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Risk factors for prolonged ventilation in patients with Chronic Obstructive Pulmonary Disease presenting with acute respiratory failure

by

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vscnas001

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18/05/2009

Declaration

I, the undersigned, hereby declare that the work contained in this thesis is my own original work and that I have not previously in its entirety or in part, submitted it at any university for a degree.

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Signature

Dr.Nasief van der Schyff

18/05/2009

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Abstract

Introduction: Patients with COPD presenting to the Emergency Unit with acute hypercapnic respiratory failure often require invasive mechanical ventilation and subsequent admission to the intensive care unit (ICU). These patients are at an increased risk of prolonged and complicated ventilation and often experience weaning difficulties. In addition, the impact of a previous episode of pulmonary tuberculosis that might have resulted in structural lung disease on the duration of mechanical ventilation in such patients has not previously been evaluated.

Methods: All patients with COPD admitted to the Respiratory ICU at Tygerberg academic hospital from the 01st January 2004 until 31st December 2007 requiring intubation and invasive mechanical ventilation for acute hypercapnic respiratory failure were included in the study. Patients were categorized into those ventilated for longer than 7 days (defined as prolonged mechanical ventilation - PMV) and those surviving 7 days after admission to the ICU and who were successfully weaned (non-PMV). Early clinical and biochemical variables recorded within the first 24 hours after admission were evaluated and compared. The primary comparison was made on patients that survived for more than 7 days, comparing those ventilated for longer than 7 days with those successfully weaned on or earlier than the 7th day.

Results: A total of 69 patients were evaluated; 45 in the non-PMV and 24 patients in the PMV group. Baseline demographic, clinical, biochemical and radiological data for the 2 groups obtained in the first 24 hours were compared. Statistically significant differences in the following early clinical variables were found on univariate analysis: the presence of chest pain ($p < 0.05$), neurological impairment on admission ($p < 0.05$), the presence of shock ($p<0.05$) and the early use of inotropes($p<0.05$), a high requirement for oxygen (FiO2; $p=0.001$), low serum albumin ($p =0.05$), low haemoglobin ($p<0.01$), the presence of a respiratory pathogen on blood culture ($p<0.05$) and a high APACHE II score($p= 0.04$).A history of previous exposure to TB, the presence of cor pulmonale, ischaemic heart disease and structural lung disease ($p = 0.07$) were not statistically significant.

Conclusion: The early clinical features that predict the need for prolonged mechanical ventilatory support in patients with acute hypercapnic respiratory failure represents the severity of acute respiratory failure (FiO2), concurrent cardiac disease and /or circulatory failure (chest pain and/or shock with need for inotropes and possibly neurological impairment), sepsis (shock and positive blood culture) and severe concurrent disease (low serum albumin and /or haemoglobin and high APACHE II score). These may be of use in planning and in policy development for ICU services in the Western Cape and similar settings with restricted availability of ICU services.

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What are the risk factors associated with prolonged mechanical ventilation in patients with Chronic Obstructive Pulmonary Disease (COPD) requiring mechanical ventilation for acute hypercapnic respiratory failure?

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Introduction

The mortality of patients with Chronic Obstructive Pulmonary Disease (COPD) has increased steadily since the 1960's (1, 2). The World Health Organization (WHO) estimates that 80 million people worldwide had moderate to severe COPD in 2005 and that 3 million people died of the disease in that year .In addition, it further estimates that COPD will become the third leading cause of death by 2030. (3)

Patients with COPD presenting to the Emergency Department (ED) with acute hypercapnic respiratory failure often require invasive mechanical ventilation and subsequent admission to the Intensive care unit (ICU) (4, 5). They are at an increased risk of prolonged ventilation, complications and often experience weaning difficulties (5, 8,9,11,13,15). These problems result in an increased morbidity and mortality and place a considerable strain on health resources globally (6).

The early identification of predictors of prolonged mechanical ventilation (PMV) could assist clinicians in the management of these patients. Recognition of these might both enable physicians to correct variables that could change the course of the ICU stay, and assist in the efficient planning of health resources and ICU bed requirements. It might also inform policy and prevent admission of patients with very poor prognoses.

COPD in the Western Cape is known to be different to that in most developed countries. The direct applicability of risk factors derived from overseas studies to our unique patient pool is thus questionable. There is a high incidence of both HIV and

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Tuberculosis as well as adult malnutrition, essential hypertension, diabetes mellitus, cardiac failure and ischemic heart disease. (7, 8). Patients with COPD thus often have multiple co-morbidities and may pose diagnostic dilemmas to attending clinicians. The impact of these factors on the mechanical ventilation of patients with COPD has not previously been evaluated in South Africa.

The aim of the current study is to identify early clinical variables predictive of prolonged mechanical ventilation (PMV) and weaning difficulties in patients with COPD admitted with acute hypercapnic respiratory failure

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Methods

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5.1 Study Design: A retrospective cohort study .

5.2 Study Population:

All patients with COPD admitted to the Respiratory ICU at Tygerberg academic hospital from the 01st January 2004 until 31st December 2007 with the problem of acute hypercapnic respiratory failure was included in the study. Since patients who died within the first 7 days of admission could not be eligible for prolonged ventilation only those that survived for 7 days were included in the study. Patients requiring intubation and invasive mechanical ventilation were evaluated and categorized into those ventilated for longer than 7 days (defined as prolonged mechanical ventilation) and those who were successfully weaned in 7 days or less (non-PMV group). Clinical variables measured and recorded within 24 hours of admission were evaluated and compared. The impact of co-morbidities including a history of pulmonary tuberculosis, was also assessed.

Where available the diagnosis of COPD was made on the basis of spirometry; a previous lung function test performed within the last 3 years or once the patient had recovered from the current ICU admission. In the absence of documented airflow obstruction, the diagnosis of COPD was made by the attending consultant clinician who was registered as a pulmonologist or critical care specialist with the Health Professions Council of South Africa. In such cases, the diagnosis of COPD was based on the PALSA (Practical Approach to Lung Health in South Africa) diagnostic

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algorithm (18). This validated algorithm which is used in resource poor settings to diagnose COPD (where pulmonary function testing is not available) employs the following questions:

- Whether symptoms suggestive of COPD started later in life (usually after the age of 35 years)
- Whether symptoms worsened slowly over a period of time
- Whether there was a long history of daily or frequent cough and sputum production
- Whether patients were short of breath for most of the day, rather than at night or during the early hours of the morning (before their acute deterioration)
- Whether there was history of heavy smoking e.g. more than 20 cigarettes/day for 15 years or more.

The decision to intubate patients for acute hypercapnic respiratory failure was made by the attending clinician. The general guidelines used by the clinicians were (17):

- apnoea or respiratory pauses with loss of consciousness or gasping for air or imminent respiratory arrest,
- acute exacerbation of COPD with hypercapnic respiratory failure, tachypnea or severe dyspnoea plus at least one of the following
    a. altered mental status or persistent uncooperativeness;
    b. acute cardiovascular instability;
    c. inability to protect the lower airway or copious secretions;
    d. patients who could not tolerate non-invasive ventilation (NIV) or the development of progressive respiratory acidosis despite intensive initial therapy

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An “exacerbation” of COPD was defined as the presence of at least 2 of the 3 respiratory symptoms of dyspnoea, cough or purulent sputum production of sufficient severity to require admission to hospital (at the admitting doctor’s discretion)(13). Acute hypercapnic respiratory failure was defined as a $PaCO2 \geq 6.6$ kPA (50 mm Hg) and $pH \leq 7.30$ as measured by the pre-intubation arterial blood gas (ABG) analysis.

Patients were excluded from the analysis if any of the following were present:

- Unknown duration of mechanical ventilation prior to admission to the ICU
- Intubated for reasons not related to acute hypercapnic respiratory failure
- Patient died before 7 days post-admission
- Insufficient clinical data (i.e. if in the judgement of the researcher there was insufficient clinical and/or laboratory data in the medical records. Information relating to details of the current presentation, relevant investigations such as arterial blood gas analysis, chest radiographs, ECGs and a previous history relating to COPD were considered essential before patients were accepted onto the study)

The decision to perform a tracheostomy was made by the attending clinicians in the ICU. A standardised protocol to perform a tracheostomy was not followed. Instead, patients had a tracheostomy if the attending clinician anticipated prolonged and complicated ventilation. Patients were only weaned once they had recovered sufficiently from the initial insult which caused their acute deterioration. The weaning process involved a gradual reduction in the synchronised intermittent and pressure support ventilation. Patients were generally kept on small amounts of PEEP during the weaning phase (2 cm water). Patients were placed on pressure support ventilation

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once they were breathing spontaneously and did not require any additional synchronized breaths from the ventilator. Those who failed their initial weaning and who required up to three Spontaneous Breathing Trials(SBT) or as long as 7 days from the first SBT to achieve successful weaning were defined as having a "prolonged wean".

Patients were only extubated when they tolerated a minimum of 30-120 minutes of minimal ventilatory support (intermittent ventilation = 0, pressure-support ventilation $\leq$ 10cm H2O), had demonstrated a significant improvement in their level of consciousness once all sedation had been stopped and had demonstrated good respiratory muscle strength. Patients who required re-intubation or who died within 72 hours of extubation were classified as having failed extubation.

Patients were routinely administered nebulised bronchodilators (using salbutamol and ipratropium bromide) before intubation, whilst being ventilated and in the post-extubation period. They were also routinely administered subcutaneous heparin (unless a bleeding diathesis existed) and sucralfate through a feeding tube. Patients who were clinically assessed to have an exacerbation of COPD due to sepsis (viral or bacterial), also received appropriate antibiotics in keeping with South African Thoracic Society guidelines.[19]. With the exception of patients admitted to the ICU for peri-operative bronchoconstriction, all other patients received systemic corticosteroids. At the discretion of the attending clinician, select cases received intravenous theophylline for ongoing bronchoconstriction despite optimal therapy listed above. Whilst on full ventilation, patients were sedated with either midazolam or morphine to attain a Ramsay sedation score between 3 and 4. As per ICU policy,

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sedation was interrupted for 2 hours in the morning from 06H00-08H00.The sedation was also weaned as patients improved, airway pressures fell and need for ventilatory support reduced.

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Statistical analysis

A health statistician, using the Statistica version 8 programme, performed the analysis. Values in the PMV and non-PMV groups were compared by univariate analysis to identify potential prognostic variables. Multiple logistic regression analysis was performed to confirm their significance. Between group differences in categoric variables assessed using the Chi-squared squared test and continuous variables by the student t-tests. Continuous variables are presented as mean ± SD (or median with range in a non-normal distribution).Categorical variables are presented as a number.

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Ethics approval

This study was approved by both the Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town, and the Committee for Human Research at Stellenbosch University. Permission to access medical records was obtained from the Tygerberg Hospital administration. The data collection sheet used during data collection was anonymised and each patient given a unique study number (001,002,003etc). The names of patients are only known to the primary investigator. The approval numbers for this study are as follows:

- Committee for Human research, Stellenbosch University, International Review Board (IRB) number: IRB0005239
- Health Sciences Faculty, Research Ethics Committee , University of Cape Town, IRB number : IRB00001938

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Results

During the 4-year period of our study, 77 patients with COPD were admitted for acute hypercapnic respiratory failure requiring mechanical ventilation. Five patients died within 7 days from admission and were excluded from the study. A further 3 patients were excluded due to insufficient clinical information in their medical records. We were thus left with a sample of 69 patients which were evaluated.

The mean age in the non-PMV and PMV group was 58($\pm$4) and 55 ($\pm$ 4) years respectively (table 1). There was a male predominance in the non-PMV group (29 males vs. 16 females) but significantly more females in the PMV group (15 females vs. 9 males) (table 2). A high proportion of current smoking was noted in both groups (59 of 69 patients (85%)), but there were no significant difference in the smoking pack year history between the 2 groups. The majority of patients in both groups who presented with acute hypercapnic respiratory failure had an established diagnosis of COPD at the time of presentation. In the non-PMV group, this diagnosis was made at a primary care facility (77%). In 42% of patients in the PMV group, their usual outpatient follow-up was at a secondary hospital. Pulmonary function testing (either prior to or upon discharge) was only performed in one third of the patients (n = 24). The FEV_1 expressed as percent predicted was 49 % and 38% in the non-PMV and PMV group respectively indicating that the majority of patients in the study were in stage III according to the Global Initiative for Chronic Obstructive Lung Disease rating of severity.

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Table 1

Baseline Demographic characteristics

		non-PMV		PMV		
		n = 45	**SD**	**n=24**	**SD**	**† p-value**
Age		58	± 4	55	± 4	0.32
Sex	Male	29		9		
	Female	16		15		
Smoking	Current	40		19		
	Previous	4		3		
	Never	2		1		
	pack years	30	±6	33	±7	0.41
Known COPD*		44		23		
FEV1 (% predicted) (n)***	(n=23)	49	+14	38	+22	0.54
FEV1/FVC ratio (n)***	(n=23)	0.55	±0.08	0.44	±0.14	0.08
Use of Inhaled Steroids (n)***	n = 12	11		1		<0.05
Follow-up	primary care facility	35		14		
	Secondary care facility	4		10		
	Tertiary care facility	6		0		
Functional status**	Mean	2.18	±0.3	2.43	±0.25	0.57
EU presentation to ICU admission (hours)		42	±24	53	±30	0.01

† Mann-Whitney analysis
*** FEV1 and FEV1/FVC ratio: n = 23; PMV = 6 patients, non-PMV = 17
*Patients established with the diagnosis of COPD prior to hospitalization
**Functional status - Grade 1- independent
- Grade 2- Restricted but leaves house
- Grade 3- Housebound but ambulant and able to perform self care
- Grade 4- Bed/chair bound, unable to perform self-care

EU = Emergency Unit, ICU = Intensive care unit

	PMV	non-PMV	Total

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Male	9	(37%)	29	(64%)	38
Female	15	(63%)	16	(36%)	31
Total	24		45		

Table 2

Chi-Square table reflecting the gender distribution in the PMV and non-PMV groups respectively

The majority of patients in both groups had a grade 2-3 functional status with no significant difference between the 2 groups. Delay in the transfer from the Emergency unit to the ICU was associated with prolonged ventilation. A further 11 hour delay in the transfer from the EU to the ICU placed the patient at a statistically significant risk of prolonged mechanical ventilation (p=0.01).

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An expected finding was that an exacerbation of COPD due to pneumonia was the predominant cause of acute deterioration requiring ventilatory support in both groups. (Figure 1).This was however not a statistically significant (p=0.42) predictor of PMV. The diagnosis of pneumonia was made if the admitting chest radiograph demonstrated pulmonary infiltrates compatible with pneumonia in a patient with a short history of cough and purulent sputum. However, neither the admitting clinician nor the attending radiologist was blinded when interpreting the chest radiograph. This raises the possibility that patients could have been overdiagnosed with pneumonia thereby limiting the assessment of pneumonia as a predictive factor for PMV. There were only 2 cases of active pulmonary tuberculosis precipitating or concurrent with an acute exacerbation of COPD and both were in the non-PMV group. In addition, there were no patients requiring PMV for acute exacerbations caused by a pneumothorax, acute heart failure, acute coronary syndrome or a surgical non-respiratory intervention.

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Figure 1: Causes and co-morbid conditions in patients with COPD requiring mechanical ventilation for acute respiratory failure. Number of patients requiring prolonged mechanical ventilation defined as more than 7 days is shown in white, and those weaned in 7days or less, in blue.

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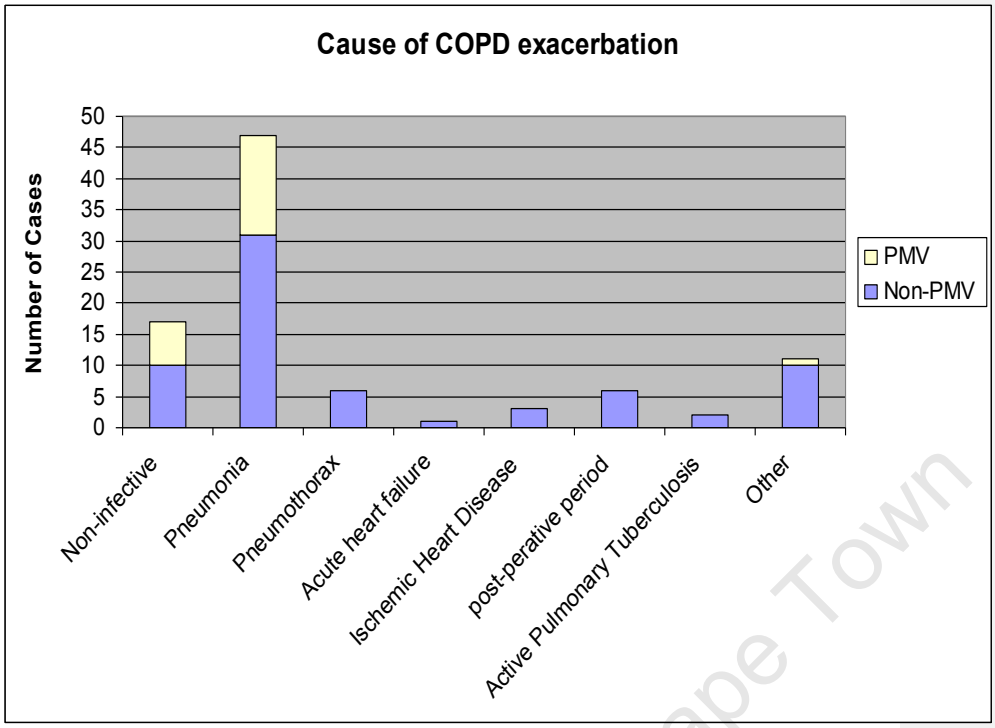

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None of several medical co-morbidities nor structural lung disease predicted PMV (Table 3). An important observation was the high frequency (21.7%) of previously treated pulmonary tuberculosis in the study cohort; 11 patients (comprising 24% of the group) in the non-PMV and 4 patients(16.7%)in the PMV group respectively. The impact of being HIV positive on the duration of mechanical ventilation could not be evaluated in this cohort due to the low frequency of HIV testing during the study period (HIV status unknown in 62% of patients). A surprise finding was that cor pulmonale and structural lung disease did not seem to predict prolonged mechanical ventilation in our study cohort.

Table 3:

Comparison of co-morbidities in COPD patients requiring prolonged mechanical ventilation for acute respiratory failure and those weaned within 7 days or less.

		non-PMV		PMV		p-value
		n = 45	Range	n = 24	Range	
Charlson Co-morbidity score*		3.42	(2.75-4.09)	3.61	(2.78-4.45)	0.94
PTB	Previous	11		4		0.65
	Current	2		0		NS
HIV	positive	1		1		NS
	negative	15		10		NS
	unknown	30		13		NS
Hepatitis/Cirrhosis		1		4		
Cor Pulmonale		20		8		0.37
Non-Cor pulmonale		2		2		NS
Chronic Renal Failure		1		3		NS
Diabetes Mellitus		5		4		0.29
Ischaemic Heart disease		9		3		0.51
Active Malignancy		6		0		NS
Structural Lung Disease**		18		4		0.07

* Charlson Co-morbidity score predicts the 1 year mortality for patients with multiple co-morbid conditions such as heart disease, stroke or malignancy (a total of 22 conditions). Each condition is assigned with a score (1, 2, 3 or) 6 depending on the risk of dying associated with this condition. The scores are then summed up and given a total score which predicts mortality.

** The presence of irreversible fibrotic changes on a chest radiograph which might be associated with volume loss.

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The clinical parameters for the 2 groups (Table 4) yielded a few interesting observations. The clinical presentation of chest pain was a statistically significant risk factor for prolonged ventilation ($p < 0.05$) with 67% of patients in the PMV group having experienced this symptom. However, coronary ischemia on the electrocardiogram was only noted in 6 patients (25%) in the PMV group suggesting an alternative aetiological explanation in most. The early occurrence of shock requiring the use of inotropes in the Emergency Unit or ICU was a statistically significant risk factor for prolonged mechanical ventilation. Not surprisingly, these patients were initially hypotensive with reduced cerebral perfusion and a depressed level of consciousness. The associated neurological impairment was thus also found to be a statistically significant risk factor. Patients who presented with severe hypoxemia requiring a higher FiO2 were at risk of prolonged mechanical ventilation ($p<0.05$). However, the level of respiratory acidosis and the degree of carbon dioxide retention did not predict prolonged ventilatory requirements.

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Table 4

Comparison of clinical data obtained within 24 hours of admission to the Emergency Unit or ICU in COPD patients requiring prolonged mechanical ventilation for acute respiratory failure and those weaned in 7 days or less.

		non-PMV		PMV		p-value
		n=45	Range	n=24	Range	
Symptoms	Cough	26		18		0.2
	Expectoration	18		15		0.12
	Chest pain	9		16		<0.05
	Neurological impairment	29		21		0.03
Shock		2		8		<0.05
Use of Inotropes within 24 hours of admission		2		8		<0.05
Arterial Blood Gas	FiO2	48.1	42-54.3	58.8	(48 - 69.5)	<0.05
	pH	7.19	7.13-7.25	7.16	7.07-7.25	0.99
	PCO2	9.9	8.5-11.4	10.3	8.5-12.1	0.79
	PO2	15.6	12.2-19	14.1	7.8-20.4	0.13
	Total CO2	26.8	23.5-30.2	30.3	26.1-34.5	0.27
	Standard bicarbonate	23.7	20.2-27.2	27.5	24.5-30.5	0.16
ECG	Right ventricular strain	19		7		0.32
	Coronary Ischemia	13		6		0.67
Chest Radiograph	Hyperinflation	45		24		NS
	Pulmonary infiltrates compatible with pneumonia	18		14		0.09
	Pulmonary infiltrates (other than pneumonia)	8		4		1
	Pneumothorax	5		2		0.72
	Structural lung disease	8		4		0.07
Albumin	g/L	27	23-31	24	19-29	0.05
Haemoglobin	g/dl	11.6	10.2-13.1	8.6	6.6-10.6	0.01
Creatinine	umol/L	103	84-122	135	98-171	0.13
ALT	mmol/L	66	16-116	120	25-256	0.07
CRP		67	33-100	102	54-151	0.2
White Blood cells	X10 9	13.5	11.6-15.5	16.6	11.9-21.4	0.36
Lactate		2.05	1.48-2.62	1.85	1.38-2.32	0.97
Blood Culture positive for respiratory pathogen		4		15		<0.05
APACHE II		15	12-17.5	19	16-23	0.04

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The presence of a pulmonary infiltrates suggestive of pneumonia on the admission chest radiograph was almost statistically significant as a risk factor for prolonged ventilation, but a syndromic diagnosis was not (p-values of 0.09 vs. 0.42). However, confirmation of pneumonia by the isolation of a respiratory pathogen in a standard blood culture was significant ($p < 0.05$). The presence of low serum albumin and/or haemoglobin was further statistically significant risk factors for PMV.

An important observation was the presence of low haemoglobin values in both groups (especially in the PMV group). The reason for this observation is not clear but a possible explanation may be an undiagnosed occult malignancy (of possible gastrointestinal origin). Unfortunately, these patients were not specifically investigated for their anaemia and our retrospective study design prevents immediate action being taken.

Table 5 summarises the associations between ventilatory patterns and risk of PMV. The duration from initial presentation to intubation was not predictive of PMV. However, as expected, mechanical ventilation with a high level of pressure support was predictive of PMV (<0.05). Interestingly, a failed extubation was not predictive of a prolonged mechanical ventilation ($p=0.89$).

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Table 5: Comparison of times to intubation and admission to the ICU, and complications and outcomes of mechanical ventilation in COPD patients requiring prolonged mechanical ventilation for acute respiratory failure and those weaned in 7 days or less.

		non-PMV		PMV		p-value
		n = 45	Range	n = 24	Range	
Presentation to intubation (Hrs)		22	3.6 - 41.4	20	0 - 44	0.7
EU presentation to ICU admission(Hrs)		42	22.4-63.4	53	14.6-92.6	0.01
Complications of MV	VAP	3		15		<0.05
	Prolonged wean	8		22		<0.05
	Failed extubation	9		5		0.89
	Tracheotomised	0		9		<0.05

The statistically significant prognostic variables are summarised in table 6.

Table 6 : Summary of variables associated with prolonged mechanical ventilation in COPD patients requiring mechanical ventilation for acute respiratory failure.

UnivariateAnalysis		
ANOVA	**Spearman**	**Spearman p-value**
FEV1/FVC Ratio	-0.42	0.08
Blood Albumin	-0.27	0.05
Creatinine	0.27	0.08
CRP	0.29	0.03
Inspired O2%(FiO2)	0.43	<0.01
Haemoglobin	-0.37	<0.01
APACHE II score ≥ 19	0.35	<0.01
Time from EU presentation to ICU admission (H)	0.34	0.01
Chi-squared test	**p-value**	
Use of Inhaled Steroids	<0.05	
Presentation with chest pain	<0.05	
Presentation with neurological impairment	<0.05	
Shock	<0.05	
Use of Inotropes	<0.05	
Respiratory pathogen isolated from blood culture	<0.05	

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Multiple logistic regression analysis was performed including variables found to be significant on univariate analysis (table 7). When these were corrected for possible confounders within the model, only an elevated creatinine and isolation of a respiratory pathogen were found to be significant.

Table 7: Logistic regression analysis of predictors of the need for prolonged mechanical ventilation in COPD patients requiring ventilatory support for acute respiratory failure.

Logistic regression analysis	p-value	odds ratio
Creatinine	0.03	1.01-48.7
Respiratory pathogen on Blood culture	0.01	1.9-20.8
FiO2	0.35	
Haemoglobin	0.87	
Neurological impairment	0.30	
Sex	0.14	

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Discussion

This is the first South African study to evaluate risk factors associated with prolonged mechanical ventilation in patients with acute hypercapnic respiratory failure associated with COPD. We have demonstrated how a few practical clinical variables may predict those at risk of prolonged mechanical ventilation and a protracted ICU stay. This is of particular relevance in the Western Cape where a relatively small number of ICU beds serve a large proportion of the population and the pressure on beds is extreme. The early identification of risk factors will identify those at risk of a prolonged stay that place a greater burden upon health resources. In resource-limited settings, this may enable clinicians to prioritize patients for ICU admission in cases where there are multiple requests for a single bed. In this regard, the finding that a delayed admission to the ICU (a greater interval between presentation to hospital and ICU admission) during which patients may or may not be placed on mechanical ventilation is associated with PMV, is of practical importance and in keeping with the general observation in critical care medicine that the first 24 hours are critical and delay in initiating full critical care measures is associated with a worse prognosis. Holding patients with acute hypercapnic respiratory failure in Emergency Units while waiting for an ICU bed is associated with additional morbidity and increased financial cost to the health system (although the latter was not studied in this project). This fact needs to be emphasized and communicated to health care administrators and planners.

An additional feature of delayed transfer is the relative lack of skills and personnel in the Emergency Unit for managing complex resuscitation and respiratory failure. In addition to medical and nursing staff shortages, there is a lack of expertise and support for use of complex equipment used for ventilating patients with respiratory

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failure with an increased risk of use of excessive pressure leading to barotrauma, poor management of fluid balance and delays in initiating appropriate antibiotics. These are some of the several problems associated with delays in admitting patients to the ICU.

Our study confirms the findings of several earlier studies. Liu *et al* (11) showed that an APACHE II > 20, the presence of shock, non-respiratory organ failure (predominantly cardiac and renal failure), refractory acidosis and age>65 years were found to be predictive of prolonged mechanical ventilation. In our study, APACHE II $\geq$19, shock and non-respiratory organ failure were also predictive of prolonged mechanical ventilation. However, since acute hypercapnic respiratory failure was an entry criterion for our study, acidosis was a feature in both groups and was not more severe in the PMV group. However, the greater refractoriness of the hypoxemia in the PMV group is suggested by the higher mean FiO2 in this group (59% versus 48% in the non-PMV and PMV groups respectively ($p<0.05$)).

Gursel (13) demonstrated that a ventilator-associated pneumonia and sepsis was predictive of mechanical ventilation longer than 7 days. This was also demonstrated in our study. However, we showed that APACHE II and albumin were also predictive of a prolonged stay after 7 days whereas these two variables were predictive only for a stay longer than 21 days in Gursel's study. As our patients were only followed up for 7 days, it is possible, that these 2 variables may also be predictive for a stay longer than 21 days.

In keeping with a study by Moran *et al* (10), we also showed that the need for a tracheostomy was predictive of PMV. However, the longer a patient was ventilated

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and subsequently stayed in the ICU, the greater the need became for a tracheostomy. A predictive relationship can therefore not be claimed.. A standardised protocol was not followed for the placement of the tracheostomy tube at a designated time after admission. The decision to perform a tracheostomy was made if the attending clinician anticipated a prolonged and complicated ventilation in view of the patient's clinical status.

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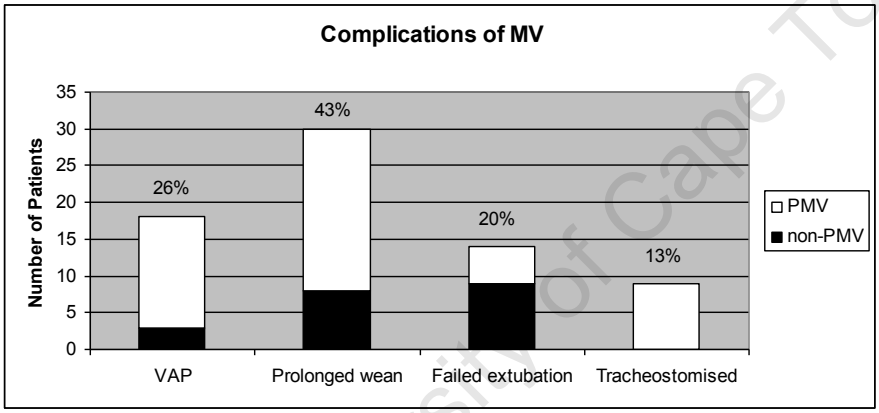
Figure 2. Complications and outcome in 69 COPD patients requiring mechanical ventilation for acute respiratory failure. VAP = ventilator-associated pneumonia, prolonged wean defined as patients who fail initial weaning and require up to three Spontaneous Breathing Trials(SBT) or as long as 7 days from the first SBT to achieve successful weaning failed extubation defined as one or more attempt to remove an endobronchial tube that necessitated replacement of the tube or tracheostomy



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In contrast to all previous studies on this topic, we also demonstrated that our patients were significantly younger (mean age = 55 years in the PMV group; SD $\pm$ 4 years); possibly indicating the relatively earlier age of onset of COPD in Cape Town. Despite our patients being 10-15 years younger than those listed in the studies above, they had similar pulmonary function tests (in those in whom it was available) and were also categorised as severe COPD (stage III GOLD).

Our study also aimed to investigate the significant co-morbidities seen in patients presenting with a severe exacerbation of COPD requiring mechanical ventilation. We are the first to investigate the relationship between pulmonary tuberculosis and the duration of mechanical ventilation in patients with COPD. Our results suggest that previous pulmonary tuberculosis is not associated with PMV. The prevalence of previous pulmonary TB in our study was 21.7%. This is comparable to the overall 14.5% prevalence (19.25% male, 11.9% female) of previous TB seen in the Cape Town cluster of the BOLD study (22). The slight difference could be explained by the significantly larger sample size used in the BOLD study (n=896). Interestingly, the patient cluster selected from Cape Town in the BOLD study were from 2 areas (Ravensmead and Uitsig) which are serviced by Tygerberg hospital. A second important observation in this study is that COPD patients who were ventilated for acute respiratory failure had a very strong smoking history with 95 % having a history of more than 30 pack years. Once again, this finding was similar to that in the BOLD study where 83% of men and 59% of women gave a history smoking at some stage in their lives. An unexpected finding was that the presence of cor pulmonale, ischemic heart disease and structural lung disease did not predict a PMV. This is particularly significant as the presence of these variables in the past were used to screen patients at

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risk for PMV and the allocation of ICU beds. As most patients did not receive an echocardiogram or a definitive test to evaluate their coronary arteries (e.g. coronary angiogram), we cannot reliably confirm or exclude the diagnosis of cor pulmonale or ischaemic heart disease in this patient group. Whether the presence of these variables conferred an increased mortality in the short to medium term is uncertain.

It makes sense that patients who are critically ill at initial presentation are at the highest risk for PMV. These patients often had severe hypoxemia and required a high FiO2 to compensate for a large alveolar-arterial gradient (A-A gradient). In addition to their profound hypoxemia, they often required aggressive fluid resuscitation and inotropic support for septic shock. They were thus at a higher risk of acute renal failure secondary to acute tubular necrosis. From a biochemical point of view, they often had significantly elevated inflammatory markers (white cell count and highly sensitive C-reactive protein) and were more likely to have positive blood cultures. The activated state of their inflammatory system often manifested with a low albumin and anaemia. It is thus readily apparent why the variables listed in table 5 were shown to be statistically significant for predicting PMV in these patients.

The finding that the presenting complaint of chest pain is an independent prognostic factor for PMV is somewhat surprising. As mentioned, 16 patients in the PMV group presented with chest pain. Of these patients, only 6 had evidence of coronary ischemia on their admitting ECG. Unfortunately, cardiac enzymes were not routinely requested and the absence of echocardiography makes it difficult to exclude pulmonary hypertension as a cause of the chest pain. Also,the possibility of acute pulmonary embolus needs to be considered as patients with COPD are at increased risk of

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thromboembolism. Other likely causes are pleurisy and rib fractures in osteopenic patients. The causes and prognostic value of chest pain in this patient cohort are thus uncertain. Due to the retrospective nature of this study, it was not possible to influence the management in these patients and thus other causes of chest pain were not evaluated.

The limitations of our study are follows:

1. The relatively small patient numbers
2. The selection bias resulting from the exclusion of patients who did not survive for 7 days post-admission. However, only 5 patients were excluded on this basis, which is unlikely to have significantly affected the statistical significance of the variables evaluated.
3. The retrospective study design
4. The fact that only 34% of patients had pulmonary function testing and documented airflow obstruction.

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In Conclusion

We have identified early clinical predictors in patients with COPD who presented with acute hypercapnic respiratory failure in an area endemic for tuberculosis. These variables may be of clinical value in assisting clinicians in the prioritization of admissions to the ICU in situations where there is great demand and insufficient ICU beds

The importance of early admission of these patients to an ICU is confirmed, especially when multiple predictors of prolonged ventilation are present (for example, shocked requiring a high FiO2 and inotropes, those with anaemia and/or a low serum albumin, and those with blood-culture positive pneumonia). The importance of current smoking and the role of pulmonary tuberculosis as contributory causes as well as the relatively early age onset of severe COPD associated with respiratory failure deserves special study in this region.

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List of Addenda

<u>Addendum 1</u> : Data Collection Sheet

1	**Patient Identifier number:**		
	Date admitted (ddmmyy)		
	Date discharged (ddmmyy)		Yes= Y No=N
	Variable	**Variable sub analysis**	
	Age (years)	Actual age	
	Gender	Sex (M=1/F=2)	
	Smoking History	Smoking History (C/P/N/U)	
		Pack Years	
	Known COPD (including Chronic Bronchitis and emphysema)		
	Usual Follow-up care provider (GP=G, PC=P, SC=S, T, V)	Follow-up	
	Functional status prior to hospitalization/deterioration	Status (1, 2, 3, 4)	
	Use of Inhaled Steroids	Seroids (Y , N)	
		Compliance (Y, N)	
	Oral steroid usage	Long term use of oral steroids (>30days)	
		Number of short (≤ 14 days) courses of oral prednisone over last year	
	Daily use of B2 agonists		
	Daily use of Ipratropium bromide		
	Daily use of oral theophylline		
	Daily use of long-acting B2-agonist		
	Daily use of B-Blockers		
	Daily use of NSAIDS/Aspirin		
	Domiciliary Home Oxygen	(Y, N)	
	Charlson Comobidity Score*	Score	
	Charslon morbidity index	Index	
	History of Pulmonary Tuberculosis	Currently on treatment	
		Previously treated	
		Never	
		Hs of non-compliance	
		Number of PTB episodes	
	HIV status	HIV (P, N, U)	
		CD4 count if known	
		On Anti-Retroviral therapy	

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2	Cirrhosis		
	Immunosuppressed		
	Cor Pulmonale (clinical or ECG)		
	Non-cor pulmonale		
	Chronic Renal Failure		
	Diabetes Mellitus		
	History of Myocardial Infarction		
	Ischemic heart disease		
	Active Malignancy		
	Previous ABG prior to current presentation	Type (1, 2) or Normal (n)	
	FEV1 (% predicted) in last 5 years	FEV1%	
	FEV1 (ml)	FEV1	
	FEV1/FVC Ratio	Actual ratio	
	Previous Hospital admission for COPD exacerbation in last year	(Y, N)	
		Number of Hospitalizations in last year	
	Number of Emergency unit visits for COPD exacerbation in preceeding year		
	Number of unscheduled medical visits to day hospital/GP in preceeding year		
	Previous Intubation for COPD	Yes/No	
		Number of previous intubations	
	Occupational exposure to gas, fumes or dust	yes/no	
	Previous Chest surgery		
	Other known Lung Disease		
	Known Drug Allergies		
	Cause of COPD	Non-infective exacerbation	
	Exacerbation	Pneumonia	
		Pulmonary Embolus	
		Pneumothorax	
		Heart Failure	
		Ischemic Heart Disease	
		Post-Operative period	
		Active Pulmonary Tuberculosis	
		Other	
	Increased recent	Dyspnoea	
		Cough	
		Expectoration	
		Chest pain	
		Sputum purulence	
	Signs of severity	Cyanosis	

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3		Neurological impairment	
		Lower limb oedema	
		unable to complete sentences	
		Use of accessory muscles	
	Heart rate (beats/min)		
	Respiratory Rate (breaths/min)		
	Arterial Blood Pressure (mm Hg)		
	Shock		
	Urine output / 24 hours (ml)		
	Treatment given	B2 agonists	
		Anti cholinergic agents	
		Inhaled steroids	
		Systemic steroids	
		Oxygen therapy	
		Antibiotics	
		Inotropes	
		Theophylline	
	Arterial Blood Gas:	Ph	
		PCO2 (Kpa)	
		PO2 (KPA)	
		Total HCO3 (mmol)	
		Standard HCO3 (mmol)	
		BE	
	ECG	Right ventricular Strain	
		Evidence of coronary Ischemia	
	Chest Radiograph	Hyperinflation	
		Pulmonary infiltrates compatible with pneumonia	
		Pulmonary infiltrates (other than pneumonia)	
		Pneumothorax	
		Structural lung disease	
	Blood Albumin(g/l)		
	Haemoglobin		
	Haematocrit		
	Creatinine (umol/L)		
	ALT		
	CRP		
	White cell count (X 10 to power 9)		
	Heart rate (beats/min)		
	Respiratory Rate (breaths/min)		
	Arterial Blood Pressure (mm Hg)		
	Shock		
	Urine output / 24 hours (ml)		
	Treatment given	B2 agonists	
		Anti cholinergic agents	
		Inhaled steroids	
		Systemic steroids	
		Oxygen therapy	
		Antibiotics	

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4		Inotropes	
		Theophylline	
	Arterial Blood Gas:	Inspired O2%	
		Ph	
		PCO2 (Kpa)	
		PO2 (KPA)	
		Total HCO3 (mmol)	
		Standard HCO3 (mmol)	
		BE	
	ECG	Right ventricular Strain	
		Evidence of coronary Ischemia	
	Chest Radiograph	Hyperinflation	
		Pulmonary infiltrates compatible with pneumonia	
		Pulmonary infiltrates (other than pneumonia)	
		Pneumothorax	
		Structural lung disease	
	Blood Albumin(g/l)		
	Haemoglobin		
	Haematocrit		
	Creatinine (umol/L)		
	ALT		
	CRP (mg/L)		
	White cell count (X 10 to power 9)		
	Lactate		
	Blood culture	Positive (p) or negative (n)	
		Respiratory pathogen	
		non-respiratory pathogen	
	Non-Invasive Ventilation	Time on NIV before Intubation(hours)	
	Time from presentation to intubation	Time (hrs)	
	Time from EU presentation to ICU admission	Time(hours)	
	APACHE II score	After 24 hours in ICU	
	Duration of mechanical ventilation(MV)	Time (days)	
	Complications of MV	VAP	
		Pneumothorax	
		Difficult wean	
		Prolonged wean	
		Failed extubation	
	Duration of ICU stay	Time (days)	
	Duration of Medical High Care		
	Duration of Hospital stay (Days)	Time (days)	
	Tracheostomised	Y/N	

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Addendum 2 : Charlson Co-morbidity score

Condition	Assigned Weight	Condition	Assigned Weight
myocardial infarction	1	Hemiplegia	2
congestive heart failure	1	renal disease moderate or severe	2
peripheral vascular disease	1	diabetes with end organ damage	2
cerebrovascular disease	1	any malignancy	2
Dementia	1	Leukemia	2
chronic pulmonary disease	1	malignant lymphoma	2
connective tissue disease	1	liver disease. moderate or severe	3
ulcer disease	1	metastatic solid malignancy	6
liver disease mild	1	AIDS	6
Diabetes	1		

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Glossary

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- Refractory Acidosis: pH persistently less than 7.3 despite optimal resuscitation
- Accessory Muscles: suprasternal, intercostal and abdominal muscles
- Chest X-Ray features:
    - Hyperinflation- Appearance on Chest radiograph of an increased lung volume suggested by more than 6 anterior ribs on the PA view.
    - Pulmonary infiltrates- the appearance of abnormal shadowing on the chest radiograph. These may be areas of opacification, reticulation or micro-nodules.
    - Structural lung disease- The presence of irreversible fibrotic changes on a chest radiograph which may be associated with volume loss.

- Complications of ventilation:
    - **Ventilator associated pneumonia**- nosocomial bacterial pneumonia that has developed in patients who are receiving mechanical ventilation
    - **Prolonged**- Patients who fail initial weaning and require up to three Spontaneous Breathing Trials(SBT) or as long as 7 days from the first SBT to achieve successful weaning
    - **Prolonged mechanical ventilation**- receiving continuous mechanical ventilation for 7 days or longer
    - **Failed extubation**- Patient having to be re-intubated or dying within 72 hours of extubation
- APACHE II – Acute Physiology and Chronic Health evaluation II. – A prognostic scoring system used in the ICU

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- Number of Pack Years - (number of cigarettes smoked per day x number of years smoked)/20
- Functional Grade
  - Grade 1- independent
  - Grade 2- Restricted but leaves House
  - Grade 3- Housebound but ambulant and able to perform self care
  - Grade 4- Bed/chair bound, unable to perform self-care
- FEV1 : Forced Expiratory Volume in 1 second
- FVC - Forced Vital capacity
- ECG diagnosis of ischaemic heart disease

  Signs of Myocardial infarction according to the Minnesota codex:
  - ST elevation or depression of at least 1.5mm
  - negative T-wave in the absence of pharmacological and extra cardiac conditions known to affect repolarization
- Cor Pulmonale
  - Clinical - Palpation of left parasternal heave with auscultatory features of a loud second heart sound in the pulmonary area
  - ECG - signs of right ventricular hypertrophy (RVH) or overload
    - Type A RVH : dominant R wave in V1 and V2, rS pattern in V5 and V6
    - Type B RVH : Rs pattern in V1, absent or marginal increase of R wave amplitude
    - Type C RVH : absent or marginal increase of R wave amplitude from V1-V6, deep S-wave in all praecordial leads
- Type 1 Respiratory Failure : $PaO_2 < 8$ kPa ; $PaCO_2 < 7$ kPA

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- Type 2 Respiratory Failure : $PaO_2 < 8$ kPa ; $PaCO_2 > 7$ kPA
- ALT : Aminoalaninetransferase
- CRP : C-Reactive Protein
- Cr = Creatinine

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