First, alveolar hypoxia causes acute hypoxic pulmonary vasoconstriction of the small muscular pulmonary arteries (Hales 1985, Staub 1985). This is the key physiological mechanism by which blood is diverted away from poorly ventilated areas of the lung to preserve ventilation/perfusion matching and minimise hypoxaemia. When there is global hypoxia, this becomes a maladaptive compensatory mechanism which substantially increases PVR (Steiner 2009). Secondly, chronic hypoxia contributes to pulmonary vascular remodelling resulting in intimal thickening and neomuscularisation of the small pulmonary arterioles which also raises PVR (Stenmark, Fagan et al. 2006). The mechanisms underpinning hypoxia-induced vascular remodelling are complex and incompletely understood (Pasha and Newman 2010). Recent advances in our understanding of endothelial dysfunction highlight that hypoxia may also play a permissive role in pulmonary vascular remodelling as hypoxia has been shown to inhibit mediators that limit remodelling such as prostacyclin and NO (Presberg and Dincer 2003).

Acute Hypoxia

The role of alveolar hypoxia in the elevation of pulmonary arterial pressure has long been recognised with supporting studies in animals and humans (Motley, Cournand et al. 1947, Nahas, Visscher et al. 1954, Fishman, Fritts et al. 1960a). Acute hypoxia has been shown to increase pulmonary arterial pressure through an increase in PVR in normal subjects and that the onset of the elevated pulmonary arterial pressure is acute and promptly restored with normoxia (Motley, Cournand et al. 1947, Fishman, Fritts et al. 1960a). Similarly, Selinger and colleagues (Selinger, Kennedy et al. 1987) showed that removal of oxygen in COPD patients receiving long-term oxygen therapy significantly increased pulmonary arterial pressure and PVR at rest and exercise, taking 2-3 hours to reach the new steady state. The increase in pulmonary arterial pressure correlated with the decrease in arterial oxygen saturation. In addition, the acute administration of 100% oxygen for 20 minutes to hypoxic COPD subjects has been shown to significantly reduce pulmonary arterial pressure and PVR (28.0 to 24.1mmHg and 415 to 389dyne.s.cm^{-5}, respectively) (Hunt, Copland et al. 1989). By comparison, in

a different cohort of COPD subjects, acute administration of 100% oxygen for 10-30 minutes did not acutely affect pulmonary arterial pressure, PVR or cardiac index (Magee, Wright et al. 1988).

Chronic Hypoxia

In the setting of COPD, chronic hypoxia has been shown to be associated with elevated pulmonary arterial pressure from numerous studies with a consistent finding of a significant correlation between pulmonary arterial pressure and PaO_2 (Bishop and Cross 1981, Keller, Shepard et al. 1986, Chaouat, Bugnet et al. 2005). Further, studies have shown that ≥15hrs/day of supplemental oxygen improves pulmonary haemodynamics and survival (Stark, Finnegan et al. 1972, Nocturnal Oxygen Therapy Trial Group 1980, Medical Research Council Working Party 1981). Long-term oxygen therapy does not normalise pulmonary haemodynamics, however stabilisation or mild improvement in pulmonary arterial pressure and PVR at rest occurs (Stark, Finnegan et al. 1972, Stark, Finnegan et al. 1973, Nocturnal Oxygen Therapy Trial Group 1980, Medical Research Council Working Party 1981, Weitzenblum, Sautegeau et al. 1985, Cooper, Waterhouse et al. 1987). Whether this reflects the "incomplete" improvement of alveolar hypoxia or chronic vascular bed changes is not clear. Supplemental oxygen has also been shown to reduce the extent of exercise or exacerbation induced increases in pulmonary arterial pressure and PVR (Timms, Khaja et al. 1985, Hanaoka, Ideura et al. 2008).

Nocturnal Hypoxia

Sleep disordered breathing, including hypoventilation and obstructive sleep apnoea-hypopnoea syndrome (OSA), can contribute to nocturnal hypoxaemia and hypercapnia in COPD patients (Chaouat, Weitzenblum et al. 1995, O'Donoghue, Catcheside et al. 2003, Weitzenblum and Chaouat 2004). Of interest, COPD subjects with OSA (known as the 'overlap syndrome') have significantly worse nocturnal oxygen desaturation (Sanders, Newman et al. 2003), hypercapnia (Resta, Foschino Barbaro et al. 2002) and higher pulmonary arterial pressure (Chaouat, Weitzenblum et al. 1995) than pure COPD or OSA patients. Consequently, in managing COPD patients with PHT, thorough evaluation for sleep disordered breathing needs to be undertaken and specific

management implemented as required, either in the form of supplemental oxygen or nocturnal non-invasive therapy.

Hypoxia - limitations

Despite the strong supporting evidence of hypoxia being an important contributor to PHT in COPD, the extent to which hypoxia causes PHT in COPD is still the subject of conjecture and investigation. This is broadly based on the following observations: (i) There is a wide variation in hemodynamic response to supplemental oxygen therapy (Ashutosh, Mead et al. 1983); (ii) The correlation between pulmonary arterial pressure and PaO_2 is not particularly strong and has not been consistently demonstrated (Bishop and Cross 1981, Scharf, Iqbal et al. 2002); (iii) Long-term oxygen therapy does not normalise pulmonary arterial pressure, unlike animal models of chronic hypoxia or humans exposed to chronic hypoxia at altitude (Naeije and Barbera 2001, Presberg and Dincer 2003); (iv) Pulmonary vascular structural changes have been observed in non-hypoxic, mild COPD subjects and in smokers with normal lung function (Barbera, Riverola et al. 1994, Peinado, Barbera et al. 1998); (v) Endothelial dysfunction has been demonstrated in non-hypoxic, mild COPD subjects (Peinado, Barbera et al. 1998, Peinado, Barbera et al. 1999); (vi) Animal models have demonstrated an elevation of pulmonary arterial pressure in response to cigarette smoke exposure prior to the development of emphysema (Wright and Churg 1991); and (vii) Hypoxic vasoconstriction alone cannot explain the physiological and pulmonary vascular pathological changes in patients with COPD (Magee, Wright et al. 1988, Wilkinson, Langhorne et al. 1988, Wright, Petty et al. 1992). Thus, although hypoxia has a key role in the development of PHT in COPD, acute hypoxic vasoconstriction is not solely responsible.

1.2.3.2 Hypercapnia / Acidosis

Early clinical studies demonstrated a relationship between $PaCO_2$ and mPAP in COPD subjects (Yu, Lovejoy et al. 1953) and subsequent physiological studies attempted to elucidate this relationship. Acute CO_2 inhalation in COPD subjects has been shown to increase pulmonary arterial pressure, largely through an increase in pulmonary blood flow and an associated increase in ventilation, but the effect on PVR has been

inconsistent (Fishman, Fritts et al. 1960b, Lim and Brownlee 1968). Further, Enson and colleagues (Enson, Giuntini et al. 1964) demonstrated a significant correlation between hydrogen ion concentration and pulmonary arterial pressure in 43 steady state patients with chronic respiratory disease ($r = 0.61$, $p < 0.001$). In contrast, alkali infusion has been shown to increase cardiac output, reduce PVR and have a variable effect on pulmonary arterial pressure (Enson, Giuntini et al. 1964, Susmano, Passovoy et al. 1977).

Taken together, these studies suggest that hypercapnia increases cardiac output, which drives an increase in mPAP. The change in PVR depends on the balance between the dilatory forces (secondary to capillary recruitment resulting from hypercapnia-induced increase in pulmonary blood flow) and the constrictive forces (due to acidaemia-induced pulmonary vasoconstriction) which will be amplified in the setting of a reduced pulmonary vascular bed as occurs in emphysema (Susmano, Passovoy et al. 1977). The situation is however confounded due to the hyperventilation that results from an induced-hypercapnia that causes an increase in the amplitude of intrathoracic pressure swings, a potential increase in PAWP and improved oxygen saturations (Harris, Segel et al. 1968, Lim and Brownlee 1968, Susmano, Passovoy et al. 1977).

Subsequent clinical trials have failed to show a consistent relationship between $PaCO_2$ and mPAP, which is probably due to additional confounders, including variable COPD severity and phenotypes (Bishop and Cross 1981, Keller, Shepard et al. 1986, Kessler, Faller et al. 2001, Thabut, Dauriat et al. 2005). Interestingly, amongst a group of severe COPD subjects assessed for LVRS or lung transplantation, the group with disproportionately severe PHT were not hypercapnic as expected (Thabut, Dauriat et al. 2005). Similarly, Chaouat and colleagues (Chaouat, Bugnet et al. 2005) identified 11 patients with severe PHT without any other cause from a cohort of 998 COPD patients and found them to be hypocapnic.

Hence, despite some clinical evidence of an association between $PaCO_2$ and elevated mPAP, this relationship does not persist into COPD patients with disproportionately severe PHT. Further, the physiological studies are limited in that they only assess acute responses. It appears that whilst hypercapnia and acidaemia play a role in pulmonary haemodynamics, their contribution to PHT in COPD is difficult to clarify in the

presence of so many potential confounders and their effect on PHT is overshadowed by other pathogenic mechanisms.

1.2.3.3 Pulmonary Hyperinflation

Patients with advanced COPD are prone to developing lung hyperinflation, gas trapping and intrinsic positive-end expiratory pressure ($PEEP_I$). In summary, loss of lung elastic recoil increases FRC and lung relaxation volume (V_r) leading to static lung hyperinflation. Increased airway resistance or reduced expiratory time can lead to gas trapping (such that FRC exceeds V_r), the generation of $PEEP_I$ and dynamic lung hyperinflation. Acutely, dynamic lung hyperinflation increases alveolar pressure, which may exceed venous and even arterial pressure thus increasing the prevalence of "West" lung zones 1 and 2 (*see* Table 5) (West, Dollery et al. 1964). This may result in an increased PVR and pulmonary arterial pressure (Banister and Torrance 1960, Howell, Permutt et al. 1961).

Table 5 West Lung Zones and The Driving Pressure in the pulmonary vessels
Adapted from (Permutt, Bromberger-Barnea et al. 1962, West, Dollery et al. 1964).

Zone	Relative Pressures
1 – Upper	Alveolar pressure > arterial pressure > venous pressure
2 – Middle	Arterial pressure > alveolar pressure > venous pressure
3 – Lower	Arterial pressure > venous pressure > alveolar pressure

In addition, hyperinflation may lead to PHT in COPD through a combination of other factors including increased lung volume (Burton and Patel 1958, Whittenberger, McGregor et al. 1960, Permutt, Howell et al. 1961, Permutt and Riley 1963, Lloyd 1967, Lim and Brownlee 1968), intrathoracic pressure swings (Buda, Pinsky et al. 1979, Pinsky 2005), cardiac effects (Butler 1990, Barr, Bluemke et al. 2010, Watz, Waschki et al. 2010b), gas exchange (Lim and Brownlee 1968, Luecke and Pelosi 2005), pulmonary vascular remodelling (Wilkinson, Langhorne et al. 1988) and even endothelial dysfunction (Yoshizumi, Kurihara et al. 1989).

Whilst many authors have listed gas trapping and lung hyperinflation amongst the causes of PHT in COPD (Wright, Lawson et al. 1983, Naeije and Barbera 2001, Scharf,

Iqbal et al. 2002, Thabut, Dauriat et al. 2005, Elwing and Panos 2008, Weitzenblum and Chaouat 2009), there is very little direct evidence to support this. An early study by Yu and colleagues (Yu, Lovejoy et al. 1953) analysed 18 emphysema patients and demonstrated a significant correlation between gas trapping (measured as residual volume to total lung capacity ratio) and mPAP and also with total pulmonary resistance, but not with PVR despite no patients with an elevated PAWP. However, this association of pulmonary arterial pressure and gas trapping has not been replicated.

Nevertheless, gas trapping and pulmonary hyperinflation have been shown to be associated with raised pulmonary arterial pressure during hyperventilation (Harris, Segel et al. 1968, Butler, Schrijen et al. 1988), exercise (Lockhart, Nader et al. 1970, Schrijen, Henriquez et al. 1989) and acute exacerbations (Akcay, Yeter et al. 2010) in COPD patients. Furthermore, it has been suggested that hyperinflation may contribute to the peculiar pulmonary vascular remodelling identified in hypoxic cor pulmonale subjects with obstructive lung disease (Wilkinson, Langhorne et al. 1988). However, whether gas trapping contributes to PHT in stable COPD patients at rest is unknown and the relationship of gas trapping to pulmonary vascular remodelling has never been explored.

The pulmonary haemodynamic consequences of pulmonary hyperinflation are discussed in greater detail in Section 1.4. In Chapter 4, the physiological effects of elevated airway pressures upon pulmonary haemodynamics in subjects with severe, stable COPD are explored.

1.2.3.4 Airway Resistance / Airway Obstruction

It would seem likely that an association would exist between a marker of COPD severity (for example, FEV_1 or airways resistance) and the severity of PHT. Several studies do support this association, demonstrating a statistical correlation between FEV_1 and mPAP on univariate analysis (Bishop and Cross 1981, Keller, Shepard et al. 1986, Scharf, Iqbal et al. 2002, Chaouat, Bugnet et al. 2005). Furthermore, Wilkinson and colleagues were able to demonstrate a significant correlation between FEV_1 and pathological changes of PHT in 10 hypoxic cor pulmonale patients with obstructive lung disease (Wilkinson, Langhorne et al. 1988). Animal studies have also revealed a

relationship between airflow obstruction and elevated pulmonary arterial pressure (Wright 1993). However, despite the apparent association between FEV_1 and pulmonary arterial pressure, the relationship is not universal and FEV_1 is not always regarded as an independent predictor of pulmonary arterial pressure (Keller, Shepard et al. 1986, Chaouat, Bugnet et al. 2005). Further, Wright and Churg (Wright and Churg 1991) have demonstrated in an animal model that the development of raised pulmonary arterial pressure in animals exposed to cigarette smoke occurs prior to the development of emphysema.

Whether airflow obstruction directly causes PHT or works via other mechanisms (such as hypoxaemia) is unclear. There is minimal direct evidence supporting the role of airway obstruction in contributing to PHT in human COPD patients due to the difficulty in study design and the presence of numerous confounders. Harris and others (Harris, Segel et al. 1968) demonstrated that hyperventilation in 6 normal subjects showed no consistent effect upon pulmonary haemodynamics. However, in 6 subjects with chronic bronchitis hyperventilation increased PVR, pulmonary arterial pressure and PAWP, with no impact upon pulmonary blood flow. Unfortunately, the authors did not examine gas trapping or $PEEP_I$ and hence it is difficult to distinguish the effects of airway resistance from pulmonary hyperinflation. Nevertheless, support for a potential role for airway resistance was obtained through an assessment of a further 41 patients with chronic bronchitis in whom they demonstrated a significant correlation between a measure of airway resistance ($1/FEV_1$) and PVR.

Finally, intravenous salbutamol (a beta 2-adrenocepter agonist causing smooth muscle relaxation) has been shown to reduce PVR in patients with chronic cor pulmonale (Vik-Mo, Halvorsen et al. 1987) and severe COPD (Mols, Ham et al. 1988). However, whether this is achieved through direct pulmonary vascular relaxation or reduced airway resistance remains speculative. Thus, it is difficult to directly implicate airways resistance or obstruction as a cause of PHT and at present, only an association is evident.

1.2.3.5 Destruction of Pulmonary Vascular Bed

It has long been held that emphysematous destruction of the pulmonary vascular bed is one of the contributors to the elevation of pulmonary arterial pressure commonly seen in COPD (Chaouat, Bugnet et al. 2005, Thabut, Dauriat et al. 2005). However, it is surprising that there is a lack of substantial direct or indirect evidence to support this mechanism. Indeed, it was recognised in the 1950s that pulmonary arterial pressure can be significantly elevated in COPD subjects despite a normal pulmonary capillary pressure, suggesting that the PHT is "pre-capillary" (Yu, Lovejoy et al. 1953). Additionally, Harris and colleagues (Harris, Segel et al. 1968) have remarked that the "labile nature of the pulmonary hypertension suggested that it has a functional rather than structural basis".

Several studies have attempted to use CT lung tissue density as a measure of emphysema severity. Whilst CT lung density is reduced in emphysema, density measurement may be increased in the presence of PVH, pulmonary oedema or pulmonary scarring (Van Grondelle, Worthen et al. 1984). Despite its limitations, CT severity of emphysema has been shown to be strongly correlated with other markers of emphysema (Gould, Redpath et al. 1991), and the relationship between CT lung density (as a marker of parenchymal destruction) and pulmonary arterial pressure has been explored.

In examining 40 patients with COPD, Shoikhet and Bednarzhevskaia (Shoikhet and Bednarzhevskaia 2004) were able to find a significant negative correlation between CT lung tissue density and the diameter of the pulmonary trunk but did not demonstrate a direct relationship with echocardiographic measurements of pulmonary arterial pressure. Others have not found any relationship between CT severity of emphysema and pulmonary haemodynamics (Biernacki, Gould et al. 1989, Scharf, Iqbal et al. 2002).

Given the potential for a reduced pulmonary vasculature to contribute to a raised pulmonary arterial pressure, there has been considerable interest in the effects of lung volume reduction surgery (LVRS) upon pulmonary haemodynamics but these have yielded inconsistent results. Criner and others (Criner, Scharf et al. 2007) compared 28 patients who underwent LVRS compared with 27 controls and found no change in

pulmonary arterial pressure or cardiac output 6 months after surgery. Other studies of smaller numbers have shown variable effects on cardiac output, PVR and mPAP after LVRS (Oswald-Mammosser, Kessler et al. 1998, Weg, Rossoff et al. 1999, Mineo, Pompeo et al. 2002, Haniuda, Kubo et al. 2003, Jorgensen, Houltz et al. 2003). These inconsistent results are most likely due to resection of variable amounts of pulmonary vessels in the study populations and a multitude of confounders post LVRS; including changes to gas trapping, capillary recruitment, ventilation-perfusion ratios and gas exchange (Sciurba, Rogers et al. 1996, Oswald-Mammosser, Kessler et al. 1998, Tschernko, Gruber et al. 1998, Mineo, Pompeo et al. 2002, Haniuda, Kubo et al. 2003, Jorgensen, Houltz et al. 2003, Hopkinson, Toma et al. 2005).

In comparison, studies in patients with pulmonary neoplasm assessing the pulmonary haemodynamic consequences of a pneumonectomy have demonstrated mild increases in pulmonary arterial pressure at rest (Deslauriers, Ugalde et al. 2011) but a 31% reduction in cardiac output and a 32% increase in PVR with exercise (Van Mieghem and Demedts 1989). Whilst significant, the magnitude of change is not as significant as the reduction in pulmonary vasculature suggesting that other factors are more important in modulating pulmonary haemodynamics.

As highlighted earlier, the dynamic nature of the pulmonary arterial pressure suggests that anatomic reduction of the pulmonary vascular bed is not the principal mechanism for PHT in COPD (Enson, Giuntini et al. 1964). Nevertheless, the dynamic responsiveness of the pulmonary circulation may be reduced with a limited vascular bed and may contribute to the presence of exercise-induced PHT often seen in COPD patients. Similarly, reduced pulmonary capillary cross-sectional area may contribute to the left ventricle (LV) diastolic dysfunction observed in COPD patients through reduced pulmonary blood flow and left ventricular underfilling (Barr, Bluemke et al. 2010).

1.2.3.6 Pulmonary Vascular Remodelling

A number of pathological changes have been identified in the pulmonary vessels of patients with COPD-associated PHT including variable medial hypertrophy, longitudinal muscle deposition, intimal hyperplasia, elastin and collagen deposition, muscularisation of the pulmonary arterioles and in-situ thrombosis (Magee, Wright et

al. 1988, Wilkinson, Langhorne et al. 1988, Wright, Petty et al. 1992, Kubo, Ge et al. 2000). Changes due to pulmonary vascular remodelling may limit the dynamic flow-resistance characteristics of the pulmonary vasculature and contribute to the development of PHT in COPD. However, studies have been inconsistent in finding a relationship between changes of pulmonary vascular remodelling and PHT (Wilkinson, Langhorne et al. 1988, Wright, Petty et al. 1992, Kubo, Ge et al. 2000).

Whilst many of the pulmonary vascular changes that have been documented in COPD-related PHT have been observed in other forms of PHT, including iPAH and high-altitude related PHT, the pattern of histological changes observed in COPD-related PHT appear to relate to the unique combination of factors including chronic hypoxia, mechanical stress, inflammation, toxic effects of cigarette smoke and repeated stretching of hyperinflated lungs (Wilkinson, Langhorne et al. 1988, Naeije and Barbera 2001).

Thus, the pulmonary vascular remodelling observed in COPD-associated PHT likely reflects a common pathway of several different pathological processes. However, it appears that vascular remodelling alone is insufficient to account for the wide variability of the pulmonary arterial pressure observed in COPD patients and their functional responses to supplemental oxygen (Wright, Petty et al. 1992).

The extent and distribution of pulmonary vascular remodelling in COPD is examined in greater detail in Section 1.3 and Chapter 3.

1.2.3.7 Inflammation

There has been renewed interest in the role of inflammation in the pathogenesis of pulmonary vascular dysfunction and remodelling in COPD (Barbera, Peinado et al. 2003, Minai, Chaouat et al. 2010). Given the fundamental role of inflammation in the development of COPD (GOLD 2009), an inflammatory component to pulmonary vascular remodelling would help explain the relatively high prevalence of PHT in COPD patients.

A number of inflammatory changes have been observed in the pulmonary vessels of patients with COPD. Increased numbers of leukocytes have been identified in the adventitia of muscular pulmonary arteries in COPD subjects compared with smoking controls and healthy controls (Peinado, Barbera et al. 1999, Saetta, Baraldo et al. 1999). The authors from both studies proposed that the leukocytes originated from the bronchial circulation rather than from adjacent bronchioles. A distinguishing feature between the two studies was that Peinado and colleagues found significantly increased intimal thickening in the muscular pulmonary arteries of COPD subjects compared to the non-smokers. Furthermore, the inflammatory infiltrate was correlated with intimal thickness of the muscular pulmonary arteries ($P < 0.01$) and negatively correlated with endothelium-dependent maximal relaxation of the small pulmonary muscular arteries ($P < 0.05$). In contrast, Saetta and coworkers did not demonstrate any changes in the intimal thickness of the muscular pulmonary arteries between COPD, asymptomatic smokers and non-smokers. The different results between the two studies may be explained by differences in methodology or patient characteristics.

Regardless, these studies demonstrate that inflammation is present in the muscular pulmonary arteries and whilst the extent and mechanism through which inflammation promotes pulmonary vascular remodelling and endothelial dysfunction is unknown, it appears likely that inflammation is integral to pulmonary vascular remodelling in subjects with COPD.

1.2.3.8 Endothelial Dysfunction

Pulmonary vascular endothelial dysfunction has been demonstrated to occur in PAH involving numerous pathways, including prostacyclin, nitric oxide and endothelin (Giaid, Yanagisawa et al. 1993, Giaid and Saleh 1995, Brett, Simon et al. 1996, Humbert, Sitbon et al. 2004, Morrell, Adnot et al. 2009). Whilst acutely these messengers and pathways may give rise to endothelial dysfunction, over time they contribute to pulmonary vascular remodelling. Endothelial dysfunction has been demonstrated in COPD subjects (Dinh-Xuan, Higenbottam et al. 1991, Peinado, Barbera et al. 1998, Barbera, Peinado et al. 2001) and appears to be mediated by similar pathways to those occurring in PAH (Chen, Chen et al. 1995, Chen, Hanaoka et al. 2009, Chen, Hanaoka et al. 2010). Furthermore, other cytokines and growth factors,

such as VEGF, may also be involved and genetic polymorphisms, inflammation and mechanical factors are likely to play an important role in modulating the endothelial dysfunction observed in COPD-related PHT (Wright, Levy et al. 2005).

Nitric oxide is a potent vasodilator, an inhibitor of platelet activation and possesses antiproliferative effects on vascular smooth-muscle (Farber and Loscalzo 2004). The role of reduced nitric oxide in COPD-associated PHT is supported by studies demonstrating reduced nitric oxide dependent relaxation in COPD subjects compared with non-smokers and smokers with normal lung function (Dinh-Xuan, Higenbottam et al. 1991, Peinado, Barbera et al. 1998, Barbera, Peinado et al. 2001). Furthermore, decreased endothelial nitric oxide synthase has been demonstrated in smokers with mild COPD (Barbera, Peinado et al. 2001) and reduced exhaled nitric oxide has been demonstrated in COPD subjects with PHT (Carratu, Scoditti et al. 2008). Finally, Clini and colleagues demonstrated a significant negative correlation between exhaled nitric oxide and pulmonary arterial pressure on echocardiogram (Clini, Cremona et al. 2000).

Endothelin-1 is a potent vasoconstrictor that stimulates the production of pulmonary-artery smooth muscle cells (Farber and Loscalzo 2004). Several studies have shown an increase in endothelin-1 levels in COPD subjects with PHT (Yamakami, Taguchi et al. 1997, Faller, Kessler et al. 1998, Carratu, Scoditti et al. 2008) however the relationship between endothelin-1 levels and pulmonary arterial pressure has been inconsistent (Stewart, Levy et al. 1991, Ferri, Bellini et al. 1995, Yamakami, Taguchi et al. 1997, Faller, Kessler et al. 1998, Fujii, Otsuka et al. 1999). Numerous factors have been shown to modulate endothelin-1 secretion (Ferri, Bellini et al. 1995). In particular, hypoxaemia has been shown to increase endothelin-1 levels (Morganti, Giussani et al. 1994, Faller, Kessler et al. 1998, Fujii, Otsuka et al. 1999). Conversely, endothelin-receptor antagonists have been shown to prevent hypoxic pulmonary vasoconstriction and attenuate hypoxia-induced pulmonary vascular remodelling in an animal model (Chen, Chen et al. 1995). Interestingly, endothelin-receptor antagonists have also been shown to attenuate emphysematous changes in an animal model suggesting that endothelin-1 is important not just in the pathogenesis of COPD-related PHT but in the development of emphysema itself (Chen, Hanaoka et al. 2010).

It has also been suggested that an imbalance between prostacyclin (a powerful vasodilator, inhibitor of platelet activation and antiproliferative agent) and thromboxane A_2 (a vasoconstrictor, platelet activator and proliferative agent) may be involved in COPD-related PHT. Zheng and colleagues (Zheng, Duan et al. 1991) reported that there was no difference in prostacyclin levels between normal subjects and COPD patients with or without PHT, however, levels of thromboxane A_2 were increased in COPD subjects with resting and exercise-induced PHT compared with healthy controls. Further, Nana-Sinkam and colleagues (Nana-Sinkam, Lee et al. 2006) demonstrated reduced prostacyclin synthase and 6-keto-PGF1α (the stable metabolite of prostacyclin synthase) in pulmonary vascular endothelial cells of emphysematous patients compared with controls. Interestingly, prostacyclin analogues have been shown to attenuate emphysematous changes induced from cigarette smoke extract in experimental models (Nana-Sinkam, Lee et al. 2007, Chen, Hanaoka et al. 2009) suggesting that prostacyclin imbalance may play a role in the pathogenesis of emphysema. Nevertheless, its role in COPD-related PHT requires further research.

Vascular endothelial growth factor is a signal protein that promotes angiogenesis and vasodilatation (through activation of nitric oxide and prostacyclin pathways). Vascular endothelial growth factor has been implicated in the development of plexiform lesions observed in iPAH (Tuder, Chacon et al. 2001) and its role in endothelial cell maintenance marks it as a possible player in the pathogenesis of emphysema and COPD-related PHT. However, there is conflicting data regarding the role of vascular endothelial growth factor in emphysema (Kasahara, Tuder et al. 2001, Santos, Peinado et al. 2003).

Numerous other chemical messengers have been suggested in the pathogenesis of PHT but their role in COPD-related PHT remains unclear. These messengers include atrial and brain natriuretic peptides (Adnot, Andrivet et al. 1990, Zhao, Winter et al. 1991, Lang, Coutie et al. 1992), serotonin (Eddahibi, Chaouat et al. 2003), vasoactive intestinal peptide (Petkov, Mosgoeller et al. 2003) and adrenomedullin (Farber and Loscalzo 2004).

Finally, shear stresses to pulmonary vascular endothelium may also cause endothelial dysfunction mediated through prostacyclin, nitric oxide and endothelin pathways.

Increases in blood flow and the introduction of pulsatile flow have been shown to increase the production of prostacyclin and nitric oxide in non-pulmonary vascular endothelium (Frangos, Eskin et al. 1985, Rubanyi, Romero et al. 1986, Buga, Gold et al. 1991). Regarding endothelin, low levels (but not high levels) of shear stress have been shown in vitro to stimulate endothelin production by endothelial cells (Yoshizumi, Kurihara et al. 1989) with slower onset and recovery than prostacyclin and nitric oxide (Frangos, Eskin et al. 1985, Rubanyi, Romero et al. 1986). Whilst far from conclusive, the effects of shear stress suggest that the haemodynamic influences of pulmonary blood flow, regional perfusion, gas trapping with wide intrathoracic pressure swings may modulate pulmonary vascular endothelial function.

1.2.3.9 Polycythaemia

Polycythaemia occurs in advanced COPD as a complication of chronic hypoxia. Defouilloy and colleagues (Defouilloy, Teiger et al. 1998) assessed 21 patients with chronic hypoxic lung disease and were unable to find a significant difference in pulmonary arterial pressure or PVR in 11 polycythaemic subjects in comparison with 10 normocythaemic subjects. However, only the polycythaemic group had impaired pulmonary vascular relaxation in response to acetylcholine (which causes release of endogenous nitric oxide and prostaglandin production), which appeared to be mediated by hyperviscosity rather than hypervolaemia.

In comparison, Nakamura and colleagues (Nakamura, Kasamatsu et al. 2000) assessed 41 subjects with severe COPD and demonstrated that haemoglobin correlated significantly with mPAP ($r = 0.466$, $P < 0.05$) and with PVR ($r = 0.467$, $P < 0.05$). Interestingly, PaO_2 was more strongly correlated with mPAP and PVR. Nevertheless, the haemoglobin effects on pulmonary arterial pressure and PVR were independent of PaO_2. The authors also hypothesised that haemoglobin may increase pulmonary arterial pressure when pulmonary vascular compliance is decreased by pulmonary vascular remodelling.

However, the relationship between polycythaemia and PHT was further complicated by a recent cohort study which demonstrated that low haemoglobin levels was associated with elevated pulmonary arterial pressure in 117 moderate-severe COPD subjects

without resting hypoxaemia (Lee, Oh et al. 2011). Consequently, the role of polycythaemia in the development of PHT remains unclear.

1.2.3.10 Genetics

Genetic predisposition appears important in the development of COPD. To date however, only alpha-1 antitrypsin deficiency has been clearly shown as causative (GOLD 2009). There appears also to be a genetic predisposition to the development of PHT in COPD subjects (Minai, Chaouat et al. 2010). Endothelial nitric oxide synthase and 5-hydroxy-tryptamine are two of the many modulators implicated in pulmonary vascular endothelial dysfunction and remodelling. Yildiz and others (Yildiz, Oflaz et al. 2003) demonstrated a significantly increased pulmonary arterial pressure amongst the BB genotype for endothelial nitric oxide synthase and this polymorphism, along with PaO_2, were found to be independent predictors of pulmonary arterial pressure in their cohort of 42 subjects with COPD. Similarly, 5- hydroxy-tryptamine mediates pulmonary artery smooth muscle cell proliferation and the LL polymorphism of the 5-hydroxy-tryptamine gene has been shown to be associated with increased mPAP in 103 subjects with severe COPD (Eddahibi, Chaouat et al. 2003). Finally, genetic predisposition for PHT in COPD may also be conferred by carrying the IL6 GG genotype (Chaouat, Savale et al. 2009).

1.2.3.11 Left Ventricle Diastolic Dysfunction

As previously mentioned in Section 1.1.6 above, there is an increased prevalence of cardiac dysfunction amongst COPD subjects in comparison with healthy controls, especially LV diastolic dysfunction (Boussuges, Pinet et al. 2000). With the lungs and heart sharing a limited space (the thoracic cavity) with circulatory continuity, it is not surprising that cardiac disease may augment PHT in patients with respiratory disease. In particular, diastolic dysfunction, which is common in COPD, can contribute to PHT whereby elevations in left atrial pressure are transmitted through to the pulmonary circulation with the development of PVH (Hoeper, Barberà et al. 2009). It has also been demonstrated that left atrial mechanical factors are significantly correlated with PHT levels in COPD subjects (Acikel, Yilmaz et al. 2004, Acikel, Kose et al. 2010). Whilst this association between LV diastolic function and PHT does not infer causation, it

reiterates that PHT due to LV diastolic dysfunction may be incorrectly classified as COPD-related PHT if cardiac structure and function are not fully assessed, including measurement of PAWP.

1.2.3.12 Thromboembolic Disease

COPD subjects may be at increased risk of pulmonary embolism due to underlying inflammation, decreased mobility, polycythaemia and other comorbidities (Bruha, Petrtyl et al. 2005, Sidney, Sorel et al. 2005, Rizkallah, Man et al. 2009). COPD subjects that develop pulmonary embolism are at increased risk of hospitalisation and mortality than patients with pulmonary embolism and no other comorbidities (Sidney, Sorel et al. 2005). Furthermore, COPD subjects with pulmonary embolism have an increased 1 year mortality in comparison with COPD subjects without pulmonary embolism (Carson, Terrin et al. 1996). Apart from the acute mortality risk of pulmonary embolism, pulmonary embolism can also progress to chronic thromboembolic PHT. Given the difficulty in diagnosing pulmonary embolism in COPD subjects, there is a danger that pulmonary embolism is being overlooked and that chronic thromboembolic PHT is being incorrectly classified as COPD-related PHT (Chaouat, Bugnet et al. 2005). This potential misdiagnosis has bearing upon treatment strategies and clinical outcomes.

1.2.3.13 Summary of Mechanisms of PHT in COPD

The aetiology of PHT in COPD is complex, multifaceted and due to both pre- and post capillary mechanisms. Whilst the strength of the evidence to support the numerous pathogenic mechanisms is variable, this probably highlights that no single mechanisms is responsible for PHT in all COPD subjects. Based on present evidence, Table 6 summarises the pathogenic mechanism and grades each factor as causative, contributory or merely associated with PHT in COPD.

Table 6 Summary of Potential Mechanisms of PHT in COPD

Reprinted from (Wrobel, Thompson et al. 2012b) with permission from Elselvier.

Mechanism	Causative	Contributory	Associated	Comments
Hypoxia	✓			Good evidence of a significant role
Hypercapnia			✓	Association mediated by increased cardiac output
Acidaemia		✓		Likely to increase pulmonary vascular resistance
Hyperinflation		✓		Contributory only during dynamic hyperinflation
Airway obstruction			✓	Association only
Loss of capillary bed		✓		Remains speculative but probably contributory
Vascular remodeling		✓		Paucity of data but likely contributory
Inflammation		✓		Likely contributory via vascular remodeling and endothelial dysfunction
Endothelial dysfunction		✓		Paucity of data but likely contributory
Polycythemia		✓		Hyperviscosity may augment endothelial dysfunction
Genetics		✓		Certain genotypes likely to be more susceptible
Comorbidities		✓		Includes obstructive sleep apnea, pulmonary emboli and left heart failure

It is important to appreciate that some COPD patients have a dynamic pattern of PHT with wide variations in pulmonary arterial pressure dependent upon blood gas derangements, pulmonary mechanics, blood viscosity, fluid status and activity level. In contrast, other COPD patients may experience a more fixed type of PHT, perhaps due to underlying structural changes of pulmonary vascular remodelling, loss of pulmonary capillaries and possible thromboembolic lesions. Dynamic and fixed patterns of PHT can also coexist which further confounds analysis of PHT pathogenesis.

Although PHT in COPD is usually of mild severity, the presence of any PHT translates into increased morbidity and mortality in this population. Consequently, as we improve our understanding for the basis of PHT in this cohort, we need to continue to explore strategies of treating COPD-related PHT. Such trials will need to ensure that improved pulmonary haemodynamics in COPD are translated into improved health outcomes. It is clear that important confounders such as hypoxia, hypercapnia, LV diastolic dysfunction and thromboembolism will need to be carefully considered in study design. Further, the use of selective pulmonary vasodilators will not cure PHT in COPD in most cases. Finally, as severe PHT is relatively uncommon in COPD subjects, patients should be adequately evaluated to exclude additional causes of PHT such as chronic thromboembolic PHT, LV diastolic dysfunction and sleep disorders which may be amenable to specific therapies (Chaouat, Bugnet et al. 2005).

It is timely to remember that COPD is not an isolated disease entity with a single phenotype, but rather represents a wide variety of pulmonary diseases with shared risk factors and a pattern of airway obstruction (Agusti and Barnes 2010, Han, Agusti et al. 2010). Ultimately, as we obtain better information on COPD phenotypes, we may be able to more precisely account for the varied pathological mechanisms of PHT occurring in different COPD patients. This would enable targeted PHT therapy for each COPD phenotype.

1.2.4 Clinical Features of PHT in COPD

The clinical symptoms of PHT in patients with COPD are usually non-specific and often attributed to the underlying COPD itself. COPD patients with PHT may present

with increasing breathlessness, symptoms of right heart failure (especially peripheral oedema), syncope or pre-syncope. Right heart failure due to underlying pulmonary disease is termed cor pulmonale. Whilst cor pulmonale was previously considered synonymous with the presence of PHT in advanced lung disease, this term has received wavering support over the years. At present, it is infrequently utilised.

The clinical signs of COPD-associated PHT are indistinguishable from PAH however, they are often less pronounced as the magnitude of pulmonary arterial pressure in COPD-associated PHT is usually less extreme than in patients with PAH. Furthermore, the cardiac signs of COPD-associated PHT may be obscured due to the hyperinflation that occurs in COPD. The clinical signs of PHT in COPD include a right ventricular heave, a prominent pulmonary heart sound, a right-sided S4 gallop rhythm, the murmur of tricuspid regurgitation, an elevated jugular venous pressure, hepatojugular reflux, a pulsatile liver and peripheral oedema (Elwing and Panos 2008).

1.2.5 Diagnosis of PHT in COPD

In addition to the clinical features of COPD-associated PHT mentioned above, clinical suspicion for COPD-associated PHT may occur when patients present with increasing breathlessness or hypoxia despite stable spirometric findings. In addition, a "disproportionately low gas transfer" relative to the degree of airflow obstruction (and CT scan parenchymal abnormalities) may also raise suspicion for the presence of PHT, however no studies are yet to define what constitutes a "disproportionately low gas transfer". A range of other investigations may alert the physician to the presence of PHT in COPD patients including hilar prominence on chest radiograph due to enlargement of the central pulmonary arteries, enlargement of the main pulmonary artery or major segmental pulmonary arteries on chest CT or magnetic resonance imaging, or features of right ventricular hypertrophy or strain on an electrocardiogram (Elwing and Panos 2008).

The gold standard diagnostic criteria for PHT is mPAP of greater than or equal to 25 mm Hg as measured by right heart catheterisation (Badesch, Champion et al. 2009). In 2008, the Fourth World Symposium on Pulmonary Hypertension classified COPD-

associated PHT into Group 3 'Pulmonary hypertension associated with lung disease and/or hypoxemia' (Simonneau, Robbins et al. 2009). However, right heart catheters are invasive and are seldom used in the clinical management of patients with COPD. Consequently, less invasive tools are often used to diagnose and monitor progression of PHT. In particular, echocardiography is often used for this purpose.

Estimates of the systolic pulmonary arterial pressure can be obtained by determining the right ventricular systolic pressure (RVSP) from echocardiography. Provided there is no obstruction to right ventricular outflow, the RVSP equals the trans-tricuspid gradient plus the estimated right atrial pressure (RAP). The trans-tricuspid gradient is estimated from the maximum jet velocity of the tricuspid regurgitant flow. The right atrial pressure may be given a nominal value or it may be estimated by the collapsibility of the inferior vena cava during inspiration. Hence;

$$\text{RVSP} = \text{trans-tricuspid gradient} + \text{RAP},$$
$$\text{Trans-tricuspid gradient} = 4\,v^2, \text{ and}$$
$$\text{RVSP} = 4\,v^2 + \text{RAP}, \text{ where}$$

RVSP = right ventricular systolic pressure,
RAP = right atrial pressure, and
v = maximum jet velocity of the tricuspid regurgitant flow

Although echocardiogram assessment of RVSP can achieve very good correlation with direct measures of systolic pulmonary arterial pressure obtained by right heart catheterisation (Laaban, Diebold et al. 1989, Arcasoy, Christie et al. 2003, Rich, Shah et al. 2011), recent studies have highlighted some pitfalls in using echocardiography (Fisher, Forfia et al. 2009, Rich, Shah et al. 2011). First, echocardiography is dependent on the presence of tricuspid insufficiency. Second, hyperinflation of the chest may reduce the quality of the echocardiography image and limit the accuracy of the measures. Recent studies assessing the accuracy of echocardiography compared with right heart catheterisation in advanced lung disease have determined a sensitivity, specificity, positive predictive value and negative predictive value of 60-85%, 55-74%, 52-68% and 67-87%, respectively (Arcasoy, Christie et al. 2003, Fisher, Criner et al. 2007). Finally, whilst echocardiography is able to supplement the RVSP measure with

information on cardiac chamber size and function, it is unable to accurately measure cardiac output and PVR that is regarded as essential information in the formal assessment of PHT. Despite these limitations, echocardiography remains the most effective non-invasive tool for the assessment of PHT in the clinical setting.

1.2.6 Treatment of PHT in COPD

Many authors report that the severity of PHT is the single most important prognostic indicator in COPD subjects (Weitzenblum, Hirth et al. 1981, Oswald-Mammosser, Weitzenblum et al. 1995, Kessler, Faller et al. 1999). Consequently, there has been significant effort to explore whether treatment of PHT in COPD patients can achieve improved pulmonary haemodynamics and clinical outcomes (Naeije, Melot et al. 1982, Weitzenblum, Sautegeau et al. 1985, Borst, Leschke et al. 1999, Holverda, Rietema et al. 2008, Lee, Chen et al. 2009, Blanco, Gimeno et al. 2010, Dernaika, Beavin et al. 2010).

1.2.6.2 General measures

First, management of COPD should be optimised including smoking cessation, hazardous exposure avoidance, inhaled bronchodilators, inhaled corticosteroids, vaccinations as appropriate, pulmonary rehabilitation, education and management of comorbidities (McKenzie, Abramson et al. 2011). Secondly, supplemental oxygen should be considered.

1.2.6.3 Supplemental oxygen

As discussed above, long-term oxygen therapy does not normalise pulmonary haemodynamics, however stabilisation or mild improvement in pulmonary arterial pressures and PVR at rest occurs (Stark, Finnegan et al. 1972, Stark, Finnegan et al. 1973, Nocturnal Oxygen Therapy Trial Group 1980, Medical Research Council Working Party 1981, Weitzenblum, Sautegeau et al. 1985, Cooper, Waterhouse et al. 1987). Supplemental oxygen may also minimise the increase in pulmonary arterial pressure and PVR associated with exercise and exacerbations (Timms, Khaja et al. 1985, Hanaoka, Ideura et al. 2008).

1.2.6.4 Non-pulmonary selective vasodilators

Morley and colleagues (Morley, Zappasodi et al. 1987) demonstrated improved pulmonary haemodynamics one hour following sublingual nifedipine administration in COPD patients with PHT (defined as mPAP > 20 mm Hg). Whilst intravenous nitroglycerin also reduced the PVR index, this was accompanied by a non-significant reduction in cardiac index.

A subsequent study using felodipine (a non-pulmonary selective calcium antagonist) for 12 weeks duration in 10 COPD patients with PHT (defined as RVSP > 30 mm Hg and/or mPAP > 20 mm Hg) demonstrated a reduction in PVR and pulmonary arterial pressure with improved cardiac output, but no improvement in exercise capacity (Sajkov, McEvoy et al. 1993).

1.2.6.5 Pulmonary Selective Vasodilators

With the development of pulmonary selective vasodilators for Group 1 PHT, there have been several studies exploring whether these agents have a role in patients with COPD.

Phosphodiesterase inhibitors

Madden and colleagues (Madden, Allenby et al. 2006) demonstrated a reduction in PVR and an improved six-minute walk distance in five out of six COPD patients with PHT treated with 8 weeks of sildenafil (a type 5 phosphodiesterase inhibitor). By contrast, Rietema and colleagues (Rietema, Holverda et al. 2008) found no change in stroke volume or exercise capacity in 15 COPD subjects (including 9 with PHT) following three months of sildenafil therapy.

Blanco and colleagues (Blanco, Gimeno et al. 2010) demonstrated a reduction in mPAP following acute sildenafil administration both at rest and during exercise in 20 COPD subjects, however, at rest there was a significant reduction in PaO_2 due to inhibition of hypoxic vasoconstriction. A subsequent double-blind, placebo-controlled, crossover, randomised controlled trial of sildenafil in 10 COPD subjects with PHT failed to show any improvement in six minute walk distance (Lederer, Bartels et al. 2012). However,

sildenafil was associated with increased alveolar-arterial oxygen gradient, worse symptoms and reduced quality of life.

Holverda and colleagues (Holverda, Rietema et al. 2008) assessed the effect of acute sildenafil administration upon the exercise-induced haemodynamic changes in 18 COPD subjects with GOLD stages II-IV. Whilst sildenafil attenuated the exercise-induced increase in mPAP during submaximal exercise, it was not associated with improved stroke volume, cardiac output or exercise capacity.

Nitric oxide

Katayama and colleagues (Katayama, Higenbottam et al. 1997) evaluated the effects of inhaled nitric oxide in 11 COPD subjects with severe PHT versus 9 COPD subjects with no documented PHT and 14 healthy controls. They demonstrated impaired transcutaneous arterial oxygenation tension in the controls and COPD group but not in the PHT subjects. Cardiac output, transcutaneous arterial carbon dioxide tension and oxygen saturations were not acutely affected amongst any of the three groups.

A subsequent study by Vonbanck and colleagues (Vonbank, Ziesche et al. 2003) evaluated the effects of oxygen alone versus oxygen and pulse nitric oxide therapy in 40 COPD patients with PHT. After acute administration, the nitric oxide group had improved pulmonary haemodynamics with reduced PVR and mPAP and an increase in cardiac output. These improvements persisted following 3 months of therapy, without decreasing arterial oxygenation. Unfortunately, exercise capacity and quality of life were not assessed.

Endothelin receptor antagonists

Finally, in a randomised, controlled trial of 30 severe COPD subjects (not restricted to patients with PHT), 12 weeks of bosentan therapy resulted in no pulmonary haemodynamic or functional improvements (Stolz, Rasch et al. 2008). However, PaO_2 was decreased, the alveolar-arterial oxygen gradient increased and the quality of life decreased in patients treated with bosentan.

Prostacyclin

Archer and colleagues (Archer, Mike et al. 1996) compared intravenous prostacyclin infusion versus placebo in 16 COPD patients with PHT (defined in this study as mPAP > 30 mm Hg or PVR > 4 Wood units) that were intubated for acute respiratory failure. Prostacyclin initially improved PVR, systemic vascular resistance and mean aortic pressure but these changes did not persist after 48 hours of therapy. Prostacyclin had no effect on cardiac output, mPAP or mean wedge pressure but significantly reduced PaO_2 at 48 hours compared to placebo.

Because of the potential for pulmonary vasodilators to reduce hypoxic vasoconstriction and hence, worsen hypoxaemia, inhaled pulmonary vasodilators have the theoretical potential to improve pulmonary haemodynamics without compromising PaO_2. Recently, Dernaika and colleagues (Dernaika, Beavin et al. 2010) evaluated the acute effects of inhaled iloprost (a synthetic analogue of prostacyclin) on 10 COPD subjects with PHT (defined as RVSP > 35 mm Hg and right ventricular morphological changes). They demonstrated improved six minute walk distance, ventilatory efficiency and alveolar-arterial oxygen gradient without compromising PaO_2. Acute haemodynamic changes were not assessed.

These studies highlight that there is currently a limited role for the use of specific pulmonary vasodilators in COPD patients with PHT. Nevertheless, selected patients may obtain some benefit with these therapies. Further research is required to better delineate which patients are likely to benefit from specific pulmonary vasodilators. This requires a better understanding of the underlying pathogenesis of PHT in COPD patients.

1.2.7 Lung transplantation and Preoperative PHT

As PHT is a poor prognostic indicator for patients with COPD and treatment options are limited, some of these patients will proceed to lung transplantation. In deed, the presence of PHT, despite oxygen therapy, is considered amongst the indications for lung transplantation in COPD (Orens, Estenne et al. 2006).

A number of risk factors have been identified for poor outcomes following transplantation for COPD as discussed above in Section 1.1.9. Despite improved registry data in recent years, information remains sparse regarding the transplant morbidity and mortality of COPD patients complicated by secondary PHT.

Boujoukos and colleagues (Boujoukos, Martich et al. 1997) retrospectively studied 30 single-lung transplant patients and compared outcomes of patients with PHT versus emphysema patients. PHT patients had longer duration of ventilation, intensive care length of stay and time until satisfactory oxygenation was achieved ($P < 0.01$). However, preoperative mean pulmonary arterial pressure did not predict for prolonged duration of mechanical ventilation in either sub-group.

Bando and colleagues (Bando, Keenan et al. 1994) studied 48 consecutive single lung transplants for a range of indications (including but not limited to pulmonary fibrosis, emphysema and PAH) and showed that pre-operative PHT (defined as mPAP > 30 mm Hg) was associated with increased intensive care length of stay ($P < 0.05$), increased episodes of infection ($P < 0.01$) and reduced 9 month and 18 month post-operative survival ($P < 0.05$). Whilst the excess mortality in the PHT group was predominantly comprised of patients with PAH, there was still greater mortality in the secondary PHT group compared with subjects without PHT (18 month survival 72% v 60%, significance not reported). This was supported by a subsequent study of 69 patients by Lee and colleagues (Lee, Martich et al. 1996) which demonstrated on multiple logistic regression that only the immediate postoperative PaO_2/fraction inspired oxygen (PaO_2/F_IO_2) ratio and the preoperative transpulmonary gradient (i.e. mPAP less PAWP) were predictive for intensive care length of stay following lung transplantation for a variety of indications (including COPD 49%, pulmonary fibrosis 20% and PHT 9%).
Recently, Fang and colleagues (Fang, Studer et al. 2011) identified preoperative elevation of pulmonary arterial pressure as a significant risk factor for the development of severe PGD (defined as the presence of radiographic infiltrates consistent with pulmonary oedema and a PaO_2/F_IO_2 ratio of less than 200 at 72 hours post-operatively) following lung transplantation for idiopathic pulmonary fibrosis.

This is consistent with Whelan and colleagues (Whelan, Dunitz et al. 2005) who performed a retrospective registry study of adult lung transplantations for idiopathic

pulmonary fibrosis. They identified elevated pre-operative mPAP as a risk factor for 90-day mortality amongst the 636 single-lung transplant recipients (P = 0.033). For bilateral-lung transplant recipients, patients with a pre-operative mPAP < 20 mm Hg or > 35 mm Hg had a higher 90-day mortality (P = 0.0045). Whitson and colleagues (Whitson, Nath et al. 2006) found a similar relationship between mPAP and bilateral lung transplantation across 146 lung transplant recipients for a variety of indications (including but not limited to idiopathic pulmonary fibrosis, COPD and PAH). They found that amongst bilateral lung transplant recipients, a mPAP ≤ 20 mm Hg or ≥ 30 mm Hg was associated with increased risk of grade 3 primary graft dysfunction within 48 hours post transplantation. The explanation for this bimodal risk for bilateral lung transplantation is not clear.

Prekker and colleagues (Prekker, Nath et al. 2006) studied 402 lung transplants for a range of indications (including COPD 61%, idiopathic pulmonary fibrosis 12% and PPH 6%) from their institution to validate the grading system for primary graft dysfunction. On multivariate analysis, they identified that elevated pre-operative mPAP was a significant risk factor for primary graft dysfunction (P = 0.04), along with single-lung transplant procedure (P < 0.01) and use of cardiopulmonary bypass (P < 0.01).

Sullivan and colleagues (Sullivan, Whitson et al. 2006) compared transplant recipient risk factors for severe primary graft dysfunction from paired single lung transplant recipients (81 donors, 162 paired recipients). They demonstrated that the only significant risk factor was preoperative pulmonary arterial pressure > 24 mm Hg (P = 0.005).

In contrast, several studies have not found preoperative pulmonary arterial pressure to be a predictor of poor outcomes following lung transplantation.

Andersen and colleagues (Andersen, Iversen et al. 2012) recently studied the clinical outcomes of 409 patients with lung transplant evaluation for COPD, and whilst patients with preoperative PHT had worse survival whilst awaiting lung transplantation, preoperative PHT did not predict for worse survival following transplantation. These results are similar to an earlier registry study by Thabut and colleagues (Thabut, Ravaud et al. 2008) of 8,182 COPD subjects which revealed that increased systolic pulmonary

arterial pressure was a risk factor for mortality on the transplant waiting list ($P < 0.001$), but did not affect survival following transplantation ($P = 0.36$).

Other negative studies have not been limited to COPD subjects.

Christie and colleagues (Christie, Bavaria et al. 1998) retrospectively reviewed 100 consecutive lung transplant recipients for a range of indications (including COPD 56%, PPH and Eisenmenger's syndrome 20% and idiopathic pulmonary fibrosis 4%) for risk factors of primary graft dysfunction. Whilst they demonstrated that there was a trend towards more primary graft dysfunction in the PPH group ($P = 0.16$), preoperative pulmonary arterial systolic pressure across all transplant indications did not predict for primary graft dysfunction overall ($P = 0.76$).

Huerd and colleagues (Huerd, Hodges et al. 2000) retrospectively reviewed 76 lung transplant recipients (including COPD 53% and idiopathic pulmonary fibrosis 32%) to assess whether preoperative secondary PHT (mPAP $\geq$ 30 mm Hg) predicted worse outcomes following transplantation. In this small study, secondary PHT did not predict for worse short-term hospital outcomes, lung function, six-minute walk distance, rejection, infection, bronchiolitis obliterans syndrome, short or long-term survival.

Conte and colleagues (Conte, Borja et al. 2001) compared lung transplant outcomes in 15 pts with PPH versus 40 patients with secondary PHT and demonstrated that amongst the subset that received a bilateral lung transplant, PPH was associated with a longer duration of mechanical ventilation ($P < 0.05$), longer intensive care length of stay ($P < 0.005$) and longer hospitalization length of stay ($P < 0.001$). Patients with PPH had better survival with bilateral compared to single lung transplant but there was no difference in survival between PPH and secondary PHT. Conte and colleagues also compared low secondary PHT (mPAP $\leq$ 40 mm Hg) versus high secondary PHT (mPAP > 40 mm Hg) but could not find any differences in either short-term hospital outcome or survival.

Fitton and colleagues (Fitton, Kosowski et al. 2005) retrospectively reviewed 87 patients for the clinical impact of secondary PHT following lung transplantation for a variety of indications (including COPD 36%, idiopathic pulmonary fibrosis 15% and

Eisenmenger's syndrome 1% but excluding PPH and heart-lung recipients). Whilst high secondary PHT (mPAP ≥ 40 mm Hg) predicted a reduced PaO_2/F_IO_2 ratio within 24 hours compared with controls, there were no differences between controls, low secondary PHT (30 ≤ mPAP < 40 mm Hg) and high secondary PHT for length of mechanical ventilation, intensive care length of stay or survival measured at 1, 2 and 4 years.

Omari and colleagues (Omari, Smith et al. 2011) retrospectively reviewed 40 lung transplant patients for a range of indications (including COPD 60% and pulmonary fibrosis 23%) to determine the effect of preoperative PHT (mPAP > 25 mm Hg on right heart catheterisation or RVSP > 35 mm Hg on echocardiogram) on transplant outcome. Whilst preoperative secondary PHT was associated with earlier onset acute rejection (65 days v 81 days), reduced 3-year survival (77% v 100%) and reduced 5-year survival (67% v 77%), these did not reach statistical significance.

1.2.8 Unresolved Questions

The clinical impact of preoperative PHT on lung transplantation outcomes has not been clearly established. In particular, no analysis has specifically addressed the short-term impact of preoperative PHT in lung transplant patients with COPD. Consequently, in Chapter 2 we explore the significance of preoperative PHT on intensive care outcomes following lung transplantation for COPD.

1.3 Pulmonary Arterial Remodelling in COPD

1.3.1 Overview of the Pulmonary Vasculature and Remodelling

The pulmonary vasculature is normally a low pressure, low resistance, high capacity circuit (Travis, Colby et al. 2002). Unlike the systemic circulation where the arterioles provide the resistance (Ham 1974), it is reported that the small muscular pulmonary arteries provide the resistance of the pulmonary circulation (Barnes and Liu 1995). There are, however, no absolute vessel features that distinguish between pulmonary arterioles, muscular pulmonary arteries and elastic pulmonary arteries (Gallagher 1997). Furthermore, structural changes can occur with aging and disease that makes differentiating these vessels more complicated.

Pulmonary arteries mostly travel and branch alongside the bronchial tree (Reid 1968, Mercer and Crapo 1998). Elastic pulmonary arteries have multiple elastic lamellae in their media, a well-defined internal and external elastic lamina and are larger than 0.50 mm diameter (Gallagher 1997, Travis, Colby et al. 2002). There is a gradual transition from elastic pulmonary arteries to muscular pulmonary arteries (Reid 1968). Muscular pulmonary arteries have a relatively thin wall with a muscular media and they often have clearly discernible internal and external elastic lamina. Muscular pulmonary arteries are generally 0.10 – 0.50 mm diameter. Pulmonary arterioles are less than 0.08 – 0.10 mm diameter, normally have no media and the wall comprises a single elastic layer (Wilkinson, Langhorne et al. 1988, Gallagher 1997, Albertine, Williams et al. 2000, Travis, Colby et al. 2002). Arterioles track with the respiratory bronchioles and eventually give rise to the capillary network responsible for gas exchange (Mercer and Crapo 1998, Albertine, Williams et al. 2000).

The capillaries drain into the pulmonary venules and then the pulmonary veins. In contrast to the pulmonary arterial circulation, the pulmonary venous system does not run with the bronchial tree but along the connective tissue planes of the sublobular and lobular septa (Mercer and Crapo 1998). Pulmonary venules and arterioles have similar

wall morphology (Overbeek, Vonk et al. 2009). The walls of pulmonary veins are less well structured than their arterial counterparts, containing smooth muscle, collagen and elastin. Pulmonary veins also lack clear and continuous elastic lamellae (Gallagher 1997).

A range of structural changes to the pulmonary vascular bed have been observed with "normal" aging and disease. More complex changes have been observed in patients with PAH. Pulmonary arterial remodelling is an umbrella term that encapsulates an array of vascular changes. In PAH, these vascular changes include medial hypertrophy, adventitial thickening, intimal hyperplasia, collagen and elastin deposition, muscularisation of the pulmonary arterioles, dilation lesions, plexiform lesions, and vasculitis with fibrinoid necrosis (Heath and Edwards 1958, Botney 1999, Farber and Loscalzo 2004). The remodelling process appears to begin in the small muscular pulmonary arteries (Heath and Edwards 1958, Travis, Colby et al. 2002) and progress proximally to involve the larger pulmonary arteries and also distally in the form of muscularisation of the arterioles (Scharf 1998).

In 1958, Heath and Edwards (Heath and Edwards 1958) developed a grading system for the severity of PAH, based on descriptive histologic findings. However, as much of the remodelling processes affect vascular wall thickness, it has become common to measure pulmonary arterial remodelling quantitatively as a ratio of intima and/or medial wall thickness to vessel diameter (Reid 1968, Shelton, Keal et al. 1977, Warnock and Kunzmann 1977a, Hale, Niewoehner et al. 1980, Hale, Ewing et al. 1984, Fernie and Lamb 1988, Wilkinson, Langhorne et al. 1988, Kubo, Ge et al. 2000).

1.3.2 Subjects without Cardiac or Respiratory Disease

Several early studies with relatively small sample sizes have explored the vascular wall changes in autopsy patients free from cardiac or respiratory disease. These studies attempted to find the effects of aging, lobar origin and pulmonary arterial size upon pulmonary arterial remodelling.

Simons and Reid (Simons and Reid 1969) compared the medial wall thickness of 5 young (ages 19-35 years) and 6 older (ages 67 – 76 years) autopsy subjects who had died from non cardiac or respiratory causes. In pulmonary arteries 0.085 to 0.2 mm diameter, they demonstrated increased overall medial wall thickness in the older subjects compared with the younger subjects (mean ± SD: 6.6% ± 2.3% versus 4.8% ± 1.3%, respectively).

Similarly, Warnock and Kunzmann (Warnock and Kunzmann 1977a) compared medial wall thickness amongst 10 autopsy subjects (age 3 – 79 years) who had died with no history of chronic lung disease. They assessed pulmonary arteries less than 0.2 mm diameter and demonstrated increased medial wall thickness in the older subjects (aged > 35 years) than the younger group (2.9% v 1.8%, $P < 0.005$, respectively).

In contrast, Fernie and Lamb (Fernie and Lamb 1988) assessed 23 autopsies (subjects aged 19 – 81 years) without cardiac or pulmonary disease and found no overall relationship between medial wall area and age amongst either the 12 non-smokers or the 11 smokers. There was also no difference in medial wall area overall between the non-smokers and the smokers.

Scant data is available but no differences have been identified in medial wall thickness between upper and lower lobe pulmonary arteries in autopsy patients without cardiac or respiratory disease (Simons and Reid 1969, Warnock and Kunzmann 1977a, Fernie and Lamb 1988). In contrast, Heath and Best (Heath and Best 1958) examined 13 controls and identified increased percentage medal wall thickness in small muscular pulmonary arteries (0.10 – 0.30 mm in diameter) from the lingula than either the upper or lower lobes.

There has been a fairly consistent finding from several studies of relatively increased remodelling (measured as wall thickness) in the smaller muscular pulmonary arteries in autopsy subjects without cardiac or respiratory disease (Reid 1968, Simons and Reid 1969, Semmens 1970, Warnock and Kunzmann 1977a). Similarly, Heath and Edwards (Heath and Edwards 1958) describe the early histologic changes of PAH occurring in muscular pulmonary arteries < 0.30 mm in diameter and in arterioles.

1.3.3 Subjects with Pulmonary Arterial Hypertension

Although PAH is defined as a mean pulmonary arterial pressure ≥ 25 mm Hg at rest (Badesch, Champion et al. 2009), the pathological hallmark is an increased PVR. This increase in PVR occurs via a combination of pulmonary arterial vasoconstriction, pulmonary arterial remodelling and in-situ thrombosis (Humbert, Sitbon et al. 2004).

Pathological changes to the pulmonary vasculature had long been recognised in patients with PAH but Heath and Edwards (Heath and Edwards 1958) described a pivotal qualitative 6-graded scale (*see* Table 7) of the histologic features in 67 cases of congenital septal defects and 2 patients with iPAH. This scale employed qualitative descriptions of the small pulmonary arteries to grade the histological severity of PHT. In a parallel paper, Heath and Best (Heath and Best 1958) quantified the percentage medial wall thickness relative to the diameter of the external elastic lamina in 13 controls and 8 patients with PHT of various aetiologies. Subsequent studies have provided a range of qualitative and quantitative descriptions of the pulmonary vasculopathy in various forms of PAH.

Table 7 Pathological grade of structural change in congenital cardiac septal defects
Adapted from (Heath and Edwards 1958).

Grade 1	The stage of retention of foetal-type pulmonary vessels
Grade 2	Stage of medial hypertrophy with cellular intimal reaction
Grade 3	Stage of progressive fibrous vascular occlusion
Grade 4	The cavernous lesion
Grade 5	Stage of chronic dilatation with formulation of numerous dilatation lesions and pulmonary hemosiderosis
Grade 6	Stage of necrotizing arteritis

Pietra and colleagues (Pietra, Edwards et al. 1989) performed histologic analysis on 58 subjects (49 with pulmonary arteriopathy, 7 with pulmonary veno-occlusive disease and 2 with uncertain pathology) and demonstrated medial hypertrophy in all 49 cases of pulmonary arteriopathy. They also demonstrated intimal or luminal lesions in 48 of these 49 cases. Amongst 26 patients with pulmonary arteriopathy on whom quantitative

measures of intimal and medial wall thickness were obtained, there was no significant difference between patients with plexiform lesions versus those with thrombotic lesions.

Chazova and colleagues (Chazova, Loyd et al. 1995) demonstrated marked increase in intimal, medial and adventitial thickness amongst 19 patients with primary pulmonary hypertension (17 autopsies and 2 explants) compared with 7 autopsy controls. They also demonstrated increased percentage intimal wall thickness in the smaller muscular pulmonary arteries (0.10 – 0.20 mm diameter) compared with the larger muscular pulmonary arteries (0.50 – 1.0 mm in diameter, P not provided). In contrast, percentage medial wall thickness was slightly increased in the larger muscular pulmonary arteries than the smaller muscular pulmonary arteries (P not provided).

Yi and colleagues (Yi, Kim et al. 2000) examined pulmonary arteriopathy in 51 patients with moderate-to-severe chronic PHT (15 with primary pulmonary hypertension, 8 with Eisenmenger's syndrome, 22 with chronic thromboembolic disease, 3 with pulmonary veno-occlusive disease, 3 other). Percentage intimal thickening in primary pulmonary hypertension was most prominent in the small muscular pulmonary arteries and arterioles (0.05 – 0.20 mm diameter) but was also increased in muscular pulmonary arteries 0.20 – 0.40 mm diameter, compared with controls ($P < 0.05$). Percentage medial wall thickness was increased in the primary pulmonary hypertension group only in arteries 0.10 – 0.60 mm diameter compared with controls ($P < 0.05$). In contrast, patients with chronic thromboembolic disease demonstrated increased percentage intimal wall thickness in pulmonary arteries 0.05 – 0.60 mm diameter compared with controls ($P < 0.05$) but there was no significant increase in percentage medial wall thickness in this group in any pulmonary arterial size range.

Overbeek and colleagues (Overbeek, Vonk et al. 2009) compared qualitative pulmonary vasculopathy in autopsies and explanted lungs amongst 8 patients with systemic sclerosis-associated PAH and 11 patients with iPAH. They demonstrated intimal fibrosis in the small pulmonary arteries and arterioles in all patients with systemic sclerosis but in only 3 patients with iPAH. Furthermore, 4 of 8 patients with systemic sclerosis had a pattern of pulmonary veno-occlusive disease. No patients with systemic sclerosis had plexiform lesions, whereas 10 of 11 iPAH patients demonstrated plexiform lesions.

Harch and colleagues (Harch, Whitford et al. 2009) performed qualitative and quantitative pulmonary vascular morphology amongst 14 PAH patients that had failed medical therapy and showed that this group mostly consisted of patients with pulmonary veno-occlusive disease (12 out of 14). Patients with "arterial-only" PAH had greater remodelling in the muscular pulmonary arteries and arterioles whereas patients with pulmonary veno-occlusive disease had greater remodelling in the intra-acinar vessels, pulmonary venules and pulmonary veins.

Finally, Stacher and colleagues (Stacher, Graham et al. 2012) evaluated explanted lungs from 62 patients with PAH (48 with "iPAH-like pattern", 12 with "collagen vascular disease-associated PAH-like pattern" and 2 with "pulmonary veno-occlusive disease-like pattern") who had been treated with selective pulmonary vasodilators and 28 controls. They demonstrated increased percentage medial wall thickness in patients with PAH compared to 22 controls without vascular remodelling ($P < 0.001$) but not compared to the 6 controls with evidence of vascular remodelling. In contrast, PAH patients had increased percentage intimal wall thickness compared to both the 22 controls without vascular remodelling ($P < 0.001$) and the 6 controls with vascular remodelling ($P < 0.001$). Percentage adventitial thickness was not different between PAH patients and controls. Plexiform lesions were found in 90% (56/62) of PAH patients and female patients had 2.8-fold higher number of plexiform lesions than males. Thrombi were present in 50% (31/62) of PAH patients of which 13 patients were receiving anticoagulation. In contrast to earlier studies with non-PAH patients, there was a negative correlation between percentage wall thickness and age amongst patients with PAH.

Stacher and colleagues also compared remodelling with pulmonary haemodynamic assessment and demonstrated only a trend between percentage wall (intima plus media) thickness to mPAP ($r = 0.235$, $P = 0.066$) and to PVR ($r = 0.247$, $P = 0.057$). Nevertheless, percentage medial wall thickness was significantly correlated to both mPAP ($r = 0.267$, $P = 0.036$) and to PVR ($r = 0.258$, $P = 0.047$). There was no significant correlation between percentage medial wall thickness and percentage intimal thickness.

1.3.4 Subjects with Chronic Obstructive Pulmonary Disease

PHT is relatively common in moderate and severe COPD. In addition, pulmonary arterial remodelling and endothelial dysfunction have been demonstrated to occur in patients with COPD (Peinado, Barbera et al. 1998). Whilst pulmonary arterial remodelling is characteristic of PAH (Hassoun, Mouthon et al. 2009), the role of pulmonary arterial remodelling in COPD-associated PHT is less well defined. This is due to several reasons including (i) the difficulty in determining the natural progression of pulmonary arterial remodelling, (ii) the inter-subject and intra-subject variability of pulmonary arterial changes, (iii) the confounder of reciprocal causation, (iv) the difficulty in obtaining specimens for analysis, and (v) the inability to accurately assess pulmonary arterial pressure using non-invasive techniques.

A number of previous studies have investigated pulmonary vasculopathy in patients with COPD. Unfortunately, many of these studies are hampered by small sample size. Furthermore, the heterogeneity of methodological options (see Table 8 and Table 9) employed in the literature makes pooling of data problematic. Table 10 provides a summary of findings from studies assessing pulmonary arterial remodelling in smokers and patients with COPD.

Table 8 Methodological Variables in Quantifying Pulmonary Vascular Remodelling

Methodological Variable	**Option**
Sampling methodology (and patient selection)	Biopsy specimen Lobar / wedge resections Explanted lung Autopsy
Specimen preparation	Injected / non-injected pulmonary artery Inflated or uninflated lung
Tissue stain	Variable
Vessel selection	Type of vessel: Elastic pulmonary arteries Muscular pulmonary arteries Arterioles Pulmonary venules Pulmonary veins Size of vessel: Highly variable
Remodelling measurement	Type of measure Width or area Average or maximal Measured directly or derived Absolute or percentage of vessel size Component of vessel wall Intima only Media only Total wall (intima plus media) Adventitia Included or not included
Statistical methods	Simple mean Weighted mean Repeated measures analysis

Table 9 Summary of Methodologies from Studies Assessing Pulmonary Arterial Remodelling in Smokers and Patients with COPD

Publication	Subjects Selection	Sampling Methodology	Specimen Preparation	Tissue Stain	Vessel Selection	Remodelling Measurement
(Shelton, Keal et al. 1977)	15 COPD patients v 6 controls	Autopsy	Inflated and injected	Not described	MPA with EEL diameter < 1.0mm and pulmonary veins with diameter < 0.90mm	• (Media x 2) / EEL Adventitia not included
(Warnock and Kunzmann 1977b)	11 symptomatic COPD v 5 asymptomatic emphysema	Autopsy; Upper and lower lobes	Inflated and injected	H & E, Wiegert elastic with Van Geison counterstain	MPA with EEL diameter: < 0.20mm, 0.20 - 0.30mm, 0.30 - 2.0mm	• (Media x 2) / EEL • (WT x 2) / EEL EEL taken as narrowest diameter; Adventitia not included
(Hale, Niewoehner et al. 1980)	25 smokers (with sudden death) v 14 non-smokers	Autopsy; All lobes sampled	Inflated and non-injected	Lawson modification of the Weigert stain	MPA with EEL diameter < 0.50mm	• (Media x 2) / EEL • (Intima x 2) / EEL EEL taken as shorter diameter; Adventitia not included
(Hale, Ewing et al. 1984)	18 COPD v 25 smokers v 14 non-smokers	Autopsy; All lobes sampled	Inflated and non-injected	Lawson modification of the Weigert stain	MPA with EEL diameter < 0.50mm	• (Media x 2) / EEL • (Intima x 2) / EEL EEL taken as shorter diameter; Adventitia not included

Table 9 (cont…)

Publication	Subjects Selection	Sampling Methodology	Specimen Preparation	Tissue Stain	Vessel Selection	Remodelling Measurement
(Fernie and Lamb 1988)	11 smokers v 12 non-smokers, all without heart-lung disease	Autopsy; Upper and lower lobes	Inflated and non-injected	Weigert elastic with Van Geison counterstain	MPA with length of IEL < 1.5 mm	• √(Medial area) Adventitia not included
(Wilkinson, Langhorne et al. 1988)	10 subjects who died from hypoxic cor pulmonale	Autopsy; 2 lobes sampled (most and least severe)	Non-injected	H & E, Miller's elastic with Van Geison counterstain	MPA with EEL diameter 0.10 - 0.50mm and arterioles < 0.08 mm diameter	• Total tissue area • Intima area / TTA • Media area / TTA • (Average media) / EEL; Adventitia not included
(Magee, Wright et al. 1988)	8 severe COPD with PHT v 14 mild-moderate COPD without PHT v 7 controls	Lobectomy, pneumo-nectomy or autopsy.	Inflated and non-injected	Verhoeff elastic stain	MPA with adventitial diameter: < 0.4 mm, 0.40-0.80mm, 0.80-1.2mm	• Total tissue area • Intima area / TTA • Media area / TTA • Adventitial area / TTA Diameter perpendicular to long diameter (Adventitia included)
(Wright, Petty et al. 1992)	29 with severe COPD stratified by mPAP v 5 controls	Autopsy	Inflated and non-injected	Humberstone's elastic stain	MPA with EEL diameter < 0.50mm	• Total tissue area • Intima area / TTA • Media area / TTA Adventitia included

Table 9 (cont…)

Publication	Subjects Selection	Sampling Methodology	Specimen Preparation	Tissue Stain	Vessel Selection	Remodelling Measurement
(Barbera, Riverola et al. 1994)	9 mild COPD with low O_2 response v 11 mild COPD with high O_2 response v 5 controls	Lobectomy or pneumo-nectomy for neoplasm	Inflated and non-injected	Elastic orcein stain	MPA with EEL diameter < 1.5mm	• Wall thickness • Media area / TTA • Intima area / TTA Diameter inferred from EEL circumference (Adventitia not included)
(Kubo, Ge et al. 2000)	10 subjects with severe COPD v 5 controls	Lobectomy for neoplasm or LVRS specimen	Non-inflated and non-injected	H & E with van Gieson elastic stain	MPA with EEL diameter 0.10 – 0.20mm	• (WT x 2) / EEL • (Media x 2) / EEL • (Intima x 2) / EEL • Adventitial thickness EEL taken as mean of 2 perpendicular measures (Adventitia included)

Injected = pulmonary artery injection prior to fixation for histologic assessment

Inflated = bronchial injection with air or fluid prior to fixation for histologic assessment

EEL, external elastic lamina; H & E, haematoxylin and eosin; MPA, muscular pulmonary artery; TTA, total tissue area; WT, wall thickness (media + intima)

Table 10 Summary of Findings in Studies Assessing Quantitative Muscular Pulmonary Arterial Remodelling in Smokers and Patients with COPD

Publication	Summary of Findings
(Shelton, Keal et al. 1977)	Increased percentage medial wall thickness in COPD with right ventricular hypertrophy (RVH) compared with COPD without RVH ($P < 0.02$) and controls ($P < 0.001$) for muscular pulmonary arteries less than 0.25 mm in diameter. COPD without RVH also demonstrated increased percentage medial wall thickness compared with controls. There was increased percentage medial wall thickness amongst the smaller vessels for both pulmonary arteries and pulmonary veins compared with larger vessels. There was no difference in remodelling between the upper and lower lobes for both pulmonary arteries and pulmonary veins.
(Warnock and Kunzmann 1977b)	Increased percentage medial wall thickness in COPD patients compared with asymptomatic emphysema controls ($4.5 \pm 1.44\%$ v $2.8 \pm 0.4\%$, respectively, $P < 0.01$). There was no significant difference in the percentage overall wall thickness in COPD compared with controls ($6.2 \pm 1.79\%$ v $5.4 \pm 1.0\%$, respectively).
(Hale, Niewoehner et al. 1980)	Increased percentage medial wall and intimal wall thickness in smokers compared with controls ($P < 0.02$ and $P < 0.04$, respectively). Remodelling correlated with severity of small airway disease and the degree of emphysema. Increased percentage intimal wall thickness in the upper lobes compared with the lower lobes in both smokers and controls ($P < 0.005$) but no difference in percentage medial wall thickness. Tendency for less remodelling in the smaller muscular pulmonary arteries.
(Hale, Ewing et al. 1984)	Increased percentage medial wall thickness and percentage intimal wall thickness in COPD compared with both smokers and non-smokers. Features of remodelling were most strongly correlated with emphysema severity and percentage of bronchioles less than 0.40 mm.

Table 10 (Cont…)

Publication	**Summary of Findings**
(Fernie and Lamb 1988)	No significant effect of age or smoking status upon medial wall area. The "predicted" percentage medial wall area in arteries with internal elastic lamina of 0.50 mm was correlated with the absolute weight of the right ventricle ($P < 0.05$).
(Wilkinson, Langhorne et al. 1988)	Considerable variability of percentage medial wall thickness and intimal wall thickness ranging from 0 - 9.4% and 0.9 - 9.4%, respectively. Remodelling did not differ between mildly or severely emphysematous areas. Similarly, there was no difference in remodelling in any subject from samples taken from different lungs or lobes. Percentage medial wall thickness was significantly correlated with percentage intimal wall thickness ($r = -0.36$, $P < 0.001$), mPAP ($r = 0.73$, $P < 0.02$) and FEV_1 ($r = -0.73$, $P < 0.03$). Nine of 10 cases demonstrated remodelling of pulmonary arterioles.
(Magee, Wright et al. 1988)	No overall difference in total tissue area of muscular pulmonary arteries amongst COPD with resting PHT, COPD without resting PHT and non-smoking controls. The percentage medial wall thickness and intimal wall thickness did not differ across muscular pulmonary artery size. There was reduced percentage medial wall thickening in COPD without PHT compared with non-smoking controls across all muscular pulmonary arteries. There was increased percentage medial wall thickness in COPD with PHT compared with non-smoking controls in larger muscular pulmonary arteries only ($P < 0.05$). There was increased percentage intimal wall thickness in COPD with and without PHT compared with controls.

Table 10 (Cont…)

Publication	**Summary of Findings**
(Wright, Petty et al. 1992)	No overall difference in total tissue area of muscular pulmonary arteries amongst COPD and controls. Increased percentage intimal wall thickness in all COPD compared with controls for medium and large muscular pulmonary arteries, but only amongst COPD with PHT in the small muscular pulmonary arteries. Increased percentage medial wall thickness in COPD compared with controls for large muscular pulmonary arteries, but only amongst COPD with PHT for the medium sized muscular pulmonary arteries. There were no significant differences in remodelling in COPD patients according to either PHT severity or response to oxygen administration.
(Barbera, Riverola et al. 1994)	Increased muscular pulmonary arterial wall thickness and reduced percentage of luminal to total tissue area was present in COPD group compared with controls. Increased percentage intimal area accounted for the difference in wall thickness between COPD and controls. Additionally, increased percentage intimal area was present in COPD with reduced oxygen response compared with COPD with high oxygen response only for arteries 0.145 - 0.470 mm in diameter. Percentage intimal area correlated with PaO_2, FEV_1 % predicted, emphysema score, V/Q inequality and inflammation score.
(Kubo, Ge et al. 2000)	Increased percentage wall thickness, percentage intimal thickness and adventitial thickness in COPD compared with controls ($P < 0.05$). Percentage wall thickness was significantly correlated with mPAP during exercise ($r = 0.721$, $P = 0.02$) and delta mPAP with exercise ($r = 0.899$, $P = 0.0004$) but not resting mPAP ($r = -0.378$, P = ns). Percentage wall thickness was not significantly correlated with other pulmonary haemodynamic measurements or pulmonary function tests.

More recently, Carlsen and colleagues (Carlsen, Hasseriis Andersen et al. 2013) investigated pulmonary arterial lesions in explanted lungs from 70 COPD patients and 18 controls with idiopathic PAH. In this study, pulmonary vascular lesions were graded using a modified form of the qualitative Heath and Edwards (Heath and Edwards 1958) scale discussed above. The authors concluded that severe PH-COPD (defined as mPAP $\geq$ 35mmHg) was associated with more advanced increased pulmonary vascular lesions compared with mild-moderate PH-COPD ($P < 0.011$) and non-PH-COPD ($P < 0.0001$). Whilst the strength of this studies lies in the relatively large number of patients sampled and the use of invasive pulmonary haemodynamic assessment (which was performed at the time of lung transplant assessment), the study is limited in that the histological assessment uses an ordinal classification based on the highest degree of pathological change observed.

1.3.5 Unresolved Questions

Despite the aforementioned studies, there is scant data regarding the lobar heterogeneity of pulmonary arterial remodelling in COPD. Furthermore, the relationship between PHT and remodelling has not been clearly established. Finally, the influence of regional emphysema severity and regional pulmonary perfusion upon pulmonary arterial remodelling has not previously been investigated in COPD. Chapter 3 investigates pulmonary arterial remodelling in explanted lungs from COPD patients with a particular focus on lobar heterogeneity and the effects of regional emphysema and perfusion upon the remodelling process.

1.4 Mechanical Lung-Heart Interactions

The respiratory and cardiovascular systems have many functions but they work together primarily for the purpose of taking oxygen from the atmosphere and delivering it throughout the body, whilst taking carbon dioxide from the body and expelling into the atmosphere. In order to achieve these aims, these systems interact at the humoral, neurological and mechanical level (Scharf, Pinsky et al. 2001).

The pulmonary circulation is a high flow, low resistance, low pressure system. It usually has very low resting pulmonary vascular tone and is under control by both active and passive factors (Barnes and Liu 1995). Active factors influence pulmonary vascular smooth muscle and are mediated by the autonomic nervous system, humoral mechanisms, endothelial function, PaO_2 and pH levels. In contrast, passive factors include right ventricular cardiac output, left atrial pressure, intrathoracic pressures and gravity.

The mechanical consequences of respiration upon the pulmonary circulation are complex, mediated through direct and indirect pressure and lung volume effects (Luecke and Pelosi 2005, Pinsky 2005). The respiratory effects upon pulmonary haemodynamics are further complicated by ventricular interdependence (Pinsky 2007).

Whilst cardiopulmonary interactions have been investigated for many decades, there are some peculiarities in COPD that may interfere with this normal physiology. In particular, mechanical derangements of the lung in COPD may affect the pulmonary circulation. For example, it has been postulated that gas trapping in pulmonary hyperinflation may contribute to PHT in patients with COPD (Wright, Lawson et al. 1983, Naeije and Barbera 2001, Scharf, Iqbal et al. 2002, Thabut, Dauriat et al. 2005, Elwing and Panos 2008, Weitzenblum and Chaouat 2009). However, there is limited direct evidence to support this.

The following sections will review the pulmonary mechanic derangements that occur in COPD and how this affects pulmonary haemodynamics.

1.4.1 Mechanical Lung Changes in COPD

Pathogenesis and Definitions

Patients with advanced COPD are prone to developing dynamic lung hyperinflation, gas trapping and $PEEP_I$. Whilst these notions are related and principally occur due to similar mechanisms, they refer to different concepts. Unfortunately, these terms have become further confused due to a variety of definitions employed to describe them and related lung volumes (Leith and Brown 1999).

Hence it is necessary to clarify these terms in the setting of COPD. FRC refers to the lung volume at end-expiration during tidal breathing. The lung volume of the relaxed respiratory system (V_r), occurs when the elastic recoil pressure of the lungs is equally opposed by the expanding pressure of the chest wall. In normal subjects during quiet breathing, FRC closely approximates V_r (Brusasco and Fitting 1996, Gibson 1996, Leith and Brown 1999).

In COPD, V_r is increased to V_r' due to loss of elastic recoil of the lungs and FRC is similarly increased to FRC′. This increase in FRC is termed static lung hyperinflation. Static lung hyperinflation develops slowly over time and is present in some patients with obstructive airway disease. It must be noted that static lung hyperinflation refers to an increased FRC and V_r which in isolation, is not associated with gas trapping or $PEEP_I$. Hence, in COPD subjects with static lung hyperinflation, FRC′ and V_r' will be greater than in normal subjects, even with an infinite period of exhalation.

If expiration is incomplete due to insufficient expiratory time and/or proximal airway closure, then FRC exceeds V_r and this is termed dynamic lung hyperinflation (O'Donnell and Laveneziana 2006). For clarification, the increase in FRC due to dynamic lung hyperinflation is termed FRC_{DH}. If progressive dynamic lung hyperinflation occurs, whereby each breath is associated with further gas trapping, then breath stacking will occur (Stather and Stewart 2005). This will result in an increase in end-expiratory lung volume and a reduction in inspiratory capacity with each breath, ultimately resulting in respiratory failure and systemic hypotension if not immediately

remedied. Figure 4 illustrates the changing lung volume during tidal breathing followed by a prolonged expiration in healthy subjects, subjects with static hyperinflation, subjects with dynamic hyperinflation and subjects with breath stacking.

Dynamic lung hyperinflation may occur at rest in stable patients with advanced obstructive lung disease, termed chronic dynamic hyperinflation. By comparison, acute dynamic lung hyperinflation occurs during acute periods of insufficient expiratory time and/or proximal airway closure. Whilst it is acknowledged that many authors do not distinguish between acute and chronic dynamic hyperinflation, this distinction helps to acknowledge that dynamic lung hyperinflation may occur at rest. Figure 5 highlights the differences between the various forms of hyperinflation.

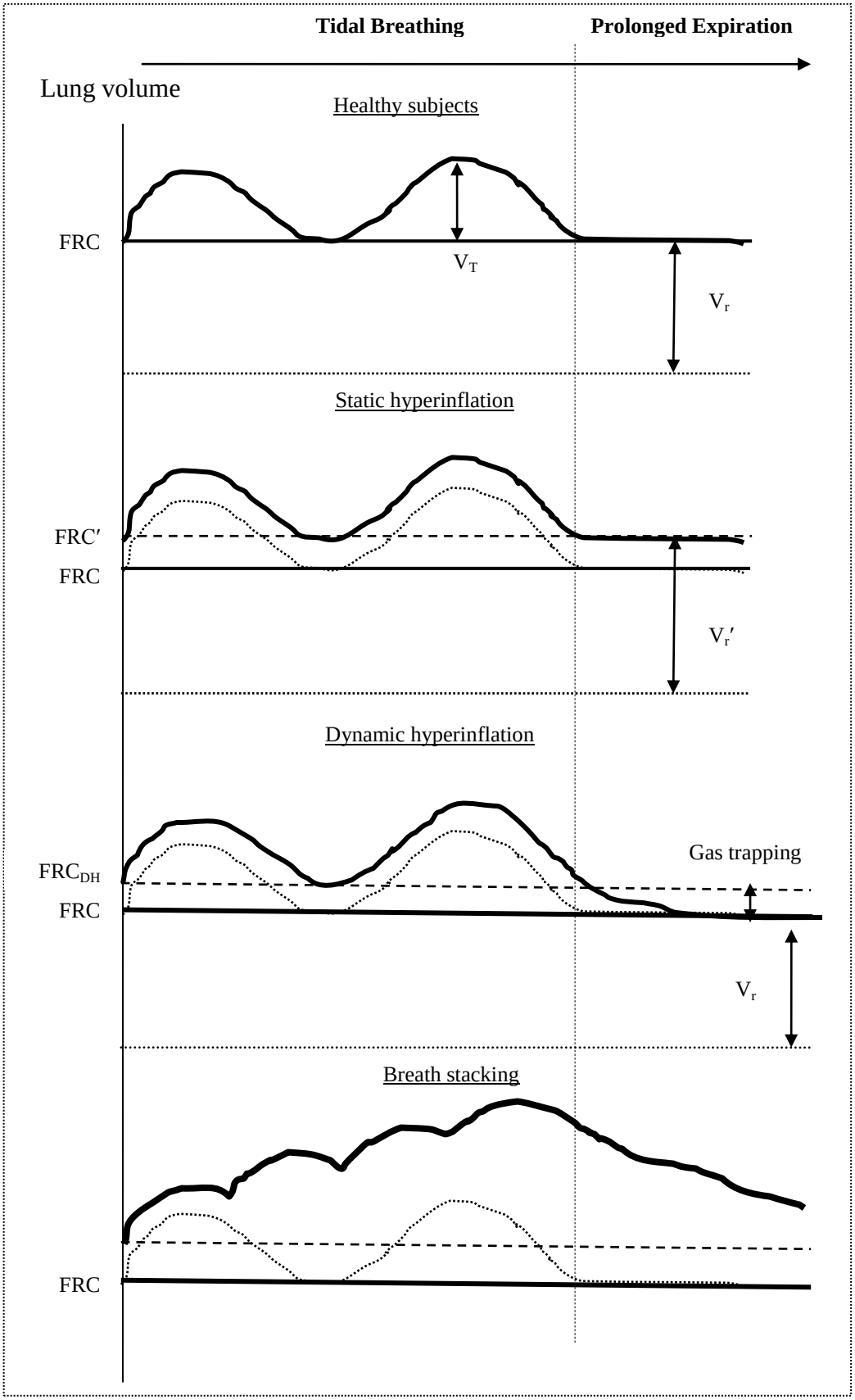

Figure 4
Functional residual capacity and relaxation lung volume. Graphical representation of tidal breathing followed by a prolonged expiration in healthy subjects, subjects with static hyperinflation, dynamic hyperinflation and breath

stacking. At end-expiration, healthy subjects reach V_r that is similar to FRC. In static lung hyperinflation, FRC increases to FRC′ and V_r increases to V_r'. At end-expiration, FRC′ approximates V_r'. In dynamic lung hyperinflation, FRC increases to FRC_{DH} and V_r is less than FRC_{DH}. With prolonged expiration, FRC_{DH} approaches V_r. FRC_{DH} less V_r is a measure of gas trapping.
FRC, functional residual capacity in healthy subjects; FRC′, functional residual capacity in static hyperinflation; FRC_{DH}, functional residual capacity in dynamic hyperinflation; V_r, volume at relaxation; V_r', volume at relaxation in static hyperinflation; V_T, tidal volume; dotted line represents healthy subjects.

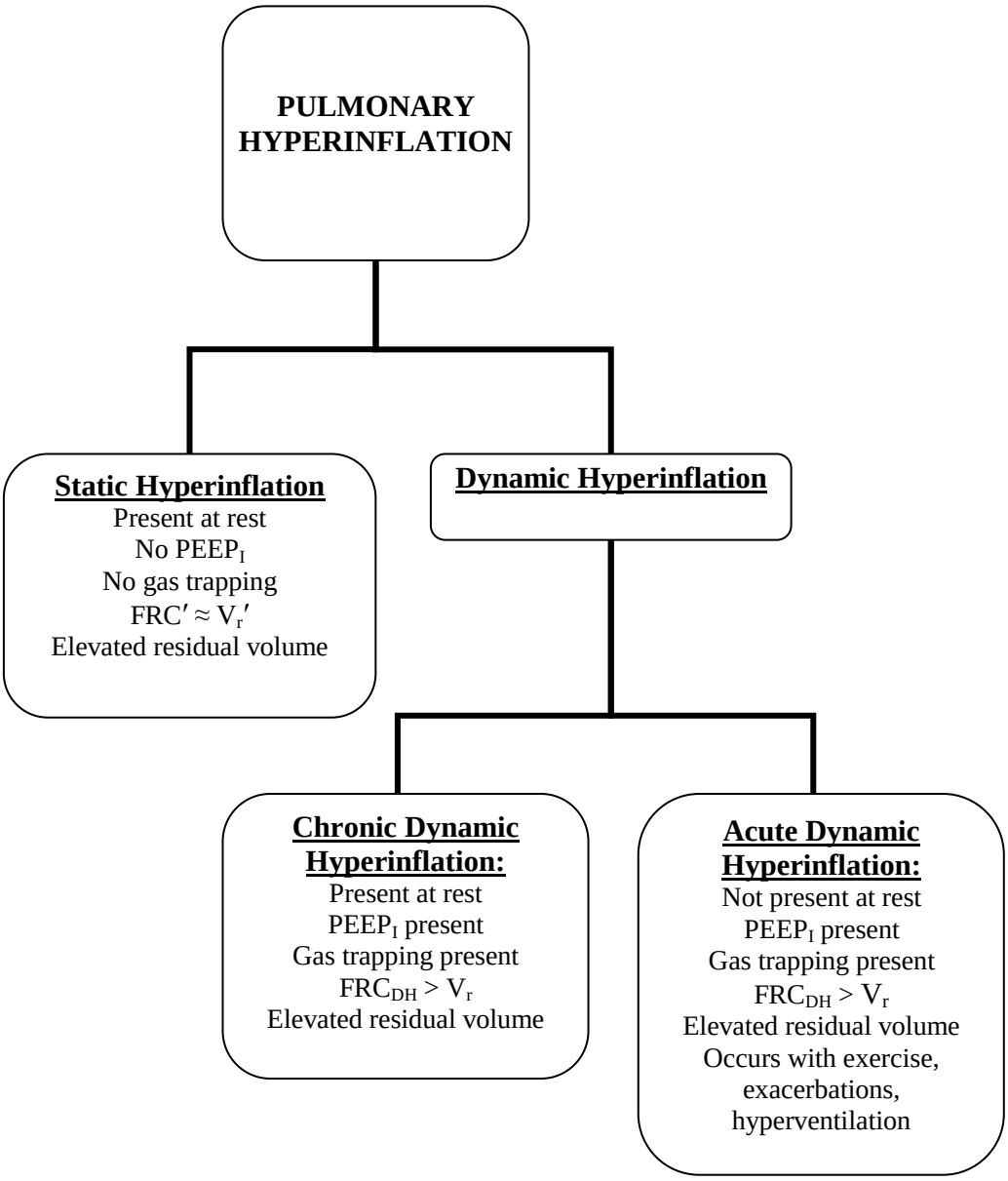

Figure 5
Static hyperinflation, chronic dynamic hyperinflation and acute dynamic hyperinflation. In both chronic and acute dynamic hyperinflation, FRC_{DH} exceeds V_r and this volume difference is a measure of gas trapping. Unfortunately, definitions are not universally applied and some authors use the term gas trapping or air trapping to denote the increase in residual volume associated with lung hyperinflation (Gibson 1996). However, residual volume may be increased due to factors other than gas trapping, for example static hyperinflation or neuromuscular disease.

Intrinsic positive end-expiratory pressure ($PEEP_I$)

The gas trapped at end-expiration creates a positive pressure within the lungs, referred to as $PEEP_I$ (or auto-PEEP) (Pepe and Marini 1982, Milic-Emili 1990, Gibson 1996, Blanch, Bernabe et al. 2005, Stather and Stewart 2005). In contrast, extrinsic positive-end expiratory pressure ($PEEP_E$) is applied at the airway opening. Static $PEEP_I$ is measured during mechanical ventilation by occluding the airway at end-expiration and determining the plateau pressure at the airway opening (which reflects alveolar pressure after adjustments for the heterogenic volume and pressure differences within the lung) (Haluszka, Chartrand et al. 1990, Ranieri, Mascia et al. 1995). Measures of static $PEEP_I$ assume that the alveoli are in communication with the proximal airway. If the airways are not in communication, static $PEEP_I$ measures will underestimate the magnitude of $PEEP_I$. In contrast, dynamic $PEEP_I$ is determined by measuring the change in oesophageal pressure in spontaneously breathing patients from the onset of an inspiratory effort to the commencement of inspiratory flow. Dynamic $PEEP_I$ measurements tend to be lower than static $PEEP_I$ as they reflect the lowest level of regional $PEEP_I$ sufficient to allow inspiration (Haluszka, Chartrand et al. 1990, Blanch, Bernabe et al. 2005). Static and dynamic $PEEP_I$ do not reflect static and dynamic hyperinflation respectively. Table 11 provides a brief glossary of relevant terms.

Table 11 Definitions of Commonly Used Terms*

Term	Definition
Acute dynamic hyperinflation	Dynamic hyperinflation that occurs during periods of reduced expiratory time and/or increased airway resistance.
Chronic dynamic hyperinflation	Dynamic hyperinflation that occurs at rest, in stable patients during tidal breathing.
Dynamic lung hyperinflation	The increase in FRC that results from insufficient expiratory time and/or elevated airway resistance. It may be classified as either acute or chronic.

Table 11 (Cont…)

Dynamic $PEEP_I$	A measure of $PEEP_I$ during spontaneous ventilation by measuring the change in oesophageal pressure from the onset of the inspiratory effort to the commencement of inspiratory flow.
Functional residual capacity (FRC)	The volume of the lungs at the end of expiration during tidal breathing. FRC′ is the FRC in patients with static hyperinflation. FRC_{DH} is the FRC in patients with dynamic hyperinflation.
Gas trapping	The volume of gas trapped during dynamic hyperinflation, defined by the difference $FRC_{DH} - V_r$.
Intrinsic positive end-expiratory pressure ($PEEP_I$)	The pressure that develops within the distal airways due to gas trapping during dynamic hyperinflation.
Relaxation volume (V_r)	The lung volume of the relaxed respiratory system when the elastic recoil pressure of the lungs equally opposes the expanding pressure of the chest wall. V_r' is the V_r in patients with static hyperinflation.
Static lung hyperinflation	The increase in FRC that results from reduced elastic recoil pressure of the lungs.
Static $PEEP_I$	A measure of $PEEP_I$ during mechanical ventilation by occluding the airway at end-expiration and determining the plateau pressure at the airway opening

* There is debate regarding the above definitions. Nevertheless, these definitions provide a working and consistent basis for this thesis.

Prevalence of Pulmonary Hyperinflation in COPD

There are difficulties in measuring chronic dynamic hyperinflation directly. Measures of inspiratory capacity or FRC do not distinguish between static hyperinflation, acute dynamic hyperinflation or chronic dynamic hyperinflation. Serial inspiratory capacity

measures may be used to assess acute dynamic hyperinflation or changes in chronic dynamic hyperinflation over time but are not a suitable method for measuring chronic dynamic hyperinflation at a static time-point. In order to distinguish static hyperinflation from chronic dynamic hyperinflation, it is necessary to measure either $PEEP_I$ and/or volume of gas trapped.

Despite several studies attempting to determine the prevalence and severity of $PEEP_I$ in respiratory patients, small sample sizes, variable clinical settings and different pathologies limit the conclusions to be drawn from this data. Nevertheless, prevalence rates of chronic dynamic hyperinflation (as determined by measures of dynamic $PEEP_I$ amongst stable COPD subjects) range from 67-84% and are significantly correlated with FEV_1 (Haluszka, Chartrand et al. 1990, Aldrich, Hendler et al. 1993). The severity of dynamic $PEEP_I$ in stable COPD subjects is approximately 3 cm H_20 for those with FEV_1 < 35% predicted versus 1 cm H_20 in those with less severe airway obstruction (Haluszka, Chartrand et al. 1990). Similarly, Dal Vecchio and colleagues (Dal Vecchio, Polese et al. 1990) measured a mean dynamic $PEEP_I$ of 2.4 cm H_20 (SD ± 1.6) in their cohort of 18 COPD patients with a mean FEV_1 of 39% predicted (SD ± 14).

By contrast, several authors have found higher levels of static $PEEP_I$ in small cohorts of COPD subjects requiring mechanical ventilation for respiratory failure. (Hence, the static $PEEP_I$ in these patients represent a combination of both chronic and acute dynamic hyperinflation.) Baigorri and others (Baigorri, de Monte et al. 1994) found that the mean static $PEEP_I$ in 10 COPD subjects receiving mechanical ventilation was 6.6 cm H_20. Ranieri and colleagues (Ranieri, Giuliani et al. 1993) found an average static $PEEP_I$ of 9.8 cm H_20 in 9 COPD subjects requiring mechanical ventilation. Finally, Georgopoulos and colleagues (Georgopoulos, Giannouli et al. 1993) found a higher average level of static $PEEP_I$ of 12 cm H_20 in their cohort of 9 COPD subjects with respiratory failure. However, the high levels of $PEEP_I$ in this study are partially due to selection bias as patient selection required the presence of dynamic hyperinflation.

Pathophysiology of Pulmonary Hyperinflation in COPD

Static hyperinflation occurs insidiously and results in several compensative mechanisms to the inspiratory muscles including a reduction in sarcomere length, an increase in the

proportion of Type I fibres and an improved mitochondrial oxidative capacity (O'Donnell and Laveneziana 2006). Over time, static hyperinflation leads to remodelling of the chest wall. Despite these adaptive mechanisms, when demand increases, as with activity, there is a reduced ability to maintain ventilatory requirements.

Dynamic hyperinflation is associated with gas trapping, the development of $PEEP_I$, a reduced IC (Schrijen, Henriquez et al. 1989, Montes de Oca, Rassulo et al. 1996, Grazzini, Stendardi et al. 2005, O'Donnell and Laveneziana 2006) and an increase in the amplitude of intrathoracic pressure (ITP) swings (Zielinski 1979, Montes de Oca, Rassulo et al. 1996).

Whilst acute dynamic hyperinflation can be a compensatory mechanism in itself allowing for increased airway diameter, improved elastic recoil and attenuation of expiratory flow limitation, it ultimately results in a range of negative consequences. These include (i) an increased requirement of inspiratory muscles to overcome the associated $PEEP_I$ that occurs (inspiratory threshold load), (ii) tidal breathing occurs at a less compliant part of the respiratory system pressure-volume curve which increases resistance and the work of breathing, (iii) flattening of the diaphragm in combination with other respiratory muscles operating at a suboptimal length-tension ratio places the respiratory muscles at a mechanical disadvantage, (iv) reduced capacity for the tidal volume to expand causes breathing frequency to increase in order to maintain ventilatory requirements, (v) an increase in breathing frequency leads to an increase in dead-space ventilation, and (vi) negative haemodynamic consequences of raised pulmonary arterial pressure, reduced right ventricular preload and variable effects to left ventricular function (Papiris, Kotanidou et al. 2002, Blanch, Bernabe et al. 2005, O'Donnell and Laveneziana 2006).

Little is known about the clinical implications of chronic dynamic hyperinflation and most analyses have not identified this as a separate entity. This is primarily because of the difficulty in distinguishing static hyperinflation from chronic dynamic hyperinflation in the clinical setting (Gibson 1996). Furthermore, most of the literature regarding dynamic hyperinflation actually refers to acute dynamic hyperinflation.

Dynamic hyperinflation is probably the principal cause for exercise limitation in COPD (O'Donnell and Laveneziana 2006, O'Donnell and Webb 2008b, Hannink, van Helvoort et al. 2010). More lung hyperinflation at rest (i.e. combined static hyperinflation and chronic dynamic hyperinflation) appears to be associated with less acute dynamic hyperinflation with exercise (O'Donnell and Webb 2008b, Hannink, van Helvoort et al. 2010). This is presumably because such patients have already encroached upon their inspiratory limitation. In addition to the aforementioned reduced breathing efficiency that occurs with lung hyperinflation, progressive dynamic hyperinflation ultimately leads to respiratory failure and is associated with other complications including barotrauma and systemic hypotension (Stather and Stewart 2005).

The interaction between lung hyperinflation and pulmonary haemodynamics is complex. This is because lung inflation exerts a range of haemodynamic consequences through volume and pressure effects, which have both direct and indirect repercussions on PVR and cardiac output that are illustrated in Figure 6. The direct volume effect of the expanding lung alters the structural configuration of pulmonary vessels whereas the indirect volume effects impact upon gas exchange within the lung. The direct pressure effects of lung inflation alter intrathoracic pressure and pulmonary vessel transmural pressure with resultant effects on pulmonary vessel calibre and vascular resistance. The indirect pressure effects of lung inflation impact both cardiac preload and afterload. The direction and magnitude of the change to pulmonary haemodynamics are discussed below and will vary depending on the clinical circumstances for the pulmonary hyperinflation.

Whilst acute dynamic hyperinflation is associated with elevations of pulmonary arterial pressure (O'Donnell and Laveneziana 2006), to date, no group has attempted to determine the specific role of increased airway pressure upon pulmonary haemodynamics in patients with COPD. Similarly, our understanding of the pulmonary haemodynamic consequences of static hyperinflation mostly comes from theoretical considerations and extrapolation of data from animal studies, intra-operative studies on non-COPD patients and on COPD subjects with acute dynamic hyperinflation.

As mentioned in section 1.2.3.3, an early study by Yu and colleagues (Yu, Lovejoy et al. 1953) demonstrated a significant correlation between gas trapping (measured as

residual volume to total lung capacity) and mPAP and also with total pulmonary resistance, but not with PVR despite no patients with an elevated PAWP. Interestingly, $PaCO_2$ was more strongly correlated with mPAP, TPR and PVR. These haemodynamic associations with gas trapping have not been replicated. Keller and colleagues (Keller, Shepard et al. 1986) assessed 89 moderate-severe COPD subjects of which 31 had PHT and they noted significantly more gas trapping in the PHT group as measured by an increased residual volume. However, upon multiple linear regression analysis residual volume was not considered an independent predictor of pulmonary arterial pressure. No other studies have identified any measure of gas trapping or hyperinflation as an independent predictor of pulmonary arterial pressure. Finally, Wilkinson and colleagues (Wilkinson, Langhorne et al. 1988) suggested that lung hyperinflation may contribute to the peculiar pulmonary vascular remodelling identified in hypoxic cor pulmonale subjects with obstructive lung disease.

The effects of changes in lung volume and airway pressure upon PVR are reviewed in the following sections.

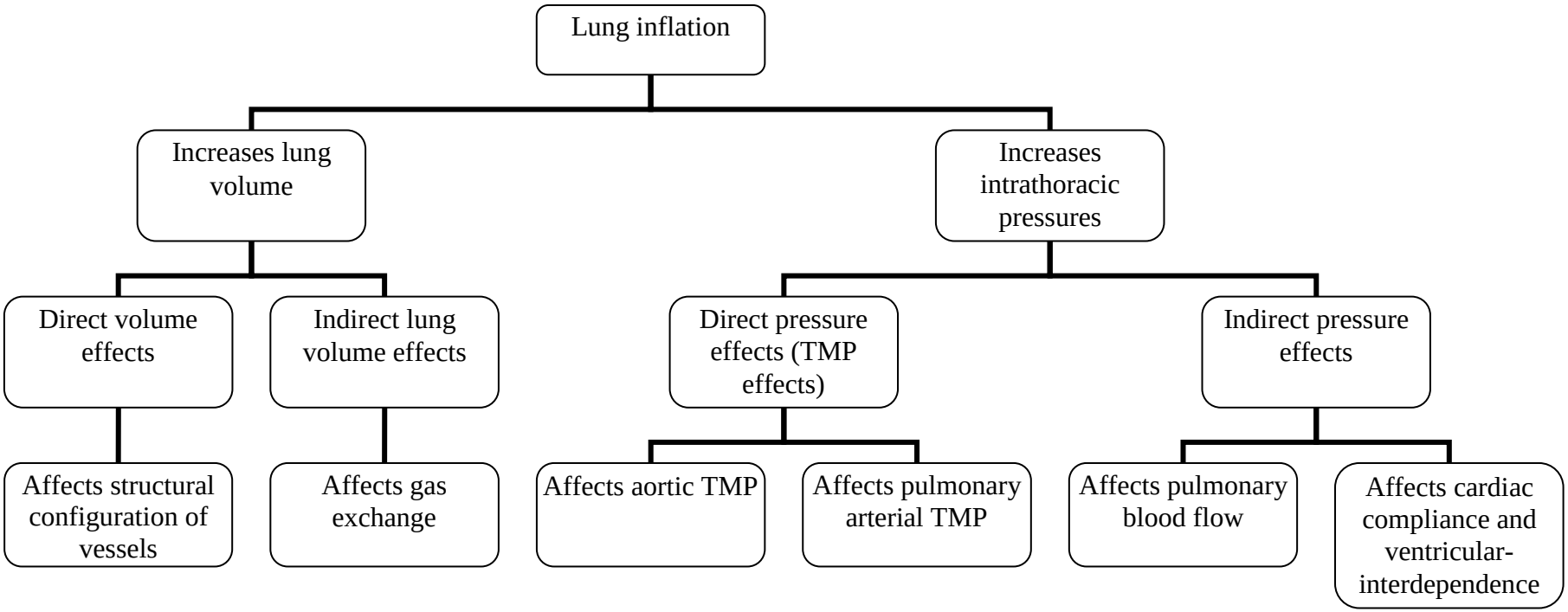

Figure 6
Direct and indirect volume and pressure consequences of lung inflation.
TMP, transmural pressure.

1.4.2 Lung Volume Effects Upon Pulmonary Vascular Resistance

The direct volume effects of the expanding lung upon the pulmonary vasculature depend on the relative inflation of the lung. As the lung volume increases, from lung collapse to small lung volumes there is a drop in PVR due to 'unkinking' of pulmonary vessels (Burton and Patel 1958). Subsequent increases in lung volume change the radial-length relationship of non-alveolar vessels and may increase PVR (Roos, Thomas et al. 1961, Lloyd 1967). Similarly, in open-chested dogs, hyperinflation with positive pressure ventilation has been demonstrated to increase PVR by stretching of alveolar capillaries and transmission of raised alveolar pressure into the pulmonary vessels (Whittenberger, McGregor et al. 1960). This creates a 'U-shape' relationship between lung volume and PVR (Burton and Patel 1958) as illustrated in Figure 7.

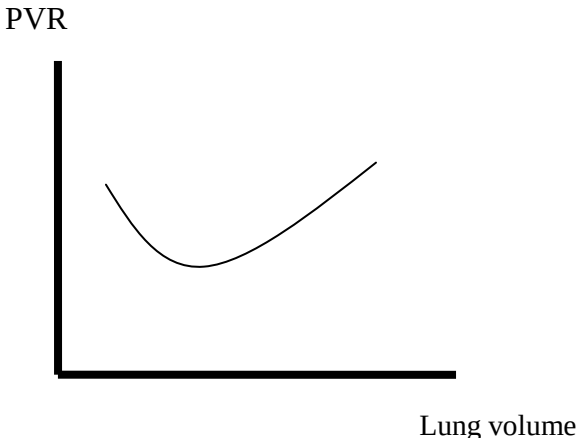

Figure 7
The relationship between pulmonary vascular resistance and lung volume. The characteristic 'U-shape' curve demonstrating the relationship between PVR and lung volume

However, these results are not supported by Cudkowicz and O'Neill (Cudkowicz and O'Neill 1965) who demonstrated that during spontaneous respiration, PVR decreases significantly as lung volumes increase from residual volume to FRC, and then further decrease at total lung capacity. They also reported a significant increase in left and right ventricular output as the lung volume increases from residual volume to FRC to total lung capacity.

This inconsistency regarding the effects of lung volume on PVR are likely due to the indirect effects on the pulmonary vessels as the lungs expand from low lung volumes. As the lung volume increases, there is an increase in the surface area of the lungs for gas exchange that reduces pulmonary shunting of blood, thereby improving PaO_2 and reducing $PaCO_2$. Improved oxygenation reduces hypoxic pulmonary vasoconstriction which will reduce PVR (Pinsky 2005). This indirect mechanism is more relevant at lower lung volumes where alveolar collapse occurs.

In addition to the structural changes that occur as the lung inflates which can affect PVR, the change in airway pressures can also exert direct and indirect effects upon the pulmonary circulation.

1.4.3 Airway Pressure Effects Upon Pulmonary Vascular Resistance

Respiration occurs due to changing pressures within the lung relative to the pressure at the mouth, regardless of the mode of ventilation (i.e. spontaneous ventilation, positive pressure ventilation or negative pressure ventilation). The extent to which pressure changes alter lung volumes depends upon the compliance of the lung and the chest wall. These changing pressures exert direct effects on the pulmonary parenchyma and pulmonary vessels, altering vessel calibre and hence, PVR. In addition, variations in the intrathoracic pressures may indirectly affect pulmonary haemodynamics through the effects on cardiac preload and afterload.

Figure 8 depicts a schematic of the human lung identifying the relevant pressures (alveolar pressure, P_A; barometric pressure, P_B; pleural pressure, P_{PL}) responsible for respiration. From this we can derive the transmural pressure of the lung (P_L), the transmural pressure of the chest wall (P_W) and the transtotal pressure of the respiratory system (P_{RS}), such that:

$$P_L = P_A - P_{PL}$$

$$P_W = P_{PL} - P_B$$

$$P_{RS} = P_L - P_W$$

$$= (P_A - P_{PL}) - (P_{PL} - P_B)$$

$$= P_A - P_B$$

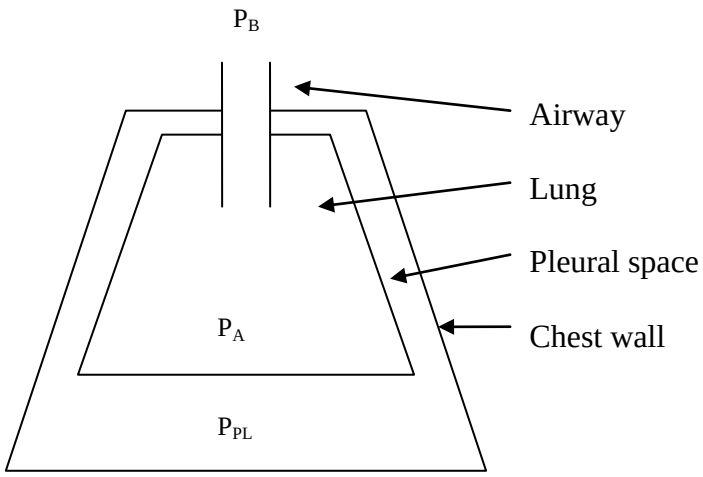

Figure 8
Pressure differences across the human chest.
P_A, alveolar pressure; P_B, barometric pressure; P_{PL}, pleural pressure

The term ITP requires clarification. ITP refers generally to the collective pressures within the thorax and hence, is more accurately termed intrathoracic pressures. Depending upon the context, ITP may refer to a specific pressure, such as airway pressure, alveoli pressure or pleural pressure. Furthermore, each intrathoracic pressure is not a single constant pressure but has a waveform which varies depending on the mode of ventilation and the timing within the respiratory cycle.

For many years there was considerable debate regarding the impact of lung inflation upon the PVR (Burton and Patel 1958, Whittenberger, McGregor et al. 1960). This debate has stemmed from variable definitions and application of 'effective pulmonary arterial pressure'. Fortunately, some resolution has come through recognition of the pertinent issues and application of uniform definitions. First, as discussed above, it was recognised that intrathoracic pressures varied markedly depending on the mode of ventilation, most notably spontaneous ventilation or positive pressure ventilation. Second, introduction of the term 'transmural pressure' clarified the relevant pressure exerting influence on the vessels such that transmural pressure is the pressure difference between the inside and the outside of a vessel (Burton and Patel 1958). Hence, the 'effective pressure' in determining the vessel size is dependent upon transmural pressures and the tension within the vessel wall, rather than on the difference between

absolute intraluminal pressure and intrathoracic pressure (Burton and Patel 1958). Similarly, the 'driving pressure' is the difference between point A and B within the pulmonary circulation rather than on the difference between intraluminal pressure and ITP (Burton and Patel 1958).

The intrathoracic pressure effects of pulmonary hyperinflation depend greatly upon the mode of ventilation as this will significantly affect P_A and P_{PL}, generating different pressure-time curves during respiration. Whilst the mode of ventilation results in different pressure-time curves, there are also regional pressure differences within the thorax with regard to pleural, juxtacardiac and oesophageal pressures. It has been recognised for decades now that alveolar pressure and pulmonary vasculature pressure are not uniform throughout the lung. Most notably, the West lung zones refer to three distinct areas within the lung that are characterised by the relative alveolar pressure, pulmonary arterial pressure and pulmonary venous pressure (*see* Table 5 above) (Permutt, Bromberger-Barnea et al. 1962, West, Dollery et al. 1964). Zone 1 occurs in the upper part of the lungs and is characterised by collapsible vessels that are closed by the relative high alveolar pressure and low vascular pressure resulting in no pulmonary blood flow. Zone 2 occurs in the middle part of the lung and is characterised by constriction of the distal end of the collapsible vessels and the driving pressure gradient is the difference between arterial and alveolar pressure. Finally, zone 3 occurs in the lower lung areas where the alveolar pressure is relatively low and the collapsible vessels remain open. The driving pressure gradient for blood flow is the difference between arterial and venous pressure.

Consequently, airway pressure changes of respiration will affect the pulmonary arterial transmural pressure and hence, the West lung zones. For example, spontaneous inspiration creates negative ITP that increases the transmural pressure of the pulmonary vasculature. Increased transmural pressure causes an increase in vessel calibre and a drop in PVR (Burton and Patel 1958). The drop in alveolar pressure during spontaneous inspiration also reduces West zone 1 conditions, thereby increasing the overall capacity of the pulmonary vasculature, which further reduces PVR.

By contrast, during inspiration with positive pressure ventilation, there is an increased ITP, reduced transmural pressure and an increased PVR (Burton and Patel 1958).

Furthermore, positive pressure ventilation increases alveolar pressure promoting increased West zones 1 and 2 conditions in the lung which has the potential to further increase PVR (Banister and Torrance 1960). This increase in PVR, coupled with the aforementioned volume effect of the expanding lung, results in an overall increase in PVR.

Alveolar and Extra-Alveolar Vessels

A distinction exists between alveolar pulmonary vessels (including pulmonary arterioles, capillaries and venules) that lie within the alveolar septa and non-alveolar vessels (larger pulmonary arteries and veins) which do not lie within the alveolar septa (Hakim, Michel et al. 1982). Alveolar vessels are greatly influenced by alveolar pressures, whereas non-alveolar vessels are more influenced by changes in the interstitium (Steingrub, Tidswell et al. 2003). As lung volume increases from residual volume to FRC, radial traction forces of the interstitium increases resulting in increased vessel calibre of the extra-alveolar vessels and a reduced PVR. In contrast, alveolar vessels will be more affected by airway pressure changes, determined by the mode of ventilation (Hakim, Michel et al. 1982). For example, during spontaneous ventilation, as alveolar pressures are negative, this will increase the transmural pressure of the alveolar vessels resulting in a reduced PVR. However, during positive pressure ventilation, the transmural pressure of alveolar vessels will decrease thereby, contributing to an increase in PVR.

In summary, PVR reflects the summation effects of alveolar vessels that are greatly influenced by airway pressure effects and extra-alveolar vessels that are more influenced by lung volume changes. PVR is mostly determined from the small muscular pulmonary arteries (Barnes and Liu 1995) and is affected by changes in both alveolar and extra-alveolar vessels.

1.4.4 Effects of Different Ventilation Modalities Upon Pulmonary Haemodynamics

As changes in ITP contribute to the altered pulmonary and systemic haemodynamics associated with respiration, it is clear that different modes of ventilation will each exert unique effects.

For example, in young adult controls, negative pressure breathing (-20 to -22 cm H_2O) reduces ITP by an average of 10.5 mm Hg and increases cardiac index due to increased heart rate with no effect on stroke volume (Kilburn and Sieker 1960). Diastolic and systolic systemic pressures did not significantly change during negative pressure ventilation. In contrast, continuous positive pressure breathing reduced cardiac index from 3.7 to 2.5 L/m in subjects who did not hyperventilate, which was associated with a reduced stroke volume and an increased heart rate. Amongst subjects who hyperventilated during continuous positive pressure breathing, their cardiac output was stable, with no significant change in cardiac output or stroke volume.

Not only is the mode of ventilation important, but an early study by Cournand and colleagues (Cournand, Motley et al. 1947) demonstrated that the haemodynamic consequences of intermittent positive pressure ventilation (IPPV) is dependent upon the pressure-curve characteristics of the respirator. The respirator with the least effect on cardiac output was described as one with a gradually increasing ITP, sudden drop in pressure during expiration and an expiratory time greater than or equal to the inspiratory time to allow for appropriate right ventricular filling. Right ventricular filling decreased with increasing mask pressure (i.e. inspiration) and increased during expiration.

Whilst traditionally, haemodynamic assessment has been conducted at end-expiration, Robotham and colleagues (Robotham, Cherry et al. 1983) argued that the hemodynamic consequences of IPPV must be examined over an entire respiratory cycle, rather than limiting the analysis to end-expiration. Furthermore, they state: “The most significant cardiopulmonary interactions may occur during inspiration”. They studied the haemodynamic consequences of IPPV with and without $PEEP_E$ in 9 dogs across end-expiration, early inspiration, late inspiration and early expiration. They demonstrated a

significant increase in aortic stroke volume and a significant decrease in pulmonary arterial stroke volume during IPPV. As the transmural aortic systolic pressure increased with IPPV but the transmural aortic diastolic pressure did not change, the authors argued that the increased aortic stroke volume was partially due to a reduced afterload. The decreased pulmonary arterial stroke volume that occurred during inspiration with IPPV was argued to be due to a reduced venous return, however the authors did not present data on the pulmonary arterial systolic or diastolic pressure during IPPV. A raised right ventricular afterload is an alternative explanation for the reduced pulmonary arterial stroke volume with IPPV.

Extrinsic Positive End Expiratory Pressure

In addition to the affects that mechanical ventilation can have upon pulmonary haemodynamics, the application of $PEEP_E$ can also alter respiratory mechanics and haemodynamics.

The application of $PEEP_E$ will increase the mean airway pressure (Luce 1984), increase FRC and reduce airway resistance. Despite the increase in FRC, there is not an increase in gas trapping per se (Tuxen 1989). Rather, the FRC is set higher due to the change in lung and chest wall pressure equilibrium. $PEEP_E$ also results in an increase in ITP (as measured by oesophageal or pleural pressure), arterial oxygen saturation and a reduced shunt fraction.

Several studies have explored the haemodynamic effects of $PEEP_E$ to mechanically ventilated dogs demonstrating a reduced cardiac output, reduced mean arterial pressure, increased central venous pressure and an increased mPAP (Manny, Patten et al. 1978, Marini, Culver et al. 1981a, Marini, Culver et al. 1981b, Hakim, Gilbert et al. 1993). $PEEP_E$ reduces cardiac output, primarily through a reduction in right ventricular preload and to a smaller extent, via an increase in right ventricular afterload (Marini, Culver et al. 1981a). There does not appear to be any direct effect of $PEEP_E$ on right ventricular contractility (Marini, Culver et al. 1981a). Furthermore, $PEEP_E$ appears to increase left atrial pressure which may be due to humoral factors (Manny, Patten et al. 1978). In close-chested dogs, PAWP overestimates left atrial pressure. This likely results from the elevated alveolar pressure leading to an increase in West zone 1 and zone 2 conditions

(Manny, Patten et al. 1978, Hakim, Gilbert et al. 1993). There are no consistent differences between experiments on open versus close-chested animals with regard to cardiac output or mPAP (Manny, Patten et al. 1978, Hakim, Gilbert et al. 1993).

Similarly, human studies have demonstrated that $PEEP_E$ increases ITP that elevates right atrial pressure and reduces venous return to the right side of the heart (Luce 1984, Blanch, Bernabe et al. 2005, Luecke and Pelosi 2005). The impact of $PEEP_E$ on right ventricular afterload is more complex. Whilst the expanding lung causes dilation of pulmonary arteries and veins which reduces PVR, the capillaries and peri-alveolar vessels lengthen and narrow which has the potential to increase PVR (Luce 1984). Furthermore, as positive airway pressure causes the increase in lung volume, there is a reduction in the transmural pressure of the pulmonary vessels resulting in a reduced calibre and increased PVR. The issue is further confounded in that the improved shunt fraction and arterial oxygen saturation decreases hypoxic pulmonary vasoconstriction which also has the potential to decrease PVR (Luecke and Pelosi 2005). Nevertheless, it appears that the final result is an increase in PVR, right ventricular afterload and a reduction in cardiac output.

Intrinsic PEEP and Extrinsic PEEP

Although $PEEP_I$ and $PEEP_E$ are often regarded as having similar pulmonary mechanical and haemodynamic consequences, debate continues as to whether their effects are equivalent. However, $PEEP_I$ and $PEEP_E$ differ with respect to site of origin, magnitude, distribution and method of measurement. For example, $PEEP_I$ originates in the distal regions of the lung due to gas trapping whereas $PEEP_E$ is delivered proximally, usually via endo-tracheal tube in mechanically ventilation patients.

Webb and colleagues (Webb, Smith et al. 1961) were able to demonstrate in dogs that the peri-alveolar pressure (as measured with a wedged bronchial catheter) is more negative than pleural pressure during inspiration and more positive than pleural pressure during expiration during spontaneous ventilation. During positive pressure ventilation, the peri-alveolar pressure remains lower than the major airway pressure. These findings suggest that $PEEP_E$ and $PEEP_I$ cannot be equated because a $PEEP_E$ of 10 cm H_20 would

generate a peri-alveolar pressure of < 10 cm H_20. Similarly, $PEEP_I$ measured at the airway opening of 10 cm H_20 would reflect a peri-alveolar pressure of > 10 cm H_20.

The haemodynamic effects of $PEEP_E$ in patient with COPD may be worse than a similar degree of $PEEP_E$ in a healthy subject as a higher fraction of the increased alveolar pressure is transmitted to the intrathoracic vessels in highly compliant lungs (Pepe and Marini 1982, Blanch, Bernabe et al. 2005). Consequently, in COPD, $PEEP_I$ may have a greater impact on vascular transmural pressure and PVR due to the compliant lungs. In contrast, asthma subjects have increased airway smooth muscle, bronchomotor tone and airway inflammation which stiffen the airway wall, resulting in less lung compliance than emphysema and transmitting a smaller amount of ITP variability to the pulmonary vasculature (Ranieri, Giuliani et al. 1993).

Pepe and Marini (Pepe and Marini 1982) have also noted that $PEEP_I$ causes an elevation of ITP during expiration which may impact upon PAWP, causing it to be spuriously elevated.

Some authors argue that $PEEP_I$ alters pulmonary haemodynamics similar to $PEEP_E$ (Ranieri, Giuliani et al. 1996, Pinsky 2005) and that matching $PEEP_E$ to a similar level of $PEEP_I$ does not have significant respiratory mechanic or haemodynamic consequences. Ranieri and colleagues demonstrated in 9 COPD patients receiving mechanical ventilation that when $PEEP_E$ exceeded $PEEP_I$ there was a decrease in cardiac index, stroke volume index, blood pressure, shunt fraction and an increase in pulmonary arterial pressure, PAWP, PVR index, systemic vascular resistance index and PaO_2.

However, other studies have shown that $PEEP_I$ and $PEEP_E$ are not equivalent and that a similar level of $PEEP_I$ resulted in significantly increased transpulmonary mean airway pressure, increase shunt fraction and reduced arterial PaO_2 in an animal study (Yanos, Watling et al. 1998). In 10 COPD subjects with acute respiratory failure, Baigorri and colleagues (Baigorri, de Monte et al. 1994) demonstrated an increase in the elastic recoil pressure of the respiratory system and an increase in right ventricular end-diastolic pressure when $PEEP_E$ was matched to $PEEP_I$. Similarly, Georgopoulos and colleagues (Georgopoulos, Giannouli et al. 1993) showed that matching $PEEP_E$ to 86% of $PEEP_I$ in

COPD patients with acute respiratory failure resulted in increased central venous pressure, mPAP and PAWP but with no change to cardiac index, stroke volume or mean arterial pressure.

1.4.5 Ventilatory Effects Upon Cardiac Function

In addition to the effects that changes in lung volume and airway pressure have upon PVR, ventilation also affects cardiac preload and afterload. At present, there is no clear evidence that ventilation directly affects contractility of the ventricles (Marini, Culver et al. 1981b, Luecke and Pelosi 2005).

The cardiac preload and afterload effects of respiration are largely dependent upon the mode of ventilation. Spontaneous inspiration generates negative ITP that reduces right atrial pressure and increases venous return to the right side of the heart. This leads to an increased right ventricular preload volume and increased right ventricular cardiac output (Montes de Oca, Rassulo et al. 1996). The effects on right ventricular afterload are more complex (as discussed below) but are partially mediated by changes in PVR that are determined by airway pressure and lung volume changes as described above.

On the left side of the heart, negative ITP increases aortic transmural pressure, increasing LV afterload pressure that reduces LV cardiac output (Buda, Pinsky et al. 1979, Peters, Fraser et al. 1989, Montes de Oca, Rassulo et al. 1996). The effect of ventilation upon pulmonary venous return appears to depend on whether lung zone 2 or zone 3 conditions predominate (Robotham, Cherry et al. 1983, Brower, Wise et al. 1985).

By comparison, during inspiration with positive pressure mechanical ventilation, there is an increase in ITP, an increase in right atrial pressure and a reduction in venous return to the right ventricle (Pinsky 2005). Positive pressure ventilation has also been shown to reduce left ventricular cardiac output and mean systemic arterial pressure following cardiac surgery (Nielsen, Ostergaard et al. 2005, Nielsen, Nygard et al. 2007) and that these haemodynamic changes were not influenced by whether the chest was opened or closed (Nielsen, Nygard et al. 2007).

1.4.6 Ventricular Interdependence

Exploring cardiopulmonary interactions is complicated further by the effects that the ventricles exert upon each other, known as ventricular interdependence. Left to right ventricular effects were first postulated by Bernheim in 1910. The right to left ventricular effects were subsequently described as the "reverse Bernheim effect" in 1956 (Dexter 1956). Santamore and Dell'Italia (Santamore and Dell'Italia 1998) define ventricular interdependence as "the forces that are transmitted from one ventricle to the other ventricle through the myocardium and pericardium, independent of neural, humoral or circulatory effects".

Ventricular interdependence occurs during both diastole and systole. In diastole, increased filling of one ventricle can lead to reduce filling compliance of the other ventricle. Systolic ventricular interdependence also occurs, whereby the pressure generated by each ventricle during systole is, in part, a result of contraction of the other ventricle. For example, Damiano and colleagues (Damiano, La Follette et al. 1991) demonstrated that left ventricular contraction contributes 37 ± 11% to peak RVSP. In contrast, right ventricular contraction contributes only 7 ± 3% to peak left ventricular systolic pressure.

Whilst ventricular interdependence may occur with an open pericardium, interactions are more pronounced if it is closed (Maruyama, Ashikawa et al. 1982, Slinker and Glantz 1986). Increased diastolic ventricular interdependence has been observed in animal studies with experimental pericardial effusion (Santamore, Heckman et al. 1986), constrictive pericarditis (Santamore, Bartlett et al. 1986) and cardiac tamponade (Gonzalez, Basnight et al. 1991). Furthermore, diastolic ventricular interdependence likely contributes to the reduced left ventricular compliance associated with increased right ventricular filling during respiratory manoeuvres (Santamore, Heckman et al. 1984, Peters, Kindred et al. 1988a, Aebischer, Malhotra et al. 1995).

Whether pulmonary hyperinflation as occurs in COPD, affects ventricular interdependence has not been studied in humans. Nevertheless, with the development of $PEEP_I$, it is expected that diastolic ventricular interdependence is increased.

Furthermore, an increased right ventricular afterload will result in leftward shift of the interventricular septum and will negatively affect both diastolic and systolic left ventricular performance. This is supported by Gomez and colleagues (Gomez, Unruh et al. 1994) who used a canine model of emphysema to demonstrate impaired left ventricular performance. Similarly, increased right ventricular afterload in PHT leads to impaired left ventricular function as a result of ventricular interdependence (Tanaka, Tei et al. 1980).

1.4.7 Pulmonary Haemodynamics During Exercise and Hyperventilation

Exercise

The causes of the reduced exercise capacity amongst COPD subjects is a source of ongoing debate and include reduced cardiac output, peripheral muscle dysfunction and dynamic hyperinflation (O'Donnell and Webb 2008a). In a study of 25 very-severe COPD subjects, 40% had pulmonary limitation alone, 24% had cardiopulmonary limitation, 12% had cardiac limitation and the remaining 24% had a submaximal effort (Montes de Oca, Rassulo et al. 1996). Of note, peak exercise capacity, maximum oxygen pulse and ITP were strongly related suggesting that mechanical derangements during exercise may contribute to the haemodynamic abnormalities.

Amongst the haemodynamic consequences of exercise, elevations in pulmonary arterial pressure occur (O'Donnell and Laveneziana 2006). Exercise-induced elevation in pulmonary arterial pressure is not unique to COPD subjects and the significance of such elevations in pulmonary arterial pressure continues to be debated (Badesch, Champion et al. 2009). Exercise-induced increases in pulmonary arterial pressure in COPD subjects may be due to any combination of an elevated PAWP, an increase in pulmonary blood flow and in increase in PVR (Lockhart, Nader et al. 1970, Bahler, Chester et al. 1977, Albert, Muramoto et al. 1985, Butler, Schrijen et al. 1988, Schrijen, Henriquez et al. 1989, Hanaoka, Ideura et al. 2008).

For example, Lockhart and colleagues (Lockhart, Nader et al. 1970) compared pulmonary haemodynamics at rest with periods of exercise in 12 mild-moderate COPD subjects and demonstrated a significant increase in mPAP during exercise (19.1 to 31.4 mm Hg, $P < 0.05$) which was associated with increases in cardiac index (3.2 to 5.3 L/min/m^3, $P < 0.05$) and PAWP (8.3 to 13.2 mm Hg, $P < 0.05$) but no change in PVR. Butler and colleagues (Butler, Schrijen et al. 1988) were able to demonstrate a significant increase in mPAP (21 to 35 mm Hg, $P < 0.01$) in 39 severe COPD subjects during exercise, which was accompanied by increases in cardiac output 5.5 to 8.7 L/min, $P < 0.01$) and PAWP (6 to 11 mm Hg, $P < 0.01$) but PVR data was not presented. The results were replicated again by Schrijen and colleagues (Schrijen, Henriquez et al. 1989) in 30 severe COPD subjects with exercise, demonstrating an increase in mPAP (21.9 to 33.3 mm Hg, $P < 0.001$), cardiac output (5.6 to 7.8 L/min, $P < 0.001$) and PAWP (5.8 to 9.2 mm Hg, $P < 0.001$) with no significant change in PVR (240 to 246 dyn.s.cm^{-5}). Similarly, in a small study of 6 COPD subjects with FEV_1 < 50% predicted, Hanaoka and colleagues (Hanaoka, Ideura et al. 2008) demonstrated a significant increase in mPAP, PAWP and cardiac index in comparison with rest but the exercise-related increase in PVR index was not significant. Whilst supplemental oxygen attenuated the exercise-induced increase in mPAP and PAWP in this study, mPAP and PAWP did not return to baseline. The authors argued that the increase in mPAP and PAWP may be partly mediated by dynamic hyperinflation and elevated ITP.

If dynamic hyperinflation occurs during exercise, this may modulate the cardiac output response to exercise (Montes de Oca, Rassulo et al. 1996). First, in the presence of dynamic hyperinflation there are wider swings in ITP associated with a more negative ITP during inspiration and a more positive ITP upon expiration. This may have the effect of exaggerating the normal haemodynamic responses to respiration. A reduced (i.e. more negative) ITP as occurs during inspiration reduces right atrial pressure and increases venous return to the right ventricle, increasing right ventricular preload. Simultaneously, the low ITP increases the transmural pressure of the aorta, thereby increasing LV afterload (Buda, Pinsky et al. 1979) which may increase left atrial pressures and PAWP. Furthermore, patients with dynamic hyperinflation may generate higher positive ITP during active expiration that may affect the West lung zones and the driving pressure across the capillary bed. This could be reflected in an elevated mPAP and measured PAWP.

However, Zielinski (Zielinski 1979) demonstrated that although there was a significant correlation between the absolute values of mPAP and ITP swings (as measured by the difference from expiratory to inspiratory diastolic pulmonary arterial pressure, dPAP) with exercise in 20 moderate-severe COPD subjects, there was no significant correlation between the changes from baseline that occurred with exercise. Furthermore, the changes in mPAP and ITP swings with recovery from exercise appeared even more independent. Unfortunately, Zielinksi did not report PAWP and hence any possible relationship between ITP and PAWP was not assessed. This study suggests that ITP swings do not significantly account for the changing mPAP observed during exercise in COPD subjects.

Another postulation is that the widened swings in ITP contribute to the elevated PAWP during exercise and hyperventilation in COPD subjects. Lim and Brownlee (Lim and Brownlee 1968) demonstrated a strong correlation ($r = 0.83$, $P < 0.001$) between peak oesophageal pressure and PAWP during both inspiration and expiration in 10 subjects with moderate-severe obstructive lung disease during hyperventilation caused by CO_2 inhalation. Similarly, Bahler and colleagues (Bahler, Chester et al. 1977) were able to demonstrate a significant correlation ($r = 0.63$, $P < 0.01$) between PAWP and respiratory variation of PAWP (defined as the amplitude of the inspiratory to expiratory peaks in PAWP) during exercise in 28 COPD subjects. In contrast, Albert and colleagues (Albert, Muramoto et al. 1985) have demonstrated that the increases in mPAP, cardiac output and PAWP during upright exercise in 8 patients with moderate-severe COPD could not be explained by increases in ITP as determined by oesophageal pressure. Hence, either a raised ITP does not increase PAWP or oesophageal pressures are not an accurate reflection of juxtacardiac and intracardiac pressures. In deed, it is acknowledged that oesophageal pressure does not necessarily reflect ITP, transmural pressure and juxtacardiac pressures (Marini, Culver et al. 1981b, Marini, Culver et al. 1981a, Butler, Schrijen et al. 1988). Alternate explanations for the raised PAWP with exercise include the effects of arterial hypoxaemia and / or left ventricular diastolic dysfunction, which are more pronounced in the setting of tachycardia.

The raised PAWP with exercise in COPD subjects may also be due to the effects of gas trapping. Butler and colleagues (Butler, Schrijen et al. 1988) argued that an increased left lower lobe lung area during exercise due to gas trapping causes an increase in

juxtacardiac and intracardiac pressures leading to increased left ventricular diastolic pressures and a raised PAWP. The authors supported this notion by demonstrating an increase in FRC with exercise (3.7 to 4.2 L, $P < 0.01$). Further, during hyperventilation they demonstrated an increased FRC (although not significant) and left lower lobe area on x-ray (140 to 154 cm^2, $P < 0.01$), in conjunction with a small but significant increase in PAWP (6 to 8 mm Hg, $P < 0.01$) in their cohort.

Whilst Schrijen and colleagues (Schrijen, Henriquez et al. 1989) found no overall change in PVR amongst 30 COPD subjects during exercise, they examined the role of a changing FRC upon pulmonary haemodynamics. They demonstrated a significant correlation between the increase in FRC and the increase in PVR with exercise ($r = 0.79$, $P < 0.001$). Further, they were able to identify two subgroups based on the change in FRC. Group I had less than 200 ml increase in FRC and had a significant reduction in PVR with exercise, whereas group II had a greater than 500 ml increase in FRC which was associated with a significant increase in PVR. Whilst this suggests that dynamic hyperinflation may increase PVR, it is noteworthy that it was the patients with the lower baseline FRC that incurred the greatest increase in FRC.

The non-uniform changes in PVR during exercise reflect that a number of factors are impacting upon PVR, including exercise-induced hypoxia causing pulmonary vasoconstriction (Bahler, Chester et al. 1977), increased blood-flow which may cause pulmonary capillary recruitment and PVR changes secondary to dynamic hyperinflation (Schrijen, Henriquez et al. 1989).

Hyperventilation

There have also been several studies exploring the role of hyperventilation upon the pulmonary haemodynamics in subjects with COPD. Early work by Harris and colleagues (Harris, Segel et al. 1968) in 6 subjects with severe COPD demonstrated that hyperventilation induced a significant increase in mPAP (28 to 43 mm Hg, P unreported), PAWP (9 to 18 mm Hg, P unreported) and PVR (457 to 657 dynes/s/cm^5, $P < 0.02$) with no significant change to pulmonary blood flow. The authors suggested that hyperventilation in association with airways resistance widened the ITP swings which increased PVR via mechanical effects on the pulmonary vessels. However,

patients were given 6% inhaled CO_2 during hyperventilation to avoid alkalosis but many patients became hypercapnic which may affect the conclusions reached.

In contrast, Lockhart and colleagues (Lockhart, Nader et al. 1970) were able to demonstrate similar changes in ventilation during hyperventilation and exercise but hyperventilation was not accompanied by the pulmonary haemodynamic changes of exercise (described above). The difference in pulmonary haemodynamics that occurred with exercise but not with hyperventilation were presumably due to the significant differences observed in mixed venous oxygen saturation, heart rate and left ventricular stroke work index during exercise. As there were similar changes to ventilation with exercise and hyperventilation, ventilatory changes could not account for the differences observed in pulmonary haemodynamics in this group of mild-moderate COPD. Although there were no measures of dynamic hyperinflation obtained, it appears very unlikely that the change in pulmonary haemodynamics with exercise were caused by dynamic hyperinflation. The differences observed between this study and Harris et al may be due to the milder severity of airway obstruction and/or the reduced intensity of hyperventilation in this study. Finally, Butler and colleagues (Butler, Schrijen et al. 1988) were able to demonstrate small but significant increases in mPAP (22 to 24 mm Hg, $P < 0.01$) and PAWP (6 to 8 mmHg, $P < 0.01$) due to hyperventilation in their cohort of 39 severe COPD subjects.

1.4.8 Measuring Lung-Heart Interactions

Diastolic Pulmonary Arterial Pressure and Diastolic Pulmonary Gradient

As discussed in Section 1.2 above, mPAP results from the product of pulmonary blood flow and total pulmonary resistance. The total pulmonary resistance represents the total resistance load on the right ventricle comprising the PVR and the resistance from the left side of the heart. Whereas a number of pulmonary haemodynamic parameters can be measured directly, PVR is a derived measure calculated as:

$$PVR = (mPAP - PAWP) / CO, \text{ where}$$

PVR = pulmonary vascular resistance
mPAP = mean pulmonary arterial pressure
PAWP = pulmonary arterial wedge pressure
CO = right ventricular cardiac output

Although invasive pulmonary arterial pressure measurements can be obtained instantaneously and continuously, right ventricular cardiac output is a dynamic measure. Even with the increasing clinical use of continuous cardiac monitoring, instantaneous assessment of PVR is not available and continuous assessment of PVR is not well validated, especially in humans (Apitzsch, Olthoff et al. 1999).

A number of animal studies have utilised invasive techniques to assess pulmonary haemodynamics, including PVR, in dogs (Visscher 1948, Whittenberger, McGregor et al. 1960, Roos, Thomas et al. 1961, Manny, Patten et al. 1978, Marini, Culver et al. 1981a, Marini, Culver et al. 1981b, Hakim, Michel et al. 1982, Peters, Kindred et al. 1988a, Peters, Kindred et al. 1988b). However, most human studies evaluating heart-lung interactions tend to employ pulmonary haemodynamic outcomes other than PVR, including cardiac output, pulse pressure, dPAP, PAWP and more recently, there is renewed interest in the diastolic pulmonary gradient, defined as:

Diastolic pulmonary gradient = dPAP – PAWP, where

dPAP = diastolic pulmonary arterial pressure, and
PAWP = pulmonary arterial wedge pressure.

In humans, Cournand and colleagues demonstrated small increases in the mean systolic and diastolic right ventricular pressures during IPPV in normal subjects (Cournand, Motley et al. 1947). However, the effect of IPPV upon the right ventricular cardiac output and the systemic arterial pressure depended upon the type of IPPV administered. Despite the increase in right ventricular pressures with IPPV noted by Cournand and colleagues, the clinical significance of the dPAP has been debated for many decades. Fowler and colleagues (Fowler, Westcott et al. 1952) investigated 54 randomly selected hospital inpatients and demonstrated a significant correlation between log dPAP and log PVR ($r = 0.92$, $P < 0.001$).

Subsequent studies suggested that dPAP could be used to estimate PAWP (Dexter, Dow et al. 1950, Kaltman, Herbert et al. 1966). Whilst Dexter and colleagues (Dexter, Dow et al. 1950) demonstrated a similar mean between dPAP and PAWP, there was no significant correlation between the two measures in 8 patients with normal haemodynamics. Whilst Kaltman and colleagues (Kaltman, Herbert et al. 1966) did show a correlation between dPAP and PAWP in 56 patients ($r = 0.908$, $P = 0.001$), this relationship was not present in 14 subjects with PHT and congenital intracardiac shunts.

Harvey and colleagues (Harvey, Enson et al. 1971) demonstrated a close correlation between dPAP and PAWP ($r = 0.879$, $P < 0.001$) amongst 44 normal subjects during rest and exercise, in recumbent and sitting positions. They subsequently concluded that dPAP reflects the end diastolic pressure of the left heart in normal subjects. Furthermore, dPAP together with stroke volume could be used to predict sPAP ($P < 0.001$) and mPAP ($P < 0.001$) in normal subjects. Harvey and colleagues also demonstrate that increases in PAWP lead to increases in sPAP, mPAP and dPAP, whereas, an increase in stroke volume lead to increases in sPAP and mPAP with minimal effect on dPAP. Finally, they demonstrated that changes in PAWP exert a greater effect upon sPAP and mPAP than changes to stroke volume.

However, in patients with COPD, there exists a persistent diastolic pulmonary gradient and consequently, PAWP is less important in predicting dPAP. Rather, dPAP is significantly associated with oxygen saturations ($r = 0.775$, $P < 0.001$), acidaemia ($r = 0.605$, $P < 0.001$) and PAWP.

Similarly, Honda and colleagues (Honda, Sunagawa et al. 1975) have demonstrated that dPAP and the diastolic pulmonary gradient are both correlated strongly with PVR index in patients with congenital heart disease with left to right shunt. They also demonstrate that these correlations are higher than between PVR and either mPAP or sPAP reinforcing the clinical importance of dPAP.

In an editorial, Stevens (Stevens 1975) advanced the notion that the diastolic pulmonary gradient could be utilised to differentiate cardiac and respiratory causes of patients presenting with respiratory failure. More recently, Gerges and colleagues (Gerges, Gerges et al. 2013) demonstrated that an elevated diastolic pulmonary gradient was

associated with increased pulmonary vascular remodelling and an increased risk of death amongst a database population with simultaneous left and right heart catheterisations.

Therefore, whilst dPAP is influenced by both the pulmonary circulation and the back pressure from the left side of the heart, the diastolic pulmonary gradient only accounts for the pulmonary circulation component.

Right Ventricular Afterload

A comprehensive discussion of right ventricular afterload is beyond the scope of this thesis. Briefly, right ventricular afterload is the load against which the heart contracts during systole to eject blood. Right ventricular afterload is dynamic, influenced by PVR, pulmonary arterial elastance, impedance and wave reflection. Consequently, it eludes instantaneous measurement and it cannot be expressed as a simple formula (Naeije and Huez 2007).

Input impedance can be defined as the ratio of pressure harmonics to flow harmonics at the entrance to the arterial system and depends upon the dimensions and compliance of the vessels, the properties of the blood and upon wave reflection (Milnor 1975, Nichols, Conti et al. 1977). Wave reflection refers to the concept that at each branching point of the arterial tree, a component of the forward travelling arterial pressure wave is reflected back towards the heart. This reflected wave is then added to the forward travelling wave resulting in wave amplification.

Ventricular afterload has been modelled using the three-element Windkessel model incorporating arterial resistance, compliance and impedance (Westerhof and Elzinga 1991). In the pulmonary circulation, Lankhaar and colleagues (Lankhaar, Westerhof et al. 2006) have demonstrated that the Windkessel components differed amongst patients with iPAH and chronic thromboembolic PHT. However, differences between the different PHT groups in their baseline haemodynamics may have confounded these results.

A major limitation of afterload assessment based on impedance is the complexity of this measurement. Alternatively, the ratio of end-systolic pulmonary arterial pressure to stroke volume based on ventricular volume-pressure curves is a surrogate measurement that is much simpler to calculate and is able to provide an accurate assessment of afterload (Sunagawa, Maughan et al. 1983, Sunagawa, Maughan et al. 1985, Kelly, Ting et al. 1992, Amin, Taghavi et al. 2011, Vonk-Noordegraaf and Westerhof 2013). Furthermore, Her and colleagues (Her, Koike et al. 2009) have demonstrated that end-systolic pulmonary arterial pressure can be estimated as 0.9 multiplied by the peak systolic pulmonary arterial pressure. Nevertheless, this simplified assessment of right ventricular afterload still requires beat-by-beat stroke volume measurements, which are not routinely performed in the clinical setting.

Cardiac Output, Stroke Volume and Pulse Pressure

The pulse pressure occurs as a result of cardiac contraction and is influenced by the characteristics of the arterial circulation. The pulse pressure is calculated as the difference between the systolic and diastolic pressures. Thus,

Pulse pressure = systolic arterial pressure – diastolic arterial pressure

Despite this simple formula, the nature of the pulse pressure is complex and influenced by vascular resistance, arterial compliance, input impedance, wave reflection and frequency dependence (Dart and Kingwell 2001). Pulmonary resistance and compliance can be measured as:

Total pulmonary resistance = CO / mPAP, and
Compliance = stroke volume / pulse pressure, or
Pulse pressure = stroke volume / compliance, where

CO = right ventricular cardiac output
mPAP = mean pulmonary arterial pressure

Measuring Lung-Heart Interactions - Summary

Whilst it is clear that respiration affects both pulmonary and systemic haemodynamics, determining the direction and magnitude of change has been difficult to establish. Many physiological studies have been conducted in animals but there have been limited quantitative analysis in humans. This is due to a range of factors including: (i) it requires invasive measurements, (ii) complex physiology and pathophysiology of cardiopulmonary interactions, (iii) cardiac consequences are confounded by ventricular interdependence, and (iv) haemodynamic changes are occurring intra-breath and intra-beat.

The complexity of analysing lung-heart interactions is further compounded by measurement difficulties. Whilst pulmonary arterial pressure measurements can be obtained continuously and instantaneously, they only represent a portion of the haemodynamic change. In contrast, more comprehensive haemodynamic assessment techniques continue to be explored but are currently hampered by their complexity of analysis and are mostly limited to the research setting. Furthermore, their inability to provide continuous and instantaneous measurement, make them difficult to employ when attempting to determine intra-beat and intra-breath haemodynamic changes.

1.4.9 Unresolved Questions

From the aforementioned discussion, it is apparent that whilst lung-heart interactions occur, their impact on pulmonary haemodynamics in COPD has not been fully established. In particular, despite considerable discussion on the matter, there is limited evidence that gas trapping, as occurs with dynamic hyperinflation, is a significant contributor to PHT in COPD subjects. Specifically, it is unknown whether increased airway pressure leads to pulmonary vascular compression in patients with severe COPD. Furthermore, it is unclear whether COPD patients with established PHT are more or less susceptible to lung-heart interactions and their clinical consequences.

1.5 Summary and Rationale for This Thesis

COPD is a major international health burden. In 2002, COPD was ranked as the fifth major cause of worldwide mortality but is expected to be the third major cause of mortality by the year 2030. Although estimates vary, up to 90% of patients with moderate-severe COPD may develop PHT that has been demonstrated to be a strong predictor of mortality and morbidity. Unfortunately, efforts to specifically treat PHT in patients with COPD have not translated into meaningful clinical outcomes.

Select patients with very severe COPD may be suitable for lung transplantation. The literature provides conflicting evidence as to the clinical impact of preoperative PHT on post transplantation outcomes generally. Furthermore, the significance of preoperative PHT on early outcomes following transplantation for COPD has not been specifically addressed. Identifying preoperative PHT as a risk factor for inferior post transplantation outcomes would not only assist better stratification of high-risk transplant patients but it would also likely contribute to our understanding of the pathophysiology of cardiopulmonary interactions and may lead to improved peri-operative management of these patients. This issue is addressed in Chapter 2.

From a pathological perspective, despite several studies demonstrating the presence of pulmonary arterial remodelling in COPD, the significance of remodelling in these patients has not been established. Greater understanding of pulmonary arterial remodelling in COPD would aid our understanding of the pathogenesis of PHT in COPD. Furthermore, it would provide the pathological basis from which to persevere with research utilising specific pulmonary vasodilator therapies in this patient group. In Chapter 3, the distribution and extent of pulmonary arterial remodelling in COPD subjects are explored. Furthermore, Chapter 3 investigates the relationship between pulmonary arterial remodelling, PHT and regional changes in perfusion and emphysema severity.

It has also been argued that PHT in COPD has a functional pathogenic component and that pulmonary hyperinflation contributes to the elevations of pulmonary arterial pressures commonly observed in these patients. Whilst there is scant data to support

this, if it can be established then it would suggest that COPD therapies aimed at reducing dynamic hyperinflation may also result in improved pulmonary haemodynamics. In Chapter 4, the impact of airway pressure changes on pulmonary haemodynamics are investigated as a model to assess whether there is a physiological basis for dynamic hyperinflation contributing to PHT in COPD.

1.6 Thesis Hypotheses

The hypotheses of this thesis have resulted in three original research studies which are presented in the chapters that follow.

Chapter 2: Preoperative Pulmonary Hypertension and Lung Transplantation in Patients with COPD

Hypothesis: That preoperative pulmonary hypertension contributes to inferior short-term outcomes following lung transplantation for COPD.

Chapter 3: Pulmonary Arterial Remodelling in COPD

Hypotheses: (a) That there is heterogeneity in pulmonary arterial remodelling between the upper and lower lobes in subject with advanced COPD, and
(b) That pulmonary hypertension in advanced COPD is associated with increased pulmonary arterial remodelling.

Chapter 4: Lung-Heart Interactions: Respiration and the Pulmonary Circulation in COPD

Hypotheses: (a) That increased airway pressure leads to pulmonary vascular compression in subjects with advanced COPD, and
(b) That baseline cardiopulmonary parameters would influence the extent of pulmonary vascular compression during positive airway pressure in subjects with advanced COPD.

Chapter 2: Preoperative Pulmonary Hypertension and Lung Transplantation in Patients with COPD

2.1 Specific Declaration for Thesis Chapter 2

2.2 Introduction to Chapter

2.3 Original Research - Published

2.4 Further Discussion

2.1 Specific Declaration (Part B) for Thesis Chapter 2

Declaration by candidate

In the case of Chapter 2, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, ethics application, data acquisition, data analysis and interpretation, manuscript preparation, final approval of manuscript	85%

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%)
1. Bruce Thompson	Study design, manuscript preparation, final approval of manuscript	
2. Greg Snell	Study design, manuscript preparation, final approval of manuscript	
3. Trevor Williams	Study design, data analysis and interpretation, manuscript preparation, final approval of manuscript	

Candidate's Signature: [redacted] **Date:** 17/5/2013

Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) Lung Function Laboratory, The Alfred, Melbourne, Australia

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[redacted]	9/4/2013
Signature 2		1/5/2013
Signature 3		6/5/2013

2.2 Introduction to Chapter

A review of the literature (Chapter 1) indicates that not only is the existence of PHT in COPD a potential indication for lung transplantation, but that the presence of preoperative PHT may lead to inferior outcomes following transplantation. Whilst two studies (Thabut, Ravaud et al. 2008, Andersen, Iversen et al. 2012) have included an assessment of the effects of preoperative PHT on long-term survival following lung transplantation for COPD, each of these studies have their limitations. Furthermore, no studies have specifically addressed the impact of preoperative PHT on short-term outcomes following lung transplantation for COPD.

In this chapter, we present a retrospective, single centre study of the impact of preoperative PHT on short-term outcomes following lung transplantation for COPD. We demonstrate that moderate-severe PHT, measured by echocardiography, leads to increased duration of mechanical ventilation, worse primary graft function at 24 hours post transplantation and a trend towards increased intensive care length of stay.

The study includes a discussion of the potential mechanisms through which preoperative PHT may affect post-operative outcomes and this is further expanded in Section 2.4. We propose that inferior post transplantation outcomes are due to effects on the right ventricle and / or through unmasking of left ventricular diastolic dysfunction and we highlight the importance of heart-lung interactions in this setting.

2.3 Original Research - Published

Wrobel JP, Thompson BR, Snell GI and Williams TJ (2012). Preoperative echocardiographic-defined moderate-severe pulmonary hypertension predicts prolonged duration of mechanical ventilation following lung transplantation for patients with COPD. Lung 190(6):635-643. [Erratum appended.]

Lung (2012) 190:635–643
DOI 10.1007/s00408-012-9423-7

PULMONARY HYPERTENSION

Preoperative Echocardiographic-Defined Moderate–Severe Pulmonary Hypertension Predicts Prolonged Duration of Mechanical Ventilation Following Lung Transplantation for Patients with COPD

Jeremy P. Wrobel · Bruce R. Thompson · Gregory I. Snell · Trevor J. Williams

Received: 21 June 2012 / Accepted: 20 September 2012 / Published online: 12 October 2012

Abstract

Purpose Recent studies have suggested that pretransplant secondary pulmonary hypertension (PHT) may be associated with worse outcomes following lung transplantation. We sought to determine whether COPD patients with secondary PHT have inferior intensive care outcomes following lung transplantation.

Methods This is a single-center, retrospective analysis of all lung transplant recipients between 2000 and 2009 for a primary diagnosis of COPD. Patients were stratified a priori into three pulmonary arterial pressure groups based on right ventricular systolic pressure (RVSP): no PHT (RVSP $<$ 35 mmHg), mild PHT ($35 \leq$ RVSP $<$ 45 mmHg), and moderate–severe PHT (RVSP $\geq$ 45 mmHg). Outcome measures were duration of mechanical ventilation, intensive care unit (ICU) length of stay, and PaO_2/fraction inspired oxygen (PaO_2/F_IO_2) ratio at 24 h posttransplantation.

Results A total of 46 COPD lung transplant recipients with documented pretransplant RVSP were included in the analysis, including 18 with no PHT, 20 with mild PHT, and eight with moderate–severe PHT. There were no differences in baseline demographics between the three pulmonary arterial pressure groups. The presence of moderate–severe PHT predicted increased duration of mechanical ventilation ($P = 0.024$), worse PaO_2/F_IO_2 ratio at 24 h ($P = 0.027$), and a trend toward increased ICU length of stay ($P = 0.055$). RVSP was the strongest risk factor for duration of mechanical ventilation and ICU length of stay. There was no difference in 1-year survival amongst the three pulmonary arterial pressure groups.

Conclusions Preoperative moderate–severe PHT predicts prolonged duration of mechanical ventilation following lung transplantation in COPD subjects.

Keywords Pulmonary hypertension · Intensive care · Lung transplantation · Prognosis · Chronic obstructive pulmonary disease

J. P. Wrobel (✉) · B. R. Thompson · G. I. Snell · T. J. Williams
Faculty of Medicine, Monash University, 55 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: jeremywrobel@gmail.com

J. P. Wrobel · B. R. Thompson · G. I. Snell · T. J. Williams
Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia

Introduction

Despite great progress during the past three decades, lung transplantation still has substantial early morbidity and mortality. Postoperative morbidity often manifests as respiratory failure requiring prolonged mechanical ventilation and is associated with increased early mortality and healthcare utilization [1]. Whilst risk factors for poor early outcomes and primary graft dysfunction (PGD) following lung transplantation have been extensively studied [2–8], the true impact of preoperative secondary pulmonary hypertension (PHT) upon both short- and long-term lung transplantation outcomes has not been established.

Recently, Fang et al. [9] identified preoperative elevation of pulmonary artery pressure as a significant risk factor for the development of severe PGD following lung transplantation for idiopathic pulmonary fibrosis. This adds to the significant body of literature suggesting a possible association between preoperative secondary PHT and inferior transplant outcomes, including reduced survival, severe PGD, increased intensive care unit (ICU) length of stay, and reduced functional class [3, 4, 7, 10–12]. In

contrast, other studies have not confirmed this association [13–16].

Limited studies have addressed the significance of preoperative secondary PHT upon transplant outcomes in COPD subjects alone. Andersen et al. [17] did not demonstrate increased mortality amongst COPD transplant recipients with preoperative PHT; however, their cohort was taken during a 20-year period and included a range of medical, surgical, and critical care practices, which may have confounded the results. In addition, short-term post-transplantation outcomes were not assessed.

Because COPD is the single largest indication for lung transplantation worldwide [18] and PHT is present in >50 % of such patients [19], the presence of preoperative PHT is potentially an important risk factor for poor outcomes following lung transplantation in these subjects. This retrospective study was performed to determine whether echocardiographic-defined PHT was associated with inferior intensive care outcomes following transplantation for COPD. In particular, we hypothesized that patients with preoperative secondary PHT would have a longer duration of mechanical ventilation, increased ICU length of stay, and more severe PGD.

Methods

A retrospective study at a single institution was conducted of all lung transplant recipients between January 2000 and December 2009 for a primary diagnosis of COPD, including alpha-1 antitrypsin deficiency. The 10 years of transplantation in the study were divided into an early transplant era (2000–2004) and a late transplant era (2005–2009). The study was approved by the institution's Human Ethics Committee.

Definition of Pulmonary Hypertension

PHT was defined as a right ventricular systolic pressure (RVSP) $\geq$ 35 mmHg on echocardiography [16, 20], which was obtained at the time of lung transplant assessment. RVSP measures were attempted on all patients based on the modified Bernoulli equation:

$$\text{RVSP} = 4v^2 + \text{RAP}$$

where v is the peak velocity of the tricuspid regurgitation jet and RAP is the right atrial pressure estimated from the collapsibility of the inferior vena cava on inspiration. Patients were stratified into three pulmonary arterial pressure groups based on a priori classification of RVSP: no PHT (if RVSP $<$ 35 mmHg), mild PHT (if $35 \leq$ RVSP $<$ 45 mmHg), and moderate–severe PHT (if RVSP $\geq$ 45 mmHg). To ensure consistency in echocardiogram assessment, patients were excluded if the echocardiogram had not been performed at our institution or if the RVSP could not be reliably estimated due to either poor echocardiographic signal and/or an insufficient tricuspid regurgitation jet. Preoperative right heart catheterizations were not routinely performed on any patient group.

Outcome Measures

The primary outcome measure was the duration of mechanical ventilation, because this has significant bearing on morbidity, mortality, and resource allocation [21–24]. Secondary outcome measures were ICU length of stay and PaO_2/F_IO_2 ratio at 24 h [15, 25, 26]. If patients were reintubated or readmitted to ICU within 24 h, then the duration of mechanical ventilation and/or ICU length of stay continued to accrue as appropriate. PaO_2/F_IO_2 ratio at 24 h was utilized as a surrogate marker of PGD, which has been well demonstrated to predict short- and long-term outcomes following lung transplantation [11, 27, 28]. Survival, which was measured at 12 months, is reported for completeness, although we anticipated that the study would be underpowered for this endpoint.

Statistical Analysis

Based on our institution's experience and previous studies [15, 25], it was estimated that a sample size of 44 subjects was required to detect a mean difference of 4 days (SD $\pm$ 6 days) in the primary outcome measure of duration of mechanical ventilation with a power of 0.8 at a significance level of 0.05. Baseline demographics and patient outcomes were compared by using the Mann–Whitney U test and Kruskal–Wallis one-way analysis of variance for nonparametric factors, and by independent samples t test and one-way ANOVA for parametric factors. Post-hoc pair wise comparisons were adjusted by a Bonferroni correction. Categorical variables were compared using the chi-square test. Spearman's correlation coefficients were calculated for outcome factors and RVSP. Univariate analysis for duration of mechanical ventilation, ICU length of stay and PaO_2/F_IO_2 ratio were determined by linear regression after log transformation for nonparametric outcomes. Twelve-month survival was compared by using the chi-square test. For all analyses, two-tailed $P < 0.05$ was considered significant. Statistical analysis was performed using PASW (SPSS) Statistics 18.0 (IBM Corporation, Somers, USA).

Results

There were 138 lung transplants for a primary diagnosis of COPD during the 10 years, of which 94 (68 %) underwent echocardiogram at our institution and 44 (32 %) underwent an external echocardiogram. Of the 94 internal

echocardiograms, 46 (49 %) had a documented RVSP, comprising 18 patients with no PHT, 20 patients with mild PHT, and 8 patients with moderate–severe PHT. The recruitment flowchart is depicted in Fig. 1. There were no differences at baseline between the included and excluded subjects (Table 1). Other than RVSP, there were no significant differences at baseline between the three pulmonary arterial pressure groups (Table 2). Furthermore, donor and surgical factors were also comparable across the three pulmonary arterial pressure groups (Table 3).

The presence of moderate–severe PHT predicted increased duration of mechanical ventilation ($P = 0.024$), a trend toward increased ICU length of stay ($P = 0.055$), and a worse PaO_2/F_IO_2 ratio at 24 h ($P = 0.027$; Fig. 2; Table 4). RVSP was significantly correlated with duration of mechanical ventilation ($r = 0.378$, $P = 0.012$) and ICU length of stay ($r = 0.327$, $P = 0.027$). The correlation between RVSP and PaO_2/F_IO_2 ratio was not significant ($r = -0.174$, $P = 0.26$). There was a nonsignificant reduced 12-month survival after lung transplantation amongst the subjects with moderate–severe PHT (12-month survival: 89 % for no PHT, 90 % for mild PHT, 75 % for moderate–severe PHT, $P = 0.54$).

The univariate predictors of ICU outcomes are presented in Table 5. RVSP was the strongest predictor for log duration of mechanical ventilation and log ICU length of stay. Transplant era was the strongest predictor for PaO_2/F_IO_2 ratio at 24 h.

Table 1 Baseline demographics and physiologic parameters

n	Patients included 46	Patients excluded 92	*P*
Age (year)	59 (56–62)	58 (53–61)	0.186
BMI (kg/m^2)	23 ± 3.7	25 ± 3.5	0.06
FEV_1 (% predicted)	20 (16–27)	21 (17–27)	0.724
FEV_1/FVC (%)	28 (23–35)	27 (24–32)	0.69
TLCO (% predicted)	26 ± 9.9	28 ± 8.8	0.586
RV/TLC (%)	66 ± 7.7	66 ± 10.7	0.832
FRC (% predicted)	193 ± 38.0	186 ± 35.3	0.434
PaO_2 (mmHg)	62 ± 14.6	65 ± 14.8	0.64
$PaCO_2$ (mmHg)	49 (40–56)	47 (44–53)	0.771
Smoking history (pack years)	30 (20–49)	45 (37.5–70)	0.088
RVEF–GBPS (%)	54 (47–60)	58 (54–64)	0.188
LVEF–GBPS (%)	61 ± 8.8	64 ± 5.4	0.21
Early transplant era (% of cases)	52	51	0.904

Values are mean ± SD, median (IQR), or percentage of cases as appropriate

GBPS gated blood pool scan; *LVEF* left ventricular ejection fraction; *RVEF* right ventricular ejection fraction

Discussion

Duration of Mechanical Ventilation and ICU Length of Stay

The present study demonstrates that echocardiography-defined, moderate–severe PHT is a significant risk factor for the duration of mechanical ventilation following lung transplantation for COPD compared with subjects with no PHT or mild PHT. This is an important outcome given the morbidity and mortality associated with an increased duration of mechanical ventilation [21, 22].

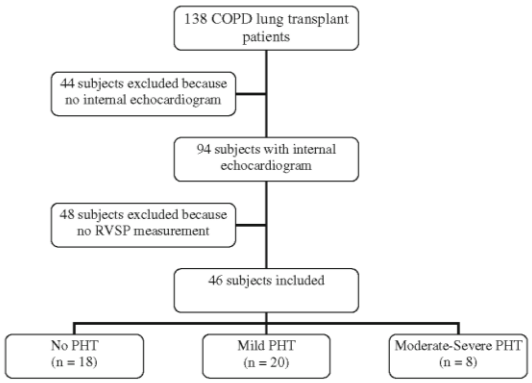

Fig. 1 Recruitment flowchart. *PHT* pulmonary hypertension, *RVSP* right ventricular systolic pressure

The duration of mechanical ventilation may be prolonged following lung transplantation for a variety of reasons, including PGD, respiratory infection, airway complications, cardiovascular or neurological events, hemodynamic instability, drug toxicity, and phrenic nerve injury [1]. Whereas recipient, donor, surgical, and critical care factors all might have bearing on this outcome, the presence of preoperative secondary PHT in COPD subjects may help to identify patients who may be at risk of prolonged mechanical ventilation following transplantation.

Whereas this study only demonstrates a trend toward increased ICU length of stay for COPD patients with moderate–severe PHT, when analyzed as a continuous variable, RVSP was significantly correlated with ICU length of stay. This significant correlation supports a negative association between elevated pulmonary arterial pressures and intensive care outcomes. Despite the inferior ICU outcomes in COPD subjects with preoperative moderate–severe PHT, there was no significant difference in 12-month survival; however, the study was not powered for this endpoint.

Table 2 Baseline demographics and physiologic parameters

	No PHT	Mild PHT	Moderate–severe PHT	*P*
n	18	20	8	
Age (year)	58 (55–61)	60 (56–64)	59 (55–60)	0.484
BMI (kg/m^2)	22 ± 4	23 ± 4	23 ± 3	0.925
Echo-transplant time (month)	8 (4–14)	7 (3–17)	5 (4–8)	0.748
FEV_1 (% predicted)	20 (15–27)	20 (18–31)	23 (19–28)	0.744
FEV_1/FVC (%)	28 (23–32)	28 (22–36)	31 (24–37)	0.81
TLCO (% predicted)	28 ± 11	27 ± 9	23 ± 10	0.481
RV/TLC (%)	67 ± 7	66 ± 10	67 ± 4	0.816
FRC (% predicted)	188 ± 26	196 ± 41	194 ± 55	0.849
PaO_2 (mmHg)	63 ± 14	64 ± 11	56 ± 22	0.461
$PaCO_2$ (mmHg)	50 (40–59)	46 (40–56)	52 (42–55)	0.839
Smoking history (pack years)	30 (20–45)	35 (25–50)	30 (27.5–80)	0.615
E/*e*′ ratio	9 (7–10)	9 (8–12)	12 (9–14)	0.357
RVEF–GBPS (%)	56 (50–61)	51 (47–59)	52 (41–55)	0.434
LVEF–GBPS (%)	61 ± 7	63 ± 10	56 ± 11	0.273
Early transplant era (% of cases)	56	45	63	0.658
RVSP (mmHg)	32 (30–33)	40 (38–44)	58 (52–69)	<0.001

Values are mean ± SD, median (IQR), or percentage of cases as appropriate

E/*e*′ peak early mitral inflow velocity to peak diastolic annular velocity; *Echo-transplant time* time between echocardiography and transplant; *GBPS* gated blood pool scan; *LVEF* left ventricular ejection fraction; *PHT* pulmonary hypertension; *RVEF* right ventricular ejection fraction; *RVSP* right ventricular systolic pressure

Table 3 Donor and surgical factors

	No PHT	Mild PHT	Moderate–severe PHT	*P*
Donor age (year)	35 ± 17	42 ± 14	38 ± 16	0.365
Donor PaO_2/F_IO_2 ratio	443 ± 78	471 ± 81	468 ± 98	0.565
Donor–recipient height diff (cm)	6 ± 9	4 ± 9	9 ± 7	0.451
Donor lung ischemic time (h)	295 ± 95	331 ± 115	353 ± 130	0.419
SLTx (% of cases)	61	40	75	0.186
CPB use (% of cases)	11	5	13	0.733

Values are mean ± SD or percentage of cases as appropriate

CPB cardiopulmonary bypass; F_IO_2 fraction of inspired O_2; *SLTx* single lung transplantation

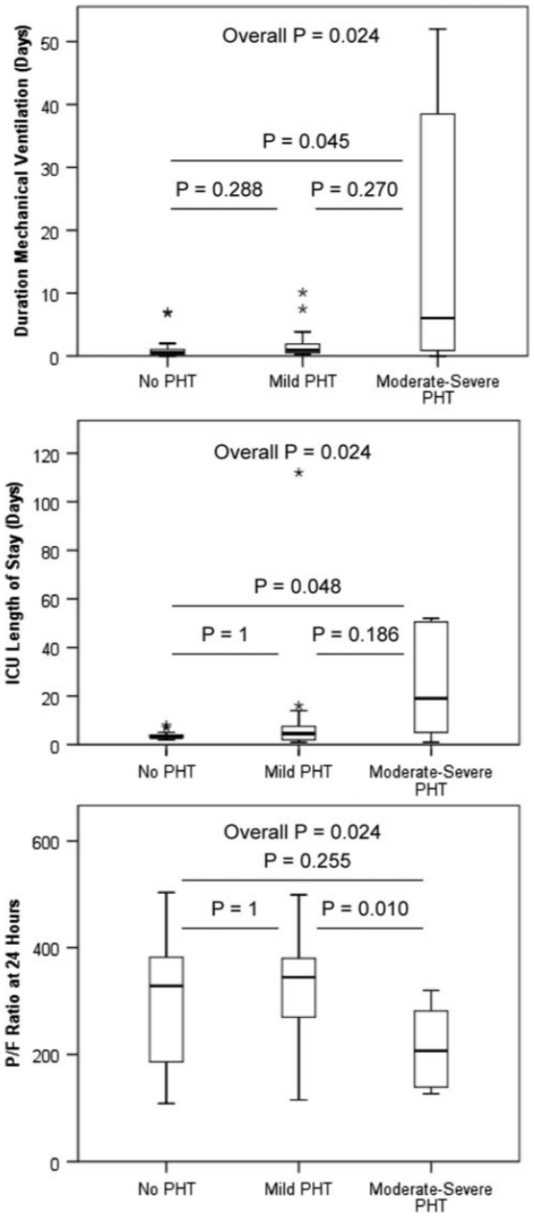

Fig. 2 Duration of mechanical ventilation (**a**), ICU length of stay (**b**), and P/F ratio at 24 h (**c**) according to pulmonary arterial pressure group. The *box plot* illustrates the minimum, lower quartile, median, upper quartile, and maximum values for each group. *Asterisk* represents outliers. *P* values are calculated using the Kruskal–Wallis one-way analysis of variance. Post-hoc pair wise comparisons were adjusted by a Bonferroni correction. *ICU* intensive care unit; *ns* not significant; *P/F ratio* PaO_2/fraction of inspired O_2 ratio; *PHT* pulmonary hypertension

Table 4 Short-term outcomes according to pulmonary arterial pressure group

Outcome	Pulmonary arterial pressure group			*P*
	No PHT	Mild PHT	Moderate–severe PHT	
Duration of mechanical ventilation (days)	0.5 (1.0), 1.3 ± 2.1	0.9 (1.7), 2.0 ± 2.7	6.0 (43.4), 17.9 ± 22.3	0.024[a]
ICU length of stay (days)	3.0 (1.3), 3.6 ± 1.7	4.5 (5.8), 10.5 ± 24.3	19.0 (46.8), 25.3 ± 22.8	0.055[a]
P/F ratio at 24 h	328 (206), 304.2 ± 127.4	345 (114), 332.8 ± 87.2	207 (162), 212.6 ± 77.7	0.027[a], 0.033[b]

Values are median (IQR), mean ± SD

ICU intensive care unit; *P/F ratio* PaO_2/fraction of inspired O_2 ratio; *PHT* pulmonary hypertension

[a] Calculated using Kruskal–Wallis one-way analysis of variance

[b] Calculated using one-way ANOVA

Table 5 Univariate analysis for short-term outcomes

	Log duration of mechanical ventilation	Log ICU length of stay	PaO_2/F_IO_2 ratio at 24 h
Age	0.062 (0.122)	0.001 (0.585)	0.028 (0.282)
BMI	0.084 (0.07)	0.001 (0.800)	0.101 (0.036)
Echo-transplant time	0.002 (0.811)	0.002 (0.756)	0.016 (0.42)
FEV_1 (% predicted)	0.135 (0.02)	0.131 (0.016)	0 (0.984)
FEV_1/FVC	0.215 (0.003)	0.138 (0.013)	0.024 (0.315)
TLCO (% predicted)	0.008 (0.606)	0.001 (0.813)	0.010 (0.541)
RV/TLC	0.031 (0.291)	0.059 (0.128)	0.005 (0.661)
FRC (% predicted)	0.067 (0.118)	0.123 (0.024)	0.038 (0.22)
PaO_2	0 (0.983)	0.025 (0.304)	0.026 (0.301)
$PaCO_2$	0.081 (0.079)	0.046 (0.156)	0.005 (0.656)
Smoking history	0.081 (0.097)	0.069 (0.107)	0.137 (0.021)
E/e′ ratio	0.116 (0.071)	0.079 (0.14)	0.014 (0.547)
RVEF–GBPS	0.016 (0.504)	0.017 (0.461)	0.001 (0.863)
LVEF–GBPS	0.100 (0.052)	0.014 (0.453)	0.090 (0.053)
Early transplant era	0.018 (0.413)	0.004 (0.669)	0.260 (<0.001)
Single lung transplant	0.009 (0.567)	0.003 (0.725)	0.233 (0.001)
RVSP	0.299 (<0.001)	0.311 (<0.001)	0.027 (0.288)

Values are r^2 (*P* value)

E/e′ peak early mitral inflow velocity to peak diastolic annular velocity; *Echo-transplant time* time between echocardiography and transplant; *GBPS* gated blood pool scan; *LVEF* left ventricular ejection fraction; *PHT* pulmonary hypertension; *RVEF* right ventricular ejection fraction; *RVSP* right ventricular systolic pressure

Primary Graft Dysfunction

Despite a range of definitions employed in the literature, PGD has been demonstrated to be a strong predictor of both short- and long-term complications [27]. In particular, PGD has been associated with increased short- and long-term mortality, longer mechanical ventilatory support, longer ICU length of stay, increased hospital length of stay, reduced bronchiolitis obliterans-free survival, reduced 6-min walk distance, and reduced FEV_1 [3, 11, 13, 29–33].

This study demonstrates that patients with moderate–severe PHT have more severe PGD, defined as PaO_2/F_IO_2 ratio at 24 h, following lung transplantation for COPD. The relationship between pulmonary arterial pressure and PaO_2/F_IO_2 ratio is not maintained when RVSP is analyzed as a continuous variable; however, this may be due to several factors. First, a threshold effect may cause RVSP to be a risk factor only above a critical level. This would suggest that mild PHT is not a risk factor for PGD and is consistent with our results showing that patients with no PHT and mild PHT had comparable levels of PGD. This threshold effect is illustrated in Fig. 3, which highlights a wide variation in PaO_2/F_IO_2 ratio when the RVSP is <45 mmHg. However, when the RVSP is >45 mmHg, the PaO_2/F_IO_2 ratio is consistently <320. Second, our utilization of PaO_2/F_IO_2 ratio for the diagnosis of PGD does not incorporate whether patients were ventilator-dependent. Extubated patients may have a relatively lower PaO_2 without the benefit of positive pressure ventilation due to pulmonary atelectasis [33]. Furthermore, the F_IO_2 may be overestimated in nonventilated patients, because delivered F_IO_2 does not necessarily equate with received F_IO_2 due to variable entrainment of room air. Consequently, patients who were extubated by 24 h would have a relatively lower PaO_2/F_IO_2 ratio, all else being equal. Hence, we have previously advocated that extubated patients automatically receive a low PGD grade [33]. Because more patients with no PHT were extubated by 24 h (78 % of no PHT, 61 % of mild PHT, and 38 % of moderate–severe PHT, P = not significant), this would bias the results toward the null hypothesis and may explain the lack of a significant correlation between RVSP and PaO_2/F_IO_2 ratio. Because the moderate–severe PHT group had a worse PaO_2/F_IO_2 ratio despite this bias toward

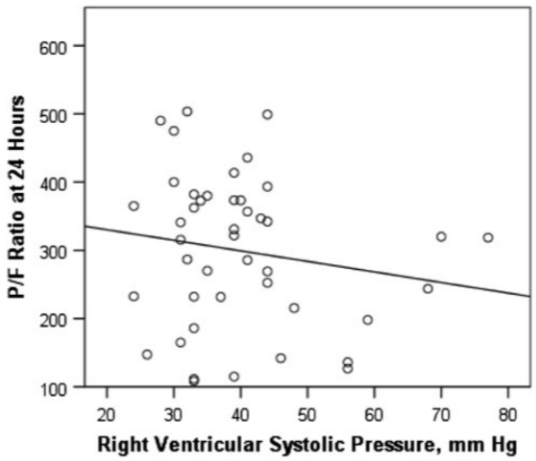

Fig. 3 P/F ratio at 24 h versus right ventricular systolic pressure (RVSP) illustrates a potential threshold effect of RVSP upon the P/F ratio. There is significant variation in the P/F ratio when RVSP < 45 mmHg; however, when RVSP > 45, the P/F ratio is consistently below 320. *P/F ratio* PaO_2/fraction of inspired O_2 ratio; *RVSP* right ventricular systolic pressure

the null, this only strengthens the association between moderate–severe PHT and more PGD.

Transplant era and single-lung transplant procedure were the strongest univariate predictors of PaO_2/F_IO_2 ratio (Table 5) and early transplant era was strongly associated with a single lung transplant procedure in our cohort ($P < 0.001$). Whilst the effect of single lung transplant on PGD has not been established due to the presence of so many confounders [2, 4–6], transplant era has been well demonstrated to affect transplant outcomes [34]. Of note, a change in the donor lung preservation solution to Perfadex was introduced at our institution toward the end of 2004, and Perfadex has been shown to be associated with reduced PGD at 48 h compared with either Euro-Collins or Papworth solution [4, 35, 36]. This change in preservation solution is likely to contribute to the strong relationship between transplant era and PaO_2/F_IO_2 ratio in this group.

The impact of cardiopulmonary bypass upon transplant outcomes has not been established, and whilst some studies have identified cardiopulmonary bypass to be an independent predictor of mortality [11, 37], other studies have found no independent relationship between cardiopulmonary bypass use and mortality, duration of mechanical ventilation, ICU length of stay, hospital length of stay, or PGD [1, 2, 38]. In the present study, the need for cardiopulmonary bypass was not significantly different amongst the pulmonary arterial pressure groups nor was it significantly associated with any of our outcome measures.

Mechanisms Leading to Prolonged Mechanical Ventilation

The mechanism by which preoperative moderate–severe PHT in COPD patients may increase the duration of mechanical ventilation is uncertain. Recently, Fang et al. [9] established preoperative PHT as a risk factor for PGD following lung transplantation for idiopathic pulmonary fibrosis but the pathogenic pathways through which preoperative PHT may contribute to PGD have not been elucidated. Various inflammatory, coagulation, and vasoactive mediators, such as protein C, type 1 plasminogen activator inhibitor, intercellular adhesion molecule-1, and soluble p-selectin, may play a role in the development of PGD [9, 39–42], and these may be modulated by the presence of PHT. Whereas moderate–severe PHT was associated with both prolonged mechanical ventilation and worse PaO_2/F_IO_2 ratio in our study, it is difficult to ascribe the prolonged mechanical ventilation to more severe PGD, because the PaO_2/F_IO_2 ratio was only measured at 24 h and was much more strongly associated with transplant era and single lung transplant procedure than RVSP.

It also has been postulated that an exacerbation of ischemic-reperfusion lung injury may result from hemodynamic forces caused by a "well-trained," hyperdynamic right ventricle contracting against a reduced pulmonary vascular resistance of the implanted lung(s) [39]. Chatila et al. [1] identified preoperative PHT and right ventricular dysfunction as the only preoperative predictors of respiratory failure (defined as mechanical ventilation greater than 48 h) following lung transplantation. The authors suggested that any allograft dysfunction (due to ischemic-reperfusion lung injury, infection, or rejection) was more likely to result in respiratory failure requiring prolonged mechanical ventilation in the presence of preoperative PHT than in subjects with normal pulmonary hemodynamics. In addition, left ventricular diastolic dysfunction may be a persistent issue contributing to respiratory decompensation following lung transplantation but to our knowledge has not been systematically studied in COPD [6].

Previous Studies

Whether preoperative secondary PHT predicts inferior short-term transplant outcomes has not been assessed previously in study populations limited to COPD patients; however, two studies have demonstrated no significant effect on long-term survival. Andersen et al. [17] assessed 246 COPD transplant patients from one institution during a 20-year period, which introduces the confounder of transplant era [34]. Whereas Thabut et al. [43] controlled for transplant era in their large registry study of 5,873 COPD

transplants, 33 % of their patients were missing estimates of pulmonary arterial pressure.

In contrast, studies limited to patients transplanted for idiopathic pulmonary fibrosis have demonstrated that preoperative secondary PHT predicts worse 90-day survival [10] and more grade 3 primary graft dysfunction [9]. Furthermore, several smaller studies (each including a variety of pretransplant diagnoses) have demonstrated that preoperative PHT (including primary and secondary PHT) is associated with worse transplantation outcomes, including longer intensive care length of stay [8] and more primary graft dysfunction [11, 12]. However, other studies have not supported this relationship [13, 14, 16].

It is expected that some positive studies were confounded by the inclusion of patients with idiopathic pulmonary arterial hypertension as this has consistently been shown to be associated with reduced 1-year survival in registry studies [18, 34]. However, Omari et al. [16] excluded pulmonary arterial hypertension in their study limited to 40 transplant recipients for end-stage lung disease and demonstrated that the presence of preoperative secondary PHT was not significantly associated with negative early or late transplantation outcomes.

The conflicting results in the literature likely stem from differences in the definition of PHT [7, 8, 16, 17], variable stratification of PHT severity [3, 8, 14, 25], heterogeneous patients groups [3, 7, 9, 15–17], choice of transplant procedure [3, 7, 8, 10], and measured outcomes [3, 7, 10, 11, 16]. Nevertheless, several studies demonstrate that preoperative secondary PHT is a risk factor for posttransplant outcomes. Our study, limited to COPD subjects and focusing on short-term outcomes, adds to the growing literature supporting preoperative secondary PHT as a poor prognostic marker. We highlight the need for further research in this area stratified by transplant indication, incorporating measures of pulmonary vascular resistance and cardiac function.

Limitations

There are several limitations of this study that need to be acknowledged. First, the retrospective nature of the study introduces potential confounders and limits the PaO_2/F_IO_2 measurements to 24 h posttransplantation, as most study subjects did not have ongoing arterial blood measurements beyond this time. Second, because it is not routine at our institution to perform right heart catheterization in patients with severe COPD, we utilized echocardiography to estimate pulmonary arterial pressure rather than the "gold standard" of right heart catheterization [20]. Despite the well-documented concerns with using echocardiography to estimate pulmonary arterial pressures, especially in COPD patients [44–46], echocardiography remains the most effective noninvasive screening tool for the assessment of PHT in the clinical setting [47] and echocardiographic-based PHT has been associated with reduced survival [48]. Whereas echocardiography was performed on all patients as part of their lung transplant assessment, we attempted to minimize the potential bias of measurement error by restricting our data to echocardiograms performed at a single institution. This restriction on patient selection resulted in only 33 % (46/138) of the potential study subjects being included in the analysis. Although there were no statistically significant differences between included and excluded study subjects, this does limit the generalizability of our findings.

Conclusions

The present study has shown that preoperative moderate–severe PHT identified on echocardiography is associated with worse ICU outcomes following transplantation for COPD. However, without transplantation, COPD patients with PHT have a worse prognosis with early mortality compared with comparable COPD patients without PHT [43]. Consequently, COPD patients with preoperative PHT should be offered lung transplantation with the recognition of possible inferior short-term outcomes. Furthermore, efforts should be made toward minimizing the risks associated with preoperative PHT and management strategies need to be directed toward (1) preoperative assessment of pulmonary arterial pressures to identify patients at risk, (2) pharmacological measures to reduce anesthetic risk, and (3) optimal pulmonary reperfusion techniques to minimize reperfusion lung injury [39].

This study supports the hypothesis that preoperative PHT predicts inferior ICU outcomes following lung transplantation for COPD. This is the first study, to our knowledge, to address specifically the role of preoperative PHT upon intensive care outcomes in the COPD-lung transplant population. This study highlights the need for prospective studies to confirm this association and to clarify the underlying mechanisms. Such studies will need to include assessment of right ventricular structure and function, cardiac output, and pulmonary vascular resistance. This important risk factor may be amenable to intervention, which will hopefully translate into improved clinical outcomes.

Acknowledgments The authors acknowledge Eldho Paul from the Department of Epidemiology and Preventive Medicine, Monash University, Australia, for assistance with the statistics presented. JPW received funding from the Australian National Health and Medical Research Council (APP1017853) to conduct this research.

Conflict of interest None.

References

1. Chatila WM, Furukawa S, Gaughan JP et al (2003) Respiratory failure after lung transplantation. Chest 123(1):165–173
2. Christie JD, Kotloff RM, Pochettino A et al (2003) Clinical risk factors for primary graft failure following lung transplantation. Chest 124(4):1232–1241
3. Whitson BA, Nath DS, Johnson AC et al (2006) Risk factors for primary graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 131(1):73–80
4. Kuntz CL, Hadjiliadis D, Ahya VN et al (2009) Risk factors for early primary graft dysfunction after lung transplantation: a registry study. Clin Transplant 23(6):819–830
5. Lee JC, Christie JD, Keshavjee S (2010) Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. Semin Respir Crit Care Med 31(2):161–171
6. Barr ML, Kawut SM, Whelan TP et al (2005) Report of the ISHLT working group on primary lung graft dysfunction part IV: recipient-related risk factors and markers. J Heart Lung Transplant 24(10):1468–1482
7. Bando K, Keenan RJ, Paradis IL et al (1994) Impact of pulmonary hypertension on outcome after single-lung transplantation. Ann Thorac Surg 58(5):1336–1342
8. Lee KH, Martich GD, Boujoukos AJ et al (1996) Predicting ICU length of stay following single lung transplantation. Chest 110(4):1014–1017
9. Fang A, Studer S, Kawut SM et al (2011) Elevated pulmonary artery pressure is a risk factor for primary graft dysfunction following lung transplantation for idiopathic pulmonary fibrosis. Chest 139(4):782–787
10. Whelan TP, Dunitz JM, Kelly RF et al (2005) Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis. J Heart Lung Transplant 24(9):1269–1274
11. Prekker ME, Nath DS, Walker AR et al (2006) Validation of the proposed international society for heart and lung transplantation grading system for primary graft dysfunction after lung transplantation. J Heart Lung Transplant 25(4):371–378
12. Sullivan VN, Whitson BA, Radosevich DM et al (2006) Elevated pulmonary artery pressure predicts development of severe primary graft dysfunction in paired single lung transplant recipients. J Heart Lung Transplant 25(2S):S47
13. Christie JD, Bavaria JE, Palevsky HI et al (1998) Primary graft failure following lung transplantation. Chest 114(1):51–60
14. Huerd SS, Hodges TN, Grover FL et al (2000) Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. J Thorac Cardiovasc Surg 119(3):458–465
15. Fitton TP, Kosowski TR, Barreiro CJ et al (2005) Impact of secondary pulmonary hypertension on lung transplant outcome. J Heart Lung Transplant 24(9):1254–1259
16. Omari MK, Smith SA, Jacobsen G et al (2011) Effect of pulmonary hypertension in patients with end-stage lung disease on posttransplantation outcomes. Transplant Proc 43(5):1881–1886
17. Andersen KH, Iversen M, Kjaergaard J et al (2012) Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant 31(4):373–380
18. Christie JD, Edwards LB, Kucheryavaya AY et al (2010) The registry of the international society for heart and lung transplantation: twenty-seventh official adult lung and heart-lung transplant report-2010. J Heart Lung Transplant 29(10):1104–1118
19. Thabut G, Dauriat G, Stern JB et al (2005) Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest 127(5):1531–1536
20. Badesch DB, Champion HC, Sanchez MAG et al (2009) Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 54(1, Supplement 1):S55–S66
21. Vincent JL (1994) Outcome from mechanical ventilation. Eur Respir J 7(4):640–642
22. Mutlu GM, Factor P (2000) Complications of mechanical ventilation. Respir Care Clin N Am 6(2):213–252
23. Feng Y, Amoateng-Adjepong Y, Kaufman D et al (2009) Age, duration of mechanical ventilation, and outcomes of patients who are critically ill. Chest 136(3):759–764
24. Gruenberg DA, Shelton W, Rose SL et al (2006) Factors influencing length of stay in the intensive care unit. Am J Crit Care 15(5):502–509
25. Conte JV, Borja MJ, Patel CB et al (2001) Lung transplantation for primary and secondary pulmonary hypertension. Ann Thorac Surg 72(5):1673–1679
26. Boujoukos AJ, Martich GD, Vega JD et al (1997) Reperfusion injury in single-lung transplant recipients with pulmonary hypertension and emphysema. J Heart Lung Transplant 16(4):439–448
27. Arcasoy SM, Fisher A, Hachem RR et al (2005) Report of the ISHLT working group on primary lung graft dysfunction part V: predictors and outcomes. J Heart Lung Transplant 24(10):1483–1488
28. Oto T, Levvey BJ, Pilcher DV et al (2005) Evaluation of the oxygenation ratio in the definition of early graft dysfunction after lung transplantation. J Thorac Cardiovasc Surg 130(1):180–186
29. Christie JD, Sager JS, Kimmel SE et al (2005) Impact of primary graft failure on outcomes following lung transplantation. Chest 127(1):161–165
30. Fiser SM, Tribble CG, Long SM et al (2002) Ischemia-reperfusion injury after lung transplantation increases risk of late bronchiolitis obliterans syndrome. Ann Thorac Surg 73(4):1041–1047
31. Fisher AJ, Wardle J, Dark JH et al (2002) Non-immune acute graft injury after lung transplantation and the risk of subsequent bronchiolitis obliterans syndrome (BOS). J Heart Lung Transplant 21(11):1206–1212
32. Whitson BA, Prekker ME, Herrington CS et al (2007) Primary graft dysfunction and long-term pulmonary function after lung transplantation. J Heart Lung Transplant 26(10):1004–1011
33. Oto T, Levvey BJ, Snell GI (2007) Potential refinements of the international society for heart and lung transplantation primary graft dysfunction grading system. J Heart Lung Transplant 26(5):431–436
34. Christie JD, Edwards LB, Kucheryavaya AY et al (2011) The registry of the international society for heart and lung transplantation: twenty-eighth adult lung and heart-lung transplant report-2011. J Heart Lung Transplant 30(10):1104–1122
35. Marasco SF, Bailey M, McGlade D et al (2011) Effect of donor preservation solution and survival in lung transplantation. J Heart Lung Transplant 30(4):414–419
36. de Perrot M, Bonser RS, Dark J et al (2005) Report of the ISHLT working group on primary lung graft dysfunction part III: donor-related risk factors and markers. J Heart Lung Transplant 24(10):1460–1467
37. Cassivi SD, Meyers BF, Battafarano RJ et al (2002) Thirteen-year experience in lung transplantation for emphysema. Ann Thorac Surg 74(5):1663–1669
38. Szeto WY, Kreisel D, Karakousis GC et al (2002) Cardiopulmonary bypass for bilateral sequential lung transplantation in patients with chronic obstructive pulmonary disease without adverse effect on lung function or clinical outcome. J Thorac Cardiovasc Surg 124(2):241–249
39. de Perrot M, Liu M, Waddell TK et al (2003) Ischemia-reperfusion-induced lung injury. Am J Respir Crit Care Med 167(4):490–511

40. Christie JD, Robinson N, Ware LB et al (2007) Association of protein C and type 1 plasminogen activator inhibitor with primary graft dysfunction. Am J Respir Crit Care Med 175(1):69–74
41. Covarrubias M, Ware LB, Kawut SM et al (2007) Plasma intercellular adhesion molecule-1 and von Willebrand factor in primary graft dysfunction after lung transplantation. Am J Transplant 7(11):2573–2578
42. Kawut SM, Okun J, Shimbo D et al (2009) Soluble p-selectin and the risk of primary graft dysfunction after lung transplantation. Chest 136(1):237–244
43. Thabut G, Ravaud P, Christie JD et al (2008) Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 177(10):1156–1163
44. Arcasoy SM, Christie JD, Ferrari VA et al (2003) Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 167(5):735–740
45. Fisher MR, Criner GJ, Fishman AP et al (2007) Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 30(5):914–921
46. Fisher MR, Forfia PR, Chamera E et al (2009) Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. Am J Respir Crit Care Med 179:615–621
47. Hoeper MM, Barberà JA, Channick RN et al (2009) Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 54(1):S85–S96
48. Stone AC, Machan JT, Mazer J et al (2011) Echocardiographic evidence of pulmonary hypertension is associated with increased 1-year mortality in patients admitted with chronic obstructive pulmonary disease. Lung 189(3):207–212

Lung (2013) 191:227–228
DOI 10.1007/s00408-013-9451-y

ERRATUM

Erratum to: Preoperative Echocardiographic-Defined Moderate–Severe Pulmonary Hypertension Predicts Prolonged Duration of Mechanical Ventilation Following Lung Transplantation for Patients with COPD

Jeremy P. Wrobel · Bruce R. Thompson · Gregory I. Snell · Trevor J. Williams

Published online: 20 February 2013

Erratum to: Lung (2012) 190(6):635–643
DOI 10.1007/s00408-012-9423-7

In Fig. 2 on page 638 of the original publication of this article, the overall *P* values were misprinted for the middle and lower panels. The middle panel should read "Overall $P = 0.055$" and the lower panel should read "Overall $P = 0.027$". The *P* values were correctly printed in the text and in Table 4. The corrected version of Fig. 2 is shown here.

The online version of the original article can be found under doi:10.1007/s00408-012-9423-7.

J. P. Wrobel (✉) · B. R. Thompson · G. I. Snell · T. J. Williams
Faculty of Medicine, Monash University, 55 Commercial Road, Melbourne, VIC 3004, Australia
e-mail: jeremywrobel@gmail.com

J. P. Wrobel · B. R. Thompson · G. I. Snell · T. J. Williams
Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, 55 Commercial Road, Melbourne, VIC 3004, Australia

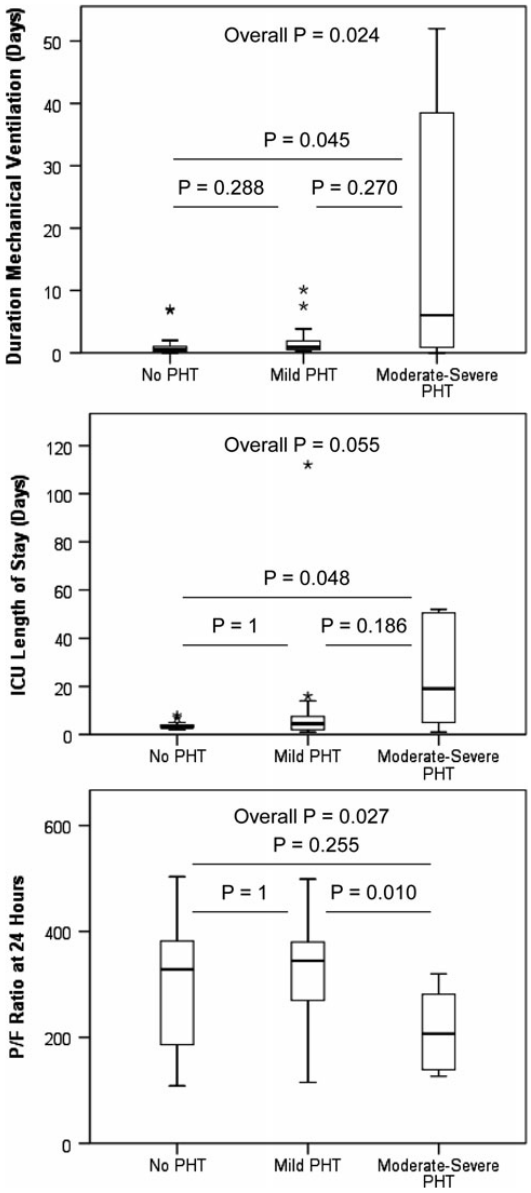

Fig. 2 Duration of mechanical ventilation (**a**), ICU length of stay (**b**), and P/F ratio at 24 h (**c**) according to pulmonary arterial pressure group. The *box plot* illustrates the minimum, lower quartile, median, upper quartile, and maximum values for each group. *Asterisk* represents outliers. *P* values are calculated using the Kruskal Wallis one-way analysis of variance. Post-hoc pair wise comparisons were adjusted by a Bonferroni correction. *ICU* intensive care unit; *ns* not significant; *P/F ratio* PaO_2/fraction of inspired O_2 ratio; *PHT* pulmonary hypertension

2.4 Further Discussion

Although this study supports the notion that preoperative PHT in COPD predicts worse intensive care outcomes following lung transplantation, the mechanisms underpinning this remain obscure. Whilst primary graft dysfunction has been proposed as a potential mechanism for poor outcomes (Chatila, Furukawa et al. 2003, Fang, Studer et al. 2011), in the present study, primary graft dysfunction was confounded by transplant era. In contrast, the notion that lung transplantation may unmask left ventricular diastolic dysfunction has not been previously investigated. Nevertheless, there is increasing literature highlighting the importance of the relationship between COPD and left ventricular diastolic dysfunction. Whilst a causative link between COPD and left ventricular diastolic dysfunction has not been established, there is clearly an association as discussed above in Section 1.1.6**.**

Furthermore, the relationship between COPD, left ventricular diastolic dysfunction and PHT is complex. COPD and left ventricular diastolic dysfunction may both contribute to the development of PHT in these patients. Indeed, left heart disease (owing to systolic dysfunction, diastolic dysfunction or valvular disease) is one of the most common causes of PHT generally (Hoeper, Barberà et al. 2009). Furthermore, Left ventricular diastolic dysfunction is a significant confounder in studies addressing COPD-associated PHT (Wrobel, Thompson et al. 2012b) as (i) it may cause PVH with or without superimposed pulmonary arterial vasoconstriction and vascular remodelling (Hoeper, Barberà et al. 2009), (ii) it is difficult to assess and quantify (Halpern and Taichman 2009), (iii) it is highly prevalent in COPD patients (Boussuges, Pinet et al. 2000), and (iv) many studies have not accounted for COPD subjects according to the presence of left ventricular diastolic dysfunction. Furthermore, it has been demonstrated that left atrial mechanical factors are significantly correlated with PHT levels in COPD subjects (Acikel, Yilmaz et al. 2004, Acikel, Kose et al. 2010).

In conclusion, it would seem that the effect of preoperative PHT in COPD patients upon transplant outcomes must be due to either effects upon the right heart (via chronically raised PVR) and / or unmasking of left heart dysfunction following implantation of the donor lungs with normal trans-pulmonary gradient. Left ventricular diastolic

dysfunction through the course of lung transplantation has not previously been investigated but it may be responsible for considerable early morbidity following transplantation, especially in the presence of COPD and PHT.

Unfortunately, it is difficult to ascertain the mechanism by which preoperative PHT may affect post transplant outcomes without a better understanding of the underlying pathogenesis of COPD-associated PHT. The next two chapters focus on improving our understanding of the mechanisms of PHT in COPD and exploring lung-heart interactions in COPD. Chapter 3 focuses on the distribution of pulmonary arterial remodelling in advanced COPD and the relationship between remodelling and PHT in these patients. Chapter 4 investigates lung-heart interactions and the airway pressure effects upon the pulmonary circulation.

Chapter 3: Pulmonary Arterial Remodelling in COPD

3.1 Specific Declaration for Thesis Chapter 3

3.2 Introduction to Chapter

3.3 Original Research - Accepted

3.4 Further Discussion

3.1 Specific Declaration (Part B) for Thesis Chapter 3

Declaration by candidate
In the case of Chapter 3, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, ethics application, data acquisition, data analysis and interpretation, manuscript preparation, final approval of manuscript	85%

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%)
1. Catriona McLean	Study design, data acquisition, manuscript preparation, final approval of manuscript	
2. Bruce Thompson	Study design, manuscript preparation, final approval of manuscript	
3. Christopher Stuart-Andrews	Data analysis and interpretation, final approval of manuscript	
4. Eldho Paul	Data analysis and interpretation, manuscript preparation, final approval of manuscript	2.5%
5. Gregory Snell	Data analysis and interpretation, manuscript preparation, final approval of manuscript	
6. Trevor Williams	Study design, data analysis and interpretation, manuscript preparation, final approval of manuscript	

Candidate's Signature: [redacted] **Date:** 17/5/2013

Declaration by co-author
The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) Lung Function Laboratory, The Alfred, Melbourne, Australia

Signature 1	[redacted]	6/5/2013
Signature 2		9/4/2013
Signature 3		15/5/2013
Signature 4		9/5/2013
Signature 5		1/5/2013
Signature 6		6/5/2013

3.2 Introduction to Chapter

Pulmonary arterial remodelling has been well documented in patients with PAH (Pietra, Edwards et al. 1989, Chazova, Loyd et al. 1995, Yi, Kim et al. 2000, Stacher, Graham et al. 2012). Unfortunately, pathological remodelling of pulmonary arteries has been less well characterised in patients with COPD. Pathological remodelling of pulmonary arteries is of interest in COPD for two main reasons. First, it may provide some insights into the pathogenesis of PHT in these patients. Second, the presence of pulmonary arterial remodelling in COPD provides the rationale from which to persevere with clinical research exploring selective pulmonary vasodilator therapies for selected COPD patients with PHT.

In this chapter, we present a quantitative pathological assessment of pulmonary arterial remodelling in explanted lungs from COPD patients. We explore the distribution of remodelling across lobar origin, muscular pulmonary arterial size and PHT severity. We also explore whether regional emphysema severity or perfusion distribution are associated with increased pulmonary arterial remodelling.

Our results demonstrate that pulmonary arterial remodelling is consistently present in end-stage COPD and that the pattern of remodelling in COPD is lobe dependent, influenced by pulmonary arterial size and pressure. It appears that increased regional perfusion partially contributes to the increased pulmonary arterial remodelling in these subjects. Further studies are required to better characterise the distribution of remodelling in COPD and to determine the relationship between remodelling and PVR.

3.3 Original Research - Accepted

Wrobel JP, McLean CA, Thompson BR, Stuart-Andrews CR, Paul E, Snell GI and Williams TJ. Pulmonary arterial remodelling in COPD is lobe dependant. *Pulmonary Circulation*. Accepted 2013.

Abstract

Pulmonary arterial remodelling has been demonstrated in patients with severe COPD but it is not known whether lobar heterogeneity of remodelling occurs. Furthermore, the relationship between pulmonary hypertension (PH) and pulmonary arterial remodelling in COPD has not been established. Muscular pulmonary arterial remodelling in arteries 0.10-0.25 mm diameter was assessed in COPD explanted lungs and autopsy controls. Remodelling was quantified as the percentage wall thickness to vessel diameter (%WT) using digital image analysis. Repeat measures mixed effects remodelling for %WT was performed according to lobar origin (upper and lower), muscular pulmonary arterial size (small, medium and large) and echocardiography-based pulmonary arterial pressure (no PH, mild PH and moderate-severe PH). Lobar perfusion and emphysema indices were determined from ventilation-perfusion and computed tomography scans respectively. Overall, %WT was greater in 42 COPD subjects compared with 5 controls ($P < 0.0001$). Within the COPD group, %WT was greater in the upper lobes ($P < 0.0001$) and in the small muscular pulmonary arteries ($P < 0.0001$). Lobar differences were most pronounced in medium and large arteries. Lobar emphysema index was not associated with arterial remodelling however, there was a significant positive relationship between the lobar perfusion index and pulmonary arterial remodelling ($P = 0.024$). The presence of PH on echocardiography showed only a trend to a small effect on lower lobe remodelling. The pattern of pulmonary arterial remodelling in COPD is complicated and lobe dependent. Differences in regional blood flow partially account for the lobar heterogeneity of pulmonary arterial remodelling in COPD.

Keywords

Emphysema

Pathology

Pulmonary circulation

Pulmonary hypertension

Regional blood flow

Main Text

Introduction

The presence of pulmonary hypertension (PH) in patients with chronic obstructive pulmonary disease (COPD) has been associated with increased mortality1,2 and morbidity.[3,4] Thus far, studies using selective and non-selective pulmonary vasodilators in COPD have not translated into improvements in meaningful clinical outcomes.[5-11] This has led to a renewed interest into the underlying pathogenesis of PH in COPD as a basis for determining the appropriateness of pursuing PH-specific therapies.[12]

The pathogenesis of COPD-associated PH is complex.[12] Whilst hypoxia plays a key role, other factors such as pulmonary arterial remodelling have been implicated.[13] Pulmonary arterial remodelling is an umbrella term that describes a range of pulmonary vascular changes observed in COPD, including medial hypertrophy, longitudinal muscle deposition, intimal hyperplasia, elastin and collagen deposition and muscularisation of the pulmonary arterioles.[14] Pulmonary arterial remodelling has often been quantified anatomically as a measure of intimal and/or medial thickness relative to arterial size.[15,16]

Although pulmonary vascular changes have been demonstrated in subjects with COPD-associated PH,[14] the relationship between PH and pulmonary arterial remodelling has been difficult to establish.[14,16,17] This is due to (i) the difficulty in determining the natural progression of pulmonary arterial remodelling, (ii) the inter-subject and intra-subject variability of pulmonary arterial changes, (iii) the inability to accurately assess pulmonary arterial pressure using non-invasive techniques and (iv) the confounder of reciprocal causation - whilst changes due to pulmonary arterial remodelling may elevate pulmonary arterial pressures, PH itself may lead to pulmonary arterial remodelling.[18] As COPD is a disease of significant parenchymal and perfusion heterogeneity,[19,20] this may partially account for the intra-subject variability of pulmonary arterial remodelling. However, it is unclear whether this heterogeneity is reflected in differences in arterial remodelling between the upper and lower lung lobes. This study primarily aims to determine whether subjects with severe COPD have lobar differences with regard to pulmonary arterial remodelling. We also seek to determine the influence of pulmonary

arterial size, pulmonary arterial pressure, regional emphysema severity and regional pulmonary perfusion upon pulmonary arterial remodelling in COPD.

Methods

Subjects and controls

From 2000 to 2009, 44 subjects with complete pre-operative assessments (including an estimate of right ventricular systolic pressure (RVSP) on echocardiography) underwent lung transplantation for severe COPD (not including patients with alpha-1 antitrypsin deficiency) at our institution. Of these subjects, 42 had adequate stored tissue for analysis. We developed normal control data by interrogating our institution's autopsy lung specimen database for age-matched, non-smoking controls with no history of chronic cardio-respiratory disease. From 153 lung autopsies during 2007-2009, only 5 were deemed true controls. The study was approved by the institution's Human Ethics Committee.

Morphologic analysis

At the time of lung transplantation, explanted lungs were placed in formaldehyde solution. The lungs were inflated but not injected prior to morphologic analysis. The lungs were sectioned, examined for macroscopic abnormalities before haemotoxylin and eosin staining and standard histologic examination. In addition, for each subject, one upper lobe and lower lobe representative paraffin-embedded section of approximately 1 cm^2 were prepared for histologic evaluation using smooth muscle actin immunohistochemistry with a Verhoeff elastin counterstain as previously described.[21]

One observer (JPW), blinded to the subjects' pulmonary arterial pressure and lobar origin of the specimen, prospectively performed morphologic assessment using digital image analysis. Pulmonary arterial remodelling was quantified by percentage wall thickness (%WT) measured as (2 x wall thickness x 100) / arterial diameter, as per previous studies (*see* Figure 1).[15,16] *See* online supplement for further details.

Vessel size

Morphologic analysis was limited to muscular pulmonary arteries 0.10-0.25 mm in diameter based on previous work by Shelton and colleagues demonstrating increased %WT in muscular pulmonary arteries of this size.[15] Muscular pulmonary artery size was categorised, rather than treated as a continuous variable,[13,17,22,23] on *a priori* basis as small (0.10-0.15 mm), medium (0.15-0.20 mm) and large (0.20-0.25 mm) in diameter.

Lobar emphysema and perfusion indices

Lobar percentage emphysema was determined prospectively via 3-dimensional reconstruction of the lung transplant assessment computed tomography (CT) chest images using the "density mask" method.[24] *See* online supplement for further details.

During lung transplant assessment, ventilation-perfusion scans were performed using inhaled Technegas and intravenous injection of technetium-99m macro-aggregated albumin, respectively. Ventilation and perfusion images were collected with a gamma camera for both phases of the investigation. The distribution and intensity of the radioactivity count from the intravenous technetium-99m allowed imputation of regional perfusion. The lobar perfusion index was calculated as the ratio of lobar-to-total pulmonary perfusion.

Pulmonary arterial pressure

All patients had an echocardiogram during lung transplant assessment. (Our institution does not routinely perform right heart catheterisation for the evaluation of severe COPD.) COPD patients where the RVSP could be determined were stratified into three pulmonary arterial pressure groups based on *a priori* classification of the RVSP obtained on the lung transplant assessment echocardiogram as follows: no PH (if RVSP < 35 mm Hg),[25] mild PH (if $35 \leq$ RVSP < 45 mm Hg) and moderate-severe PH (if RVSP ≥ 45 mm Hg).

Statistical analysis

Statistical analysis was performed using the SAS software version 9.2 (SAS Institute, Cary, NC, USA). Repeat measures mixed effects models for %WT were fitted using lobar origin, pulmonary arterial size and pulmonary arterial pressure as main effects. Post-hoc pair wise comparisons were adjusted by a Bonferroni correction. The effects of lobar percentage emphysema and lobar perfusion index on %WT were assessed after adjusting for lobar origin and pulmonary arterial size. Weighted Pearson correlation compared lobar percentage emphysema and perfusion index. Intra-observer and inter-observer reliability were determined using the Bland-Altman method. For all analyses, statistical significance was set at a two-tailed $P < 0.05$.

Results

Five controls were identified. They were appropriately age-matched against 42 COPD subjects (59.0 ± 5.1 v 58.8 ± 4.9 yrs respectively, $P = 0.9$). Amongst the COPD subjects, there were 15 with no PH, 19 with mild PH and 8 with moderate-severe PH. Baseline demographics are presented in Table 1.

Qualitative assessment

In the explanted COPD lungs, the parenchyma showed moderate to extensive acinar tissue loss. The vessel changes of PH varied from minor intimal myofibroblastic thickening to significant medial muscular hypertrophy. Plexiform lesions and fibrinoid necrosis were not seen. The large pulmonary arteries showed variable degrees of atherosclerosis. Chronic bronchitis was seen in three cases. There was one subject each with extensive fibrosis, pneumonic consolidation and fibrin thrombi. Scant interstitial granulomata were seen in six cases. There was no evidence of neoplasia.

Vessel size and measurement

From 42 COPD subjects and 5 controls, we analysed 1,513 muscular pulmonary arteries (*see* Table 2). Intra-observer and inter-observer reliability for measures of %WT were

excellent with an absolute bias (95% limits of agreement) of %WT of only 0.5% (-2.2 to 2.7) and 1.8% (-4.5 to 8.1), respectively.

Pulmonary arterial remodelling in COPD

The %WT was substantially increased in the COPD subjects (irrespective of the presence of PH) compared with controls (%WT ± SEM: 30.4 ± 1.1 v 13.2 ± 3.1 respectively, $P < 0.0001$). Amongst controls, there were no significant differences across pulmonary arterial size or lobar origin. However, in COPD subjects, %WT was significantly increased in the upper lobes compared with the lower lobes ($P < 0.0001$) and %WT was significantly increased in the small muscular pulmonary arteries compared with the medium and large muscular pulmonary arteries ($P < 0.0001$, Figure 2).

Interaction effects between lobar origin and pulmonary arterial size

For the COPD subjects, interaction effects were present between lobar origin and muscular pulmonary arterial size such that %WT was significantly less for the medium ($P < 0.0001$) and large ($P < 0.01$) muscular pulmonary arteries in the lower lobe compared with the upper lobe, whereas %WT for the small muscular pulmonary arteries was not different across lobar origin (Figure 3a). %WT values are presented according to lobar origin and muscular pulmonary arterial size in Table 3.

Lobar emphysema and perfusion indices

Lobar percentage emphysema and lobar perfusion index measures were only available on 20 and 17 COPD subjects, respectively. Lobar percentage emphysema was greater in the upper lobes than the lower lobes (index ± SD: 54 ± 19 v 45 ± 16 % respectively, $P = 0.02$), but was not significantly associated with %WT ($P = 0.48$).

The lobar perfusion index was not different between the upper and lower lobes (index ± SD: 0.24 ± 0.05 v 0.24 ± 0.07 respectively, $P = 0.93$). Nevertheless, the lobar perfusion index was positively associated with %WT ($P = 0.024$, Table 4). There were only 14

COPD subjects with measures for both lobar percentage emphysema and lobar perfusion index and these were not significantly correlated (weighted r = -0.23, P = 0.43).

Pulmonary arterial pressure and pulmonary arterial remodelling

Overall, there were no significant differences in %WT across the pulmonary arterial pressure groups (P = 0.45, Figure 2c). Interaction effects were present between lobar origin and pulmonary arterial pressure group such that COPD subjects without PH had less %WT in the lower lobes compared with the upper lobes ($P < 0.0001$) but %WT did not change for the other PH categories across lobe origin (Figure 3b). Despite this interaction, within each lobe there were no significant differences between the PH groups. There were no interaction effects between muscular pulmonary arterial size and pulmonary arterial pressure group (Figure 3c).

Discussion

The key findings of our study are (i) that pulmonary arterial remodelling is consistently present in end-stage COPD; (ii) in COPD, there is increased pulmonary arterial remodelling in the upper lobes compared with the lower lobes; (iii) in COPD, there is greater remodelling in the small muscular pulmonary arteries compared with the medium and larger arteries; and (iv) an increase in regional lung perfusion is associated with increased pulmonary arterial remodelling.

Additionally, no consistent relationship between PH (determined on echocardiography) and pulmonary arterial remodelling was found. Nevertheless, interaction effects are present between lobar origin, pulmonary arterial size and PH. These findings demonstrate the complexity of the distribution of pulmonary arterial remodelling in COPD.

(i) COPD versus controls

Our study confirms the presence of pulmonary arterial remodelling universally in end-stage COPD compared with age-matched, non-smoking controls. Our small number of controls free from chronic cardiac or respiratory disease reflects a small subset of our

usual hospital autopsy population. By way of comparison, our measures for pulmonary arterial remodelling amongst COPD subjects are slightly less compared to those obtained by Kubo and colleagues[16] who studied an older cohort of 10 subjects with severe COPD undergoing lung volume reduction surgery (%WT: 30% v 36% respectively). Similarly, our controls had reduced %WT compared to Kubo and colleagues (13% v 22% respectively) but their controls were older, non-smoking lung cancer patients which likely accounts for this difference. In addition, slight differences in methodology suggest that our study represents a more conservative estimate of pulmonary arterial remodelling.

Whilst we have not examined patients with idiopathic pulmonary arterial hypertension in this study, Chazova et al[26] examined 19 patients with idiopathic pulmonary arterial hypertension and demonstrated a mean percentage wall thickness of approximately 60% compared with only 10% in their 7 controls. In our institution, we have previously demonstrated increased mean percentage intimal and smooth muscle thickness in muscular pulmonary arteries of patients with pulmonary veno-occlusive disease compared with 6 controls (19.3% and 34.1% v 9.0% and 25.3%, respectively).[21] Unfortunately, each study employs slightly different methodology and assesses different pulmonary artery sizes so direct comparisons must be made with caution.

(ii) Lobe effects

There was increased pulmonary arterial remodelling in the upper lobes compared with the lower lobes in COPD subjects. Due to the difficulty in finding true controls, we were unable to assess for lobar differences in remodelling amongst controls with adequate statistical power. Few previous studies have examined whether differences in pulmonary arterial remodelling exist across different lobes. To our knowledge, the only other study to find increased remodelling in the upper lobes identified increased intimal thickness, but not medial thickness, in the upper lobes of non-smokers and smokers without significant lung disease.[23] However, the authors did not elaborate further on this finding – they did not control their results for pulmonary arterial size nor did they provide any measure of pulmonary arterial pressure. A subsequent study by the same group[22] included subjects with severe COPD but did not report any lobar information regarding pulmonary arterial remodelling.

Other studies reporting lobar-specific measures of pulmonary arterial remodelling have not shown lobar differences.[14,27-30] These negative results are consistent with a hypothesis that the entire pulmonary arterial bed is under that same pulmonary arterial pressure and hence, should have a similar degree of pulmonary arterial remodelling. However, this presumes that it is the pulmonary arterial pressure that drives the remodelling process independent of pulmonary arterial size or location. In contrast, Botney[31] has proposed a two-hit hypothesis requiring both increased pulmonary blood flow and endothelial injury prior to the development of neointimal pulmonary arterial remodelling. In reality, pulmonary arterial pressures and remodelling are likely co-dependent, moderated by arterial resistance, shear forces and blood flow. Consequently, muscular pulmonary arterial size and location are likely to affect this interaction.

(iii) Lobe and pulmonary arterial size

Pulmonary arterial remodelling was increased in the small muscular pulmonary arteries compared with the medium and larger arteries, and this is consistent with some previous studies.[15,17,27,29,32] However, other studies have not supported this relationship.[13,30] Some caution is needed in inferring a predilection for remodelling of smaller pulmonary arteries as our measure of remodelling is partially dependent on the size of the vessel.

The distribution of pulmonary arterial remodelling in different sized pulmonary arteries is also lobe dependant, with relative sparing of lower lobe pulmonary arterial remodelling in the medium and large muscular pulmonary arteries. Of note, the distribution of muscular pulmonary arterial sizes is different between the lower and upper lobes (repeated measures weighted mean diameter ± SEM: 0.154 ± 0.002 mm v 0.160 ± 0.002 mm respectively, $P < 0.01$), a relationship that was not present in the control group. From our data, we are not able to determine whether this difference in the distribution of pulmonary arterial sizes is associated with greater arterial remodelling in the upper lobes. Nevertheless, the notion that the distribution of vessel size can influence pulmonary haemodynamics is supported by a recent study[33] which demonstrated that having fewer small pulmonary vessels was associated with increased pulmonary arterial pressure in a cohort of patients with severe emphysema enrolled in the National Emphysema and Treatment Trial.

(iv) Lobar emphysema and perfusion indices

CT quantification of emphysema has been found to be a good marker of the anatomical distribution and severity of emphysema[24,34] but the relationship between histologic emphysema severity and pulmonary arterial remodelling has been inconsistent.[14,22,23] Although we demonstrated greater upper lobe emphysema, there was no significant relationship between lobar severity of emphysema and pulmonary arterial remodelling. Furthermore, there was no significant relationship between lobar severity of emphysema and pulmonary artery density, measured as the number of pulmonary arteries identified per lobe per subject.

In contrast, the lobar perfusion index was found to have a significant positive relationship to pulmonary arterial remodelling after adjusting for lobe and muscular pulmonary arterial size. It would be expected that emphysematous areas of the lung receive less perfusion due to destruction of the pulmonary capillary bed and this would be further exacerbated by hypoxic pulmonary vasoconstriction. However, if emphysema causes localised pulmonary arterial remodelling, one would expect reduced perfusion to these areas and a negative relationship between pulmonary arterial remodelling and the lobar perfusion index. Surprisingly, we have demonstrated that pulmonary arterial remodelling and lobar perfusion index are positively associated suggesting that pulmonary arterial remodelling may occur secondary to increased pulmonary perfusion. Hence, our data supports the aforementioned two-hit hypothesis of remodelling.[31]

Nevertheless, the explanation for increased upper lobe remodelling in this COPD cohort is uncertain. Whilst not directly associated with increased upper lobe emphysema, the increased upper lobe remodelling may be a result of vascular changes induced by cigarette smoke which, due to regional differences in ventilation, perfusion, inflammation and clearance of toxins, appear to have a predilection for the upper lobes.[35] Furthermore, cigarette smoke exposure has been demonstrated to cause pulmonary vascular changes, independent of the development of emphysema in a guinea-pig model.[36]

(v) Pulmonary arterial pressure

Invasive pulmonary haemodynamics are not performed as part of routine lung transplant assessment in our centre, however, all COPD patients are assessed by echocardiography. The interaction effects observed between lobe and pulmonary arterial pressure suggest that upper lobe remodelling occurs in the absence of PH. Within the lower lobes, there was a trend to increased pulmonary arterial remodelling amongst COPD subjects with moderate-severe PH compared to COPD subjects without PH (unadjusted $P < 0.05$, adjusted $P = 0.32$). It is not apparent whether lower lobe pulmonary arterial remodelling occurs prior or subsequent to the development of PH.

Limitations

The present study has two main limitations. First, lobar percentage emphysema and lobar perfusion index were only performed on a subset of COPD subjects. Although percentage emphysema scores were calculated prospectively, they were measured using the archived 7.5mm thick, contrast-enhanced CT chest scans performed during the lung transplant assessment. Whilst thinner slice, non-contrast CT is generally the preferred mode from which to quantify emphysema scores, the correlation between percentage emphysema and quantitative histology is similar across a range of CT section thicknesses ranging from 1 to 10 mm.[34]

The second main limitation is that pulmonary arterial pressures were estimated from echocardiography rather than the gold standard of right heart catheterisation. Clearly determining COPD to have a high transpulmonary gradient and correlating the vascular remodelling with pulmonary vascular resistance would lead to a more definitive study. Despite the well documented concerns with using echocardiography to estimate pulmonary arterial pressures, especially in COPD patients,[37,38] echocardiography remains the most accepted non-invasive tool for the assessment of PH in the clinical setting[39] and echocardiographic-determined PH has been associated with increased mortality in COPD patients.[40]

Conclusion

This study confirms that severe COPD is associated with a complex pattern of significant pulmonary arterial remodelling. Utilising histological, radiological and clinical data, the distribution of remodelling in COPD is lobe dependent, influenced by pulmonary arterial size and pressure. Increased regional blood flow partially contributes to the increased pulmonary arterial remodelling in these subjects. These findings have not been previously demonstrated.

To explain lobar differences in pulmonary arterial remodelling, and the interactions between regional blood flow, arterial remodelling and PH requires further research. The present study would support future studies utilising invasive pulmonary haemodynamics, particularly measurement of pulmonary vascular resistance.

References

1. Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, Kessler R. Prognostic factors in COPD patients receiving long-term oxygen therapy: importance of pulmonary artery pressure. Chest 1995;107:1193-1198.
2. Doi M, Nakano K, Hiramoto T, Kohno N. Significance of pulmonary artery pressure in emphysema patients with mild-to-moderate hypoxemia. Respir Med 2003;97:915-920.
3. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158-164.
4. Sims MW, Margolis DJ, Localio AR, Panettieri RA, Kawut SM, Christie JD. Impact of pulmonary artery pressure on exercise function in severe COPD. Chest 2009;136:412-419.
5. Stolz D, Rasch H, Linka A, Di Valentino M, Meyer A, Brutsche M, Tamm M. A randomised, controlled trial of bosentan in severe COPD. Eur Respir J 2008;32:619-628.
6. Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, Roca J, Barbera JA. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am J Respir Crit Care Med 2010;181:270-278.
7. Sajkov D, McEvoy RD, Cowie RJ, Bradley JA, Antic R, Morris RG, Frith PA. Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. Chest 1993;103:1354-1361.
8. Morley TF, Zappasodi SJ, Belli A, Giudice JC. Pulmonary vasodilator therapy for chronic obstructive pulmonary disease and cor pulmonale: treatment with nifedipine, nitroglycerin, and oxygen. Chest 1987;92:71-76.
9. Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, Westerhof N, Postmus PE, Boonstra A, Vonk-Noordegraaf A. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Respir J 2008;31:759-764.
10. Vonbank K, Ziesche R, Higenbottam TW, Stiebellehner L, Petkov V, Schenk P, Germann P, Block LH. Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. Thorax 2003;58:289-293.

11. Lederer DJ, Bartels MN, Schluger NW, Brogan F, Jellen P, Thomashow BM, Kawut SM. Sildenafil for chronic obstructive pulmonary disease: A randomized crossover trial. COPD 2012;9:268-275.
12. Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. J Heart Lung Transplant 2012;31:557-564.
13. Magee F, Wright JL, Wiggs BR, Pare PD, Hogg JC. Pulmonary vascular structure and function in chronic obstructive pulmonary disease. Thorax 1988;43:183-189.
14. Wilkinson M, Langhorne CA, Heath D, Barer GR, Howard P. A pathophysiological study of 10 cases of hypoxic cor pulmonale. Q J Med 1988;66:65-85.
15. Shelton DM, Keal E, Reid L. The pulmonary circulation in chronic bronchitis and emphysema. Chest 1977;71:303-306.
16. Kubo K, Ge RL, Koizumi T, Fujimoto K, Yamanda T, Haniuda M, Honda T. Pulmonary artery remodeling modifies pulmonary hypertension during exercise in severe emphysema. Respir Physiol 2000;120:71-79.
17. Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: national institutes of health nocturnal oxygen therapy trial. Lung 1992;170:109-124.
18. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease: a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958;18:533-547.
19. Wagner PD, Dantzker DR, Dueck R, Clausen JL, West JB. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. J Clin Invest 1977;59:203-216.
20. Wedzicha JA. The heterogeneity of chronic obstructive pulmonary disease. Thorax 2000;55:631-632.
21. Harch S, Whitford H, McLean C. Failure of medical therapy in pulmonary arterial hypertension: is there an alternative diagnosis? Chest 2009;135:1462-1469.
22. Hale KA, Ewing SL, Gosnell BA, Niewoehner DE. Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction. Am Rev Respir Dis 1984;130:716-721.

23. Hale KA, Niewoehner DE, Cosio MG. Morphologic changes in the muscular pulmonary arteries: relationship to cigarette smoking, airway disease, and emphysema. Am Rev Respir Dis 1980;122:273-278.

24. Muller NL, Staples CA, Miller RR, Abboud RT. "Density mask": an objective method to quantitate emphysema using computed tomography. Chest 1988;94:782-787.

25. Badesch DB, Champion HC, Gomez Sanchez MA, Hoeper MM, Loyd JE, Manes A, McGoon M, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55-S66.

26. Chazova I, Loyd JE, Zhdanov VS, Newman JH, Belenkov Y, Meyrick B. Pulmonary artery adventitial changes and venous involvement in primary pulmonary hypertension. Am J Pathol 1995;146:389-397.

27. Simons P, Reid L. Muscularity of pulmonary artery branches in the upper and lower lobes of the normal young and aged lung. Br J Dis Chest 1969;63:38-44.

28. Warnock ML, Kunzmann A. Changes with age in muscular pulmonary arteries. Arch Pathol Lab Med 1977;101:175-179.

29. Warnock ML, Kunzmann A. Muscular pulmonary arteries in chronic obstructive lung disease. Arch Pathol Lab Med 1977;101:180-186.

30. Fernie JM, Lamb D. Assessment of the effects of age and smoking on the media of muscular pulmonary arteries. J Pathol 1988;155:241-246.

31. Botney MD. Role of hemodynamics in pulmonary vascular remodeling: implications for primary pulmonary hypertension. Am J Respir Crit Care Med 1999;159:361-364.

32. Barbera JA, Riverola A, Roca J, Ramirez J, Wagner PD, Ros D, Wiggs BR, Rodriguez-Roisin R. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:423-429.

33. Matsuoka S, Washko GR, Yamashiro T, Estepar RS, Diaz A, Silverman EK, Hoffman E, et al. Pulmonary hypertension and computed tomography measurement of small pulmonary vessels in severe emphysema. Am J Respir Crit Care Med 2010;181:218-225.

34. Gierada DS, Bierhals AJ, Choong CK, Bartel ST, Ritter JH, Das NA, Hong C, et al. Effects of CT section thickness and reconstruction kernel on emphysema

quantification relationship to the magnitude of the CT emphysema index. Acad Radiol 2010;17:146-156.

35. Takahashi M, Fukuoka J, Nitta N, Takazakura R, Nagatani Y, Murakami Y, Otani H, Murata K. Imaging of pulmonary emphysema: a pictorial review. Int J Chron Obstruct Pulmon Dis 2008;3:193-204.
36. Wright JL, Churg A. Effect of long-term cigarette smoke exposure on pulmonary vascular structure and function in the guinea pig. Exp Lung Res 1991;17:997-1009.
37. Arcasoy SM, Christie JD, Ferrari VA, Sutton MSJ, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med 2003;167:735-740.
38. Fisher MR, Criner GJ, Fishman AP, Hassoun PM, Minai OA, Scharf SM, Fessler AH, Group NR. Estimating pulmonary artery pressures by echocardiography in patients with emphysema. Eur Respir J 2007;30:914-921.
39. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-1263.
40. Stone AC, Machan JT, Mazer J, Casserly B, Klinger JR. Echocardiographic evidence of pulmonary hypertension is associated with increased 1-year mortality in patients admitted with chronic obstructive pulmonary disease. Lung 2011;189:207-212.

Table 1 Baseline demographics and physiologic parameters for COPD subjects.

	Subjects with COPD
n	42
Age, years	58.8 ± 4.9
Ax-Tx time, months	10.5 ± 10.2
BMI, kg/m^2	23.0 ± 3.7
FEV_1, % predicted	22.7 ± 8.0
FEV_1/FVC, %	30.0 ± 9.6
TLCO, % predicted	26.5 ± 10.0
RV/TLC, %	66.0 ± 7.3
PaO_2, mm Hg	62.1 ± 15.2
$PaCO_2$, mm Hg	49.4 ± 10.8
Smoking history, pack yrs	38.3 ± 23.5
RVEF-GBPS, %	51.6 ± 11.5
LVEF-GBPS, %	60.7 ± 9.1
RVSP, mm Hg	40.6 ± 11.7

Values are mean ± SD.

Ax-Tx time, duration between lung transplant assessment and lung transplantation; BMI, body mass index; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GBPS, gated blood pool scan; LVEF, left ventricular ejection fraction; $PaCO_2$, partial pressure of arterial carbon dioxide; PaO_2, partial pressure of arterial oxygen; RV, residual volume; RVEF, right ventricular ejection fraction; RVSP, right ventricular systolic pressure; TLC, total lung capacity; TLCO, transfer factor of the lung for carbon monoxide.

Table 2 The number of vessels analysed, according to lobar origin and muscular pulmonary arterial size.

Lobe	Artery Size	Control subjects (n = 5)	COPD (n = 42)
Upper			
	Small	50 (10.0)	279 (6.6)
	Medium	13 (2.6)	197 (4.7)
	Large	7 (1.4)	103 (2.5)
Lower			
	Small	73 (14.6)	420 (10.0)
	Medium	31 (6.2)	205 (4.9)
	Large	8 (1.6)	127 (3.0)
Total		182 (36.4)	1,331 (31.7)

Values are total number of vessels (average number of vessels per subject). All vessels that met the inclusion criteria where included in the analysis.

Table 3 Mean percentage wall thickness (%WT), according to lobar origin and muscular pulmonary arterial size.

Lobe	Artery Size	Control subjects (n = 5)	COPD (n = 42)
Upper			
	Small	13.6 ± 1.3	33.0 ± 1.3
	Medium	13.9 ± 1.8	32.1 ± 1.3
	Large	10.2 ± 2.2	29.1 ± 1.4
Lower			
	Small	13.4 ± 1.2	31.9 ± 1.2
	Medium	13.1 ± 1.4	27.0 ± 1.3
	Large	12.2 ± 2.1	25.2 ± 1.4

Values are adjusted mean of %WT ± SEM.

Table 4 Effect of lobar percentage emphysema and lobar perfusion index on the percentage wall thickness.

	Parameter Estimate[a]	Adjusted[a] P Value
Lobar Percentage Emphysema	0.36 ± 0.5	0.482
Lobar Perfusion Index	1.69 ± 0.7	0.024

Estimates are incremental effects on %WT ± SEM, for every 10% increase in index value.

[a]Adjusted for lobe and pulmonary arterial size.

%WT, percentage wall thickness.

Figures

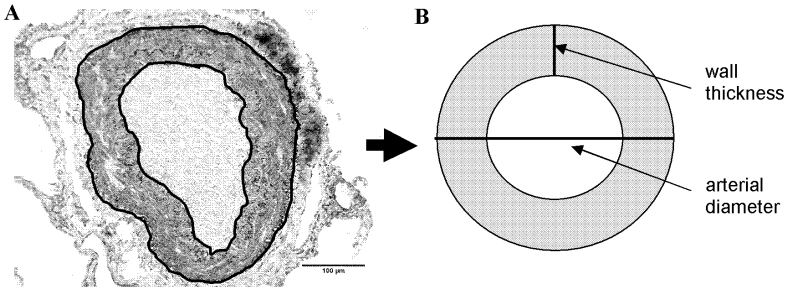

Figure 1 The lumen and external elastic lamina circumference were measured from image A. This enabled an idealised artery to be drawn (image B), based on the radius which was derived from the circumference measures. The percentage wall thickness (%WT) was then calculated as 2 x wall thickness x 100 / arterial diameter.

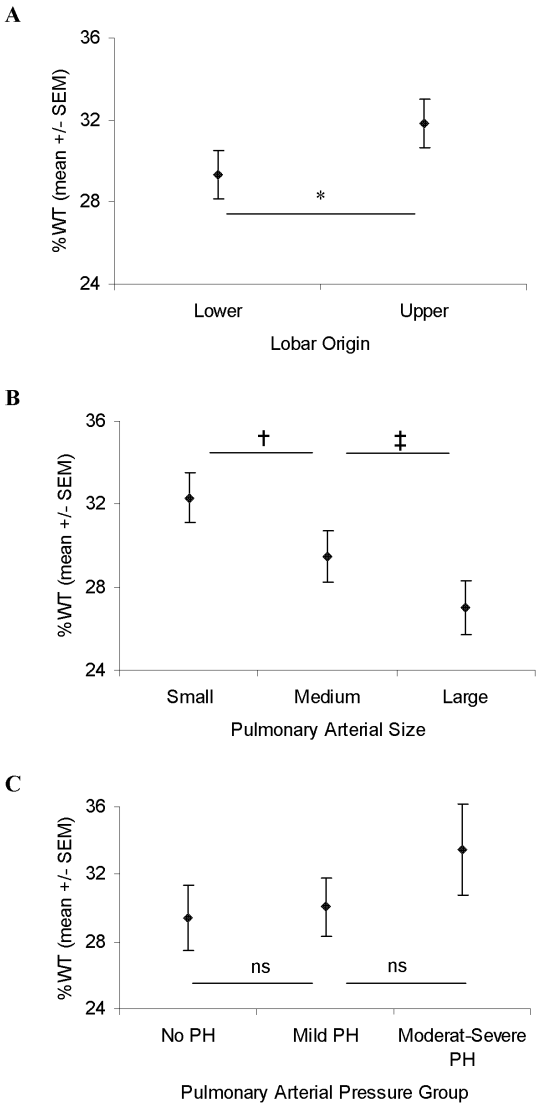

Figure 2 Overall, %WT is greater in the upper lobe compared with the lower lobe (panel A) and greater in the small muscular pulmonary arteries compared with the medium and large muscular pulmonary arteries (panel B). %WT did not vary significantly amongst pulmonary arterial pressure group (panel C).

* $P < 0.0001$, † $P < 0.001$, ‡ $P < 0.01$.

ns, not significant; PH, pulmonary hypertension; %WT, percentage wall thickness.

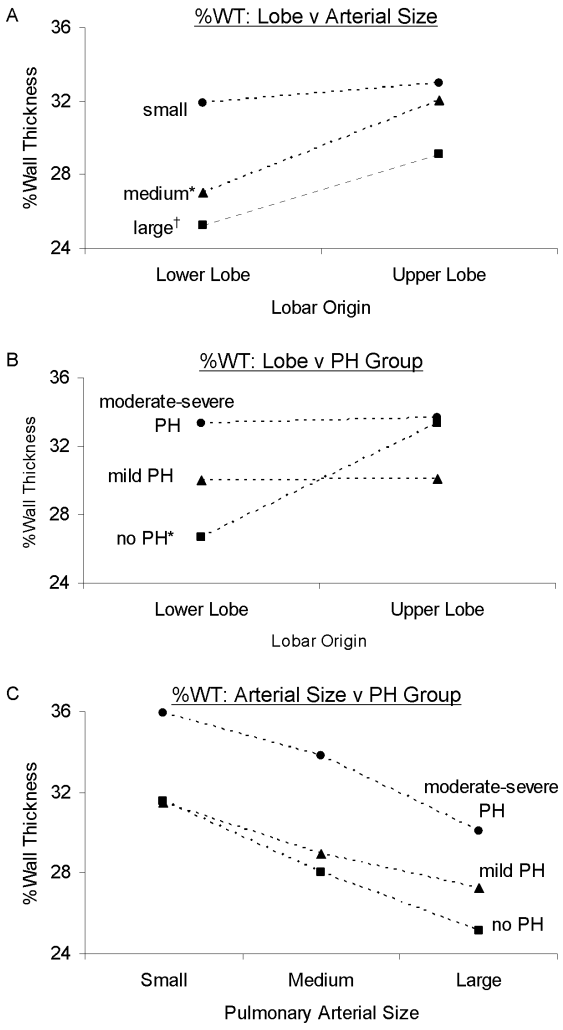

Figure 3 Interaction effects of lobar origin, arterial size and PH group upon %WT: %WT for medium and large pulmonary arteries are less in the lower lobes compared with the upper lobes, however there is no difference in the small pulmonary arteries across lobar origin (panel A). %WT for the no PH group is less in the lower lobes compared with the upper lobes, however there is no difference for mild and moderate-severe PH groups across lobar origin (panel B). There are no interaction effects between pulmonary arterial size and pulmonary arterial pressure group (panel C).

P values are for comparisons between lower and upper lobe.

* $P < 0.0001$, † $P < 0.01$.

PH, pulmonary hypertension, %WT, percentage wall thickness.

Online Supplement

Morphologic Analysis Supplement

Lung morphology was assessed prospectively (Olympus BH2 microscope, Olympus, Japan) and all muscular pulmonary arteries were photographed (Optronics MircoFire® microscope digital CCD camera, Optronics, USA) from non-consolidated, non-fibrotic lung tissue with a magnification of either 200x or 400x depending on the size of the vessel. Photographs were calibrated using a 1 mm stage micrometer at the appropriate magnification.

Muscular pulmonary arteries were identified primarily by vessel location within the parenchyma.[1] A continuous and clearly identifiable internal elastic lamina was used as an adjunct to help distinguish pulmonary arteries from pulmonary veins and venules.[2]

Morphologic assessment was performed using digital image analysis (Image Pro Plus, version 5.0, Media Cybernetics Inc., Rockville, USA; ImageJ software, version 1.44b, National Institute of Health, Bethesda, USA). The outline of the arterial lumen was carefully traced using ImageJ, which digitally calculated values for circumference and area. To improve reliability of the measures, repeated tracings were performed on each lumen until two consecutive tracings provided both luminal circumference and luminal area within ±3%. The latter of the two reproducible measures was used in the analysis. The same process was repeated for the external elastic lamina. To ensure data validity, intra-observer (JPW) and inter-observer (JPW and CAM) reliability were assessed.

Arterial diameter was defined as the diameter of the external elastic lamina.[3] All muscular pulmonary arteries ranging from 0.10 to 0.25 mm in diameter were included in the analysis if the lumen and external elastic lamina were complete. If the ratios of the long diameter to the short diameter of both the lumen and external elastic lamina were greater than two, the vessel was excluded in order to ensure that the arteries included for analysis had been cross-sectioned in an approximate transverse plane.[4]

The luminal area was calculated using the radius derived from the luminal circumference (i.e. radius = circumference / ($2.\pi$)) rather than using the digitally

measured area[4] as it was considered less prone to significant variation resulting from arterial collapse or non-circular arteries.[5] The arterial area was subsequently adjusted for the increase in luminal area so as to obtain a derived arterial area. The average arterial wall thickness (WT) was defined as the difference between the derived arterial radius less the derived luminal radius. Pulmonary artery remodelling was then defined as %WT and calculated as 2 x average wall thickness x 100 / arterial diameter.

Lobar Percentage Emphysema Supplement

At time of lung transplant assessment, contrast-enhanced CT chest with 7.5mm thick sections was undertaken at full inspiration. Three-dimensional images of the upper and lower lung lobes were reconstructed by tracing the lung lobe on successive images using digital analysis software (Advantage Workstation 4.3, General Electric Medical Systems, Connecticut, USA). Lobar volume was measured as the volume of tissue with a pixel threshold of less than negative 500 Hounsfield Units (HU).[6-7] The percentage emphysema was defined for each lobe as the percentage of pixels less than negative 900 HU compared to the corresponding lobar volume.[6-8]

There is presently no consensus on the optimal threshold with which to measure emphysema on CT but most studies have used a threshold of between -890 and -960 HU. We utilised a relatively high threshold of less than -900 HU for emphysema as the use of contrast and thicker slice (i.e. 7.5mm compared with 1.25mm) both increase lung density.[7,9] Hence, a threshold of less than -960 HU would underestimate the quantity of emphysema. As lobar percentage emphysema was designed in this study to examine the relative distribution of emphysema between the upper and lower lobe, rather than emphysema severity, a higher threshold was desirable. Furthermore, Gierada and colleagues[6] have previously demonstrated that a higher threshold (i.e. less negative) for emphysema provides more robust measures of emphysema scores across a variety of reconstruction kernel and CT section thickness.

Online Data Supplement References

1. Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease: a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. Circulation 1958;18:533-547.
2. Gallagher PJ. Blood vessels. In: Sternberg SS, ed. Histology for pathologists. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1997:772.
3. Semmens M. The pulmonary artery in the normal aged lung. Br J Dis Chest 1970;64:65-72.
4. Barbera JA, Riverola A, Roca J, Ramirez J, Wagner PD, Ros D, Wiggs BR, Rodriguez-Roisin R. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:423-429.
5. Fernie JM, Lamb D. New method for measuring intimal component of pulmonary arteries. J Clin Pathol 1985;38:1374-1379.
6. Gierada DS, Bierhals AJ, Choong CK, Bartel ST, Ritter JH, Das NA, Hong C, et al. Effects of CT section thickness and reconstruction kernel on emphysema quantification relationship to the magnitude of the ct emphysema index. Acad Radiol 2010;17:146-156.
7. Gierada DS, Yusen RD, Pilgram TK, Crouch L, Slone RM, Bae KT, Lefrak SS, Cooper JD. Repeatability of quantitative CT indexes of emphysema in patients evaluated for lung volume reduction surgery. Radiology 2001;220:448-454.
8. Muller NL, Staples CA, Miller RR, Abboud RT. "Density mask": an objective method to quantitate emphysema using computed tomography. Chest 1988;94:782-787.
9. Newell JD, Jr. Quantitative computed tomography of lung parenchyma in chronic obstructive pulmonary disease: an overview. Proc Am Thorac Soc 2008;5:915-918.

3.4 Further Discussion

This study demonstrates that lobar heterogeneity of pulmonary arterial remodelling does exist between the upper and lower lobes in patients with advanced COPD. Furthermore, by examining interaction effects between lobar origin, muscular pulmonary artery size and pulmonary arterial pressure, this study reveals that the pattern of remodelling in advanced COPD is complex.

Whilst the mechanism for this lobar heterogeneity in remodelling is not clear, it may be in part due to differences in regional blood flow, supported by the relationship between remodelling and increased regional blood flow. This is supported by the "two-hit hypothesis" of remodelling whereby vascular injury and increased blood flow are both required for the development of neointimal lesions in the pulmonary vasculature (Botney 1999). It must be noted however, that during perfusion scanning in our study, patients were in the supine position. Consequently, this may artificially increase the upper lobe perfusion score as the gravitation effects on perfusion are not present. It is not clear how patient positioning during perfusion scanning affects the relationship between regional perfusion and pulmonary arterial remodelling.

The second aim of this study was to determine the relationship between pulmonary arterial remodelling and PHT. Whilst there was no significant relationship between PHT and remodelling in this study, there was a strong difference in lobar remodelling amongst patients with no PHT. Furthermore, the relationship between regional blood flow and pulmonary arterial remodelling serves to highlight that pulmonary arterial pressure and pulmonary arterial remodelling are not only co-dependent, but regional blood flow is intimately involved. Indeed, it is well recognised that pulmonary arterial pressure, resistance and blood flow are connected by Ohm's law, such that:

$$\text{Flow} = \text{pressure} / \text{resistance}$$

Unfortunately, this study does not have right heart catheterisation data and hence, data on PVR is not available. Although we may postulate that increased pulmonary arterial remodelling leads to greater PVR, further study is required to confirm this relationship.

Such studies will also need to recognise that PVR is comprised of structural and dynamic factors. The structural factors include the anatomy of the pulmonary arterial tree (the distribution of the size and number of the pulmonary arteries) and pulmonary arterial remodelling (wall thickness which affects lumen calibre).

Furthermore, as Burton and Patel (Burton and Patel 1958) argue, it is the vessel wall tension in addition to transmural pressure that affect the vessel calibre and hence, resistance to flow. Consequently, it may be hypothesised that vessels with increased vascular remodelling with resultant thickening of the vessel wall will lead to a reduced vascular compliance. Further, reduced vascular compliance may be less prone to changes in transmural pressure as a greater transmural pressure change is required to effect a change in the vessel calibre. This would imply that vessels with vascular remodelling could be less subject to dynamic PHT that occurs in the setting of hypoxia and acidaemia.

The relationship between pulmonary arterial remodelling, flow and pressure are further compounded by the complexities of fluid mechanics and the recognition that there are regional differences within the lung of each of these factors. Pulmonary arterial pressure and flow cause shear stresses upon the pulmonary arterial endothelium which regulates acute vessel tone and chronic remodelling of the vessel (Botney 1999). A number of cellular responses occur secondary to shear stress that depend on the duration of the stress (*see* Table 12). In addition, the type of flow (laminar or turbulent) may also have bearing on the pulmonary endothelial response to shear stress (Malek, Alper et al. 1999, Stone, Coskun et al. 2003).

In conclusion, this study highlights that the distribution of pulmonary arterial remodelling in advanced COPD is complex. The relationship between blood flow and remodelling suggest that haemodynamic factors contribute towards the development of PHT. Nevertheless, further studies are required to investigate the relationship between pulmonary arterial remodelling and PVR. In addition, regional differences in pressure, flow, resistance and remodelling will help aid our understanding of the interactions between these factors. The following chapter addresses another potential contributor to PHT in advanced COPD, namely lung-heart interactions and the role of increased airway pressure.

Table 12 Pulmonary Vascular Response to Shear Stress

Adapted from (Botney 1999).

Duration of stress	**Response**
Milliseconds to seconds	Potassium channel activation G protein activation IP_3, DAG elevation Calcium fluxes
Minutes	Nitric oxide and PG_I2 release MAP kinase signalling NF-κβ activation bFGF upregulation Cytoskeleton begins rearranging
Hours	Changes in gene regulation Focal adhesion rearrangements Change in cell shape
Hours to days	Cell proliferation Cell alignment

bFGF, basic fibroblast growth factor; DAG, diacylglycerol; IP3, inositol 1,4,5-triphosphate; MAP, mitogen-activated protein; NF-kβ, nuclear factor kappa β; PGI_2, prostaglandin I_2.

Chapter 4: Lung-Heart Interactions: Respiration and the Pulmonary Circulation in COPD

4.1 Specific Declaration for Thesis Chapter 4

4.2 Introduction to Chapter

4.3 Original Research - Submitted

4.4 Further Discussion

4.1 Specific Declaration (Part B) for Thesis Chapter 4

Declaration by candidate
In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Study design, ethics application, data acquisition, data analysis and interpretation, manuscript preparation, final approval of manuscript	85%

The following co-authors contributed to the work.

Name	Nature of contribution	Extent of contribution (%)
1. Bruce Thompson	Study design, manuscript preparation, final approval of manuscript	
2. Christopher Stuart-Andrews	Data acquisition, data analysis and interpretation, final approval of manuscript	
3. Kirk Kee	Data analysis and interpretation, final approval of manuscript	2.5%
4. Gregory Snell	Study design, manuscript preparation, final approval of manuscript	
5. Mark Buckland	Study design, data acquisition, final approval of manuscript	
6. Trevor Williams	Study design, data analysis and interpretation, manuscript preparation, final approval of manuscript	

Candidate's Signature: [redacted] **Date:** 17/5/2013

Declaration by co-autho [redacted]
The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.
(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;
(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;
(4) there are no other authors of the publication according to these criteria;
(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and
(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s) Lung Function Laboratory, The Alfred, Melbourne, Australia

Signature 1	[redacted]	9/4/2013
Signature 2		15/5/2013
Signature 3		9/4/2013
Signature 4		2/5/2013
Signature 5		14/5/13
Signature 6		6/5/2013

4.2 Introduction to Chapter

PHT is common in moderate-severe COPD and is due to a combination of structural and functional factors (Wrobel, Thompson et al. 2012b). Lung-heart interactions are known to occur continuously throughout the respiratory and cardiac cycles (Scharf, Pinsky et al. 2001). Whilst pulmonary hyperinflation is speculated to contribute to PHT in COPD there is limited direct evidence to support this. Hence, we sought to determine the effects of changes in airway pressure upon pulmonary and systemic haemodynamics in patients with severe COPD.

In this chapter, we investigate lung-heart interactions in patients with severe COPD receiving IPPV immediately prior to lung transplantation. In particular, we quantify the effect of IPPV upon pulmonary haemodynamics. We also investigate the relative importance of changing lung volume and changing airway pressure upon pulmonary haemodynamics, paying particular attention to the effect of IPPV upon dPAP. Finally, we investigate the effects of IPPV upon right ventricular stroke volume, measured by the pulmonary pulse pressure.

We demonstrate that IPPV increases dPAP and that these changes are largely mediated by positive airway pressure changes rather than due to increases in lung volume. Whilst this study provides 'in principle' support of the notion that gas trapping and $PEEP_I$ may increase pulmonary arterial pressures in COPD patients with dynamic hyperinflation, the magnitude of this interaction is relatively small and unlikely to have clinical relevance in non-mechanically ventilated COPD patients. On the other hand, the effect of IPPV upon right ventricular stroke volume may contribute to right ventricular failure in the critical care setting. Further studies are required to more fully evaluate the effects of different ventilation strategies upon right ventricular function in the critical care setting.

4.3 Original Research - Submitted

Wrobel JP, Thompson BR, Stuart-Andrews CR, Kee K, Snell GI, Buckland M, and Williams TJ. Intermittent positive pressure ventilation increases diastolic pulmonary arterial pressure in advanced COPD. *Heart & Lung*. Submitted 2013.

Title:

Intermittent positive pressure ventilation increases diastolic pulmonary arterial pressure in advanced COPD

Authors:

Jeremy P. Wrobel[1,2,3] MPH, FRACP, Bruce R. Thompson[1,2] PhD, Christopher R. Stuart-Andrews[2] PhD, Kirk Kee[1,2] FRACP, Gregory I. Snell[1,2] MD, FRACP, Mark Buckland[4] FRANCA, and Trevor J. Williams[1,2] MD, FRACP

Departments and institutions:

[1] Department of Medicine, Monash University, Melbourne, Australia

[2] Allergy, Immunology & Respiratory Medicine, The Alfred, Melbourne, Australia

[3] Advanced Lung Disease Unit, Royal Perth Hospital, Perth, Australia

[4] Department of Anaesthesia, The Alfred, Melbourne, Australia

Corresponding author:

Jeremy Wrobel

Royal Perth Hospital

Wellington Street

Perth WA 6000

Australia

[redacted]

F: +61 8 9224 3866

[redacted]

Abstract

Objectives

To measure the impact of intermittent positive pressure ventilation (IPPV) on diastolic pulmonary arterial pressure (dPAP) and pulmonary pulse pressure in patients with advanced COPD.

Background

The physiological effects of raised intrathoracic pressures upon the pulmonary circulation have not been fully established.

Methods

22 subjects with severe COPD receiving IPPV were prospectively assessed with pulmonary and radial arterial catheterisation. Changes in dPAP were assessed from end-expiration to early inspiration during low and high tidal volume ventilation.

Results

Inspiration during low tidal volume IPPV increased the median [IQR] dPAP by 3.9 [2.5-4.8] mm Hg ($P<0.001$). During high tidal volume, similar changes were observed. The IPPV-associated change in dPAP was correlated with baseline measures of PaO_2 (rho=0.65, P=0.005), pH (rho=0.64, P=0.006) and right atrial pressure (rho=-0.53, P=0.011).

Conclusions

In severe COPD, IPPV increases dPAP and reduces pulmonary pulse pressure during inspiration.

Keywords

Diastolic pulmonary gradient
Intrathoracic pressure
Pulmonary arterial wedge pressure
Pulmonary haemodynamics
Pulmonary hypertension

Introduction

Chronic obstructive pulmonary disease (COPD) is frequently complicated by the development of pulmonary hypertension[1] which is associated with increased mortality,[2-4] increased hospitalisations[5] and reduced functional status.[6] Efforts to treat the pulmonary hypertension in these patients have been disappointing.[7-11] Consequently, there has been renewed interest in the pathogenesis of pulmonary hypertension in patients with COPD[12] in an effort to explore novel therapeutic management strategies.

Although several authors have postulated that gas trapping and dynamic lung hyperinflation contribute to pulmonary hypertension in COPD,[13-18] there is limited evidence to support this. Nevertheless, previous studies have demonstrated that increased intrathoracic pressures are associated with reductions in right ventricular preload, right ventricular cardiac output[19, 20] and left ventricular cardiac output.[21] Recently, Pinsky[22] has reviewed heart lung interactions during mechanical ventilation, focussing on pulse pressure and stroke volume variation as a means of identifying volume responsiveness due to the effect of raised intrathoracic pressures on right ventricular preload. However, whether raised intrathoracic pressures, as occurs with pulmonary hyperinflation, increase pulmonary vascular resistance (PVR) and whether this subsequently affects right ventricular cardiac output have not been established.

Exploring airway pressure effects upon pulmonary haemodynamics is challenging due to the concurrence of direct and indirect pressure and lung volume effects, pulsatile cardiac contractions, ventricular inter-dependence, pulmonary blood volume changes and the shared anatomical space of the heart and lungs.[23, 24] Furthermore, continuous measures of PVR are not readily available nor well validated,[25] especially in human studies. The PVR is also limited in that it is prone to error as an increased cardiac output may recruit more pulmonary vascular bed and thereby reduce PVR in normal subjects. In contrast, the diastolic pulmonary arterial pressure (dPAP) is a useful measure of pulmonary haemodynamics as it reflects both the pulmonary circulation and the back pressure from the left side of the heart, it can be assessed beat-by-beat, is correlated

with pulmonary vascular resistance and is minimally affected by right ventricular stroke volume.[26, 27]

In this study, we examine the airway pressure effects upon pulmonary haemodynamics in mechanically ventilated patients with severe, stable COPD in the operating theatre immediately prior to a lung transplant procedure. We hypothesised that increased airway pressure (as occurs during inspiration with intermittent positive pressure ventilation, IPPV) would increase dPAP. Secondly, we sought to determine whether baseline cardiopulmonary parameters could predict the dPAP response to inspiration during IPPV.

Methods

Subjects

The study was approved by the institution's Human Ethics Committee. Patients with end-stage COPD were prospectively recruited from the lung transplant waiting list at a single institution and all subjects provided written and informed consent. Baseline demographic and physiologic parameters were taken from lung transplant assessment data. All haemodynamic responses during IPPV were captured once the subjects were anaesthetised at the time of lung transplantation, immediately prior to the commencement of surgery.

Primary outcome – diastolic pulmonary arterial pressure (dPAP)

The primary outcome was the change from end-expiration to early inspiration in dPAP. To investigate whether IPPV principally affects dPAP or all systemic and pulmonary pressures equally, the change in dPAP was compared with changes in systolic pulmonary arterial pressure (sPAP), diastolic systemic arterial pressure (dBP), systolic systemic arterial pressure (sBP), right atrial pressure (RAP) and pulmonary arterial wedge pressure (PAWP).

Secondary outcomes

To investigate predictors of the dPAP response to IPPV, we examined the relationship between the percentage change in dPAP and a range of cardiopulmonary parameters that may affect pulmonary vascular compliance, namely $PaCO_2$, PaO_2, PAWP, pH, PVR, RAP, stroke volume index (SVI) and tidal volume (V_T).

Ventilation strategy

Patients were anaesthetised using propofol, fentanyl, midazolam and rocuronium. All patients were intubated in preparation for transplantation with an appropriately sized Bronchocath^{TM} (Mallinckrodt, Covidien, Mansfield, Massachusetts, USA) double lumen endotracheal tube. During the study period, patients were ventilated (Aisys Anesthesia Carestation, GE Healthcare, Wisconsin, Milwaukee, USA) with both endotracheal tube lumens connected to a common ventilator.

To determine whether the inspiratory changes to dPAP during IPPV were driven by airway pressure or lung volume changes, we compared the haemodynamic responses during low V_T versus high V_T without changing the delivered inspiratory positive airway pressure.

The "low" V_T protocol comprised inspiratory pressure 15-25 cm H_2O, zero extrinsic positive end-expiratory pressure, respiratory rate of 10 breaths.min^{-1}, inspiratory-to-expiratory ratio of 1:3.5, and inspired oxygen fraction of 60%. Ventilation was then adjusted by anaesthetist preference to achieve stable haemodynamics, arterial oxygenation of greater than 94% saturation and a stable minute ventilation of 4-6 L.min^{-1}. (Hypercapnia was permitted.) The respiratory rate was then reduced to 6 breaths.min^{-1} without adjusting inspiratory positive airway pressure, in order to achieve a "high" V_T, whilst attempting to minimise gas trapping and maintain minute ventilation. After 5 minutes with the high V_T strategy, haemodynamic assessment was repeated.

Haemodynamic assessment

All patients had a pulmonary arterial catheter (Edwards Lifesciences, Irvine, California, USA) inserted via the right internal jugular vein. Zero reference was at the midthorax with the patient lying horizontally. Cardiac output was measured using the thermodilution method as the average of three dilutions within 10% of each other. Systemic arterial pressures were measured by a radial artery catheter (Pressure Monitoring Kit with TruWave Disposable Pressure Transducer, Edwards Lifesciences, Irvine, California, USA). Haemodynamics were calculated by the patient monitor (IntelliVue MP90, Philips Healthcare, Andover, Massachusetts, USA) and continuous waveform data was captured by data acquisition software (TrendFace, ixellence GmbH, Wildau, Germany) for off-line analysis.

Pressure measurements

Commencement of inspiration was determined by change in direction of airway flow (*see* Figure 1). For systolic pressure measurement, the complete upstroke limb of the arterial pressure cycle was required to occur during the appropriate phase of ventilation (the upstroke and downstroke limbs were required for diastolic pressure measurement). RAP and PAWP were measured as the mean pressure over a single cardiac cycle during the appropriate phase of respiration. Measurements were averaged over three consecutive breaths during steady state.[28] Changes in PAP, BP, RAP and PAWP were measured from end-expiration to early inspiration.

Statistics

Based on previous animal studies[29] we estimated that a sample size of 14 was required to detect a mean difference of 2 mm Hg (SD ± 1.5 mm Hg) in the primary outcome measure of dPAP with a power of 0.80 at a significance level of 0.05. Differences between low V_T and high V_T parameters were assessed using Wilcoxon signed rank tests. Pulmonary and systemic arterial pressure changes were compared using the Friedman test. Post-hoc pair wise comparisons were calculated using the Wilcoxon signed rank test with a Bonferroni correction. For all analyses, two tailed

P<0.05 was considered significant. Statistical analysis was performed using PASW/SPSS Statistics 18.0 (IBM Corporation, Somers, USA).

Results

Baseline values

22 COPD lung transplant patients were recruited for the study and baseline demographics are described in Table 1. Ventilation, blood gas parameters and haemodynamics at the different ventilation strategies are presented in Table 2 confirming that we were able to achieve higher V_T without increasing the delivered inspiratory positive airway pressure. Although minute ventilation was slightly reduced with the higher V_T ventilation, alveolar ventilation was unchanged, evidenced by the stable (albeit elevated) $PaCO_2$. This indicates that the reduced minute ventilation was associated with reduced dead-space ventilation.

IPPV and dPAP

During low V_T ventilation, dPAP, sPAP, dBP, sBP, RAP and PAWP each increased significantly from end-expiration to early inspiration (P<0.001). The median [IQR] dPAP increased by 3.9 [2.5-4.8] mm Hg which was greater than the other pressure increases as illustrated in Figure 2A. A similar pattern was observed during high V_T ventilation whereby all pressures increased. Again, the greatest effect was on dPAP which increased by 3.8 [3.0-4.4] mm Hg (P<0.001) as shown in Figure 2B. There were no significant differences in the IPPV-associated pressure changes between low V_T and high V_T ventilation (*see* Figure 3).

Correlates of increased pulmonary vascular tone

At low V_T ventilation, the percentage change in dPAP was significantly correlated with baseline pH, PaO_2 and RAP (*see* Table 4 and Figure 3). During high V_T ventilation, there were no significant baseline correlates with the percentage change in dPAP. Percentage change in dPAP was significantly correlated with the inspiratory change in pulmonary pulse pressure during low and high V_T ventilation.

Discussion

The main findings of this study in severe, stable COPD patients during general anaesthesia are: (i) IPPV increases dPAP during early inspiration. Although sPAP, dBP, sBP, RAP and PAWP all increased, the effects were smaller in magnitude than the effect on dPAP. (ii) Arterial oxygenation, acidaemia and right atrial pressure are associated with the dPAP response to IPPV.

Diastolic PAP is influenced by both the pulmonary circulation and the back pressure from the left side of the heart. Nevertheless, the physiological underpinnings and clinical relevance of dPAP have been debated for decades.[27, 30, 31]. In normal subjects, dPAP is predominantly influenced by the back pressure from the left side of the heart (which can be measured by PAWP).[32] However, in patients with pulmonary disease, including COPD, there exists a persistent gradient between dPAP and PAWP (i.e. the diastolic pulmonary gradient).[27]

An early study by Fowler and colleagues[33] demonstrated a significant relationship between log dPAP and log PVR amongst a hospital inpatient population with a variety of pathologies. Honda et al[26] subsequently demonstrated that both dPAP and the diastolic pulmonary gradient are significantly correlated with PVR index in patients with congenital heart disease with left to right shunt. Laskey and colleagues[34] have shown an inverse relationship between dPAP and the stroke volume response during exercise in primary pulmonary hypertension. More recently, Gerges and colleagues[35] demonstrated that an elevated diastolic pulmonary gradient was associated with increased pulmonary vascular remodelling and an increased risk of death amongst a database population with simultaneous left and right heart catheterisations.

(i) IPPV and dPAP

Whilst IPPV increases all pulmonary and systemic arterial pressures, there is a greater effect on dPAP. That the dPAP increased immediately and consistently upon inspiration with IPPV, at both low and high V_T ventilation, suggests that the dPAP was increased via directly transmitted intrathoracic pressure effects upon the pulmonary vascular bed rather than through indirect effects mediated by changes in pulmonary blood volume or

gas exchange. This is consistent with Tyberg and colleagues[36] who suggested that with increasing intrathoracic pressures, the pulmonary vasculature transmural pressure is reduced leading to narrowing of the pulmonary vessels and increased pulmonary vascular resistance. In contrast, Pinsky[37] questioned the significance of intrathoracic pressures upon PVR by previously commenting that changes to intrathoracic pressures that are not accompanied by lung volume changes, cannot affect PVR.

In the present study, the extent to which haemodynamic changes are mediated by intrathoracic pressures rather than increasing lung volume are difficult to distinguish. We observed a similar pattern of haemodynamic changes occurring at both low and high V_T ventilation (*see* Figure 2). Although V_T increased by nearly 52% during the high V_T ventilation strategy, there was no significant change in pulmonary or systemic haemodynamics (*see* Figure 3). This may be partly due to our inspiratory measurements being taken at early inspiration.

It is important to acknowledge that although dPAP significantly increased with IPPV, the magnitude of this change was small. Hence, it is unlikely that COPD patients with pulmonary hyperinflation and relatively low intrinsic positive end-expiratory pressures, in the order of 2.4-3 cm H_2O as demonstrated in earlier studies,[38, 39] significantly contributes to adverse haemodynamics in spontaneously breathing patients.

As the IPPV-associated change in dPAP was greater than the effect on PAWP, early inspiration was associated with a significant increase in the diastolic pulmonary gradient ($P<0.001$). However, late inspiration was associated with no further change in dPAP ($P=0.345$) but a further significant increase in PAWP ($P<0.001$) such that the diastolic pulmonary gradient was not significantly different from end-expiration to end-inspiration ($P=0.686$).

The IPPV-associated increase in dPAP in early inspiration was also greater than the increase in sPAP leading to a drop in the pulmonary pulse pressure, suggesting a fall in right ventricular stroke volume. Whilst this is likely due to a combination of reduced right ventricular preload and increased right ventricular afterload, we consider that an increased right ventricular afterload is the predominant mechanism in this study. This is supported by the strong negative relationship observed between the percentage change

in dPAP and the change in pulmonary pulse pressure (although we accept that dPAP is part of our pulse pressure measurement, i.e. pulse pressure = sPAP – dPAP). In contrast, the pulse pressure drop was not associated with delta RAP. Similarly, previous studies have demonstrated the importance of increased right ventricular afterload in the observed stroke volume reduction in patients with acute respiratory distress syndrome.[40]

Consequently, this study highlights the pathophysiological importance of an increased dPAP which contributes to the reduced right ventricular stroke volume observed during positive pressure ventilation in COPD. Our results are in contrast to the preload predominant mechanism observed in a recent study of spontaneous breathing COPD subjects during active expiration which demonstrated a fall in both sPAP and dPAP.[41]

(ii) Pulmonary vascular response to IPPV

There is considerable interest in assessing whether baseline haemodynamic factors can predict the response to a fluid challenge in ventilated patients.[42, 43] Similarly, we sought to determine whether factors which may influence pulmonary vascular compliance would predict the dPAP response to IPPV. We demonstrate that reduced arterial oxygenation and acidaemia were both associated with a smaller percentage increase in dPAP during inspiration with IPPV, which likely results from greater pulmonary vasoconstriction and reduced pulmonary vascular compliance. It is interesting that arterial oxygenation affects the dPAP response to IPPV across the range of hyperoxaemia that was present in this study. Higher baseline RAP was also associated with a smaller percentage increase in dPAP during inspiration with IPPV. Hypercapnia was not associated with the change in dPAP consistent with a recent review highlighting the complex relationship between hypercapnia and pulmonary haemodynamics.[12] Whilst we did not assess static lung compliance, there was no association between the percentage change in dPAP and dynamic lung compliance, measured as V_T / delivered positive airway pressure (rho=0.19, P=0.396).

It had been suggested that in the presence of pulmonary hypertension, the respiratory variation upon the PVR may have more profound cardiac consequences.[29] However, Boerrigter and colleagues[41] recently demonstrated that COPD patients with

pulmonary hypertension had reduced heart-lung interactions during active expiration. In the present study, we found no significant relationship between baseline PVR and the dPAP response to IPPV.

Limitations

Despite performing invasive pulmonary and systemic haemodynamic assessment, meticulous intra-breath analysis and employment of reasonably consistent ventilation strategies, there are several limitations that need to be acknowledged. First, we were unable to directly record intrathoracic pressures using oesophageal manometry. Whilst we had endeavoured to do this, it became impossible due to the placement of a trans-oesophageal echocardiographic probe which between planning and the commencement of the study became part of routine clinical management. Secondly, systemic pressures were taken from the radial artery whereas pulmonary pressures were obtained centrally. Whilst peripheral pulse pressures are amplified due to pressure wave reflection, this amplification is less significant in the upper limb compared with the lower limb, and is of smaller magnitude with increasing age.[44]

This study assesses the effects of IPPV on pulmonary haemodynamics in severe, stable COPD patients that were ventilated because of their imminent transplant, rather than due to an acute exacerbation. Although, there was no healthy control group, we were able to assess the ventilatory effects on the COPD group throughout the respiratory cycle and at different V_T using each patient as their own internal control.

Conclusions

We demonstrate that IPPV increases dPAP during inspiration. These haemodynamic consequences reflect the summation effects caused by changes to preload, afterload, intrathoracic pressures and lung volume. The relative importance of each continues to be debated.[29, 30, 36, 45] Nevertheless, we demonstrate that the increased dPAP contributes to the reduced right ventricular stroke volume observed during inspiration with IPPV in COPD. Further research is required to assess whether this pathophysiological pathway can be manipulated in the critical care setting in fluid non-

responsive patients in an effort to minimise the deleterious effects of positive pressure ventilation on pulmonary and systemic haemodynamics.

ACKNOWLEDGEMENTS

We would like to thank the following cardiothoracic anaesthetists at The Alfred whose patience and support enabled this project to be undertaken: Christopher Bain, David Daly, Christopher Duffy, Enjarn Lin, Howard Machlin, John Moloney and Paul Myles. We acknowledge the lung transplant surgeons for allowing this research to be performed in the time critical environment of the pre-operative transplantation period. We also acknowledge the support of the lung transplant coordinators for their assistance in patient recruitment. Finally, we thank the patients who volunteered to participate in this study.

CONFLICTS OF INTERESTS

None.

SOURCES OF SUPPORT

The research was made possible from funding provided to Jeremy P Wrobel through an Australian National Health and Medical Research Council Postgraduate Scholarship (APP1017853).

REFERENCES

[1] Hoeper MM, Barberà JA, Channick RN, Hassoun PM, Lang IM, Manes A, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol. 2009;54:S85-S96.

[2] Andersen KH, Iversen M, Kjaergaard J, Mortensen J, Nielsen-Kudsk JE, Bendstrup E, et al. Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. J Heart Lung Transplant. 2012;31:373-80.

[3] Doi M, Nakano K, Hiramoto T, Kohno N. Significance of pulmonary artery pressure in emphysema patients with mild-to-moderate hypoxemia. Respir Med. 2003;97:915-20.

[4] Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest. 1995;107:1193-8.

[5] Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159:158-64.

[6] Sims MW, Margolis DJ, Localio AR, Panettieri RA, Kawut SM, Christie JD. Impact of pulmonary artery pressure on exercise function in severe COPD. Chest. 2009;136:412-9.

[7] Blanco I, Gimeno E, Munoz PA, Pizarro S, Gistau C, Rodriguez-Roisin R, et al. Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. Am J Respir Crit Care Med. 2010;181:270-8.

[8] Morley TF, Zappasodi SJ, Belli A, Giudice JC. Pulmonary vasodilator therapy for chronic obstructive pulmonary disease and cor pulmonale. Treatment with nifedipine, nitroglycerin, and oxygen. Chest. 1987;92:71-6.

[9] Rietema H, Holverda S, Bogaard HJ, Marcus JT, Smit HJ, Westerhof N, et al. Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. Eur Respir J. 2008;31:759-64.

[10] Sajkov D, McEvoy RD, Cowie RJ, Bradley JA, Antic R, Morris RG, et al. Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. Chest. 1993;103:1354-61.

[11] Stolz D, Rasch H, Linka A, Di Valentino M, Meyer A, Brutsche M, et al. A randomised, controlled trial of bosentan in severe COPD. Eur Respir J. 2008;32:619-28.

[12] Wrobel JP, Thompson BR, Williams TJ. Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: A pathophysiologic review. J Heart Lung Transplant. 2012;31:557-64.

[13] Wright JL, Lawson L, Pare PD, Hooper RO, Peretz DI, Nelems JM, et al. The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease. The effect of oxygen and exercise. Am Rev Respir Dis. 1983;128:702-7.

[14] Naeije R, Barbera JA. Pulmonary hypertension associated with COPD. Crit Care. 2001;5:286-9.

[15] Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med. 2002;166:314-22.

[16] Thabut G, Dauriat G, Stern JB, Logeart D, Levy A, Marrash-Chahla R, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest. 2005;127:1531-6.

[17] Elwing J, Panos RJ. Pulmonary hypertension associated with COPD. International Journal of COPD. 2008;3:55-70.

[18] Weitzenblum E, Chaouat A. Cor pulmonale. Chron. 2009;6:177-85.

[19] Baigorri F, de Monte A, Blanch L, Fernandez R, Valles J, Mestre J, et al. Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. Crit Care Med. 1994;22:1782-91.

[20] Manny J, Patten MT, Liebman PR, Hechtman HB. The association of lung distention, PEEP and biventricular failure. Ann Surg. 1978;187:151-7.

[21] Nielsen J, Ostergaard M, Kjaergaard J, Tingleff J, Berthelsen PG, Nygard E, et al. Lung recruitment maneuver depresses central hemodynamics in patients following cardiac surgery. Intensive Care Med. 2005;31:1189-94.

[22] Pinsky MR. Heart lung interactions during mechanical ventilation. Curr Opin Crit Care. 2012;18:256-60.

[23] Peters J, Kindred MK, Robotham JL. Transient analysis of cardiopulmonary interactions. II. Systolic events. J Appl Physiol. 1988;64:1518-26.

[24] Peters J, Kindred MK, Robotham JL. Transient analysis of cardiopulmonary interactions. I. Diastolic events. J Appl Physiol. 1988;64:1506-17.

[25] Apitzsch H, Olthoff D, Lange S, Thiem V. A method for continuous monitoring of total peripheral and pulmonary vascular resistance in high risk cardiac patients. Anaesthesiol Reanim. 1999;24:116-9.

[26] Honda S, Sunagawa H, Tasaki H, Hirose M, Fukushige J. Correlation between pulmonary vascular resistance and pulmonary arterial diastolic pressure in congenital heart diseases with left to right shunt. Jpn Heart J. 1975;16:629-38.

[27] Harvey RM, Enson Y, Ferrer MI. A reconsideration of the origins of pulmonary hypertension. Chest. 1971;59:82-94.

[28] Denault AY, Gasior TA, Gorcsan J, 3rd, Mandarino WA, Deneault LG, Pinsky MR. Determinants of aortic pressure variation during positive-pressure ventilation in man. Chest. 1999;116:176-86.

[29] Robotham JL, Cherry D, Mitzner W, Rabson JL, Lixfeld W, Bromberger-Barnea B. A re-evaluation of the hemodynamic consequences of intermittent positive pressure ventilation. Crit Care Med. 1983;11:783-93.

[30] Cournand A, Motley HL, Werko L, Richards DW. Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. Am J Physiol. 1947;152:162-74.

[31] Stevens PM. Assessment of acute respiratory failure: cardiac versus pulmonary causes. Chest. 1975;67:1-2.

[32] Kaltman AJ, Herbert WH, Conroy RJ, Kossmann CE. The gradient in pressure across the pulmonary vascular bed during diastole. Circulation. 1966;34:377-84.

[33] Fowler NO, Jr., Westcott RN, Scott RC. Pulmonary artery diastolic pressure: its relationship to pulmonary arteriolar resistance and pulmonary capillary pressure. J Clin Invest. 1952;31:72-9.

[34] Laskey WK, Ferrari VA, Palevsky HI, Kussmaul WG. Pulmonary artery hemodynamics in primary pulmonary hypertension. J Am Coll Cardiol. 1993;21:406-12.

[35] Gerges C, Gerges M, Lang MB, Zhang L, Jakowitsch J, Probst P, et al. Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. Chest. 2013;143:758-66.

[36] Tyberg JV, Grant DA, Kingma I, Moore TD, Sun Y, Smith ER, et al. Effects of positive intrathoracic pressure on pulmonary and systemic hemodynamics. Respir Physiol. 2000;119:171-9.

[37] Pinsky MR. Cardiovascular issues in respiratory care. Chest. 2005;128:592S-7S.

[38] Haluszka J, Chartrand DA, Grassino AE, Milic-Emili J. Intrinsic PEEP and arterial PCO2 in stable patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1990;141:1194-7.

[39] Dal Vecchio L, Polese G, Poggi R, Rossi A. "Intrinsic" positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. Eur Respir J. 1990;3:74-80.

[40] Vieillard-Baron A, Loubieres Y, Schmitt JM, Page B, Dubourg O, Jardin F. Cyclic changes in right ventricular output impedance during mechanical ventilation. J Appl Physiol. 1999;87:1644-50.

[41] Boerrigter B, Trip P, Bogaard HJ, Groepenhoff H, Oosterveer F, Westerhof N, et al. Right atrial pressure affects the interaction between lung mechanics and right ventricular function in spontaneously breathing COPD patients. PLoS ONE. 2012;7:e30208.

[42] De Backer D, Heenen S, Piagnerelli M, Koch M, Vincent JL. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. Intensive Care Med. 2005;31:517-23.

[43] Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. Chest. 2002;121:2000-8.

[44] Dart AM, Kingwell BA. Pulse pressure--a review of mechanisms and clinical relevance. J Am Coll Cardiol. 2001;37:975-84.

[45] Morgan BC, Martin WE, Hornbein TF, Crawford EW, Guntheroth WG. Hemodynamic effects of intermittent positive pressure respiration. Anesthesiology. 1966;27:584-90.

Table 1. Preoperative baseline demographics

Male:Female	5:17
Age, yrs	58 [51-61]
Height, m	1.65 [1.61-1.70]
Weight, kg	67 [58-76]
BMI, $kg.m^{-2}$	25.3 [21.8-27.4]
Smoking history, pack years	39 [27-60]
Ax-surgery time, months	9 [5-18]
FEV_1 post BD, % predicted	21 [19-26]
FEV_1/FVC post BD, %	31 [27-34]
$TLCO_{hb}$, % predicted	24 [21-40]
FRC, % predicted	191 [170-221]
TLC, % predicted	137 [122-150]
IC/TLC, %	16.2 [12.4-23.4]
RV/TLC, %	72 [59-78]

Values are median [IQR]. Respiratory function tests were obtained during lung transplant assessment.

Ax-surgery time, time duration between lung transplant assessment and lung transplant surgery; BMI, body mass index; FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; TLC, total lung capacity; $TLCO_{hb}$, transfer factor of the lung for carbon monoxide corrected for haemoglobin.

Table 2. Ventilation and blood gas parameters at different tidal volumes

	Low V_T	High V_T [a]	P
IPAP, cmH_2O	20 [20.0-25.0]	20 [19.5-25.0]	0.068 [C]
$PEEP_E$, cmH_2O	0 [0-0]	0 [0-0]	1
Tidal volume, ml	478 [421-577]	725 [662-796]	< 0.001
Minute ventilation, $L.min^{-1}$	4.78 [4.21-5.77]	4.35 [3.97-4.78]	< 0.001
RR, min^{-1}	10 [10-10]	6 [6-6]	< 0.001
I:E ratio	0.29 [0.29-0.29]	0.29 [0.29-0.29]	0.066 [C]
FiO_2	0.6 [0.6-0.6]	0.6 [0.6-0.6]	1
PaO_2, mm Hg	264 [178-313]	266 [197-300]	0.784
$PaCO_2$, mm Hg	55.9 [45.5-64.5]	54.1 [49.3-62.2]	0.480
pH, units	7.35 [7.31-7.39]	7.36 [7.34-7.38]	0.695
Base excess, units	3.6 [0.6-4.3]	3.1 [0.4-4.0]	0.327
Bicarbonate, $mmol.L^{-1}$	29.0 [26.6-32.2]	29.4 [27.3-31.5]	0.574
PAWP, mm Hg	10.0 [8.0-12.0]	9.0 [8.0-12.0]	0.977
RAP, mm Hg [b]	8.3 [4.7-9.8]	7.7 [5.5-9.8]	0.848
mPAP, mm Hg [b]	23.1 [21.0-27.0]	23.0 [22.0-27.0]	0.904
sPAP, mm Hg [b]	32.1 [30.1-37.3]	32.3 [28.1-35.7]	0.191
dPAP, mm Hg [b]	16.1 [12.9-19.0]	15.3 [13.9-18.3]	0.641
sBP, mm Hg [b]	124 [86-142]	111 [88-133]	0.958
dBP, mm Hg [b]	66 [52-75]	63 [53-72]	0.931
Pulmonary pulse pressure, mm Hg	17.8 [14.1-20.9]	16.9 [13.8-18.6]	0.232
Systemic pulse pressure, mm Hg	58.9 [30.2-66.6]	47.9 [35.6-63.0]	0.931
HR, min^{-1}	83 [73-97]	83 [69-91]	0.076 [C]
CI, $L.min^{-1}.m^{-2}$	2.6 [1.8-2.9]	2.4 [1.9-2.5]	0.542
SVI, $ml.m^{-2}$	30.3 [25.9-34.4]	29.9 [26.6-36.5]	0.629
PVR, WU	4.1 [2.2-4.6]	3.8 [2.8-4.7]	0.420

Values are median [IQR]. P values calculated using the Wilcoxon signed rank test.

[a] Subjects were ventilated at high V_T for 6:08 [4:09-8:18] minutes prior to reassessment.

[b] RAP, mPAP, sPAP, dPAP, sBP and dBP measured at end-expiration.

[c] These borderline P values with similar median [IQR] values reflect small but consistent changes amongst only a few subjects from low to high V_T.

CI, right ventricular cardiac index; dBP, diastolic systemic arterial blood pressure; dPAP, diastolic pulmonary arterial pressure; FiO_2, fraction of inspired oxygen; HR, heart rate; I:E, inspiratory to expiratory; IPAP, inspiratory positive airway pressure;

mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; $PEEP_E$, extrinsic positive end-expiratory pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RR, respiratory rate; sBP, systolic systemic arterial blood pressure; sPAP, systolic pulmonary arterial pressure; SVI, right ventricular stroke volume index; V_T, tidal volume.

Table 3. Correlates with percentage change in dPAP at different tidal volumes

	Low V_T	High V_T
$PaCO_2$	-0.38 (0.130)	-0.12 (0.676)
PaO_2	0.65 (0.005)	-0.14 (0.630)
PAWP	-0.32 (0.144)	-0.31 (0.191)
pH	0.64 (0.006)	0.37 (0.173)
PVR	-0.01 (0.982)	0.10 (0.694)
RAP	-0.53 (0.011)	-0.40 (0.075)
SVI	0.10 (0.662)	-0.21 (0.395)
V_T	0.21 (0.339)	0.22 (0.330)
Delta pulmonary pulse pressure	-0.64 (0.001)	-0.57 (0.007)

Values are Spearman's rho (P value). Percentage change in dPAP calculated from end-expiration to early inspiration.

dPAP, diastolic pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SVI, stroke volume index; V_T, tidal volume.

Figures

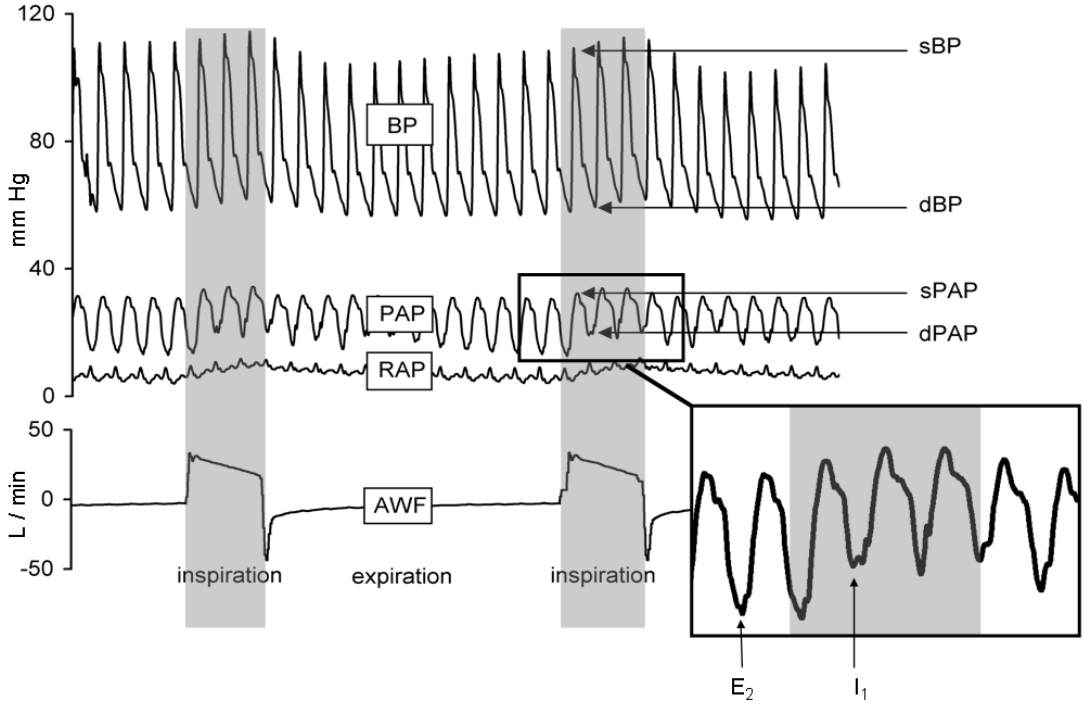

Figure 1. Respiratory effects upon the systemic and pulmonary arterial pressures are demonstrated in a representative subject. Inspiration (shaded bars) occurs during positive airway flow and expiration during negative airway flow. The callout box indicates dPAP at end-expiration (E_2) and early inspiration (I_1). From E_2 to I_1, there are increases in systemic and pulmonary arterial pressures, most pronounced in dPAP.

AWF, airway flow; BP, systemic arterial pressure; dBP, diastolic systemic arterial pressure; dPAP, diastolic pulmonary arterial pressure; E_2, end-expiration; I_1, early inspiration; PAP, pulmonary arterial pressure; RAP, right atrial pressure; sBP, systolic systemic arterial pressure; sPAP, systolic pulmonary arterial pressure.

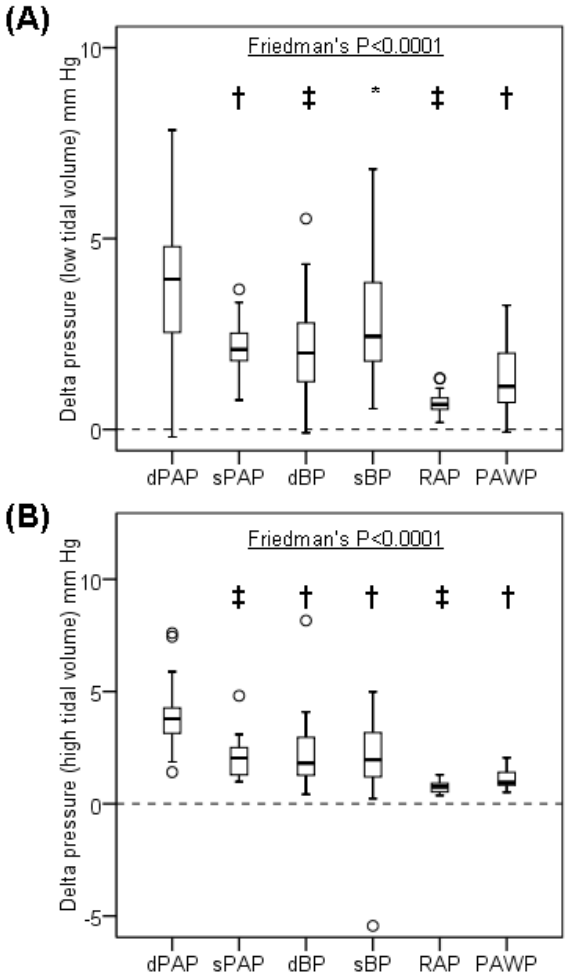

Figure 2. Change in pulmonary and systemic pressures measured from end-expiration to early inspiration with a low V_T ventilation strategy (panel A) and a high V_T ventilation strategy (panel B). Boxplot illustrates the minimum, lower quartile, median, upper quartile and maximum values. "o" represent outlier values. * P<0.05, † P<0.01, ‡ P<0.001 compared with dPAP.

dBP, diastolic systemic arterial pressure; dPAP, diastolic pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; sBP, systolic systemic arterial pressure; sPAP, systolic pulmonary arterial pressure; V_T, tidal volume.

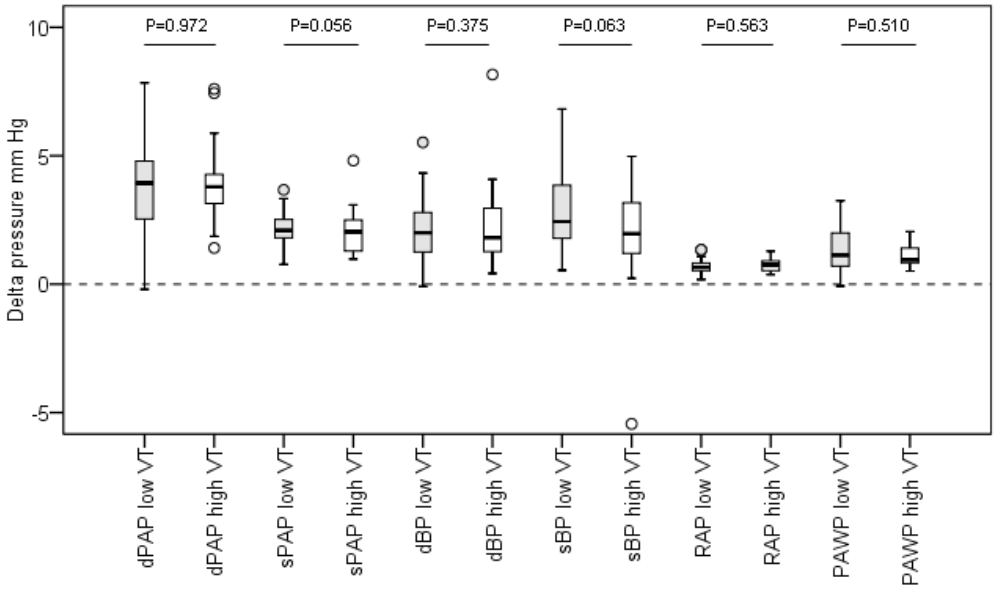

Figure 3. Changes in pulmonary and systemic pressures measured from end-expiration to early inspiration with different V_T strategies (shaded bars are at low V_T, unshaded bars are at high V_T). Boxplot illustrates the minimum, lower quartile, median, upper quartile and maximum values. "o" represent outlier values.

dBP, diastolic systemic arterial pressure; dPAP, diastolic pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; RAP, right atrial pressure; sBP, systolic systemic arterial pressure; sPAP, systolic pulmonary arterial pressure; V_T, tidal volume.

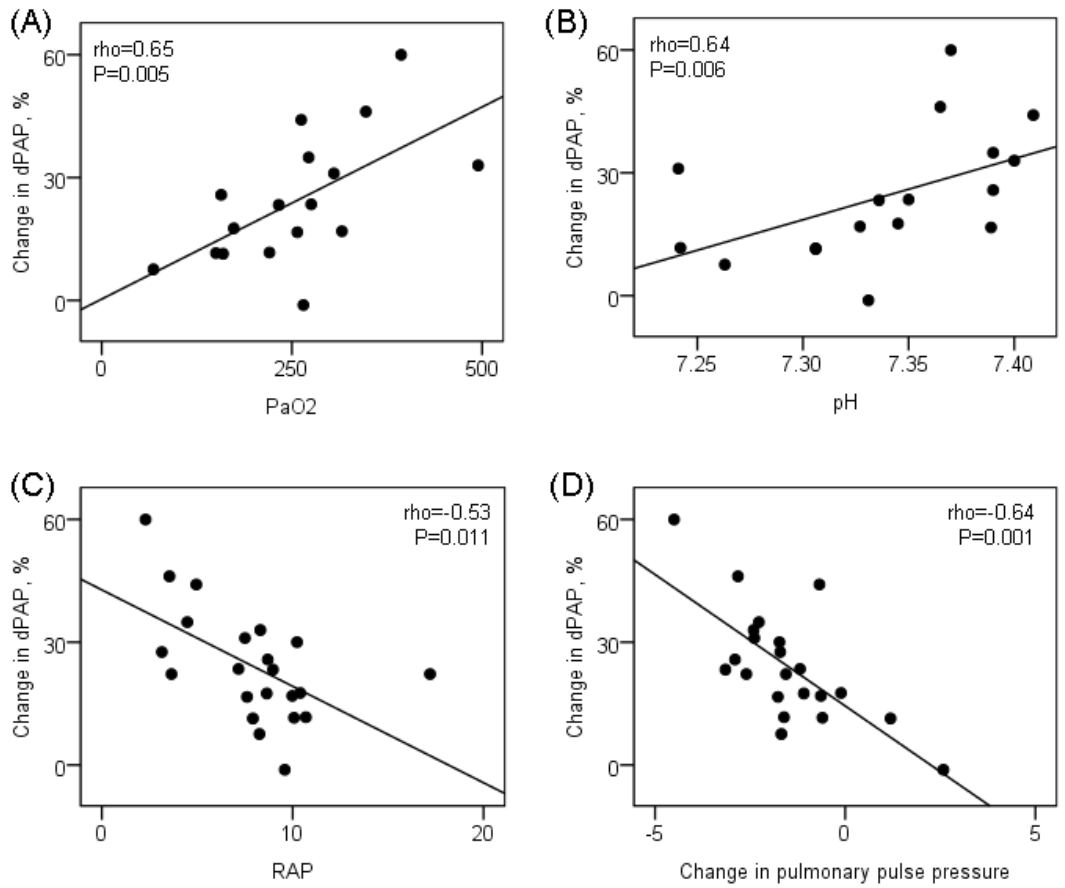

Figure 4. Scatterplots for percentage change in dPAP versus PaO_2 (panel A), pH (panel B), RAP (panel C) and change in pulmonary pulse pressure (panel D) during low tidal volume ventilation. Percentage change in dPAP measured from end-expiration to early inspiration.

dPAP, diastolic pulmonary artery pressure; RAP, right atrial pressure.

4.4 Further Discussion

This study demonstrates that positive pressure ventilation transiently increases dPAP during inspiration. The rationale for the study was to determine whether it was physiologically plausible that $PEEP_I$ and gas trapping could contribute to elevation of pulmonary arterial pressure in patients with advance COPD. Whilst we were able to demonstrate this, the magnitude of change is rather small and unlikely to have clinical bearing in COPD patients during spontaneous ventilation. Nevertheless, the application of our findings to patients receiving mechanical ventilation is most interesting.

By examining the changes to pulmonary and systemic pulse pressures we can infer the haemodynamic effects of IPPV upon pulmonary and systemic stroke volume (Mesquida, Kim et al. 2011). We demonstrate that IPPV reduces pulmonary pulse pressure during inspiration. As pulmonary pulse pressure equals right ventricular stroke volume divided by pulmonary vascular compliance (Dart and Kingwell 2001), we can infer that the observed fall in pulmonary pulse pressure during IPPV underestimates the actual stroke volume reduction.

pulse pressure = stroke volume / vascular compliance

This is because, with inspiration during IPPV, the pulmonary vascular transmural pressure falls leading to a reduction in pulmonary vascular compliance. Hence, with all else being equal, a drop in pulmonary vascular compliance would actually increase pulmonary pulse pressure. However, as the pulmonary pulse pressure fell, this infers a reduction in right ventricular stroke volume greater than the percentage decrease in vascular compliance.

IPPV and left ventricular stroke volume

Whilst the systemic arterial pressures also increase during IPPV, the increase in sBP is greater than the increase in dBP, leading to a small but significant increase in systemic pulse pressure ($P = 0.006$). Stroke volume generally is determined from the combination of preload, afterload and contractility. Although not directly measured in this study,

there is no clear evidence in the literature that positive pressure ventilation alters left ventricular contractility (Marini, Culver et al. 1981a, Luecke and Pelosi 2005). Similarly, there is presently no consensus regarding the immediate effects of ITP on left ventricular filling (Luecke and Pelosi 2005). Nevertheless, changing ITP may affect pulmonary venous return depending on which lung zone characteristics predominate (Robotham, Cherry et al. 1983, Brower, Wise et al. 1985). Furthermore, a reduced right ventricular preload may improve left ventricular compliance through ventricular interdependence (Robotham, Cherry et al. 1983, Peters, Kindred et al. 1988a, Shekerdemian and Bohn 1999, Luecke and Pelosi 2005).

Peters and colleagues (Peters, Kindred et al. 1988b) have previously demonstrated in a canine study that negative ITP increases left ventricular afterload and reduces left ventricular stroke volume. This is consistent with previous studies (Scharf, Brown et al. 1979, Summer, Permutt et al. 1979). Conversely, in the present study, IPPV leads to reduced aortic transmural pressure, reduced left ventricular afterload and increased systemic pulse pressure during inspiration. Our results are consistent with Robotham and colleagues (Robotham, Cherry et al. 1983) who demonstrated an inspiratory increase in left ventricular stroke volume during IPPV. This implies a reduced left ventricular stroke volume would occur in association with reduced ITP, as occurs in inspiration during spontaneous ventilation, providing an additional mechanism to explain the well recognized phenomenon of pulsus paradoxus. The reduced left ventricular stroke volume during spontaneous inspiration may also help account for the negative clinical outcomes associated with dynamic hyperinflation in COPD (O'Donnell, Revill et al. 2001, Casanova, Cote et al. 2005, O'Donnell and Webb 2008b).

Finally, as the relationship between stroke volume and pulse pressure is partially dependent upon vascular compliance, the increase in systemic pulse pressure observed in this study may be partially due to the reduced aortic compliance that would inevitably occur during inspiration with IPPV.

It is also important to distinguish the resistance vessels of the systemic and pulmonary circulations. Whereas the small muscular pulmonary arteries are responsible for the pulmonary arterial resistance, it is the systemic arterioles that are responsible for the systemic vascular resistance and these lie outside thoracic cavity and, hence, are not

directly affected by IPPV. Consequently, the driving pressure of the systemic circulation from the left ventricle would increase during inspiration with IPPV. This also helps to explain the difference observed between the pulmonary and system pulse pressure changes.

Returning to Figure 6, it is possible to speculate further upon the haemodynamic consequences that will secondary to increasing lung inflation with positive pressure ventilation as illustrated below in Figure 9. Further research is necessary to determine if these cardiopulmonary interactions can be manipulated in order to improve clinical outcomes.

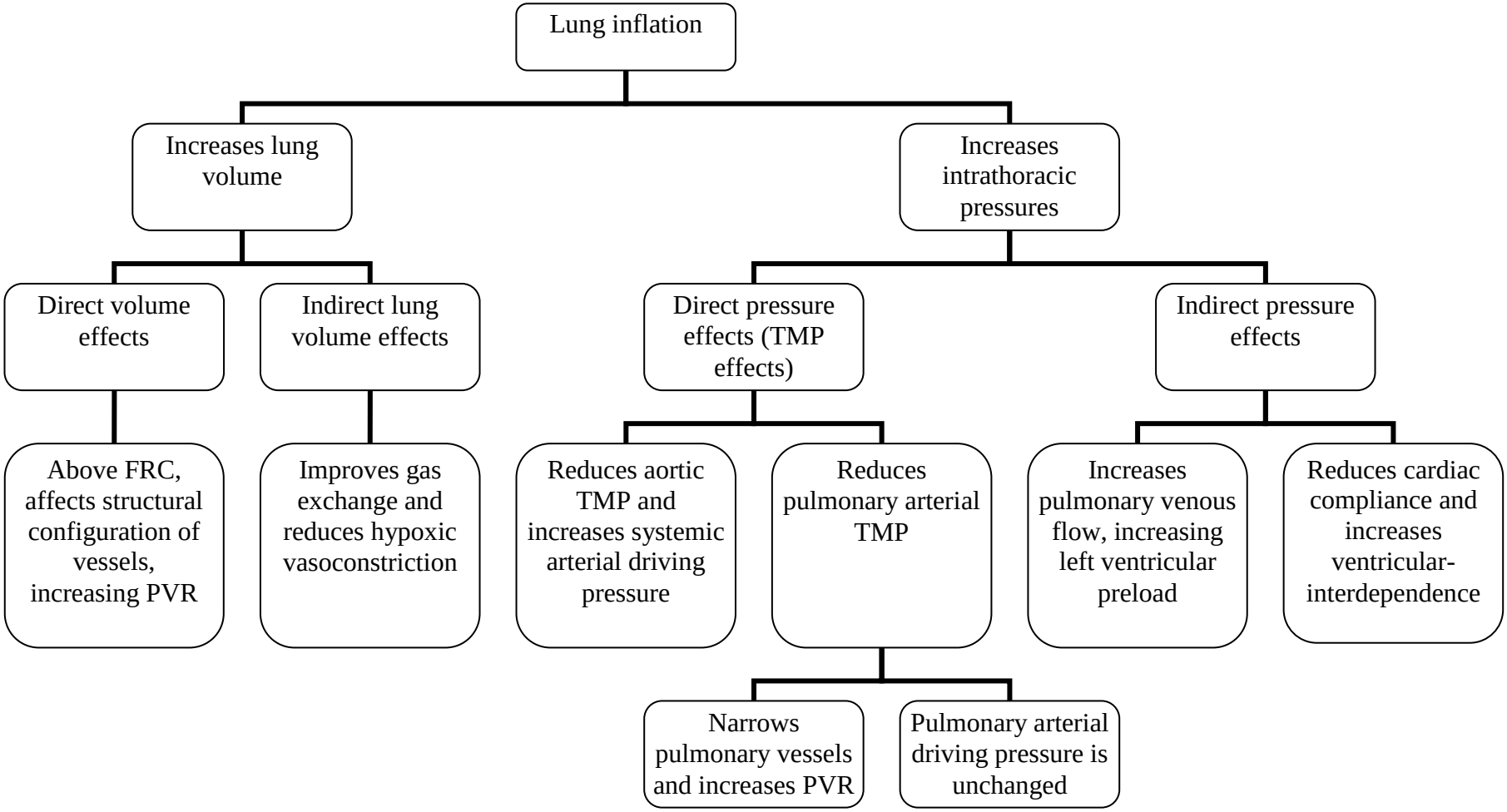

Figure 9
Direct and indirect volume and pressure consequences of lung inflation.
FRC, functional residual capacity; PVR, pulmonary vascular resistance; TMP, transmural pressure.

Chapter 5: Integrative Discussion

5.1 Overview of Salient Findings

5.2 Integrated Discussion and Clinical Findings

5.3 Limitations and Future Directions

5.1 Overview of Salient Findings

The salient findings of this thesis are as follows:

1. Despite the many postulated mechanisms contributing to PHT in COPD, other than for hypoxaemia, the evidence supporting each of these factors is very limited and largely circumstantial.
2. Preoperative moderate-severe PHT is associated with prolonged duration of mechanical ventilation following lung transplantation for COPD.
3. Preoperative moderate-severe PHT is also associated with a worse early allograft function (as evidenced by the PaO_2 to fraction of inspired oxygen ratio) and a trend towards longer intensive care length of stay following lung transplantation for COPD.
4. There is significant pulmonary arterial remodelling in patients with severe COPD compared with non-smoking controls, determined by the percentage wall thickness of muscular pulmonary arteries.
5. Amongst patients with severe COPD, there is increased pulmonary arterial remodelling in the upper lobes and in the small muscular pulmonary arteries.
6. Pulmonary arterial remodelling in severe COPD is heterogeneous and that there are interactions between pulmonary arterial size, pulmonary arterial pressure and lung lobe upon the magnitude of pulmonary arterial remodelling.
7. The positive association between regional perfusion and pulmonary arterial remodelling in severe COPD suggests that increased perfusion contributes to the remodelling process.
8. Inspiration with IPPV is associated with a small but consistent increase in dPAP. The change in dPAP is largely associated with increased airway pressure rather than increases in lung volume. Inspiration with IPPV is also associated with a reduction in right ventricular stroke volume, as measured by pulmonary pulse pressure.
9. Lower oxygenation, acidaemia and higher right atrial pressures at baseline are associated with a reduced dPAP response to inspiration with IPPV.
10. Cardiopulmonary interactions contribute to the pathophysiology and clinical outcomes in COPD patients with PHT.

5.2 Integrative Discussion and Clinical Implications

COPD is a major international health burden. Amongst patients with moderate-severe COPD, PHT is relatively common and is widely regarded as a poor prognostic marker. Whilst supplemental oxygen has some proven clinical benefit, therapies to specifically target the PHT in patients with COPD have not translated into meaningful clinical outcomes. This thesis investigates PHT in patients with COPD with a focus on clinical, pathological and physiological issues.

The literature suggests that preoperative PHT may be associated with inferior outcomes following lung transplantation (Whelan, Dunitz et al. 2005, Prekker, Nath et al. 2006, Sullivan, Whitson et al. 2006, Whitson, Nath et al. 2006, Fang, Studer et al. 2011) but no studies have assessed the short-term outcomes in patients with COPD. We performed a retrospective analysis of a single institution's experience and demonstrated that preoperative PHT is associated with prolonged duration of mechanical ventilation following lung transplantation for COPD (Wrobel, Thompson et al. 2012a).

This raises a number of pathophysiological questions. In particular, the mechanism by which preoperative PHT affects post transplantation outcomes has not been elucidated. Some authors have suggested that these inferior outcomes occur as a result of primary graft dysfunction secondary to a "primed" right ventricle contracting against a pulmonary circulation with relatively low PVR (Chatila, Furukawa et al. 2003, Fang, Studer et al. 2011). However, this is not supported by our data. Alternatively, it would appear that post transplantation unmasking of left ventricular diastolic dysfunction provides a possible explanation. To date this question remains unanswered as left ventricular diastolic dysfunction has not been systematically studied in the peri-transplant period.

This study highlights the need for further research to confirm the association between preoperative PHT and inferior outcomes following lung transplantation. In addition, systematic assessment of preoperative PHT (including presence and severity of LV

diastolic dysfunction) may lead to improved clinical outcomes through the identification of high risk patients and improved peri-operative care.

One of the major limitations of this study was that PHT was determined by echocardiography. Despite the common clinical use of echocardiography to screen for PHT, there are significant concerns regarding the accuracy of this modality to assess pulmonary arterial pressures (Arcasoy, Christie et al. 2003, Fisher, Criner et al. 2007, Fisher, Forfia et al. 2009). Consequently, in Chapter 3 we sought to determine whether there was a relationship between echocardiography-based assessment of PHT and pulmonary arterial remodelling utilising stored lung tissue samples from 42 of the 46 subjects studied in Chapter 2.

Although pulmonary arterial remodelling has been demonstrated in patients with COPD, the significance of this is unclear and the relationship between pulmonary arterial remodelling and PHT has not been established. We were unable to demonstrate a direct relationship between pulmonary arterial remodelling and echocardiography-based PHT severity. However, in the lower lobes, there was a strong trend to greater pulmonary arterial remodelling in the moderate-severe PHT group compared with patients with no PHT (unadjusted $P < 0.05$). Somewhat to our surprise, the impact of PHT on remodelling was small relative to the effect of having COPD. Furthermore, we identified complex interactions that were present between lobar origin, muscular pulmonary artery size and pulmonary arterial pressure. We also demonstrated novel findings of an increase in pulmonary arterial remodelling in the upper lobes compared with lower lobes and a positive association between remodelling and regional perfusion.

The pathogenesis of pulmonary arterial remodelling in COPD is unclear. Although pulmonary arterial remodelling appears necessary for the development of PHT in patients with COPD, it is not sufficient in isolation to cause PHT in these patients.

This study contributes to the literature by suggesting that interactions between regional pulmonary blood flow, pulmonary arterial size and pulmonary arterial pressure are integral to the remodelling process. As this study employed echocardiography to assess pulmonary arterial pressures, we were unable to evaluate the relationship between PVR and pulmonary arterial remodelling.

Further research is required to better elucidate the relationship between regional blood flow, pulmonary arterial remodelling, pulmonary arterial pressure and PVR. A better understanding of pulmonary arterial remodelling in COPD, would help establish the basis from which to consider further studies using selective pulmonary vasodilators as a therapy for select COPD patients with PHT.

The aforementioned studies implicate cardiopulmonary interactions as the basis for inferior post transplantation outcomes in COPD patients with moderate-severe PHT (Chapter 2) and as contributing to the pathogenesis of pulmonary arterial remodelling in COPD patients (Chapter 3). Cardiopulmonary interactions are complex in health and disease (Scharf, Pinsky et al. 2001). In COPD, cardiopulmonary interactions may be more pronounced due to the unique combination of pathological features such as lung parenchymal destruction, systemic inflammation and altered lung mechanics.

In Chapter 4, we prospectively investigated the lung-heart interactions of IPPV upon pulmonary haemodynamics using the accepted gold standard of right heart catheterisation to assess the pulmonary circulation.

It has been postulated that dynamic hyperinflation contributes to PHT in patients with COPD however there is limited evidence to support this. We demonstrate that inspiration with IPPV was associated with a small but consistent increase in dPAP. However, the magnitude of this effect appears to be of limited clinical relevance in COPD patients during spontaneous ventilation.

IPPV was also associated with a reduction in right ventricular stroke volume, independent of changes to preload, and these results are likely to be of significant clinical importance in patients receiving mechanical ventilation. Previous research on lung-heart interactions during mechanical ventilation have mostly focused on the effects upon cardiac preload, however this study highlights that afterload effects must not be ignored.

Whilst this study focuses only on the mechanical heart-lung interactions of increased airway pressure, it is evident that the respiratory and cardiovascular systems are intimately connected and this has both pathophysiological and clinical implications. We

demonstrate that lower baseline oxygenation, acidaemia and higher right ventricular filling pressures reduce the dPAP response to IPPV. This suggests that we may be able to stabilise the pulmonary haemodynamic responses to IPPV through manipulation of baseline physiologic parameters. For example, aiming for near-normal levels of PaO_2 may reduce the respiratory fluctuations in right ventricular stroke volume during mechanical ventilation. Furthermore, future research directed at refining patient specific ventilation protocols based on their current haemodynamic status could minimise some of the deleterious clinical effects of mechanical ventilation.

This thesis answers several questions but poses many more. Cardiopulmonary interactions are complex and contribute to the pathophysiology and clinical outcomes of patients with severe COPD and PHT. Nevertheless, it remains to be seen whether greater appreciation and understanding of these interactions can be translated into improved clinical outcomes for COPD patients with PHT.

5.3 Limitations and Future Directions

The major limitation of this thesis is that PHT in Chapters 2 and 3 have been diagnosed using echocardiography rather than the accepted gold standard of right heart catheterisation. Unfortunately, our institution (like many) does not perform routine right heart catheterisation on patients with severe COPD and invasive catheterisation is difficult to justify in pathophysiological research that does not have therapeutic potential for the study subjects. Whilst right heart catheterisation is performed at the time of lung transplantation, formal baseline haemodynamic assessments are not obtained.

Nevertheless, invasive pulmonary haemodynamics could be collected routinely at the time of transplantation with minimal increase in risk for patients and this would enable a more accurate assessment of the impact of preoperative PHT upon post transplantation outcomes. Furthermore, the retrospective nature of the study in Chapter 2 raises the potential for confounding. Consequently, further research employing prospective right heart catheterisation on a larger group of subjects is required to determine whether

preoperative PHT influences post transplantation outcomes in the modern treatment era of lung transplantation.

Similarly, prospective formalised invasive haemodynamic assessment at the time of lung transplantation could be used to provide a more comprehensive assessment of the relationship between pulmonary haemodynamics and pulmonary arterial remodelling.

In Chapter 3, pulmonary arterial remodelling was measured as percentage wall thickness of the muscular pulmonary arteries. Several studies have distinguished between intimal thickness and medial thickness with mixed results (Hale, Niewoehner et al. 1980, Hale, Ewing et al. 1984, Wilkinson, Langhorne et al. 1988, Wright, Petty et al. 1992, Barbera, Riverola et al. 1994, Kubo, Ge et al. 2000) Whilst our experience is that delineating between intima and media is often subjective, improved digital image analysis programs might enable more objective methods for making this distinction.

Future research should also be directed towards developing non-invasive, computerised methods for assessing pulmonary arterial remodelling which would enable a larger volume of lung to be sampled from more subjects than is currently feasible. Improved understanding of the basis for pulmonary arterial remodelling would provide the foundation from which to better target COPD patients that may be amenable to pulmonary vasodilator therapy. Ultimately, we might also be able to prevent the remodelling process in susceptible patients.

The major limitation of Chapter 4 was the lack of non-COPD control subjects. Whilst this thesis focussed solely on COPD patients due to the unique mechanical lung derangements of this patient group, it is likely that cardiopulmonary interactions are also clinically important in non-COPD patients. Future research should be aimed at elucidating cardiopulmonary interactions in non-COPD patients to help identify susceptible patient groups at high risk of the deleterious effects of mechanical ventilation.

Finally, given the high prevalence of cardiovascular disease in COPD and the complex cardiopulmonary interactions at play, future research should be aimed at identifying COPD patient groups that may benefit from therapies that have traditionally been

targeted for cardiovascular disease. Such therapies may ultimately lead to improved clinical outcomes in patients with severe COPD.

Chapter 6: Conclusion

This thesis investigated PHT in COPD from a clinical, pathological and physiological perspective. We provide the first published analysis of the impact of preoperative PHT on short-term outcomes following lung transplantation for COPD. Whilst this needs to be confirmed in prospective studies, it highlights the potential for cardiopulmonary interactions to impact upon clinical outcomes in the peri-transplant period.

The pathological analysis of COPD pulmonary arterial remodelling is amongst the largest of its kind. We have demonstrated novel findings of complex interactions between lung lobe, pulmonary arterial size, pulmonary arterial pressure and regional lung perfusion, which have not been previously investigated. Despite the limitations of this study, it illustrates that cardiopulmonary interactions contribute to the pathogenesis of pulmonary arterial remodelling in COPD which is fundamental to the development of PHT.

Finally, we have prospectively demonstrated that cardiopulmonary interactions occur during mechanical ventilation in patients with severe COPD. This is the first time that the direction and magnitude of these interactions have been investigated in this patient group. We also demonstrate that these cardiopulmonary interactions impact upon cardiac function and that these changes appear to be independent of changes to cardiac preload.

This thesis demonstrates that cardiopulmonary interactions are integral to our understanding of the pathophysiology of PHT in COPD. Not only is improved understanding of cardiopulmonary interactions in COPD fundamental to advancing our knowledge of COPD-associated PHT, but such interactions likely contribute to other clinical aspects of patients with severe COPD, such as the increased prevalence of cardiovascular disease. Consequently, further research is required to improve our understanding of cardiopulmonary interactions in COPD and how best to translate this knowledge into improved clinical outcomes for the millions of COPD patients worldwide.

Bibliography

Access Economics (2008). Economic impact of COPD and cost effective solutions, The Australian Lung Foundation.

Acikel M, Kose N, Aribas A, et al. (2010). The effect of pulmonary hypertension on left ventricular diastolic function in chronic obstructive lung disease: a tissue Doppler imaging and right cardiac catheterization study. *Clinical Cardiology* 33(8):E13-18.

Acikel M, Yilmaz M, Gurlertop Y, et al. (2004). The effect of pulmonary hypertension on left atrial mechanical functions in chronic obstructive lung disease. *International Journal of Cardiology* 97(2):187-192.

Adir Y, Shachner R, Amir O and Humbert M (2012). Severe pulmonary hypertension associated with emphysema: a new phenotype? *Chest* 142(6):1654-1658.

Adnot S, Andrivet P, Chabrier PE, et al. (1990). Plasma levels of atrial natriuretic factor, renin activity, and aldosterone in patients with chronic obstructive pulmonary disease. Response to O2 removal and to hyperoxia. *American Review of Respiratory Disease* 141(5 Pt 1):1178-1184.

Aebischer N, Malhotra R, Connors L, Kappenberger L and Parisi AF (1995). Ventricular interdependence during Valsalva maneuver as seen by two-dimensional echocardiography: new insights about an old method. *Journal of the American Society of Echocardiography* 8(4):536-542.

Agusti A and Barnes PJ (2010). What the journal would like to publish on chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 182(1):1-2.

Agusti A, Edwards LD, Rennard SI, et al. (2012). Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS ONE [Electronic Resource]* 7(5):e37483.

Agusti A and Vestbo J (2011). Current controversies and future perspectives in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 184(5):507-513.

Akcay M, Yeter E, Durmaz T, et al. (2010). Treatment of acute chronic obstructive pulmonary disease exacerbation improves right ventricle function. *European Journal of Echocardiography* 11(6):530-536.

Albert RK, Muramoto A, Caldwell J, Koepsell T and Butler J (1985). Increases in intrathoracic pressure do not explain the rise in left ventricular end-diastolic pressure that occurs during exercise in patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 132(3):623-627.

Albertine KH, Williams MC and Hyde DM (2000). Anatomy and development of the respiratory tract. *Textbook of Respiratory Medicine*. Murray JF and Nadel JA. Philadelphia, W.B. Saunders Company. 1**:**3-34.

Aldrich TK, Hendler JM, Vizioli LD, et al. (1993). Intrinsic positive end-expiratory pressure in ambulatory patients with airways obstruction. *American Review of Respiratory Disease* 147(4):845-849.

Almagro P, Calbo E, Ochoa de Echaguen A, et al. (2002). Mortality after hospitalization for COPD. *Chest* 121(5):1441-1448.

Amin A, Taghavi S, Esmaeilzadeh M, et al. (2011). Pulmonary arterial elastance for estimating right ventricular afterload in systolic heart failure. *Congestive Heart Failure* 17(6):288-293.

Andersen KH, Iversen M, Kjaergaard J, et al. (2012). Prevalence, predictors, and survival in pulmonary hypertension related to end-stage chronic obstructive pulmonary disease. *Journal of Heart and Lung Transplantation* 31(4):373-380.

Anderson WJ, Lipworth BJ, Rekhraj S, Struthers AD and George J (2013). Left ventricular hypertrophy in COPD without hypoxemia: the elephant in the room? *Chest* 143(1):91-97.

Anthonisen NR, Connett JE, Enright PL and Manfreda J (2002). Hospitalizations and mortality in the Lung Health Study. *American Journal of Respiratory and Critical Care Medicine* 166(3):333-339.

Apitzsch H, Olthoff D, Lange S and Thiem V (1999). A method for continuous monitoring of total peripheral and pulmonary vascular resistance in high risk cardiac patients. *Anaesthesiologie und Reanimation* 24(5):116-119.

Arcasoy SM, Christie JD, Ferrari VA, et al. (2003). Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. *American Journal of Respiratory and Critical Care Medicine* 167(5):735-740.

Archer SL, Mike D, Crow J, Long W and Weir EK (1996). A placebo-controlled trial of prostacyclin in acute respiratory failure in COPD. *Chest* 109(3):750-755.

Ashutosh K, Mead G and Dunsky M (1983). Early effects of oxygen administration and prognosis in chronic obstructive pulmonary disease and cor pulmonale. *American Review of Respiratory Disease* 127(4):399-404.

Australian Institute of Health and Welfare (2010). Australia's Health 2010. Australia's health series no. 12. Cat. no. AUS 122. Canberra: AIHW.

Badesch DB, Champion HC, Gomez Sanchez MA, et al. (2009). Diagnosis and assessment of pulmonary arterial hypertension. *Journal of the American College of Cardiology* 54(1, Supplement 1):S55-S66.

Bahler RC, Chester EH, Belman MJ and Baum GL (1977). Multidisciplinary treatment of chronic pulmonary insufficiency. 4. The influence of intrathoracic pressure variations on increases in pulmonary vascular pressure during exercise in patients with chronic obstructive pulmonary disease. *Chest* 72(6):703-708.

Baigorri F, de Monte A, Blanch L, et al. (1994). Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. *Critical Care Medicine* 22(11):1782-1791.

Bando K, Keenan RJ, Paradis IL, et al. (1994). Impact of pulmonary hypertension on outcome after single-lung transplantation. *Annals of Thoracic Surgery* 58(5):1336-1342.

Banister J and Torrance RW (1960). The effects of the tracheal pressure upon flow: pressure relations in the vascular bed of isolated lungs. *Quarterly Journal of Experimental Physiology and Cognate Medical Sciences* 45:352-367.

Barbera JA, Peinado VI and Santos S (2003). Pulmonary hypertension in chronic obstructive pulmonary disease. *European Respiratory Journal* 21(5):892-905.

Barbera JA, Peinado VI, Santos S, et al. (2001). Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. *American Journal of Respiratory and Critical Care Medicine* 164(4):709-713.

Barbera JA, Riverola A, Roca J, et al. (1994). Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 149(2 Pt 1):423-429.

Barnes PJ and Liu SF (1995). Regulation of pulmonary vascular tone. *Pharmacological Reviews* 47(1):87-131.

Barr RG, Bluemke DA, Ahmed FS, et al. (2010). Percent emphysema, airflow obstruction, and impaired left ventricular filling. *New England Journal of Medicine* 362(3):217-227.

Berger JS, Sanborn TA, Sherman W and Brown DL (2004). Effect of chronic obstructive pulmonary disease on survival of patients with coronary heart disease having percutaneous coronary intervention. *American Journal of Cardiology* 94(5):649-651.

Biernacki W, Gould GA, Whyte KF and Flenley DC (1989). Pulmonary hemodynamics, gas exchange, and the severity of emphysema as assessed by quantitative CT scan in chronic bronchitis and emphysema. *American Review of Respiratory Disease* 139(6):1509-1515.

Bishop JM and Cross KW (1981). Use of other physiological variables to predict pulmonary arterial pressure in patients with chronic respiratory disease. multicentre study. *European Heart Journal* 2(6):509-517.

Bishop JM and Cross KW (1984). Physiological variables and mortality in patients with various categories of chronic respiratory disease. *Bulletin Europeen de Physiopathologie Respiratoire* 20(6):495-500.

Blanch L, Bernabe F and Lucangelo U (2005). Measurement of air trapping, intrinsic positive end-expiratory pressure, and dynamic hyperinflation in mechanically ventilated patients. *Respiratory Care* 50(1):110-123.

Blanco I, Gimeno E, Munoz PA, et al. (2010). Hemodynamic and gas exchange effects of sildenafil in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine* 181(3):270-278.

Borst MM, Leschke M, Konig U and Worth H (1999). Repetitive hemodilution in chronic obstructive pulmonary disease and pulmonary hypertension: effects on pulmonary hemodynamics, gas exchange, and exercise capacity. *Respiration* 66(3):225-232.

Botney MD (1999). Role of hemodynamics in pulmonary vascular remodeling: implications for primary pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine* 159(2):361-364.

Boujoukos AJ, Martich GD, Vega JD, Keenan RJ and Griffith BP (1997). Reperfusion injury in single-lung transplant recipients with pulmonary hypertension and emphysema. *Journal of Heart and Lung Transplantation* 16(4):439-448.

Boussuges A, Pinet C, Molenat F, et al. (2000). Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. *American Journal of Respiratory and Critical Care Medicine* 162(2 Pt 1):670-675.

Brett SJ, Simon J, Gibbs R, Pepper JR and Evans TW (1996). Impairment of endothelium-dependent pulmonary vasodilation in patients with primary pulmonary hypertension. *Thorax* 51(1):89-91.

Brower R, Wise RA, Hassapoyannes C, Bromberger-Barnea B and Permutt S (1985). Effect of lung inflation on lung blood volume and pulmonary venous flow. *Journal of Applied Physiology* 58(3):954-963.

Bruha R, Petrtyl J, Urbanek P, et al. (2005). Hepatic vein stenosis and inferior vena cava stenosis in a patient with chronic obstructive pulmonary disease. *Hepato-Gastroenterology* 52(66):1867-1868.

Brusasco V and Fitting JW (1996). Lung hyperinflation in airway obstruction. *European Respiratory Journal* 9(12):2440.

Buch P, Friberg J, Scharling H, Lange P and Prescott E (2003). Reduced lung function and risk of atrial fibrillation in the Copenhagen City Heart Study. *European Respiratory Journal* 21(6):1012-1016.

Buda AJ, Pinsky MR, Ingels NB, Jr., et al. (1979). Effect of intrathoracic pressure on left ventricular performance. *New England Journal of Medicine* 301(9):453-459.

Buga GM, Gold ME, Fukuto JM and Ignarro LJ (1991). Shear stress-induced release of nitric oxide from endothelial cells grown on beads. *Hypertension* 17(2):187-193.

Burgess MI, Mogulkoc N, Bright-Thomas RJ, et al. (2002). Comparison of echocardiographic markers of right ventricular function in determining prognosis in chronic pulmonary disease. *Journal of the American Society of Echocardiography* 15(6):633-639.

Burrows B, Fletcher CM, Heard BE, Jones NL and Wootliff JS (1966). The emphysematous and bronchial types of chronic airways obstruction. A clinicopathological study of patients in London and Chicago. *Lancet* 287(7442):830-835.

Burrows B, Niden AH, Fletcher CM and Jones NL (1964). Clinical types of chronic obstructive lung disease in London and in Chicago. A study of one hundred patients. *American Review of Respiratory Disease* 90:14-27.

Burton AC and Patel DJ (1958). Effect on pulmonary vascular resistance of inflation of the rabbit lungs. *Journal of Applied Physiology* 12(2):239-246.

Butler J (1990). The heart is not always in good hands. *Chest* 97(2):453-460.

Butler J, Schrijen F, Henriquez A, Polu JM and Albert RK (1988). Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 138(2):350-354.

Carlsen J, Hasseriis Andersen K, Boesgaard S, et al. (2013). Pulmonary arterial lesions in explanted lungs after transplantation correlate with severity of pulmonary hypertension in chronic obstructive pulmonary disease. *Journal of Heart and Lung Transplantation* 32(3):347-354.

Carratu P, Scoditti C, Maniscalco M, et al. (2008). Exhaled and arterial levels of endothelin-1 are increased and correlate with pulmonary systolic pressure in COPD with pulmonary hypertension. *BMC Pulmonary Medicine* 8:20.

Carson JL, Terrin ML, Duff A and Kelley MA (1996). Pulmonary embolism and mortality in patients with COPD. *Chest* 110(5):1212-1219.

Casanova C, Cote C, de Torres JP, et al. (2005). Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 171(6):591-597.

Cassivi SD, Meyers BF, Battafarano RJ, et al. (2002). Thirteen-year experience in lung transplantation for emphysema. *Annals of Thoracic Surgery* 74(5):1663-1669.

Celli BR, Cote CG, Marin JM, et al. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *New England Journal of Medicine* 350(10):1005-1012.

Chang CL, Robinson SC, Mills GD, et al. (2011). Biochemical markers of cardiac dysfunction predict mortality in acute exacerbations of COPD. *Thorax* 66(9):764-768.

Chaouat A, Bugnet A-S, Kadaoui N, et al. (2005). Severe pulmonary hypertension and chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 172(2):189-194.

Chaouat A, Savale L, Chouaid C, et al. (2009). Role for interleukin-6 in COPD-related pulmonary hypertension. *Chest* 136(3):678-687.

Chaouat A, Weitzenblum E, Krieger J, et al. (1995). Association of chronic obstructive pulmonary disease and sleep apnea syndrome. *American Journal of Respiratory and Critical Care Medicine* 151(1):82-86.

Chatila WM, Furukawa S, Gaughan JP and Criner GJ (2003). Respiratory failure after lung transplantation. *Chest* 123(1):165-173.

Chazova I, Loyd JE, Zhdanov VS, et al. (1995). Pulmonary artery adventitial changes and venous involvement in primary pulmonary hypertension. *American Journal of Pathology* 146(2):389-397.

Chen SJ, Chen YF, Meng QC, et al. (1995). Endothelin-receptor antagonist bosentan prevents and reverses hypoxic pulmonary hypertension in rats. *Journal of Applied Physiology* 79(6):2122-2131.

Chen Y, Hanaoka M, Chen P, et al. (2009). Protective effect of beraprost sodium, a stable prostacyclin analog, in the development of cigarette smoke extract-induced emphysema. *Am J Physiol Lung Cell Mol Physiol* 296(4):L648-656.

Chen Y, Hanaoka M, Droma Y, et al. (2010). Endothelin-1 receptor antagonists prevent the development of pulmonary emphysema in rats. *European Respiratory Journal* 35(4):904-912.

Christie JD, Bavaria JE, Palevsky HI, et al. (1998). Primary graft failure following lung transplantation. *Chest* 114(1):51-60.

Christie JD, Edwards LB, Kucheryavaya AY, et al. (2010). The registry of the International Society for Heart and Lung Transplantation: Twenty-seventh official adult lung and heart-lung transplant report-2010. *Journal of Heart and Lung Transplantation* 29(10):1104-1118.

Christie JD, Edwards LB, Kucheryavaya AY, et al. (2012). The registry of the International Society for Heart and Lung Transplantation: 29th adult lung and heart-lung transplant report-2012. *Journal of Heart and Lung Transplantation* 31(10):1073-1086.

Clini E, Cremona G, Campana M, et al. (2000). Production of endogenous nitric oxide in chronic obstructive pulmonary disease and patients with cor pulmonale. Correlates with echo-Doppler assessment. *American Journal of Respiratory and Critical Care Medicine* 162(2 Pt 1):446-450.

Come CE, Divo MJ, San Jose Estepar R, et al. (2012). Lung deflation and oxygen pulse in COPD: results from the NETT randomized trial. *Respiratory Medicine* 106(1):109-119.

Conte JV, Borja MJ, Patel CB, et al. (2001). Lung transplantation for primary and secondary pulmonary hypertension. *Annals of Thoracic Surgery* 72(5):1673-1679.

Cooper CB, Waterhouse J and Howard P (1987). Twelve year clinical study of patients with hypoxic cor pulmonale given long term domiciliary oxygen therapy. *Thorax* 42(2):105-110.

Cournand A, Motley HL, Werko L and Richards DW (1947). Physiological studies of the effects of intermittent positive pressure breathing on cardiac output in man. *American Journal of Physiology* 152(1):162-174.

Criner GJ (2011). Alternatives to lung transplantation: lung volume reduction for COPD. *Clinics in Chest Medicine* 32(2):379-397.

Criner GJ, Scharf SM, Falk JA, et al. (2007). Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. *American Journal of Respiratory and Critical Care Medicine* 176(3):253-260.

Cudkowicz L and O'Neill A (1965). Effects of lung volume changes on cardiac output in man. *Thorax* 20:242-247.

Dal Vecchio L, Polese G, Poggi R and Rossi A (1990). "Intrinsic" positive end-expiratory pressure in stable patients with chronic obstructive pulmonary disease. *European Respiratory Journal* 3(1):74-80.

Damiano RJ, Jr., La Follette P, Jr., Cox JL, Lowe JE and Santamore WP (1991). Significant left ventricular contribution to right ventricular systolic function. *American Journal of Physiology* 261(5 Pt 2):H1514-1524.

Dart AM and Kingwell BA (2001). Pulse pressure--a review of mechanisms and clinical relevance. *Journal of the American College of Cardiology* 37(4):975-984.

Defouilloy C, Teiger E, Sediame S, et al. (1998). Polycythemia impairs vasodilator response to acetylcholine in patients with chronic hypoxemic lung disease. *American Journal of Respiratory and Critical Care Medicine* 157(5 Pt 1):1452-1460.

Dernaika TA, Beavin M and Kinasewitz GT (2010). Iloprost improves gas exchange and exercise tolerance in patients with pulmonary hypertension and chronic obstructive pulmonary disease. *Respiration* 79(5):377-382.

Deslauriers J, Ugalde P, Miro S, et al. (2011). Adjustments in cardiorespiratory function after pneumonectomy: results of the pneumonectomy project. *Journal of Thoracic and Cardiovascular Surgery* 141(1):7-15.

Dexter L (1956). Atrial septal defect. *British Heart Journal* 18(2):209-225.

Dexter L, Dow JW, Haynes FW, et al. (1950). Studies of the pulmonary circulation in man at rest; normal variations and the interrelations between increased pulmonary blood flow, elevated pulmonary arterial pressure, and high pulmonary 'capillary" pressures. *Journal of Clinical Investigation* 29(5):602-613.

Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. (1991). Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. *New England Journal of Medicine* 324(22):1539-1547.

Doi M, Nakano K, Hiramoto T and Kohno N (2003). Significance of pulmonary artery pressure in emphysema patients with mild-to-moderate hypoxemia. *Respiratory Medicine* 97(8):915-920.

Dornhorst AC (1955). Respiratory insufficiency. *Lancet* 268(6876):1185-1187.

Eddahibi S, Chaouat A, Morrell N, et al. (2003). Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. *Circulation* 108(15):1839-1844.

Eisner MD, Anthonisen N, Coultas D, et al. (2010). An official American Thoracic Society public policy statement: Novel risk factors and the global burden of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 182(5):693-718.

Elwing J and Panos RJ (2008). Pulmonary hypertension associated with COPD. *International Journal of COPD* 3(1):55-70.

Enson Y, Giuntini C, Lewis ML, et al. (1964). The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. *Journal of Clinical Investigation* 43:1146-1162.

Faller M, Kessler R, Sapin R, et al. (1998). Regulation of endothelin-1 at rest and during a short steady-state exercise in 21 COPD patients. *Pulmonary Pharmacology and Therapeutics* 11(2-3):151-157.

Fang A, Studer S, Kawut SM, et al. (2011). Elevated pulmonary artery pressure is a risk factor for primary graft dysfunction following lung transplantation for idiopathic pulmonary fibrosis. *Chest* 139(4):782-787.

Farber HW and Loscalzo J (2004). Pulmonary arterial hypertension. *New England Journal of Medicine* 351(16):1655-1665.

Fernie JM and Lamb D (1988). Assessment of the effects of age and smoking on the media of muscular pulmonary arteries. *Journal of Pathology* 155(3):241-246.

Ferri C, Bellini C, De Angelis C, et al. (1995). Circulating endothelin-1 concentrations in patients with chronic hypoxia. *Journal of Clinical Pathology* 48(6):519-524.

Fisher MR, Criner GJ, Fishman AP, et al. (2007). Estimating pulmonary artery pressures by echocardiography in patients with emphysema. *European Respiratory Journal* 30(5):914-921.

Fisher MR, Forfia PR, Chamera E, et al. (2009). Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *American Journal of Respiratory and Critical Care Medicine* 179(7):615-621.

Fishman A, Martinez F, Naunheim K, et al. (2003). A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. *New England Journal of Medicine* 348(21):2059-2073.

Fishman AP, Fritts HW, Jr. and Cournand A (1960a). Effects of acute hypoxia and exercise on the pulmonary circulation. *Circulation* 22:204-215.

Fishman AP, Fritts HW, Jr. and Cournand A (1960b). Effects of breathing carbon dioxide upon the pulmonary circulation. *Circulation* 22:220-225.

Fitton TP, Kosowski TR, Barreiro CJ, et al. (2005). Impact of secondary pulmonary hypertension on lung transplant outcome. *Journal of Heart and Lung Transplantation* 24(9):1254-1259.

Fowler NO, Jr., Westcott RN and Scott RC (1952). Pulmonary artery diastolic pressure: its relationship to pulmonary arteriolar resistance and pulmonary capillary pressure. *Journal of Clinical Investigation* 31(1):72-79.

Frangos JA, Eskin SG, McIntire LV and Ives CL (1985). Flow effects on prostacyclin production by cultured human endothelial cells. *Science* 227(4693):1477-1479.

Fujii T, Otsuka T, Tanaka S, et al. (1999). Plasma endothelin-1 level in chronic obstructive pulmonary disease: relationship with natriuretic peptide. *Respiration* 66(3):212-219.

Gallagher PJ (1997). Blood Vessels. *Histology for Pathologists*. Sternberg SS. Philadelphia, Lippincott-Raven Publishers**:**771-772.

Garcia-Aymerich J, Gomez FP, Benet M, et al. (2011). Identification and prospective validation of clinically relevant chronic obstructive pulmonary disease (COPD) subtypes. *Thorax* 66(5):430-437.

Georgopoulos D, Giannouli E and Patakas D (1993). Effects of extrinsic positive end-expiratory pressure on mechanically ventilated patients with chronic obstructive pulmonary disease and dynamic hyperinflation. *Intensive Care Medicine* 19(4):197-203.

Gerges C, Gerges M, Lang MB, et al. (2013). Diastolic pulmonary vascular pressure gradient: a predictor of prognosis in "out-of-proportion" pulmonary hypertension. *Chest* 143(3):758-766.

Giaid A and Saleh D (1995). Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension. *New England Journal of Medicine* 333(4):214-221.

Giaid A, Yanagisawa M, Langleben D, et al. (1993). Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *New England Journal of Medicine* 328(24):1732-1739.

Gibson GJ (1996). Pulmonary hyperinflation a clinical overview. *European Respiratory Journal* 9(12):2640-2649.

GOLD (2009). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (updated 2009), Global Initiative for Chronic Obstructive Lung Disease (GOLD).

GOLD (2011). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (revised 2011), Global Initiative for Chronic Obstructive Lung Disease (GOLD).

Gomez A, Unruh H and Mink S (1994). Left ventricular systolic performance is depressed in chronic pulmonary emphysema in dogs. *American Journal of Physiology* 267(1 Pt 2):H232-247.

Gonzalez MS, Basnight MA and Appleton CP (1991). Experimental cardiac tamponade: a hemodynamic and Doppler echocardiographic reexamination of the relation of right and left heart ejection dynamics to the phase of respiration. *Journal of the American College of Cardiology* 18(1):243-252.

Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M and Zielinski J (1997). Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. *Thorax* 52(8):674-679.

Gould GA, Redpath AT, Ryan M, et al. (1991). Lung CT density correlates with measurements of airflow limitation and the diffusing capacity. *European Respiratory Journal* 4(2):141-146.

Grazzini M, Stendardi L, Gigliotti F and Scano G (2005). Pathophysiology of exercise dyspnea in healthy subjects and in patients with chronic obstructive pulmonary disease (COPD). *Respiratory Medicine* 99(11):1403-1412.

Hakim TS, Gilbert E and Camporesi E (1993). Positive end-expiratory pressure increases capillary pressure relative to wedge pressure in the closed and open chest. *Journal of Critical Care* 8(2):80-86.

Hakim TS, Michel RP and Chang HK (1982). Effect of lung inflation on pulmonary vascular resistance by arterial and venous occlusion. *Journal of Applied Physiology* 53(5):1110-1115.

Hale KA, Ewing SL, Gosnell BA and Niewoehner DE (1984). Lung disease in long-term cigarette smokers with and without chronic air-flow obstruction. *American Review of Respiratory Disease* 130(5):716-721.

Hale KA, Niewoehner DE and Cosio MG (1980). Morphologic changes in the muscular pulmonary arteries: relationship to cigarette smoking, airway disease, and emphysema. *American Review of Respiratory Disease* 122(2):273-278.

Hales CA (1985). The site and mechanism of oxygen sensing for the pulmonary vessels. *Chest* 88(4 Suppl):235S-240S.

Halpern SD and Taichman DB (2009). Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. *Chest* 136(1):37-43.

Haluszka J, Chartrand DA, Grassino AE and Milic-Emili J (1990). Intrinsic PEEP and arterial PCO2 in stable patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 141(5 Pt 1):1194-1197.

Ham AW (1974). Histology. *The Circulatory System*. Philadelphia, J.B. Lippincott Company**:**559-568.

Han MK, Agusti A, Calverley PM, et al. (2010). Chronic obstructive pulmonary disease phenotypes: the future of COPD. *American Journal of Respiratory and Critical Care Medicine* 182(5):598-604.

Hanaoka M, Ideura G, Ito M, et al. (2008). Pulmonary haemodynamic changes in patients with severe COPD. *Respirology* 13(6):919-922.

Haniuda M, Kubo K, Fujimoto K, et al. (2003). Effects of pulmonary artery remodeling on pulmonary circulation after lung volume reduction surgery. *Thoracic and Cardiovascular Surgeon* 51(3):154-158.

Hannink JD, van Helvoort HA, Dekhuijzen PN and Heijdra YF (2010). Dynamic hyperinflation during daily activities: does COPD Global Initiative for Chronic Obstructive Lung Disease stage matter? *Chest* 137(5):1116-1121.

Harch S, Whitford H and McLean C (2009). Failure of medical therapy in pulmonary arterial hypertension. Is there an alternative diagnosis? *Chest* 135(6):1462-1469.

Harris P, Segel N, Green I and Housley E (1968). The influence of the airways resistance and alveolar pressure on the pulmonary vascular resistance in chronic bronhcitis. *Cardiovascular Research* 2(1):84-92.

Harvey RM, Enson Y and Ferrer MI (1971). A reconsideration of the origins of pulmonary hypertension. *Chest* 59(1):82-94.

Hassoun PM, Mouthon L, Barberà JA, et al. (2009). Inflammation, growth factors, and pulmonary vascular remodeling. *Journal of the American College of Cardiology* 54(1, Supplement 1):S10-S19.

Heath D and Best PV (1958). The tunica media of the arteries of the lung in pulmonary hypertension. *Journal of Pathology and Bacteriology* 76(1):165-174.

Heath D and Edwards JE (1958). The pathology of hypertensive pulmonary vascular disease; a description of six grades of structural changes in the pulmonary arteries with special reference to congenital cardiac septal defects. *Circulation* 18(4 Part 1):533-547.

Her C, Koike H and O'Connell J (2009). Estimated right ventricular systolic time intervals for the assessment of right ventricular function in acute respiratory distress syndrome. *Shock* 31(5):460-465.

Hoeper MM, Barberà JA, Channick RN, et al. (2009). Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. *Journal of the American College of Cardiology* 54(1, Supplement 1):S85-S96.

Hole DJ, Watt GC, Davey-Smith G, et al. (1996). Impaired lung function and mortality risk in men and women: findings from the Renfrew and Paisley prospective population study. *BMJ* 313(7059):711-715.

Holverda S, Rietema H, Bogaard HJ, et al. (2008). Acute effects of sildenafil on exercise pulmonary hemodynamics and capacity in patients with COPD. *Pulmonary Pharmacology and Therapeutics* 21(3):558-564.

Honda S, Sunagawa H, Tasaki H, Hirose M and Fukushige J (1975). Correlation between pulmonary vascular resistance and pulmonary arterial diastolic pressure in congenital heart diseases with left to right shunt. *Japanese Heart Journal* 16(6):629-638.

Hopkinson NS, Toma TP, Hansell DM, et al. (2005). Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. *American Journal of Respiratory and Critical Care Medicine* 171(5):453-460.

Hosenpud JD, Bennett LE, Keck BM, Edwards EB and Novick RJ (1998). Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. *Lancet* 351(9095):24-27.

Howell JB, Permutt S, Proctor DF and Riley RL (1961). Effect of inflation of the lung on different parts of pulmonary vascular bed. *Journal of Applied Physiology* 16:71-76.

Huerd SS, Hodges TN, Grover FL, et al. (2000). Secondary pulmonary hypertension does not adversely affect outcome after single lung transplantation. *Journal of Thoracic and Cardiovascular Surgery* 119(3):458-465.

Humbert M, Sitbon O and Simonneau G (2004). Treatment of pulmonary arterial hypertension. *New England Journal of Medicine* 351(14):1425-1436.

Hunt JM, Copland J, McDonald CF, et al. (1989). Cardiopulmonary response to oxygen therapy in hypoxaemic chronic airflow obstruction. *Thorax* 44(11):930-936.

Hurst JR, Vestbo J, Anzueto A, et al. (2010). Susceptibility to exacerbation in chronic obstructive pulmonary disease. *New England Journal of Medicine* 363(12):1128-1138.

Incalzi RA, Fuso L, De Rosa M, et al. (1999). Electrocardiographic signs of chronic cor pulmonale: A negative prognostic finding in chronic obstructive pulmonary disease. *Circulation* 99(12):1600-1605.

Iversen KK, Kjaergaard J, Akkan D, et al. (2008). Chronic obstructive pulmonary disease in patients admitted with heart failure. *Journal of Internal Medicine* 264(4):361-369.

Iversen KK, Kjaergaard J, Akkan D, et al. (2010). The prognostic importance of lung function in patients admitted with heart failure. *European Journal of Heart Failure* 12(7):685-691.

Jorgensen K, Houltz E, Westfelt U, et al. (2003). Effects of lung volume reduction surgery on left ventricular diastolic filling and dimensions in patients with severe emphysema. *Chest* 124(5):1863-1870.

Jorgensen K, Muller MF, Nel J, et al. (2007). Reduced intrathoracic blood volume and left and right ventricular dimensions in patients with severe emphysema: an MRI study. *Chest* 131(4):1050-1057.

Kaltman AJ, Herbert WH, Conroy RJ and Kossmann CE (1966). The gradient in pressure across the pulmonary vascular bed during diastole. *Circulation* 34(3):377-384.

Kasahara Y, Tuder RM, Cool CD, et al. (2001). Endothelial cell death and decreased expression of vascular endothelial growth factor and vascular endothelial growth factor receptor 2 in emphysema. *American Journal of Respiratory and Critical Care Medicine* 163(3 Pt 1):737-744.

Katayama Y, Higenbottam TW, Diaz de Atauri MJ, et al. (1997). Inhaled nitric oxide and arterial oxygen tension in patients with chronic obstructive pulmonary disease and severe pulmonary hypertension. *Thorax* 52(2):120-124.

Keller CA, Shepard JW, Jr., Chun DS, Vasquez P and Dolan GF (1986). Pulmonary hypertension in chronic obstructive pulmonary disease. Multivariate analysis. *Chest* 90(2):185-192.

Kelly RP, Ting CT, Yang TM, et al. (1992). Effective arterial elastance as index of arterial vascular load in humans. *Circulation* 86(2):513-521.

Keogh AM and Pettersson R (2009). Australia and New Zealand Cardiothoracic Organ Transplant Registry: 2009 report. Sydney, St Vincent's Hospital.

Keogh AM, Williams TJ and Pettersson R (2012). Australia and New Zealand Cardiothoracic Organ Tranplant Registry: 2011 report. Sydney, St Vincent's Hospital.

Kessler R, Faller M, Fourgaut G, Mennecier B and Weitzenblum E (1999). Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 159(1):158-164.

Kessler R, Faller M, Weitzenblum E, et al. (2001). "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. *American Journal of Respiratory and Critical Care Medicine* 164(2):219-224.

Kilburn KH and Sieker HO (1960). Hemodynamic effects of continuous positive and negative pressure breathing in normal man. *Circulation Research* 8:660-669.

Kubo K, Ge RL, Koizumi T, et al. (2000). Pulmonary artery remodeling modifies pulmonary hypertension during exercise in severe emphysema. *Respiration Physiology* 120(1):71-79.

Laaban JP, Diebold B, Zelinski R, et al. (1989). Noninvasive estimation of systolic pulmonary artery pressure using Doppler echocardiography in patients with chronic obstructive pulmonary disease. *Chest* 96(6):1258-1262.

Lang CC, Coutie WJ, Struthers AD, et al. (1992). Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. *Clinical Science* 83(5):529-533.

Lankhaar JW, Westerhof N, Faes TJ, et al. (2006). Quantification of right ventricular afterload in patients with and without pulmonary hypertension. *American Journal of Physiology - Heart and Circulatory Physiology* 291(4):H1731-1737.

Lederer DJ, Bartels MN, Schluger NW, et al. (2012). Sildenafil for chronic obstructive pulmonary disease: a randomized crossover trial. *COPD* 9(3):268-275.

Lee JH, Oh YM, Seo JB, et al. (2011). Pulmonary artery pressure in chronic obstructive pulmonary disease without resting hypoxaemia. *International Journal of Tuberculosis and Lung Disease* 15(6):830-837.

Lee KH, Martich GD, Boujoukos AJ, Keenan RJ and Griffith BP (1996). Predicting ICU length of stay following single lung transplantation. *Chest* 110(4):1014-1017.

Lee TM, Chen CC, Shen HN and Chang NC (2009). Effects of pravastatin on functional capacity in patients with chronic obstructive pulmonary disease and pulmonary hypertension. *Clinical Science* 116(6):497-505.

Leith DE and Brown R (1999). Human lung volumes and the mechanisms that set them. *European Respiratory Journal* 13(2):468-472.

Lim TP and Brownlee WE (1968). Pulmonary hemodynamics in obstructive lung disease. *Diseases of the Chest* 53(2):113-125.

Lloyd TC, Jr. (1967). Analysis of the relation of pulmonary arterial on airway conductance to lung volume. *Journal of Applied Physiology* 23(6):887-894.

Lockhart A, Nader F, Tzareva M and Schrijen F (1970). Comparative effects of exercise and isocapnic voluntary hyperventilation on pulmonary haemodynamics in chronic bronchitis and emphysema. *European Journal of Clinical Investigation* 1(1):69-76.

Luce JM (1984). The cardiovascular effects of mechanical ventilation and positive end-expiratory pressure. *Journal of the American Medical Association* 252(6):807-811.

Luecke T and Pelosi P (2005). Clinical review: Positive end-expiratory pressure and cardiac output. *Critical Care* 9(6):607-621.

MacNee W (2007). Pathogenesis of chronic obstructive pulmonary disease. *Clinics in Chest Medicine* 28(3):479-513, v.

Madden BP, Allenby M, Loke T-K and Sheth A (2006). A potential role for sildenafil in the management of pulmonary hypertension in patients with parenchymal lung disease. *Vascular Pharmacology* 44(5):372-376.

Magee F, Wright JL, Wiggs BR, Pare PD and Hogg JC (1988). Pulmonary vascular structure and function in chronic obstructive pulmonary disease. *Thorax* 43(3):183-189.

Malek AM, Alper SL and Izumo S (1999). Hemodynamic shear stress and its role in atherosclerosis. *Journal of the American Medical Association* 282(21):2035-2042.

Manny J, Patten MT, Liebman PR and Hechtman HB (1978). The association of lung distention, PEEP and biventricular failure. *Annals of Surgery* 187(2):151-157.

Marini JJ, Culver BH and Butler J (1981a). Effect of positive end-expiratory pressure on canine ventricular function curves. *Journal of Applied Physiology* 51(6):1367-1374.

Marini JJ, Culver BH and Butler J (1981b). Mechanical effect of lung distention with positive pressure on cardiac function. *American Review of Respiratory Disease* 124(4):382-386.

Marsh SE, Travers J, Weatherall M, et al. (2008). Proportional classifications of COPD phenotypes. *Thorax* 63(9):761-767.

Maruyama Y, Ashikawa K, Isoyama S, et al. (1982). Mechanical interactions between four heart chambers with and without the pericardium in canine hearts. *Circulation Research* 50(1):86-100.

Matthay RA, Schwarz MI, Ellis JH, Jr., et al. (1981). Pulmonary artery hypertension in chronic obstructive pulmonary disease: determination by chest radiography. *Investigative Radiology* 16(2):95-100.

McKenzie DK, Abramson M, Crockett AJ, et al. (2011). The COPD-X plan: Australia and New Zealand guidelines for the management of chronic obstructive pulmonary disease. V2.30.

McKenzie DK, Frith PA, Burdon JG and Town GI (2008). The COPD-X plan: Australian and New Zealand Guidelines for the management of chronic obstructive pulmonary disease.

Medical Research Council Working Party (1981). Long term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Report of the Medical Research Council Working Party. *Lancet* 1(8222):681-686.

Mejia M, Carrillo G, Rojas-Serrano J, et al. (2009). Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. *Chest* 136(1):10-15.

Mercer RR and Crapo JD (1998). Normal anatomy and defence mechanisms of the lung. *Textbook of Pulmonary Diseases*. Baum GL, Crapo JD, Celli BR and Karlinsky JB. Philadelphia, Lippincott - Raven. 1**:**23-46.

Mesquida J, Kim HK and Pinsky MR (2011). Effect of tidal volume, intrathoracic pressure, and cardiac contractility on variations in pulse pressure, stroke volume, and intrathoracic blood volume. *Intensive Care Medicine* 37(10):1672-1679.

Meyer DM, Bennett LE, Novick RJ and Hosenpud JD (2001). Single vs bilateral, sequential lung transplantation for end-stage emphysema: influence of recipient age on survival and secondary end-points. *Journal of Heart and Lung Transplantation* 20(9):935-941.

Milic-Emili J (1990). Dynamic pulmonary hyperinflation and intrinsic PEEP: consequences and management in patients with chronic obstructive pulmonary disease. *Recenti Progressi in Medicina* 81(11):733-737.

Milnor WR (1975). Arterial impedance as ventricular afterload. *Circulation Research* 36(5):565-570.

Minai OA, Chaouat A and Adnot S (2010). Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective. *Chest* 137(6 Suppl):39S-51S.

Mineo TC, Pompeo E, Rogliani P, et al. (2002). Effect of lung volume reduction surgery for severe emphysema on right ventricular function. *American Journal of Respiratory and Critical Care Medicine* 165(4):489-494.

Mols P, Ham H, Naeije N, et al. (1988). How does salbutamol improve the ventricular performance in patients with chronic obstructive pulmonary disease? *Journal of Cardiovascular Pharmacology* 12(2):127-133.

Montes de Oca M, Rassulo J and Celli BR (1996). Respiratory muscle and cardiopulmonary function during exercise in very severe COPD. *American Journal of Respiratory and Critical Care Medicine* 154(5):1284-1289.

Morganti A, Giussani M, Ghio F, et al. (1994). Endothelin-releasing stimuli and calcium antagonists in normal and pathological conditions. *Journal of Hypertension. Supplement* 12(1):S27-31.

Morley TF, Zappasodi SJ, Belli A and Giudice JC (1987). Pulmonary vasodilator therapy for chronic obstructive pulmonary disease and cor pulmonale. Treatment with nifedipine, nitroglycerin, and oxygen. *Chest* 92(1):71-76.

Morrell NW, Adnot S, Archer SL, et al. (2009). Cellular and molecular basis of pulmonary arterial hypertension. *Journal of the American College of Cardiology* 54(1, Supplement 1):S20-S31.

Motley HL, Cournand A and et al. (1947). The influence of short periods of induced acute anoxia upon pulmonary artery pressures in man. *American Journal of Physiology* 150(2):315-320.

Naeije R and Barbera JA (2001). Pulmonary hypertension associated with COPD. *Critical Care* 5(6):286-289.

Naeije R and Huez S (2007). Right ventricular function in pulmonary hypertension: physiological concepts. *European Heart Journal Supplements* 9(Supplement H):H5-9.

Naeije R, Melot C, Mols P and Hallemans R (1982). Reduction in pulmonary hypertension by prostaglandin E1 in decompensated chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 125(1):1-5.

Nahas GG, Visscher GW, Mather GW, Haddy FJ and Warner HR (1954). Influence of hypoxia on the pulmonary circulation of nonnarcotized dogs. *Journal of Applied Physiology* 6:10.

Nakamura A, Kasamatsu N, Hashizume I, et al. (2000). Effects of hemoglobin on pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic emphysema. *Respiration* 67(5):502-506.

Nana-Sinkam SP, Lee JD, Sotto-Santiago S, et al. (2007). Prostacyclin prevents pulmonary endothelial cell apoptosis induced by cigarette smoke. *American Journal of Respiratory and Critical Care Medicine* 175(7):676-685.

Nana-Sinkam SP, Lee JD, Stearman R, et al. (2006). Prostacyclin synthase in smoking-related lung disease. *Proceedings of the American Thoracic Society* 3(6):517.

Nichols WW, Conti CR, Walker WE and Milnor WR (1977). Input impedance of the systemic circulation in man. *Circulation Research* 40(5):451-458.

Nielsen J, Nygard E, Kjaergaard J, Tingleff J and Larsson A (2007). Hemodynamic effect of sustained pulmonary hyperinflation in patients after cardiac surgery: open vs. closed chest. *Acta Anaesthesiologica Scandinavica* 51(1):74-81.

Nielsen J, Ostergaard M, Kjaergaard J, et al. (2005). Lung recruitment maneuver depresses central hemodynamics in patients following cardiac surgery. *Intensive Care Medicine* 31(9):1189-1194.

Nocturnal Oxygen Therapy Trial Group (1980). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease: a clinical trial. Nocturnal Oxygen Therapy Trial Group. *Annals of Internal Medicine* 93(3):391-398.

O'Donnell DE and Laveneziana P (2006). The clinical importance of dynamic lung hyperinflation in COPD. *COPD* 3(4):219-232.

O'Donnell DE, Revill SM and Webb KA (2001). Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 164(5):770-777.

O'Donnell DE and Webb KA (2008a). Last word on point:counterpoint: The major limitation to exercise performance in COPD is 1) inadequate energy supply to the respiratory and locomotor muscles, 2) lower limb muscle dysfunction, 3) dynamic hyperinflation. *Journal of Applied Physiology* 105(2):765.

O'Donnell DE and Webb KA (2008b). The major limitation to exercise performance in COPD is dynamic hyperinflation. *Journal of Applied Physiology* 105(2):753-755.

O'Donoghue FJ, Catcheside PG, Ellis EE, et al. (2003). Sleep hypoventilation in hypercapnic chronic obstructive pulmonary disease: prevalence and associated factors. *European Respiratory Journal* 21(6):977-984.

Omari MK, Smith SA, Jacobsen G and Kaza V (2011). Effect of pulmonary hypertension in patients with end-stage lung disease on posttransplantation outcomes. *Transplantation Proceedings* 43(5):1881-1886.

Orens JB, Estenne M, Arcasoy S, et al. (2006). International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. *Journal of Heart and Lung Transplantation* 25(7):745-755.

Oswald-Mammosser M, Kessler R, Massard G, et al. (1998). Effect of lung volume reduction surgery on gas exchange and pulmonary hemodynamics at rest and during exercise. *American Journal of Respiratory and Critical Care Medicine* 158(4):1020-1025.

Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. (1995). Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. *Chest* 107(5):1193-1198.

Overbeek MJ, Vonk MC, Boonstra A, et al. (2009). Pulmonary arterial hypertension in limited cutaneous systemic sclerosis: a distinctive vasculopathy. *European Respiratory Journal* 34(2):371-379.

Papiris S, Kotanidou A, Malagari K and Roussos C (2002). Clinical review: severe asthma. *Critical Care* 6(1):30-44.

Pasha MA and Newman JH (2010). High-altitude disorders: pulmonary hypertension: pulmonary vascular disease: the global perspective. *Chest* 137(6 Suppl):13S-19S.

Pauwels RA, Buist AS, Calverley PM, Jenkins CR and Hurd SS (2001). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *American Journal of Respiratory and Critical Care Medicine* 163(5):1256-1276.

Peinado VI, Barbera JA, Abate P, et al. (1999). Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 159(5 Pt 1):1605-1611.

Peinado VI, Barbera JA, Ramirez J, et al. (1998). Endothelial dysfunction in pulmonary arteries of patients with mild COPD. *American Journal of Physiology* 274(6 Pt 1):L908-913.

Pepe PE and Marini JJ (1982). Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *American Review of Respiratory Disease* 126(1):166-170.

Permutt S, Bromberger-Barnea B and Bane HN (1962). Alveolar pressure, pulmonary venous pressure, and the vascular waterfall. *Medicina Thoracalis* 19:239-260.

Permutt S, Howell JB, Proctor DF and Riley RL (1961). Effect of lung inflation on static pressure-volume characteristics of pulmonary vessels. *Journal of Applied Physiology* 16:64-70.

Permutt S and Riley RL (1963). Hemodynamics of collapsible vessels with tone: the vascular waterfall. *Journal of Applied Physiology* 18:924-932.

Peters J, Fraser C, Stuart RS, Baumgartner W and Robotham JL (1989). Negative intrathoracic pressure decreases independently left ventricular filling and emptying. *American Journal of Physiology* 257(1 Pt 2):H120-131.

Peters J, Kindred MK and Robotham JL (1988a). Transient analysis of cardiopulmonary interactions. I. Diastolic events. *Journal of Applied Physiology* 64(4):1506-1517.

Peters J, Kindred MK and Robotham JL (1988b). Transient analysis of cardiopulmonary interactions. II. Systolic events. *Journal of Applied Physiology* 64(4):1518-1526.

Petkov V, Mosgoeller W, Ziesche R, et al. (2003). Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. *Journal of Clinical Investigation* 111(9):1339-1346.

Pietra GG, Edwards WD, Kay JM, et al. (1989). Histopathology of primary pulmonary hypertension. A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation* 80(5):1198-1206.

Pinsky MR (2005). Cardiovascular issues in respiratory care. *Chest* 128(5 Suppl 2):592S-597S.

Pinsky MR (2007). Heart-lung interactions. *Current Opinion in Critical Care* 13(5):528-531.

Pochettino A, Kotloff RM, Rosengard BR, et al. (2000). Bilateral versus single lung transplantation for chronic obstructive pulmonary disease: intermediate-term results. *Annals of Thoracic Surgery* 70(6):1813-1818.

Prekker ME, Nath DS, Walker AR, et al. (2006). Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. *Journal of Heart and Lung Transplantation* 25(4):371-378.

Presberg KW and Dincer HE (2003). Pathophysiology of pulmonary hypertension due to lung disease. *Current Opinion in Pulmonary Medicine* 9(2):131-138.

Puhan MA, Garcia-Aymerich J, Frey M, et al. (2009). Expansion of the prognostic assessment of patients with chronic obstructive pulmonary disease: the updated BODE index and the ADO index. *Lancet* 374(9691):704-711.

Ranieri VM, Giuliani R, Cinnella G, et al. (1993). Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *American Review of Respiratory Disease* 147(1):5-13.

Ranieri VM, Giuliani R, Mascia L, et al. (1996). Patient-ventilator interaction during acute hypercapnia: pressure-support vs. proportional-assist ventilation. *Journal of Applied Physiology* 81(1):426-436.

Ranieri VM, Mascia L, Petruzzelli V, et al. (1995). Inspiratory effort and measurement of dynamic intrinsic PEEP in COPD patients: effects of ventilator triggering systems. *Intensive Care Medicine* 21(11):896-903.

Reid L (1968). Structural and functional reappraisal of the pulmonary artery system. *Scientific Basis of Medicine Annual Reviews*:289-307.

Resta O, Foschino Barbaro MP, Brindicci C, et al. (2002). Hypercapnia in overlap syndrome: possible determinant factors. *Sleep & Breathing* 6(1):11-18.

Rich JD, Shah SJ, Swamy RS, Kamp A and Rich S (2011). Inaccuracy of Doppler echocardiographic estimates of pulmonary artery pressures in patients with pulmonary hypertension: implications for clinical practice. *Chest* 139(5):988-993.

Rietema H, Holverda S, Bogaard HJ, et al. (2008). Sildenafil treatment in COPD does not affect stroke volume or exercise capacity. *European Respiratory Journal* 31(4):759-764.

Rizkallah J, Man SF and Sin DD (2009). Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest* 135(3):786-793.

Robotham JL, Cherry D, Mitzner W, et al. (1983). A re-evaluation of the hemodynamic consequences of intermittent positive pressure ventilation. *Critical Care Medicine* 11(10):783-793.

Roos A, Thomas LJ, Jr., Nagel EL and Prommas DC (1961). Pulmonary vascular resistance as determined by lung inflation and vascular pressures. *Journal of Applied Physiology* 16:77-84.

Rubanyi GM, Romero JC and Vanhoutte PM (1986). Flow-induced release of endothelium-derived relaxing factor. *American Journal of Physiology* 250(6 Pt 2):H1145-1149.

Saetta M, Baraldo S, Corbino L, et al. (1999). CD8+ve cells in the lungs of smokers with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 160(2):711-717.

Sajkov D, McEvoy RD, Cowie RJ, et al. (1993). Felodipine improves pulmonary hemodynamics in chronic obstructive pulmonary disease. *Chest* 103(5):1354-1361.

Sanders MH, Newman AB, Haggerty CL, et al. (2003). Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *American Journal of Respiratory and Critical Care Medicine* 167(1):7-14.

Santamore WP, Bartlett R, Van Buren SJ, Dowd MK and Kutcher MA (1986). Ventricular coupling in constrictive pericarditis. *Circulation* 74(3):597-602.

Santamore WP and Dell'Italia LJ (1998). Ventricular interdependence: significant left ventricular contributions to right ventricular systolic function. *Progress in Cardiovascular Diseases* 40(4):289-308.

Santamore WP, Heckman JL and Bove AA (1984). Right and left ventricular pressure-volume response to respiratory maneuvers. *Journal of Applied Physiology* 57(5):1520-1527.

Santamore WP, Heckman JL and Bove AA (1986). Right and left ventricular pressure-volume response to elevated pericardial pressure. *American Review of Respiratory Disease* 134(1):101-107.

Santos S, Peinado VI, Ramirez J, et al. (2003). Enhanced expression of vascular endothelial growth factor in pulmonary arteries of smokers and patients with moderate chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 167(9):1250-1256.

Scharf SM (1998). The normal adult pulmonary circulation. *Textbook of Pulmonary Diseases*. Baum GL, Crapo JD, Celli BR and Karlinsky JB. Philadelphia, Lippincott - Raven. 2**:**1257-1272.

Scharf SM, Brown R, Saunders N and Green LH (1979). Effects of normal and loaded spontaneous inspiration on cardiovascular function. *Journal of Applied Physiology* 47(3):582-590.

Scharf SM, Iqbal M, Keller C, et al. (2002). Hemodynamic characterization of patients with severe emphysema. *American Journal of Respiratory and Critical Care Medicine* 166(3):314-322.

Scharf SM, Pinsky MR and Magder S, Eds. (2001). *Respiratory-circulatory interactions in health and disease*. Lung biology in health and disease. New York, Marcel Dekker.

Schrijen FV, Henriquez A, Carton D, Delorme N and Butler J (1989). Pulmonary vascular resistance rises with lung volume on exercise in obstructed airflow disease. *Clinical Physiology* 9(2):143-150.

Schunemann HJ, Dorn J, Grant BJ, Winkelstein W, Jr. and Trevisan M (2000). Pulmonary function is a long-term predictor of mortality in the general population: 29-year follow-up of the Buffalo Health Study. *Chest* 118(3):656-664.

Sciurba FC, Rogers RM, Keenan RJ, et al. (1996). Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. *New England Journal of Medicine* 334(17):1095-1099.

Selinger SR, Kennedy TP, Buescher P, et al. (1987). Effects of removing oxygen from patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 136(1):85-91.

Semmens M (1970). The pulmonary artery in the normal aged lung. *British Journal of Diseases of the Chest* 64(2):65-72.

Shekerdemian L and Bohn D (1999). Cardiovascular effects of mechanical ventilation. *Archives of Disease in Childhood* 80(5):475-480.

Shelton DM, Keal E and Reid L (1977). The pulmonary circulation in chronic bronchitis and emphysema. *Chest* 71(2 suppl):303-306.

Shoikhet IN and Bednarzhevskaia TV (2004). Computed tomography and study of external respiratory function in the diagnosis of complications due to chronic obstructive lung disease. *Klinicheskaia Meditsina* 82(7):65-68.

Sidney S, Sorel M, Quesenberry CP, Jr., et al. (2005). COPD and incident cardiovascular disease hospitalizations and mortality: Kaiser Permanente Medical Care Program. *Chest* 128(4):2068-2075.

Simonneau G, Galie N, Rubin LJ, et al. (2004). Clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology* 43(12 Suppl S):5S-12S.

Simonneau G, Robbins IM, Beghetti M, et al. (2009). Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology* 54(1, Supplement 1):S43-S54.

Simons P and Reid L (1969). Muscularity of pulmonary artery branches in the upper and lower lobes of the normal young and aged lung. *British Journal of Diseases of the Chest* 63(1):38-44.

Sims MW, Margolis DJ, Localio AR, et al. (2009). Impact of pulmonary artery pressure on exercise function in severe COPD. *Chest* 136(2):412-419.

Sin DD, Anthonisen NR, Soriano JB and Agusti AG (2006). Mortality in COPD: role of comorbidities. *European Respiratory Journal* 28(6):1245-1257.

Sin DD and Man SF (2003). Why are patients with chronic obstructive pulmonary disease at increased risk of cardiovascular diseases? The potential role of systemic inflammation in chronic obstructive pulmonary disease. *Circulation* 107(11):1514-1519.

Sin DD and Man SF (2005). Chronic obstructive pulmonary disease as a risk factor for cardiovascular morbidity and mortality. *Proceedings of the American Thoracic Society* 2(1):8-11.

Sin DD, Wu L and Man SF (2005). The relationship between reduced lung function and cardiovascular mortality: a population-based study and a systematic review of the literature. *Chest* 127(6):1952-1959.

Skwarski K, MacNee W, Wraith PK, Sliwinski P and Zielinski J (1991). Predictors of survival in patients with chronic obstructive pulmonary disease treated with long-term oxygen therapy. *Chest* 100(6):1522-1527.

Slinker BK and Glantz SA (1986). End-systolic and end-diastolic ventricular interaction. *American Journal of Physiology* 251(5 Pt 2):H1062-1075.

Snell GI, Holsworth L, Borrill ZL, et al. (2003). The potential for bronchoscopic lung volume reduction using bronchial prostheses: a pilot study. *Chest* 124(3):1073-1080.

Snell GI, Hopkins P, Westall G, et al. (2009). A feasibility and safety study of bronchoscopic thermal vapor ablation: a novel emphysema therapy. *Annals of Thoracic Surgery* 88(6):1993-1998.

Stacher E, Graham BB, Hunt JM, et al. (2012). Modern age pathology of pulmonary arterial hypertension. *American Journal of Respiratory and Critical Care Medicine* 186(3):261-272.

Stark RD, Finnegan P and Bishop JM (1972). Daily requirement of oxygen to reverse pulmonary hypertension in patients with chronic bronchitis. *British Medical Journal* 3(5829):724-728.

Stark RD, Finnegan P and Bishop JM (1973). Long-term domiciliary oxygen in chronic bronchitis with pulmonary hypertension. *British Medical Journal* 3(5878):467-470.

Stather DR and Stewart TE (2005). Clinical review: mechanical ventilation in severe asthma. *Critical Care* 9(6):581-587.

Staub NC (1985). Site of hypoxic pulmonary vasoconstriction. *Chest* 88(4 Suppl):240S-245S.

Steiner MK (2009). World Health Organization class III COPD-associated pulmonary hypertension: are we there yet in understanding the pathobiology of the disease? *Chest* 136(3):658-659.

Steingrub JS, Tidswell M and Higgins TL (2003). Hemodynamic consequences of heart-lung interactions. *Journal of Intensive Care Medicine* 18(2):92-99.

Stenmark KR, Fagan KA and Frid MG (2006). Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. *Circulation Research* 99(7):675-691.

Stevens PM (1975). Assessment of acute respiratory failure: cardiac versus pulmonary causes. *Chest* 67(1):1-2.

Stewart DJ, Levy RD, Cernacek P and Langleben D (1991). Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? *Annals of Internal Medicine* 114(6):464-469.

Stolz D, Rasch H, Linka A, et al. (2008). A randomised, controlled trial of bosentan in severe COPD. *European Respiratory Journal* 32:619-628.

Stone AC and Nici L (2007). Other systemic manifestations of chronic obstructive pulmonary disease. *Clinics in Chest Medicine* 28(3):553-557, vi.

Stone PH, Coskun AU, Yeghiazarians Y, et al. (2003). Prediction of sites of coronary atherosclerosis progression: in vivo profiling of endothelial shear stress, lumen, and outer vessel wall characteristics to predict vascular behavior. *Current Opinion in Cardiology* 18(6):458-470.

Sullivan VN, Whitson BA, Radosevich DM, et al. (2006). Elevated pulmonary artery pressure predicts development of severe primary graft dysfunction in paired single lung transplant recipients. *Journal of Heart and Lung Transplantation* 25(2S):S47.

Summer WR, Permutt S, Sagawa K, Shoukas AA and Bromberger-Barnea B (1979). Effects of spontaneous respiration on canine left ventricular function. *Circulation Research* 45(6):719-728.

Sunagawa K, Maughan WL, Burkhoff D and Sagawa K (1983). Left ventricular interaction with arterial load studied in isolated canine ventricle. *American Journal of Physiology* 245(5 Pt 1):H773-780.

Sunagawa K, Maughan WL and Sagawa K (1985). Optimal arterial resistance for the maximal stroke work studied in isolated canine left ventricle. *Circulation Research* 56(4):586-595.

Susmano A, Passovoy M and Carleton RA (1977). Mechanisms of hypercapneic pulmonary hypertension. *Cardiovascular Research* 11(5):440-445.

Tanaka H, Tei C, Nakao S, et al. (1980). Diastolic bulging of the interventricular septum toward the left ventricle. An echocardiographic manifestation of negative interventricular pressure gradient between left and right ventricles during diastole. *Circulation* 62(3):558-563.

Thabut G, Christie JD, Ravaud P, et al. (2008). Survival after bilateral versus single lung transplantation for patients with chronic obstructive pulmonary disease: a retrospective analysis of registry data. *Lancet* 371(9614):744-751.

Thabut G, Dauriat G, Stern JB, et al. (2005). Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. *Chest* 127(5):1531-1536.

Thabut G, Ravaud P, Christie JD, et al. (2008). Determinants of the survival benefit of lung transplantation in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 177(10):1156-1163.

Timms RM, Khaja FU and Williams GW (1985). Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. *Annals of Internal Medicine* 102(1):29-36.

Tockman MS, Pearson JD, Fleg JL, et al. (1995). Rapid decline in FEV1. A new risk factor for coronary heart disease mortality. *American Journal of Respiratory and Critical Care Medicine* 151(2 Pt 1):390-398.

Todd JL and Palmer SM (2010). Lung transplantation in advanced COPD: is it worth it? *Seminars in Respiratory & Critical Care Medicine* 31(3):365-372.

Traver GA, Cline MG and Burrows B (1979). Predictors of mortality in chronic obstructive pulmonary disease. A 15-year follow-up study. *American Review of Respiratory Disease* 119(6):895-902.

Travis MD, Colby TV, Koss MN, et al. (2002). Pulmonary hypertension and other vascular disorders. *Non-Neoplastic Disorders of the Lower Respiratory Tract*. Armed Forces Institute of Pathology. Washington, American Registry of Pathology**:**767-792.

Tschernko EM, Gruber EM, Jaksch P, et al. (1998). Ventilatory mechanics and gas exchange during exercise before and after lung volume reduction surgery. *American Journal of Respiratory and Critical Care Medicine* 158(5 Pt 1):1424-1431.

Tuder RM, Chacon M, Alger L, et al. (2001). Expression of angiogenesis-related molecules in plexiform lesions in severe pulmonary hypertension: evidence for a process of disordered angiogenesis. *Journal of Pathology* 195(3):367-374.

Tuxen DV (1989). Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *American Review of Respiratory Disease* 140(1):5-9.

Van Grondelle A, Worthen GS, Ellis D, et al. (1984). Altering hydrodynamic variables influences PGI2 production by isolated lungs and endothelial cells. *Journal of Applied Physiology* 57(2):388-395.

Van Mieghem W and Demedts M (1989). Cardiopulmonary function after lobectomy or pneumonectomy for pulmonary neoplasm. *Respiratory Medicine* 83(3):199-206.

Vestbo J, Anderson W, Coxson HO, et al. (2008). Evaluation of COPD longitudinally to identify predictive surrogate end-points (ECLIPSE). *European Respiratory Journal* 31(4):869-873.

Vik-Mo H, Halvorsen FJ, Thorsen E, Walde NH and Rosland GA (1987). Improved cardiac performance by salbutamol, a selective beta 2-agonist, in chronic cor pulmonale. *Journal of Cardiovascular Pharmacology* 9(2):129-134.

Visscher MB (1948). The capacity changes in the pulmonary vascular bed with the respiratory cycle. *Federation Proceedings* 7(1 Pt 1):128.

Vonbank K, Ziesche R, Higenbottam TW, et al. (2003). Controlled prospective randomised trial on the effects on pulmonary haemodynamics of the ambulatory long term use of nitric oxide and oxygen in patients with severe COPD. *Thorax* 58(4):289-293.

Vonk-Noordegraaf A and Westerhof N (2013). Describing right ventricular function. *European Respiratory Journal* 41(6):1419-1423.

Warnock ML and Kunzmann A (1977a). Changes with age in muscular pulmonary arteries. *Archives of Pathology and Laboratory Medicine* 101(4):175-179.

Warnock ML and Kunzmann A (1977b). Muscular pulmonary arteries in chronic obstructive lung disease. *Archives of Pathology and Laboratory Medicine* 101(4):180-186.

Watz H, Waschki B, Boehme C, et al. (2008). Extrapulmonary effects of chronic obstructive pulmonary disease on physical activity: a cross-sectional study. *American Journal of Respiratory and Critical Care Medicine* 177(7):743-751.

Watz H, Waschki B and Magnussen H (2010a). Emphysema, airflow obstruction, and left ventricular filling. *New England Journal of Medicine* 362(17):1638-1639.

Watz H, Waschki B, Meyer T, et al. (2010b). Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. *Chest* 138(1):32-38.

Webb WR, Smith JR and Campbell GD (1961). Peri-alveolar pressures: measurement and significance in pulmonary dynamics. *Annals of Surgery* 153:650-657.

Weg IL, Rossoff L, McKeon K, Michael Graver L and Scharf SM (1999). Development of pulmonary hypertension after lung volume reduction surgery. *American Journal of Respiratory and Critical Care Medicine* 159(2):552-556.

Weitzenblum E and Chaouat A (2004). Sleep and chronic obstructive pulmonary disease. *Sleep Medicine Reviews* 8(4):281-294.

Weitzenblum E and Chaouat A (2009). Cor pulmonale. *Chronic Respiratory Disease* 6(3):177-185.

Weitzenblum E, Hirth C, Ducolone A, et al. (1981). Prognostic value of pulmonary artery pressure in chronic obstructive pulmonary disease. *Thorax* 36(10):752-758.

Weitzenblum E, Kessler R, Oswald M and Fraisse P (1994). Medical treatment of pulmonary hypertension in chronic lung disease. *European Respiratory Journal* 7(1):148-152.

Weitzenblum E, Sautegeau A, Ehrhart M, et al. (1984). Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 130(6):993-998.

Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M and Pelletier A (1985). Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. *American Review of Respiratory Disease* 131(4):493-498.

Wells JM, Washko GR, Han MK, et al. (2012). Pulmonary arterial enlargement and acute exacerbations of COPD. *New England Journal of Medicine* 367(10):913-921.

West JB, Dollery CT and Naimark A (1964). Distribution of blood flow in isolated lung; relation to vascular and alveolar pressures. *Journal of Applied Physiology* 19:713-724.

Westerhof N and Elzinga G (1991). Normalized input impedance and arterial decay time over heart period are independent of animal size. *American Journal of Physiology* 261(1 Pt 2):R126-133.

Whelan TP, Dunitz JM, Kelly RF, et al. (2005). Effect of preoperative pulmonary artery pressure on early survival after lung transplantation for idiopathic pulmonary fibrosis. *Journal of Heart and Lung Transplantation* 24(9):1269-1274.

Whitson BA, Nath DS, Johnson AC, et al. (2006). Risk factors for primary graft dysfunction after lung transplantation. *Journal of Thoracic and Cardiovascular Surgery* 131(1):73-80.

Whittenberger JL, McGregor M, Berglund E, Borst HG and McGregor M (1960). Influence of state of inflation of the lung on pulmonary vascular resistance. *Journal of Applied Physiology* 15:878-882.

Wilkinson M, Langhorne CA, Heath D, Barer GR and Howard P (1988). A pathophysiological study of 10 cases of hypoxic cor pulmonale. *Quarterly Journal of Medicine* 66(249):65-85.

World Health Organization. (2008). World Health Statistics.

Wright JL (1993). Relationship of pulmonary arterial pressure and airflow obstruction to emphysema. *Journal of Applied Physiology* 74(3):1320-1324.

Wright JL and Churg A (1991). Effect of long-term cigarette smoke exposure on pulmonary vascular structure and function in the guinea pig. *Experimental Lung Research* 17(6):997-1009.

Wright JL, Lawson L, Pare PD, et al. (1983). The structure and function of the pulmonary vasculature in mild chronic obstructive pulmonary disease. The effect of oxygen and exercise. *American Review of Respiratory Disease* 128(4):702-707.

Wright JL, Levy RD and Churg A (2005). Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. *Thorax* 60(7):605-609.

Wright JL, Petty T and Thurlbeck WM (1992). Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health nocturnal oxygen therapy trial. *Lung* 170(2):109-124.

Wrobel JP, Thompson BR, Snell GI and Williams TJ (2012a). Preoperative echocardiographic-defined moderate-severe pulmonary hypertension predicts prolonged duration of mechanical ventilation following lung transplantation for patients with COPD. *Lung* 190(6):635-643.

Wrobel JP, Thompson BR and Williams TJ (2012b). Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. *Journal of Heart and Lung Transplantation* 31(6):557-564.

Yamakami T, Taguchi O, Gabazza EC, et al. (1997). Arterial endothelin-1 level in pulmonary emphysema and interstitial lung disease. Relation with pulmonary hypertension during exercise. *European Respiratory Journal* 10(9):2055-2060.

Yanos J, Watling SM and Verhey J (1998). The physiologic effects of inverse ratio ventilation. *Chest* 114(3):834-838.

Yi ES, Kim H, Ahn H, et al. (2000). Distribution of obstructive intimal lesions and their cellular phenotypes in chronic pulmonary hypertension. A morphometric and immunohistochemical study. *American Journal of Respiratory and Critical Care Medicine* 162(4 Pt 1):1577-1586.

Yildiz P, Oflaz H, Cine N, et al. (2003). Gene polymorphisms of endothelial nitric oxide synthase enzyme associated with pulmonary hypertension in patients with COPD. *Respiratory Medicine* 97(12):1282-1288.

Yoshizumi M, Kurihara H, Sugiyama T, et al. (1989). Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. *Biochemical and Biophysical Research Communications* 161(2):859-864.

Yu PN, Lovejoy FW, Jr., Joos HA, Nye RE, Jr. and McCann WS (1953). Studies of pulmonary hypertension. I. Pulmonary circulatory dynamics in patients with pulmonary emphysema at rest. *Journal of Clinical Investigation* 32(2):130-137.

Zhao L, Winter RJ, Krausz T and Hughes JM (1991). Effects of continuous infusion of atrial natriuretic peptide on the pulmonary hypertension induced by chronic hypoxia in rats. *Clinical Science* 81(3):379-385.

Zheng L, Duan SF and Zhang ZX (1991). Changes of thromboxane A2 (TXA2) and prostacyclin (PGI2) in COPD patients with pulmonary hypertension. *Zhonghua Nei Ke Za Zhi* 30(2):91-93, 126.

Zielinski J (1979). Intrathoracic pressure variations and pulmonary artery pressure in patients with chronic obstructive lung disease. *Bulletin Europeen de Physiopathologie Respiratoire.* 15(2):397-405.

Zielinski J, MacNee W, Wedzicha J, et al. (1997). Causes of death in patients with COPD and chronic respiratory failure. *Monaldi Archives for Chest Disease* 52(1):43-47.

Zvezdin B, Milutinov S, Kojicic M, et al. (2009). A postmortem analysis of major causes of early death in patients hospitalized with COPD exacerbation. *Chest* 136(2):376-380.

Appendix 1

Appendix 1 Specific Declaration (Part B) for Thesis Appendix

Declaration by candidate

In the case of Appendix 1, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Extent of contribution (%)**
Literature search, critical appraisal of literature, manuscript preparation, final approval of manuscript	90%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	**Nature of contribution**	**Extent of contribution (%)**
1. Bruce Thompson	Manuscript preparation, final approval of manuscript	
2. Trevor Williams	Manuscript preparation, final approval of manuscript	

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature		**Date**

Main Supervisor's Signature		**Date**

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Appendix 1 Review Article - Published

Wrobel JP, Thompson BR and Williams TJ (2012). Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: a pathophysiologic review. Journal of Heart and Lung Transplantation 31(6):557-564.

ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

STATE OF ART

Mechanisms of pulmonary hypertension in chronic obstructive pulmonary disease: A pathophysiologic review

Jeremy P. Wrobel, MBBS(Hons), MPH, FRACP,[a,b] Bruce R. Thompson, PhD,[a,b] and Trevor J. Williams, MBBS, MD, FRACP[a,b]

From the [a]Department of Medicine, Monash University, and [b]Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, Melbourne, Victoria, Australia.

KEYWORDS:
chronic obstructive pulmonary disease; emphysema; pulmonary hypertension; pulmonary vascular resistance

Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity worldwide and is often complicated by the development of pulmonary hypertension (PHT). The presence of PHT in COPD subjects is associated with increased mortality, morbidity and use of health-care resources. Thus, there has been significant effort to treat PHT in COPD patients to achieve improved clinical outcomes, but with only minimal success. There is renewed interest in understanding the mechanisms contributing to PHT in COPD as the basis for exploring new therapeutic strategies. In this study we review the evidence supporting the postulated mechanisms contributing to PHT in COPD. Hypoxia plays a pivotal role in the development of COPD-associated PHT. However, other mechanisms are also likely involved in the pathogenesis of increased pulmonary vascular resistance in this cohort, including acidemia, dynamic pulmonary hyperinflation, parenchymal destruction, pulmonary vascular remodeling, endothelial dysfunction and inflammation. These mechanisms are interdependent, modulated by genetic factors, and may be confounded by comorbidities such as sleep-disordered breathing, left heart failure and pulmonary thromboembolism. Despite significant research in recent decades, there is surprisingly little evidence of a causal relationship between many of these factors and the development of COPD-associated PHT. The pathogenesis of PHT in COPD is complex and multifaceted. Ultimately, as we obtain better information on COPD phenotypes, we may be able to more precisely account for the varied pathologic mechanisms of PHT occurring in various COPD patients. This may ultimately enable targeted PHT therapy for each COPD phenotype.

J Heart Lung Transplant 2012;31:557–64

Chronic obstructive pulmonary disease (COPD) is a major international health burden. It is responsible for substantial morbidity and mortality[1] and is currently the fourth leading cause of death worldwide.[2] COPD may be complicated by the development of pulmonary hypertension (PHT) and, although the severity of PHT in COPD patients is usually mild,[3] the presence of PHT in COPD is nevertheless associated with increased mortality,[4,5] increased hospitalizations[6] and reduced exercise function.[7] The reported prevalence of PHT in moderate/severe COPD ranges from 23% to 91%, depending on patient selection and diagnostic criteria.[7–10]

PHT is defined as a mean pulmonary artery pressure (mPAP) of ≥25 mm Hg, as measured by right heart catheterization at rest.[11] Pulmonary arterial hypertension (PAH) and pulmonary venous hypertension (PVH) are traditionally distinguished on the basis that PAH patients have a pulmonary arterial wedge pressure (PAWP) of ≤15 mm Hg. In 2008, the Dana Point Symposium on Pulmonary Hypertension classified COPD-associated PHT into Group 3 "Pulmonary hypertension associated with lung disease and/or hypoxemia," but did not specifically distinguish between PAH and PVH in this group.[12]

In broad terms, PHT in COPD may be due to structural and/or functional factors (Table 1). These structural changes

Reprint requests: Trevor J. Williams, MBBS, MD, FRACP, Department of Allergy, Immunology and Respiratory Medicine, The Alfred Hospital, 55 Commercial Road, Melbourne VIC 3004, Australia. Telephone: [redacted] Fax: 61-3-9076-3601.
E-mail address: [redacted]

1053-2498/$ -see front matter
doi:10.1016/j.healun.2012.02.029

Table 1 Structural and Functional Pulmonary Hypertension in COPD

Structural/fixed PHT	Functional/dynamic PHT
Loss of pulmonary vascular bed	Hypoxia
Pulmonary vascular remodeling	Acidemia
Inflammation	Pulmonary hyperinflation
Thromboembolic disease	Airway resistance
	Endothelial dysfunction
	Polycythemia

would be expected to cause fixed elevations of PAP and functional changes tend to have more dynamic effects. Figure 1 illustrates the principal site of action for each mechanism. Although genetics and environmental exposures play a significant role in the development of COPD itself, they are also likely to contribute to the development of PHT in COPD subjects.[9]

The development of PHT in COPD is not simply of academic interest. Many investigators have reported that the severity of PHT is the single most important prognostic indicator in COPD subjects.[4,6] Consequently, there has been significant effort undertaken to determine whether treatment of PHT in COPD patients can lead to improved pulmonary hemodynamics and clinical outcomes, but with only limited success.[9] This has led to renewed interest in understanding the mechanisms underpinning PHT in COPD to determine which patients are likely to benefit from specific PHT treatment and also to explore new therapeutic strategies.[13] Hence, it seems timely to review the current literature exploring the postulated mechanisms contributing to PHT in COPD. Unfortunately, any such review is complicated by the interactions between each of the mechanisms contributing to COPD-associated PHT. This complexity is illustrated in Figure 2. Nevertheless, despite significant interplay between each of these mechanisms, our review focuses on the evidence and importance of each in turn.

Review methodology

The initial search was conducted using OVID Medline (from 1946) with the subject headings "Pulmonary Disease, Chronic Obstructive" and "Pulmonary Hypertension." All abstracts were assessed for relevance and articles of the relevant studies were retrieved. Subsequent searches utilized the following combinations of subject headings: "Pulmonary Disease, Chronic Obstructive" or "Emphysema" or "Pulmonary Emphysema" or "Respiratory Mechanics" or "Lung Compliance" and "Hypertension, Pulmonary" or "Pulmonary Heart Disease" or "Pulmonary Artery" or "Pulmonary Circulation" or "Vascular Resistance" or "Sleep Apnea, Obstructive" or "Sleep Apnea Syndromes" or "Pulmonary Embolism" or "Heart Failure, Diastolic." For relevant titles, the abstracts were reviewed and, if still relevant, the article was retrieved. References within the selected articles, especially for review articles, were also reviewed for their relevance. In addition, for selected references, the "related citations" feature was explored using PubMed.

Hypoxia

At present, there is broad agreement that hypoxia contributes to PHT via two mechanisms. First, alveolar (and perhaps low mixed venous saturation) hypoxia causes acute hypoxic pulmonary vasoconstriction of the small muscular pulmonary arteries,[14] and in the setting of global hypoxia this mechanism may substantially increase pulmonary vascular resistance (PVR).[15] Second, chronic hypoxia contributes to pulmonary vascular remodeling, resulting in intimal thickening and neo-muscularization of the small pulmonary arterioles, which also raises PVR.[16] The mechanisms underpinning hypoxia-induced vascular remodeling are complex and incompletely understood.[17] Recent advances in our understanding of endothelial dysfunction highlight that hypoxia may also play a permissive role in pulmonary vascular remodeling as hypoxia has been shown to inhibit mediators that limit remodeling such as prostacyclin and nitric oxide.[18]

Despite strong supporting evidence of hypoxia being an important contributor to PHT in COPD, the full extent to which hypoxia causes PHT in COPD is still the subject of conjecture and investigation. This is broadly based on the following observations: (i) there is a wide variation in hemodynamic response to supplemental oxygen therapy[19]; (ii) the correlation between pulmonary arterial pressure (PAP)

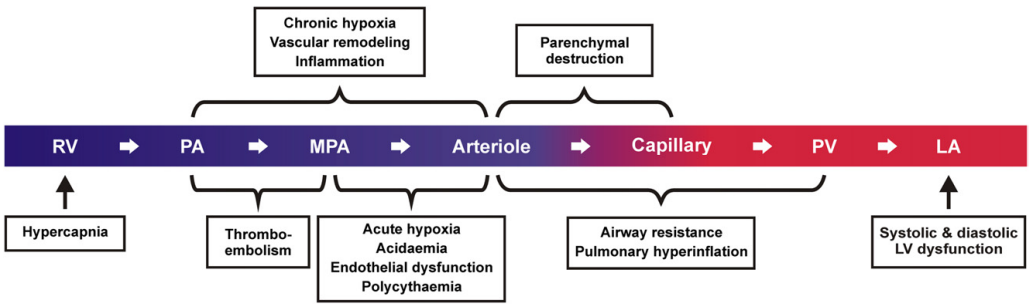

Figure 1 This schema illustrates the site of action for each of the pathogenic mechanisms for pulmonary hypertension in COPD. LA, left atrium; LV, left ventricle; MPA, muscular pulmonary artery; PA, pulmonary artery; PV, pulmonary vein; RV, right ventricle.

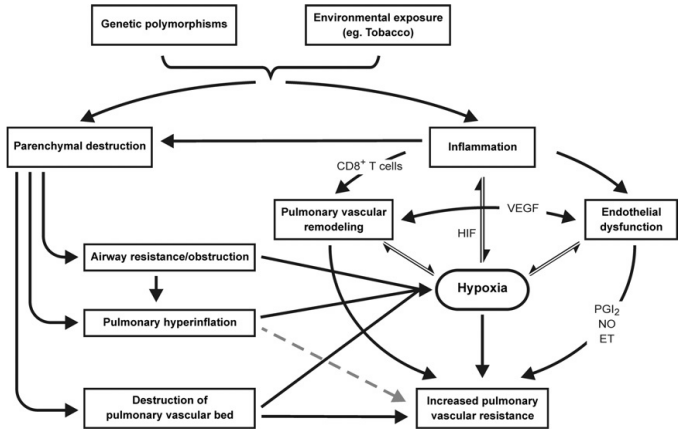

Figure 2 The complex interactions between each of the pathogenic mechanisms which may lead to an increased pulmonary vascular resistance in subjects with COPD. In COPD, genetic and environmental exposures contribute to the development of parenchymal destruction and inflammation. Parenchymal destruction alters respiratory mechanics and causes destruction of the pulmonary vascular bed, which leads to hypoxia and contributes directly toward an increased pulmonary vascular resistance. Inflammation is likely to be intimately involved in pulmonary vascular remodeling and endothelial dysfunction, which also leads to hypoxia and increased pulmonary vascular resistance. The schema highlights the central role of hypoxia but also indicates that hypoxia is not essential to the development of an increased pulmonary vascular resistance in COPD. VEGF, vascular endothelial growth factor; HIF, hypoxia-inducible factors; PGI_2, prostacyclin; NO, nitric oxide; ET, endothelin.

and partial pressure of oxygen (PaO_2) is not strong and has not been consistently demonstrated[8,20]; (iii) long-term oxygen therapy does not normalize PAP, unlike animal models of chronic hypoxia or humans exposed to chronic hypoxia at altitude[18]; (iv) pulmonary vascular structural changes have been observed in non-hypoxic, mild COPD subjects and in smokers with normal lung function[21,22]; (v) endothelial dysfunction has been demonstrated in non-hypoxic, mild COPD subjects[22,23]; (vi) animal models have demonstrated an elevation of PAP prior to the development of COPD[24]; and (vii) hypoxic vasoconstriction alone cannot explain the physiologic and pulmonary vascular pathologic changes in patients with COPD.[25,26] Thus, although hypoxia plays a key role in the development of PHT in COPD, acute hypoxic vasoconstriction and chronic hypoxic vascular remodeling do not fully account for the deranged pulmonary hemodynamics observed in COPD subjects.

Hypercapnia/acidosis

Despite early studies showing a relationship between partial pressure of carbon dioxide ($PaCO_2$) and mPAP in COPD subjects,[27] the role of hypercapnia in contributing to PHT in COPD is unclear. From a range of physiologic studies exploring this relationship[28–30] it has become apparent that hypercapnia increases cardiac output, which drives an increase in mPAP. However, changes in PVR depend on the balance between the dilatory forces (secondary to capillary recruitment resulting from hypercapnia-induced increases in pulmonary blood flow) and the constrictive forces (due to acidemia-induced pulmonary vasoconstriction), which will be amplified in the setting of a reduced pulmonary vascular bed, such as what occurs in emphysema.[31] The pathophysiology is further complicated by hyperventilation that results from an induced hypercapnia, which causes an increase in the amplitude of intrathoracic pressure swings, a potential increase in PAWP and improved oxygen saturation levels.[29,31,32] Interestingly, COPD patients identified as having disproportionate PHT are not hypercapnic as expected but have low or normal $PaCO_2$ levels.[3,33]

Although hypercapnia and acidemia affect pulmonary hemodynamics, their contribution to PHT in COPD is difficult to clarify in the presence of so many potential confounders and their effect on PHT is overshadowed by other pathogenic mechanisms.

Pulmonary hyperinflation

It has been postulated that dynamic lung hyperinflation in COPD may contribute to the development of PHT through a combination of mechanisms, including increased lung volume,[29] widened intrathoracic pressure swings,[34,35] cardiac effects,[36,37] altered gas exchange,[29,38] pulmonary vascular remodeling[26] and even endothelial dysfunction.[39]

Many investigators have listed gas trapping and lung hyperinflation among the causes of PHT in COPD,[8,33,40] but there is a lack of direct supporting evidence. Nevertheless, gas trapping and pulmonary hyperinflation have been shown to be associated with raised PAP during hyperventilation,[41] exercise[42] and acute exacerbations.[43] However, whether gas trapping causes PHT in stable COPD patients at rest is unknown and the relationship between gas trapping and pulmonary vascular remodeling has not been explored.

Airway resistance/airway obstruction

Studies have demonstrated a statistical correlation between forced expiratory volume in 1 second (FEV_1; as a marker of airway obstruction) and mPAP.[20,44] However, this relationship is not always seen and FEV_1 is not universally considered to be an independent predictor of pulmonary arterial pressure.[3,44] Further, Wright and Churg have demonstrated in an animal smoking model that raised pulmonary arterial pressure occurs prior to the development of emphysema.[45] Thus, there is currently limited evidence supporting a causal relationship between airflow obstruction and PHT. If such a relationship exists, it is likely mediated through other mechanisms such as hypoxemia or pulmonary hyperinflation.[32]

Destruction of pulmonary vascular bed

It has long been held that emphysematous destruction of the pulmonary vascular bed contributes to the elevation of PAP and is often listed among the mechanisms of PHT in COPD.[3,33] The lack of substantial direct or indirect evidence to support this mechanism is surprising. For example, studies comparing computed tomography lung tissue density with pulmonary hemodynamics have not indicated any significant relationships.[8,46]

Furthermore, resection of the pulmonary vascular bed in lung volume reduction surgery (LVRS) yielded inconsistent effects upon PAP.[47–49] These inconsistent results are most likely due to resection of variable amounts of pulmonary vessels in the study populations and a multitude of confounders post-LVRS, including changes to gas trapping, capillary recruitment, ventilation–perfusion ratios and gas exchange.[50]

It was noted in the 1960s that the variable nature of the PAP in COPD suggests that parenchymal destruction with loss of the pulmonary vascular bed is not the principal mechanism for PHT in COPD.[30,32] Nevertheless, the dynamic responsiveness of the pulmonary circulation may be reduced with a limited vascular bed and may contribute to the presence of exercise-induced PHT often seen in COPD patients. Similarly, reduced pulmonary capillary cross-sectional area may contribute to the left ventricular diastolic dysfunction observed in COPD patients through reduced pulmonary blood flow and left ventricular underfilling.[36]

Pulmonary vascular remodeling

A number of pathologic changes have been identified in the pulmonary vessels of patients with COPD-associated PHT, including variable medial hypertrophy, longitudinal muscle deposition, intimal hyperplasia, elastin and collagen deposition, muscularization of the pulmonary arterioles and in situ thrombosis.[18,26] Changes due to pulmonary vascular remodeling may alter the pulmonary vascular responsiveness and contribute to the development of PHT in COPD. However, studies have been inconsistent in finding a relationship between changes of pulmonary vascular remodeling and PHT.[25,26,51]

Although many of the pulmonary vascular changes that have been documented in COPD-related PHT have been observed in other forms of PHT, including idiopathic PAH and high-altitude–related PHT, the pattern of histologic changes observed in COPD-related PHT appears distinct and may relate to the unique combination of factors, including chronic hypoxia, mechanical stress, inflammation, toxic effects of cigarette smoke, endothelial dysfunction and repeated stretching of hyperinflated lungs.[26,52] Thus, the pulmonary vascular remodeling observed in COPD-associated PHT likely reflects the net effects of several different pathologic processes. However, it appears that vascular remodeling alone is not sufficient to account for the wide variability of the PAP nor to the varied functional responses to supplemental oxygen.[25]

Inflammation

There has been renewed interest in the role of inflammation in the pathogenesis of pulmonary vascular remodeling and endothelial dysfunction in COPD.[9] Increased numbers of leukocytes have been identified in the adventitia of muscular pulmonary arteries in COPD subjects compared with smoking controls and healthy controls, but with an inconsistent relationship between the inflammatory infiltrate and intimal thickness.[23,53] Nevertheless, this leads to speculation that inflammation may promote pulmonary vascular remodeling and endothelial dysfunction in subjects with COPD.

Endothelial dysfunction

Pulmonary vascular endothelial dysfunction has been demonstrated to occur in idiopathic PAH[54] involving numerous pathways, including prostacyclin, nitric oxide and endothelin.[55] Although acutely these mediators and pathways may give rise to endothelial dysfunction, over time they contribute to pulmonary vascular remodeling. Endothelial dysfunction has been demonstrated in COPD subjects[22,56,57] and appears to be mediated by pathways similar to those seen in idiopathic PAH.[58–60] Other cytokines and growth factors, such as vascular endothelial growth factor,[61] atrial and brain natriuretic peptides,[62,63] serotonin,[64] vasoactive intestinal peptide[65] and adrenomedullin,[55] may contribute to endothelial dysfunction in COPD-related PHT. Furthermore, genetic polymorphisms, inflammation and mechanical factors are likely to play an important role in modulating the endothelial dysfunction observed in COPD-related PHT.[66]

Polycythemia

Polycythemia (with resultant increased blood viscosity) occurs in advanced COPD as a complication of chronic hyp-

oxia. Although it may reflect COPD severity, polycythemia may be reduced by oxygen therapy, potentially masking any association of polycythemia to COPD-associated PHT. Not surprisingly, earlier work has provided inconsistent data regarding this relationship.[67–69] Consequently, the role of polycythemia in the development of PHT remains unclear.

Genetics

Genetic predisposition appears to be important in the development of COPD, but only α_1-anti-trypsin deficiency has been clearly shown as causative.[70] There also appears to be genetic predisposition to the development of PHT in COPD subjects.[9] Genetic polymorphisms of endothelial nitric oxide synthase and 5-hydroxytryptamine have been implicated in pulmonary vascular endothelial dysfunction and remodeling in COPD subjects.[64,71] Furthermore, genetic predisposition for PHT in COPD may also be conferred by carrying the interleukin-6 GG genotype.[72] These studies highlight the need for further investigation into the role of genetics in the development of PHT in COPD subjects.

Comorbidities

Nocturnal hypoxia. COPD subjects with obstructive sleep apnea (OSA) have significantly greater nocturnal oxygen desaturation,[73] hypercapnia[74] and PAP[75] compared with pure COPD or OSA patients. Although well-designed studies showing the benefit of treatment are lacking, it would seem prudent that in COPD patients with PHT, thorough evaluation for sleep-disordered breathing needs to be undertaken and specific management should be implemented.

Left ventricular diastolic dysfunction. Left heart disease (owing to systolic dysfunction, diastolic dysfunction or valvular disease) is one of the most common causes of PHT generally.[10] Left ventricular diastolic dysfunction is a significant confounder in studies addressing COPD-associated PHT because: (i) it may cause PVH with or without superimposed pulmonary arterial vasoconstriction and vascular remodeling[10]; (ii) it is difficult to assess and quantify[76]; (iii) it is highly prevalent in COPD patients[77]; and (iv) many studies have not accounted for COPD subjects according to the presence of left ventricular diastolic dysfunction. Indeed, it has been demonstrated that left atrial mechanical factors are significantly correlated with PHT levels in COPD subjects.[78,79] Consequently, it is apparent that left ventricular diastolic dysfunction can confound the assessment of COPD-associated PHT if cardiac structure and function are not adequately assessed.

Thromboembolic disease. COPD subjects may be at increased risk of developing pulmonary embolism[80] and, once present, the prognosis is poor.[81] Diagnosing pulmonary embolism in COPD subjects can be difficult, leading to a misdiagnosis. A small proportion of COPD subjects with pulmonary embolism, even if treated in a timely manner, may develop chronic thromboembolic pulmonary hypertension (CTEPH). Consequently, CTEPH may be incorrectly classified as COPD-related PHT if such patients are not thoroughly evaluated.[3]

"Out-of-proportion" pulmonary hypertension

As discussed previously, PHT is frequently seen in moderate to severe COPD, but it is usually of mild severity.[10] Moderate to severe elevations of PAP (i.e., mPAP > 35 mm Hg) have been documented to occur in up to 9.8% of subjects with advanced COPD.[33] Patients with mild to moderate COPD (i.e., GOLD Stages I and II) with any severity PHT, and patients with more severe COPD (i.e., GOLD Stages III and IV) and moderate to severe PHT (i.e., PAP > 35 mm Hg) are unexpected. Consequently, such patients have been described as having "out-of-proportion" PHT.[82,83] These patients tend to have severe hypoxemia, hypocapnia, very low diffusing capacity for carbon monoxide and a worse prognosis.[3,33] Nevertheless, there is presently no clearly described phenotype nor data suggesting a specific therapeutic approach for managing PHT in this setting. Debate will continue as to whether out-of-proportion PHT is part of the normal spectrum of PHT-associated COPD, represents a distinct clinical phenotype, or reflects the coexistence of COPD and idiopathic pulmonary arterial hypertension.[82,84]

By way of comparison, among patients listed for lung transplantation with idiopathic pulmonary fibrosis the prevalence of PHT is 46.1%, of which 9.1% is considered severe (i.e., mPAP > 40 mm Hg).[85] These patients with severe PHT are similarly considered to have out-of-proportion PHT. Although several studies have assessed the role of endothelin antagonists as anti-proliferative drugs in patients with interstitial lung disease, some of whom have PHT, there are no high-quality clinical studies looking at the role of selective vasodilators in this subgroup.

Until much more data become available, the definition, pathogenesis and implication for out-of-proportion PHT in lung disease will remain the subject of vigorous conjecture. Experienced investigators suggested that, in patients with mPAP ≥40 to 45 mm Hg and respiratory function derangement insufficient to account for the degree of dyspnea,[83] further assessment for other causes of PHT should be sought[3] and, in their absence, these patients should be considered for clinical trials.

Conclusions

The etiology of PHT in COPD is complex, multifaceted and due to both pre- and post-capillary mechanisms. Although the strength of the evidence to support the numerous pathogenic mechanisms is variable, this probably highlights that no single mechanism is responsible for PHT in all COPD subjects. Hypoxia clearly plays a pivotal role in the development of PHT in COPD patients, but the presence and

Table 2 Summary of Potential Mechanisms of PHT in COPD

Mechanism	Causative	Contributory	Associated	Comments
Hypoxia	✓			Good evidence of a significant role
Hypercapnia			✓	Association mediated by increased cardiac output
Acidaemia		✓		Likely to increase pulmonary vascular resistance
Hyperinflation		✓		Contributory only during dynamic hyperinflation
Airway obstruction			✓	Association only
Loss of capillary bed		✓		Remains speculative but probably contributory
Vascular remodeling		✓		Paucity of data but likely contributory
Inflammation		✓		Likely contributory via vascular remodeling and endothelial dysfunction
Endothelial dysfunction		✓		Paucity of data but likely contributory
Polycythemia		✓		Hyperviscosity may augment endothelial dysfunction
Genetics		✓		Certain genotypes likely to be more susceptible
Comorbidities		✓		Includes obstructive sleep apnea, pulmonary emboli and left heart failure

magnitude of contributions by other pathogenic mechanisms remain unproven. Table 2 provides a summary of the contribution of each pathogenic mechanism based on the present evidence. Factors are judged to be either causative, contributory or merely associated with PHT in COPD.

Due to the complex mechanisms of PHT in COPD, trials of selective pulmonary vasodilators are challenging. As we improve our understanding for the basis of PHT, we need to continue to explore strategies of treating COPD-related PHT. Such trials will need to ensure that improved pulmonary hemodynamics in COPD are translated into improved clinical outcomes (hopefully without exacerbating hypoxia). It is clear that important confounders, such as sleep-disordered breathing, left ventricular diastolic dysfunction and thromboembolism, will need to be carefully considered in study designs. It is also likely that the use of selective pulmonary vasodilators will not substantially alter COPD-associated PHT in most cases. Further studies that lead to an improved understanding of the pathobiology of COPD-associated PHT may allow us to better target these agents.

As severe PHT is relatively uncommon in COPD subjects, such patients should be adequately evaluated to exclude additional causes of PHT, such as sleep-disordered breathing, left ventricular diastolic dysfunction and CTEPH, which may be amenable to specific therapies.[3]

It is timely to remember that COPD is not an isolated disease entity with a single phenotype, but rather represents a wide variety of pulmonary diseases with shared risk factors and a pattern of airway obstruction.[86,87] Ultimately, as we obtain better information on COPD phenotypes, we may be able to more precisely account for the varied pathologic mechanisms of PHT occurring in different COPD patients. This would enable targeted PHT therapy for each COPD phenotype.

Disclosure statement

The authors have no conflicts of interests to disclose.

Funding was provided by the National Health and Medical Research Council of Australia (to J.P.W.).

References

1. Pauwels RA, Buist AS, Calverley PM, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) workshop summary. Am J Respir Crit Care Med 2001;163:1256-76.
2. World health statistics. Geneva: World Health Organization; 2008.
3. Chaouat A, Bugnet A-S, Kadaoui N, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005;172:189-94.
4. Oswald-Mammosser M, Weitzenblum E, Quoix E, et al. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 1995;107:1193-8.
5. Doi M, Nakano K, Hiramoto T, et al. Significance of pulmonary artery pressure in emphysema patients with mild-to-moderate hypoxemia. Respir Med 2003;97:915-20.
6. Kessler R, Faller M, Fourgaut G, et al. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:158-64.
7. Sims MW, Margolis DJ, Localio AR, et al. Impact of pulmonary artery pressure on exercise function in severe COPD. Chest 2009;136:412-9.
8. Scharf SM, Iqbal M, Keller C, et al. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med 2002;166:314-22.
9. Minai OA, Chaouat A, Adnot S. Pulmonary hypertension in COPD: epidemiology, significance, and management: pulmonary vascular disease: the global perspective. Chest 2010;137(suppl):39S-51.
10. Hoeper MM, Barberà JA, Channick RN, et al. Diagnosis, assessment, and treatment of non-pulmonary arterial hypertension pulmonary hypertension. J Am Coll Cardiol 2009;54(suppl):S85-96.
11. Badesch DB, Champion HC, Gomez Sanchez MA, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54(suppl):S55-66.
12. Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol 2009;54(suppl):S43-54.
13. Hoeper MM. Treating pulmonary hypertension in COPD: where do we start? Eur Respir J 2008;32:541-2.
14. Hales CA. The site and mechanism of oxygen sensing for the pulmonary vessels. Chest 1985;88(suppl):235S-40.
15. Steiner MK. World Health Organization class III COPD-associated pulmonary hypertension: are we there yet in understanding the pathobiology of the disease? Chest 2009;136:658-9.

16. Stenmark KR, Fagan KA, Frid MG. Hypoxia-induced pulmonary vascular remodeling: cellular and molecular mechanisms. Circ Res 2006;99:675-91.
17. Pasha MA, Newman JH. High-altitude disorders: pulmonary hypertension: pulmonary vascular disease: the global perspective. Chest 2010;137:13S-9.
18. Presberg KW, Dincer HE. Pathophysiology of pulmonary hypertension due to lung disease. Curr Opin Pulm Med 2003;9:131-8.
19. Ashutosh K, Mead G, Dunsky M. Early effects of oxygen administration and prognosis in chronic obstructive pulmonary disease and cor pulmonale. Am Rev Respir Dis 1983;127:399-404.
20. Bishop JM, Cross KW. Use of other physiological variables to predict pulmonary arterial pressure in patients with chronic respiratory disease. Multicentre study. Eur Heart J 1981;2:509-17.
21. Barbera JA, Riverola A, Roca J, et al. Pulmonary vascular abnormalities and ventilation-perfusion relationships in mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1994;149:423-9.
22. Peinado VI, Barbera JA, Ramirez J, et al. Endothelial dysfunction in pulmonary arteries of patients with mild COPD. Am J Physiol 1998; 274:L908-13.
23. Peinado VI, Barbera JA, Abate P, et al. Inflammatory reaction in pulmonary muscular arteries of patients with mild chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159:1605-11.
24. Wright JL, Churg A. A model of tobacco smoke-induced airflow obstruction in the guinea pig. Chest 2002;121(suppl):188S-91.
25. Wright JL, Petty T, Thurlbeck WM. Analysis of the structure of the muscular pulmonary arteries in patients with pulmonary hypertension and COPD: National Institutes of Health Nocturnal Oxygen Therapy Trial. Lung 1992;170:109-24.
26. Wilkinson M, Langhorne CA, Heath D, et al. A pathophysiological study of 10 cases of hypoxic cor pulmonale. Q J Med 1988;66:65-85.
27. Yu PN, Lovejoy FW Jr, Joos HA, et al. Studies of pulmonary hypertension. I. Pulmonary circulatory dynamics in patients with pulmonary emphysema at rest. J Clin Invest 1953;32:130-7.
28. Fishman AP, Fritts HW Jr, Cournand A. Effects of breathing carbon dioxide upon the pulmonary circulation. Circulation 1960;22:220-5.
29. Lim TP, Brownlee WE. Pulmonary hemodynamics in obstructive lung disease. Dis Chest 1968;53:113-25.
30. Enson Y, Giuntini C, Lewis ML, et al. The influence of hydrogen ion concentration and hypoxia on the pulmonary circulation. J Clin Invest 1964;43:1146-62.
31. Susmano A, Passovoy M, Carleton RA. Mechanisms of hypercapneic pulmonary hypertension. Cardiovasc Res 1977;11:440-5.
32. Harris P, Segel N, Green I, et al. The influence of the airways resistance and alveolar pressure on the pulmonary vascular resistance in chronic bronchitis. Cardiovasc Res 1968;2:84-92.
33. Thabut G, Dauriat G, Stern JB, et al. Pulmonary hemodynamics in advanced COPD candidates for lung volume reduction surgery or lung transplantation. Chest 2005;127:1531-6.
34. Buda AJ, Pinsky MR, Ingels NB Jr, et al. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 1979;301: 453-9.
35. Pinsky MR. Cardiovascular issues in respiratory care. Chest 2005; 128(suppl):592S-7.
36. Barr RG, Bluemke DA, Ahmed FS, et al. Percent emphysema, airflow obstruction, and impaired left ventricular filling. N Engl J Med 2010; 362:217-27.
37. Watz H, Waschki B, Meyer T, et al. Decreasing cardiac chamber sizes and associated heart dysfunction in COPD: role of hyperinflation. Chest 2010;138:32-8.
38. Luecke T, Pelosi P. Clinical review: positive end-expiratory pressure and cardiac output. Crit Care 2005;9:607-21.
39. Yoshizumi M, Kurihara H, Sugiyama T, et al. Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. Biochem Biophys Res Commun 1989;161:859-64.
40. Weitzenblum E, Chaouat A. Cor pulmonale. Chron Respir Dis 2009; 6:177-85.
41. Butler J, Schrijen F, Henriquez A, et al. Cause of the raised wedge pressure on exercise in chronic obstructive pulmonary disease. Am Rev Respir Dis 1988;138:350-4.
42. Schrijen FV, Henriquez A, Carton D, et al. Pulmonary vascular resistance rises with lung volume on exercise in obstructed airflow disease. Clin Physiol 1989;9:143-50.
43. Akcay M, Yeter E, Durmaz T, et al. Treatment of acute chronic obstructive pulmonary disease exacerbation improves right ventricle function. Eur J Echocardiogr 2010;11:1530-6.
44. Keller CA, Shepard JW Jr, Chun DS, et al. Pulmonary hypertension in chronic obstructive pulmonary disease. Multivariate analysis. Chest 1986;90:185-92.
45. Wright JL, Churg A. Effect of long-term cigarette smoke exposure on pulmonary vascular structure and function in the guinea pig. Exp Lung Res 1991;17:997-1009.
46. Biernacki W, Gould GA, Whyte KF, et al. Pulmonary hemodynamics, gas exchange, and the severity of emphysema as assessed by quantitative ct scan in chronic bronchitis and emphysema. Am Rev Respir Dis 1989;139:1509-15.
47. Mineo TC, Pompeo E, Rogliani P, et al. Effect of lung volume reduction surgery for severe emphysema on right ventricular function. Am J Respir Crit Care Med 2002;165:489-94.
48. Weg IL, Rossoff L, McKeon K, et al. Development of pulmonary hypertension after lung volume reduction surgery. Am J Respir Crit Care Med 1999;159:552-6.
49. Criner GJ, Scharf SM, Falk JA, et al. Effect of lung volume reduction surgery on resting pulmonary hemodynamics in severe emphysema. Am J Respir Crit Care Med 2007;176:253-60.
50. Sciurba FC, Rogers RM, Keenan RJ, et al. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med 1996;334:1095-9.
51. Kubo K, Ge RL, Koizumi T, et al. Pulmonary artery remodeling modifies pulmonary hypertension during exercise in severe emphysema. Respir Physiol 2000;120:71-9.
52. Naeije R, Barbera JA. Pulmonary hypertension associated with COPD. Crit Care 2001;5:286-9.
53. Saetta M, Baraldo S, Corbino L, et al. CD8+ve cells in the lungs of smokers with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;160:711-7.
54. Morrell NW, Adnot S, Archer SL, et al. Cellular and molecular basis of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54(suppl): S20-31.
55. Farber HW, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med 2004;351:1655-65.
56. Dinh-Xuan AT, Higenbottam TW, Clelland CA, et al. Impairment of endothelium-dependent pulmonary-artery relaxation in chronic obstructive lung disease. N Engl J Med 1991;324:1539-47.
57. Barbera JA, Peinado VI, Santos S, et al. Reduced expression of endothelial nitric oxide synthase in pulmonary arteries of smokers. Am J Respir Crit Care Med 2001;164:709-13.
58. Chen SJ, Chen YF, Meng QC, et al. Endothelin-receptor antagonist bosentan prevents and reverses hypoxic pulmonary hypertension in rats. J Appl Physiol 1995;79:2122-31.
59. Chen Y, Hanaoka M, Chen P, et al. Protective effect of beraprost sodium, a stable prostacyclin analog, in the development of cigarette smoke extract-induced emphysema. Am J Physiol Lung Cell Mol Physiol 2009;296:L648-56.
60. Chen Y, Hanaoka M, Droma Y, et al. Endothelin-1 receptor antagonists prevent the development of pulmonary emphysema in rats. Eur Respir J 2010;35:904-12.
61. Santos S, Peinado VI, Ramirez J, et al. Enhanced expression of vascular endothelial growth factor in pulmonary arteries of smokers and patients with moderate chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:1250-6.
62. Adnot S, Andrivet P, Chabrier PE, et al. Plasma levels of atrial natriuretic factor, renin activity, and aldosterone in patients with chronic obstructive pulmonary disease. Response to O_2 removal and to hyperoxia. Am Rev Respir Dis 1990;141:1178-84.
63. Lang CC, Coutie WJ, Struthers AD, et al. Elevated levels of brain natriuretic peptide in acute hypoxaemic chronic obstructive pulmonary disease. Clin Sci 1992;83:529-33.

64. Eddahibi S, Chaouat A, Morrell N, et al. Polymorphism of the serotonin transporter gene and pulmonary hypertension in chronic obstructive pulmonary disease. Circulation 2003;108:1839-44.
65. Petkov V, Mosgoeller W, Ziesche R, et al. Vasoactive intestinal peptide as a new drug for treatment of primary pulmonary hypertension. J Clin Invest 2003;111:1339-46.
66. Wright JL, Levy RD, Churg A. Pulmonary hypertension in chronic obstructive pulmonary disease: current theories of pathogenesis and their implications for treatment. Thorax 2005;60:605-9.
67. Defouilloy C, Teiger E, Sediame S, et al. Polycythemia impairs vasodilator response to acetylcholine in patients with chronic hypoxemic lung disease. Am J Respir Crit Care Med 1998;157:1452-60.
68. Nakamura A, Kasamatsu N, Hashizume I, et al. Effects of hemoglobin on pulmonary arterial pressure and pulmonary vascular resistance in patients with chronic emphysema. Respiration 2000;67:502-6.
69. Lee JH, Oh YM, Seo JB, et al. Pulmonary artery pressure in chronic obstructive pulmonary disease without resting hypoxaemia. Int J Tuberc Lung Dis 2011;15:830-7.
70. Global Initiative for Chronic Obstructive Lung Disease: global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease (updated 2009); 2009.
71. Yildiz P, Oflaz H, Cine N, et al. Gene polymorphisms of endothelial nitric oxide synthase enzyme associated with pulmonary hypertension in patients with COPD. Respir Med 2003;97:1282-8.
72. Chaouat A, Savale L, Chouaid C, et al. Role for interleukin-6 in COPD-related pulmonary hypertension. Chest 2009;136:678-87.
73. Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. Am J Respir Crit Care Med 2003;167:7-14.
74. Resta O, Foschino Barbaro MP, Brindicci C, et al. Hypercapnia in overlap syndrome: possible determinant factors. Sleep Breath 2002;6:11-8.
75. Chaouat A, Weitzenblum E, Krieger J, et al. Association of chronic obstructive pulmonary disease and sleep apnea syndrome. Am J Respir Crit Care Med 1995;151:82-6.
76. Halpern SD, Taichman DB. Misclassification of pulmonary hypertension due to reliance on pulmonary capillary wedge pressure rather than left ventricular end-diastolic pressure. Chest 2009;136:37-43.
77. Boussuges A, Pinet C, Molenat F, et al. Left atrial and ventricular filling in chronic obstructive pulmonary disease. An echocardiographic and Doppler study. Am J Respir Crit Care Med 2000;162:670-5.
78. Acikel M, Kose N, Aribas A, et al. The effect of pulmonary hypertension on left ventricular diastolic function in chronic obstructive lung disease: a tissue Doppler imaging and right cardiac catheterization study. Clin Cardiol 2010;33:E13-8.
79. Acikel M, Yilmaz M, Gurlertop Y, et al. The effect of pulmonary hypertension on left atrial mechanical functions in chronic obstructive lung disease. Int J Cardiol 2004;97:187-92.
80. Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. Chest 2009;135:786-93.
81. Carson JL, Terrin ML, Duff A, et al. Pulmonary embolism and mortality in patients with COPD. Chest 1996;110:1212-9.
82. Mal H. Prevalence and diagnosis of severe pulmonary hypertension in patients with chronic obstructive pulmonary disease. Curr Opin Pulm Med 2007;13:114-9.
83. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219-63.
84. Weitzenblum E, Chaouat A. Severe pulmonary hypertension in COPD: Is it a distinct disease? Chest 2005;127:1480-2.
85. Shorr AF, Wainright JL, Cors CS, et al. Pulmonary hypertension in patients with pulmonary fibrosis awaiting lung transplant. Eur Respir J 2007;30:715-21.
86. Agusti A, Barnes PJ. What the journal would like to publish on chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:1-2.
87. Han MK, Agusti A, Calverley PM, et al. COPD phenotypes: the future of COPD. Am J Respir Crit Care Med 2010;182:598-604.