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THREE ASPECTS IN THE TREATMENT OF ACUTE EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE: THE RÔLE OF NEBULISED MAGNESIUM, THE RISKS OF OXYGEN AND THE UTILITY OF THE CRB-65 SCORE

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SUMMARY OF THESIS: POSTGRADUATE RESEARCH DEGREES

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SECTION A: TO BE COMPLETED BY THE CANDIDATE AND SUBMITTED WITH THE THESIS

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Full Title of Thesis	Three aspects in the treatment of acute exacerbations of chronic obstructive pulmonary disease: The role of nebulised magnesium, the risks of oxygen and the utility of the CRB-65 score

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Summary of Thesis:

Chronic Obstructive Pulmonary Disease (COPD) is one of the commonest long-term conditions worldwide. It is characterised by chronic airflow limitation, pathological changes in the lung and significant extra-pulmonary manifestations.

The treatment of an acute exacerbation of COPD (AECOPD), involves glucocorticoids and bronchodilators supplemented by antibiotics if needed. In-hospital, oxygen, which has potential risks as well as benefits, and additional respiratory support can be given if the patient deteriorates. Clinicians need to decide which treatment to provide and who can be safely discharged. This has led to the advent of scoring systems to define severity in COPD.

This thesis examines the evidence base for the use of magnesium in airways disease and presents the results of the first randomised double-blind placebo-controlled trial using nebulised magnesium in the treatment of AECOPD. 116 patients were randomised, but after 3 nebulisations over 90 minutes, there was no significant difference in FEV_1 compared to placebo ($p=0.67$).

In a second study, the CRB65 score was retrospectively assigned to a cohort of patients presenting to the emergency department with AECOPD, using data collected from a previous audit. Patients with a CRB65 score of 0 or 1 had a low risk of in-hospital and 30-

day mortality and could be considered for discharge, whereas those with scores between 2-4 required admission with mortality increasing with the score. The CRB65 score showed a similar utility in AECOPD as it does in pneumonia.

Finally, 18 subjects with stable but severe COPD were randomised in a crossover study to two nebulisations with salbutamol and ipratropium over 15 minutes with a five minute interval between nebulisations, using air or oxygen as the driving gas. When oxygen was used there was a 3.1mmHg difference ($p<0.001$) at 35 minutes, compared to air, illustrating the potential risks of repeated nebulisations to those with severe COPD.

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I would like to thank both my supervisors, Professor Richard Beasley of the Medical Research Institute of New Zealand (MRINZ) and Otago University in Wellington and Professor Dennis Shale of Cardiff and Vale University Health Board and Cardiff University. I would like to thank Professor Beasley in particular, who oversaw the clinical trials aspect of my work which was undertaken in Wellington, for his inspirational leadership of MRINZ and for the encouragement and support he provided me during my time in New Zealand.

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I would like to express my heartfelt gratitude on behalf of myself and my family to the residents of Wellington, especially those of the Kilbirnie/Lyall Bay area where we lived

and were made to feel a most welcome part of the community. In particular I would like to thank the staff and students of Lyall Bay Kindergarten and St. Patrick's Primary School, Kilbirnie as well as Fr. Mathew Clerkin and the parishioners of St. Patrick's Church, Kilbirnie.

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Finally, I would like to thank my wife Linda and our 3 boys for following me all the way there and back and for encouraging me to complete and submit this work.

STUDY CONTRIBUTORS

The magnesium study was a collaborative effort involving the whole of the MRINZ team, in particular the Magnesium COPD Study Team. All investigators recruited patients to the trial and I was involved in coordinating the study (which involved ensuring relevant study materials were available) and collecting and reviewing the data. The study had been designed prior to my arrival in New Zealand and continued when I left. Professor Beasley and Dr. Pip Shirtliffe were involved in writing the manuscript of the study with input from the rest of the MRINZ team.

The CRB-65 study was based on previously published audit data which was held on the MRINZ database. For this study I was involved in extracting the data that was required. I did this under the supervision of Dr. Kyle Perrin and the final manuscript was finished by him based upon an earlier draft that I had written.

The oxygen study was jointly conceived by Professor Beasley, Dr. Perrin and myself following on from previous oxygen trials that had been performed at MRINZ. However, I was solely responsible for recruitment and the day-to-day running of the trial. Again, Dr. Perrin provided assistance with completion of the manuscript following on from an earlier draft by me.

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My MD thesis was entirely self-funded apart from a grant of £750 courtesy of the HM Foreman fund.

PUBLICATIONS

The three studies described in the thesis have been published in the scientific literature as follows:

Edwards L, Shirtcliffe P, Wadsworth K, et al. Use of nebulised magnesium sulphate as an adjuvant in the treatment of acute exacerbations of COPD in adults: a randomised double-blind placebo-controlled trial. *Thorax* 2013; **68**:338-343.

Edwards L, Perrin K, Williams M, et al. Randomised controlled crossover trial of the effect on P_{tCO2} of oxygen-driven versus air-driven nebulisers in severe chronic obstructive pulmonary disease. *Emerg Med J* 2012; **29**:894-898

Edwards L, Perrin K, Wijesinghe M, et al. The value of the CRB-65 score to predict mortality in exacerbations of COPD requiring hospital admission. *Respirology* 2011; **16**:625-629

PRIZES

Edwards L, Perrin K, Wijesinghe M, et al. The value of the CRB-65 score to predict mortality in exacerbations of COPD requiring hospital admission. *Respirology* 2011; **16**:625-629

The above paper won the Welsh Thoracic Society prize at the Spring meeting in 2011 for best published work by a respiratory trainee from the Welsh deanery.

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CHAPTER 1

INTRODUCTION

The definition, aetiology and prevalence of chronic obstructive pulmonary disease

Chronic Obstructive Pulmonary Disease (COPD) is one of the commonest long-term conditions worldwide with significant mortality, morbidity and economic costs.

COPD, as stated in the GOLD (Global Initiative for Chronic Obstructive Lung Disease) guide 2012

"..(is) a common, preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients."[1]

Tobacco smoking is by far the main risk factor for the development of COPD in developed countries[2] though air pollution[3] and domestic cooking smoke exposure[4] are factors in some settings. The risk of developing COPD from cigarette smoking is related to the dose inhaled over time.[5] However, not all smokers will develop COPD to the same degree and some do not develop it at all.[6] Additionally, airflow limitation, as measured by forced expiratory volume in 1 second (FEV_1), the traditional means by which COPD is diagnosed, does not always correspond to symptoms.[1] Nevertheless,

the use of FEV_1 allows the clinician to assess the severity of airflow limitation and to fit patients into groups based upon these measurements which broadly, but not universally, define a sufferer's expected symptomatology, treatment category and prognosis.

The table below shows how COPD was diagnosed in the past based primarily upon spirometric data alongside a likely history of COPD (cough, breathlessness and smoking history). Figure 1 shows the new GOLD classification based upon symptoms, breathlessness, spirometry and risk of exacerbation. Figures 2 and 3 provide further detail of the assessments used.

Stage I	Mild COPD	FEV1/FVC<0.70	$FEV_1 \geq$ 80% normal
Stage II	Moderate COPD	FEV1/FVC<0.70	FEV_1 50-79% normal
Stage III	Severe COPD	FEV1/FVC<0.70	FEV_1 30-49% normal

Stage IV	Very Severe COPD	FEV1/FVC<0.70	FEV_1 <30% normal

Figure 1

COPD Assessment using symptoms, breathlessness, spirometric classification and risk of exacerbation

From the Global Strategy for Diagnosis, Management and Prevention of COPD 2013. Used with permission from the Global Initiative for Chronic Obstructive Lung Disease (GOLD), available from http://www.goldcopd.org.

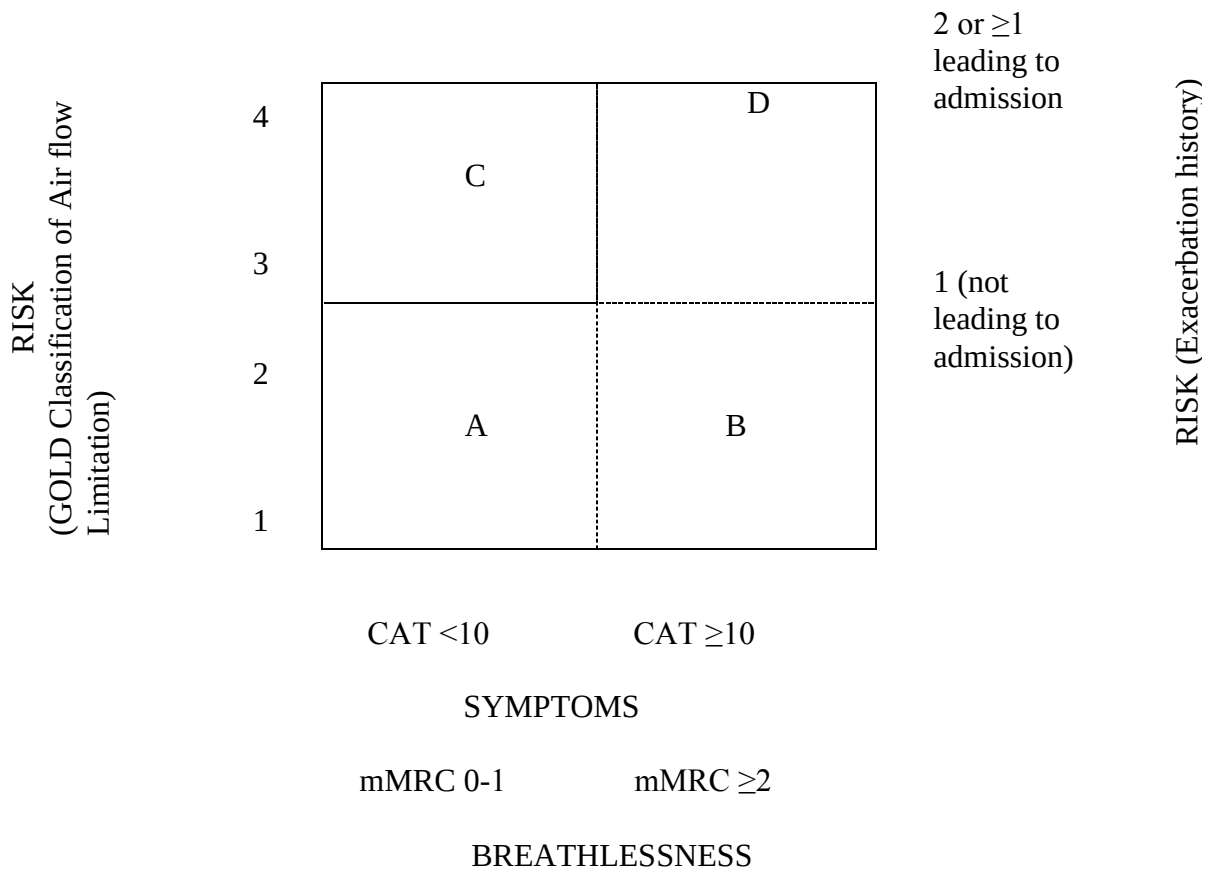


Figure 2

Modified MRC (mMRC) breathlessness scale[7]

Grade	Degree of breathlessness
0	Not breathless except with strenuous exercise
1	Breathlessness when walking up an incline or hurrying on the level
2	Walks slower than most on the level, or stops after 15 minutes of walking on the level
3	Stops after a few minutes of walking on the level
4	With minimal activity such as getting dressed, too breathless to leave the house

Figure 3

COPD Assessment Test (CAT)[8]

SYMPTOM (ABSENT)	SCORE (0-5)	SYMPTOM (SEVERE)	SCORE (OUT OF 5)
I never cough	0 1 2 3 4 5	I cough all the time	
I have no phlegm in my chest at all	0 1 2 3 4 5	My chest is full of phlegm	
My chest does not feel tight at all	0 1 2 3 4 5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	0 1 2 3 4 5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	0 1 2 3 4 5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	0 1 2 3 4 5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	0 1 2 3 4 5	I don't sleep soundly because of my lung condition	
I have lots of energy	0 1 2 3 4 5	I have no energy at all	
		TOTAL SCORE:	

The prevalence of COPD in the UK is 1%, rising to 10% in men over the age of 75, figures which are broadly similar worldwide.[9] However, whilst around 900,000 people in the UK have an official diagnosis of COPD, it is estimated that up to 3.7 million actually have the condition. Those without a diagnosis have been dubbed the "missing millions".[10] COPD accounts for more than 1 million bed days per year in the UK with over 111000 admissions in 2004, 20% of all respiratory admissions. In the same year there were 27478 deaths due to COPD.[11] Worldwide, it is likely that COPD will go from being the sixth to the third leading cause of death by 2020.[12] Between 1965 and 1998 the mortality from COPD in the USA increased by 163% whilst mortality from stroke and coronary vascular disease fell.[13] COPD accounts for 56% of all European healthcare costs of €48.4 billion.[14]

Acute exacerbations of COPD and their treatment

In recent years, in recognition of the complexities of COPD and the difficulties and controversies that arise in its diagnosis, treatment and monitoring, global cooperation has increased, driven by organisations such as GOLD. In turn, national organisations have produced numerous well researched guidelines for the diagnosis and treatment of asthma and COPD with the British Thoracic Society (BTS) taking the lead in the UK. The treatment of an acute exacerbation of COPD (AECOPD) is characterised by the recognition of an exacerbation followed by treatment with glucocorticoids and either inhaled or nebulised bronchodilators (usually beta-agonists and anticholinergics), supplemented by antibiotics if needed. In the hospital setting oxygen and intravenous bronchodilators (beta-agonist or theophylline) can be provided, with the additional option of respiratory support if the patient deteriorates. Unlike in asthma exacerbations, where there is some evidence if its efficacy as a bronchodilator when given by infusion[15], magnesium, given either intravenously or by nebuliser, is not generally used in AECOPD. Within 2 weeks of discharge, acute pulmonary rehabilitation has been shown to improve walking distance and quality of life, as well as reducing the risk of readmission.[16, 17] The ultimate aims of treatment are firstly to return the patient to their usual equilibrium, ideally without the added risks and costs involved in admission to hospital, and secondly to prevent or delay further exacerbations which are associated with an accelerated decline in lung function and reduced quality of life.[18, 19]

In an age of preventative medicine there is much interest in elucidating the factors involved in exacerbations of COPD and those that might predict readmission to hospital. Many of these are well characterised and will be described in more detail later. Additionally, once in hospital, doctors need to know which patients are at highest risk in comparison to others. This has led to the advent of scoring systems to define severity in many conditions, the prime example in respiratory medicine being pneumonia with the CURB-65[20] score now well established in the UK, and others such as the pneumonia severity index (PSI)[21] in use elsewhere.

Much interest recently has focused on the use of oxygen, with an increasing evidence base for its potential ill-effects seemingly offset by its continued abuse as a drug even though practitioners from all of the caring professions are made aware of its dangers. This is true especially in COPD where the patients tend to be older than the asthmatic population, with multiple co-morbidities requiring numerous medications and where physiological reserves are less robust. Despite this education however, there remains the possibility that in the maelstrom of an exacerbation, health practitioners at every step of a patient's journey from their home to hospital (possibly via ambulance transfer) may still utilise oxygen in an incorrect and potentially dangerous manner, leading to adverse health outcomes.

Aims of this thesis

This thesis will look at the use of nebulised magnesium as a bronchodilator in acute exacerbations of COPD (AECOPD). The vast majority of work done on the bronchodilator properties of magnesium and its subsequent application to patient care has been done in asthma. Necessarily therefore, much of the literature review with respect to that issue will deal mostly with trials on asthmatic subjects. The evidence base for magnesium's use in COPD is sparse with researchers surmising that due to the similarities between asthma and COPD and their usual treatment, what appears to work for one may well be useful in the other. This remains to be seen.

The thesis will also look at the utility of biomarkers, including magnesium levels, and severity scores in COPD, especially their value in prognostication during an AECOPD.

Finally, it will evaluate the evidence regarding the use, and potential abuse, and therefore the dangers of oxygen therapy in AECOPD, especially with regards to the early stages of an exacerbation.

The thesis will be clinically orientated in its outlook, with the three main themes mirroring the patient's journey during an AECOPD from treatment at home and in the ambulance, to initial evaluation of the patient in the emergency department and the therapy they receive when they get there. In doing so, it aims to provide clinicians with

novel information that will inform their practice when dealing with the common problem of AECOPD.

CHAPTER 2

LITERATURE REVIEW

1) The theoretical basis for magnesium's bronchodilatory properties
2) Clinical trials of intravenous and nebulised magnesium in adults with acute exacerbations of asthma and COPD
3) Prognostic markers and severity scores in stable COPD and during exacerbations
4) Pre-hospital care in AECOPD: The use of oxygen

The theoretical basis for magnesium's bronchodilatory properties

Magnesium is the second most abundant cation in the extracellular fluid and its rôle in physiological processes is now well understood. This in turn has led to its use as a therapeutic agent especially in the fields of cardiology, obstetrics and lately, respiratory medicine.[22]

From an evolutionary standpoint the place of magnesium in animal cell biology is closely tied to that of another bivalent ion, calcium.[23] Indeed the requirement for magnesium developed in tandem with, and in competition to that of calcium. Magnesium has been referred to as

> *"Nature's physiologic calcium blocker"* [24]

Following the development of animal cells containing adenosine triphosphate (ATP), magnesium became essential for energy transformation and cell metabolism whereas calcium was required for structural stability and motility via neuromuscular activity. This latter rôle became more important when an organism's ability to move directly affected its capacity for survival.[24]

Excitable tissues, including bronchial smooth muscle, require the generation of electrochemical potential differences across the cell membrane in order for muscular contraction to occur. This is modulated by calcium flux in and out of the cell though the

exact mechanism differs depending on the type of muscle involved.[25] Magnesium appears to block the excitatory effects of calcium in various ways including inhibiting calcium flux through the sarcolemma, competing with calcium for binding sites on actin and modulating the adenylate cyclase-cyclic AMP (adenylate monophosphate) system.[26] It has also been demonstrated that it affects neuromuscular transmission directly by antagonising calcium, leading to a reduction in the amount of transmitter liberated at the motor nerve terminals, diminishing the depolarising action of acetylcholine at the end-plate and depressing the excitability of the muscle fibre membrane.[27] Experimental depletion of magnesium leads to hypocalcaemia[28] and it is now thought that magnesium modulates calcium balance through its effect on parathyroid hormone (PTH). Magnesium deficiency inhibits the direct action of PTH on bone and may also impair PTH secretion.[29]

Total body stores of magnesium are around 24g[30], of which less than 1% is extracellular. More than half of extracellular magnesium exists in its free ionised form with the remainder either protein bound or complexed to anions.[31] The normal reference range is 0.7-1.0 mmol/L though it varies between laboratories. It is estimated that between 53% and 67% of total body magnesium rests in bone. Whilst the total amounts of magnesium in various compartments may vary according to need, stores are regulated by metabolic and hormonal effects on absorption and excretion via the gastrointestinal tract and kidneys respectively. Gut absorption varies according to the dietary magnesium ingestion with only 40% of that swallowed being absorbed normally (assuming an ideal intake of 36-48 mg per day).[32] Absorption may be as high as 70%

in magnesium deficient diets and falls below 30% where dietary intake is high. Seeds, nuts and pulses tend to be richer in magnesium than meat or fruit and it is absorbed equally well in the jejunum or ileum[33] though the former is Vitamin D dependent.[34] Around 10% of ingested magnesium is lost each day via gastrointestinal tract secretions, though this figure can increase in diarrhoeal illnesses or malabsorptive states.[22] Renal excretion accounts for the remainder of the magnesium balance with only 3% being filtered by the glomerulus, though practically all of this is reabsorbed either in the proximal tubule (30%) or the loop of Henle(65%).[35] Commonly used drugs such as digoxin, aminoglycosides and both loop and thiazide diuretics can cause renal magnesium wasting.[36]

Though easy to measure, serum magnesium level does not necessarily correlate with either total body stores or with disease.[37] Severe deficiency may cause no symptoms.[38] However, hypomagnesaemia is relatively common, especially in critical care settings where prevalence can be as high as 65%.[39] One study has suggested that 43% of those admitted to an intensive care unit (ICU) with severe asthma are hypomagnesaemic[40] whilst in a study of 93 chronic stable asthmatics, Alamoudi showed that 27% had hypomagnesaemia and that these had a higher rate of hospitalisations (40% compared with 11.8% in those with magnesium levels in the normal range). Additionally low magnesium and chronic asthma tended to result in more severe asthma.[41] A contrasting study by Falkner found no difference in serum magnesium levels between non-asthmatic subjects and those with acute asthma though the population observed was small.[42] A further study with 25 patients found no

increase in serum magnesium levels after magnesium infusion in chronic stable asthmatics with magnesium levels in the normal range. Perhaps more significantly there was no bronchodilator response as measured by FEV_1 either.[43]

Rolla found that 11% of a group of patients with severe COPD were hypomagnesaemic and that those had a lower mean FEV_1 compared to patients with levels in the normal range.[44] The authors found that the use of diuretics was associated with lower magnesium levels, a fact that had previously been noted.[45] Additionally there was a negative correlation between serum magnesium and length of oral steroid therapy but β-agonists had no effect. Magnesium levels have also been postulated to be a possible marker for COPD among at-risk smokers. Concentrations of biologically active ionised magnesium are lower in those with COPD and the ratio of total calcium to total magnesium (tCa/tMg) was higher in the polymorphonuclear cells of those with COPD than those of healthy smokers and non-smokers.[46]

Another population of patients with COPD had lower serum magnesium levels than other patients with acute respiratory disease (pneumonia, pulmonary embolism and asthma) at the end of treatment (though the length of treatment is unspecified). At baseline, there was no significant difference in serum magnesium concentration whilst at the end mean serum concentration in the COPD group was 0.87mmol/L compared to 0.94mmol/L for the other group ($p<0.05$). Additionally, serum levels fell in 17.2% of COPD patients, compared with 5.3% of the others by the end of treatment ($p<0.05$). Those with COPD also had higher 24 hour urine magnesium levels, both at baseline

(3.98mmol/day compared to 3.04mmol/day, $p<0.015$) and at the end of treatment (4.28mmol/day compared to 2.67mmol/day, $p<0.01$). This may reflect an older population with multiple co-morbidities such as cor pulmonale, and polypharmacy, especially with diuretics and more prolonged use of steroids, than the other group.[40]

Unpublished studies on COPD patients have suggested an inverse correlation between magnesium levels and inspiratory muscle strength as measured by P_{imax} (maximal inspiratory mouth pressure). Furthermore, higher serum calcium to magnesium coefficient correlated with a lower P_{imax} suggesting that an imbalance in the levels of calcium and magnesium may be an indication of respiratory muscle dysfunction.[47] This had been suggested earlier in a speculative study which measured respiratory muscle power in 17 hypomagnesaemic patients(11 with alcoholism and 6 with COPD) both before and 3 days after an infusion of 6g of magnesium salt. As expected, there were significant increases in blood and urine magnesium levels, and all indices of muscle power that were measured also showed improvement from baseline after treatment (though there was no difference between the alcoholics and those with COPD). This reached significance for P_{imax}-FRC (maximal inspiratory power at functional residual capacity) and P_{emax}-TLC (maximal expiratory power at total lung capacity) with a p-value of ≤ 0.05.[48] See figures 4 and 5.

Figure 4

Improvement from baseline in P_{imax}-FRC with magnesium compared to placebo

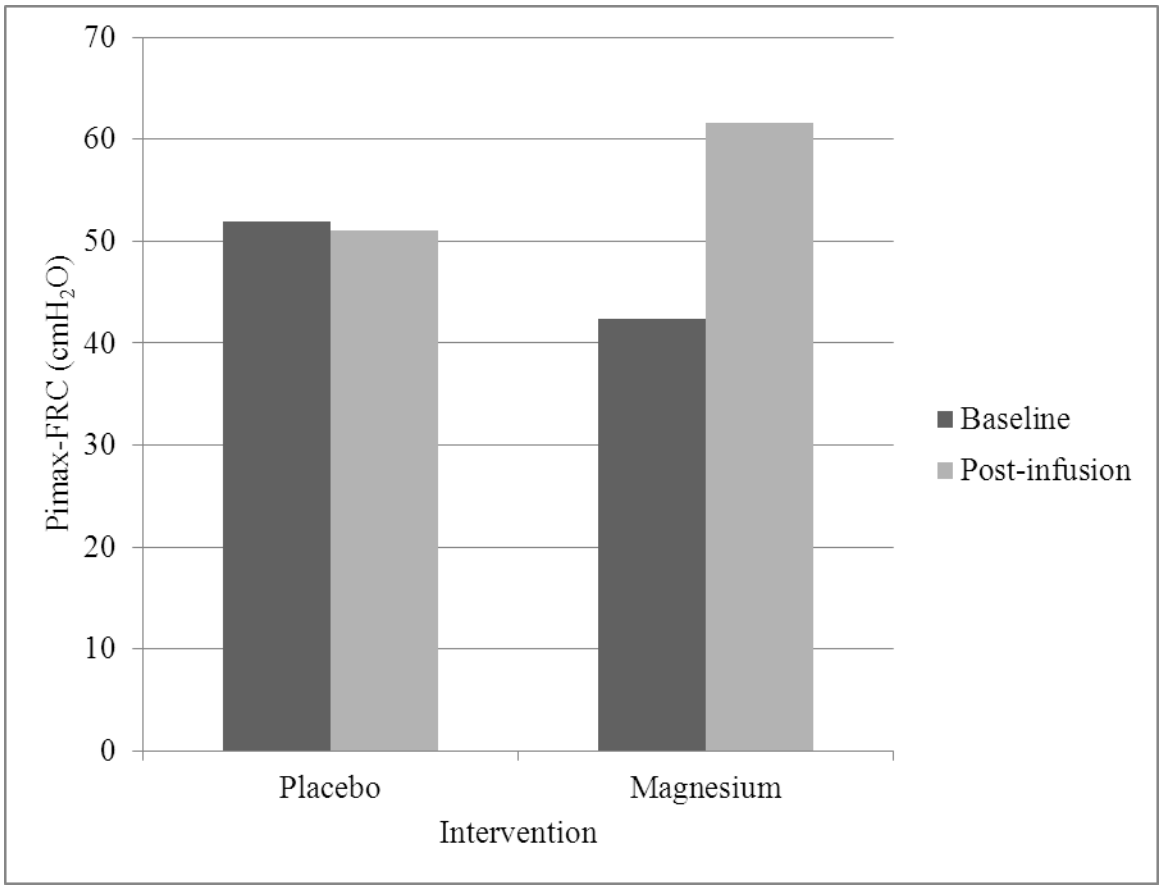
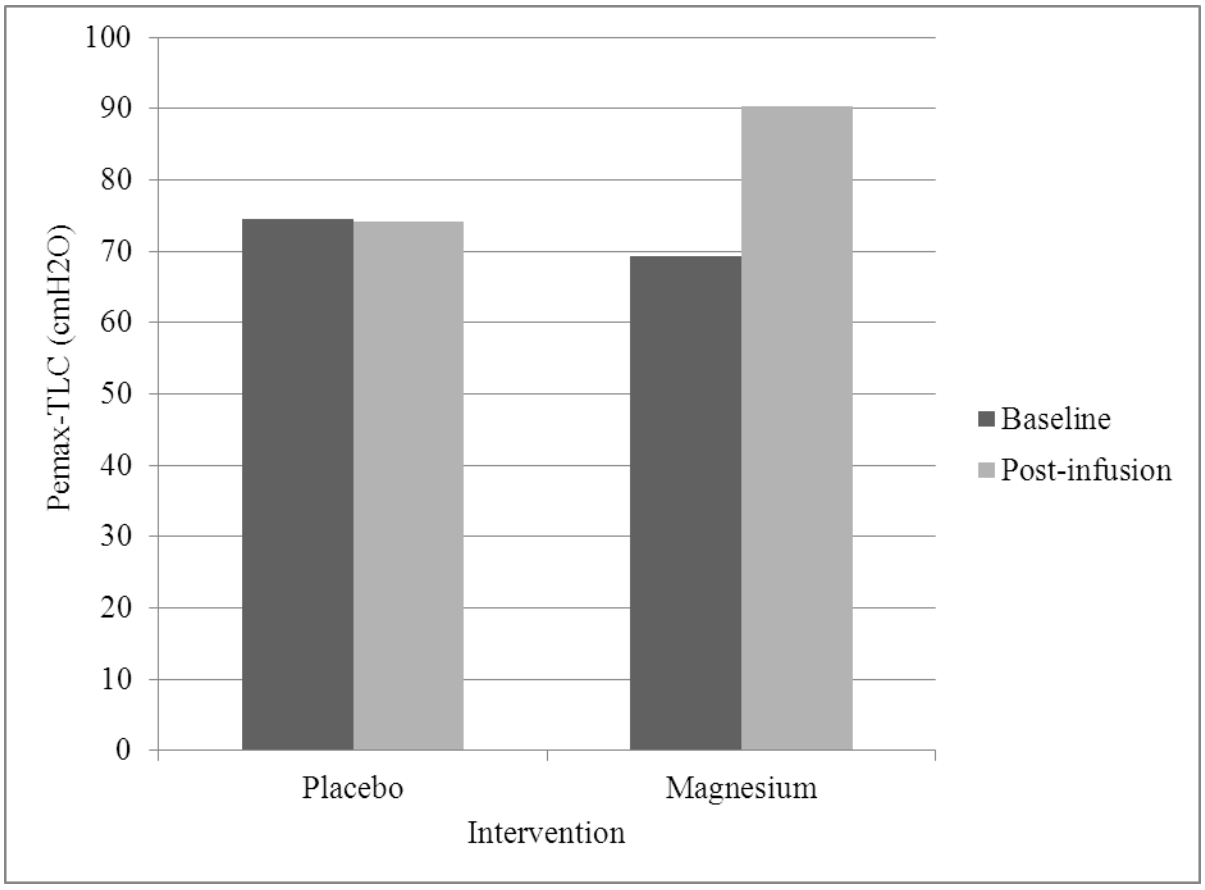


Figure 5

Improvement from baseline in P_{emax}-TLC with magnesium compared to placebo



Another outpatient study on 22 stable patients with COPD saw acute loading with 2g of magnesium sulphate lead to an improvement in respiratory muscle strength and decreased lung hyperinflation, though this was only marginally statistically significant. However, there was no effect on FEV_1 ($p=0.06$).[49] A smaller, more recent study published only in abstract form did show an improvement in FEV_1 (from 1.44L to 1.67L at 60 minutes, $p<0.05$) when nebulised magnesium was used as an adjuvant with salbutamol in stable outpatients. Details regards randomisation and blinding are lacking and it is difficult to draw any firm conclusions from published data.[50]

Other studies in asthmatic patients have looked at magnesium levels in different compartments to try and correlate them with disease, though there are no large-scale studies. De Valk found no difference in magnesium levels between plasma and erythrocytes and mononuclear lymphocytes.[51] Contrastingly, though Emelyanov found no differences in serum magnesium levels between a group of stable asthmatics and controls, the concentration of magnesium in erythrocytes was significantly lower. This was not related to airways obstruction but a magnesium tolerance test showed a greater retention of magnesium in the asthmatic subjects. As the authors conclude:

"This may reflect a relative magnesium deficiency in several cell types, including inflammatory cells, smooth muscle and skeletal muscles." [52]

This has been shown in the skeletal muscle of asthmatics treated with oral β-agonists, although drug withdrawal led to no significant rise in magnesium after two months. It is therefore unclear whether this finding of skeletal muscle magnesium deficiency is due to pathophysiology or treatment.[53] A further interesting finding of the Emelyanov study was the discovery that the erythrocyte magnesium concentration was significantly correlated with PC_{20} to acetylcholine. (PC_{20} is defined as the provocative concentration of a bronchoconstrictor agent-in this case acetylcholine-which causes a fall in FEV_1 of 20% from baseline). This suggests that low intracellular magnesium promotes airway hyperresponsiveness.

Following on from this there is further evidence in the literature that magnesium plays a role in bronchial hyperresponsiveness (BHR) though some studies are contradictory on this point as well as on the clinical utility of intracellular magnesium concentrations. A Greek study found that although intracellular magnesium levels fell during histamine challenge, presumably so that it could block histamine channels, this could not be correlated with bronchial hyperreactivity. Additionally, plasma levels were within normal ranges and did not change. The authors put the negative results down to the Greek diet, which tends to be rich in magnesium, and also to the lower average age of the subjects compared to other studies.[54] In a separate Mediterranean study however, intracellular magnesium levels were significantly lower in asthmatic patients compared to those with rhinitis and there was a strongly positive correlation ($r=0.72$, $p<0.001$) between bronchial reactivity to methacholine and the level of intracellular magnesium. The authors make no direct mention of the protective effect or otherwise of the regional diet but the average

age of the study population was 13 years older than the Greek study, though still only 33.[55] Two similar studies using inhaled magnesium sulphate showed that whilst it had no effect on FEV_1 itself, it significantly increased PD_{20} FEV_1 to both histamine and methacholine.[56, 57] This effect is very similar to that observed with nifedipine[58], suggesting that magnesium inhibits calcium handling of bronchial smooth muscle cells. Further experiments on animal tracheal tissue have shown that verapamil blocks calcium influx in response to acetylcholine[59] and nifedipine inhibits calcium dependent intrinsic tone and histamine responses.[60] The fact that magnesium appears to interfere with processes that require calcium to occur is supported by evidence from experiments on vascular beds and subsequent studies on rabbit smooth muscle.

Altura exposed rat aortic tissue to varying concentrations of magnesium and showed that lowering the extracellular concentration led to an increased magnitude of contractile response in the vascular smooth muscle with response times shortening the lower the magnesium concentration fell.[61] Tissue bathed in magnesium free solution had a decreased threshold for calcium induced contraction. Conversely, subsequent elevation of the magnesium concentration led to a reversal of these effects and also lowered baseline tension by up to 20%. The authors therefore conclude that magnesium acts at the cell membrane. They also report that it acts intracellularly as the fact that a certain concentration of magnesium, 1.2mM, actually increases the maximal contractile response of depolarised aorta to calcium suggests that it might be competing with calcium for some intracellular sites, in that the presence of magnesium on intracellular calcium binding sites means that there is more free ionised calcium available for contraction. The

same investigators had previously shown that magnesium displaced cellular calcium in smooth muscle.[62] Exposure of tissues to a magnesium free media also differentially affects contractile responses of vasoactive agents such as adrenaline, 5-hydroxytryptamine and oxytocin, compared to when the tissues are subsequently exposed to magnesium. As these agents have different sites of action, it suggests that magnesium acts in different ways.

In experiments on New Zealand white rabbits, Spivey showed that when magnesium chloride was added to tissue baths where the bronchial rings were stimulated either by histamine, bethanechol or electricity, it produced statistically significant dose-dependent relaxation of the bronchial tissue. Furthermore, the addition of calcium salt did not significantly reverse the magnesium induced relaxation. This led the investigators to conclude that magnesium acts to relax smooth muscle and is a bronchodilator, likely through non-competitive antagonisation of the effects of calcium. Another interesting aspect of the study is that the three bronchoconstrictor agents act in different ways, yet magnesium significantly altered smooth muscle tension when compared against all of them, adding further weight to the theory that magnesium has many different modes of action.[63]

Electrical stimulation leads to the production of action potentials at voltage gated calcium channels on smooth muscle membranes, leading to contraction via calcium ion flux into the cell. We know from previous studies that magnesium prevents postganglionic nerve stimulation of smooth muscle cells at the motor end plate[27], but its actions against

bethanechol suggests that it blocks autonomic impulses at the level of the cell wall, thus keeping calcium channels closed and inhibiting calcium release. As regards histamine, it had previously been shown that magnesium could stabilise mast cells, thus inhibiting histamine release which in turn would make the smooth muscle membrane less permeable to the influx of calcium.[64] We also know that in atopic asthmatics during an attack, the level of magnesium in blood and erythrocytes correlates with the rise in histamine and number of eosinophils. This provides further basis for the role of magnesium not just in asthma, but in allergic conditions as a whole.[65]

Despite this apparently good evidence of magnesium's potentially beneficial role in BHR, two studies by Hill and colleagues might serve to diminish expectations about magnesium's potential use in respiratory disease. Both studies are well conducted randomised, double-blind crossover trials. The subjects were young and clinically stable with mild to moderate asthma. In the first, 2g of intravenous magnesium sulphate resulted in what they termed "weak" though statistically significant bronchodilatation. 20 non-smokers with what was termed mild to moderate asthma were studied. All were on regular beta-agonists, but interestingly 18 were on regular oral steroids. There is no documentation regards inhaled steroid use. Magnesium or placebo was infused over 20 minutes in a double-blinded crossover trial, followed on each occasion by inhalation of doubling doses of histamine. Mean change in FEV_1 from baseline was 1.71L higher with magnesium than placebo ($p=0.049$). Magnesium did not alter airway reactivity to histamine however ($p=0.70$). [66] This is in contrast to an earlier trial by the same team which concluded that magnesium was not a bronchodilator, where 4 different doses of

nebulised magnesium sulphate was given to 20 control subjects and 19 asthmatics (mean age 42, mean FEV_1 2.3L, 66.7% predicted. All were on inhaled steroids and 3 used oral theophyllines). There was no significant difference in the mean change from baseline in FEV_1, FVC or Vmax25 (flow at 25% FVC).[67] No definite explanation is provided for why there is a differing result between the studies or for why magnesium did not alter airway reactivity to histamine. The second, smaller study with 10 non-smoking asthmatics with a mean FEV_1 of 2.38L, 8 of whom were on oral steroids, showed that nebulised magnesium actually lowered PD_{20} FEV_1 to both AMP ($p=0.023$) and, more significantly, histamine ($p=0.01$). Again, no definite conclusions are reached as to why this occurred and its apparent incongruity to prior experiments by Rolla[56, 57] was noted by the authors.[68] It is interesting to find that a different paper accepted at the same time showed magnesium to have a significant effect on the bronchodilator response, though the bronchoconstrictor agent was sodium metabisulphate rather than histamine.[69] A subsequent study by Schenk using methacholine found that 30% of asthmatic subjects given intravenous magnesium reached a normal PC_{20} 30 minutes after infusion compared to 10% in the placebo group.[70]

It has previously been stated that asthmatics tend to have lower serum magnesium levels than normal subjects.[41] Brittle asthmatics also have lower dietary intakes of magnesium, other trace elements and antioxidants than controls.[71] The reasons for this are not clear and the results may be due to the inherent weakness of a single dietary survey. However the authors also point out that many of these patients have perceived or real food intolerances, as well as the need to reduce caloric intake due to steroid

associated weight gain, such that they may alter their diets to produce nutritional deficiency. Though there is no clear evidence that magnesium supplementation improves asthmatic symptoms or objective measures of airway function, higher magnesium intake in asthmatics can lead to higher FEV_1, reduced BHR and less self reported wheeze.[72, 73]

At a cellular level, there is evidence to suggest that magnesium deficiency leads to increased levels of substance P which triggers the release of histamine and subsequently the release of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tissue necrosis factor-α (TNF-α).[74] There is also a rise in intracellular calcium.[75] This would tie in with our current knowledge about the inflammatory processes in asthma. Magnesium may indeed have a direct anti-inflammatory action, especially in clinically relevant concentrations, by attenuating the neutrophil respiratory burst through its negative effects on calcium influx.[76]

Recently, much research has concentrated on the effect of nitric oxide (NO) in asthma. It is known that when produced in high concentrations in the airway it can lead to hyperaemia, oedema and exudation, contributing to worsening asthmatic symptoms.[77] We also know that higher levels of exhaled NO correlate with markers of airway inflammation[78], and that NO levels can be use to guide treatment.[79] However, at low concentrations, NO acts as a vasodilator and smooth muscle relaxant and this may be mediated through magnesium.[80] There is also evidence to show that magnesium can

lead to increased prostacyclin production thus potentially augmenting vasodilator responses.[81]

Clinical trials of intravenous and nebulised magnesium in adults with acute exacerbations of asthma and COPD

Experimental data from as far back as 1912 suggested that magnesium relaxed bronchial smooth muscle of animals[82], but it was not until 1936 that the first description of the use of magnesium salts in acute asthma in humans was published.[83] Following a report in the French literature regarding the potential use of magnesium as an anti-anaphylactic agent[84] and due to increasing realisation at the time of the similarities between bronchospasm and anaphylaxis, those with experience of scientific studies involving magnesium began using it clinically in selected patients. This led Haury to publish his studies of magnesium levels in asthmatics and reports of the successful treatment of two patients with acute asthma with intravenous and intramuscular magnesium salt. This is the first mention of magnesium treatment of asthma in the English language medical press, though he does not document whether magnesium was tried unsuccessfully on other patients.[85]

Numerous studies on the potential mechanisms for magnesium's bronchodilating effects followed, along with studies looking at magnesium and its effect on BHR, many of which have already been discussed. It was not until 1987 that the clinical use of magnesium in asthma attacks resurfaced in the literature. Given intravenously, it reportedly acted as a bronchodilator and improved subjective dyspnoea in mild asthma attacks, though the

study was unblinded and not placebo controlled.[86] In contrast to their earlier studies, Italian investigators also found evidence of improved FEV_1 when magnesium was given intravenously. Considering other studies that were to be conducted using magnesium in airways obstruction, including the author's, they also discovered that adding salbutamol further aided bronchodilatation.[87]

Another case report from the USA[88] encouraged further research, including the first randomised controlled trial. In the trial performed in Philadelphia by Skobeloff, Spivey, Mcnamara and Greenspon, 38 patients with moderate to severe asthma who attended the emergency department with an exacerbation (based only upon having an average of 3 PEFR recordings of less than 200L/min) were studied. All these patients initially received usual treatment including either nebulised albuterol or metaproterenol, followed by 125mg of intravenous methylprednisolone, a theophylline loading dose and a continuous infusion. 60 minutes after the initial nebuliser, a further nebuliser was given and if, 15 minutes after this, the PEFR was less than double the initial PEFR, subjects were then given an infusion of saline placebo in 50ml of saline or 1.2g of magnesium sulphate in 50ml of saline over 20 minutes. Physiological measurements, including PEFR were taken by an investigator at intervals up to 45 minutes post-infusion. The decision to admit was taken by the physician in the emergency department, not the investigator. Both groups were equally matched in terms of demographic data as well as usual asthma medications with 4 in the placebo group and 5 in the magnesium group on regular oral steroids. The peak expiratory flow rate (PEFR) in the treatment group increased from 225 L/min to 297 L/min compared with 208L/ min to 216 L/min in the placebo group, and this was

statistically significant. Divergence in PEFR between the two groups was seen as early as 5 minutes post infusion but became significant at 20 minutes. This continued until the end of the study period at 45 minutes. Significantly fewer patients were admitted to hospital in the magnesium group compared to those who received placebo (7 versus 15, P<0.01). There were no differences in physiological parameters such as heart rate, blood pressure and respiratory rate and no serious adverse events were reported. The authors point out that the sample size was small, which might affect the study's power, and that most patients were black and female, limiting its generalisability. However, as this was the first randomised controlled trial looking at magnesium in acute asthma, it is a significant moment in the research of magnesium use in acute asthma.[89] Noppen subsequently confirmed the bronchodilator effect of magnesium in severe asthma though the trial was small (6 patients) and unblinded. Known asthmatics were given usual treatment which consisted of nebulised albuterol, 40mg intraveneous methylprednisolone, intravenous theophylline and antibiotics if there was infection. If FEV_1 was <40% of predicted then they were considered for enrollment. The next morning albuterol was stopped and they had a baseline FEV_1 taken followed by in infusion of 3g magnesium sulphate over 20 minutes. Spirometry was performed at the end of the infusion and again 30 minutes later at which point nebulised albuterol was given, followed by repeat spirometry. This process was replicated the next day. Both bronchodilators improved FEV_1 significantly (0.94L to 1.3 L for magnesium, 1.13L to 1.72L for albuterol, both p values <0.05), but albuterol was better than magnesium (p<0.02). The authors could not account for this apart from suggesting that the use of both had additive bronchodilating

effects and also that they studied a more severe group of asthmatics than other investigators.[90]

With the potential effects of magnesium on acute asthma slowly being realised it was no surprise that clinicians turned to using magnesium in the critical care setting, especially with hypomagnesaemia being so common in ICU patients. Trials specifically looking at this have not been performed but there are a number of case reports suggesting that intravenous magnesium decreases airway resistance and peak airway pressures, as well as facilitating weaning in ventilated asthmatics.[91-93] However, waiting to treat with magnesium until after a patient has been intubated is a risky and expensive undertaking and the priority has therefore been attempting to stabilise patients in the emergency department with a view to potential discharge. Schiermeyer showed that rapid infusion of 2g of magnesium sulphate obviated the need for intubation in asthmatics with impending respiratory failure, but only two patients were treated in this way.[94]

Two important studies published in the early 1990's seemed to cast doubt upon the apparent benefits of intravenous magnesium in an emergency setting. The first involving 120 patients was not physician blinded and the patients were randomised to treatment or placebo by the "odd or even' days method. 2g of intravenous magnesium sulphate was given following usual treatment and within 45 minutes of standard treatment initiation. This is sooner than in the Skobeloff study in which magnesium infusion did not start until at least an hour had elapsed from initial treatment. No differences in PEFR or admission rates were noted between the two groups.[95]

The second study, though smaller, was a double-blinded, placebo controlled trial in which randomisation occurred via computer, more in line with current studies. Again, neither magnesium infusion nor 2g bolus resulted in any meaningful effects on PEFR or FEV_1 in moderate to severe asthmatics.[96] In their discussion, the authors make an interesting point when comparing their study to Skobeloff's. The earlier study had a preponderance of women which was not as marked in the latter. However, there was still a trend, albeit non-significant, towards responsiveness to magnesium infusion in females. There are well documented hormonal influences on airway reactivity[97] and oestrogen can augment the bronchodilator effect of magnesium.[98] To date, no further trials have been performed looking at magnesium's effect on bronchial smooth muscle solely in females.

Later studies have tended to be more positive in their outcomes regarding the utility of magnesium in an emergency setting, with a definite trend towards its use in more severe cases. A well conducted trial, again using 2g of intravenous magnesium sulphate showed a non-significant trend towards reduced admission rates in the magnesium arm and no difference between placebo and treatment groups in the change in FEV_1. However, when a sub-group analysis was performed (the decision to do this was taken prior to unblinding but patients were randomised as one group), looking at those that were classed as severe (baseline FEV_1 <25% predicted on presentation) versus moderately severe asthmatics (baseline FEV_1 25-75% of predicted at presentation), the admission rates were much less in the severe group compared with placebo (33.3% as opposed to

78.6%, p= 0.009) and there was also a significant improvement in FEV_1 (p=0.014 at 120 minutes). The reason for this difference was not clear but the authors suggested that those with severe asthma may be less responsive to β-agonists.[99]

At the end of the twentieth century therefore, despite some evidence that magnesium might be beneficial, further trials were needed as two of the main studies had shown little or no benefit. Two systematic reviews at the time concluded that there was no place for the routine use of magnesium in an emergency setting, though the second did suggest its use in severe asthma.[100, 101] All studies, including systematic reviews concluded that magnesium was safe. Although it had been shown that magnesium could potentiate terbutaline's effects on diastolic blood pressure and calcium levels, the magnitude of the effects were modest.[102] Potentially serious was magnesium's capability to decrease R-R interval and increase QTc interval in league with terbutaline, but these are thought to be offset by its known antitachydysrhythmic effects, particularly in patients post myocardial infarction.[103] It is important to recognise however that the latter trial was not set up to study asthmatic subjects.

Two Thai studies further clouded the issue by reporting the statistically nonsignificant effects of 2g intravenous magnesium sulphate on severity scores. Airway obstruction was not measured and both studies were small.[104, 105] Additionally, the second study suggested that nebulised salbutamol alone had no effect on serum magnesium and those improvements that were seen in severity scores were independent of rises in serum magnesium. This is in slight contrast to an earlier study suggesting that repeated

nebulisation of β-agonists could lead to significant decreases in serum electrolytes, including magnesium.[106] If this is true, it has certainly not been borne out by an excess of adverse events related to magnesium in trials to date.

The final published trial using intravenous magnesium in asthmatics with an $FEV_1 \leq 30\%$ of predicted on arrival in the emergency department showed a small but significant benefit in favour of magnesium over placebo. Regression analysis showed a greater effect compared to placebo when the FEV_1 was <25% predicted with a mean difference of 9.7% at 240 minutes (p=0.001). There was no benefit compared to placebo in the group with an FEV_1 >25% predicted on arrival.[107]

In 2003, intravenous magnesium sulphate was first recommended by the BTS in its guidelines on acute severe asthma.[108] However, only one reference was included in relation to this, that being the earlier systematic review by Rowe. The results of this review are slightly equivocal stating that magnesium only "appears" to be beneficial in severe acute asthma. Subsequently there have been no further published trials using intravenous magnesium in adults, but it continues to be part of the updated BTS guidelines[15].

With evidence suggesting that intravenous magnesium was beneficial in the treatment of acute asthma, especially those with more severe attacks (and possibly females), researchers turned to the potential use of nebulised magnesium as this would be easier to administer. A French study, published in abstract form, suggested that inhaled

magnesium, in addition to β-agonists, improved severity scores in the emergency department as measured by the Fischl[109] index. There was an effect in mild and severe asthmatics but the other treatments given to the two groups differed markedly and there also seems to have been a significant placebo response.[110] Previous trials had shown that inhaled magnesium had an effect on BHR and to a lesser extent FEV_1 [56, 57, 111], though its precise role was still unclear. In the first major study using nebulised magnesium, Mangat showed that it had a significant bronchodilating effect, similar to that of salbutamol.[112] Further work confirmed that when used as a vehicle for nebulised salbutamol, isotonic magnesium significantly improved bronchodilator response, especially in more severe asthmatics.[113]

Another randomised placebo-controlled trial on 74 patients in 2002 failed to show any statistically significant effect on FEV_1 when magnesium was nebulised immediately after albuterol 3 times in an hour in mild to moderate asthma exacerbations as defined by PEFR between 40-80% of predicted. However, p-values are not quoted in the published paper. [114] A further study, albeit small and single-blinded also failed to show an effect of isotonic nebulised magnesium over and above that of salbutamol. Average PEFR's however were above 44% of predicted and nobody had PEFR< 30% predicted on arrival.[115]

More positively, a New Zealand study showed significant differences in the nebulised magnesium group compared with placebo. The study was a double-blinded, randomised placebo-controlled trial. 58 subjects with a known history of asthma and who presented to

the emergency department with an exacerbation in which their FEV_1 was <50% of predicted were randomised. Patients requiring immediate intubation, those with hypotension (systolic blood pressure <100mmHg), those diagnosed with pneumonia or COPD at admission or patients with known cardiac or renal disease or current pregnancy were not enrolled. 28 out of 30 patients in the magnesium group and 24 out of 28 in placebo group completed the protocol. 6 subjects were excluded from the analysis as they were found to have a diagnosis of either pneumonia or COPD. The initial power calculation based upon a standard deviation of 0.4L for FEV_1, suggested that 29 patients were needed in each group to detect an effect size of 0.3L, with 80% power at a two-sided α of 0.05. Patients were equally matched for demographic data, baseline and presentation FEV_1, smoking status and beta-agonist use. The saline group had a higher daily inhaled steroid use (1680µg/day compared to 1258µ/day), but it is unclear whether this is of statistical significance.

Following baseline spirometry, potential participants were given 2.5mg salbutamol by nebuliser as well as 100mg intravenous hydrocortisone. 30 minutes after this, patients were randomised if FEV_1 was <50% of predicted. Patients were then given by nebuliser either 2.5 mg salbutamol mixed with 2.5ml isotonic saline or 2.5ml isotonic magnesium sulphate on three occasions at 30 minute intervals. Physiological parameters and spirometry were measured every 30 minutes. At 90 minutes the mean difference in FEV_1 (the primary outcome variable) between treatment and placebo groups was 0.37L ($p=0.003$). Post-hoc analysis showed that those with FEV_1 <30% predicted on arrival had an even more significant difference when given magnesium (0.64L, $p<0.0001$). There

was also a difference in admission rates between the magnesium and placebo group which reached statistical significance (12 versus 17, $p<0.04$).[116]

Subsequently, two systematic reviews of nebulised magnesium trials, using broadly similar data, reached slightly different conclusions. Both reviews comprised of only six studies, with five appearing in each review. There was a significant heterogeneity between studies with mixed adult and paediatric study populations. In Villeneuve's review, which was mainly descriptive and did not attempt any formal meta-analysis, five studies were double-blinded prospective randomised trials and the other single-blinded. The authors suggest that the bronchodilator dosage regimes did not mirror common practice in that the doses of salbutamol were small and sometimes titrated and no anticholinergics were used. Additionally, the dosage of magnesium varied between studies. On the whole, magnesium appeared to work better when given with a β-agonist but the primary outcomes tended to be related to lung function, whereas in the emergency department, final patient location is more clinically relevant.[117] Blitz also excluded non- randomised trials and it was unclear for only one of them the exact nature of the blinding. This review included statistical analysis as well as a description of the studies. For pulmonary function tests, magnesium with or without a β-agonist worked better than β-agonist given alone for lung function. They calculated a standardised mean difference (SMD) of 0.37 ($p=0.006$). Magnesium's effect was similar in severe and non-severe asthma. For admission rates, magnesium alone was superior to β-agonist alone, especially in severe asthma with a relative risk (RR) of 0.61 ($p=0.05$), but whether this has clinical significance is another matter. Additionally, ipratropium was not used in the trials, even

though this tends to be standard practice. Despite these caveats, this review, (which was co-authored by some of those involved in the more successful New Zealand study described earlier), though agreeing that heterogeneity was an issue, tended towards the positive, especially with respect to nebulised magnesium's role as an adjunct to β-agonists. They concluded there were definite benefits, especially in pulmonary function measurements in those with more severe asthma.[118]

Two published trials since that review have shown markedly differing results in those with acute asthma. The first failed to show a benefit when magnesium was added to standard treatment. During the trial, 100 patients presenting to the emergency department who were known to have asthma or whose history and examination findings were suggestive of asthma were randomised equally with one group (A) receiving magnesium and salbutamol, the other (B) only salbutamol. Each group had 3 nebulisations at 20 minute intervals. PEFR did increase significantly in both groups (from 118.6 l/min to 237.8 l/min in group A and from 111.6 l/min to 236.2 l/min in group B. P value for both groups 0.0001) but the lack of additional benefit seen in the magnesium group suggests it was due to an effect of β-agonists. Interestingly, despite the severity of the asthma, both groups had serum magnesium levels at baseline within the normal range. The only caution with this study, which the authors point out, is that it was underpowered to detect true differences in PEFR and as such, possible differences between the groups may have been masked by the small sample size, despite it being the largest trial yet undertaken with nebulised magnesium.[119] In the second trial, which randomised 60 patients with acute asthma presenting at the emergency department, an intravenous dose of steroid was

followed by nebulisation with albuterol and ipratropium or 333mg of magnesium sulphate. The magnesium group had higher post-bronchodilator FEV_1 and oxygen saturations and was less likely to need to be admitted (5 versus 13, $p<0.047$).[120]

Finally, a further systematic review looking at all trials involving magnesium in asthma, both intravenous and nebulised, adult and paediatric, suggested that further trials were required in adults using both delivery modalities before any firm conclusions could be drawn. Again, they revisited the trials from the earlier reviews and combined them with the more recent studies. Evidence of benefit was weak on the whole, but those given magnesium tended to have better pulmonary function tests at the end than controls, with an SMD of 0.17 ($p=0.09$), and admission data trended towards benefit, though it did not reaching statistical significance as RR was 0.68 ($p=0.06$). They conclude,

"We can neither clearly state nor rule out a useful role for either nebulised or intravenous magnesium sulphate in adults"

However, they do go on to say that due to the low risk of serious side effects, intravenous magnesium could reasonably be tried in any adult with life-threatening features, as possible benefits would outweigh the risks.[121]

Clinical trials of intravenous and nebulised magnesium in AECOPD

Little work has been done specifically looking at the effects of magnesium in COPD. It is unclear exactly why magnesium levels may be important in COPD but loop diuretic and steroid use may be a factor.[40] Additionally, nutritional status in COPD is often poor[122] and there is some evidence to suggest that a diet higher in fruits and grains and lower in alcohol can lead to a small (139ml) but significant ($p<0.001$) improvement in FEV_1 in subjects with COPD.[123] There is little evidence to suggest that smoking in itself reduces serum magnesium, but it is well described that in controlled situations, smokers with higher magnesium levels, smoke less cigarettes than those with lower levels.[124] This is probably due to a magnesium mediated reduction in noradrenaline release within the brain.[125]

There are only three published studies though all are prospective randomised controlled trials. The first involved the administration of 1.2g of intravenous magnesium sulphate to patients with severe COPD with an exacerbation, in addition to usual treatment. The PEFR was significantly higher in those receiving magnesium compared to placebo at both 30 and 45 minutes. There was also a trend towards reduced hospitalisation in that group. However, in contrast to the stable group of patients in the earlier quoted study by Do Amaral, indices of respiratory muscle strength did not improve, suggesting that

magnesium acted solely as a bronchodilator. Again, there were no significant adverse effects associated with magnesium therapy.[126] Another trial with small numbers suggested that intravenous magnesium had no bronchodilatory effects when given alone in COPD exacerbations but that it did enhance the bronchodilating effects of β-agonists.[127] Recently, a further study randomised 62 patients to multiple nebulisations of terbutaline and ipratropium or terbutaline plus a one-off bolus of 1.5g magnesium followed by nebulised terbutaline and magnesium. There was no difference in hospital admission or intubation rates.[128] Hogg presented a small randomised double-blinded placebo-controlled study involving 24 patients given 1.2g of intravenous magnesium sulphate in abstract form. Results were promising, suggesting an improvement in breathlessness (as measured by Borg score) and a reduced length of stay in those given magnesium.[129]

Prognostic markers and severity scores in stable COPD and during exacerbations

Much work has been done in the last 30 years on the search for biomarkers of prognosis and disease progression, both in stable COPD and during exacerbations. A great deal of this has been due to the development of immunohistocytochemistry and the discovery of cytokines and their link to inflammatory processes. However, before we are able to look properly at biomarkers in exacerbations, we must first be able to define what constitutes an AECOPD. COPD exacerbations are very heterogenous, making definition difficult. They have many different aetiologies[130] and are treated in contrasting ways.[131] Additionally, many exacerbation events resolve spontaneously or with home management and are not reported to medical practitioners.[19]

Attempts have been made to reach consensus regards the definition of COPD[132] and international guidelines have been developed to this end.[133] As described, COPD can be defined as

"..(is) a common, preventable and treatable disease, is characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.

Exacerbations and co-morbidities contribute to the overall severity in individual patients."[1]

COPD is an inflammatory disorder which is mainly neutrophilic in character.[134] This ultimately leads to airways obstruction which may be irreversible, or partly reversible by bronchodilators.[135] As described, there has been much interest in attempting to stratify patients with COPD into prognostic groups. This has been done on the basis of lung physiology, anthropometric measurements, markers of inflammation (mainly in blood and exhaled breath), and examination of sputum and histopathological specimens. One of the best known prognostic scoring systems in stable COPD is the BODE index (**B**ody Mass Index, Airflow **O**bstruction, **D**yspnoea and **E**xercise Capacity Index) which was devised and validated by Celli and colleagues.[136] Initially, 207 patients were evaluated and out of a number of variables, the four chosen had the strongest association with mortality. Subsequently, in a further 625 patients, the index was validated by giving points for each threshold value of the variables. The final index ranged between 0 and 10. For every one point increase in the score, the hazard ratio for death was 1.34 and for death from a respiratory cause 1.62. BODE index was also better able to predict death than FEV_1. Recently, Ong has shown that the index can predict hospitalisation in COPD[137] and Marin has shown that it can also be used to predict the number and severity of exacerbations.[138]

Many potential biomarkers have now been identified and well studied with regards to COPD but it is beyond the scope of this work to detail them all.[139, 140] It is now well

established that there is a link between the reduced lung function seen in COPD and ongoing systemic inflammation as measured by serum markers such as c-reactive protein (CRP), fibrinogen, TNF-α, and interleukins 6 and 8.[141, 142] Furthermore, it is well understood that COPD is a disorder with clinical manifestations beyond pulmonary inflammation and structural remodeling. Effects on body mass, especially fat-free mass (FFM), bone and wasting in muscles are all thought to be due to the systemic inflammatory response which occurs in COPD.[143]

A recent study looking at a new way of profiling serum biomarkers using protein microarray platform (PMP) technology examined 143 potential serum biomarkers in COPD. This was a case control study on 48 patients and controls and numerous analyses were performed on the data. Following univariate analysis, 43 markers differed significantly between patients and controls. Further analysis revealed 24 of these biomarkers correlated with traditional markers of severity such as lung physiology, exacerbation frequency and BODE index.[144] Whether, in time, these will become part of the prognostic work-up of COPD patients remains to be seen.

There is even less evidence regarding the clinical usefulness of measuring serum magnesium levels in COPD exacerbations. Only two published studies specifically look at whether levels predict response to treatment or can act as a future prognostic indicator for the COPD sufferer. The first study retrospectively looked at magnesium levels in 50 patients with AECOPD and 50 stable patients. Subjects were not matched for lung function and despite there being no effort made to match for age and gender, there were

no significant differences between the groups in these two aspects. Though both groups had baseline serum magnesium levels within normal ranges, the exacerbating group had a significantly lower level of magnesium. (0.77 mmol/L compared to 0.91 mmol/L) At the higher end of magnesium concentrations, the probability of exacerbating approached zero. The investigators also attempted to find a serum magnesium level below which patients were more likely to exacerbate. Statistical analysis indicated this to be around 0.85 mmol/L, giving a sensitivity of 84% and specificity of 68%.[145]

The second study also looked retrospectively at a group of patients presenting with AECOPD. They looked at 16 variables to try to discover which, if any, would predict readmission. These variables were age, sex, FEV_1, use of inhaled or oral steroids, home oxygen therapy, statin and diuretic treatment, smoking status, pneumonia and influenza vaccination rates, serum brain natriuretic peptide (BNP) and magnesium levels, duration of stay during admission and time to readmission. None predicted frequent readmission rate following multivariate analysis apart from serum magnesium level. Additionally, hypomagnesaemic patients had a shorter time to next admission, though this did not reach statistical significance.[146]

A meta-analysis in 2006 looked at biomarkers other than those found in serum.[147] Bronchial biopsies provide an opportunity to look directly at structural changes and the expression of inflammatory biomarkers which might underlie changes such as apoptosis or cell proliferation. However, biopsy of a proximal airway may not reflect changes at a parenchymal level. Additionally, two biopsies (pre and post treatment) are needed to

study an effect of treatment often requiring multiple biopsies each time. Patients with COPD often have other co-morbidities which make the procedure more risky and recruitment to biopsy studies can be difficult. Bronchoalveolar lavage (BAL) is slightly safer in COPD research[148] and can be advantageous in that it samples inflammation in the lung periphery. This can give details about cellular composition of the airways as well as any inflammatory mediators that are present. Repeat BAL can give information on the effects of treatment though to date there are few studies, and in that it still requires bronchoscopy, there remains some inherent risk. Sputum, either spontaneously produced or induced, can also give information about cellular composition and the presence of inflammatory mediators. However, it may not reflect changes in peripheral airways and there may be a problem with sample collection and degradation during analysis. The use of exhaled gases such as NO and breath condensates (EBC) has sparked interest in recent years but NO levels are affected by cigarette smoke and the technical expertise required, cost and the high variability of EBC biomarkers during repeated measurements limits their use. The authors conclude that what biomarker is used will depend on the type of study being undertaken, especially when the effects of drugs are being measured.[147]

The first major study of outcomes following AECOPD was performed by Connors in 1996 where 1016 patients were enrolled, with all of them being hypercarbic on admission. Outcomes were evaluated over a six month period. The median age was 70 and median FEV_1 0.80L (though this applied to only 131 who had had lung function testing in the preceding year). 89% survived their admission though only 26% reported good, very good or excellent quality of life at six months. Additionally, the mortality rate

of survivors was 33% at six months, increasing to almost 50% at 2 years. 50% of survivors were also readmitted in the first six months following discharge, some more than once. Physiological and serological variables associated independently with survival following multivariate analysis were acute physiology score and PaO_2/FiO_2 (arterial oxygen tension/fractional inspired oxygen concentration), which are markers of the severity of the acute illness, age, functional status in the two weeks prior to the event and co-morbidities (chronic health state), body mass index (BMI) and albumin (nutritional status) and the presence of cardiac disease as evidenced by cor pulmonale or chronic heart failure (CHF). The total direct cost of care for the patients during the index exacerbation was a staggering $16.4 million and this did not include primary care costs, social care costs or days off work. This study was the first to show on such a large scale which factors independently affect prognosis following an AECOPD.[149]

A more recent study by Garcia-Aymerich has linked worse pre-bronchodilator lung function, as defined by the GOLD criteria of the time (see table on page 3), with an increased risk of AECOPD in a cohort of 20571 patients. Those with GOLD stage 4 COPD[150] had a 25 times higher incidence of hospitalisation compared to normal controls. Additionally, hospitalisation increased all- cause mortality (Hazard Ratio 2.7) over a median 10 year follow-up period and the increase was similar across all GOLD stages. Mortality rate in this study was 50% at 5 years post AECOPD and, as alluded to above, this is irrespective of lung function. As the authors state, a COPD-related hospitalisation is a key so-called “sentinel” event in the lives of these patients.[151]

Several other studies have followed looking at a plethora of biomarkers and physiological variables in COPD exacerbation and attempting to link them with both short and long term prognosis. In a retrospective chart analysis in 2000, Dewan and colleagues studied 107 patients with AECOPD.[152] They looked at factors associated with treatment failure which they defined as the need for a second course of antibiotics within four weeks of the index exacerbation. They found that FEV_1 <35% of predicted, use of home oxygen, frequency of exacerbation, history of previous pneumonia or sinusitis and use of maintenance steroids were independently associated with failure of treatment (defined as a return visit for persistent respiratory symptoms that required a change of antibiotic in less than 4 weeks). Use of home oxygen and frequency of exacerbations were the most sensitive indicators following logistic regression analysis. Those who had more than four exacerbations over the 24 month period of the study had almost 100% chance of treatment failure. Additionally, the failure rate for a more severe Type 1 exacerbation as judged by the Anthonisen[153] criteria was higher than for a Type 3 exacerbation (see below). Age and presence of co-morbidities had no bearing on treatment success or otherwise.

Anthonisen criteria for use of antibiotics in AECOPD (where antibiotics are more useful in Type 1>Type 2>Type 3 AECOPD)

TYPE 1	TYPE 2	TYPE 3
Increased dyspnoea Increased sputum volume Increased sputum purulence	Any two out of the three for Type 1	Any one out of the three for Type 1 in addition to at least one of: Sore throat or nasal discharge in last 5 days Increased wheeze Increased cough Fever without an obvious source 20% increase in respiratory rate or heart rate from baseline

A Turkish study found that in-hospital mortality was associated with lower initial PaO_2, higher $PaCO_2$ and longer hospital stay. Longer term mortality, which approached 50% at 3 years, was associated with longer disease duration, lower PaO_2 and poor nutritional status (low albumin and BMI).[154] A further Middle Eastern study confirmed acidaemia and hypercapnia to be associated with in-hospital mortality along with disease severity, number of prior hospitalisations and co-morbidities.[155] These studies and others suggest that factors involved in mortality are fairly similar worldwide.[156, 157] However, an Indian study of 94 patients matched for age and sex, whilst noting that CO_2 was lower and PaO_2 higher in survivors rather than non-survivors, found that only hypotension on admission was independently associated with increased mortality after multivariate analysis.[158] Non-survivors though had a mean number of 604.5 pack years of smoking versus 478.42 for survivors. No comment is made whether this was statistically significant or not and there is no indication of current smoking status.

More recent studies have suggested that age is an adverse factor along with a number of clinical signs of severity such as cyanosis (which was also found by Chandra[158] after initial analysis), lower limb oedema, impaired conciousness, asterixis (flapping tremor) and the use of accessory muscles. They also derived a mortality prediction score based upon these clinical signs and reported good discrimination for mortality in the derivation and validation cohorts of their study. However, they accept the need for further prospective validation of these results in other centres.[159] It is also important to note

that no mention is made of blood gas values in the paper so it is impossible to say whether this would have added any further discriminatory power either way.

In the last few years, much more research interest has focused on the use of plasma biomarkers, including cytokines, to aid prognosis in AECOPD. Malo showed a general increase in cytokines including TNF-α, IL-6 and IL-8 as well as CRP in exacerbating subjects compared to stable COPD controls and that despite treatment with intravenous glucocorticoids, there was little decline up to 2 months after the event.[160] This suggests that inflammation continues long after the exacerbation has ceased to be a clinical problem. This has subsequently been confirmed by others [161] and it is likely related to the slow recovery in lung function following AECOPD.[162] Pinto-Plata showed however that whilst cytokine levels were high during an admission, they did fall during recovery and at 8 weeks, levels of IL-6, IL-8 and leukotriene B4 (LTB4) were significantly lower. Furthermore, the decreasing levels of inflammatory cytokines, especially IL-6 and IL-8 were correlated with symptomatic improvements in dyspnoea and a rise in FEV_1. FEV_1 improved more slowly than inspiratory capacity (IC), suggesting that reduction in dynamic hyperinflation is more important from a symptomatic basis in the early stages of treatment.[163]

Much work has gone into looking at CRP as a potential biomarker as it is easily measured and readily available as an assay in most developed countries. It is an acute phase reactant produced in the liver and elevated levels are seen in inflammatory and malignant conditions. CRP levels are known to rise in AECOPD[141] and it has been linked to lung

function decline.[164] Hurst found that out of a panel of 36 potential markers, CRP was the most selective though it was neither sensitive nor specific enough by itself. When allied with a major symptom of exacerbation (dyspnoea, increased sputum volume or increased sputum purulence), specificity improved markedly such that a CRP≥8 mg/L and one major symptom would have a 95% specificity for an exacerbation.[165] In a similar vein, Ruiz-Gonzalez showed that although a particular level of elevated CRP was associated with adverse outcomes (death in hospital or within 15 days of discharge, need for ICU transfer or development of clinically defined heart failure during hospitalisation), again it was neither sensitive nor specific enough by itself. When combined with other variables such as current smoking status, confusion and multiple co-morbidities, this greatly enhanced its ability to predict adverse outcome. However, the cut-off level of 50 mg/L is rather higher than the previous study.[166] Stolz also looked at CRP and noted it to be significantly higher during Type 1 Anthonisen exacerbations but could not conclusively link it to long term outcomes.[167] The same was true using procalcitonin but not so copeptin which is the stable C-terminal part of the vasopressin molecule precursor. Vasopressin is known to be released in infectious and shock states[168] and copeptin remains stable for several days in the serum, reflecting directly the levels of vasopressin.[169] Copeptin levels on admission predicted prolonged hospital stay and long-term treatment failure, independently of age, co-morbidity, hypoxaemia and lung function. A level of above 40 pmol/L when combined with a history of hospitalisation in the previous year increased the chances of a poor outcome. Again, age and blood gas values had no bearing on outcome although the authors do not offer an explanation why this was the case. It may be that the level of the inflammatory response during AECOPD

is a more important determiner of treatment failure than variables, such as age, which are more fixed.

Recently, serum amyloid A (SAA) has been identified as a potential biomarker in exacerbation and compared with CRP. Both SAA and CRP rise during AECOPD but SAA rises in all types of exacerbation compared to the stable state whereas CRP only rises significantly in a Type 1 exacerbation. Combining SAA with dyspnoea or Anthonisen criteria did not add to its discriminative value, but a lack of twofold rise in SAA from baseline indicated that an exacerbation could be excluded with 100% sensitivity.[170]

Perhaps of more relevance than SAA or copeptin, given its ubiquitous use in hospitals, is the measurement of cardiac Troponin T (cTnT). Two recent studies, both published in the same issue of Thorax suggest that elevated levels during AECOPD are associated with increased mortality subsequently. In a Danish study, 73 out of 99 patients had elevated levels of high-sensitivity (hs) cTnT, i.e above 14ng/L. The hazard ratios for death over a median follow-up period of 1.9 years in those with hs-cTnT levels of 14-39.9ng/L and ≥40ng/L were 4.5 and 8.9 respectively compared to those with normal levels. There was an even stronger association if the patient was tachycardic on admission.[171] Chang et al used a non-hs-cTnT test and, as such, only 16.6% (40/241) of patients had elevated levels (>0.03µg/L) during AECOPD. This still predicted mortality at 30 days (Odds Ratio 6.3) but not in the longer term. If patients also had an elevated N-terminal pro-brain natriuretic peptide (NT-proBNP), which can be associated with left ventricular failure or right ventricular overload, there was a 15-fold higher mortality at 30 days compared with

those who had normal levels of both biomarkers. In fact, NT-proBNP predicted 30-day mortality better than cTnT (Odds ratio 9.0).[172]

Subsequent to AECOPD, further exacerbations are more likely.[173] Following 340 patients for a mean period of just over a year, Spanish investigators revealed a 29% mortality rate and 63% readmission rate.[174] A prior exacerbation increased a patient's risk of a further exacerbation as did, unexpectedly, being looked after by a specialist and being on anticholinergics. However, the last two factors may well be a reflection of previous exacerbations, so called "confounding by indication". This was also seen in a previous study by the same investigators looking at risk factors for hospitalisation.[175] Encouragingly, the 2003 study showed that physical activity reduced the risk of readmission, with activity beyond 232 kcal in 24 hours almost leading to a 50% drop in expected admissions. This however is independent of whether the patient had pulmonary rehabilitation in the past, so the mechanism of this reduction is unclear. A later study showed that health status as measured by the St. George's Respiratory Questionnaire (SGRQ) was an independent predictor of readmission and that the closest relationship was seen with the activity scale, with higher levels of physical activity associated with reduced risk of readmission. There was a significant correlation between SGRQ and Hospital Anxiety and Depression (HAD) score. In those with low health status, higher HAD score was associated with an increased risk of rehospitalisation.[176]

The accumulation of evidence from biomarker studies and from other studies looking at physiological and psychological variables in COPD had led to the development of prognostic indices. The BODE index remains one of the best known but a more recent

index derived from an analysis of 12 randomised controlled trials predicts not only mortality but also COPD exacerbations and hospital episodes and which the authors suggest can be used in primary care. Most of the variables are easily measured but the quality of life (QoL) indices such as SGRQ and chronic respiratory questionnaire (CRQ) are not routinely used, even in secondary care, as the authors point out. This may make the index impractical to use in a busy clinic with limited time but further validation studies are required.[177]

The two aforementioned indices deal with the long term prognosis of stable COPD. Interest has naturally turned to short term prognostic indices in AECOPD. A review looking at 268 studies over 25 years with 142, 407 patients found that breathing rate and arterial carbon dioxide tension were significantly different between all types of exacerbations in both outpatient and inpatient settings. Other variables showed some correlations with levels or settings but were not consistent throughout. Additionally, blood gas data were absent for outpatient settings and level 2 and 3 exacerbations were merged to create the inpatient settings as most patients in these groups were hospitalised.[178] The study already discussed by Roche[159] suggested that age and certain clinical signs could predict in-hospital mortality. However, no scoring system to predict mortality during AECOPD has to this time been properly validated.

Scoring systems for other acute respiratory illnesses are well described with perhaps the best analogy being the systems in place for community acquired pneumonia (CAP). In the United States, Fine and colleagues developed and validated the pneumonia scoring

index (PSI).[21] By looking at patient demographics, co-morbid states, physiological variables and laboratory and radiographic finding on admission, a score is built up allowing the physician to discriminate with a reasonable degree of certainty who might be suitable for outpatient treatment, The main problem is that due to its dependence on radiographic and laboratory analyses, it is unsuitable for use in primary care. In the UK and Europe, the CURB-65 score has been introduced.[20] Patients score one point each for a new confusional state, urea > 7 mmol/L, respiratory rate > 30/min, low systolic (<90 mmHg) or diastolic (< 60 mmHg) blood pressure and age > 65 years. Risk of mortality varies between 0.7% for a score of 0 to 57% for a score of 5. This allows the physician also to identify those who might be suitable for treatment at home. It is much easier to use than the PSI and has been modified for use in primary care by the removal of urea to become CRB-65. Comparisons between the PSI and CURB-65 scores found both to be equally as effective in most situations [179], but the simplicity of CURB-65 is preferred by the BTS. Despite this, neither is foolproof and caution needs to be taken, especially when applying them to a young patient who may be quite significantly compromised even if their scores do not reflect it.[180]

As yet, there is no validated or recognised clinical scoring system for AECOPD. However, an audit in a New Zealand hospital looking at all COPD related admissions in May and October of 2004 suggested that as well as low BMI, an increased CURB-65 score led to a higher mortality for those with a score ≥ 3 as compared to those with a score of 0 or 1. However the score was applied retrospectively which may have introduced bias and the numbers in the study were small. There was also a significant

exclusion rate due to coding error and the two chosen months may not have been representative of the year as a whole[181]. The authors have followed this up with a recently published prospective study where CURB-65 was calculated on admission for 252 consecutive patients with AECOPD. Complete 30-day data was collected on 249 patients and of these, 4.8% died in hospital and the 30-day mortality was 8.4%. Scores of 0-1 were classified as low risk; a score of 2 meant a moderate risk and a score of 3 or above signified a high risk of death at 30 days. Mortality rates respectively were 2%, 6.7% and 21.3% and the differences in death rates between groups was highly statistically significant (p=0.001). These are very similar figures to those found in some pneumonia cohorts when looking at CURB-65 score and mortality.[182]

Pre-hospital care in AECOPD: The use of oxygen

Should a patient suffer from an AECOPD requiring hospitalization, transfer is often accomplished by ambulance where oxygen is frequently provided. Patients may have oxygen themselves at home which in the UK this is now generally provided via a fixed flow concentrator. Oxygen is prescribed in a formal way following a thorough assessment of the patient's needs. This is known as long-term oxygen therapy (LTOT), after definitive studies showed a survival advantage in selected patients with COPD.[183, 184] Recent guidelines have discouraged the use of oxygen cylinders as the evidence for the benefits of short burst oxygen therapy (SBOT) are not conclusive.[185] Given this, patients are rarely now able to alter the flow of oxygen they receive at home.

Oxygen remains one of the most commonly used drugs in medical emergencies, not just AECOPD, and around 34% of all ambulance journeys involve its use.[186] In AECOPD, oxygen is given to reduce breathlessness and also to correct and prevent hypoxaemia. However, it has been recognised for over 50 years that high concentrations of oxygen can have adverse effects in AECOPD, primarily through an increase in arterial $PaCO_2$.[187] Standard teaching in medical schools, including the author's own, was that this was due to a reduction in hypoxic drive caused by the sudden increase in PaO_2. Whilst this may occur, the most important mechanism is now thought to be due to an increase in ventilation/perfusion inequality caused by release of hypoxic vasoconstriction.[188, 189]

A further analysis of the physiological principles involved is not within the scope of this thesis but whatever the mechanism that leads to hypercarbia, high concentrations of oxygen can also cause hyperoxia which can lead to worse clinical outcomes, including a higher likelihood of requiring assisted ventilation.[190, 191] Additionally, it is known that even in healthy subjects, hyperoxia can cause reduced coronary and cerebral blood flow as well as decreased myocardial oxygen consumption.[192, 193] It is unclear whether these effects are more pronounced in those with COPD, who have an increased risk of vascular disease.

The recent guideline on emergency oxygen use in adults formulated by the BTS has provided a valuable reference point for physicians and first responders alike in deciding on appropriate oxygen therapy when approaching patients with medical conditions causing hypoxia, including AECOPD. Whilst generally recognising the potential benefits of high oxygen concentrations in critical illness and recommending immediate administration in this circumstance, it cautions its use in conditions, such as COPD, where there is a risk of hypercapnic respiratory failure and states that achieving normal or near-normal should not be the goal in this group.[185]

The danger of incorrectly prescribed or monitored oxygen therapy was officially recognised in the UK in 2009 by the National Patient Safety Agency (NPSA) in its report on oxygen safety in hospitals. It was acknowledged that since 2004 there had been 281 serious incidents, including 9 deaths involving prescription errors or omissions, poor monitoring, problems with oxygen administration and faulty or missing equipment.[194]

For its work in the highlighting the perils and pitfalls of oxygen prescribing, the BTS was jointly awarded the National Patient Safety Award for Patient Safety in Clinical Practice in 2011.

Until recently, there was little evidence in terms of randomised trials comparing high flow or high concentration oxygen (HCO) with controlled or titrated oxygen therapy in AECOPD. Much of the earlier work consisted of case series and audits of oxygen use. Earlier versions of national oxygen guidelines attested to this dearth of evidence and erred on the side of avoiding severe hypoxaemia, suggesting an initial oxygen concentration of 40%, whilst accepting that the evidence either way was sparse and the recommendation was therefore based upon expert opinion.[195] In a later audit, Durrington commented that this was

> *"... an extraordinary state of affairs....."*

considering how common AECOPD is.[190] However, prior to 2004, it had been recognised that prolonged ambulance transfer, particularly in rural areas, posed a greater risk of hypercapnia, and thus tighter control of oxygen therapy may be appropriate.[196]

A pilot study that year suggested that lower arterial oxygen tension might indeed be harmful with a group of exacerbating patients in whom PaO_2 was not allowed to rise above the equivalent of 50mmHg tending to have worse outcomes than a group with a

maximum PaO_2 of 68mmHg, though this was not statistically significant.[197] However, as Howard noted in a review of oxygen toxicity, neither group were allowed to achieve normal PaO_2 values and translating the PaO_2 values to the oxygen dissociation curve suggests that the lower PaO_2 group had saturations of 74% compared to 89% in the higher group.[198] The latter value is most consistent with recent guidelines.[185]

Furthermore, an audit conducted in Norwich clearly showed that exacerbating subjects receiving HCO in the ambulance and on arrival in hospital had higher rates of respiratory acidosis and other complications, including assisted ventilation and death, than those who had oxygen concentrations of ≤28% throughout the study period (64.7% versus 25.2%, $p<0.05$). A second audit showed that intervention can change practice such that fewer patients received HCO, although the complication rate was unchanged. However, those who spent more than 30 minutes in an ambulance and received HCO had a far higher complication rate than those on shorter journeys who had lower oxygen concentrations delivered (60% versus 19.4%, $p<0.05$). Causation could not be proved as it was an audit, not a randomised controlled trial. [190] In a similar audit in New Zealand, higher oxygen flow and PaO_2 at presentation to the emergency department were associated with poorer outcomes. Other pre-existing factors such as home oxygen or nebuliser use, previous respiratory failure or previous ventilation, which could point to worse functional status pre-exacerbation, were also associated with poor outcomes at exacerbation.[199] Earlier, Denniston had shown a mortality rate of 14% in a group of 57 out of 97 exacerbating subjects who had received >28% oxygen, compared to 2% mortality in those who did not receive HCO.[200]

The first randomised controlled trial comparing titrated oxygen with HCO in presumed AECOPD was published in 2010. It was conducted in Tasmania where HCO treatment was the default standard within the local ambulance service at the time. Accordingly, the local ethics committee waived patient consent and interestingly, paramedics rather than patients were the units of randomisation. Just over half the 405 patients were known to have COPD. Subjects received oxygen titrated to saturations of 88-92% with nebulisers driven by air, or HCO at 8-10L/min and nebulisers driven by oxygen (6-8L/min). Despite a high rate of protocol violation (56% in the titrated arm, where subjects received HCO which the authors conclude was down to the entrenched attitudes of emergency care providers), those subjects receiving titrated oxygen had a 58% lower mortality compared to the HCO group. In those with known COPD, the reduction was 78%. Additionally, there was a significantly lower rate of respiratory acidosis, although the authors bemoan as a limitation of the study a low rate of arterial blood gas sampling. Again, they felt that entrenched practices were, in part at least, to account for this. The authors were unable to tease out whether any in-hospital change to the amount of oxygen delivered had any effect on outcomes as this was beyond the scope of the study, but felt that any change would have reduced the differences between the treatment arms, thus leading to an underestimation of the risk associated with HCO.[201]

Recognising that nebulisers were, and indeed still are, almost universally used by paramedics when treating AECOPD, Gunawardena studied changes in arterial PaO_2 and $PaCO_2$ in 23 inpatients, including asthmatics, with chronic airways obstruction.

Comparison was made between the rise in CO_2 in the subjects when air or HCO was used as the driving gas. Those who normally retained CO_2 and who were therefore most at risk of developing respiratory acidosis had a mean $PaCO_2$ rise of 7.7mmHg when HCO was used as a driving gas for 15 minutes. There was no rise in $PaCO_2$ when air was used. There was no significant rise in $PaCO_2$ with HCO or air in subjects with normal baseline CO_2. As the $PaCO_2$ returned to normal within 20 minutes of stopping the nebuliser, the authors concluded that caution should be exercised when using oxygen as a driving gas in those with baseline CO_2 retention.[202] However, a subsequent Australian pilot study using 6L/min of oxygen as a driver (though with no control arm), concluded that despite a mean rise of 6.7mmHg (from 59.7 to 66.4) this was neither statistically or clinically significant. They concluded that HCO may be safe in chronically hypercapnic subjects but counseled the need for further studies.[203]

CHAPTER 3

STUDY SETTING

Setting

All the studies described in this thesis were undertaken under the auspices of MRINZ, which is an independent medical research organisation established in 2001. It is based in Wellington, the capital city of New Zealand, which is located at the southern tip of the North Island.

MRINZ was initially run out of offices in the central business district but in 2010 moved to a purpose built unit co-located within the new Wellington Regional Hospital (WRH). The unit contains an inbuilt respiratory laboratory and MRINZ has access to a Phase 2 clinical trials unit with 14 beds as well as the Clinical Measurement Unit (CMU), which encompasses respiratory, cardiac and neurophysiological testing.

Clinical trials were undertaken in WRH, either in the Emergency Department (ED) or CMU. Subjects were also recruited to the magnesium study at the Hutt Hospital ED, which serves the population of the Hutt Valley to the north of Wellington

CHAPTER 4

SUBJECT CHARACTERISTICS

Patients and Ethnicity

According to 2006 census figures, almost 449,00 people live in the Wellington district region with just over 55,000 (12.8%) classifying themselves as Maori-the original inhabitants of New Zealand. A further 8% are from other Pacific Island nations.
Maori and Pacific Islander populations tend to be disadvantaged compared to other populations within New Zealand although they are, broadly speaking, better off in Wellington than Maori populations elsewhere in New Zealand. For instance, the median Wellington income for people over the age of 15 in Wellington in 2006 was $28,000. Median Maori income was $24,100 in Wellington compared to $20,900 for Maori elsewhere in New Zealand. However, Maori unemployment in Wellington stood at 10%, compared to 5.2% for other populations. 39.9% of Maori in New Zealand and 32.8% in the Wellington region left school with no qualifications, compared with a figure of 19.8% for the Wellington region as a whole.
Wellington Maori also tend to be younger (male median age 23.1 years compared with 35.3 years for the whole population and only 3.3% are over 65 compared to 11.5%).[204]

In New Zealand as a whole, smoking prevalence in those above the age of 15 is around 26%, but it is 50% in some Maori populations. The average incidence of COPD in 2004 was 120 per 100000 people, but again the figure was higher in Maori (285/100000).[205] In the Wellington area, a recent study showed that out of 736 people invited for health screening, 16% of the total and 23% of Maori had previously undiagnosed COPD.[206]

Total direct costs of healthcare for COPD have been estimated to be between $102 million and $192 million. In 1999, COPD accounted for 7400 (1.05%) of all coded discharges from public hospitals and there were 1443 deaths due to COPD in New Zealand (5.1% of the total).[205] Unfortunately, more accurate up-to-date figures are not available.

Medical research involving Maori

For all clinical trials conducted in New Zealand there is a specific requirement to consider the impact the proposed research will have on the Maori population and to consult with them (to varying degrees depending on how specific the research is to Maori issues) before embarking on a study. This is doubly important when a trial involves removal and/or retention of blood or tissue samples as some Maori populations totally reject research which involves genetics.[207]

As far as the trials described here are concerned, there were no difficult issues to resolve. Consultation was undertaken with the assistance of Dr. Matire Harwood, a researcher affiliated with MRINZ with a special interest in Maori health, who confirmed that no special dispensation or wider consultation would be required.
Blood samples were taken either as part of usual medical care or were used for a specific test which was explained in the consent form. No samples were retained and all were disposed of according to local laboratory protocols.

CHAPTER 5

STATISTICS AND ETHICS

Statistics

Statistical analysis of the studies was undertaken using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) by Dr. Mark Weatherall, University of Otago.

Ethical approval

Where relevant, ethical approval was sought and gained through the Central Regional Ethics Committee, apart from the CRB-65 study which was based on historical audit data. Further approval for the use of WRH's CMU for research purposes was granted by Dr. Collin Feek the medical director at WRH. With the exception of the CRB-65 study, the trials were registered with the Australia and New Zealand Clinical Trials Registry.

CHAPTER 6

METHODS AND MATERIALS

Spirometry

Spirometry was performed using a hand-held spirometer (Micro Spirometer, Micro Medical Ltd, Rochester, UK). Where possible, the subject was asked to perform three attempts and the best was recorded. Spirometry was performed in the sitting or standing position, depending on how unwell the subject was but all three attempts by the same subject were performed in the same position. Prior to performing spirometry independently, I was provided with training by a respiratory scientist (Mr. Mathew Williams).

Arterial Blood Gases

Arterial blood gases were performed during the nebulised magnesium study and as part of the oxygen-driven versus air-driven nebuliser study. This was done with the subject breathing room air or oxygen if required. Samples were obtained by radial puncture with a 22 gauge needle and analysed immediately (Radiometer ABL800 FLEX, Copenhagen, Denmark). If the initial attempt was unsuccessful, a second attempt would be made using 2-3ml 1% lignocaine local anaesthetic for patient comfort. Some of the subjects recruited into the nebulised magnesium trial had already had blood gases performed by ED staff prior to an investigator seeing them.

Oxygen Saturations

The oxygen saturations of study subjects were monitored during the nebulised magnesium and air-driven versus oxygen-driven nebuliser study with a probe on the subject's finger. (Avant 2120, Nonin Medical, Minnesota, USA).

Nebulisation

Nebulised drugs were delivered using a portable high flow air-compression device (Portaneb, Respironics, Murrysville, PA, USA) unless otherwise stated in the study protocols.

Height and Weight

Height was measured using a standard wall-mounted measure. However, due to the physical condition of some of the subjects in the nebulised magnesium trial, it was not always possible to accurately measure this in all participants. In these cases, height would be estimated by the investigator or by direct questioning of the subject. Standard conversion tables were used for non-metric heights. Weight was measured in the CMU using calibrated scales (BWB 620, Tanita Corp., Illinois, USA).

Transcutaneous carbon dioxide measurement ($_tCO_2$)

The arterial partial pressure of carbon dioxide ($PtCO_2$) was estimated with a $PtCO_2$ monitor (TOSCA 500, Radiometer, Basel AG, Switzerland) during the air-driven versus oxygen-driven nebuliser study. This was done by cleaning the earlobe with an alcohol swab and then, after allowing the earlobe to dry, a probe was attached using a clip and contact gel. A minimum of 10 minutes was allowed for arterialisation to occur and $PtCO_2$ readings to stabilise.

The $PtCO_2$ monitor relies on the fact that CO_2 diffuses easily through the skin. The sensor is warmed to 42^oC (and subjects are informed of the fact they may feel a warm sensation) which leads to local hyperaemia resulting in an increased blood supply to dermal capillary beds.

CHAPTER 7

USE OF NEBULISED MAGNESIUM SULPHATE AS AN ADJUVANT IN THE TREATMENT OF ACUTE EXACERBATIONS OF COPD IN ADULTS: A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

USE OF NEBULISED MAGNESIUM SULPHATE AS AN ADJUVANT IN THE TREATMENT OF ACUTE EXACERBATIONS OF COPD IN ADULTS: A RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED TRIAL

INTRODUCTION

Magnesium has a key role in numerous physiologic processes.[23, 24] Important underlying mechanisms of action of magnesium include calcium antagonism via calcium channels, regulation of energy transfer (such as the production and function of ATP) and membrane stabilization. In the airways, magnesium is a bronchodilator through various mechanisms including an inhibitory effect on bronchial smooth muscle contraction mediated by calcium[63] and an inhibitory effect on acetylcholine release from cholinergic nerve terminals[27] and histamine from mast cells.[63]

Experimental studies have variably demonstrated a benefit of magnesium in acute severe asthma since the first report over 50 years ago.[83] Magnesium has been administered via the intravenous route [70, 89, 99, 107]and via nebuliser[112, 113, 116, 118], with interest in the latter route of administration because of practical and potential safety advantages. In a randomised double-blind placebo controlled trial, it has been shown that isotonic nebulised magnesium sulphate results in an enhanced bronchodilator response in severe exacerbations of asthma.[116] However there are fewer studies which have addressed the effects of magnesium in chronic obstructive pulmonary disease (COPD)[49, 50, 126-129]

even though asthma and COPD share some pathophysiologic characteristics (such as bronchial hyper-responsiveness) as well as numerous therapies, particularly bronchodilator treatments.

As previously discussed, I could find only six studies investigating the bronchodilator efficacy of magnesium sulphate in COPD. Three studies have reported positive efficacy of intravenous magnesium in the setting of acute exacerbations of COPD (AECOPD), improving patient symptoms and reduced length of stay[129], increasing peak expiratory flow rate (PEFR)[126] and increasing forced expiratory volume in one second (FEV_1).[127] This last study only showed an effect as an adjunct to inhaled $beta_2$-agonist. A fourth study compared the effect of nebulised terbutaline and a bolus of intravenous saline against nebulised magnesium combined with one bolus of intravenous magnesium in a randomised, double-blinded trial of 124 patients. There was no difference in the primary combined outcome of hospital admission, intubation and hospital death rate compared with terbutaline and ipratropium although the latter group showed a greater improvement in peak expiratory flow. Unfortunately, no power calculation was performed and it is therefore difficult to comment on the significance of these results.[128] Two studies in stable COPD have been undertaken, reporting a reduction in hyperinflation with intravenous magnesium[49] and an increase in FEV_1 when magnesium was added to nebulised salbutamol.[50]

Nebulised magnesium is attractive as a therapeutic option because it is easily administered, relatively cheap and has minimal side effects. In light of some evidence for

an effect when nebulised in severe exacerbations of asthma, the similarities between asthma and COPD (especially with regards to bronchodilator therapy) and the practical advantages of administration via nebuliser, this trial sought to focus on the nebulised route of delivery in AECOPD. The hypothesis was that adjuvant magnesium therapy administered via nebuliser was more effective than placebo in the management of patients with AECOPD.

METHODS

Participants

Patients with an AECOPD, presenting to the emergency departments of two university hospitals in New Zealand (Wellington Regional Hospital and Hutt Hospital), were invited to participate in the study between June 2008 and July 2011. Inclusion in the study required age of 35 years or greater, a doctor diagnosis of COPD, a ratio of the FEV_1 to forced vital capacity (FVC) (FEV_1/FVC) <70 % and an FEV_1 ≤50 % predicted 20 minutes after initial treatment with 2.5 mg salbutamol and 500 µg ipratropium bromide by nebulisation. Patients were excluded if they required intubation or non-invasive ventilation (NIV), were unable to perform spirometry, or had evidence of pneumothorax, hypotension, any other serious medical condition that would prevent their participation in the trial, or were pregnant.

Study protocol

On presentation to the emergency department with a provisional diagnosis of an AECOPD, potential subjects were clinically assessed and received standard initial treatment (2.5 mg salbutamol and 500 µg ipratropium bromide by jet nebulisation and 40mg prednisone). Oxygen (2 L/min nasal prongs) was given if oxygen saturations on room air were less than 92 %. Only subjects with an $FEV_1 \leq 50\%$ predicted measured 20 minutes after commencement of the initial salbutamol/ipratropium nebulisation were enrolled in the trial. During this 20 minute period informed consent was obtained and a brief questionnaire administered, obtaining information with regard to duration and

severity of symptoms, medication use and smoking status. Routine blood tests were performed, as well as a serum magnesium level. After randomisation, patients received by jet nebulisation 2.5mg of salbutamol (GlaxoSmithKline, London, UK) mixed with 2.5ml isotonic magnesium sulphate (250mmol/L, tonicity 289 mosmol; 151mg per dose) or 2.5 mL isotonic saline (placebo) on three occasions at 30 min intervals. The majority of the nebulisers were driven by air, 14 patients received supplemental oxygen via nasal prongs during the nebuliser (1-2L/min) and 21 had their nebuliser driven by oxygen (6L/min), most commonly because medical air was not available.

FEV_1 was recorded using a hand-held spirometer (Micro Medical, Rochester, Kent, England) at presentation, before the first study nebuliser, before each subsequent nebulisation and and 30 minutes after the final nebulisation. Three measurements were made at each time point and the best recording used for analysis. All investigators received training from a respiratory scientist regarding the use of the spirometer. Pulse oximetery was done as part of routine clinical observations and arterial blood gases were performed if clinically indicated. After the final recordings, the decision to admit the patients was made at the discretion of the clinical team, independent of the investigator.

Randomisation and masking

Patients were randomly allocated in a double blind fashion to receive one of two treatment regimens. The study statistician performed block randomisation, with a block size of eight, using computer generated random sequence. This was administered by a third-party process so that participants and investigators were unaware of treatment allocation through provision by the hospital pharmacy of pre-prepared identical syringes containing the study drug or control according to this random allocation.

Ethics and registration

The trial was approved by the Central Regional Ethics Committee and written informed consent was obtained from all patients. The trial was registered on the Australian New Zealand Clinical Trials Registry ACTRN12608000167369.

Statistical Analysis

Analysis was by intention-to-treat. The primary outcome was FEV_1 at 90 minutes. Secondary outcomes were FEV_1 at 30 and 60 minutes, hospital admission, episodes of NIV, and admission to ICU.

The significance level was set at p=0.05. The primary analysis was a t-test comparing FEV_1 between the randomised groups at 90 minutes. Secondary analyses were t-tests to compare FEV_1 at 30 and 60 minutes as well as ANCOVA with adjustment for baseline FEV_1. The calculation of relative risk of the secondary categorical outcome

measurements, with appropriate confidence intervals, was planned, but in the event there were no episodes of NIV or ICU admissions and this could only be calculated for hospital admissions. An exploratory analysis of the relationship between the change in FEV_1 and serum magnesium was carried out using simple correlation coefficients and ANCOVA. SAS version 9.2 was used for the analysis.

The planned sample size of 200 participants was estimated based on the standard deviation of the FEV_1 at the last measurement time from our previous study.[116] In that study the difference between the mean FEV_1 in the magnesium group, 1.94 litres, and in the saline group, 1.58 litres, was 0.36 litres with a pooled standard deviation of 0.74 litres. To detect an absolute difference in FEV_1 of 0.30 L, at an alpha of 5% and a power of 80% required 194 subjects in a two arm trial.

RESULTS

161 patients were assessed between May 2008 and December 2011. Following exclusion of 45 patients, 116 patients were randomised. Reasons for exclusion included not meeting the inclusion criteria (lack of formal COPD diagnosis, significant other co-morbidity such as pneumonia and congestive heart failure, receiving NIV on arrival at the Emergency Department, FEV_1 >50% predicted post-bronchodilator), declined to participate, and other (for example unable to consent secondary to language barrier or dementia, unable to perform adequate spirometry, given intravenous magnesium by Emergency Department staff).

Of the 116 remaining patients, 52 were randomly allocated to the magnesium adjuvant group. Two patients in the placebo group and three in the magnesium group were inadvertently enrolled twice and the second presentation was excluded from the analysis (5 events). Two other patients were excluded prior to analysis because of an inaccurate calculation of the per cent predicted FEV_1 and initial failure to recognize pneumonia as the primary diagnosis. See Figure 1.

Figure 1 Consort trial profile

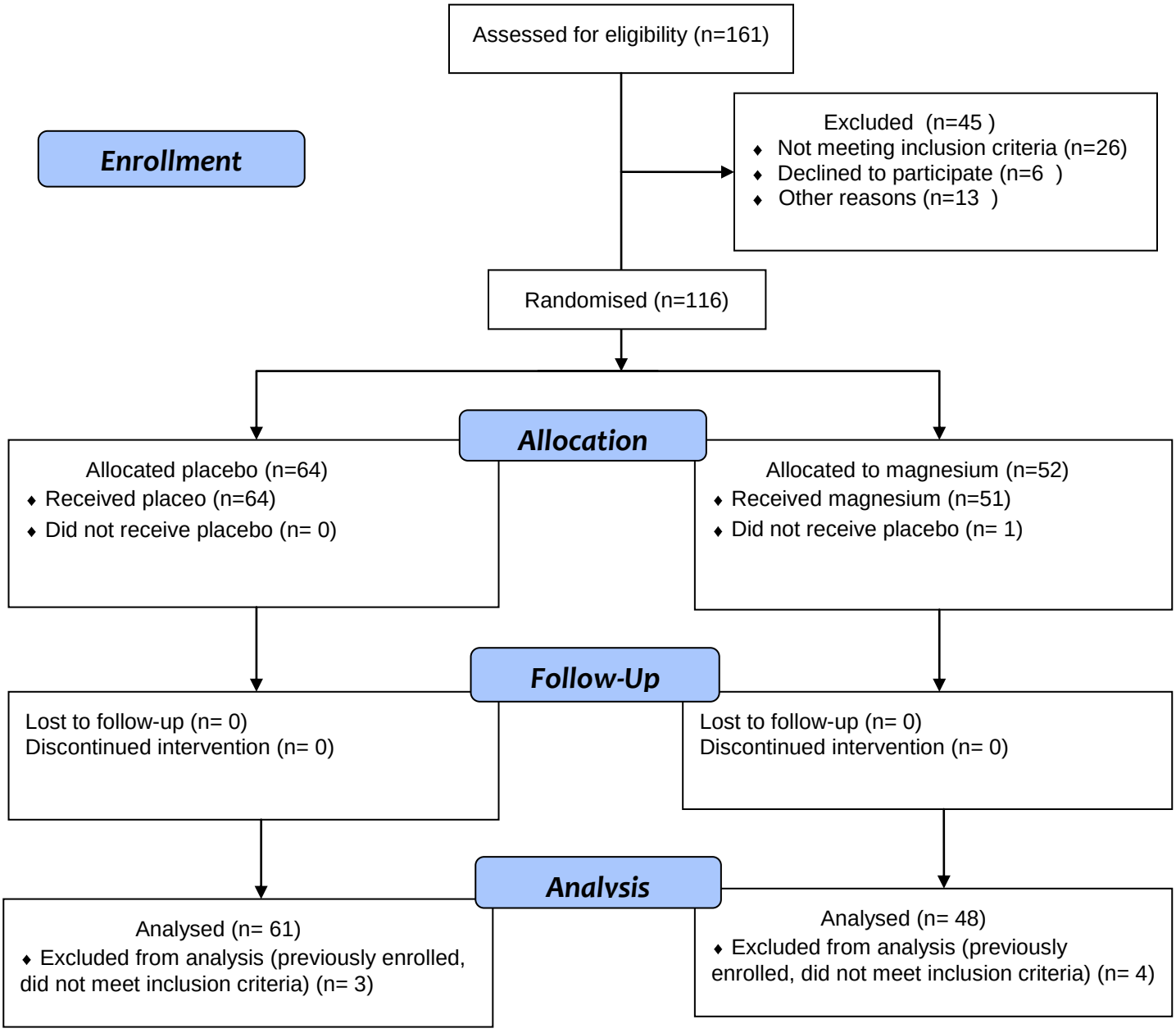


Table 1 shows baseline characteristics of the 109 patients included in the analysis. The denominator for some of the characteristics varies due to missing data for 8 patients (5 in the placebo group and 3 in the magnesium group). The mean age was 71 and ranged from 36 to 89 years. Fifty three per cent were male and 40% were current smokers. Nearly 20% were on domiciliary oxygen and the average number of admissions in the last year was one. FEV_1 (SD) on arrival was 0.71L (0.25) with a range of 0.15 to 1.43L. The proportion of patients with an FEV_1 on arrival of >1000ml was 8/48 (16.7%) in the magnesium group and 6/61 (9.8%) in the placebo group (p=0.29).

TABLE 1: **Baseline characteristics of patient group**

	Placebo N=61	Magnesium N=48
Age (yrs) (SD)	69.5 (11.9)	73.2 (9.8)
Female sex (%)	30 (49.2)	21 (43.8)
Current smokers (%)	22/56 (39.3)	18/45 (40.0)
Pack years (SD)	45.0 (30.7) N=55	41.3 (21.3) N=42
Never smoker	2/56 (3.6)	1/45 (2.2)
Long term oral steroid use	6/56 (10.7)	5/45 (11.1)
Inhaled corticosteroid	44/56 (78.6)	37/45 (82.2)
Home nebuliser	17/56 (30.4)	11/45 (24.4)
Home oxygen	10/56 (17.9)	8/45 (17.8)
Diuretic use	12/61 (19.7)	13/48 (27.1)
Hospital admission in last year	1.3 (N=55)	1.0 (N=45)
Presentation FEV1	0.72 (0.25)	0.69 (0.26)
%predicted presentation FEV1	29.7 (9.2)	28.2 (9.3)
Baseline FEV1	0.74 (0.28)	0.74 (0.28)
Magnesium level (mmol/l)	0.78 (0.10) N=42	0.81 (0.08) N=36

For the primary outcome variable, FEV_1 at 90 minutes (30 minutes after the third administration of the study drug), the mean (SD) FEV_1 in the magnesium group (N=47) was 0.78L (0.33) compared to 0.81L (0.30) in the saline group (N=61), difference -0.026L (95% CI -0.15 to 0.095, p=0.67). After adjustment for baseline FEV_1 the difference was -0.024L (95% CI -0.07 to 0.026), p=0.34. See Table 2 and figure 2.

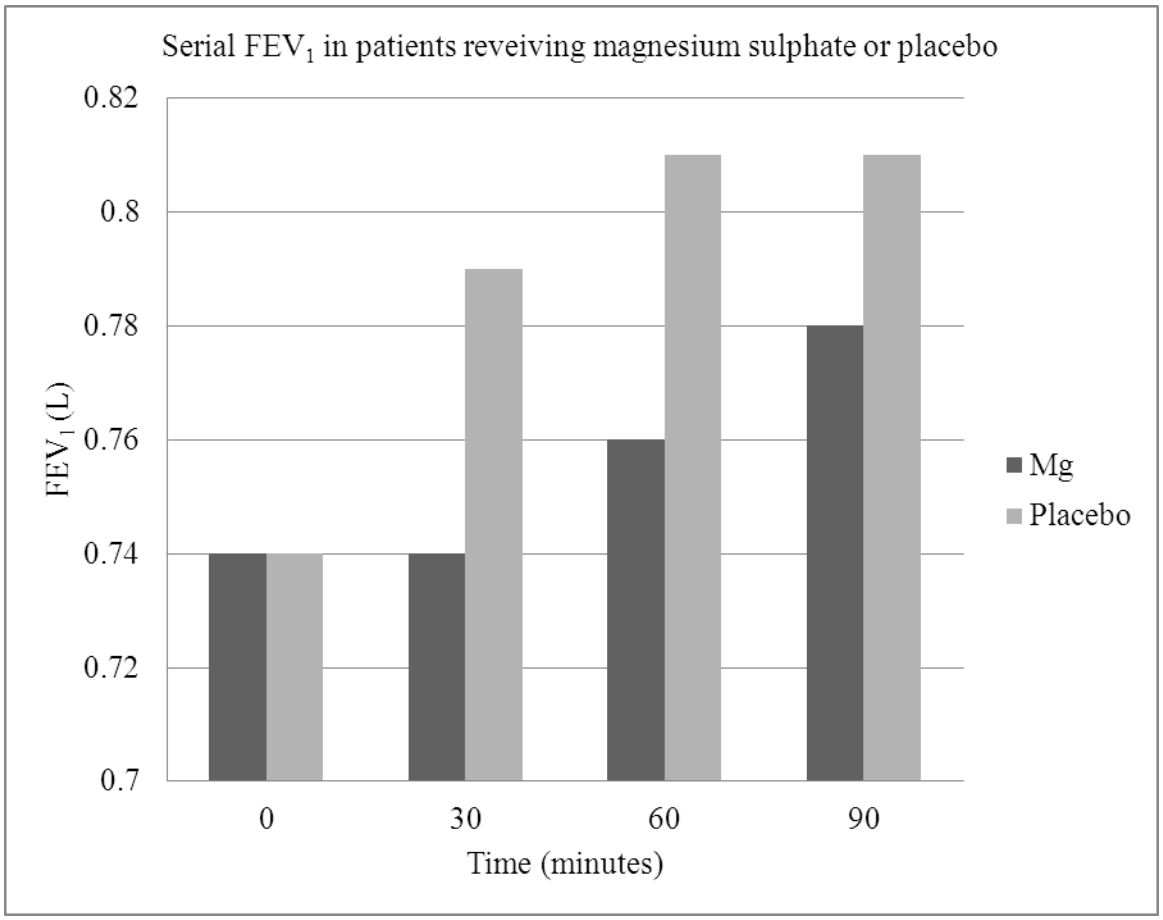
For FEV_1 at 30 and 60 minutes, ANCOVA showed an adjusted difference of -0.043L (95% CI -0.08 to -0.009, p=0.014) and -0.042L (95% CI -0.08 to -0.007, p=0.02) respectively, i.e. FEV_1 lower in the magnesium group after adjustment for baseline. No patients required assisted ventilation and there were no ICU admissions in either group. There were 43/48 (89.6%) admissions to hospital in the magnesium group and 56/61 (91.8%) in the saline group (RR of admission magnesium versus placebo 0.98, 95% CI 0.86 to 1.10, p= 0.69).

Reversibility (based on absolute change in FEV_1 of at least 200ml and >12% from baseline using 90 minute and baseline FEV_1) by randomised group was as follows: 5/47 (10.6%) in the magnesium group and 6/61 (9.8%) in the placebo group (RR 1.08, 95% CI 0.35 to 3.33, p=0.89). One participant in the magnesium group had missing spirometric data at 90 minutes.

TABLE 2: Serial FEV_1 in patients receiving magnesium sulphate or placebo

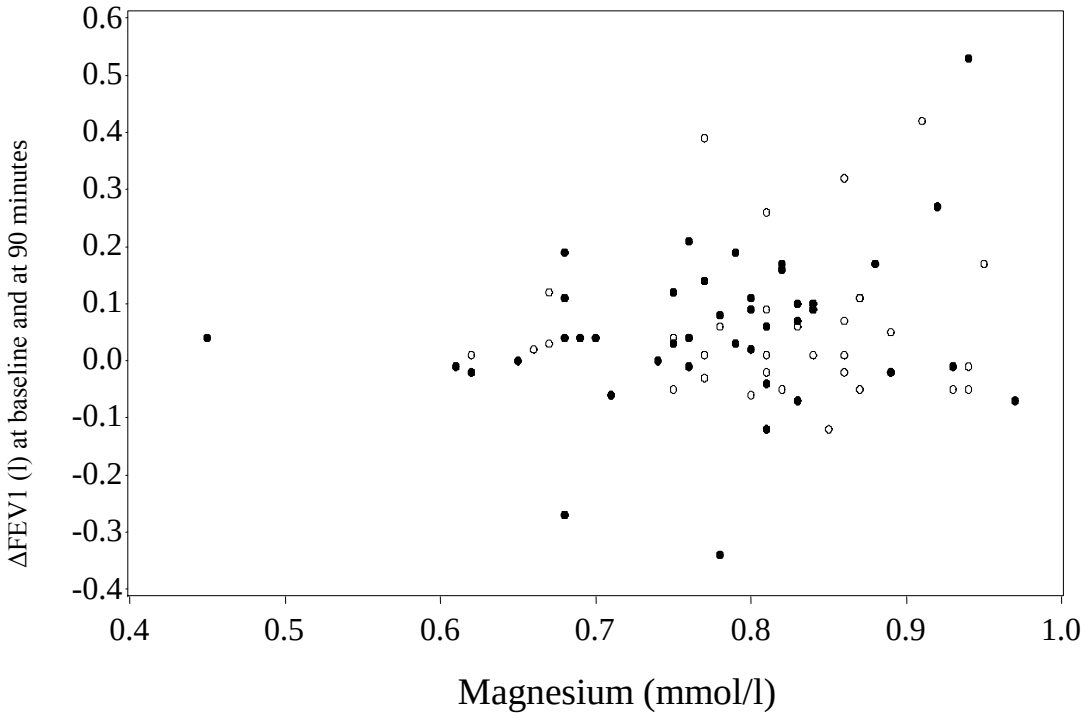
	Mean (SD)	Median (IQR)	Min to Max
FEV_1 Time 0			
Magnesium N=48	0.74 (0.28)	0.70 (0.50 to 0.89)	0.34 to 1.41
Placebo N=61	0.74 (0.28)	0.74 (0.53 to 0.92)	0.17 to 1.74
All N=109	0.74 (0.28)	0.71 (0.51 to 0.92)	0.17 to 1.74
FEV_1 Time 30			
Magnesium N=48	0.74 (0.29)	0.68 (0.48 to 0.94)	0.25 to 1.53
Placebo N=61	0.79 (0.29)	0.76 (0.57 to 0.97)	0.17 to 1.63
All N=109	0.76 (0.29)	0.71 (0.55 to 0.96)	0.17 to 1.63
FEV_1 Time 60			
Magnesium N=48	0.76 (0.31)	0.69 (0.50 to 0.98)	0.30 to 1.47
Placebo N=61	0.81 (0.31)	0.80 (0.58 to 0.98)	0.24 to 1.97
All N=109	0.79 (0.31)	0.74 (0.57 to 0.98)	0.24 to 1.97
FEV_1 Time 90			
Magnesium N=47	0.78 (0.33)	0.69 (0.54 to 0.97)	0.28 to 1.54
Placebo N=61	0.81 (0.30)	0.77 (0.58 to 1.0)	0.32 to 1.50
All N=108	0.79 (0.31)	0.74 (0.55 to 0.99)	0.28 to 1.54

Figure 2


Serial FEV1 in patients reveiving magnesium sulphate or placebo
0.82
0.8
0.78
0.76
0.74
0.72
0.7
FEV1 (L)
0
30
60
90
Time (minutes)
Mg
Placebo

Baseline serum magnesium levels ranged from 0.45 to 0.97mmol/l (normal reference range 0.76-0.99mmol/l). There was no statistically significant evidence of an interaction between treatment and serum magnesium (p=0.51), and Pearson's correlation coefficient for the association between change in FEV_1 at 90 minutes and time zero was 0.17 (p=0.13, N= 77 with complete data). See figure 3.

Figure 3 Change between forced expiratory volume in 1 sec (FEV_1) at baseline and at 90 min in relation to serum magnesium levels (open symbols represent magnesium, closed symbols represent placebo)



No clinically significant adverse events were reported, and no patients in either group needed additional bronchodilator therapy within the 90 minute time period, or were withdrawn from the study because of clinical deterioration.

DISCUSSION

This randomised double blind placebo controlled trial was unable to demonstrate any spirometric benefit with single or repeated administration of nebulised magnesium given as an adjunct to bronchodilator treatment on presentation to hospital with an AECOPD. This study, the largest to date of nebulised magnesium in COPD, was also unable to show any evidence of a relationship between baseline serum magnesium and change in FEV_1 in either placebo or active treatment group. However, it is reasonable to conclude that despite an apparent lack of benefit, an absence of adverse events suggests that it is a safe treatment.

There are several methodological issues in the design of the study that are relevant to its interpretation. The primary reason for including only subjects with an FEV_1 less than 50% predicted (measured 20 minutes after commencement of initial salbutamol and ipratropium) was that in groups with asthma, an effect with intravenous magnesium has been found in those with more severe disease.[101] FEV_1 was chosen as the primary outcome variable as a sensitive, objective and repeatable measure of bronchodilator response in AECOPD.[208, 209] Specifically, the administration of a bronchodilator during AECOPD can increase the FEV_1 and the FVC by 15 to 29 per cent over a period of 60 to 120 minutes.[210] Additionally, FEV_1 had been successfully used as an outcome measure in previous trials using magnesium, including one conducted by our group.[114, 116]

With regards to the protocol of bronchodilator administration, the reason for the initial salbutamol/ipratropium nebulisers at presentation was safety as well as ensuring some standardisation of bronchodilator treatment in the 20 minutes prior to randomisation. Guidelines for managing an AECOPD generally agree that bronchodilators are considered first line therapy[195]but may not recommend a specific dose. In stable COPD, it has been shown that 88% of patients achieved 90% of maximal bronchodilation with doses of inhaled salbutamol ≤ 1.2mg.[211] It could be argued that this pre-dosing with bronchodilators meant patients had already reached their maximal bronchodilator response before administration of magnesium. Additionally, the combination of ipratropium and salbutamol is known to be superior to either agent alone.[212] It is also possible that due to the generally slower time-course of an AECOPD compared to an exacerbation of asthma, patients may also have received oral steroids at home. The magnesium used was formulated as an isotonic solution. This was important because both hypotonic and hypertonic nebuliser solutions can induce bronchoconstriction in patients with bronchial hyper-responsiveness.[213]

Recruitment proved difficult with only 109 of a planned 200 patients studied, despite the extension of the study by 10 months. Post-hoc analysis suggests the study was still adequately powered due to the smaller standard deviation for FEV_1 in the study as compared with that used in the power calculations (based on our previous study of nebulised magnesium in acute severe asthma).[116] This resulted in the 95% confidence intervals that excluded the pre-nominated clinically important difference. The reason for the unequal numbers in the two groups was that the batches of magnesium and placebo

provided by the hospital pharmacy were often incompletely used before expiring and a new batch being issued.

The findings of this study raise a number of points for discussion. The first is the relation of this study to other studies of magnesium in COPD. There are only six placebo controlled trials involving intravenous[49, 126, 127, 129] or nebulised[50] magnesium (or both)[128] in either acute exacerbations[126-129] or in the stable outpatient setting[49, 50] and three are in abstract from only.[50, 127, 129]

In the two that involve intravenous magnesium in the setting of AECOPD, 1.2g was administered following standard nebulised bronchodilator treatment. In their randomised double-blind placebo-controlled trial of 24 subjects with an AECOPD, Hogg et al report a significant reduction in the Modified Borg Dyspnoea Score 30 minutes after the start of the infusion (2.33 vs 1.08, $p<0.01$) and a reduced length of inpatient stay in the intravenous magnesium group compared to placebo (4.27 vs 7.33 days, $p<0.05$).[129] In their trial of 72 subjects with AECOPD, Skorodin et al report a significant increase in peak expiratory flow from initiation to 30 and 45 minutes later (25.1L/min vs 7.4L/min, $p=0.03$) and a statistically non significant trend towards a reduced need for hospitalization with intravenous magnesium.[126] Gonzalez et al administered either 1.5g of magnesium or placebo the first day and then vice versa the other day in a randomised, double-blind crossover design of 24 patients. Salbutamol was administered 45 minutes after the placebo or magnesium. The mean increase in FEV_1 was 0.18L compared to 0.081L after placebo, $p=0.004$. Interestingly, this bronchodilating effect was

only observed after salbutamol administration.[127] It could be argued that this confirms the work of Skorodin to some extent, where magnesium potentiated the effect of beta-agonists on adenyl cyclase.[102] Increased local magnesium concentration also allows for increased respiratory muscle power, which may account for the increased bronchodilatation seen subsequently with salbutamol.[48]

In a further randomised double-blind placebo-controlled trial of 22 subjects with stable COPD, Do Amaral et al report that an intravenous infusion of magnesium sulphate resulted in a significant reduction in lung hyperinflation measured as functional respiratory capacity (-0.53L vs -0.05L, p=0.04) and an increase in respiratory muscle strength, measured as maximum inspiratory pressure (6.9cmH20 vs -3.1cmH20, p=0.02).[49] Together these studies indicate that a single intravenous dose of magnesium has some clinical benefit in both stable and AECOPD.

More recently, Nouira et al randomised 62 patients presenting to the ED with an AECOPD to receive either multiple nebulisations of terbutaline plus ipratropium or terbutaline plus a once-only bolus of intravenous magnesium (1.5g) followed by repeated nebulised terbutaline and nebulised magnesium (150mg/nebule). There was no significant difference between the two groups in their primary outcome variable (which included hospital admission, intubation and hospital death rates). Patients who were given ipratropium (and terbutaline) had an average improvement in peak expiratory flow of 32 l/min (95% CI 19 to 43) compared with the magnesium group. Their reason for

combining an intravenous bolus and repeated nebulisations was to ensure an adequate dose but to avoid potentially toxic blood levels.[128]

The only other study of nebulised magnesium investigated its effect in 18 outpatients with stable COPD and an FEV_1 <50% predicted. Baseline measurements of PEFR and FEV_1 were taken and the subjects then divided into four groups (Group A: Nebulised saline, Group B: Nebulised magnesium sulphate 300mg, Group C: Nebulised salbutamol 2mg plus saline, Group D: Nebulised salbutamol 2mg plus 300mg magnesium sulphate). It is not stated how this was done, nor the number of subjects in each group and there is no demographic data. The group that received magnesium as an adjunct to nebulised salbutamol showed a significant increase in FEV_1 from 1.44L to 1.67L, $p<0.05$ at 60 minutes.[50] However, given that this study is small and details are sparse (presented in poster form at the American Thoracic Society meeting 2004), it is difficult to reach any conclusion about nebulised magnesium in COPD on the basis of this trial. The design of our trial, with its greater power provides a higher level of evidence that nebulised magnesium as an adjunct to salbutamol treatment in the setting of AECOPD has no effect.

The second point is consideration of the trial's findings in relation to the asthma literature. This is relevant because the reported efficacy in asthma exacerbations is the pretext for its use in COPD. However, it is now recognised that they are not always distinct and mutually exclusive clinical entities and there is much heterogeneity between them.[214] This is a bigger problem in the older age group where fewer than 20% of

those with COPD have the classical phenotypes of chronic bronchitis or emphysema and in the UK 19% of those with an obstructive lung disease have an overlap between asthma and the phenotypes of COPD.[215] Better defining the patient group who may respond to magnesium may be crucial in clarifying its therapeutic effect.

In asthma, magnesium has been administered both intravenously and via the nebulised route. The recent Cochrane meta-analysis of intravenous magnesium reported an improvement only in the severe subgroup in whom peak expiratory flow improved by 52.3L/min (95% CI 27 to 77.5) and FEV_1 by 9.8% predicted (95% CI 3.8 to 15.8).[101] This subgroup was not consistently defined throughout the studies though, varying from a rather vague "failure to respond to initial therapy" to a more precise measurement of either 25% or 30% predicted PEFR at presentation. The more recent Cochrane review of nebulised magnesium as an adjunct in acute asthma reported a non significant improvement in pulmonary function in the nebulised magnesium group, but significant heterogeneity between trials precluded a definitive conclusion.[118]

This leads on to the third point which concerns the route of administration. Although individual trials in acute asthma, including our own, may show some benefit with nebulised magnesium,[113, 116] this was not conclusively shown in the meta-analysis[118] and the efficacy of this route must remain in question. The benefits of repeated administration of nebulised magnesium include ease of administration without the need for an intravenous line. With regard to the dose of magnesium, this was based on the work in asthma.[116]

The fourth point concerns association between serum magnesium levels and COPD. Aziz et al retrospectively reviewed charts of 50 patients with stable COPD and 50 with an AECOPD. Those in the latter group had a significantly lower magnesium levels, and 22% had levels below the lower limit of normal compared to none in the stable group.[145] Bhatt et al also retrospectively reviewed magnesium levels and readmission rate and death in 100 patients with AECOPD. The sole predictor of frequent readmissions was serum magnesium.[146] Rolla et al measured magnesium levels in a group of 95 with severe but stable COPD. 11% had hypomagnesemia and there was a significant inverse relationship between serum magnesium and the use of diuretics or length of oral steroid treatment. The authors concluded that serum magnesium should be routinely checked because of potential negative effects on respiratory muscle power.[44] Earlier work with 17 stable patients has shown that correction of hypomagnesaemia is associated with improved respiratory muscle power. However, only 6 of these had COPD (the others being alcoholics). The applicability of this study to AECOPD is therefore uncertain.[48] Interestingly, we did not find any relationship between serum magnesium, change in FEV_1 and randomised treatment group. Given, however, that there is evidence as described above showing that magnesium levels can be lower in exacerbating subjects and that it can improve respiratory muscle power, it is possible that the dose we used was not big enough to provide an effect.

In conclusion, this randomised double-blind placebo-controlled trial has shown no evidence of efficacy of single or repeated nebulised magnesium as an adjunct to

nebulised salbutamol in AECOPD. These findings, together with previous studies, suggest that the priority for further investigation of magnesium in AECOPD should be with the intravenous route of administration.

CHAPTER 8

THE VALUE OF THE CRB65 SCORE TO PREDICT MORTALITY IN EXACERBATIONS OF COPD REQUIRING HOSPITAL ADMISSION

THE VALUE OF THE CRB65 SCORE TO PREDICT MORTALITY IN EXACERBATIONS OF COPD REQUIRING HOSPITAL ADMISSION

INTRODUCTION

Acute exacerbations of COPD (AECOPD) are common, often require hospitalisation and may necessitate intensive care. It is estimated that in the United Kingdom, hospitalisation with AECOPD costs, on average, £ 1960.[122] The burden to health-care systems could be reduced using alternatives to hospital admission such as a hospital at home model of care.[216] However, AECOPD are associated with significant mortality and a reduced level of health care is inappropriate for high-risk patients. A simple risk score that could identify mortality risk in AECOPD would be clinically desirable. Such a score could be used to triage patients presenting to hospital and identify those who may be suitable for a lower level of health care. An effective risk score would also identify a high-risk group where more intensive monitoring and care could be considered.

Previous research has linked clinical variables at the time of hospital presentation with future health status. These include low FEV_1, use of long-term oxygen therapy, frequency of exacerbations,[149, 152] hypercapnia[154] and more recently serological variables such as CRP[165] and serum amyloid A.[170] However, many of the markers correlate only weakly with mortality, with one review concluding that only respiratory rate and arterial carbon dioxide tension have shown consistency as independent predictors of outcome between studies over time.[178] A subsequent study developed and validated a

risk score incorporating elevated urea, confusion, heart rate and age to predict in-hospital mortality or the need for mechanical ventilation in a large cohort with AECOPD.[217] The value of risk stratification also applies to individuals presenting with community-acquired pneumonia. Severity scores such as the PSI[21] and the simpler CURB65 score[20] have been developed and validated. These scores can identify low-risk individuals with pneumonia who may be suitable for home treatment and have been widely adopted in clinical decision making.[218] Recent studies conducted at Waikato Hospital, New Zealand, suggest that the CURB65 score predicts early mortality in AECOPD, possibly as effectively as it does for pneumonia.[182, 219] The CRB65 score is a further simplification of the CURB65 score for pneumonia with similar predictive characteristics.[220]Removing the requirement to measure serum urea allows the CRB65 score to be evaluated in primary care or immediately upon arrival to hospital, allowing earlier triage decisions.

The use of the CRB65 score in AECOPD has the potential advantage that a single, easily remembered clinical score could be applied to both pneumonia and AECOPD, the two most common causes of severe respiratory illness in the older adult. This study investigated whether the CRB65 score could effectively predict mortality in patients admitted to hospital with AECOPD.

METHODS

Patients with AECOPD admitted to Wellington Hospital, New Zealand, between June 2006 and June 2007 as part of the Wellington Ambulance Audit were included in this study.[199] Patients who were brought by ambulance to the Emergency Department were included. Patients were identified by the medical records department by a hospital discharge code compatible with a primary diagnosis of COPD (ICD Codes J40 to J44).

Markers of COPD severity, variables of the CRB65 score and clinical outcomes following presentation to the Emergency Department were retrospectively reviewed. Sources of information included the ambulance case records for details of pre-hospital respiratory rate, blood pressure and documentation of confusion. Emergency Department case records were examined where ambulance case records were incomplete. Vital status was obtained from hospital records. All study data were collected as part of an audit of hospital and ambulance services so research ethics committee approval and participant informed consent were not required.

The CRB65 score assigns one point to each of: confusion, respiratory rate 30/min, low systolic (<90 mm Hg) or diastolic (<60 mm Hg) blood pressure and age 65 years at the time of presentation to hospital. Possible CRB65 scores range from 0 to 4.Confusion was defined as a Glasgow Coma Score of 13 or lower.[217]

STATISTICAL ANALYSIS

Logistic regression was used to describe the strength of association between CRB65 and the outcome of death at the three measurement times; in-hospital, 30 days and 12 months. The ‘c’ statistic representing the area under the curve of the receiver operating characteristic curve was calculated to describe how well each instrument discriminated between those who died or survived. A value of 0.5 means discrimination is poor and a value of 1.0 means it is perfect. CRB65 scores of 0 and 1 were grouped together because of an expected low mortality rate in these groups. CRB65 scores of 3 and 4 were grouped together because of expected low patient numbers in these groups, in line with methods used in studies based in other centres.[219]

Statistical significance of mortality differences between CRB65 groups was tested by the chi-square test with Yates’ correction because of the small numbers involved. Mortality differences in the presence or absence of individual score components was evaluated using Fisher’s exact test with Bonferroni correction for multiple comparisons. For participants with missing values of each component of the CRB65, a sensitivity analysis was carried out by assigning missing values a score of zero (see chapter appendix).

RESULTS

Of 250 patient admissions, 76 were excluded as repeat admissions leaving 174 first patient admissions. Of these, 41 had incomplete data that did not allow the CRB65 score to be calculated. The remaining 133 patients were included in the analysis. Of the patients in the analysis, 133, 131 and 126 had valid in-hospital, 30-day and 12-month mortality data, respectively.

The characteristics of the 133 patients included in the analysis are shown in Table 1. Most patients were 65 years of age or older. Long-term oral corticosteroid and domiciliary oxygen therapy were relatively uncommon.

In-hospital mortality rates in the presence and absence of each element of the CRB65 score and for the CRB65 groups are shown in Table 2. Mortality rates were relatively low except in the highest group and increased progressively with increasing CRB65 group. Low blood pressure was the only individual element of the score to be significantly associated with in-hospital mortality ($P = 0.002$). This association remained statistically significant after correcting for multiple comparisons. An increased respiratory rate was associated with reduced in-hospital mortality.

The 30-day and 1-year mortality rates are shown in Table 3. Similar to in-hospital mortality, mortality rates at 30 days were low except in the highest CRB65 group and increased progressively with increasing CRB65 group. The differences between groups

defined by CRB scores of 0 or 1 and 2 were less apparent after 12 months. Of the individual components of the CRB65 score, confusion and low blood pressure were significantly associated with 30-day mortality (P = 0.03 and 0.01, respectively). These associations were not statistically significant after adjustment for multiple comparisons. No individual component of the CRB65 score was significantly associated with 1-year mortality.

The CRB65 score demonstrated modest performance in predicting in-hospital and 30-day mortality with a c statistic of 0.68 at both time points. The c statistic was unchanged when CRB65 scores were grouped. The odds ratios for in-hospital, 30-day and 1-year mortality for each increase in CRB65 group are shown in Table 4. The CRB65 score was a statistically significant predictor of in-hospital and 30-day mortality but not of 1-year mortality. There was no significant change to the reported mortality frequencies following the sensitivity analysis.

Table 1 Characteristics of the 133 patients with AECOPD

	Mean (SD)
Age	72.7 (10)
	Number (percent)
	n=133
Female gender	65 (48.9)
Use of home nebulizer	24 (18.8)
Use of long-term oral corticosteroid	20 (15.0)
Use of long-term oxygen	19 (14.3)
Previous non-invasive ventilation	15 (11.3)
Previous invasive ventilation	4 (3.0)
Non-invasive ventilation during hospital admission	24 (18.0)
Invasive ventilation during hospital admission	2 (1.5)
Confusion	10 (7.5)
Increased respiratory rate	60 (45.1)
Low blood pressure	13 (9.8)
Age >65	111 (83.5)
CRB65 score	
0	12 (9.0)
1	57 (42.9)
2	57 (42.9)
3	6 (4.5)
4	1 (0.8)

Table 2 In-hospital mortality by severity score factor and severity score group

		Fractional mortality	Percent mortality
Confusion	Present	2/9	22
	Absent	5/124	4
Increased respiratory rate	Present	1/60	2
	Absent	6/73	8
Low blood pressure	Present	4/13	31*
	Absent	3/120	3
Age >65 years	Present	7/111	6
	Absent	0/22	0
CRB65 score group	0–1	2/69	3
	2	3/57	5
	3-4	2/7	29
Total deaths		7/133	5

* $P < 0.05$ compared with factor absent.

Table 3 30-day and 1-year cumulative mortality by severity score factor and severity score group

		30 day		1 year	
		Fractional mortality	Percent mortality	Fractional mortality	Percent mortality
Confusion	Present	3/9	33*	3/9	33
	Absent	8/122	7	30/117	26
Increased respiratory rate	Present	4/60	7	13/59	22
	Absent	7/71	10	20/67	30
Low blood pressure	Present	4/13	31*	6/13	46
	Absent	7/118	6	27/113	24
Age >65	Present	10/110	9	31/108	29
	Absent	1/21	5	2/18	11
CRB65 score group	0–1	3/67	4	15/63	24
	2	5/57	9	14/56	25
	3-4	3/7	43	4/7	57
Total		11/131	8	33/126	26

* $P < 0.05$ compared with factor absent.

Table 4 Odds ratios for cumulative mortality for each increase in CRB65 group

Time point	Odds ratio	Confidence interval	P value
In-hospital	3.5	(1.0–11.8)	0.04
30 days	3.7	(1.3–10.3)	0.01
1 year	1.4	(0.7–2.6)	0.37

DISCUSSION

This study has confirmed that in patients admitted to hospital with AECOPD, the CRB65 score is a predictor of both in-hospital and 30-day mortality. These findings suggest that the utility of the CRB score extends beyond its use as a risk stratification model for community-acquired pneumonia. The CRB65 score was able to identify a group of patients with AECOPD who are at high risk of short-term mortality, for whom intensive hospital care may be required, as well as a low risk group in whom hospital at home management may be considered. The CRB65 score was less effective at predicting 1-year mortality, suggesting that factors that reflect the severity of the acute physiologic disturbance during an exacerbation do not predict the long-term prognosis in COPD with as much accuracy as they do in the short-term. It may be that other factors such as low BMI, poor nutrition and co-morbidities have more bearing on longer-term mortality.[149] These results should be considered in light of the strengths and weaknesses of this study, which was a retrospective review of data recorded at the time of the Wellington Ambulance Audit.[199] This meant that some patients did not have sufficient data recorded to allow the CRB65 score to be calculated; however, sensitivity analyses suggested that these missing data had little impact on the results (see chapter appendix). This audit was conducted during all seasons so was representative of presentations with AECOPD where ambulance transport was used. However, this data does not include patients who arrived other than by ambulance or those who were already inpatients when they developed an AECOPD.

Measuring urea may have added some predictive power to the severity score. We chose not to use urea in the predictive score as it is not a routinely performed test at Wellington Hospital and is not available in the assessment of AECOPD in the community setting. Avoiding using a blood test in the risk score allows an immediate calculation of risk in the Emergency Department, before the effect of initial treatment complicates the assessment of disease severity. It also allows the risk prediction score to be calculated in a pre-hospital setting such as an ambulance or general practitioner's office.
Caution must be used in extrapolating the results of studies performed in hospital populations to patients in primary care. Definition of confusion was based on the Glasgow Coma Scale. This is consistent with some previous studies[217] but others have used the abbreviated mental test.[182] Some caution should be applied in comparing results between studies using different methods to assess confusion.

The power of a clinical score to predict 30-day mortality can be expressed as a 'c' statistic, equivalent to the area under the receiver-operating curve. Our observed 'c' statistic of 0.68 is similar to the value of 0.73 reported by the Waikato Hospital group.[182, 219] This provides independent confirmation of the value of this score in AECOPD. These 'c' statistic estimates in AECOPD are similar to reported CRB65 and CURB65 scores in pneumonia (0.69 and 0.73, respectively), and this was the rationale for using it in this study.[221] These findings suggest that the CRB65 score has similar utility in predicting mortality in AECOPD to that in community-acquired pneumonia.The observation of the Waikato Hospital group that the score at the time of an acute exacerbation was a poor predictor of longer-term mortality in COPD is also confirmed by

our study.[182, 219] This supports the role of the score as a signal of acute end-organ dysfunction, rather than a measure of chronic poor health.

However, it should be remembered that the 'c' statistic may not be optimal at assessing models that predict future risk or stratify individuals into risk groups, where calibration (how well predicted probabilities agree with actual observed risk) is as important. Studies of cardiovascular risk factors have shown that individual variables can have a statistically significant effect on risk stratification in large populations, whilst having only a marginal effect on the 'c' statistic. Therefore, over-reliance on it as a predictor of risk in a prognostic sense, especially in the long-term, could lead to potentially important variables being overlooked.[222]

A study of a large hospital database examined many parameters that may be predictive of mortality in AECOPD.[217] The presence of confusion, elevated heart rate, elevated urea and age >65 years were associated with mortality and were incorporated into a BAP-65 score. This score demonstrated similar but slightly better predictive characteristics to the CRB65 score with a 'c' statistic of 0.75 for predicting in-hospital mortality. An increased respiratory rate was not predictive of mortality, consistent with the results of our study. This is in contrast to studies in pneumonia where an increased respiratory rate is predictive of increased mortality.[20] Although this discrepancy may be simply a statistical aberration, we speculate that it may be due to differences in pathophysiology between pneumonia and AECOPD. The increased respiratory rate in pneumonia is due to the degree of lung consolidation and sepsis, whereas in AECOPD, it may be related to

other factors less closely related to mortality such as anxiety, dynamic hyperinflation and innate respiratory drive.[158, 178] Unfortunately, as our data was extracted from an audit looking at ambulance records, information regards the presence or absence of consolidation on x-rays was not collected.

The application of a clinical risk score is to assist clinical decision making. Based on the results of this study and those of the Waikato group, the CRB65 score might be used to guide whether hospital admission is required, and the intensity of monitoring and management. For patients with a score of 0 or 1, the low risk of mortality may allow for early hospital discharge or hospital at home treatment, which has been shown to have similar low mortality rates in carefully selected cohorts.[223] For intermediate risk patients with a score of 2, standard hospital admission is required. Patients with a score of 3 or 4 are at high risk of mortality and intensive monitoring and management is likely to be needed during the hospital stay. The clinical benefit of applying the CRB65 score to AECOPD may be most apparent in the Emergency Department or medical admission unit setting.

In conclusion, the CRB65 score shows similar characteristics for predicting short-term mortality in AECOPD as it does in pneumonia. Its use in clinical practice is recommended, particularly in patients with a score of 3 or 4, which is associated with a high risk of early mortality and suggests the need for intensive hospital monitoring and care.

CHAPTER APPENDIX

CRB-65 score versus death in COPD ambulance data set

Statistical methods

Logistic regression was used to describe the strength of association between the disease severity instruments and the outcome of death at the three measurement times. The 'c' statistic representing the Area Under the Curve of the Receiver Operating Characteristic Curve describes how well each instrument discriminates between those who die or survive. A value of 0.5 means discrimination is poor and a value of 1.0 means it is perfect.

For participants with missing values of each component of the CRB-65, a sensitivity analysis was carried out by assigning missing values a score of zero. A further analysis is also presented by merging those with a CRB-65 score of 4 with those with a score of 3.

Another analysis is presented merging CRB-65 scores of zero and one as one category, CRB-65 of two as another category, and finally scores of three and four as the final category.

Some participants were missing values for vital status at the one and twelve month time

Hospital deaths

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0	0/12 (0)	0/17 (0)
1	2/57 (3.5)	3/79 (3.8)
2	3/57 (5.3)	3/71 (4.2)
3	2/6 (33.3)	2/6 (33.3)
4	0/1 (0)	0/1 (0)
Total	7/133 (5.3)	8/174 (4.6)

Deaths at One Month

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0	1/11 (9.1)	1/16 (6.3)
1	2/56 (3.6)	3/76 (4.0)
2	5/57 (8.8)	5/71 (7.0)
3	3/6 (50.0)	3/6 (50.0)
4	0/1 (0)	0/1 (0)
Total	11/131 (8.4)	12/170 (7.1)

Deaths at Twelve Months

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0	1/8 (12.5)	1/12 (8.3)
1	14/55 (25.5)	17/75 (22.7)
2	15/56 (26.8)	17/70 (24.3)
3	3/6 (50.0)	3/6 (50.0)
4	0/1 (0)	0/1 (0)
Total	33/126 (26.2)	38/164 (23.2)

Odds Ratio for association

OR per one point score higher on the instrument

	OR (95% CI), P value	
	CRB-65 with complete data	**CRB-65, Missing data set to zero**
Death in Hospital	2.75 (0.99 to 7.63) 0.052	2.50 (0.95 to 6.53) 0.062
Death at One Month	2.40 (1.02 to 5.62) 0.044	2.33 (1.03 to 5.29) 0.042
Death at Twelve Months	1.32 (0.76 to 2.29) 0.33	1.42 (0.85 to 2.37) 0.19

'c' statistic

	CRB-65 with complete data	CRB-65, Missing data set to zero
Death in Hospital	0.69	0.66
Death at One Month	0.67	0.65
Death at Twelve Months	0.55	0.56

Merging CRB-65 score of 4 with those with 3

Hospital deaths

	CRB-65 with complete data	**CRB-65, missing data set to zero**
	Deaths/N (%)	
0	0/12 (0)	0/17 (0)
1	2/57 (3.5)	3/79 (3.8)
2	3/57 (5.3)	3/71 (4.2)
3	2/7 (28.6)	2/7 (28.6)
Total	7/133 (5.3)	8/174 (4.6)

Deaths at One Month

	CRB-65 with complete data	**CRB-65, missing data set to zero**
	Deaths/N (%)	
0	1/11 (9.1)	1/16 (6.3)
1	2/56 (3.6)	3/76 (4.0)
2	5/57 (8.8)	5/71 (7.0)
3	3/7 (42.9)	3/7 (42.9)
Total	11/131 (8.4)	12/170 (7.1)

Deaths at Twelve Months

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0	1/8 (12.5)	1/12 (8.3)
1	14/55 (25.5)	17/75 (22.7)
2	15/56 (26.8)	17/70 (24.3)
3	3/7 (42.9)	3/7 (42.9)
Total	33/126 (26.2)	38/164 (23.2)

Odds Ratio for association, merged CRB-65 level 4

OR per one point score higher on the instrument

	OR (95% CI), P value	
	CRB-65 with complete data	**CRB-65, Missing data set to zero**
Death in Hospital	3.39 (1.03 to 11.0) 0.044	2.89 (0.97 to 8.57) 0.056
Death at One Month	2.78 (1.07 to 7.19) 0.036	2.63 (1.07 to 6.9) 0.036
Death at Twelve Months	1.38 (0.77 to 1.45) 0.28	1.47 (0.86 to 2.52) 0.16

The 'c' statistics were unchanged.

Merged CRB-65 zero and one, two, and three and four

Hospital deaths

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0,1	2/69 (2.9)	3/96 (3.1)
2	3/57 (5.3)	3/71 (4.2)
3,4	2/7 (28.6)	2/7 (28.6)
Total	7/133 (5.3)	8/174 (4.6)

Deaths at One Month

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0,1	3/67 (4.5)	4/92 (4.4)
2	5/57 (8.8)	5/71 (7.0)
3,4	3/7 (42.9)	3/7 (42.9)
Total	11/131 (8.4)	12/170 (7.1)

Deaths at Twelve Months

	CRB-65 with complete data	CRB-65, missing data set to zero
	Deaths/N (%)	
0,1	15/63 (23.8)	18/87 (20.7)
2	15/56 (26.8)	17/70 (24.3)
3,4	3/7 (42.9)	3/7 (42.9)
Total	33/126 (26.2)	38/164 (23.2)

Odds Ratio for association, merged CRB-65 level 4

OR per one level higher on the three levels

	OR (95% CI), P value	
	CRB-65 with complete data	**CRB-65, Missing data set to zero**
Death in Hospital	3.5 (1.0 to 11.8) 0.044	3.0 (0.95 to 9.3) 0.06
Death at One Month	3.7 (1.3 to 10.3) 0.012	3.4 (1.3 to 9.0) 0.01
Death at Twelve Months	1.4 (0.7 to 2.6) 0.37	1.4 (0.8 to 2.6) 0.26

'c' statistic

	CRB-65 with complete data	**CRB-65, Missing data set to zero**
Death in Hospital	0.68	0.64
Death at One Month	0.68	0.66
Death at Twelve Months	0.54	0.55

CHAPTER 9

RANDOMISED CONTROLLED CROSSOVER TRIAL OF THE EFFECT ON P_tCO_2 OF OXYGEN-DRIVEN VERSUS AIR-DRIVEN NEBULISERS IN SEVERE COPD

RANDOMISED CONTROLLED CROSS-OVER TRIAL OF THE EFFECT ON $PtCO_2$ OF OXYGEN-DRIVEN VERSUS AIR-DRIVEN NEBULISERS IN SEVERE COPD

INTRODUCTION

It is well recognised that administering high concentration oxygen (HCO) therapy to patients with AECOPD may lead to CO_2 retention.[224] The clinical relevance of this physiological response in the pre-hospital setting has been demonstrated in the recent randomised controlled trial of oxygen therapy in AECOPD.[201] In this study, HCO therapy during ambulance transfer to hospital was more likely to causes severe hypercapnia and respiratory acidosis than oxygen titrated to achieve oxygen saturations between 88% and 92%, with a mean difference in $PaCO_2$ of 34mmHg and pH of 0.12. Importantly, HCO therapy was associated with a 2.4-fold increased risk of death compared with controlled oxygen therapy. To reduce this risk the BTS Oxygen Guidelines recommend that oxygen should only be administered to patients with AECOPD if oxygen saturations are <88%, and that oxygen therapy should be adjusted to maintain saturations between 88 and 92%.[185]

One of the potential difficulties in administering controlled oxygen during hospital transfer is the need to initiate treatment with bronchodilator drugs by nebulizer, which are usually oxygen-driven. This inevitably results in the administration of HCO therapy during the period of nebulisation. The BTS COPD guidelines note that compressed air is rarely available in the majority of ambulance, and recommends that oxygen-driven

nebulisers be limited to six minutes.[185] Whilst this may limit the risk of hypercapnia to some extent, it does not overcome the risks associated with longer journey times, or the potential for nebuliser masks to be inadvertently left in place for longer.

The objective of this study was to compare the effect of bronchodilator nebulisers driven by oxygen versus air on the time course and severity of CO_2 retention in subjects with severe stable COPD. The hypothesis was that administration of bronchodilator drugs by oxygen-driven nebuliser would result in an increase in $PaCO_2$ compared with room air, and that this effect would be greater after the second nebulised bronchodilator administration.

METHODS

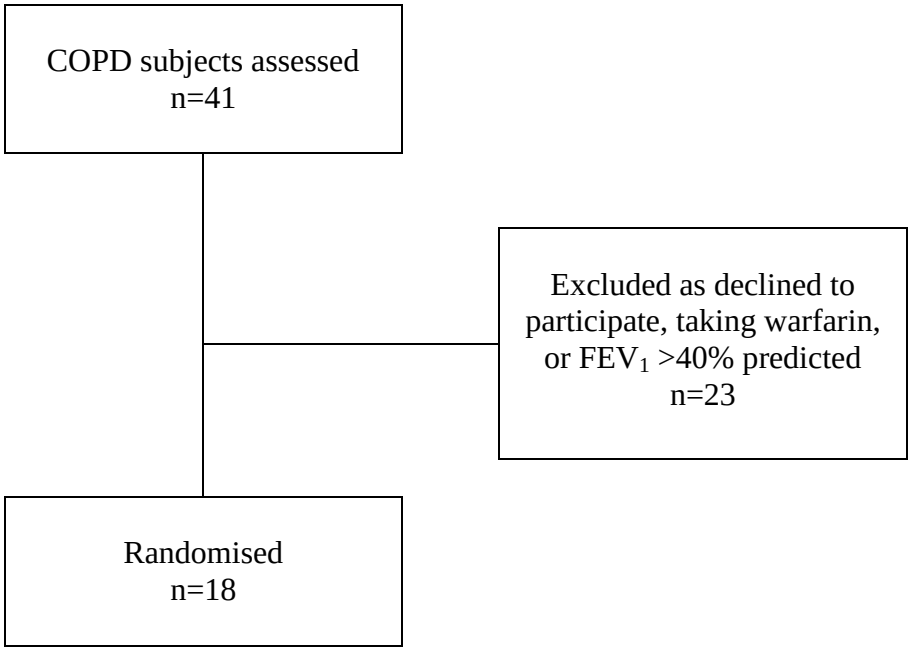
The trial was an open label, randomised, controlled, crossover study.

Subjects

Eligible participants were aged over 40 years with a doctor diagnosis of COPD and an FEV_1 ≤40% of predicted. Exclusion criteria were: sensitivity or other contra-indications to salbutamol or ipratropium bromide, additional risk factors for hypercapnic respiratory failure (BMI >40 kg/m^2, severe musculoskeletal weakness, chest wall restriction), long term oxygen therapy with >4 L/min of oxygen via nasal cannulae, and receiving warfarin therapy (due to the need for arterial blood gas measurement). Participants were recruited from existing outpatient COPD databases and the study was undertaken in the Clinical Measurement Unit (CMU) of Wellington Regional Hospital. Figure 1 shows the flow of subjects in the study.

Figure 1:

Flow of subjects in the study



Study intervention

The study comprised two visits one week apart. The reason for this was to minimise the risk that an exacerbation might occur, which might have led to a change in treatment or altered the response to the intervention. At the first visit, weight and height were recorded and spirometry was performed using a handheld spirometer (Micro Spirometer, Micro Medical Ltd, Rochester, UK) with the best of three attempts recorded. An arterial blood gas (ABG) was performed with the subject breathing room air, or if hypoxaemic (oxygen saturations <88%) on oxygen titrated to maintain SpO_2 between 88 and 92%. The ABG samples were obtained by radial puncture with a 22 gauge needle into a heparinised syringe and analysed immediately (Radiometer ABL800 FLEX, Copenhagen, Denmark).

The arterial partial pressure of carbon dioxide ($PaCO_2$) was estimated with a transcutaneous carbon dioxide ($PtCO_2$) monitor (TOSCA 500; Radiometer Basel AG; Switzerland). Subjects that required nasal cannula oxygen at baseline due to oxygen saturations below 88% continued to receive this throughout the nebuliser treatment periods. An earlobe was cleaned with an alcohol swab and allowed to dry, and the $PtCO_2$ probe was attached using an attachment clip and contact gel. A minimum of 10 minutes was allowed for arterialisation to occur and $PtCO_2$ readings to stabilise, at which stage the first randomised treatment was started.

Subjects received the two treatments in random order at study visits one week apart. The study treatments were identical apart from the nebuliser delivery method. Salbutamol (5 mg) and ipratropium bromide (500 µg) were nebulised over 15 minutes followed by a 5

minute interval, and then a further 5mg of salbutamol was nebulised over 15 minutes. After the second nebulisation, monitoring was continued for a further 15 minutes. Oxygen-driven nebulisers were delivered using a wall supply of oxygen at a flow rate of 8 l/min. Air-driven nebulisers were delivered with a portable high flow air-compression device (Portaneb, Respironics, Murrysville PA, USA). The $PtCO_2$, oxygen saturation, and heart rate were monitored continuously throughout the 45 minute study period and measurements recorded at 5 minute intervals. The FEV_1 was measured at baseline and at the end of each study treatment.

A computer generated randomisation schedule was provided by the statistician. Subjects were allocated to their treatment order by the study investigator. Blinding of the investigator and participants was not possible due to the use of the compressed air-driven device and wall mounted oxygen. The protocol was terminated if a subject demonstrated an increase in their $PtCO_2$ >10mmHg from baseline at any stage during either of the treatment periods.

Statistical analysis

The primary outcome variable was the change in $PtCO_2$ from baseline at the end of the second nebulisation period (t = 35 min). Secondary outcomes included the time course of $PtCO_2$ over the study period, the number of patients experiencing a rise in $PtCO_2$ >10 mmHg, the time course of heart rate and oxygen saturation responses during the study period, and change in FEV_1 at the end of monitoring. The primary analysis was a mixed linear model with the visit order and baseline measurement of the particular variable treated as a covariate. For the variables $PtCO_2$, heart rate and oxygen saturation, the sandwich estimator of variance-covariance structure of repeated measurements was used and the pre-specified comparisons were at 15, 35 and 50 minutes. FEV_1 was measured twice, at baseline before each treatment and at 50 minutes and a simple unstructured variance-covariance matrix was modelled.

Power calculations

For a difference of 4 mmHg (increase from baseline in the oxygen arm compared to the room air arm) with a standard deviation of 5.6, a sample size of 18 had 80% power to detect the nominated difference with a type I error rate of 5%. 6. A previous study looking at hypoventilation and ventilation-perfusion redistribution during oxygen-induced hypercarbia in AECOPD had noted that patients whose $PaCO_2$ increased by 3mmHg (8.3 ± 5.6, mean ± SD) had significant hypoventilation ($p=0.007$) and ventilation-perfusion mismatch ($p<0.05$) compared to those whose $PaCO_2$ did not rise.[225]

Ethics approval

Ethics approval was granted by the Central Regional Ethics Committee (CEN/09/12/093). The study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12610000080022).

RESULTS

Between April and May 2010 a total of 41 subjects were approached for inclusion in the study. Of these, 17 declined to participate, three were not eligible as currently taking warfarin, and three were not eligible due to an FEV_1 >40% predicted (Figure 1). The characteristics of the 18 randomised subjects are shown in Table 1.

The subjects had a mean age of 73, were predominantly male, and had severe airflow obstruction with a mean FEV_1 of 27% predicted. The mean $PaCO_2$ was 47.8 mmHg (range 38 to 56 mmHg) and mean oxygen saturation was 92.7%. In one subject the protocol was stopped during the oxygen treatment arm because the $PtCO_2$ increased by 11 mmHg after 15 minutes. At the end of the final nebulised treatment (t=35 minutes) the mean (SD) $PtCO_2$ was 53.0 (6.9) mmHg in the oxygen-driven arm and 49.9 (7.1) mmHg in the air-driven arm. In the mixed linear model incorporating baseline $PtCO_2$ and accounting for repeated measures, the mean $PtCO_2$ difference between the oxygen and air treatment arms was 3.0 mmHg (95% CI 0.08 to 5.2, P<0.01) and 3.1 mmHg (95% CI 1.6 to 4.5, P<0.001) at 15 and 35 minutes respectively.

Table 1: Baseline characteristics of subjects

Continuous variables	**Mean (SD)**
Age (years)	73.2 (6.1)
BMI (kg/m^2)	26.3 (6.3)
Pack years of smoking	50.2 (25.0)
Baseline arterial blood gas†	
• pH	7.41 (0.024)
• PaO_2 (mmHg)	61.8 (8.6)
• $PaCO_2$ (mmHg)	47.8 (5.5)
• Bicarbonate (units)	29.4 (3.0)
• Oxygen Saturation (%)	92.7 (2.7)
FEV_1 (litres)	0.71 (0.27)
FEV_1 (% predicted)	27.3 (10.3)
Categorical variables	**N/N (%)**
Male	13/18 (72.2)
Current smoker	2/18 (11.1)
Use long term oxygen	12/18 (66.7)
Home nebuliser	5/18 (27.8)
Long term oral steroids	7/18 (38.9)
Long-acting beta agonist	13/18 (72.2)
Long-acting antimuscarinic	9/18 (50.0)
Previous hospital admission	14/18 (77.8)

† Two subjects had ABG measurements while receiving supplementary oxygen in accordance with the protocol.

The change in $PtCO_2$ over the 50 minute study period is shown in Table 2 and Figure 2. Over the 50 minute study period the oxygen treatment arm demonstrated a progressive rise in $PtCO_2$ over the 15 minute duration of the first nebulisation, followed by a decrease towards baseline during the 5 minute interval, and a further rise over the 15 minutes of the second nebulisation. At the end of the study period, 15 minutes after the second nebulisation, the $PtCO_2$ had returned to baseline in the oxygen treatment arm. In the mixed linear model, the mean $PtCO_2$ difference between the oxygen and air treatment arms was -0.1 mmHg (95% CI -0.6 to 0.4, p=0.69) at 50 minutes.

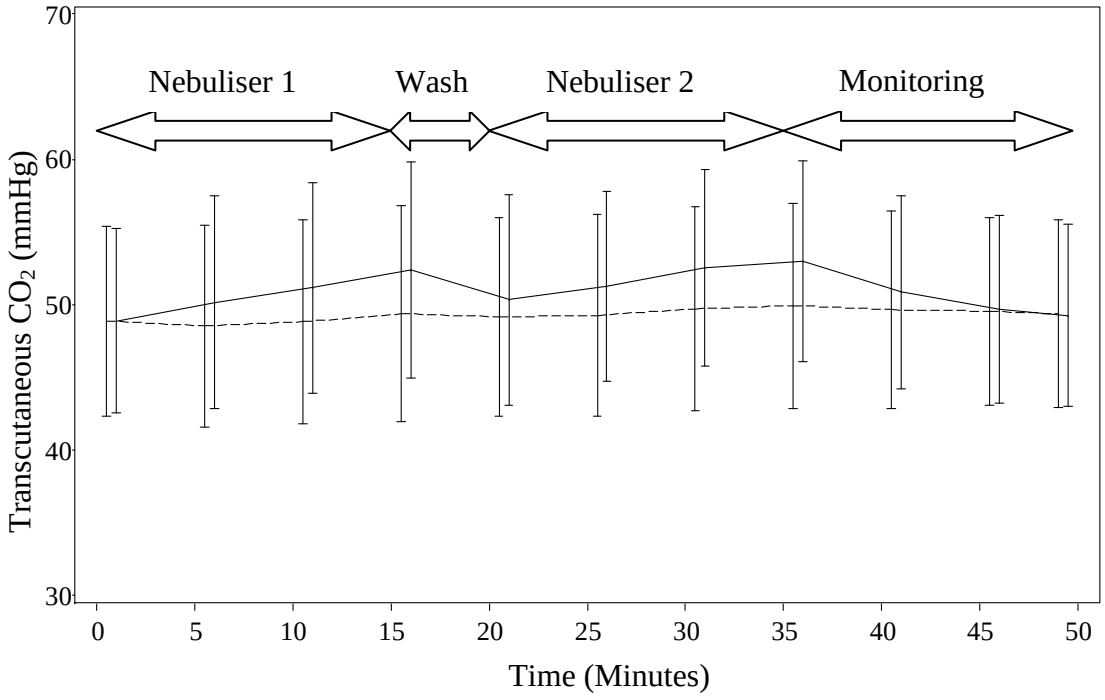
Table 2: Time course of $PtCO_2$ changes over the study period

Time (min)	Oxygen minus air $PtCO_2$ mean (SD) (mmHg)	95% CI†	P
0	0 (2.3)	-1.1 to 1.1	1.0
5	1.6 (3.7)	-0.2 to 3.4	0.8
10	2.3 (4.4)	0.2 to 4.5	0.038
15	3.0 (4.4)	0.8 to 5.2	0.01
20	1.2 (2.6)	-0.2 to 2.5	0.78
25	2.0 (2.8)	0.6 to 3.4	0.008
30	2.8 (2.7)	1.5 to 4.2	<0.001
35	3.1 (3.0)	1.6 to 4.5	<0.001
40	1.2 (2.2)	0.2 to 2.3	0.028
45	0.1 (1.8)	-.8 to 1.0	0.8
50	-0.1 (2.0)	-1.1 to 0.9	0.82

† Paired t-test

Figure 2:

$PtCO_2$ vs time for oxygen (solid line) and air-driven (dashed line) nebulisers over the study period. Vertical bars are ±1 standard deviation. One subject was withdrawn at time 15 minutes during oxygen treatment as the $PtCO_2$ increased 11 mmHg.



There was no significant difference between the two treatments in the change in heart rate, FEV_1, or FEV_1 percent predicted over the duration of the study period. There was a significant increase in oxygen saturation in the oxygen treatment arm throughout the study period (Table 3, Figure 3). In the mixed linear model incorporating baseline oxygen saturation and accounting for repeated measures, the difference in oxygen saturation was maximal at the end of the second nebuliser, (6.8%, 95% CI 5.5 to 8.1, $P<0.001$) and remained significantly greater at the end of the study period (1.5%, 95% CI 0.8 to 2.2, $P<0.001$).

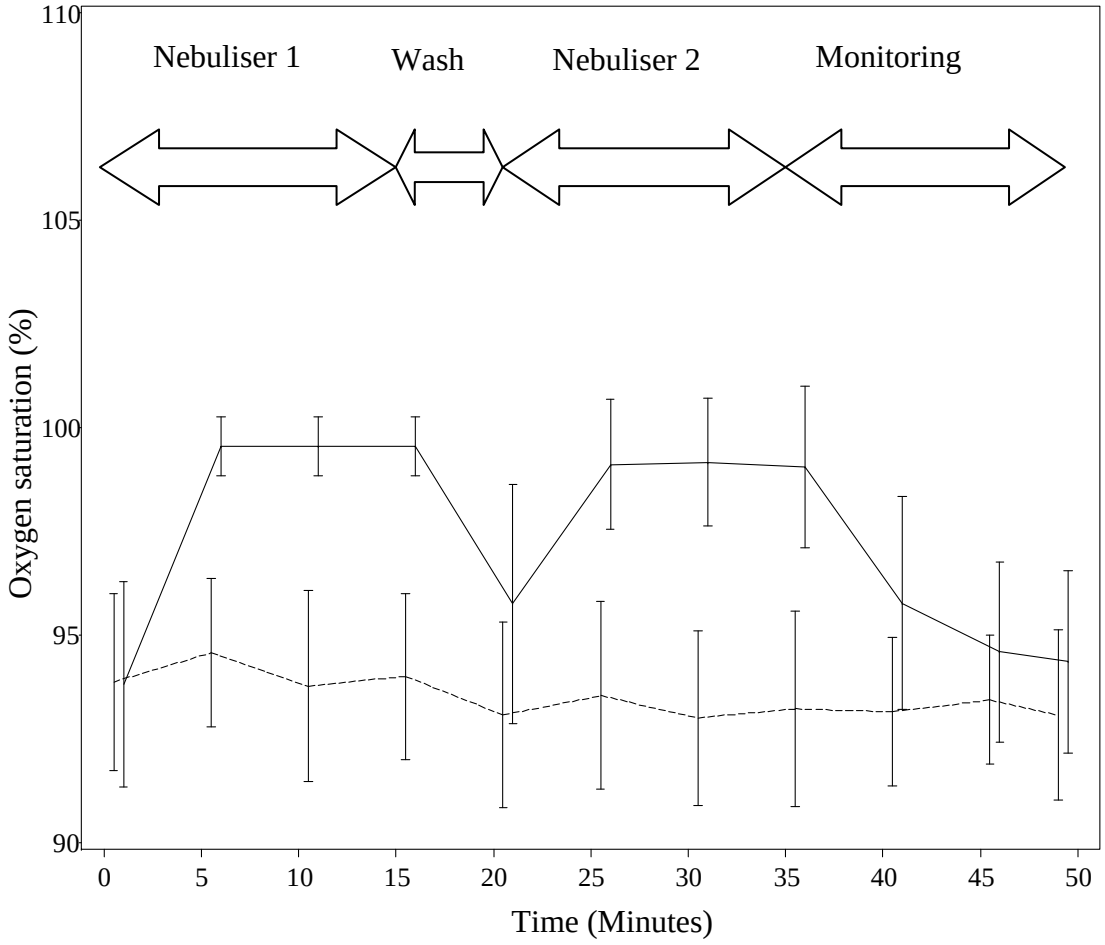
Table 3: Time course of oxygen saturation changes over the study period†

Time (min)	Oxygen minus Air Oxygen saturation % Mean (SD)	95% CI	P
0	0.3 (2.4)	-0.9 to 1.5	0.57
5	5.7 (2.3)	4.5 to 6.8	<0.001
10	6.1 (2.5)	4.9 to 7.4	<0.001
15	6.9 (3.0)	5.4 to 8.4	<0.001
20	2.8 (3.1)	1.3 to 4.4	0.001
25	6.7 (3.0)	5.2 to 8.2	<0.001
30	7.1 (2.8)	5.7 to 8.4	<0.001
35	7.0 (2.9)	5.6 to 8.4	<0.001
40	3.3 (2.8)	1.9 to 4.7	<0.001
45	2.0 (2.3)	0.8 to 3.2	0.002
50	1.7 (1.8)	0.7 to 2.6	0.001

†: Paired t-test

Figure 3:

Oxygen saturation vs time for oxygen (solid line) and air driven (dashed line) nebulises over the study period. Vertical bars are ±1 standard deviation



DISCUSSION

This randomised controlled trial has demonstrated that two oxygen-driven bronchodilator nebulisations resulted in a significant rise in $PtCO_2$ compared to air-driven nebulisation in subjects with stable severe COPD. The mean $PtCO_2$ level increased by 3.0 mmHg throughout the first 15 minute period of oxygen-driven nebulisation, and although it decreased during the 5 minute interval period, there was a similar increase of 3.1 mmHg during the second nebulisation, returning to the baseline level during the subsequent 15 minute observation period. Of concern, in one of the subjects who had chronic respiratory failure, the $PtCO_2$ increased by 11 mmHg after 15 minutes of the first nebulisation, illustrating the potential risk of worsening hypercapnia if bronchodilator nebulisation is driven by oxygen.

These findings complement those of Gunawardena et al[202] who investigated the effects of a single oxygen-driven bronchodilator nebuliser on $PaCO_2$ in three groups of inpatients: normocapnic subjects with an acute exacerbation of asthma, normocapnic subjects with AECOPD, and hypercapnic subjects with AECOPD. They demonstrated a significant rise in $PaCO_2$ of 7.7 mmHg in the hypercapnic group after 15 minutes of nebulised salbutamol treatment driven by oxygen at a flow rate of 8l/min. There was no significant difference in $PaCO_2$ in the other two groups. Our study extends these findings by demonstrating that when oxygen driven bronchodilator nebuliser is administered on a second occasion after a short interval of 5 minutes, the $PtCO_2$ again increases but not to a

higher level, than after the first nebulisation. Similar to the Gunawardena et al study we observed that the $PtCO_2$ fell to baseline levels in the 15 minute period following nebulisation.

There are a number of methodological issues relevant to the interpretation of the study results. Firstly, enrolled subjects had stable COPD rather than an acute severe exacerbation. This facilitated the study of subjects on two separate days and thereby conduct a randomised cross over trial. As a result, the magnitude of the increase in $PtCO_2$ with oxygen-driven nebuliser use in AECOPD is likely to have been underestimated as patients with stable COPD are less likely to develop oxygen-induced hypercapnia.[224] However, COPD sufferers with severe airflow obstruction were recruited, with a mean FEV_1 of 27% and mean baseline $PaCO_2$ of 47.8 mmHg. As a result, the subjects were representative of COPD patients likely to experience severe exacerbations of COPD requiring ambulance transfer to hospital, although ultimately it is not possible to be absolutely certain that we can extrapolate the data to an acute setting.[226]

Secondly, subjects were recruited from a local database of patients with COPD who were under respiratory follow-up or who had previously been admitted with AECOPD. The basis for the diagnosis of COPD was not revisited and neither did the inclusion criteria stipulate that subjects had to have a certain number of pack years, as is usual for COPD studies. This could have influenced the type of patient recruited, although all had repeat spirometry which confirmed they had COPD, at least according to spirometric criteria.

Thirdly, as the data within the database was not complete with regards to inclusion and exclusion criteria, it was not always possible to ascertain before contacting people who might be eligible to participate. Further information was gleaned from the hospital database (clinic and discharge letters) which enabled the database to be trimmed but the investigator could still not be entirely sure when potential participants were initially telephoned as to whether they might still be eligible. Additionally, patients were contacted in a random order from the database, in an attempt to get as representative a sample of the Wellington COPD population as possible. This may have introduced bias, though it does appear that no single region was over-represented.

Fourthly, the "declined to participate" rate is quite high at 41%. Some gave no reasons, whilst others felt they were too unwell or did not wish to travel. It is likely that these patients would require ambulance transfer should they have a severe exacerbation so the final study population may not be a true reflection of those most at risk of hypercapnia. One declined to participate due to illiteracy and did not wish to have any further information read out by an independent person.

Fifthly, it could be argued that some of the patients recruited were comparatively undertreated. Given the severity of COPD within the group, one would expect all of them to be on long-acting antimuscarinics and probably beta-agonists as well. A possible explanation for the lack of antimuscarinic prescription could be that fact that tiotropium had only been added to the approved prescribable list of medications in New Zealand in 2005 and it was being utilised less than had been predicted.[227]

The study was designed to replicate the initial ambulance management approach to AECOPD. In a recent audit of pre-hospital management of AECOPD, the average duration of ambulance transfer was 49 minutes (although data regarding the number of nebulisers received in the ambulance was not collected),[199] and similar ambulance transfer times of 33 and 45 minutes have been reported from the United Kingdom[190] and Australia.[201] It is tempting to suggest that these findings are likely to underestimate the risk associated with longer ambulance transfers where there is an opportunity for patients to receive a greater number of, or continuous, nebulised bronchodilator treatments. However, no specific studies have been performed looking at the number of nebulisers provided to a COPD patient in an ambulance, or if longer journeys increase the amount given. While the study design was based on pre-hospital management, the findings also apply to in-hospital care in the Emergency Department, medical ward or High Dependency Unit, in which bronchodilator nebulisers driven by oxygen may be administered frequently and/or continuously, without such close monitoring of oxygen saturations and CO_2. To ensure further generalisability to current local practice, the bronchodilator regime was an initial nebulisation of salbutamol and ipratropium bromide, followed by a second nebulisation with salbutamol.

Measurement of $PtCO_2$ as a non-invasive assessment of $PaCO_2$ was done to minimise the risk of complications associated with the insertion of in-dwelling arterial catheters on two separate visits. The $PtCO_2$ device we used has been validated in a previous study of patients with acute asthma and pneumonia, and has minimal bias and acceptable limits of agreement.[228]

The potential for oxygen-driven nebulisers to result in a rapid and marked increase in $PtCO_2$ was demonstrated by the subject who experienced an increase in $PtCO_2$ of 11 mmHg during the first nebulisation. This subject was a 67 year old female with a 44 pack year history of smoking though had been abstinent for 5 years. She'd had 2 admissions in the last year but never been admitted to intensive care. She was on LTOT with a baseline PaO_2 of 57mmHg, $PaCO_2$ of 55mmHg, FEV_1 of 0.55L (26% predicted) and a BMI of 22. This kind of physiological response poses a significant risk to patients transferred by ambulance, especially in the context of longer trip times, rising number of transfers and frequent dosing. Although the BTS COPD guidelines suggest limiting the length of oxygen-driven treatments to no longer than six minutes,[185] this poses practical problems and compliance uncertainties. A safer approach would be to use alternative methods of bronchodilator administration, such as multiple MDI actuations through a spacer, a technique that has demonstrated efficacy in COPD.[229] A second option would involve ambulance units carrying portable air jet compressor nebulisers for the administration of bronchodilators to COPD patients, which has been demonstrated to be effective in pre-hospital setting a recent randomised controlled trial.[201] Oxygen could then be continuously titrated as required by the use of nasal prongs, with the nebuliser mask applied over the prongs for drug delivery.

In conclusion this study has shown that the administration of bronchodilator via oxygen driven nebulisers results in worsening hypercapnia in stable patients with severe COPD. Given the weight of evidence demonstrating harm with high concentration oxygen in AECOPD, it is surely critical that health professionals in both the community and

hospital settings prioritise the implementation of alternative methods of drug delivery in this high risk group.

Table S1: Time course of heart rate changes over the study period

Time (min)	Oxygen minus Air HR Mean (SD)	95% CI	P†
0	2.6 (9.6)	-2.2 to 7.4	0.27
5	-1.4 (10.0)	-6.4 to 3.5	0.55
10	-1.1 (9.7)	-5.9 to 3.7	0.63
15	-1.1 (8.7)	-5.4 to 3.3	0.61
20	1.8 (11.6)	-4.0 to 7.	0.52
25	-0.6 (8.7)	-4.9 to 3.	0.79
30	-0.5 (8.4)	-4.7 to 3.7	0.80
35	-0.9 (7.9)	-4.8 to 3.0	0.62
40	1.1 (9.1)	-3.5 to 5.6	0.63
45	0.8 (9.3)	-3.8 to 5.4	0.73
50	1.0 (8.5)	-3.2 to 5.2	0.63

†**:** Paired t-test

Table S2: The FEV_1 response to nebulised bronchodilator treatment

Variable	Oxygen	Air
	Mean (SD)	**Mean (SD)**
Initial FEV_1 (L)	0.71 (0.27)	0.71 (0.27)
Initial FEV_1 (% predicted)	27.3 (10.3)	27.1 (9.7)
FEV_1 at 50 min (L)	0.76 (0.32)	0.77 (0.32)
FEV_1 at 50 min (% predicted)	29.2 (12.2)	29.4 (12.8)

Oxygen minus Air, at 50 min	Difference Mean (SD)	95% CI (P-value)†
FEV_1 (L)	-0.005 (0.075)	-0.042 to 0.033 (0.78)
FEV_1 (% predicted)	-0.22 (3.22)	-1.9 to 1.4 (0.78)

Mixed linear model with baseline measurement as a covariate	Estimate (95% CI)	P-value
FEV_1 (L)	-0.003 (-0.063 to 0.056)	0.91
FEV_1 (% predicted)	-0.50 (-3.2 to 2.2)	0.72

†: Paired t-test

CHAPTER 10

FINAL DISCUSSION AND CONCLUSION

Medical knowledge is constantly expanding and our understanding of the biological mechanisms underlying diseases, as well as the ways of treating them, are continually evolving. Well conducted clinical trials lead to a stronger theoretical basis for our knowledge, and they encourage clinicians to favour treatments with a proven evidence-base over those where evidence for their efficacy is weak or non-existent. This is not always true, of course, especially in rare diseases where clinical trials can be sparse.

Similarly, this thesis has evolved in its nature as the original intention was to look at nebulised magnesium in asthma and COPD, as well as the use of pre-hospital inhaled therapy by those patients suffering an acute exacerbation. Shifting research emphasis, time and labour constraints and my own interests (which were allowed to develop during my time at MRINZ) led to a change whereby I concentrated on AECOPD and three discrete but interlinked aspects of its management.

However, I feel that the end result is a cogent and coherent body of work looking at important clinical matters of current interest, namely new treatments in AECOPD, risk stratification in AECOPD and oxygen therapy in AECOPD. Each study looks at a different aspect of AECOPD, from ambulance trip through to emergency treatment and the decision to admit or discharge. The thesis reflects clinical pathways and the patient's

journey that I see every day in my current post as an acute physician with an interest in respiratory disease.

Unfortunately, I was unable to obtain enough good data to include a paper looking at the use of inhaled therapy by patient at home prior to hospital admission. I feel that this would have added another layer to the thesis. Additionally, I had intended to look at serum magnesium levels in COPD within a separate study, but again due to the difficulties in recruiting to the magnesium trial, it was felt that this should be included within that paper as a small part of the final analysis.

Looking at the studies themselves, despite the difficulty in recruitment, I believe that the study of nebulised magnesium is an important one in the treatment of AECOPD. Trials that cannot reject the null hypothesis are increasingly recognised as being of clinical usefulness. Medical journals have been accused of concentrating on positive outcomes, thus denying to the literature an important canon of work with the potential of influencing the results of meta-analyses of drug treatments, and the conclusions of guideline development groups. This leads to publication bias. Our randomised double-blind placebo-controlled trial is one of the few done in an emergency setting for AECOPD, and was therefore an important trial to have been performed. As mentioned, the use of nebulised magnesium as an adjunct to salbutamol did not lead to any additional statistically significant bronchodilatation. Given this, it would seem that the future of research into the utility of magnesium in COPD should concentrate on the intravenous

route. Whether it has the same effect as in asthma, especially at the severe end of the exacerbation spectrum remains to be seen.

The CRB65 study added to work already performed in New Zealand by the Waikato group headed by Chang and it shows the value of the score in predicting mortality in the short-term from AECOPD. However, whilst statistically valid (with a 'c' statistic estimate similar to that found when it is used in pneumonia) and potentially useful, it will only be truly helpful if utilised in day-to-day clinical practice. In developed countries, in hospital settings, this is not likely to be the case especially when alternatives are available. Even in primary care, it will probably be difficult to get general practitioners to use it, as the default setting is often the local hospital when faced with a patient with AECOPD who is breathless, and when other factors such as patient and family wishes, social support, frailty and availability of nebulised therapy are factored in. Many patients with AECOPD are likely to be quite dyspnoeic and they tend to be older than pneumonia cohorts, thus immediately giving many a CRB65 score of at least 2, which practically mandates admission. Future work in this field may concentrate upon finding scores that are more specific to AECOPD, rather than attempting to translate work that has been done with a different pathological process and with a different cohort of patients.

This brings us on to the oxygen trial which contributes to the growing body of evidence related to oxygen toxicity in COPD and other conditions.[230, 231] Although the trial was performed in an outpatient setting on selected stable patients with some respiratory compromise, evidenced by severe airflow obstruction and borderline hypoxaemia, the

results do not require such a huge leap of faith as to make one believe that they would not be replicated (even possibly to a worse degree) if a further study was to be conducted in a real-world setting of AECOPD, which would be the ideal scenario. There is no reason to suggest that it cannot be done, as trials looking at high-flow oxygen versus controlled oxygen have shown.[201] I believe that the trial I performed will further assist in the development of guidelines related to oxygen therapy and, in conjunction with those guidelines and future trials put an onus on ambulance services to standardise the care given to patients with AECOPD in the pre-hospital setting.

Finally therefore, I feel that this thesis is strongly clinically based and patient-centred with immediate implications for respiratory care. Together, these studies add to the evidence base concerning the acute treatment of COPD.

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