MONASH University

PHENOTYPING HOSPITALIZED EXACERBATIONS OF COPD BY UNDERLYING AETIOLOGY AND INTERACTION WITH CARDIAC DISEASE

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ABSTRACT

Studying phenotypes within chronic obstructive pulmonary disease (COPD) populations may improve prediction of therapeutic responses and clinical outcomes. Acute exacerbations of COPD (AECOPD) are heterogenous events which are currently poorly defined. Despite their known heterogeneity, there is minimal characterization of AECOPD in clinical practice or research studies. Differences in treatment response and prognosis between exacerbation *phenotypes* may be obscured as a result.

We utilized techniques routinely employed in clinical practice to characterize AECOPDs. In Chapter 2 we report comprehensive characterization of an unselected hospitalized AECOPD cohort having examined viral, bacterial, embolic, cardiac, psychological and social precipitants for hospitalized AECOPD. The data indicate that the traditional dichotomy between infective and non-infective exacerbations may be misleading as most exacerbations feature a combination of both components. The findings also suggest that this complex patient cohort may benefit from in-depth assessment to permit individualized therapy.

The enormous clinical burden imposed by AECOPD requires simple markers to inform swift therapeutic decision-making. High blood eosinophil counts may predict increased exacerbation frequency and shorter exacerbation duration but during AECOPD blood eosinophil counts are often abnormally low. This may be important since eosinopenia is a marker of infection and associated with adverse outcomes. To date studies of eosinophils in this context have only considered 2 categorizations (“high” and “not high”). In Chapter 3 we report that low, normal and high blood eosinophil counts were equally distributed at AECOPD, both in a derivation and a validation cohort. Eosinophils correlated inversely with C-reactive protein, a marker of putative infection. Eosinopenic exacerbations were associated with evidence of infection, longer hospital stay and may be associated with reduced survival at 12 months.

Blood lactate levels are routinely reported as a component of blood gas analysis, but have never been studied in AECOPD. Lactate has potential implications as a driver

of hyperventilation but also as a marker of β-agonist excess. In Chapter 4, we detail findings indicating that blood lactate levels are frequently elevated in AECOPD. Raised lactate was associated with adverse outcomes and treatment with inappropriately high doses of β-agonists.

Cardiac disease is increasingly recognised as a key determinant of COPD outcomes, particularly mortality. A plethora of cardiac therapies have established mortality benefit in general populations, but although they are a key population to target, COPD patients have generally been excluded from studies. Characterizing cardiac disease in this population is challenging and in Chapter 5 we applied cutting-edge CT technology to systematically assess combined heart-lung pathologies in AECOPD. Occult coronary, pulmonary vascular and ventricular dysfunction was frequently identified by 256-multidetector CT (MDCT) and measurements of troponin and natriuretic peptides were often raised. Elevated biomarkers of cardiac dysfunction were associated with a variety of cardiac pathologies.

This body of research has demonstrated that clinically feasible strategies can be used to phenotype AECOPD. Studies have also identified key areas to target that may permit a personalised medicine approach. Overall, phenotyping strategies in AECOPD have potential to advance our understanding of pathologies and to optimise management.

DECLARATION

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution. 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 2 original papers published in peer reviewed journals and 2 submitted publications. The core theme of the thesis is the application of clinically available methods to phenotype hospitalized exacerbations of COPD. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within the Monash Lung and Sleep Department, Monash Medical Centre, Clayton under the supervision of Dr Paul King and Prof Philip Bardin.

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 following chapters, my contribution to the work involved:

Thesis Chapter	Publication title	Status	Nature and % of student contribution	Co-authors names. Nature and % of co-authors contributions	Co-author(s) Monash Student
1	Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease	Published	50%. For this chapter I performed the literature review, wrote the manuscript and submitted for publication.	1) E Shafuddin, literature review manuscript preparation. Input 30% 2)C Chang, review of manuscript. Input 5% 3)RJ Hancox, preparation of manuscript. Input 5%. 4) PT King, review of	No

				manuscript. Input 5% 5) PG Bardin. Preparation of manuscript. Input 5%.	
2	Exacerbation phenotyping in chronic obstructive pulmonary disease	Published	For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 70%.	1) K Hamza, aided in data analysis. Input 10% 2) PT King, review of manuscript. Input 5% 3) PG Bardin, aided with hypothesis generation and manuscript preparation. Input 15%.	No
3	Implications of low and high blood eosinophils in hospitalized exacerbations of COPD	Submitted for publication	For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 60%.	1) C Osadnik, aided with data analysis and manuscript preparation. Input 25%. 2) P King. Review of manuscript. Input 5% 3) PG Bardin. Interpretation of results and manuscript preparation. Input 10%.	No

4	Lactate is associated with adverse outcomes in AECOPD and reflects β-agonist dosages	Submitted for publication	For this chapter I was responsible for hypothesis generation, data collection, data analysis, interpretation of results and manuscript preparation. The extent of my contribution was 75%.	1) K Polkinghorne. Aided with data analysis. Input 10%. 2) PT King. Review of manuscript. Input 5%. 3) PG Bardin. Interpretation of results and manuscript preparation. Input 10%	No

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

DR MARTIN IAN MACDONALD:……Date:…….

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

PROF PHILIP G BARDIN……Date…….

DR PAUL T KING ……,Date:…….

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I would like to thank Anne, Lauren and Liz for research assistance, particularly their capacity to corral patients through consecutive Cardiology, Respiratory and Radiology examinations and still leave them happy and smiling at the end of the day, mostly. I would also like to thank Christian for expert help and advice across all domains!

Our cardiac study would not have been feasible without the dedication and expertise of John, Ahilan and Marcus at Monash Radiology who provided phenomenal technical and logistic support to our project.

Finally to my wife Clare, and sons Ben and Alex, it would not have been possible to complete this work without your support and patience. Thank you for keeping me going through the last 4 years and I look forward to seeing a whole lot more of you all very soon!

CONTENTS

LIST OF ABBREVIATIONS

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
BODE	Body-mass index, airflow Obstruction, Dyspnea, and Exercise
CAT	chronic obstructive pulmonary disease assessment tool
cMRI	cardiac magnetic resonance imaging
COPD	chronic obstructive pulmonary disease
CRP	C-reactive protein
CTPA	computer tomography pulmonary angiography
CXR	chest x-ray
DH	dynamic hyperinflation
DLP	dose length product
DSM-IV	Diagnostic Statistical Manual of Psychological Illnesses Version 4
ED	emergency department
FBE	full blood examination
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global initiative for chronic Obstructive Lung Disease
HADS	Hospital anxiety and depression scale
Hb	haemoglobin
HRCT	high resolution computer tomography
HREC	Hospital research ethics committee
hs-TnI	high-sensitivity troponin I
ICS	inhaled corticosteroids
ICU	intensive care unit
IL	interleukin-6
IQR	interquartile range
LABA	long acting beta-agonist
LAMA	long acting muscarinic antagonist
MDCT	multi-detector computer tomography
mMRCD	modified Medical Research Council Dyspnoea score
mSV	millisievert
NIV	non-invasive ventilation
NT-proBNP	N-terminal pro-natriuretic peptide
OCS	oral corticosteroid
PaCO2	arterial pressure of carbon dioxide
PCR	polymerase chain reaction
PE	pulmonary embolism
PM10	particulate matter 10
PWV	pulse wave velocity
RCT	randomized controlled trial
RV	rhinovirus

SABA	short acting beta-agonist
SAMA	short acting muscarinic antagonist
SD	standard deviation
ULN	upper limit of normal
URTI	upper respiratory tract infection
WCC	white cell count

ABSTRACTS PRESENTED AT NATIONAL CONFERENCES

ORAL PRESENTATION

MacDonald M, Wong A, King P, Lockwood S, Troupis J, Bardin P

Occult cardiac disease can be identified by dynamic CT during COPD exacerbation

TSANZSRS Annual Scientific Meeting 2016, 1 - 6 April 2016, Perth, Australia

MacDonald M, Wong A, King P, Lockwood S, Troupis J, Bardin P

Reduced pulmonary artery distensibility on dynamic CT correlates with emphysema and impaired right ventricular function

TSANZSRS Annual Scientific Meeting 2017, 24-28 March 2016, Canberra, Australia

SCIENTIFIC POSTERS

MacDonald M, Polkinghorne K, Laska I, Qiu M, Barberi A, MacDonald C, King P, Bardin P

Lactate is a routinely available biomarker in COPD exacerbation of prognostic and therapeutic relevance

TSANZSRS Annual Scientific Meeting 2016, 1 - 6 April 2016, Perth, Australia

MacDonald M, Osadnik C, Vasanthakumar S, Qiu M, King P, Bardin P

Blood Eosinophilia is Common in COPD Exacerbation and Associated with Non-infectious Aetiology

TSANZSRS Annual Scientific Meeting 2016, 1 - 6 April 2016, Perth, Australia

Dalgleish G, MacDonald M, King P, Hamilton G, Bardin P

Impaired sleep quality is a key symptom at COPD exacerbation and is perpetuated during hospitalization

TSANZSRS Annual Scientific Meeting 2016, 1 - 6 April 2016, Perth, Australia

ABSTRACTS PRESENTED AT INTERNATIONAL CONFERENCES

SCIENTIFIC POSTERS

MacDonald M, Wong A, King P, Lockwood S, Troupis J, Bardin P

Occult cardiac disease can be identified by dynamic CT during COPD exacerbation

American Thoracic Society Conference 2016, 13-18 May 2016, San Francisco, USA

MacDonald M, Polkinghorne K, Laska I, Qiu M, Barberi A, MacDonald C, King P, Bardin P

Lactate is a routinely available biomarker in COPD exacerbation of prognostic and therapeutic relevance

American Thoracic Society Conference 2016, 13-18 May 2016, San Francisco, USA

MacDonald M, Osadnik C, Vasanthakumar S, Qiu M, King P, Bardin P

Blood Eosinophilia is Common in COPD Exacerbation and Associated with Non-infectious Aetiology

American Thoracic Society Conference 2016, 13-18 May 2016, San Francisco, USA

PUBLISHED PAPERS

The following papers were accepted for publication during PhD candidature and form the basis of this thesis:

MacDonald MI, Shafuddin E, King PT, Chang CL, Bardin PG, Hancox RJ (2016). **Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease.**
Lancet Respir Med, 4(2), 138-148. doi: 10.1016/S2213-2600(15)00509-3

MacDonald MI, Korman T, King P, Hamza K, & Bardin P.(2013).
Exacerbation phenotyping in chronic obstructive pulmonary disease.
Respirology, 18(8), 1280-1281. doi: 10.1111/resp.12197

The following papers were published during PhD candidature but are not presented in this thesis:

Ruwanpura SM, McLeod L, Dousha LF, Seow HJ, Alhayyani S, Tate M, Deswaerte V, Brooks G, Bozinovski S, MacDonald M, Garbers C, King PT, Bardin PG, Vlahos R, Rose-John S, Anderson GP, Jenkins BJ. (2016).
Therapeutic Targeting of the IL-6 Trans-Signaling/Mechanistic Target of Rapamycin Complex 1 Axis in Pulmonary Emphysema.
Am J Respir Crit Care Med, 194(12), 1494-1505. doi: 10.1164/rccm.201512-2368OC

Kan-o K, Ramirez R, MacDonald MI, Rolph M, Rudd PA, Spann KM, Mahalingam S, Bardin PG, Thomas B (2017).
Human metapneumovirus infection in chronic obstructive pulmonary disease: impact of glucocorticosteroids and interferon
Journal of Infectious Diseases (accepted)

1.1 DECLARATION FOR THESIS CHAPTER 1

Declaration by candidate

In the case of Chapter 1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Contribution
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

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	Contribution (student co-authors only)
Dr E Shafuddin	Aided in hypothesis generation, data analysis and manuscript preparation.	
Dr C Chang	Aided in manuscript preparation.	
Dr RJ Hancox	Aided in hypothesis generation, data analysis and manuscript preparation.	
Dr PT King	Aided in hypothesis generation, data analysis and manuscript preparation.	
Prof PG Bardin	Aided in hypothesis generation, data analysis and manuscript preparation.	

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**

CHAPTER 1

REVIEW OF THE LITERATURE

1.2 REVIEW OF THE LITERATURE

Parts of this chapter have been published in *Lancet Respiratory Medicine* and are included as a pdf at the end of this chapter.

Definition of COPD

"Chronic Obstructive Pulmonary Disease" (COPD) describes a chronic respiratory disease characterized by progressive chronic airflow limitation caused by a mixture of small airways disease and emphysema. COPD is currently diagnosed by expiratory airflow obstruction not fully reversible by bronchodilators(Vogelmeier et al., 2017) and does not require distinction of the underlying disease elements. The population encompassed by "COPD" therefore demonstrate great heterogeneity, not only in disease severity, but in the nature of the underlying contributory pathologies. In addition, COPD disease impact is further modulated by the interaction of COPD with a plethora of associated physical and psychosocial morbidities(Sin, Anthonisen, Soriano, & Agusti, 2006). The airflow obstruction in COPD usually develops as a consequence of significant exposure to noxious particles or gases(Vogelmeier et al., 2017). The COPD patients reported in this thesis were all former or current cigarette smokers.

Phenotyping stable obstructive lung disease

The existence of different phenotypes within the COPD population has long been recognized(Burrows, Fletcher, Heard, Jones, & Wootliff, 1966). Heterogeneity within the population of patients with obstructive lung diseases including COPD and asthma, has traditionally been represented by an overlapping theoretical Venn diagram(Soriano et al., 2003). For the purposes of research studies, a stereotypical subset of COPD has been identified and studied, however this group may represent as little as 10% of the group labeled 'COPD' in the community(Beasley, Weatherall, Travers, & Shirtcliffe, 2009). Even within this subset, there remains marked heterogeneity, and as a result, there is burgeoning interest in sub-classifying COPD patients into distinct phenotypes based on clinical characteristics (e.g. 'bronchitic'/'emphysematous' phenotype), patient behaviours (e.g. 'frequent exacerbator') or association with asthma and other comorbidities ('overlap syndromes').

Alternatively, statistical techniques have been used to identify phenotypes within stable COPD. Cluster analysis in 175 community subjects identified 5 distinct phenotypes in patients with applicable respiratory symptoms or obstructive spirometry(Weatherall et al., 2009), including a group characterized by severe and markedly variable airflow obstruction with features of chronic bronchitis, emphysema and atopic asthma. A combination of component and cluster analysis in 322 patients who met spirometry criteria for COPD, identified 4 clusters or phenotypes(Burgel et al., 2010). Importantly, patients with similar levels of airflow limitation belonged to different phenotypes with different symptoms, comorbidities, exacerbation rates and estimated prognosis.

The heterogeneity and complexity of COPD means that sub-classification of patients with COPD according to key characteristics may be required to improve COPD management. Clinical phenotypes defined by responses to treatment have been proposed for stable COPD, with the potential to direct optimal patient care(Miravitlles, Soler-Cataluña, Calle, & Soriano, 2013).

Phenotyping exacerbations of COPD

Exacerbations of COPD are also complex and heterogeneous. Acute exacerbations of COPD (AECOPD) are episodic acute deteriorations in airflow limitation that punctuate the natural history of the disease. AECOPD are associated with accelerated lung function decline(Kanner, Anthonisen, & Connett, 2001), reduced quality of life(Wedzicha, Decramer, & Seemungal, 2012), mortality(Soler-Cataluna et al., 2005) and substantial healthcare costs(Sullivan, Ramsey, & Lee, 2000). AECOPDs are the second leading cause of avoidable hospitalization in Australia(Page A, 2007) and constitute the bulk of COPD health care costs(Sullivan et al., 2000). AECOPD shows a tendency towards temporal clustering(Hurst et al., 2009) and patients with previous exacerbations are at highest risk of future exacerbations(Hurst et al., 2010).

Readmission to hospital following AECOPD is common, with 35.1% of patients readmitted within 90 days in a prospective audit of 15191 AECOPD discharges(Hartl et al., 2016). There are currently few effective strategies to mitigate this. With the burden of COPD projected to increase(Lozano et al., 2012) there is an urgent need

for novel approaches that may improve AECOPD management. Despite their high prevalence and importance, our understanding of exacerbations is incomplete, and even a satisfactory definition of AECOPD remains elusive.

Symptom-based definition

The current consensus definition of AECOPD as an acute worsening of respiratory symptoms requiring an increase in therapy(Vogelmeier et al., 2017) reflects some key observations. Symptoms are present at baseline and increase during exacerbation however COPD symptoms show inherent variability, the cause of which is not fully understood, and in clinical practice the threshold which defines an exacerbation is fundamentally subjective. In research studies, daily symptom scores to define exacerbation events consistently identify frequent spikes in symptoms not reported by the patient to researchers. These ‘mini-exacerbations’ are associated with worsened health status and may outnumber exacerbations by two to one, particularly in older patients with severe disease(Langsetmo, Platt, Ernst, & Bourbeau, 2008). Given the difficulty in defining an exacerbation by symptoms alone, the inclusion of “an increase in therapy” to the definition reflects the relevance of clinician evaluation and the core issue of therapeutic intervention. To date no sensitive and/or specific biomarkers to define a COPD exacerbation have been validated.

Health-care based definition

An alternative to the symptom-based definition is one based on increased health care utilization(Rabe et al., 2007) - hospitalizations, clinic visits or episodes where key exacerbation therapies (e.g. oral corticosteroids and/or antibiotics) are initiated. The location in which an exacerbation is managed - community, hospital, intensive care unit - provides a crude surrogate for exacerbation severity, but ultimately each AECOPD is a unique patient-clinician-healthcare system encounter.

Just as COPD diagnosis does not require identification of constituent disease components, “exacerbations” of COPD do not identify an underlying aetiology or mechanism. Exacerbation rate reduction is a key target for interventional trials in COPD(Calverley et al., 2007; Decramer et al.; Tashkin et al., 2008) but exacerbations are reported as discrete nonspecific events. This lack of

characterization implies an equivalence between exacerbations which may be misleading, but is difficult to overcome given the uncertainty in defining and recording exacerbations(Cazzola, MacNee, Martinez, & Rabe, 2008). As some exacerbation therapies have a relatively specific mechanism of action (e.g. antibiotics to reduce bacterial exacerbations) the benefits (or harm) of therapies could be obscured by failure to distinguish exacerbation subtypes. Greater exacerbation reduction with inhaled corticosteroids, particularly in patients with elevated blood eosinophil counts(Pascoe, Locantore, Dransfield, Barnes, & Pavord, 2015; Watz et al., 2016), may reflect the benefits of phenotyping AECOPD. With the advent of biological therapies with a highly specific mechanism of action(Brightling et al., 2014), phenotyping COPD and potentially AECOPD may have increasing appeal.

COPD phenotype and exacerbator phenotype

COPD severity

Exacerbation frequency increases with worsening airflow obstruction(Dewan et al., 2000) and numerous classification systems for COPD severity exist. The Global Obstructive Lung Disease (GOLD) Class I-IV grades patients by severity of expiratory airflow limitation with prognostic and therapeutic implications(Rabe et al., 2007). Multi-dimensional assessment such as the Body-mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) Index(Celli et al., 2004) which incorporates functional and nutritional status, permits more accurate prediction of exacerbation risk(Marin et al., 2009).

Exacerbation history

Independent of disease severity, some patients with COPD appear prone to frequent exacerbations, leading to the concept of a “frequent exacerbator” phenotype in COPD(Hurst et al., 2010). A self-reported health care utilization exacerbation rate of ≥2/year appears the best predictor of future exacerbation rates(Hurst et al., 2010). The mechanisms underlying the frequent exacerbator phenotype have not yet been elucidated but in the case of roflumilast, the frequent exacerbator phenotype has been used to identify patients most likely to benefit from new therapies(Wedzicha, Rabe, et al., 2013). Frequent exacerbators may themselves be a heterogeneous

group with various specific susceptibilities to different exacerbation aetiologies(Wedzicha, Brill, Allinson, & Donaldson, 2013). The most recent International COPD GOLD guidelines have recommended incorporating symptoms, exacerbation frequency and severity of airflow obstruction to create a more informative patient phenotype(Vogelmeier et al., 2017).

What underpins hospitalized exacerbations of COPD and how can we characterize them?

A hospitalized 'COPD exacerbation' could be considered an episode where a patient's ability to cope with symptoms in the community is overwhelmed, most often by an acute insult. By this definition, an exacerbation occurs when the delicate balance of disease impact and functional capacity is disturbed. This implies that composite factors including the patient's baseline physical condition, severity of the provocative factor(s) and available community support may all determine whether a patient is hospitalized for a COPD exacerbation.

Classifying exacerbations by severity

Scoring systems to classify the severity of hospitalized exacerbation have been validated as predictors of inpatient mortality or need for mechanical ventilation(Shorr, Sun, Johannes, Derby, & Tabak, 2012; Steer, Gibson, & Bourke, 2012). Acute prognostic indicators include severity of ventilatory insufficiency or parameters of multi-organ dysfunction, such as reduced conscious state, renal impairment, and haemodynamic instability. Predictive factors identified for inpatient and post discharge mortality from a large European hospital audit included many fixed variables such as age, previous admissions, severity of airflow limitation and number of comorbidities(Hartl et al., 2016). However, exacerbation aetiology and phenotype as determinants of outcome in AECOPD have been minimally researched.

Biomarkers which guide AECOPD therapy

For the various therapeutic interventions prescribed in AECOPD, the availability of biomarkers or endotypes to guide clinical management is limited.

Ventilatory support

The value of biomarkers to predict treatment benefit in AECOPD is evident with non-invasive ventilation (NIV). Hypercapnoea on arterial blood gas analysis identifies an

AECOPD population in whom NIV improves prognosis(Lightowler, Wedzicha, Elliott, & Ram, 2003).

Bronchodilators

In contrast to the COPD "mega-trials" investigating bronchodilator effectiveness and safety in stable COPD(Calverley et al., 2007; Tashkin et al., 2008; Vestbo et al.), there is a paucity of data to guide bronchodilator strategies in acute exacerbations of COPD. The benefit of using bronchodilators in very high doses or combining β_2-agonists and antimuscarinic agents in AECOPD has not been established(Moayyedi, Congleton, Page, Pearson, & Muers, 1995) but may be common in clinical practice. Tachycardia and subclinical cardiac dysfunction are frequently observed in COPD and associated with adverse prognosis(Hoiseth, Omland, Hagve, Brekke, & Soyseth, 2012). Very high-dose β_2-agonist and antimuscarinic therapy could have adverse cardiac effects during AECOPD but this has not been adequately studied and there is currently no evidence base to guide maximal or optimal beta-agonist administration in COPD. Lactate has shown a direct relationship with β_2-agonist doses in asthma, and we therefore explored associations of lactate in AECOPD with β-agonist dose and clinical outcomes in Chapter 4.

Corticosteroids

Corticosteroids reduce exacerbation duration and severity in AECOPD(Walters et al., 2014). Inhaled and oral corticosteroids improve airflow limitation in the subset of stable COPD patients with higher sputum and blood eosinophil levels(Brightling et al., 2005; Brightling et al., 2000). In acute exacerbations of COPD treated with systemic corticosteroids, exacerbations were shorter among patients with "high" blood eosinophils than those whose eosinophils were "not high" (>2% versus <2% total white cell count)(Bafadhel et al., 2016). This has been proposed to reflect increased corticosteroid responsiveness. Eosinophil profiles in hospitalized AECOPD however, are different from stable COPD. Absolute eosinophil counts in an AECOPD population designated "not high", are often abnormally low ("eosinopenic").. Eosinopenia is a marker of sepsis and has been associated with increased mortality and longer hospitalization(Abidi et al., 2011; Holland, Alkhalil, Chandromouli, Janjua, & Babores, 2010). In the absence of suppression by exogenous corticosteroids, eosinopenia may reflect the presence or severity of infection in AECOPD(Abidi et al.,

2008). The blood eosinophil count may therefore have implications for antibiotic as well as corticosteroid therapy in AECOPD. We explored a strategy categorizing AECOPD according to peripheral blood eosinophil count - eosinopenic, normal or eosinophilic - in Chapter 3.

Antibiotics

Bacterial infection is implicated in up to 50% of AECOPD(Sapey & Stockley, 2006). Current guidelines recommend antibiotics for exacerbations where clinical signs of infection such as fever, leucocytosis or sputum purulence are present(Yang, 2016). A meta-analysis found antibiotic prescription to be associated with reduced treatment failure in hospitalized exacerbations (RR=0.77), particularly those requiring Intensive Care Unit (ICU) management (RR=0.19)(Vollenweider, Jarrett, Steurer-Stey, Garcia-Aymerich, & Puhan, 2012). Antibiotic benefit would be anticipated to be restricted to those with bacterial involvement, however confirming bacterial involvement in AECOPD can be difficult. Sputum purulence is a simple clinical observation to identify likelihood of benefit from antibiotics(Anthonisen et al., 1987; Stockley, O'Brien, Pye, & Hill, 2000). Blood markers of inflammation are commonly used to identify infection in AECOPD, although the ability of individual biomarkers to reliably distinguish bacterial and viral infection is controversial(Daniels, Schoorl, et al., 2010). Prediction of antibiotic benefit is enhanced in the presence of sputum purulence and C-reactive protein (CRP) levels >40mg/L(Miravitlles et al., 2013). A placebo controlled trial of doxycycline in hospitalized AECOPD without fever or consolidation reported no overall difference in clinical success rates at Day 30(Daniels, Snijders, et al., 2010), but indicated a clear benefit in those patients with either sputum purulence or measurements of CRP>50mg/L. Other biomarkers of infection have been studied in AECOPD. Serum amyloid A is an acute phase reactant that appears to be a sensitive marker of AECOPD(Bozinovski et al., 2008). Procalcitonin has been proposed as a more specific marker of bacterial infection to guide rational antibiotic prescription in hospitalized AECOPD(Stolz et al., 2007) although numerous studies have failed to confirm it’s ability to accurately distinguish bacterial from viral exacerbations(Chang et al., 2015; Daniels, Schoorl, et al., 2010; Falsey et al., 2012). However, withholding antibiotics in AECOPD with low procalcitonin levels appears to be safe and may reduce overall antibiotic exposure(Corti et al., 2016). Whether this

translates into a cost-effective strategy with long-term benefits for patients is yet to be established.

Cardiovascular medications in AECOPD

There are no placebo controlled randomized clinical trials (RCT) of cardiovascular medications as therapy in AECOPD. Observational studies have suggested lower mortality and exacerbation rates in patients on statins(Huang et al., 2011), antiplatelet(Harrison et al., 2014), angiotensin converting enzyme inhibitors(Mortensen et al., 2009) or β-blocker therapy(Dransfield, Rowe, Johnson, Bailey, & Gerald, 2008). The only RCT in this field studied exacerbation rates in COPD patients without a conventional indication for statin therapy and found no benefit from simvastatin(Criner et al., 2014). However, cardiac dysfunction during AECOPD as manifest by elevated troponins and natriuretic peptides is common(Chang et al., 2011), and cardiac investigation and therapy may be a neglected facet of AECOPD management. In Chapter 5 we report cardiac biomarker analysis integrated with a novel dynamic 256-slice multidetector cardiopulmonary computed tomography (256-MDCT) in hospitalized AECOPD. This approach has not been previously reported and provides the first opportunity to simultaneously assess coronary arteries, lung, pulmonary vasculature and cardiac function.

Imaging phenotypes

MDCT can characterize and quantify structural changes in individual COPD patients to enhance disease phenotyping. Some imaging abnormalities have shown relevance to exacerbations of COPD. Increased emphysema predicts reduced survival post exacerbation(Cheng et al., 2015). At a basic level, a crude assessment of heart-lung interaction in AECOPD has been explored by measurement of pulmonary artery:aorta (PA:A) on conventional CT acquisitions. Dilatation of the pulmonary artery is observed in established pulmonary hypertension (PH) and a PA:A>1 predicts an increased risk of past and future AECOPD(Wells et al., 2012). A retrospective study of hospitalized AECOPD suggested that increased PA:A on standard CT may be associated with increased troponin levels and adverse clinical outcomes(Wells, Morrison, Bhatt, Nath, & Dransfield, 2015).

Integrating clinical, blood and CT markers appears to be a promising strategy to improve phenotyping of COPD exacerbations. The work presented in this PhD aims to assess the feasibility and utility of clinically orientated aetiological AECOPD phenotyping. Unlike previous small research studies in selected outpatients (in studies outlined in Chapter 2) we used routinely available techniques to implement comprehensive aetiological phenotyping in hospitalized AECOPD. The use of readily available blood markers to identify exacerbation phenotypes is explored further in Chapter 3 where we investigate the implications of low, normal and high eosinophil counts in AECOPD with relation to infective aetiology and clinical outcomes. In Chapter 4, we explore the associations of lactate levels measured as a routine component of blood gas analysis in AECOPD, in particular the association with excessive β_2-adrenergic stimulation. In Chapter 5, we report the first use of dynamic 256-MDCT to simultaneously examine cardiopulmonary structure and function in patients with COPD during acute exacerbation and after recovery. MDCT results were integrated with cardiac biomarker analysis to elucidate the clinical implications of raised troponins and natriuretic peptides during AECOPD.

The rationale for Chapters 3, 4 and 5 are explored in greater detail in the introduction to those Chapters. The literature reviewed below summarizes evidence regarding known aetiological contributors to AECOPD and follows the framework reported in Chapter 2. A comprehensive literature review of cardiac dysfunction in AECOPD was also conducted as part of the current doctoral studies and was published in *Lancet Respiratory Medicine* in 2016. The paper is enclosed as an Adobe Acrobat document at the end of this chapter.

Phenotyping AECOPD by aetiology

Several lines of evidence indicate that AECOPD is not a homogeneous event. Published literature frequently reports the aetiology of exacerbations as infective in around 70% of cases(Sapey & Stockley, 2006). In relative terms, the other 30% have barely been researched. Additional factors putatively implicated include eosinophilic airway inflammation, or non-infectious aetiologies such as cardiac dysfunction, pulmonary embolism, anxiety and depression and social factors. As a first step we proposed an acronym to aid clinician characterization of COPD exacerbations by aetiological phenotype(MacDonald, Korman, King, Hamza, & Bardin, 2013). Several

aetiologies may contribute to hospitalization for AECOPD and each possible cause should be considered in turn to promote comprehensive assessment. Ultimately it may be possible to integrate the exacerbation phenotype with the underlying individual patient COPD disease phenotype.

This approach may offer multiple potential benefits. It may identify patterns of disease activity and exacerbation ‘behaviour’ within groups of patients and individuals. For example, patterns of recurrence may suggest immune dysfunction, susceptibility to viral infection or the role of chronic bacterial colonization. A previous study has demonstrated a familial exacerbation phenotype, thereby implicating a potential inherited susceptibility(Foreman, DeMeo, Hersh, Reilly, & Silverman, 2007) In addition, separating phenotypes into those of an infective nature and non-infective causes will help direct exacerbation treatments. Positive identification of triggers such as anxiety/depression or heart failure will prompt alternative validated management strategies that can improve patient care and may reduce exacerbation rates and ultimately the costs associated with COPD.

An acronym to phenotype acute exacerbations of COPD by underlying aetiology – ABCDEFGX

Infective aetiologies and AECOPD

A – Airway viral infection

Circumstantial evidence for respiratory virus infection exists in seasonality(Jenkins et al., 2011), reductions in risk of exacerbations by influenza vaccination(Poole, Chacko, Wood-Baker, & Cates, 2000), and the presence of coryzal symptoms as a frequent precursor of exacerbations(Seemungal et al., 2001). Multiplex respiratory virus polymerase chain reaction (PCR) testing has made detection of viruses in routine clinical care possible. Nasopharyngeal virus PCR at the time of COPD exacerbation is positive around 25-50% of cases(Hewitt et al., 2016) with similar rates observed in inpatient or community studies. The most commonly detected viruses are generally rhinovirus (RV), respiratory syncytial virus and influenza(Zwaans, Mallia, van Winden, & Rohde, 2014). However, PCR detects viral nucleic acid, not replicating virus, and therefore detection of viral nucleic acid at AECOPD does not confirm causality. Some studies have detected virus during stable state. In a study with exacerbation and stable state matched samples in 68/83 community-based patients, viral PCR was positive in 38.7% of cases at exacerbation versus 16.2% when stable (Seemungal et al., 2001). The same study however, found viral PCR positivity at exacerbation was significantly associated with upper respiratory tract infection (URTI) symptoms.

Compelling evidence for the role of RV came from a study of experimentally induced RV infection in COPD subjects and healthy controls(Mallia et al., 2011). In this study, inoculation with human RV of 13 patients with COPD (mean FEV_1 1.94L) and 13 smoking control subjects was successful in 23/26. URTI symptoms developed in 21/23. COPD patients had more upper and lower respiratory tract symptoms and almost all infected COPD patients developed an exacerbation. Compared to the control subjects, COPD patients developed a higher viral load and higher sputum neutrophils but a reduced interferon response, suggesting defective anti-viral host responses in COPD patients.

Coryzal symptoms can be a useful surrogate for viral infection(Kherad et al., 2010). Exacerbations featuring coryzal symptoms or respiratory virus detection have been associated with longer duration and greater lung function decline(Donaldson et al., 2015). A study that used virus PCR in outpatient AECOPD observed a mean recovery time of 13 versus 6 days for viral versus non-viral exacerbations (p=0.006)(Seemungal et al., 2001). Relevant to the importance of disease phenotyping, patients who presented with symptoms of a common cold at first exacerbation have been shown to be more likely to present with a cold at a subsequent exacerbation(Perera et al., 2007). Whether this reflects a specific immune deficiency or an increased rate of exposure merits investigation.

Studies have reported on various sampling techniques for virus detection in AECOPD; nasal aspirate, nasopharyngeal aspirate, nasal swab, spontaneously expectorated or induced sputum(Zwaans et al., 2014). A higher prevalence of virus has generally been observed in lower respiratory tract samples. A study in hospitalized AECOPD using PCR on both nasal lavage and induced sputum found higher viral detection rates in induced sputum(Rohde et al., 2003). Sputum induction is not routinely performed in clinical practice and in hospitalized AECOPD spontaneously expectorated sputum may often not be available. In the European COPD audit 35.2% of AECOPD admissions did not have increased sputum and 50% did not report sputum purulence(Hartl et al., 2016). Nasopharyngeal viral PCR is easier to obtain, although possibly at the expense of reduced sensitivity.

B – Bacterial infection

Most studies have suggested that bacterial infection is causative of 30-50% of exacerbations(Gallego et al., 2016) and in up to 70% of exacerbations which require mechanical ventilation(Soler et al., 1998). Loss of innate immunity through structural damage is likely to be a major factor in bacterial interaction with COPD and impaired mucosal antibody and cellular immunity may be relevant. The most commonly isolated bacteria are *Haemophilus influenzae, Streptococcus pneumoniae* and *Moraxella catarrhalis*. Infections with *Pseudomonas* spp, *Stenotrophomonas* spp, and Gram negative bacteria occur in more severe exacerbations, often affecting the most debilitated patients(Miravitlles et al., 1999). In severe COPD, many patients

have bacterial colonization of their lower airway and recently HRCT chest imaging has identified a significant subset of COPD patients with associated bronchiectasis(Du, Jin, Liu, & Sun, 2016). Colonizing bacteria may contribute to the natural history of COPD in a manner analogous to that observed in cystic fibrosis and bronchiectasis. A recent study identified Pseudomonas in 34.7% of severe COPD patients post exacerbation, particularly those with coexistent bronchiectasis(Gallego et al., 2014), many of which demonstrated chronic colonization on longitudinal follow up. One proposed explanation for exacerbations in colonized patients is bacterial strain change since the humoral immune response to pathogenic bacteria is highly strain specific. A prospective study of 81 COPD outpatients having monthly sputum examinations isolated a new strain of *Haemophilus influenzae*, *Streptococcus pneumoniae* or *Moraxella catarrhalis* more commonly at exacerbation than at stable times of review(33.0 v 15.4%, $p<0.001$)(Sethi, Evans, Grant, & Murphy, 2002). A similar finding was reported following development of new strains of *Pseudomonas aeruginosa*(Murphy et al., 2008). New bacterial strains elicit increased pulmonary and systemic inflammatory responses during AECOPD in comparison with pre-existing or nonpathogenic bacteria(Sethi et al., 2008).

Colonized patients have increased inflammatory markers in induced sputum, suggesting that bacterial colonization may be a factor increasing airway inflammation(Sethi, Maloney, Grove, Wrona, & Berenson, 2006). However, these patients remain colonized when symptomatically stable, albeit at lower bacterial loads(Wedzicha, 2002). Bacterial load has been shown to relate directly to sputum neutrophilia and may be a causal factor in airway inflammation(Papi et al., 2006). Patients with bacteria identifiable in sputum at baseline appear more likely to have a bacterial aetiology associated with subsequent exacerbations(Bafadhel et al., 2011).

The seminal report on COPD exacerbations by Anthonisen et al(Anthonisen et al., 1987) classified exacerbations according to the pattern of symptoms, with increased sputum volume and purulence being markers of bacterial infection and predictive of antibiotic response(Anthonisen et al., 1987). In a study of 121 community exacerbations, sputum purulence predicted the likelihood of a positive bacterial culture and higher CRP(Stockley et al., 2000) and lack of sputum purulence

predicted successful resolution without antibiotics. Of note, only 89/121 (73.6%) patients in this study could provide a sputum sample for analysis. A pilot study in hospitalized AECOPD restricted antibiotic use to patients with sputum purulence and found no difference in rates of short-term clinical failure(Soler et al., 2012). Although sputum purulence appears a reliable marker of infection recent studies have cast doubt on its ability to differentiate bacterial from viral infection(Papi et al., 2006). Bacterial and virus co-infection can also occur frequently(Papi et al., 2006).

Beyond sputum purulence, systemic inflammatory markers can aid identification of bacterial exacerbations although the evidence is conflicting. A prospective study of 265 outpatients with severe COPD and Anthonisen Type I-II exacerbations examined sputum for both bacterial culture and viral PCR. CRP levels were higher in bacterial versus viral (median 58.3 v 37.3mg/L) and in hospitalized versus community exacerbations (67.4 v 37.3mg/L), although a median CRP of 36.4mg/L was observed even where no infection was identified(Gallego et al., 2016). Higher CRP values have been generally associated with bacterial aetiology(Garcha et al., 2012) although a prospective study of 86 hospitalized patients with AECOPD but without pneumonia found no significant difference in CRP levels between exacerbations with bacteria, virus or no infection identified(Kherad et al., 2010). Infact, in one study using nasopharyngeal swabs and sputum culture in 137 hospitalized AECOPD without consolidation on chest X-ray, CRP levels were higher in viral and mixed infections (Clark et al., 2015).

Procalcitonin is a calcitonin precursor normally produced in the neuroendocrine cells of the thyroid and the lungs, but in response to bacterial infections, procalcitonin may be produced by cells throughout the body(Becker, Nylen, White, Muller, & Snider, 2004). Procalcitonin has therefore been evaluated as a guide antibiotic therapy in respiratory tract infections(Stolz et al., 2007). In AECOPD, a high procalcitonin has been associated with pneumonia on chest X-ray and markers of infection such as fever, white cell count, CRP and clinical severity(Falsey et al., 2012). To date, evidence that procalcitonin can discriminate between bacterial and viral exacerbations, is limited. Whilst some studies have suggested slightly better discriminant value in distinguishing bacterial versus viral AECOPD(Tanriverdi et al., 2015), studies in hospitalized AECOPD have not verified this benefit(Chang et al.,

2015; Soler et al., 2012). Furthermore, analysis of an RCT of doxycycline in hospitalized AECOPD suggested CRP that may perform better than procalcitonin to guide antibiotic therapy(Daniels, Schoorl, et al., 2010). Serum amyloid A (SAA) has been proposed as an alternative to CRP and has shown marginally better prediction of severe exacerbations compared to CRP (AUC 0.88 v 0.80, p=0.05)(Bozinovski et al., 2008). In the latter study both SAA and CRP progressively increased when exacerbations with no pathogen, virus only, bacteria only and co-infection were compared. Increases in $\log_e$ CRP (OR=1.57) and $\log_e$SAA (OR=1.39) were able to discriminate between bacterial versus non-bacterial, but not between bacterial and viral aetiologies.

CRP is routinely available to clinicians and its utility as a blood biomarker of infection in AECOPD appears non-inferior to proposed alternatives. However, CRP testing alone cannot adequately differentiate viral from bacterial exacerbation. Indeed given the limitations of viral sampling techniques, bacterial culture(Garcha et al., 2012) and the high frequency of bacterial colonization, co-infection and pre-hospital antibiotic exposure, definitively establishing the nature of microbiological aetiology in hospitalized AECOPD is currently not possible.

Correctly identifying the bacterial infection phenotype would seem important since these patients are the logical candidates for antibiotic therapy. Chronically colonized patients and those with coexistent bronchiectasis may be an important specific subgroup. The importance lies not just in diagnostic purism but also because injudicious antibiotic prescription is likely to contribute to microbial resistance patterns that could potentially adversely affect the natural history of the disease. Antibiotics carry the risk of allergy and increased rates of diarrhea(Ram, Rodriguez-Roisin, Granados-Navarrete, Garcia-Aymerich, & Barnes, 2006). Changing the practice of near universal antibiotic prescription however, may be difficult until clinicians have confidence in accurate identification of bacterial infection. To change current clinical practice, high-level evidence establishing the benefits of a rational and targeted approach is likely to be needed.

C – Co-infection

Confusion about the relative contribution of either bacteria or viruses in COPD exacerbations may reflect a failure of some studies to test for both concurrently. Co-infection with both virus and bacteria is thought to occur in around 25% of exacerbations and is associated with more severe exacerbations than either agent alone(Wilkinson et al., 2006). A study of 56 community exacerbations found co-infection with RV/Haemophilus to be associated with higher bacterial load and serum IL-6 than exacerbations without both pathogens(Wilkinson et al., 2006). When associated with new or worsening coryzal symptoms, isolation of *Haemophilus influenzae* at exacerbation onset is associated with more respiratory symptoms and lung function impairment(Wilkinson et al., 2006). Whether co-infected patients are those with underlying colonization and whether certain bacteria and viruses preferentially interact are fascinating areas for further research**.** Intriguingly, viral infection appears a frequent precursor to bacterial infection. Experimental RV infection was induced in a study of 31 patients with COPD without sputum bacteria at baseline, 28 smokers without COPD and 19 non-smoker control subjects(Mallia et al., 2012). In RV infected COPD patients, subsequent bacterial infection appeared at Day 9 and peaked at Day 15 post viral inoculation. Mean baseline FEV_1 (L) was significantly lower (1.76 v 2.18, p=0.04) in patients who developed secondary bacterial infection. A study of 92 community exacerbations compared exacerbation onset PCR with PCR from a time-matched stable member of the same cohort(A. F. Hutchinson et al., 2007). In that study 36% of AECOPD with positive viral PCR at exacerbation onset had developed bacteria by Day 7 and 78% of AECOPD with *Haemophilus influenza* detected in the first 5 days had viral symptoms as a prodrome. From our own published work in hospitalized AECOPD, co-infection appeared to be associated with longer duration of hospitalization(MacDonald et al., 2013).

Non-infective aetiologies and AECOPD

Even in studies employing meticulous examination, a significant proportion of COPD exacerbations are deemed to be non-infective. These may potentially represent infections that elude current diagnostic techniques, increased inflammation of non-infective origin or the impact of alternative pathologies. In clinical practice where failure to identify a specific pathogen is common and treatment is often empirical, it is essential to review individual patients comprehensively to exclude important additional - or alternative diagnoses.

D - Depression/anxiety

Anxious and depressive symptoms are frequently present in patients with COPD(van Manen et al., 2002), and predict poorer quality of life and functional status(Eisner et al.). Depression has been linked with both frequent exacerbations and an increased risk of mortality from exacerbations(Almagro et al., 2002). Depression has not been proven to cause exacerbations but it does impair functional performance, quality of life and is a key issue in the holistic care of COPD (Quint, Baghai-Ravary, Donaldson, & Wedzicha, 2008).

The prevalence of panic disorder in COPD has been estimated to be at least 10 times higher than the prevalence of 1.5 to 3.5% in the general population(Hynninen, Breitve, Wiborg, Pallesen, & Nordhus, 2005). Anxiety has been shown to predict a higher risk of COPD exacerbations(Eisner et al.). Anxiety augments symptoms of breathlessness and diminishes the patient's ability to cope with symptoms thereby promoting presentations to health care services.

Dynamic hyperinflation (DH) refers to the increase in end-expiratory lung volume that may occur in patients with airflow limitation when minute ventilation increases (*e.g.* during exercise, hypoxia, anxiety etc.). The abnormal pulmonary mechanics of COPD predispose to DH whenever hyperventilation occurs, and DH underpins the pathophysiology of COPD exacerbation. The mechanical forces exerted by hyperinflation may even be pro-inflammatory(A. Agusti & Soriano, 2007). Dynamic hyperinflation provides a potential mechanism by which anxiety may amplify the natural variability in symptoms, provoking physiological deterioration and increased

healthcare utilization in the absence of an infective insult. This group may respond well to bronchodilators and anxiolytic agents and may represent a small but expensive and poorly managed cohort.

E - Embolism/Eosinophils

Acute breathlessness caused by pulmonary embolism can closely resemble COPD exacerbation. The prevalence of pulmonary embolism (PE) in COPD has been an area of controversy and may be underestimated(Gunen, Gulbas, In, Yetkin, & Hacievliyagil, 2010). Patients with COPD exacerbation have risk factors of poor mobility and systemic inflammation and have been designated as a 'high-risk' group for developing venous thromboembolism(NHMRC, 2009). One study identified PE in 25% of patients hospitalized for COPD exacerbation where infective causes were not clinically suspected(Tillie-Leblond et al., 2006). In this study, factors predictive of risk were malignancy, previous thromboembolic disease and reduction in P_aCO_2 of at least 5mmHg from baseline. In contrast, a study using universal D-dimer testing followed by CTPA and limb ultrasound found the prevalence to be 3.3% overall - 6.2% in those with and only 1.3% in those without clinical suspicion of PE(Rutschmann et al., 2007). Statistically significant predictors of PE in this study were chest pain, severe hypoxia and absence of purulent sputum. Studies featuring higher prevalence of PE excluded patients with infective symptoms and had higher rates of malignancy. The negative predictive value of D-dimer to exclude PE in AECOPD appears high(Gunen et al., 2010). A rational approach would be to consider investigation for PE when clinically suspected or when no inflammatory reaction is evident, particularly in the presence of risk factors such as malignancy or previous venous thrombosis.

Eosinophilic inflammation has been proposed as the cause of around a quarter of COPD exacerbations(Bafadhel et al., 2011). A sputum WCC of >3% predicts corticosteroid response in COPD(Brightling et al., 2005; Brightling et al., 2000). A blood eosinophil level of >2% total white cell count appears a fairly reliable surrogate marker for airway eosinophil count and predicts corticosteroid response(Bafadhel et al., 2011; Bafadhel et al., 2012). A review of the literature regarding blood eosinophils and COPD exacerbations is reported in the Introduction to Chapter 3.

F - Failure (cardiac)

Cardiac dysfunction is increasingly recognized as an important facet of AECOPD. Exacerbations may provoke acute cardiovascular events as rates of myocardial infarction and stroke are higher in the post exacerbation period(Donaldson, Hurst, Smith, Hubbard, & Wedzicha, 2010). A substantial subset of hospital AECOPD may be precipitated by acute cardiac dysfunction(Connors et al., 1996). Furthermore, increased levels of troponin and natriuretic peptides are frequently observed during AECOPD in the absence of clinically diagnosed cardiac dysfunction(Campo et al., 2015; Chang et al., 2011; Pavasini et al., 2015). Cardiac biomarker elevation appears more common in COPD patients with concomitant cardiac diagnoses(Patel et al., 2013). This suggests that AECOPD may impose significant strain upon the heart, particularly in those with underlying heart disease.

The clinical implications of raised cardiac biomarkers during AECOPD have not yet been elucidated but elevated measurements are associated with increased mortality and may identify a group who require specific cardiovascular therapies. A comprehensive review of cardiac dysfunction in AECOPD published in *Lancet Respiratory Medicine* is included at the end of this Chapter. A review of available imaging techniques to evaluate cardiac structure and function including their role in COPD is reported in the Introduction to Chapter 5. A study integrating cardiac biomarker analysis with functional cardiac imaging during AECOPD and following exacerbation recovery is reported in Chapter 5.

G – General environment

Ambient environmental triggers to acute exacerbation have been identified. Environmental pollution may trigger exacerbations and increasing concentrations of microparticulates (PM_{10}) have been associated with increased AECOPD hospitalizations(H. R. Anderson et al., 1997). Cold temperature can exacerbate symptoms and impair lung function in COPD(Donaldson, Seemungal, Jeffries, & Wedzicha, 1999). Indoor air pollution in the form of a second hand tobacco smoke exposure has also been identified as a possible contributor to exacerbation risk(Garcia-Aymerich et al., 2003). A broader environmental context must also be considered in hospitalized AECOPD. Many COPD patients are frail and elderly with

multi-morbidity(Lahousse et al., 2016; Vanfleteren et al., 2013) and may be dependent upon social and therapeutic support systems to cope in the community. Disruption or dysfunction in social support systems may prompt hospital admission but these are seldom considered and it has been difficult to quantify their importance.

X – Unknown

The explanation for day-to-day fluctuation in COPD symptoms is not yet understood. Exacerbations without an evident aetiological precipitant may reflect underlying COPD disease activity. Alternatively, the baseline functional condition of some patients may be so precarious that subtle perturbations will be sufficient to result in exacerbated symptoms followed by hospitalization. The group of patients with exacerbations of unidentifiable aetiology may be very important and can potentially be an informative group to study.

As per Monash University guidelines for thesis by publication the remainder of this chapter is presented as a PDF as it has been published.

Cardiac dysfunction during exacerbations of chronic obstructive pulmonary disease

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See Online for appendix

Chronic obstructive pulmonary disease (COPD) and cardiovascular disease often coexist, and acute cardiac events frequently occur during COPD exacerbations. Even when cardiac complications are not clinically apparent, biochemical evidence of cardiac dysfunction is often noted during exacerbations and portends poor prognosis. Diagnosis of cardiac disease in COPD can be difficult and necessitates a high degree of clinical suspicion. However, the additional strain of an exacerbation could be a pivotal moment, during which previously unsuspected cardiac dysfunction is exposed. In this Review, we present evidence about cardiac involvement in exacerbations of COPD, and discuss diagnostic challenges and treatment opportunities.

Introduction

Patients with chronic obstructive pulmonary disease (COPD) often have cardiovascular comorbidities.[1] Patients with cardiovascular complications tend to have more symptoms and higher mortality than do patients with COPD alone.[2] To distinguish symptoms of cardiac disease from those of COPD can be difficult, however, and cardiac disease is often unrecognised.[3,4] Exacerbations of COPD are characterised by symptomatic deterioration or increased use of health care; definitions do not ascribe cause, and primary cardiovascular instability precipitating acute deterioration in COPD symptoms is probably common.[3] At one extreme, decompensated cardiac failure could be mistaken for COPD exacerbation.[3,5] But even without clinical signs of cardiac involvement, biochemical evidence of cardiac dysfunction is often present.[6–19] Increased cardiac biomarkers during COPD exacerbations are associated with poor prognosis, but their wider implications are uncertain.[6,18,19] In this Review, we examine the evidence for cardiac dysfunction during exacerbations of COPD and provide diagnostic, prognostic, and therapeutic perspectives.

Key messages

- Diagnosed cardiac comorbidities are common in patients with chronic obstructive pulmonary disease (COPD) and are associated with worse outlook. Prevalence might be underestimated because of underdiagnosis.
- COPD exacerbations are often complicated by acute cardiac dysfunction, which can be difficult to recognise clinically.
- Biochemical evidence of myocardial stretch (B-type natriuretic peptides) and myocardial injury (troponins) is often noted in exacerbations of COPD and is associated with increased mortality.
- Results of observational studies suggest that cardiac treatments could improve outcomes from COPD exacerbations, but no prospective controlled trials have been done.
- Further research into the pathogenesis and treatment of acute cardiac dysfunction in COPD exacerbations is urgently needed.

Epidemiology

COPD can be an important comorbidity in patients with cardiovascular disease: it is identified in 7–16% of patients with acute myocardial infarction and up to 52% of patients with heart failure (appendix). The presence of COPD is associated with an increased risk of readmission to hospital and long-term mortality.[20] Patients with comorbid cardiac disease and COPD are less likely to be given β blockers for cardiac dysfunction or β agonists for airflow obstruction.[21,22]

About 20% of patients with COPD have a diagnosed cardiovascular comorbidity (appendix). Cardiovascular diagnoses are more common in those with severe airflow obstruction. Both airflow obstruction and low forced vital capacities are established cardiovascular risk factors,[23,24] and the results of population-based studies show at least a 30% higher risk of cardiovascular death in patients with impaired lung function, even after adjustment for age, smoking status, and traditional cardiovascular risk factors.[23–25] Accurate estimation of cardiovascular mortality in COPD is difficult, however, because death certificates can be unreliable. When cause of death is meticulously reviewed, cardiovascular disease (including cerebrovascular disease) seems to account for 25% of all-cause mortality.[26] Cardiac deaths outnumber respiratory deaths in mild and moderate COPD—only in advanced disease does respiratory failure predominate.[25] Comorbid heart failure in COPD is associated with a doubling of the mortality rate, poor quality of life, and low exercise tolerance.[27–29]

Cardiovascular disease can be detected in as many as 55% of patients admitted with exacerbations of COPD (table 1). Furthermore, around 20% of exacerbations of COPD could be due to acute decompensated heart failure and cardiac arrhythmias.[38] Comorbid cardiac failure, ischaemic heart disease, and arrhythmias have all been associated with reduced survival from exacerbations of COPD (table 1), and particularly with early inpatient mortality.[36,38,39] Retrospective studies have shown that 8–25% of patients with exacerbations of COPD have

	Study type	Population (n)	Key findings
Agabiti et al, 2010[30]	Retrospective cohort	Patients admitted to hospital (12 756)	Past history of IHD (15% of population; RR 1·3 [95% CI 1·1–1·5]), heart failure (10%; 1·7 [1·4–2·0]), and atrial fibrillation (11%; 1·2 [1·0–1·4]) predicted mortality at 30 days
Almagro et al, 2002[31]	Prospective cohort	Patients admitted to hospital (135)	Past history of heart failure (33% of population) predicted long-term (>2 years) mortality (OR 2·30 [95% CI 1·39–2·83])
Almagro et al, 2015[32]	Prospective cohort	Patients admitted to hospital (606)	Past history of IHD (21% of population; HR 1·29 [95% CI 1·04–1·61]), heart failure (33%; 2·31 [1·05–5·1]), and atrial fibrillation (21%; 2·8 [1·28–6·15]) predicted mortality at 3 months
Brekke et al, 2008[33]	Retrospective cohort	Patients admitted to hospital (897)	Past history of IHD (29% of population; HR 1·54 [95% CI 1·05–2·26]) and current atrial fibrillation (10%; 1·4 [1·03–1·9]) predicted mortality at 2 years, past history of heart failure (10%; 1·26 [0·91–1·75]) did not
Bustamante-Fermosel et al, 2007[34]	Retrospective cohort	Patients admitted to hospital (972)	Current heart failure (28% of population) predicted in-hospital mortality (RR 3·47 [95% CI 1·24–9·66])
Chang et al, 2011[35]	Prospective cohort	Patients admitted to hospital (250)	Past history of cardiac disease (30% of population) did not predict mortality at 30 days (OR 0·7 [95% CI 0·25–1·99])
Connors et al, 1996[5]	Prospective cohort	Patients admitted to hospital (1016)	Current heart failure (26% of population; HR 0·66 [95% CI 0·45–0·97]) predicted mortality at 6 months, past history of any cardiac disease did not (1·06 [0·74–1·5])
Dransfield et al, 2008[36]	Retrospective cohort	Patients admitted to hospital (825)	Past history of heart failure (28% of population) predicted in-hospital mortality (OR 4·54 [95% CI 1·53–13·5])
Escande et al, 2014[37]	Prospective cohort	Patients admitted to hospital (29)	Current heart failure (52% of population) predicted mortality at 5 years (HR 3·37 [95% CI 1·19–9·56])
Fruchter et al, 2009[37]	Retrospective cohort	Patients admitted to hospital (182)	Past history of IHD (43% of population) predicted mortality at 3 years (HR 2·34 [95% CI 1·38–3·95])
Fuso et al, 1995[38]	Retrospective cohort	Patients admitted to hospital (590)	Cardiac arrhythmia (19% of population; OR 1·91 [95% CI 1·10–3·31]) and current atrial fibrillation (8%; 2·27 [1·14–4·51]) predicted in-hospital mortality, past history of IHD (3%; 2·69 [0·91–7·97]) did not
Harrison et al, 2014[39]	Prospective cohort	Patients admitted to hospital (1343)	Past history of heart failure (proportion of participants with heart failure not reported) predicted in-hospital mortality (OR 1·75 [95% CI 1·06–2·91]) and mortality at 1 year (1·52 [1·11–21])
Hasegawa et al, 2014[40]	Retrospective cohort	Patients admitted to hospital (177 207)	Past history of heart failure (18% of population) predicted in-hospital mortality (OR 1·31 [95% CI 1·23–1·40])
Incalzi et al, 1997[41]	Prospective cohort	Patients admitted to hospital (270)	Current IHD (6% of population; HR 1·42 [95% CI 1·02–1·96]) predicted mortality at 5 years, past history of IHD (4%; 1·05 [0·54–2·05]) did not
Lainscak et al, 2011[42]	Retrospective cohort	Patients admitted to hospital (968)	Past history of heart failure (27% of population) predicted mortality at 4 years (HR 1·72 [95% CI 1·39–2·14])
Lindenauer et al, 2013[43]	Retrospective cohort	Patients admitted to hospital (150 035)	Past history of heart failure (42% of population; OR 1·34 [95% CI 1·28–1·39]) and atrial fibrillation (37%; 1·17 [1·12–1·22]) predicted mortality at 30 days; past history of IHD (50%; 0·87 [0·83–0·90]) did not
Marcun et al, 2012[44]	Prospective cohort	Patients admitted to hospital (127)	Current heart failure (55% of population) did not predict mortality at 6 months (HR 0·97 [95% CI 0·23–3·97])
McGhan et al, 2007[45]	Retrospective cohort	Patients admitted to hospital (51353)	Past history of heart failure (20% of population) predicted mortality at 5 years (HR 1·36 [95% CI 1·32–1·40])
Raurich et al, 2004[46]	Retrospective cohort	Patients admitted to intensive-care unit (101)	Past history of IHD (16% of population; RR 1·0 [95% CI 0·4–2·4]) and heart failure (15%; 1·7 [0·8–3·6]) did not predict in-hospital mortality
Roberts et al, 2011[47]	Retrospective cohort	Patients admitted to hospital (9201)	History of atrial fibrillation (10% of population) predicted in-hospital mortality (RR 1·31 [95% CI 1·05–1·62]) and mortality at 3 months (1·35 [1·17–1·55]), past history of heart failure (7%) predicted mortality at 3 months (1·61 [1·37–1·89]). Past history of IHD (25%) did not predict in-hospital mortality (0·98 [0·83–1·16]) or mortality at 3 months (0·96 [0·85–1·08])
Slenter et al, 2013[48]	Retrospective cohort	Patients admitted to hospital (260)	Past history of heart failure (22% of population) predicted mortality at 1 year (HR 1·75 [95% CI 1·03–2·97])
Soyseth et al, 2007[49]	Retrospective cohort	Patients admitted to hospital (854)	Past history of IHD (29% of population; 1·3 [95% CI 1·0–1·7]), heart failure (20%; 1·6 [1·2–2·2]), and atrial fibrillation (20%; 1·6 [1·2–2·1]) predicted mortality at 2 years
Steer et al, 2012[50]	Prospective cohort	Patients admitted to hospital (920)	Current atrial fibrillation (13% of population) predicted in-hospital mortality (OR 2·66 [95% CI 1·39–5·09])
Stiell et al, 2014[51]	Prospective cohort	Patients admitted to hospital (945)	Neither past history of IHD (11% of population; OR 2·03 [95% CI 0·84–4·92]), current IHD (1%; 3·25 [0·95–11·04]), nor current heart failure (10%; 1·88 [0·94–3·78]) predicted mortality at 30 days
Tabak et al, 2013[52]	Retrospective cohort	Patients admitted to hospital (102 626)	Past history of heart failure (28% of population) predicted in-hospital mortality (OR 1·46 [95% CI 1·33–1·61])
Terzano et al, 2010[53]	Prospective cohort	Patients admitted to hospital (288)	Past history of IHD (16% of population) predicted mortality at 7 years (HR 3·43 [95% CI 1·02–11·55])
Wildman et al, 2009[54]	Prospective cohort	Patients admitted to intensive-care unit (832*)	Current atrial fibrillation (12% of population) did not predict mortality at 6 months (OR 1·58 [95% CI 0·98–2·54])

IHD=ischaemic heart disease. RR=risk ratio. OR=odds ratio. HR=hazard ratio. *Of these 832 patients, 752 had exacerbations of chronic obstructive pulmonary disease, and 80 had asthma exacerbations.

***Table 1*: Studies of prevalence of cardiac disease and association with mortality in exacerbations of chronic obstructive pulmonary disease**

abnormal cardiac troponin concentrations and electrocardiograms, fulfilling diagnostic criteria for acute coronary syndromes.[4,7] Only a small proportion of these events are recognised in routine clinical practice.[4,8]

Evidence for cardiac dysfunction in exacerbations

Cardiac muscle injury

Biochemical evidence of cardiac injury during COPD exacerbations is common (table 2) and predicts both short-term and long-term mortality.[6] Troponins are globular protein complexes bound to the actin filaments of myocytes that regulate contraction of skeletal and cardiac muscle. These proteins are released into the peripheral blood from cardiomyocytes after myocardial injury. Troponin measurements are mainly used to diagnose acute myocardial infarction, but, although they are specific for myocardial necrosis, they are not specific for ischaemic injury because cardiac troponins can also be raised in heart failure, renal dysfunction, pulmonary embolism, pulmonary hypertension, tachyarrhythmias, and sepsis. Although increased cardiac troponin concentrations in these disorders do not necessarily suggest an acute coronary syndrome, they are nonetheless consistently associated with poor prognosis.[70]

In patients with stable COPD, baseline concentrations of high-sensitivity cardiac troponins tend to be higher than those in matched controls who do not have COPD, albeit within normal limits.[71] During exacerbations, high-sensitivity measurements show circulating cardiac troponin concentrations higher than the upper limit of normal in most cases, particularly in patients with known ischaemic heart disease.[6,9,10]

Although patients with clinically apparent acute cardiac disease have been excluded from previous investigations of raised cardiac troponin concentrations during COPD exacerbations,[6,7,9,10] the nature of cardiac injury in this setting was not assessed beyond basic clinical examination, electrocardiography, and chest radiographs—all of which have poor sensitivity for characterisation of cardiac disease in this setting. Thus, what troponin release during an exacerbation of COPD represents at a pathophysiological level remains unclear. Some evidence shows that the mortality associated with increased troponin concentrations in patients with COPD exacerbations might be linked to tachycardia.[10] Underlying left ventricular hypertrophy is also common in patients with COPD and could contribute to troponin increases in this setting.[72] Cardiac dysfunction during COPD exacerbations could also be caused by acute pulmonary hypertension and right ventricular dysfunction (raised troponin concentrations also occur in pulmonary hypertension caused by pulmonary embolism and predict adverse outcomes).[73]

Cardiac strain or stretch

B-type natriuretic peptides (BNPs) are secreted from ventricular cardiomyocytes in response to cardiac wall stretch as a result of either volume or pressure overload under sympathetic drive.[74] BNPs downregulate the sympathetic nervous system and the renin–angiotensin–aldosterone system, enable natriuresis, decrease peripheral vascular resistance, increase smooth-muscle relaxation, stimulate myocardial relaxation, and inhibit cardiac remodelling.[74] Assays for detection of physiologically active BNP and the metabolically inactive cleavage by-product, amino-terminal pro-BNP (NT-proBNP), are valuable in the diagnosis of heart failure and correlate with impaired left ventricular function detected by echocardiography.[74] However, mild-to-moderate increases also occur in situations other than clinical heart failure: BNP concentrations rise with age, and can be increased in renal impairment, hyperdynamic states including sepsis, and pulmonary hypertension.[74] Raised BNP concentrations are also noted in patients after acute myocardial infarction without symptoms of heart failure, when they are associated with an adverse short-term outlook.[75] High concentrations of BNPs predict an increased risk of cardiovascular events and death in asymptomatic people without heart failure, even after adjustment for other cardiovascular risk factors.[76] Serum BNP and NT-proBNP concentrations are often raised during exacerbations of COPD (table 2) and predict poor short-term and long-term prognosis.[18,19,35,44]

Taken together, evidence shows that cardiovascular diseases are common in stable COPD and that exacerbations of COPD are associated with an increased risk of both overt and subclinical acute cardiac dysfunction, both of which are associated with increased mortality. After acute exacerbations of COPD, the short-term (30 day), and, to some extent, long-term mortality of patients with high concentrations of BNPs and cardiac troponins are much higher than are those of patients with normal BNP and cardiac troponin concentrations, even after adjustment for exacerbation severity.[35,44] Furthermore, NT-proBNP and cardiac troponins are better indicators of short-term prognosis in COPD than are widely used clinical prognostic instruments, such as the confusion, urea, respiratory rate, blood pressure, and age older than 65 years (CURB-65) and elevated blood urea nitrogen, altered mental status, pulse greater than 109 beats per minute, and age older than 65 years (BAP-65) scores.[35] The dyspnoea, eosinopenia, consolidation, acidaemia, and atrial fibrillation (DECAF) score, which includes a cardiac parameter (ie, atrial fibrillation), might be more accurate than CURB-65 or BAP-65.[50]

Cardiac biomarkers could help to phenotype exacerbations of COPD to improve stratification of prognosis. They could also help to identify the cause of the exacerbation, but not enough is known about the mechanisms of cardiac dysfunction in COPD exacerbations to provide definitive guidelines for diagnosis and management.

	Study design	Study population (n)	Biomarkers	Key findings
Abroug et al, 2006[11]	Cross-sectional	Patients admitted to intensive-care unit (148)	NT-proBNP, troponin T	High NT-proBNP and troponin T concentrations were significantly associated with left ventricular dysfunction (p<0·0001)
Baillard et al, 2003[55]	Prospective cohort	Patients admitted to intensive-care unit (71)	Troponin I	High troponin I concentrations (>0·5 μg/L) were noted in 18% of population and associated with increased risk of in-hospital mortality (OR 6·52 [95% CI 1·23–34·47])
Brekke et al, 2008[33]	Retrospective cohort	Patients admitted to hospital (396)	Troponin I	High troponin I concentrations (≥0·04 μg/L) were associated with increased risk of all-cause mortality (HR 1·64 [95% CI 1·15–2·34])
Brekke et al, 2009[56]	Cross-sectional	Patients admitted to hospital (441)	Troponin T	High troponin T concentrations (>0·04 μg/L) were noted in 27% of population; independent determinants of increased concentrations were high neutrophil count, creatinine, heart rate, cardiac infarction injury score, and low haemoglobin concentrations
Campo et al, 2015[57]	Prospective cohort	Patients admitted to hospital (694)	Troponin T	High troponin T concentrations were noted in 70% of patients and associated with increased risk of cardiac mortality and non-fatal myocardial infarction (composite HR 1·73 [95% CI 1·2–2·7])
Chang et al, 2011[35]	Prospective cohort	Patients admitted to hospital (250)	NT-proBNP, troponin T	High NT-proBNP (>1864 ng/L; OR 9·0 [95% CI 3·1–26·2]) and troponin T (>0·03 μg/L; 6·3 [2·4–16·5]) concentrations were associated with increased risk of 30 day mortality
Fruchter et al, 2009[37]	Retrospective cohort	Patients admitted to hospital (182)	Troponin I	High troponin I concentrations (>0·03 μg/L) were noted in 59% of population and associated with increased risk of 3 year mortality (HR 1·32 [95% CI 1·08–2·25])
Gale et al, 2011[58]	Prospective cohort	Patients admitted to hospital (140)	NT-proBNP	The highest quartile NT-proBNP concentrations (>298 ng/L) were associated with increased risk of 1 year mortality (RR 3·02, p=0·001)
Gariani et al, 2011[15]	Cross-sectional	Patients admitted to hospital (57)	BNP	Increased BNP (>100 ng/L) in 81% of population, which had sensitivity of 92% and negative predictive value of 91% to detect left ventricular systolic failure and sensitivity of 93% and negative predictive value of 91% to detect left ventricular diastolic failure
Harvey et al, 2004[8]	Retrospective case series	Patients admitted to hospital (188)	Troponin I, troponin T	High troponins (>0·4 μg/L for troponin I or >0·03 μg/L for troponin T) in 25% of population, which were associated with longer hospital stays (5 days *vs* 3 days, p=0·001)
Hoiseth et al, 2011[59]	Prospective cohort	Patients admitted to hospital (99)	High-sensitivity troponin T	High troponin T concentrations (≥0·014 μg/L) were associated with increased long-term mortality (HRs 4·5 [95% CI 1·2–16·0] for troponin T 0·014–0·0399 μg/L and 8·9 [2·4–32·0] for troponin T ≥0·04 μg/L)
Hoiseth et al, 2012[10]	Cross-sectional	Patients admitted to hospital (99)	High-sensitivity troponin T	High troponin T concentrations were associated with older age, arterial hypertension, tachycardia, and increased serum creatinine (all p values <0·05)
Hoiseth et al, 2012[18]	Prospective cohort	Patients admitted to hospital (99)	NT-proBNP	Highest tertile NT-proBNP concentrations (≥909 ng/L) were noted in 74% of population and were associated with increased risk of long-term mortality (HR 3·2 [95% CI 1·3–8·1])
Hoiseth et al, 2014[60]	Prospective cohort	Patients admitted to hospital (83)	High-sensitivity troponin T, NT-proBNP	Stable increased troponin concentrations were associated with higher mortality (HR 2·4 [95% CI 1·1–5·3]), as were NT-proBNP concentrations >1181 ng/L (5·6 [1·8–17·0])
Inoue et al, 2009[61]	Prospective cohort	Patients with stable COPD admitted to hospital (60)	BNP	BNP concentration was higher during exacerbations of COPD than in stable disease (p=0·004) and correlated with left ventricular ejection fraction (r=–0·41, p=0·0197)
Kanat et al, 2007[62]	Randomised controlled trial	Patients with stable COPD admitted to hospital (45)	BNP	BNP concentrations were higher during exacerbations of COPD than in stable disease (p=0·0001) and significantly decreased from day 1 to day 10 of exacerbation (p<0·05); the decrease was more substantial with diuretic treatment and was independent of right ventricular dysfunction
Kelly et al, 2013[63]	Retrospective cohort	Patients admitted to hospital (252)	Troponin I	High troponin I concentrations (>0·04 μg/L, in 31 % of population) were associated with increased risk of in-hospital mortality (OR 8·3 [95% CI 1·58–43·70])
Marcun et al, 2012[44]	Prospective cohort	Patients admitted to hospital (127)	NT-proBNP, troponin T	High NT-proBNP concentrations (>95th percentile) were noted in 60% of population and predicted 6 month mortality (HR 4·2 [95% CI 1·07–14·01]), high discharge troponin T concentrations (>0·012 μg/L) were noted in 19% of population and predicted future admission to hospital (2·89 [1·13–7·36])
Martins et al, 2009[64]	Retrospective cohort	Patients admitted to hospital (173)	BNP, troponin I	High troponin I concentrations (>0·012 μg/L) in 70% of patients, which were associated with increased use of non-invasive ventilation and long-term mortality (p<0·01); high BNP concentrations (>100 ng/L) were noted in 76% of population
McAllister et al, 2012[7]	Case series	Patients admitted to hospital (242)	Troponin I, troponin T	High troponin concentrations (>99th percentile) in 10% of population
McCullough et al, 2003[65]	Cross-sectional	Emergency presentation (417*)	BNP	High BNP concentration (>100 ng/L, in 37 % of population) was the strongest predictor of heart failure (OR 12·1 [95% CI 5·4–27·0])
Medina et al, 2011[19]	Prospective cohort	Patients admitted to hospital (192*)	NT-proBNP	High NT-proBNP concentrations (>588 ng/L) were noted in 44% of population and predicted 1 year mortality (OR 3·9 [95% CI 1·46–10·47])
Nishimura et al, 2014[16]	Prospective cohort	Patients with stable COPD admitted to hospital (251)	BNP	BNP concentrations were higher during exacerbations of COPD than in stable disease, and higher during exacerbation than before and after exacerbation (all p values <0·001)
Ouanes et al, 2012[12]	Cross-sectional	Patients admitted to intensive-care unit (120)	NT-proBNP	Left ventricular dysfunction was noted in 48% of patients; high NT-proBNP concentrations were associated with left ventricular dysfunction (p<0·0001)
Patel et al, 2013[13]	Prospective cohort	Patients with COPD exacerbations in the community (98)	NT-proBNP, troponin T	NT-proBNP and troponin T concentrations were higher during the exacerbation than during stable disease, higher in patients with known ischaemic heart disease, and persistently increased more than 5 weeks after exacerbation (all p values <0·01)

(Table 2 continues on next page)

	Study design	Study population (n)	Biomarkers	Key findings
(Continued from previous page)				
Pavasini et al, 2015[6]	Systematic review and meta-analysis	Patients admitted to hospital (2062)	High-sensitivity troponin T, troponin I, troponin T	High troponin concentrations (high troponin T in 17–74% of the population and high troponin I in 18–70%) were associated with increased risk of all-cause mortality (OR 1·69 [95% CI 1·25–2·29]), mortality within 6 months (3·22 [1·31–7·91]), and mortality after more than 6 months (1·38 [1·02–1·86])
Sanchez-Marteles et al, 2009[66]	Case series	Patients admitted to hospital (99)	NT-proBNP	NT-proBNP concentrations were higher in patients older than 65 years and in patients with atrial fibrillation (p values <0·01)
Sanchez-Marteles et al, 2010[67]	Prospective cohort	Patients admitted to hospital (192)	NT-proBNP	High NT-proBNP concentrations (>500 ng/L) were noted in 53% of population and associated with increased risk of mortality at 6 months (OR 11·0 [95% CI 1·39–86·99)
Soyseth et al, 2013[9]	Cross-sectional	Patients with stable COPD admitted to hospital (174)	High-sensitivity troponin T	Troponin T concentrations were four-times higher during exacerbations than during stable disease (relative change 4·26 [95% CI 3·02–6·00)
Stiell et al, 2014[51]	Prospective cohort	Emergency presentation (945)	NT-proBNP, troponin T, troponin I	High NT-proBNP (>5000 ng/L) concentrations in 11% of patients and raised troponins (>99th percentile) in 13%; no significant difference in NT-proBNP (p=0·5) and troponin (p=0·9) concentrations between patients with and without serious adverse events
Stolz et al, 2008[14]	Prospective cohort	Emergency department presentations and recovery (208)	BNP	BNP concentrations were higher during exacerbation than during recovery (p<0·001); increased BNP concentrations were associated with admission to the intensive-care unit (HR 1·13 [95% CI 1·03–1·24] for an increase of 100 ng/L), but not associated with in-hospital, 6 month, or 2 year mortality
Yang et al, 2010[68]	Randomised controlled trial	Patients admitted to intensive-care unit (56)	BNP	Invasive ventilation reduced BNP concentrations more efficaciously after 24 hours' treatment than did non-invasive ventilation (p<0·05)
Youssef et al, 2013[69]	Cross-sectional	Patients admitted to hospital (60)	Troponin I	High troponin I concentrations (≥0·01 µg/L) were noted in 70% of population and associated with severity of exacerbations, right ventricular dysfunction, weaning failure from mechanical ventilation, and increased risk of in-hospital mortality (all p values <0·05)

COPD=chronic obstructive pulmonary disease. BNP=B-type natriuretic peptide. NT-proBNP=amino-terminal pro B-type natriuretic peptide. OR=odds ratio. RR=risk ratio. HR=hazard ratio. *Included patients with chronic asthma.

***Table 2*: Studies of cardiac biomarkers in exacerbations of COPD**

Possible mechanisms of cardiac dysfunction

Several mechanisms could plausibly be implicated in provoking cardiac distress during COPD exacerbation (figure 1). Respiratory infections increase the risk of vascular events and are the most common precipitant of exacerbation.[77] In a large prospective cohort of 20 101 exacerbations of COPD resulting in hospital admission (in which antibiotic prescription was a criterion to define exacerbation), myocardial infarction and stroke risk within the early period after admission were more than double the baseline risk.[78] Cardiac troponin and BNP concentrations are also increased in community-acquired pneumonia, suggesting an increased risk of acute cardiac dysfunction during acute respiratory infections.[79]

Hypoxaemia and tachycardia associated with a COPD exacerbation can lead to adverse cardiac effects, especially in patients with pre-existing coronary disease or left ventricular dysfunction. Infective COPD exacerbations also provoke acute increases in arterial stiffness (as assessed by aortic pulse wave velocity),[13] which then increases left ventricular afterload.

COPD is associated with systemic inflammation, which is increased during acute exacerbations. Plasma fibrinogen concentrations are associated with risk of COPD exacerbations and adverse outcomes.[80] Platelet activation is present in stable COPD and increases during exacerbations.[81] Concentrations of other pro-atherothrombotic biomarkers, such as interleukins 6 and 8 and tumour necrosis factor α, and prothrombin fragments are also raised during exacerbations. These findings suggest that exacerbations of COPD lead to systemic inflammation, hypercoagulability, increased platelet activation, and oxidative stress. These factors can cause endothelial dysfunction and precipitate atherosclerotic plaque rupture and thrombosis.[82]

Emphysema in stable patients is associated with reduced left ventricular filling and diastolic dysfunction on echocardiography.[83] Cardiac MRI studies show reduced biventricular filling and blood volumes in severe and even mild emphysema, which are thought to be secondary to lung hyperinflation raising intrathoracic pressures and impeding venous return.[84] High intrathoracic pressures generated by dynamic hyperinflation in acute exacerbations of COPD would be expected to further impede venous return.

β_2 agonists are part of standard treatment for COPD exacerbations, but have been associated with adverse cardiovascular effects.[85] In comorbid cardiorespiratory disease, increasing doses of β_2 agonists have been associated with an increase in admissions to hospital associated with heart failure and increased all-cause mortality.[86] Thus high doses of β_2 agonists given during acute severe COPD exacerbations could plausibly contribute to cardiac stress. β-agonist-induced cardiac

toxic effects in the setting of hypoxia were thought to be a possible cause of asthma deaths;[87] patients with COPD have a greater risk than do those with asthma because they are generally older, more hypoxaemic, and are more likely to have pre-existing cardiac comorbidities. Although β_2 agonists are thought to be safe at standard doses in stable COPD, the safety of the very high doses that are often used in COPD exacerbations has not been established in clinical trials. It is noteworthy that high-dose β_2-agonist therapy has been linked to cardiovascular mortality in COPD exacerbations[88] and that COPD exacerbations and overuse of β_2 agonists are increasingly recognised as a cause of stress cardiomyopathy.[89,90]

COPD exacerbations are associated with acute increases in pulmonary artery pressure,[91] and cardiac biomarker derangement might be a result of acute right heart strain. Acute right heart strain can also be associated with left ventricular dysfunction: raised pulmonary pressures in patients with stable COPD are associated with left ventricular diastolic dysfunction on echocardiograms,[92] and poor right heart function is usually associated with impaired left heart function in patients with COPD.[93]

COPD is associated with persistent autonomic dysfunction that is amplified during acute exacerbations. The physiological mechanism is not entirely understood, but includes blunted sensory and stretch receptor responses, arterial chemoreceptor upregulation due to hypoxaemia and hypercapnia, arterial and cardiac baroreceptor changes as a result of large fluctuations of intrathoracic pressure, neurohormonal activation secondary to systemic inflammation and the effect of exogenous β sympathomimetics. Taken together, these physiological processes result in increased sympathetic tone, loss of parasympathetic tone, reduced autonomic reflexes, and altered baroreceptor sensitivity, all of which are associated with adverse cardiac events.[94]

Determining how all these different mechanisms contribute to cardiac dysfunction in COPD exacerbations is a key challenge for research.

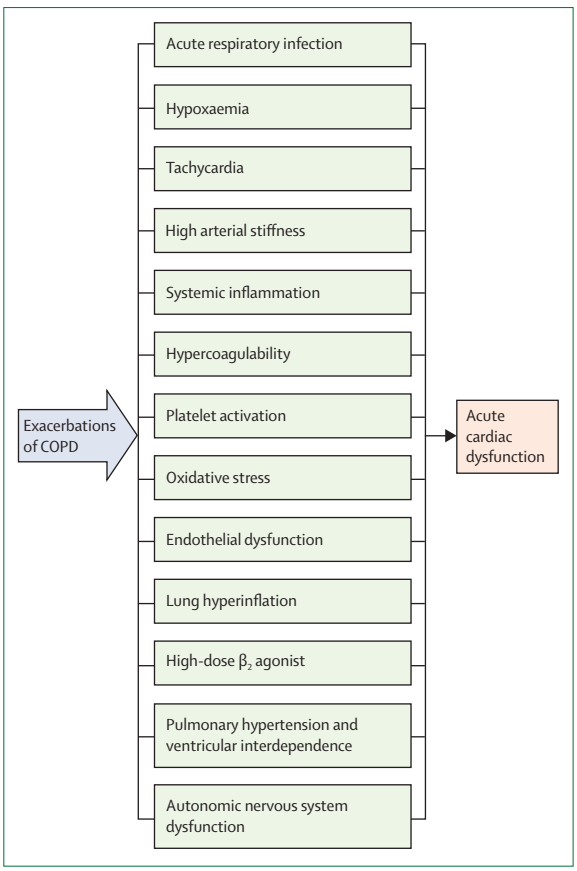

***Figure 1*: Potential factors contributing to acute cardiac dysfunction in exacerbations of COPD**
COPD=chronic obstructive pulmonary disease.

Recognition of cardiac dysfunction

Diagnosis of cardiac disease in COPD is difficult (figure 2). Electrocardiographic abnormalities are common in COPD exacerbations but under-recognised in clinical practice.[4,7] Additionally, recognition of an acute coronary syndrome is challenging because the traditional complex of chest pain, electrocardiographic changes, and increased troponin concentrations might be unreliable during an exacerbation of COPD. Many patients have electrocardiographic changes in the absence of acute cardiac injury,[7] chest discomfort associated with COPD exacerbation can be difficult to distinguish from cardiac pain, and troponins are frequently increased without other evidence of myocardial infarction.[6–8,10]

Assessment of the cardiothoracic ratio and interstitial oedema by chest radiography is obscured in patients with emphysema.[95] Transthoracic echocardiography is the most frequently used technique to assess cardiac failure. It is non-invasive and does not expose patients to radiation, but is associated with interobserver variability, necessitates assumptions about cardiac morphology and—pertinent to patients with COPD—works poorly in patients with emphysema because of impairment of the acoustic window.[12,16] Cardiac MRI is currently thought to be the gold standard for assessment of cardiac function (particularly the right ventricle).[96] However, the cost, duration, and claustrophobic nature of an MRI scanner are impractical for patients with an exacerbation of COPD.

Hence, as a result of the limitations of available techniques, the relative contributions of acute coronary disease and left ventricular or right ventricular pathological changes to the biomarker derangements and associated mortality noted in COPD exacerbations are difficult to distinguish. Dynamic cardiac CT is an emerging technique that can be used to assess biventricular function, pulmonary artery anatomy, coronary artery calcification, and pulmonary structure, and might inform future research and clinical

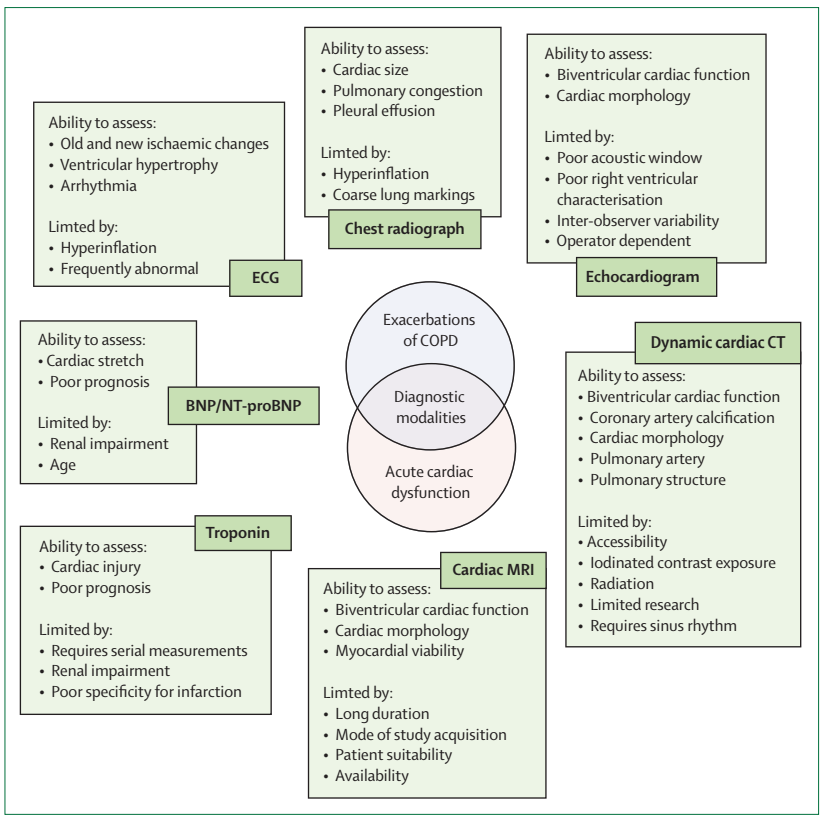

***Figure 2*: Advantages and limitations of diagnostic modalities of acute cardiac dysfunction in exacerbations of COPD**

COPD=chronic obstructive pulmonary disease. BNP=B-type natriuretic peptide. NT-proBNP=amino-terminal pro B-type natriuretic peptide. ECG=electrocardiography.

assessment of cardiac dysfunction in patients with COPD.

Treating cardiac disease in COPD exacerbations

Almost no evidence from clinical trials is available as a basis for management of cardiovascular disease during COPD exacerbations. In view of the prevalence and adverse consequences, cardiac involvement is an important topic for future research. Few existing COPD treatments reduce mortality from exacerbations and treatment of cardiovascular comorbidities could possibly have a greater effect on overall mortality than do specific respiratory treatments.

A particularly urgent question is whether cardioselective β blockers should routinely be used in patients with COPD. β blockers are an important component of the management of both ischaemic heart disease and heart failure, but have often been avoided in patients with airways disease for fear of inducing bronchospasm. Patients with COPD were excluded from the major randomised controlled trials[97] that showed the substantial mortality benefit associated with β blockers in heart failure. Short-term clinical trials suggest that patients with stable COPD can tolerate cardioselective β blockers,[98,99] but no long-term clinical trial evidence of the benefits and harms is available.

Despite the absence of evidence, there are good reasons to suspect that β blockers might have cardiovascular benefits in exacerbations of COPD. Patients with COPD often have high resting heart rates and sympathetic dominance of cardiac autonomic modulation,[100] which will be accentuated during exacerbations. In apparently healthy populations and those with known cardiac disease, resting heart rate is an independent risk factor for all-cause mortality.[101] The results of observational studies have shown that cardioselective β blockers are associated with lower mortality in stable COPD.[102] β blockers have also been associated with reduced exacerbation rates.[103] Furthermore, retrospective observational studies suggest that mortality is lower in patients who are taking β blockers at the time of an exacerbation than in those who are not,[36] but no prospective controlled trials have been done. Many considerations would have to be taken into account in an appropriate study. Use of a highly cardioselective β blocker in patients who depend on β_2-agonist bronchodilators seems logical. Identification of the target population at high cardiovascular risk could be based on predictive risk-scoring algorithms,[104] simple clinical markers such as tachycardia, serum cardiac biomarkers, or imaging (eg, coronary artery calcium scoring), depending on the balance between cost, accessibility, and precision.

Other perhaps less controversial options for treating cardiac disease in COPD exacerbations also need to be investigated. Ivabradine lowers the heart rate by specifically blocking the sinoatrial node, and could be an alternative to β blockers for patients in sinus rhythm.[105] Thrombocytosis has been associated with increased mortality from COPD exacerbations and patients taking antiplatelet drugs at the time of an exacerbation had lower 1 year mortality in an observational study.[39] Although in a 2014 randomised controlled trial, statins did not prevent COPD exacerbations,[106] the study was not designed or powered to assess cardiac outcomes and patients at high cardiovascular risk were excluded. Results of retrospective studies[107,108] suggest that mortality might be lower in patients with COPD who are taking statins than in those who are not. The results of observational studies[107,108] also suggest that angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers could reduce mortality in stable COPD and during exacerbations of disease, but these drugs have also not been assessed in clinical trials.

Many cardiac therapies have proven efficacy for primary indications in selected groups of patients. However, patients with COPD tend to be excluded from clinical trials of cardiac treatments (most notably trials of β blockers[109–111]). Although patients with COPD have a high risk of cardiac events and deaths, they might also

Search strategy and selection criteria

We searched PubMed with the terms "chronic obstructive pulmonary disease" or "COPD", "exacerbation", "cardiac failure" or "heart failure", "myocardial infarction", "troponin", and "BNP" or "NT-proBNP" for original research and reviews published in any language on or before Sept 1, 2015. We did not do a systematic review, and used the most relevant results. Further studies were identified from the reference lists of reviewed papers. For foreign language studies, translations were used.

be prone to increased adverse effects from cardiac treatments and the balance of risks and benefits of these treatments, even in stable disease, remains unclear. Future studies of cardiovascular treatments should include patients with COPD to determine whether both stable patients and those with disease exacerbations would benefit from cardiac treatment. However, we identified no ongoing clinical trials of cardiac treatment during COPD exacerbations on ClinicalTrials.gov or the Australian New Zealand Clinical Trials Registry when we used the search terms "chronic obstructive pulmonary disease" or "COPD", "cardiac treatment", "beta-blocker", and "statin". A feasibility study of β blockers in COPD exacerbations (ACTRN12614001095651) has been done and a randomised controlled trial of metoprolol for prevention of exacerbation (NCT02587351) has not yet commenced recruitment.

Conclusions

Accumulating evidence suggests that cardiac dysfunction during exacerbations of COPD is common and portends poor prognosis. The emphasis for treatment has been placed on optimisation of therapies for COPD itself—scant attention has been paid to the management of cardiovascular complications. However, convincing evidence suggests that a pulmonary exacerbation is often associated with cardiac exacerbations, but this co-occurrence is often not suspected and can be difficult to detect clinically with the current approach to assessment of patients with COPD exacerbations.

Few respiratory treatments substantially affect mortality from COPD exacerbations. Identification of cardiac dysfunction during exacerbations represents an opportunity to treat the primary, non-respiratory cause of mortality in COPD. Treating the heart could also have a greater effect on outcomes than treatment solely directed at the airways. Although there is tantalising evidence that active management of cardiac disease with β blockers, statins, and antiplatelet drugs could be beneficial, no randomised controlled trials have been done and none seem to be underway. There is an urgent need to understand cardiac dysfunction in COPD exacerbations and establish whether cardiac treatments improve outcomes.

Contributors

MIM and ES are the first authors. MIM, ES, CLC, PGB, and RJH conceived and designed the review, and contributed to data acquisition and critical analysis of published work. MIM and ES wrote the first draft. All authors contributed to critical revision of the report for important intellectual content and approved the final version to be published.

Declaration of interests

RJH has received lecture fees from Novartis and Glaxo Wellcome, lecture and advisory board fees from AstraZeneca, and non-financial support (ie, workshop attendance) from Boehringer, all of which were unrelated to this work . All other authors declare no competing interests.

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CHAPTER 2

CLINICAL PHENOTYPING OF COPD EXACERBATIONS BY UNDERLYING AETIOLOGY

2.1 DECLARATION 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	**Contribution**
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

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**	**Contribution** **(student co-authors only)**
Dr C Osadnik	Aided in data analysis.	
Ms E Leahy	Aided in data collection.	
Ms L Bulfin	Aided in data collection.	
Ms A Tran	Aided in data collection.	
A/Prof. K Hamza	Aided in data analysis.	
Dr PT King	Aided in hypothesis generation, data analysis and manuscript preparation.	
Prof PG Bardin	Aided in hypothesis generation, data analysis and manuscript preparation.	

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**

2.2 INTRODUCTION TO CHAPTER

The current consensus definition of an acute exacerbation of COPD (AECOPD) is an acute worsening of respiratory symptoms requiring an increase in therapy(Vogelmeier et al., 2017). AECOPDs are associated with accelerated lung function decline(Kanner et al., 2001), reduced quality of life(Wedzicha et al., 2012), mortality(Soler-Cataluna et al., 2005) and substantial healthcare costs(Sullivan et al., 2000). Susceptibility to exacerbations increases with worsening disease severity(Sullivan et al., 2000), however, some individuals appear to be particularly susceptible to exacerbations(Hurst et al., 2010).

In clinical practice no specific symptom threshold defines an exacerbation and in medication trials, AECOPD are often defined by hospitalization or courses of antibiotics or oral corticosteroids(Erdal et al., 2016). Both the symptom-based and healthcare utilization-based definitions are nonspecific and do not identify the cause of the exacerbation. Hospitalized AECOPD can be precipitated by diverse aetiological triggers(Wedzicha, 2015) and while clinicians often try to identify the cause(s) of AECOPD, there is no recognized methodology to establish this distinction. The difficulty in accurately discriminating between exacerbation aetiologies or exacerbation “phenotypes” is a challenge to the field. It is logical to expect that improved understanding of exacerbation aetiology could enhance patient care and limited evidence to date supports this hypothesis. Currently however, exacerbations of COPD are generally reported as undifferentiated events, implying an assumption of equivalence. This may obscure the impact of therapies that target distinct exacerbation mechanisms (e.g. antibiotics in bacterial AECOPD). In part this reflects clinicians’ difficulty in confidently ascribing a specific aetiology in AECOPD.

While much is known about the impact of exacerbations generally, there has been little attention given to any differential impact of exacerbations resulting from distinct aetiologies(Kherad, Bridevaux, Kaiser, Janssens, & Rutschmann, 2014). In clinical practice, exacerbations are often broadly defined as infective or non-infective. A prospective study using detailed paired sputum and serum biomarker analysis in community exacerbations identified 4 key exacerbation phenotypes - viral, bacterial, eosinophilic and pauci-inflammatory(Bafadhel et al., 2011). Whilst such rigorous

methodology would not be feasible to replicate in routine practice, some simple markers can predict exacerbation aetiology with direct implications for treatment. Purulent sputum at exacerbation is associated with increased bacterial load and predicts response to antibiotic therapy(Stockley et al., 2000). Distinctions within 'infective' exacerbations - viral, bacterial or dual (co-infection) - may carry further therapeutic and prognostic relevance. Viral exacerbations have been associated with longer duration and poor recovery (Aaron et al., 2012; Donaldson et al., 2015) although these studies assessed viral status by symptoms rather than molecular detection. Co-infection has been associated with an increased inflammatory response, greater lung function impairment and prolonged hospitalization(Papi et al., 2006; Wilkinson et al., 2006). The implications for clinicians of distinguishing viral and bacterial aetiologies are unclear however, as primary viral infection is frequently followed by bacterial infection in AECOPD(Mallia et al., 2012).

Even when meticulous virological and microbiological assessment is performed, up to 30% of exacerbations appear to have a non-infective aetiology. Non-infective exacerbations are poorly understood and have been subject to far less research than infective exacerbations. Whilst some may simply represent infection that has eluded detection, processes other than infection may be responsible. Inflammation of non-infective origin is one possibility. A study using detailed blood and sputum analyses attributed 28% of community exacerbations to "eosinophilic" inflammation(Bafadhel et al., 2011) although the blood eosinophil counts in these "eosinophilic" exacerbations were generally within the normal population reference range. Amongst those patients with relatively higher blood eosinophil counts, infectious agents were not identified and typical sputum and blood markers of infection including C-reactive protein (CRP) were low(Bafadhel et al., 2011). A further study by the same researchers identified oral corticosteroid benefit in community AECOPD only in the higher eosinophil group(Bafadhel et al., 2012).

Another alternative is that "exacerbations of COPD" may result from destabilization of COPD by comorbid pathologies. Pulmonary embolism in a COPD patient could masquerade as an exacerbation and was identified in 3.3% of unselected AECOPD ED attendances undergoing routine D-dimer, CTPA and USS(Rutschmann et al., 2007). Cardiac dysfunction is increasingly recognized as an important precipitant and cofactor in AECOPD(MacDonald, Shafuddin, et al., 2016). Left ventricular

failure, coronary ischaemia and tachyarrhythmmia are all common comorbidities in COPD and deterioration in cardiac function is often indistinguishable at a clinical level from AECOPD(McCullough et al., 2003). Indeed, even in the absence of clinically detected cardiac dysfunction, elevated troponin or natriuretic peptides are common in AECOPD and associated with reduced survival(Baillard et al., 2003; Brekke, Omland, Holmedal, Smith, & Soyseth, 2008; Chang et al., 2011; Pavasini et al., 2015) although the mechanisms underlying their release has not been elucidated.

Psychological comorbidity is often overlooked despite an extremely high prevalence in severe COPD(Yohannes, Willgoss, Baldwin, & Connolly, 2010). Anxiety and depression are associated with increased exacerbation frequency(Laurin, Moullec, Bacon, & Lavoie, 2012). An acute anxiety attack could directly provoke a symptom complex resembling AECOPD and psychological morbidity could augment symptoms or lower the threshold for healthcare utilization. Furthermore, healthcare utilization in chronic disease reflects the interaction between the patient and their social, physical and therapeutic environment. Hospitalized patients with COPD are often frail, elderly and highly dependent upon support networks(Kennedy et al., 2015). Disruptions to therapeutic or social support systems may result in increased healthcare resource utilization, including hospital admission.

Given the heterogeneity of hospitalized exacerbations of COPD we have proposed a framework to classify exacerbations by putative aetiology(MacDonald, Beasley, Irving, & Bardin, 2011). The methodology employed routinely available diagnostic techniques and was conceived to be implementable in routine hospital practice. This exacerbation assessment is comprehensive, encompassing “core” aetiologies such as infection and key co-factors in AECOPD such as cardiac dysfunction, psychological distress and environmental instability. The results of our pilot study (n=52) which did not include cardiac biomarker analysis have been published(MacDonald et al., 2013) and are included in Appendix 1. In Chapter 2 we report the findings of implementing our “exacerbation phenotyping” approach in a prospective observational study in hospitalized AECOPD (n=155).

2.3 CLINICAL PHENOTYPING OF COPD EXACERBATIONS BY UNDERLYING AETIOLOGIES

Introduction

Given the heterogeneity of the COPD population and diversity of aetiological triggers, exacerbations are clearly multifactorial and the quest to classify AECOPD using a single unique biomarker is therefore likely to fail. Previous studies have identified exacerbation subtypes according to their underlying aetiology but have generally been conducted in pre-selected community patients using techniques unavailable in routine clinical practice(Bafadhel et al., 2011; Quint et al., 2010). The burden of COPD hospitalizations is enormous and approaches to improve our understanding and management of AECOPD are urgently required. We have therefore proposed a practical framework to ascribe putative aetiology to hospitalized exacerbation episodes(MacDonald et al., 2011). This clinically-oriented and pragmatic approach was adopted given the limitations of current diagnostic methodologies and the clinical environment within which phenotyping has to be implemented. We used routinely available methods to explore the diversity of hospitalized AECOPD using an aetiological phenotyping process.

Methods

Study population

The study was approved by the Human Research Ethics Committee, Monash Health, Melbourne (HREC13134A). Written informed consent was obtained from all patients.

Patients with a clinical diagnosis of AECOPD admitted to the Respiratory Unit at a tertiary referral centre (Monash Medical Centre) in Melbourne, Australia, were recruited to a prospective observational study at the time of hospital admission. Exclusion criteria were direct admission to the Intensive Care Unit (ICU) for mechanical ventilation, presence of an alternative respiratory diagnosis deemed responsible for admission or clinician-diagnosed left ventricular failure. Peripheral oedema was not an exclusion criterion if deemed secondary to right ventricular failure but was recorded as a categorical variable. Sufficient cognitive capacity to provide informed consent and complete questionnaires was required. COPD was diagnosed by spirometry demonstrating a forced expiratory ratio (forced expiratory volume in the first second [FEV_1]:forced vital capacity [FVC]) <0.7 in accordance with Global Initiative for Chronic Obstructive Lung disease (GOLD) criteria(Vogelmeier et al., 2017). Where spirometry results were not available at the time of enrolment, spirometry was arranged for ≥6 weeks post hospital discharge and clinical recovery was verified prior to testing. Patients with spirometry inconsistent with COPD were excluded from the final analyses.

COPD symptoms were assessed using the COPD Assessment Tool (CAT)(Jones, 2013). Symptoms of anxiety or depression were measured using the Hospital Anxiety and Depression Scale (HADS)(Zigmond & Snaith, 1983). The number of days between patient perceived exacerbation onset and presentation to hospital, prior contact with healthcare providers, and pre-hospital antibiotic or oral corticosteroid therapy were recorded.

Clinical management was at the discretion of the treating clinicians and not influenced by the study team. Readmissions were included in the overall cohort but the primary analyses reported are based upon the first (index) admission for each individual.

Clinical and Laboratory measurements

Demographic variables, co-morbidities, baseline dyspnoea grade (evaluated by modified Medical Research Council Dyspnoea (mMRCD) scale(Mahler & Wells, 1988), domiciliary oxygen therapy and baseline medication prescription were identified from patient interview and the hospital case record. Self-reported hospital and community exacerbations in the preceding 12 months were recorded. Previous hospitalizations for AECOPD within the Monash Health network (Monash Medical Centre, Dandenong Hospital, Casey Hospital) were verified by reference to the electronic medical record.

Virus testing was performed using nasopharyngeal flocked swab with respiratory virus multiplex PCR (AusDiagnostics Highplex, Beaconsfield, Australia). Spontaneously expectorated sputum was examined for white blood cell count and bacterial culture. Total white cell count (WCC), differential white cell count and haemoglobin (Hb) (Beckman Coulter DxH800) were taken from the first Full Blood Examination (FBE) performed at the time of Emergency Department presentation. The highest C-reactive protein (CRP) level (Beckman Coulter DXC800) obtained in the first 48 hours of admission was the value used for analysis. In addition, serum taken within the first 24 hours of admission was retrieved and stored at -80°C. At study completion, N-terminal pro B-type natriuretic peptide (NT-proBNP, electrochemiluminescence immunoassay, ECLIA, Roche e411) and high-sensitivity Troponin-I (hs-TnI, chemiluminescent microparticle immunoassay, CMIA, Abbott Archicentre ci16200) were performed where adequate serum was available.

Aetiological categorization - ABCDEFGX

The rationale for this framework to ascribe aetiological contributors to hospitalized AECOPD has been published previously(MacDonald et al., 2011) and has been reviewed in Chapter 1. The aetiology ascribed to each exacerbation event was based on clinically based diagnostic criteria (see Figure 1):

A - Airway virus

Detection of viral nucleic acid by nasopharyngeal respiratory virus PCR was assumed to be diagnostic of virus infection (A - airway virus infection), with negative

virus PCR accepted as absence of virus infection. Symptoms of upper respiratory tract infection were not specified within the study questionnaire.

B - Bacteria

Given the difficulty in establishing definitive proof of bacterial aetiology in AECOPD, 2 categories of bacterial aetiology were assigned;

Bi) Potentially pathogenic micro-organism (PPM) identified on sputum culture.

Bii) Fever (temperature ≥38 degrees Celsius) or CRP≥20mg/L, with negative virus PCR but no PPM identified on sputum culture.

C – Co-infection

(C-Co-infection) was established only when sputum culture for PPM (Bi) and virus PCR (A – Airway virus) were both positive.

D - Depression/Anxiety

Symptoms of anxiety and depression at the time of AECOPD admission were quantified using the Hospital Anxiety and Depression Scale (HADS). HADS is a 14-item questionnaire with seven questions relating to anxiety and seven questions relating to depressive symptoms. The optimal cut-off point to identify cases of anxiety or depression has been identified at >8 for HADS A and HADS D respectively(Bjelland, Dahl, Haug, & Neckelmann, 2002). Various optimal cut-offs ranging from 8-21 have been reported to identify cases using the combined HADS Total (HADS T) in different patient populations(Bjelland et al., 2002).

For the purpose of reporting exacerbation phenotypes, we sought to identify AECOPDs where poorly controlled anxiety/depression symptoms were a relevant contributor to the exacerbation episode. We therefore applied a very high cut-off score to assign a category of “D”. A total score (HADS T) ≥27 or scores in the subscales for anxiety (HADS A) or depression (HADS D) ≥15 were used as these thresholds have shown 95% specificity for Anxiety/Depression as diagnosed by Diagnostic Statistical Manual of Psychological Illnesses (Version 4) (DSM-IV) in an acute inpatient population(Singer et al., 2009). A history of doctor diagnosed anxiety,

depression, psychiatric disorder, or alcohol/substance abuse and use of antidepressant, anxiolytic or antipsychotic medication were also recorded.

E - Embolism/Eosinophils

Due to the low prevalence of PE in previous studies(Rutschmann et al., 2007) and implications of radiation exposure and intravenous iodinated contrast loading, patients did not undergo routine exclusion of pulmonary embolism (PE) by computerised tomography pulmonary angiography (CTPA). For the principal study, a diagnosis of pulmonary embolism therefore relied upon detection by the treating clinical team as part of routine clinical care. A subset of the patient cohort (n=58) had CT pulmonary angiography assessed as a component of cardiopulmonary dynamic 256-slice multi-detector computerized tomography (MDCT) in AECOPD with results reported in Chapter 5.

To investigate the utility of blood eosinophil counts in AECOPD phenotyping, we analysed the first eosinophil count on admission among those patients not exposed to pre-hospital oral corticosteroids. Exacerbations were categorized as eosinopenic ($<0.05*10^9$), normal ($\geq 0.05*10^9$ but <2% eosinophils:total white cell count) or eosinophilic (>2% eosinophils:total white cell count). Details of this analysis are reported in Chapter 3.

F - Failure (cardiac)

Patients with clinically diagnosed overt left ventricular failure or acute coronary syndromes as primary admission diagnoses were excluded. Samples for NT-proBNP and high-sensitivity troponin I (hs-TnI) testing were retrieved from admission blood samples where adequate serum was available. These samples were analysed in batches at completion of the study.

A category of “F” was assigned to exacerbations where high-sensitivity troponin or NT-proBNP levels were above the upper limit of normal (ULN) for a reference population(Galasko, Lahiri, Barnes, Collinson, & Senior, 2005; Trambas et al., 2016). Samples with a value below the lower limit of quantification were assigned a value that was half that limit in accordance with previous studies(Hurst et al., 2010).

Integration of cardiac biomarkers analyses with ECG-gated dynamic MDCT, including coronary artery calcium scoring, pulmonary artery distensibility and biventricular cardiac function quantification is reported on a subset of this study cohort (n=58) in Chapter 5.

G – General environment

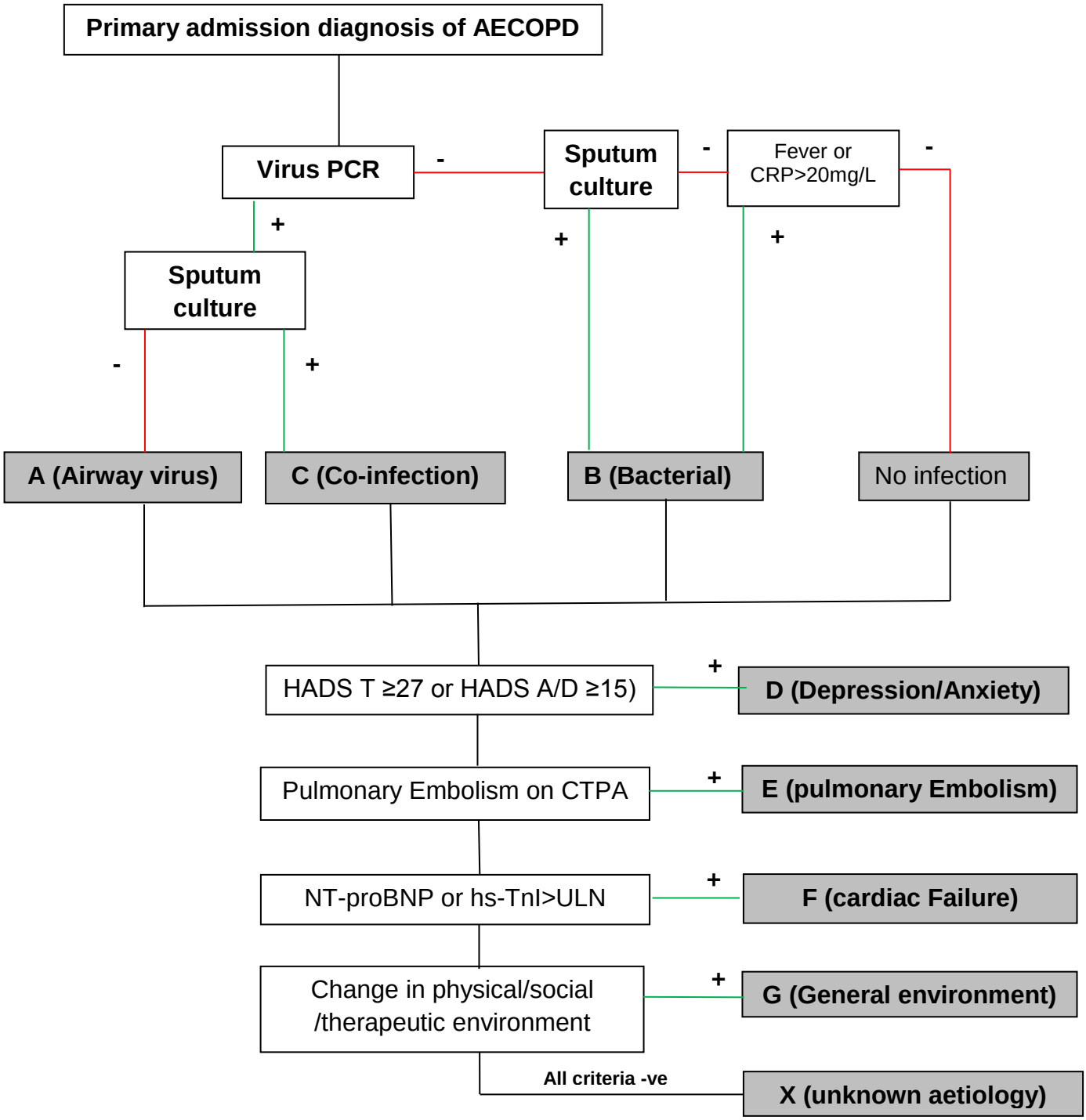
Patients were asked to rate their self-perception of capacity to cope at home when stable. Specifically, any acute disruptions to the physical environment, usual medical therapy or social support network that had substantially contributed to admission were recorded. Assessments of the treating Medical, Physiotherapy and Occupational Therapy Team that identified clear disruptions to the patient's physical, social or therapeutic environment deemed contributory to AECOPD were also taken into account.

X – Unknown

Admissions where none of the aforementioned aetiological contributors were identified were categorized as **X.**

It should be appreciated that each admission could be identified as having more than one aetiological contributor (e.g. PPM on sputum culture, NT-proBNP>ULN = BF or Virus PCR positive, HADS T ≥27 = AD).

Figure 1. Methodology for aetiological phenotyping hospitalized AECOPD



PCR = polymerase chain reaction, CRP = C-reactive protein, Fever = temperature≥38^{o}C, CTPA = CT pulmonary angiography, ULN = upper limit of normal (>95th percentile) for a reference age and gender matched healthy population.

Figure 1. Each AECOPD episode is reviewed to assess which diagnostic criteria for each of the putative aetiologies are fulfilled. A cumulative phenotype is thus constructed including all identified aetiological factors.

Clinical outcomes

Clinical outcomes recorded included non-invasive ventilation (NIV) in the emergency department (ED) or during hospital admission, mechanical ventilation occurring subsequent to ward admission and inpatient mortality. Patients intubated for mechanical ventilation at the time of initial hospital presentation were excluded. Length of hospital stay was recorded as a continuous variable.

Statistical Analysis

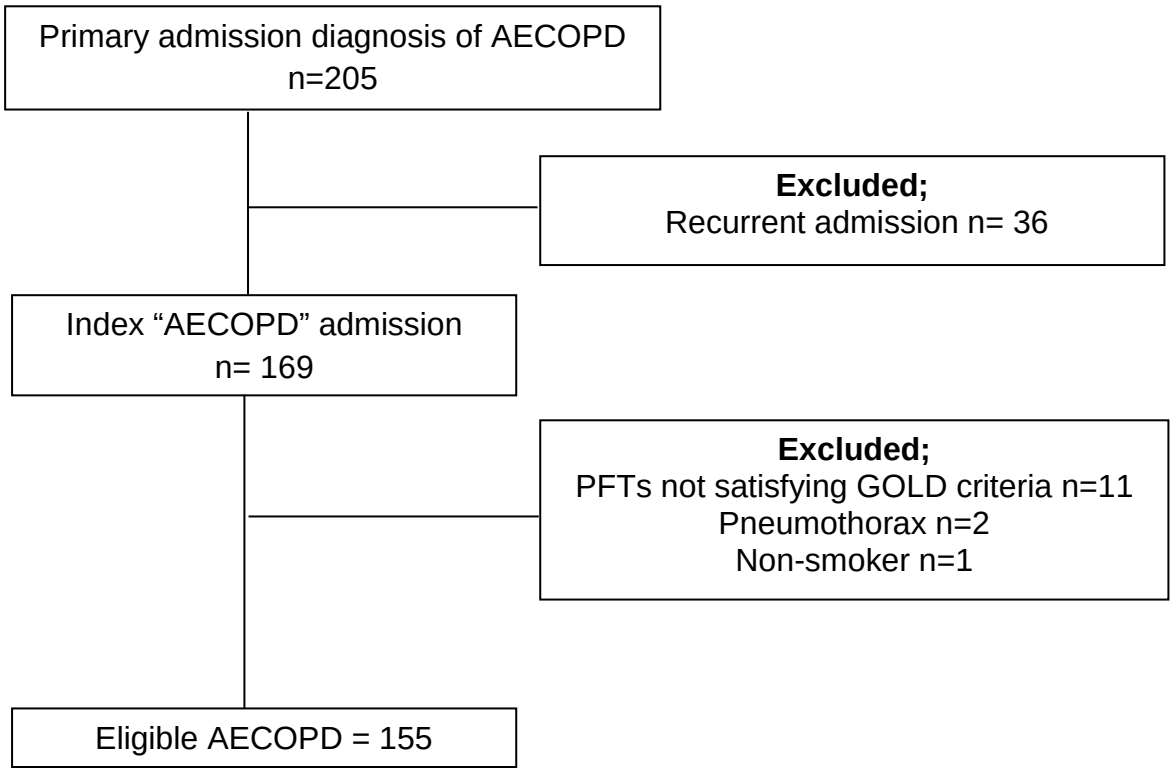
All data is presented as number (percentage), mean (standard deviation, SD), or median (interquartile range, IQR) where appropriate. The principal analysis used data from patients' first admission only. Data normality was examined by the Shapiro-Wilk statistic and visual inspection of frequency histograms. Comparisons were made between aetiological groups. Relationships between characteristics and different aetiological groups were analysed by unpaired t-test and one-way analysis of variance (ANOVA) for normally distributed data or Mann-Whitney and Kruskal-Wallis testing for non-parametric data. Chi-square analyses were used to determine differences between groups for categorical data. Statistical significance was accepted at $p<0.05$ for all analyses. All analyses were conducted on Stata MP 14.1 (Statacorp, College Station, Texas, USA).

Results

Study population

205 admissions (169 individuals) with a primary admission diagnosis of acute exacerbation of COPD were enrolled. Spirometry results were available for 163/169 individuals, with 6/169 (3.6%) without confirmatory lung function results accepted as AECOPD (details of these individuals are shown in Appendix 2). 14 enrolled patients were excluded from analysis - 11 because spirometry was inconsistent with GOLD criteria for diagnosis of COPD, two had pneumothoraces and one was a non-smoker.

Figure 2. CONSORT diagram of participant flow.



Demographics, lung function, comorbidities and medication use in the study population is shown in Table 1.

Table 1. Baseline characteristics of enrolled patients

Demographics		**Comorbidities, n (%)**		**Medication, n (%)**	
Age (mean/SD)	71.8/10.4	Bronchiectasis	16 (10.3)	LAMA	133 (85.8)
Male, n (%)	97 (62.6)	OSA	14 (9.0)	LABA	129 (83.2)
BMI (kg/m^2)(mean/SD)	24.8/6.5	Hypertension	71 (45.8)	ICS	126 (81.3)
FEV_1 (L) (mean/SD)	1.1/0.5	AF/flutter	19 (12.3)	OCS¤	13 (8.4)
FEV_1 (%) (mean/SD)	45.2/18.6	IHD	43 (27.7)	Antibiotic¤	5 (3.2)
TLCO (%) (mean/SD)	38.3 (16.2)	Cardiac failure	32 (20.6)	Antiplatelet	55 (35.5)
LTOT continuous, n (%) LTOT exertional, n (%)	19 (12.2) 40 (25.8)	CVD	15 (9.7)	Anticoagulant	18 (11.6)
mMRC-D (mean/SD)	2.9/1.2	Diabetes Mellitus	29 (18.7)	Beta-blocker	19 (12.3)
Current smoker, n (%) Former smoker, n (%) Pack years (mean/SD)	48 (31) 117 (69) 44.1/26.4	Malignancy*	15 (9.7)	Sinus node blocker	4 (2.6)
AECOPD in previous year *Hospital (mean/SD)* *Community (mean/SD)*	 1.5/2.3 1.7/2.5	Renal impairment (egfr<30ml/min)	3 (1.9)	Rate-limiting Ca2RA	13 (8.2)
		Anxiety	36 (23.2)	ACE-I/ARB	52 (33.5)
Frequent exacerbators, n (%) (≥ 2 AECOPD hospital admissions in previous year)	47 (30.3)	Depression	35 (22.6)	Statin	57 (36.8)
		Other psychiatric disorder**	3 (1.9)	Loop diuretic	33 (21.3)
		Alcohol misuse (current)	12 (7.7)	Benzo-diazepine***	20 (12.6)
		Substance misuse (current)	2 (1.3)	Anti-depressant/ Antipsychotic	39 (24.5)

BMI = body mass index, FEV_1 = Forced expiratory volume in 1 second, TLCO = gas transfer, LTOT = long term oxygen therapy, mMRC-D = modified Medical Research Council Dyspnoea score, OSA = obstructive sleep apnoea, IHD = ischaemic heart disease, CVD = cerebrovascular disease, LAMA = long acting muscarinic antagonist, LABA = long acting beta-agonist, ICS = inhaled corticosteroid, OCS = oral corticosteroid, ¤ = maintenance, ACE-I/ARB = Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker, Ca2RA = calcium antagonist, *receiving treatment or palliation **bipolar affective disorder, schizophrenia, post-traumatic stress disorder, ***(excluding nocte Temazepam)

A classification of COPD severity within the study cohort is represented using the refined GOLD assessment tool(Vogelmeier et al., 2017) - FEV_1 (Class 1-4) and exacerbation risk (A,B,C,D) - is shown in Figure 3.

Figure 3. Patients by GOLD class (FEV_1) and Group (symptoms/exacerbations)

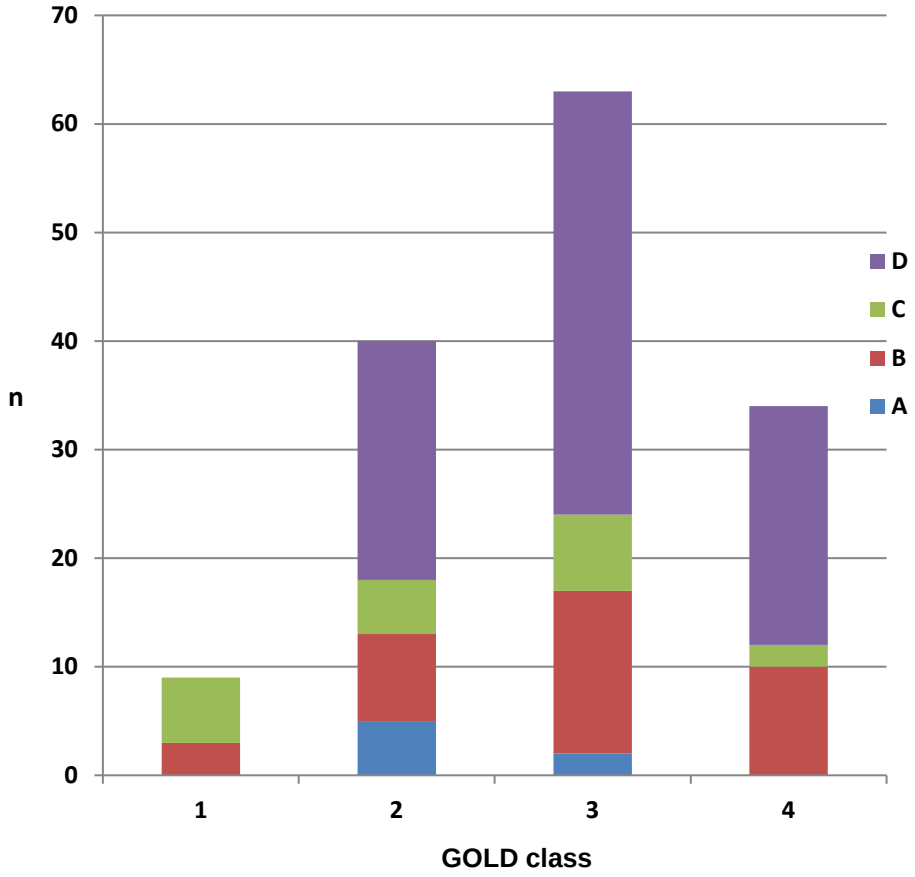
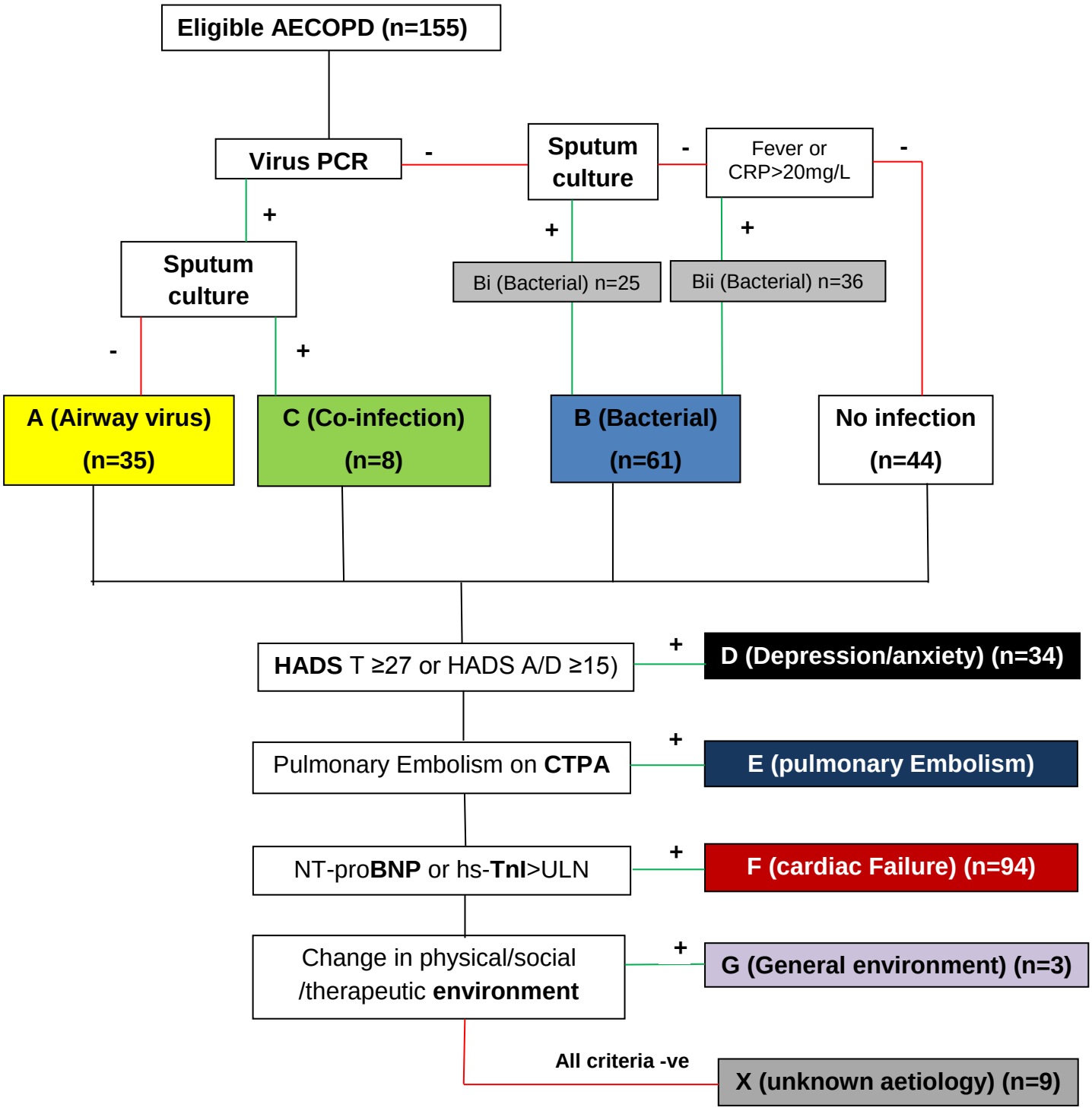


Figure 3. COPD severity within the study population represented according to level of airflow limitation (GOLD Class) on the x-axis, with symptoms and exacerbation history reflected according to the A, B, C, D quadrants described in the GOLD 2017 report.

The prevalence of identified exacerbation aetiologies according to the pre-specified criteria is shown in Figure 4.

Each exacerbation was assigned aetiological classifications based upon the criteria previously described (see Table 2). Patients who had both virus and bacteria identified are reported as co-infection and are not included in the individual viral or bacterial aetiology category. Patients were only designated “no infection” if virus PCR was negative, sputum culture was negative, fever was absent and CRP was <20mg/L.

Figure 4. Aetiologies identified in hospitalized AECOPD



PCR = polymerase chain reaction, MCS = microscopy and culture of sputum, CRP = C-reactive protein, HADS = Hospital Anxiety and Depression Scale, PE = pulmonary embolism, CTPA = computer tomography pulmonary angiography. NT-proBNP = N-terminal brain natriuretic peptide, Hs-TnI = high sensitivity troponin I

Table 2. Aetiologies identified according to pre-specified criteria

	Data available, n (%)	Criteria to assign aetiological category	Criteria fulfilled, n (%)
Airway virus	146/155 (94.2)	+ve virus PCR only	35/146 (24.0)
Bacterial **(Bi)**	136/155 (87.7)	+ve PPM only	25/136 (18.4)
(Bii)	155/155 (100)	CRP>20/Virus-ve/ Sputum-ve/	32/155 (20.6)
		CRP<20/fever-ve/Sputum-ve/Virus-ve	4/155 (2.6)
Coinfection	133/155 (85.8)	A + Bi	8/133 (6.0)
Depression/Anxiety	143/155 (92.3)	HADS Total ≥27 / HADS A or D≥15	34/133 (25.6)
Embolism	6/155 (3.9)	+ve CTPA	0/155 (0)
Failure (cardiac)	128/155 (82.6)	Cardiac biomarkers >ULN	94/128 (59.1)
General environment	155/155 (100)	Environmental factors identified	3/155 (1.9)
X - unknown	111/155 (71.6)	None of the above (complete data)	9/111 (8.1)

A - airway virus:

Virus PCR results were available for 146/155 (94.2%). Viruses were detected in 43/146 (29.4%) of exacerbations, 35 cases of virus alone and 8 cases of co-infection with bacteria (Table 3). One patient had 2 viruses detected from the same sample.

B - Bacteria:

Sputum culture results were available in 136/155 (87.1%) of cases. Bi aetiology was assigned to 25/136 (18.4%) where potential pathogenic microorganisms (PPM) were identified on sputum culture (Table 2). One patient had 2 PPMs identified from the same sample. Bii aetiology was used where no PPM was cultured but either fever or CRP ≥20mg/L were identified and virus PCR was negative 36/155 (23.2%).

C – Co-infection: Co-infection was ascribed when both virus PCR (A) and sputum culture (Bi) were positive. This was observed in 8/135 (6%) of cases with results available for both tests.

Table 3. Bacteria and viruses identified at AECOPD

Virus only	**n**	**Bacteria only**	**n**	**Virus with Bacteria**	***n***
Rhinovirus	12	Pseudomonas. aerug.	8	*Rhinovirus/Strep.*	*2*
HMPV	8	Haem. influenzae	10	*Rhinovirus/Pseudomonas*	*2*
Influenza A	7	Strep. pneumoniae	1	*RSV/Streptococcus*	*2*
RSV	3	Moraxella catarrhalis	3	*Influenza A /Pseudomonas*	*1*
Influenza B	2	MRSA	1	*HMPV/Moraxella*	*1*
Adenovirus	0	MSSA	1	**Total**	**8**
Parainfluenza 1	1	Pseudomonas + MRSA	1		
Parainfluenza 2	1	**Total**	**25**		
Rhinovirus + HMPV	1				
Total	**35**				

RSV = Respiratory syncytial virus

MRSA = Methicillin resistant Staphylococcus aureus

MSSA = Methicillin sensitive Staphylococcus aureus

HMPV = human metapneumovirus

D - Depression/Anxiety

HADS scores were available for 143/155 (92.3%) of cases. The baseline prevalence of doctor diagnosed psychiatric comorbidities was as follows: anxiety (23.2%); depression (22.6%); major psychiatric disorder (1.9%); current alcohol/substance misuse (9%). HADS scores on admission for the overall population and for those with and without various diagnosed psychiatric comorbidities are shown in Table 4 and Figure 5. HADS scores were significantly higher in those with a psychiatric comorbidity than those without (20.2/8.7 v 14.6/8.0, $p<0.001$). A psychiatric comorbidity diagnosis was more common in females than males but this did not reach statistical significance (44.8% v 31.9% $p=0.11$) and there was no difference in HADS scores between males and females (16.5/9.4 v 16.9/7.5). Mean/SD COPD assessment Tool (CAT) scores were not different between those with or without psychiatric comorbidity (29.6/6.1 v 28.4/7.4, $p=0.32$).

Table 4. Hospital anxiety and depression scale scores within various subgroups with or without psychological comorbidity

	Overall Population (n=143)	Anxiety (n=35)	Depression (n=32)	Alcohol Misuse (n=11)	None (n=89)
Male, n (%)	89 (62.2)	19 (54.3)	14 (43.8)	8 (72.7)	59 (66.3)
Antidepressant, n (%)	36 (25.2)	23 (65.7)	28 (87.5)	7 (63.6)	2 (2.3)
HADS Anxiety (mean/SD)	8.8/5.1	10.7/5.3	11.8/5.1	10.7/5.7	7.7/4.7
HADS Depression (mean/SD)	8.0/5.0	10.9/5.0	10.6/4.8	10.1/4.1	6.8/4.6
HADS Total (mean/SD)	16.7/8.7	20.8/9.0	21.8/8.4	19.3/8.4	14.6/8

Figure 5. HADS scores according to underlying psychiatric disorder

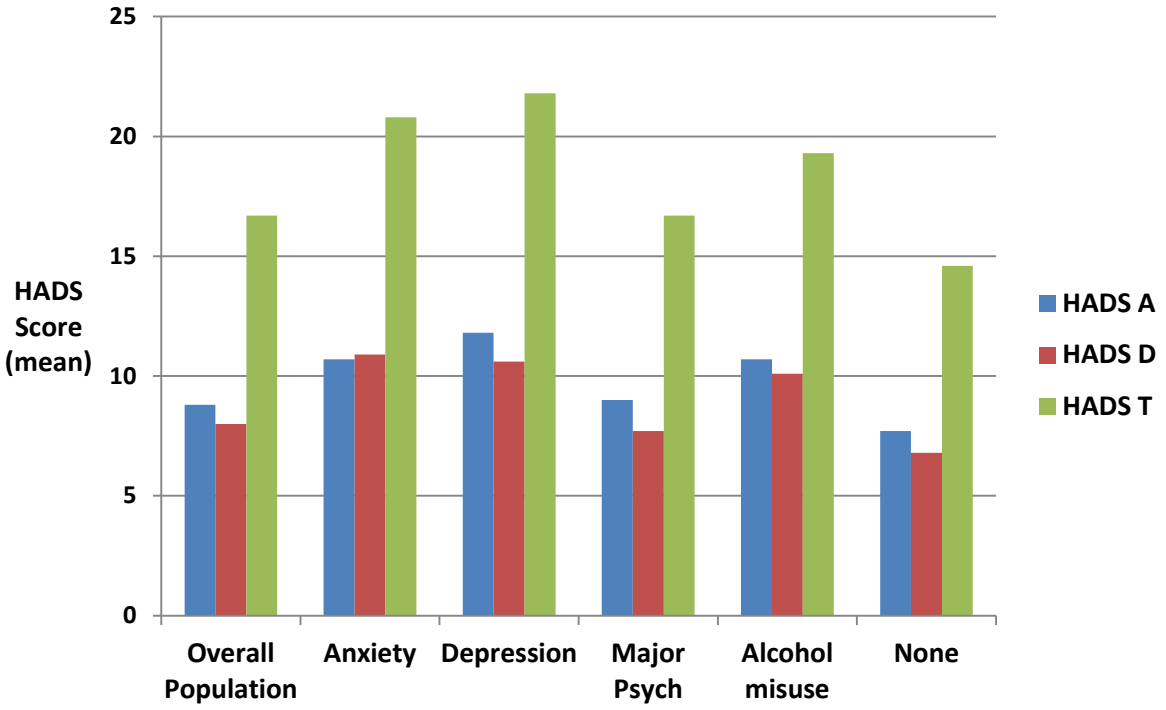


Figure 5. Bar graph showing Hospital Anxiety and Depression Scale (HADS) scores across various subgroups with or without psychological comorbidity.

E - Embolism/Eosinophils

Investigation of pulmonary embolism was at the discretion of the treating clinical team with 6/155 (3.9%) undergoing CTPA. No pulmonary emboli were identified. Computer tomography pulmonary angiography (CTPA) as a component of ECG-gated 256-MDCT is reported in a subset of patients (n=58) enrolled in a sub-study - Comprehensive Cardiopulmonary CT in COPD (4C). High quality CTPA images using the 4C protocol were obtained in 47/58 (81.0%) with no pulmonary emboli identified.

Eosinophil profiling as a basic exacerbation phenotype was explored in a study of AECOPD patients without pre-hospital oral corticosteroid exposure (see Chapter 3). Patients were categorized according to the first blood eosinophil count on admission as high (>2% total white blood cells), low (<0.05 10^9) or normal (<2% but >0.05 10^9).

F - Failure (cardiac)

Serum was available for analysis of high sensitivity Troponin I (hs-TnI) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in 128/155 (82.6%) of cases. Hs-TnI was above the upper limit of normal (ULN) in 35/128 (27.3%) and NT-proBNP was >ULN in 79/128 (61.7%). Cardiac biomarkers in those with and without established cardiovascular diagnoses are shown in Table 5.

Table 5. Cardiac biomarker levels in those with and without known cardiovascular disorders

	Overall Population	HTN	IHD	Heart Failure	No known cardio-vascular disorder*
n	128	58	35	29	44
hs-TnI [median/IQR]	9 [5-24]	10 [6-29]	10 [5-27]	16.5 [6-36]	7 [4-16]
hs-TnI >ULN, n (%)	35 (27.3)	19 (32.8)	10 (28.6)	13 (44.8)	8 (18.2)
NT-proBNP (ng/L) [median/IQR]	359.5 [163-1211]	442 [175-1941]	351 [185-1545]	618 [185-2016]	289.5 [130.5-567.5]
NT-proBNP>ULN, n (%)	90 (70.3)	43 (74.1)	26 (74.2)	22 (75.9)	31 (70.5)
TnI or NTproBNP >ULN, n (%)	94 (73.4)	44 (75.9)	27 (77.1)	23 (79.3)	32 (72.7)

*no known history of hypertension, ischaemic heart disease, heart failure, cerebrovascular disease, arrhythmia or diabetes mellitus

Patients with a history of heart failure had significantly higher NT-proBNP (p=0.02) and troponin (p=0.04) than patients with no known cardiovascular disorder (Figure 6a, b).

Figure 6. a) NT-proBNP and b) hs-TnI in those with a baseline comorbidity of cardiac failure versus those with no cardiovascular diagnosis

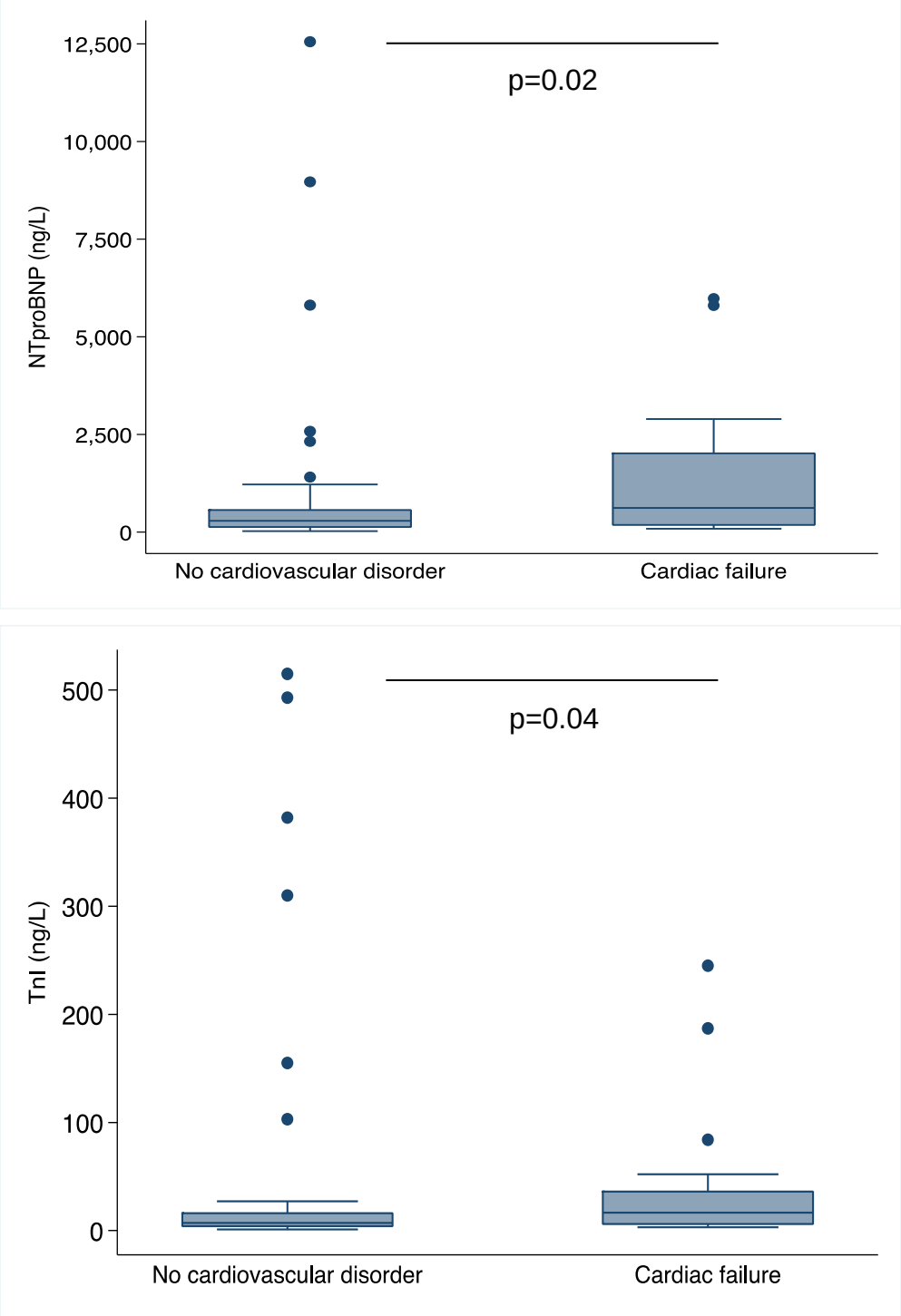


Figure 6. NT-proBNP and high-sensitivity Troponin I levels were significantly higher in patients with a background diagnosis of cardiac failure than those without any known cardiovascular diagnosis

G - General environment

Data to categorize G (General environment) was available in 155/155 (100%). Self-reported assessment of baseline domestic circumstances is shown in Figure 7. Of the overall study population, 149/155 (96.1) were living in the community. Amongst community dwellers, 69/149 (46.3%) considered themselves dependent upon others to complete basic activities of daily living at baseline, while 9/149 (6%) perceived that they were not coping in their home environment even when their COPD was stable.

Figure 7. Domestic circumstances of AECOPD population

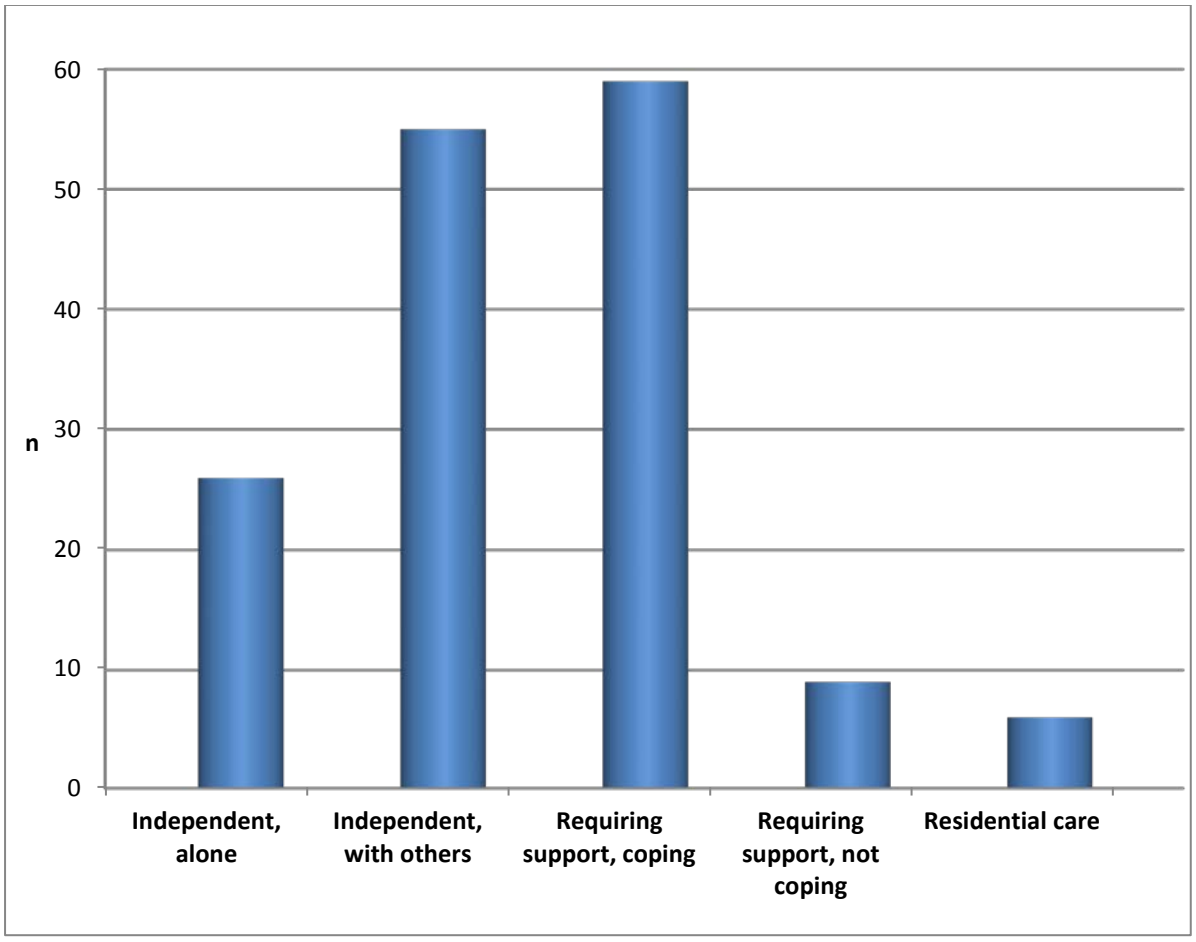


Figure 7. The majority of the hospitalized AECOPD population perceived themselves as requiring support to maintain functional independence at home.

Environmental factors directly contributing to AECOPD presentation were only identified in 3/155 (1.9%) and included acute dust exposure, air conditioner malfunction during an extreme heatwave and loss of regular medications.

X - unknown

Of patients with complete data available to assign all exacerbation phenotypes, none of the pre-specified criteria were satisfied in 9/111 (8.1%). This group in whom no identified aetiological precipitant was evident, had the highest rates of High Dependency Unit admission (66.7% vs. 26.9% for infective exacerbations, p=0.013) and a trend towards earlier hospital presentation (3 vs. 5 days for infective exacerbations, p=0.08). Almost 80% had a history of frequent exacerbations and a high proportion used ambulatory oxygen at home (44.4% vs. 22.1 for infective exacerbations, p=0.13).

Using our ABCDEFGX model, and after excluding 9 cases who were category X (i.e. no positive identification of any specific aetiology), only 48/155 (31%) were assigned a single aetiological category, 2 aetiologies were identified in 77/155 (48.4%) and 3 aetiologies were identified in 8/155 (5.2%). Poorly controlled anxiety/depression and cardiac dysfunction were prevalent in all exacerbation subtypes. The distribution of exacerbation aetiologies is represented in Figure 8.

Figure 8. Distribution of aetiologies in AECOPD

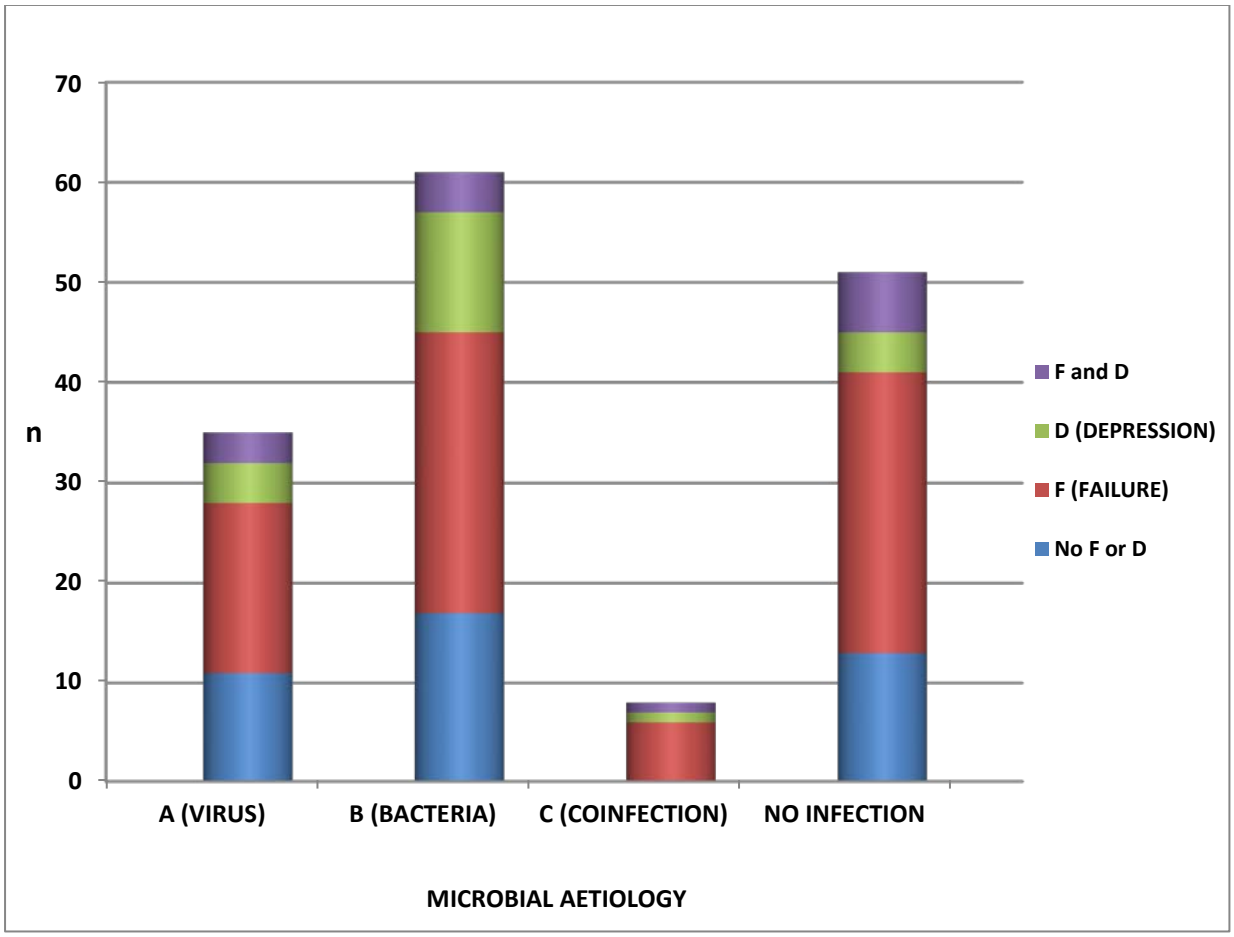


Figure 8. Exacerbation aetiology is represented by baseline infective status with cardiac dysfunction (F) or acute psychological distress (D) included with each infective subtype. The proportion of exacerbations featuring F or D was high across all infective categorizations.

No significant difference was observed in the distribution of exacerbation phenotypes after exclusion of patients receiving pre-hospital antibiotics or oral corticosteroids (n=70) (see Figure 9).

Figure 9. Aetiologies identified in those with and without pre-hospital treatment

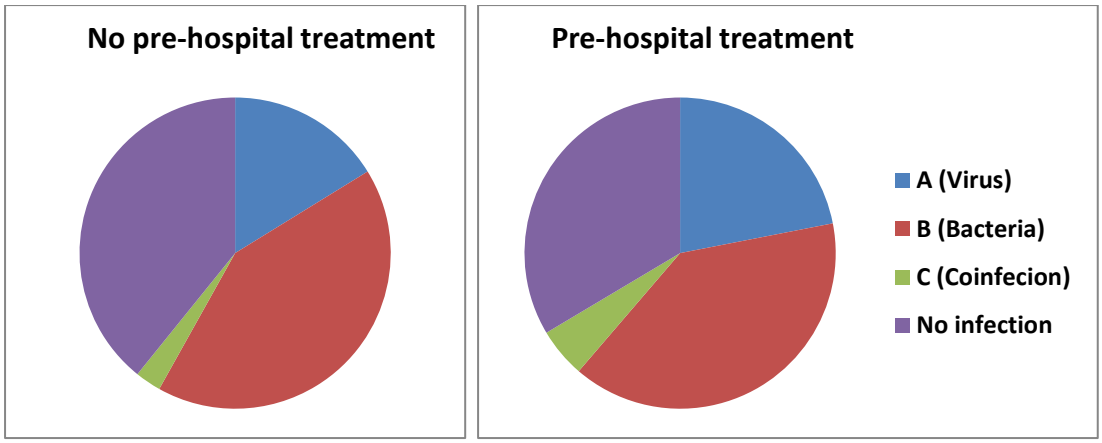


Figure 9. The distribution of infection subtypes was similar between those who did and did not commence exacerbation therapy prior to hospital attendance.

Comparison between aetiological phenotypes

Infective versus non-infective exacerbations

Patient characteristics, exacerbation characteristics and exacerbation outcomes were first compared using a broad categorization of infective versus non-infective aetiology. Infective status was assigned when positive virus PCR, positive sputum culture, CRP≥20mg/L or fever was present (70.3%). A non-infective status was only assigned when all of the aforementioned criteria were negative (29.7%).

Baseline Demographics, COPD severity and Comorbidities

There were no significant differences in baseline demographics, severity of lung function impairment or common comorbidities between the infective and non-infective groups. A higher prevalence of alcohol misuse in non-infective exacerbations approached statistical significance (13.6% v 4.8%, p=0.06).

Table 6. Baseline Demographics, COPD severity and Comorbidities

Demographics	Infective	Non infective	p
n	104	44	
age (mean/SD)	72.4/10.2	69.8/10.7	0.17
male, n (%)	66 (63.5)	26 (59.1)	0.62
Frequent exacerbator (hospital), n (%)	31 (29.8)	12 (27.3)	0.62
Frequent exacerbator (any), n (%)	62 (59.6)	26 (59.0)	0.95
Current smoker, n (%)	32 (30.7)	15 (34.1)	0.69
Pack year (mean/SD)	46.7/28.5	38.7/21.6	0.1
BMI (kg/m2)	25.1/5.8	23.9/7.6	0.29
FEV_1 L (mean/SD)	1.2/0.5	1.1/0.7	0.07
FEV_1 (% predicted) (mean/SD)	50.6/17.9	44.0/20.1	0.11
TLCO (mean/SD)	8.8/3.6	10.9/6.0	0.16
TLCO (% predicted) (mean/SD)	37.0/14.8	42.7/19.7	0.14
mMRC [median/IQR]	4 [3–5]	4 [3–5]	0.86
Comorbidities			
Bronchiectasis, n (%)	11 (10.6)	5 (11.4)	0.88
Obstructive Sleep Apnoea, n (%)	8 (7.7)	6 (13.6)	0.26
Hypertension, n (%)	49 (47.1)	20 (45.5)	0.85
Ischaemic heart disease, n (%)	30 (28.9)	10 (22.7)	0.44
Cardiac failure, n (%)	20 (19.2)	9 (20.5)	0.86
Cerebrovascular disease, n (%)	12 (11.5)	3 (6.8)	0.38
Diabetes, n (%)	20 (19.2)	9 (20.5)	0.86
Arrhythmmia, n (%)	14 (13.5)	4 (9.1)	0.46
Malignancy, n (%)	12 (11.5)	3 (6.8)	0.38
Anxiety, n (%)	22 (21.1)	12 (27.3)	0.42
Depression, n (%)	22 (21.1)	12 (27.3)	0.42
Alcohol misuse, n (%)	5 (4.8)	6 (13.6)	0.06

Table 6. BMI = body mass index, FEV_1 = Forced expiratory volume in 1 second, TLCO = gas transfer, LTOT = long term oxygen therapy, mMRC-D = modified Medical Research Council Dyspnoea score

Exacerbation symptoms and prehospital care

Total CAT scores (mean/SD) were similar in infective versus non-infective exacerbations (28.9 v 29.2, p=0.62). Individual CAT item responses were generally similar although increased phlegm rated higher in infective exacerbations (p=0.056. Figure 10). HADS scores (mean/SD) were similar between infective and non-infective exacerbations(16.6/8.9 v 17.4/8.5, p=0.63).

Outpatient consultation with a medical practitioner had occurred prior to hospital presentation in 101/155 (65%) of admissions. An increase in baseline therapy had been prescribed prior to hospital attendance in 71/155 (45.8%) - antibiotics (45.2%) or oral corticosteroids in 36/155 (23.2%). Non-infective exacerbations appear less likely to attend a GP prior to hospital presentation (54.5% v 67.3%, p=0.08) and were less frequently taking pre-hospital OCS (13.6% v. 28.7%, p=0.049). Non-infective exacerbations showed a trend towards lower median exacerbation severity scores as indicated by BAP-Class (2 vs. 3, p=0.08).

Figure 10. CAT item responses in infective and non-infective exacerbations

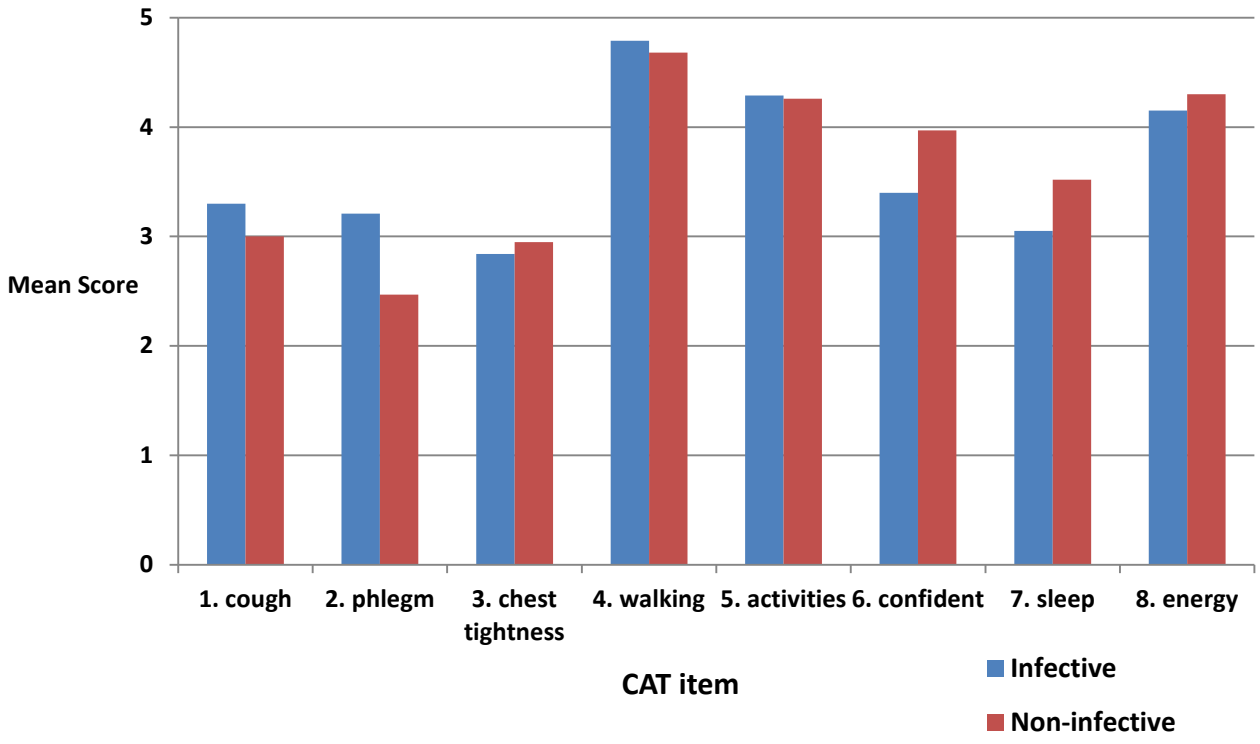


Figure 10. Individual COPD assessment Tool (CAT) item responses were broadly similar between infective and non-infective exacerbations.

Table 7. Prehospital care and assessment scoring

Exacerbation characteristics	Infective	Non infective	p
Days since symptom onset [median/IQR]	5 [3-7]	4 [2-14]	0.89
Prior contact with healthcare provider, n (%)	70 (67.3)	24 (54.5)	0.08
Change in therapy prehospital, n (%)	51 (49.0)	17 (38.6)	0.14
Prehospital antibiotics, n (%)	52 (50)	16 (36.4)	0.13
Prehospital oral corticosteroids, n (%)	30 (28.8)	6 (13.6)	0.049*
CAT total (mean/SD)	28.9/7.2	29.2/5.8	0.98
HADS total (mean/SD)	16.6/8.9	17.4/8.5	0.63
BAP-65 Class [median/IQR]	3 [2-3]	2 [2-3]	0.08

Laboratory indices

Typical markers of infection such as total white cell count, neutrophils and CRP were significantly higher in infective exacerbations. Blood eosinophil counts were lower in infective exacerbations ($p<0.001$) and the median eosinophil count in infective exacerbations was in the eosinopenic range ($<0.05\ 10^9$). Markers of ventilatory failure were higher in the non-infective exacerbations group (see Table 8). Elevation of cardiac biomarkers was highly prevalent in both groups.

Table 8. Laboratory markers in infective and non-infective AECOPD

Laboratory results	Infective	Non-infective	p
WCC (mean/SD)	12.3/4.7	10.0/3.0	<0.001*
Neutrophils (mean/SD)	9.6/4.3	7.0 (2.4)	<0.001*
CRP mg/L [median/IQR]	52.9 [18.7 - 130.9]	4.2 [1.7 – 7]	<0.001*
Eosinophils [median/IQR]	0.035 [0 - 0.14]	0.243 [0.08 - 0.46]	<0.001*
pH (mean/SD)	7.36/0.08	7.33/0.08	0.007*
pCO2 (mean/SD)	48.4/11.5	54.5/13.8	0.009*
Bicarbonate (mean/SD)	27.6/4.4	29.3/5.7	0.07
Base excess (mean/SD)	2.8/4.0	4.1/5.2	0.11
Glucose (mean/SD)	8.06/3.02	7.85/3.12	0.43
Lactate (mean/SD)	1.71/0.84	1.76/0.74	0.53
NT-proBNP [median/IQR]	406 [174 – 1277]	263 [152 – 853]	0.38
BNP>ULN, n (%)	58 (71.6)	27 (67.5)	0.64
Hs-TnI [median/IQR]	9 [5 -33]	8 [5 – 20]	0.32
Hs-TnI>ULN, n (%)	25 (30.9)	8 (20)	0.21
Egfr<60ml/min, n (%)	15 (14.6)	6 (14.0)	0.92
Creatinine (mean/SD)	79.6/26.4	81.0/64.4	0.12

Clinical management and outcomes

Non-infective exacerbations were more frequently treated with non-invasive ventilation (22.7% vs. 7.7%, p=0.01). No difference was observed in rates of mechanical ventilation, inpatient mortality or length of hospital stay. Antibiotics were prescribed in 90.9% of exacerbations designated as non-infective by our pre-specified criteria, although this was significantly lower than antibiotic prescription rate in infective exacerbations (100%) (p=0.002).

Table 9. Clinical management and outcomes in infective and non-infective AECOPD

Clinical management/outcomes	Infective	Non-infective	p
Antibiotics (inpatient), n (%)	104 (100)	40 (90.9)	0.002*
Systemic corticosteroids (inpatient), n (%)	101 (97.1)	42 (95.5)	0.61
NIV (ED), n (%)	18 (17.3)	15 (34.1)	0.025*
NIV (ward), n (%)	8 (7.7)	10 (22.7)	0.011*
HDU/ICU, n (%)	28 (26.9)	18 (40.9)	0.09
Mechanical ventilation, n (%)	4 (3.8)	1 (2.3)	0.63
Inpatient mortality, n (%)	1 (1)	0 (0)	0.51
Length of hospital stay (days) [median/IQR]	5 [4-8]	5 [3-8]	0.2

NIV = non-invasive ventilation, ED = Emergency Department, HDU = High Dependency Unit, ICU = Intensive Care Unit

Comparison between infection subtypes

Exacerbations were compared according to infection subgroups – viral, bacterial, coinfection or no infection identified (see Table 10).

Baseline Demographics, COPD severity and Comorbidities

The bacterial group had significantly higher prevalence of frequent hospital exacerbator status (p=0.02). The non-infective group had the lowest FEV_1 and significantly lower gas transfer (p=0.012). The viral group had the lowest baseline dyspnoea scores (p<0.001).

No significant difference was seen when major common comorbidities were compared between viral, bacterial, co-infection and non-infective exacerbations.

Compared to non-viral exacerbations, exacerbations with positive virus PCR (A and C) had lower prevalence of bronchiectasis (2.9% v 11.7%, p=0.12) and cardiac failure (5.7% v 23.4% p=0.02).

Exacerbation symptoms and prehospital care

There was no significant difference in median total CAT scores between exacerbation subtypes with the exception of CAT item 2 (phlegm) which was highest in co-infection (p=0.007. Figure 10). There was no significant difference in BAP-65 scores between the exacerbation subtypes. Rates of medical consultation prior to hospital attendance were highest in the co-infection group and lowest in the non-infective group (p=0.019). Rates of pre-hospital antibiotic (p=0.024) and oral corticosteroid (p=0.029) followed the same pattern.

Table 10. Exacerbation characteristics according to infection subtype

Patient characteristics; n (%), (mean/SD), median [IQR]	**A (Viral)**	**B (Bacterial)**	**C (Coinfection)**	**No Infection**	**p**
n	35	61	8	44	
age	71.5/10.1	73.3/9.5	69.5/15.8	69.8/10.7	0.36
Male	22 (63)	39 (64)	5 (63)	26 (59)	0.97
Freq. exacerbator (hospital)	3 (9)	27 (44)	1 (13)	12 (27)	0.02*
Current smoker	14 (40)	15 (25)	3 (38)	15 (34)	0.43
Pack year	39 [25-55]	45 [28-60]	46 [25-114]	32 [22.5-47.5]	0.35
BMI (kg/m2)	25.0/5.4	25.2/6.1	25.1/5.8	23.9/7.6	0.78
FEV_1 (L)	1.05 [0.9-1.4]	1.09 [0.78-1.32]	1.41 [1.13-2.6]	0.88 [0.6-1.39]	0.14
FEV_1 (% predicted)	49.2 [36-62]	46.8 [36-55]	71.2 [47-73]	39.2 [29-54]	0.18
TLCO (% predicted)	39.1 [35-52]	31.3 [25.-40]	36.9 [24-51]	42.4 [28-55]	0.01*
mMRC	3 [2-4]	5 [4-5]	4 [3-5]	4 [3-5]	<0.01*
Days since symptom onset	5 [3-10]	4 [3-7]	6.5 [4-18.5]	4 [2-14]	0.55
Exacerbation characteristics					
Prior contact with HCP	27 (77)	35 (57)	8 (100)	24 (55)	0.019*
Pre-hospital antibiotics	22 (63)	24 (39)	6 (75)	16 (36)	0.024*
Pre-hospital OCS	13 (37)	13 (21)	4 (50)	6 (14)	0.029*
CAT total	31.5 [25-36]	28.5 [24-33]	32 [29-37]	30 [26-33]	0.18
HADS total	17.1/8.0	16.1/9.1	17.5/11.8	17.4/8.5	0.9
BAP-65 Class	2 [2 – 3]	3 [2 – 3]	2 [2 – 3]	2 [2 – 3]	0.15
Fever	3 (9)	19 (31)	2 (25)	0 (0)	<0.001*
WCC	10.4/3.7	13.0/5.1	14.8/3.7	10.0/3.0	0.0002*
Neutrophils	7.9 [5.6-10.4]	9.6 [6.5-12.9]	11.0 [9.4-14.3]	6.8 [5.6-8.4]	0.0001*
CRP (mg/L)	19 [5–44]	67 [33-156]	113 [65-167]	4 [2-7]	0.0001*
Eosinophils	0.03 [0-0.16]	0.04 [0-0.13]	0.04 [0-0.13]	0.24 [0.08-0.46]	0.001*
pH	7.35 [7.33-7.4]	7.38 [7.31-7.42]	7.41 [7.39-7.43]	7.32 [7.27-7.38]	0.004*
P_vCO_2	48.2/10.71	49.4/12.54	42.6/5.79	54.5/13.8	0.03*
Bicarbonate (mmol/L)	26.6/4.4	28.5/4.5	26.4/3.6	29.3/5.7	0.075
Base excess	1.6/4.0	3.7/3.9	2.0/3.5	4.1/5.2	0.066
Glucose (mmol/L)	7.1/6.5	7.1/6.1	8.3/6.7	6.9/6.1	0.41
Lactate (mmol/L)	1.55/1.1	1.4/1.15	1.75/1.4	1.6/1.2	0.26
NT-proBNP (ng/L)	422 [117-1190]	406 [176-1545]	351 [234-2580]	263 [152-853]	0.71
BNP>ULN	20 (69)	32 (71)	6 (86)	27 (68)	0.805
Hs-TnI (ng/L)	8 [4-23]	10 [6-33.5]	33 [4-74]	8 [5-20]	0.52

Hs-TnI>ULN	5 (17.2)	16 (35.6)	4 (57.1)	8 (20.0)	0.065
Creatinine (micromol/L)	72.5/64	77/62	81/54.5	66/55	0.39
Clinical management/outcomes					
Antibiotics (inpatient), n (%)	35(100)	61(100)	8(100)	40(90.9)	0.02*
Systemic CS (inpatient), n (%)	35(100)	58(95.1)	8(100)	42(95.5)	0.55
NIV (ED), n (%)	5(14.3)	12(19.7)	1(12.5)	15(34.1)	0.14
NIV (ward), n (%)	5(14.3)	3(4.9)	0(0)	10(22.7)	0.03
HDU/ICU, n (%)	10(28.6)	14(23)	4(50)	18(40.9)	0.15
Mechanical ventilation, n (%)	2(5.7)	2(3.3)	0(0)	1(2.3)	0.8
Inpatient mortality, n (%)	0(0)	1(1.6)	0(0)	0(0)	0.7
Length of stay [median/IQR]	6 [5-9]	5 [3-8]	6 [5-7.5]	5 [3-8]	0.15

Figure 11. Individual CAT score elements by infective status

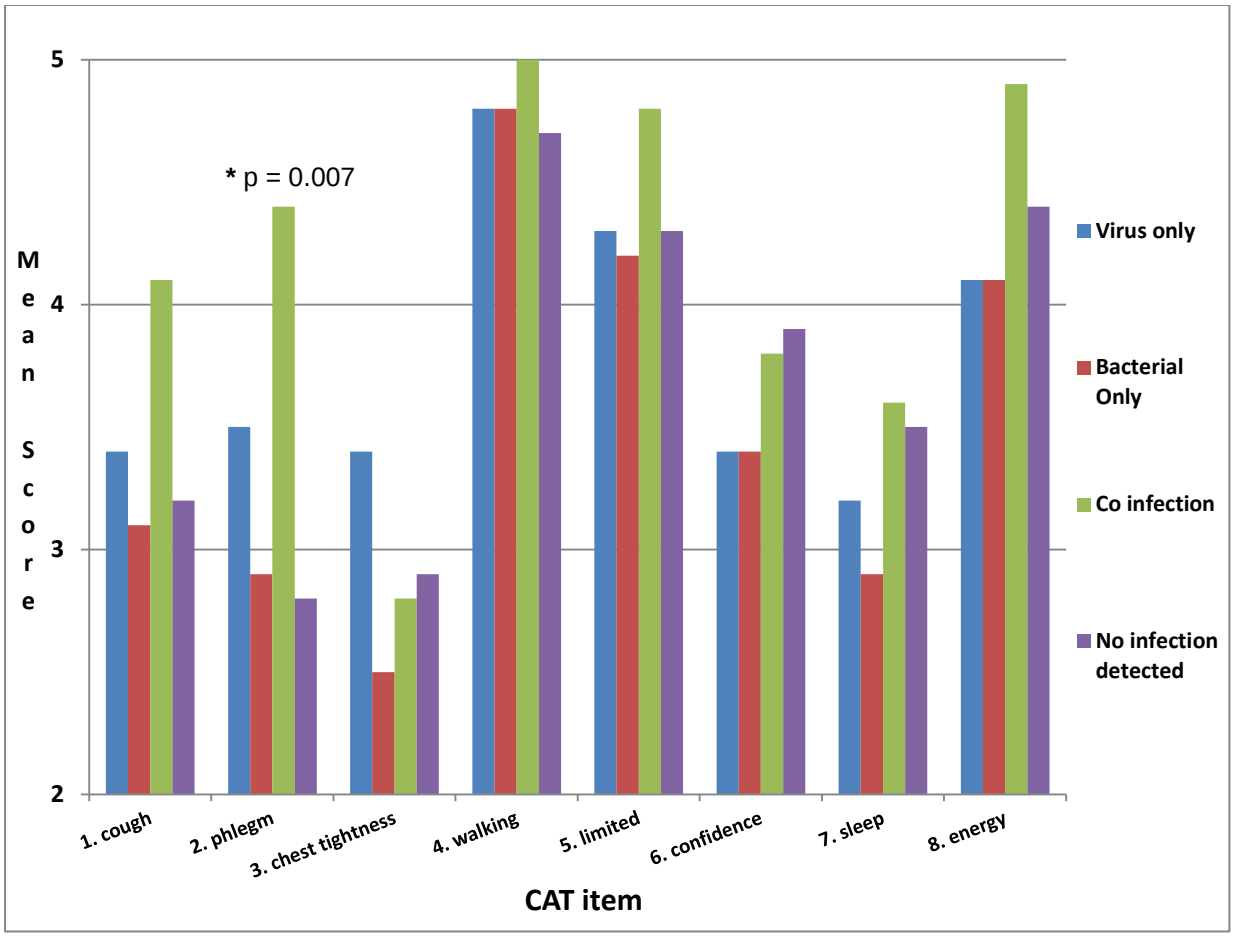


Figure 11. Patients with co-infection rated sputum volume (CAT item 2) significantly higher than other infection subtypes.

Laboratory indices

Co-infection was associated with the highest CRP, white cell count and neutrophil count ($p<0.001$). Non-infective exacerbations were associated with significantly higher eosinophil counts ($p=0.001$). Non-infective exacerbations were also associated with lower pH ($p=0.004$) and higher P_vCO_2 ($p=0.03$). There was no significant difference in lactate between any infective group and the non-infective group. An elevated cardiac biomarker was identified in 60.6% of the overall population with similar prevalence of NT-proBNP and hs-TnI >ULN across all exacerbation infective subtypes. Median NT-proBNP was >ULN in all exacerbation subtypes. The frequency of elevated troponin appeared highest in the co-infection group (57.1%, $p=0.065$).

Clinical management and outcomes

Clinical management was at the discretion of treating clinicians independent of the study team. Antibiotic prescription was significantly lower in non-infective exacerbations ($p=0.02$). Non-invasive ventilation was applied more often in viral and non-infective exacerbations compared to those featuring bacteria ($p=0.03$). The median length of hospital stay for the overall population was 5 days and there was no significant difference in median length of hospital stay between exacerbation subtypes. Short admissions (≤4 days) were most common in the non-infective groups and least common in the groups featuring viral infection (viral 22.9% v bacterial 39.3% v co-infection 12.5% v non-infective 47.7%, $p=0.06$). The short admissions in the non-infective group were observed despite a high need for ventilatory support at the time of admission and frequent high dependency unit admission. Inpatient mortality was very low at 1/155 (0.7%).

Discussion

This study used clinically available methods to assign putative aetiology to hospitalized AECOPDs. The decision rules to define aetiologies were specifically chosen to be applicable in routine hospital practice. A comprehensive perspective was employed to capture not only core aetiologies such as infection but also major associated comorbidities such as anxiety/depression and cardiac dysfunction. While

many previous studies have investigated the aetiologies of AECOPD, particularly those associated with infection, to our knowledge this is the first study to comprehensively assess the full spectrum of AECOPD aetiologies. Our study highlights the diversity and complexity of hospitalized AECOPD with the majority of patients matching more than one categorization.

Exacerbations are sometimes distinguished as infective or non-infective in clinical practice, although this distinction is not made in medication trials. This reflects the difficulty in accurately identifying or excluding infection in AECOPD. Our categorization system identified infection in just over two thirds of AECOPD with the other third deemed non-infective. This distribution is remarkably consistent across almost all studies of AECOPD(Sapey & Stockley, 2006).

We used respiratory virus multiplex PCR on nasopharyngeal swabs to identify or exclude viral infection. Nasopharyngeal swabs were chosen as sputum production does not always feature in hospitalized AECOPD(Hartl et al., 2016) and our intention was to devise a strategy implementable in clinical practice. Our detection rate of around 30% positive viral swabs is similar to previous studies(Hewitt et al., 2016) although lower than some(Papi et al., 2006; Seemungal et al., 2001). This may reflect lower virus detection rates using upper rather than lower respiratory tract samples(Zwaans et al., 2014). In addition, 27.1% of cases were sampled more than a week after perceived exacerbation onset. Studies testing naturally occurring RV in AECOPD have shown marked reduction in viral load over the first week of exacerbation. In common with previous studies, we observed RV to be the most frequently identified virus in AECOPD.

A pragmatic approach was employed to define bacterial infection. Definitive proof of bacterial infection in AECOPD is challenging due to the frequent presence of PPMs in sputum in stable COPD(Hurst, Perera, Wilkinson, Donaldson, & Wedzicha, 2006; Wilkinson et al., 2006), difficulty in obtaining high quality sputum samples, and antibiotic administration prior to sample collection (45.2% in our study). As suggested by other studies we compensated for the relatively low sensitivity of sputum culture in this patient cohort by attributing a bacterial aetiology to exacerbations with fever or raised CRP and negative virus PCR. The CRP threshold used was based on a previous study showing a CRP level of 20mg/L to be optimal to

distinguish bacterial from nonbacterial AECOPD and superior to sputum purulence(Peng et al., 2013). In our cohort of elderly hospitalized patients, often frequent exacerbators with some having coexistent bronchiectasis, *Pseudomonas* and *Haemophilus* were the bacteria most frequently identified and were equally prevalent.

We attributed co-infection as the aetiology only where identification of both bacteria and virus was confirmed by microbiological testing on samples taken at the time of admission. Using these criteria in this cohort, only 5.2% of exacerbations were deemed due to co-infection. This is almost certainly an underestimate since bacterial superinfection is known to be a frequent sequel of viral infection in AECOPD(Mallia et al., 2012). The low prevalence in our study is likely to reflect reduced sensitivity of microbiological testing in a clinical setting, sampling days after exacerbation onset, antibiotic exposure and the effect of only obtaining microbiological samples at a single time point (i.e. admission). In keeping with previous studies, systemic inflammatory markers and symptom scores were highest in patients with co-infection(Wilkinson et al., 2006).

We observed significantly higher CRP in exacerbations associated with bacteria than those without ($p<0.0001$). In contrast, eosinophil counts were significantly higher in non-infective exacerbations ($p<0.0001$). Previous studies have attributed the observation of shorter hospitalization in eosinophilic exacerbations to enhanced corticosteroid responsiveness(Salturk et al., 2015). Absence of infection may be an alternative explanation for faster recovery in this group.

We also systematically examined for presence of common non-infective comorbidities associated with exacerbations. A psychological comorbidity was a baseline diagnosis in 36.8% of the population and 24.5% were taking antidepressant/anxiolytic medication. Numerous studies have associated anxiety and depression with increased hospitalization rates, longer hospitalizations and increased mortality in COPD(Al Aqqad et al., 2016; Eisner et al., 2010; Gudmundsson et al., 2005; Laurin et al., 2012; Yohannes et al., 2010) however the nature and direction of the relationship between physical frailty, psychological morbidity and exacerbation rates remains unclear. Symptoms of anxiety/depression may potentially represent a “treatable trait” in AECOPD. We therefore only

categorized depression/anxiety as a relevant contributor to our exacerbation phenotyping process when symptom scores were acutely elevated. Although significantly more common amongst those with established diagnoses of psychological morbidities, very high HADS scores were identified in 21.9% of the AECOPD population. Of this highly symptomatic group, over half had no diagnosed psychological disorder and only 40% were taking antidepressant/anxiolytic medication.

The prevalence of pulmonary embolism (PE) in AECOPD is controversial(Chan, Colice, & Shorr, 2009). Studies reporting a high prevalence of up to 25% have restricted their evaluation to AECOPD of unclear aetiology(Tillie-Leblond et al., 2006) or diagnosed PE in the absence of visualized thrombus(Shapira-Rootman, Beckerman, Soimu, Nachtigal, & Zeina, 2015). Over-diagnosis of PE, particularly when solitary or subsegmental emboli appears high(B. D. Hutchinson, Navin, Marom, Truong, & Bruzzi, 2015). In contrast, a study of unselected moderate to severe COPD presentations (similar to our study population) reported a prevalence of only 3.3% overall, and only 1.3% where clinical suspicion of pulmonary embolism was low(Rutschmann et al., 2007). In our study, exclusion of pulmonary embolism was at the discretion of the treating physician and 6/6 (100%) CTPAs were negative for PE.

Cardiovascular disease is common in COPD(Feary, Rodrigues, Smith, Hubbard, & Gibson, 2010) and exacerbations are associated with higher rates of major cardiovascular events(Donaldson et al., 2010). In addition, recent studies have found elevated cardiac biomarkers such as high-sensitivity troponin and NT-proBNP during exacerbation in the absence of diagnosed acute cardiac disorder. While the underlying causes of this “subclinical“ cardiac dysfunction in AECOPD are unclear, elevated cardiac biomarkers are associated with reduced survival and increased rates of cardiovascular events(Baillard et al., 2003; Campo et al., 2015; Fruchter & Yigla, 2009; Hoiseth et al., 2016; Pavasini et al., 2015). Our cohort had a similar baseline prevalence of diagnosed cardiovascular disorder to previous studies(Aliyali, Mehravaran, Abedi, Sharifpour, & Yazdani Cherati, 2015; Almagro et al., 2012; Antonelli Incalzi et al., 1997). We found levels of cardiac biomarkers at AECOPD to be greater than the upper limit of normal in the large majority of cases. Absolute levels of troponin and NT-proBNP were higher in those with known cardiovascular

diagnoses, particularly cardiac failure, however elevated levels remained common in those with no cardiovascular diagnosis. This raises the possibility that undiagnosed cardiac disorder may be common and potentially unmasked by the acute stress of exacerbation.

Environmental pollutants have been linked to higher levels of respiratory symptoms in COPD(Peacock et al., 2011) and increased hospitalizations(Li et al., 2016). Measurement of local environmental pollution was beyond the scope of this study but environmental factors identified by the patient were assessed. The scope of environmental factors was broadened to encompass the social and therapeutic support networks that many patients require to maintain daily living in the community. Almost half of the study population were dependent upon others for activities of daily living either in the community or residential accommodation. Despite this, our assessment only identified an environmental factor as a direct precipitant for admission in 2% of admissions.

A small group was identified in whom no specific aetiology was identified by our categorization. This group had the highest rate of frequent exacerbator status, earliest presentation to hospital and the highest rates of non-invasive ventilation. They likely represent a group with minimal ventilatory reserve amongst whom hospital admission can be precipitated by a relatively minor factors leading to deterioration followed by hospital presentation.

Deliberations regarding infective and non-infective exacerbations have often implicated alternative pathologies such as cardiac dysfunction as potential explanations for non-infective exacerbations. Our data suggests that major comorbidities such as cardiac dysfunction or psychological morbidity are highly prevalent in all exacerbation subtypes and should be considered as co-factors in exacerbation rather than unique causes. Indeed, a striking finding of this study is that most exacerbations featured multiple aetiologies, highlighting the complexity of AECOPD and the need for detailed assessment.

We first made comparisons between infective and non-infective exacerbations, and subsequently between infection subtypes. Comparing infective to non-infective exacerbations, there were no statistically significant differences in demographics or lung function. As expected markers of infection such as white cell count and CRP

were higher in the infective group. Notably, eosinophils were significantly lower in the infective group. This may reflect either acute suppression of eosinophil counts by infection, the presence of eosinophilic inflammation in the non-infective group, or both, and is explored in Chapter 3. Indices of ventilatory failure and provision of non-invasive ventilation were greater in the non-infective exacerbations, suggesting poorer ventilatory function in this group despite a similar FEV_1. Despite a high need for high dependency unit care, non-infective exacerbations were frequently discharged relatively quickly from hospital suggesting rapid resolution of exacerbations in the absence of infection.

Comparison between infective subtypes identified a number of differences between the groups. Frequent hospital exacerbator status was most common in the bacterial group and the non-infective group that may reflect the effects of both bacterial colonization and advanced disease. Markers of inflammation were highest in the coinfection group and lowest in the non-infective group. The non-infective group had higher levels of ventilatory failure on admission despite not scoring higher on a severity score (BAP-65). Exacerbations featuring viral infection appeared to take longer to resolve.

There were no differences in mortality or mechanical ventilation rates in this study cohort and the overall mortality rate was extremely low. In data from a separate retrospective study in our health care network, we observed an inpatient mortality rate of 3% in all AECOPD between 2 major hospitals over 1 year. The extremely low mortality rate of 0.7% in this prospective study may reflect exclusion of patients with altered conscious state, those admitted directly to the Intensive Care Unit and restriction of the study cohort to admissions under the Respiratory Unit and excluding General Medicine Unit admissions, patients who would generally be older with more comorbidity. In addition, severe outcomes of AECOPD such as inpatient mortality and mechanical ventilation are known to relate primarily to patient factors such as age, severity of airflow obstruction and diagnosed multi-morbidity whereas we compared patient outcomes according to exacerbation aetiology.

The current study has important limitations. Identifying the cause of an AECOPD using a clinically applicable methodology requires some assumptions, chiefly that the tests employed are sensitive and specific. We categorized viral infection using a

single nasopharyngeal swab at admission that may have generated both false positive (patients are ‘colonised’) and false negative results. However, rates of virus detection in stable COPD and hence ‘colonisation,’ are relatively low(Papi et al., 2006). Accurate identification of bacterial infection as the cause of an exacerbation is difficult and we adopted a pragmatic approach assuming that other evidence of infection with negative virus PCR is likely to be attributable to bacterial infection. CRP is established as a marker of infection in AECOPD(Chang et al., 2015; Clark et al., 2015; Gallego et al., 2016), however, the threshold of 20mg/L that we employed may have led to some misclassification. A very high proportion of our study cohort had also already commenced antibiotic or oral corticosteroid therapy prior to the phenotyping process. Exclusion of this group did not alter the overall distribution of aetiologies in the population but may have affected some individuals results. Similarly, the HADS score thresholds we used to indicate anxiety/depression as an active contributory aetiology to exacerbation can only be considered exploratory. We categorized cardiac dysfunction based upon either a high-sensitivity troponin I or NT-proBNP value above the upper limit of normal. Elevated cardiac biomarker levels were extremely common in this population and to a similar degree in all exacerbation subtypes. This suggests that acute cardiac dysfunction should be considered a frequent component of hospitalized AECOPD - not an alternative aetiology. Levels were highest in those with baseline cardiovascular diagnoses suggesting that these blood biomarkers reflect underlying cardiovascular health. High levels were also observed in those without known cardiovascular diagnoses suggesting that cardiovascular disease may be under diagnosed in an AECOPD population. Using a higher biomarker threshold to define cardiac dysfunction may have greater specificity to detect cardiac dysfunction and to assess the impact on clinical outcomes.

Our study demonstrates that a comprehensive aetiological phenotyping process using routine methods in hospitalized AECOPD is feasible. The strategy also reveals the complexity and diversity of AECOPD. Important differences in patient behaviour and admission outcomes were identified between aetiological phenotypes. The impact of exacerbation aetiological phenotype on post discharge outcomes such as readmissions and survival should be explored in future studies. Ultimately, the most informative phenotyping may be achieved through integration of key patient factors with key exacerbation factors in larger research cohorts. The most feasible

methodology to achieve this is also an area for future study but our reported methodology is practical, simple and clinically applicable and can be tested in general hospital populations.

CHAPTER 3

IMPLICATIONS OF LOW AND HIGH EOSINOPHILS IN HOSPITALIZED EXACERBATIONS OF COPD

3.1 DECLARATION 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	**Contribution**
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

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**	**Contribution (student co-authors only)**
Dr C Osadnik	Aided in data analysis and manuscript preparation.	
Dr A Wong	Aided in data collection.	
Dr AM Wong	Aided in data collection.	
Dr Michael Qiu	Aided in data collection and analysis.	
Ms A Tran	Aided in data collection.	
A/Prof. K Hamza	Aided in data analysis.	
Dr PT King	Aided in hypothesis generation, data analysis and manuscript preparation.	
Prof PG Bardin	Aided in hypothesis generation, data	

	analysis and manuscript preparation.	

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**

3.2 INTRODUCTION TO CHAPTER

As outlined in Chapter 1, peripheral blood eosinophil counts may be a useful biomarker to guide therapy in COPD. Corticosteroids are an established therapy in both stable COPD and exacerbations of COPD, however their role is controversial(Vogelmeier et al., 2017). A subset of COPD patients exhibit evidence of eosinophilic inflammation(Singh et al., 2014). Corticosteroids effectively suppress eosinophilic inflammation and this process may underlie the modest benefits from corticosteroids in unselected COPD populations. In a double-blind, placebo-controlled crossover randomized controlled trial (RCT) of Prednisolone in stable COPD, improvements in airflow obstruction, respiratory symptoms and walk distance studies were only observed in the subset with the highest sputum eosinophil counts(Brightling et al., 2005). In a similar study comparing inhaled mometasone and placebo in stable COPD, improvement in FEV_1 was again only seen in those with the highest sputum eosinophils(Brightling et al., 2005). Sputum eosinophil counts >3% were identified at exacerbation onset in 28% of a small community AECOPD cohort(Bafadhel et al., 2011). Unfortunately, technical challenges in obtaining and processing sputum eosinophil samples mean that it has not become established in routine clinical practice. However, a high correlation between sputum and blood eosinophil counts has been identified, with an area under the receiver-operating curve (ROC) of 0.95 (95% CI 0.87-1.00) for percentage blood eosinophils to predict a sputum eosinophil-associated exacerbation(Bafadhel et al., 2011). In this study, a cutoff of >2% blood eosinophils gave a sensitivity of 90% and specificity of 60% for identifying sputum eosinophilia of >3% at exacerbation. In contrast to sputum eosinophils, the blood eosinophil count is routinely available. As a result, numerous studies have investigated a threshold of >2% eosinophils to dichotomize patients as “eosinophilic” versus “non-eosinophilic” in COPD.

“Eosinophilic” COPD has been associated with greater exacerbation risk(Vedel-Krogh, Nielsen, Lange, Vestbo, & Nordestgaard, 2015) but with shorter exacerbation duration(Bafadhel et al., 2016; Salturk et al., 2015) and greater benefit from oral corticosteroids(Bafadhel et al., 2012). A logical hypothesis is that a difference in outcomes between the 2 groups is due to increased corticosteroid responsiveness in the group with the higher eosinophil count. The converse may also be true, low eosinophils may identify a population with poorer exacerbation outcomes. The

association of low eosinophils and infection may even indicate that corticosteroids might delay bacterial clearance and prolong exacerbation in eosinopenic patients.

The reported normal range of blood eosinophils is between 0.05-0.5 10^9. Studies in stable COPD have identified a prevalence of >2% eosinophils in around 70% of COPD patients. At exacerbation, the prevalence of >2% eosinophils is much lower at around 30%(Kang et al., 2016). This suggests that the proportion of blood eosinophils is dynamic in COPD and often falls at the time of exacerbation. A characteristic fall in blood eosinophil counts in response to acute infection was first described as far back as 1893(Bass, 1975). Originally conceived as a response to increased glucocorticoid release from the “stress” of infection, it was subsequently shown to be a specific response to bacterial infection, independent of adrenal function(Bass, 1975; Bass et al., 1980). Very low eosinophils or “eosinopenia” (<0.05 10^9) are a marker sepsis in critical illness(Abidi et al., 2008), and in hospitalized AECOPD, eosinopenia was one of 4 factors predicting inpatient mortality(Steer et al., 2012). Small observational studies have reported longer hospital stays and increased inpatient mortality in eosinopenic AECOPD(Holland et al., 2010; Rahimi-Rad, Asgari, Hosseinzadeh, & Eishi, 2015).

Eosinophil counts may therefore reflect divergent exacerbation characteristics at opposite ends of the spectrum, which in turn underlie the differences in response to corticosteroids. While effective in reducing eosinophilic inflammation, corticosteroids are associated with reduced bacterial clearance and may offer less benefit in infective exacerbations than non-infective exacerbations. Blood eosinophil counts may have the potential to identify both benefit and harm from corticosteroids in AECOPD. Of note, comparing prednisolone versus placebo in a small RCT of AECOPD found prednisolone to shorten duration of eosinophilic exacerbations but be associated with prolonged non-eosinophilic exacerbations(Bafadhel et al., 2012). The presence or absence of infection may be a key determinant of blood eosinophil counts at AECOPD, which in turn, may underlie differential outcomes and treatment responses in those with high and low blood eosinophils.

In the studies outlined, we have revised the commonly used dichotomous classification of eosinophilic versus non-eosinophilic exacerbation. Instead, we have

classified patients as eosinopenic, eosinophilic or normal (neither eosinopenic nor eosinophilic). Patients exposed to oral corticosteroid prior to blood eosinophil count measurement were excluded from the study. To investigate the underlying mechanism for the impact of eosinophils on AECOPD outcomes, we related eosinophil categorization to a putative clinical diagnosis of infection versus non-infection. Analyses were first performed on a retrospective cohort admitted across 2 tertiary hospitals between Sep 2012 and October 2013, identified by searching an emergency department database. AECOPD diagnosis was verified by individual casenote review by a senior clinician. The analyses were then replicated in the prospectively enrolled AECOPD cohort described in Chapter 2.

CHAPTER 3

IMPLICATIONS OF LOW AND HIGH BLOOD EOSINOPHILS IN HOSPITALIZED EXACERBATIONS OF COPD

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3.3 IMPLICATIONS OF LOW AND HIGH BLOOD EOSINOPHILS IN HOSPITALIZED EXACERBATIONS OF COPD

ABSTRACT

Rationale*:* Patients with acute exacerbations of COPD and elevated blood eosinophil counts may derive benefit from corticosteroid treatment and recover more swiftly. Conversely, low eosinophil counts may reflect the presence of infection.

Objectives: We categorized hospitalized exacerbations of COPD according to their admission blood eosinophil count as low, normal, or high, and evaluated associations with infection and clinical outcomes.

Methods*:* Studies were done in patients with hospitalised exacerbations of COPD, first in a retrospective derivation cohort and subsequently in a prospective validation cohort. Patients eligible for the derivation cohort were identified from hospital case notes (n=242). The validation cohort was prospectively recruited on hospital admission (n=99). Blood eosinophil counts were categorized as low ($<0.05*10^9$L), normal ($>0.05*10^9$ but <2%) or high (>2%). Exacerbations were adjudged as being infective if either virus PCR was positive *or* CRP ≥20mg/L. Associations of eosinophils with clinical outcomes were examined and groups compared via Chi-square and Kaplan-Meier statistics.

Main results*:* Findings in the derivation cohort were highly reproducible in the validation cohort. Patients with low eosinophil counts had a higher incidence of infection (low counts - 91%; normal - 67%; high - 48%; p=0.003) and prolonged hospital admission >7 days (low - 34%; normal - 27%; high - 6%; p=0.022). Eosinophil counts were inversely correlated with CRP (r = -0.224, p<0.001). Conclusions*:* Low blood eosinophil counts in exacerbations of COPD portend poorer outcomes. Studies of both high and low blood eosinophil counts in exacerbations of COPD are needed to examine therapeutic and prognostic implications.

Word count: 243

Introduction

Blood eosinophil counts are deemed to be a reliable surrogate of induced sputum eosinophil counts with both measures believed to mirror airway eosinophil-associated inflammation(Bafadhel et al., 2011; Negewo et al., 2016). Higher blood eosinophil levels may identify a 'treatable trait' in COPD(A. Agusti et al., 2016) although the optimal threshold to define eosinophilia in this context has not yet been resolved(Negewo et al., 2016). In stable COPD, higher blood eosinophil counts predict increased risk of severe acute exacerbations (AECOPD)(Vedel-Krogh et al., 2015), and greater exacerbation risk reduction with inhaled corticosteroids(Pascoe et al., 2015). If a threshold of >2% blood eosinophils is used to define eosinophilic exacerbations, it predicts oral corticosteroid (OCS) benefit in community managed AECOPD(Bafadhel et al., 2012), and shorter hospitalization in severe AECOPD(Bafadhel et al., 2016; Salturk et al., 2015). It may not be appropriate however, to dichotomize COPD exacerbations as simply 'high' (eosinophilia) or 'not high' (non-eosinophilia). The non-eosinophilia group will include some eosinophil counts within the normal range but also abnormally low counts. This can have clinical relevance since limited studies have reported that low blood eosinophil counts (eosinopenia) may be a marker of sepsis(Abidi et al., 2008) and may be a predictor of mortality in critical illness(Abidi et al., 2008; Bass et al., 1980) including AECOPD (Duman et al., 2015; Holland et al., 2010; Steer et al., 2012).
The potential benefit of taking both eosinophilia and eosinopenia into account during AECOPD has not been examined. Moreover, complex interactions between infections causing AECOPD and blood eosinophil counts require investigation. We postulated that taking both high and low blood eosinophils into account could improve characterisation of AECOPD and predict key clinical outcomes with the potential to direct therapy. We also explored the impact of using different thresholds to define eosinophilia on associations with clinical outcomes. Some of the results of these studies have been previously reported in the form of abstracts(MacDonald, Osadnik, Qiu, Vasanthakumar, et al., 2016; MacDonald, Osadnik, Qiu, Vasathankumar, et al., 2016).

Methods

Both the derivation (HREC13291Q) and validation cohort (HREC13134A) studies were approved by the Human Research Ethics Committee, Monash Health, Melbourne, Australia.

Patient selection

Derivation cohort: Patients aged >40 years with AECOPD admitted to 2 metropolitan hospitals in Melbourne, Australia, between September 2012 - October 2013 were identified via an emergency department (ED) electronic database. Records were inspected by a Respiratory Physician (MM) to confirm AECOPD and exclude alternative diagnoses. COPD was diagnosed according to GOLD criteria(Vogelmeier et al., 2017) in 161/242 patients or clinical history (applicable symptoms, >10 pack years smoking and absence of diagnosed asthma) where spirometry was unavailable. Patients taking oral corticosteroids (OCS) pre-admission were excluded. Demographics, comorbidities and pharmacotherapy were identified from electronic medical records. Full blood examination, C-reactive protein (CRP; highest value recorded during the first 48 hours of admission), respiratory virus polymerase chain reaction (PCR) from nasopharyngeal swab and sputum culture results, were retrieved from hospital pathology databases. Patients with ≥2 AECOPD hospitalizations in the 12 months prior to the index admission were identified as frequent exacerbators(Hurst et al., 2010).

Validation cohort: Consecutive admissions to Monash Medical Centre with AECOPD were recruited to a prospective observational study of AECOPD. Informed, written consent was obtained. Data from the first AECOPD admission of patients without OCS exposure prior to blood eosinophil count measurement were included. Data obtained from the derivation cohort were collected in the validation cohort. Patients included in the derivation cohort were not eligible for recruitment into the validation cohort leaving a total of 99 patients.

Eosinophil profiling

The eosinophil count from the first full blood examination obtained in hospital was used to designate eosinophil group. Low eosinophil count (eosinopenia) was defined

as <0.05*10^9L(Abidi et al., 2008). High eosinophil counts were defined as >2% total White Cell Count (WCC). Eosinophil counts with neither eosinopenia (<0.05*10^9L) nor eosinophilia (>2% total WCC) were classified as normal (i.e. neither low nor high). Associations between eosinophil classification and clinical outcomes were further explored using different thresholds to define eosinophilia (2%, >0.3*10^9L and >0.5*10^9L).

Exacerbation aetiology

Exacerbations were classified as infective or non-infective using results of virus PCR (AusDiagnostics Highplex, Beaconsfield, Australia) and C-reactive protein (CRP). Detection of virus nucleic acid was considered to reflect virus infection, while a CRP ≥20mg/L in the absence of detectable virus was employed as a surrogate measure of bacterial infection(Peng et al., 2013). Exacerbations were defined as infective when *either* virus PCR was positive *or* CRP ≥20 mg/L. Exacerbations were defined as non-infective when *both* virus PCR was negative *and* CRP<20 mg/L. Exacerbation severity was classified using the blood urea nitrogen, altered mental status, pulse >109 beats per minute, and age> 65 years (BAP-65) criteria (Shorr, Sun, Johannes, Yaitanes, & Tabak, 2011).

Statistical analysis

The principal analysis used data only from patients' first admission. Where possible we normalised non-normally distributed data by application of natural log transformations. Comparisons were made between the three eosinophil groups (low, normal, high). Relationships between clinical outcomes and eosinophil groups were analysed by unpaired t-test and one-way ANOVA (normally distributed data) or Mann-Whitney and Kruskal-Wallis testing (non-parametric data). Chi square analyses were used for categorical data. Survival analyses were conducted using Kaplan-Meier curves and log-rank tests. Statistical significance was accepted at $p<0.05$. All analyses were conducted on Stata MP 14.1(Statacorp, College Station, Texas, USA).

Results

For the derivation cohort, electronic case-note review of 1781 Emergency Department (ED) presentations with potential AECOPD identified 518 confirmed AECOPD admissions in 374 individuals. After excluding patients with pre-hospital OCS use (n = 132), 242 admissions were eligible for analyses (Figure 1).

The validation cohort comprised 193 AECOPD admissions in 153 individuals, of which 115 index events involved no pre-hospital OCS treatment. Sixteen of these were ineligible for inclusion due to prior representation within the derivation cohort, leaving 99 for analysis (Figure 1).

Baseline demographic data were similar in both cohorts across the three eosinophil groups (Table 1). Eosinopenia was more common than normal counts and eosinophilia in both the derivation (39% vs 31% vs 30%, respectively) and validation (36% vs 33% vs 31%, respectively) cohorts. Eosinophil profiles and their relationship to WCC, neutrophil counts and CRP are shown in Table 2. Low eosinophil counts were associated with higher neutrophil counts. CRP measurements differed markedly between the eosinophil groups across both cohorts ($P < 0.001$ for both; Table 2)

Eosinophil profiles and infection

Most patients with AECOPD had evidence of infection based on the criteria used in the study. Infection was detected in 84.2% of patients in the retrospective cohort and in 71.4% of patients in the validation cohort. However, infection was less frequently detected in patients who had higher blood eosinophils (incidence for those with low eosinophils - 90.6%; normal - 66.6% and high eosinophils - 47.6%; p=0.003 in validation cohort; Figure 2a). In both cohorts absolute eosinophil counts were significantly higher in AECOPDs not associated with infection vs. AECOPDs categorised as having infection (data for validation cohort: median $0.185*10^9$L vs. $0.04*10^9$L, respectively, $P < 0.001$; Figure 2b). Blood eosinophil counts correlated negatively with CRP (r=-0.262 and -0.244 across both cohorts, $P < 0.001$; Figure 2c,d)

Eosinophil profiles and clinical outcomes

Patients with eosinopenia had slightly greater exacerbation severity as reflected by median BAP-65 scores compared to those with normal or high eosinophil counts in the derivation cohort (*P* = 0.037; Table 3), although no difference was seen in the validation cohort. Prescription of systemic corticosteroids or antibiotics did not differ significantly between the low, normal and high eosinophil groups in either cohort (Table 3). Kaplan-Meier analysis identified a significant difference between eosinophil groups in hospital length of stay (derivation cohort *P* = 0.009 and validation cohort *P* < 0.001; Figure 3a, b). Admissions lasting >7 days were higher in low vs. normal vs. high eosinophil categories, respectively, in the derivation (30% vs 17% vs 14%; *P* = 0.03) and validation cohorts (34% vs 27% vs 6%, *P* = 0.022; Table 3).

Eosinophil profiles defined by different cut-offs

Changes to the cut-off threshold to define eosinophilia (from >2% to >0.3*10^9 to >0.5*10^9, for all comparisons) resulted in a decrease in the proportion of patients classified as eosinophilic (mean of both cohorts) from 30.2% to 22.3% to 10.9%, respectively (pooled data). The incidence of eosinophilic AECOPDs associated with infection progressively decreased with changing cut-off from 14.0% to 10.0% to 5.2%, respectively. Associations between eosinophil groups and total WCC, neutrophil counts and CRP measurements were unchanged as were associations with clinical outcomes.

Discussion

This study in hospitalized AECOPD investigated the full profile of eosinophil counts (low, normal and high) and evaluated outcomes as well as associations with putative infection. Low eosinophil counts were linked to evidence of infection and these patients demonstrated a significantly longer in-hospital stay. Distinguishing exacerbations with low, normal and high eosinophil counts may be a simple first step towards 'phenotyping' of AECOPDs(MacDonald et al., 2011). Associations of high eosinophils with corticosteroid response and low eosinophils with infection, suggest direct relevance to AECOPD therapy.

There is considerable interest in blood eosinophils as a biomarker to guide corticosteroid prescription in COPD(Pascoe et al., 2015; Watz et al., 2016). Higher eosinophil counts in sputum identify the subset of stable patients who derive benefit from oral or inhaled corticosteroids(Brightling et al., 2005; Brightling et al., 2000). The strong correlation between sputum and blood eosinophil counts in stable and exacerbated COPD(Bafadhel et al., 2011; Negewo et al., 2016) provided the opportunity to explore broader application of this concept. Prevalence of eosinophilia (>2%) may be as high as 70% in stable COPD(DiSantostefano, Hinds, Van Le, & Barnes, 2016; Pavord, Lettis, Anzueto, & Barnes, 2016) but in the current studies was approximately 30% in both the derivation and validation studies. This was consistent with other studies in AECOPD(Bafadhel et al., 2016; M. Bafadhel et al., 2016; Kang et al., 2016) Importantly, the lower prevalence of eosinophilia was observed in the absence of oral corticosteroid use suggesting lower counts were likely due to other factors such as acute infection.

This study is the first to concurrently examine the clinical implications of low, normal and high blood eosinophil counts in AECOPD. Previous comparable studies have either grouped patients as having 'high or normal'(Bafadhel et al., 2016; Duman et al., 2015; Salturk et al., 2015) or 'low or normal' eosinophils(Holland et al., 2010; Rahimi-Rad et al., 2015). Even after exclusion of patients with pre-hospital OCS exposure in our studies, eosinopenia was the most prevalent eosinophil profile. A significant inverse relationship between eosinophil counts and CRP was also observed across both cohorts (Table 2 and Figure 2). This finding is consistent with previous literature(Bafadhel et al., 2016; Bafadhel et al., 2011; Kang et al., 2016)

and, in conjunction with the inverse relationship of eosinophils to blood neutrophils, likely reflects a response to acute infection(Bass et al., 1980).
The reduced hospital length of stay in patients with eosinophilia may indicate not only greater corticosteroid responsiveness, but also a lesser burden of infection. Moreover, whilst patients with high blood eosinophils may benefit from corticosteroids, in those with a blood eosinopenia there may be less benefit or possibly even harm due to delayed clearing of infection. This hypothesis is supported by the observation of slower exacerbation recovery with Prednisolone compared to placebo in outpatient AECOPD with eosinophils *below* 2%(Bafadhel et al., 2012).Our data evaluating the impact of different cut-offs to define eosinophilia in AECOPD suggests use of a stricter threshold (>0.5*10^9L) appears to increase the robustness of group classifications, without altering the nature of associations with clinical outcomes. The 'optimal' threshold to define eosinophilia is therefore likely to depend upon the specific clinical context in which it is being applied.

Some aspects of this study warrant specific attention. Derivation cohort data were retrospectively collected, however inclusion was based upon individual case record review by a respiratory physician rather than hospital discharge codes. Patients were excluded if exposed to OCS prior to hospital admission and no eosinophil data were missing in either cohort. As retrospective studies have inherent weaknesses that may limit potential prospective or 'real-world' application, results from the derivation cohort were corroborated with an independent, prospective validation cohort. Definitive proof of infection in AECOPD can be difficult in routine clinical practice. The definition of infection we employed was pertinent in a clinical context and based on evidence that PCR for virus infections and CRP as a proxy for bacterial infection can identify infection in a majority of AECOPD(George et al., 2014; Peng et al., 2013). Virus detection by PCR is a sensitive diagnostic technique that provides same-day results as a result of advances in molecular virology and diagnosis(Mahony, 2008). However, detection of bacteria in sputum is insensitive and takes longer. CRP has therefore been used as a proxy measure, with a cut-off of 10mg/L shown to exhibit 65% sensitivity and specificity to identify bacteria associated exacerbations(Bafadhel et al., 2011), and levels >50mg/L predictive of antibiotic benefit in hospitalized AECOPDs(Daniels, Snijders, et al., 2010). We opted for a level of ≥20mg/L as it appears to be the best predictor of bacteria in sputum at

the time of exacerbation(Peng et al., 2013). This method, however, would benefit from prospective confirmation.

In summary, our data demonstrate, for the first time, the importance of evaluating the full spectrum of high, normal and low blood eosinophil counts in hospitalised AECOPD. Studies are indicated to determine whether low and high blood eosinophils can be integrated into AECOPD management algorithms to target populations for either antibiotics and/or corticosteroids.

Word count 2209

Figure 1. CONSORT diagram of participant flow

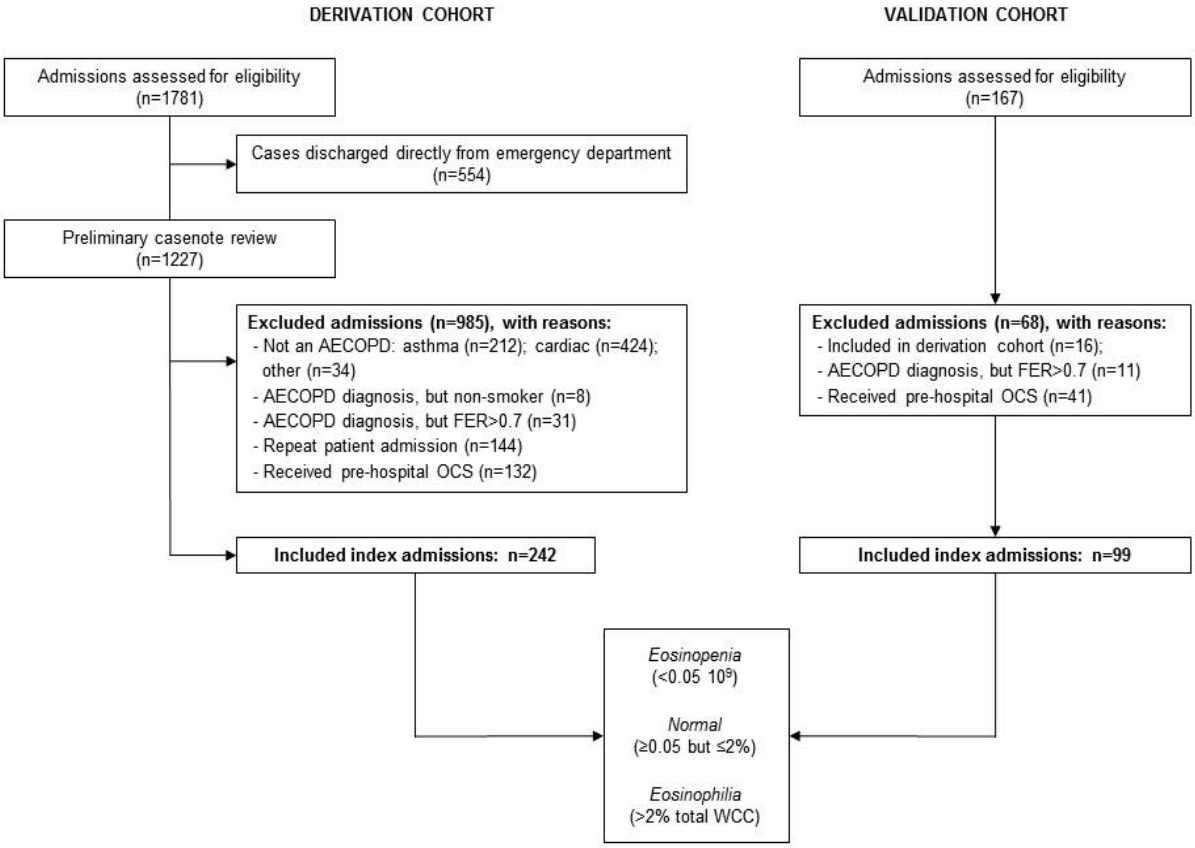


Figure 1. In the derivation cohort AECOPD were identified by individual casenote review of patients identified by an emergency department database search. For the validation cohort, AECOPD patients were recruited prospectively to an observational study. Analyses were performed on the 2 cohorts independently.

Table 1. Low, normal and high eosinophil counts in AECOPD: baseline demographic and comorbidity data

	Retrospective derivation cohort (n=242)						Prospective validation cohort (n=99)					
	N	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**	**N**	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**
Distribution, n (%)	*242*	242 (100%)	95 (39%)	75 (31%)	72 (30%)	N/A	*99*	99 (100%)	35 (36)%	33 (33)%	31 (31%)	N/A
Male:Female	*242*	136:106	52:43	41:34	43:29	0.772	*99*	64:35	19:16	21:12	24:7	0.144
Age (years)	*242*	73.6 (9.9)	74.7 (10.3)	73.5 (8.6)	72.1 (10.6)	0.259	*85*	70.9 (10.7)	71.8 (11.2)	71.1 (10.5)	69.9 (10.7)	0.943
BMI kg/m^2	*161*	26.8 (7.1)	25.6 (6.5)	27.1 (6.4)	28.0 (8.5)	0.211	*85*	25.7 (6.1)	25.2 (6.9)	26.6 (6.9)	25.4 (4.2)	0.657
FEV_1 (L)	*161*	1.1 (0.5)	1.1 (0.4)	1.2 (0.5)	1.2 (0.5)	0.318	*84*	1.2 (0.6)	1.1 (0.5)	1.0 (0.5)	1.3 (0.7)	0.082
FEV_1 (% predicted)	*161*	50 (19)	47 (16)	53 (22)	51 (17)	0.209	*84*	46 (20)	46 (22)	44 (20)	49 (20)	0.658
FEV_1/FVC	*161*	48 (13)	45 (11)	48 (14)	50 (14)	0.160	*84*	46 (14)	47 (14)	45 (16)	46 (12)	0.867
Post-BD ΔFEV_1 (%)	*142*	8 (10)	7 (9)	9 (11)	7 (10)	0.584	*74*	6 (11)	5 (12)	5 (10)	8 (12)	0.444
TLCO	*129*	9.2 (4.3)	9.1 (3.8)	8.5 (4.3)	10.1 (4.8)	0.243	*74*	10.1 (4.8)	9.6 (3.8)	8.4 (3.3)	12.1 (6.1)	0.022*
TLCO (% predicted)	*129*	39 (16)	38 (14)	36 (17)	42 (16)	0.163	*74*	40 (16)	40 (13)	35 (13)	44 (19)	0.130
IHD, n (%)	*242*	56 (23.1)	20 (21.1)	19 (25.3)	17 (23.6)	0.801	*98*	27 (28)	9 (26)	9 (27)	9 (30)	0.927
CCF, n (%)	*242*	51 (21.1)	18 (18.9)	20 (26.7)	13 (18.1)	0.356	*98*	21 (21)	6 (17)	7 (21)	8 (27)	0.647
AF/flutter, n (%)	*242*	55 (22.7)	20 (21.1)	20 (26.7)	15 (20.8)	0.618	*98*	12 (12)	5 (14)	2 (6)	5 (17)	0.395
Diabetes, n (%)	*242*	60 (24.8)	19 (20.0)	19 (25.3)	22 (30.6)	0.292	*98*	15 (15)	5 (14)	6 (18)	4 (13)	0.848
Malignancy, n (%)	*242*	17 (7.0)	9 (9.5)	4 (5.3)	4 (5.6)	0.487	*98*	7 (7)	3 (9)	2 (6)	2 (7)	0.916
Psychiatric disorder, n (%)	*242*	14 (5.8)	6 (6.3)	5 (6.7)	3 (4.2)	0.778	*98*	3 (3)	1 (3)	2 (6)	0 (0)	0.377
Anxiety/Depression, n (%)	*242*	41 (16.9)	8 (8.4)	16 (21.3)	17 (23.6)	0.017*	*98*	31 (32)	11 (31)	12 (36)	8 (27)	0.710
Frequent exacerbator, n (%)	*240*	29 (12.1)	6 (6.5)	12 (16.0)	11 (15.3)	0.103	*98*	22 (22)	7 (20)	8 (24)	7 (23)	0.907
ICS use, n (%)	*242*	194 (80.2)	76 (80)	63 (84)	55 (76.4)	0.511	*98*	77 (79)	27 (77)	27 (82)	23 (77)	0.855
ICS dose/day, mg[1]	*242*	2000 [1000 - 2000]	1800 [1000 - 2000]	2000 [1000 - 2000]	2000 [800 - 2000]	0.660	*98*	1000 [400 - 2000]	1000 [400 - 2000]	1000 [500 - 2000]	800 [256 - 2000]	0.958

Data are mean (standard deviation) or median [interquartile range] unless otherwise specified; * denotes statistical significance between the three eosinophil groups. [1]Reported as budesonide equivalent units. Lung function data (from laboratory database) were available in a subset of patients (n=161 for spirometry; n=129 for TLCO). AF = atrial fibrillation, BD = bronchodilator, BMI = body mass index, CCF = congestive cardiac failure, FEV_1 = forced expiratory volume in the first second, FVC = forced vital capacity, IHD = ischaemic heart disease, TLCO = transfer factor of carbon monoxide.

Table 2. Eosinophil profiles: relationship to WCC, neutrophil counts and CRP.

	Retrospective derivation cohort						Prospective validation cohort					
	N	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**	***n***	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**
Eosinophils (*10^9L)	*242*	0.09 [0.01-0.24]	0.01 [0.00-0.02]	0.11 [0.07-0.16]	0.38 [0.27-0.63]	<0.001*	*99*	0.10 [0.00-0.30]	0.00 [0.00-0.01]	0.10 [0.08-0.16]	0.45 [0.30-0.79]	<0.001*
Eosinophils[1]	*197*	0.11 (0.09-0.13)	0.02 (0.02-0.02)	0.11 (0.09-0.12)	0.40 (0.34-0.46)	<0.001*	*73*	0.16 (0.13-0.22)	0.02 (0.02-0.04)	0.11 (0.09-0.12)	0.46 (0.37-0.58)	<0.001*
WCC[1]	*242*	10.4 (9.9-10.9)	11.3 (10.3-12.4)	10.8 (10.0-11.6)	9.0 (8.3-9.7)	<0.001*	*99*	10.5 (9.7-11.3)	11.1 (9.4-13.0)	10.5 (9.4-11.6)	9.9 (8.8-11.1)	0.484
Neutrophils[1]	*242*	7.4 (7.1-7.9)	8.7 (7.9-9.6)	7.9 (7.3-8.7)	5.6 (5.0-6.3)	<0.001*	*99*	7.6 (6.9-8.3)	8.3 (6.8-10.1)	7.9 (6.9-9.0)	6.6 (5.7-7.6)	0.10
CRP (mg/L)[1]	*193*	23.6 (18.2-30.5)	55.2 (40.5-75.2)	25.1 (15.7-40.1)	6.9 (4.4-10.8)	<0.001*	*95*	22.0 (15.6-30.9)	60.2 (36.5-99.2)	19.4 (12.0-31.6)	8.0 (4.3-14.7)	<0.001*

Data are mean (95% confidence interval) or median [interquartile range] unless otherwise specified; CRP = C-reactive protein, WCC = white cell count. [1]Denotes available data after log-transformation; *Denotes statistical significance between the three eosinophil groups.

Table 3. Low, normal and high eosinophil counts in AECOPD: in-hospital demographic data, comorbidities and clinical outcome data.

	Retrospective derivation cohort (n=242)					Prospective validation cohort (n=99)					
	n	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**	***n***	**Overall**	**Low (<0.05)**	**Normal**	**High (>2%)**	**p**
Distribution, n	*242*	242	95 (39%)	75 (31%)	72 (30%)		*99*	99	35 (36)	33 (33)	31 (31)	
Infection, n (%)	*152*	128 (84.2)	68 (93.2)	38 (82.6)	22 (66.7)	0.002*	*77*	55 (71)	29 (91)	16 (67)	10 (48)	0.003*
No infection, n (%)	*152*	24 (15.8)	5 (6.8)	8 (17.4)	11 (33.3)		*77*	22 (29)	3 (9)	8 (33)	11 (52)	
BAP-65 score	*242*	3 [2-3]	3 [3-3]	3 [2-3]	3 [2-3]	0.037*	*99*	3 [2-3]	3 [2-3]	3 [2-3]	3 [2-3]	0.607
BAP-65 (age>65), n (%)	*242*	195 (80.6)	77 (81.1)	62 (82.7)	56 (77.8)	0.747	*99*	67 (68)	24 (69)	24 (73)	19 (61)	0.614
BAP-65 (urea>9), n (%)	*242*	59 (24.4)	26 (27.4)	16 (21.3)	17 (23.6)	0.650	*99*	14 (14)	5 (14)	5 (9)	4 (13)	0.967
BAP-65 (GCS<14), n (%)	*242*	9 (3.7)	3 (3.2)	4 (5.3)	2 (2.8)	0.668	*99*	4 (4)	3 (9)	0 (0)	1 (3)	0.192
BAP-65 (HR>109), n (%)	*242*	121 (50.0)	58 (61.1)	33 (44.0)	30 (41.7)	0.021*	*99*	49 (49)	14 (40)	17 (52)	18 (58)	0.328
Systemic corticosteroids, n (%)	*241*	226 (93.8)	87 (91.6)	69 (92.0)	70 (98.6)	0.135	*94*	91 (97)	33 (100)	29 (97)	29 (94)	0.340
Antibiotics, n (%)	*242*	230 (95.0)	94 (98.9)	69 (92.0)	67 (93.1)	0.076	*94*	91 (97)	31 (94)	30 (100)	30 (97)	0.393
NIV in ED, n (%)	*242*	67 (27.7)	30 (31.6)	12 (16.0)	25 (34.7)	0.022*	*98*	23 (23)	6 (17)	8 (24)	9 (30)	0.472
NIV outside ED, n (%)	*242*	38 (15.7)	17 (17.9)	10 (13.3)	11 (15.3)	0.714	*98*	12 (12)	4 (11)	6 (18)	2 (7)	0.373
Mechanical ventilation, n (%)	*242*	8 (3.3)	3 (3.2)	1 (1.3)	4 (5.6)	0.357	*98*	5 (5)	3 (9)	1 (3)	1 (3)	0.508
Hospital length of stay, days	*240*	5 [2-7]	6 [2-9]	5 [2-6]	5 [2-6]	0.101	*99*	5 [3-7]	6 [4-8]	5 [4-8]	4 [3-5]	<0.001*
Patients discharged at day 7, n (%)	*240*	190 (79)	66 (70)	62 (83)	62 (86)	0.03	*99*	76 (77)	23 (66)	24 (73)	29 (94)	0.022*
In-hospital mortality, n (%)	*237*	9 (3.8)	4 (4.4)	3 (4.0)	2 (2.8)	0.867	*98*	0 (0)	0 (0)	0 (0)	0 (0)	N/A

Data are median [interquartile range] unless otherwise specified; BAP-65 = Blood urea nitrogen (>9), Altered GCS (<14), Pulse (>109), Age (>65) Scale, GCS = Glasgow Coma Scale, HR = heart rate (beats per minute), ED = Emergency Department, ICU = intensive care unit, NIV = non-invasive ventilation; *Denotes statistical significance between the three eosinophil groups.

Figure 2a. Eosinophils, infective status and CRP

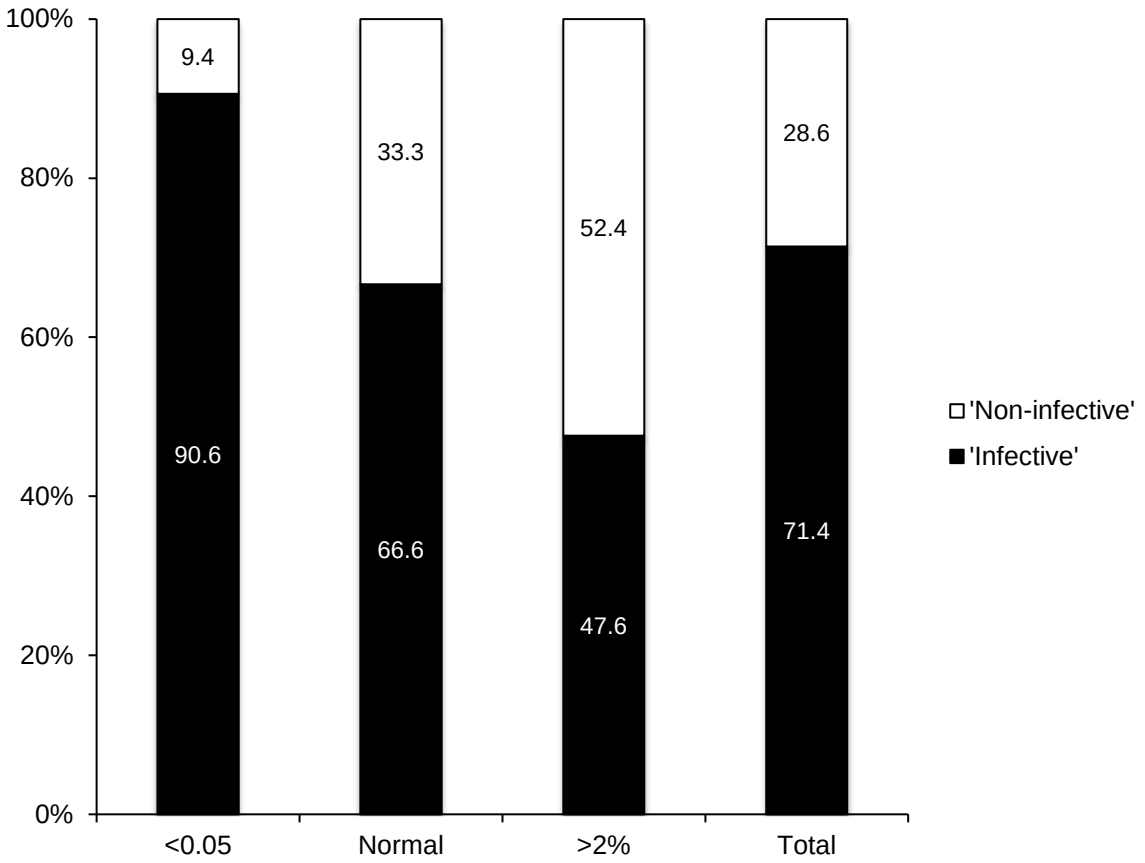


Figure 2a. Proportion of AECOPD with evidence of infection according to eosinophil groups in the validation cohort (*denotes statistical significance between groups; *P* = 0.003);

Figure 2b. Absolute eosinophil counts in infective and non-infective exacerbations

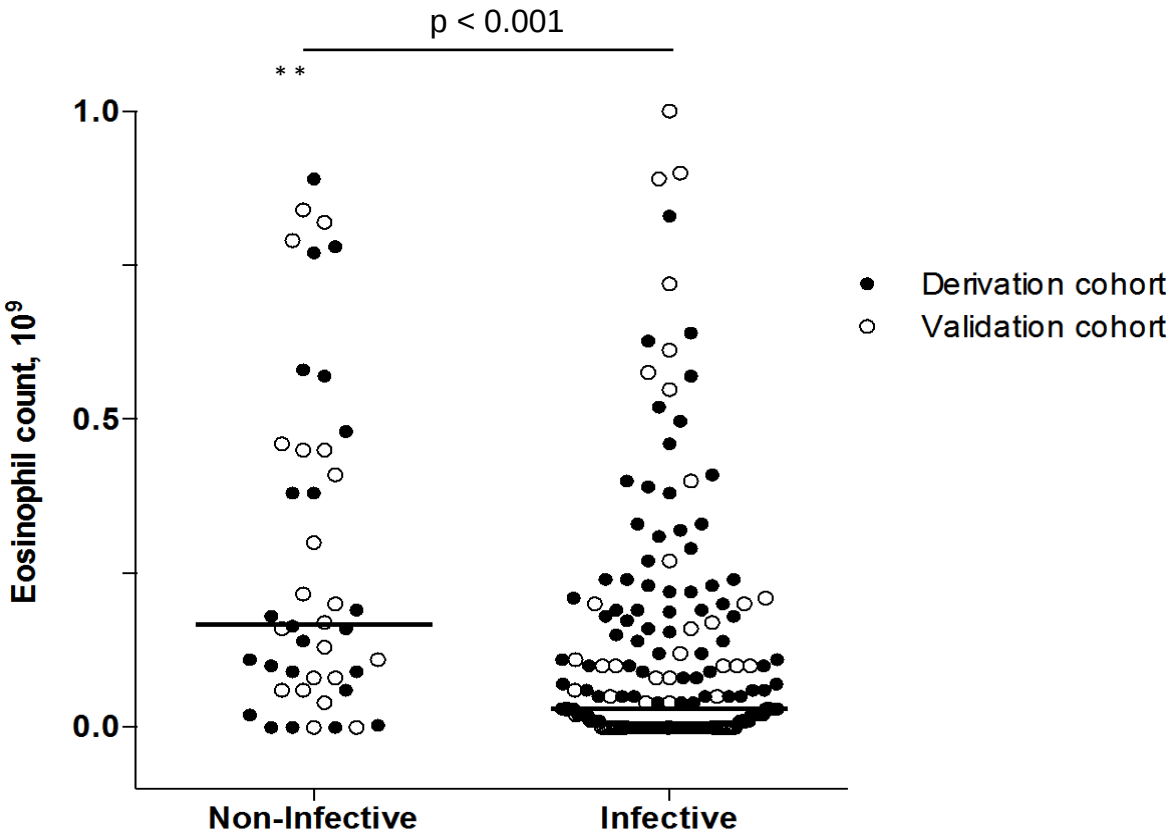


Figure 2b. Relationship between infective status and eosinophil counts. *Denotes outliers (eosinophil count 1.46 for retrospective cohort, 2.67 for prospective cohort); *P* < 0.001 between group with infection vs. group without infection.

Figure 2c. CRP measurements across eosinophil categories

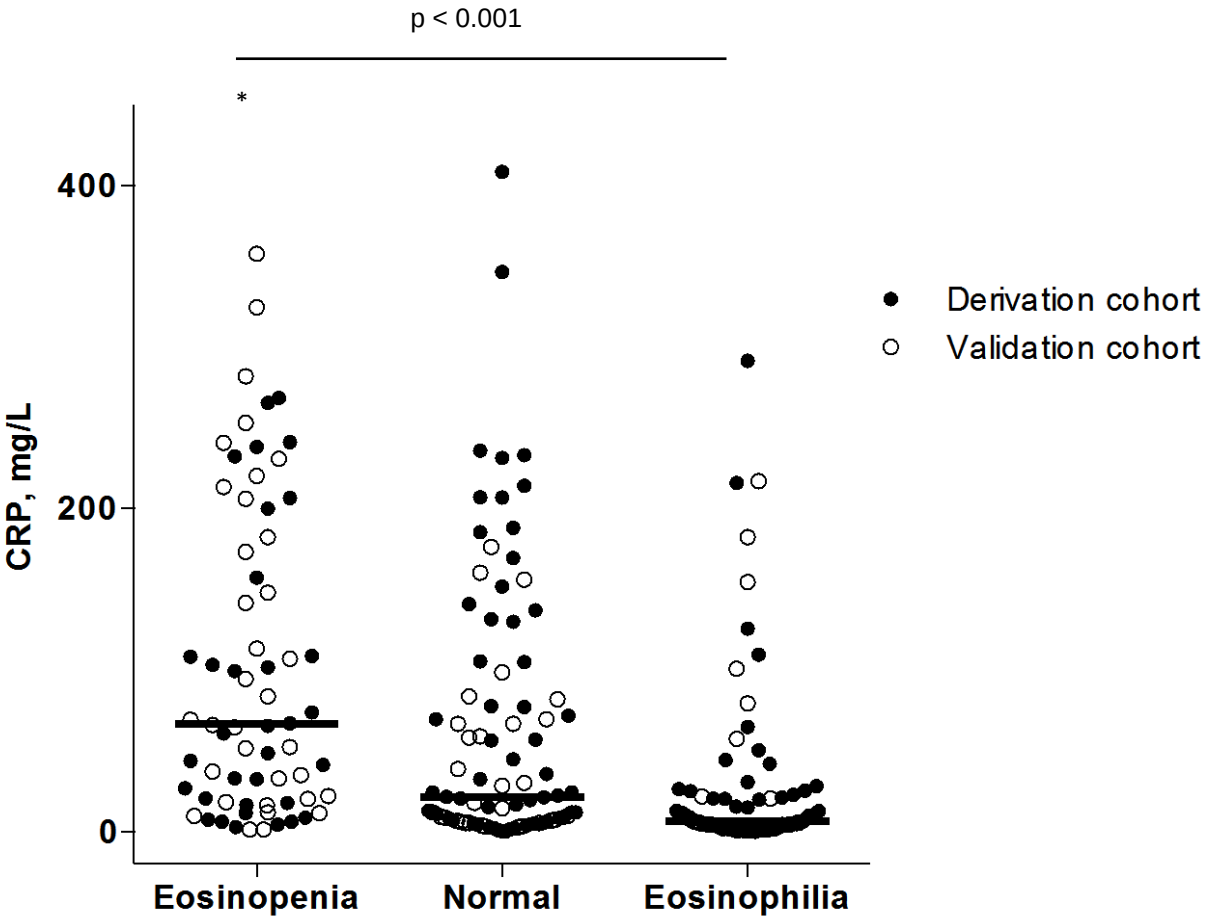


Figure 2c. C-reactive protein levels are shown for each of the 3 categories of eosinophil levels at acute exacerbation of COPD for the derivation (closed circles) and validation (open circles) cohorts.

Figure 2d. Correlation of blood esoinophils and CRP

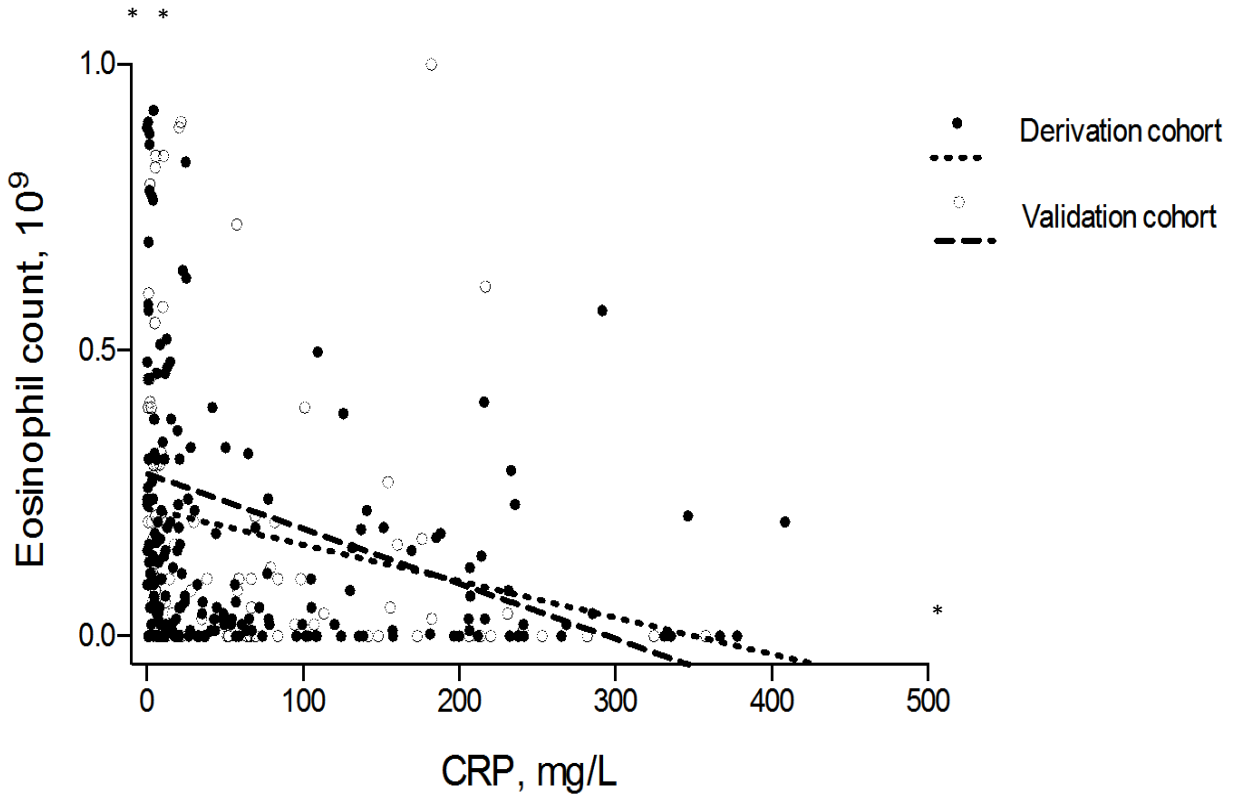


Figure 2d. Correlation between initial blood eosinophil counts and peak 48-hour CRP level for the derivation cohort (closed circles r=-0.262, *P* < 0.001) and validation cohort (open circles r=-0.224, *P* < 0.001). *Denotes outliers at (4.4:1.46), (4.5:2.67) and (530.4:0.0).

Figure 3a. Kaplan-Meier analysis of length of hospital stay in derivation cohort

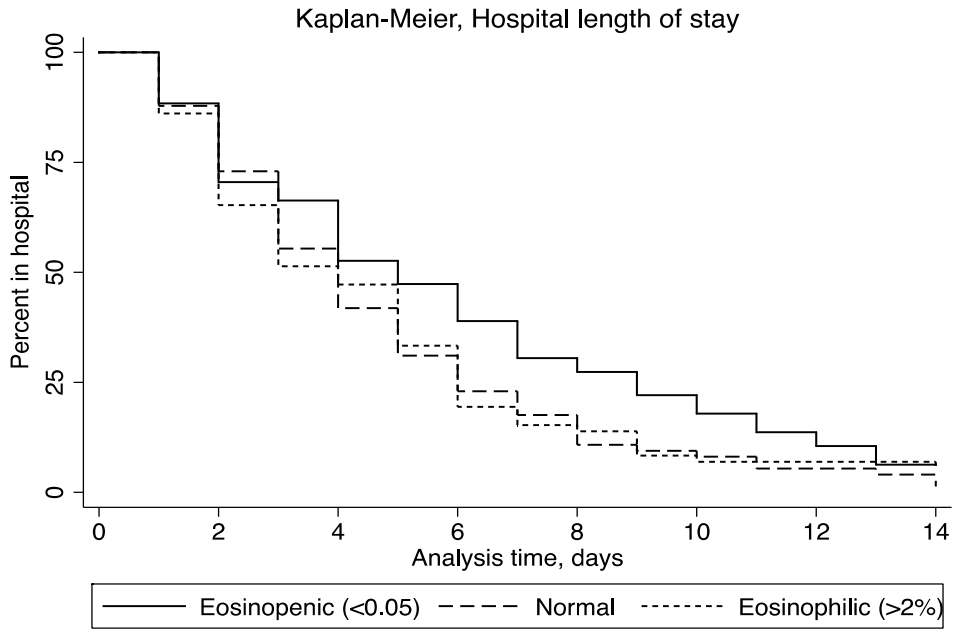


Figure 3a. Kaplan-Meier analysis of length of hospital stay in validation cohort

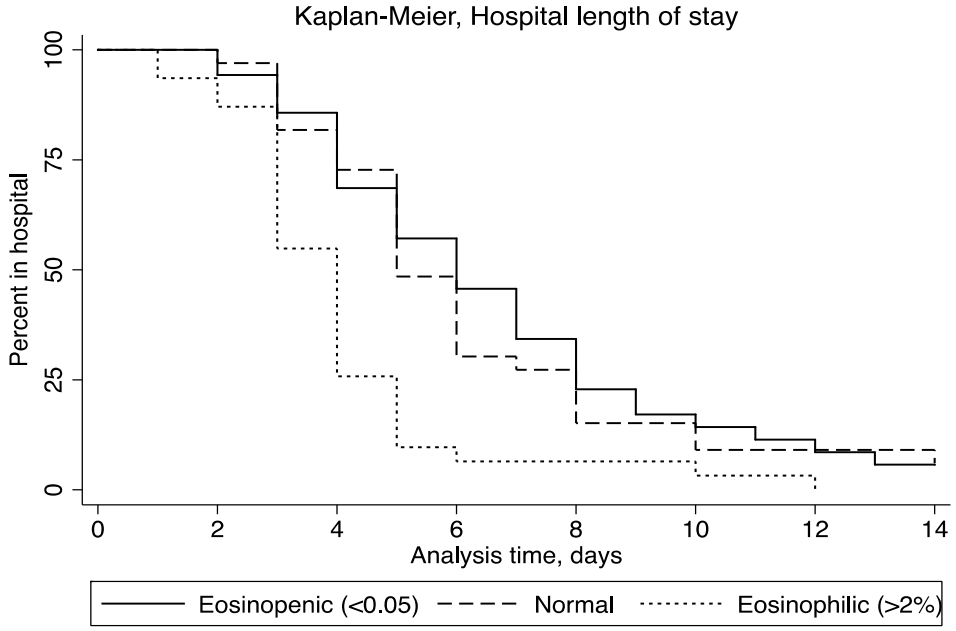


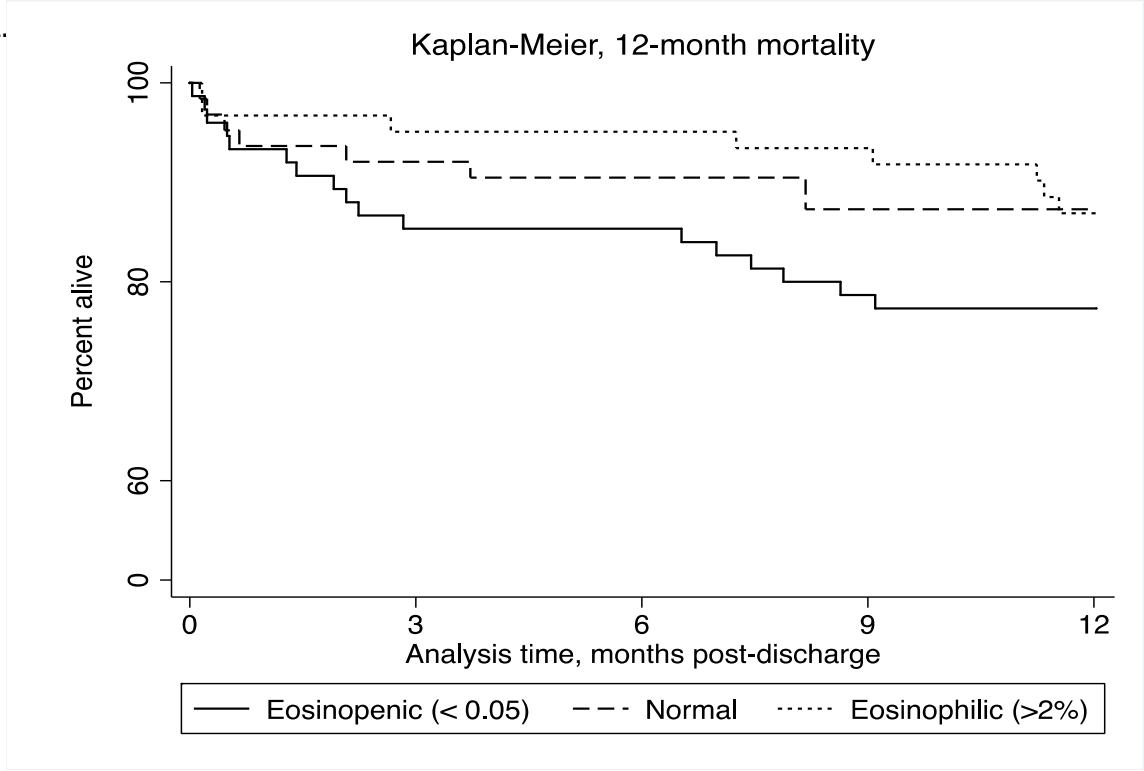
Figure 3. Kaplan-Meier analysis, hospital length of hospital stay in **a)** retrospective cohort (*P* = 0.009 for between group differences) and **b)** prospective cohort (*P* < 0.001 for between group differences). Figures depict admission data for up to 14 days of hospitalisation.

Supplementary data: eosinophil category and survival at 12 months

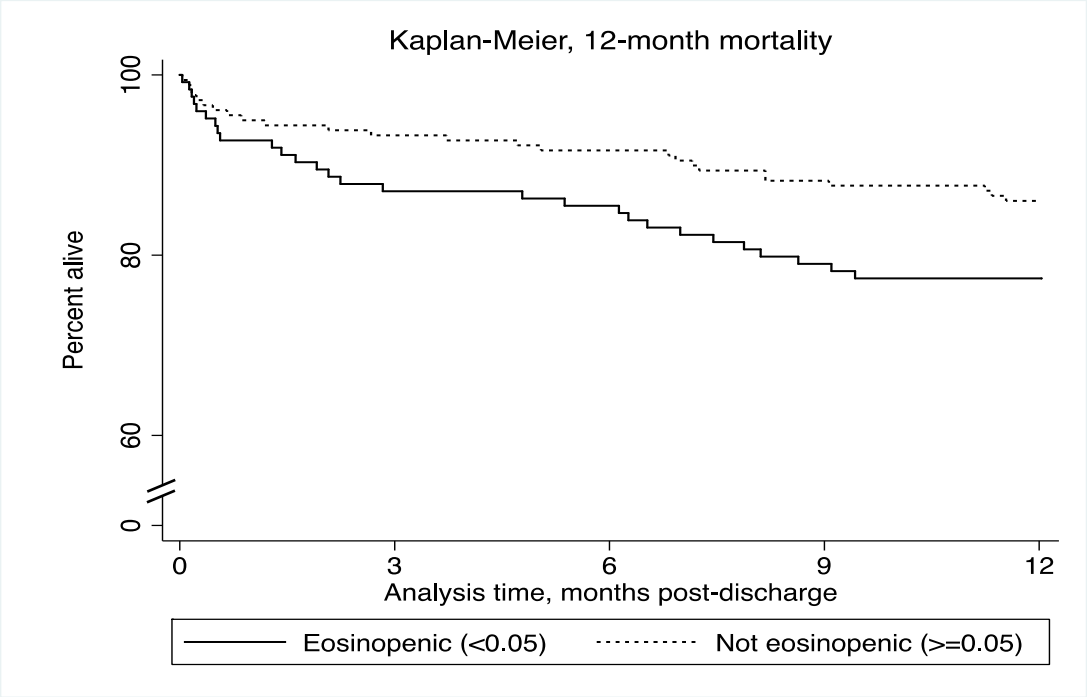
The data shown below was not included in the submission for publication as full data regarding survival at 12 months was not available for the validation cohort at the time of submission. In the derivation cohort eosinopenia was associated with reduced survival at 12 months.

Supplementary Figure Eosinophil categorization and survival at 12 months

S1a.



S1b.



Supplementary Figure 1. Kaplan-Meier analysis for survival at 12 month in derivation cohort according to categorization by blood eosinophil count at exacerbation **a)** eosinophilic versus normal versus eosinopenic (p=0.183); **b)** eosinopenic versus non-eosinopenic (p=0.049)

4.1 DECLARATION 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	Contribution
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

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	Contribution (student co-authors only)
Prof K Polkinghorne	Aided in data analysis.	
Dr C Osadnik	Aided in data analysis.	
Dr I Laska	Aided in data collection.	
Dr CJ MacDonald	Aided in data collection.	
Mr S Jeyakumar	Aided in data collection.	
A/Prof. K Hamza	Aided in data analysis.	
Dr PT King	Aided in hypothesis generation, data analysis and manuscript	
Prof PG Bardin	Aided in hypothesis generation, data analysis and manuscript	

	preparation.	

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**

4.2 INTRODUCTION TO CHAPTER

As outlined in Chapter 1, bronchodilation is a cornerstone of COPD exacerbation therapy(Vestbo et al., 2013; Vogelmeier et al., 2017). Relaxation of bronchial smooth muscle can be achieved via stimulation of β_2-receptors and/or inhibition of antimuscarinic receptors. In AECOPD therapy, a combination of short-acting beta-agonist (SABA) and short-acting muscarinic antagonist (SAMA) therapy is routinely prescribed. The recommended maximal dose of SAMA therapy is 2g nebulized Ipratropium bromide in divided dosages over 24 hours(Actavis, 2015). In contrast, there are no explicit guideline recommendations regarding a dose limit for β_2-agonist therapy. Indeed, although universally accepted as recommended therapy, there is minimal evidence base to guide the optimal strategy for short-acting bronchodilator therapy in AECOPD. In severe asthma exacerbation, guidelines recommend very high dose β_2-agonist therapy(GINA, 2017). Given the similarities in clinical presentation and management, emergency medicine practitioners may be prescribing similar β_2-agonist dosages in AECOPD.

Tachycardia in AECOPD

β_2-adrenergic receptors are found in the heart at a ratio of β_1:β_2 of 3:1(Bristow, 2000) and β_2-agonist medications cause cardiac excitation. A heart rate >109/minute(Shorr et al., 2012) and tachyarrhythmia(Steer et al., 2012) predict mortality/mechanical ventilation in AECOPD. Tachycardia (HR>100bpm) has been associated with increased high-sensitivity Troponin T (hs-TnT) during AECOPD(Hoiseth et al., 2012). Elevated hs-Tn levels have been associated with reduced short and medium term survival following hospitalized AECOPD(Brekke, Omland, Holmedal, et al., 2008; Chang et al., 2011). The extent to which tachycardia reflects acute infection, exacerbation severity, underlying cardiovascular disease or a side effect of β_2-agonist therapy is difficult to discern. This is further confounded by a presumed inherent relationship between greater exacerbation severity and increased clinician prescription of β_2-agonist.

β_2-agonists in COPD and AECOPD

Safety studies of β_2-agonists in asthma or COPD have generally been of short duration (often single dose) in outpatients, small in sample size and excluded those with unstable cardiac disease. A meta-analysis of such RCTs assessing LABA/SABA therapy in stable COPD/asthma identified a mean increase in heart rate of 9 beats/minute(bpm) after a single β_2-agonist dose, and increased sinus tachycardia (RR3.06, 95%CI 1.7-5.5)(Salpeter, Ormiston, & Salpeter, 2004). Observational studies have raised concern regarding the cardiovascular safety of standard dosages of inhaled β_2-agonists in stable COPD(Macie, Wooldrage, Manfreda, & Anthonisen, 2008). Reassuringly, large scale RCTs involving standard doses of LABA therapy in stable COPD have not identified an excess of cardiovascular events(Calverley et al., 2010), including among patients with cardiovascular risk factors(Vestbo et al.). In contrast, the safety of very high-dose SABA during AECOPD, where comorbid heart failure is frequently present, is unknown. High-dose β_2 agonist during AECOPD has been reported as a cause of cardiac arrhythmia(McCord & Borzak, 1998), cardiomyopathy(Rajwani, Adam, & Hall, 2015) and even death(Buajordet, Ebbesen, Erikssen, Brors, & Hilberg, 2001). Cardiotoxicity may be enhanced by co-administration of high-dose systemic corticosteroids with high-does SABA(Aziz, McFarlane, & Lipworth, 1998).

4.2.3 β_2-agonist and blood lactate

Lactate can be generated via either anaerobic tissue metabolism (Type A) or catecholamine-driven glycolysis (Type B)(Kraut & Madias, 2014). High lactate is frequently observed in asthma exacerbations and appears secondary to β_2-agonist-induced hyperadrenergism causing increased glycolysis(Dodda & Spiro, 2012). This process may be enhanced by concomitant glucocorticoid administration. Intravenous β_2-agonists have been associated with lactic acidosis in management of preterm labour(Cotton, Strassner, Lipson, & Goldstein, 1981; Richards, Chang, & Stempel, 1983), in healthy volunteers, and in acute asthma, including exacerbations where respiratory muscle paralysis has been administered (Appel, Rubenstein, Schrager, & Williams, 1983; Braden, Johnston, Germain, Fitzgibbons, & Dawson, 1985; Dodda & Spiro, 2012; Maury, Ioos, Lepecq, Guidet, & Offenstadt, 1997). Case reports have identified hyperlactataemia as provoking respiratory failure in asthma

due to hyperventilation and worsening hyperinflation(Tobin & Santamaria, 2005). Two prospective studies have assessed the relationship between lactate and β_2-agonist dosage in acute asthma presentations to the Emergency Department. In a RCT of an intravenous β_2-agonist in acute severe asthma, sub-analysis in the placebo arm observed lactate above the upper limit of normal in 69.2% of patients receiving standardized prednisolone, ipratropium and albuterol (salbutamol) nebulization. In the same study, serial blood measurements identified a positive correlation between lactate and blood albuterol levels ($r=0.45$, $p<0.001$)(Lewis et al., 2014). Patients with a markedly elevated lactate (>4.0mg/L, n=10) showed a non-significant trend to increased need for hospitalization (50% v 40%, $p=0.26$). In a prospective RCT of 18 acute asthma presentations to the emergency department a rise in lactate levels was observed in all subjects following inhaled albuterol dosages, with levels >4mmol/L in 4/18 (22.2%)(Rodrigo & Rodrigo, 2005). In the same study, lactate elevation was greater among patients with evidence of a pretreatment hyperadrenergic state.

Is lactate relevant in AECOPD?

In contrast to asthma, lactate has barely been studied in acute exacerbation of COPD, although in one small observational study, high lactate predicted increased need and longer duration of non-invasive ventilation(Terzano et al., 2012).
The lack of investigation of lactate in AECOPD is surprising given the high risk for both Type A and Type B lactic acidosis. AECOPDs are often associated with hypoxaemia and infection with an attendant risk of Type A lactic acidosis(anaerobic metabolism). Alternatively, lactate production may be increased due to respiratory muscle workload during AECOPD. In addition, high dose β_2-agonist therapy may drive Type B (catecholamine-driven glycolysis) in AECOPD.

Reasons why lactate may be of greater clinical relevance in AECOPD than in asthma included;

1) direct impact on acid-base balance and blood gas interpretation.
2) lactate provokes hyperventilation and panic attacks(Cowley & Arana, 1990), which will worsen dynamic hyperinflation during AECOPD.

3) lactate is an established predictor of mortality in shock(Manikis, Jankowski, Zhang, Kahn, & Vincent, 1995), sepsis(Mikkelsen et al., 2009) and more recently pulmonary embolism(Vanni et al., 2015). Mortality rates in AECOPD are higher than in hospitalized asthma attacks(Dougherty & Fahy, 2009)
4) AECOPD frequently involve bacterial infection and lactate is elevated in sepsis.
5) β_2-agonist hyper-stimulation is likely to be more deleterious in an elderly COPD population with frequent cardiometabolic comorbidity, than in an asthma population.

In this paper we explored the prevalence and associations of increased blood lactate in the retrospectively identified cohort of AECOPDs described in Chapter 3. β_2-agonist therapy from paramedics and the first 24 hours of hospital admission was recorded. Blood lactate levels were recorded as a component of peripheral arterial or venous blood gas samples(Bloom, Pott, Freund, Grundlingh, & Harris, 2014).

CHAPTER 4

LACTATE IS ASSOCIATED WITH ADVERSE OUTCOMES IN COPD EXACERBATION AND REFLECTS β_2-AGONIST DOSAGE

MacDonald MI, Polkinghorne K, Osadnik C, Laska I, MacDonald CJ, King PT, Bardin PG

4.3 LACTATE IS ASSOCIATED WITH ADVERS OUTCOMES IN EXACERBATIONS OF COPD AND REFLECTS β_2-AGONIST DOSAGE

ABSTRACT

Background

Lactate predicts mortality in shock and sepsis, but not in asthma exacerbations where it reflects β_2-agonist dosage. Lactate has not been investigated in acute exacerbations of COPD (AECOPD).

Methods

We assessed 1781 acute hospital presentations and identified 199 patients hospitalized with AECOPD who had blood lactate levels recorded. Baseline demographics, comorbidities and clinical outcomes were compared between patients with normal (≤2.0mmol/L) versus elevated (>2.0mmol/L) lactate. Multiple linear regression was used to assess the relationship between peak (log) lactate level and albuterol dose.

Results

Lactate was elevated (>2.0mmol/L) in 51.7% of AECOPD. Patients with lactate >2.0mmol/L had similar baseline demographics and comorbidities to those with lactate ≤2.0mmol/L. High lactate was associated with lower pH (7.34 v 7.37, *P* =0.04), increased non-invasive ventilation (29.8% v 9.6%, *P* =0.001), increased mechanical ventilation (7.7% v 1%, *P* <0.001) and increased length of stay (5.5 v 4 days, *P* =0.01). No difference in mortality was observed. Patients with lactate>3.0mmol had significantly higher rates of new onset tachyarrhythmia (20% v 7.6%, *P* =0.013). Raised lactate was significantly associated with high albuterol doses (p<0.001) and hyperglycaemia (p<0.001).

Conclusions

Raised blood lactate was common during hospitalized AECOPD and associated with adverse outcomes. The association of high lactate with β_2-agonist treatment

suggests that lactate may be a valuable marker of overtreatment with β_2-agonists in an at-risk population.

Introduction

Lactate accumulation in acute disease states can be a consequence of both anaerobic tissue metabolism (Type A lactic acidosis) and catecholamine-driven glycolysis (Type B lactic acidosis)(Kraut & Madias, 2014). High blood lactate levels are associated with increased mortality in sepsis(Mikkelsen et al., 2009), shock(Manikis et al., 1995) and pulmonary embolism(Vanni et al., 2015). High lactate is also observed in acute asthma exacerbations and appears linked to albuterol treatment(Alberts, Williams, & Ramsdell, 1986; Appel et al., 1983; Lewis et al., 2014; Rodrigo & Rodrigo, 2005). In asthma however, high lactate is not associated with increased mortality, although rare adverse effects have been described(Tobin & Santamaria, 2005).

There has been minimal investigation of lactate in acute exacerbations of COPD(AECOPD) despite the inherent risk for both Type A and Type B lactic acidosis. High blood lactate levels may have direct implications in AECOPD via increasing ventilatory drive thereby worsening dynamic hyperinflation(Tobin, Pellizzer, & Santamaria, 2006). In addition, as an anion it will increase acid-base imbalance and may prolong the need for non-invasive ventilation (NIV)(Terzano et al., 2012). Alternatively, high lactate levels may provide a marker of excessive adrenergic stimulation by high dose β_2-agonists administered in AECOPD. There is increasing concern about acute cardiovascular events during AECOPD(MacDonald, Shafuddin, et al., 2016) with plausible benefits from β-blockade during AECOPD postulated(Bhatt et al., 2015; Dransfield et al., 2008). While deleterious effects from β_2-agonists are rarely observed in adult asthma, excessive β_2-agonism may be more detrimental in an elderly COPD population with comorbid cardiac disease(Au, Curtis, Every, McDonell, & Fihn, 2002; Au, Lemaitre, Curtis, Smith, & Psaty, 2000; Au et al., 2003; Cazzola, Matera, & Donner, 2005).

The aim of this study was to examine the prevalence of raised blood lactate in hospitalized AECOPD and compare clinical outcomes between those patients with high versus normal lactate levels. We also explored the relationship between lactate and albuterol dosage.

Materials and Methods

This study was approved by the Ethics Committee of Monash Health (HREC13291Q).

Study Population

Consecutive admissions to 2 major metropolitan hospitals (Monash Medical Centre and Dandenong Hospital, Monash Health, Melbourne, Australia) with AECOPD between September 2012 - October 2013 were identified via the Emergency Department (ED) database (*Symphony, EMIS Healthcare, Leeds, UK*) (Figure 1). Records were inspected by a Respiratory Physician (MM) to confirm AECOPD and exclude alternative diagnoses. Cases were included if the admission diagnosis of exacerbation of COPD was corroborated by lung function testing in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria(Vogelmeier et al., 2017). In the absence of available spirometry results, cases were only included where a Pulmonologist diagnosis of COPD had been documented in conjunction with applicable respiratory symptoms, >10 pack year smoking history and absence of a diagnosis of asthma. Cases with a primary admission diagnosis of AECOPD underwent comprehensive record review. For patients with multiple hospital admissions only the first admission was included for analysis. Mortality at 12 months was established by electronic medical record review or confirmed by telephone contact with next-of-kin.

Study Measurements

Primary outcome

The primary outcome of the study was to compare hospitalized AECOPD with elevated versus normal blood lactate levels. Lactate levels were available as a component of blood gas analyses in the Emergency Department (Radiometer ABL827, Copenhagen, Denmark) and Intensive Care Units (Radiometer ABL825, Copenhagen, Denmark). Lactate levels were obtained from either venous or arterial blood gas samples since several studies have confirmed that venous and arterial blood lactate measurements are comparable and closely matched(Adams & Hazard, 1988; Middleton, Kelly, Brown, & Robertson, 2006; Younger, Falk, & Rothrock,

1996). For patients who had repeat analyses during admission, the highest lactate recorded was used.

Secondary outcomes

We compared inpatient mortality, need for mechanical or non-invasive ventilation and length of hospital stay between patients with high versus normal lactate levels. In addition, we calculated the cumulative dosage of aerosolized albuterol administered during the first 24 hour hours of hospital admission, to explore its relationship with blood lactate levels. Patient demographics, comorbidities and inpatient management were obtained from inspection of individual electronic medical records and not based on discharge coding. To facilitate dose comparison of inhaled albuterol exposure, 10 puffs via metered dose inhaler (MDI) albuterol with spacer was considered equivalent to 2.5mg of nebulized albuterol(G. Rodrigo & Rodrigo; Yang, 2016). The cumulative dose of aerosolized albuterol administered by both ambulance paramedics and during the first 24 hours of hospitalization is therefore reported as units of '2.5mg nebulized equivalents'. Following the initiation of Paramedic or Emergency Department care, hypoxaemia was generally eliminated by supplemental oxygen or ventilatory support. Severe hypoxaemia was therefore reported as a categorical variable based upon pulse oximetry oxygen saturation recordings (SpO2)<88% at the time of initial ambulance or ED presentation. COPD exacerbations were managed according to international guidelines(Vogelmeier et al., 2017). Survival at 12 months was confirmed by inspection of the electronic medical record or telephone contact with patient/next of kin. Exacerbation severity was assessed by the elevated blood urea nitrogen, altered mental status, pulse greater than 109 peats per minute and age older than 65 years (BAP-65) score(Shorr et al., 2012).

Statistical analyses

All data are presented as number (percentage), mean±standard deviation, or median [interquartile range] where appropriate. Blood lactate levels were highly skewed and were therefore log transformed prior to the regression analysis. Univariate associations between (log) lactate levels and the patient and laboratory

characteristics were explored using students t-test, and χ^2 test where appropriate. Multiple linear regression was used to assess the relationship between peak (log) lactate level and standardised albuterol dose while controlling for potential confounding variables. All factors with P<0.2 on univariate analysis were entered into the final model. In addition, age, gender, and acid-base factors were kept in the model irrespective of significance as they were felt to be important determinants and/or confounding factors on the lactate/salbutamol relationship. Stepwise backward elimination was used beginning with the variable with the highest p-value. Inspection of the change in the adjusted R^2 & performance of a likelihood ratio test were both used to confirm that deleted factors did not contribute to the model. The assumptions underlying multiple linear regression analyses were examined and confirmed. We considered results to be statistically significant if the two-sided p-value was less than 0.05. All analyses were conducted on Stata MP 14.1 (Statacorp, College Station, Texas, USA).

Results

Review of 1781 Emergency Department attendances identified 547 admissions with a primary clinical diagnosis of AECOPD, of which 244 (213 patients) had lactate results recorded (Figure 1). Spirometry results were available for 130/213 (61%) of patients. 14/130 (10.8%) of cases were excluded due to spirometry results inconsistent with GOLD criteria(Global Strategy for the Diagnosis, 2015) and a further 12 excluded due to administration of intravenous albuterol. Where spirometry results were unavailable, patients were included if diagnosed by a Pulmonologist as AECOPD with no history of asthma and >10 pack year smoking history, leaving 199 cases for the principal analyses.

Clinical characteristics of patients with AECOPD on admission

The demographic and clinical characteristics of patients included in the studies are shown in Table 1. Mean±SD lactate for the overall population was 2.2±1.4mmol/L and lactate was elevated (>2.0mmol/L) in 103/199 (51.8%) of AECOPD. There was no difference in baseline demographics, severity of airflow obstruction or prevalence of major common comorbidities between the groups with normal or raised lactate (Table 1). Chronic liver disease was relatively infrequent overall, but more common in the high lactate population (7.7% v 0%, *P* =0.006). A high exacerbation severity score (BAP-65 score ≥3) was more common in the group with raised lactate (79.4% v 64.9%, *P* =0.023).

Association of blood lactate measurements with clinical outcomes

Patients in the high lactate group had lower median pH (7.34 v 7.37, *P* =0.033) and lower bicarbonate (26.9 v 29.6, *P* <0.001) (Table 2). In cases with elevated lactate, rates of NIV in the Emergency Department (44.2% v 21.9%, *P* =0.001), NIV following admission 29.8% v 9.6%, *P* p=0.001) and mechanical ventilation (7.7% v 1.0%, *P* =0.02) were all higher. Median hospital length of stay was also significantly longer (5.5 v 4 days, *P* =0.01) (Table 2). No significant difference was observed in mortality during the inpatient admission (5.8% v 5.2%, *P* =0.98) or at 12 months post discharge (15.4% v 17.7%, *P* =0.9).

Predictors of elevated blood lactate measurements

Factors associated with Type A lactic acidosis (anaerobic metabolism)

There was no significant difference observed between the groups in frequency of severe hypoxaemia (SpO2<88%) at initial presentation (48% v 43.6%, *P* =0.7) or circulatory shock (systolic blood pressure≤80mmHg) (6.7% v 4.2%, *P* =0.28).

Factors associated with Type B Lactic acidosis (catecholamine-driven glycolysis)

Patients with AECOPD treated with intravenous albuterol (n=12) had elevated lactate in 11/12 (91.7%) but were excluded from the reported analyses. Aerosolized albuterol was delivered by nebulizer alone (67.9%), a combination of nebulizer and metered dose inhaler (MDI) via spacer (30.2%), or MDI alone (1.9%). The median standardised aerosolized albuterol dose was significantly higher in the in high lactate versus the normal lactate group (40mg v 25mg, *P* =0.0001) and salbutamol dose demonstrated moderate correlation with lactate (r=0.4, p<0.0001. Figure 3). Peak heart rate and peak lactate were significantly correlated (r=0.21, p=0.003. Figure 4). Adrenergic stimulation as manifest by rates of tachycardia (>100bpm) on initial presentation (60.1 v 48.9% *P* =0.1) or during ED treatment (79.4% v 66%, *P* =0.09), and new onset tachyarrhythmia (atrial fibrillation, atrial flutter, supraventricular tachycardia, 13.7% vs 8.5%, *P* =0.25) were all higher in the group with lactate >2mmol/L but did not reach statistical significance. When patients with lactate >3.0mmol/L were compared to those with lactate ≤3.0mmol/, new onset tachyarrhythmia was significantly more frequent (20% v 7.6%, *P* =0.013).
Lactate was also highly correlated with glucose (r=0.56, *P* <0.001). The normal and high lactate groups had a similar prevalence of diabetes (20.6% vs 22.3%, *P* =0.77) and metformin prescription (6.9% vs 9.6%, *P*=0.49). Systemic corticosteroids were administered more frequently in the high lactate group (98% v 91.5%, *P* =0.04).

Multivariate linear regression analyses (Table 3) identified only albuterol dose (*P* <0.001), blood glucose (*P* <0.0001) and a higher exacerbation severity score (*P* =0.03) to be predictive of lactate levels.

Physician recognition of elevated lactate was documented in only 24.5% of cases with lactate >2.0mmol/L. In 3/103 (2.9%) of patients with high lactate, abdominal imaging or surgical review was requested but no alternative pathology was identified in any patient.

Discussion

Our study is the first to investigate lactate in AECOPD and found elevated levels in the majority of cases. Unlike studies in shock and sepsis, hospital mortality rates were not higher in the population with high lactate, but other markers of adverse clinical outcomes were increased. In particular the need for non-invasive and mechanical ventilation, admission to a critical care ward, and hospital length of stay were significantly higher when lactate was elevated.

To date, there has been minimal investigation of lactate in AECOPD and it may be a neglected facet of AECOPD management. High lactate levels may have direct clinical implications through increasing ventilatory drive and reducing expiratory time, thereby worsening the dynamic hyperinflation which underpins AECOPD(Tobin et al., 2006). High lactate levels have been shown to stimulate hyperventilation, anxiety and even induce panic attacks(Cowley & Arana, 1990; Maddock, Buonocore, Copeland, & Richards, 2009). Lactate will contribute to acidosis and the only previous study to examine lactate in AECOPD observed prolonged need for non-invasive ventilation (NIV) in a very small subgroup of hypercapnoeic AECOPD with hyperlactataemia(Terzano et al., 2012). In our study we found that patients with high lactate were frequently prescribed NIV in the Emergency Department, and often this was done to alleviate increased work of breathing. Lactate may be contributing to the perceived need for NIV by driving hyperventilation and anxiety, and/or through it's effect on acid-base balance. Clinicians managing AECOPD should be aware of the potential for lactate to modulate both dyspnoea and acid-base balance.

Elevated lactate levels in AECOPD are likely to be multifactorial in origin. In our study, Type A (anaerobic metabolism) lactic acidosis appeared less likely to be the predominant factor as circulatory shock was uncommon and pre-hospital hypoxaemia appeared similar in both groups. Albuterol dosage was correlated with lactate and remained a significant predictor of lactate on multivariate analysis, consistent with the hypothesis that lactate production in AECOPD is driven predominantly by β_2-hyperstimulation (Type B lactic acidosis - catecholamine-driven glycolysis). In asthma, serum albuterol levels have been shown to relate directly with lactate levels(Lewis et al., 2014). In our study, the albuterol dosages administered in

the first 24 hours after admission were very high. International guidelines suggest relatively conservative dosages of inhaled bronchodilators in AECOPD although there is a limited evidence base on which to draw recommendations(Vogelmeier et al., 2017; Yang, 2016). Our COPD study population were elderly with high levels of comorbid cardiac disease, a patient group rarely investigated in randomized controlled trials but likely at greatest risk of adverse effects. Tachycardia and new onset tachyarrhythmia appeared more common in the high lactate/high albuterol group, a finding that was statistically significant at a higher lactate threshold of >3.0mmol/L. It is highly plausible that hyperadrenergism may be deleterious in AECOPD, with observational studies reporting reduced mortality in AECOPD patients receiving β_2-blocker therapy(Dransfield et al., 2008). While this has not yet been assessed in a prospective study, avoiding unnecessary β_2-stimulation may be an important consideration. Lactate as a marker of β_2-hyperstimulation in AECOPD could be of interest where either limitation of β-stimulation or even β-blockade are deemed beneficial and requires prospective evaluation.

Elevated lactate was also strongly associated with hyperglycaemia despite a similar prevalence of diagnosed diabetes in the high and normal lactate groups. Hyperlactataemia and hyperglycaemia are frequently observed concurrently, a phenomenon known to reflect β_2-adrenergic stimulation(Reverte, Garcia-Barrado, & Moratinos, 1991). Hyperglycaemia has been reported as an independent predictor of inpatient mortality, prolonged hospitalization(Baker et al., 2006) and failure of NIV(Chakrabarti, Angus, Agarwal, Lane, & Calverley, 2009) in previous AECOPD studies, but these studies did not report concurrent lactate levels. Of note, no benefit from intensive glucose control has been observed, and the prognostic implications of hyperglycaemia may be linked to lactate. In a retrospective study of sepsis in non-diabetic subjects, hyperglycaemic patients were more likely to have hyperlactatemia (OR 4.14) and the increased mortality observed in concurrent hyperglycaemia and hyperlactataemia (OR 3.96) was not seen with isolated hyperglycaemia (OR 0.78)(Green et al., 2012).

Other potential sources of lactate include increased respiratory muscle workload(Mountain, Heffner, Brackett, & Sahn, 1990), although hyperlactataemia has been observed even in asthmatic patients who have received muscle

paralysis(Liem, Mnookin, & Mahla, 2003). The lungs themselves may be a potential source of lactate production, however this has only been described in the context of acute lung injury(Brown, Clark, & Gutierrez, 1996; Routsi et al., 1999).

In our study, clinician awareness of lactate accumulation appeared low, suggesting that elevated lactate is a frequent but under-appreciated clinical observation. From our data, it can be reasonably inferred that a high peak lactate may be a marker of 'cardiometabolic stress' and that lactate may have prognostic value and identify over-treatment with β_2-agonists. Prospective studies are needed to substantiate these findings.

These studies have a number of potential limitations. Data was collected retrospectively, although medical records were individually reviewed for accuracy by a senior clinician. Distinction between COPD and asthma is difficult but patients included in this study had either spirometry available to confirm COPD, or >10 pack year smoking history with pulmonologist-diagnosed COPD documented in medical records. Blood gas analyses were predominantly obtained from venous blood. This is unlikely to have affected our results since pH, bicarbonate and lactate measurements are closely matched between venous and arterial blood gases in AECOPD(McKeever et al., 2016). A key limitation in assessing the relationship of albuterol, lactate and clinical outcomes in this study is confounding by exacerbation severity. It is likely that exacerbations receiving the highest doses of albuterol were adjudged by treating clinicians to be the most severe and therefore may have been at greatest risk of adverse outcomes. We gained an estimation of exacerbation severity from BAP-65 scores. The small differences in BAP-65 scores were mainly due to higher heart rates - which may be a result of high dose albuterol treatments.

Conclusions

In conclusion, elevated lactate is a frequent but under-appreciated clinical finding in exacerbations of COPD. Lactate stimulates hyperventilation, impacts blood gas interpretation and appears to be a consequence of high dose β_2-agonist therapy. It should be incorporated into the assessment of the dyspnoeic AECOPD patient and has the advantage of being routinely available on blood gas analysis and immediately accessible at no additional cost. Associations of elevated blood lactate with adverse clinical outcomes and β_2-agonist treatments in AECOPD merit prospective investigation.

Figure 1. CONSORT diagram of participant flow

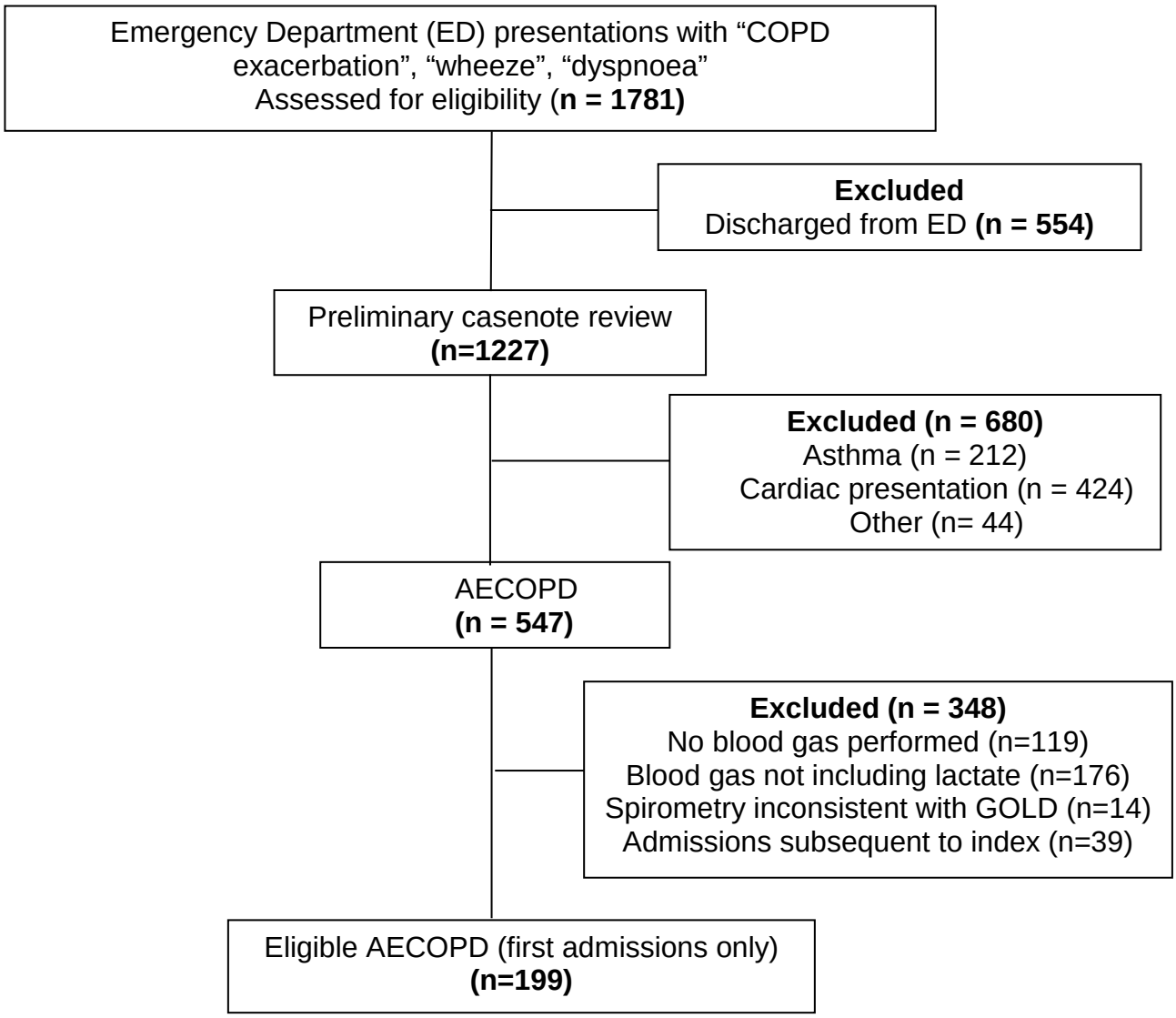


Figure 2. Distribution of peak lactate levels

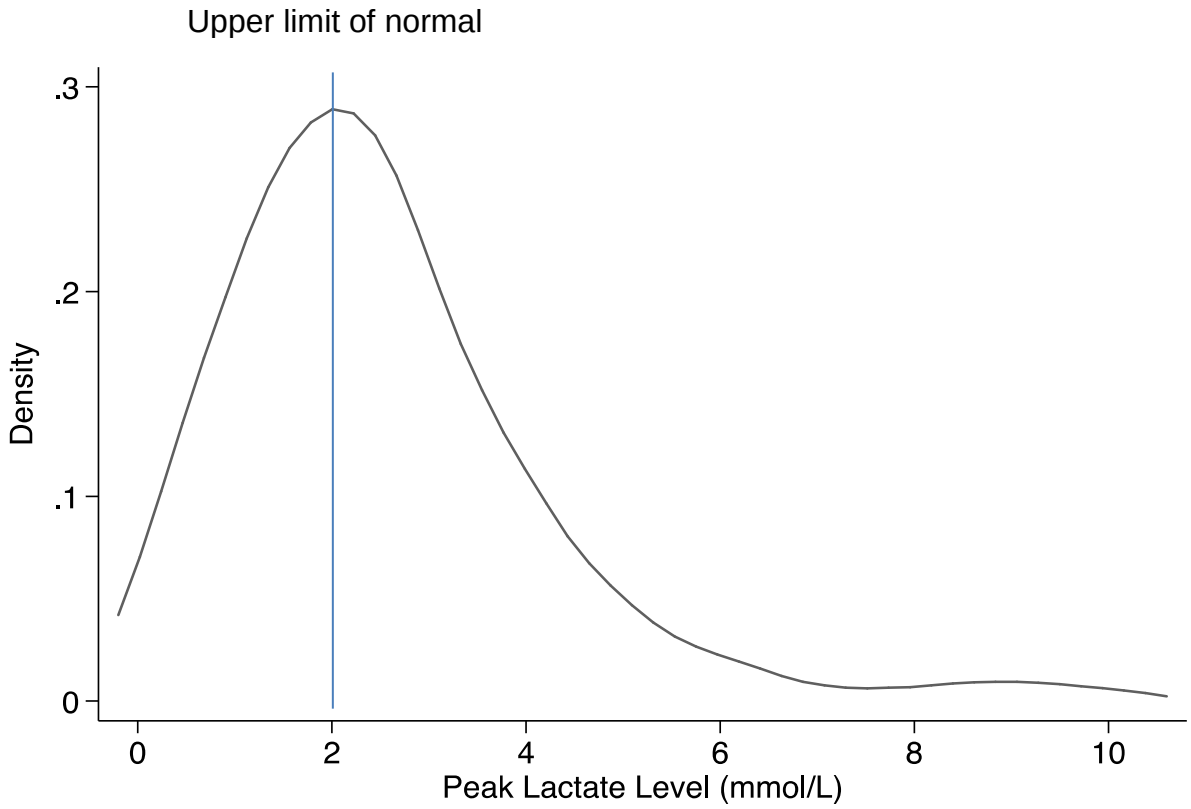


Figure 2. Density map showing the distribution of peak lactate levels observed in a hospitalized AECOPD population. Levels above 2mmol/L are above the upper limit of normal for our local reference population.

Table 1. Baseline characteristics of patients with AECOPD stratified by lactate

Baseline Demographics	**Lactate≤2.0mmol/L**	**Lactate>2.0mmol/L**	**P**
n (%)	96 (48.3)	103 (51.7)	
Age, years, median [IQR]	73.3 [67.0-82.1]	73.8 [67.7-79.2]	0.89
Male, n (%)	48 (50.0)	59 (57.3)	0.3
FEV_1 (L), (mean±SD)	1.04±0.44	1.13±0.51	0.26
FEV_1 (% predicted), (mean±SD)	45.2±17.5	49.0±19.3	0.23
Bronchodilator reversibility (%ΔFEV_1), (mean±SD)	7.4±9.8	8.0±10.3	0.76
TLCO (% predicted), (mean±SD)	37.6±15.8	37.5±16.2	0.98
BMI (kg/m^2), (mean±SD)	25.9±6.7	26.2±5.4	0.79
Comorbidities			
Ischaemic Heart Disease, n (%)	36 (37.5)	39 (37.5)	1.0
Cardiac failure, n (%)	24 (25.0)	21 (20.4)	0.42
Atrial fibrillation/flutter, n (%)	19 (19.8)	19 (18.3)	0.78
Diabetes mellitus, n (%)	21 (22.3)	21 (20.2)	0.64
Creatinine (mean±SD)	86.2±19.8	93.2±32.9	0.3
Metformin, n (%)	10 (10.4)	7 (6.7)	0.35
Chronic liver disease, n (%)	0 (0)	8 (7.7)	0.006*
Malignancy¤, n (%)	6 (6.3)	6 (5.8)	0.88
Exacerbation characteristics			
BAP-65 score parameters, n (%)			
- age > 65	75 (78.1)	85 (81.7)	0.52
- Urea>9/BUN>25	20 (20.8)	30 (28.9)	0.19
- GCS<14	0 (0)	0(0)	-
- Heart rate >109bpm	54 (56.3)	65 (62.5)	0.37
BAP-65 score ≥3, n (%)	63 (65.6)	83 (79.8)	0.02*
SpO_2<88%, n (%)	41 (43.6)	49 (48)	0.7
SBP<80mmHg, n (%)	4 (4.2)	7 (6.7)	0.28

¤Malignancy = malignancy diagnosis currently being treated or palliated. FEV_1 = Forced expiratory volume in 1 second, TLCO = transfer factor carbon monoxide, BMI = body mass index, BAP-65 = blood urea nitrogen>25, age>65 years, pulse>109 beats per minute score, BUN = blood urea nitrogen, GCS = Glasgow coma scale, SpO_2 = Oxygen saturation, SBP = systolic blood pressure,

Table 2. Association of blood lactate with exacerbation outcomes

Clinical outcomes	Lactate ≤2.0 n=96	Lactate >2.0 n=103	*P*
NIV in Emergency Dept, n (%)	21 (21.9)	46 (44.2)	0.001*
NIV post admission, n (%)	9 (9.6)	31 (29.8)	0.001*
HDU/ICU admission, n (%)	12 (12.3)	36 (35.6)	0.001*
Mechanical ventilation, n (%)	1 (1.0)	8 (7.7)	0.02*
Vasopressor/Inotrope, n (%)	3 (3.1)	4 (3.9)	0.78
Length of stay, days, median [IQR]	5.5 [3-9]	4 [2-6]	0.01*
Inpatient Mortality, n (%)	5 (5.2)	6 (5.8)	0.98
Mortality at 1 year, n (%)	16 (17.7)	16 (15.4)	0.9
Pharmacological management			
Systemic corticosteroids, n (%)	88 (91.7)	102 (98.1)	0.04*
Antibiotics, n (%)	90 (93.8)	103 (99.0)	0.04*
Albuterol dosage*, median [IQR]	25 [10.2-35]	40 [20-55]	<0.001*
√Albuterol dosage, mean±SD	5±1.9	6.3±1.9	<0.001*
Blood gas parameters			
pH, median [IQR]	7.37 [7.3-7.4]	7.34 [7.3-7.4]	0.02*
pCO_2, median [IQR	52.0 [45.0-59.8]	50.5 [43.3-60.6]	0.41
pO_2, median [IQR]	40.3 [29.5-55.5]	47.4 [34.0-61.2]	0.043*
Glucose (mmol/L), median [IQR]	7.2 [6.1-8.8]	9.8 [8.2-12.5]	<0.001*
Bicarbonate, median [IQR]	29.6 [26.6-32.0]	26.9 [23.6-30.3]	<0.001*
Cardiac parameters			
Initial heart rate (bpm), mean±SD	106±21.6	110.9±20.6	0.23
Peak heart rate (bpm), mean±SD	114.8±23.1	118.5±20.1	0.24
New onset tachyarrhythmia, n (%)	8 (8.5)	14 (13.7)	0.25

NIV = non-invasive ventilation, HDU = High Dependency Unit, ICU = Intensive Care Unit, *standardized albuterol dose (excluding intravenous albuterol) in first 24hours of care, bpm=beats per minute

Figure 3. Scatterplot of lactate versus albuterol dose

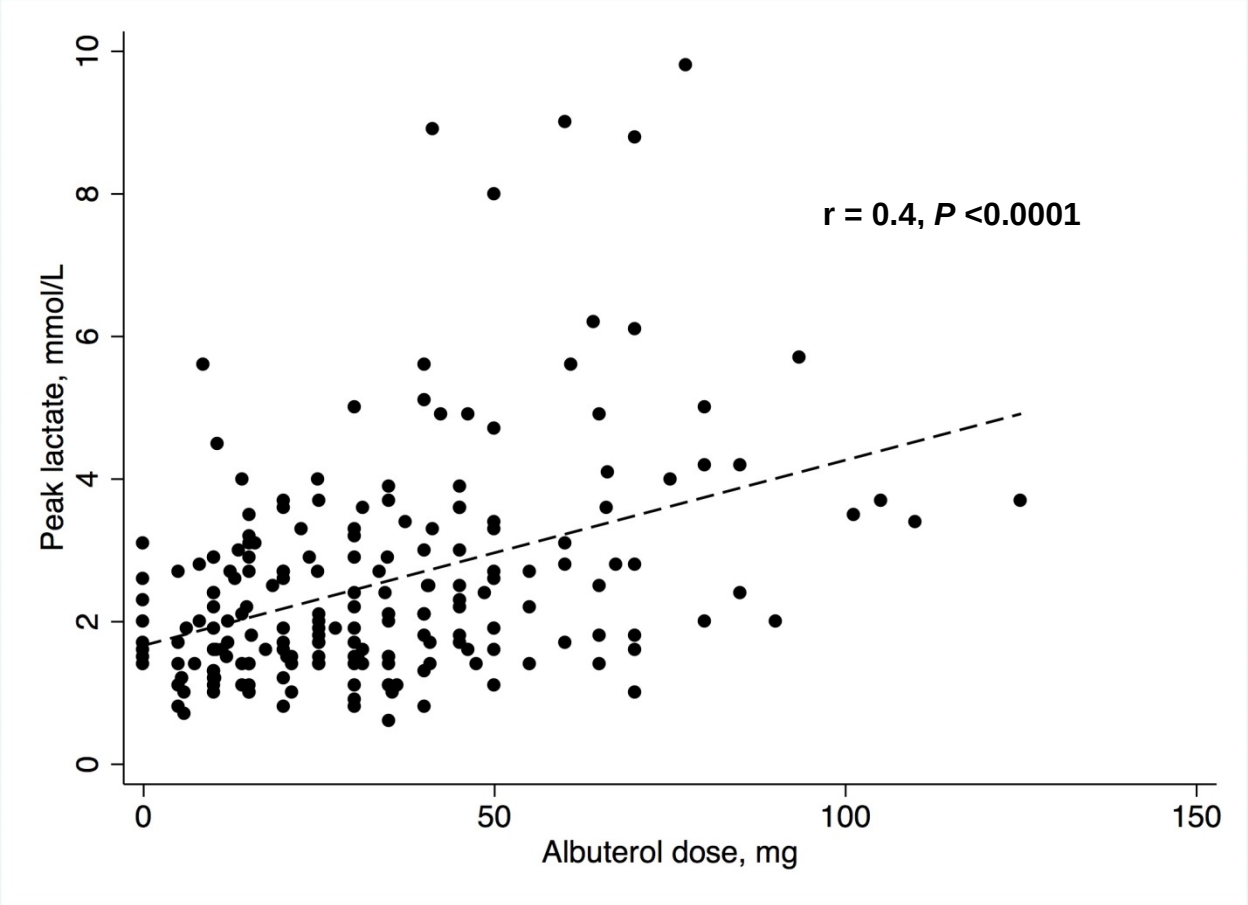


Figure 3. Scatterplot demonstrating correlation between cumulative albuterol dosage administered by paramedics and during the first 24 hours of hospital care (mg nebulized equivalent) and peak lactate level (mmol/L).

Figure 4. Scatterplot of peak heart rate versus lactate

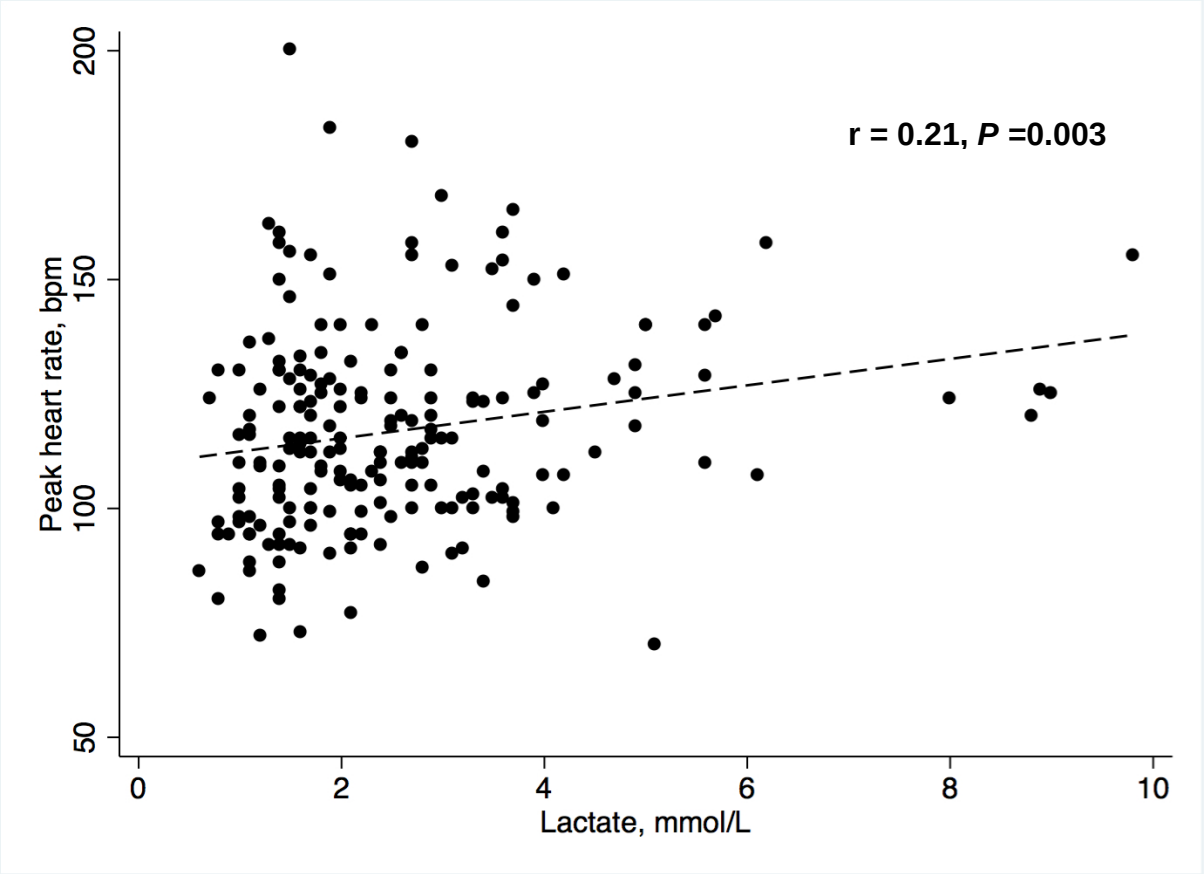


Figure 4. Scatterplot showing correlation between peak lactate level and the highest heart rate recorded during emergency department care.

Table 3. Predictors of elevated (log transformed) lactate by regression analyses

	Un-Adjusted				Adjusted			
(log) lactate	**Beta Coefficient**	**CI (95%)**		***P***	**Beta Coefficient**	**CI (95%)**		***P***
Age	0.004	-0.004	0.012	0.297	0.003	-0.004	0.009	0.430
pH	-1.663	-2.690	-0.636	0.002*	-1.615	-5.375	2.144	0.398
pCO_2	-0.004	-0.009	0.002	0.189	-0.008	-0.036	0.021	0.599
pO_2	0.002	-0.002	0.005	0.324	-0.003	-0.006	0.000	0.061
Glucose	0.071	0.056	0.087	<0.001*	0.052	0.036	0.069	<0.001*
Bicarbonate	-0.030	-0.043	-0.017	<0.001*	-0.007	-0.063	0.048	0.796
Albuterol dosage	0.009	0.006	0.012	<0.001*	0.004	0.001	0.007	0.003*
Gender	-0.086	-0.238	0.066	0.264	-0.071	-0.192	0.049	0.244
ICU/HDU	0.383	0.218	0.547	<0.001*	0.133	-0.020	0.287	0.087
BAP-65 Class 3-5 (vs 1-2)	0.33	0.17	0.50	<0.001*	0.158	0.016	0.300	0.030*
Metformin	-0.052	-0.329	0.226	0.714				
Chronic Liver Disease	0.390	-0.047	0.828	0.080				
NIV in Emergency Dept	0.283	0.127	0.438	<0.001*				

ICU = Intensive Care Unit, HDU = High Dependency Unit, BAP-65 = elevated blood urea nitrogen, altered mental status, pulse greater than 109 peats per minute and age older than 65 years, NIV = Non-invasive ventilation

Table 3. Beta-coefficient (95% CI) for factors predictive of peak lactate in unadjusted (left) and adjusted (right) linear regression model.

5.1 DECLARATION FOR THESIS CHAPTER 5

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	**Contribution**
For this chapter I was responsible for hypothesis generation, data analysis, interpretation of results and manuscript preparation.	80%

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**	**Contribution (student co-authors only)**
Dr AM Wong	Aided in data collection.	
Ms A Tran	Aided in data collection.	
Ms L Bulfin	Aided in data collection.	
Dr C Osadnik	Aided in data analysis.	
Mr Marcus Crossett	Aided in data collection and data analysis.	
Mr Ahilan Kuganesan	Aided in data collection and data analysis.	

Dr Siobhan Lockwood	Aided in hypothesis generation and data analysis.	
Dr Mark McCusker	Aided in data collection and data analysis.	
Dr Sinan Al-Hadethi	Aided in data collection and data analysis.	
Prof J Troupis	Aided in hypothesis generation, data analysis and manuscript preparation.	
Dr PT King	Aided in hypothesis generation, data analysis and manuscript preparation.	
Prof PG Bardin	Aided in hypothesis generation, data analysis and manuscript preparation.	

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**

5.2 INTRODUCTION TO CHAPTER

CARDIAC ASSESSMENT DURING AECOPD

Assessing the acutely breathless patient is one of the most common clinical scenarios encountered by hospital clinicians. However, distinguishing cardiac and pulmonary dysfunction in the breathless patient can be extremely difficult and it represents a key clinical conundrum in AECOPD. Troponins and natriuretic peptides aid identification of myocardial infarction and cardiac failure in the appropriate clinical context but are also observed in a wide variety of clinical scenarios where the clinical implications are less clear. In acute exacerbations of COPD (AECOPD) elevated cardiac biomarkers are associated with increased all-cause mortality(Chang et al., 2011; Hoiseth, Omland, Hagve, Brekke, & Soyseth, 2012). Overall, the mechanism and clinical implications of myocardial injury at AECOPD are poorly understood.

Current clinical investigations for cardiac dysfunction have specific limitations in a COPD population. Chest X-ray (CXR) assessment of heart failure by cardiothoracic ratio and interstitial oedema are obscured by emphysema and hyperinflation(Hublitz & Shapiro, 1969). ECGs frequently satisfy technical criteria for myocardial infarction which is not corroborated clinically(McAllister, Maclay, Mills, Leitch, Reid, Carruthers, O'Connor, et al., 2012). Echocardiography is limited by the impaired acoustic window of emphysema(Vizza, Lynch, Ochoa, Richardson, & Trulock, 1998). Cardiac MRI (cMRI) is the 'gold standard' investigation for myocardial function(Kumar, Patton, & Friedrich, 2010) but the prolonged acquisition protocols are impractical in a severe COPD population and availability in a clinical setting is often limited.

The role of computed tomography (CT) in cardiac imaging thus far has primarily focussed on CT contrast coronary arteriography as an alternative to invasive coronary angiography. Dynamic CT provides estimation of ventricular function that correlates well with MRI and is more accurate than Echocardiography(Greupner et al., 2012; K. Nasir et al., 2008). Clinical application of functional cardiac CT has been limited, largely due to concerns regarding radiation exposure and established preferences for traditional alternatives such as Echocardiography and MRI. Modified iterative reconstruction algorithms in the latest generation of CT imaging technologies permits marked reduction in radiation exposure, making functional

cardiac CT a viable clinical possibility. In the current studies we used novel CT imaging technologies (Philips i256 slice MDCT) and apposite algorithms to perform comprehensive cardiopulmonary assessment during COPD exacerbations.

General technical considerations in cardiac CT(Abramson, 2012)

Some basic principles regarding dynamic MDCT acquisition are outlined below:

Respiratory motion

CT requires breath hold and recumbent posture

Spatial resolution

Spatial resolution is the ability of an imaging system to **separate adjacent objects** within a volume as being distinct. In a 2-dimensional axial CT image, a grid of boxes forms a matrix of pixels that comprise the image on a computer monitor or film. Although 2-dimensional in shape, the pixel on screen represents a 3-dimensional object comprised of height, width and depth - the elemental unit of CT image known as a voxel. Each voxel is assigned a single density value for its entire volume, measured in Hounsfield Units (HU). A greyscale value is associated with the attenuation measurement assigned to each voxel to produce a visual image. Voxels cannot be further subdivided. Voxel dimensions are described as:

x-axis: the line drawn in the plane of scanning from the patient's right to left

y-axis: the line drawn in the plane of scanning from the patent's front to back (anteroposterior)

z-axis: the line drawn along the direction of scanning (the plane of collimation), from the patient's head to toe, orthogonal to the x- and y-axes.

Spatial resolution of a CT image is determined by the image matrix and field-of view (FOV). Longitudinal z-axis resolution is determined by the x-ray beam collimation and z-axis width of the CT detector beams.

(e.g. for a FOV of 500mm diameter and 512x512 image matrix,
x- and y-axis resolution is 512/500 = around 1mm pixels
for a FOV of 250mm/512 pixels = around 0.5mm pixels

z-axis detectors are typically set at 0.5x0.5x0.5mm.

Contrast resolution

Contrast resolution is the ability to **distinguish regions of differing density** or attenuation. The Hounsfield Unit (HU) value relates to how effectively the object

stops x-ray beams passing through its substance (linear attenuation coefficient). This is a function of the electron density of tissues - a property that parallels physical density. Low contrast resolution is the specific ability to discriminate small differences in attenuation among nearby structures - MDCT can discriminate density differences as low as 3HU. CT density measurements are greatly influenced by the specifics of imaging acquisition and technique, including slice thickness and reconstruction kernel.

Image noise and the contrast to noise ratio

Image noise is a random fluctuation in CT density values that do not represent the true nature of the structure being imaged. By convention, the entire contents of a container of pure water should have an HU density of 0 on CT scanning. In reality, the voxels which form that image will have a range of values that centre about a mean of zero with a pattern of variation which forms a normal distribution. This variation defines the concept of image noise. The **higher the image noise the greater the spread of values** and the larger the standard deviation of density measurements for that image. Most image noise arises from statistical variation in the number of x-ray photons ultimately striking the detector after passing through the object being imaged. When the amount of image noise exceeds the true difference in density among objects, they cannot be discriminated. Iodinated contrast serves to increase image contrast by widening the difference in attenuation between among various tissues. Thus, tissue differentiation can be improved without increased radiation dose.

The contrast to noise ratio (CNR) defines the ratio of true signal to random noise in a specified object. Image noise has the greatest impact in low-contrast CT imaging of small objects. Low contrast resolution is dependent on tube current (milliamperes, mA), x-ray beam energy (kV), slice thickness, pitch and reconstruction algorithm.

Tube current

The more photons in the x-ray beam, the higher the signal ultimately reaching the detector, resulting in less statistical variation in attenuation values, and less image noise. The flow of photons, or power, in CT is controlled by the tube current and expressed in milliamperes (mA). The product of mA and the imaging length of time in

seconds are expressed in milliampere seconds (mAs). As the product of power and time, mAs represents the total amount of energy in photons applied to obtain an image. There is a linear relationship between the patient radiation dose and changes in mAs. Noise varies with the square root of mAs (e.g. reducing mAs from 200 to 100 reduces the radiation dose by half and increases the image noise by a factor of 1.4).

X-ray energy

Kilovolts (kV) refers to the energy of the x-rays rather than the amount of x-rays (mA). Higher energy photons have greater penetration through tissue, allowing more photons to reach the detector beam. Lower energy X-rays are more easily stopped by tissues, resulting in greater image noise. Radiation dose changes as the second power of change in kV: a doubling of kV results in a fourfold increase in radiation dose.

Pixel size and slice thickness

The smaller the dimensions of an image voxel, the fewer photons contribute to calculation of its attenuation value and the greater the image noise. The noise in a voxel varies to the fourth power of a change in its 3-D measurements. E.g. an improvement in isotropic resolution from $0.5mm^3$ to $0.25mm^3$ results in a 2^4 or 16-fold increase in radiation dose. Changing slice thickness alone alters the z-axis but not the x- or y- axis and has less impact on image noise.

Pitch

Pitch describes the rate at which the patient and table move through the CT scanner with respect to the z-axis width of the irradiated detector. Radiation dose is always inversely proportional to pitch in helical CT: the lower the pitch, the greater the radiation.

Reconstruction algorithm or Kernel

Independent of the number of photons reaching the detector, image noise can be greatly affected by the specific mathematical tools utilized to reconstruct CT data. Reconstruction algorithms sharpen or smooth the contours of objects, enhancing or degrading detection of image detail. Choosing among reconstruction algorithms

represents a balance between higher spatial resolution with increased noise and higher contrast resolution with decreased noise.

Temporal resolution

Temporal resolution is the ability to resolve fast moving objects as if they were motionless. The acquisition time for MDCT scanners is tied to the rotation speed of the x-ray and detector gantry unit. The scanner rotation speed must be faster than the moving anatomy to obtain an image free of motion artefact.

Image Reconstruction

Iterative reconstruction computational technology in the latest generation of MDCT scanners, uses statistical modelling to reduce image noise, while maintaining spatial resolution and other features of image quality. The reduced image noise allows for a marked reduction in the tube current (i.e. radiation dosage).

Retrospective ECG gating

Traditional coronary CT angiography (CTA) is acquired with continuous irradiation of the patient, with imaging synchronized to the patient's ECG tracing and using a slow pitch - the coronary anatomy is oversampled at multiple points of the cardiac cycle. Retrospective image reconstruction isolates the narrow moments of least coronary artery motion using processing tools after the scan is acquired. Acquiring the data with retrospective ECG gating gives great latitude in optimizing image quality on a vessel by vessel basis but involves more radiation.

Prospective ECG gating

The scanner samples 3-7 heart beats immediately before the diagnostic image acquisition to predict diastole and trigger scanning accordingly. The patient is motionless on the table and then incremented to the next range of contiguous anatomy and the process repeated ("stop and shoot"). This technique performs best for patient with BMI<30kg.m^2, heart rate <70/minute and minimal heart rate variability. Radiation exposure is markedly reduced.

Multisegment reconstruction

In single segment reconstruction, the projections used to form an image are all derived from one heartbeat of data. As phase length is dependent on the heartbeat, the proportion of the R-R interval that is used for image reconstruction is adjusted to meet the minimum required data acquisition. For a HR of 60bpm, a 10% window of the cardiac phase will occur over only 100msec.

Components of the Combined Cardiopulmonary CT in COPD (4C) Study CT algorithm and their relevance to AECOPD

The aim of the Combined Cardiopulmonary CT in COPD (4C) Study methodology was to obtain key clinical information from i256 MDCT. In addition to standard CT thorax image acquisition, 6 key components of cardiopulmonary pathophysiology were assessed:

CT coronary artery calcium score

Emphysema quantification

Right and left ventricular functional assessment

CT pulmonary angiography

CT pulmonary artery distensibility

Aortic pulsatility

A brief background to each component and the relevance to AECOPD are outlined below;

Coronary artery calcification and COPD exacerbation

Coronary artery calcification is considered pathognomonic of coronary artery disease. CT can quantify the extent and density of coronary artery calcification to generate a coronary artery calcium score (CACS) expressed in Agatston's Units (AU)(Agatston et al., 1990). Population reference values for CACS in patients without clinical cardiovascular disease or treated diabetes have been derived from prospective multicentre patient cohorts (McClelland, Chung, Detrano, Post, & Kronmal, 2006). CACS can therefore also be expressed as a percentile for an age/gender/race matched reference population free of *diagnosed* cardiovascular disease. CACS measured by CT has been shown to correlate with coronary plaque identified at post-mortem examination(Rumberger, Simons, Fitzpatrick, Sheedy, & Schwartz, 1995), coronary stenosis at invasive angiography(Guerci et al., 1997), future cardiovascular event rates(Detrano et al., 1996) and all-cause mortality(Shaw, Raggi, Schisterman, Berman, & Callister, 2003).

A coronary artery calcium score provides a quantitative representation of the overall burden of coronary artery plaque. However, symptomatic coronary artery disease (i.e. *ischaemic* heart disease) is generally the result of flow limiting coronary stenosis or unstable plaque, reflecting focal regions of critical pathology rather than the global burden of atherosclerosis. Therefore while CACS shows a statistical association with likelihood of coronary stenoses, unlike *CT contrast coronary angiography*, it cannot be used to identify symptomatic coronary stenoses. However, in distinction to CT contrast coronary angiography, CACS does not require iodinated contrast or heart rate reduction (i.e. β-blockade) and can be performed at a very low radiation dose (<1mSV). Optimal assessment of CACS is achieved using ECG-gating to acquire coronary images during diastole when cardiac motion is minimized and CT resolution optimized. Application of CACS to standard non-ECG gated CT thorax is feasible but less accurate(Xie et al., 2013).

Utility of Coronary artery calcium score (CACS)

CACS outperforms risk calculators or blood biomarkers in predicting the rate of future cardiac events(K. Nasir, Shaw, Budoff, Ridker, & Pena, 2012) and is particularly useful for the following purposes:

1) Exclusion of coronary artery disease in asymptomatic populations

The absence of coronary artery calcification (i.e. CACS of 0) is strongly suggestive of very low coronary risk, particularly in asymptomatic populations(Church et al., 2007). Coronary plaque can be non-calcified however and the prognostic value of a CACS of zero may be less robust when applied to symptomatic or high-risk populations such as elderly diabetics(Ergun et al., 2011).

2) Improved stratification of intermediate risk patients

Estimation of future coronary risk in asymptomatic patients is generally based upon prediction algorithms integrating risk factors(Wilson et al., 1998). For patients with multiple risk factors, CACS was able to re-stratify 55% of those considered intermediate risk as either low or high risk of future coronary events(K. Nasir et al., 2012).

3) Guiding rational prescription of primary prevention therapy

Benefit from statin therapy in primary prevention of cardiovascular events is greatest amongst those with high LDL cholesterol(Shepherd et al., 1995) or low HDL cholesterol(Downs et al., 1998). Paradoxically however, in such a prevalent disease, the majority of cardiovascular events will ultimately occur in individuals without adverse lipid profiles. Benefit from statin therapy was identified amongst patients without hyperlipidaemia but with hs-CRP>2mg/L in the JUPITER trial(Ridker et al., 2008), although the overall event rate was low. Applying coronary artery calcium scoring can reduce the number needed to treat (NNT) with statin therapy to reduce cardiovascular event rates. Integrating CACS with the same hs-CRP criteria for the JUPITER trial, the predicted NNT to prevent 1 coronary heart disease event was 549 for CAC 0, 94 for CAC1-100, and 24 for CAC>100(Blaha et al., 2011). In a placebo-controlled trial, atorvastatin treatment was associated with a lower event rate in CACS>400 (8.7% v 15%, p=0.046)(Arad, Spadaro, Roth, Newstein, & Guerci, 2005) although this was not a primary endpoint.

In contrast to statins, aspirin is not infrequently associated with serious adverse effects with an estimated number needed to harm (NNH) over 5 years of 442(Miedema et al., 2014). In a primary prevention population, this risk of harm likely outweigh potential benefits in patients with CACS of 0(Miedema et al., 2014),

whereas net benefit is anticipated in those with CACS>100(Divakaran et al., 2015). Moreover, knowledge of the coronary artery calcium score appears to increase physician prescription and patient adherence to appropriate pharmacological and lifestyle modification strategies(Khurram Nasir et al., 2010; Orakzai et al., 2008).

A meta-analysis of studies reporting on cardiovascular comorbidity in COPD identified an odds ration (OR) = 2.28 for diagnosed ischaemic heart disease, OR = 2.7 for myocardial infarction and an OR = 8.16 for angina pectoris(Chen, Thomas, Sadatsafavi, & FitzGerald). The prevalence and impact of undiagnosed coronary artery disease in a COPD population is unknown. CACS was assessed in stable COPD patients, smokers with normal lung function and non-smoking controls in the ECLIPSE COPD cohort using non-gated CT chest in a stable outpatient population(Williams et al., 2014). Self-reported cardiovascular disease was higher in the COPD v smoking control v non-smoking control (53% v 23% v 34%) patients. Median/IQR CACS was higher in the COPD (128/492) v smoker (0/75) v non-smoker (0/3) ($p<0.001$). CACS in COPD was associated with age, pack year history, FEV_1 and history of self–reported cardiovascular disease and was independently associated with reduced walk-distance, increased BODE index and mMRC-D scores but not exacerbation frequency. In a Cox-proportional hazards model adjusted for age, gender and pack years, CACS was associated with increased mortality in COPD patients.

CACS may therefore have an important role in COPD patient management. Despite common major risk factors, IHD remains underdiagnosed in COPD. Even symptomatic IHD may be missed in COPD, including COPD exacerbations, due to symptom overlap(Brekke, Omland, Smith, & Soyseth, 2008; McAllister, Maclay, Mills, Leitch, Reid, Carruthers, O'Connor, et al., 2012). Observational studies of antiplatelets, statins, beta-blockers, and ACE-inhibitors have frequently suggested prognostic benefit in COPD populations. Given the additional potential values of chest imaging by CT in COPD, integration of coronary risk assessment into the CT acquisition is an attractive concept, and has already been proposed for lung cancer screening protocols(Hecht, Henschke, Yankelevitz, Fuster, & Narula, 2014). CACS could be used in COPD to identify high coronary risk patients with greatest likelihood of benefit from primary prevention therapy.

Criticisms of CACS implementation have mainly centred on costs, radiation exposure, downstream costs of incidental findings (e.g. pulmonary nodules) and availability of viable alternatives in lipid and hs-CRP profiling. Concerns regarding cost and radiation exposure may be less relevant in a moderate to high-risk, elderly COPD population. The potential for malignancy in incidentally discovered lung nodules may be higher in a COPD population(de Torres et al., 2007). Use of hs-CRP in COPD and particularly COPD exacerbation is likely to be confounded by concomitant systemic inflammation.

To assess whether an alternative blood biomarker at COPD exacerbation could predict the likelihood of a positive CT CACS result, we analysed high-sensitivity troponin at exacerbation admission. Troponin elevation during community COPD exacerbations is more frequently observed amongst those with a past history of ischaemic heart disease(Patel et al., 2013). Minor troponin elevations during AECOPD may therefore potentially identify a subgroup with significant IHD who could be targeted for cardiovascular primary prevention therapy.

For evaluation of coronary artery disease, CACS offers the specific advantage of integration into a comprehensive ECG-gated cardiopulmonary MDCT in a patient group for whom evaluation of lung CT, pulmonary vasculature and cardiac function is particularly relevant.

Emphysema quantification

COPD is diagnosed on the basis of lung function impairment rather than identification of the structural pathologies of emphysema and bronchitis. Lung high resolution CT (HRCT) has a potentially important role however, in the differential diagnosis and phenotyping of COPD.

Identification of emphysema

Emphysema is defined as abnormal permanent enlargement of the airspaces distal to the terminal airspaces, accompanied by destruction of their walls, without obvious fibrosis due to alveolar wall destruction and apoptosis of epithelial and endothelial cells following exposure to cigarette smoke and other noxious particles(Vogelmeier et al., 2017). Although emphysema is a pathological diagnosis, HRCT provided the first opportunity to directly visualize this pathology *in vivo* and more recent advances in CT technology have made it possible to quantify emphysema utilizing the different density thresholds of emphysema as represented by low attenuation areas on CT. Volumetric analysis of a 3-dimensional chest CT permits expression of the emphysema component as a percentage of lung volume(Cavigli et al., 2009). This process identifies and quantifies a distinct component of COPD pathology and is a key component of COPD patient phenotyping.

Techniques to quantify degree of Emphysema

X-ray CT passes an x-ray beam through an object to obtain multiple one-dimensional line integrals, or projections, of the object. An inverse radon transform is performed on the one-dimensional line integrals to produce a true two-dimensional axial image of the object at a particular level. Multiple two-dimensional axial images are then stacked on top of each other to produce a true three-dimensional image of the scanned object. The smallest unit of measurement in CT is the voxel and each voxel has a single density value. A 3-D lung volume is composed of a series of voxel densities that reflect the x-ray beam attenuation by tissue density. The increase in respiratory airspace size and decrease in tissue that occurs in emphysema causes the density (weight per unit volume) to decrease. Emphysematous lung destruction results in replacement of normal lung (which has a typical attenuation about -850 HU on inspiratory CT) by air-containing spaces, with CT attenuation close to -1000

HU(Lynch & Al-Qaisi, 2013). A CT “density mask” can thus be applied to the CT dataset to identify those voxels with a low attenuation typical of emphysema thus producing an “emphysema map”. The lung volume occupied by low attenuation areas (LAA) is then expressed as a % of the total lung volume (%LAA). Although often referred to as the ‘emphysema index’, %LAA measures attenuation levels which correlate with histological emphysema rather than directly measuring emphysema.

Correlation with histology

Genevois et al compared quantitative pathological measurements of emphysema with density-mask measurements made using 1mm slice HRCT (reconstructed with an edge enhancing algorithm) and identified a density cut-off of-950HU as having the best correlation with the extent of emphysema(Gevenois et al., 1996).

Figure1. Emphysema quantification by density mask volumetry

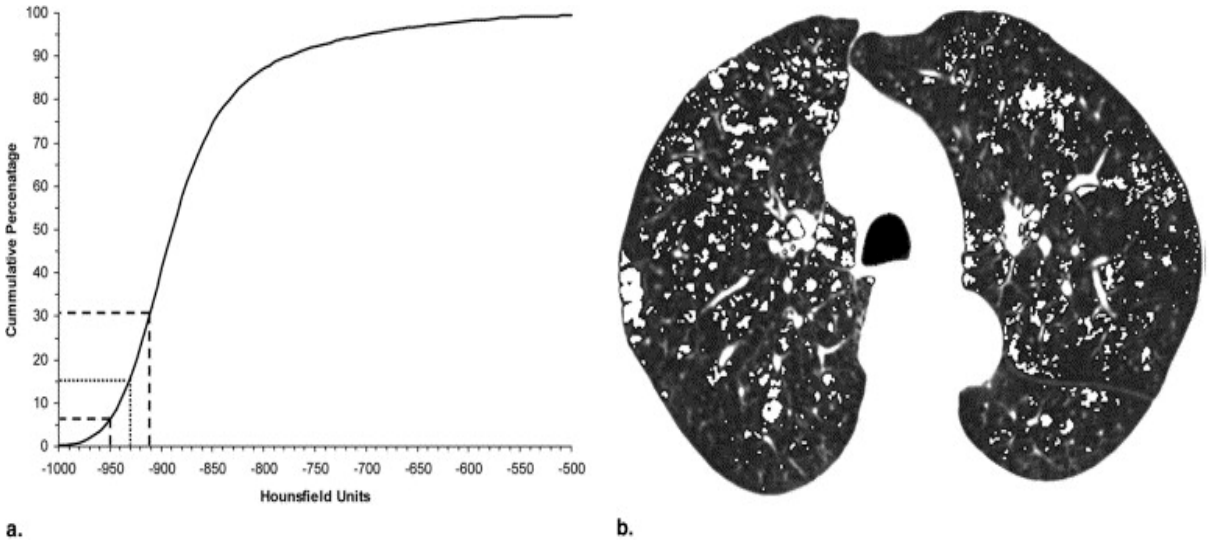


Figure 1a) cumulative distribution of X-ray attenuation values from a CT thorax. Cut-off values of-910Hu and -950HU are shown in dashed lines. The intersection of these lines on the y-axis indicates the percentage of emphysema in the CT scan using this technique. **1b)** Voxels with a HU<-950 are shown in white. Adapted from (Gevenois et al., 1996)

Factors influencing emphysema quantification measurements

Reconstruction algorithm

A low spatial-frequency algorithm provides optimal image contrast at the expense of spatial resolution. A high spatial frequency algorithm provides high spatial resolution at the expense of contrast resolution. The standard algorithm has been used predominantly in studies using 10 mm collimation and the high spatial resolution algorithm has been used primarily in studies using 1 mm collimation.

Lung volume

Scans should be performed as close to total lung capacity as possible. Estimates of LAA% are similar between 90-100% of total lung capacity but submaximal inspiration will underestimate LAA%(Madani, Van Muylem, & Gevenois, 2010). Spirometrically controlling lung volumes however, does not appear to be necessary(Gierada et al., 2001).

Intravenous contrast media

Intravenous contrast media have been shown to cause a small increase in estimated lung density from -820 to -832U(Coxson et al., 1999).

Smoking status

Current smokers can appear to have a lower emphysema level than former smokers on quantitative CT(Camiciottoli et al., 2009). The extent of emphysema appears to increase rapidly after smoking cessation, reflecting a fall in lung attenuation. This is presumed to reflect a reduction in smoke induced inflammatory cell infiltrate, such that partial voluming masks the areas of low attenuation in smokers(Ashraf et al., 2011).

Distinction of normal from near-normal

The identification of emphysema presupposes knowledge of normal airspace size, which varies considerably with height, weight, sex and the degree of lung inflation. This creates problems in separating fully expanded normal lung from mild emphysema, and makes it difficult to detect the transition from health to earliest stage disease. In addition, a “*normal range*” for pulmonary emphysema index

(%LAA) has not been established. A study of 70 healthy young men with normal spirometry and minimal smoking history identified an upper limit of normal (ULN) of 2.73% using a -950HU threshold or 0.87% using -960HU threshold(Mets, van Hulst, Jacobs, van Ginneken, & de Jong, 2012).

Emphysema index and lung function parameters

Data relating Emphysema index to traditional lung function parameters is relatively scarce. Early studies compared PFT measurements with emphysema quantification by fully automated analysis of 4-slice MDCT, in a retrospective cohort including 179 COPD patients(Heussel et al., 2009). CT derived volumetric measurements correlated well with static lung plethysmography measurements (r=0.8-0.88). Correlation of emphysema index with forced expiratory ratio(r=-0.81), FEV_1 (r=-0.49) and residual volume (RV)/total lung capacity (TLC) (r=0.6) was moderate. The largest study relating %LAA to spirometry in COPD examined -950HU on inspiratory CT in 2145 patients with COPD and 1917 control subjects(Schroeder et al., 2013). Correlation was moderate between %LAA and FEV_1 (r=-0.67) and FER (r=-0.76). Correlation was stronger between quantitative expiratory CT parameter of gas trapping (HU-856) with FEV_1(r=-0.77) and FER (r=-0.84). %LAA shows moderate correlation with TLCO (r=-0.63) and KCO (r=-0.59)(Desai et al., 2007).

Relation of emphysema index to clinically significant endpoints

In a study of 251 patients with a median follow up of 8 years, %LAA had the strongest association with respiratory related mortality(Haruna et al., 2010). The GenKols study of 947 smokers, half of whom had COPD, found %LAA to be a strong independent predictor of respiratory and cardiovascular mortality(Johannessen et al., 2013). %LAA also demonstrates a strong association with 6 minute walk distance and BODE index(Ostridge & Wilkinson, 2016). Increased exacerbation rates have been associated with increased %LAA(Han et al., 2011; Jairam, van der Graaf, Lammers, Mali, & de Jong, 2015). Higher %LAA observed on CT chest at the time of exacerbation predicted increased rates of disability and death at 1 year in a prospective study of 104 AECOPD admissions(Cheng et al., 2015).

Clinical utility of emphysema quantification by %LAA

The anatomical distribution of emphysema is now of key importance in patient selection for bronchoscopic lung volume reduction surgery (LVRS). CT imaging to quantify and map emphysema permits detailed anatomical interlobar comparisons, but a global %LAA assessment has not yet become an integral part of clinical COPD management. It has value as a prognostic tool, including among patients who have not yet developed spirometric obstruction(Martinez & Han, 2012; Mohamed Hoesein et al., 2011). It is also useful as a more sensitive marker to observe longitudinal change in emphysema in studies of alpha-1 antitrypsin deficiency(Dirksen et al., 1999).

Ventricular function assessment

Image processing

A multi-phase reformatted dataset of maximally thick 1.5mm axial images without overlap are reconstructed at 10% increments (10 phases) for single source or 5% increments (20 phases) for dual source CT scanners. Images are reconstructed in a cine mode, from R wave onset throughout the cardiac cycle, for global and regional ventricular function assessment.

Assessment of Left and Right Ventricular function

Measurements of the internal boundaries of the left ventricle (LV) are performed at end-diastole and end-systole. End diastole can be defined as onset of the QRS complex but preferably as the frame following mitral valve closure, or the frame in which the cardiac dimension is largest, which is after atrial contraction in patients in sinus rhythm.

Assessments of ventricular function and left ventricular (LV) mass by MDCT are comparable to cardiac magnetic resonance imaging (cMRI)(Brodoefel et al., 2007; Busch et al., 2008). A reasonable correlation has even been achieved with non-contrast CT imaging(K. Nasir et al., 2008). A meta-analysis comparing the assessment of left ventricular ejection fraction (LVEF) by cardiac CT, cMRI and TTE showed no difference between modalities(Asferg, Usinger, Kristensen, & Abdulla, 2012). Excellent correlation between cardiac CT and cMRI to estimate LV size, volume and function has been confirmed across a wide range of clinical severity (LVEF 30-72%)(Asferg et al., 2012). Cardiac CT shows better agreement with cMRI than with biplane ventriculography or 2D transthoracic echocardiography(Dewey et al., 2006) for global LV function and equivalent wall motion assessment to echocardiography. Abnormal left ventricular volumes and impaired left ventricular ejection fraction as determined by MDCT predict mortality and risk discrimination in a prospective study of 7758 patients(Arsanjani et al., 2014).

Cardiac MRI (cMRI) is the “gold standard” investigation for assessment of right ventricular function(Goetschalckx, Rademakers, & Bogaert, 2010). The right ventricle (RV) has a complex asymmetrical shape. It is morphologically different from the LV wall as its walls are much thinner and more trabeculated. This can make edge

recognition by echocardiography difficult(Ho & Nihoyannopoulos, 2006). A study comparing cMRI, MDCT and real-time 3-dimensional echocardiography (RT3DE) showed high correlation between MDCT and cMRI(Sugeng et al., 2010). CT showed a slight (4%) but consistent overestimation of RV volumes, whereas RT3DE showed a slight underestimation. Obtaining RV assessment via MDCT requires extending the duration of the contrast infusion by 10 seconds to ensure adequate RV filling. Retrospectively ECG-gated image reconstruction is required to reconstruct images throughout all phases of the cardiac cycle. Tube current modulation can be applied which limits the tube output in systole. Functional analysis can be performed prospectively if sufficient “padding” is added. The timing of contrast is standardized for arterial phase imaging (typically the scan acquisition starts 4-6 seconds after time to peak aortic opacification). Contrast injection for LV and coronary imaging is typically performed for a time period that is equal to the duration of data acquisition (but at least 10 seconds if data acquisition is <10 seconds). To obtain adequate RV opacification an additional 10 seconds of contrast injection should be added but may be given at a slower flow rate (e.g. 2ml/sec) if the injector permits.

MDCT provides a reliable alternative to cMRI for assessment of the right ventricle(Surkova, Muraru, Iliceto, & Badano, 2016). Right ventricular functional assessment by MDCT shows significant correlation with right heart catheterization measures in patients with pulmonary hypertension(Abel et al., 2012) and excellent correlation with cardiac MRI in patients with suspected coronary disease(Plumhans et al., 2008).

Pulmonary hypertension and pulmonary artery distensibility

The pulmonary circulation is a high flow, low resistance circuit. The pulmonary vasculature can be considered as comprising of two units - the pulmonary arteries (PA) and the capillary bed. High distensibility in the proximal PAs permits transformation of pulsatile right ventricular (RV) output into the near steady blood flow at the capillary level(Fourie, Coetzee, & Bolliger, 1992). The distal pulmonary vasculature is also highly distensible, and during exercise can recruit the pulmonary microvasculature to reduce pulmonary vascular resistance (PVR) and accommodate large increases in cardiac output without marked elevations in pulmonary pressure. Due to this physiological reserve, elevation in resting pulmonary artery pressure is not seen until over 50% of the vascular bed is obstructed(Dalen et al.). The pulmonary arteries and microcirculation have distinct effects on RV afterload. Peripheral vascular resistance modulates a steady component to drive and maintain forward flow, whereas an oscillatory component reflects proximal and distal pulmonary arterial stiffness(Weir-McCall, Struthers, Lipworth, & Houston, 2015).

Healthy pulmonary arterioles do not possess a muscular layer. In COPD related pulmonary hypertension (COPD-PH), remodelling and muscularization of pulmonary arterioles occurs, characterized by intimal proliferation of poorly differentiated smooth muscle cells and the deposition of elastic and collagen fibres. Pulmonary vascular changes occur early in the course of COPD, before the onset of hypoxaemia. Inflammatory mediators released from the pulmonary parenchyma and direct effects of cigarette smoke on vascular endothelium may underlie the apoptosis and endothelial dysfunction observed in smokers with and without COPD(Barbera, 2013). Subsequent vascular remodelling, capillary loss and small vessel thrombosis can ensue. Alveolar hypoxia causes reflex pulmonary vasoconstriction resulting in increased pulmonary vascular resistance (PVR) and increased pulmonary artery pressure (*Ppa*). In combination, cigarette smoking and alveolar hypoxia induce greater pulmonary vascular remodelling than either noxious stimulus alone although substantial inter-individual variability is observed in healthy and COPD populations(Weitzenblum, Schrijen, Mohan-Kumar, Colas des Francs, & Lockhart, 1988). Chronic hypoxaemia results in endothelial dysfunction favouring increased vasomotor tone(Faller, 1999), another determinant of Ppa. Destruction of the pulmonary microvasculature and reduction in PA compliance in COPD patients can

therefore result in a spectrum of pathophysiology in COPD, from exercise-induced pulmonary hypertension through to cor pulmonale.

Ventriculo-arterial coupling

The distensibility of the PA is determined by it's intrinsic stiffness and the driving pressure. A highly compliant and distensible PA allows the right ventricle to work at optimal efficiency and protects the microcirculation from large pressure gradients.(Fourie et al., 1992). In COPD, a pathological rise in PA pressure with exercise is seen among those individuals with and without established resting PH(Hilde et al., 2013) which directly correlates with PA wall thickness(Kubo et al., 2000). Increasing PA stiffness appears to initially provoke exercise-induced PH (EIPH), which can progress to resting PH, RV hypertrophy and diastolic dysfunction and ultimately RV systolic dysfunction.

Definition of pulmonary hypertension

PH is defined as a mean resting pulmonary artery pressure (mPAP)>25mmHg measured during right heart catheterization (RHC)(Badesch et al., 2009). Pulmonary artery pressure represents the sum of the pulmonary capillary wedge pressure (*P*pw) and the driving pressure across the pulmonary circulation - cardiac output (CO) x pulmonary vascular resistance (PVR). Pulmonary wedge pressure is often high in severe COPD patients(Scharf et al., 2002) possibly reflecting concomitant left heart disease. Alternatively lung hyperinflation has been proposed to increase juxtacardiac pressures, with pressures rising with exercise and tachypnoea(Butler, Schrijen, Henriquez, Polu, & Albert, 1988).

Prevalence of PH in COPD

Estimates of pulmonary hypertension in COPD (PH-COPD) prevalence are confounded by variable COPD severity, comorbid left-sided heart disease, PH thresholds and diverse techniques used for estimation. In clinical practice, RHC is rarely performed in COPD patients outwith the lung transplantation setting. One study of 98 stable COPD patients without left sided heart disease, found a prevalence of PH as determined by RHC mPAP>25mmHg in 5%, 27% and 53% of patients in GOLD stages II, III and IV, respectively(Hilde et al., 2013). In hospitalized COPD patients, prevalence of mild PH had been estimated at 50%, with rates of 70-

90% in those evaluated for lung transplantation (Chaouat, Naeije, & Weitzenblum, 2008). Exercise-induced pulmonary hypertension (EIPH) appears common in COPD and predicts the onset of resting PH(Kessler et al., 2001).

Pathophysiology of PH in COPD

In healthy patients, pulmonary vascular resistance drops during exercise to accommodate the increased cardiac output. In COPD, this drop does not occur and the increased cardiac output results in increased pulmonary artery pressure thus provoking exertional dyspnoea(Fletcher, Luckett, Miller, & Fletcher, 1989).

COPD exacerbation has been associated with a transient elevation in Ppa of up to 20mmHg (Abraham et al., 1969). Significant spikes in pulmonary artery pressure at exacerbation are more common in patients exhibiting peripheral oedema and correlate with hypoxaemia(Weitzenblum, Apprill, Oswald, Chaouat, & Imbs, 1994).

Pulmonary hypertension in COPD also predicts increased hospitalization for exacerbation(Kessler, Faller, Fourgaut, Mennecier, & Weitzenblum, 1999). Surrogates for pulmonary hypertension in COPD such as an increased pulmonary artery:aorta (PA:A) have also been shown to predict risk of severe exacerbation(Wells et al., 2012).

Detection of PH in COPD

Right heart catheterization

The gold standard investigation to detect PH remains right heart catheterization (RHC). This allows direct measurement of pulmonary pressures, assessment of the left heart contribution via pulmonary capillary wedge pressure and testing of vasodilator responsiveness. Due to the risks associated with RHC and the resources required, there is considerable interest in identifying reliable non-invasive parameters to assess PH, particularly in COPD populations.

Cardiac biomarkers

Brain natriuretic peptide (BNP) and N-terminal proBNP (NTproBNP) are a cardiac hormone and prohormone released into the circulation in response to “cardiac stretch”(Bozkanat et al., 2005). BNP blunts hypoxic vasoconstriction in healthy

volunteers and patients with cor pulmonale, resulting in decreased PVR, decreased mPAP and suppression of aldosterone(Cargill & Lipworth, 1996). BNP correlates with pulmonary artery pressure as measured by RHC and has been proposed as a non-invasive screening tool for PH(Leuchte et al., 2006). Patients with COPD exhibiting lower oxygen saturation, higher pulmonary artery pressure and cor pulmonale demonstrate significantly higher BNP levels(Bozkanat et al., 2005). BNP predicts functional impairment and is a stronger predictor of mortality in stable COPD than lung function impairment(Leuchte et al., 2006).

Transthoracic Echocardiography (TTE)

Whilst the diagnosis of PH is based upon mean PAP (mPAP) at RHC, Doppler echocardiography can estimate *systolic* pulmonary artery pressure via measurement of the peak velocity of a regurgitant tricuspid jet. Right ventricular systolic pressure is estimated based on the modified Bernoulli equation and considered to be equivalent to sPAP in the absence of right ventricular outflow tract (RVOT) obstruction. This can be summarized as follows:

sPAP = RVSP = trans-tricuspid gradient + right atrial pressure (RAP)

where trans-tricuspid gradient is $4v^2$ (v = peak velocity of tricuspid regurgitation (metres/second). RAP is estimated based on variation in the size of the inferior vena cava with inspiration

Complete collapse - RAP = 5mmHg

Partial collapse - RAP = 10mmHg

No collapse - RAP = 15mmHg

A statistically significant correlation between sPAP via TTE and RHC is well established in cardiac disease(Currie et al., 1985). In contrast, TTE performs poorly in severe obstructive lung disease due to impairment of the acoustic window by hyperinflated lungs. An estimate of pulmonary artery pressure by Echocardiography could only be made in 38% of patients with severe obstructive lung disease(Arcasoy et al., 2003). Moreover, although a statistically significant relationship between estimated sPAP and RHC confirmed sPAP existed, the diagnostic accuracy of echocardiography was poor.

Magnetic Resonance Imaging

Cardiac MRI is the gold standard for quantification and evaluation of right ventricular function (Pennell et al., 2004). Dynamic imaging allows visualization of the PAs throughout the cardiac cycle. The fractional area change of the PA through the cardiac cycle is frequently referred to as PA distensibility in the literature. When area change alone is assessed it is more correctly termed pulsatility. Assessment of true distensibility, requires not only knowledge of the change in vessel calibre but also of the driving pressure that induced that change. Pulmonary artery “pulsatility” or “distensibility” have been investigated as surrogates for pulmonary hypertension. To be consistent with the literature the terms pulsatility or distensibility are used in accordance with the term proposed in the original paper. In pulmonary arterial hypertension (PAH), gradual muscularization of the pulmonary arteries in response to markedly elevated pulmonary pressures reduces the capacity of the proximal pulmonary arteries to offload the pressure delivered by the right ventricular output. Pulmonary artery distensibility is markedly reduced in patients with established PAH compared to controls(Bogren et al., 1989; Wu et al., 2008) and correlates well with mPAP as measured by RHC(Sanz et al., 2009). Reduced PA distensibility is strongly predictive of mortality(Sanz et al., 2009).

Pulmonary hypertension in COPD is generally milder than in PAH and reflects both increased hypoxic vasomotor constriction and vascular remodelling(Elwing & Panos, 2008). An MRI study assessing PA distensibility in 290 patients free of clinical cardiovascular disease observed progressive decline in PA distensibility from controls (20.6%) to mild(20%), moderate (16.7%) and severe (12.9%) COPD(Liu et al., 2013). The same patient cohort had %emphysema data available from a separate CT examination. Main and right PA distensibility on MRI were inversely related to %emphysema on CT after adjustment for age, gender, weight, race, smoking history, lipids, statin use, hypertension and oxygen saturation.

Patients often progress through an evolution from normal resting Ppa to exercise-induced pulmonary hypertension, ultimately culminating in resting pulmonary hypertension. Importantly, decreased pulmonary artery distensibility may be detectable early in the evolution of this process, before resting pulmonary hypertension is established(Sanz et al., 2009).

MDCT

PH confirmed on RHC is associated with a dilated PA on MRI(Boerrigter et al., 2010) or CT(Devaraj et al., 2010). A ratio of the PA:Aorta diameters >1 has a PPV of 92% in a PAH population(Boerrigter et al., 2010). Using standard, non ECG-gated CT, PA:Aorta>1 was a strong predictor of severe exacerbations in COPD (OR 3.44)(Wells et al., 2012). A retrospective study of 134 patients suggested a significant increase in mean PA:A from 0.91 when stable to 0.97 at exacerbation ($p<0.001$)(Wells et al., 2015). In the same study, increased PA:A was associated with biochemical evidence of cardiac injury and adverse exacerbation outcomes.

Pulmonary artery dilation reflects established pulmonary hypertension and therefore has a high specificity but relatively lower sensitivity to detect PH. ECG-gated MDCT has the capacity to measure pulsatility of the PA, rather than a single diameter observed at an unknown phase of the cardiac cycle. Impaired distensibility of the PA appears to occur earlier in the evolution of PH than established dilation of the PA(Sanz et al., 2009). PA distensibility measured by MDCT correlates well with both MRI PA distensibility and with RHC measurement of Ppa(Abel et al., 2012; D'Agostino, Valerio, Bracciale, & Valerio, 2013; Plumhans et al., 2008; Revel et al., 2009). Impaired pulmonary artery distensibility during exercise(Sanz et al., 2009) or exacerbation may identify a population at high risk for future established pulmonary hypertension. One previous study has related ECG-gated MDCT PA distensibility to RHC measurements in COPD patients(D'Agostino et al., 2013). PA pulsatility (PA*puls*) was inversely related to PVR ($r^2=0.274$, $p=0.0177$) and PAP ($r^2=0.219$, $p=0.0371$). PA*puls* was around 20% in the COPD group (n=20) compared to 10% in the COPD-PH (n=20) group (<0.0001) (D'Agostino et al., 2013).

Once established, PH is associated with markedly reduced 5-year survival in COPD patients(Andersen et al., 2012; Weitzenblum et al., 1981) and so early detection is of paramount importance.

Aortic distensibility (pulsatility)

Distensibility of the aorta absorbs pulsatile pressure from the left ventricular output. Stiffening of the aorta occurs progressively with ageing and reduces aortic distensibility, resulting in increased shear stress on distal vessels, increased left ventricular afterload and reduced coronary blood flow in diastole.

Aortic stiffness can be measured using carotid-femoral Doppler pulse wave velocity (PWV) - a stiff aorta transmits the aortic pulse wave more quickly. Carotid-femoral PWV is predictive of cardiovascular events and mortality in healthy individuals(Vlachopoulos, Aznaouridis, & Stefanadis, 2010). PWV is known to be increased in COPD patients(Mills et al., 2008) and relates to the degree of CT quantified emphysema and FEV_1(McAllister et al., 2007). Aortic distensibilty has been measured using cMRI(Nelson et al., 2009) and ECG-gated MDCT(Rose et al., 2010). Distensibility is calculated based upon the change in cross-sectional area of the ascending aorta through the cardiac cycle(Groenink, de Roos, Mulder, Spaan, & van der Wall, 1998):

$$\text{Distensibility } (10^{-3}\text{mmHg}) = \frac{A_{max} - A_{min}}{A_{min}\,(P_{max} - P_{min})}$$

A_{max} = maximum cross-sectional area of ascending aorta
A_{min} = minimum cross-sectional area of ascending aorta
P_{max} = systolic blood pressure (mmHg)
P_{min} = diastolic blood pressure (mmHg)

In a COPD population, CT has numerous advantages over the alternative non-invasive modalities currently available. Echocardiography performs particularly poorly in emphysematous patients. The mode and duration of MRI acquisition would be difficult to tolerate for severe stable COPD patients and certainly impractical during an exacerbation. ECG-gated MDCT also has the enormous advantage of simultaneous lung field assessment. Finally, only MDCT has the potential to explore the relationship between emphysema, pulmonary vascular disease and cardiac function within the same study acquisition.

5.3 CARDIOPULMONARY EVALUATION IN COPD EXACERBATION USING DYNAMIC CT

Introduction

Cardiovascular disease is a leading cause of mortality in COPD and is likely to be significantly under-diagnosed(Brekke, Omland, Smith, et al., 2008; Sin et al., 2006). The interaction of heart and lung disease in COPD is complex and varied but improved diagnosis of cardiac disease may provide an opportunity for therapeutic intervention.

Cardiac disease is of key relevance during acute exacerbations of COPD (AECOPD) on a number of levels. An established diagnosis of cardiac disease at the time of AECOPD is associated with greater short-term mortality(Agabiti et al., 2010; Almagro et al., 2012). Acute cardiac dysfunction may be the primary cause of hospitalized AECOPD(Connors et al., 1996). Alternatively, exacerbations may provoke major cardiovascular events, with increased rates of myocardial infarction(McAllister, Maclay, Mills, Leitch, Reid, Carruthers, O'Connor, et al., 2012), atrial fibrillation(C. Terzano et al., 2014) and stroke(G. C. Donaldson, Hurst, Smith, Hubbard, & Wedzicha, 2010) observed during or post exacerbation.

More commonly however, elevated levels of troponin or brain natriuretic peptide are observed in the absence of a clinically detected acute cardiac disorder. Elevation of cardiac biomarkers appears clinically important as it is associated with reduced survival(Singanayagam, Schembri, & Chalmers, 2013). Limited data suggests elevated troponins during AECOPD may be more common in those with diagnosed coronary artery disease(Patel et al., 2013) and BNP levels higher in those with left ventricular dysfunction(Abroug et al., 2006). Elevated cardiac biomarkers during AECOPD may therefore identify COPD patients with underlying cardiac disease who could be targeted for therapeutic intervention. Observational studies suggest COPD patients may benefit from anti-platelet agents(Harrison et al., 2014), statins(Mortensen et al., 2009), β-blockers(Dransfield et al., 2008) and angiotensin blockade(Mancini et al., 2006) although this has never been evaluated in randomized trials. However, raised troponins and natriuretic peptides at exacerbation are not specific for coronary artery disease and left ventricular failure. High levels

have been observed in pulmonary hypertension(Leuchte et al., 2004), pulmonary embolism(ten Wolde et al., 2003), right ventricular failure(Kruger et al., 2004), renal failure(Jain & Hedayati, 2011) and sepsis(Altmann et al., 2010), where benefit from the aforementioned therapies would not be anticipated

The mechanisms provoking elevation of cardiac biomarkers during AECOPD and any therapeutic implications are not clear, although these may be of considerable prognostic relevance. Diverse processes including coronary artery disease, left ventricular systolic and diastolic dysfunction, increased arterial stiffness, hyperadrenergism, pulmonary hypertension and right ventricular dysfunction may all be implicated to varying degrees. Distinguishing coronary, pulmonary vascular and myocardial disorders in each exacerbation is required to individualize medical therapy, but accurately identifying cardiac comorbidities in severe COPD exacerbations presents a particular diagnostic challenge.

Transthoracic echocardiography (TTE) performs poorly in the presence of emphysema(Arcasoy et al., 2003). Cardiac magnetic resonance imaging (cMRI) represents the gold standard investigation to evaluate cardiac function(Hendel et al., 2006) however, the duration and mode of acquisition is impractical during AECOPD. Dynamic multidetector computed tomography (MDCT) provides a novel opportunity to identify and quantify these various pathologies at COPD exacerbation. Cardiac MDCT shows excellent agreement with cMRI for quantification of ventricular function(Asferg et al., 2012) and is more accurate than transthoracic echocardiography(Greupner et al., 2012). In a COPD population, MDCT enjoys specific advantages over cMRI, with rapid study acquisition, simultaneous lung assessment and potential for coronary artery calcium scoring.

Hypotheses and aim

We hypothesized that:

1) Low-radiation dynamic cardiac function CT during acute COPD exacerbation would identify previously undiagnosed cardiac disorders, and
2) Elevations of cardiac biomarkers at exacerbation would be associated with cardiac abnormalities identified on CT.

The overall **aims** were therefore:

1) To assess the prevalence of cardiac pathology identified using 256-MDCT in a hospitalized AECOPD cohort.

2) To examine the impact of acute exacerbation on cardiac function using MDCT during acute exacerbation and following exacerbation recovery.

3) To correlate cardiac biomarkers in peripheral blood with various indices of cardiac function and dysfunction as detected on MDCT.

The protocol included prospective ECG-gated non-contrast coronary artery calcium scoring, followed by retrospective ECG-gated contrast enhanced 256-slice MDCT thorax. The CT parameters measured and their relevance are briefly discussed below;

Coronary artery calcium score (CACS)

Coronary artery calcium scoring (CACS) permits non-invasive detection and quantification of coronary atherosclerosis, although unlike CT coronary *contrast arteriography*, calcium scoring cannot identify flow-limiting stenoses. CACS can be reported as an absolute value expressed in Agatston Units(AU)(Agatston et al., 1994) or as a percentile relative to matched individuals without clinical cardiovascular disease(McClelland et al., 2006). CACS predicts risk of future cardiovascular events(Church et al., 2007) and likelihood of coronary stenoses at invasive angiography(Guerci et al., 1997). In large stable outpatient COPD populations, CACS independently predicts mortality and major adverse cardiovascular events (MACE) rates (Gaisl et al., 2015; Williams et al., 2014),

Emphysema Index

CT voxels of <-950 Hounsfield Units (HU) are termed ‘low attenuation areas’ (LAA) and correlate with histologically confirmed emphysema(Gevenois et al., 1996). The ‘emphysema index’ (%LAA) quantifies emphysema as percentage of intrathoracic volume occupied by voxels of emphysema density(Cavigli et al., 2009).

CT pulmonary angiography (CTPA)

CTPA identifies pulmonary embolism through direct contrast visualization. Pulmonary embolism is an infrequent cause of AECOPD(Rutschmann et al., 2007) but a potential cause of elevated cardiac biomarkers(Bajaj et al., 2015).

Pulmonary artery distensibility

A highly compliant and distensible pulmonary artery is required to help transform the pulsatile right ventricular output to a near steady flow at the level of the pulmonary capillaries(Fourie et al., 1992). As pulmonary pressure increases the pulmonary arteries become progressively less compliant with reduced distensibility(Bogren et al., 1989). Pulsatility of the PA (fractional change in cross-sectional area over the cardiac cycle) can be measured by MRI or MDCT and is usually >40% in healthy individuals(Gan et al., 2007; Sanz et al., 2009). PA pulsatility is reduced in pulmonary hypertension and correlates inversely with pulmonary pressure as measured by right heart catheterization(D'Agostino et al., 2013; Sanz et al., 2009). Impaired pulmonary artery pulsatility is an independent predictor of mortality in pulmonary arterial hypertension(Gan et al., 2007; Swift et al.).

Aortic pulsatility

Elevated arterial stiffness is a known predictor of cardiovascular risk and all-cause mortality(Vlachopoulos et al., 2010) and is prevalent in COPD patients(McAllister et al., 2007). Previous studies measuring arterial stiffness via ultrasound Doppler carotid-femoral aortic pulse wave velocity (PWV) have suggested that arterial stiffness increases at the time of exacerbation and is higher among frequent exacerbators(Patel et al., 2013). We report pulsatility of the aorta as a marker of aortic stiffness as aortic *distensibility* measurement requires knowledge of the systemic blood pressure which was not recorded at the time of supine CT scanning.

Cardiac function CT

Biventricular systolic function assessment using contrast enhanced ECG-gated MDCT in sinus rhythm is equivalent to cardiac MRI(Greupner et al., 2012). MDCT shows greater accuracy than conventional 2-dimensional transthoracic

Echocardiography in estimating ventricular volumes, particularly for the right ventricle(Plumhans et al., 2008; Surkova et al., 2016).

We utilized this novel multidimensional cardiopulmonary MDCT approach to evaluate the complex cardiopulmonary pathophysiology of AECOPD. Cardiovascular diagnoses based on MDCT findings were compared to rates of diagnosed conditions from the medical record. High sensitivity troponin I (hs-TnI) and NT-proBNP levels in those with clinically or MDCT diagnosed cardiac disorders were compared. Follow-up imaging and biomarker analysis was performed to assess the acute impact of exacerbation.

Methods

Study design and patients

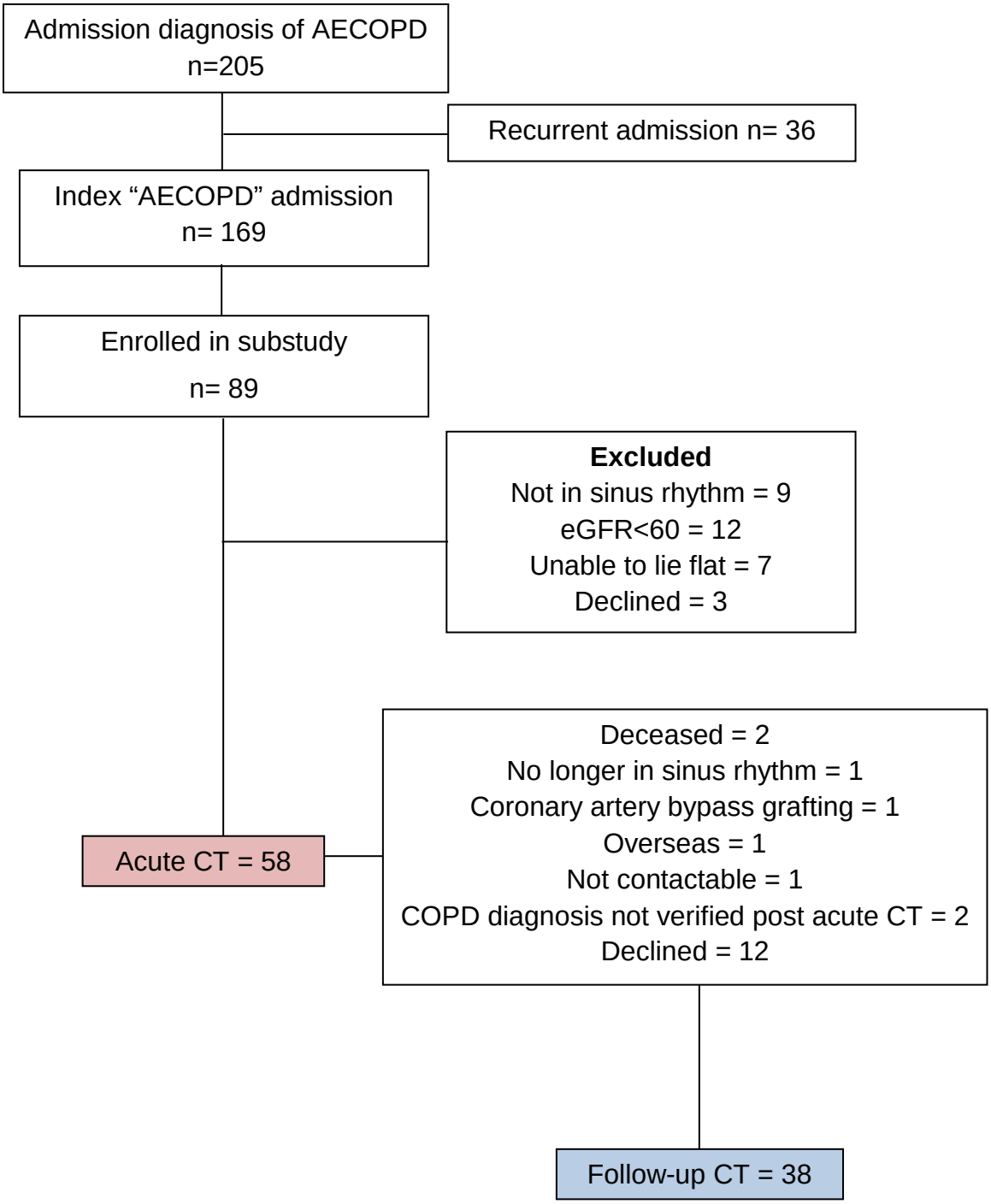
The study was approved by the Human Research Ethics Committee, Monash Health, Melbourne (HREC14261A).

Patient selection

Patients at a tertiary referral centre in Melbourne, Australia, with a primary admission diagnosis of AECOPD were enrolled in a prospective observational study (HREC13134A). A subset of eligible patients, were enrolled to a sub-study utilizing contrast enhanced 256-slice multi-detector computed tomography (256-MDCT) between November 2014 and March 2016 (HREC14261A). Patients enrolled to the CT study required to be in sinus rhythm at the time of CT to facilitate retrospective ECG-gated assessment of cardiac function. As iodinated intravenous contrast was used, patients with iodine allergy or estimated glomerular filtration rate (eGFR)<60ml/min were excluded. Coronary artery contrast angiography was not a study objective therefore heart rate reduction therapy (i.e. β-blockade) was not required and any patient with a heart rate <130 beats per minute was eligible. Patients were required to be capable of lying flat and performing a breath-hold at full inspiration for 6 seconds.

All patients were current or former cigarette smokers. COPD was established by post-bronchodilator forced expiratory ratio <0.7 in accordance with Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria(Vogelmeier et al., 2017).

Figure 1. CONSORT diagram of study participants



Patient assessment

All patients who were recruited underwent a comprehensive exacerbation phenotyping process comprising nasopharyngeal viral PCR, sputum culture, full blood examination (FBE), C-reactive protein (CRP), venous blood gas (VBG), study specific questionnaire, COPD Assessment Tool (CAT)(P. Jones, Harding, Wiklund, Berry, & Leidy, 2009) and Hospital Anxiety and Depression Scale (HADS)(Zigmond & Snaith, 1983). Serum from admission blood samples was retrieved and frozen at -80C where available. These samples were analysed at study completion for high-sensitivity troponin I (hs-TnI) using STAT High Sensitivity Troponin chemiluminescent microparticle immunoassay, Abbott Archicentre ci162) and N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) measure using an electrochemiluminescence immunoassay (Roche e411). High sensitivity troponin I and NT-proBNP levels are reported both as absolute values and as dichotomous variables based on values above or below the upper limit of normal for age and gender matched reference population(Galasko et al., 2005; Trambas et al., 2016).

256-MDCT parameters

All CT imaging was performed with a 256-slice CT machine *(Philips iPatent iCT, Philips Healthcare, Cleveland, USA).* Patients underwent two consecutive CT acquisitions as outlined below. Assessments were undertaken using the IntelliSpace Portal Workstation (*V6 Philips Healthcare, Cleveland, USA*).

Prospective ECG-gated coronary artery calcium score

The acquisition parameters were as follows; collimation of 96/128 x 0.625mm (dependant on z-axis coverage), rotation time of 0.33sec, pitch 0.2, kVp selection of 120 and tube current modulated depending on patient size with an average patient mAs of 61mAs. Contiguous 2.5mm thick images were reconstructed for coronary artery calcium scoring. Coronary artery calcium was considered present in a coronary artery when a density threshold of >130HU was detected in ≥3 consecutive pixels overlying that coronary artery and quantified using the previously described Agatston's score(Agatston et al., 1994)**.**

Figure 2. Coronary artery calcium scoring

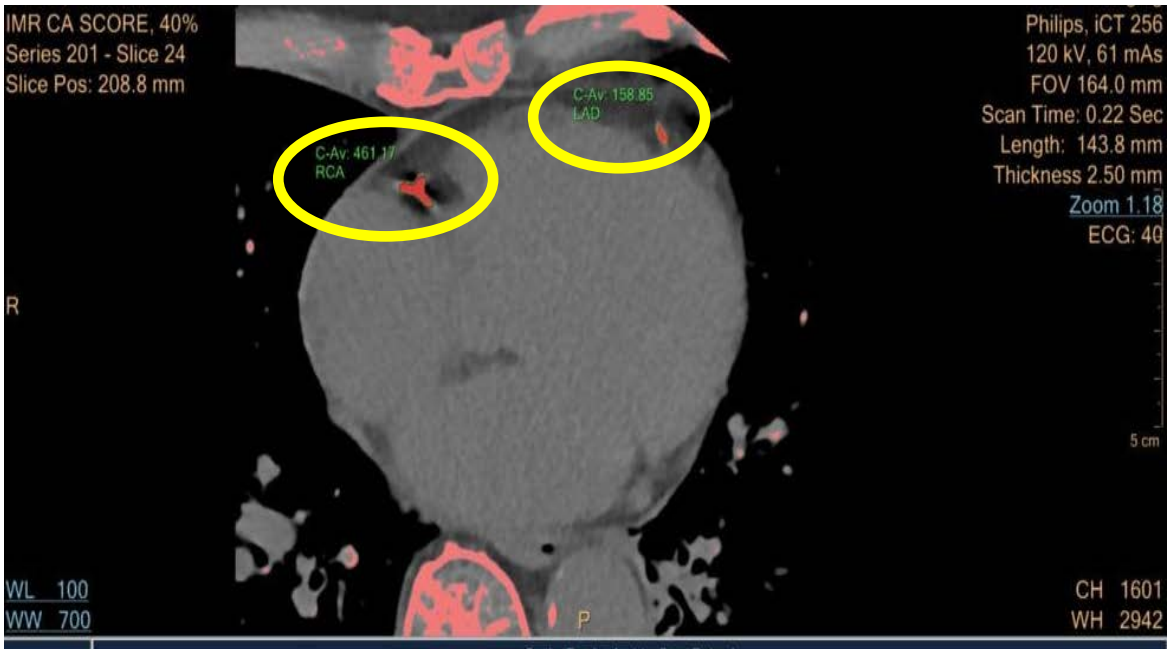


Figure 2. Areas of density over 130 Hounsfield Units (HU) in the coronary arteries are shown (yellow circles, RCA = right coronary artery, LAD = left anterior descending artery). Note areas of non-coronary calcific density in the vertebral body, sternum, costal cartilage, and anterior ribs. Coronary artery calcium score is calculated for individual coronary arteries and then summed to give a total score, expressed in Agatston's Units (AU) (table at bottom of figure).

Retrospective ECG-gated CT full chest

The acquisition parameters were as follows; collimation of 128 x 0.625mm, kVp selection of 100 or 120 dependent on patient weight (100kVp for <80kg and 120 for ≥80kg), rotation time of 0.27sec, pitch of 0.2 and tube current modulated depending on patient size (average patient mAs of 86mAs <80kg and 51mAs ≥80kg). The patients were scanned from cranial to caudal, holding their breath at the end of a maximal inspiratory effort. A total of 75 ml of non-ionic low-osmolar contrast agent (*Omnipaque 350, Iohexol, GE Healthcare, Milwaukee US*) was administered intravenously at a flow rate of 5 ml per second using a biphasic injection protocol (40mL contrast followed by 60mL 50:50 contrast:normal saline mix). CT scanning was commenced when contrast was visualised in the left ventricle using a contrast bolus tracking method. No heart rate control was employed. Full chest assessment was conducted using a dataset reconstructed with 1mm thick contiguous images of the 40% phase of the coronary R-R interval dataset. Pulmonary emphysema was quantified by CT densitometry and volumetry with emphysema identification based upon a density threshold of -950Hounsfield Units (HU). The % low attenuation areas (%LAA) or ‘emphysema index’ was calculated by dividing the total lung volume (TLV) by the lung volume with a density <-950HU.

Figure 3. Emphysema index (%LAA)

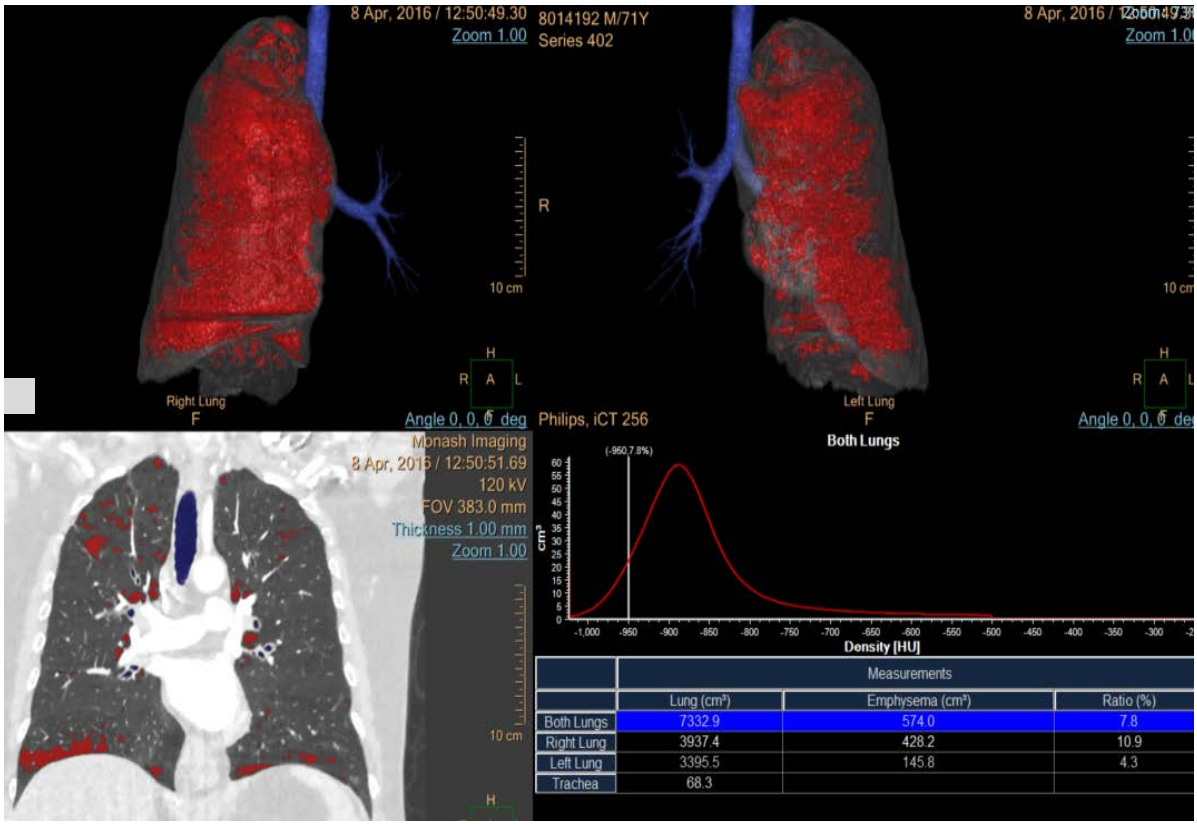


Figure 3. Volumetric CT acquisition of the chest is performed. Lung parenchyma and large proximal airways are segmented; the airways (in blue) are excluded from lung volume calculations. A Hounsfield Unit (HU) density mask is applied to identify all voxels in the lung parenchyma with HU<-950 (in red). The % low attenuation area (%LAA) or 'emphysema index' is calculated by dividing the total volume of voxels with HU<-950 by the total volume of the lung parenchyma. The distribution of voxel densities in the lung is shown in histogram format (middle right) with a vertical line marking the -950HU threshold.

Cardiac function assessments were determined using 1mm thick contiguous image datasets reconstructed at 10% intervals from 0%-90% of the coronary R-R interval. Short-axis multiplanar sections were defined, including the whole ventricular chamber, from base to apex. Then, the observers modified if necessary, the automatic outlining of the cardiac cavities on the end-systolic and end-diastolic images. Once all slices were outlined, the software automatically calculated the end-systolic and end-diastolic volumes by Simpson's rule. The papillary muscles were excluded in the right ventricular volumes. Volumes are reported both in absolute values and indexed against body surface area calculated using Mosteller's method(Mosteller, 1987).

Figure 4. Cardiac function assessment

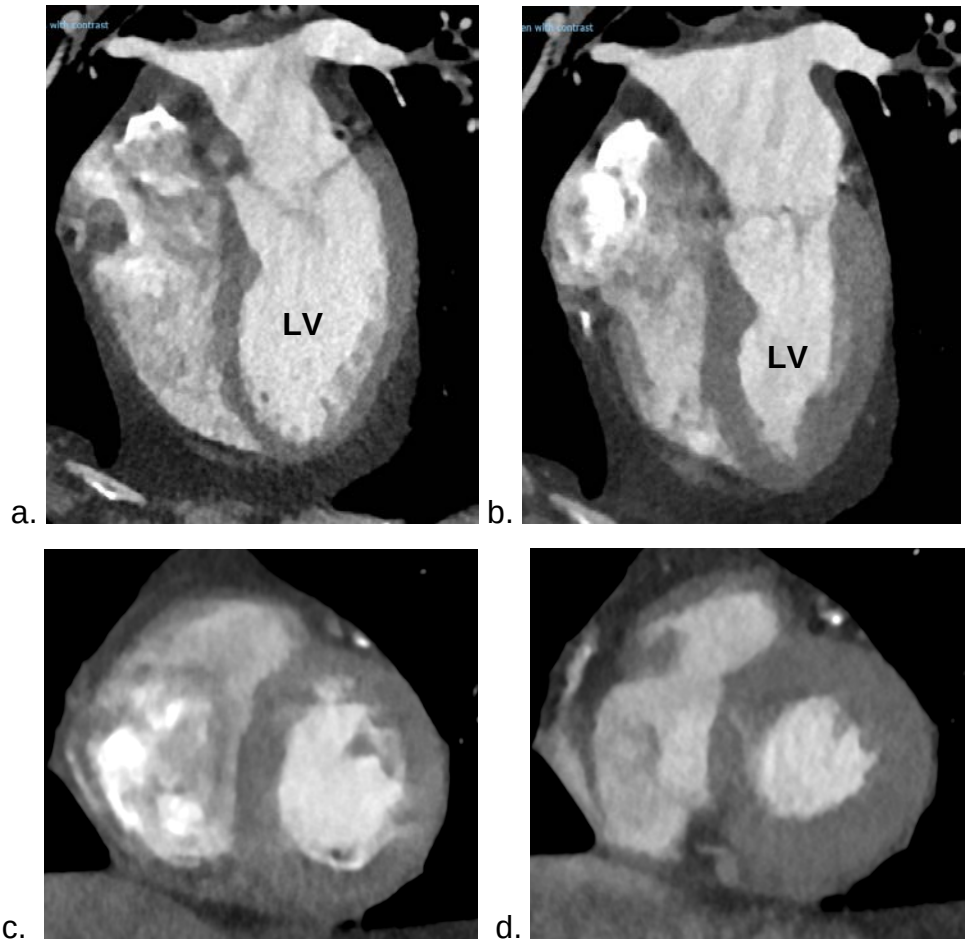


Figure 4. A 3D volume of the heart is acquired during an entire cardiac cycle; multiplanar images are reconstructed at 10% of the R-R interval from 0% to 90%. For example: **a**. end-diastole (4 chamber view) **b**. end-systole (4 chamber view) **c.** short end-diastole (LV short axis) d. end-systole (LV short axis).

Pulmonary artery (PA) surface area was defined on a cross-sectional plane of the PA trunk, perpendicular to its long axis, on sagittal and axial views, at the midpoint between the pulmonary valve and the bifurcation of the PA. The PA cross-sectional area (CSA) was measured in each cardiac phase using semi-automatic calipers with manual correction if required. Fractional area change (FAC) or PA pulsatility (PA*puls*) was then calculated using the highest and the lowest of the 10 CSA measurements: PA pulsatility (%) = ((CSA max-CSAmin)/CSA max) x 100(Revel et al., 2009).

Figure 5. Pulmonary artery pulsatility

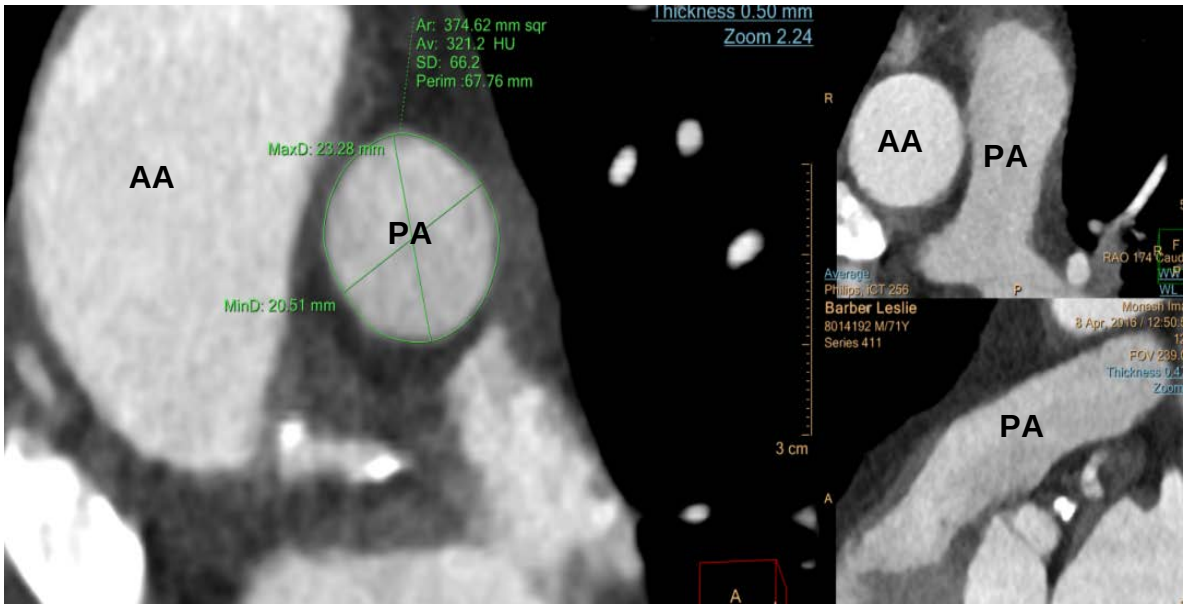


Figure 5. The midpoint of the main pulmonary artery (PA) is defined on parasagittal oblique (bottom right) and axial (top right) views. Multiplanar reformats are used to establish the optimal plane for PA cross-sectional area (CSA) measurement (perpendicular to two orthogonal planes through the long axis of the PA). CSA of the main PA is then measured at 10% intervals throughout the cardiac cycle. Pulmonary artery pulsatility (%) is reported as fractional area change (CSA max-CSAmin)/CSA max) x 100.

Aortic pulsatility

Ascending aorta measurements were taken at the midpoint of the ascending aorta (midpoint between aortic valve and the first branch of the ascending aorta). Fractional area change (FAC) or ‘aortic pulsatility’ was then calculated using the highest and the lowest of the 10 CSA measurements: Aortic pulsatility (%) = ((CSA max-CSAmin)/CSA max) x100.

Figure 6. Aortic pulsatility

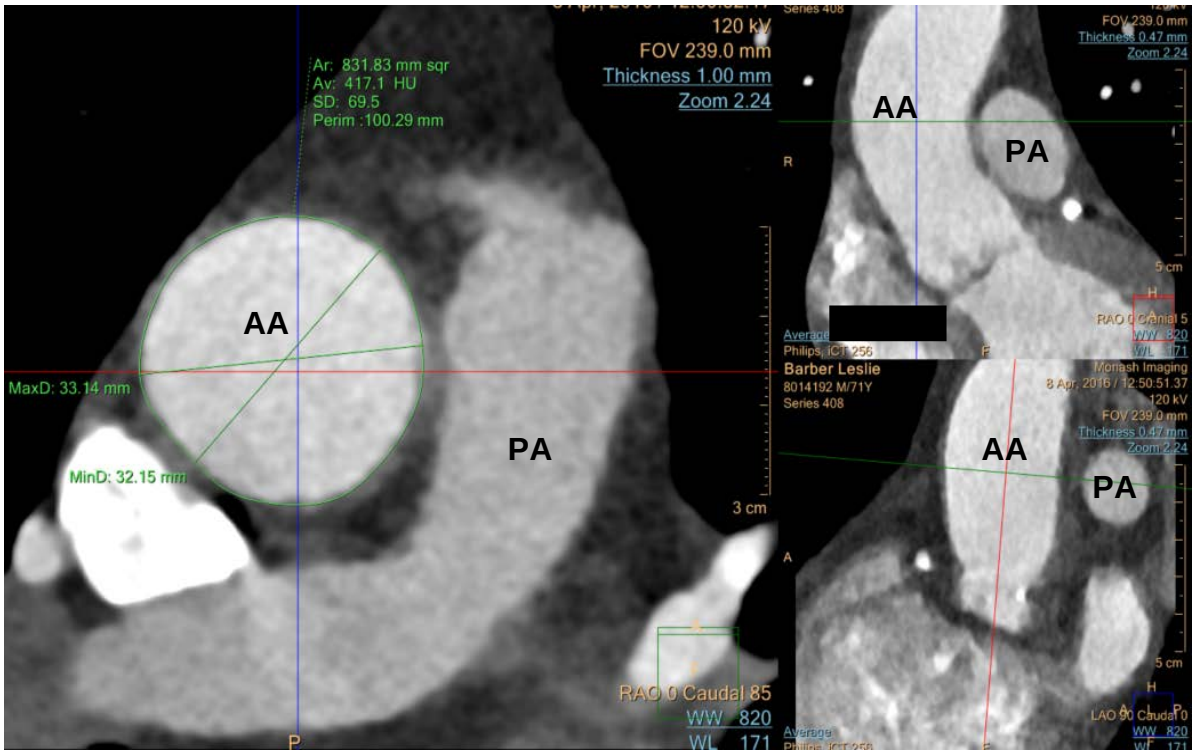


Figure 6. The midpoint of the ascending aorta (AA) is defined on sagittal (bottom right) and coronal (top right) views. Multiplanar reformats are used to establish the optimal plane for AA cross-sectional area (CSA) measurement (perpendicular to two orthogonal planes through the long axis of the AA). CSA of the AA is then measured at 10% intervals throughout the cardiac cycle. AA pulsatility (%) is reported as fractional area change (CSA max-CSAmin)/CSA max) x 100.

Clinical parameters

Baseline demographics, comorbidities and medications were prospectively collected via patient interview and with reference to the electronic medical record. Requirements for ventilatory support, length of hospital stay and inpatient mortality were recorded. Symptoms at admission were evaluated using the COPD Assessment Tool (CAT). As part of a comprehensive exacerbation phenotyping strategy, a Hospital Anxiety and Depression Scale (HADS) and study specific questionnaire were performed.

Follow up investigations

All patients were invited to attend a follow-up review at 2 months post hospital discharge where clinical stability was confirmed by Physician review. Contrast enhanced 256-MDCT and cardiac biomarker analyses were repeated. Coronary artery calcium scoring was not repeated as no significant change would be anticipated in this time period and the additional radiation exposure was deemed unnecessary. Patients also underwent pulmonary function testing and CAT, HADS and study questionnaires on the same day as the follow-up CT. Survival to 180 days was ascertained by reference to the hospital electronic medical record or telephone contact.

Statistical analyses

Although hypotheses have been presented, the study was exploratory and no formal hypothesis testing was conducted. All data are presented as number (percentage), mean/standard deviation, or median [interquartile range] where appropriate. Relationships between CT findings and cardiac biomarker levels were analysed by unpaired t-test and one-way analysis of variance (normally distributed data) or Mann-Whitney and Kruskal-Wallis testing (non-parametric data). Chi square analyses were used for categorical data. Paired data were analysed using paired t-test if normally distributed or Wilcoxon signed rank test if non-normally distributed. Survival analyses were conducted using Kaplan-Meier curves and log-rank tests. Associations between cardiac biomarker measurements and MDCT parameters were tested using

univariate linear regression analyses following log transformation of the biomarker data. Univariate logistic regression analysis was conducted to identify predictors of survival at 180 days after MDCT scan. We declared a finding to be statistically significant if the two-sided p-value was less than 0.05. All analyses were conducted on Stata MP 14.1 (Statacorp, College Station, Texas, USA).

Results

Demographics, comorbidities and medication prescription for the study population are shown in Table 1.

Table 1. Patient demographics of subjects in cardiac subtudies

	n (%), mean/SD, median [IQR]
Age	68.7/10.0
Male	33/58 (56.9%)
Post bronchodilator FEV_1 (L)	1.16/0.64
FEV_1 (% predicted)	48.9/25.8
TLCO (% predicted)	39.8/18.2
KCO (% predicted)	45.0/22.7
Current smoker	21/58 (36.2%)
Former smoker	37/58 (63.8%)
Pack years	45.7/27.3
BMI (kg/m^2)	24.6/7.5
mMRC-D	4 [3-5]
Frequent exacerbator (hospital)	22/58 (37.9%)
Frequent exacerbator (any)	35/58 (60.3%)
Established cardiovascular disease	
Hypertension	25/58 (43.1%)
Ischaemic heart disease	12/58 (20.7%)
Heart failure	8/58 (13.8%)
Pulmonary hypertension	7/58 (12.1%)
Cerebrovascular disease	6/58 (10.3%)
Peripheral vascular disease	1/58 (1.7%)
Arrhythmmia	3/58 (5.2%)
Diabetes mellitus	7/58 (12.1%)
Obstructive Sleep Apnoea,	10/58 (17.2%)
Cardiovascular medications	
Antiplatelet	20/58 (34.5%)
Anticoagulant	2/58 (3.4%)
Heart rate limiting agent	8/58 (13.8%)
Statin	19/58 (32.8%)
ACE-I/ARB	21/58 (36.2%)
Diuretic	10/58 (17.2%)

FEV_1 = Forced expiratory volume in 1 second, TLCO = gas transfer, KCO = gas transfer corrected for alveolar volume, BMI = body mass indexmMRC-D = modified Medical Research Council Dyspnoea score Antiplatelet = Aspirin/Clopidogrel/Dipyrimadole/Ticagrelor, Anticoagulant = Warfarin/Direct oral anticoagulant, Heart rate limiting agent = β-blocker/Diltiazem/Verapamil/Ivabradine, ACE-I/ARB = Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker, Diuretic = Frusemide/Spironolactone

Full data acquisition was successfully achieved across all parameters in almost all studies. The mean/SD radiation dose was low at 4.3/1.5mSV. CT scans were well tolerated with no significant adverse events. Results for the overall population are shown in Table 2.

Table 2. Results of 256-MDCT imaging in acute exacerbation of COPD

Population Results	mean/SD (range), median [IQR]
Radiation dose (mSV)	4.3/1.5
Heart rate (bpm)	84.1/15.5
Systolic BP (mmHg)	127.4/19.4
Diastolic BP (mmHg)	84.6/93.4
SpO2 (%)	93.4/2.8
Coronary artery calcium score (AU)	119.2 [7.8 - 967.8]
Emphysema Index (%LAA)	16.3/13.8: Optimal 55/58, Motion artefact 3/58
CTPA	Pulmonary embolism 0/58
- Image quality	Optimal 37/58 / Adequate 13/58 / Inadequate 8/58
Pulmonary Artery CSA max (mm^2)	718/225 (316 - 1082)
Pulmonary Artery CSA min (mm^2)	614/201 (4.1 - 34.5)
Pulmonary Artery Pulsatility (%)	17.8/7.3
Ascending Aorta CSA max (mm^2)	893/190 (495 - 1405)
Ascending Aorta CSA min (mm^2)	821/192 (399 - 1340)
Aortic pulsatility (%)	9.5/6.4
Right Ventricle	
RV EF (%)	49.0/10.5 (22.7-66.9)
RV EDV absolute (ml)	150.6/38.5 (75.7-240)
RV EDV indexed (ml)	88.9/22.0 (25-160.7)
RV ESV absolute (ml)	78.4/31.6 (28-177.6)
RV ESV indexed (ml)	46.6/20.2 (19.2-124.2)
RV SV absolute(ml)	72.2/19.2 (38-124)
RV SV indexed(ml)	42.4/9.2 (24-62.7)
Left Ventricle	
LV EF (%)	62.3/12.3 (24.2-79.6)
LV EDV absolute(ml)	122.1/38.5 (75.7-240)
LV EDV indexed(ml)	71.7/13.1 (48.1-113)
LV ESV absolute(ml)	46.9/24.6 (20.8-150)
LV ESV indexed(ml)	27.1/12.9 (12.6-72)
LV SV absolute(ml)	75.0/21.0 (34.6-127.6)
LV SV indexed(ml)	43.9/9.9 (14.4-62.8)

mSV = milliSieverts, bpm = beats per minute, mmHg = millimetres mercury, BP = blood pressure, SpO2 = pulse oximetry oxygen saturation, AU = Agatston Units, LAA = low attenuation areas, CTPA = computer tomography pulmonary angiography, RV = right ventricle, LV = left ventricle, EDV = end-diastolic volume, ESV = end-systolic volume, SV = stroke volume, EF = ejection fraction, indexed = adjusted for body surface area (Mosteller method)

Coronary artery calcium scores

Coronary artery calcium scores (CACS) were available in 58/58(100%). Coronary artery disease as indicated by CACS>0 was observed in 45/58 (77.6%), while ischaemic heart disease was a documented diagnosis in only 13/58 (22.4%). Median [IQR] CACS percentile in our AECOPD cohort was 70 [27-92] and significantly higher in those with diagnosed IHD than those without (88.5 [77 - 95] v 54 [25 - 83], p=0.04). A grading system for CACS has been validated to estimate the likelihood of coronary stenoses at invasive angiography and future risk of cardiovascular events(Greenland et al., 2007). CACS>100 indicates at least moderate atherosclerotic plaque while CACS>400 indicates extensive plaque with high likelihood of coronary stenoses. In Table 3, the prevalence of diagnosed IHD, cardiac biomarker results and cardio-protective medication use are shown according to CACS grade. Extensive coronary artery calcification (CACS>400) was identified in 23/58 (39.6%), of whom 16/23 (69.6%) had no known IHD diagnosis. Amongst patients with CACS>400, the proportion receiving antiplatelet (47.8%), statin (56.5%) or heart-rate reduction therapy (0%) was low.

Median troponin levels were similar in those with or without a documented history of IHD (8 [4-16] v 8 [5-29], p=0.58). In contrast, the population with coronary artery disease identified by CACS>100 (n=30/58) had significantly higher troponin levels than those with CACS≤100 (10 [5-29] v 6 [3-13], p=0.032 - Figure 6). Elevated NT-proBNP was common regardless of coronary artery calcium score.

Table 3. Coronary artery calcium grades, IHD diagnosis and therapy, and cardiac biomarker results

	CACS 0	CACS 1-99	CACS 100-399	CACS 400-999	CACS >/=1000	p
Likelihood of coronary plaque	None	Minimal/mild	Moderate	Extensive	Severe	
n, (%)	13/58 (22.4)	15/58 (25.9)	7/58 (12.1)	9/58 (15.5)	14/58 (22.4)	N/A
Known IHD, n (%)	2/13 (15.4)	1/15 (6.7)	1/7(14.3)	1/9 (11.1)	7/14 (50)	*0.04
Hs-TnI (ng/L) [median/IQR]	6 [3.5-13]	6 [3-9]	8 [5-21]	10 [4-52]	10 [8-29]	0.23
Hs-TnI > ULN, n (%)	1/12 (8.3)	2/14 (14.3)	2/6 (33.3)	2/7(28.6)	4/13 (30.1)	0.55
NT-proBNP (ng/L) [median/IQR]	200 [165-1336]	178.6 [136-290]	1570 [170-2596]	406 [262-1927]	216 [111-499]	0.35
NT-proBNP >ULN, n (%)	7/12 (58.2)	9/14 (64.3)	5/6 (83.3)	6/7 (85.7)	6/13 (46.2)	0.53
Antiplatelet, n (%)	3/13 (23.1)	3/15 (20)	2/7 (28.6)	2/9(22.2)	9/14 (64.3)	0.08
Statin, n (%)	1/13 (7.7)	3/15 (33.3)	3/7 (42.9)	4/9 (44.4)	9/14 (64.3)	*0.02
Heart rate limiting therapy, n (%)	2/13 (15.4)	2/15 (13.3)	0/7 (0)	0/9 (0)	0/14 (0)	0.34

Antiplatelet = Aspirin, Clopidogrel, Ticagrelor, Heart rate-limiting therapy = beta-blocker, sinus node blocker, rate-limiting calcium antagonist

Figure 6. High-sensitivity troponin levels and coronary artery calcium score

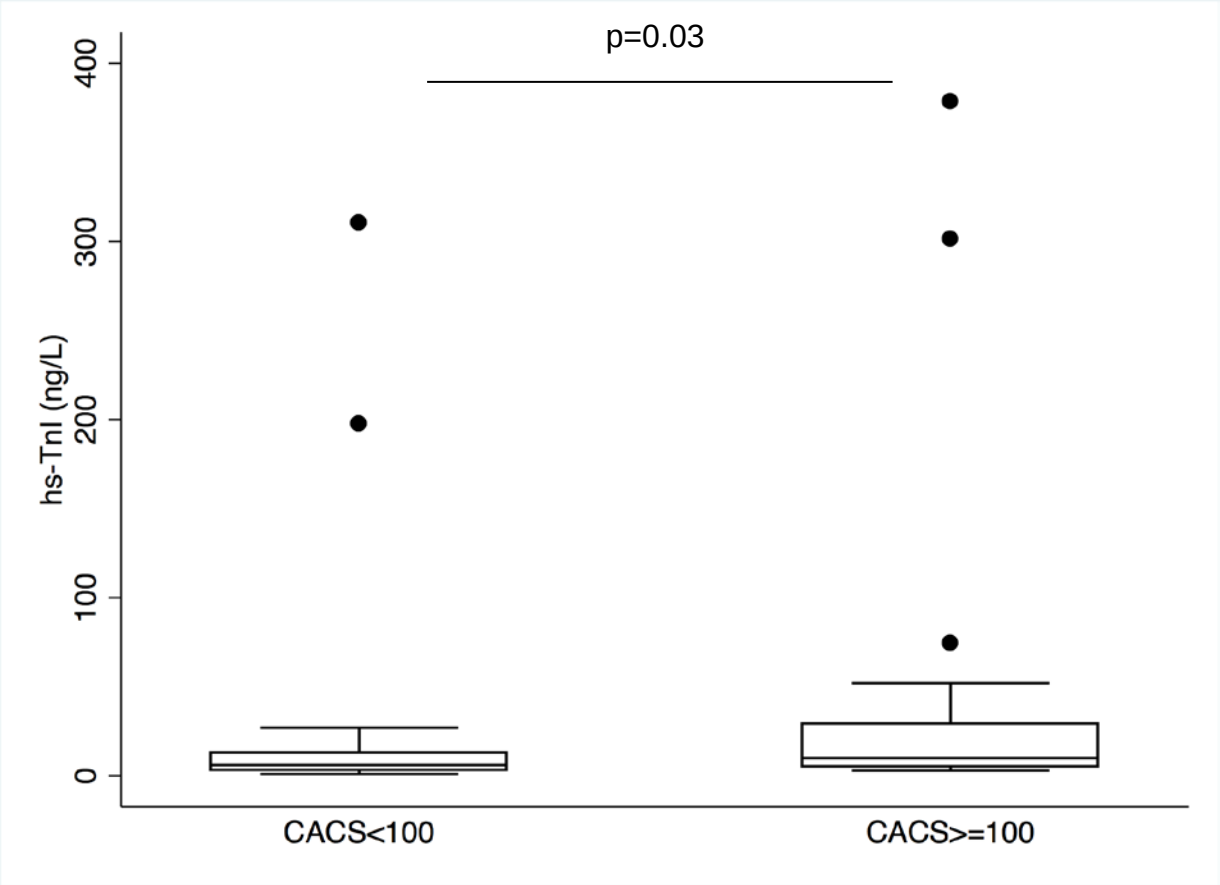


Figure 6. High-sensitivity Troponin I levels at the time of exacerbation amongst patients with coronary artery calcium score <100 versus ≥100.

Left ventricular function

Left ventricular functional data were available for 56/58 patients (96.6%). Data were unavailable in 2/58 (3.4%) due to image mis-registration secondary to ectopic beats. Left ventricular ejection fraction (LVEF) <50% was identified in 10/56 (17.9%) including LVEF<40% in 4/56 (7.1%). In 2/4 cases with LVEF<40%, left ventricular systolic dysfunction was not previously known. Only 4/10 patients with LVEF<50% were receiving ACE-I/ARB therapy and only 1/10 was taking β-blockers.

NT-proBNP levels above the upper limit of normal were observed in 65.4% of the population overall, including among 65% of those with LVEF>55%. Associations of left ventricular ejection fraction with hs-TnI and NT-proBNP levels and relevant medications are shown in Table 4. Patients with LVEF<50% appeared to have higher hs-TnI (18.5 [10-33] v 7 [4-13], p=0.056) and NT-proBNP (540[190-1347] v 227[139-426], p=0.2) than those with LVEF>50%. Patients with clearly reduced LVEF (<40%) compared to those with clearly normal LVEF(>55%) had higher median troponin (37 v 7, p=0.036) and NT-proBNP (716 v 238.5, p=0.08) levels.

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Table 4. Ventricular ejection fraction, heart failure diagnosis and therapy, and cardiac biomarker measurements

	LVEF(%) >60	LVEF(%) 50-60	LVEF(%) <50	p
n	36	10	10	NA
Age (mean/SD)	69.2/11.1	63.0/4.9	72.2/7.0	0.06
CACS (AU) [median – IQR]	82.2 [22-757]	69.2 [0-388]	1224.5 [0-2523]	0.15
Heart Failure diagnosis n (%)	4/36 (11.1)	1/10 (10)	3/10 (30)	0.29
NT-proBNP (ng/L) [median/IQR]	239 [144-426]	175 [92.5-1355]	540 [190-1347]	0.35
NT-proBNP>ULN, n (%)	22/34 (64.8)	6/8 (75)	5/8 (62.5)	0.83
hs-TnI (ng/L) [median/IQR]	6.5 [4-10]	13 [4.5-192]	18.5 [10-33]	0.06
hs-TnI >ULN, n (%)	4/34 (11.8)	3/8 (37.5)	3/10 (30)	0.11
ACE-I/ARB, n (%)	16/36 (44.4)	1/10 (10)	4/10 (40)	0.14
Beta-blocker, n (%)	2/36 (5.6)	1/10 (10)	1/10 (10)	0.83

CACS = coronary artery calcium score, AU = Agatstons Units, NT-proBNP= N-terminal pronatriuretic peptide, hs-TnI = high=sensitivity troponin I, ULN = upper limit of normal, ACE-I/ARB = Angiotensin converting enzyme inhibitor/angiotensin receptor blocker

Emphysema Index (%LAA)

Emphysema index (%LAA) was calculated in 54/58 (93.1%). Data was unavailable due to image degradation by respiratory motion in 3/58 (5.2%) or presence of cystic changes in 1/58 (1.7%). A wide range of emphysema was observed (0.1 - 49%) with a high %LAA (mean/SD) for the overall population of 16.2/13.8. Emphysema index (mean/SD) was significantly higher in those with hyperinflation identified on chest X-ray (20.3/14.1 v 8.7/10.1, p=0.005).

Pulmonary artery assessment

CTPA was not the primary objective of the study acquisition but high quality CTPA images were obtained for most patients. Contrast density in the main pulmonary artery was above the recommended threshold of 211HU in 50/58 (86.2%) with image degradation by motion artefact in 1/58 (1.7%). CTPA images were graded as optimal in 38/58 (65.5), adequate 10/58 (17.2%) and suboptimal in 10/58 (17.2%). No pulmonary emboli were identified.

Pulsatility of the main pulmonary artery (PA*puls*) was calculated in 57/58 (98.3%). Previous studies have estimated a PA pulsatility of >40% in control subjects(Sanz et al., 2009). In our AECOPD cohort, PA*puls* (mean/SD) was low at 17.8/7.4%. PA*puls* was inversely related to %LAA/emphysema (r=-0.302, p=0.028) (Figure 7). Patients with PA*puls*<10% had the highest hs-TnI (median 44.5, p=0.03) and NT-proBNP (median 1272.5, p=0.29) with hs-TnI above the upper limit of normal in 83.3%.

%LAA(emphysema) and PA*puls* were inversely related (r=-0.3, p=0.028. Figure 7a). Correlation was also observed between PA*puls* and pulsatility of the aorta (Ao*puls*) (r= 0.44, p<0.001, Figure 7b)

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Table 5. Pulmonary artery distensibility, emphysema, right ventricular function and cardiac biomarkers

	Overall	PA pulsatility >20%	PA pulsatility 10-20%	PA pulsatility <10%	p
n (%)	57/58 (100)	19/57 (33.3)	30/57 (52.7)	8/57 (14.0)	N/A
Age (mean/SD)	68.7/10	67.3/10.8	68.5/10.2	73.9/6.4	0.32
FEV_1 (%)	48.9/25.8	50.6/28.4	52.4/25	31.3/9.8	0.21
TLCO (%)	39.7/18.2	44.0/18.0	38.7/19.5	32.0/14.6	0.16
Emphyema (%LAA)	16.2/13.8	11.9/12.6	15.3/13.0	30.5/13.6	0.02
RV EDV (indexed)	88.9/22.0	85.6/14.6	89.8/23.5	93.2/31.0	0.92
RV ESV (indexed)	46.6/20.2	41.7/12.0	47.5/22.9	54.5/24.0	0.48
RV SV (indexed)	42.4/9.2	43.2/7.3	43.0/12.1	38.4/8.5	0.51
RVEF (%)	49.0/10.5	51.7/7.2	48.9/12.1	43.3/9.8	0.12
NT-proBNP, median [IQR]	238.5 [141.5-601]	198.5 [165-388]	276 [124.4-577.5]	1272.5 [246-5810]	0.29
NT-proBNP >ULN	34/52 (65.4)	10/18 (55.6)	19/28 (67.9)	5/6 (83.3)	0.43
Hs-TnI, ng/L median [IQR]	8 [4-18.5]	7.5 [3-10]	7.5 [4-14.5]	44.5 [21-74]	0.03*
Hs-TnI>ULN	11/52 (21.2)	2/18 (11.1)	4/28 (14.3)	5/6 (83.3)	<0.001*

Figure 7a. Correlation of PA pulsatility with emphysema

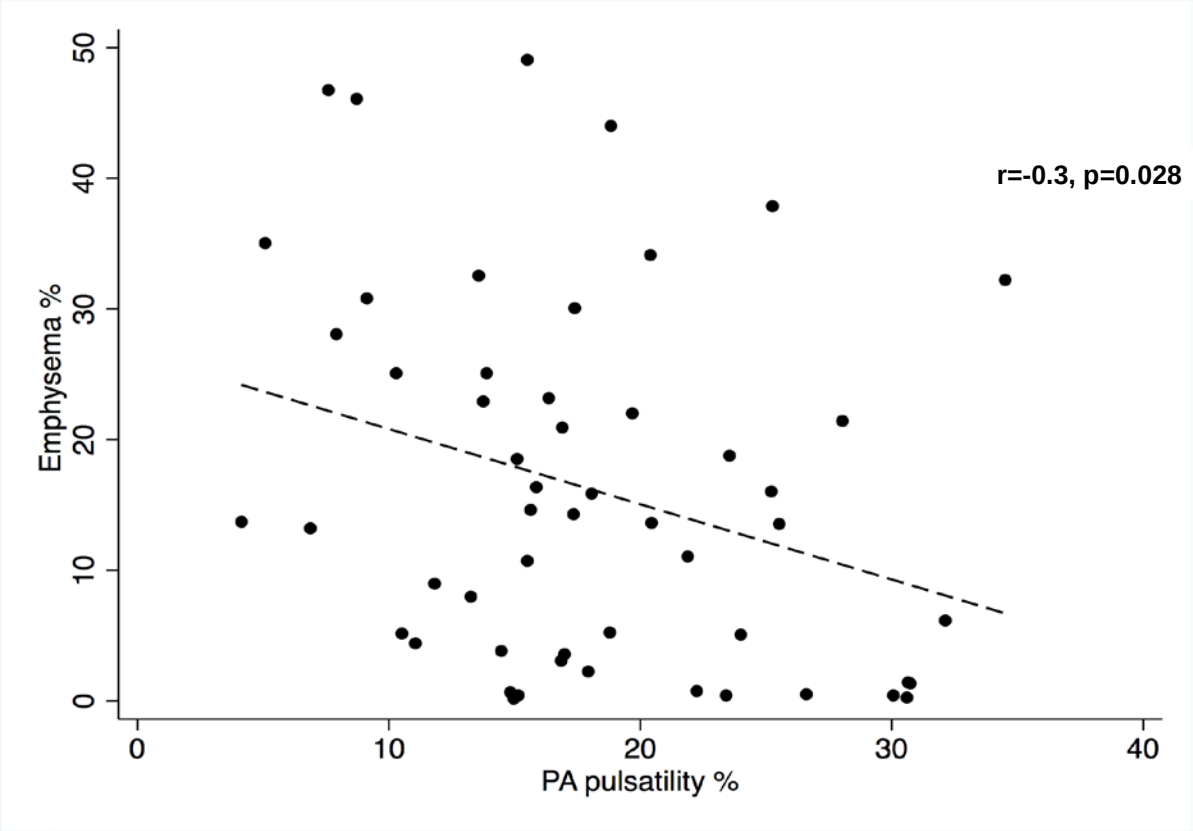
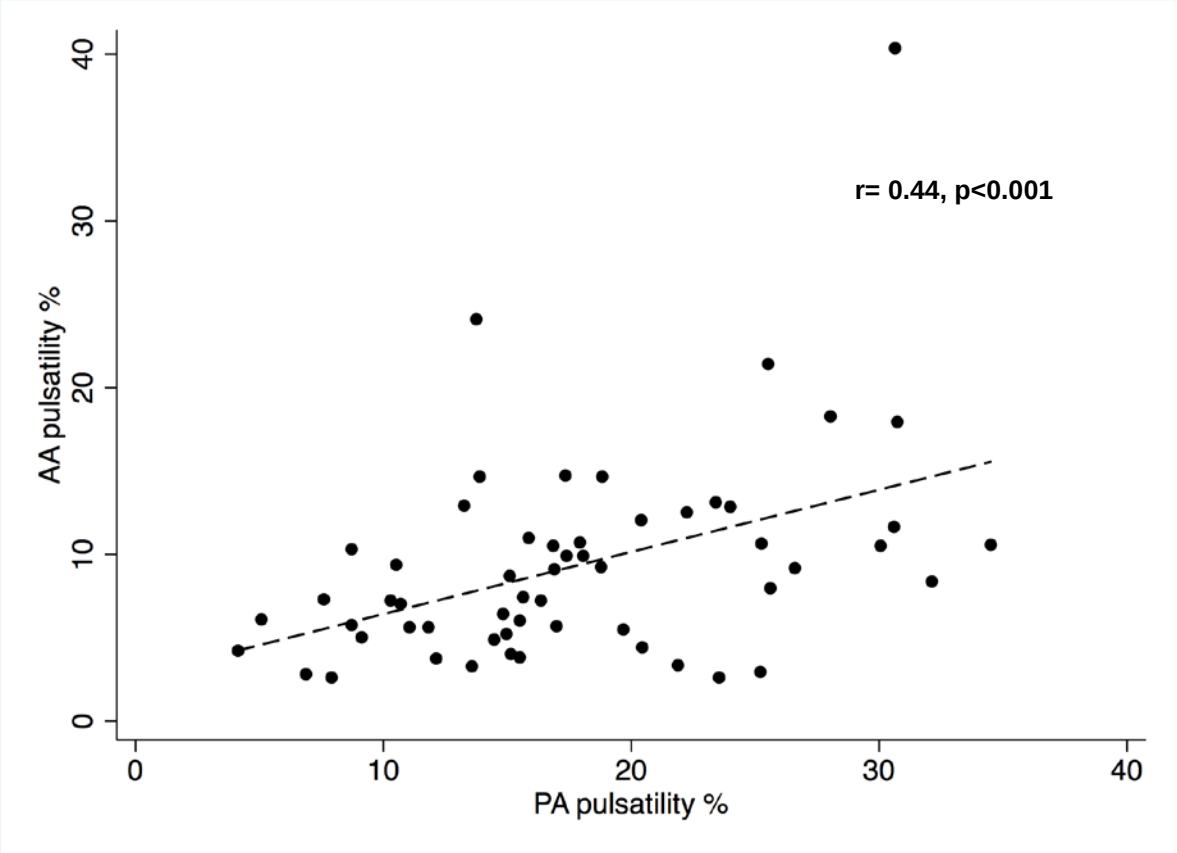


Figure 7a. correlation coefficient for pulsatility (%) of the main pulmonary artery versus emphysema (%) as a proportion of total lung volume

Figure 7b. Correlation of PA pulsatility with aortic pulsatility

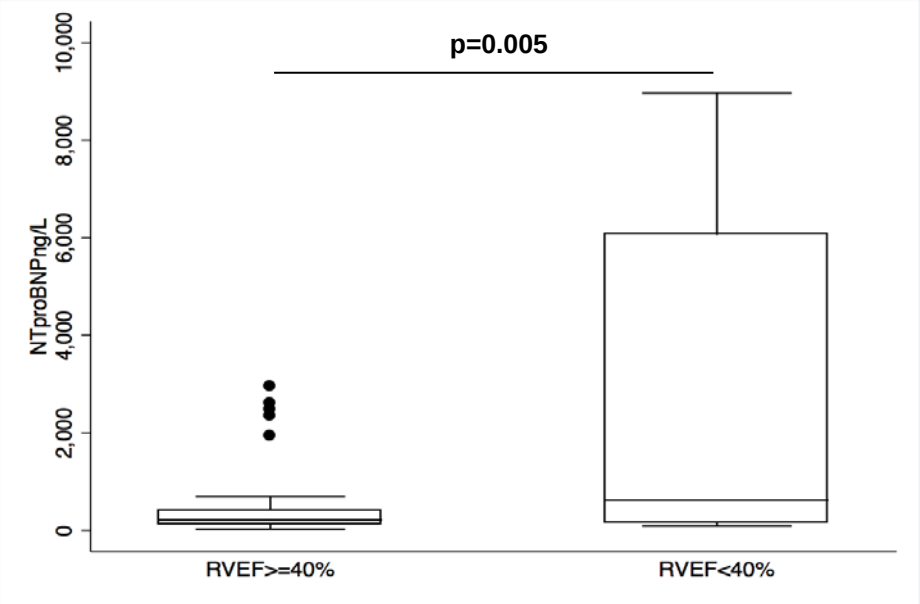


b. correlation for pulsatility of the main pulmonary artery (PA) versus pulsatility of the mid ascending aorta (AA pulsatility).

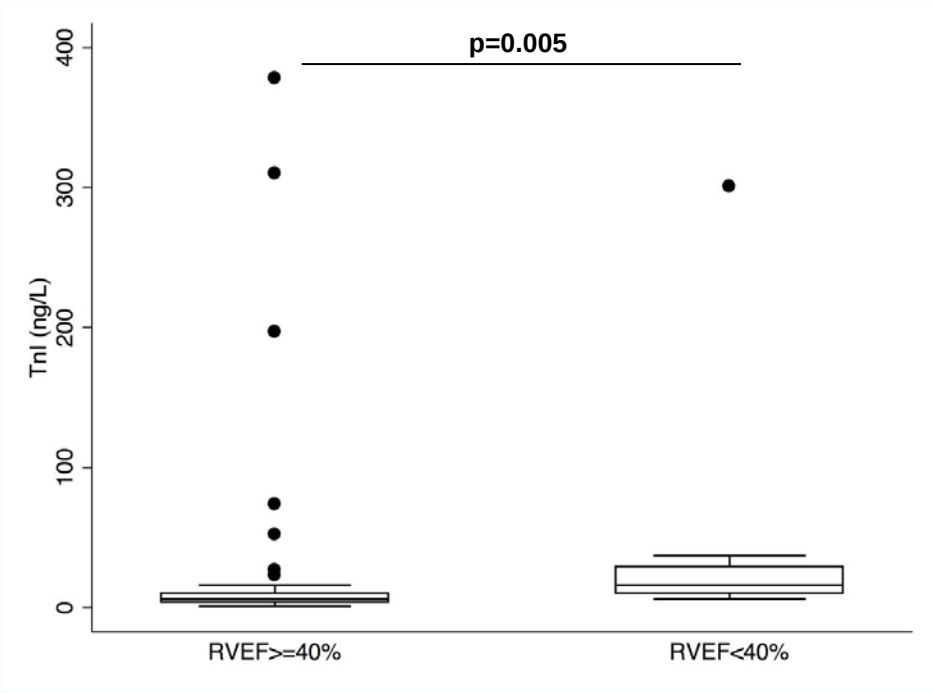
Right ventricle

An inverse relationship was observed between %LAA (emphysema) and RVEF (%) (r=-0.42, p=0.002) and RVESV (r=-0.28, p<0.05). RVEF was <40% in 20% of the AECOPD population. When compared to those with RVEF>40%, patients with RVEF<40% had higher median hs-TnI (16 [10-29] v 6 [4-10], p=0.005) and NT-proBNP (618 [164-6055] v 216 [139-422], p=0.065).

Figure 8a. Cardiac biomarker measurements in patients with normal versus reduced right ventricular ejection fraction (RVEF).



a. NT-proBNP in those with RVEF≥40% v <40%



b. Hs-TnI in those with RVEF≥40% v <40%

Figure 8a. NT-proBNP and **b.** high sensitivity Troponin I were both significantly higher in patients with right ventricular ejection fraction below 40%

Table 6. Right ventricular systolic dysfunction and cardiac biomarkers

	RVEF (%) ≥40	RVEF (%) <40	p
n	44	11	
Age (mean/SD)	68.2/10.4	70.7/8.0	0.46
Heart Failure diagnosis, n (%)	4/44 (9.1)	4/11 (36.4)	0.016*
NT-proBNP (ng/L), [median/IQR]	216 [139-422]	618 [164-6055]	0.065
NT-proBNP>ULN, n (%)	26/41 (63.4)	8/11 (72.7)	0.56
hs-TnI (ng/L) [median/IQR]	6 [4-10]	16 [10-29]	0.005*
hs-TnI>ULN, n (%)	7/41 (17.1)	4/11 (36.4)	0.16

Aortic pulsatility

Aortic pulsatility was calculated in 58/58 (100%). Median [IQR] fractional area change (% pulsatility) of the ascending aorta was 8.5 [5.5-11.6]. We compared patient groups with aortic pulsatility below or above this median level. Patients with lower aortic pulsatility had significantly higher levels of troponin (p=0.02) and NT-proBNP (p=0.003). Lower aortic pulsatility was associated with older age (mean/SD 73.3/8.4 v 64.1/9.4, p=0.0002) but not with other comorbidities, frequent COPD exacerbator status or any CT parameters. There was no difference in aortic pulsatility between infective versus non-infective exacerbations.

Figure 9. Cardiac biomarkers and aortic pulsatility

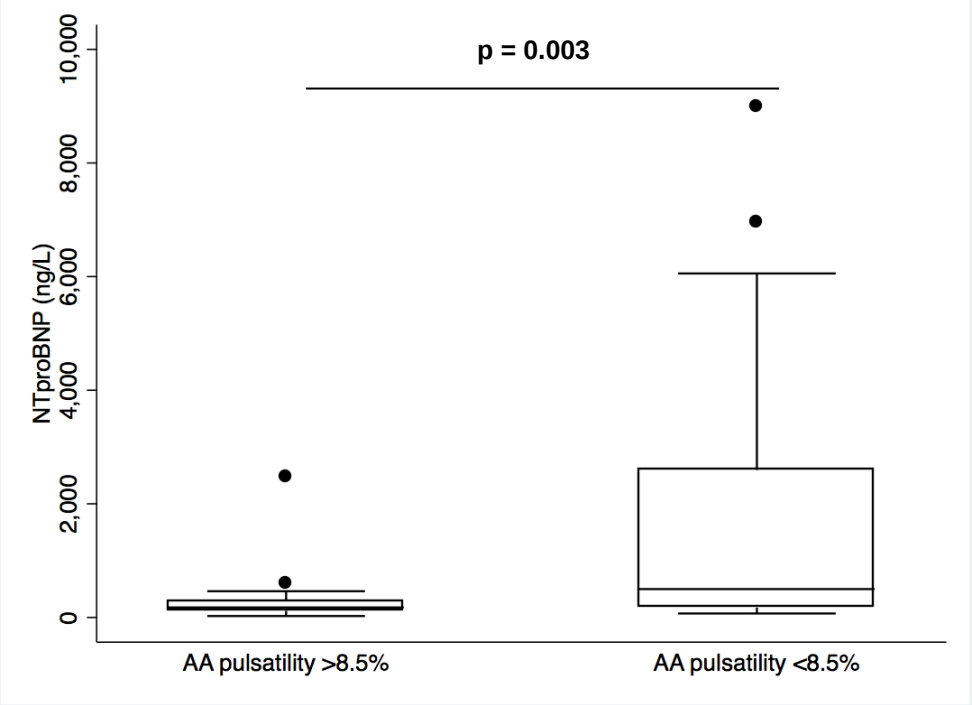


Figure 9a. NTproBNP measurements were significantly higher in the population with aortic pulsatility below the cohort population median.

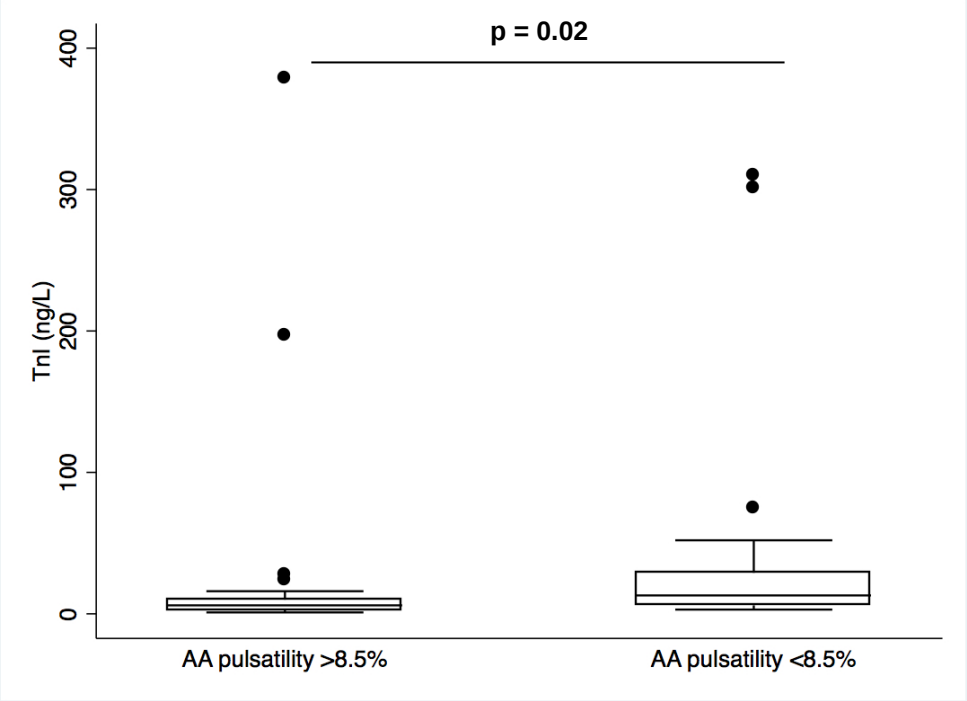


Figure 9b. High sensitivity Troponin I measurements were significantly higher in the population with aortic pulsatility below the cohort population median.

Blood biomarkers to identify underlying cardiac disorder in AECOPD

Given the heterogeneity of cardiovascular dysfunction in AECOPD, acute elevation of cardiac enzymes may reflect multiple pathologies within the same individual. Complete data to simultaneously assess CACS, biventricular function and PA pulsatility was available for 55/58 (94.8%). We set a threshold for identifying pathology across key elements of CT assessment - CACS>0, LVEF<50%, RVEF<40% and PA pulsatility<20%. A completely 'normal' MDCT was observed in only 3/55 (5.4%). At the other extreme, pathology was identified in all of the MDCT elements in 4/55 (7.2%). The overwhelming majority of AECOPD therefore had a cardiac pathology identified by MDCT but with marked heterogeneity between individuals.

We then explored the capacity of biomarker results to identify the underlying pathologies. Neither hs-TnI nor NT-proBNP alone or in combination could predict the nature of the cardiac abnormality identified on MDCT. Exacerbations where neither biomarker was elevated tended to have CT measurements closer to the normal range (lower CACS, higher LVEF, higher RVEF, higher PA*puls*) although this only approached statistical significance for PA*puls* (p=0.06)(Table 7).

Univariate linear regression analysis was performed to identify predictors of log transformed hs-TnI and NT-proBNP (Table 8). RVEF was the only significant predictor of (log)hsTnI, although LVEDV and LVESV approached statistical significance. RVEF, RVEDV, RVESV were significant predictors of (log)NT-proBNP, along with age and aortic pulsatility.

We assessed the ability of hs-TnI to predict the likelihood of a CACS≥100. The area under the receiver operating characteristic (AUROC) was 0.67 during exacerbation and 0.61 when stable(Figure 10.). During exacerbation, hs-TnI >13 demonstrated a specificity of 73% for CACS≥100, which increased to 84.6% when hs-TnI was >16. Under stable conditions (post exacerbation recovery), specificity for CACS≥100 was 57.1% when hs-TnI >13 and 71.4% when hs-TnI >16.

Table 7. Cardiac biomarker measurements and associated MDCT findings and clinical outcomes

	Both normal	Only hsTnI >ULN	Only NT-proBNP >ULN	Both >ULN	p
n	22	3	19	8	-
Age (years) (mean/SD)	66/10.5	65.1/5.6	69.7/11.2	72.4/6.2	0.31
FEV_1 (%), (mean/SD)	45.5/24.4	54.5/36.9	51.5/21.9	48.1/31.1	0.83
TLCO (%), (mean/SD)	40.6/18	37.6/13.4	35.9/17	42.2/17.4	0.78
Freq exac (hospital), n (%)	54.5	33.3	52.6	12.5	0.3
IHD, n (%)	27.3	33.3	10.5	25	0.55
HF, n (%)	9.1	33.3	10.5	37.5	0.19
CACS, median [IQR]	53 [0-740]	1371 [50 - 2523]	133 [3-968]	501 [208-1724]	0.31
CACS percentile, median [IQR]	49 [0-85]	95 [47-96]	70 [36-93]	78 [56-93]	0.41
LVEF (%), (mean/SD)	65.6/9.7	60.1/12.5	62.3/12.6	56.6/16.0	0.41
RVEF (%), (mean/SD)	50.7/8.4	43.2/8.1	49.3/12.9	42.5/8.9	0.15
Emphysema (%),(mean/SD)	13.6/10.8	23.3/20.5	19.1/15.1	11.8/12.9	0.52
PA pulsatility (%), (mean/SD)	20.4/5.9	12.3/4.9	17.8/7	14.5/9.2	0.06
NIV ward, n (%)	5 (22.7%)	0 (0)	3 (15.8)	2 (25)	0.75
Mechanical ventilation, n (%)	0	0	1(5.3)	1 (12.5)	0.44
Length of stay, median [IQR]	5 [3-5]	5 [3-8]	5 [4-11]	8 [6-9.5]	0.31
Survival to 180 days, n (%)	19 (90.5)	3 (100)	18 (94.7)	6 (75)	0.41

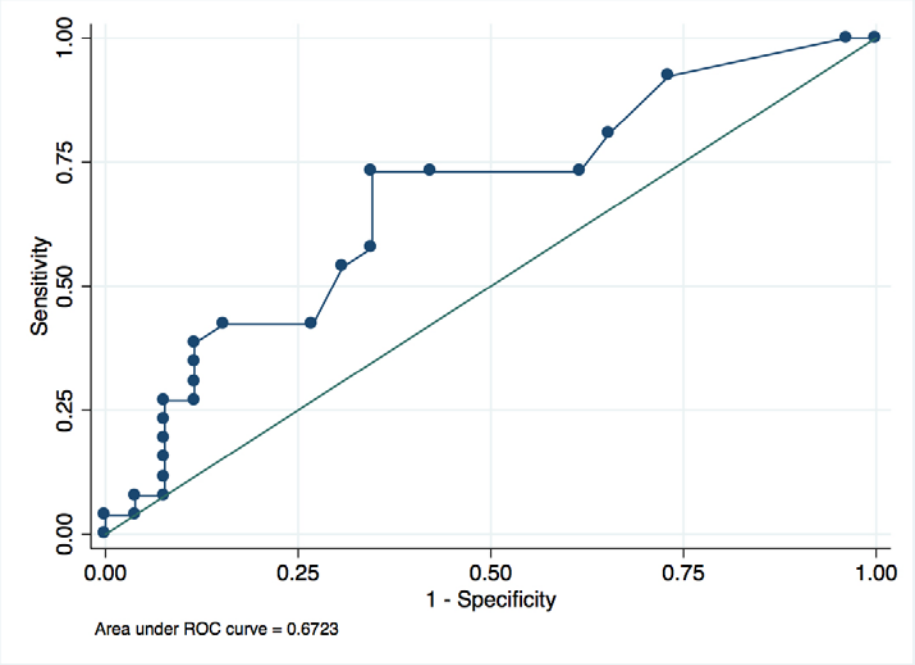
Table 8. Univariate predictors of elevated a. hs-TnI and b. NT-proBNP

Factor ((log) hs-TnI)	**Beta coefficient**	**95% CI**		**p**
Age (years)	0.0258	-0.0094	0.0611	0.147
LV EDV (ml)	0.0228	-0.0035	0.0491	0.087
LV ESV (ml)	0.0253	-0.0017	0.0522	0.066
LV SV (ml)	-0.0063	-0.0473	0.0347	0.760
LV EF (%)	-0.0244	-0.0548	0.006	0.113
LV mass index (g/m^2)	0.0233	-0.007	0.0532	0.122
RV EDV (ml)	0.0103	-0.0059	0.0266	0.205
RV ESV (ml)	0.0158	-0.0017	0.0333	0.075
RV SV (ml)	-0.0165	-0.0596	0.0266	0.446
RV EF (%)	-0.0345	-0.0686	-0.0005	0.047*
PA*puls* (%)	-0.0287	-0.0796	0.0222	0.263
AA*puls* (%)	-0.063	-0.138	0.012	0.1
CACS (AU)	0.0002	-0.0001	0.0006	0.17

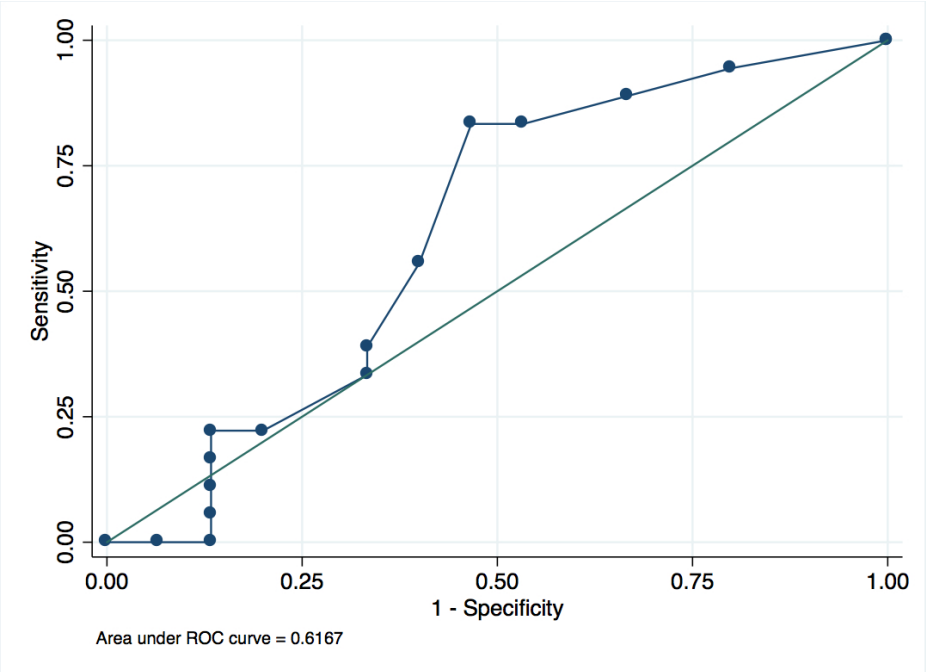
Factor ((log)NT-proBNP)	**Beta coefficient**	**95% CI**		**p**
Age (years)	0.0436	0.007	0.0807	0.022
LV EDV (ml)	0.0167	-0.0119	0.0452	0.246
LV ESV (ml)	0.0208	-0.0083	0.0501	0.157
LV SV (ml)	-0.0103	-0.0540	0.0333	0.636
LV EF (%)	-0.0243	-0.0568	0.0082	0.139
LV mass index (g/m^2)	-0.008	-0.041	0.0238	0.6
RV EDV (ml)	0.0291	0.0137	0.0445	<0.001*
RV ESV (ml)	0.0355	0.0192	0.0518	<0.001*
RV SV (ml)	-0.0013	-0.0476	0.0449	0.954
RV EF (%)	-0.0526	-0.0873	-0.0180	0.004*
PA*puls* (%)	-0.0508	-0.1049	0.0032	0.065
AA*puls* (%)	-0.1160	-0.1927	-0.0392	0.004*
CACS (AU)	-0.0017	-0.0123	0.0089	0.752

Table 8a. the only significant predictor of high-sensitivity troponin I was right ventricular ejection fraction. **8b.** Age, right ventricular end diastolic volume, right ventricular end systolic volume, right ventricular ejection fraction and aortic pulsatility were all significant predictors of NT-proBNP.

Figure 10. AUROC for hs-TnI to predict CACS≥ 100



10a. Hs-TnI measured at acute exacerbation of COPD demonstrated AUROC= 0.67 to predict CACS≥100.

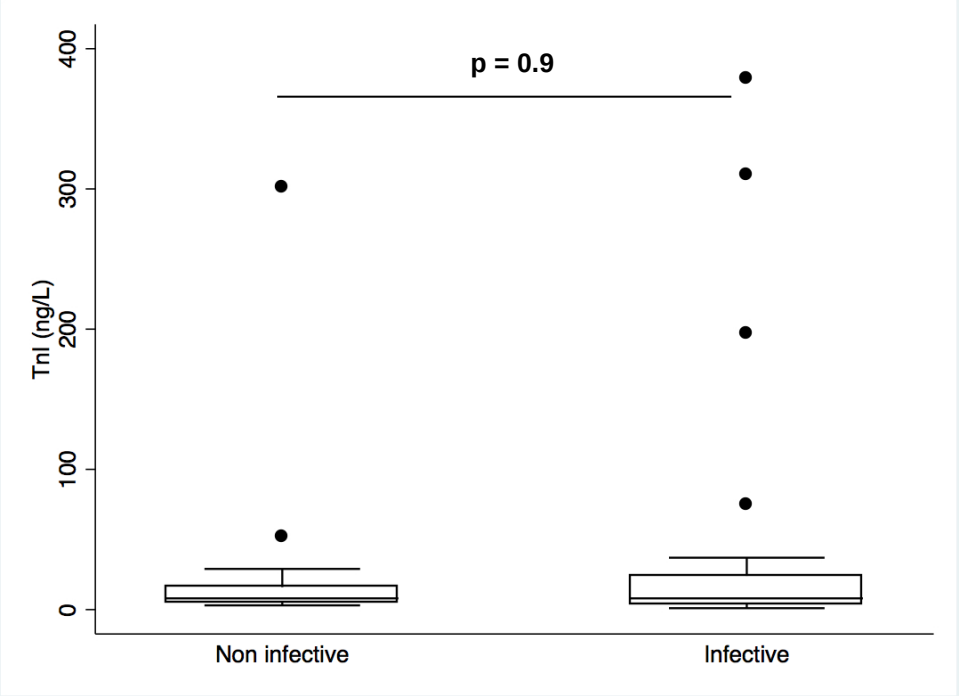


10b. Hs-TnI measured at acute exacerbation of COPD demonstrated AUROC= 0.62 to predict CACS≥100.

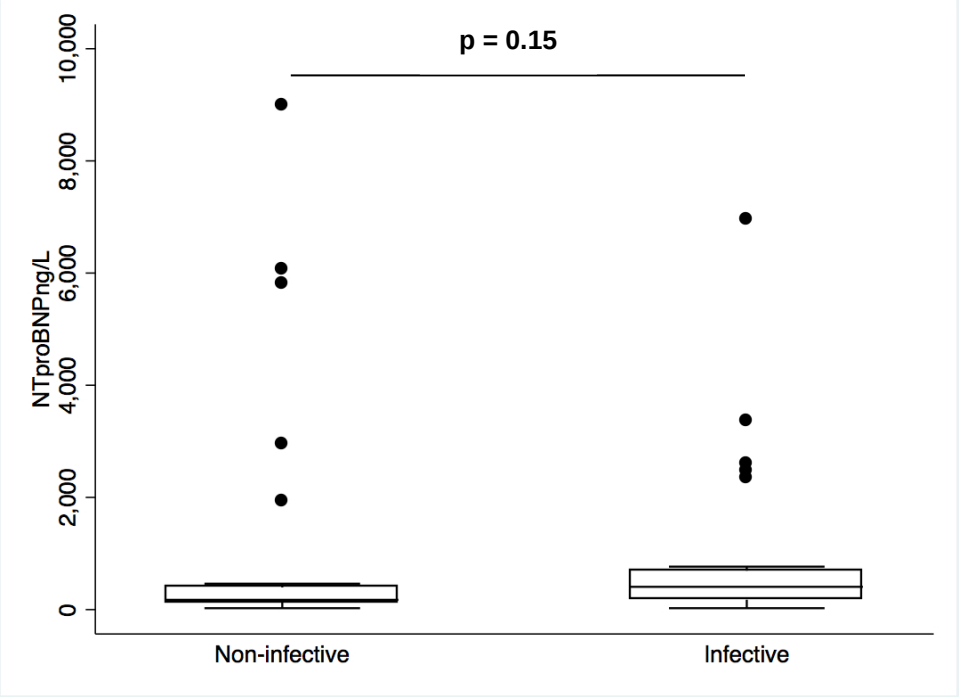
Exacerbation characteristics and outcomes according to biomarkers and 256-MDCT

Exacerbations were categorized as infective (n=30) if *either* nasopharyngeal swab virus PCR was positive *or* CRP was ≥20mg/L and non-infective (n=28) when *both* virus PCR was negative *and* CRP<20mg/L. Hs-TnI and NT-proBNP levels were similar in infective v non-infective AECOPD (Figure 11). Tachycardia (heart rate>100bpm) during emergency department (ED) care was observed in 32/58 (55.2%) but did not appear to be associated with elevation of cardiac biomarkers. Surprisingly, tachycardia in ED was associated with a lower frequency of raised troponin (10.7% v 33.3%, p=0.04) and NT-proBNP (42.9 v 62.5, p= 0.16).

Figure 11. Cardiac biomarkers and infective status at AECOPD



a. high sensitivity troponin I measurements in patients with non-infective and infective AECOPD.



b. NT-proBNP measurements in patients with non-infective and infective AECOPD.

Adverse exacerbation outcomes in this small study population were rare - inpatient mortality (n=1), mechanical ventilation (n=2), non-invasive ventilation (n=10). We did not identify statistically significant differences in acute exacerbation outcomes between subpopulations identified by either MDCT parameters or cardiac biomarkers. Notably, three patients had critical cardiac disorders identified by MDCT, which treating clinicians were alerted to. Two of these patients proceeded to invasive coronary angiography and subsequent urgent coronary artery bypass graft surgery - one with CACS>3000 and another with LVEF 24.3% - both of whom had no diagnosis of CAD prior to MDCT scanning as part of the study protocol. In another patient, incidental note was made of a left atrial thrombus which was corroborated by transthoracic Echocardiography (TTE) resulting in therapeutic anticoagulation.

Survival data at Day 180 was available for 57/58 patients. 6/57 (10.5%) were deceased by Day 180. On univariate logistic regression analysis, FEV_1 (p=0.006), pulmonary artery distensibility (p=0.019) and aortic pulsatility (p=0.023) were the only significant predictors of survival at 180 days post discharge. Survival curves according to thresholds of PA*puls* are shown in Figure 11. A PA*puls* of ≤10% was associated with markedly increased risk of death by day 180 compared to PA*puls* >20% (hazard ratio =14 (1.6-127)).

Figure 12. Kaplan-Meier analysis of survival to 180 days, according to pulmonary artery pulsatility thresholds.

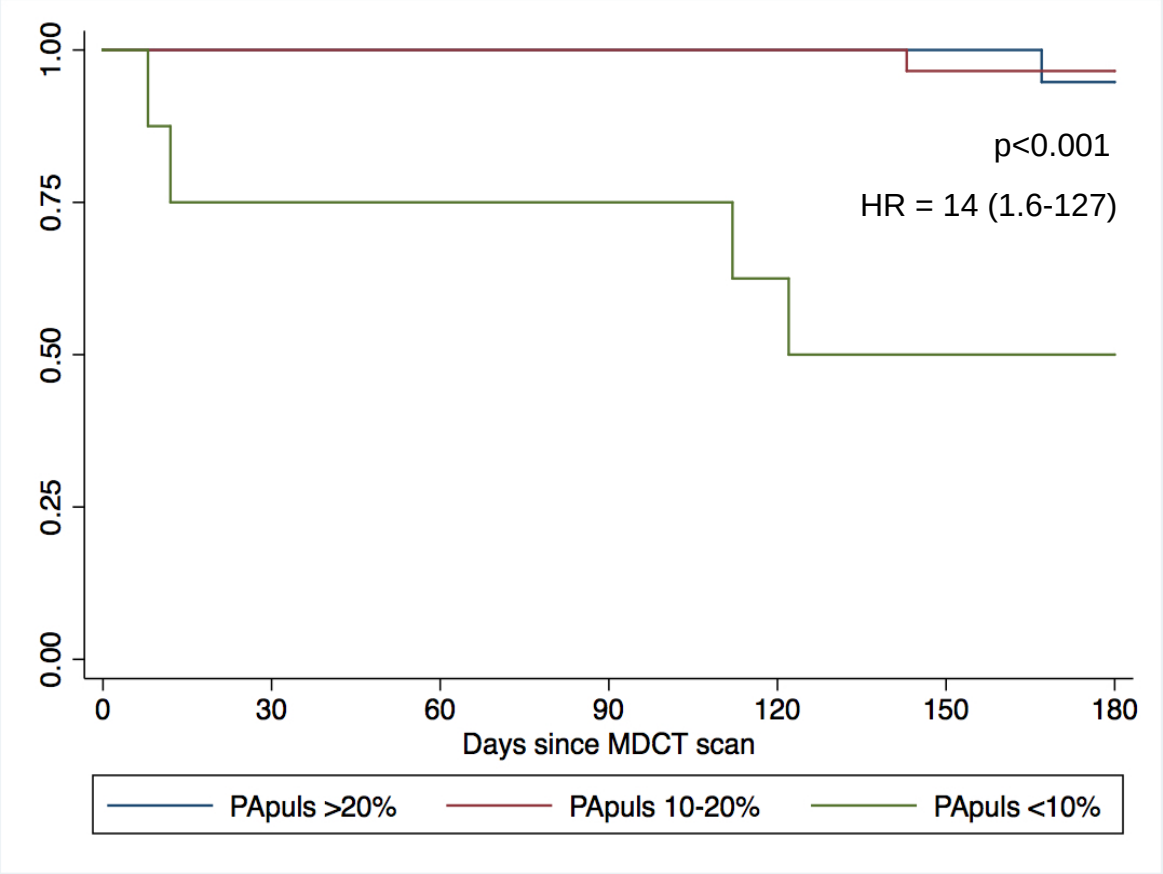


Figure 11. Survival at 180 days was significantly lower among patients with pulmonary artery pulsatility<10%.

Cardiac assessment at acute exacerbation versus stable visit

Follow-up CT was performed in 38/58 patients (65.5%). Reasons why 20/58 patients (34.4%) did not undergo follow-up CT are shown in Figure 1. The only significant difference in baseline characteristics in the group who did not undergo follow-up CT was older age (median 74 v 70 years, p=0.003). Changes in CT parameters from acute to stable conditions are shown in Table 5. As would be expected, mean heart rate was significantly higher at the time of exacerbation (84 v 78 bpm, p=0.041). Mean right ventricular end-diastolic (p=0.03) and end-systolic volumes (p=0.045) were significantly greater at acute exacerbation versus recovery. In contrast, mean left ventricular volumes did not show significant change. The change in RVEDV from acute to stable remained significant after exclusion of patients with detectable peripheral oedema at exacerbation (n=6) (p=0.037).

Patients who underwent follow-up scan (n=38) had hs-TnI and NT-proBNP measured on the same day as their follow-up MDCT. Cardiac biomarker levels were significantly lower at recovery compared to exacerbation (median NT-proBNP (153 [67-297] v 238[127-542], p =0.0003) and hs-TnI (5 [3-8] v 8.5 [4-22], p=0.026. Figure 12). Univariate linear regression analysis was used to identify significant predictors of hs-TnI and NT-proBNP from the same day MDCT acquisition (i.e. MDCT parameters when stable to predict biomarkers when stable).Significant predictors of (log)hs-TnI at exacerbation recovery were LVEF (0.053 (0.002 – 0.104), p=0.044) and LV mass index (0.042 0.02 – 0.064, p<0.001). Coronary artery calcium score percentile (p=0.06) and LVESV (p=0.08) approached statistical significance.

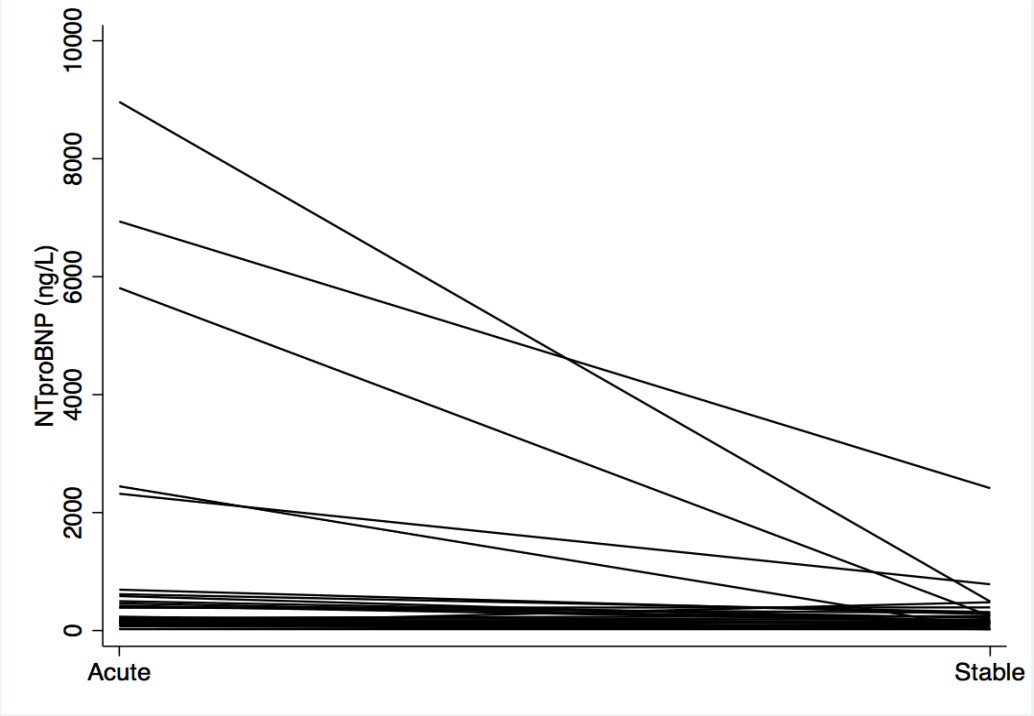
Significant predictors of stable (log) NT-proBNP identified on stable MDCT included RVEDV (0.023 (0.004 – 0.042), p=0.02), RVESV (0.022(0.002 – 0.043), p=0.03), aortic pulsatility (-0.149(-0.25 - -0.047), p=0.006) and LV mass index (0.042(0.021 – 0.063), p<0.001).

Table 8. MDCT parameters during acute exacerbation versus stable

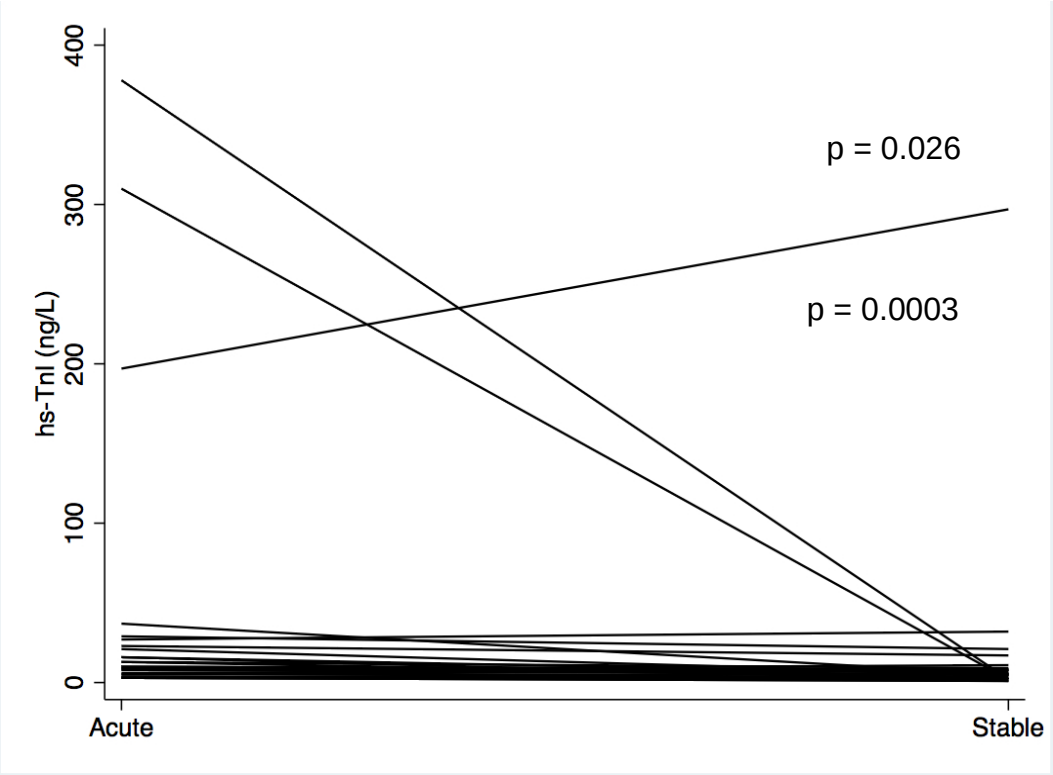
	Acute	Stable	p
Heart rate (bpm) (mean/SD)	84.1/15.5	77.6/11.4	0.041*
Emphysema (%) median [IQR]	14 [4-25]	16 [4-25]	0.9
PA pulsatility (%) (mean/SD)	17.8/7.3	17.1/5.3	0.5
Aortic pulsatility (%) median [IQR]	8.5 [5.5-11.6]	8.4 [5.1-11.4]	0.5
LV EDVa (ml) (mean/SD)	121.7/31.7	124.5/29.8	0.75
LV EDVi (ml) (mean/SD)	71.2/14.1	71.8/13.2	0.75
LV ESVa (ml) (mean/SD)	46.2/23.3	48.4/19.8	0.375
LV ESVi (ml) (mean/SD)	26.7/12.1	27.8/10.4	0.421
LV SVa (ml) (mean/SD)	75.3/19.4	75.5/18.5	0.94
LV SVi (ml) (mean/SD)	43.7/9.7	43.6/8.1	0.92
LV EF (%) (mean/SD)	62.6/11.4	61.5/8.6	0.49
RV EDVa (ml) (mean/SD)	153.4/30.0	144.5/33.1	0.02*
RV EDVi (ml) (mean/SD)	90.3/24.4	84.7/21.4	0.032*
RV ESVa ((ml) mean/SD)	80.7/35.0	74.6/27.5	0.032*
RV ESVi (ml) (mean/SD)	48.1/23.4	44.5/19.6	0.045*
RV SVa (ml) (mean/SD)	72.5/16.4	69.8/18.4	0.23
RV SVi (ml) (mean/SD)	42.8/8.2	40.4/8.2	0.15
RVEF (%)	48.9/11.2	47.5/10.2	0.3

LV = left ventricle, RV = right ventricle, EDV = end diastolic volume, ESV = end systolic volume, SV = stroke volume, EF = ejection fraction, a = absolute, i = indexed to body surface area

Figure 12. Change in cardiac biomarkers from exacerbation to recovery



a. NT-proBNP measurements at acute exacerbation and stable recovery



b. high sensitivity troponin I measurements at acute exacerbation and stable recovery.

Discussion

Comprehensive 256-MDCT cardiopulmonary assessment in AECOPD was technically successful and achieved at low radiation doses without adverse events. MDCT could identify and differentiate key cardiac and respiratory pathologies in breathless patients with severe emphysema, a patient group in whom traditional cardiac imaging techniques perform poorly. MDCT demonstrated the potential to guide specific therapeutic intervention and inform prognosis.

Identification of cardiac pathology by MDCT

Coronary artery disease

Coronary artery calcification was present in 77.6% of the population and was severe (>400AU) in around one third. Two thirds of those with severe coronary calcification had no diagnosed coronary artery disease. Primary prevention therapy was under-prescribed, indicating an immediate opportunity to improve patient outcomes. Of note however, almost a quarter of our AECOPD population had no coronary artery calcification and therefore indiscriminate provision of coronary therapy to COPD patients is not likely to be indicated.

Left ventricular systolic dysfunction

Assessment of left ventricular systolic function was successfully achieved irrespective of heart rate at the time of study acquisition. LVEF<40% was relatively uncommon among this cohort where patients with overt left heart failure identified by clinical examination and chest X-ray were excluded. Half of those with LVEF<40% had no known diagnosis of heart failure and were not receiving appropriate medical therapy.

Pulmonary embolism

Pulmonary angiography did not identify any pulmonary emboli. This finding is in keeping with the low prevalence observed in studies of unselected AECOPD(Rutschmann et al., 2007).

Pulmonary hypertension

Detection of pulmonary hypertension in COPD (PH-COPD) is challenging as the acoustic window for echocardiography is impaired by emphysema, and right heart catheterization is rarely performed outside of a lung transplantation setting. Pulsatility of the proximal pulmonary arteries can be measured by MRI or CT and has been shown to reflect pulmonary pressure as measured by right heart catheterization(Abel et al., 2012; K. W. Kang et al., 2011; Revel et al., 2009) including in a stable COPD population measuring PA*puls*(D'Agostino et al., 2013). Established PH-COPD as indicated by pulmonary artery:aorta diameter >1 on conventional CT predicts increased exacerbation rates(Wells et al., 2012) and cardiac enzyme release at exacerbation(Wells et al., 2015). Studies indicate that only a minority of patients with COPD progress to established resting pulmonary hypertension(Elwing & Panos, 2008) but exercise-induced pulmonary hypertension (EIPH) is very common(Hilde et al., 2013). Of clinical relevance, impaired pulmonary artery distensibility is detectable in EIPH before resting PH has been established(Sanz et al., 2009). Reduced PA pulsatility therefore has potential to identify COPD patients with earlier stages of pulmonary hypertension where therapeutic intervention has greater prospects of improving clinical outcomes. Reduced PA pulsatility offers prognostic value, predicting reduced survival in pulmonary arterial hypertension(Gan et al., 2007; D. A. J. Swift et al., 2017). In our population, patients with PA*puls* <10% had significantly reduced survival, with only 50% alive at 180 days. PA*puls* was significantly correlated with both emphysema and right heart function and may serve as a composite marker of heart and lung dysfunction in COPD.

Cardiac biomarker elevation and structural and functional abnormality on MDCT

Interpreting cardiac biomarker elevation AECOPD is complex. Clearly there is considerable overlap and some interdependence between pathologies. Levels above the upper limit of normal for hs-TnI and NT-proBNP were observed in 21.2% and 65.4% of the overall population respectively. Previous studies have suggested that elevated cardiac biomarkers may be higher in COPD with known cardiac disease. In our study there was no significant difference in hs-TnI or NT-proBNP levels between those with or without diagnosed cardiac disease. Our CT data however, shows that

clinical diagnosis of cardiac disease in a COPD population appears unreliable. A third of those without known CAD had severe coronary artery calcification, and hs-TnI was significantly higher in the population with CACS>100(p=0.03). Troponins do not appear to be specific for coronary artery disease in an AECOPD population however, as levels were predicted by right ventricular ejection fraction on univariate linear regression. Higher hs-TnI levels at exacerbation were observed in patient groups with left and right ventricular systolic dysfunction, and impaired pulmonary artery and aortic pulsatility.

As in previous studies, NT-proBNP levels were frequently elevated in hospitalized AECOPD(Vallabhajosyula et al., 2016). Significant predictors of (log) NT-proBNP at AECOPD were predominantly parameters of right ventricular function. The specificity of NT-proBNP in AECOPD appears poor and elevated NT-proBNP levels may reflect right ventricular failure and/or left heart failure with preserved ejection fraction (HFpEF). Left ventricular hypertrophy is particularly common in COPD populations(W. J. Anderson, Lipworth, Rekhraj, Struthers, & George, 2013; Vallabhajosyula et al., 2016) and diastolic dysfunction may explain high natriuretic peptide levels in the presence of normal systolic function. This hypothesis is supported by the association we observed between (log) NT-proBNP with aortic stiffness at exacerbation and left ventricular mass index at recovery. Application of MDCT to diagnose diastolic dysfunction has been limited to date(Agrawal, Agrawal, Dwivedi, & Tripathi, 2016; Boogers et al., 2011) and was not specifically assessed as part of our study. Unlike systolic dysfunction, the impact of medical therapy in HFpEF is limited and can generally be guided by monitoring of systemic blood pressure(Borlaug & Paulus, 2011).

It can be argued that key priorities in COPD management should be improved identification of coronary artery disease and left ventricular systolic dysfunction as these are morbidities where mortality benefit from medical intervention is clearly established. Whilst elevated hs-TnI was uncommon in the absence of coronary artery calcification, hs-TnI cannot reliably identify or exclude CAD in an AECOPD population, although from our data, it could be used to identify a high risk population.

Only 2/58 patients had a “normal” MDCT (no coronary calcification, LVEF≥60%, RVEF≥40% and pulmonary artery pulsatility≥20%) and both had normal hs-TnI and

NT-proBNP levels. Conversely, of 37/58 AECOPD patients with an elevated cardiac biomarker, at least one element of the MDCT was “abnormal” in 36/37. Accurate delineation of cardiac pathophysiology in COPD patients will therefore require anatomical and/or functional assessment.

In our study, significantly predictors of mortality at 180 days were stiffness of the pulmonary artery(p=0.019) and aorta(p=0.023). A PApuls≤10% appears to be associated with markedly reduced survival at 180 days. Populations identified with reduced survival following AECOPD associated with elevated cardiac biomarkers(Chang et al., 2011; Gale et al., 2011; Hoiseth et al., 2012, 2012; Medina et al., 2011; Sanchez-Marteles et al., 2010) likely include substantial proportions with pulmonary hypertension and right heart dysfunction for whom mortality cannot be substantially modified by current therapy.

Changes in cardiac function between acute exacerbation and recovery

Overall cardiac functional parameters showed relatively minor changes between exacerbation and stable state while biomarker levels changed substantially. A previous small RCT in stable COPD patients found a small improvement in pulmonary artery pulsatility and increase in right ventricular volumes following relief of hyperinflation with bronchodilator therapy(Stone et al., 2016). In contrast, right ventricular end-diastolic and end-systolic volumes were significantly higher at exacerbation in our study, a time when hyperinflation would be increased. We found minimal change in left ventricular volumes between acute and stable state. Our findings may potentially reflect impaired capacity of a poorly distensible pulmonary circulation to accommodate an increased heart rate and cardiac output at the time of COPD exacerbation.

Limitations

Whilst MDCT enjoys specific advantages over echocardiography and MRI it also holds a number of disadvantages. Concern regarding radiation exposure has been a limiting factor in the uptake of cardiac function CT. In our study however, the mean radiation dose was low at approximately 4mSV reflecting both the impact of advances in CT iterative reconstruction algorithms and the low body weight of many study subjects. Due to concern for potential nephrotoxicity of iodinated contrast

material we adopted a conservative approach to contrainidication by renal impairment which excluded 13.5% of potential candidates. Absence of sinus rhythm (to facilitate ECG-gating) excluded a further 10.1%. Significant renal impairment and atrial fibrillation are both associated with increased likelihood of cardiac disease and their exclusion will likely have resulted in a lower prevalence of cardiac disorders in our study population than would be anticipated in an unselected population. From a practical perspective, CT acquisition requires a 6 second breath-hold while lying flat and therefore patients in severe acute respiratory distress cannot be assessed. Follow up CT data was only available for 38/58 (65.5%) for a variety of reasons. The CT data could not be corroborated against the accepted gold standard: cardiac MRI. MRI would not be feasible in acutely breathless AECOPD patients however equivalence of cardiac function parameters as assessed by MRI and MDCT has been established in previous studies(Busch et al., 2008; Plumhans et al., 2008; Surkova et al., 2016).

The anticipated benefit of treating coronary disease and left ventricular dysfunction in COPD patients has been extrapolated from studies demonstrating prognostic benefit of various therapies in a general population. Whilst COPD patients are known to have a high mortality from cardiovascular disease(Sin et al., 2006) cardiac therapies have not yet been studied specifically in a COPD population. Some of the population in this study appear to have severe pulmonary hypertension and right ventricular failure and may have a poor prognosis refractory to medical intervention.

Conclusions

To the best of our knowledge, this is the first reported application of cardiopulmonary dynamic MDCT in AECOPD. The technique appears practical, well tolerated and capable of identifying a broad spectrum of relevant pathology with potentially important therapeutic implications.

6.1 OVERVIEW

Hospitalized AECOPD are events associated with substantial morbidity, mortality and healthcare costs. Although known to be heterogenous in nature, to date there has been minimal in-depth characterization of AECOPD in clinical practice or research.

The enormous burden of COPD is projected to increase further(Lozano et al., 2012), but there has been limited innovation in the management of AECOPD and outcomes remain poor. In the absence of new therapeutic agents for COPD, clinicians ~~are compelled~~ should seek to optimize investigation and management of AECOPD using existing resources. Much of the previous research identified prognostic factors in AECOPD rather than focussing on exploring mechanisms of disease and identifying feasible targets for intervention. The overall aim of these doctoral studies was therefore to characterize AECOPD using clinically accessible methodologies, focussing on factors that: i) elucidate pathology, ii) function as disease biomarkers, and iii) may enhance optimised management. Key areas for study were exacerbation aetiologies, biomarkers and gaining a better understanding of the nature of cardiac dysfunction occurring in AECOPD.

Given the heterogeneity of AECOPD, the benefit of therapies with a specific mechanism of action may be obscured by failure to study the appropriate COPD subpopulation. In clinical practice, AECOPD management is often relatively uniform and with the exception of NIV, there is a paucity of evidence to identify those who benefit from specific therapies. While clinicians may make a broad distinction between infective and non-infective exacerbations, there is no established methodology to achieve this goal. Importantly, exacerbations are rarely characterized in interventional and medication studies.

The strategy devised for this body of research was to study a cohort of patients with AECOPD, representative of a population typically encountered by hospital clinicians. We explored phenotypes with emphasis on those factors with feasible therapeutic implications.

In Chapter 2, comprehensive assessment of AECOPD aetiology was performed encompassing known infective and non-infective aetiologies. Studies again highlighted the heterogeneity of hospitalized AECOPD and suggested that aetiology may be better considered as a composite of multiple contributory factors rather than being attributable to a single cause.

The detailed characterization in Chapter 3 may not be feasible in large-scale research studies or in primary care. As a result, we explored categorization by three categories of blood eosinophil counts (low, normal and high). This identified divergent profiles and exacerbation outcomes between exacerbations associated with low and high blood eosinophil counts. The findings suggest that low eosinophil counts may accompany infections whereas high eosinophil counts may indicate absence of infection and thus other mechanisms at play. This in turn may have therapeutic implications meriting further investigation. Eosinophil categorization is easily accessible in clinical practice and should be integrated into large-scale AECOPD studies for new therapies.

The impact of AECOPD upon cardiac function is gaining increasing attention. Troponins and natriuretic peptides are frequently elevated and although associated with adverse prognosis there is no evidence to date that they should be used to direct or alter current therapy. In the absence of such evidence their costs may not be justified in routine AECOPD care. As with blood eosinophil counts, lactate levels are already routinely available to clinicians as a component of blood gas analysis. We explored lactate as a marker of excessive treatments with β-agonists during AECOPD, an issue of considerable relevance given interest in β-blockade as therapy for AECOPD and stable COPD. This was the first study of blood lactate in hospitalized AECOPD and we observed elevated blood lactate levels in the majority of cases. A raised peak lactate was associated with adverse exacerbation outcomes and correlated with administered beta-agonist dosages; these doses were often very high. Of concern, there appeared to be a significantly higher rate of new onset tachyarrhythmia in the patient group with the highest lactate measurements.

To understand the implications of cardiac biomarker elevation in AECOPD we utilised cutting-edge CT technologies to perform comprehensive cardiopulmonary ECG-gated MDCT, using equipment potentially available at any tertiary-care hospital. Studies demonstrated that MDCT is feasible, required low radiation doses and provided highly informative data. Cardiac dysfunction was identified frequently in patients with AECOPD but this aspect of their overall disease burden was often unknown to treating clinicians. MDCT demonstrated that the underlying nature of cardiac dysfunction in AECOPD is varied and indicated that interpretation extrapolation of biomarker elevations based on extrapolation from other disease contexts may not be appropriate in COPD. Accurate identification of cardiac pathologies rather than depending on nonspecific marker of cardiac distress may be of paramount importance given the potential benefits of directed therapy in appropriately targeted populations. Individualizing appropriate cardiac therapy in COPD patients will require detailed evaluation and only MDCT has the capacity to provide simultaneous coronary, lung, heart and pulmonary vascular assessment.

6.2 IMPLICATIONS OF FINDINGS

6.2.1 CLINICAL PHENOTYPING OF EXACERBATIONS OF COPD BY UNDERLYING AETIOLOGY

The specific underlying aetiology of AECOPD is often not pursued in clinical practice and rarely reported in clinical research. In part, this reflects the difficulty in definitively establishing a specific aetiology with currently available methods. No specific biomarker accurately defines an exacerbation, and given the heterogeneity and complexity of these events, it is unlikely that this can be achieved.

Traditionally, exacerbation aetiology has been regarded as either infective or non-infective. More detailed aetiological phenotyping using cluster analysis in outpatients with COPD introduced a concept of 4 exacerbation types - viral, bacterial, eosinophilic and pauci-inflammatory(Bafadhel et al., 2011). While pauci-inflammatory exacerbations were not further characterised in previous studies, non-inflammatory aetiologies such as cardiac dysfunction are increasingly recognized and may fit into this group.

It has been suggested that clinical evaluation of stable COPD should be approached from the concept of “treatable traits”(Alvar Agusti et al., 2016). To an extent this concept was extended and applied to hospitalized exacerbations of AECOPD. A simple acronym (ABCDEFGX), with potential to act as an *aide memoire* for hospital clinicians, was used to inform a comprehensive assessment of AECOPD aetiology. During the study itself *a priori* assumptions were made regarding exacerbation aetiology and this was based on results of simple, clinically relevant and routinely accessible investigations. Microbiological, pathophysiological, psychological and social factors were all assessed to build a cumulative exacerbation phenotype reflecting treatable facets of the event.

Overall these studies indicated that clinical phenotyping of AECOPD is both feasible and informative. Conceptualization of exacerbations as either infective or non-infective appears to be incorrect since components such as cardiac dysfunction and psychological distress were prevalent to a similar degree in exacerbations deemed as being either infective or non-infective.

With the exception of sputum, symptoms appear to be poor discriminators of exacerbation aetiology. Viral detection appeared to be associated with prolonged admission that may reflect more intense bronchospasm in the viral group or conversely reflect benefits of antibiotics in the non-viral group. Bacterial infection appeared more common in those with frequent previous hospital exacerbations. Co-infection was associated with the highest CRP but bacterial detection rates were relatively low (given sputum samples collected using routine clinical methods at a single time-point).

Depression and anxiety symptoms were extremely prevalent and psychological comorbidity may represent an element of AECOPD that is under-diagnosed and undertreated. Attention to anxiety management may benefit patients and potentially even reduce resource utilization.

Clinicians rarely pursued a diagnosis of pulmonary embolism. The results detailed in Chapter 5 supports the view that pulmonary embolism is uncommon in unselected AECOPD cohorts.

Blood eosinophil counts were inversely related to CRP and may be useful as a crude measure of potential infection that is broadly applicable in AECOPD.

Elevation of cardiac biomarkers was very common, particular in those patients with underlying cardiac disease.

Our findings indicate that assessment of healthcare provision for AECOPD should be cognisant of patient's social support. Most patients were dependent upon others to maintain functional independent living in the community even at baseline.

Interestingly, a small group of patients had no identifiable aetiology to their exacerbation. They appear to represent a distinct phenotype with severe baseline disease and early hospital presentation but early hospital discharge. Rapid recovery may reflect the fact that only a minor deterioration was required to necessitate hospitalization and that this could often be rapidly resolved.

Taken together studies show that exacerbations should be considered as multi-dimensional and that most hospitalized AECOPD encompass multiple potentially treatable aetiological components. This implies that systematically examining AECOPD episodes for aetiological contributors could provide a framework for an individualized management approach. The protocol we used is sufficiently simple and accessible to be utilized in hospital practice. As a next step this approach can be employed in a prospective study using aetiologically-driven therapies and management strategies.

6.2.2 IMPLICATIONS OF LOW AND HIGH EOSINOPHILS IN HOSPITALIZED EXACERBATIONS OF COPD

A simplified approach to phenotyping AECOPD, if feasible, may help to improve management. One possible technique is to use blood eosinophil counts since this measure appears to be a reliable surrogate for airway eosinophil populations and eosinophil blood counts have been shown to predict some outcomes in COPD(Pascoe et al., 2015; Vedel-Krogh et al., 2015). Studies have suggested that

exacerbations featuring blood eosinophil counts >2% total white cell count resolve faster than those featuring eosinophil counts <2%(Bafadhel et al., 2012). This has been assumed to reflect increased corticosteroid responsiveness in the group with “high” eosinophils. However, comparing patients with “eosinophilic” versus “non-eosinophilic” blood counts during AECOPDs fails to take into account an important third group of patients - those with abnormally low eosinophils (eosinopenia). Eosinopenia can be a marker of sepsis and may be associated with adverse clinical outcomes(Abidi et al., 2008).

We therefore compared exacerbation aetiology and outcomes between 3 patient groups categorized according to their blood eosinophil counts: high, normal and low. An equal distribution of high, normal and low eosinophil counts at exacerbation in both a derivation and validation cohort was observed. An inverse correlation observed between blood eosinophil counts and CRP suggested that acute infection may cause some suppression of blood eosinophils. Eosinophilic exacerbations were often associated with absence of detectable infection and shorter times of hospitalization. In contrast, eosinopenic exacerbations were associated with infection and longer periods of hospitalization. In the derivation cohort, survival at 12 months was significantly lower in eosinopenic compared to eosinophilic exacerbations. This data was not yet available for the validation cohort.

Our studies therefore imply that both low and high blood eosinophil counts may have therapeutic and prognostic implications for AECOPD. The key therapeutic decision in current AECOPD management is whether antibiotics or corticosteroids, or both should be prescribed. Our findings suggest that higher blood eosinophils identify a target group for treatment with oral corticosteroids. Low eosinophils may reflect infection and merit antibiotic prescription. Finally, it remains a possibility that oral corticosteroids are contributing to prolonged exacerbations in eosinopenic AECOPD by impairing host immunity and subsequent bacterial clearance.

Integration of blood eosinophil counts into AECOPD management algorithms should therefore be prospectively assessed. If shown to assist therapeutic decision-making, the simplicity and cost of the test would make it widely accessible, including in primary care. Furthermore, reporting the eosinophil category of exacerbations in

research studies may elucidate the impact of therapy - e.g. whether the observed benefit of ICS in frequent exacerbators with higher blood eosinophil counts is due specifically to inhibition of eosinophilic exacerbations.
The relationship between eosinopenia and CRP may indicate a role for low eosinophils to detect chronic low grade inflammation in stable COPD, perhaps as a result of bacterial colonization. One previous study identified greater pneumonia risk from ICS therapy in COPD amongst patients who had eosinophils<2%(Pavord et al., 2016). Many questions are unresolved and nuanced studies are needed to define the role and use of blood eosinophil counts in therapy and management of AECOPD – and beyond.

6.2.3 LACTATE IS ASSOCIATED WITH ADVERSE OUTCOMES IN COPD EXACERBATION AND REFLECTS BETA-AGONIST DOSAGE

As a component of blood gas analysis, lactate is another blood marker routinely available to hospital clinicians managing AECOPD. Lactate correlates with mortality in shock and sepsis but has not been investigated in AECOPD. In acute asthma it is associated with β-agonist doses administered but has not been shown to link with adverse outcomes(Lewis et al., 2014). Lactate has potential relevance to AECOPD through disturbance of acid-base balance and ventilatory stimulation. It may also identify excessive β-agonism. Concerns regarding cardiac risks of β-agonists in COPD patients have been raised in observational studies. Conventional doses of inhaled LABA appear safe in stable COPD in patients enrolled in clinical trials. It cannot be assumed however, that the same applies to extremely high doses of short-acting β-agonists given to patients experiencing severe acute exacerbations, particularly those with underlying cardiac disease.

In the current studies elevated lactate was common in AECOPD, particularly among those patients requiring ventilatory support and longer hospitalization. While a causal relationship cannot be inferred from these observational data, it raises some noteworthy issues. Lactate may be directly contributing to the need for ventilatory support by worsening acid-base balance but also by worsening hyperventilation and anxiety - which then contribute to a clinical impression of worsening AECOPD and

possibly to application of NIV for increased work of breathing. It is feasible that excessive β-agonist treatments followed by increases in lactate contribute to a paradoxical perception of a need for additional ventilatory support.

Current guidelines recommend conservative doses for β-agonist use in AECOPD but there is a paucity of data from which to draw specific recommendations. Our study observed extremely high doses of β-agonist being administered in the first 24 hours after onset of AECOPD, chiefly as part of pre-hospital and emergency department care. It is therefore of significant concern that the safety of β-agonists in the context of AECOPD appears to have been largely forgotten and that it has not been studied. Moreover, there is burgeoning interest in the therapeutic use of β-blockers in AECOPD as a form of cardio-protection and the same rationale would suggest that excessive β-agonist use might have damaging consequences in patients with compromised cardiac function. In this context the utility of lactate as a marker of hyper-adrenergism warrants further exploration.

In summary, correlations between lactate and administered salbutamol doses in AECOPD are consistent with observations in asthma populations. We found that raised lactate was frequently observed, particularly in those patients with adverse exacerbation outcomes and clinician awareness of the problem was limited. Since lactate was associated with hyperglycaemia, tachycardia and new onset tachyarrhythmia this retrospective review is cautionary regarding the safety of extremely high dose β-agonists in AECOPD. As detailed in Chapter 5, severe cardiac comorbidity is common in AECOPD and often not recognised or identified by the treating clinician.

6.2.4 CARDIOPULMONARY EVALUATION IN COPD EXACERBATION USING DYNAMIC CT

The consistent association of elevated cardiac biomarkers with reduced survival post AECOPD(Chang et al., 2011) has flagged this area as a priority for clinical research, particularly since highly effective therapies are available for coronary artery disease (CAD) and left ventricular systolic dysfunction. Current cardiac investigations perform poorly in COPD and there is a pressing need for improved assessment of cardiac

status in this group, particularly in severe COPD. Based on its imaging and computational attributes MDCT has unique potential to achieve comprehensive cardiopulmonary assessment, but this has never been examined in COPD. We therefore applied 256-MDCT to assess coronary artery disease, pulmonary vasculature, cardiac function and degrees of emphysema in hospitalized AECOPD. The techniques used have been validated individually, but have never been integrated to conduct a comprehensive study in an AECOPD population. The findings demonstrate that comprehensive cardiopulmonary MDCT is feasible, even during AECOPD, with high technical success rates achieved at low radiation dosages. Importantly, MDCT frequently identified major and relevant cardiac pathology and disease.

Coronary artery calcium scores reflect coronary atherosclerosis and predict cardiovascular event rates and mortality(Greenland et al., 2007). We observed coronary calcification in a large majority of COPD patients and these findings had direct therapeutic implications for coronary therapy. Primary prevention therapy with statins, anti-platelet agents and intensive risk factor management has never been specifically studied in a COPD population. Given the high cardiovascular event rate in COPD this could have a major impact on mortality. Alternatively, the impact of COPD on prognosis may be such that the benefits of coronary primary prevention therapy will not be achieved in this patient group. Coronary artery calcium scoring could be used to identify CAD in COPD patients and target rational prescription of primary prevention coronary therapy.

MDCT identified left ventricular systolic dysfunction where clinical evaluation was insensitive, highlighting the difficulty in identifying left ventricular failure in AECOPD and the need for an accurate diagnostic tool. The combination of COPD and heart failure is associated with higher hospitalization rates(Roversi, Fabbri, Sin, Hawkins, & Agusti, 2016) and undiagnosed cardiac dysfunction may be a key factor contributing to admission in frequent exacerbators.

The applicability of echocardiography and MRI for detection of pulmonary hypertension in COPD (PH-COPD) is very limited. Conventional CT can identify PH-COPD when the PA measures wider than the adjacent ascending aorta, a finding

associated with increased exacerbation frequency(Wells et al., 2012). With dynamic MDCT we were able to measure PA pulsatility, a parameter shown to be the best predictor of survival in PAH populations(Swift et al.). PA pulsatility correlated with emphysema severity, right ventricular dysfunction and aortic stiffness, and this simple metric may provide a summary statistic reflecting the global impact of COPD and associated left and right heart disease. Impaired PA pulsatililty is observed at early stages of PH development with potential to identify high-risk patients and treat them before resting PH has become established.

Elevation of natriuretic peptide, and to a lesser extent troponin, was common in our AECOPD cohort. Consistent with previous literature, levels were significantly higher at exacerbation than recovery. Both measures appear to indicate acute ‘cardiac strain’ but with limited ability to discriminate between different underlying cardiac diagnoses. The current studies found that patients without coronary artery calcification had lower troponin levels at AECOPD as well as when recovered. However, raised troponin levels also showed a significant association with both left and right ventricular dysfunction. NT-proBNP measurements were significantly higher among patients with either left or right ventricular systolic dysfunction but high levels were also prevalent among patients with normal biventricular systolic function. This finding is most likely to reflect diastolic dysfunction which was not specifically assessed in the current study protocol but can also potentially be identified using MDCT{Boogers, 2011 #990}.

The cardiac parameter demonstrating the greatest change from acute to stable state was heart rate. Exercise-induced pulmonary hypertension is common in COPD and AECOPD has been associated with a spike in pulmonary pressure{Abraham, 1969 #515}. Although the mean PA pulsatility did not significantly change from exacerbation to stable review, the altered right ventricular function parameters indicate increased right ventricular afterload at AECOPD. Both troponin and BNP levels were significantly higher in patients with tachycardia. Whether heart rate reduction therapy in AECOPD could improve exacerbation outcomes, perhaps by improving exacerbation ‘tolerance’, should be prospectively investigated.

The poor diagnostic accuracy of clinical signs, symptoms, ECG and CXR in distinguishing cardiac dysfunction in COPD means that more advanced techniques are required to answer this cardinal question in clinical practice. Unravelling the complexity of heart-lung disease interaction in COPD through cardiopulmonary MDCT offers an enticing possibility. The previous barrier of radiation exposure has been largely overcome. A more relevant concern may be whether comprehensive cardiac CT could be a cost effective investigation. The patient population with hospitalized COPD exacerbations and cardiac disease currently consume a vast amount of healthcare resources. Investigations to modify treatment and clarify prognosis in this patient group could well be cost-effective and merits prospective study.

APPENDIX 1.

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SCIENTIFIC LETTER

Exacerbation phenotyping in chronic obstructive pulmonary disease

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Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are crucial events but causes remain poorly defined. A method to clinically 'phenotype' AECOPD have been proposed, and 52 hospitalized chronic obstructive pulmonary disease exacerbations according to underlying aetiology have now been prospectively phenotyped. Multiple exacerbation phenotypes were identified. A subpopulation coinfected with virus and bacteria had a significantly longer length of hospital stay, and this pilot study indicates that exacerbation phenotyping may be advantageous.

Key words: clinical respiratory medicine, chronic obstructive pulmonary disease, emphysema, infection and inflammation, viral infection.

Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) are the cardinal factor associated with mortality, morbidity, impaired quality of life and health-care costs in the disease.[1] Current definitions of exacerbation are non-specific,[2] implying an inherent assumption that exacerbation events have equivalent aetiologies. However, AECOPD are clearly heterogenous, and we proposed that routine clinical methods may be employed to attribute presumptive clinical aetiology to exacerbations.[3] Application of this process would permit identification of differences in population characteristics and clinical outcomes between different exacerbation subpopulations or 'phenotypes'. This may in turn have therapeutic consequences.

Following literature review, the established aetiologies of AECOPD have been précised in the acronym—ABCDEFGX;[3] **A**irway viral infection, **B**acterial infection, **C**oinfection, **D**epression/Anxiety, **E**mbolism (pulmonary), **F**ailure (cardiac, or failure of lung integrity—pneumothorax), **G**eneral environment, **X** (unknown) (Table S1 online).

The aim of this pilot study was to investigate the feasibility and putative benefits of our proposed exacerbation phenotyping. Methods employed for phenotype allocation are shown in the online supplement (Table S1 online).

Consecutive patients hospitalized with AECOPD ($n = 52$) provided informed consent and were evaluated prospectively. Those with known alternative respiratory diagnoses or inability to complete questionnaires were excluded. Demographic data included age, gender and smoking status/pack year history, Medical Research Council Dyspnoea score, current medications and vaccination history. Presenting symptoms and symptom duration prior to emergency room presentation were recorded. Each patient underwent nasopharyngeal sampling for respiratory virus multiplex polymerase chain reaction in addition to sputum culture, chest X-ray, serum white blood cell and C-reactive protein. A Hospital Anxiety and Depression Score,[4] and any changes in physical, social or therapeutic environment were recorded. Investigation for pulmonary embolism was at the discretion of the treating physician.

Patient demographics, exacerbation presentation, clinical severity and outcomes were compared between aetiological subgroups. Groups were compared using univariate analysis of variance.

The study population as a whole was elderly with severe disease. Distribution of aetiologies and demographics of phenotypes were shown in the online supplement (Table S2 online). Length of stay was normally distributed after exclusion of four outliers (>2 standard deviation from mean) who had protracted complications not clearly linked to AECOPD. Univariate analysis of variance comparing demographic factors between subpopulations did not identify a statistically significant difference between groups.

Mean length of hospital stay was 8 ± 5.9 days for the cohort as a whole. Coinfection resulted in a statistically significant longer length of hospital stay (coinfection 15.7 ± 10.8 vs bacterial 7.0 ± 3.3 ($P = 0.001$), coinfection vs viral 7.7 ± 4.8 ($P < 0.001$), coinfection vs non-infectious 4.63 ± 1.2 ($P < 0.001$); see Fig. 1). Coinfection group included the only

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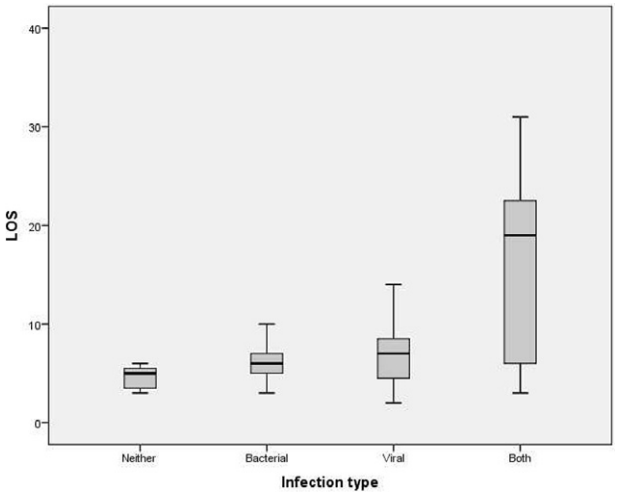

Figure 1 Length-of-stay (LOS) comparison between aetiological phenotype.

fatality and viral/coinfection had highest rates of non-invasive ventilation (NIV) requirement (not significant).

This pilot study emphasizes the heterogeneity of AECOPD and demonstrates that refining the term 'COPD exacerbation' to reflect underlying exacerbation aetiology may be feasible and clinically relevant. This proposition is supported by our finding that coinfection predicts poorer outcomes. Coinfection identified using more advanced research methods has shown a similar finding,[5] but our study has clinical utility as routinely available methods were employed. Other important subpopulations may be identifiable in larger studies. For example, patients in our study with poorly controlled anxiety/depression reported increased symptoms and attended emergency department (ED) earliest but had the least clinically severe exacerbations and shortest length of hospital stay (not significant). This subgroup may benefit from intensive psychosocial interventions rather than routine corticosteroids and antibiotics. Larger studies of AECOPD phenotyping are indicated.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1 ABCDEFGX classification system for COPD exacerbation aetiology.

Table S2 Comparison between aetiological subgroups.

Online Table S1. *ABCDEFGX classification system for COPD exacerbation aetiology*

Code	***Aetiology***	***Rationale***
A	*Airway viral infection*	*Viral PCR +ve on nasopharyngeal flocculated swab* *(nasopharyngeal flocked swab sampling was performed in preference to sputum viral analysis to endure a sample could be collected from each participant)*
B	*Bacterial infection*	*Bacteria identified on sputum MCS* *CXR consolidation* *Clinically evident infection – fever, purulent sputum*
C	*Coinfection*	*Viral PCR +ve* *And* *Bacteria identified on sputum MCS*
D	*Depression/Anxiety*	*Hospital anxiety or depression score (HADS) > 11*
E	*Embolism (pulmonary)*	*Pulmonary embolism confirmed on CTPA or V/Q scan*
F	*Failure (cardiac)*	*Cardiac failure evident on CXR or clinical examination*
G	*General Environment*	*Change in physical, social or therapeutic environment identifiable as trigger for hospitalization*
X	*X = unknown*	*None of the above factors identified – exacerbation unexplained*

Online Table S2. *Comparison between aetiological subgroups*

	n	***Age (years)***	***FEV1 (%pred)***	***MRC-D***	***BMI kg/m²***	***Current smoking (%)***	***Pack Years***	***NIV required (%)***
A	*13*	*67.3 ±8.3*	*36.9 ±16.6*	*3.6 ±1.0*	*28.7 ±5.9*	*46*	45.3 ±22.1	*31*
B	*24*	*74.1 ±10.4*	*39.7 ±15.8*	*4.5 ±0.7*	*24.9 ±7.9*	*17*	46.5 ±40.6	*17*
C	*7*	*70.0 ±5.7*	*43.5 ±18.0*	*3.6 ±1.0*	*26.5 ±8.2*	*29*	39.3 ±13.1	*29*
D	*3*	*71.7 ±9.2*	*32.3 ±10.7*	*4.3 ±1.2*	*21.1 ±2.0*	*0*	50.0 ±10.0	*0*
E	*1*	*84*	*N/A*	*4.0*	*N/A*	*0*	50.0	*0*
F	*0*							
G	*0*							
X	*4*	*71.5 ±11.9*	*26.7 ±8.7*	*3.7 ±1.5*	*22.6 ±2.6*	*75*	47.5 ±35.9	*25*

Each exacerbation event was comprehensively analysed for underlying aetiology – if multiple aetiologies were identified then a "dominant" aetiology was ascribed to permit comparison between aetiological phenotypes.

APPENDIX 2.

Subjects included as AECOPD without spirometry confirmation.

Subject	Respiratory Physician diagnosis	Age	Pack Years	Radiological evidence	Reason no PFTs available
1	Yes	78.0	60	10.7% LAA on CT	Declined testing
2	Yes	77.3	50	18.5% LAA on CT	Incapable of techniques
3	Yes	83.8	70	CXR hyperinflation	Deceased
4	Yes	77.4	23	CXR hyperinflation	Uncontactable post discharge
6	Yes	54.0	30	5.2% LAA on CT	Uncontactable post discharge

%LAA= low attenuation areas on computed tomography (CT) (i.e. %emphysema), CXR = Chest X-ray

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