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EFFECTIVENESS OF CONTINUOUS OR BILEVEL POSITIVE AIRWAY PRESSURE VERSUS STANDARD MEDICAL THERAPY FOR ACUTE ASTHMA

Silmara Guanaes Hanekom

A dissertation submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in fulfillment of the requirements for the degree of Masters of Science in Physiotherapy

Johannesburg, 8 November 2007

DECLARATION

I, Silmara Guanaes Hanekom, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science in Physiotherapy at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree of examination at this or any other University.

……..

8 of November, 2007

PUBLICATIONS AND PRESENTATIONS ARISING FROM THIS STUDY

POSTER PRESENTATION

Hanekom, S.G., van Aswegen, H., Eales, C., Engelbrecht, L. & Becker, P. 2006. Noninvasive positive pressure ventilation in acute asthma exacerbation at an emergency department. South African Critical Care Congress, 3-7 September, Bloemfontein, South Africa.

VERBAL PRESENTATION

Hanekom, S.G., van Aswegen, H., Eales, C., Engelbrecht, L. & Becker, P. 2007. Effectiveness of continuous and bilevel positive airway pressure versus standard medical therapy for acute asthma. South African Critical Care Congress, 14-17 August 2007, Sun City, South Africa.

ABSTRACT

Patients with respiratory failure secondary to acute asthma exacerbation (AAE) frequently present at emergency units. Some patients may develop respiratory muscle fatigue. Current guidelines for the treatment of an AAE center on pharmacological treatment and invasive mechanical ventilation. Noninvasive positive pressure ventilation (NPPV) has an established role in COPD exacerbations. The role it can play in an AAE remains unanswered although it is frequently used in the clinical setting. *Aims:* The present study proposed to investigate if the early use of NPPV in the forms of continuous positive airway pressure (CPAP) or bilevel positive pressure ventilation (BPPV) together with standard medical therapy in AAE can decrease time of response to therapy compared to standard medical therapy alone. We further tested the effect of BPPV against CPAP. *Methods:* Asthmatic patients who presented with a severe AAE (PEFR % predicted < 60 %) at the emergency unit were randomized to either standard medical therapy (ST), ST and CPAP or ST and BPPV. Thirty patients fulfilled the inclusion criteria for the study. Groups presented similar baseline characteristics. The mean age for the group was 42.1 ± 12.6 years. Mean baseline PEFR % predicted was 35.2 ± 10.7 % (ST), 30.5 ± 11.7 % (ST + CPAP) and 33.5 ±13.8 % (ST + BPPV). *Results:* Hourly improvement (Δ) in respiratory rate and sensation of breathlessness was significantly better in the BPPV intervention group. Improvement (Δ) from baseline to end of treatment in respiratory rate and sensation of breathlessness was significant for both CPAP and BPPV ($p = 0.0463$; $p = 0.0132$ respectively) compared to ST alone. Lung function was significantly improved in the CPAP intervention group hourly and from baseline to end of treatment ($p = 0.0403$ for PEFR and $p = 0.0293$ for PEFR % predicted) compared to ST + BPPV and ST alone. The mean shift (Δ) in PEFR from baseline to 3 hours of treatment was 67.4, 123.5 and 86.8 L/min ($p = 0.0445$) for ST, ST + CPAP and ST + BPPV respectively. This corresponded to a 38.1, 80.8 and 51.7 % improvement in lung function respectively. *Discussion:* The effect of BPPV on the reduction of respiratory rate and sensation of breathlessness could be related to the inspiratory assistance provided by BPPV. The significant improvement in lung function in the CPAP group could be related to its intrinsic effect on the airway smooth muscle and / or on the airway smooth muscle load. *Conclusion:* The present results suggest that adding NPPV to standard treatment for an AAE not only improves clinical signs faster but also improves lung function faster. CPAP seems to have an intrinsic effect on the airway smooth muscle so rendering it more effective in ameliorating lung function.

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LIST OF ABBREVIATIONS

AAE	acute asthma exacerbation
ABG	arterial blood gases
AHR	airway hyperresponsiveness
AM	accessory muscle use
ANOVA	analysis of variance
ASM	airway smooth muscle
BiPAP®	bilevel positive airway pressure (Respironics trademark name)
BP	blood pressure
bpm	breaths per minute or beats per minute
BPPV	bilevel positive pressure ventilation
β	beta
cmH_2O	centimeters water
$cmH_2O.L^{-1}.s^{-1}$	centimeters water per liter per second
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
DBP	diastolic blood pressure
DH	dynamic hyperinflation
EELV	end expiratory lung volume
EPAP	expiratory positive airway pressure
FEV_1	forced expiratory volume in one second
FRC	functional residual capacity
GW	general ward
HC	high-care ward
ICU	intensive care unit
IPAP	inspiratory positive airway pressure
ITL	inspiratory threshold load
ITP	intrathoracic pressure
L/min	liters per minute
L	liters
LS	lung sounds
mmHg	millimeters mercury

M/F	male / female
NaCl	natrium chloride
NPPV	noninvasive positive pressure ventilation
OW	overnight ward
PEEP	positive end expiratory pressure
PEEPi	intrinsic positive end expiratory pressure
PEFR	peak expiratory flow rate
PEFR % pred	peak expiratory flow rate percentage of predicted
Pes/PImax	esophageal pressure divided by maximum inspiratory pressure
$PaCO_2$	partial pressure of carbon dioxide
pH	potential of hydrogen ion
PaO_2	partial pressure of arterial oxygen
$PD_{20}FEV_1$	drug dosage at which a 20 % fall in FEV_1 is achieved
RR	respiratory rate
SB	sensation of breathlessness
SBP	systolic blood pressure
ST	standard therapy
sGaw	specific airway conductance
Ti/Ttot	total inspiratory time divided by total breathing time

CHAPTER I

INTRODUCTION

1.1 BACKGROUND

Acute asthma exacerbation is a major cause of respiratory failure that patients present with at emergency departments. Lack of response or a delayed response to treatment can result in respiratory muscle fatigue and the need for ventilatory assistance.

Clinical presentation of a patient with an acute exacerbation of asthma can range from a high respiratory rate, the presence of wheezes and use of accessory muscles to extreme agitation and hypercarbia. Patients mainly complain of "shortness of breath", "tight chest" and "can't get air in". This sensation of breathlessness is a consequence of respiratory muscles that are severely overloaded. Much of the inspiratory effort by these muscles is not rewarded with airflow and the excessive positive pressure in the lung places these muscles in a shortened position rendering them less efficient (Macklem, 1984; Decramer, 1997; De Troyer, 1997). Although asthma is a reversible airflow obstruction pathology, some of the patients will recover in a few hours while others will have to be admitted for longer and more intensive care and monitoring.

The intensity of bronchospasm, the time since the exacerbation started and the degree of response to treatment will determine if these patients develop respiratory muscle fatigue or not. Although not many AAE patients need intubation, the intubation procedure can initially worsen the obstruction, hyperinflation and cause laryngospasm (Papiris et al., 2002; Phipps & Garrard, 2003). This is usually followed by a prolonged stay in the intensive care unit (ICU) with difficult ventilation and often the need to use paralytic agents. Add to this the use of steroids and the perfect conditions are set for increased risk of ventilator acquired pneumonia and critical illness polyneuropathy with difficulty to wean from ventilation (Fagon, Chastre & Hance, 1993; Papiris et al., 2002; Phipps & Garrard; 2003).

Predictors of good outcome in the management of AAE in the emergency unit have been shown to be a faster improvement in lung function in the first half an hour of treatment (Rodrigo & Rodrigo, 1998; Rodrigo, Rodrigo & Hall, 2004). One of the newer ways of providing patients in respiratory failure with ventilatory support is noninvasive positive pressure ventilation (NPPV). Noninvasive ventilation refers to the application of positive airway pressure to the lungs without the need for an artificial airway (Meyer & Hill, 1994; Meduri et al., 1996; Jasmer, Luce & Mathay, 1997; Evans, 2001). This has the potential to avoid many complications associated with intubation like soft tissue trauma during intubation, sinusitis, increased risk of hospital acquired pneumonia, increased hospital stay and increased bronchospasm (Fagon, Chastre & Hance, 1993). Noninvasive ventilation has been extensively researched in chronic obstructive pulmonary disease (COPD) patients with its indication as first-line treatment in COPD exacerbations (Brochard et al., 1990; Brochard et al., 1995; Liesching, Kwok & Hill, 2003). Chronic obstructive pulmonary disease, although a chronic pathology, has some similarities with an acute asthma exacerbation namely, increased airway resistance and dynamic lung hyperinflation. Patients with COPD have an increased mortality if intubated. In the COPD population NPPV is used to bridge the exacerbation and not so much to improve lung function which is irreversibly compromised (Ram et al., 2004). NPPV has been shown to reduce hospital stay and mortality in the COPD population.

1.2 SIGNIFICANCE OF RESEARCH

A small number of studies have looked at the effect of NPPV in the asthma population with promising results (Martin et al., 1982; Shivaram et al., 1987; Shivaram et al.,1993; Lin et al.,1995; Lougheed et al., 1995; Pollack, Fleisch & Dowsey, 1995; Meduri et al., 1996; Wang et al., 1996; Fernandez et al., 2000; Gelbach et al., 2002; Soroksky et al., 2003). A limitation is that most of the studies use small sample sizes without a control group and the application of NPPV is done for short periods. Yet most of the studies have concluded that there is some benefit in adding NPPV to asthma treatment. Only one study has compared NPPV to standard asthma medical therapy in a clinical setting (Sorosky, Stav & Shpirer, 2003). The Cochrane Review on the use of NPPV in acute asthma states that no conclusion can be drawn on this single study (Ram, Wellington, Rowe, & Wedzicha, 2005). Yet NPPV is frequently

used in acute asthma exacerbations and in status asthmaticus patients (Fernandez et al., 2000; Gelbach et al., 2002). Status asthmaticus can be defined as an acute asthma exacerbation that is refractory to medical therapy (Scoggin et al., 1977). Guideliness on NPPV to date all agree that positive results exist but larger studies need to be performed to find conclusive results. A need exists for higher quality research like randomized controlled trials and studies that compare different modes of NPPV. Noninvasive positive pressure ventilation can be applied in different modes. The most used ones are one level of positive airway pressure (CPAP) and two levels of positive pressure or bilevel positive pressure ventilation (BPPV). In the COPD population it has been found that the application of bilevel positive pressure ventilation is superior to that of continuous positive airway pressure. In the asthma population, to our knowledge, no study has ever compared these two modes of NPPV.

1.3 RESEARCH QUESTION

The question therefore remains; does NPPV when added to standard medical therapy promote a faster improvement in patients presenting with an acute asthma exacerbation as compared to standard therapy alone?

1.4 RESEARCH OBJECTIVES

The aim of the present study was to evaluate the effectiveness of standard medical therapy combined with noninvasive ventilation against standard medical therapy alone in:

- ameliorating clinical, physiological and spirometric values in acute asthma exacerbation,
- response time to treatment in the emergency department, and
- outcomes such as length of time that NPPV was administered, intubation rate, mortality rate and length of hospital stay.

1.5 HYPOTHESIS

a).Early use of noninvasive ventilation in the forms of CPAP and BPPV together with standard medical therapy in acute asthma exacerbation can decrease time of response to therapy compared to standard medical therapy alone.

b) Patient's response to therapy is expected to be faster with the administration of BPPV together with standard therapy due to the inspiratory assistance provided to the positive end-expiratory pressure (PEEP).

The following chapter consists of an in-depth discussion of the literature found on the management of acute asthma exacerbation. Noninvasive positive pressure ventilation and its potential role in asthma will also be discussed.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

The present work has within its aims to look deeper into one of the adjunct therapies for the management of an acute asthma exacerbation (AAE). Although plenty research and guidelines exist as for the best pharmacological treatment to administer during an acute asthma attack (Hallstrand & Fahy, 2002; Marik, Varon & Fromm, 2002; Papiris et al., 2002; Rodrigo, Rodrigo & Hall, 2004; Edmonds et al., 2005; Manser, Reid & Abramson, 2005), the role of therapies like noninvasive positive pressure ventilation, although recommended, still remains to be established by researched studies.

The South African Pulmonology Society defines asthma as a chronic inflammatory condition of the airways which is usually allergic in origin and is characterised by hyperresponsive airways (South African Pulmonology Society Adult Asthma Working Group, 2000). The prevalence of asthma increased worldwide in the last 20 years carrying with it a large cost burden to health-care systems (Rodrigo et al., 2004). Countries like Spain, Canada and Australia report that 1 to 12% of all adult visits to the emergency unit (EU) are due to acute asthma exacerbations. In the USA 14 million are affected by asthma and nearly 2 million cases of acute asthma present at their emergency departments yearly costing around 6 billion US dollars per year (Rodrigo et al., 2004). Hospitalization and emergency department visits are the main contributors to the asthma cost burden in health-care (Rodrigo et al., 2004). In the International Study of Asthma and Allergies in Childhood (ISAAC) report on asthma symptoms in 13 to 14 year old children, one participating community assessed in Cape Town had a 16.1% presence of wheezing, 21.4% incidence of exercise induced wheezing, 31.1% “ever had asthma” incidence and a 5.2% presence of an episode of severe wheeze limiting speech. To the question of “has your child in the last 12 months been disturbed by wheezing during sleep once or more times a week” South Africa ranked seventh among the 56 countries that participated (International Study of Asthma and Allergies in Childhood (ISAAC), 1998). In another study of 12 year old

children comparing asthma prevalence in four countries, South Africa reported 11.5% of children presenting with a history of asthma at any time (Burr et al., 1994).

2.2 PATHOPHYSIOLOGY OF ASTHMA

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, reversible airflow obstruction and inflammatory changes in the submucosa (National Heart, Lung and Blood Institute, 1992; Hallstrand & Fahy, 2002; Marik et al., 2002; Rodrigo et al., 2004). An acute asthma exacerbation is characterized by respiratory symptoms such as cough, wheezing, chest tightness, shortness of breath and a decrease in expiratory airflow (Shim & Williams, 1983; Teeter & Bleecker, 1998; Rodrigo et al., 2004). These exacerbations are usually reversible but can sometimes be severe and even fatal. The main feature in an asthma exacerbation is progressive narrowing of the airways as a result of airway inflammation and/or increase in airway smooth muscle tone. This leads to an increase in flow resistance, hyperinflation and ventilation/perfusion mismatch (Rodrigo et al., 2004). Authors seem to agree that two types of acute asthma present at emergency units (Hallstrand & Fahy, 2002). Type 1 or slow-onset acute asthma presents with a major inflammatory component which develops slowly over many hours, days or weeks. Upper respiratory tract infection seems to be the most common trigger and response to therapy is slow (Rodrigo & Rodrigo, 2000; Rodrigo et al., 2004). Type 2 or acute-onset asthma is usually triggered by respiratory allergens, exercise or psychological factors. The dominant feature here is bronchospasm. It develops fast yet shows a quicker response to therapy (Rodrigo & Rodrigo, 2000). Between 80 to 90 percent of AAE presenting at emergency units are type one (Rodrigo et al., 2004). An acute asthma attack is usually classified according to the severity of the attack. Several guidelines exist that classify the severity of an attack using parameters like respiratory rate, use of accessory muscle, wheeze, heart rate, pulsus paradoxus and peak expiratory flow rate (PEFR). The Global Initiative for Asthma classifies an attack as mild when PEFR % of predicted is above 80%, moderate when PEFR % of predicted is 60 to 80 % and severe if PEFR % predicted is below 60 % (Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2006).

Similarities exist between patients that suffer an exacerbation of chronic obstructive pulmonary disease (COPD) and those that suffer an exacerbation of asthma. The most important similarities are: a) increase in expiratory flow resistance and b) dynamic hyperinflation. These two events have mechanical, sensory and physiologic consequences on the respiratory system. Interestingly the major mechanical consequence of this expiratory loading on the respiratory system is the loading of the inspiratory muscles (Martin, Shore & Engel, 1983; Chen & Yan, 1999). This effect is better understood under the consequences of dynamic lung hyperinflation (DH).

2.2.1 Dynamic Lung Hyperinflation

Macklem describes lung hyperinflation as one of the "commonest functional abnormalities in diseases leading to airways obstruction and loss of lung recoil" (Macklem, 1984). Dynamic hyperinflation (DH) refers to the increase in end expiratory lung volume (EELV). At the end of a normal breathing cycle the lung volume that remains in the lung (functional residual capacity) is determined by the "static balance between the opposing elastic recoil of the lung and chest wall" (Tobin & Lodato, 1989). Hyperinflation occurs when due to the increase in expiratory resistance associated with increased breathing frequency the expiratory time becomes insufficient for lung volumes to reach functional residual capacity (FRC) before the next inspiratory effort begins.

Dynamic hyperinflation was first seen as a passive event evolving as a consequence of increased expiratory resistance. Martin and colleagues examined the mechanism of hyperinflation in asthma patients. They looked at the activity of the respiratory muscles during hyperinflation in induced asthma and found that persistent tonic activity of the inspiratory muscles during expiration substantially influenced the increase in functional residual capacity (Martin, Powel, Shore, Emrich & Engel, 1980). This showed that there is an active component to DH. Wheatley and colleagues looked at the effects that DH in induced asthma had on respiratory muscle work. They found that DH due to bronchoconstriction actually reduced the total positive respiratory muscle work just by decreasing the expiratory muscle component (Wheatley, West, Cala & Engel, 1990).

Although DH has an active component due to the contraction of the inspiratory muscles during expiration so reducing the expiratory muscle work, the loading on the inspiratory muscles during inspiration results in major negative mechanical and sensory consequences (Martin et al., 1983; O'Donnell, 1994). Martin and colleagues (1983) studied the effects that lung hyperinflation had on inspiratory muscle action. They found that when forced expiratory volume in one second (FEV_1) fell to 49.5 ± 3.9 % the inspiratory work rate increased ten times. The elastic component was found to be the biggest contributor towards inspiratory work. Since elastic recoil is a consequence of dynamic hyperinflation they concluded that hyperinflation was the main reason for increased inspiratory muscle work (Martin et al., 1983).

Basically then we can say that dynamic hyperinflation has an active component due to the contraction of the inspiratory muscles during expiration. This is however obscured by the fact that DH overloads the inspiratory muscles. Since elastic recoil is at its strongest at end of inspiration, the more hyper inflated a lung becomes the more elastic recoil the inspiratory muscles will have to overcome during the inspiration.

It is this increase in elastic loading on the inspiratory muscles that deserves further discussion. The effects that dynamic hyperinflation has on the respiratory system can be divided into its effect on the:

2.2.1.1 respiratory muscles;
2.2.1.2 respiratory muscle energy spending;
2.2.1.3 inspiratory threshold load created and
2.2.1.4 the sensory effect of DH.

2.2.1.1 Dynamic Hyperinflation and the respiratory muscles

Looking at the effect DH has on the breathing muscles we start with the diaphragm. The diaphragm in its crural and costal parts has a parallel mechanical arrangement when lung volumes are normal. This means that the force generated by the diaphragm will be a sum of the forces generated by each part (Macklem, 1984; Decramer, 1997; DeTroyer, 1997). This enables the diaphragm to tolerate large loads. Once

hyperinflation exists the arrangement of the diaphragm parts becomes one in series (Macklem, 1984). In this arrangement the diaphragm is no longer capable of generating the same force as when in parallel thus becoming less able to handle large increases in workload (Macklem, 1984; Decramer, 1997; De Troyer, 1997). The accessory muscles also suffer under the effect of DH. The internal and external intercostals muscles' function is to approximate the ribs so reducing the intercostal spaces. Whether this will move the ribs up or down will depend on the rib cage impedance (Macklem, 1984). The rib cage impedance is determined by the lung volumes. At low volumes the scalene and sternomastoid muscles are in a stretched position while the abdominal muscles are shortened. This favors inspiration as the impedance for the rib cage to move up is less. On the contrary, at high lung volumes the abdominal muscles will be in a relatively stretched position while the scalene and sternomastoid muscles are shortened. Again this favors rib movement downward (Macklem, 1984; Decramer, 1997; De Troyer, 1997). This is comfortable during normal expiration following inspiration but in the presence of DH there will be a permanent tendency of the rib cage to move downward even when inspiration is required imposing extra work on the inspiratory muscles (Macklem, 1984; Decramer, 1997; De Troyer, 1997).

2.2.1.2 Dynamic Hyperinflation and muscle energy spending

The effect of dynamic hyperinflation on respiratory muscle energetics has two components. Firstly the muscles are placed in an inefficient part of their force length relationship. This comes as a consequence to the distortion of the thorax that occurs due to the increase in end-expiratory lung volumes. The rib cage position at end-expiration is altered with the ribs displaced more horizontally (Decramer, 1997). This means that to produce the same results the respiratory muscles will have to increase their excitation. This was observed in a study done by Martin and colleagues. They found that after inducing bronchoconstriction in stable asthma patients the tension-time product of the inspiratory muscles all together had increased fivefold (Martin et al., 1983). Since the tension-time index is an indicator of the metabolic cost for the respiratory muscles it clearly shows that hyperinflation increases the energy spent by the respiratory muscles. The second component is related to the increased velocity of shortening by the respiratory muscles. This is a direct consequence of the increased ventilatory need as bronchospasm worsens and DH increases. The consequence of

these two factors is an increase in energy consumption together with a decrease in efficiency (Macklem, 1984). Another problem that can be added occurs when muscle contractions are strong enough to cause a reduction in the blood supply to the inspiratory muscles. The reduction in blood/energy supply added to a constant increase in energy demand, further compromises muscle function (Macklem, 1984).

2.2.1.3 Dynamic Hyperinflation and the inspiratory threshold load (ITL)

While dynamic hyperinflation has a compromising effect on the pressure generating ability of the inspiratory muscles, it also leads to an increase in end expiratory lung volume (EELV) with a resultant auto or intrinsic positive end expiratory pressure (PEEPi). In normal breathing airflow ceases when equilibrium is reached between the lung and chest wall elastic recoil. In the presence of bronchoconstriction expiration is terminated before passive equilibrium is reached (Martin et al., 1980). The PEEPi created by this then acts as an inspiratory threshold load for the inspiratory muscles. With the presence of PEEPi the "initial part of the inspiratory effort by the inspiratory muscle contraction does not produce any flow or volume change" (Yan, 1999). This means that the inspiratory muscles are required to overcome this load before flow is initiated. This increase in EELV means that the lung operates at a higher level of it's pressure-volume curve resulting in an increase in elastic recoil and a reduction in compliance (Martin et al., 1983). Appendini and colleagues divided the inspiratory effort in the presence of PEEPi into two components. They described it as an initial isometric contraction by the inspiratory muscles with the function of counterbalancing the PEEPi. This was recorded by tracing the flow, pleural pressure, gastric pressure and transdiaphragmatic pressure curves of patients breathing with the presence of a PEEPi. While contraction of the inspiratory muscles was evident due to the fall in pleural pressure and increase in the transdiaphragmatic pressure at the start of inspiration, no inspiratory flow was recorded. This was followed by the second component, the isotonic contraction which then produced a recorded inspiratory flow curve. This clearly shows that the initial inspiratory effort in the presence of PEEPi is not compensated by change in flow as would be expected under normal breathing. (Appendini et al.,1994). In conclusion DH therefore overloads the inspiratory muscles due to the PEEPi.

2.2.1.4 Dynamic hyperinflation and sensation of breathlessness

Finally DH has an important and many times overlooked effect on sensation of breathlessness experienced by asthmatic patients. There is a need for better understanding of the relationship between what is obtained from objective parameters like PEFR and FEV_1 and a patient's perception of breathlessness (Lougheed et al., 1993). Burdon and colleagues found a close linear relationship between the decline in FEV_1 and breathlessness. Yet they found great inconsistency between the degree of obstruction and the severity of breathlessness related by patients (Burdon et al.,1982). Lougheed and colleagues defined breathlessness due to bronchoconstriction as a "complex sensory experience that is expressly linked to perceptions of heightened inspiratory-muscle contractile effort, unrewarded inspiratory effort, and reduced inspiratory capacity" (Lougheed, Webb & O'Donnell, 1995). Chen and colleagues studied the effects that the inspiratory threshold load (ITL) and increase in EELV had on subjects' perception of inspiratory difficulty. They used healthy subjects and induced increases in ITL by the application of external PEEP. Increase in EELV was achieved by external application of continuous positive airway pressure (CPAP). Their results suggest that both ITL and increased EELV independently and significantly increased the perception of inspiratory difficulty but ITL was found to contribute the strongest to this sensation (Chen & Yan, 1999). Lougheed and colleagues also evaluated the effects of hyperinflation on breathlessness. They induced bronchoconstriction in 21 stable asthma subjects with a consequent significant ($p < 0.001$) increase in EELV and asked each to grade their breathlessness on a modified Borg scale. Subjects were also asked to rate their inspiratory and expiratory difficulty in breathing at maximum bronchoconstriction. They concluded that at maximum bronchoconstriction their subjects' breathlessness was significantly increased ($p < 0.001$) mainly due to the increase in the inspiratory difficulty (Lougheed et al., 1995). This was directly related to the increase in EELV.

2.2.1.4.1 Neurophysiologic Basis for Breathlessness

The thorax, lungs and airways are rich in sensory receptors. These afferent receptors are sensitive to changes in muscle tension and length, changes of air flow and volume and also changes in the chest wall position (O'Donnell, 1994). During a normal breath the motor output i.e. contraction of the inspiratory muscles is compensated by sensory feedback of the respiratory mechanoreceptors. A complete understanding of

breathlessness is still not fully known. However two factors that seem to contribute to this uncomfortable sensation are the motor output or muscle effort and the sensory feedback (O'Donnell, 1994). When these two work harmoniously it is referred to as neuromechanical coupling of the respiratory pump (O'Donnell, 1994; Lougheed et al., 1995). When airflow obstruction occurs there is a consequent disruption of this relationship. An imbalance between the level of effort done by the inspiratory muscles and the anticipated ventilatory consequence occurs. This disruption is then called neuromechanical dissociation of the ventilatory pump (O'Donnell, 1994; Lougheed et al., 1995). During an acute asthma exacerbation the dynamic hyperinflation and the functional inspiratory muscle weakness will lead to neuromechanical dissociation of the respiratory pump.

It is clear therefore that DH carries with it real consequences to the respiratory mechanics. It overloads the inspiratory muscles due to the ITL increasing their energy spending and finally creating the unpleasant sensory experience of breathlessness.

2.3 MEDICAL MANAGEMENT OF ACUTE ASTHMA

Acute asthma exacerbation is a typical medical emergency that patients present with at emergency units. Authors of current guidelines for treatment of an acute exacerbation agree on supplemental oxygen to maintain adequate arterial oxygenation ($SpO_2 \geq 92\%$), repetitive administration of rapid-acting inhaled bronchodilators like β-agonists and anticholinergics to relief airflow obstruction (Rodrigo, 2003) and the use of systemic corticosteroids (Manser et al., 2005) to reduce airway inflammation (Rodrigo et al., 2004; Global strategy for asthma management and prevention, Global initiative for asthma (GINA), 2006). Although symptoms and physical examination findings are widely used outcome measures to evaluate the patient's response to treatment, the best objective measurement remains the improvement in peak expiratory flow rate (PEFR) or forced expiratory volume in one second (FEV_1) over

time (Rodrigo & Rodrigo, 1993; Corbridge & Hall, 1995; Rodrigo et al., 2004). Teeter and Bleecker (1998) compared asthma symptoms to FEV_1 and PEFR in 67 chronic asthma patients and found that asthma symptoms correlated poorly with the level of obstruction as showed by FEV_1 and PEFR. Time spent in the emergency unit during an acute attack can range from one to six hours until symptoms fully resolve. In many instances patients are discharged based on clinical criteria rather than on improvement of lung function as measured objectively by PEFR or FEV_1 as recommended in the International Consensus Report on Diagnosis and Treatment of Asthma guidelines and the Advanced Cardiac Life Support recommendations for asthma (National Heart, Lung and Blood Institute, National Institutes of Health Bethesda (NHLBI), 1992; Cumins, 2003). Early response to therapy is seen as one of the best predictors of outcome. This refers to the improvement in PEFR % predicted or in PEFR in the first 30 minutes of intense treatment (Rodrigo & Rodrigo, 1998). Rodrigo and colleagues found that a variation of more than 50 L/min of the PEFR over baseline and a PEFR % predicted of above 40% after thirty minutes of treatment were predictors of good outcome (Rodrigo et al., 2004).

Other therapies indicated and debated in recent reviews on the management AAE are theophylline, magnesium sulfate, leukotriene modifying agents, heliox, humidification, antibiotics and positive pressure ventilation whether invasive or noninvasive (Corbridge & Hall, 1995; Hallstrand & Fahy, 2002; Marik et al., 2002; Rodrigo et al., 2004;). Until recent years patients with AAE who failed to improve despite optimal therapy and developed respiratory muscle fatigue together with increased hypercapnia and hypoxia were intubated and admitted to an ICU. Endotracheal intubation remains a life saving intervention yet carries with it well known complications. These can range from damage to local tissue during the intubation procedure, sinusitis, pneumothorax, increased need for sedation and neuro-muscular blocking agents to increased ICU stay and morbidity and increased incidence of nosocomial pneumonia (Stauffer, Olson & Petty, 1981; Fagon et al., 1993). In asthmatic patients the intubation procedure leads to increase in airway narrowing, hyperresponsiveness and inflammation (Rodrigo et al., 2004). Marik et al states that the only real indication for endotracheal intubation in these patients is total respiratory muscle fatigue (Marik et al., 2002). The decision to intubate a patient with

an AAE remains a challenge since the clinical condition can worsen after the intubation procedure (Cumins, 2003).

Despite the fact that research is aimed at a common and protocolized approach to asthma treatments (GINA, 2006), recent studies have started looking at factors like individual behaviour, environmental factors and individual genetic make-up which could affect response to therapy (Morrow, 2007). It is known that variation exists between patients in their response to different asthma therapies. Research has also found some genetic mutations linked to these different responses. Specific gene mutations have been linked to variability in response to beta 2-agonists, leukotrine response modifiers, glucocorticoids and theophylline. Yet these gene mutations have not been linked to huge population groups. As research into gene-based therapies continuous guidelines will continue to be used. The certainty exists though, that changes will occur that will improve treatment outcome but will also have significant social and economic effects. (Morrow, 2007).

Presently the management of an AAE consists of supplemental oxygen, continuous administration of rapid-acting bronchodilators and systemic corticosteroids. Objective measurements of the improvement or not of lung function are essential for best management of these patients. One of the best predictors of outcome is an early response to therapy. Although endotracheal intubation remains a life saving intervention it can lead to complications like nosocomial pneumonia and increased morbidity. It should be very carefully considered.

2.4 NONINVASIVE VENTILATION AND ASTHMA

2.4.1 Overview of Noninvasive Ventilation

Noninvasive positive pressure ventilation (NPPV) dates back to the 1930s when Alvan Barach used a device generating continuous positive airway pressure. He succesfully treated patients with acute pulmonary oedema (Mehta & Hill, 2001). After the advent of invasive ventilation together with endotracheal intubation, noninvasive ventilation became dormant only to resurface in the 1980s with its use in obstructive

sleep apnea (Mehta & Hill, 2001). This was followed by a proliferation in the use of noninvasive positive pressure to treat different causes of acute and chronic respiratory failure. Research into the application of NPPV to these pathologies also increased. A Pubmed search done on the word "noninvasive positive pressure ventilation" revealed only one article published in 1970. The same search of the years 1990 and 2000 revealed 8 and 32 articles respectively. Using the same word a search of the last 40 years revealed 487 articles of which 125 were reviews. This shows the increase in published research in this area. Presently noninvasive ventilation has a great variety of applications. It has been used in acute and chronic respiratory failure in settings varying from hospital to home use. Probably one of the big propellants of research into noninvasive ventilation has been the complications associated with the use of invasive ventilation (Stauffer et al., 1981; Fagon et al., 1993). Extensive research has been done on the use of noninvasive ventilation in acute respiratory failure due to hypercapnic and hypoxemic causes. One of the conclusions of the international consensus conference on NPPV held in 2000 was that "NPPV has the potential of reducing the morbidity and possibly mortality associated with hypercarbic or hypoxemic respiratory failure" if adequate alveolar ventilation and oxygenation can be safely delivered (Evans, 2001). Chronic obstructive pulmonary disease has been extensively researched in relation to the use of NPPV in patients presenting with acute respiratory failure (Keenan et al., 2000; Keenan et al., 2003; Lightowler et al., 2003). Peter and colleagues in a recent meta-analysis of noninvasive ventilation in acute respiratory failure concluded that the use of NPPV led to a significant reduction in mortality, a reduction in the need for mechanical ventilation as well as in the hospital length of stay mainly in the COPD subgroup (Peter et al., 2002).

2.4.2 Noninvasive Ventilation and its application in Asthma

Noninvasive ventilation in AAE presents as an ideal option to avoid the side effects of intubation and alleviate the sensation of breathlessnesss. Although used more frequently in the clinical scenario, its role remains to be defined in the management of an AAE. Recent reviews and guidelines on the management of AAE mention noninvasive ventilation as a possibility (Corbridge & Hall, 1995; Hallstrand & Fahy, 2002; Marik et al., 2002; Rodrigo et al., 2004). Rodrigo and colleagues (2004) stated that a trial of noninvasive ventilation is worthwhile in patients who are at risk of

developing respiratory failure or "as an alternative to intubation". They recommend the early use of NPPV even in the emergency department. Marik and colleagues (2002) recommend a trial of noninvasive ventilation in alert and cooperative patients who did not respond to aggressive medical therapy alone. They recommend that this should not be attempted in rapidly deteriorating patients or in somnolent or confused patients. Hallstrand and Fahy (2002) note that NPPV may decrease the work of breathing during an acute asthma attack but comment that controlled trials are necessary to provide statistically significant evidence. The advanced cardiac life support reference book also recommends the use of NPPV for AAE with strict indications and contraindications outlined (Cumins, 2003). In one of the most recent systematic reviews on NPPV the author suggests that despite the lower-level evidence NPPV should not be dismissed as a treatment in acute asthma exacerbation (Hess, 2004).

2.4.3 Definition of Noninvasive Ventilation

Noninvasive ventilation refers to the application of positive pressure ventilatory support to the airways without the need for endotracheal intubation (Meyer & Hill, 1994; Meduri et al., 1996; Jasmer et al., 1997; Evans, 2001; Baudouin et al., 2002; Diaz Lobato & Mayoralas Alises, 2003). Positive pressure is applied to the airways through various interfaces like full face or nasal masks, nasal prongs and helmets. Some of the advantages of NPPV are that it can be applied intermittently, there is no need for sedation, the airway protection mechanism is preserved and it allows for patients to communicate, eat and drink (Ram et al., 2005). The most important advantage of NPPV is the reduction in the incidence of ventilator associated pneumonia compared to endotracheal intubation (Guerin et al., 1997; Nourdine et al., 1999).

For the present study the following modalities of noninvasive positive pressure were considered:

- Continuous Positive Airway Pressure (CPAP) and
- Bilevel Positive Pressure Ventilation (BPPV).

CPAP is defined as the application of a constant positive airway pressure throughout the ventilatory cycle. This means that the "baseline pressure is elevated above the

atmospheric pressure in a spontaneously breathing patient" (Vines, 2003).With one level of positive pressure being provided during inspiration and expiration no inspiratory assistance is provided. (American Respiratory Care Foundation, 1997) The main difference between CPAP and other modes of noninvasive positive pressure is this lack of inspiratory assistance which leads to smaller tidal volumes. Debate exists as to whether CPAP should be included under the term of ventilation due to the lack of this inspiratory assistance, yet it was not the objective of this study to define nomenclature. In order to simplify terminology CPAP and BPPV have been included under the term "noninvasive positive pressure ventilation" (NPPV).

Bilevel positive pressure ventilation on the other hand refers to the delivery of two levels of positive pressure, an inspiratory pressure and an expiratory pressure. The inspiratory assistance can be provided by volume- or pressure targeted ventilation depending on the device used. It can be referred to as pressure support or inspiratory positive airway pressure (IPAP). The expiratory pressure is provided by positive end-expiratory pressure (PEEP). With BPPV the increase in airway pressure during inspiration provides for bigger tidal volumes than with CPAP (ARCF, 1997).

2.4.4 Studies on NPPV and asthma

Few studies exist to date on the use of noninvasive ventilation in the asthma population. In a literature search eleven clinical studies were found which investigated the effect of NPPV in patients presenting with an AAE (Martin et al., 1982; Shivaram et al., 1987; Shivaram et al.,1993; Lin et al.,1995; Lougheed et al., 1995; Pollack, Fleisch & Dowsey, 1995; Meduri et al., 1996; Wang et al., 1996; Fernandez et al., 2000; Gelbach et al., 2002; Soroksky et al., 2003). Seven of these studies used patients with AAE and the other four studies looked at patients with induced asthma. As for the location where NPPV was applied three were in an ICU setting, four were done in lung function laboratories, three were done in an emergency unit with only one being conducted on ward based patients. Only one out of the eleven studies randomly assigned patients to two treatment groups (Soroksky et al., 2003). This was also the only study included in a Cochrane Review to date (Ram et al., 2005). The studies are discussed according to their results on the effect of NPPV in relation to:

2.4.4.1 dynamic hyperinflation,

2.4.4.2 the respiratory muscles and their work of breathing,

2.4.4.3 the airway smooth muscle tone

2.4.4.4 the inspiratory threshold load,

2.4.4.5 lung function and

2.4.4.6 patient's sensation of breathlessness.

2.4.4.1 NPPV and dynamic hyperinflation in acute asthma

As previously discussed the increase in airflow resistance, dynamic hyperinflation and ventilation/perfusion mismatch, if not corrected can lead to increased work of breathing, gas exchange inefficiency and respiratory muscle fatigue (Macklem, 1980; Meduri et al., 1996; Rodrigo et al., 2004). The notion that the application of positive pressure to bronchoconstricted lungs could further increase hyperinflation is still existent. This has been challenged by the findings of Appendini and colleagues. In their study the application of noninvasive CPAP and PEEP levels of 4.9 ± 1.6 cmH_2O on acute COPD exacerbation did not significantly increase pulmonary hyperinflation (Appendini et al., 1994). Smith and colleagues showed that in mechanically ventilated COPD patients PEEP levels of 5 and 10 cmH_2O improved expiratory resistance without substantial increase in peak pressure or in the risk of barotrauma (Smith & Marini, 1988). Two studies on the asthma population have found similar results. Martin and colleagues (1982) found that the application of CPAP levels of 12.0 ± 0.9 cm H_2O caused end expiratory volume to change by 0.27 ± 0.12 litres which was considered to be small. Lougheed and colleagues (1995) also measured the change in EELV in induced asthma before CPAP (3.47 ± 0.24 L) and with CPAP (3.58 ± 0.27 L). The change in these volumes was not significant with CPAP levels of 5.3 ± 0.6 cmH_2O. It is interesting to note that the levels of CPAP used by Martin et al (12 – 16 cm H_2O) are much higher than usually used on asthma and COPD patients in general. Most studies use levels of 5 to 8 cmH_2O (Shivaram et al., 1987; Shivaram et al., 1993; Lin et al., 1995; Lougheed et al., 1995; Pollack et al.,1995; Wang et al., 1996; Soroksky et al., 2003;). This higher CPAP level could be the cause of the small increase in EELV noted in their study. Shivaram and colleagues (1987) added another

aspect to this issue. They used CPAP levels of 5, 7, 10 and 12 cmH_2O on acute asthma patients and noted their sensation of comfort at each level. The best sensation of comfort reported by the patients was on levels of 5.3 ± 2.8 cmH_2O. The authors note that 71% of the patients complained that a CPAP level of 12 cmH_2O caused increased discomfort. In the Lougheed study similar outcome was observed. They induced bronchoconstriction until FEV_1 fell by 54 ± 3% predicted. The PEEPi of their subjects was found to be 6.9 ± 1.0 cmH_2O. Their patients were also encouraged to choose the level of optimal CPAP where they felt the greatest degree of symptom relief. The chosen levels were close to the levels of PEEPi, namely 5.3 ± 0.6 cmH_2O. Any level above their optimal CPAP level caused increased sensation of breathlessness and increase in dynamic hyperinflation (Lougheed et al., 1995). It seems then that the application of these studied levels of CPAP to asthma patients does not cause further hyperinflation. It is also clear that levels of CPAP or PEEP higher than the PEEPi presented by the patient caused increased sensation of discomfort which is probably related to an increase in EELV. The patient's input as to the level of CPAP seems a useful tool for situations where it is not possible to measure the intrinsic PEEP.

2.4.4.2 NPPV and Work of Breathing of the Inspiratory Muscles

The following studies have looked into the effect that CPAP could have on the inspiratory muscles during an asthma exacerbation. Shivaram and colleagues (1987) investigated the short term effect of CPAP on asthmatics presenting with peak expiratory flow rate below 200L/min. CPAP levels of 5, 7.5 and 10 cmH_2O were applied for one to two minutes. They found that the fractional inspiratory time, that is, the ratio of inspiratory time to the duration of the total respiratory cycle (Ti/Ttot) was significantly reduced at all levels of CPAP. This indicated a reduction of the workload on the inspiratory muscle when CPAP was applied. Martin and colleagues (1982) also investigated the effect of short periods of CPAP on histamine induced asthma. They noted that CPAP levels of 12 ± 0.9 cmH_2O significantly reduced the inspiratory pleural pressure that the inspiratory muscles generated as also the inspiratory swing of the diaphragmatic pressure generated by the diaphragm. This indicates that CPAP unloaded the inspiratory muscles and so decreased the energy cost of their action. In a study by Lougheed and colleagues (1995) in induced bronchoconstriction they found

that CPAP levels of 5.3 ± 0.6 cmH_2O significantly reduced the total inspiratory effort which is expressed by the oesophageal pressure divided by the maximum inspiratory pressure (Pes/PImax). CPAP also significantly reduced the peak inspiratory oesophageal pressure by 27% and the inspiratory work rate per liter of ventilation by 14%. This means that the application of CPAP in this study, bypassed the ITL so reducing the inspiratory work. These three studies show evidence that CPAP reduced the work load on the inspiratory muscles by unloading them. Unfortunately they applied CPAP for very short periods (one to ten minutes), so the prolonged treatment effect of CPAP could not be seen. Only one study used asthma exacerbation while the other two used induced asthma and it could be argued that they would not be a real reflection of an acute asthma attack. The Lougheed study induced bronchoconstriction to a change in FEV_1 of 50% which can be considered to be an equivalent of a severe attack. They also note that after the application of CPAP a second maximal dose of methacoline was administered to maintain the level of bronchoconstriction that had been achieved (Lougheed et al., 1995). Martin and colleagues (1982) induced bronchospasm until the subjects judged it to be the equivalent of a moderate attack so this leaves room for queries as to what real level of bronchoconstriction was achieved. They did however note that during bronchoconstriction the lung resistance had increased from 4.2 ± 0.5 to 22.5 ± 3.0 $cmH_2O.L^{-1}.s^{-1}$ and functional residual capacity had increased from 3.65 ± 0.19 to 5.76 ± 0.32 L.

2.4.4.3 NPPV and its effect on the airway smooth muscles

The increase in airway smooth muscle tone in asthmatics that results in an increase in airway resistance has also been evaluated in the presence of CPAP. Lin and colleagues (1995) investigated the effect that a CPAP level of 8 cmH_2O had on airway smooth muscle in induced asthma subjects. They found that CPAP reduced bronchial reactivity and sensitivity. This indicates that CPAP reduced the level of bronchoconstriction of the airway smooth muscles resulting from different drug dosages and also affected the intrinsic properties of these muscles by reducing their sensitivity to the extrinsic stimuli acting on it. Although these results mainly apply to methacholine-induced bronchospasm it cannot be overlooked that CPAP does seem to act directly on the properties of the airway smooth muscle. This evidence provides support for the use of CPAP as an adjunct therapy for patients presenting with AAE.

2.4.4.4 NPPV and its effect on lung function

Four studies were found that investigated changes in lung function as measured by peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV_1) (Shivaram et al., 1987; Shivaram et al., 1993; Pollack et al., 1995; Soroksky et al., 2003). Two studies by Shivaram et al found no significant change in these parameters (Shivaram et al., 1987; Shivaram et al., 1993). The first study used applications of CPAP levels of 5, 7.5 and 10 cmH_2O for one or two minutes only and this might explain why no major change in lung function was found (Shivaram et al., 1987). In the second study by Shivaram (1993) CPAP levels of 5 and 7.5 cmH_2O was applied for 30 minutes twice with a 20 minutes interval when no CPAP was applied. No bronchodilators were used during the study period and also 30 minutes prior to the study. Again no significant improvement in FEV_1 was found. In a study done by Pollack and colleagues (1995), bi-level positive airway pressure (BiPAP®) was used to administer bronchodilators to 60 patients presenting at the emergency department with acute bronchospasm. Patients were randomly assigned to receive albuterol inhalations via a small volume nebulizer (n = 40) or via BiPAP® (n = 60) twenty minutes apart. No intra-venous medication was administered to these patients. The mean PEFR % predicted at beginning of treatment was 37.3% for the control group and 40.3% for the BiPAP® group which would classify these patients as severe exacerbations. A significant increase in PEFR % predicted ($p = 0.0013$) was found compared to the control group from baseline to completion. The increase in the absolute peak expiratory flow rate was also more significant in the BiPAP® group ($p = 0.0001$). In a more recent study, Soroksky and colleagues (2003) compared BiPAP® and standard treatment with standard treatment alone as first line treatment for 30 patients presenting at their emergency department with a FEV_1 below 60% predicted. Significance was found when percentage improvement was analysed for PEFR % predicted and FEV_1 % predicted. This significance was found for values measured after three hours of treatment. In this study patients were randomly assigned, medical treatment was not standardized and statistical analysis of PEFR and FEV % predicted did not include analysis of variance which would correct for baseline values and would be indicated in such a study. Yet this is one of the best studies done to date using the early application of BPPV in this patient population. Some evidence exists for the improvement of lung functions when NPPV was applied to AAE but there remains a dearth of evidence.

2.4.4.5 NPPV and the inspiratory threshold load

As previously described dynamic hyperinflation leads to an increase in EELV which in turn creates an intrinsic PEEP and this acts as an inspiratory threshold load to the inspiratory muscles. Understanding how NPPV bypasses the ITL and counteracts the PEEPi is key to the adequate indication and application of NPPV in patients with AAE. With the presence of the PEEPi the alveolar pressures will be above atmospheric pressures at the end of the breathing cycle. This means that at the beginning of the next inspiration the inspiratory muscles would have to generate a pressure equal and opposite to the PEEPi since airflow only occurs in the presence of a difference of pressure between alveolar and atmospheric pressures (Macklem, 1984; Gay, Rodarte & Hubmayr,s 1989; Appendini et al., 1994; Lougheed et al., 1995; Tobin & Lodato, 1989). This difference in pressure that has to be generated is equal to the ITL. It has been proposed that the external application of a positive pressure like CPAP or PEEP could reduce the work of breathing of the inspiratory muscles (O'Donnell, 1994; Fessler, Brower & Permutt, 1995). With external PEEP, ambient pressure would be elevated. Inspiration would then be easier to achieve since alveolar pressure would need to be decreased below the external PEEP/CPAP level rather than below atmospheric pressure. Tobin and Lodato (1989) refer to this as a paradox. While PEEP is usually used to treat atelectases, to recruit lung volume and treat hypoxemia, in the presence of hyperinflation it can be used to reduce the work of breathing. Tobin and Lodato (1989) use a waterfall analogy to explain this concept. The upstream river represents the hyperinflated lung with PEEPi, the waterfall represents the magnitude of the ITL and the downstream river represents atmospheric pressure. If the level of the downstream river is lifted up to that of the upstream river, the two levels equalize so bypassing the waterfall. Continuous positive airway pressure or PEEP would represent the elevated downstream river bypassing the waterfall / PEEPi. This was first researched in mechanically ventilated COPD patients. It was observed that in COPD patients with PEEPi the application of an external PEEP on the ventilator improved the patient's triggering of the ventilator, reduced their work of breathing and did not cause further hyperinflation as long as the external PEEP did not pass the level of the PEEPi (Smith & Marini, 1988; Gay et al., 1989; MacIntyre, Cheng & McConnell, 1997).

The effect of NPPV on respiratory mechanics in the COPD patient was studied by Appendini and colleagues (1994). They compared pressure support ventilation, CPAP and pressure support together with PEEP to spontaneous breathing in acute exacerbation of COPD. There was a significant and progressive decrease in transdiaphragmatic pressure, that is, in the inspiratory muscle effort with all three modalities. The application of levels of mask CPAP or PEEP between 80 - 90 % of dynamic PEEPi significantly reduced inspiratory workload by replacing PEEPi. The best results were seen when PEEP was applied together with pressure support ventilation. With this combination, PEEP counterbalanced PEEPi and hence the amount of isometric contraction required to overcome the inspiratory threshold throughout inspiration, whereas pressure support ventilation assisted the isotonic contraction and improved ventilation and arterial blood gas. Lougheed and colleagues (1995) looked at the effect that noninvasive CPAP would have compared to inspiratory pressure (IPAP) on induced asthma. While CPAP maintained one level of positive pressure throughout the breathing cycle the IPAP caused an increase in positive pressure during inspiration only. Once expiration started no additional positive pressure was kept in the airways. A fall in FEV_1 of 50 % was induced after which lung mechanics were measured. They found that while both CPAP and inspiratory positive airway pressure reduced the oesophageal pressure over maximal inspiratory pressure (Pes/Pimax) ratio as well as the elastic and resistive work only CPAP counterbalanced the effects of the ITL. CPAP significantly reduced the ITL and PEEPi. The measured ITL fell significantly with CPAP and continued to fall even after CPAP had been removed. The EELV also fell significantly after CPAP but not after IPAP. They used levels of CPAP just below the levels of the ITL. These studies support the “waterfall analogy” in the clinical settings. This study shows that the expiratory pressure (CPAP or PEEP) and not IPAP bypasses the ITL and reduces the sensation of breathlessness while both CPAP and IPAP favourably affected work of breathing.

2.4.4.6 NPPV and its effect on breathlessness

Breathlessness remains an important clinical feature in acute asthma attacks. Lougheed and colleagues (1993) found breathlessness in acute bronchoconstriction to be a complex sensory experience linked to perceptions of heightened inspiratory muscle contractile effort, "unrewarded" inspiratory effort and reduced inspiratory

capacity. They tested the effect of CPAP on 12 asthmatic patients. Methacholine bronchoprovocation was done until a fall of 54 ± 3 % of the FEV_1 was achieved. CPAP was then started from two cmH_20 and increased until patients experienced optimal reduction in breathlessness. Breathlessness was recorded on a modified Borg scale. They found that CPAP levels of 5.3 ± 0.6 cmH_2O significantly reduced the patients' breathlessness ($p < 0.001$). Shivaram and colleagues (1993) applied CPAP levels of 5 and 7.5 cmH_20 to asthmatic patients presenting at the emergency room with PEFR of 80 to 200 L/min. Both levels of CPAP were applied to each patient for 30 minutes with 20 minutes intervals. They also found a significant decrease in breathlessness ($p < 0.05$) as assessed by a breathlessness score and a reduction in the respiratory rate with CPAP. Shorter applications of CPAP in induced asthma also had similar effects as shown in a study by Wang and colleagues. They applied CPAP for ten minutes and also found a significant reduction in their subjects' breathlessness ($p< 0.01$) (Wang et al., 1996). Interestingly Lougheed and colleagues (1993) found that during bronchoconstriction, breathlessness was more strongly related to inspiratory capacity than to FEV_1 or any other parameter. As inspiratory capacity reflects change in dynamic end-expiratory volume it would explain why CPAP or PEEP reduced sensation of dyspnoea as it bypasses PEEPi and with prolonged application has been found to reduce EELV (Lougheed et al., 1995).

Most studies used NPPV on asthma patients for short periods. Meduri and colleagues (1996) applied NPPV in the form of pressure support and PEEP for longer periods to status asthmaticus patients who failed to improve with initial management. There was a significant reduction in $PaCO_2$ and pH compared to a control group, as also reduction in dyspnea and respiratory rate. Of the 17 patients who received NPPV only two required intubation. Unfortunately the patients were not randomized and the control group consisted of only four patients who had to be intubated before reaching ICU. Presentation parameters were also much worse in the control group. Their study was a retrospective patient record review. A seven year retrospective observational study by Fernandez and colleagues (2000) identified 33 patients who would have been eligible for NPPV. Of these 22 (67 %) were treated with NPPV. Of those that received NPPV, three (14 %) needed to be intubated. They reported no difference in ICU and hospital stay or mortality between those who received NPPV and those who underwent invasive mechanical ventilation. The authors suggest that non-invasive

ventilation improves pulmonary function and is a safe treatment technique in status asthmaticus and hypercapnic patients who fail to improve with initial medical management.

The International Consensus Conference in Intensive Care Medicine published a report on the use of noninvasive ventilation in acute respiratory failure (Evans, 2001). Under the recommendations given was the need for studies that would evaluate the clinical difference of using an inspiratory assistance like pressure support or inspiratory positive airway pressure and an end-expiratory pressure like PEEP or CPAP in diagnoses like asthma COPD and cardiogenic pulmonary oedema. They also suggested investigation into the different responses to NPPV between asthma and COPD patients. The present study addresses some of these issues as patients were randomized to receive either CPAP or BPPV (inspiratory pressure plus PEEP) and the patients' response was compared between these groups. The British Thoracic Society on the other hand in their guidelines on NPPV said that there was insufficient evidence to recommend its use in asthma patients (Baudouin et al., 2002). These guidelines where published in 2002 when no randomized control study had yet been published. Since then the Soroksky study was published with promising results (Soroksky et al., 2003). In a more recent update on this topic done by Hess, the Soroksky study is mentioned. They noted that there is less evidence for the use of NPPV in the asthma population compared to the COPD population. They commented that lower-level of evidence research together with the Sorosky study suggested that the use of NPPV for asthma patients should not be dismissed. Additional studies with larger populations were recommended (Hess, 2004).

Corbridge and Hall (1995) stated that by decreasing work of breathing, NPPV may lessen inspiratory muscle fatigue, buy time for concurrent pharmacological therapy to become effective and thereby avert the need for intubation in some. The literature above provides supportive evidence for the use of NPPV in acute asthma exacerbation. A need for randomized studies on asthma and NPPV still exists for better support of its acceptance and institution as adjunct therapy for acute asthma exacerbations.

In light of the evidence presented, the methodology followed to investigate the use of NPPV in acute asthma exacerbation, will be discussed in the next chapter.

CHAPTER 3

MATERIALS AND METHODS

An acute asthma exacerbation can severely distress patients as the respiratory muscles become overloaded. This can lead to muscle fatigue and exhaustion. Noninvasive positive pressure ventilation such as CPAP and BPPV has been used in a few studies on patients with an asthma exacerbation but a lack of more evidence to support its use still exists. To further investigate the effects that CPAP and BPPV can have on AAE this chapter will explain the methods and materials used to execute the present study.

3.1 SAMPLE SELECTION

Asthmatic patients who presented with an acute asthma exacerbation at the Emergency Unit, Kalafong Hospital between January 2004 and October 2006 were recruited for the study. Only severe exacerbations were included into the study.

3.1.1 Sample Size:

n Query 6.0 software was employed and computations were based on recovery time. For the standard treatment the assumption was made that recovery time was between 2 and 6 hours (Kelsen et al, 1978; Fanta et al, 1982, McFadden et al, 1995; Rodrigo & Rodrigo, 1998) suggesting a standard deviation of 0.67 hours (range/6). A sample of 10 patients per group provided an 85% power to detect a reduction of 1 hour in recovery time where mean recovery time for the standard treatment is 4 hours.

3.1.2 Inclusion Criteria:

a) Male and female patients between the ages of 18 to 70 years

b) A previous diagnosis of asthma as defined by the South African Pulmonology Society

c) An acute severe exacerbation of asthma. This classification was made according to the Global Initiative for Asthma guidelines (Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2006) for initial peak expiratory

flow rate percentage predicted (PEFR% pred). Patients were classified as severe if their PEFR% predicted was below 60 %.

d) Patients who presented with the above at the emergency department between 07h00 and 16h00.

3.1.3 Exclusion Criteria:

a) A systolic blood pressure < 90 mmHg or

b) Use of vasopressors

c) Electrocardiographic instability (evidence of ischaemia or arrhythmia)

d) Neurologic disorder (coma, seizure or mental disorder)

e) Cardiorespiratory arrest

f) Evidence of pneumonia or tuberculosis

g) An axillary temperature equal or above 38 degrees Celsius

h) Previous established cardiac pathology

i) Chronic obstructive pulmonary disease

j) Moderate and mild exacerbations of asthma

k) Pregnancy

l) Inadequate peak flow technique

3.1.4 Criteria for discontinuation of noninvasive positive pressure:

If the patient demonstrated any one of the following criteria NPPV was discontinued;

a) Inability to correct blood gas values (pH < 7.30, $PaCO_2$ > 45 mmHg or PaO_2 < 45 mmHg) after one hour of treatment

b) Inability to decrease dyspnoea after one hour of treatment,

c) Inability of patient to protect his airways such as poor cough reflex, reduced consciousness

d) Intolerance of CPAP or BiPAP® (patients who feel claustrophobic, patients who pull of their masks or refuse mask after a few attempts)

e) Haemodynamic instability,

f) Poorly fitting mask and

g) Patient request.

3.1.5 Intubation Criteria:

Major Criteria

a) Respiratory arrest

b) Respiratory pauses with loss of consciousness or gasping for air

c) Psychomotor agitation making nursing care impossible and requiring sedation

d) A heart rate < 50 beats per minute with loss of alertness

e) Haemodynamic instability with systolic arterial blood pressure < 70 mmHg.

Minor Criteria:

a) Respiratory rate > 35/min or above the value of admission,

b) Arterial pH < 7.30 or below value of admission,

c) An arterial partial pressure of oxygen (PaO_2)< 45 mmHg despite oxygen therapy

d) An increase in the score of encephalopathy [1=mild asterixis (abnormal muscle tremor with involuntary jerking of the hands), 2=marked asterixis,mild confusion or sleepiness during the day, 3=major confusion with daytime sleepiness or agitation and 4=obtundation or major agitation]

The presence of one of the major criteria at any time was considered an indication for intubation. The presence of two of the minor criteria after one hour of treatment was also considered an indication of the need for intubation (Brochard, Mancebo & Wysocki,1995).

3.2-PROCEDURES

A three group randomized parallel open study (1:1:1) was conducted. Patients who presented at the Emergency Unit with symptoms of an acute asthma exacerbation immediately received an initial dose of bronchodilator inhalations. The dosage consisted of 1.25 mg of β_2-agonist (Fenoterol) and 0.5 mg of anticholinergic (Ipatropium bromide). This was administered by the emergency unit nurse. They were then evaluated by the casualty officer and severity was determined according to the Global Initiative for Asthma guidelines from the PEFR% predicted reading (Global

Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA), 2006). If the patient had a peak expiratory flow rate less than 60% of predicted the investigator was contacted through a pager. Nebulised bronchodilators were continued accordingly. The researcher then proceeded to evaluate the patient to determine if they fitted the inclusion criteria. A short explanation of the study procedures was read to the patient (appendix A). It was made clear that participation was voluntarily and that the patient could withdraw from the study at any time with no detrimental effect to his health status as standard therapy would be continued. A consent form (appendix B) was then given to the patient to sign. In the case of a patient being unable to deal with this, consent from family was obtained. In extreme situations were the patient's clinical condition was too severe a verbal consent was procured until patient stabilized and then the written consent was obtained from the patient. Once consent had been given patients were randomized into one of three groups: a) Standard medical Therapy (ST), b) Standard Therapy + Continuous Positive Airway Pressure or c) Standard Therapy + Bilevel Positive Pressure Ventilation. **Randomization** was done by the sealed opaque envelope method. All envelopes were put inside a box and mixed frequently. At the time of randomization an envelope was retrieved from the box by either the medical officer present, one of the sisters or by the investigator.

3.2.1 Standard Therapy

For an acute exacerbation, standard therapy consisted of oxygen therapy (to maintain peripheral saturation $\geq 90\%$) together with β_2-agonist (Fenoterol) and anticholinergic agent (Ipatropium bromide) nebulisation given continuously with a small volume nebulizer until the episode resolved. Beta $_2$-agonist was administered at 1.25 mg and anticholinergic was administerd at 0.5 mg. Both were given from unit dose vials which had 2 ml isotonic saline already mixed to the bronchodilator medication. Methylprednisone was administered at 125 mg (prescribed 6 hourly) via intra-venous infusion. Aminophylin was also administered intravenously at 250 mg bolus if the patient was not on oral theophylin.

3.2.2 Noninvasive Devices:

In the study we made use of the **Solo Plus Lx CPAP System** for the CPAP applications **and the BiPAP® Harmony S/T Ventilatory Support System** for the BPPV application. Both are from Respironics Inc, Murraysville, Pa. USA . The CPAP provided a continuous flow of at least 100 L/min and positive pressure levels from 4 to 15 cmH_2O. The BiPAP® provided a flow of 140 L/min and cycled between adjustable inspiratory (IPAP) and expiratory pressures (EPAP) utilizing the patient flow-triggered mode. The inspiratory pressures ranged from 4 to 30 cmH_2O and the EPAP from 4 to 15 cmH_2O. Oxygen was added from a flow meter and connected to a small port on the mask. A **full-face mask and headgear** from Spectrum ® Disposable Full Face Mask, Respironics Inc, Murrysville, Pa. USA was used. Masks were available in sizes small, medium and large and the patient's face was fitted for the right size. These masks are designed for optimal patient comfort and minimal leak and were fitted to the patient's face with head straps. In acute respiratory failure a full-face mask has been suggested as the best option. (Mehta & Hill, 2001) This type of mask had a quick release cord so that patients could remove it from the face in case of vomiting without the need to first loosen straps. Another safety feature was an entrainment valve flapper, which allowed patients to breathe through an opening behind this valve in case of an electrical failure.

Figure 3-1



Patient being ventilated on the BiPAP device

3.2.3 Continuous and Bilevel Positive Airway Pressure protocol:

A full-face mask was used. (figure 3-2) The mask was connected to flexible tubing through a whisper swivel connection, which functions as an exhalation port. A T-piece nebulizer was added to the circuit. (figure 3-3) before fixing the mask on the patient's face the explanation in appendix A was read to the patient on how the pressure worked what sensation he/she would feel and that he/she were allowed to ask for it to be removed at any time. The mask was then fitted on the patient (figure 3-1) by the researcher with CPAP or BiPAP® on initial settings as described below.

Figure 3-2



Noninvasive full face mask and straps

Figure 3-3



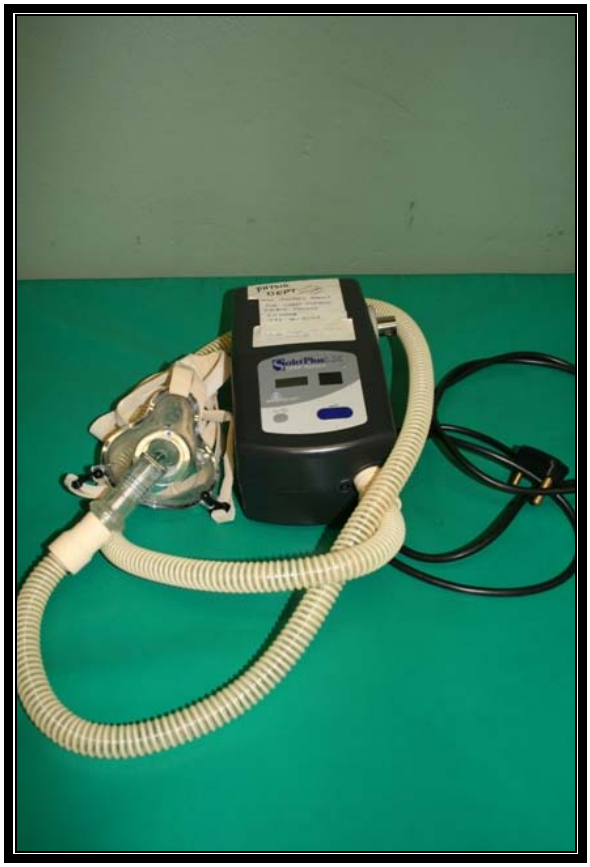
T-piece inhalator connected in NPPV circuit

3.2.4 Initial settings:

3.2.4.1 Continuous Positive Airway Pressure

This was started at 5 cmH_2O. This level has already been studied on patients with asthma with good patient tolerance and reduction of dyspnoea and inspiratory effort (Shivaram et al., 1987; Wang et al., 1996) (figure 3-4). The CPAP settings were adjusted one cmH_2O at a time.

Figure 3-4



CPAP device

3.2.4.2 Bilevel Positive Airway Pressure

The BiPAP® (figure 3-4) was set on an inspiratory pressure (IPAP) of 10 cm H_2O and an expiratory pressure (EPAP) of 5 cmH_2O. These settings have also been previously used on patients with asthma (Pollack et al., 1995; Soroksky et al., 2003). The EPAP settings were adjusted one cmH2O at a time and IPAP at two cmH_2O at a time. The

adjustments were done at the investigator's discretion and according to the patient's clinical condition.

Figure 3-5



BiPAP device

3.2.4.3 Oxygen

Oxygen was delivered via an entry port on the mask and started at 5 L/min. The decision to start oxygen on 5 L/min was taken based on the researcher's personal experience. Both oxygen and pressures were titrated to achieve an oxygen saturation of ≥ 90% and a respiratory rate of < 30/min.

3.2.5 Bronchodilator administration

Bronchodilator medication (beta 2-agonist and anticholinergic agent) was administered through the T-piece nebulizer connected on the NPPV circuit when patients were on CPAP or BiPAP. For those patients who were randomized to the standard therapy group these drugs were administered through a small volume nebulizer.

3.2.6 Humidification

The CPAP and BiPAP® generated high flows. This could dehydrate the airways easily which would not be recommended for asthma patients (Moloney et al., 2002). Therefore it was determined that in between the bronchodilators isotonic saline (0.9% NaCl) would be added into the T-piece nebulizer to make sure adequate humidification could be maintained. Administration of isotonic inhalations for the purpose of humidifying the airways of patients is standard protocol in the physiotherapy department when no other means of humidification is available. The same was done for the standard therapy group with the small volume nebulizer. This was only necessary after patients had reached a PEFR % predicted > 60 % as initially bronchodilators were administered continuously.

3.2.7 Disconnection from NPPV

Patients randomized to receive either CPAP or BiPAP® were kept continuously on the devices. Disconnection from these was only done for measurements of lung function. If patients wanted to drink water this was also done during this same disconnection period. Disconnection during this period was kept as briefly as possible so as to not loose the effect of the positive pressure. Since bronchodilators were administered on the circuit it was not necessary to disconnect patients for inhalations.

3.2.8 Stabilizing Parameters

These were considered to be an oxygen saturation ≥ 95%, a respiratory rate < 20 breaths per minute, no accessory muscle use and a FEV_1 ≥ 65 to 70% of predicted. After stabilizing parameters were achieved and maintained for at least 30 minutes a trial of 15 minutes on an oxygen mask was given. If the patient maintained oxygen saturation ≥ 90% and respiratory rate < 24/min CPAP or BiPAP® was discontinued. If the patient showed an increase in respiratory rate > 30/min and use of accessory muscles the CPAP or BiPAP® protocol was reinstated. If a patient was still in need of noninvasive ventilation once he was to be transferred from the emergency department he was transferred with it. The decision to re-instate or continue NPPV in the ward was taken in consultation with the casualty officer. Patients were examined regularly for abdominal distention, ability to clear secretions and to protect their airways.

Patients were followed up until discharge, whether from the emergency department or from the ward if they were admitted. The investigator did not interfere in the admission or discharge decisions taken by the medical officer on duty. Data was collected until patients were discharged from the emergency department or transferred to the internal medicine ward. Data collection sheets were awarded serial numbers in order to maintain anonymity and these sheets were only handled by the investigator. All measures were taken to prevent any physical and psychological risks for the patient. As this is an emergency care setting there was a casualty doctor and nursing staff present permanently monitoring patient evolution. The investigator was also permanently present. All criteria were followed strictly and patient safety took prevalence above research outcomes.

3.3 DATA COLLECTION

3.3.1 Data collected: age, gender, weight, height, temperature, duration of attack in hours, asthma history in years, if patient was a smoker or non-smoker.

3.3.2 Dependant variables:

3.3.2.1 Clinical variables: patient's sensation of breathlessness, accessory muscle use, evidence of muscle fatigue, heart rate, blood pressure, respiratory rate and lung sounds.

3.3.2.2 Physiological variables: oxygen saturation, arterial blood gas values (pH, PaO_2, $PaCO_2$, HCO_3). Arterial blood gases were done at attending casualty officer's discretion.

3.3.2.3 Spirometry: peak expiratory flow rate (PEFR)

3.3.3 Independent variable was the allocation to one of the three treatment regimes, that is: standard therapy, standard therapy and CPAP or standard therapy and BiPAP®.

3.3.4 Secondary outcome measures

a) Outcome after emergency department stay. The outcome could be one of the following: discharged from the emergency unit to go home, admitted to an overnight observation ward, general ward, high-care ward or intensive care unit with intubation and mechanical ventilation and finally discharged from the hospital.

b) Total time of NPPV administration. This was calculated as the number of hours since the patient was put on the non-invasive ventilation until it was discontinued.

c) Total length of hospital stay. This was calculated as the length of stay in hours in the emergency department. For those patients admitted to the hospital for further treatment the length of stay in each ward was noted in hours and summed up to get the total hours spend in the hospital.

d) Mortality rate.

3.3.5 Data collection methodology

Once patients had been randomized to the different treatment regimes baseline data were collected (Appendix C). After baseline data the following data were collected at 30 and 60 minutes:

3.3.5.1 Arterial blood gas obtained from blood drawn anaerobically from the radial or brachial artery into a heparinized syringe. This was done only at the medical officer's discretion for those patients that he felt it necessary. An *ABL 500 or 700 Radiometer, Radiometer A/S, Copenhagen, Denmark* was used to analyze the arterial blood gas samples.

3.3.5.2 Heart rate expressed in beats per minute,

3.3.5.3 Oxygen saturation expressed in percentage,

Peripheral oxygen saturation and heart rate were monitored by a **pulse oxymeter model** *515C, Novametrix Medical Systems Inc, Wallingford, CT, USA* and more unstable patients had their electrocardiogram monitored on the *defibrilator Diascope 2, type 2011, S&W Medico Teknik NS, Albertslund, Denmark*.

3.3.5.4 Respiratory rate in breaths per minute, counted over thirty seconds and multiplied by two,

3.3.5.5 Blood pressure in mmHg. Blood pressure was measured by the *Dinamap pro 400, Critikon Company LLC, Tampa FL.* In the case of this device not being available or being broken a *sphygmomanometer* was used.

3.3.5.6 Peak expiratory flow rate (L/min). The best of three efforts were taken according to American Thoracic Society recommendations (American Thoracic Society, 1987). Patients were in a seated position while doing the measurement. If a patient was unable to perform an initial maneuver due to the respiratory distress the number zero was noted at baseline. After 30 minutes of treatment the next peak flow maneuver was performed. Percentage of predicted values of the above was also used for analysis. The percentage of predicted values were calculated according to age, weight and length using the Gregg and Nunn reference table for predicted peak expiratory flow rate (Gregg & Nunn,1973). Lung function was measured on the *Asthma Monitor ® AM1, Jaeger, Hoechberg, Germany*. The device allowed for three or more attempts to be made by the patient an then the best attempt was displayed.

3.3.5.7 Sensation of breathlessness. This was measured using a visual analogue scale of 10 centimeters where zero was not breathless at all, and 10 equaled the maximal breathlessness the patient had ever felt. The patient encircled the number that most expressed his sensation of breathlessness.

3.3.5.8 Accessory muscle use. This was defined as visible retraction of the sternomastoid muscles and graded as 0 = absent, 1 = mild, 2 = moderate, 3 = severe (Rodrigo, 1993).

3.3.5.8 Evidence of muscle fatigue was defined as the inability to continue to develop or maintain a predetermined force. The clinical evidence was the development of rapid shallow breathing, alternation between rib cage and abdominal movement during inspiration, abdominal paradox and finally increase in the level of arterial carbon dioxide ($PaCo_2$) (Macklem, 1980).

3.3.5.9 Lung sounds were classified according to the following: 0 = no wheezes, 1 = expiratory wheezing, 2 = inspiratory and expiratory wheezing and 3 = "silent" lungs (Rodrigo, 1993).

3.3.5.10 Body mass index was calculated at the end of the study for each patient using the weight in kilograms divided by the height multiplied by the height in meters.

Data collection continued then on an hourly basis until one hour after discontinuation of CPAP or BiPAP® or until patient was transferred to another ward or discharged. The investigator collected all data in order to limit the amount of bias that could occur. Arterial blood gases were collected by the medical officer on duty if deemed necessary according to sterile technique.

3.4 DATA MANAGEMENT AND ANALYSIS

The data collected between January 2004 and October 2006 was analyzed using the Kruskal-Wallis test (parametric one way ANOVA). Software STATA 8 was used. All analysis of the variables were corrected for baseline values. Testing was done at the 0.5 level of significance. Due to the fact that the ANOVA tells us only that there was a significant difference between the groups but does not identify which groups were significantly different from each other, post-hoc comparisons were done. Data was summarized by group using descriptive statistics, mean, SD, minimum and maximum. The ANOVA for the primary outcomes (respiratory rate, sensation of breathlessness, accessory muscle use, lung sounds, PEFR and PEFR % predicted) was done analysing the actual mean shift between baseline and the next data collection time. For the rest of the data the ANOVA was done comparing the mean values at each data collection. This was done with the assistance of a statistician.

3.5 ETHICAL CONSIDERATIONS

Ethical clearance was obtained from the University of the Witwatersrand Ethics Committee [03-05-53 (appendix D)] and from the Kalafong Emergency Unit (appendix E) for the present study. Consent was obtained from each patient who agreed to participate in the study (appendix B).

Having described the methods used to collect the data for the present study, we will proceed to describe the results obtained through these methods in the following chapter.

CHAPTER 4

RESULTS

4.1 INTRODUCTION

A total of 85 patients with acute asthma exacerbation was admitted to the Emergency unite of Kalafong hospital during the day between January 2004 and October 2006. Thirty of these patients fulfilled the inclusion criteria for the study. For the purpose of this chapter the treatment groups were referred to in the following way: the standard therapy group was named *Standard Therapy group*; the standard therapy and CPAP group was referred to as *CPAP group* and the standard therapy and BiPAP® group was referred to as *BPPV group*. The ANOVA analyses of the three treatment groups was referred to as **Group A** (standard therapy group versus the CPAP group versus the BPPV group). We also analyzed the data by joining the *CPAP* and *BPPV groups* (noninvasive groups) and analyzing them against the *Standard Therapy group*. This was referred to as **Group B**.

4.2 POPULATION CHARACTERISTICS

The mean age for the group as a whole was 42 ± 12.5 years [*standard therapy group* (44.7 ± 15 years), *CPAP group* (43 ± 10.8 years) and *BPPV group* (38.6 ± 11.8 years)]. Gender representation was as follows: the *standard therapy group* and *CPAP group* had 30% males and 70 % females while the *BiPAP group* had 20 % males and 80% females. The mean hours lapsed between the onset of the asthma exacerbation and the arrival at the emergency unit was 10.11 ± 5.08 hours for the group as a whole [*standard therapy group* (11.35 ± 5.32 hours), *CPAP group* (10.6 ± 6.15 hours) and *BPPV group* (8.4 ± 3.47 hours)]. The body mass index was 26.76 ± 5.67 for the *standard therapy group,* 26.46 ± 3.69 for the *CPAP group* and 27.97 ± 5.37 for the *BPPV group.* The majority were non smokers. (Table 4-1)

Table 4-1
Population characteristics

	Groups (n=30)	Standard Therapy group (n=10)	CPAP group (n=10)	BPPV group (n=10)	*p* value Group A	*p* value Group B
Age (years) (mean ± SD)	42.1 ± 12.57	44.7 ± 15.16	43 ± 10.780	38.6 ± 11.87	0.5505	0.4327
Gender M/F (%)	M= 26.67 F= 73.33	M = 30 F = 70	M = 30 F = 70	M = 20 F = 80	----------	--------
Hours of attack before arrival (hours)	10.11 ± 5.08	11.35 ± 5.32	10.6 ± 6.14	8.4 ± 3.47	0.4177	0.3569
BMI (mean ± SD)		26.76 ± 5.67	26.46 ± 3.69	27.97 ± 5.37	0.7780	0.8155
Smoker (%)	3.33		10		---------	-------
Non-smoker (%)	90	80	90	100	---------	-------
Ex-smoker (%)	6.67	20			----------	-------

F = *female*, **M** = *male*, **BMI** = *body mass index*, **ST group** = *standard therapy group,* **CPAP group** = *continuous positive airway pressure group with standard therapy*, **BPPV group** = *bilevel positive airway pressure with standard therapy*; **Group A** = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group,*

4.3 BASELINE CHARACTERISTICS

The following baseline data was collected: respiratory rate, heart rate, temperature, systolic and diastolic blood pressure, peripheral saturation, PEFR and PEFR % predicted. Baseline characteristics are listed in table 4-2. The respective mean values and standard deviations, minimal and maximum values are presented. None of these initial parameters showed statistically significant difference between the treatment groups with exception of the baseline systolic blood pressure in the Group B analysis.

Although the one-way ANOVA did not show significance among the systolic blood pressures the post-hoc analysis showed a marginal significance between the NPPV groups [CPAP (p=0.0538) and BPPV (p=0.0915)] and the standard therapy group. This means that patients in both NPPV groups had a slightly increased mean systolic blood pressure at the beginning of the study.

4.3.1. Blood Pressure variation over time

The systolic blood pressure was significantly different among the treatment groups at one and two hours of treatment (p=0.0494 and 0.0332 respectively) and marginally at three hours of treatment (p=0.918). The diastolic blood pressure showed a marginally significant difference among the groups from half an hour up to four hours of treatment when it was significantly different (p= 0.0288). The main contributor to this significance was the BPPV group. The BPPV group showed a decrease in both systolic and diastolic blood pressures as treatment time progressed (table 4-3, graphics 4-1 and 4-2).

4.3.2. Arterial Blood Gases

Arterial blood gases (ABG) were done at the medical officer's discretion. A total of seven patients had blood drawn for ABG. Three patients refused a second ABG. The pH, PaO_2 and $PaCO_2$ of the four patients who had a follow-up ABG after half an hour of treatment are in table 4-4. Two patients (patient 2 and 3) showed hyperventilation with lower $PaCO_2$
values while patient one and 18 were hypercapnic initially and had improved after half an hour of treatment. Patients oxygenated well except patient two whose baseline ABG was done on room air and not on 5 L/O_2/min as was the case with the others. Some patients presented with hyperoxia after first half an hour of treatment but this was corrected by reducing supplied oxygen.

Table 4-2
Baseline characteristics of population

	Mean	SD	Min	Max	*p* value Group A	*p* value Group B
Respiratory rate (bpm)						
ST group (n=10)	24	6.75	14	38		
CPAP group (n=10)	25.7	7.12	18	39		
BPPV group (n=10)	28.9	5.86	20	36		
Groups (n=30)	26.2	6.69	14	39	0.2586	0.2084
Temperature (°C)						
ST group (n=10)	36.7	0..52	36.0	37.8		
CPAP group (n=10)	36.83	0.41	36.0	37.2		
BPPV group (n=10)	36.83	0.41	36.0	37.6		
Groups (n=30	36.79	0.43	36	37.8	0.7552	0.4495
Blood Pressure Systolic (mmHg)						
ST group (n=10)	118.3	17.35	98	158		
CPAP group (n=10)	135.7	18.67	110	167		
BPPV group (n=10)	133.4	21.62	108	180		
Groups (n=30)	129.13	20.20	98	180	0.1098	0.0353
Blood Pressure Diastolic (mmHg)						
ST group (n=10)	76.1	18.01	60	119		
CPAP group (n=10)	83.5	14.41	62	106		
BPPV group (n=10)	81.2	8.64	69	94		
Groups (n=30)	80.27	14.07	58	119	0.5009	0.2587
Heart rate (bpm)						
ST group (n=10)	110.8	26.17	79	154		
CPAP group (n=10)	119.8	24.92	78	155		
BPPV group (n=10)	114	21.88	81	148		
Groups (n=30)	114.87	23.84	78	155	0.7079	0.5183
Saturation (%)						
ST group (n=10)	97.2	1	95	99		
CPAP group (n=10)	97.7	1	96	100		
BPPV group (n=10)	95.1	5	84	99		
Groups (n=30)	96.7	3.09	84	100	0.1356	0.5132
PEFR (L/min)						
ST group (n=10)	178.8	70.01	59	297		
CPAP group (n=10)	150.8	50.31	50	240		
BPPV group (n=10)	162.2	60.10	50	250		
Groups (n=30)	163.9	59.71	50	297	0.3426	0.3426
PEFR%pred (%)						
ST group (n=10)	35.185	10.71	12.82	49.09		
CPAP group (n=10)	30.552	11.70	10.86	48.97		
BPPV group (n=10)	33.524	13.80	7.94	53.76		
Groups (n=30)	33.09	11.87	7.94	53.76	0.6915	0.5034

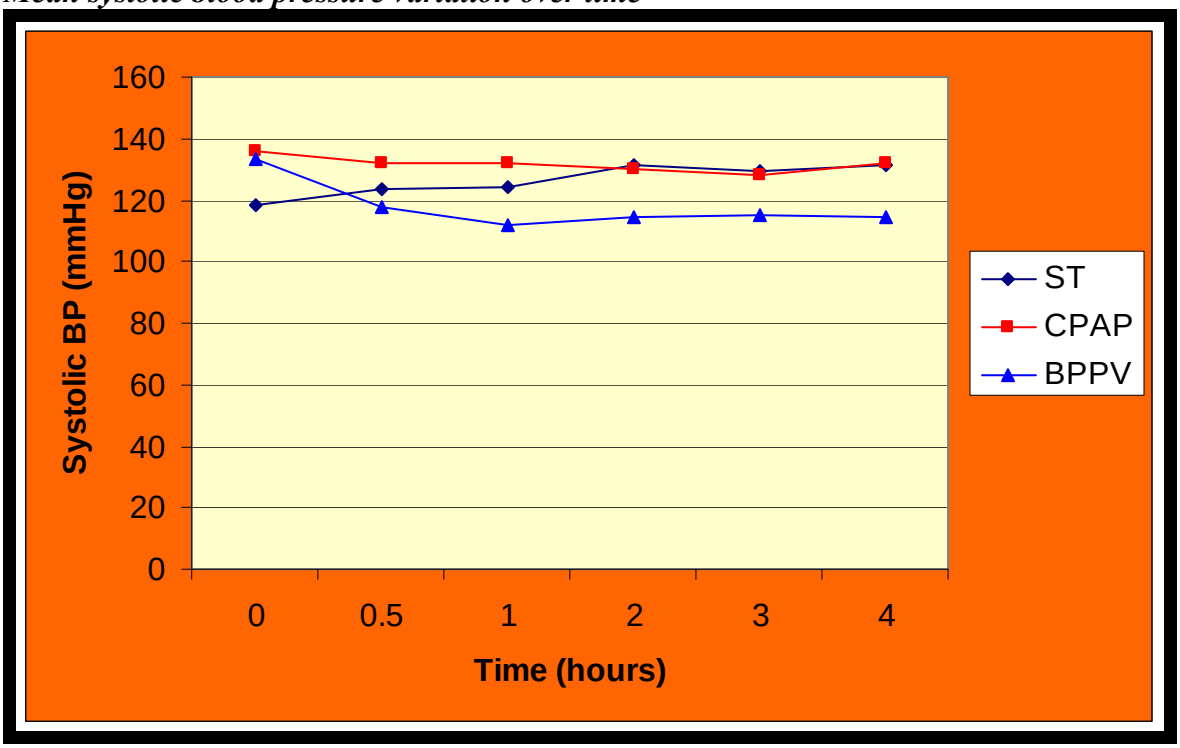
PEFR= *peak expiratory flow rate*, **PEFR% pred** = *peak expiratory flow rate percentage predicted*, **ST group** = *standard therapy group,* **CPAP group** = *continuous positive airway pressure group with standard therapy*, **BPPV group** = *bilevel positive pressure ventilation with standard therapy*; **Group A** = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group,* **bpm** = *beats per minute for heart rate and breaths per minute for respiratory rate*. ***mmHg*** = *millimeters mercury,*
°C = *degrees Celsius*, **L/min** = *liters per minute*

Table 4-3
Mean systolic and diastolic blood pressure analysis over time

	Baseline	*0.5 hr*	*1 hr*	*2 hr*	*3 hr*	*4 hr*
SYSTOLIC BLOOD PRESSURE						
ANOVA	0.1098	0.2336	O.0494 †	0.0332 †	0.0918 ‡	0.1252
Post-hoc:						
-ST x CPAP	0.0538 ‡	0.2909	0.3456	0.8516	0.8628	0.9134
-ST x BPPV	0.0915 ‡	0.5159	0.1193	0.0189 †	0.0523 ‡	0.0821 ‡
-CPAP x BPPV	0.7919	0.0940 ‡	0.0161 †	0.0288 †	0.0673 ‡	0.0766 ‡
DIASTOLIC BLOOD PRESSURE						
ANOVA	0.5009	0.0608 ‡	0.0730 ‡	0.0846 ‡	0.0647 ‡	0.0288 †
Post-hoc:						
-ST x CPAP	0.2547	0.0488 †	0.1058	0.4568	0.7231	0.3460
-ST x BPPV	0.4295	0.8565	0.5165	0.1377	0.0701 ‡	0.0624 ‡
-CPAP x BPPV	0.7204	0.0331 †	0.0275 †	0.0304 †	0.0292 †	0.0103 †

ST = standard therapy, CPAP = Continuous positive airway pressure, BPPV = bilevel positive pressure ventilation, post-hoc = post-hoc comparisons, † = significant, ‡ = marginally significant

Graphic 4-1
Mean systolic blood pressure variation over time

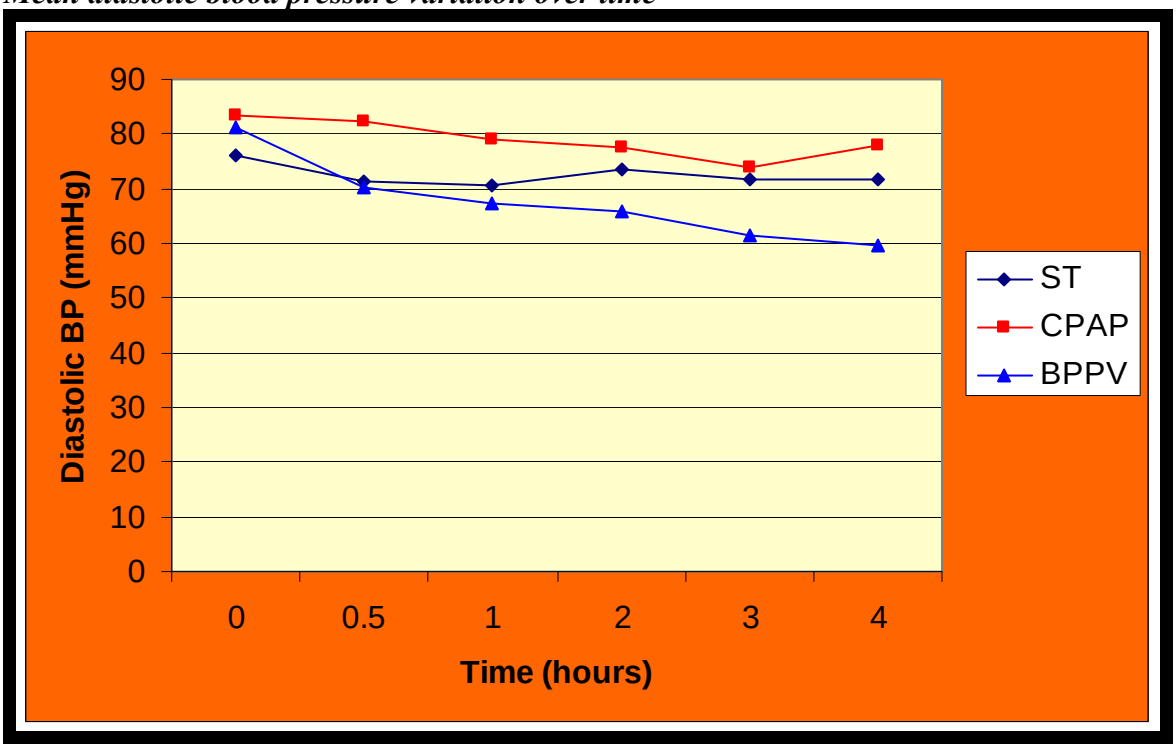


ST = standard therapy, CPAP = Continuous positive airway pressure, BPPV = bilevel positive pressure ventilation, BP = blood pressure.

It is clear that the systolic BP lowered mostly in the BPPV group.

Graphic 4-2

Mean diastolic blood pressure variation over time



ST = standard therapy, CPAP = Continuous positive airway pressure, BPPV = bilevel positive pressure ventilation, BP = blood pressure

It is clear that the diastolic BP lowered mostly in the BPPV group.

Table 4-4

Arterial blood gas results

	Treatment group allocation	ABG	Baseline	After half an hour of treatment
Patient 2	**ST + BPPV**	pH	7.42	7.42
		PaO_2	54.6	79.1
		$PaCO_2$	35.7	36.7
Patient 3	**ST + CPAP**	pH	7.34	7.42
		PaO_2	112.4	89.3
		$PaCO_2$	24.7	30.0
Patient 1	**ST + CPAP**	pH	7.22	7.32
		PaO_2	197.9	275.0
		$PaCO_2$	48.8	35.6
Patient 18	**ST + BPPV**	pH	7.36	7.33
		PaO_2	105	355
		$PaCO_2$	57.5	42.4

ST = standard therapy, CPA = continuous positive airway pressure, BPPV = bilevel positive pressure ventilation, pH = potential of hydrogen ion, PaO2 = partial pressure of arterial oxygen, PaCO2 = partial pressure of carbon dioxide

4.4 TIME ANALYSIS

The following times periods are expressed as means and standard deviation per treatment group in table 4-5:

a) Time before intervention started: this meant time from arrival at the Emergency Unit until the patient was enrolled in the study and baseline measurements were done.

b) Time in Emergency Unit: this comprised the total time spend in the emergency unit, from arrival until transfer to another ward or discharge

c) Time of intervention: this was calculated as the time from when baseline measurements were done until the last measurement was taken from the patients.

No significant difference was found among the groups for these time periods.

Table 4-5
Time table

TIME	ST Group	CPAP Group	BPPV Group	Groups	*p* value GroupA	*p* value GroupB
	n = 10	n = 10	n = 10	n = 30		
Before intervention	0.49	0.49	1.17	0.58	0.2612 NS	0.4264 NS
In emergency unit	5.37	4.55	5.19	5.17	0.6048 NS	0.4069 NS
Of intervention	4.06	4.06	4.12	4.08	0.9734 NS	0.9068 NS

Time *= expressed in hours and minutes.* ***Abbreviations:*** **ST group** *= standard therapy group,* **CPAP group** *= continuous positive airway pressure group with standard therapy*, **BPPV group** *= bilevel positive pressure ventilation with standard therapy*; **Group A** *= three group ANOVA*, **Group B** *= CPAP+ BPPV groups analyzed against the standard therapy group,* ***NS*** *= not significant*

4.5 ANALYSIS OF PRIMARY OUTCOMES

The following variables were analyzed as primary outcomes: respiratory rate (RR), patient's sensation of breathlessness (SB), use of accessory muscles (AM), lung sounds (LS), peak expiratory flow rate (PEFR) and peak expiratory flow rate percentage of predicted value (PEFR % pred).

The initial analyses of the variables at half an hour of treatment was done with 30 patients, 10 in each treatment group. As treatment time progressed the patient numbers became less as their acute episode resolved or they were admitted to the hospital. Table 4-6 shows how many patients were used in the hourly analyses as treatment progressed. After 4 hours of treatment the sample size became too small for analysis as many patients recovered before that. End of treatment was defined as the stage where the investigator ended all measurements and was usually due to a patient reaching a PEFR % predicted ≥ 65 % or being admitted to the ward or being discharged from the emergency unit even if PEFR % predicted had not reached 65% of predicted value. The mean time from baseline to end of treatment for the group was a 4.08 hours.

Table 4-6
Patient numbers according to time elapsed

	0.5 hr	**1 hr**	**2 hr**	**3 hr**	**4 hr**	**5 hr**	**6 hr**	**End Rx**
Total n =	30	30	30	29	20	13	3	30
***ST Group* n=**	10	10	10	9	7	5	1	10
***CPAP Group* n=**	10	10	10	10	6	5	0	10
***BPPV Group* n=**	10	10	10	10	7	3	2	10

0.5 hr *= first half an hour of treatment,* ***End Rx*** *= end treatment and corresponded to the point were al data collection was ceased due to patient being discharged or transferred to a ward.* **ST group** *= standard therapy group,* **CPAP group** *= continuous positive airway pressure group with standard therapy*, **BPPV group** *= bilevel positive pressure ventilation with standard therapy*

The above table shows the number of patients that was used in the statistical analyses per hour. As patients recovered the number reduced, so that it became impossible to do statistical analyses from 5 hours onwards

4.5.1. Respiratory Rate

The one-way ANOVA of the shift in respiratory rate showed that there was significant difference between the groups at two hours of treatment and at the end of treatment. In the post-hoc comparisons BPPV significantly reduced the respiratory rate compared to the control group at one hour and two hours. Continuous positive airway pressure added to standard therapy reduced respiratory rate significantly at two hours. At the end of treatment both the CPAP and BPPV intervention groups showed significance when compared to the Standard Therapy group. The biggest contributor to the significant changes in respiratory rate was the BPPV group (graphic 4-3). The *p* values are presented on table 4-6. A p-value < 0.05 was considered significant and a p-value $> 0.05 <$ but ≤ 0.1 was considered moderately significant. When the two intervention groups were analyzed together in relation to the Standard Therapy group (**Group B**) they showed a significant shift in respiratory rate at two and three hours and at the end of treatment.

Table 4-7
Respiratory rate mean shift analysis – p-values

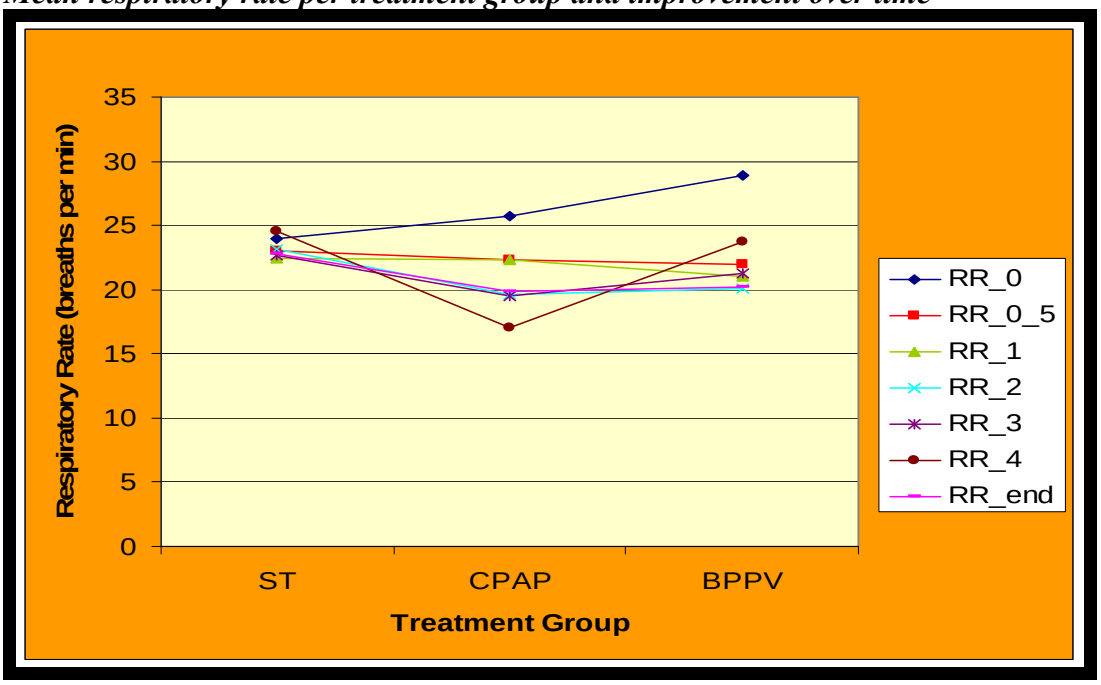
	0.5 hr	1 hr	2 hr	3 hr	4 hr	End Rx
Total n =	30	30	30	29	20	30
Δ RR						
Group A	0.1615	0.0618 ‡	0.0133 †	0.1110	0.1509	0.0328 †
ST x CPAP	0.3850	0.5173	0.0258 †	0.0820 ‡	0.0603 ‡	0.0463 †
ST x BPPV	0.0591 ‡	0.0236 †	0.0051 †	0.0569 ‡	0.5980	0.0132 †
CPAPxBPPV	0.2573	0.0795 ‡	0.4220	0.8072	0.1554	0.5078
Group B	0.1226	0.1151	0.0043 †	0.0354 †	0.1853	0.0107 †

Group A = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group. STxCPAP, STxBPPV, CPAPxBPPV are the post-hoc comparisons. RR = respiratory rate*

† = $p < 0.05$, ‡ = $0.05 < p \leq 0.1$

Graphic 4-3

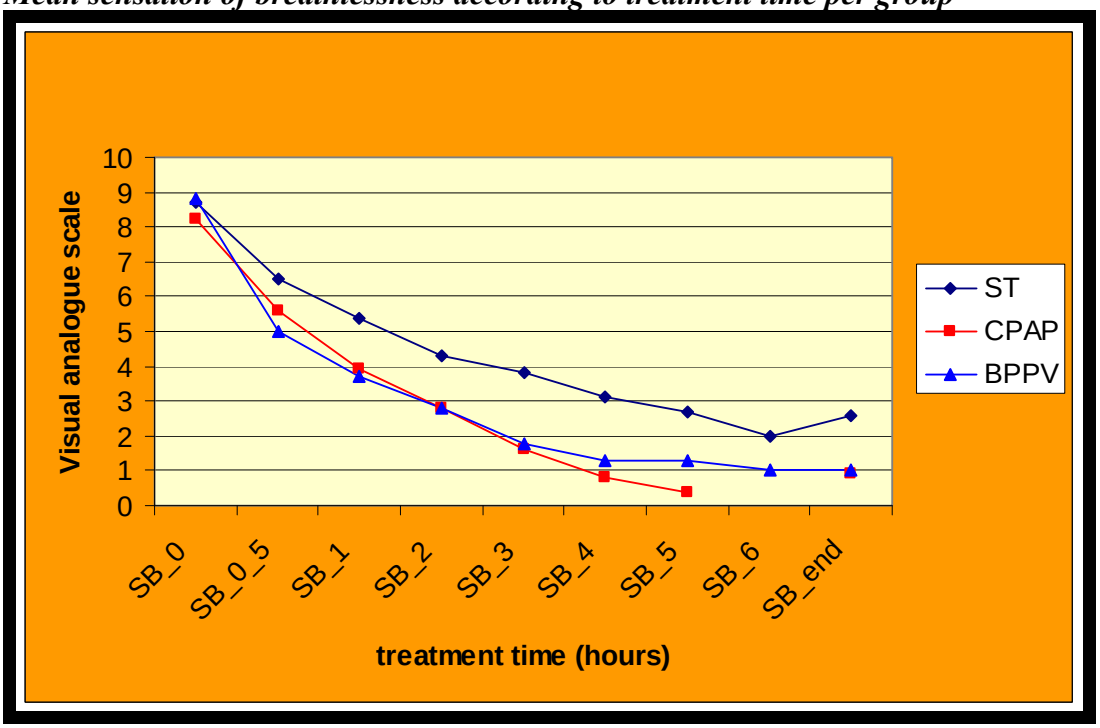
Mean respiratory rate per treatment group and improvement over time



ST *= standard therapy group,* ***CPAP*** *= CPAP intervention group and* ***BPPV*** *= BPPV intervention group. Respiratory rate is given in breaths per minute.* ***RR_0,0.5,1,2,3,4,5,6,end*** *= treatment time when data was collected where 0 is baseline and 0.5 is first half an hour of treatment and so forth.*

Graphic 4-4

Mean sensation of breathlessness according to treatment time per group



SB_0*=sensation of breathlessness at baseline,* ***SB_0.5****=sensation of breathlessness after first half an hour of treatment* ***SB_1,2,3,4,5,6****=sensation of breathlessness after one,2,3,4,5,6 hour/s of treatment.****SB_end****=sensation of breathlessness at end of treatment, did not take into consideration time.****Visual Analogue scale*** *from zero to ten, zero = no breathlessness at all, 10 = most breathlessness ever****ST*** *= standard therapy group,* ***CPAP*** *= CPAP intervention group,* ***BPPV*** *= BPPV intervention group*

4.5.2. Sensation of Breathlessness

Patients graded their sensation of breathlessness on a visual analogue scale. Ten out of ten was the most "short of breath" that they had ever felt and zero out of ten was no shortness of breath at all. The **Group A** analyses showed significant difference between the treatment groups in the first half an hour, becoming marginally significant after one hour and significant again at three hours and at end of treatment. In the post-hoc comparisons the BPPV group showed significant contribution towards the reduction of breathlessness throughout the treatment compared to the Standard Therapy group (graphic 4-4). The CPAP group was also significant at three hours and at the end of treatment but not as much as the BPPV group when they were compared to the Standard Therapy group. The *p* values are described in table 4-8. When the CPAP and BPPV groups were compared to the Standard Therapy group (**Group B**) they significantly improved the patients' sensation of breathlessness in the first half an hour, one hour, three and four hours and at end of treatment.

Table 4-8
Sensation of breathlessness mean shift analysis – p-values

	0.5 hr	1 hr	2 hr	3 hr	4 hr	End Rx
Total n =	30	30	30	29	20	30
Δ SB						
Group A	0.0169 †	0.0595	0.1257	0.0300 †	0.0696	0.0237 †
ST x CPAP	0.3526	0.1394	0.1773	0.0311 †	0.0575 ‡	0.0061 †
ST x BPPV	0.0054 †	0.0197 †	0.0477 †	0.0142 †	0.0393 †	0.0263 †
CPAPxBPPV	0.0507 ‡	0.3591	0.5094	0.7560	0.9419	0.0122 †
Group B	0.0369 †	0.0271 †	0.0519	0.0079 †	0.0191 †	0.0061 †

Group A = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group.* ***ST x CPAP, ST x BPPV and CPAP x BPPV*** *are the post-hoc comparisons. SB = sensation of breathlessness*
† = $p<0.05$, ‡ = $0.05 < p \leq 0.1$

4.5.3. Accessory Muscle Use

Accessory muscle use was significantly improved between the treatment groups (**Group A**) from baseline to end of treatment. In the post-hoc comparisons the CPAP and BPPV groups contributed to this significance (graphic 4-5). The BPPV intervention group did not show significance in the hourly analyses while the CPAP

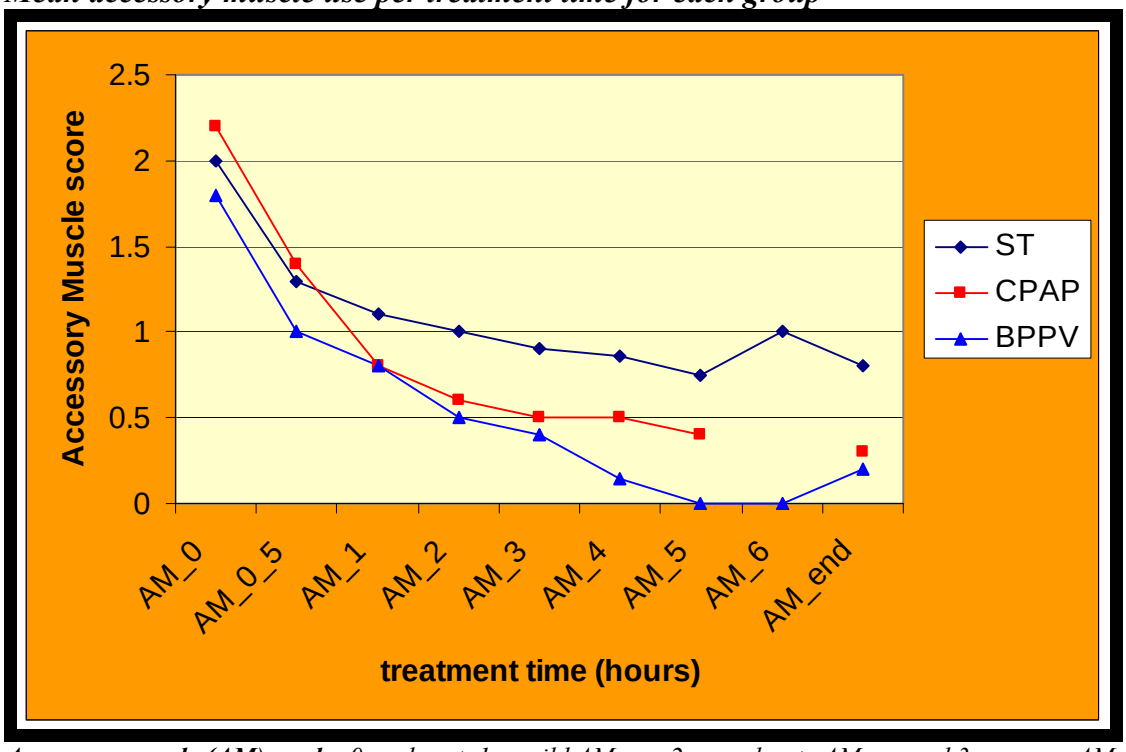
group showed significance at one hour of treatment and then marginally at two and three hours of treatment. In the **Group B** analyses the intervention groups significantly reduced the use of accessory muscle at two hours and at end of treatment compared to the Standard Therapy group. The *p* values are described in table 4-9.

Table 4-9
Accessory muscle use mean shift analysis- p-values

	0.5 hr	1 hr	2 hr	3 hr	4 hr	End Rx
Total n =	30	30	30	29	20	30
Δ AM				-		
Group A	0.7785	0.1324	0.1221	0.2084	`0.4484	0.0253 †
ST x CPAP	0.8897	0.0475 †	0.0586 ‡	0.0991 ‡	0.2382	0.0129 †
ST x BPPV	0.5033	0.4242	0.1092	0.1681	0.3840	0.0290 †
CPAPxBPPV	0.6016	0.2244	0.7568	0.7872	0.8255	0.7286
Group B	0.6335	0.1077	0.0407 †	0.0771 ‡	0.2054	0.0066 †

Group A = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group.* ***ST x CPAP, ST x BPPV, CPAP x BPPV*** *are the post-hoc comparisons.* ***AM*** = *accessory muscles*
† = $p < 0.05$, ‡ = $0.05 < p \leq 0.1$

Graphic 4-5
Mean accessory muscle use per treatment time for each group



Accessory muscle (AM) scale :*0 = absent, 1 = mild AM use, 2 = moderate AM use and 3 = severe AM use (Rodrigo and Rodrigo 1993),* ***AM_0*** *= AM at baseline,* ***AM_0.5*** *= AM after first half an hour of treatment,* ***AM_1,2,3,4,5,6*** *= AM after one,2,3,4,5,6 hour/s of treatment,* ***AM_end =*** *AM at end of treatment, did not take into consideration time,* ***ST*** *= standard therapy group,* ***CPAP*** *= CPAP intervention group,* ***BPPV*** *= BPPV intervention group*

4.5.4. Lung Sounds

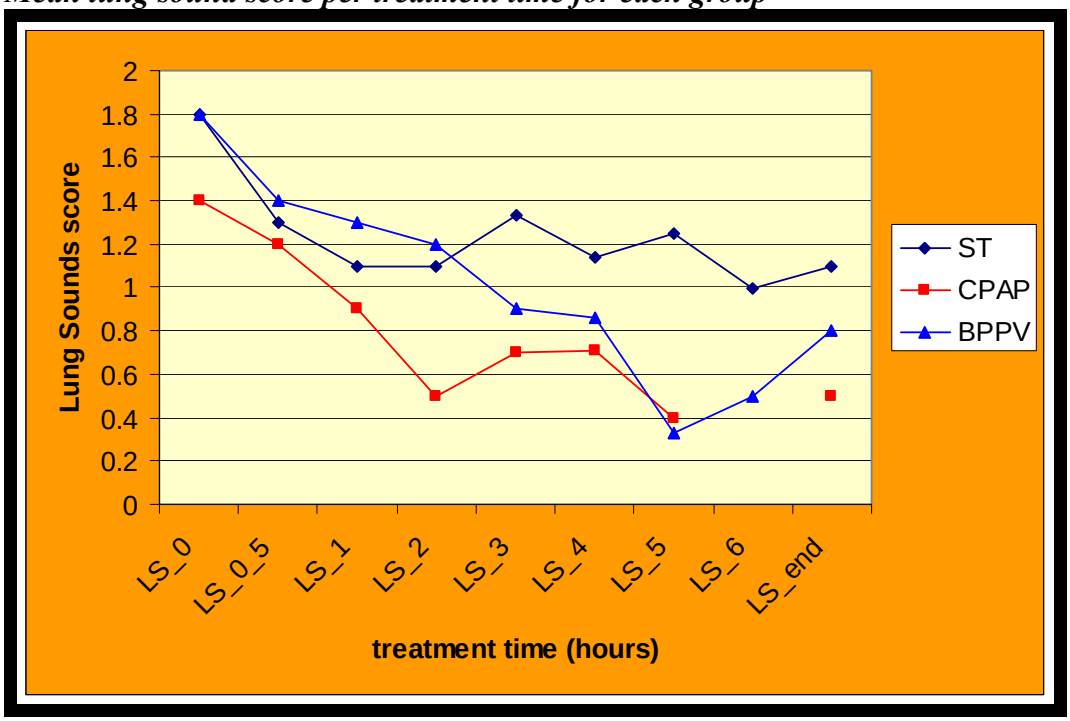
Lung sounds only showed significant improvement at two hours of treatment. In the post-hoc comparisons the main difference was between the Standard Therapy group and the CPAP intervention group (graphic 4-6). This was significant at two hours of treatment and at end of treatment. The *p* values are noted on table 4-10.

Table 4-10
Lung sounds mean shift analysis – p-values

	0.5 hr	1 hr	2 hr	3 hr	4 hr	End Rx
Total n =	30	30	30	29	20	30
Δ LS						
Group A	0.9381	0.6151	0.0309 †	0.1690	0.5511	0.1023
ST x CPAP	0.9366	0.7682	0.0352 †	0.0737 ‡	0.2875	0.0345 †
ST x BPPV	0.7336	0.4982	0.6564	0.1600	0.4601	0.2645
CPAPxBPPV	0.8027	0.3447	0.0133 †	0.6431	0.6940	0.2695
Group B	0.7983	0.8018	0.3963	0.0650 ‡	0.3025	0.0659 ‡

Group A = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group.* ***ST x CPAP, ST x BPPV and CPAP x BPPV*** *are the post-hoc comparisons.* ***LS*** *= the lung sounds*
† = $p < 0.05$, ‡ = $0.05 < p \leq 0.1$

Graphic 4-6
Mean lung sound score per treatment time for each group



Lung sounds score: *0 = no wheezes, 1 = expiratory wheezes, 2 = inspiratory and expiratory wheezes and 3 = silent lungs (Rodrigo and Rodrigo 1993),* ***LS_0*** *= lung sounds at baseline,* ***LS_0.5*** *= lung sounds after first half an hour of treatment,* ***LS_1,2,3,4,5,6*** *lung sounds after one,2,3,4,5,6 hour/s of treatment,* ***LS_end*** *= lung sounds at end of treatment, did not take into consideration time,* ***ST*** *= standard therapy group,* ***CPAP*** *= CPAP intervention group,* ***BPPV*** *= BPPV intervention group*

4.5.5. Lung Function

The change in peak expiratory flow rate (PEFR) and peak expiratory flow rate % predicted (PEFR % predicted) was significant from the first half an hour of treatment to three hours of treatment between the groups (one-way ANOVA). From four hours to end of treatment PEFR lost significance between the groups and PEFR % predicted was marginally significant at end of treatment. Two patients (patient one and 18) who were so severely distressed at presentation to the emergency unit were unable to perform a peak flow maneuver. The noted value on their data sheets for baseline was zero. For statistical analyses this was not an accepted value so it was changed to the lowest value that we considered would be comparable to these patient's lung function at that point. The value of a PEFR of 50 L/min was used for the statistical analyses of these two patients. The post-hoc comparison showed that the values for lung function in the CPAP intervention group were significantly different from that of the Standard Therapy group in these first three hours of treatment. The CPAP group was also the only intervention group that displayed significance in lung function at the end of treatment. The *p* values are described in table 4-11.

Table 4-11
Peak expiratory flow rate and PEFR percentage of predicted mean shift analysis – p- values

	0.5 hr	1 hr	2 hr	3 hr	4 hr	End Rx
Total n =	30	30	30	29	20	30
Δ PEFR						
Group A	0.0030 †	0.0264 †	0.0428 †	0.0445 †	0.2024	0.1149
ST x CPAP	0.0007 †	0.0092 †	0.0190 †	0.0154 †	0.0792 ‡	0.0403 †
ST x BPPV	0.0643 ‡	0.3999	0.6411	0.3738	0.5153	0.3712
CPAPxBPPV	0.0622 ‡	0.0558 ‡	0.0486 †	0.0912 ‡	0.2460	0.2117
Group B	0.0041 †	0.0576 ‡	0.1225	0.0659 ‡	0.1721	0.0948 ‡
Δ PEFR% pred						
Group A	0.0035 †	0.0138 †	0.0224 †	0.0265 †	0.2715	0.0877
ST x CPAP	0.0009 †	0.0048 †	0.0108 †	0.0089 †	0.1120	0.0293 †
ST x BPPV	0.0823 ‡	0.3917	0.6898	0.3481	0.4605	0.3294
CPAPxBPPV	0.0566 ‡	0.0337 †	0.0257 †	0.0635 ‡	0.3480	0.1938
Group B	0.0053 †	0.0444 †	0.1088	0.2715	0.1854	0.0732 ‡

ST = *standard therapy*, **CPAP** = *continuous positive airway pressure and* **BPPV** = *bilevel positive pressure ventilation.* **Group A** = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group.* ***ST x CPAP, ST x BPPV, CPAP x BPPV*** *are the post-hoc comparisons for the one-way ANOVA,.* ***PEFR*** = *the peak expiratory flow rate,* ***PEFR % pred*** = *peak expiratory flow rate percentage of predicted*
† = $p < 0.05$, ‡ = $0.05 < p \leq 0.1$

Lung function improvement in the present study was calculated by the shift in liters per minute or in percentage points from baseline. This was different from the way the Sorosky study (2003) calculated their patients' improvement in lung function. In their study they compared the means. We opted to compare the real shift in parameters between the groups as this would represent real improvement. Tables 4-12 and 4-13 show the actual shift (Δ) in PEFR in liters per minute and the shift in PEFR % predicted in percentage points for each treatment group. Table 4-13 was illustrated in graphic 4-7 and it shows that both the CPAP and BPPV groups improved lung function faster and better than the standard therapy group. It is also easily seen that the CPAP group had a significantly greater improvement. The BPPV group also improved more than the standard therapy group even if significance was not reached.

Table 4-12
PEFR improvement (Δ) in L/min

	0_5 hr	1 hr	2 hr	3 hr	4 hr	end Rx
ST	15.4899	36.9995	61.2357	67.4266	74.2513	86.3864
CPAP	54.1417	87.5314	110.63	123.508	132.575	140.993
BPPV	34.7683	52.1692	70.4339	86.8133	93.6123	109.121

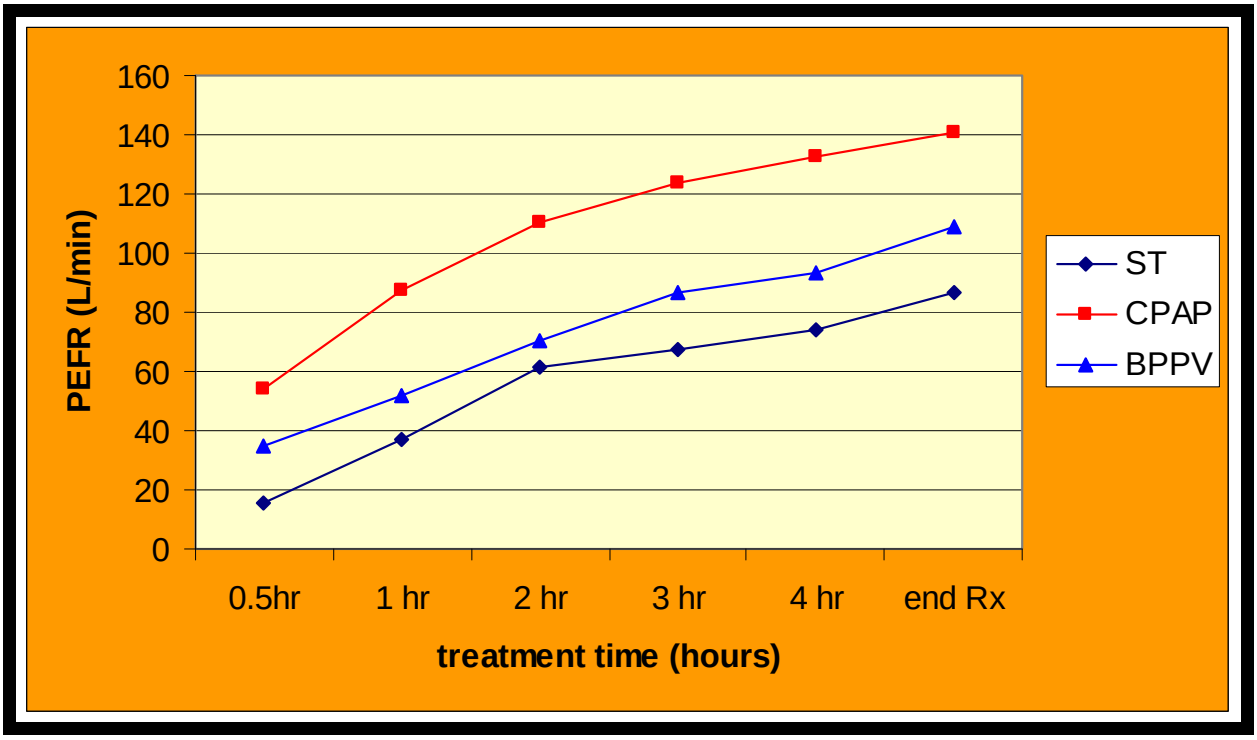
ST = *standard therapy*, **CPAP** = *continuous positive airway pressure and* **BPPV** = *bilevel positive pressure ventilation.*

Table 4-13
PEFR % predicted improvement (Δ) in % points

	0_5 hr	1 hr	2 hr	3 hr	4 hr	end Rx
ST	3.1465	7.4265	12.2037	13.4105	15.2043	17.1096
CPAP	11.0085	17.4219	22.1571	24.6949	25.3574	28.0621
BPPV	6.8759	10.2156	13.6492	17.1877	19.3272	21.7763

ST = *standard therapy*, **CPAP** = *continuous positive airway pressure and* **BPPV** = *bilevel positive pressure ventilation.*

Graphic 4-7
Mean shift in the peak expiratory flow rate L/min as lung function improved over time



ST *= standard therapy group,* ***CPAP*** *= CPAP intervention group,* ***BPPV*** *= BPPV intervention group,* ***PEFR*** *= peak expiratory flow rate,* ***L/min*** *= liters per minute*

The CPAP intervention group clearly stands out, yet the BPPV group also performed better than the standard therapy group.

Table 4-14
Percentage improvement in PEFR % predicted

	0_5 hr	1 hr	2 hr	3 hr	4 hr	end Rx
ST	8.94	21.11	34.68	38.11	43.21	48.63
CPAP	36.03	57.02	72.52	80.83	82.99	91.85
BPPV	20.51	30.47	40.71	51.27	57.65	64.96

ST *= standard therapy,* **CPAP** *= continuous positive airway pressure and* **BPPV** *= bilevel positive pressure ventilation.* ***PEFR % predicted*** *= peak expiratory flow rate percentage predicted*

Table 4-15
Comparison of three studies

	n	Baseline PEFR % predicted	*p*	3 hr PEFR % predicted	*p* value for means	Shift in percentage points	% improvement	*p*	*p* value for shift
Sorosky									
Control	15	34 ± 11.1	NS	41.9 ± 18.6	0.03	7.9	21.9 ± 32.3	0.02	not available
BPPV	15	38 ± 11.9		57.9 ± 20		19.9	55.5 ± 43.9		
Pollack									
Control	40	37.3 ± 13	NS	57.2 ± 21	0.0011	20	53.61	not availa-ble	not available
BPPV	60	40.3 ± 14		68.8 ± 18.9		28	68.47		
Hanekom									
Control	10	35.2 ± 10.7	NS	47.8±15.2		13.6 ± 7.8	38.11		ANOVA p= 0.0265
CPAP	10	30.5 ± 11.7		54.8 ± 18.5		24.2 ± 9.5	80.83	not availa-ble	CPAPxST p=0.0089
BPPV	10	33.5 ± 13.8		50.8 ± 16.1		17.3 ± 8.7	51.27		BPPVxST p=NS

Control *= standard medical treatment, it did vary from study to study,* ***n*** *= sample size,* ***NS*** *= non significant,* ***PEFR*** *= peak expiratory flow rate,* ***PEFR % predicted*** *= peak expiratory flow rate percentage predicted,* ***CPAP*** *= continuous positive airway pressure,* ***BPPV*** *= bilevel positive pressure ventilation,* ***ST*** *= standard therapy*

For comparison with the Sorosky study (table 4-14) the percentage improvement according to the shift in PEFR % predicted was calculated. Table 4-15 further compares the Sorosky and Pollack studies with the present study. The Pollack study had a higher PEFR % predicted at baseline especially in their BPPV group. Our CPAP group showed the lowest mean PEFR % predicted at baseline (30.55 %).

After three hours of treatment the mean PEFR % predicted was highest in the BPPV group of the Pollack study (68.8 %). The shifts in PEFR % predicted in percentage points and in percentage improvement were similar for the BPPV group in the Sorosky and present study while much higher in the Pollack study. Note that the Pollack study had a bigger sample size (n=100). The Sorosky study had the lowest improvement in PEFR % predicted in the control group. The CPAP group in the present study had the biggest percentage improvement in PEFR % predicted when compared to the BPPV groups of all three studies [80.83 % versus 55.5 % (Sorosky) and 68.47 % (Pollack)].

4.5.6 Separate analyses of the CPAP group against the BPPV group

In the separate covariance analyses of the CPAP group against the BPPV group what stood out were the results of lung function as shown by the PEFR. When compared to the BPPV group the CPAP group tended to improve lung function (PEFR and PEFR % predicted) faster over the four hour period (table 4-11 and graphic 4-7).

4.5.7 Expiratory Positive Airway Pressure and Continuous Positive Airway Pressure

The mean values and standard deviation of the level of expiratory positive airway pressure (EPAP) and continuous positive airway pressure (CPAP) are listed on table 4-16. No significant difference between the mean levels of applied EPAP and CPAP was found among the two intervention groups.

Table 4- 16
Applied levels of EPAP and CPAP(mean ± SD) over time

	Baseline	**0.5 hr**	**1 hr**	**2 hr**	**3 hr**	**4 hr**
***p* value**	0.3306	1.0000	0.1456	0.6601	0.8297	0.4017
CPAP cmH20	5 ± 0	5.7 ± 0.21	6.2 ± 0.25	6.4 ± 0.27	6.6 ± 0.31	7.2 ± 0.54
min	5	5	5	5	5	5
max	5	7	7	7	8	8
EPAP cmH20	5.2 ± 0.63	5.7 ± 0.33	5.6 ± 0.31	6.2 ± 0.36	6.5 ± 0.34	6.6 ± 0.43
min	5	5	5	5	5	5
max	7	7	7	8	8	8

EPAP *= expiratory positive airway pressure;* ***CPAP*** *= continuous positive airway pressure;* ***min*** *= minimum;* ***Max*** *= maximum*

4.5.8 Inspiratory Positive Airway Pressure

The mean inspiratory positive airway pressure (IPAP) applied to the patients in the BPPV group is shown on table 4-17. The maximum IPAP level applied during the study was 15 cmH_20.

Table 4-17
Mean levels of inspiratory positive airway pressures applied (mean ± SD) over time

	Baseline	**0.5 hr**	**1 hr**	**2 hr**	**3 hr**	**4 hr**
IPAP cmH20	10.5 ± 1.58	10.9 ± 1.66	11.1 ± 1.91	11.2 ± 2.1	11.4 ± 2.1	11.4 ± 2.06
Min	10	10	10	10	10	10
Max	15	15	15	15	15	15

IPAP *= inspiratory positive airway pressure,* ***min*** *= minimum.* ***Max*** *= maximum*

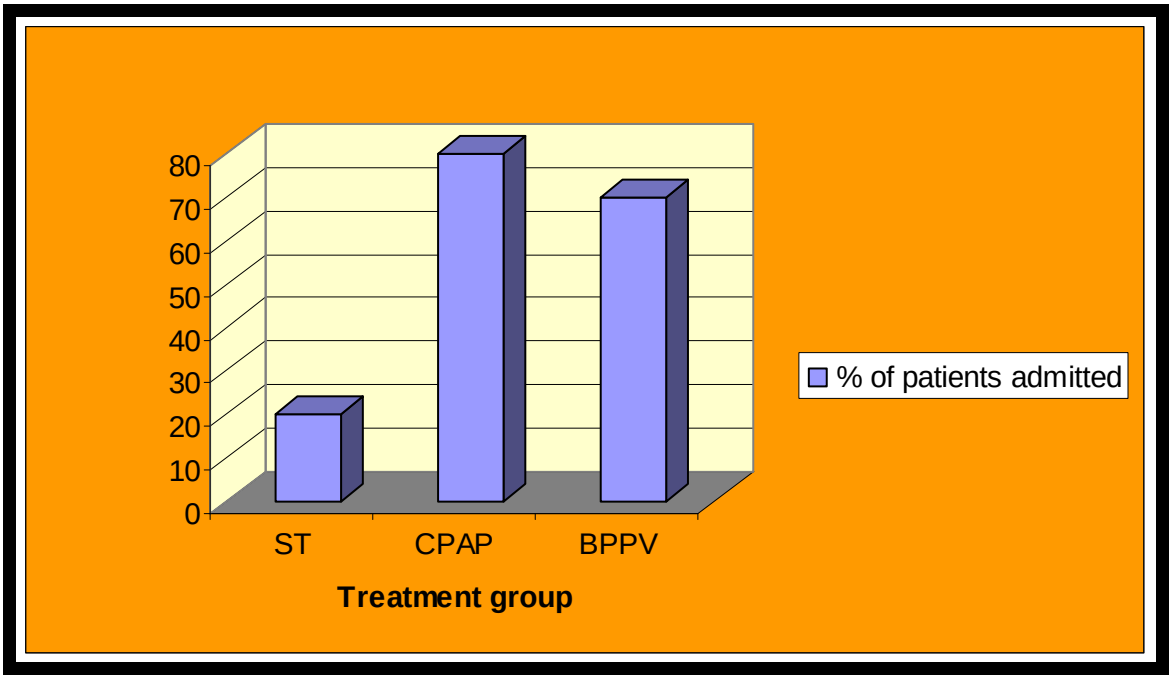
4.6 ANALYSIS OF SECONDARY OUTCOMES

4.6.1 Outcome from the emergency unit

Patient recovery was observed to see if they were discharged after emergency unit treatment or admitted to one of the wards. There was a significant difference between the treatment groups in the number of patients who were discharged after the emergency unit treatment and those admitted to the hospital. (p = 0.02) In the

Standard Therapy group, 80% of the patients were discharged from the emergency unit and 20% were admitted. In the CPAP group, 20 % of the patients were discharged and 80 % admitted while in the BPPV group, 30 % was discharged and 70 % admitted. From the total group (n = 30) 13 patients (43.33 %) were discharged from the emergency unit while 17 (56.67 %) were admitted to the hospital for further treatment ($p = 0.020$). See graphic 4-8

Graphic 4-8
Percentage of patients in each treatment group that were admitted after emergency unit treatment

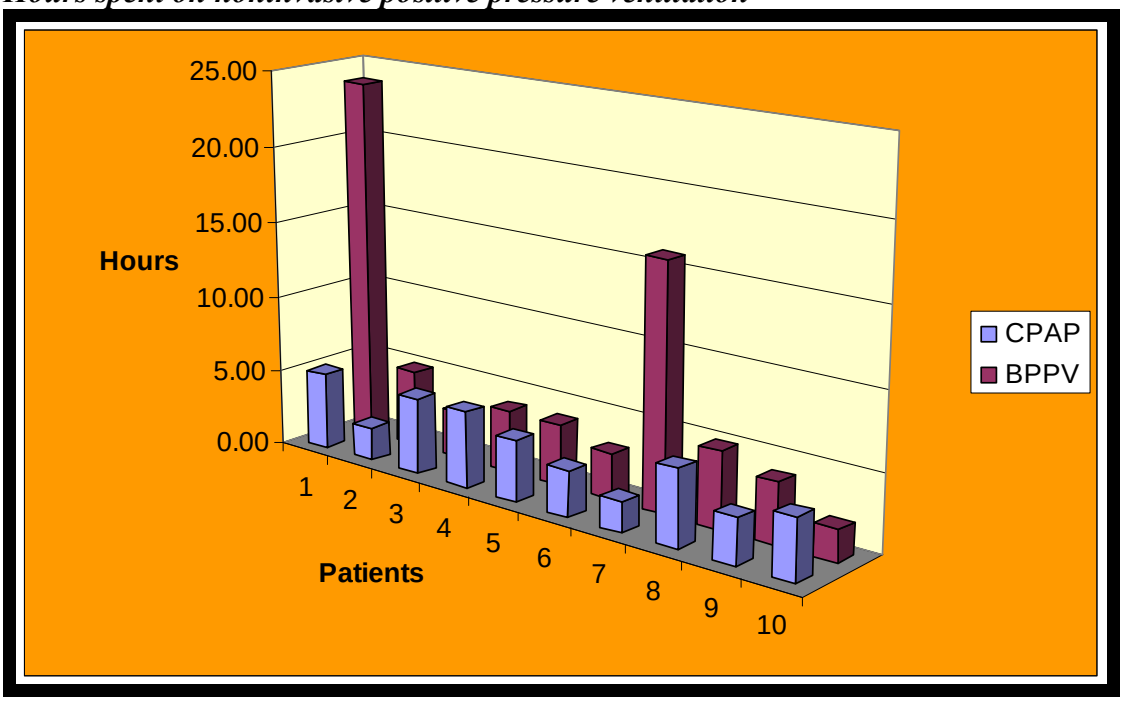


ST *= standard therapy group,* ***CPAP*** *= continuous positive airway pressure group,* ***BPPV*** *= bilevel positive pressure ventilation group*

4.6.2 Time spent on Noninvasive Ventilation

Patients in the CPAP group and those in the BPPV group spent a mean of 3.82 ± 1.202 hours and 6.98 ± 7.092 hours respectively on noninvasive ventilation. Two patients in the BPPV group had to sleep on noninvasive ventilation. Patient two spent 23.75 hours and patient 18 spend 16 hours on noninvasive ventilation respectively (graphic 4-9).

Graphic 4-9
Hours spent on noninvasive positive pressure ventilation



Numbering on the x-axis are a serious of numbers, not the codes allocated to each patient. Patients two and 18 are represented by number one and seven of the BPPV group (burgundy) in the x-axis. CPAP=continuous positive airway pressure group,BPPV=bilevel positive pressure ventilation group

4.6.3. Intubation Rate

No patients were intubated in the Emergency Unit. Patient 11 was intubated five days later in ICU after having been put on non-invasive ventilation again in the High-care ward.

4.6.4. Mortality Rate

None of the patients enrolled in the study died in the emergency unit or in the wards. There was therefore a zero mortality rate.

4.6.5. Length of Stay

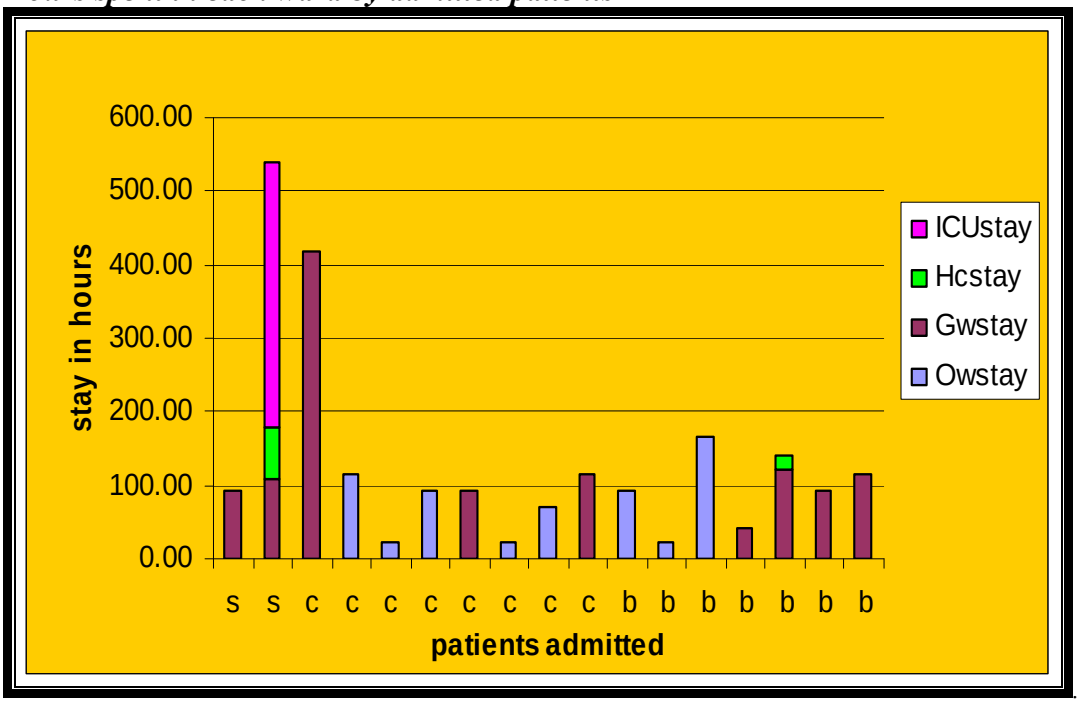
The length of stay was divided into emergency unit stay and hospital stay. The mean length of stay in the emergency unit for the group (n = 30) was 5.28 ± 1.52 hours. For those patients who were admitted to the hospital for further treatment (n = 17) the total length of stay in hospital was 5.53 ± 5.58 days. The length of stay in the emergency unit and the stay in hospital per treatment group is described in table 4-18. No significant difference (p = 0.1444) was found among the hospital length of stay between the treatment groups (**Group A analyses**). The Standard Therapy group with only two admissions shows clearly a longer mean length of stay in hospital compared to the CPAP and BPPV groups. This was mainly due to patient 11 who worsened once in the ward and had to be taken to the intensive care unit for intubation and ventilation. In the **Group B** analysis the Standard Therapy group had a significant longer hospital stay than the intervention groups (p = 0.0481). Patients were mostly admitted to the overnight and general wards (graphic 4-10). Only two patients were first sent to the high care ward.

Table 4-18
Mean emergency unit stay and hospital length of stay (mean ± SD)

	LOS in EU (hours)	Number of patients admitted	LOS in hospital (days)
ST	5.61 ± 1.60	2	13.19 ± 13.17
CPAP	4.91 ± 1.33	8	4.98 ± 5.68
BPPV	5.31 ± 1.68	7	3.98 ± 2.08
p value group A	0.6048	0.020 †	0.1444
p value group B	0.4069		0.0481 †

ST = *standard therapy group*, **CPAP** = *continuous positive airway pressure group*, **BPPV** = *bilevel positive pressure ventilation group,* ***EU*** *= emergency unit,* ***LOS*** *= length of stay*, **Group A** = *three group ANOVA*, **Group B** = *CPAP+ BPPV groups analyzed against the standard therapy group* ***Time*** *= was expressed in hours*, † = $p < 0.05$, ‡ = $0.05 < p \leq 0.1$

Graphic 4-10
Hours spent in each ward by admitted patients

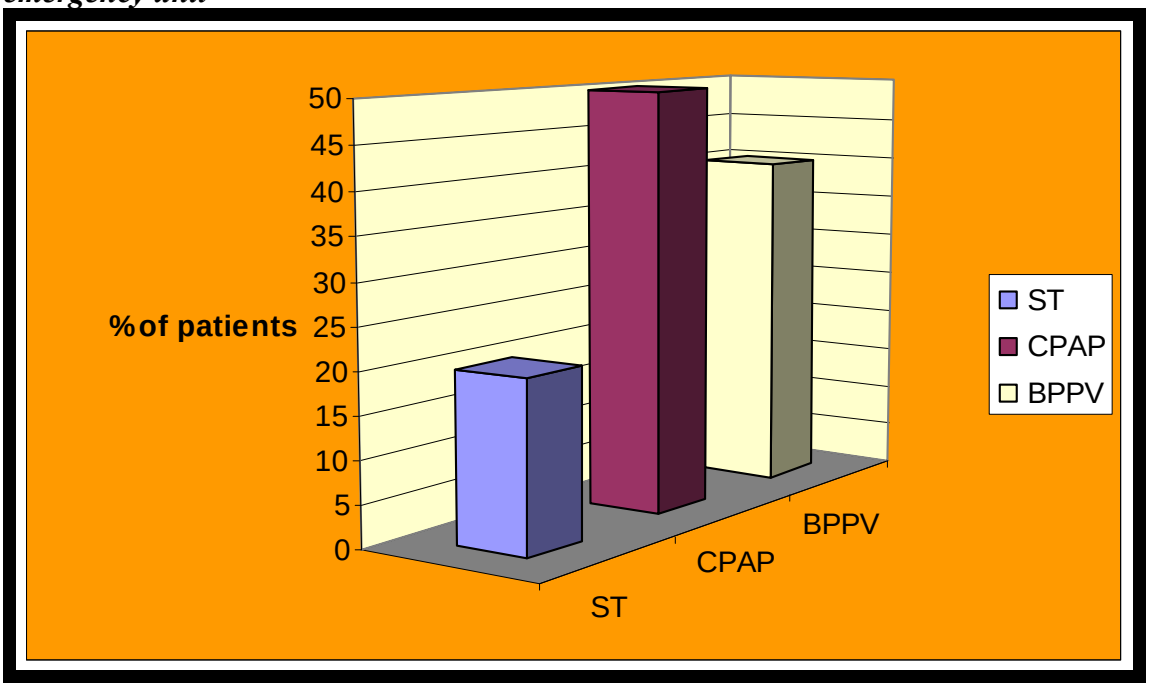


Patients were named according to their treatment group for this graphic namely: ***s****=standard therapy patient,* ***c*** *= continuous positive airway pressure patient and* ***b****= bilevel positive pressure ventilation patient.*
OW *= overnight stay ward,* ***GW****= general wards,* ***HC****= high care ward,* ***ICU****=intensive care unit*

4.6.6. Patients that reached PEFR > 65 % predicted

Out of the total group (n = 30) nineteen (63.33 %) failed to reach a PEFR of at least 65% in the emergency unit. In the Standard Therapy group, two patients (20 %) reached a PEFR % predicted > 65 %. In the CPAP and BPPV groups there were 5 (50 %) and 4 (40 %) patients respectively who reached a PEFR > 65 % predicted. There was no statistical difference between the group of patients who managed to reach a PEFR % predicted > 65 % in the emergency unit and those who did not (p = 0.510).The clinical significance of these findings will be discussed in the following chapter.

Graphic 4-11
Percentage of patients who reached a peak expiratory flow rate > 65% in the emergency unit



ST = *standard therapy group,* **CPAP** = *continuous positive airway pressure group,*
BPPV = *bilevel positive pressure ventilation*

4.7 CONCLUSION

The results of the present investigation revealed that both CPAP and BPPV improved patients' clinical signs faster than standard therapy alone. BPPV seemed to improve respiratory rate and sensation of breathlessness earlier in the course of treatment while the effect of CPAP was more evident in the reduction of accessory muscle use and disappearance of wheezes on auscultation in the lungs. Lung function was clearly and significantly improved by CPAP from the first half an hour of treatment. In the following chapter we will proceed to discuss these results in more details as well as their clinical relevance.

CHAPTER 5

DISCUSSION

5.1 INTRODUCTION

Asthma is a reversible airway obstruction disease characterized by airway hyperresponsiveness and inflammation. Acute asthma exacerbation (AAE) is a medical emergency that patients present with frequently at emergency units. While the main problem in an acute exacerbation is an increased expiratory resistance the main consequence is a loading of the inspiratory muscles. Symptoms like tachypnoea, dyspnoea and accessory muscle use always accompany an AAE. If treatment is delayed or ineffective to reduce the level of bronchoconstriction present, patients may develop respiratory muscle fatigue and they may need ventilatory support. Noninvasive positive pressure ventilation has an established role in acute exacerbations of COPD. Its role remains to be established in asthma.

The present study was undertaken to investigate the use of two modes of noninvasive positive pressure ventilation in AAE. We hypothesized that the early use of CPAP or BPPV added to standard medical therapy would decrease time of response to therapy compared to standard therapy alone. We further hypothesized that BPPV would improve patients' symptoms faster than CPAP due to the inspiratory assistance added to the PEEP in the bilevel positive pressure ventilation.

In the population studied there was no significant difference among the three treatment groups in age and also in hours of attack prior to presenting at the emergency department for treatment. The mean age of the group was 42 ± 12.57 years. The group was comprised mainly of females (80 % females) for n = 30. This was consistent with previous studies which have shown a higher prevalence of acute asthma exacerbations in the female population (Singh et al., 1999; Rodrigo et al., 2004). The majority of the group (90 %) consisted of non smokers. There were similar findings for baseline characteristics namely heart rate, respiratory rate, temperature,

PEFR and PEFR % predicted, peripheral saturation and blood pressure among the three treatment groups.

The results of the present investigation revealed that both CPAP and BPPV improved patients' clinical signs faster than standard therapy alone. Lung function was clearly and significantly improved by CPAP from the first half an hour of treatment. This was an unexpected finding and proved our second hypotheses wrong. As far as secondary outcomes there were significantly more admissions to hospital wards in the two noninvasive groups but hospital length of stay was significantly longer in the standard therapy group. Mortality rate was zero for all three groups.

The results will be discussed under two main themes namely: a) results on lung function tests and b) results on clinical signs. Under each theme we will discuss a) the results obtained between each intervention group and the control group (CPAP versus ST and BPPV versus ST) b) the results between the two intervention groups (CPAP versus BPPV) and c) the results between the noninvasive therapy groups (CPAP and BPPV) and the standard therapy group (NPPV versus ST).

5.2 LUNG FUNCTION

5.2.1 Continuous Positive Airway Pressure versus Standard Therapy in its effect on lung function

The CPAP intervention group showed an outstanding improvement in lung function compared to the standard therapy group (tables 4-11, 4-12, 4-13 and graphic 4-7). It could be argued that this improvement was related to the administration of bronchodilator inhalations. In the first hours of treatment of an AAE the reduction in bronchospasm is mostly due to the continuous administration of nebulized β-agonists and anticholinergic drugs. The β-agonist has an onset action of 5 minutes with this action continuing for up to 6 hours (Rodrigo, 2003). The administration of intra-venous steroids only initiates its action after 4 hours and can take 6 to 24 hours to improve lung function (Manser et al., 2005). Nebulised anticholinergics usually start

acting 20 minutes after administration. Studies on the use of inhaled anticholinergics have shown that the addition of ipatropium bromide together with β-agonists improved lung function, reduced hospital admission and reduced costs (Rodrigo, 2003). Since all intervention groups received standardized nebulized ipatropium bromide together with β-agonists and intra-venous medication it seems evident that the improvement is due to the addition of noninvasive CPAP. Yet two studies have shown that administering bronchodilators with a noninvasive device improved lung function more in this group compared to those who received bronchodilators through small volume nebulizers. (Pollack et al., 1995; Lin et al., 1995)

A number of studies have looked at the effect of CPAP on AAE (Martin et al.,1982; Shivaram et al., 1987; Shivaram et al., 1993; Lin et al., 1995; Lougheed et al., 1995; Wang et al., 1996). Two of these studies looked at lung function in induced bronchoconstriction and found a significant improvement in FEV_1 between the control and CPAP groups (Lin et al., 1995; Wang et al., 1996). Of the above mentioned studies only two studies investigated CPAP in AAE in clinical conditions (Shivaram et al., 1987, Shivaram et al., 1993). In the first of these two studies (1987) patients received intra-venous aminophyline and no mention was made about nebulized bronchodilators. Patients were fitted with face mask CPAP after being selected for the study (n = 21). Nineteen patients were selected as a control group. The CPAP pressures used in this study were 5, 7.5 and 10 cmH_2O. They concluded that the application of these levels of CPAP on acutely ill asthmatic patients reduced the workload on the inspiratory muscles. The second study (1993) selected all patients (n = 21) presenting at their emergency unit with a PEFR of 80 – 200 L/min and applied nasal mask CPAP of 5 and 7.5 cm H2O intermittently for 30 minutes. The control group consisted of six selected patients. They withheld bronchodilators and oxygen 30 minutes prior to the study. They found that CPAP reduced the respiratory rate and dyspnoea of the asthma patients. It would seem that these studies tested the effect of CPAP alone in the intervention group. To our knowledge the present study is the first that has looked at the effect of CPAP when added to standard medical treatment (ST) (as suggested by present treatment guidelines) (Rodrigo, 2003; Global Strategy for Asthma Management and Prevention (GINA), 2006) for an AAE and compared it to ST alone. An asthma exacerbation is a serious and distressing situation for a patient. Changing or withholding treatment that has been shown to be effective does not make

sense to us. We preferred to investigate whether the addition of noninvasive positive pressure to the existing standard treatment could alleviate the distressing sensations experienced by patients with AAE faster than standard medical treatment alone.

Ongoing investigation exists into the possible mechanisms of airway hyperresponsiveness (AHR) or excessive airway narrowing in asthma. Most authors seem to agree that the remodeling that occurs in the asthmatic airway due to the inflammatory response is a definite contributor to the AHR found in asthma. The mainframe of research to date suggests the following mechanisms as contributors to AHR: a) increase in airway smooth muscle (ASM) mass, b) a decrease of the load against which the ASM must shorten and c) an alteration or decrease of the fluctuating load that would perturb the myosin bindings during breathing (Fredberg, 2004). Alteration in the airway smooth muscle load in the asthmatic lung could be due to many factors like airway cartilage softening, decreased tethering effect of the lung parenchyma, increased ASM proportion in the circumference, increased airway wall thickness and increased secretions in the airway lumen (Brusasco & Pellegrino, 2003; Moreno, Hogg & Pare, 1986). Further research has also been done into the mechanisms that modulate AHR in non-asthmatic persons but seem to be absent or weakened in patients with asthma. The main mechanisms that are accepted today are the effects of deep inspiration and the effects of tidal stretching acting as bronchodilator and bronchoprotective mechanisms (Scichilone, Permutt & Togias, 2001; Brusasco & Pellegrino, 2003). Deep inspiration has been shown to have a potent bronchodilator effect on normal lungs after these have undergone bronchoprovocation (Pellegrino et al., 1998; Scichilone, Permutt & Togias 2001; Brusasco & Pellegrino, 2003). On the other hand this effect seems to be absent or very reduced in moderate to severe asthma patients (Lim et al., 1989; Macklem, 1996; Pellegrino et al., 1998). Tidal stretching causing load fluctuations during spontaneous breathing was shown to be the most potent bronchodilator mechanism present in normal lungs (Brusasco & Pellegrino, 2003; Fredberg et al., 1997; Gump, Haughney & Fredberg, 2001). Again this mechanism seems to be altered in the asthmatic lung due to decreased loads altering the transmission of these tidal stretches to the level of the myosin bindings in the ASM cell (Pellegrino et al., 1998; Brusasco et al., 1999; Wang, McParland & Pare, 2003; Fredberg, 2004). It was based upon these findings

that we looked for an explanation for the unexpected improvement in lung function observed with the application of CPAP.

Several reasons could be presented for this outstanding improvement in lung function with the addition of CPAP to the standard medical treatment. Firstly a few authors (Shivaram et al., 1993; Wang et al., 1996) have suggested that CPAP could pneumatically splint the airway lumen. If this theory were sustainable one would expect lung function to worsen once CPAP and the "splinting" effect had been removed. Martin and colleagues (1982) did notice an important increase in pulmonary resistance in his induced asthma subjects after the removal of the CPAP. It is however important to notice that CPAP in their study was applied for only one minute once off. Wang and colleagues (1996) on the other hand reported an improvement in lung function as measured by FEV_1 at least up to 5 minutes after the removal of the CPAP. An interesting study that could support this effect of "splinting" was done by Collet and colleagues. They monitored cross-sectional glottic area in asthmatic subjects before and after induced bronchoconstriction. They found that after induced bronchoconstriction cross-sectional glottic area fell significantly at mid-expiration. Once a CPAP of 10 cmH_2O was applied to these patients the expiratory constriction was abolished. The possible mechanism for this improvement in cross-sectional glottic area during expiration remains unanswered. The authors conjectured that mechanoreceptors located in the pharynx and larynx could be responsible for this phenomenon (Collet, Brancatisano & Engel, 1983). We suggest the possibility of CPAP "splinting" the glottic area during the expiratory phase. This suggestion could be supported by the widespread use of CPAP in obstructive sleep apnea (Wright & White, 2000). If the splinting effect exists, as CPAP raises the transpulmonary pressure, it could explain the improvement in lung mechanics and in the patient's sensation of breathlessness found in our study. Yet the fact that Wang and colleagues and the present author observed continued improvement in lung function after the removal of CPAP could suggest that CPAP probably has a more intrinsic effect on the airways of asthmatic lungs. This intrinsic effect could lie in the contraction mechanisms of the ASM.

A second explanation for the significant improvement in PEFR with the application of CPAP could be the effect of CPAP directly on the ASM. In a study done by Lin and

colleagues, they looked at the effect of CPAP on airway smooth muscle (ASM) by evaluating lung responses of subjects with asthma during methacholine-induced bronchoconstriction. They specifically looked at bronchial reactivity and sensitivity. Bronchial reactivity represents the level of bronchoconstriction reached in response to different drug doses. Bronchial sensitivity on the other hand reveals the intrinsic property of the ASM like the number of drug receptors that act on the ASM. In other words bronchial sensitivity shows how easily or how difficult airways narrow (Orehek et al., 1977; Woolcock, Salome & Yan, 1984; Lin et al., 1995). Two groups of asthmatic patients were used in this study. Continuous positive airway pressure of 8 cmH_2O was initiated in one group for 10 minutes while the control group received a mask without positive pressure. Methacoline challenge was then started in both groups until a decrease in FEV_1 of 20% was achieved. The CPAP was only removed for inhalation of methacholine or performance of lung function in the intervention group. Their results showed that the use of CPAP reduced both the bronchial reactivity and sensitivity of the asthmatic subjects. This means that the level of bronchoconstriction reached at different drug doses was smaller with CPAP than without CPAP. The CPAP also acted on the intrinsic properties of the ASM in response to stimuli reducing their sensitivity. Another important finding in their study was a fall in the cumulative dose of methacholine needed to cause a 20% fall in FEV_1 ($PD_{20}FEV_1$). The authors comment that this could be due to a protective effect of CPAP on the ASM against the spasmogen stimuli. Our results concur with the above results as the group that received CPAP in the present study had a very significant improvement in their lung function when compared to the standard therapy group. It could be suggested that CPAP in our study also reduced bronchial reactivity and sensitivity. However the mechanism by which this happens remains open to speculation. There is however a difference between these two studies. In the Lin study CPAP was applied before and during the exposure to spasmogen stimuli. In our study patients had already been exposed to whatever had irritated their airways and a relative level of bronchoconstriction was established and advanced before CPAP was applied. It could be that the CPAP in the Lin study acted through a different mechanism as it was applied prior to bronchoconstriction.

A further mechanism to consider would be the contractile mechanisms of the ASM in itself. It could be argued that the ASM of the subject with asthma enters into such a

contraction state that exiting from this state is nearly impossible. MacParland and colleagues (2005) studied length change in bronchial smooth muscle in conditions that mimicked real bronchoconstriction. They found that ASM adapted to its shortened position and then regained the ability to generate maximal force. This is also referred to as ASM plasticity (Fredberg, 2004). A further explanation arises when we look at the tidal stretching theories. As airway smooth muscle contracts myosin-actin cycling commences. These form a number of interactions also called bridges. If nothing disrupts these bridges they will reach what is called an isometric steady state (Fredberg, 2004). Research into this phenomenon has revealed that the tidal stretches that occur with tidal breathing are transmitted to the myosin head detaching it from the actin filament and so disrupting the bridges formed by the isometric contraction. This has been named a "perturbed equilibrium of myosin binding" (Fredberg, 2004). However tidal stretches of smaller amplitudes than tidal stretching from tidal breaths actually worsen ASM narrowing (Fredberg et al., 1997). Gump and colleagues (2001) have observed in their study that the tidal stretches that occur during quiet tidal breathing in healthy lungs were the "first line of defense against bronchospasm". They tested the effect of length fluctuations on bovine tracheal smooth muscle. They found that tidal fluctuations of length of amplitudes equal to those that are present during quiet tidal breathing had a potent inhibitory effect on the smooth muscle. It seems that in asthmatic lungs factors like inflammatory thickening of the lamina reticulosa, peribronchial adventitia thickening and loss of elastic recoil permits the myosin bindings to collapse in the isometric steady state so causing the bronchoconstriction seen in clinical conditions (Moreno et al., 1986; Fredberg, 2004; Postma & Timens, 2006). Therefore we proposed in our study that since CPAP increases intraluminal pressures and also transpulmonary pressures, it could disrupt these bridge dynamics at ASM level owing to the constant applied pressure. The ASM would consequently return to the perturbed equilibrium of myosin binding state, similar to what happens when tidal stretches are transmitted to the ASM in healthy lungs.

A further possible mechanism could lie in the load against which the airway smooth muscle contracts. Bronchoprovocation tests are used to draw a dose-response curve of the lung to a stimulus. The dose-response curve shows bronchial reactivity to stimuli like histamine or methacholine and they can further discriminate between bronchial reactivity and sensitivity as described above (Woolcock et al., 1984; Cockcroft,

Killian & Mellon, 1977; Orehek et al., 1977). In normal individuals and mild asthmatics the dose-response curve achieves a plateau while in moderate asthma this plateau is not existent. This means that in normal individuals and mild asthmatics maximal shortening of ASM can be achieved without asphyxia (Moreno, Hogg & Pare, 1986). Increasing stimulus from the plateau level causes no further constriction of the airways. This means that in these individuals a mechanism exists that inhibits any further constriction beyond a certain point. On the other hand patients with moderate and severe asthma seem to lack this mechanism that would inhibit the ASM shortening. The lack of this inhibitory factor is believed to lead to AHR. Macklem (1991) argued that to find this mechanism one would have to look at postjunctional events acting on the ASM rather than at prejunctional events. An important postjunctional factor is the load against which the ASM contracts. The smooth muscle structure is subject to the requirement of an antagonism. This means that every time a smooth muscle contracts an external force is required to lengthen it. The length of the ASM is determined by the balance between two static forces. On the one side would be the isometric force generated by the muscle. Balancing it would be the load against which this muscle shortens. This load would act as a passive reaction force (Fredberg et al., 1999). The interdependence between airways and parenchyma represent a load that regulates ASM contraction. The alteration of the function and structure of the airway epithelium could therefore increase AHR (Brusasco & Pellegrino, 2003). A decrease in the ASM load can occur due to a number of factors: a) the softening of airway cartilage due to the chronic inflammatory process that is present in asthma, b) a decreased reduction in transmission of lung elastic recoil through altered parenchyma, c) increased proportion of ASM in the airway circumference and finally d) increased airway wall thickness due to the inflammatory process (Moreno et al., 1986). These factors lead to a loss in interdependence between the airways and the parenchyma (Macklem, 1991). If the hypothesis that CPAP pneumatically splints the airways were considered under the above mentioned factors we could speculate that as CPAP increases the intraluminal pressure this could serve to restore the load against which ASM contracts so limiting the level of constriction by the ASM.

Another explanation for this improvement in lung function may be that CPAP could have an effect on the airway wall oedema and inflammation by reducing the vascular leak. One of the characteristics of an asthma exacerbation is the consequent

inflammatory processes occurring in the airways. This inflammatory process is characterized by an increased vascularity, leaky capillaries, increased mucosal blood flow, exudates and oedema (Burns & Gibson, 2002). The equilibrium between the flow of intra- and extravascular fluid is directly affected by the changes in hydrostatic pressures. On the other hand dynamic hyperinflation leads to an increase in negative intrathoracic pressure swings. This could lead to a pressure gradient across the capillary walls. Since the asthmatic airways have an increased vascularity, this increase in the pressure gradient could cause larger amounts of fluid to leak into the airway wall, so increasing its thickness. Burns and Gibson (2002) have tested this hypothesis in normal and asthmatic lungs. They tested the effect of deep inspiration on specific airway conductance (sGaw). Deep inspiration was done from residual volume to total lung capacity with and without a resistance. The resistance was added to create the negative intrathoracic pressure effect. They found that in the asthmatic population the sGaw was significantly reduced when three consecutive deep inspirations were done through a resistance. This was not the case in the population with normal lungs. The authors argued that the increased negative intrathoracic pressure swings could have lead to increased fluid extravasation to the airway walls so reducing their lumen and thickening them and so reducing the sGaw. This could result in increased bronchoconstriction (Brown, Zerhouni & Mitzner, 1995). As described earlier anything that alters the ASM load leads to an imbalance between the ASM and this load thereby increasing AHR. Burns and Gibson (2002) suggested that an intervention that could manipulate this fall in intrathoracic pressure would have clinical benefits. They suggested that noninvasive positive pressure could reduce airway wall oedema. Two studies have shown that the application of CPAP to patients with asthma reduced the negative pleural and gastric pressure swings (Martin et al., 1982; Lougheed et al., 1995). Based on this it could be argued that in the present study the application of CPAP to patients with AAE and dynamic hyperinflation, reduced the negative intrathoracic pressure swings and so reduced the airway wall oedema. This would then remove one of the stimuli for increased bronchoconstriction and so aid in the improvement in lung function observed in the CPAP group.

The outstanding improvement in lung function in the present study with the application of CPAP pressures of 5-8 cmH_2O together with standard therapy compared to standard therapy alone was unexpected. Several mechanisms could

explain this improvement. It could be due to a splinting effect of the increased intraluminal positive pressure or due to the fact that CPAP acted on the contracting mechanism of the ASM and / or finally due to CPAP increasing the load against which the ASM should contract so counterbalancing its excessive contraction.

5.2.2 BPPV versus Standard Therapy in their effect on lung function

The BPPV group did not show a significant improvement in lung function when compared to the standard therapy group. Patients had similar baseline characteristics and pharmacologic treatment was standardized, and therefore this could not have influenced these results. Despite the fact that in our study no significance was found in the shift in PEFR and PEFR % predicted, we did notice a clinical improvement when BPPV together with standard therapy was compared to the standard therapy group (graphic 4-7).

In a similar study Soroksky and colleagues (2003) also compared BPPV and standard medical therapy with standard medical therapy alone in patients with acute asthma presenting at their emergency department. They had a sample size of 15 patients per group. Our findings differ from those of Soroksky and colleagues who found significant improvement at three hours in the PEFR % predicted and FEV_1 % predicted in the BiPAP intervention group. In their study the mean PEFR % predicted at three hours of treatment was 41.9 ± 18.6 % in the control group and 57.9 ± 20 % in the BPPV group (p = 0.03). They calculated the percentage improvement from baseline to three hours of treatment and this was 21.9 ± 32.3 % and 55.5 ± 43.9 % for the control and BPPV groups respectively (p = 0.02). Their study compared the mean percentage improvements by t-test. In our study the mean PEFR % predicted at three hours of treatment for the standard therapy (ST) and standard therapy plus BPPV groups was 47.76 ± 15.22 and 50.79 ± 16.10 % respectively. We analyzed the shift (Δ) from baseline which would show the real improvement over time. The difference in statistical analysis makes it difficult to compare the two studies. If the percentage

improvement was calculated in our study as in the Soroksky study it would be 38.11 % and 51.27 % for ST and ST + BPPV groups respectively (table 4-13). The percentage improvement in PEFR % predicted in our study (51.27 %) was quite similar to that in the Soroksky study (55.5 ± 43.9 %) for the BPPV intervention group. The control group in the Soroksky study showed very little improvement in PEFR % predicted (Δ = 7.9 % points) while in our study the control group had a much bigger improvement in PEFR % predicted (Δ = 13.61 ± 7.79 % points). This could be due to the fact that the control group in the Sorosky study only received hourly inhalations while in our study we followed the asthma guidelines (Rodrigo et al., 2004; NHLBI, 1997) that recommend continuous bronchodilator inhalations for an AAE. In fact in their control group 6 out of the 15 patients received only two nebulizations and one received no intravenous methylprednisolone during the four hour intervention. So it could be argued that their control group did not receive optimal medical treatment. Although their BPPV group also had only hourly nebulizations, 11 patients received three nebulizations while four received only two during the four hour intervention.

The Soroksky study protocol for the BiPAP® pressures were inspiratory pressures (IPAP) from 8 to 15 cmH_20 and expiratory pressures (EPAP) of 3 to 5 cmH_20. They stated that the maximum inspiratory pressure administered to patients was 14 cmH_20. Their pressure values were chosen in an arbitrary manner. In the present study the BiPAP® pressures given to the patients were similar for the inspiratory pressures, that is, we started at 10 cmH_20 and went up to 15 cmH_20 according to the patient's respiratory requirements. Our treatment did differ however on the level of the expiratory positive airway pressures. We started at 5 cmH_20 and went up to a maximum of 8 cmH_20. We decided on these levels because they have been previously used on asthma patients by other investigators without adverse effects (Shivaram et al., 1987; Pollack et al., 1995; Wang et al., 1996; Soroksky et al., 2003). It would seem to the author that the present study showed similar clinical improvements in lung function as the Soroksky study for the BPPV intervention group. The bigger sample size and the small improvement in the control group of the Soroksky study could have contributed to the differences in results.

Pollack and colleagues (1995) also reported significant improvement in PEFR % predicted in their study. They did not use BiPAP® continuously but used it to

administer bronchodilator inhalations twice, 20 minutes apart for the intervention group. The control group received bronchodilator inhalations through a small volume nebulizer. They reported a significant improvement in PEFR in the intervention group after each BiPAP® period ($p = 0.0011$) and from baseline to completion ($p = 0.0013$). In the Pollack study the patient's baseline PEFR % predicted was slightly higher than in the Soroksky and in the present study although their patients were still classified under severe attacks (table 4-15). This could be the reason why they had bigger percentage improvement in their PEFR % predicted. They also had a large sample size (n=100).

5.2.3 CPAP versus BPPV in the improvement in lung function

Continuous positive airway pressure improved lung function more as determined by PEFR than BPPV. When the results on lung function improvement were compared for the CPAP and BPPV groups there was a marginal to significant difference. This was an unexpected finding. As explained earlier under point 5.2.2. BPPV had a clinically better improvement in lung function than standard therapy. Continuous positive airway pressure however showed significant improvement in lung function compared to standard therapy and it was nearly significantly different from the improvement shown in the BPPV group. This means that CPAP clearly stood out in its effect on lung function in an AAE for the population studied.

The question to be asked is why? To our knowledge no study to date has compared CPAP with BPPV in patients with severe AAE. It is generally rationalized that BPPV offers with the PEEP/EPAP the same as CPAP and adds an inspiratory pressure which assists inspiratory muscles in their effort. But is this really the case? This seems logical and has been demonstrated in COPD patients. Appendini and colleagues (1994) studied the effect of CPAP, pressure support alone and PEEP plus pressure support against spontaneous breathing in COPD patients. They found that the inspiratory muscle effort reduced progressively with CPAP, pressure support and PEEP plus pressure support. The best effect in improvement of gas exchange and reduction in the breathing work load was obtained with PEEP and pressure support. It

is usually based on results like these that BPPV would seem a better option in asthma as it provides both pressure support in the forms of IPAP and PEEP in the form of EPAP. This was the reasoning of Soroksky and coworkers (2003) in their study that compared BPPV added to medical treatment with medical treatment alone in AAE. They did not consider using CPAP because they explained its use as only to improve oxygenation.

This was the original use of CPAP in lungs without flow limitation. The use of CPAP in these cases was to increase functional residual capacity and so oxygenation (Boch & Alba 1990, Keenan, Sinuff, Cook & Hill, 2005). In flow limited lungs the application of CPAP becomes a mechanical indication where CPAP is used to elevate atmospheric pressure and so bypass or negate the PEEPi. This reduces the inspiratory threshold created by the PEEPi and so unloads the inspiratory muscles. It has been shown in numerous studies that CPAP and PEEP do not increase end expiratory lung volume in flow limited lungs, so their effect does not reach alveolar level (Appendini et al., 1994; Lougheed et al., 1995). It is interesting to note that before BPPV became available, CPAP was the main form of NPPV used. Most of the researchers who wanted to test the use of NPPV on asthma made use of CPAP. They all reported improvements in lung mechanics and also in respiratory rate, dyspnoea and some even in lung function (Martin et al., 1982; Shivaram et al., 1987; Shivaram et al., 1993; Lougheed et al., 1995; Wang et al., 1996). We suppose that it is acceptable to always want to use the best available technology to improve patient's health but in this case is the best really the best for the condition of asthma? Our results seem to question this. One study in the asthma population has compared CPAP with inspiratory positive airway pressure (IPAP) which is the same as pressure support. Lougheed and colleagues (1995) found that IPAP reduced the elastic and resistive work of breathing and also improved the contractile force ratio (oesophageal pressure/ maximal inspiratory pressure ratio) of the inspiratory muscles. This was similar to the effects of CPAP. The main difference found was that CPAP counterbalanced the effects of the inspiratory threshold load but IPAP without a PEEP did not. In their study CPAP relieved patients' perceived inspiratory difficulty more than IPAP. They did not test IPAP with PEEP like the Appendini study. What stands out in their study is that noninvasive positive pressure for patients with asthma must always include a PEEP or CPAP.

One factor that should be taken into consideration is the differences that exist between asthma and COPD pathologies. Although both present with expiratory airflow limitation, COPD is a chronic presentation of disease. Patients with COPD have proven muscle weakness that not only affects the limbs but also the respiratory muscles. Asthma presents with a reversible obstruction while COPD presents with an irreversible obstruction. Patients with COPD can become distressed by mild levels of exercise showing that their respiratory muscles which are chronically overloaded cannot cope with increased loads. It could be that during an acute exacerbation they would need the inspiratory assistance given by IPAP or pressure support more than patients with asthma. Furthermore the aims of using NPPV in asthma and COPD may vary. Although the main aim in both asthma and COPD exacerbation is to relief respiratory distress the aim in asthma also includes improvement in lung function which has deteriorated from the onset of the exacerbation. The aim in COPD is possibly more directed at resting overloaded and fatigued respiratory muscles. It could then be suggested that IPAP or pressure support is not as necessary in an AAE as in COPD exacerbation. Tobin and Lodato (1989) have commented that external PEEP (and for that matter CPAP also) would act more like a pressure support ventilation. This would be due to the fact that once it bypasses PEEPi it consequently augments inspiration.

A further explanation as to the better improvement in lung function noticed in the CPAP group could lie in the different reactions of normal and asthma lungs to a deep inspiration. It has been established that deep inspiration after induced bronchoconstriction in normal subjects and mild asthmatics produces bronchodilatation (Pellegrino, Violante & Crimi, 1993; Brown et al., 2001; Brusasco & Pellegrino, 2003). The explanation for this bronchodilatory effect has been much researched. Airway caliber is determined by the balancing of two opposing forces. One tends to constrict the airways (airway smooth muscle) while the other prevents this narrowing (lung elastic recoil) (Pellegrino et al., 1998). Lung volume and volume history are the determinants of lung elastic recoil during normal tidal breathing. This means that lung volume generated by a breath creates the elastic recoil that counterbalances contraction of ASM. This happens due to the forces of interdependence between the airways and lung parenchyma. It is therefore important

that the structures where the forces of interdependence operate are maintained integral (Pellegrino et al., 1998).

Based on this model then when bronchoconstriction is induced in normal lungs, the balance tips towards the constricting forces of the airways, the ASM. The consequent deep inspiration taken would increase the opposing mechanism, that is, the elastic load which then would be transmitted down to the lung parenchyma and so limit smooth muscle shortening. For deep inspiration to be effective the mechanism by which an inflation stimulus is transmitted from the pleura to the external wall of the airways needs to be integral. A further determinant of the success of a deep inspiration is the thickness of the airway wall. Pellegrino and colleagues have stated that "the elastic recoil pressure provided by lung parenchyma seems to be the strongest modulator of airway narrowing in humans in vivo" (Pellegrino et al., 1998). This mechanism is absent in spontaneous bronchoconstriction. Deep inspiration in spontaneous bronchoconstriction actually worsens bronchoconstriction (Lim et al., 1989; Macklem, 1996; Pellegrino et al., 1998). Acute asthma exacerbation is associated with an inflammatory response which compromises the integrity of the structures where the forces of interdependence operate. This would not allow for normal transmission of increased elastic loading during a deep inspiration, so favouring further constriction.

Based on these explanations of deep inspiration we speculated that the better improvement in lung function observed in the CPAP group could be due to the fact that CPAP could reestablish the balance between the forces of interdependence and so facilitate bronchodilation. On the other hand BPPV despite the improvement seen in clinical signs could be provoking a repeat of the imbalance created by the deep inspiration in spontaneous bronchoconstriction. We further suggest that the balance created by the CPAP could come from one or both sides of these opposing forces. Firstly as described under point 5.2.1 continuous positive airway pressure could act on the intrinsic properties of the ASM, breaking the steady-state isometric condition of the constricted ASM. On the other hand CPAP could act on the parenchyma by decreasing fluid extravasation from the inflammatory process as discussed earlier.

Continuous positive airway pressure outperformed BPPV in improving lung function. This could be due to the fact that although the PEEP in BPPV acted like CPAP bypassing the threshold load, the inspiratory pressure on the other hand created a similar effect to that done by a deep inspiration on asthmatic lungs and increased bronchoconstriction. This could have slowed down the possible improvement promoted by the PEEP.

5.2.4. Noninvasive Ventilation versus standard therapy in the improvement in lung function

Lung function was significantly improved in the first half an hour of treatment when the NPPV groups were compared to the standard therapy group (Analyses B). It then maintained a marginal significance until the end of treatment. This was similar to what Sorosky and colleagues (2003) found although they did not compare CPAP but only BPPV in their study. Pollack and colleagues also found similar improvement in lung function with the use of BPPV in AAE (Pollack et al., 1995). To our knowledge no study up to date has compared both CPAP and BPPV independently with standard medical therapy in AAE. Our results suggest that adding NPPV to standard medical treatment could improve patient's lung function faster than standard medical treatment alone.

5.3 CLINICAL SIGNS

5.3.1 BPPV versus standard therapy and their effect on the clinical signs

The main finding in the BPPV intervention group was a significant reduction in clinical signs like respiratory rate, sensation of breathlessness and accessory muscle use over time compared to the standard therapy group. BPPV reduced accessory muscle use at what was called end of treatment while respiratory rate and sensation of breathlessness could be seen to improve significantly already from the first half an hour of treatment. Although end of treatment did not take into consideration time, the mean time for end of treatment was calculated to be 4.13 hours for the group. So we can postulate that up to 4 hours of treatment BPPV significantly reduced the use of accessory muscle compared to the standard therapy group alone.

As described in the literature review chapter, during an asthma exacerbation the lungs develop dynamic hyperinflation. Dynamic hyperinflation is a consequence of air trapped in the lungs due to increased airway resistance and increased breathing frequency. Dynamic hyperinflation caries with it deleterious effects like placing the inspiratory muscles in a disadvantaged position, increasing their energy spending, creating an inspiratory threshold load due to the PEEPi and finally leading to the uncomfortable sensation of breathlessness or neuromechanical dissociation of the ventilatory pump.

Bi-level positive airway pressure has been suggested to counter act the effects of dynamic hyperinflation. The BPPV aids the inspiratory muscles, which are positioned at an unfavourable place of the length-tension relationship, by providing an inspiratory assistance with the increase in positive pressure during inspiration. This inspiratory help would also decrease their energy spending of the inspiratory muscles. On the other hand the PEEP applied by the BPPV at the end of expiration would counterbalance the inspiratory threshold load created by the DH and its consequent PEEPi. The externally applied PEEP would then lead to a neuromechanical coupling

of the respiratory pump and so reduce the sensation of breathlessness (O'Donnell, 1994, Lougheed et al., 1995).

Our results show that the patients who received BPPV as a method NPPV benefited from the inspiratory assistance in relation to their respiratory rate and accessory muscle use. These two are clear clinical signs of respiratory distress. Similar results were described by Sorosky and colleagues (2003). They reported a significant reduction in the respiratory rate of their BPPV intervention group at three hours of treatment but not at four hours of treatment. Meduri and Cook (1996) also reported a significant reduction in respiratory rate on their status asthmaticus patients. They used a normal ventilator to administer noninvasive positive pressure with pressure support and PEEP. This has the same effect as BPPV. They reported a reduction in respiratory rate for up to 12 hours of treatment. In our study the reduction in respiratory rate was already marginally significant in the first half an hour of treatment and continued until three hours of treatment. At end of treatment it was significant and as mentioned above end of treatment was a mean of 4.13 hours for the group as a whole. In a study by Pollack and colleagues (1995) no significant improvement in respiratory rate was noted with the use of BPPV in acute asthma exacerbations. This could be due to the fact that they only used BPPV to administer bronchodilator inhalations twice, 20 minutes apart. The continuous administration of NPPV probably has a cumulative effect where inspiratory muscles are supported and also rested. The effect that we noted on the accessory muscle use has to our knowledge not been described previously in a study where noninvasive ventilation was investigated in AAE. Since the use of accessory muscles are related to increased respiratory work, we believe that the reduction in their use could be related to the assistance provided by the inspiratory pressure of the BPPV.

Furthermore BPPV significantly reduced the patients' sensation of breathlessness. A visual analogue scale was given to the patients with numbers from zero to 10. Although breathlessness can be considered to be a subjective parameter, in asthma it seems to be related to an imbalance between the effort done by the inspiratory muscles and the mechanical consequence like change in flow/volume, that is expected (Lougheed et al., 1993). Breathlessness was defined by Lougheed and colleagues (1993) as a complex sensory experience related to the perception that the contractile

effort of the inspiratory muscles has increased while their capacity has been reduced. The main causative factor for breathlessness seems to be the ITL created by the PEEPi. Chen and colleague have studied the effect of ITL as well as EELV on breathlessness. They found that both ITL and EELV independently and significantly increased the perception of inspiratory difficulty but ITL was found to contribute the strongest to this sensation (Chen & Yan, 1999).

Inspiratory threshold load is a mechanical consequence of the PEEPi created by DH. This basically means that as the inspiratory muscles contract at the beginning of an inspiration no flow or volume change is produced (Yan, 1999). The inspiratory muscles now have to bypass the increased elastic recoil of the chest wall that is directed inwards due to the hyperinflation (Tobin & Lodato, 1989). During a normal breath decreasing the pleural pressure takes minimal contraction of the inspiratory muscles. To create the difference between ambient and alveolar pressures, in the presence of PEEPi, the inspiratory muscle will be required to increase their contractile effort. To add to this overload is the fact that these muscles are working from a shortened position as described in point 2.2.1.1.rendering them less effective.

The solution to this mechanical imbalance would be the elevation of ambient pressure to the level of the alveolar pressure or as close to it as possible (Tobin & Lodato, 1989). This can be accomplished by the application of external positive airway pressure in the forms of PEEP or CPAP. By elevating the ambient pressure the negative pressure required to create a difference of pressure would be much less. Since breathlessness in airway obstruction has been linked to the imbalance between the muscle effort and the anticipated ventilatory changes the application of external PEEP or CPAP can serve to negate the inspiratory threshold load (O'Donnell, 1994). Lougheed and colleagues (1995) in a study on induced asthma patients found that CPAP reduced the total inspiratory effort. They also found that CPAP reduced the net tension-time index which is a reflection of the metabolic cost of breathing. Breathlessness was significantly (p<0.001) reduced in their study and mainly due to a reduction in the inspiratory effort. We have found similar results in our study with a reduction in the sensation of breathlessness from the first half an hour of treatment with the use of noninvasive BPPV. As described above BPPV provides an inspiratory pressure and also a PEEP at the end of expiration. We believe that the PEEP had the

effect of negating the PEEPi present in our patients with AAE and so relieved the sensation of breathlessness experienced by them. A few patients were seen to fall asleep while on the BPPV. Shivaram and colleagues (1987, 1993) reported similar findings in two studies done on patients with AAE. Both studies found that CPAP reduced the patients' breathlessness. In the Shivaram studies CPAP was applied for short periods. In one study CPAP was applied for one to two minutes (1987) while in the second study (1993) it was applied for 30 minutes twice with a 20 minute break in between. Even these short applications revealed an improvement on breathlessness which probably suggests that the external elevation of ambient pressure immediately caused a coupling of the neuromechanical ventilatory pump.

5.3.2 CPAP versus Standard Therapy and their effect on clinical signs

The addition of CPAP to standard therapy showed significant improvement in the clinical signs of respiratory rate, sensation of breathlessness, accessory muscle use and lung sounds at the end of treatment. BPPV had an early effect on respiratory rate and sensation of breathlessness while CPAP significantly improved respiratory rate only at two hours, sensation of breathlessness at three hours and accessory muscle use at one hour of treatment and all of them at end of treatment. The small sample size could have influenced the hourly results. Since end of treatment was a mean of 4.13 hours for the group as a whole, it seems that CPAP also improved the clinical signs faster than the standard therapy group, but it became apparent later in the treatment compared to BPPV.

For lung sounds we observed that CPAP was the only intervention to show a significant reduction in wheezes at two hours and at the end of treatment. BPPV showed no significance at all. We believe this could be due to two reasons. Firstly it could be due to the improvement in lung function by CPAP as discussed later. A general relationship exists between the type of wheezes and the level of obstruction (Shim & Williams, 1983). Despite this it has been shown that asthma symptoms

cannot be directly related to the severity of an obstruction in asthma (Teeter & Bleecker, 1998). Secondly, wheezes occur due to air flowing through airways with narrowed airway lumen (Shim & Williams, 1983). Because CPAP applies a constant positive pressure continuously to the airways, patients breathe with much smaller tidal volumes compared to BPPV. It could be postulated that these smaller airflow dislocations inside the airways would then create less vibrations of an audible frequency. Authors have suggested that CPAP would "splint" the airways (Shivaram et al., 1993). This would also impede some of the airway narrowing that increases during expiration and so also causes less flow vibration which could lead to a reduction in wheezes on auscultation.

The improvement in the respiratory rate, sensation of breathlessness and accessory muscle use can be explained by the same reasoning as for the PEEP in the BPPV intervention. Continuous positive airway pressure counterbalanced the effects of the ITL and so reduced the work of breathing. Tobin and Lodato (1989) have referred to the effect of CPAP as an external increase in positive pressure which would function like a pressure-support aiding inspiration. At expiration this PEEP would be functionally absent.

Martin and coworkers in what was probably one of the first studies in this area evaluated the effects of CPAP on subjects with induced asthma. They measured lung function and chest wall and lung mechanics after bronchococonstriction, with CPAP and after CPAP removal. They found that CPAP unloaded the inspiratory muscles. This was seen by the reduction in the inspiratory pleural pressure generated by the inspiratory muscles and also by the reduction in the swing of the trans-diaphragmatic pressure. Furthermore CPAP reduced the energy utilization by the inspiratory muscles. This was evident by the significant reduction in the pressure-time product of the inspiratory muscles and of the diaphragm ($p<0.05$). Pressure-time product reflects the metabolic cost of breathing. Continuous positive airway pressure also improved the efficiency of contraction of the muscles reflected by a 50% increase in the inspiratory flow rate. Finally they found a significant fall in pulmonary resistance ($p<0.02$) with CPAP (Martin et al., 1982).

The present study did not measure lung mechanics yet the improvement in clinical symptoms matched what Martin and colleagues (1982) found in the laboratory setting. It could be argued against the Martin study that they used induced asthma and not spontaneous asthma exacerbations. Shivaram published two studies on acute asthma exacerbation. In both studies they applied CPAP for different periods and found a reduction in respiratory rate and dyspnea (Shivaram et al., 1987; Shivaram et al., 1993). These results are similar to our study. Compared to the standard therapy group the clinical improvement in respiratory rate in the CPAP intervention group is much greater.

5.3.3 CPAP versus BPPV in their action on clinical signs

Respiratory rate and sensation of breathlessness improved faster in both CPAP and BPPV groups compared to the standard therapy group. Although BPPV seemed to make a bigger difference this was not statistically significant. Continuous positive airway pressure and BPPV both reduced the use of accessory muscles by the end of treatment compared to standard therapy alone.

It would seem then that both noninvasive positive pressure methods used in this study helped patients' symptoms to improve faster. This was due to the previously described effect of CPAP and PEEP in bypassing PEEPi and so unloading the inspiratory muscles. Although improved symptoms on their own cannot determine that the acute episode has been resolved, this has a major implication for the patient. The anxiety that respiratory distress causes to a patient is probably underestimated. Even if the present noninvasive interventions did not improve lung function, just the fact that they aided patients by reducing their respiratory rate and accessory muscle use as well as improving their sensation of breathlessness would have proven them worthy interventions.

5.3.4. Noninvasive Ventilation versus standard therapy

When the CPAP and BPPV groups were grouped together and analyzed against the standard therapy group similar results were obtained. The noninvasive groups exhibited significantly ameliorated respiratory rates, sensation of breathlessness and accessory muscle use at the end of treatment. This is in line with the findings of several other authors (Martin et al., 1982; Shivaram et al., 1987; Lougheed et al., 1995; Meduri et al., 1996; Pollack et al., 1995; Wang et al., 1996). Yet each of these authors' studies tested only CPAP or BPPV individually in AAE. As far as lung sounds, the NPPV groups of the present study exhibited a marginal improvement at the end of treatment.

5.4 NPPV AND ARTERIAL BLOOD GASES

It was not possible to statistically analyze the arterial blood gases (ABG) done in the study as they were few and only four patients had a repeat ABG after the first half an hour of treatment. Of these two presented the classic hyperventilation – hypocapnic result. This is common at presentation of a patient with AAE at the emergency unit. These patients are in respiratory distress and so tachypneic (Rodrigo, 2004). The other two ABG were from patients who already started with respiratory muscle fatigue. They presented with hypercapnea which improved after the first half an hour of treatment. All these patients had been randomized either to CPAP or BPPV and the improvement noticed in the first half an hour of treatment was with the use of one of these devices. We can however not conclude that this was solely due to the action of NPPV as ABG were not taken for any of the patients in the standard therapy group.

5.5 HAEMODYNAMIC EFFECTS OF NPPV

When the NPPV groups were analyzed together against the standard therapy group there was a difference in baseline systolic blood pressure (SBP). Patients in both the CPAP and BPPV groups had higher initial SBP. This difference was however not strong enough to show in the one-way ANOVA analyses. From two hours of treatment onwards it seemed that the SBP lowered more in the BPPV group compared to the CPAP and the standard therapy groups. The same occurred with the diastolic blood pressure (DBP).

A few reasons could exist for these lower blood pressure values in the BPPV intervention group. Beta adrenergics like fenoterol used for inhalations during an AAE are known to have the potential to lead to a reduction in peripheral vascular resistance (Zanoni & Palhares, 2002). The fact that only the BPPV group showed this significant reduction in blood pressure means that it could not be due to the effect of beta adrenergics only as all patients received the same inhalations. Blood pressure can be influenced by emotional factors like anxiety and stress. Patients in an AAE experience both these emotions as they try to breath with the severe bronchospasm. It could be that since BPPV relieved the sensation of breathlessness and reduced respiratory rate earlier in the treatment that this could have resulted in a relief of the distress experienced by the patients. This may have contributed to lower blood pressures in the BPPV group. A further reason could be that some of the patients could have become dehydrated during the treatment time. Most of the patients had started the exacerbation the previous night coming to the emergency unit only in the morning. They were all on a maintenance drip of saline (0.9 % NaCl). In children presenting with AAE it has been noted that they can present to the emergency unit with dehydration (Potter, Klein & Weinberg, 1991). Dehydration could have been present in some patients of the BPPV group. The mean SBP at four hours of treatment was 131.3, 132.3 and 114.4 mmHg for the standard therapy, CPAP and BPPV groups respectively. Mean DBP at end of treatment was 71.8, 78 and 59.7 mmHg respectively. While the SBP did not fall below acceptable values the DBP was quite low at four hours of treatment. A further possibility could be the effect of the increase in intrathoracic pressure (ITP) due to positive pressure ventilation. While ITP falls

during spontaneous breathing it increases when positive pressure ventilation is initiated. Hyperinflation is also known to increase pressure around the heart chambers. Pinsky (2005) has noted that it is the increase in lung volume more than the increase in pressure that affects the ITP. He has also noted that although hyperinflation increases pulmonary vascular resistance so impeding right ventricular filling, adding an external PEEP that does not surpass the PEEPi will cause no further haemodynamic effects. Having previously mentioned the differences between CPAP and BPPV we speculate that due to the larger lung volumes that patients could breathe with the BPPV, this could have had the effect of lowering these patients' blood pressures due to a reduction in venous return and consequent reduction in cardiac output.

These results differ from the Shivaram study. Shivaram and colleagues (1993) found that the application of CPAP levels of 5 and 7.5 cmH2O had no untoward effects on mean arterial pressures. In the Soroksky study (2003) no mention was made in their results about their patients' blood pressure. We cannot determine the reason for the drop in blood pressures observed in the BPPV group as this was not the aim of the present study. We speculate that the possible dehydration and/or improvement in these patients' sensation of breathlessness could have contributed to this phenomenon.

5.6 SECONDARY OUTCOMES

5.6.1. Outcome from the emergency unit

Significantly more patients were discharged after the emergency unit treatment from the standard therapy group (80%) than from the groups that received noninvasive ventilation (CPAP group = 80%, BPPV group = 70%). This result is very different from those obtained by Soroksky and colleagues (2003). In their study 37.5% of the control group were discharged compared to 82.4% of the BPPV intervention group. This was however calculated on an intention-to treat analysis including 3 patients who had actually withdrawn from the study.

This finding could be explained by several factors. Firstly a discharge protocol did not form part of our study so most of the patients were discharged or admitted to hospital at the medical officer's discretion. The emergency department had guidelines for the discharge of a patient after an AAE but again these were not strictly enforced. The researcher also did not contribute to the decision as to whether a patient should be discharged or not as this would create a bias. Patients were mostly discharged if they had achieved a PEFR % predicted above 65% and did not worsen once inhalations were stopped. Other factors that also contributed to the decision to discharge a patient were social conditions for example female patients who had children at home without anyone to look after them and patients who simply refused to be admitted. Another problem experienced included the availability of beds in the hospital (if no beds were available patients who seemed stable and might have been admitted overnight were rather discharged). Factors influencing admission of patients were again social factors for example patients who would not have transport overnight to return to the hospital in case of a new asthma attack, were admitted. It is important to know that Kalafong hospital is situated in a needy area and serves patients of low or no income. This had an important effect on the decision making process to admit or to discharge patients.

Taking all the above into consideration our results showed more hospital admissions in the noninvasive groups yet this was severely influenced by social circumstances.

5.6.2. Time spent on noninvasive positive pressure ventilation

Patients spent nearly double the amount of hours on the BPPV ventilation compared to CPAP. This was however due to two patients in the BPPV group that continued to make use of it after the emergency unit treatment. Time spent on the NPPV devices was calculated in total and not only in the emergency unit. If the patient needed to continue on NPPV after the emergency unit treatment NPPV was continued and included in the total NPPV time calculation. To our knowledge no study so far has compared CPAP with BPPV noninvasive ventilation. This means that we could not compare the results with existent research findings. In the Soroksky study it was stipulated that patients would receive maximal 4 hours of noninvasive ventilation (Soroksky et al., 2003). We continued NPPV until patients had reached a PEFR % predicted above 65% or until they were transferred to a ward in the hospital. This meant that our patients receiving BPPV spent a mean of 6.98 ± 7 hours on the NPPV while the CPAP group spent a mean of 3.84 ± 1 hour on NPPV. Meduri and colleagues (1996) reported a mean of 16 ± 21 hours spent on noninvasive ventilation. It is important to note that they ventilated patients with status asthmaticus while in the present study we included AAE at presentation. The present study did however have one patient which evolved into a status asthmaticus and was later intubated. This is probably the reason why the present study showed shorter hours of NPPV when compared to the Meduri study.

Therefore we can report that the number of hours that the patients spent on NPPV was a mean of 5.4 hours which was adequate to improve their lung function and clinical signs faster than the standard therapy alone. We therefore suggest that it would be worthwhile to make use of NPPV in the emergency unit as most patients spend an average three to four hours in the unit.

5.6.3. Intubation rate and mortality rate

No patients needed to be intubated in any of the three treatment groups while still in the emergency unit. There was one intubation (patient 18) which was avoided in the emergency unit. Patient 11 from the standard therapy group was intubated five days after hospital admission after deteriorating in the ward. Noninvasive ventilation with the BiPAP® was initiated still in the ward and continued in the High-Care ward for 24 hours intermittently due to the patient's confused mental state. Nearly 48 hours later the decision was made in ICU to intubate the patient due to a $PaCO_2$ of 60mmHg. The researcher did not agree with this decision as the patient had by then survived the worst part of her status asthmaticus condition. She was still mildly confused but improved whenever she was on the BPPV. Unfortunately an arterial blood gas was not taken the previous day when she was probably more hypercapnic. After being intubated mechanical ventilation was very difficult and by 12 hours into mechanical ventilation her $PaCO_2$ remained above 60 mmHg. The patient eventually spent 15 days in ICU and had a tracheostomy performed on her in this period. The total length of hospital stay for this patient was 22.5 days. This patient presented a clear example of what complications can arise if an asthma patient is intubated. Ventilating an acute asthma patient requires fine tuning of the ventilator settings, especially of peak and mean airway pressures. If noninvasive positive pressure ventilation is applied correctly and successfully such complications could be avoided. It is also imperative that the whole team (doctors, nurses and physiotherapists) are familiar with indications for NPPV, its applications and advantages.

Finally the intubation rate for the patients that were admitted to hospital was 3.3% (that is one patient) for the group as a whole. Mortality rate was zero. It is important to note that our treatment protocol applied only to the emergency unit. This meant that once in the wards patients were treated according to the discretion of the internal medicine doctor responsible for the patient which made any comparison among the initial treatment groups impossible.

5.6.4. Emergency unit and Hospital length of stay

There was no difference in the hours that the patients spent in the emergency unit among the three treatment groups. Although the patients in all three groups spent more or less the same time in the emergency unit, we did notice faster improvement in lung function and clinical signs in the noninvasive treatment groups up to 4 hours of treatment as already discussed. Again the time spent in the emergency unit was influenced by factors such as the number of nursing staff and doctors available on that day and also the time it took for the casualty doctor to reevaluate the patient and refer the patient to internal medicine if necessary. Our data was similar to that of the Soroksky study. Their BPPV group spent a mean of 5.9 ± 1.3 hours in the emergency unit while their control group spent 5.6 ± 1.3 hours (Soroksky et al., 2003). Noninvasive positive pressure ventilation did not affect the length of stay in the emergency unit in the present study. If NPPV would become standard protocol in the emergency unit it might require an additional dedicated professional to initiate NPPV and monitor a patient's response to therapy.

As far as the hospital length of stay is concerned, the patients in the two NPPV groups spent significantly fewer days in hospital than the standard therapy group ($p=0.0481$). It is interesting to note that this was despite the fact that the standard therapy group had only 2 admissions. Our results differ from the Soroksky study. The mean hospital length of stay in their study was 4 ± 0 and 2.5 ± 1.4 days for the BPPV and control groups respectively. They did not test for significance (Soroksky et al., 2003). In their study the control group had significantly more admissions which also differed from our results. This could be explained by the difference in hospital setting. Unfortunately our admissions and discharges were influenced by social and hospital factors out of our control. We suspect that the Soroksky study might have been performed under more stable conditions. The fact that the present results on length of hospital stay were influenced by social and hospital factors made a direct conclusion on NPPV influencing hospital length of stay impossible. Yet the fact that NPPV was associated with shorter hospital length of stay could indicate a possibility of reduction in costs for the hospital. Future studies with larger samples could clarify this better.

In the present study therefore we have found that in the admitted patients the standard therapy group patients had a longer hospital length of stay.

5.6.5. Patients that reached PEFR > 65% predicted

A bigger percentage of patients in the CPAP (50 %) and BPPV (40 %) groups reached a PEFR > 65%. Although this was not statistically significant when compared to the 20% of the standard therapy group who also reached a PEFR > 65% it had a clinical significance. This meant that double or more of the patients who received NPPV reached an acceptable lung function level while in the emergency department. Several investigators have shown that response to treatment in the emergency department is a predictor of outcome (Kelsen, Kelsen, Fleegler, Jone & Rodman, 1978; Fanta, Rossing & McFadden, 1982; Nowak, Tomlanovich, Sarkar et al., 1983; Rodrigo & Rodrigo, 1988; Rodrigo & Rodrigo, 1993). Although more patients in the NPPV treatment groups reached a PEFR > 65%, more of them were also admitted yet this could have been due to the factors out of our control described in the previous paragraph.

5.7 CONCLUSION

In conclusion we have found the following: a)noninvasive positive pressure ventilation in the form of CPAP or BPPV when added to standard medical treatment for an acute asthma exacerbation improved lung function and clinical signs like respiratory rate, sensation of breathlessness and accessory muscle use faster than standard therapy alone up to three and four hours of treatment, b) the effect of BPPV stood out in the improvement of clinical signs and we believe that it could be due to the inspiratory assistance provided in this form of NPPV, c) CPAP improved lung function faster than BPPV and it could be due to the effect of CPAP on the load of the airway smooth muscle or its effect on the actin-myosin bridge cycling of the ASM.

As far as secondary outcomes a) the use of NPPV in the emergency unit did not reduce the number of patients admitted to the hospital, b)those admitted from the standard therapy group had a longer hospital length of stay but this should be interpreted in the light of patients' social circumstances, hospital staffing and administration shortages, c) mortality rate and intubation rate were not influenced by the initial treatment received in the emergency unit c) mortality rate and intubation rate were zero for all the treatment groups d) NPPV assisted more patients to achieve a PEFR > 65% while still in the emergency unit.

The results confirm our first hypothesis which stated that early use of noninvasive ventilation in the forms of CPAP and BPPV together with standard medical therapy in acute asthma exacerbation can decrease time of response to therapy compared to standard medical therapy alone. Our results further support part of the second hypothesis, that is, that BPPV acts faster than CPAP in improving clinical, physiological and spirometric values due to the inspiratory assistance added to the PEEP. Bilevel positive pressure ventilation did show a tendency to improve clinical signs like respiratory rate and sensation of breathlessness faster than CPAP with standard therapy and standard therapy alone. As far as lung function however our results contradict the second hypothesis. Continuous positive airway pressure clearly outperformed BPPV when it came to the improvement in lung function. Further on when time was not taken into consideration both CPAP and BPPV significantly improved patients' clinical signs.

The limitations of this study will be discussed in the following chapter.

CHAPTER 6
LIMITATIONS and RECOMMENDATIONS

6.1 LIMITATIONS

The following limitations were observed in the present study:
1-The main limitation to this study was the small sample size. A bigger sample size would have delivered better statistical results especially in the BPPV group which in some analysis like the improvement in PEFR was marginally significant. This was however not possible as the author was also the only data collector and patients were only enlisted during day time. We believe that a potential number of patients were lost due to their presentation at the emergency unit in the early hours of the morning. Another limitation was that the referring doctor from the emergency unit went on maternity leave for a few months during the data collection phase and during that period fewer patients with asthma were referred to the researcher.

2- Another potential limitation was that the study was not blinded to the data collector or to the medical officers on duty. Knowledge of the group to which each patient was randomized as also the objective of the study is a cause for bias. A suggestion for less bias would be the use of independent data collectors and also that the medical officers of the emergency unit would not know the end points of the study. This was not possible in the present study as the researcher was the only available person at the hospital to collect data. Further on as this was a first study in cooperation between two departments it was necessary to explain the study to the medical officers for better cooperation and patient referral for the study.

3-The hand held peak expiratory flow meter used in this study posed another limitation. In the Soroksky study spirometry was performed which allowed for better control of the technique and quality of measurement than the small hand held devices used in this study. At the start of the study a device for complete spirometry was not available at Kalafong

Hospital and patients who needed this were referred to another hospital. We did however explain to and monitor the technique of our patients and had two patients who were not enrolled due to poor technique. The hand held device used in the present study was however better than a Wrights Peak Flow meter as it electronically displayed the values performed by the patients and stored the best of three attempts for recording. With the Wrights Peak Flow meter the value is observed on a visual scale and the observer will estimate on the visual scale what the PEFR was thus rendering data collection less accurate.

4-The fact that a single centre study was conducted limited the results to the specific population studied. A better study would have been a multiple center randomized study where patients with asthma from different socio-economic areas were included. The population serviced by the Kalafong hospital is mainly a low income population. This added many uncontrollable social-economic variables to the study as described in our discussion chapter. A multicenter trial would require a few experienced data collectors. Presently the researcher is the only experienced staff in NPPV in the region.

5-The lack of a discharge/admission criteria in the present study protocol is a further limitation. This compromised the interpretation of the secondary results like treatment outcome (admitted or discharged). As described in the discussion chapter many patients were admitted or discharged due to factors other than clinical and objective parameters.

6-The fact that there was not a uniform treatment protocol for patients admitted to the ward posed a further limitation to the study. This meant that the secondary outcomes had to be interpreted in light of this as treatment in the wards differed according to the admitting physician and also according to the nursing staff. This could have had a significant influence on the length of hospital stay.

6.2 RECOMMENDATIONS

The following recommendations are made in relation to the present study:

1. A study with a similar protocol but a larger sample size would be highly recommended.

2. A multi-center randomized study with similar end-points would enhance the present results.

3. We applied NPPV on AAE patients until they had reached a PEFR % predicted > 65 % or were admitted. Future studies could determine to apply NPPV for a limited period (3 to 4 hours) as it seemed to be the mean time up to which a significant difference was detected among the intervention groups.

4. The present study concentrated on severe AAE at presentation in the emergency unit. The results cannot be extrapolated to status asthmaticus. Further research would be necessary to compare the use of NPPV in the status asthmaticus population.

5. A study that included hospital costing as one of the secondary outcomes would also be highly recommended. This was not possible in the present study as no reliable source for hospital costing could be found.

6. An investigation into the role of the physiotherapist in the application of NPPV to patients with acute respiratory failure as also their role in the emergency department would be relevant.

CHAPTER 7

CONCLUSIONS

The aim of the present study was to evaluate the effectiveness of noninvasive positive pressure ventilation when added to standard medical therapy against standard medical therapy alone in the management of acute asthma exacerbation. The following hypotheses were tested: a) early use of NPPV in the forms of CPAP or BPPV together with standard medical therapy in acute asthma exacerbation can decrease time of response to therapy compared to standard medical therapy alone. b) patient's response to therapy is expected to be faster with the administration of BPPV together with standard therapy due to the inspiratory assistance provided to the positive end-expiratory pressure (PEEP).

The present results suggest that adding CPAP or BPPV to standard medical (ST) therapy in an AAE improves clinical signs and lung function faster than ST alone. This extends on previous research that showed that adding BPPV to ST in AAE improves lung function more than ST alone. As previously discussed the clinical signs like increased respiratory rate (RR) and sensation of breathlessness (SB) are a consequence of the dynamic hyperinflation (DH) present in an AAE. Both CPAP and the PEEP in BPPV bypass the DH so reducing the inspiratory load. This will reduce the SB and RR. The additional inspiratory assistance provided by the BPPV seems to support breathing thus reducing their inspiratory efforts. To our knowledge this is the first study to compare CPAP with BPPV in the management of AAE. Contrary to our hypothesis CPAP improved lung function more than BPPV. This seems to be related to two possibilities. Firstly CPAP could have an intrinsic effect on the airway smooth muscle (ASM) and it could replace the ASM load which is altered by the inflammatory changes. A second possibility is that BPPV with the inspiratory assistance provides for a bigger tidal volume, a larger stretching of lung tissue so mimicking the effect of a deep inspiration which is known to increase bronchospasm in patients with asthma. This could be a possible reason why CPAP had a better effect on lung function compared to BPPV.

As far as secondary outcomes are concerned the results showed that:

a) The use of NPPV in the emergency unit did not reduce the number of patients admitted to the hospital,

b) Admission to the hospital and discharge from the emergency unit were influenced by socio-economic factors,

c) Patients admitted from the standard therapy group had a longer hospital length of stay

d) Mortality rate was zero for the three groups

e) Only one patient was intubated in the whole group

f) More patients in the NPPV groups achieved a PEFR > 65% in the emergency unit.

In the clinical setting would this mean that while BPPV is the first line of treatment indicated for a COPD exacerbation, the results of the present study suggest that CPAP might be a better option for respiratory assistance when it comes to an AAE. This could differ with a patient with status asthmaticus as they can develop severe muscle fatigue. Further research is needed to compare the use of CPAP in an AAE with its use in status asthmaticus. Finally as a direct result of the present study CPAP has been added to the standard medical management of patients presenting with an AAE at the emergency unit at Kalafong hospital.

APPENDICES

APPENDIX A

SUBJECT INFORMATION SHEET

Hi, I am Silmara G. Hanekom and I am doing a study with people who have asthma.

This is how the study will be conducted: the asthma patients that want to be part of the study will continue to get their normal medication prescribed by the doctor. At casualty you always get oxygen through a mask as part of your normal treatment. In addition to this treatment we have three different masks and want to see how you feel when receiving treatment with one of the three masks. Each of the masks gives you oxygen and helps your breathing in different ways. The masks are connected to a pipe which is then connected to a machine or to the oxygen on the wall. I want to see how the mask that will be put on your face will help you to breath.

If you agree to be part of the study you will be asked to sign a form. An envelope will then be drawn from a box and inside the envelope is written what kind of mask you will use.

Before I put you on the mask, I will write down how your lungs are and you will tell me how you are breathing. You will also be asked to blow into a flow meter so I can measure your lung function. I will then hold the mask over your face so you can feel how it is. When you feel comfortable I will put the straps that keep the mask in place around your head. You will feel air coming through the mask and you must continue to breathe in and out. I will be next to you all the time seeing how you are doing. I will write down how your lungs are from time to time and you will help me by telling me how your breathing is feeling and by blowing into the flow meter. This will show me how your lungs are doing. It may be necessary for the doctor to draw blood from your artery in your arm and this can be painful. This will only be done if necessary.

Your participation in the study is voluntary and you can decide at any time that you do not want to be part of it anymore. Your treatment will continue as usual. Please ask questions at any time that you feel you do not understand what is happening or if you want to know more.

Contact person: Silmara Hanekom Celular phone 084 – 461 8020
Hospital pager number 25
Physiotherapy department x 6765

APPENDIX B

CONSENT FORM

I fully understand this study that was explained to me by Silmara G. Hanekom

I understand that if I refuse to take part in this study, I will not be penalized in any way and that I can decide to not be part of it at any time.

Name_____

Relative_____

I agree to participate_____

Date_____

Place_____

APPENDIX C

DATA COLLECTION SHEET

DATA COLLECTION SHEET

SERIALNUMBER_____

PATIENT NAME_____HOSPITALNUMBER _____

DATE_____

AGE_____ WEIGHT_____

GENDER_____ HEIGHT_____

ADMISSION TIME_____ SMOKER_____

NONSMOKER_____

DURATION OF ATTACK _____ hours

DURATION OF SYMPTOMS _____ days/hours

ASTHMA HISTORY

_____

_____

_____

NUMBER OF HOSPITALIZATIONS 2002____2003____2004____2005_____

PRESENT EXACERBATION CLASSIFICATION GY GINA GUIDELINESS:

MODERATE_____

SEVERE_____

RANDOMIZED TO: STANDARD THERAPY_____

ST + CPAP _____

ST + BiPAP _____

TIME INITIATED NONINVASIVE VENTILATION_____

REASON FOR DISCONTINUATION OF NPPV _____

TIME DISCONTINUED NPPV _____

DESTINATION FROM THE EMERGENCY UNIT:

DISCHARGED_____

OVERNIGHT OBSERVATION WARD_____

GENERAL WARD_____

HIGH-CARE_____

ICU, INTUBATION + VENTILATION_____

DATA TABLE

	ZERO	30’	60’	2hrs	3hrs	4hrs	5hrs	6hrs
Heart rate								
Blood pressure								
Temp								
Resp rate								
ABG								
pH								
PaCO2								
PaO2								
HCO3								
BE								
Sats								
Dysp score								
Acc M use (0-3)								
Muscle fatigue (1-4)								
Lung sounds (1-3)								
PEF								
% pred								
FVC								
% pred								
FEV1								
% pred								
FEV1/FVC								
Sats								

Accessory muscle use : 0=absent, 1=mild, 2=moderate, 3=severe

Evidence of muscle fatigue: 1=rapid shallow breathing, 2=alternation between rib cage and abdominal movement during inspiration, 3=abdominal paradox, 4= increase in PaCO2

Lung sounds: 1=expiratory wheezes, 2=inspiratory and expiratory wheezes, 3=silent lungs

Reasons for intubation _____

Complications after intubation _____

Reasons for patient exiting trial _____

LENGHT OF HOSPITAL STAY (hours)

OVERNIGHT OBS WARD _____

GENERAL WARD _____

HIGH-CARE _____

ICU _____

EMERGENCY UNIT _____

TOTAL HOURS_____

FINAL HOSPITAL OUTCOME : D/C _____

DISSEASED _____

	Starting	Adj 1	2	3	4	5	6
Time of adj							
CPAP cm H_2O							
O_2 L/min							
FiO_2							
BiPAP							
IPAP (cmH_2O)							
EPAP (cmH_2O)							
O_2 L/min							
FiO_2							

VISUAL ANALOGUE SCALE FOR SHORTNESS OF BREATH

SERIAL NUMBER_____

ZERO



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

30’



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

60’



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

2 hrs



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

3 hrs



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

4 hrs



0_____1_____2_____3____ 4_____5_____6_____7____8____9_____10

APPENDIX D

ETHICAL CLEARANCE UNIVERSITY OF THE WITWATERSRAND

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Hanekom

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER 03-05-53**
PROJECT	Effectiveness of Continous & Bilevel Positive Airway Pressure Versus Standard Medical Therapy for Acute Asthma
INVESTIGATORS	Ms SG Hanekom
DEPARTMENT	School of Therapeutic Sci
DATE CONSIDERED	03-05-30
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application. This ethical clearance will expire on 30 July 2007.

DATE 04-01-09 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Ms H van Asweegen
School of Therapeutic Sci

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.** .....

This ethical clearance will expire on 1 February 2005
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX E

ETHICAL CLEARANCE KALAFONG HOSPITAL

FORM CRHS (2002)

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

APPLICATION[1] TO THE KALAFONG COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL) FOR CLEARANCE OF RESEARCH INVOLVING HUMAN SUBJECTS, OR PATIENT RECORDS.

☐ CLEARANCE NUMBER (for office use only): ____ // ____

This application must be typed or handwritten in capitals

NAME: Prof/Dr/Mr/Miss/(Ms) SILMARA GUANAES HANEKOM

PROFESSIONAL STATUS (if student, year of study)

UNIVERSITY DEPARTMENT[2] PHYSIOTHERAPY

HOSPITAL/INSTITUTION WHERE EMPLOYED KALAFONG HOSPITAL

FULL-TIME OR PART-TIME FULL-TIME

TELEPHONE AND EXTENSION 012-3186764/5 FAX NO

TITLE OF RESEARCH PROJECT: (Use no abbreviations)
EFFECTIVENESS OF CONTINUOUS AND BILEVEL POSITIVE AIRWAY PRESSURE VERSUS STANDARD MEDICAL THERAPY FOR ACUTE ASTHMA

WHERE WILL THE RESEARCH BE CARRIED OUT? (Please furnish name of hospital/institution and particular department) KALAFONG HOSPITAL EMERGENCY DEPARTMENT

All the following sections must be completed[3]. Please tick all relevant boxes.

1. PURPOSE OF THE RESEARCH:
   - postgraduate: degree/diploma (state which) ☒
   - undergraduate: degree/diploma (state which) ☐
   - not for degree purposes ☐

2. OBJECTIVES OF THE RESEARCH (please list):
The aim of this study is to evaluate according to severity, the effectiveness of standard medical therapy with noninvasive ventilation versus standard medical therapy alone:
a) in ameliorating clinical, physiological and spyrometric values in acute asthma exacerbation.
b) in response time to treatment in the emergency department,
c) in outcomes such as length of noninvasive ventilation, intubation rate, mortality rate, length of hospital stay and hospital costing.

1. Unless received by the 7th of the month, applications will be carried over to the next month for consideration.
2. If not employed by the University or one of the University's teaching hospitals, please indicate clearly where correspondence should be sent.
3. This requirement holds even if, to assist the Committee, a protocol detailing the background to the research, the design of the investigation and all procedures, is submitted with the application.

3. SUMMARY OF THE RESEARCH (give a brief outline of the research plan):

Acute exacerbation of asthma many times leads to the need for mechanical ventilation. Noninvasive ventilation has been proven efficient in COPD patients reducing intubation rate and hospital stay. We want to see if the early use of noninvasive ventilation improves patient condition faster than medical therapy alone and if it affects hospital stay and costing

4. REQUIREMENTS

4.1 If this project involves studies with drugs at a teaching hospital associated with this University, approval must be first obtained from the Protocol Review Committee.[4]
Has application been made? . Yes ☐ No ☐
(If not, this application cannot be considered) N/A

4.2 If radiation or isotopes are to be used, written approval must be obtained from the Nuclear Medicine Department, Diagnostic Radiology Department, Radiation Therapy Department or NUCOR representative.
N/A
Is this attached? If not, the application cannot be considered. Yes ☐ No ☐

4.3 Subject Information Sheet[5] is attached. (For written and verbal consent)
Yes ☒ No ☐

Informed Consent Form[6] is attached. (For written consent). Yes ☒ No ☐

Consent will be verbal Yes ☐ No ☐

Informed consent is not necessary. State why not. Yes ☐ No ☐

4.4 If a questionnaire or interview is to be used in the research, it must be attached.
Is it attached? If not, the application cannot be considered. Yes ☐ No ☐
N/A

5. SUBJECTS FOR STUDY

5.1 If patients are being studied, state where and how the subjects are selected:

Acute asthma exacerbation pathents, presenting at Kalafong Emergency department will be included.
Age 18 to 70
Moderate to severe exacerbations
Male and female

4. NB. If any doubt exists, the Secretary of the Protocol Review Committee should be approached.
Ms Mary-Ann Richardson, 717-2207, Room 3P09, Wits Medical School.

5. Whether written or verbal consent is to be obtained, the CRHS requires a Subject information sheet written in language understandable to the subject (or guardian) detailing what the subject will be told. This should normal include the following:(1) participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled; (2) the subject may discontinue participation at any time without penalty or loss of benefits;(3)a brief description of the research, its duration, procedures and what the subject may expect and/or be expected to do; (4) any foreseeable risks, discomforts, side-effects or benefits, including those for placebo; and (5) disclosure of alternatives available to the subject. If risks are involved: (6) a professional contact and telephone number; and(7) explanation whether medical treatment will be provided in the case of a complication developing. The Subject Information Sheet may be incorporated into the consent form, or the consent form may be submitted separately.

6. The Informed Consent Form should include a clear statement that the subject is consenting to involvement in research and not to treatment which will necessarily provide personal benefit. Any personal benefit should be mentioned when this is possible. In a trial containing a placebo, the subject must be made aware that, although the potential risks and benefits of all the substances under trial have been explained, none of the active substances may be administered and it will not be possible for the researcher to reveal whether an active substance or placebo is being administered. An important piece of information is that the subject is free to withdraw from the trial at any time without prejudicing any treatment that is required for existing or future medical conditions. If this is not made clear, the researcher risks the accusation that consent was obtained by subtle coercion (that is, the possibility of prejudice against the subject as a current or future patient).

5.2 Where the subjects are not patients, they will be asked to volunteer ☐ they will be selected ☐
State how the subjects are selected, or who is asked to volunteer: N/A

Are the subjects subordinate to the person doing the recruiting? Yes ☐ No ☐
If yes, justify the selection of subordinate subjects: N/A

5.3 Will control subjects be used? If yes, explain how they will be recruited: Yes ☐ No ☒

5.4 Subject records: state what records will be used and how they will be selected: N/A

5.5 Age range of patients/subjects/controls: 18 - 70 years
If under 18 years, from who will consent be obtained?

5.6 Sex: Male ☒ Female ☒

5.7 Number of patients 90 ; non-patient subjects ..... ; controls .....

5.8 Benefit to patient or subjects: will the research benefit the patient(s) or subject(s) in any direct way. If yes, explain in what way. Yes ☒ No ☐
If hypothesis is proven correct this new method will improve patients discomfort faster and save money for the hospital.

5.9 Disadvantages to patients/subjects/controls. Will participation or non-participation disadvantage them in any way? If yes, explain in what way: Yes ☐ No ☒

6. PROCEDURES

6.1 Mark research procedure(s) that will be used:

- ☐ Record review
- ☐ Interview form (must be attached)
- ☐ Questionnaire (must be attached)
- ☒ Examination (state below nature and frequency of examination) see protocol.
- ☐ Drug or other substance administration (state below name(s) of drug(s)/substance(s) and dose(s) and frequency of administration)
- ☐ X-rays
- ☐ Isotope administration (state below name(s) of isotope(s) and frequency)
- ☒ Blood sampling; ☐ venous; ☒ arterial (state below amount to be taken and the frequency of blood sampling)
  3ml at initial assessment, after 30' and 60'. Only some exacerbati will have arterial blood gases done.
- ☐ Biopsy
- ☐ Other procedures (explain)

Use this space to elaborate procedures marked above:

6.2 Is/are procedure(s) routine for diagnosis/management? ☒ Specific to research? ☐

6.3 Who will carry out the procedure(s)? (State name(s) and position(s) held)?
Silmara G. Hanekom - Chief Physiotherapist.
Casualty officer on duty will draw arterial blood.

6.4 When will the research commence, and over what approximate time period will the research be conducted?

June or July 2003.

Aproximately 9 to 12 months.

7. RISKS OF THE PROCEDURE(S) subjects/controls will suffer:

- [X] No risk
- [X] Discomfort
- [ ] Pain
- [ ] Possible complications
- [ ] Side effects from agents used

If you have checked any of the above except "No risk" provide details here:

CPAP mask may cause initial discomfort

8. GENERAL

8.1 Has permission of relevant authority/ies been obtained? Yes[ ] No[ ] N/A[ ]

State name of authority/ies: Kalafong Hospital.

Has been applied.

8.2 Confidentiality: how will confidentiality be maintained so that patients/ subjects/controls are not identifiable to persons not involved in the research?

Serial numbers will be awarded to data collection sheets

8.3 Results: to whom will result be made available?

Only to investigator

8.4 Finances. There will be financial costs to:

Patient/subject	Yes[ ]	No[X]
Hospital/institution	Yes[ ]	No[X]
Other	Yes[X]	No[ ]

Explain any box marked "yes": Costs with protostats

How will the research be funded?

8.5 Any other information which may be of value to the committee should be provided here:

Date: 22/05/2003 Applicant's Signature: Silmara Gfforelom.

Who will supervise the project? At Kalafong Hospital.

Name Dr L. Engelbrecht. Department Emergency Dept. LEngelbrecht

Telephone No. Date 22/05/2003 Signature

Head/Research Coordinator of Department/Institute in which study was conducted:

SUPERINTENDENT KALAFONG HOSPITAL.

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