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The efficacy of a 'spacer' in the delivery of salbutamol for the prevention of exercise-induced asthma

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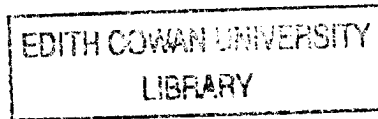
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The Efficacy of a 'Spacer' in the delivery of salbutamol for the
prevention of Exercise-induced asthma

by
David G. Reed

A Thesis Submitted in Partial Fulfilment of the
Requirements for the Award of
Bachelor of Science Honours.

At the Faculty of Science, Technology and Engineering.
Edith Cowan University, Joondalup

Date of Submission: 16th November 1998.

DECLARATION

I certify that this thesis does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any institution of higher education; and that to the best of my knowledge and belief it does not contain any material previously written by another person except where due reference is made in the text.

Signature

A black rectangular box redacting the signature.

Date

5.2.99

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Abstract

Salbutamol is a Beta-2-agonist, commonly prescribed for the prevention and reversal of Exercise induced asthma (EIA). The purpose of this study was to compare the efficacy of a spacer device in the delivery of salbutamol for the prevention of EIA. Thirteen confirmed asthmatic subjects (10 female and 3 male), completed 3 exercise test sessions consisting of three treatments a) Ventolin via MDI (metered dose inhaler) and placebo via spacer, b) Ventolin via spacer and placebo via MDI and c) Placebo via spacer and MDI, randomly administered utilising a single blind, cross-over design. Following treatment, subjects completed an asthmogenic physical challenge (8-minute, graded treadmill run at 75-85% predicted heart rate maximum). The lung function variables: FEV₁, FVC, PEFR, FEF₅₀, and FEF₂₅₋₇₅ were recorded pre-treatment, pre-exercise and 0,3,5,7,10,20 and 30 minutes post-exercise. Of the 13 subjects, only 7 demonstrated sufficient decrement in FEV₁ to be classified as EIA. In the subjects who demonstrated EIA, no significant differences were found for post-exercise lung function measures between the spacer and MDI mean scores. Administration of salbutamol via the spacer resulted in significant improvements over the placebo scores in MEF₅₀ and FEF₂₅₋₇₅, and significant test/time interactions for FVC and FEV₁, however the MDI scores were not significantly different to the placebo. The findings were congruent with previous findings which suggest that spacer delivery offers no significant advantage in preventing EIA in subjects who are skilled in MDI administration techniques. The inability to induce EIA in 6 of the 13 subjects may relate to the high lability scores recorded for several subjects suggesting that bronchoconstriction was evident prior to testing. This may have been due to the high pollen count recorded during testing. Secondly, the asthmogenic nature of the testing environment may have been hindered

due to the high level of fluctuation in the relative humidity recorded for each test. Although conclusions have been made concerning spacer efficacy, this study should be replicated under more asthmogenic conditions to confirm the findings of this study.

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CHAPTER ONE

1.0 Introduction

The phenomena of asthma, otherwise known as 'airways narrowing', has been recognised and documented for nearly 19 centuries. Today, asthma is one of the most common respiratory diseases with at least 10% of the Australian adult population affected and 20% of the adolescent population (Rees & Price, 1989). It is estimated that 30% of the population will exhibit asthma type symptoms at some time during their lives (National Asthma Campaign, 1996). The relationship between asthma and exercise has been described as being 'paradoxical' (Morton & Fitch, cited in Skinner, 1993, p.211) in that although exercise can improve the symptoms of asthma (Cox, Van-Herwaarden, Folgering, & Binkhorst, 1988), it has the potential to induce several clinical signs and symptoms of bronchoconstriction. (Chen & Horton, 1977)

Exercise-induced asthma (EIA) is a term used to describe the transitory increase in airway resistance which follows vigorous exercise in most asthmatic individuals (Anderson, 1988). EIA is categorised within the broad definition of asthma in that the airway narrowing process is similar in action to that of other asthmatic bronchospasms. However the severity and duration are usually reduced. (National Asthma Campaign, 1996).

Prevention of EIA is now achieved through pre-exercise medication which is taken in unison with additional medication for the control of general asthma. Inhaled Ventolin™ is the most readily used form of the Beta-2-agonist, salbutamol, a bronchodilator which aids in the non-ergogenic reduction of the symptoms of EIA that disadvantage asthmatic athletes. Few studies have been undertaken into the delivery of salbutamol. For elite and non-elite athletes, the question still persists over whether

metered dose inhalers (MDI's) or spacers present the best delivery options. The spacer is a chamber designed to hold the spray of medication from an MDI before it is inhaled. This theoretically overcomes the problem that many asthmatics, especially young children, have in coordinating the deep inhalation with the actuation of the MDI. Both have advantages and disadvantages, yet no study has been done on the efficacy of each with regard to the effects on lung function pre and post-exercise with asthmatics prone to exercise-induced attacks. The purpose of this study is to investigate what consequential differences exist between the spacer delivery and metered dose delivery of salbutamol with reference to EIA and relevant lung function measures. Falls in the forced expiratory volume in the first second (FEV_1) will be the primary measure to assess if EIA has occurred as it is widely considered the benchmark in pulmonary function indication.

1.2 Significance of the Study

Asthmatics perform exercise and sport with a significant respiratory disadvantage. It is important therefore, to examine all possible means of allowing the asthmatic to participate on an equal basis with the non-asthmatic and without suffering the discomfort and performance limitations produced by EIA. More importantly, the benefits of reducing this discomfort in asthmatic sufferers whilst exercising may see a renewal in exercise thus having a large improvement on lifestyle and overall health.

This study will generate a greater understanding of the delivery of salbutamol to such individuals, so that when participating in sport, respiratory equality between competitors is approached or achieved and discomfort that bronchospasm produces minimised or even prevented.

1.3 Research Questions

The purpose of this study was to determine whether the use of a 'spacer' to deliver salbutamol (Ventolin™) provides better protection from exercise-induced asthma than delivery via a metered dose inhaler (MDI). The specific research questions concerning changes in selected lung function measures after exercise are:

1. Does a spacer assisted pre-exercise inhalation of salbutamol increase post-exercise Forced Expiratory Volume in one second (FEV₁) in comparison to the metered dose inhalation method using a MDI.
2. Does a spacer assisted pre-exercise inhalation of salbutamol increase post-exercise Peak Expiratory Flow Rate (PEFR) in comparison to the metered dose inhalation method using a MDI?
3. Does a spacer assisted pre-exercise inhalation of salbutamol increase post-exercise Forced Vital Capacity (FVC) in comparison to the metered dose inhalation method using a MDI?
4. Does a spacer assisted pre-exercise inhalation of salbutamol increase post-exercise Forced Expiratory Flow rate (after 50% of the forced vital capacity manoeuvre is complete) and Forced Expiratory Flow rate (during the middle half of the forced vital capacity manoeuvre) in comparison to the metered dose inhalation method using a MDI. (MEF₅₀ & FEF₂₅₋₇₅)

1.4 Definition of Terms

Salbutamol The name given to the most widely used form of the beta-2-agonist drug which is used as a reliever for asthma patients and as a preventer of EIA. Retailed as Ventolin™

Ventolin The trade name of the form of salbutamol manufactured by Glaxo Pharmaceuticals company. The most commonly used form of salbutamol.

Exercise-induced asthma (EIA) Asthma triggered by physical activity

Forced Vital Capacity (FVC) Vital capacity when performed with a maximally forced expiratory effort following a maximal inhalation.

Forced Expiratory Volume in 1 second (FEV_1) The volume of air exhaled in the first 1 second of a forced vital capacity manoeuvre

Forced Expiratory Volume 1% ($FEV_1\%$) The FEV_1 value expressed as a percentage of FVC; $FEV_1 \div FVC \times 100$

Peak Expiratory Flow Rate (PEFR) The highest forced expiratory flow rate measured during a forced vital capacity manoeuvre.

Forced Expiratory Flow rate (25%-75%) (FEF_{25-75}) Mean forced expiratory flow rate during the middle half of the forced vital capacity manoeuvre.

Forced or Maximal expiratory flow rate (50%) (FEF_{50} or MEF_{50}) Forced expiratory flow rate when 50% of FVC has been exhaled during a forced vital capacity manoeuvre.

Metered Dose Inhaler (MDI). An aerosol container used to administer a fixed dose of inhaled medication.

Spacer A clear plastic tube used to aid in the delivery of inhaled medication.

Bronchial Lability The maximum post-exercise percent increase plus the maximum post-exercise percentage decrease. Usually applied to FEV_1 and PEFR.

1.5 Abbreviations

| | | |
|----------------------|---|---|
| ANOVA | - | Analysis of Variance |
| BP | - | Blood pressure |
| EIA | - | Exercise-Induced Asthma |
| FVC | - | Forced Vital Capacity |
| FEV ₁ | - | Forced Expiratory Volume during the first second of a FVC manoeuvre |
| FEV ₁ % | - | FEV ₁ ÷ FVC expressed as a percentage |
| FEF ₂₅₋₇₅ | - | Forced Expiratory Flow rate in the middle half of a FVC manoeuvre. |
| MEF ₅₀ | - | Maximal Expiratory Flow rate after 50% of the FVC manoeuvre is complete. |
| PEFR | - | Peak Expiratory Flow Rate |
| HR | - | Heart Rate |
| HR _{max} | - | Maximum heart rate |
| MDI | - | Metered Dose Inhaler |
| RHL | - | Respiratory Heat Loss |
| RWL | - | Respiratory Water Loss |
| RPB | - | Rate of Perceived Breathlessness. |

CHAPTER TWO

2.0 Literature Review

2.1 Asthma

Asthma is defined as being;

“A chronic disorder of the airways in which many cells play a role. In susceptible individuals, this inflammation causes symptoms which are usually associated with widespread but variable airflow obstruction that is often reversible either spontaneously or with treatment and it also causes an associated increase in airway responsiveness to a variety of stimuli.” (National, heart, lung and blood institute, 1992)

Bundgaard, (1985) states that asthma is a disease characterised by airways inflammation typified by mucosal infiltration with inflammatory cells, thickened airway walls, spasms of bronchial smooth muscle, oedema, hypertrophy of glands and smooth muscle, damaged epithelium and increased production of mucous. Although these symptoms vary in response to therapy, the underlying inflammation persists.

Swimburn, (1976) adds that the disease is characterised by intermittent attacks with fluctuating severity. Anderson (1988, p.1156) supports this notion by terming asthma as ‘transitory’ thus placing emphasis on the short-term nature of the diseases symptoms.

2.1.1 Population Particulars of Asthma

Asthma is one of the most common respiratory diseases in modern industrialised nations affecting between 4-16% of the population (Morton, Fitch & Hahn 1981). Since the early 1980’s, the incidence of asthma within Australia has increased at a rate higher than that accountable for population increases, with Australians and New Zealanders having the highest rate of asthma in the Westernised world. Swimburn, (1976) suggests that within these populations, males have a higher incidence of asthma than females at a ratio of 7:3. Anderson (1986) argues that this ratio would be more realistic at 3:2, with

young children having the highest rate. Later in life, this figure is reversed, with females over the age of 55 having the higher rate than males of the same age.

2.2 Exercise-induced asthma

Exercise Induced Asthma is defined as being any asthmatic episode provoked by the incidence of vigorous physical activity (Katz & Pierson, 1988). EIA is characterised by an increase in airway resistance that occurs after 6 to 8 minutes of strenuous exercise and appears in 70% to 80% of asthma patients. Of this group, 70% will require pre-exercise medication. The majority of EIA sufferers recover spontaneously, with little after-effect from exercise (Anderson 1986). Bundgaard (1985, p. 256), states that EIA should be referred to as 'hyperpnoea-induced asthma' due to the fact that EIA is facilitated by the heavy breathing associated with physical activity.

2.2.1 Mechanisms of Exercise-Induced Asthma

2.2.1.1 Previous Findings

In 1864, speculation existed on the effects cold air had on the stimulation of nervous system irritability that caused asthma (Katz and Pierson, 1988). Since then, research has been centred upon the causes of asthma with particular emphasis on respiratory response to airway cooling and drying. Engstrom, Karlberg, and Kraepelein (1960) found that with the onset of EIA there was a significant difference in lung function measurements between normal and asthmatic children. Jones, Buston, and Wharton (1962) showed that a correlation existed between the type and duration of exercise and the severity of the asthma attack. Since these discoveries, research was undertaken into all forms of exercise including stairways, treadmills, cycle-ergometers and swimming to give a greater understanding of the mechanisms and attributes of EIA.

Unfortunately, these tests caused greater contradiction with many conflicting results causing discrepancies with past and present findings. Katz and Pierson (1988) state that from these findings, EIA was related to a plethora of disorders including; hypoxemia, hypocapnia, acidosis, bicarbonate decrease, and reflex bronchial apposition.

Argument exists that asthma is caused by hyperventilation (Bundgaard, 1985) which contradicts Beaudry, Wise and Seely (1967) and McFadden and Lyon's (1968) findings that hypoxemia is a more probable cause of EIA.

Hypocapnia or depressed plasma carbon dioxide contradicts the hypoxemia theory and is argued against by Sterling (1968) stating that changes in partial pressures of carbon dioxide cause respiratory resistance in all individuals whether they suffer from asthma or not. Vassalo, Gee, and Domm, (1972) argue that metabolic acidosis is associated with increased airway resistance in asthmatics and normal subjects. This process is given credence due to the theory that an increase in arterial hydrogen ions occurs with a corresponding fall in bicarbonate and partial pressures of oxygen within the respiratory system. This function is concomitant with the processes described by Anderson (1986), where respiratory water loss may increase osmolarity and concentrations of the pre-mentioned substrates. Today, argument is centred upon the theories that EIA is triggered by either; respiratory water loss (RWL) or respiratory heat loss (RHL), both of which are discussed later.

2.2.1.2 Influence of Exercise on the Respiratory System

During the first few minutes of exercise, bronchodilation occurs. Due to this increase in air space within the upper respiratory system, peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV₁) increase (Anderson, 1986). As the exercise intensity increases, there is an increase in minute ventilation resulting in

an increase in heat and water loss from the mucosal surface of the respiratory tract. (Anderson & Schoeffel, 1982). This process, first demonstrated by Otis (1964), showed that under resting conditions, this heat and water loss only accounted for 10% of the total heat and water loss from the body. During exercise, ventilation can increase by up to 40 times (5 litres/min up to 200 litres/min) with water and heat loss from the airways being markedly increased. It is argued by Novinski, Bar-Yishay, Gur and Godfrey (1987), that RHL is the triggering factor in EIA. A theory initially manifested by Deal, McFadden, Ingram and Jaeger, (1979), and reaffirmed by McFadden (1983).

According to Anderson (1986), the temperature of the inhaled air is not critical to the EIA response. She states that the rate of water loss from the mucosal wall of the respiratory tract, otherwise known as respiratory water loss (RWL), is of far greater importance to the triggering of EIA. A theory widely supported within the academic community. (Hahn, Anderson, Morton, Black & Fitch, 1984; Anderson, Schoeffel, Follet, Perry, Daviskas, & Kendall, 1982)

2.2.1.3 Respiratory Response to EIA

There is little difference in the asthma bronchoconstriction caused by exercise and that induced by other pathophysiological factors such as dust and pollen allergies. According to Hahn (1985) the incidence of EIA is directly related to the type of exercise undertaken and the environmental factors associated with it. Jones, Buston, and Wharton (1962) state that the potency of exercise as a stimulus is an integrated function of its duration, intensity and type. However, later research has proven that external factors such as temperature and humidity also play a major role in the severity of an asthmatic attack.

According to Godfrey (1975), EIA occurs after exercise has ceased and peaks in severity at 5 to 10 minutes post-exercise. Some asthmatics must cease activity during exercise, however the majority demonstrate bronchoconstriction post-exercise. EIA is initiated by the abnormally high rate of water and heat loss from the airways when conditioning large volumes of air in a relatively short period of time. According to Anderson (1986), the increase in respiratory airflow associated with intense exercise causes a high rate of water loss from the lining of the respiratory tract leading to greater osmolarity of the periciliary fluid. This evaporative process can instigate a bronchoconstrictive reaction. Many researchers argue to the contrary stating that heat loss through airway cooling is the primary trigger of an EIA attack (Deal, McFadden, Ingram & Jaeger 1979). Katz and Pierson (1988) support Anderson by stating that airway cooling in children can be as low as 4% of the total temperature change between inspired and expired air (with ambient temperatures above 37° celcius) thus supporting the argument that more than just airway cooling is needed for EIA. The actual process by which an increase in osmolarity and or a reduction in temperature leads to a contraction of bronchial smooth muscle is not known (Anderson, 1985). However several theories exist on the subject. As osmolarity of the lining fluid of the respiratory tract increase, reflex bronchoconstriction occurs mediated by the parasympathetic nervous system and the release of substances that contract bronchial smooth muscle, either directly or via the vagus nerve (Anderson, 1986). According to Togias, Naclerio, Proud, Fish, Adkinson, Kagey-Sobotka, Norman and Lichtenstein (1985), this process can increase the release of histamine from mast cells within the respiratory mucosa. They add that this local release of inflammatory mediators can cause localised respiratory tract dysfunction. Contradiction to this theory is supplied by O'Cain, Dowling, Slutsky, Hensley, Strohl, McFadden and Ingram, (1980), who debate that this

constrictive process is due to airway cooling not osmolarity and that mast cell mediator release due to hyperventilation is not a major effector mechanism in either normal or asthmatic bronchoconstriction. Figure 2.1 shows the general reaction that mast cells have to exercise and how the released mediators are in contradiction to catecholamines that aids in airway dilation. This explains the initial dilatory response exercise has on the airway due to the time differences displayed in the release of catecholamine in comparison to the mast cells' mediators.

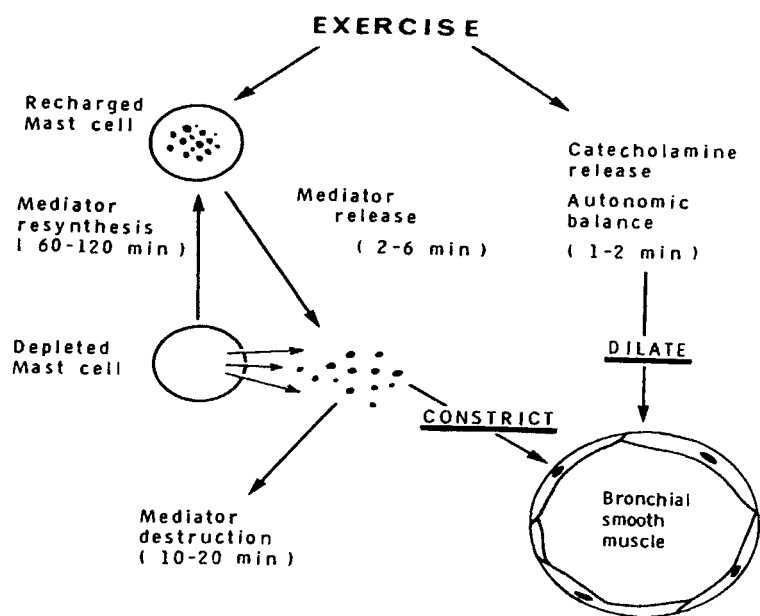


Figure 2.1. Hypothetical pathways concerned in Exercise-induced Asthma.
(Godfrey, Silverman and Anderson, 1973, p.199)

Questions still remain as to how the inflammatory mediators reach the smooth muscle, however, it has been reported that this may be facilitated by a change in permeability of the bronchial mucosa brought about by the fore-mentioned stimuli Anderson (1986). The activity of mast cells can also lead to the release of leukotrienes from epithelial cells, that in turn enhance the release and action of other mediators from the mast cells in the sub-mucosa.

2.2.1.4 Pulmonary Function Response to EIA

According to Eggleston, Kagey-Sabotka, Schleimer & Lichtenstein (1984), hyperosmolar fluid surrounding mast cells trigger the release of inflammatory mediators including histamines, causing a subsequential cascade of other immunological events that leads to bronchoconstriction. The effects on lung function are drastic, with difficulty in breathing being most prevalent in the exhalation phase of the respiratory cycle. Exercise often, but not always, induces an initial bronchodilation which is maintained throughout the exercise period (Fig. 2.2). After the cessation of the exercise, bronchospasm ensues, and lung function reaches its lowest level after 3 to 5 minutes in children and 5 to 7 minutes in adults (Weiss, Segal, & Stein 1985). For the purpose of this study, quantification of EIA was indexed using percent post-exercise fall in FEV₁ of 10%. Figure 2.2 shows two possible expected trends for the PEFR in asthmatic subjects after an 8-minute exercise challenge. Figure 2.3, shows the expected trends for FEV₁ after a similar exercise protocol. Both graphs show normal and asthmatic results.

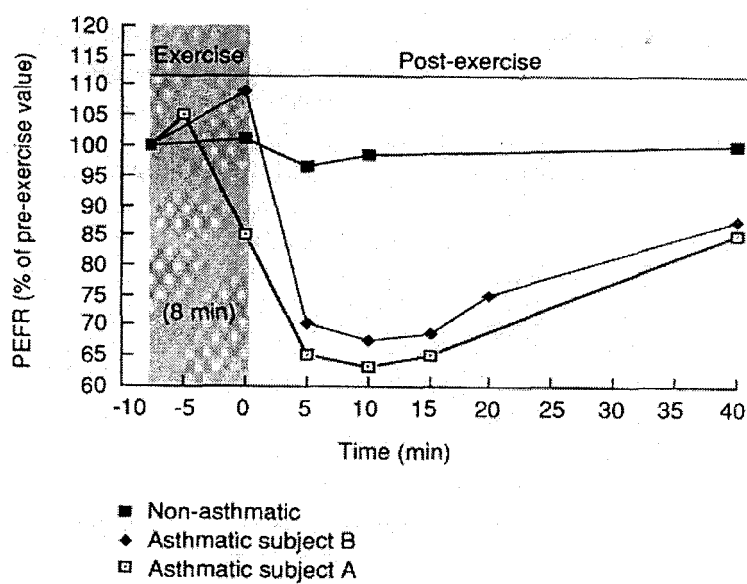


Figure 2.2. Typical PEFR response in asthmatic and non-asthmatic subjects.
(Morton; in Bloomfield, Fricker & Fitch, 1992, p.536)

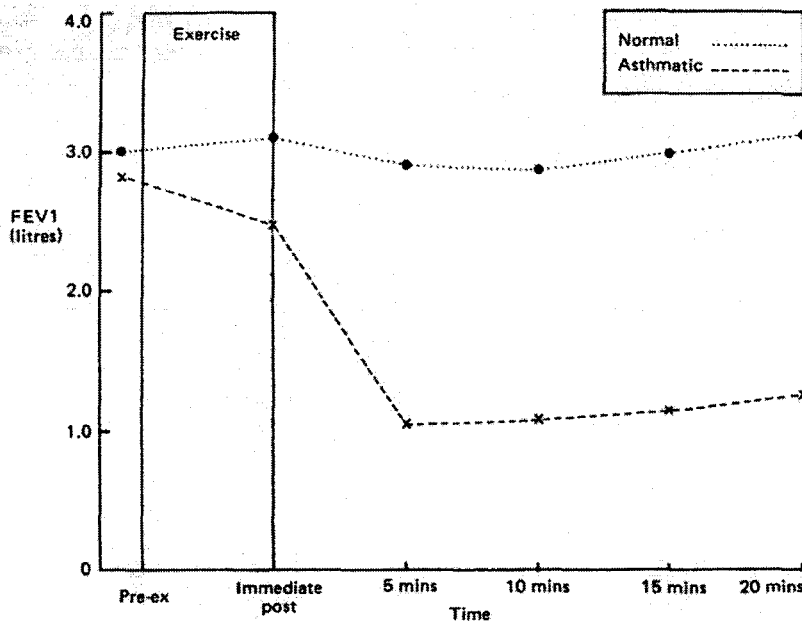


Figure 2.3 . Typical effects of exercise on FEV₁ in normal and asthmatic subjects.

(Hahn, 1985, p.4)

2.2.2 Current treatment

Asthmatics participate in a wide range of sports and at all levels. According to Hahn (1985), the type of treatment received is dependent on type and severity of the asthma suffered. EIA has several specific treatments which are presented in Table 2.1. Today, salbutamol is the most widely used anti-asthma drug available. Salbutamol is a Beta-2 agonist that has a selective stimulant action on beta-receptors in bronchial muscle (Hill, Davies & Geary, 1976). Howarth, Durham, Lee, Kay, Church and Holgate (1985) state that albuterol (US equivalent of salbutamol) inhibits the mast cell histamine release associated with an asthma attack. It is also reported that inhaled salbutamol is of greater effect in preventing EIA than the orally taken form (Bloomfield, Carmichael, Petrie, Jewell and Crompton, 1979). While inhaled salbutamol is permitted by the International Olympic Medical Commission, the oral route of administration is forbidden.

Boulet, Turcotte and Tennina (1989) demonstrated that salbutamol gave the highest level of protection against all forms of asthma and prevented EIA to a greater

degree than other popular drugs (Cromoglycate and Ipratropium). Not only is salbutamol effective in preventing EIA, research shows that there is little or no tolerance or resistance generated by the asthmatic who uses the drug on a regular basis (Harvey, Baldwin, Wood, Alberti and Tattersfield 1981). Thus making it a suitable drug for EIA study concerned with delivery methods of the drug and the effects different delivery systems has on the severity of EIA.

Table 2.1.

Drugs for the prevention and relief of EIA (most common forms and delivery techniques)

| Drug Type | Name | Administration | Effects | Duration |
|-----------------------|---------------------|--|--|----------------------|
| Beta-2 Agonists | Salbutamol | Inhaled or orally taken. prior to ex. (5-10 mins) or day before for pill. | Decreases severity of asthma attack | 2 hours (inhaled) |
| Methyl Xanthines | Theophylline | Oral (10-20µg) 90 mins prior | Decreases incidence of EIA | 1-2 hours |
| Khellin Derivatives | Cromolyn sodium | Inhalation of dried powder. 5 minutes prior | Longer term protection of EIA | < 5 hours. |
| Glucocortico-steroids | Budesonide | Inhaled prior to ex. 5-10 mins. | Similar to Beta 2. Mainly control of some symptoms | Immediate to 1 hour |
| Belladonna Alkaloids | Ipratropium bromide | Inhaled in combination | ↓ | ↓ |

2.2.3 Relevant Studies

Past studies into EIA, have explored the range of ‘bronchial lability’ in normal subjects and asthmatics. Non-asthmatic individuals usually demonstrate an average rise

in peak flow during exercise of 3 to 4% with a maximal post exercise drop of up to 10% (Silverman and Anderson 1972). A study by Burr, Eldridge and Borysiewicz (1974) found that 89% of asthmatic subjects had a fall in PEFr greater than 10%. For the purpose of this study, Anderson's definition of EIA has been used with FEV₁ and PEFr declines greater than 10% post-exercise being considered. With regard to reproducibility, Godfrey, Silverman and Anderson (1973) found that repeated tests within 1 week intervals had average coefficient variations in pulmonary function of 21%. This was caused by changes in the sensitivity of the asthmatic to exercise rather than experimental error whilst conducting the tests.

2.2.3.1 Provocation of EIA via Running.

Running is the most widely used physical challenge in attempting to produce EIA. Fitch and Morton (1971) demonstrated that running causes more asthma provocation than cycling and swimming. Anderson, Connolly, and Godfrey (1971) confirmed this finding by stating that the asthmogenic nature of running is far more effective in generating bronchoconstriction than most other modes of exercise. Several studies have demonstrated that an 8-minute exercise challenges produce the highest rate of asthma (Figure 2.4). Godfrey in Dempsey and Reed (1977) found that in many asthmatic patients, continuation of exercise for more than 8 minutes causes progressive reduction in the severity of EIA. Silverman and Anderson (1972) found that such declines in the magnitude of the airway's response can occur when prolonging the duration of exercise from 8 to 12 minutes.

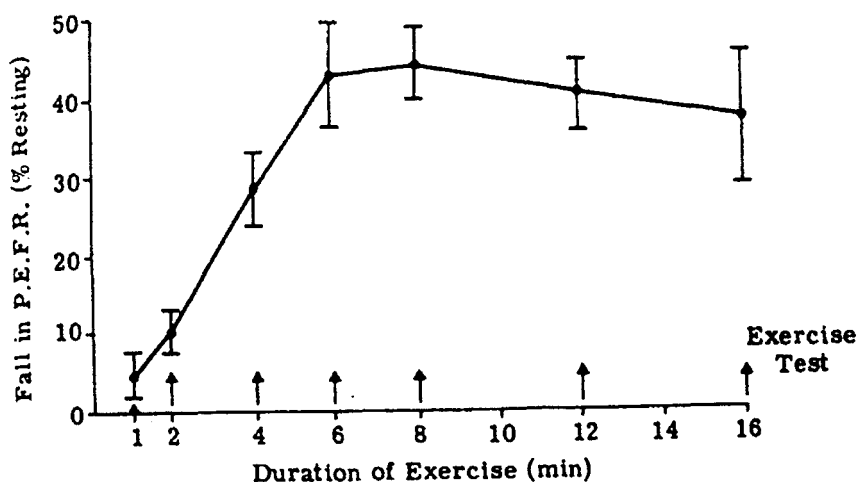


Figure 2.4. The effect of duration of exercise on asthma induced by treadmill running.

(Godfrey, Silverman and Anderson, 1973, p.201).

2.2.4 Delivery of salbutamol

Past research into the delivery of salbutamol for the prevention of asthma has been based primarily on optimal inhaler technique, deposition patterns of inhaled drug using different inhaler devices and the effects different drugs and drug forms have on lung function. As mentioned earlier, research into the area of EIA has been relatively limited and although many related studies have been accomplished in the area of asthma, these findings cannot be transferred or linked to the more specific EIA therefore leaving a small void of information. To date, the nebulizer technique of delivering aerosol medication to the lungs has been considered the most effective method of delivery, however it is quite impractical (Devadason & Le Soeuf, 1992)

Delivery of salbutamol is achieved in the most efficient way through the use of the MDI and 'spacer'. The MDI is a dose-controlled mechanism that delivers 100µg of salbutamol in a dried powder form. The spacer is a clear plastic tube with an insertion at one end for an MDI and a uni-directional valve mouth-piece at the other. The medication (salbutamol) is fired into the chamber and then inhaled over several respiratory cycles. Morton and Fitch (1992) state that the device overcomes the

requirement for co-ordination of the actuation of the MDI with the inhalation phase. The problem of MDI misuse is extensive due to the number of differing inhalation techniques and the relatively high level of coordination required to effectively inhale the medication (Hindle, Newton and Chrystyn 1993). Gurwitz, Mindorff, Levison and Reilly (1983) found that incorrect inhalation technique can be traced back to childhood where the ratio of equally effective oral and inhaled doses in children is about 25:1. Appendix C shows the instructions that prompted research by Epstein, Manning, Ashley and Corey (1979) who found that most adults with asthma are unable to perform all of the manoeuvres correctly. Even after extensive training, 14% of all asthmatics totally misuse their inhalers (Patterson & Crompton 1976). Crompton (1984) placed this percentage at above 50% when referring to the coordination of inhalation with MDI actuation. This poor use or misuse of the MDI can lead to a reduction in the therapeutic efficacy of inhaled bronchodilators due to inadequate airway deposition of the medication. (Orehek, Gayrard, Grimaud & Charpin 1976)

By using the spacer, a greater lung deposition of the medication is achievable. According to Rivlin, Mindorff, Reilly and Levison, (1984), this delivery system is significantly more effective in delivering aerosol drug to the lungs. The common problem of fast inhalation coupled with poor hand lung coordination whilst using an MDI is overcome by use of a spacer device leading to greater deposition of medication within the lung (Newman, Clarke, Talae & Clarke 1989). A study conducted by Newman, Millar, Lennard-Jones, Moren and Clarke (1984) found that a large volume spacer deposited 21% of the medication into the lungs and 16% in the oropharynx, with about 56% remaining in the spacer. Without a spacer, only 10-15% is deposited in the lungs and 70-80% on the oropharynx. The benefits of spacer use are supported by

Cushley, Lewis and Tatterfield (1983) and Tobin, Jenouri, Donta, Kim, Watson and Sackner (1982) who both argue that the spacer device not only aids in the delivery of drug to the lung but reduces the waste caused by poor MDI inhalation techniques.

Theoretically, by slowing aerosol particle speed during the inhalation phase of MDI actuation, the spacer allows greater lung deposition by preventing the drug from depositing at the back of the throat and being swallowed as shown in Figure 2.5 (Gurwitz, Levison, Mindorff, Reilly & Worsley, 1983). However, more recent research questions the spacer's credentials.

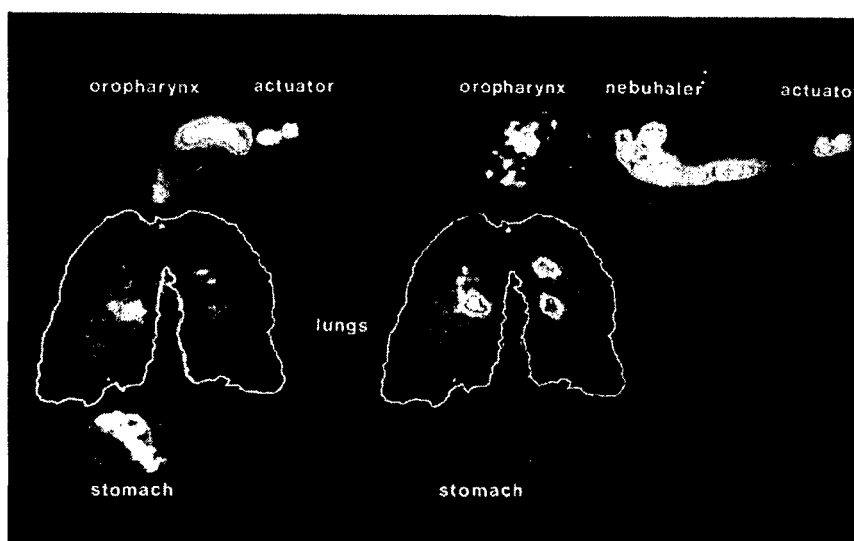


Figure 2.5. Typical deposition patterns for the MDI alone (left) and for MDI with spacer attachment (right).

(Newman, Millar, Lennard-Jones, Moren & Clarke. 1984, p.939)

Konig (1985) refers to spacers as gimmicks and argues that they are neither a breakthrough nor aid in the drug delivery process for the majority of asthmatic patients. Barry and O'Callaghan (1994) noted similar delivery patterns when comparing the inhalation of aerosol drug from a Volumatic™ spacer device to an MDI. However, they did record a lower oropharyngeal deposition with the use of the spacer, yet there was no significant difference between the 2 devices with regard to lung deposition. Christensson, Arborelius and Lilja (1981) argue that MDI use is as effective as all other

delivery systems and shows no significant difference even when compared to the nebulizer delivery system. Findings by Pedersen and Bundgaard (1983) support the notion that spacers aren't more effective over MDI's by showing that the spacer was no more efficacious in the delivery of aerosol medication with asthmatics who have proper inhalation coordination when using the MDI. Current research is centered upon static charge surrounding the spacer devices and how this can disrupt the drug delivery (Wilhaber, Devadason, Eber, Hayden, Everard, Summers & LeSouef, 1996). Such research has lead to further study on how the multiple actuation process of releasing the salbutamol into the spacer disrupts medication flow to the lungs (Wildahaber, Devadason, Hayden, James, Dufty, Fox, Summers & LeSouef, 1996). No research has been done on the effects the delivery systems have on EIA and post-exercise lung function. A question that this study endeavours to answer.

2.3 Summary

With the majority of past asthma study concentrating on drug development and effectiveness in preventing asthma, research on the topic of delivery systems of these drugs has been neglected. Causation of an asthmatic episode has been defined and described within the body of this proposal, however, the lack of discussion on the spacer and MDI is representative of the deficiency in published research in the area of study in question. To this authors knowledge, spacers and MDI's have never been compared with regard to EIA.

CHAPTER THREE

3.0 Methodology

3.1 Sample

Thirteen (10 female and 3 male, mean age = 24 yrs SD = 7.44yrs) healthy asthmatics were recruited from the Edith Cowan University Joondalup and TAFE student populations. Subjects were considered active, based on their participation in sport over the past 3 months (all participated in some form of exercise at least 3 times per week for no less than 1 hour per session). All subjects consistently experienced EIA and were prescribed Ventolin™ by their physician for preventative measures against the condition. A general medical information questionnaire and signed consent was completed prior to any testing (Appendix B). All subjects had the procedures explained to them and were provided with information sheets that addressed consistency procedures and research procedures to ensure standardised testing and standardised preparation was maintained. (Appendix B) Medical clearance was compulsory and obtained for each subject either through their own general practitioner or the Edith Cowan campus doctor.

The research was approved by the Human Rights Committee of Edith Cowan University.

3.2 Study Design

This study employed a single-dose, single blind, placebo controlled cross-over study. There were three laboratory treatment sessions for each subject. No two treatments were conducted on the same day with a minimum of 2 days and a maximum of 5 days

between tests. Five specific lung function measures were recorded post-exercise to investigate the efficacy of two different delivery systems of aerosol salbutamol.

3.3 Reliability Study

To ensure experimenter familiarity with the autspirometer and to establish reliability, a pilot study was undertaken to determine the consistency of the Minato Autospiral spirometer. Thirty non-asthmatic subjects performed lung function tests on 2 occasions over 2 weeks. Reliability was determined using an interassay test-retest protocol and the results examined by a Pearson Product Moment correlation and by application of the Student t-test for related groups. The pulmonary function variables examined for the determination of reliability were those measured in the major research project.

3.4 Instruments and Materials

- Track master Tm400 treadmill
- Polar edge heart rate monitor
- Glaxo Wellcome Volumatic™ Spacer device
- Glaxo Wellcome Metered dose inhaler
- Ventolin™ (3 canisters)
- Placebo (3 canisters)
- Auto spirometer 'Minato AUTOSPIRAL PAL'.
- Mouth pieces
- Borg scale of Perceived Breathlessness
- Nose clip
- Toshiba Pentium Laptop computer
- PalSoft software (Switzerland)

3.5 Research Protocols

Each subject completed 3 testing sessions involving a standard asthma exercise challenge following pre-exercise inhalation of either:

- 1) salbutamol via MDI and placebo via spacer
- 2) placebo via MDI and salbutamol via a spacer
- 3) placebo via MDI and placebo via spacer.

The severity of EIA was assessed from FEV₁ and other selected lung function measurements obtained pre and post-exercise. Pre-medication measures were used as a baseline figure with which all subsequent lung function results were compared. Lung function tests took place at pre-medication, 5 minutes post-medication, pre-exercise and at 7 given post-exercise time periods: Immediately post exercise and at 3, 5, 7, 10, 20 and 30 minutes. See Figure 3.1.

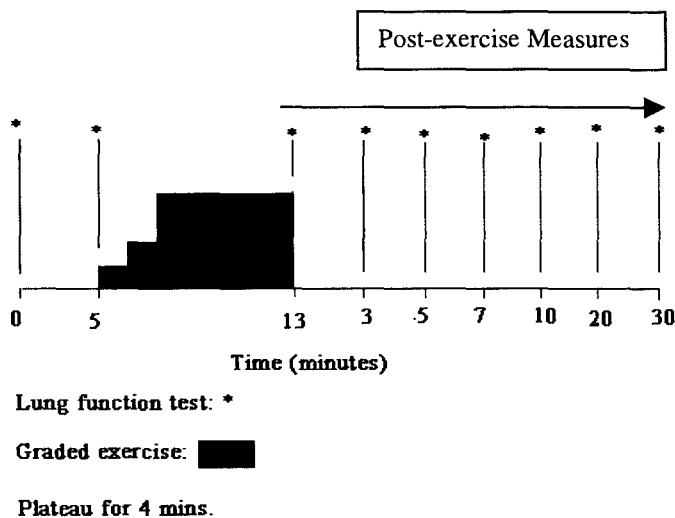


Figure 3.1. Time display for graded running protocol with Lung Function test times shown.

In order to assess subjects perceived level of breathlessness, the Borg Scale of Perceived Breathlessness (Appendix D) was used and scores recorded every minute during the 8-minute exercise challenge and whenever post-exercise lung function measures were conducted. The 8-minute exercise challenge involved a multi-stage-continuous treadmill run with gradual increases in severity over the first 3 to 4 minutes, achieved by adjusting speed and grade. The increases in workload were manipulated so that the subject was exercising at 75-85% predicted HRmax by the 4th minute thus ensuring at least 4 minutes of exercise at this level. All testing was carried out in a laboratory where the environment maintained at 19°Celsius (range = 17°-21°) with humidity remaining relatively consistent at 55% (range = 47%-63%).

Prior to testing, all environmental measures were recorded (temperature, barometric pressure and humidity) for calibration purposes. All lung function measures were corrected to body temperature, ambient atmospheric pressure and saturated with water vapour (BTPS).

3.5.1 Experimental Testing Sessions

Each subject attended three exercise testing sessions in the physiology laboratory at Edith Cowan University, Joondalup. The order of pre-exercise treatments was randomly assigned to each of the three experimental testing sessions with single blind administration of the salbutamol and placebo. The placebo, salbutamol, spacers and metered dose inhalers were supplied by the Human Movement department at The University of Western Australia. Both the placebo and salbutamol canisters were identical except for code numbers (see Figure 3.2). The placebo consisted of aerosol propellant only.

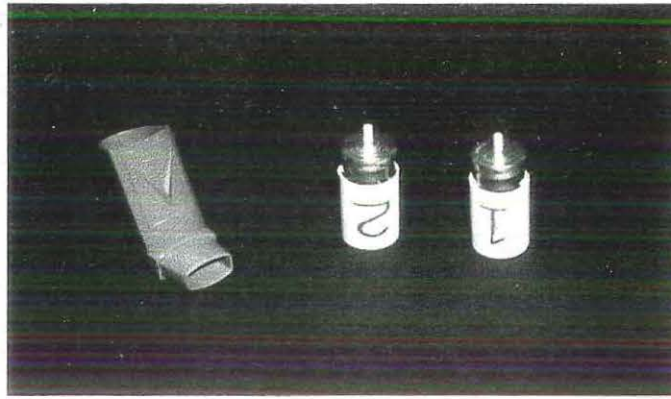


Figure 3.2 Metered dose inhaler with Ventolin cannister (2) and placebo cannister (1).

On arrival for each testing session, the subject's body mass and height were determined and entered into the Autospiral data bank. The subject was then fitted with a Polar Edge heart rate monitor and instructed to sit alongside the spirometer. Once seated, pre-treatment lung function measures were recorded involving the best of two trials utilising the FVC manoeuvre, with nose clip in place to prevent air escaping through the nasal passages (Figure 3.3). All data were recorded by the Autospiral autospirometer and immediately downloaded to an adjoining Toshiba laptop computer.



Figure 3.3 FVC manoeuvre employed for lung function testing with Autospiramer and attached Laptop computer. Subject seated and nose-clip attached.

Following a revision of spacer and MDI use techniques, the subject self-administered the allocated treatment (Figures 3.4 & 3.5). Placebo and/or salbutamol were administered via the MDI and spacer as two actuations one minute apart according to the instructions in Appendix C. Each actuation provided 100 µg of the medication/placebo.



Figure 3.4 Correct spacer assisted MDI actuation.



Figure 3.5 Correct metered MDI actuation.

All subjects were closely observed during treatment to ensure optimal technique was used. After 5 minutes seated rest, the pulmonary function tests were repeated. Immediately after the ‘post-medication’ scores were completed, the subject began the exercise challenge on the treadmill with nose clip attached (Figure 3.6).

The initial speed and grade was determined by feedback given from the subject on what they considered as being a ‘comfortable’ warm-up level. For the following 2 minutes, speed and grade was manipulated by the tester to attain a HR which corresponded to the required test level. After the first 3-minutes of exercise, which represented a warm-up, the subject achieved a running pace which induced a heart rate equivalent to 75-85% predicted HR_{max}. This was maintained until a total of 8 minutes was completed. Each minute, reports of perceived breathlessness and heart rate were obtained.



Figure 3.6. Subject performing a Graded Treadmill exercise challenge with nasal clip attached.

Immediately (< 30 seconds) after the cessation of exercise, the pulmonary function testing was performed and repeated at 3, 5, 7, 10, 20 and 30 minutes post-exercise. Borg scale readings and heart rate were also measured at these time intervals. At the end of the 30-minute post exercise period, the subject's lung function results were checked to ensure adequate recovery (> 75% of initial value) before allowing them to leave the laboratory. If this level of recovery was not attained, Ventolin was administered and lung function monitored until the criteria was achieved.

3.5.2 Measurement Procedures

3.5.2.1 Total Body Mass

Body mass was determined with the subject wearing minimal clothing, running shorts (male) or running shorts and lightweight singlet (female) without foot attire. Subjects stood erect on the centre of a Mettler electronic scale ensuring minimal movement. Mass was recorded to the nearest 10 grams.

3.5.2.2 Standing Height

Standing height was obtained using a Holtain Stadiometer. Subjects stood erect with heels, buttocks, posterior aspect of the thoracic region and head against the vertical plane of the stadiometer. Heels were slightly apart and the arms hanging in a relaxed state. Using a pistol grip, the subjects head was manipulated into the Frankfurt plane by applying slight upward pressure on the jaw and occipital bone. Height was read from the scale and rounded to the nearest centimetre.

3.5.2.3 Ambient temperature, Barometric pressure and Relative humidity

Ambient temperature and relative humidity within the air-conditioned physiology laboratory was determined using an aspirated psychrometer (whirling hygrometer). This was carried out prior to each subject's initial pulmonary function measurement. Barometric pressure was determined using a mercury barometer. As the barometric scale was in mm of Hg and the Autospiral required this parameter to be expressed in kPa, the value, expressed in mmHg, was multiplied by 0.13333. The barometric pressure, ambient temperature and relative humidity were all used to calibrate the Minato Autospiral pal and used to correct lung function values to BTPS.

3.5.2.4 Pulmonary Function Testing

The Minato: Autospiral Pal autspirometer was used for all lung function testing. Each subject used a separate sterilised filter and a new cardboard mouthpiece for each testing session. A small amount of tape was used to guarantee a tight seal between the mouthpiece and the Autospiral transducer. Prior to each testing session, the Autospiral Pal was calibrated to the manufacturers instructions, as described in Appendix E.

To determine the influence of two different methods of Ventolin on exercise-induced asthma following a standardised exercise challenge, nine separate tests were carried out during each of the three sessions. A flow volume test (FVC pre-test) was applied to record the 5 lung functions in question (FVC, FEV₁, FEF₅₀, FEF₂₅₋₇₅ and PEF_R). Subjects were given 2 trials at each time point with a short break of approximately 5 seconds between trials. During each pulmonary function test, subjects sat comfortably on a chair with feet flat on the ground. A nose clip was worn for all tests (Figure 3.3). Subjects were required to have the lips sealed around the mouthpiece, the end of which was positioned just beyond

the teeth. Throughout the inhalation and exhalation procedure, subjects were given verbal encouragement to ensure an optimal result was achieved for every FVC manoeuvre.

3.5.2.5 Rating of Perceived Breathlessness

Rating of Perceived Breathlessness was recorded during the last 10 seconds of each test using the Borg category scale (breathlessness) with ratio properties (Appendix D) The Borg scale chart was placed at eye level in front of the treadmill. Indication of the rate of breathlessness was obtained verbally or by physical sign.

3.5.3 Data Analysis

Heart rate, treadmill protocols and lung function measures were recorded on data collection forms for the 3 visits (Appendix F). All post-medication; pre-exercise and post-exercise scores from each test session for each subject were expressed as a percentage of the pre-medication score obtained at that session.

EIA was determined achieved if maximum decrement on FEV_1 was greater than 10%. The significance of the differences between the means were tested over the three different treatments and seven post-exercise time periods by application of a treatment x treatment x subjects design analysis of variance (T x T x S ANOVA). Using this test, F ratios were computed for three factors. These being; treatment, time and the treatment/time interaction. When significant main effects were obtained ($p < 0.05$) for treatment only, the post hoc all possible simple contrasts function was implemented to locate the significant simple main effects between the three tests. A oneway ANOVA with repeated measures was then

applied to each of the 7 time periods to locate where significant F ratios existed between treatments. The post hoc; all possible simple contrasts method was used to isolate the simple main effects between the treatments for each time period that showed a significant F ratio ($p < 0.05$). When the treatment/time interaction showed a significant F ratio, regardless of the other two factors, the significant F values were investigated by examining the simple effect of treatment at each level of time using a related samples t-tests. When the time factor demonstrated a significant F ratio, the mean value at each time period was tested using related samples t-tests. This test ignored differences shown across treatments and concerned the mean value of all three tests at each time, it was therefore considered not central to the research questions and thus reported rarely within the results section.

Maximum decrement and bronchial lability statistical analysis was completed by a oneway repeated measures ANOVA. Where significant F ratios were obtained, thus indicating a significant difference between tests, a post hoc test of within subjects contrasts was applied to distinguish which tests differed to the $p < 0.05$. Raw data for all tests are presented in Appendix A.

3.6 Limitations

1. Subjects were unpaid volunteers whose level of motivation during tests could be expected to vary. Although subjects were continuously encouraged, motivation could not be controlled.
2. Variation in severity of airways disease and responsiveness to the exercise challenge.
3. It is uncertain how each subject's level of fitness will influence the results.
4. The equipment required to measure effort independent airways resistance was unavailable.

5. Availability of a climatic chamber was also a limiting factor as conditions in the laboratory are controlled for temperature only and not humidity. This may hinder asthmogenic effect of the exercise challenge.

5. Although subjects were instructed to abstain from medication prior to testing (see Appendix G), the pro-longed effects of some drugs on bronchoconstriction are unknown and may prevent some asthma symptoms.

3.7 Delimitations

1. Subjects were 18-40 years of age with a history of EIA.
2. All were prescribed Ventolin for their condition by their physician.
3. Sedentary subjects were excluded
4. **Exercise Induced Asthma was confirmed with subject's general practitioners.**

CHAPTER FOUR

4.0 Results

4.1 Reliability

Repeated measures of lung function tests used in this study proved reliable based on the high correlation coefficient and coefficients of variation for repeated measures (Table 4.1). The application of a paired samples t-test confirmed that there were no significant differences between the two test sessions (See Table 4.2). Raw data for the reliability study is presented in Appendix H. The FVC and FEV₁ variables proved most reliable (< 5% Coefficient of Variation), with the MEF₅₀ and PEFR showing the least reliable statistics.

Table 4.1 Correlation, Method error and the coefficient of variation for FVC, FEV₁, FEF₅₀, FEF₂₅₋₇₅ and PEFR values obtained from reliability study. (n=30)

| | Pearsons product moment Correlation | Coefficient of variation (V) | Method Error |
|----------------------|--|---------------------------------|--------------|
| FEV ₁ | .961 ^a | 4.14 | 0.165 |
| FVC | .957 ^a | 4.21 | 0.200 |
| FEF ₂₅₋₇₅ | .923 ^a | 7.49 | 0.312 |
| PEFR | .857 ^a | 7.51 | 0.690 |
| MEF ₅₀ | .887 ^a | 9.62 | 0.466 |

^a indicates significant correlation $p < 0.01$.

Table 4.2. Mean, Standard deviation and significant differences of test – retest pulmonary function scores using the Minato Autspirometer. (n=30)

| Variable | Test-1 mean (\pm SD) | Test-2 mean (\pm SD) | t-value | p value |
|---|----------------------------|----------------------------|---------|---------|
| FEV ₁ (L) | 3.98 (\pm 0.79) | 4.00 (\pm 0.84) | -0.602 | 0.552 |
| FVC (L) | 4.71 (\pm 0.87) | 4.74 (\pm 0.95) | -0.635 | 0.530 |
| FEF ₂₅₋₇₅ (L.min ⁻¹) | 4.15 (\pm 1.11) | 4.18 (\pm 1.13) | -0.510 | 0.614 |
| PEFR L.min ⁻¹) | 9.19 (\pm 1.86) | 9.16 (\pm 1.76) | 0.133 | 0.895 |
| MEF ₅₀ (L.min ⁻¹) | 4.81 (\pm 1.40) | 4.87 (\pm 1.36) | -0.526 | 0.603 |

4.2 Subjects

Although fifteen subjects were recruited, only thirteen subjects (10 female and 3 male) completed the study. After the three 8-minute exercise challenges, only 7 subjects displayed falls in FEV₁ consistent with the criteria for an EIA episode (ie > 10% decrease in post-exercise FEV₁) even though EIA had been confirmed with all subjects General Practitioners. Subsequent data analysis was limited to results obtained from within this group (Subject characteristics are shown in Table 4.3).

Table 4.3 Subject characteristics (n = 7)

| Subject Characteristics | mean | SD |
|-------------------------|--------|--------|
| Age (yr) | 24.50 | ± 7.14 |
| Height (cm) | 176.90 | ± 7.64 |
| Weight (kg) | 71.64 | ± 9.22 |
| Male/Female | 3/4 | |

To allow for variation in age, sex and physique when comparing the results of each ventilatory function test, all values for each subject were expressed as a percentage of the pre-medication, pre-exercise score where appropriate.

4.3 Pre-Treatment Baseline Pulmonary Function

When the scores obtained prior to treatment (pre-treatment scores) for each of the three sessions were analysed using a repeated measures ANOVA, the F ratio was not significant for between tests comparisons except for the PEF_R pulmonary variable where a simple post hoc contrast demonstrated a simple main effects significant F value between the mean MDI value and the mean placebo value (F = 8.123, p = 0.029). Table 4.4 shows the mean baseline pulmonary values for each of the five variables. Temperature and relative humidity did not vary significantly between testing sessions.

Table 4.4. Baseline pulmonary values pre-medication. (n = 7)

| Pulmonary function variable | <u>MDI</u> | <u>Spacer</u> | <u>Placebo</u> |
|--------------------------------|---------------------|--------------------|---------------------|
| | mean (\pm SD) | mean (\pm SD) | mean (\pm SD) |
| FVC (L) | 4.47 (\pm 0.95) | 4.36 (\pm 0.94) | 4.16 (\pm 0.76) |
| FEV ₁ (L) | 3.31 (\pm 0.85) | 3.06 (\pm 0.88) | 2.92 (\pm 0.71) |
| FEF ₂₅₋₇₅ (L.min-1) | 2.82 (\pm 1.33) | 2.48 (\pm 1.27) | 2.42 (\pm 1.18) |
| PEFR (L.min-1) | 7.73 (\pm 2.70)# | 6.15 (\pm 1.90) | 5.64 (\pm 1.53)# |
| MEF ₅₀ (L.min-1) | 3.27 (\pm 1.50) | 2.82 (\pm 1.54) | 2.73 (\pm 1.38) |

indicates significant differences between MDI and Placebo to the $p < 0.05$ level.

4.4 Pulmonary Function Variable Results

4.4.1 FEV₁

4.4.1.1 Pulmonary Changes post-exercise.

The mean FEV₁ changes for the 3 different treatment groups (Figure 4.1), demonstrated that only the spacer treatment had a positive effect on FEV₁ post-exercise scores. Table 4.5 shows the normalised mean post-exercise values for each pulmonary measure. The spacer achieved a mean change in post-exercise FEV₁ of 11.7%. (\pm 24.8) whereas the MDI and placebo scores achieved -1.7% (\pm 10.2) and -13.3% (\pm 16.5) respectively. It is apparent that, although the MDI treatment had little effect in increasing FEV₁ function post-exercise, it did prevent the EIA that was evident in the placebo scores. A treatment by treatment by subjects ANOVA demonstrated a significant F ratio between the test/time interaction ($F = 2.514$, $p = 0.008$), which was isolated between the mean spacer treatment score and the mean placebo treatment score at the 7th post-exercise minute only ($p = 0.045$). No significant differences between placebo and Ventolin via MDI or between Ventolin via spacer or MDI were found for any time period.

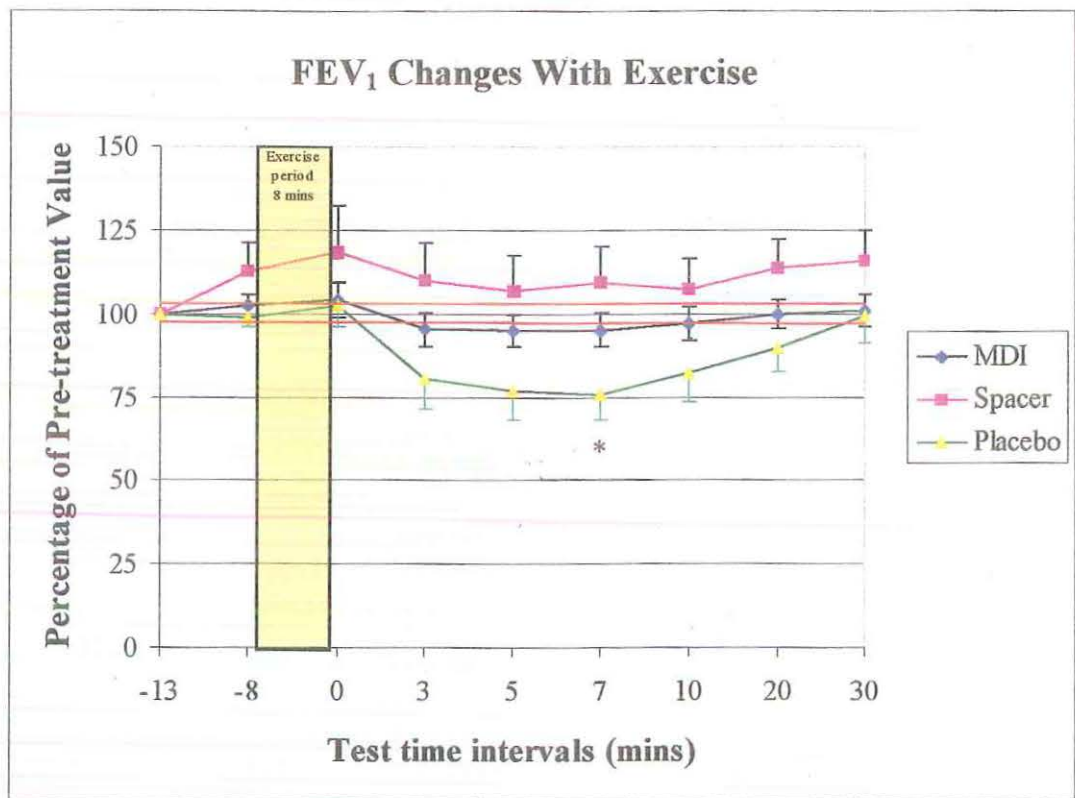


Figure 4.1. Mean and Standard Error for FEV₁ Changes Expressed as a Percentage of the Pre-treatment value. (n = 7).

* = indicates significant difference between Spacer and Placebo scores ($p < 0.05$)
 ~ Red line represents the % range in normal values expressed as a standard error as found for non-asthmatics during the reliability study.

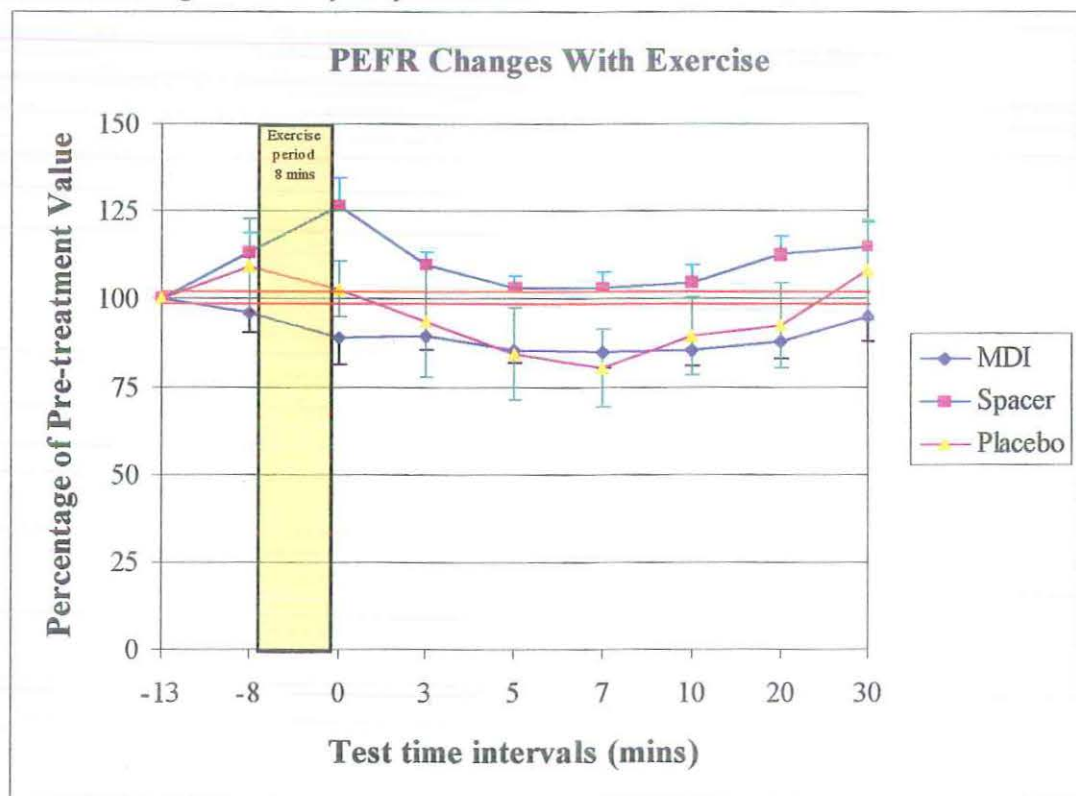


Figure 4.2. Mean and Standard Error for PEFR Changes Expressed as a Percentage of the Pre-treatment value. (n = 7).

~ Red line represents the % range in normal values expressed as a standard error as found for non-asthmatics during the reliability study.

Table 4.5. Percentage Change in Post-Exercise Lung Function Mean and Standard Deviation (n=7).

| Pulmonary function variable | <u>MDI</u> mean (\pm SD) | <u>Spacer</u> mean (\pm SD) | <u>Placebo</u> mean (\pm SD) |
|-----------------------------|--------------------------------|-----------------------------------|------------------------------------|
| FVC | 99.30 (\pm 5.75) | 105.80 (\pm 13.99) | 90.03 (\pm 12.54) |
| FEV ₁ | 98.26 (\pm 10.26) | 111.69 (\pm 24.80) | 86.66 (\pm 16.55) |
| FEF ₂₅₋₇₅ | 100.18 (\pm 27.19) | 124.47* (\pm 39.88) | 82.61* (\pm 20.31) |
| PEFR | 88.21 (\pm 9.78) | 110.81 (\pm 33.76) | 93.06 (\pm 28.21) |
| MEF ₅₀ | 101.19 (\pm 30.22) | 130.88* (\pm 44.48) | 83.79* (\pm 21.76) |

* indicates significance between the spacer and placebo scores to the $p < 0.05$ level.

4.4.1.2 Maximum Decrement and Bronchial Lability

Mean results for maximum decrement and bronchial lability are presented in Figures 4.6 and 4.7. Comparison of FEV₁ scores over the 3 treatments indicated that the greatest drop occurred after the placebo test (mean = 28.6% \pm 20.7). The MDI recorded a decrease of 12.2% (\pm 11.2) and the spacer displayed a mean maximum decrement of 9.6% (\pm 11.7). Note that no significant differences between tests were found. ($F = 2.876$, $p = 0.095$) Lability scores between the 3 treatments demonstrated that MDI resulted in less lability than the spacer, with the placebo treatment generating the greatest score (Figure 4.6), again no significant differences were obtained between the bronchial lability scores for FEV₁ post-exercise ($F = 3.641$, $p = 0.058$). Raw data for maximum decrement and bronchial lability are presented in Appendix A; Tables A2 and A3.

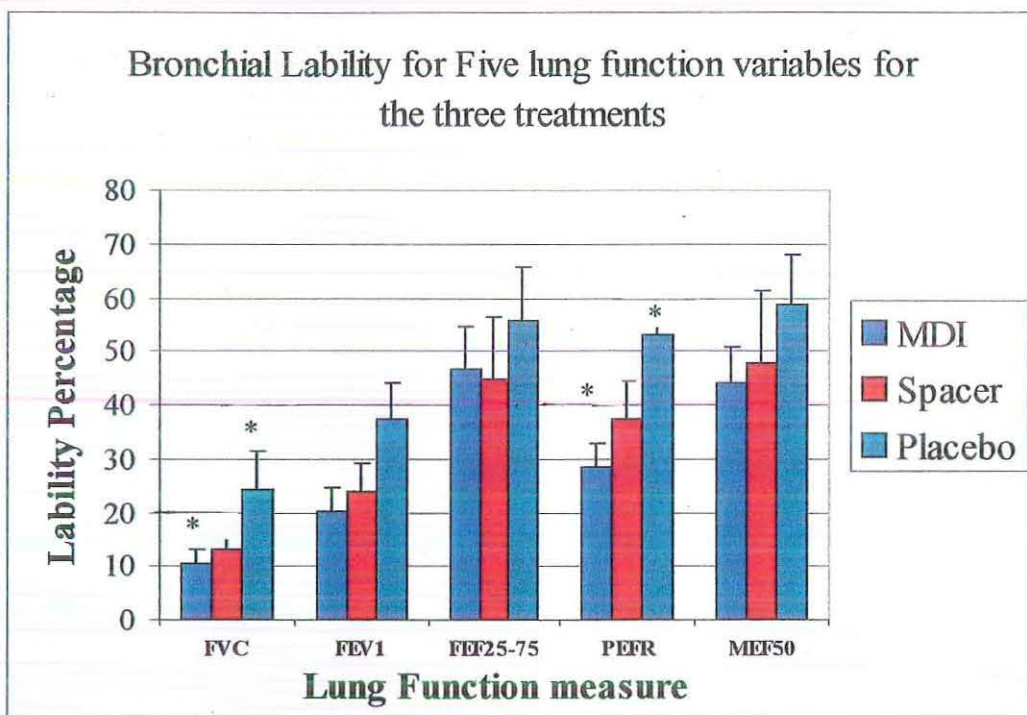


Figure 4.6 Mean and Standard Error for Bronchial Lability Scores obtained for the three treatments.

* = indicates significant difference between MDI and Placebo scores ($p < 0.05$)

4.4.2 PEFR

4.4.2.1 Pulmonary Changes post-exercise.

The mean PEFR changes after the 3 different treatments are shown in figure 4.2. The placebo and spacer treatment scores showed a tendency to increase immediately post-treatment, however Ventolin via MDI showed a slight decrease at this time and did not show any improvement until after the 20th minute. All three treatments showed a declining trend in PEFR immediately post-exercise with improvements only apparent after the 7th minute post-exercise. No significant F ratios were obtained between the tests, however, a significant increase in all PEFR scores occurred between the 10th and 20th minute ($p = 0 < 0.01$). Note that this significant difference refers to the difference recorded between the 10th and 20th minutes and not in comparison to the pre-treatment values. The Spacer treatment maintained PEFR function above the pre-treatment value throughout the testing procedures with a mean post-exercise increase of +10.8% (\pm

33.7). MDI scores had a tendency to remain below the pre-treatment value through out the test with a mean post-exercise fall of 11.8% (± 9.8) being recorded. Placebo scores displayed a smaller fall than the MDI scores with a mean post-exercise value of -6.9% (± 28.2). No significant F ratios were obtained for any of these differences.

4.4.2.2 Maximum Decrement and Bronchial Lability

A oneway ANOVA with repeated measures indicated that bronchial lability scores between the three treatments showed a significant F value of 4.151 ($p = 0.043$) for PEFR. The placebo test recorded the greatest lability score of 53.1% (± 18.7) with the MDI recording the lowest lability of 28.2% (± 12.6). Significance was achieved between these two scores only ($p = 0.037$). Spacer bronchial lability scores were not significantly different from the MDI results. No significant differences in the maximum decrement scores occurred between the 3 treatments. (see Figure 4.7).

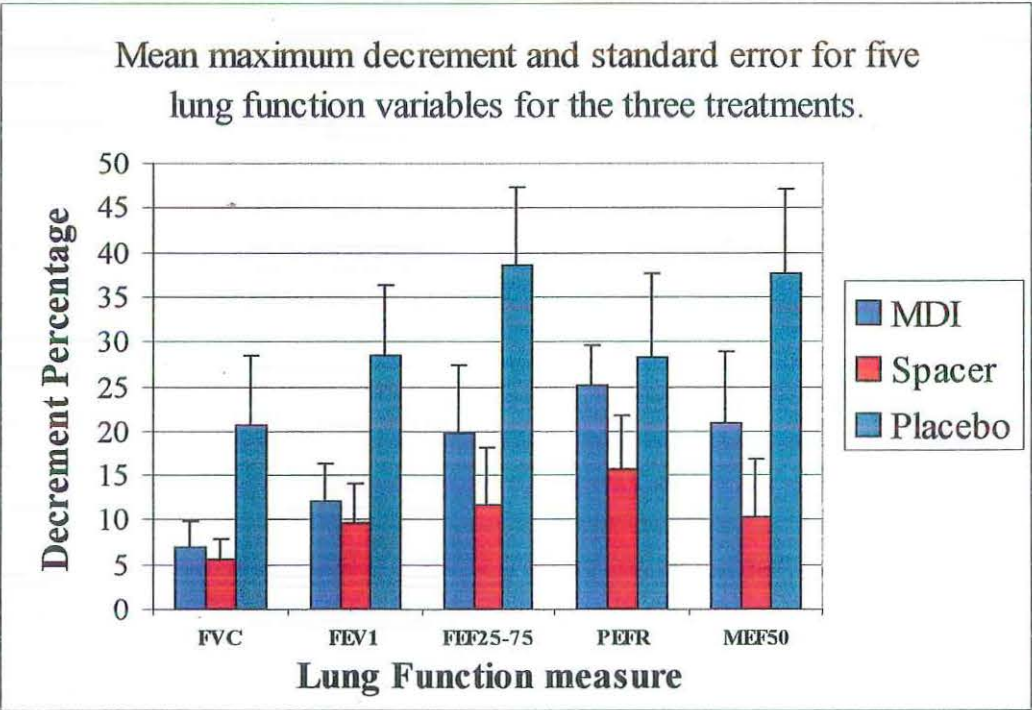


Figure 4.7 Mean and Standard Error for Maximum Decrement Scores obtained for the three treatments.

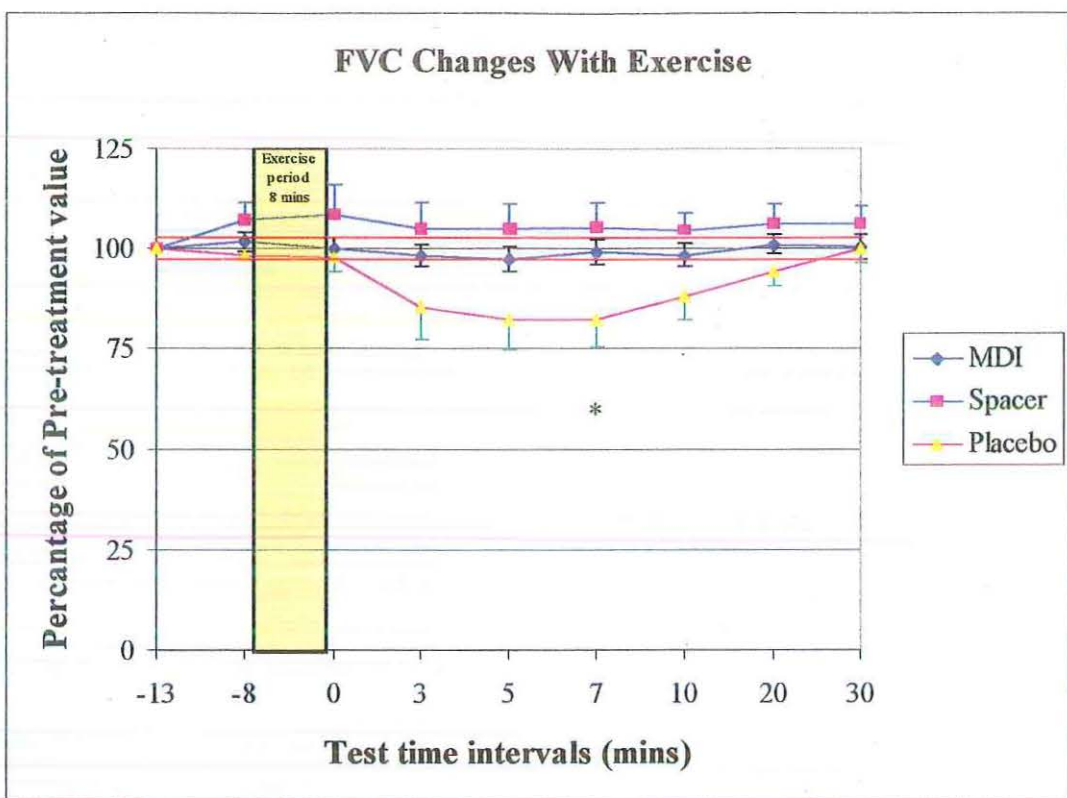


Figure 4.3. Mean and Standard Error for FVC Changes Expressed as a Percentage of the Pre-treatment value. (n = 7).

* = indicates significant difference between Spacer and Placebo scores ($p < 0.05$)

~ Red line represents the % range in normal values expressed as a standard error as found for non-asthmatics during the reliability study.

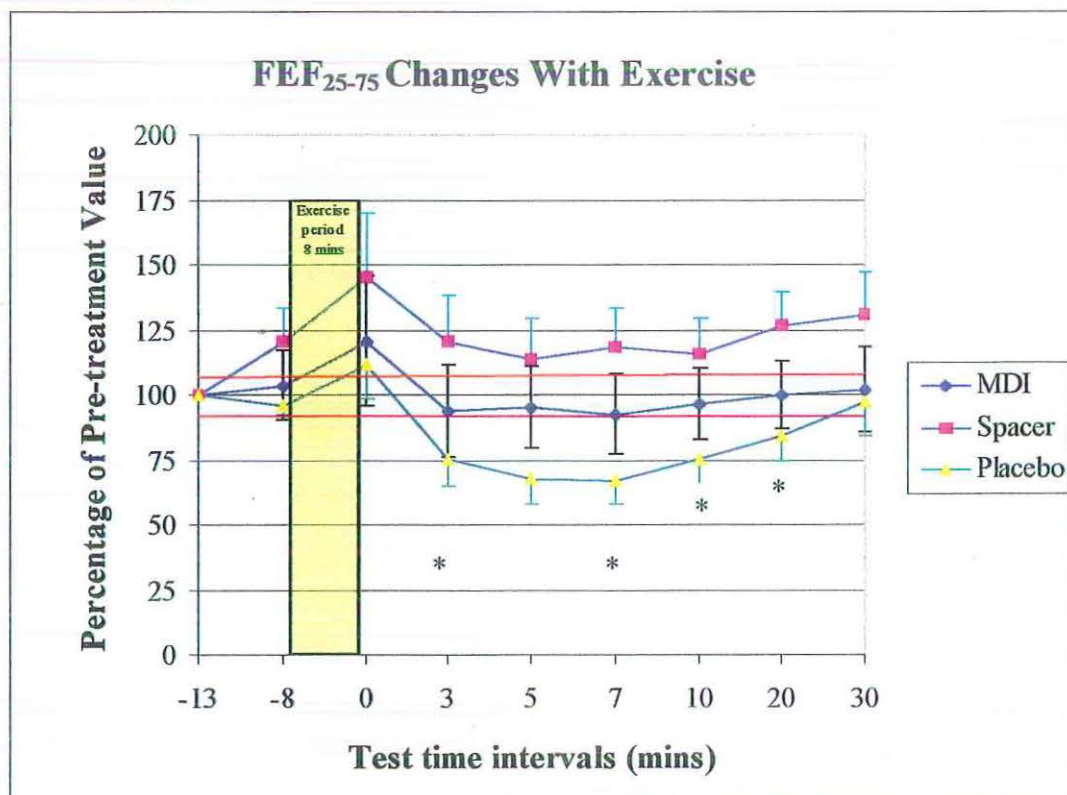


Figure 4.4. Mean and Standard Error for FEF₂₅₋₇₅ Changes Expressed as a Percentage of the Pre-treatment value. (n = 7).

* = indicates significant difference between Spacer and Placebo scores ($p < 0.05$)

~ Red line represents the % range in normal values expressed as a standard error as found for non-asthmatics during the reliability study

4.4.3 FVC

4.4.3.1 Pulmonary Changes post-exercise.

The mean FVC changes after the 3 different treatments shown in Figure 4.3, show similar trends to that reported in section 4.4.1.1. The spacer treatment was the only test that maintained mean post-exercise lung function scores above the pre-treatment value ($+105.8\% \pm 13.9$). Although the MDI and the placebo had negative mean post-exercise scores for FVC (see Table 4.5), the MDI prevented the FVC from falling below the pre-treatment value by more than $-2.57\% (\pm 7.99)$. A significant F ratio was obtained for the test/time interaction and the analysis of simple main effects showed that the only significant difference occurred at the 7th post-exercise test time between the placebo treatment and spacer treatment scores. ($p = 0.048$). No other significant differences were found between tests.

4.4.3.2 Maximum Decrement and Bronchial Lability.

A significant difference within the sample data was found for bronchial lability only ($F = 4.145$, $p = 0.043$), with the placebo lability score $24.4\% (\pm 17.9)$ being significantly greater than the MDI score $10.6\% (\pm 6.1)$ ($p < 0.05$). Maximum decrement scores were $20.7\% (\pm 19.9)$ for the placebo treatment and only $6.9\% (\pm 7.6)$ and $5.6\% (\pm 6.7)$ for the MDI and spacer tests respectively (difference N.S).

4.4.4 FEF₂₅₋₇₅

4.4.4.1 Pulmonary Changes post-exercise.

The mean FEF₂₅₋₇₅ changes after the 3 different treatments (Figure 4.4), show substantially larger differences in the three treatment scores. This is to be expected since these last two pulmonary variables are far more sensitive than the initial variables.

All three treatments show positive trend scores at post-treatment and immediately post-exercise with regard to their pre-treatment values. The spacer treatment recorded the fastest rate at this point with the score reaching +45.3% (± 65.8) above the pre-treatment value. Declines in all three treatments between 0 and 3 minutes occurred, which leveled off until the 10th minute post-exercise. Note that only the spacers mean scores were above the 100% value between these times (Figure 4.4). The MDI recorded a mean post-exercise FEF₂₅₋₇₅ score of 100.2% (± 27.2) implying that it prevented bronchoconstriction even though there was no significant F ratio between it and the placebo scores. (See Table 4.5 for the mean post-exercise pulmonary function scores). Significant F ratios were obtained between tests ($F = 3.992$, $p = 0.047$). Analysis of the simple main effects demonstrated significant differences between the mean placebo scores and mean spacer scores only at the 3rd, 7th, 10th and 20th time intervals ($p < 0.05$).

4.4.4.2 Maximum Decrement and Bronchial Lability

Decrement scores for FEF₂₅₋₇₅ shows that the placebo had the greatest maximum mean decrement between all three tests; 38.48% (± 23.22), with the MDI and the spacer recording 19.6% (± 20.2) and 11.8% (± 16.8) respectively. No significant F ratios were found for any of the maximum decrements or the lability scores recorded for FEF₂₅₋₇₅ ($F = 3.387$, $p = 0.068$ & $F = 0.546$, $p = 0.593$ respectively). The highest lability score was obtained by the placebo test, followed the MDI and spacer treatments results (See Figure 4.6).

4.4.5 MEF₅₀

4.4.5.1 Pulmonary Changes post-exercise.

The mean MEF₅₀ changes after the 3 different treatments are shown in Figure 4.5. The trend demonstrated is very similar to that recorded for FEF₂₅₋₇₅ due to the fact that MEF₅₀ is a measurement taken within the middle of the for FEF₂₅₋₇₅ score. As with the results in section 4.4.4.1, all three treatments had an upward trend until immediately post-exercise whereafter they all declined and leveled off at the 3rd minute post-exercise. The spacer treatment for MEF₅₀ peaked at the 0 minute post-exercise interval with an increase of 52.1% (± 75.3) compared to the pre-treatment value. From the 3rd to 10th minute, this value stayed within a range of +20% to +26%. The MDI had a mean post-exercise value of 101.2% (± 30.2), however, as found within section 4.4.4.1, the mean score was below the 100% data line from the 3rd to 10th post-exercise time intervals. The placebo treatment recorded a mean post-exercise fall of -16.2% (± 21.8) and was found to be significantly different from the spacer treatment scores at the 3rd, 7th, 10th and 20th time intervals post-exercise ($p < 0.05$). No significant differences between placebo and Ventolin via MDI or between Ventolin via spacer or MDI were found for any time period.

4.4.5.2 Maximum Decrement and Bronchial Lability

Maximum decrement and bronchial lability scores for MEF₅₀ over the 3 treatments demonstrated no significant differences between tests. ($F = 3.098$, $p = 0.082$ & $F = 0.846$, $p = 0.453$ respectively). The trends shown within the other pulmonary variables were repeated by the MEF₅₀ scores with the placebo showing the greatest bronchial lability and maximum mean decrement. The MDI had a greater

decrement over the spacer treatment but showed a lower mean lability. These results are presented in Figures 4.6 and 4.7.

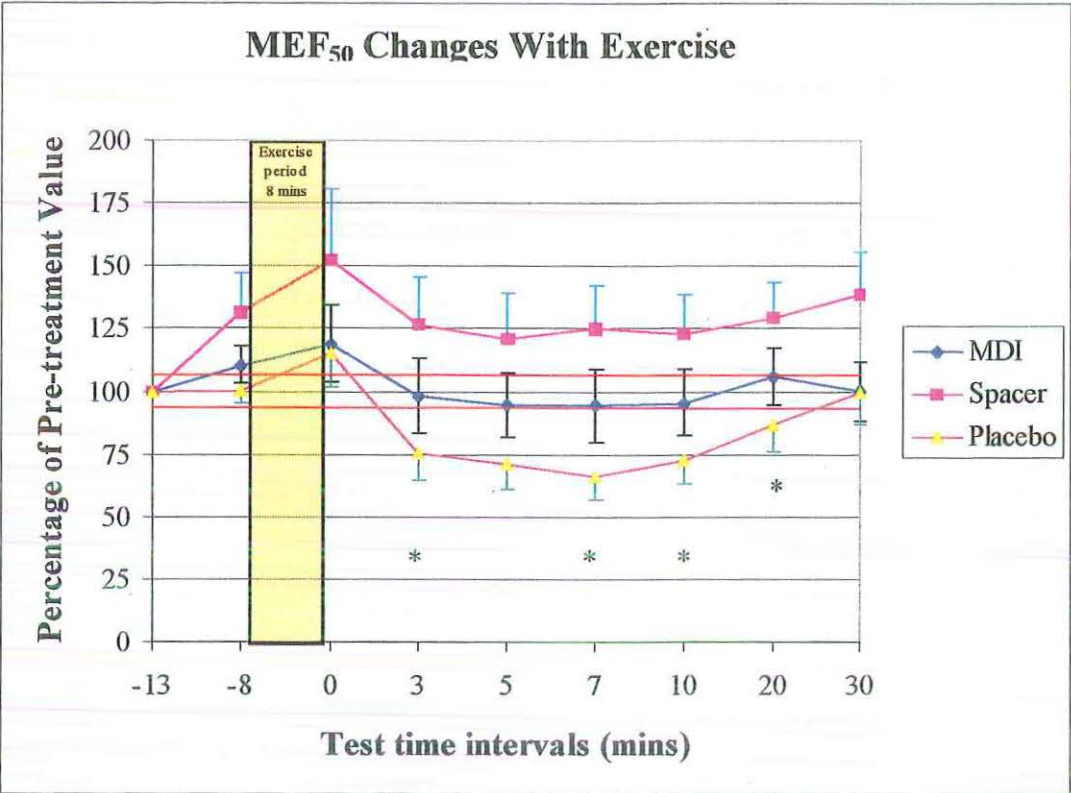


Figure 4.5. Mean and Standard Error for MEF₅₀ Changes Expressed as a Percentage of the Pre-treatment value. (n = 7).

* = indicates significant difference between Spacer and Placebo scores (p < 0.05)
~ Red line represents the % range in normal values expressed as a standard error as found for non-asthmatics during the reliability study

4.5 Heart Rate and Rate of Perceived Breathlessness (RPB).

The recovery and exercise heart rate and RPB scores are shown in table 4.6.

The mean heart rates recorded during exercise and recovery were within 3bpm for each test. Mean exercise and recovery RPB scores also varied only slightly, with a range of 0.5 and 0.4 for exercise and recovery respectively. Using a repeated measures ANOVA, there were no significant differences between the three treatment values for exercise and post-exercise recovery heart rates and RBP scores.

Table 4.6 Mean HR and RPB results for the 3 test periods

| | <u>MDI</u> | | <u>Spacer</u> | | <u>Placebo</u> | |
|-----------------|-----------------------|----------------------|-----------------------|----------------------|-----------------------|----------------------|
| | mean (\pm SD) | | mean (\pm SD) | | mean (\pm SD) | |
| | Heart rate | RPB | Heart rate | RPB | Heart rate | RPB |
| Exercise | 163 (\pm 13.07) | 2 (\pm 1.39) | 160 (\pm 13.82) | 1.8 (\pm 0.99) | 163 (\pm 13.58) | 2.3 (\pm 1.10) |
| Recovery | 104 (\pm 8.24) | 2.4 (\pm 0.62) | 107 (\pm 9.88) | 2.3 (\pm 0.45) | 105 (\pm 10.30) | 2.7 (\pm 0.92) |

CHAPTER FIVE

5.0 Discussion

The purpose of this study was to compare the efficacy of a spacer device to that of the metered dose inhaler in the delivery of the aerosol medication, salbutamol for the prevention of exercise-induced asthma. Although the spacer assisted delivery demonstrated no significant benefit over the MDI method, the data obtained raises questions over the circumstances under which testing occurred. Only 7 of the 13 subjects displayed falls in FEV₁ sufficient to be classified as exercise-induced asthma, even after proven steps were taken to stimulate such responses. Subjects stated that during exercise, they experienced an asthma attack on a regular basis. Furthermore, all medical practitioners confirmed each of the subjects' asthmatic condition. All subjects were non-smokers and healthy; so why didn't 6 of the 13 subjects show a fall in FEV₁ over the three tests, large enough to be classified as EIA?

Chapter 3 explained the steps taken to provoke an EIA episode. Nasal breathing was employed to enhance RWL and RHL and subjects were instructed to refrain from medication according to the guidelines in Appendix G. Laboratory ambient temperature remained constant however a relatively large variation in the relative humidity was recorded. Henriksen, Dahl and Lundqvist (1981) demonstrated that humid air can decrease the bronchospastic response in asthmatic subjects, with the range of relative humidity recorded during this study (47% to 63%), causing up to 30% fewer cases of EIA than in relative humidities of 15% to 20%. Secondly, as EIA is defined as a fall in FEV₁ of more than 10%, attainment of EIA may have been hindered by the relatively large bronchial lability scores implying that some bronchoconstriction was evident in subjects prior to testing. This suggestion is supported by the normative pulmonary

function values generated by the Minato Autspirometer suggesting that on each visit, subjects obtained mean pre-treatment FEV₁ scores that were only 85% their normal expected value.

One may question the reliability of such norms, however the Minato Autspirometer processes the norm calculation on previously calculated norms based on age, sex, height and weight collected from 25 year old Caucasians. All subjects in this study were Caucasian with a mean age of 24.07.

An asthmatic patient suffering from no bronchoconstriction will often achieve near normal lung function results. If it was the case that bronchoconstriction was evident in a number of subjects prior to testing, then an explanation for this must be addressed. Asthma can be caused by allergies, exercise or certain climatic scenarios. The testing was undertaken in the middle of spring thus suggesting environmental conditions may have caused the pre-exercise constriction. According to Kaliner, Eggleston and Mathews (1987), the most important technique for preventing an asthmatic episode is avoidance of airborne allergens. Avoidance of such allergens was difficult at the laboratory used for testing as it's location within a pine plantation may have exposed subjects to abnormally high airborne pollen which is a known asthmogenic allergen. (Morton, in Bloomfield, Fricker & Fitch, 1992, p.537). The pollen count for Perth (presented in Appendix J) shows that the testing period for this study coincided with the highest pollen counts taken for spring. Also note that the pine pollen count represented a large percentage of the total pollen count thus supporting the suggestion that the location of the laboratory was perhaps contributory to the significant bronchoconstriction evident in some subjects. This problem could easily be avoided if testing occurred in the late summer months therefore ensuring lower pollen counts and the added security of warm, less humid conditions.

Due to the nature of this study, time and equipment constraints prevented the use of controlled air conditions for testing. Hahn (1984), Papalia (1991) and Rossi (1995) all found that nearly 100% of subjects achieved post-exercise EIA with the use of a climatic chamber which maintained a low relative humidity and regular temperature. To ascertain whether or not the data obtained in this study presents a true indication of spacer efficacy, the research should be replicated with the use of a climatic chamber to ensure a higher level of consistency and asthmogenic conditions.

It is also a possibility that the occurrence of EIA may have been reduced if subjects demonstrated a relaxed approach to the instructions concerning short and long-term preventative medications. This fact is unproven, however future study should encompass the importance of following the medication guidelines to optimise EIA development in subjects.

Due to time constraints, it was not possible to pre-determine, using a 'familiarisation' session, whether or not the subjects had a tendency to demonstrate EIA under the provided laboratory conditions. Again, this extra visit would have exempted several subjects from the study who were not prone to EIA under the given circumstances. Eggleston (1979) suggests that such familiarisation sessions can improve the reproducibility of the airways response to exercise. Through this kind of subject selection process, a sample that was likely to experience EIA would have been ensured.

Variation between tests could also have negatively influenced the achievement of EIA. According to Silverman and Anderson (1972), tests for EIA that were performed on separate days within one week generated average coefficients of variation in pulmonary function of 21%. They state that this was due to changes in the sensitivity of the asthmatic to exercise rather than experimental error. Fortunately, the airways response is more consistent, however, the more chronic the subjects asthma, the greater their

sensitivity to exercise. This fact coupled with the finding in this study that significant variation occurred within the subject's scores at the baseline, pre-treatment level, presents a hindrance to the reproducibility of similar testing conditions between tests. Sly (1970) and Eggleston and Guerrant (1976) argue that such changes in an asthmatics resting airways calibre influences EIA testing results minimally thus ruling this concern unwarranted. By implementing an incremental exercise challenge, Godfrey (1974, p.34) believes that more variable results are obtained than in tests that maintain a single work rate throughout the entire tests. This study employed an incremental protocol which, even though it was replicated across treatments, may have caused some variation in results.

Data obtained over the three treatments illustrate that the spacer device resulted in significantly less airway obstruction following exercise compared to the post-exercise results obtained following placebo treatment. The MDI presented no significant differences when compared to both the spacer and placebo scores. FEV₁ will be discussed in depth as it is the benchmark pulmonary variable for the measurement and diagnosis of EIA.

5.1 FEV₁

The occurrence of EIA between treatments was limited due to only 7 subjects demonstrating adequate falls in FEV₁. The spacer treatment prevented 4 subjects from suffering EIA, with the placebo and MDI preventing 3 subjects post-exercise. The severity of EIA may have been greater than recorded if lability scores weren't as elevated as they were. Jones, Buston and Wharton (1962) recorded similar lability scores as this study, yet these were not accounted for and their conclusions made

concerning the effect exercise has on FEV₁ have been repeatedly disputed (Morton, Lawrence, Fitch & Hahn, 1983). From the results obtained in this study, the efficacy of the spacer to improve post-exercise FEV₁ values obtained under EIA conditions proved not significantly superior to the MDI treatment when administering salbutamol. The recorded lack of contrariety between the two devices in question may be due to the capable and coordinated approach the majority of subjects possessed with regard to MDI use. It is apparent that the subjects within this sample were experienced MDI users. This was confirmed by all subjects carrying their MDI's on their person at all times. With a mean age of 24yrs, the results obtained from this study are comparable to similar studies by Gomm, Keaney, Winsey and Stretton (1980) who, using a cognate sample, found no statistical significance between the MDI and the aerochamber when measuring post-treatment FEV₁, FVC and PEFR. Adult asthmatics were also used in studies performed by Newman et al (1984); Comis, Valletta, Sette, Andreoli and Boner (1993) and Dolovich, Eng, Ruffin, Corr and Newhouse (1983). These studies all concluded that the application of a spacer device compared to an MDI provides no significant improvement in FEV₁ or drug deposition within the airways.

Based on the mean change in FEV₁, the spacer prevented EIA to a greater extent than what the MDI achieved. Although the difference between the treatment devices did not prove statistically significant, in the case of elite athletes competing in highly competitive sports, the smallest of advantages can improve placing's or even mean the difference between a win and a loss. Findings by Newman, Moren, Pavia, Little and Clarke (1981), and Newman, Clarke, Talae and Clarke (1989), argue in favour of the spacer over the MDI when being used by mature asthmatics due to a significantly greater amount of aerosol medication reaching the lungs with significantly lower stomach and oropharyngeal deposition. The opposite has also been proven by

Bloomfield and Crompton (1979), who demonstrated with accustomed asthmatics that the MDI has the capability to deliver a greater amount of drug when correct actuation is achieved. Without the ability to radiolabel the drug, it is impossible to determine which of these two theories can be applied to the sample in the current study. However, from the mean values obtained, it could be concluded that the spacer did deliver a greater amount of drug, without a significant difference in lung function variables between it and the MDI scores being achieved. Given the fact that all subjects in this who encountered EIA, were long-term asthmatics with good MDI actuation technique, may explain why no significant differences between the 2 devices was recorded. In this context, it would be interesting to compare these findings with a group of asthmatic subjects having poor inhalation technique. It is conceivable that for young asthmatics, the spacer is the best delivery method for aerosol medication. This is maintained by Rivlin et al (1984), who showed that the spacer device can increase FEV₁ from baseline scores by up to 36% in asthmatic children, almost double that of the MDI. Further research into this hand lung 'discoordination' could provide asthmatics with the knowledge of when to adopt the MDI without the spacer device. Even though this study presented evidence that the spacer provides no real improvement over the MDI in mature asthmatics, many elite sporting teams still utilise the spacer to administer quick medication to breathless athletes who may be unable to effectively actuate an MDI without the aid of a spacer. This also presents an opportunity for further research into the effect that physical activity induced breathlessness has on the efficacy of the delivery of an aerosol medication via the MDI to proven coordinated MDI users.

5.2 PEFR

PEFR is a measure of the velocity or rate at which air can be forcefully exhaled from the lungs. It is particularly useful in measuring EIA due to the difficulty in exhaling demonstrated during bronchoconstriction. This difficulty is directly linked to the degree of bronchoconstriction, therefore the slower the PEFR, the greater the bronchospastic response to exercise.

The trends demonstrated in this study are consistent with prior findings involving EIA in that post-exercise PEFR decrement is comparable to that achieved for FEV₁ scores. Unfortunately, the baseline values for PEFR showed a significant difference between treatments. This supports the suggestion that several subjects had some form of bronchoconstriction prior to testing. This variation could also be due to the high coefficient of variation obtained for PEFR in the reliability study (Table 4.2). Silverman and Anderson (1972) and Eggleston and Guerrant (1976) found that when asthmatics perform treadmill based EIA studies on separate days within short periods, the average coefficient of variation for PEFR decrement can be at least 20%. From this finding, they concluded that, because one third of all trials produce a maximum fall in PEFR of either more than 1.2 times or less than 0.8 times the overall mean value, the airways response of asthmatic subjects to exercise is only moderately reproducible. PEFR is highly dependent on the subject's willingness to perform a 'maximal effort' exhalation consistently and correctly, which, due to psychological factors, may have caused some variation. This problem is not restricted to PEFR and can be applied to most other lung function variables.

In answering the 2nd research question, PEFR did not differ significantly between the three treatments thus suggesting that there is little difference between the 2 devices in preventing EIA symptoms as recorded by PEFR decrement. Again, the spacer was the

only treatment that maintained post-exercise lung function above the pre-treatment value with the MDI falling lower than the placebo value for 5 of the 7 post-exercise time intervals. No firm conclusions can be made because of the lack of statistical support available from a small sample, however, the spacer would be the best option under situations where any slight improvement in lung function would be desirable, ie elite athletes.

5.3 FVC

The FVC is a measure of the voluntary lung capacity that an individual is able to exhale. In asthmatic subjects, this measure can fall by 20% in severe cases, however the main measure that concerns EIA is the rate at which the air can be exhaled. FVC only varies when swelling within the pulmonary system reduces the space within the lungs, thus reducing the capacity to breath or the difficulty to exhale increases the lung residual volume therefore reducing the amount of air moving in and out of the lungs (Rasmussen, Elkjaer & Juhl, 1988). Airway swelling and oedema following exercise only accounts for a small portion of the possible airway space therefore having only a slight influence on the final FVC figure. Due to the increase in residual volume caused by the swelling, many subjects shorten the breath cycle to puffs, which can lead to a smaller FVC reading. Gimeno, Berg, Sluiter and Tammeling (1972) also discovered that asthmatics who show declines in FVC may exasperate the condition by performing spirometry tests. Gimeno et al (1972) argue that with lung oedemas, the FVC manoeuvre can irritate the swelling thus causing premature closure of the lower airways during the FVC manoeuvre leading to an increase in the residual volume. This can produce subsequent falls in all of the lung function variables. The severity of FVC was

minimal in this study and generated similar scores for the spacer and MDI. Even though the placebo fell close to 15% post-exercise, the only significant F value was obtained at the 7th minute between it and the spacer treatment. As there was no significant differences noted between the MDI and spacer scores, it must be concluded that there was no added benefit in using the spacer over the MDI for the prevention of FVC decrement within the context of EIA.

The relatively blunted response FVC had to exercise in this study, particularly following the spacer treatment can be attributed to an increase in pulmonary blood flow, thus increasing intra-thoracic blood volume and pressure that corresponds with a proportional decrease in the available gas volume. (Fox & Matthews, 1981, p.244). Buono, Wilmore and Roby (1983) state that FVC is relatively insensitive to increases in intra-thoracic blood volume thus maintaining a relatively undisturbed residual volume in the lung. The scenarios presented by Rasmussen et al (1988) show residual volume only increasing in severe asthmatic episodes, of which none were recorded in this study.

5.4 MEF₅₀ and FEF₂₅₋₇₅.

MEF₅₀ and FEF₂₅₋₇₅ represent the rate of airflow during a FVC manoeuvre at specific times. MEF₅₀ represents the rate after half the FVC manoeuvre is completed and FEF₂₅₋₇₅ represents the rate recorded during the middle half of the FVC manoeuvre. These measures of pulmonary function are therefore good indicators of smaller airway functioning. Due to the relatively large degree of bronchodilation recorded during exercise for these variables, proportionately well above that recorded for any other pulmonary variable, it can be concluded that the drug did have an effect on the smaller airways above that what normal exercise causes. According to McArdle, Katch and

Katch (1996, p.358), adrenalin release into the bloodstream causes some bronchodilation within the airways post-exercise. A study by Burr, Eldridge and Borysiewicz (1974) and Godfrey (1975) demonstrated that PEF_R and FEV₁ scores can increase up to 25% post-exercise due to these hormonal releases in non-asthmatic individuals. The subjects in this study demonstrated an increase in post-exercise PEF_R and FEV₁ with the spacer treatment only, however the mean post-exercise increase was only ~10%. This suggests bronchodilatory inhibition occurred due to EIA for all treatments. Although little information exists on MEF₅₀ and FEF₂₅₋₇₅ with regard to hormonal induced increases, the results demonstrate that a greater amount of drug reached the smaller airways during the spacer treatments due to the lower amount of mean decrement recorded during these tests. Again, the lack of a significant difference between the MDI and spacer prevents any formal conclusions concerning this. Support for Crompton and Bloomfields' theory concerning the benefits of MDI use over the spacer device was given credence by Dolovich et al (1983). The latter groups research found that after a five-fold reduction in aerosol medication delivery to the lungs, which can frequently occur with MDI use, similar lung function results are achievable (as recorded by MEF₅₀ and FEF₂₅₋₇₅), if the medication reaches the lower respiratory tract. This may have been the case in this study as both MEF₅₀ and FEF₂₅₋₇₅ scores were proportionately higher than the other lung function variables, thus bronchoconstriction may have been prevented within the smaller airways for both the MDI and spacer treatments. The spacer method of aerosol drug delivery is very successful at achieving this level of delivery and therefore maintaining post-exercise MEF₅₀ and FEF₂₅₋₇₅ scores, though no more so if MDI actuation coordination is well developed in asthmatic subjects (Collier, Dobb & Williams, 1980). There were no significant differences demonstrated between MDI and spacer with regard to MEF₅₀ and FEF₂₅₋₇₅, therefore, in

answering the 4th research question, the spacer exhibited no benefit over the MDI for the purpose of preventing post-exercise decrement in MEF_{50} and FEF_{25-75} under EIA conditions.

5.5 RPB and Heart rate

Heart rates were recorded in order to determine whether there was a difference in the cardiovascular stresses produced by the three different treatments, and to monitor the exercise intensity that was consequential to the degree of EIA achieved. Salbutamol is a specific beta-2-agonist with slight beta-1-adrenoreceptor activity (Sly, Puapan, Ghazanshahi and Midha 1975). Past studies have found that administration by inhalation minimises the quantity of salbutamol absorbed into the bloodstream through the alimentary canal therefore preventing beta-1-adrenoreceptor stimulation (Choo-Kang, Simpson & Grant. 1969). As seen with the pulmonary function variables, no treatment caused significant differences in the post-exercise recovery periods for HR. This trend supports findings by Bedi, Gong and Horvath (1988) and McKenzie, Rhodes, Stirling, Wiley, Dunwoody, Filsinger, Jang and Stevens (1983), who found low blood salbutamol concentrations in asthmatics who showed good MDI actuation coordination, therefore preventing drug induced HR fluctuations. Nebulisers have a similar aerosol drug delivery pattern to the spacer and have been proven to increase the HR in asthmatics above that which the MDI can instigate (Newhouse & Dolovich 1987). This finding was based on earlier research that showed spacers and nebulisers contribute greater amounts of drug to the stomach than the MDI counterpart in subjects with excellent MDI coordination. As there were no differences in HR's between treatment groups in this study it suggests that little or no drug was swallowed during spacer actuation.

The rate of perceived breathlessness recorded in this research found the post-exercise values were higher in the recovery for MDI treatment than the spacer but showed no significant differences between the two. Stark and Gambles (1981) used the RPB within a similar study and concluded that for non-asthmatics, exercise breathlessness was not altered by pre-exercise administration of salbutamol as did Freeman, Packe and Cayton (1989). Schmidt, Diamant, Bundgaard and Masden (1988), reported no change in sub-maximal RPB when asthmatics exercised after the inhalation of aerosol medication, however few studies consider the RPB post-exercise/recovery period. RPB recorded at these times can give a better understanding of the post-exercise EIA stresses that are encountered by subjects that are often misunderstood by non-asthmatic individuals.

CHAPTER SIX

6.0 Summary and Conclusions.

Research into spacer efficacy has demonstrated that for uncoordinated asthmatics, usually younger asthmatics, the spacer provides a significantly greater amount of aerosol drug to the lungs. This is achieved by the spacer's ability to reduce the aerosol particle speed prior to inhalation thus preventing oropharyngeal deposition which leads to swallowed medication (Newman et al, 1981). Support for the spacer is extensive with many researchers arguing that any level of increase in drug delivery is of paramount importance to overcome the effects of an asthmatic episode (Tobin et al, 1982; Cushley, Lewis & Tatterfield, 1983).

More recently, the efficacy of the spacer has been questioned with Konig (1985) referring to them as gimmicks and Barry and O'Callaghan (1994) demonstrating the poor delivery patterns that a spacer can also produce. Wildahaber et al (1996) debates that electrostatic charge and poor valve quality on the spacer can lead to a reduction in drug delivery. Such conflicting views have lead to the opinion that the MDI is quite effective in delivering aerosol medication for coordinated asthmatics, however the spacer should be adopted for those asthmatics who display inhalation and actuation coordination difficulty. The question put before this researcher was centred on how applicable this recommendation is to EIA.

On 3 separate occasions, 13 asthmatics who acted as subjects, completed a typical asthmogenic exercise challenge for the purpose of producing EIA that was followed by 7 post-exercise pulmonary function tests measuring FEV₁, PEF_R, FVC, MEF₅₀ and FEF₂₅₋₇₅. The different drug delivery effects offered by the use of a spacer and MDI were analysed by comparing the post-exercise pulmonary values with those obtained pre-treatment and pre-exercise. Using a single-blind, random, double cross-over, placebo controlled study design for the administration of Ventolin over three tests, it was concluded that there was no significant benefit in using the spacer over the MDI for the prevention of EIA as measured by the recorded pulmonary function variables. Note that the subjects were all excellent MDI users thus suggesting that this conclusion can only be applied to asthmatics who demonstrate similar abilities in MDI actuation as demonstrated by this sample.

6.1 Recommendations for further study

In this study, several scenarios prevented 6 subjects from producing sufficient falls in FEV₁. High pollen counts and varying relative humidity may have reduced the

ability of subjects to generate asthma due to a significantly high bronchial constriction evident in some subjects prior to testing and the lowered asthmogenic nature of the tests caused by the humidity level. Future research should replicate this study in controlled environmental conditions to ensure the asthmogenic nature of the research. If a climatic chamber is unavailable, as was the case in this research, summer testing should be adopted to take advantage of the lower humidities, lower pollen counts and higher temperatures. A double blind study could be applied to reduce the chances of tester interference and could be achieved by having treatments prepared by an independent technician prior to subject and tester arrival.

Future research could analyse the poor actuation techniques employed by breathless athletes during competitive scenarios such as football and other sports where 'on field' maintenance is permitted, and study the efficacy of the spacer and MDI under these conditions. Other research into the MDI design, such as employing a small lamina flow grid could measure the reduction in particle speed (if any) and reduce the need for spacer devices. Medical practitioners often promote the use of several devices in the pursuit of maximal asthma prevention. Newhouse (1997, p. 585) argues that the 'juggling' of two or even possibly three accessory devices would be unacceptable due to the greater problem of confusion and therefore poor compliance such a move could generate. Researchers must accept that the MDI is a small and highly portable method of administering aerosol medication and even though the spacer presents some benefits in certain cases, the MDI will always be the favoured choice for asthmatics. Therefore rendering itself to closer study and scrutiny for the benefit of the asthmatic population.

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APPENDIX A

Raw Data

- | | |
|-----------|--|
| Table A1. | Normalised Raw Data Collected for 5 Lung functions over three treatments |
| Table A2. | Mean and Standard Deviations for Bronchial Lability results over 3 test periods. |
| Table A3. | Mean and Standard Deviations for Decrement results over 3 test periods. |

RAW NORMALISED DATA FOR 5 LUNG FUNCTIONS.

NB: Constrict and Dilate categories are based on FEV1 values.

Table A1. Normalised Raw Data Collected for 5 Lung functions over three treatments

| | | MDI TREATMENT | | | | | | | | |
|----------------------|-----------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEF ₂₅₋₇₅ | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 100.44 | 115.11 | 122.22 | 116.44 | 102.22 | 112.44 | 100.44 | 100 |
| 2 | constrict | 100 | 93.64 | 140.17 | 72.54 | 73.41 | 73.99 | 69.65 | 84.1 | 87.57 |
| 3 | dilate | 100 | 114.71 | 122.55 | 116.67 | 113.07 | 109.15 | 110.46 | 110.46 | 106.86 |
| 4 | constrict | 100 | 82.07 | 49.51 | 59.26 | 64.52 | 52.44 | 75.44 | 67.45 | 64.33 |
| 5 | constrict | 100 | 118.55 | 90.32 | 78.23 | 84.68 | 91.13 | 97.58 | 103.23 | 120.16 |
| 6 | constrict | 100 | 100.31 | 148.93 | 110.09 | 107.03 | 109.17 | 96.64 | 105.2 | 89.91 |
| 7 | dilate | 100 | 101.88 | 111.53 | 103.53 | 99.53 | 95.29 | 101.18 | 99.53 | 103.76 |
| 8 | dilate | 100 | 101.95 | 120.49 | 106.83 | 105.85 | 114.63 | 104.39 | 99.02 | 101.46 |
| 9 | constrict | 100 | 141.67 | 170.83 | 148.61 | 153.82 | 150 | 153.13 | 148.26 | 161.81 |
| 10 | constrict | 100 | 89.26 | 130.2 | 65.1 | 67.11 | 69.13 | 69.8 | 92.62 | 92.62 |
| 11 | dilate | 100 | 108.41 | 123.36 | 119 | 116.82 | 115.26 | 121.81 | 116.51 | 122.12 |
| 12 | dilate | 100 | 101.01 | 120.35 | 109.55 | 99.5 | 105.28 | 101.26 | 99.25 | 101.76 |
| 13 | dilate | 100 | 101.65 | 107.76 | 100.47 | 104 | 102.35 | 100.24 | 103.53 | 106.82 |

| | | SPACER TREATMENT | | | | | | | | |
|----------------------|-----------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEF ₂₅₋₇₅ | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 101.69 | 116.88 | 102.53 | 89.45 | 82.28 | 93.25 | 100.84 | 100 |
| 2 | constrict | 100 | 113.37 | 144.39 | 120.05 | 118.38 | 110.98 | 116.47 | 118.38 | 118.62 |
| 3 | dilate | 100 | 112.15 | 115.89 | 108.72 | 103.74 | 107.17 | 104.36 | 109.66 | 113.08 |
| 4 | constrict | 100 | 76.42 | 77.27 | 70.74 | 56.25 | 84.38 | 80.4 | 98.3 | 82.95 |
| 5 | constrict | 100 | 173.91 | 138.04 | 126.09 | 132.61 | 136.96 | 118.48 | 146.74 | 161.96 |
| 6 | constrict | 100 | 158.78 | 285.14 | 212.16 | 179.73 | 191.22 | 183.11 | 186.49 | 208.78 |
| 7 | dilate | 100 | 105.85 | 108.91 | 103.82 | 103.56 | 101.78 | 105.34 | 99.24 | 101.02 |
| 8 | dilate | 100 | 114.58 | 130.73 | 127.6 | 114.58 | 110.94 | 97.4 | 117.71 | 110.94 |
| 9 | constrict | 100 | 126.86 | 140 | 135.14 | 138.57 | 139.43 | 136.57 | 144.86 | 142 |
| 10 | constrict | 100 | 92.81 | 115.11 | 79.14 | 80.58 | 82.01 | 81.29 | 92.09 | 102.16 |
| 11 | dilate | 100 | 113.68 | 122.19 | 113.07 | 118.54 | 120.67 | 120.06 | 117.33 | 123.1 |
| 12 | dilate | 100 | 113.95 | 117.11 | 112.37 | 109.47 | 106.58 | 111.84 | 106.32 | 109.21 |
| 13 | dilate | 100 | 103.69 | 114.29 | 102.76 | 100.46 | 108.53 | 104.15 | 106.91 | 105.76 |

| | | PLACEBO TREATMENT | | | | | | | | |
|----------------------|-----------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEF ₂₅₋₇₅ | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 97.5 | 94.58 | 97.92 | 76.25 | 75.83 | 104.17 | 85 | 88.75 |
| 2 | constrict | 100 | 90.09 | 98.82 | 50 | 53.07 | 38.68 | 41.75 | 54.48 | 76.18 |
| 3 | dilate | 100 | 106.15 | 112.31 | 100.31 | 94.15 | 97.23 | 94.46 | 99.08 | 98.15 |
| 4 | constrict | 100 | 97.72 | 84.79 | 92.02 | 97.72 | 98.48 | 94.3 | 109.13 | 164.26 |
| 5 | constrict | 100 | 82.3 | 93.81 | 41.59 | 47.79 | 50.44 | 53.1 | 68.14 | 72.57 |
| 6 | constrict | 100 | 101.84 | 181.6 | 113.5 | 100.61 | 94.48 | 104.29 | 114.11 | 101.23 |
| 7 | dilate | 100 | 99.71 | 103.48 | 97.39 | 98.84 | 95.65 | 96.52 | 94.2 | 95.36 |
| 8 | dilate | 100 | 106.54 | 110.75 | 102.34 | 98.6 | 97.2 | 91.12 | 95.79 | 100.47 |
| 9 | constrict | 100 | 91.16 | 91.71 | 74.03 | 40.61 | 56.91 | 74.86 | 99.72 | 111.33 |
| 10 | constrict | 100 | 111.72 | 138.28 | 56.25 | 57.03 | 55.47 | 54.69 | 58.59 | 64.84 |
| 11 | dilate | 100 | 98.15 | 109.23 | 100.92 | 102.15 | 101.23 | 99.38 | 103.69 | 112 |
| 12 | dilate | 100 | 97.33 | 111.47 | 104.8 | 97.87 | 99.2 | 101.07 | 96.53 | 96 |
| 13 | dilate | 100 | 93.5 | 97.18 | 88.42 | 93.5 | 94.35 | 96.05 | 92.94 | 91.53 |

| | | MDI TREATMENT | | | | | | | | |
|------|-----------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEV1 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 101.63 | 104.61 | 106.5 | 104.61 | 100.54 | 102.98 | 104.34 | 100.81 |
| 2 | constrict | 100 | 98.66 | 109.41 | 88.71 | 88.71 | 89.25 | 87.63 | 94.62 | 97.04 |
| 3 | dilate | 100 | 103.56 | 101.78 | 104.27 | 103.56 | 102.85 | 102.14 | 101.78 | 105.34 |
| 4 | constrict | 100 | 96.06 | 73.09 | 87.47 | 89.56 | 83.53 | 94.9 | 85.61 | 89.56 |
| 5 | constrict | 100 | 116.76 | 104.86 | 93.51 | 94.05 | 97.84 | 103.78 | 109.19 | 114.59 |
| 6 | constrict | 100 | 97.19 | 109.21 | 101.28 | 100.77 | 102.05 | 95.14 | 95.91 | 87.21 |
| 7 | dilate | 100 | 101.58 | 94.72 | 101.32 | 100 | 98.42 | 101.32 | 101.06 | 100 |
| 8 | dilate | 100 | 105.04 | 111.51 | 107.91 | 108.27 | 109.71 | 108.63 | 103.96 | 104.32 |
| 9 | constrict | 100 | 114.38 | 116.61 | 115.97 | 114.06 | 117.25 | 117.89 | 117.57 | 122.68 |
| 10 | constrict | 100 | 91.09 | 112.02 | 74.81 | 73.26 | 76.36 | 76.74 | 92.25 | 94.57 |
| 11 | dilate | 100 | 104.72 | 108.33 | 106.67 | 106.39 | 105.83 | 107.5 | 108.06 | 106.94 |
| 12 | dilate | 100 | 101.02 | 106.14 | 106.39 | 103.07 | 102.3 | 102.56 | 101.02 | 101.79 |
| 13 | dilate | 100 | 103.61 | 103.89 | 101.94 | 103.89 | 101.67 | 98.89 | 102.5 | 101.67 |

| | | SPACER TREATMENT | | | | | | | | |
|------|-----------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEV1 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 105.04 | 105.88 | 99.16 | 93.28 | 86.83 | 84.87 | 98.04 | 100.56 |
| 2 | constrict | 100 | 103.95 | 106.58 | 106.84 | 106.05 | 102.11 | 104.74 | 106.84 | 107.63 |
| 3 | dilate | 100 | 104.95 | 107.07 | 105.65 | 104.95 | 106.71 | 107.07 | 105.3 | 104.95 |
| 4 | constrict | 100 | 86.42 | 85.93 | 81.73 | 71.36 | 91.6 | 89.14 | 95.31 | 88.64 |
| 5 | constrict | 100 | 153.16 | 135.44 | 126.58 | 130.38 | 134.81 | 123.42 | 143.67 | 138.61 |
| 6 | constrict | 100 | 134.41 | 192.31 | 168.02 | 155.47 | 156.28 | 150.61 | 147.37 | 158.7 |
| 7 | dilate | 100 | 106.37 | 98.34 | 106.93 | 104.71 | 106.09 | 103.6 | 104.16 | 105.82 |
| 8 | dilate | 100 | 109.26 | 118.52 | 115.56 | 113.7 | 111.85 | 106.67 | 117.41 | 110.37 |
| 9 | constrict | 100 | 108.04 | 96.73 | 106.25 | 109.82 | 112.5 | 111.01 | 112.5 | 113.1 |
| 10 | constrict | 100 | 97.69 | 107.31 | 81.92 | 79.62 | 83.46 | 88.08 | 93.85 | 101.92 |
| 11 | dilate | 100 | 105.83 | 106.39 | 107.22 | 107.5 | 108.33 | 107.78 | 107.78 | 108.06 |
| 12 | dilate | 100 | 103.7 | 109.26 | 107.67 | 105.03 | 104.23 | 106.08 | 103.7 | 104.5 |
| 13 | dilate | 100 | 103.06 | 105.01 | 104.18 | 102.51 | 105.57 | 104.46 | 104.74 | 103.62 |

| | | PLACEBO TREATMENT | | | | | | | | |
|------|-----------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FEV1 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 99.11 | 99.11 | 105.33 | 96.75 | 90.24 | 104.14 | 96.75 | 98.22 |
| 2 | constrict | 100 | 95.83 | 98.44 | 75 | 74.74 | 64.06 | 67.45 | 76.04 | 89.32 |
| 3 | dilate | 100 | 97.63 | 100 | 98.64 | 97.97 | 99.66 | 100.34 | 98.64 | 98.31 |
| 4 | constrict | 100 | 106.27 | 93.42 | 100.63 | 104.39 | 107.21 | 105.64 | 112.54 | 136.68 |
| 5 | constrict | 100 | 87.29 | 92.82 | 41.44 | 46.41 | 51.38 | 55.25 | 67.96 | 75.69 |
| 6 | constrict | 100 | 98.5 | 136.09 | 103.01 | 97.37 | 92.86 | 100.75 | 105.64 | 107.14 |
| 7 | dilate | 100 | 100.64 | 99.68 | 101.93 | 102.57 | 100.96 | 102.89 | 99.68 | 101.29 |
| 8 | dilate | 100 | 103.79 | 107.93 | 106.9 | 105.17 | 104.14 | 98.28 | 102.76 | 104.48 |
| 9 | constrict | 100 | 97.6 | 83.53 | 74.25 | 56.59 | 64.97 | 78.44 | 94.61 | 104.79 |
| 10 | constrict | 100 | 105.33 | 113.78 | 65.33 | 63.11 | 61.33 | 62.22 | 72.44 | 81.33 |
| 11 | dilate | 100 | 99.44 | 103.37 | 99.72 | 101.4 | 101.69 | 101.12 | 102.53 | 103.93 |
| 12 | dilate | 100 | 99.19 | 107.55 | 105.39 | 103.5 | 101.62 | 103.23 | 97.84 | 96.77 |
| 13 | dilate | 100 | 96.42 | 99.67 | 98.05 | 100.65 | 99.02 | 100.33 | 99.02 | 96.74 |

| | | MDI TREATMENT | | | | | | | | |
|-----|-----------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FVC | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 103.16 | 100.53 | 100 | 102.81 | 101.58 | 99.65 | 103.86 | 101.93 |
| 2 | constrict | 100 | 100.44 | 93.44 | 97.16 | 96.5 | 96.72 | 97.59 | 99.12 | 100.88 |
| 3 | dilate | 100 | 99.4 | 91.54 | 97.58 | 97.89 | 95.47 | 96.68 | 95.77 | 100.6 |
| 4 | constrict | 100 | 98.82 | 91.55 | 99.61 | 98.43 | 99.21 | 96.27 | 96.27 | 98.62 |
| 5 | constrict | 100 | 112.64 | 113.72 | 101.81 | 99.64 | 102.17 | 106.14 | 110.11 | 109.03 |
| 6 | constrict | 100 | 97.19 | 99.4 | 99 | 100.2 | 101.2 | 95.58 | 94.18 | 86.55 |
| 7 | dilate | 100 | 100.25 | 92.84 | 97.53 | 97.04 | 99.26 | 100.25 | 99.51 | 100.25 |
| 8 | dilate | 100 | 106.61 | 107.94 | 108.47 | 110.58 | 107.94 | 110.05 | 106.35 | 104.76 |
| 9 | constrict | 100 | 107.01 | 101.3 | 106.75 | 104.16 | 109.61 | 109.09 | 109.35 | 110.39 |
| 10 | constrict | 100 | 93.27 | 101.16 | 83.99 | 80.28 | 83.29 | 84.92 | 94.9 | 96.06 |
| 11 | dilate | 100 | 102.91 | 98.66 | 101.34 | 101.57 | 102.01 | 102.24 | 103.13 | 101.12 |
| 12 | dilate | 100 | 100.86 | 98.71 | 103.43 | 102.79 | 100.21 | 101.93 | 101.29 | 101.72 |
| 13 | dilate | 100 | 103.37 | 101.69 | 101.45 | 103.13 | 102.41 | 99.52 | 102.65 | 100.72 |

| | | SPACER TREATMENT | | | | | | | | |
|-----|-----------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FVC | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 103.78 | 102.52 | 97.84 | 97.66 | 97.3 | 96.76 | 96.04 | 96.58 |
| 2 | constrict | 100 | 101.14 | 92.5 | 98.86 | 101.14 | 98.18 | 98.64 | 101.14 | 102.27 |
| 3 | dilate | 100 | 102.47 | 96.6 | 101.85 | 102.16 | 104.63 | 105.25 | 101.85 | 101.54 |
| 4 | constrict | 100 | 100.19 | 97.09 | 96.9 | 100 | 100.39 | 100.19 | 98.84 | 98.26 |
| 5 | constrict | 100 | 131.6 | 123.79 | 118.96 | 120.82 | 121.93 | 117.1 | 129.37 | 117.47 |
| 6 | constrict | 100 | 113.18 | 147.01 | 139.55 | 133.08 | 131.09 | 126.12 | 121.39 | 128.11 |
| 7 | dilate | 100 | 102.67 | 93.2 | 103.16 | 97.33 | 101.21 | 99.76 | 101.7 | 101.94 |
| 8 | dilate | 100 | 106.08 | 112.17 | 109.52 | 111.64 | 110.32 | 108.99 | 114.29 | 108.73 |
| 9 | constrict | 100 | 104.87 | 94.62 | 97.18 | 100.51 | 105.13 | 102.05 | 103.08 | 105.13 |
| 10 | constrict | 100 | 97.06 | 101.47 | 84.87 | 80.46 | 84.87 | 89.5 | 93.7 | 96.85 |
| 11 | dilate | 100 | 103.41 | 98.86 | 105.68 | 102.27 | 103.41 | 102.73 | 102.5 | 102.5 |
| 12 | dilate | 100 | 101.75 | 104.6 | 105.47 | 104.16 | 103.72 | 104.16 | 102.63 | 102.63 |
| 13 | dilate | 100 | 102.66 | 101.69 | 104.35 | 102.9 | 104.83 | 103.14 | 104.11 | 102.17 |

| | | PLACEBO TREATMENT | | | | | | | | |
|-----|-----------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| FVC | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 104.92 | 101.97 | 107.48 | 104.72 | 100.98 | 103.35 | 102.17 | 105.91 |
| 2 | constrict | 100 | 96.18 | 92.81 | 88.99 | 86.29 | 80.67 | 84.04 | 88.76 | 94.16 |
| 3 | dilate | 100 | 98.84 | 85.76 | 96.51 | 98.26 | 99.42 | 100 | 98.26 | 97.97 |
| 4 | constrict | 100 | 95.38 | 95.58 | 97.99 | 99.4 | 101.61 | 103.21 | 99.6 | 103.61 |
| 5 | constrict | 100 | 91.72 | 93.79 | 42.76 | 46.55 | 55.86 | 63.1 | 77.59 | 84.83 |
| 6 | constrict | 100 | 98.28 | 115.69 | 98.04 | 97.3 | 93.63 | 101.47 | 104.41 | 111.76 |
| 7 | dilate | 100 | 102.92 | 95.92 | 100.58 | 102.62 | 100.87 | 101.17 | 100.87 | 101.46 |
| 8 | dilate | 100 | 103.06 | 107.65 | 109.95 | 109.44 | 109.95 | 107.14 | 109.18 | 107.4 |
| 9 | constrict | 100 | 101.58 | 83.42 | 76.84 | 68.42 | 69.47 | 82.37 | 95 | 101.84 |
| 10 | constrict | 100 | 101.31 | 102.35 | 84.6 | 74.93 | 73.89 | 79.11 | 91.12 | 97.91 |
| 11 | dilate | 100 | 101.15 | 99.31 | 98.62 | 102.07 | 102.53 | 102.99 | 104.14 | 100.46 |
| 12 | dilate | 100 | 100 | 104.49 | 105.39 | 105.17 | 102.47 | 103.82 | 97.75 | 98.43 |
| 13 | dilate | 100 | 96.39 | 99.44 | 102.5 | 102.5 | 100.28 | 101.39 | 100.28 | 98.89 |

| | | MDI TREATMENT | | | | | | | | |
|-------|-----------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|
| MEF50 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 111.54 | 115.77 | 138.46 | 116.54 | 114.62 | 103.46 | 120.77 | 102.69 |
| 2 | constrict | 100 | 93.28 | 134.33 | 74.88 | 76.12 | 75.62 | 69.15 | 84.58 | 90.3 |
| 3 | dilate | 100 | 102.36 | 105.77 | 102.89 | 98.95 | 89.76 | 93.96 | 93.18 | 88.45 |
| 4 | constrict | 100 | 103.6 | 44.18 | 60.96 | 68.49 | 48.63 | 68.49 | 80.82 | 54.11 |
| 5 | constrict | 100 | 126.03 | 95.21 | 76.03 | 82.88 | 86.99 | 100 | 102.74 | 115.75 |
| 6 | constrict | 100 | 101.01 | 152.91 | 106.33 | 99.24 | 106.33 | 100 | 107.34 | 91.9 |
| 7 | dilate | 100 | 100.91 | 112.3 | 103.19 | 100.46 | 97.04 | 101.59 | 101.59 | 107.29 |
| 8 | dilate | 100 | 105.45 | 105.06 | 102.33 | 106.61 | 112.45 | 108.95 | 96.89 | 103.5 |
| 9 | constrict | 100 | 148.16 | 165.03 | 162.27 | 159.82 | 163.19 | 163.5 | 165.64 | 156.75 |
| 10 | constrict | 100 | 90.45 | 125.28 | 67.98 | 60.67 | 65.17 | 65.17 | 80.9 | 90.45 |
| 11 | dilate | 100 | 109.83 | 121.91 | 117.7 | 112.64 | 117.98 | 118.82 | 115.45 | 121.63 |
| 12 | dilate | 100 | 100.66 | 112.11 | 101.98 | 92.95 | 99.78 | 92.73 | 93.17 | 103.74 |
| 13 | dilate | 100 | 90.36 | 97.16 | 96.22 | 95.27 | 100.38 | 98.87 | 99.24 | 103.4 |

| | | SPACER TREATMENT | | | | | | | | |
|-------|-----------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| MEF50 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 105.24 | 117.23 | 100.37 | 98.5 | 85.39 | 102.25 | 110.11 | 110.49 |
| 2 | constrict | 100 | 113.98 | 136.42 | 111.61 | 118.31 | 113.39 | 112.99 | 106.3 | 113.39 |
| 3 | dilate | 100 | 105.19 | 97.4 | 95.06 | 88.05 | 91.69 | 88.05 | 93.77 | 101.04 |
| 4 | constrict | 100 | 84.75 | 75.75 | 74 | 53.75 | 82 | 85 | 99.25 | 86.5 |
| 5 | constrict | 100 | 196.15 | 146.15 | 134.62 | 138.46 | 146.15 | 128.85 | 159.62 | 169.23 |
| 6 | constrict | 100 | 172.67 | 313.66 | 232.3 | 206.83 | 209.94 | 200.62 | 193.79 | 225.47 |
| 7 | dilate | 100 | 104.33 | 108.41 | 106.97 | 101.68 | 98.8 | 102.4 | 104.81 | 97.6 |
| 8 | dilate | 100 | 118.1 | 130.17 | 125.43 | 119.83 | 119.4 | 106.9 | 99.14 | 135.78 |
| 9 | constrict | 100 | 146.41 | 146.67 | 136.41 | 141.54 | 147.95 | 143.08 | 141.79 | 139.49 |
| 10 | constrict | 100 | 104.93 | 128.87 | 97.18 | 88.73 | 90.14 | 91.55 | 95.77 | 125.35 |
| 11 | dilate | 100 | 110.68 | 119.18 | 106.03 | 112.33 | 124.38 | 120.27 | 109.04 | 120.27 |
| 12 | dilate | 100 | 107.46 | 101.81 | 99.6 | 106.85 | 99.8 | 95.16 | 99.6 | 98.19 |
| 13 | dilate | 100 | 93.77 | 103.74 | 98.75 | 93.77 | 100.71 | 101.78 | 99.82 | 97.51 |

| | | PLACEBO TREATMENT | | | | | | | | |
|-------|-----------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| MEF50 | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 104.33 | 116.25 | 102.53 | 84.12 | 73.29 | 88.81 | 83.75 | 87 |
| 2 | constrict | 100 | 87.22 | 94.93 | 50.91 | 54.16 | 38.34 | 41.38 | 56.39 | 73.83 |
| 3 | dilate | 100 | 101.33 | 105.33 | 97.33 | 88.27 | 88.8 | 90.4 | 94.93 | 93.33 |
| 4 | constrict | 100 | 111.11 | 87.81 | 88.53 | 111.11 | 99.64 | 91.4 | 115.05 | 166.31 |
| 5 | constrict | 100 | 82.81 | 89.06 | 39.06 | 45.31 | 46.88 | 50.78 | 65.63 | 71.09 |
| 6 | constrict | 100 | 101.09 | 183.61 | 114.75 | 102.73 | 92.35 | 106.01 | 123.5 | 109.29 |
| 7 | dilate | 100 | 97.79 | 106.63 | 99.17 | 97.79 | 95.86 | 95.86 | 91.99 | 96.69 |
| 8 | dilate | 100 | 104.18 | 100.38 | 106.46 | 145.25 | 93.54 | 84.79 | 95.82 | 101.9 |
| 9 | constrict | 100 | 97.55 | 97.06 | 74.26 | 41.67 | 57.35 | 78.43 | 101.47 | 115.2 |
| 10 | constrict | 100 | 118.57 | 136.43 | 59.29 | 61.43 | 54.29 | 52.86 | 60 | 75 |
| 11 | dilate | 100 | 103.63 | 103.35 | 100.84 | 105.87 | 102.23 | 101.12 | 109.5 | 112.57 |
| 12 | dilate | 100 | 93.26 | 103.37 | 113.26 | 103.15 | 102.02 | 98.65 | 102.02 | 100.9 |
| 13 | dilate | 100 | 98.05 | 96.53 | 81.34 | 92.41 | 88.29 | 87.2 | 83.95 | 93.28 |

| | | MDI TREATMENT | | | | | | | | |
|------|-----------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|
| PEFR | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 98.07 | 73.89 | 89.1 | 78.77 | 66.63 | 74.69 | 71.17 | 67.99 |
| 2 | constrict | 100 | 101.37 | 108.24 | 92.29 | 92.08 | 93.88 | 82.47 | 94.51 | 96.73 |
| 3 | dilate | 100 | 105.84 | 113.18 | 102.45 | 107.53 | 104.52 | 105.65 | 106.78 | 99.62 |
| 4 | constrict | 100 | 97.89 | 61.27 | 90.56 | 93.52 | 88.03 | 97.46 | 78.03 | 91.55 |
| 5 | constrict | 100 | 113.18 | 106.35 | 99.29 | 85.65 | 89.18 | 92 | 100.47 | 113.65 |
| 6 | constrict | 100 | 67.24 | 71.45 | 77.56 | 73.93 | 71.78 | 75.83 | 71.95 | 76.16 |
| 7 | dilate | 100 | 94.05 | 100.96 | 96.3 | 108.04 | 77.17 | 91.48 | 99.84 | 84.57 |
| 8 | dilate | 100 | 106.89 | 106.09 | 108.34 | 98.41 | 106.36 | 110.2 | 108.61 | 109.67 |
| 9 | constrict | 100 | 92.33 | 89.64 | 103.23 | 97.31 | 100 | 104.71 | 100.67 | 104.17 |
| 10 | constrict | 100 | 102.62 | 113.51 | 74.6 | 76.81 | 84.48 | 72.38 | 98.59 | 114.11 |
| 11 | dilate | 100 | 95.01 | 104.2 | 98.42 | 93.82 | 95.4 | 90.28 | 101.71 | 97.77 |
| 12 | dilate | 100 | 93.39 | 95.87 | 95.16 | 97.64 | 92.8 | 94.92 | 94.57 | 98.58 |
| 13 | dilate | 100 | 97.52 | 94.04 | 89.4 | 116.39 | 102.81 | 101.32 | 93.21 | 105.96 |

| | | SPACER TREATMENT | | | | | | | | |
|------|-----------|------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| PEFR | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 129.32 | 109.51 | 113.4 | 94.95 | 83.88 | 76.7 | 106.21 | 112.04 |
| 2 | constrict | 100 | 82.2 | 105.73 | 93.19 | 86.38 | 78.14 | 81.36 | 87.34 | 79.57 |
| 3 | dilate | 100 | 103.53 | 115.58 | 111.5 | 111.69 | 110.95 | 103.71 | 105.75 | 106.49 |
| 4 | constrict | 100 | 68.24 | 72.01 | 62.45 | 56.26 | 79.54 | 66.76 | 68.37 | 71.74 |
| 5 | constrict | 100 | 161.75 | 165.96 | 161.75 | 156.84 | 143.86 | 168.42 | 178.6 | 177.54 |
| 6 | constrict | 100 | 149.14 | 203.3 | 151.18 | 143.96 | 154.16 | 149.76 | 143.01 | 164.68 |
| 7 | dilate | 100 | 112.6 | 107.52 | 93.29 | 110.37 | 114.02 | 121.14 | 89.43 | 126.63 |
| 8 | dilate | 100 | 104.03 | 114.09 | 110.06 | 110.44 | 108.81 | 111.7 | 109.06 | 109.06 |
| 9 | constrict | 100 | 103.52 | 98.96 | 94.91 | 100.78 | 98.83 | 101.83 | 105.61 | 96.08 |
| 10 | constrict | 100 | 99.43 | 131.24 | 90.86 | 84.38 | 84 | 89.71 | 100 | 103.81 |
| 11 | dilate | 100 | 101.07 | 103.33 | 103.73 | 101.46 | 96.67 | 103.2 | 101.73 | 97.87 |
| 12 | dilate | 100 | 87.6 | 115.44 | 111.74 | 107.26 | 101.32 | 101.72 | 106.99 | 111.48 |
| 13 | dilate | 100 | 92.06 | 93.59 | 91.76 | 90.08 | 107.18 | 112.21 | 102.9 | 90.69 |

| | | PLACEBO TREATMENT | | | | | | | | |
|------|-----------|-------------------|--------|--------|--------|--------|--------|--------|--------|--------|
| PEFR | mins | -13 | -8 | 0 | 3 | 5 | 7 | 10 | 20 | 30 |
| 1 | constrict | 100 | 87.9 | 129.44 | 156.85 | 129.44 | 96.17 | 120.36 | 127.42 | 152.62 |
| 2 | constrict | 100 | 117.1 | 124.69 | 104.28 | 100.28 | 86.62 | 87.17 | 75.59 | 98.34 |
| 3 | dilate | 100 | 101.31 | 109.01 | 94.93 | 95.31 | 100.94 | 95.5 | 104.69 | 100.94 |
| 4 | constrict | 100 | 187.1 | 105.84 | 129.93 | 117.76 | 130.17 | 131.14 | 144.53 | 169.1 |
| 5 | constrict | 100 | 88.54 | 78.04 | 37.47 | 40.57 | 45.11 | 47.73 | 58.71 | 66.83 |
| 6 | constrict | 100 | 96.66 | 111.13 | 89.15 | 93.88 | 87.9 | 100 | 95.55 | 100.83 |
| 7 | dilate | 100 | 105.79 | 93.75 | 98.61 | 107.18 | 103.7 | 105.09 | 111.11 | 111.11 |
| 8 | dilate | 100 | 105.15 | 106.08 | 102.38 | 101.06 | 98.81 | 101.72 | 99.74 | 107 |
| 9 | constrict | 100 | 96.03 | 74.42 | 66.62 | 43.37 | 53.63 | 68.67 | 77.02 | 89.88 |
| 10 | constrict | 100 | 92.43 | 97.1 | 69.49 | 65.03 | 62.14 | 71.27 | 69.04 | 81.51 |
| 11 | dilate | 100 | 100.4 | 107.52 | 102.82 | 96.91 | 99.33 | 98.79 | 97.32 | 99.33 |
| 12 | dilate | 100 | 93.25 | 92.27 | 92.02 | 90.31 | 93.99 | 92.76 | 88.1 | 94.85 |
| 13 | dilate | 100 | 92.9 | 86.89 | 72.68 | 94.17 | 79.42 | 90.71 | 86.89 | 92.71 |

Table A2 Mean and Standard Deviations for Bronchial Lability results over 3 test periods.

| Pulmonary function variable | <u>MDI</u> | <u>Spacer</u> | <u>Placebo</u> |
|--|--------------------------|-------------------------|---------------------------|
| | mean (\pm SD) | mean (\pm SD) | mean (\pm SD) |
| FVC (l) | 10.61# (\pm 6.13) | 12.98 (\pm 7.93) | 24.45# (\pm 17.90) |
| FEV ₁ (l) | 20.17 (\pm 12.37) | 24.04 (\pm 13.22) | 37.36 * (\pm 17.54) |
| FEF ₂₅₋₇₅ l.min ⁻¹ | 46.86 (\pm 20.03) | 44.77 (\pm 30.80) | 55.60 (\pm 27.23) |
| PEFR l.min ⁻¹ | 28.27# (\pm 12.60) | 37.45 (\pm 18.49) | 53.04# (\pm 18.67) |
| MEF ₅₀ l.min ⁻¹ | 43.97 (\pm 18.35) | 47.81 (\pm 35.67) | 58.80 (\pm 24.60) |

indicates significance between the MDI and placebo treatments to the $p < 0.05$ level.

Table A3. Mean and Standard Deviations for Decrement results over 3 test periods.

| Pulmonary function variable | <u>MDI</u> | <u>Spacer</u> | <u>Placebo</u> |
|--|-------------------------|-------------------------|-------------------------|
| | mean (\pm SD) | mean (\pm SD) | mean (\pm SD) |
| FVC (l) | 6.98 (\pm 7.56) | 5.64 (\pm 6.70) | 20.72 (\pm 19.93) |
| FEV ₁ (l) | 12.19 (\pm 11.24) | 9.62 (\pm 11.72) | 28.58 (\pm 20.71) |
| FEF ₂₅₋₇₅ l.min ⁻¹ | 19.64 (\pm 20.25) | 11.76 (\pm 16.80) | 38.48 (\pm 23.22) |
| PEFR .min ⁻¹ | 25.17 (\pm 11.76) | 15.71 (\pm 15.74) | 28.19 (\pm 24.98) |
| MEF ₅₀ l min ⁻¹ | 20.90 (\pm 21.04) | 10.30 (\pm 17.01) | 37.74 (\pm 24.64) |

APPENDIX B

Consent Documents and Subject Information/instruction forms

1. Initial Subject Information Form.
2. Covering Letter
3. Consent Form.
4. Medical Questionnaire.
5. Consistency Procedures

Subject Information

School of Biomedical and Sports Sciences

Edith Cowan University

A study conducted by Professor A.R. Morton and Mr. D. G. Reed to investigate the efficacy of a 'spacer' in the delivery of salbutamol for the prevention of Exercise Induced Asthma.

WE REQUIRE ACTIVE INDIVIDUALS WHO UNDERTAKE REGULAR EXERCISE WHO ARE 18-35 YEARS OF AGE WHO REGULARLY EXHIBIT EXERCISE INDUCED ASTHMA

You would be required to attend 3 test sessions, all at the Joondalup campus of Edith Cowan University each lasting for 1 hour. All testing will be carried out by qualified personnel.

All sessions will involve the initial testing of lung function using a spirometer and then the administration of an inhaled substance followed by an 8 minute run on a motor driven treadmill. Lung function will then be measured intermittently over a period of 30 minutes post exercise.

On each of the visits, a different protocol will exist for the administration of the inhaled substance. On 2 of the 3 sessions, salbutamol (Ventolin) will be inhaled via a Metered Dose Inhaler or a 'Spacer' devise. The other visit **will incur no active drug administration.** (placebo)

It is the purpose of this study to induce a mild asthmatic bronchospasm and study the potential effect that differing delivery systems have on post exercise lung function. During the test, your heart rate will be monitored by a Polar heart rate monitor and the perceived exertion via the Borg Scale. Discomfort may be experienced with this study during the 8-minute treadmill run (mild fatigue) with possible side-effects caused by the bronchospasm also generating some uncomfortable symptoms. Heart rate will be monitored at all times and if at any stage during the test, your asthma becomes distressing, or it takes longer than usual to recover, you will be given your usual 'reliever' medication. The exercise challenge used during this study is a safe and routine procedure, which has been performed many hundreds of times under similar laboratory conditions conducted by Professor Morton (supervisor)

The treadmill running test will consist of a multistage continuous exercise test that will last for 8 minutes and correspond to a speed and gradient that generates a 75%-85% predicted maximal heart rate. (220 – age). No warm up will be given; however, the first 2 –3 minutes will be easy enough to generate desired preparation.

Lung function will be measured pre-medication, then five minutes later it will be repeated (post-medication pre-exercise.) Following 8 minutes of exercise, lung

function will be measured immediately, then after 3, 5, 7, 10, 20 and 30 minutes post exercise.

Salbutamol is the most commonly prescribed asthma medication and is used regularly by asthmatics to prevent EIA, occasionally side effects of palpitation and muscle tremor may occur. A doctor will be on call during all testing sessions.

It is your right to withdraw your consent at any time and to discontinue your participation in the study generally or in any specific aspect of it. Data obtained from the results of the tests to be conducted will be placed in a thesis; names of individual subjects will not be used.

You will be provided with your test results that will be explained and compared to norms for your age, height, sex and weight. You will also gain clearer understanding of the management of your exercise-induced asthma.

Please note that all subjects must be salbutamol users on a regular basis. Participation in this study will only be allowed if your family doctor prescribes this drug to you for your asthma.

Tuesday, 01 September 1998

Dear,

Thankyou very much for volunteering your time to be a part of this study that aims to distinguish the most effective delivery system of Ventolin for the prevention of exercise induced asthma. The ramifications of this research will give asthmatics reliable information on which delivery system best prevents EIA. (between Metered dose inhalers and spacers).

It is important to carefully read all documents within this package and truthfully complete all enclosed forms.

Forms that will require your attention are:

- Medical Questionnaire
- Consent Form
- Covering letter (GP's phone number and name)

During the next few days, you will be required to obtain medical clearance that will be conducted by the ECU Joondalup medical practitioner. This service is only available from 9.00 am to 12.30pm each weekday. I will call you to organise times in the near future. (This medical will incur no cost to you)

All forms must be completed by the time of the medical and will be collected from you at this time. Could you please fill in the name of your Doctor and his/her phone number in case of emergency and for consultation on your participation in this study.

I do realise how busy you are so it cannot be emphasised how grateful I am that you are giving your time to this research.

Thanking you again

David Reed

Name of Doctor _____

Phone number _____

CONSENT FORM

School of Biomedical and Sports Sciences

Edith Cowan University

I, the undersigned _____

Of _____

Do freely and voluntarily give consent to be a subject in a study conducted by Mr. David Reed and Prof. Alan Morton to investigate the efficacy of the 'spacer' in the delivery of salbutamol (Ventolin™) for the prevention of exercise-induced asthma.

I have been informed that this medication is commonly prescribed and used regularly by asthmatics to prevent and reverse attacks of asthma. I have been informed that occasionally side effects of palpitation and muscle tremor may occur. A doctor will be on call during all testing sessions.

I declare that the purpose of this study has been fully explained to me and that I understand them. I realise that I will be required to attend 3 sessions all at the Physiology Laboratory at Edith Cowan University, Joondalup. During each of my 3 visits, I will be required to complete an 8-minute running exercise on a motor driven treadmill at a rate of 75-85% of my predicted maximal heart rate. Before each of these tests, either a placebo, salbutamol via a metered dose inhaler or salbutamol via a 'Spacer' will be administered by inhalation through the mouth. (A Spacer is a clear plastic cylinder approximately 20 cm long which combines air and medication to aid in the full inhalation of the salbutamol).

Before and after the test, my lung function will be measured a total of 10 times which requires me to forcefully exhale into a spirometer for a short period of time.

Whilst I hereby indicate my willingness to act as subject in the study, I retain the right to withdraw my consent at any time and to discontinue my participation in the study generally or in any specific aspect of it. I understand that should I have any questions concerning this project they can be directed to David Reed.

I wave all possible responsibility from Edith Cowan University and participate at my own risk. Finally, I declare that any research data obtained from the results of the test to be conducted can be published in scientific papers, provided my name is not used.

Subject: _____ (sign)

Witness: _____ (sign)

Date: _____

Medical Questionnaire

The following questionnaire is designed to establish a background of your medical history, and identify any injury or illness that may influence your testing or performance.
Please answer all questions as accurately as possible and if you are unsure about any thing please ask.
All information provided is strictly confidential.

Personal Details

Name:

DOB: Sex:

Height: Weight:

Medical History

Have you ever had, or do you currently have any of the following?

| | | | If you answered YES please give details |
|---------------------------------|---|---|---|
| High or abnormal blood pressure | Y | N | <input type="text"/> |
| High cholesterol | Y | N | <input type="text"/> |
| Rheumatic fever | Y | N | <input type="text"/> |
| Heart abnormalities | Y | N | <input type="text"/> |
| Asthma | Y | N | <input type="text"/> |
| Diabetes | Y | N | <input type="text"/> |
| Epilepsy | Y | N | <input type="text"/> |
| Back pain | Y | N | <input type="text"/> |
| Neck pain | Y | N | <input type="text"/> |
| Severe allergies | Y | N | <input type="text"/> |
| Any infectious diseases | Y | N | <input type="text"/> |

If you answered YES please give details

Are you currently on any medications?Y N

Have you had the flu in the last two weeks?Y N

Have you recently had any injuries or accidents?

Do you have any recurring muscle or joint injuries? Y N _____

Is there any other condition not previously mentioned which may affect your exercise performance? Y N _____

Family History

Are any of the following known to exist in your family?

| | Y | N | If you answered YES please give details |
|-------------------|---|---|---|
| Cardiac disease | | | _____ |
| Pulmonary disease | | | _____ |
| Stroke | | | _____ |

Lifestyle Habits

| | | |
|---|-------|---|
| Do you exercise regularly? | Y | N |
| If YES how many hours per week? | _____ | |
| Do you smoke tobacco or any other nicotine products | Y | N |
| If YES please how much per day? | _____ | |
| Do you consume alcohol? | Y | N |
| If YES how many standard drinks per week? | _____ | |
| Do you consume tea and or coffee? | Y | N |
| If YES how many cups per day? | _____ | |
| Do you take any recreational drugs? | Y | N |
| If YES how much or how often per week? | _____ | |

Declaration

I acknowledge that the information provided on this form, is to the best of my knowledge, a true and accurate indication of my current state of health.

Name: _____ Date: _____

Signature: _____

Consistency Procedures

Preparation for and the performance of any scientific test must be controlled to ensure consistency especially when dealing with multiple tests performed by the same subject. As is the case with this research, subjects will be required to undertake similar tests over a period of 1 to 2 weeks.

The aim of this study is to examine the effects that differing delivery protocols of ventolin have on bronchoconstriction post exercise. It is therefore necessary to maintain similar circumstances during each test which is in some cases the responsibility of the subject. Below is a list of 'constants' that you as a subject should endeavour to adhere to prior to any test:

Pre-test activities

- Please ensure that all foodstuff consumption prior to test is identical in terms of time and type as well as quantity.

Other factors of consideration:

- **Food consumption** prior must be similar for a period of no less than 12 hours
- **Maintain same exercise patterns** ~ no exercise 24 hours prior to test
- **Keep same sleeping patterns**
- **Consume no caffeine products** (coffee, chocolate or Coke)

Test activities

For the test, please regulate and repeat:

- Clothing worn = shoes (runners), shorts, socks! All same please.
- Drink no alcohol for 24 hours
- No smoking for 12 hours
- Fast for 3 hours prior
- Be relaxed. (It's not as bad as it sounds!)

The test facilitators will ensure that all the constants under their control will be maintained for all tests. It would be greatly appreciated if subjects could please do the same. The most important factor is that the same activities occur each week. Also record any details that you believe may become 'forgotten' by your next test.

It is very important for you to take note of the list of drugs/treatments that are permitted prior to the test. These are listed on the attached form.

Also note that your Doctor's (GP) phone number and name is required on the covering letter you received in this package so that contact can be made with him/her concerning your participation in this study.

The information on this sheet is very important so please undertake the consistency procedures and understand that it's up to you!

Please do not hesitate to call me on [REDACTED] if there are any queries or questions.

APPENDIX C

Instructions for MDI use & Spacer use.

Techniques for the administration of Aerosol salbutamol via the Metered Dose Inhaler (MDI).

Subjects were instructed to follow the following steps in administering Ventolin via the MDI.

1. Remove cap
2. Shake inhaler
3. Hold inhaler upright
4. Tilt the head back
5. Place the inhaler into the mouth
6. Breath in and simultaneously activate the inhaler
7. Continue to inhale slowly and deeply
8. Hold breath for 10 seconds.

For each aerosol treatment, 2 MDI actuations were administered 1 minute apart. To ensure optimal administration technique, subjects were verbally reminded of the correct technique and closely observed during all steps of treatment administration.

Techniques for the administration of Aerosol salbutamol via the Spacer device (connected to a MDI).

Subjects were instructed to follow the following steps in administering Ventolin via the Spacer device.

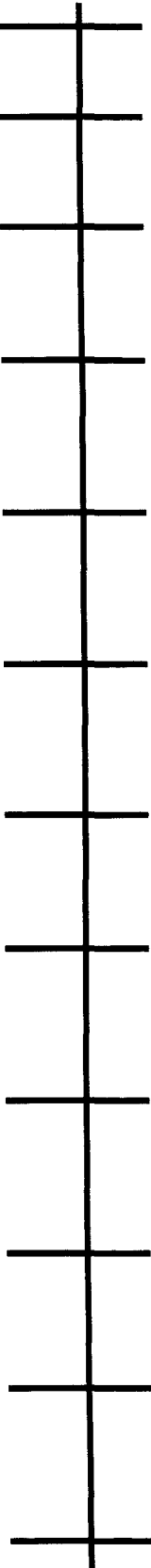
1. Remove cap of MDI
2. Shake inhaler
3. Connect MDI to spacer at correct end.
4. Tilt the head back
5. Place the spacer uni-directional mouthpiece into the mouth
6. Activate the inhaler with 2 actuations into chamber
7. Breath in deeply and slowly
8. Hold for 3 seconds
9. Continue to inhale and exhale through mouthpiece for 3 breaths.

To ensure optimal administration technique, subjects were verbally reminded of the correct technique and closely observed during all steps of treatment administration.

APPENDIX D

Borg Scale of the Rate of Perceived Breathlessness 'RPB'

**BORG SCALE OF BREATHLESSNESS
(RPB)**

| | | |
|-------------------|--|-----|
| nothing at all |  | 0 |
| very, very slight | | 0.5 |
| very slight | | 1 |
| slight | | 2 |
| moderate | | 3 |
| somewhat severe | | 4 |
| severe | | 5 |
| | | 6 |
| very severe | | 7 |
| | | 8 |
| very, very severe | | 9 |
| MAXIMAL | | 10 |

Borg, G., & Noble, B. (1974). Perceived exertion. In: Exercise and Sports Sciences Review, J.H. Wilmore (Ed). New York: Academic Press. pp 131-153

APPENDIX E

Calibration Instructions For the Minato Autspirometer PAL

Calibration of the Autospiral Autspirometer PAL

Calibration of the Minato comprises of two separate calibration tasks. These are known as 'Offset calibration' and 'Volume calibration'. The manufacturers recommend that calibration occur once a week, however, for the purpose of this study, calibration was undertaken prior to each subject due to changes in temperature and humidity.

Offset Calibration

1. Depress [Cal] key to access the calibration display screen.
2. Depress the [1] key to select offset calibration.
3. Connect the filter end of the transducer (ie the non-mouth end), to a piston syringe, preferably with a 2 liter volume. Move the piston several times.
4. Next, cover the open end of the transducer with your hand (to prevent airflow) and depress the [START] key.
5. Offset calibration will then be complete within 2 to 3 seconds.
6. If airflow is detected, the word 'unusual' will appear and by pressing the [ce] key, the process is repeated.

Volume Calibration

This is performed straight after an offset calibration.

1. Depress [Cal] key to change the screen to CALIBRATION display
2. Depress [2] key to select Volume Calibration function.
3. With syringe piston connected, press the [START] key
4. Reciprocate the plunger from one end to the other moderately at least five times namely in order to draw five loops on the screen before you hear a short signal in approximately 20 seconds after the start of calibration.
5. The calibration data is displayed on the screen and Volume Calibration is complete.
6. The volume of the syringe calibrator can be changed within the owners menu prompt, however 2 liters is the recommended level.

APPENDIX F

Data Collection Form

HR pred max range:

Data Collection: Subject No: test category: A B C

| Time (min) | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|--------------|---|---|---|---|---|---|---|---|
| Speed (km) | | | | | | | | |
| Gradient (%) | | | | | | | | |

Post exercise→

| | Pre-med | Pre-ex | 0 min | 3 min | 5 min | 7 min | 10 min | 20 min | 30 min |
|-----------------------|---------|--------|-------|-------|-------|-------|--------|--------|--------|
| FEV1 (l) | | | | | | | | | |
| FVC l (l) | | | | | | | | | |
| FEV1% | | | | | | | | | |
| PEFR (l.min-1) | | | | | | | | | |
| FEF50 (l.min-1) | | | | | | | | | |
| FEF25-75 (l.min-1) | | | | | | | | | |

Data collected during exercise

| | 1 min | 2 min | 3 min | 4 min | 5 min | 6 min | 7 min | 8 min |
|-------------------------|-------|-------|-------|-------|-------|-------|-------|-------|
| Borg Scale | | | | | | | | |
| Heart Rate (b.min-1) | | | | | | | | |

Data collected post exercise

| | 0 min | 3 min | 5 min | 7 min | 10 min | 20 min | 30 min |
|----------------------|-------|-------|-------|-------|--------|--------|--------|
| Borg Scale | | | | | | | |
| Heart Rate (b.min-1) | | | | | | | |

APPENDIX G

Drug Information Sheet.

Drugs That must be avoided prior to testing.

Subjects should abstain from medication for 24 hours prior to testing.

If this is not possible, the following guidelines should be adhered to.

Do not take for 24 hours:

- Cromolyn sodium (Intal)
- Methyl xanthines
- Antihistamines

Do not take for 8 hours:

- Aerosol corticosteroids (Becotide, Budesonide)
- Anticholinergics

Do not take for 12 hours:

- Long acting beta-2 agonists

Do not take for 4 hours:

- Short acting beta-2 agonists (Ventolin)

If you are unsure about any of these drugs, contact your doctor to discuss what medications you are on.

APPENDIX H

Raw Data for Reliability Study

Raw Data for the reliability study of the Minato Autospirometer (n = 30)

| | FEV1 (l) | | FVC (l) | | FEF ₂₅₋₇₅ (l.min ⁻¹) | | PEFR (l.min ⁻¹) | | MEF ₅₀ (l.min ⁻¹) | |
|--------------|----------|--------|---------|--------|---|--------|-----------------------------|--------|--|--------|
| Subject | test 1 | test 2 | test 1 | test 2 | test 1 | test 2 | test 1 | test 2 | test 1 | test 2 |
| 1 | 4.28 | 4.88 | 5.1 | 5.9 | 4.48 | 4.98 | 7.95 | 10.07 | 5.45 | 5.94 |
| 2 | 3.54 | 3.73 | 4.02 | 4.28 | 4.4 | 4.34 | 12.13 | 12.62 | 5.4 | 5.07 |
| 3 | 3.16 | 2.72 | 3.64 | 3.18 | 4.17 | 3.42 | 7.85 | 7.4 | 5.83 | 4.93 |
| 4 | 2.76 | 2.36 | 3.49 | 2.97 | 2.42 | 2.08 | 7.07 | 6.19 | 2.89 | 2.5 |
| 5 | 3.92 | 4.21 | 5.04 | 4.99 | 3.21 | 4.3 | 12.4 | 9.2 | 3.83 | 5.21 |
| 6 | 3.44 | 3.92 | 4.26 | 4.63 | 3.09 | 3.8 | 7.59 | 9.28 | 3.19 | 4.2 |
| 7 | 4.39 | 4.44 | 5.42 | 5.4 | 4.13 | 4.35 | 9.26 | 8.74 | 4.44 | 5.06 |
| 8 | 3.16 | 3.47 | 4 | 4.25 | 2.65 | 3.21 | 9.17 | 8.98 | 3.05 | 3.62 |
| 9 | 4.88 | 5.03 | 5.58 | 5.68 | 5.86 | 5.96 | 11.75 | 12.19 | 7.36 | 7.48 |
| 10 | 4.77 | 4.96 | 5.28 | 5.88 | 5.5 | 5.49 | 9.41 | 10.75 | 6.91 | 6.11 |
| 11 | 3.06 | 3.09 | 3.9 | 3.97 | 2.63 | 2.49 | 9.01 | 9.35 | 3.09 | 2.94 |
| 12 | 3.76 | 3.86 | 4.45 | 4.52 | 4.18 | 4.52 | 8.39 | 8.12 | 5.11 | 4.85 |
| 13 | 3.48 | 3.51 | 4.02 | 4.2 | 3.5 | 3.77 | 8.09 | 8.89 | 4.65 | 4.72 |
| 14 | 5.07 | 4.84 | 6.04 | 6.37 | 4.38 | 4.57 | 9.01 | 9.06 | 4.67 | 5.28 |
| 15 | 4.82 | 4.73 | 5.67 | 5.56 | 5.09 | 4.96 | 10.51 | 9.66 | 6.02 | 5.48 |
| 16 | 4.42 | 4.28 | 5.38 | 5.38 | 4.25 | 3.86 | 9.99 | 9.86 | 4.89 | 4.56 |
| 17 | 4.75 | 4.89 | 5.9 | 5.58 | 5.08 | 5.24 | 10.56 | 11.11 | 5.79 | 5.91 |
| 18 | 3.35 | 3.37 | 3.76 | 3.75 | 3.76 | 3.69 | 6.25 | 6.35 | 3.75 | 3.66 |
| 19 | 5.25 | 5.24 | 5.85 | 5.97 | 6.09 | 5.78 | 11.49 | 10.81 | 7.25 | 7.01 |
| 20 | 4.31 | 4.18 | 4.8 | 4.72 | 4.44 | 4.15 | 9.94 | 9.68 | 4.76 | 4.37 |
| 21 | 4.76 | 4.8 | 5.56 | 5.29 | 4.89 | 5.8 | 11.15 | 11.1 | 5.08 | 6.7 |
| 22 | 4.48 | 4.4 | 4.88 | 4.99 | 5.44 | 4.87 | 8.95 | 8.77 | 6.22 | 5.77 |
| 23 | 4.49 | 4.52 | 5.77 | 5.74 | 3.85 | 3.89 | 10.06 | 10.63 | 4.42 | 4.58 |
| 24 | 3.11 | 3.14 | 3.4 | 3.48 | 3.89 | 3.84 | 6.3 | 5.99 | 4.44 | 4.22 |
| 25 | 4.62 | 4.77 | 5.29 | 5.28 | 4.97 | 5.5 | 11.04 | 9.41 | 5.58 | 6.91 |
| 26 | 3.26 | 3.28 | 4.02 | 4.12 | 2.99 | 2.97 | 8.94 | 8.69 | 3.73 | 3.55 |
| 27 | 3.47 | 3.46 | 4.25 | 4.21 | 3.21 | 3.24 | 7.98 | 7.88 | 3.52 | 3.62 |
| 28 | 2.88 | 2.5 | 3.72 | 3.32 | 2.42 | 1.95 | 6.27 | 6.41 | 3.05 | 2.43 |
| 29 | 2.63 | 2.72 | 3.3 | 3.31 | 2.81 | 2.58 | 5.69 | 6.58 | 2.51 | 2.95 |
| 30 | 5.13 | 4.87 | 5.68 | 5.53 | 6.39 | 5.8 | 11.53 | 11.25 | 7.48 | 6.63 |
| Mean | 3.98 | 4.01 | 4.72 | 4.75 | 4.14 | 4.18 | 9.19 | 9.17 | 4.81 | 4.88 |
| SD± | 0.80 | 0.84 | 0.87 | 0.96 | 1.11 | 1.13 | 1.86 | 1.76 | 1.40 | 1.36 |
| Diff T1 & T2 | -0.03 | | -0.03 | | -0.04 | | 0.02 | | -0.06 | |
| ME | 0.165 | | 0.2 | | 0.312 | | 0.69 | | 0.466 | |
| V | 4.14% | | 4.21% | | 7.49% | | 7.51% | | 9.62% | |

APPENDIX I

ANOVA Summaries

| | | | | | |
|---|-------------|----|----------|-------|-------|
| Test of within subjects effects | | | | | |
| Baseline values for lung functions | | | | | |
| | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | 10.456 | 2 | 5.228 | 2.912 | 0.093 |
| Lung*Test | 8.91 | 8 | 1.114 | 3.097 | 0.007 |
| Baseline PEFR value | | | | | |
| Test A TestB | 30.619 | 1 | 30.619 | 8.123 | 0.029 |
| Test A TestC | 1.835 | 1 | 1.835 | 0.807 | 0.404 |
| HR ex A vs B vs C | | | | | |
| Test | 4.46E-02 | 2 | 2.23E-02 | 0.003 | 0.997 |
| HR resrt A vs B vs C | | | | | |
| Test | 111.867 | 2 | 55.933 | 1.865 | 0.197 |
| RPB ex A vs B vs C | | | | | |
| Test | 1.249 | 2 | 0.624 | 2.16 | 0.137 |
| RPB rest A vs B vs C | | | | | |
| | 6.109 | 2 | 3.054 | 3.763 | 0.054 |
| Test of within subjects Effects | | | | | |
| Lablity | | | | | |
| FVC | | | | | |
| Test | 767.251 | 2 | 383.625 | 4.145 | 0.043 |
| Test of within subjects Contrasts | | | | | |
| Test C Test A | 670.548 | 1 | 670.548 | 5.142 | 0.044 |
| Test C Test B | 96.703 | 1 | 96.703 | 1.768 | 0.232 |
| Test of within subjects Effects | | | | | |
| FEV1 | | | | | |
| Test | 1138.03 | 2 | 569.015 | 3.641 | 0.58 |
| Test of within subjects Effects | | | | | |
| FEV1% | | | | | |
| Test | 127.474 | 2 | 63.737 | 1.181 | 0.34 |
| Test of within subjects Effects | | | | | |
| FEF25-75 | | | | | |
| Test | 461.89 | 2 | 230.945 | 0.546 | 0.593 |
| Test of within subjects Effects | | | | | |
| PEFR | | | | | |
| Test | 2194.112 | 2 | 1097.056 | 4.151 | 0.043 |
| Test of within-subjects contrast | | | | | |
| PEFR | | | | | |
| Test C Test A | 2146.197 | 1 | 2146.197 | 8.699 | 0.026 |
| Test C Test B | 47.915 | 1 | 47.915 | 0.17 | 0.694 |

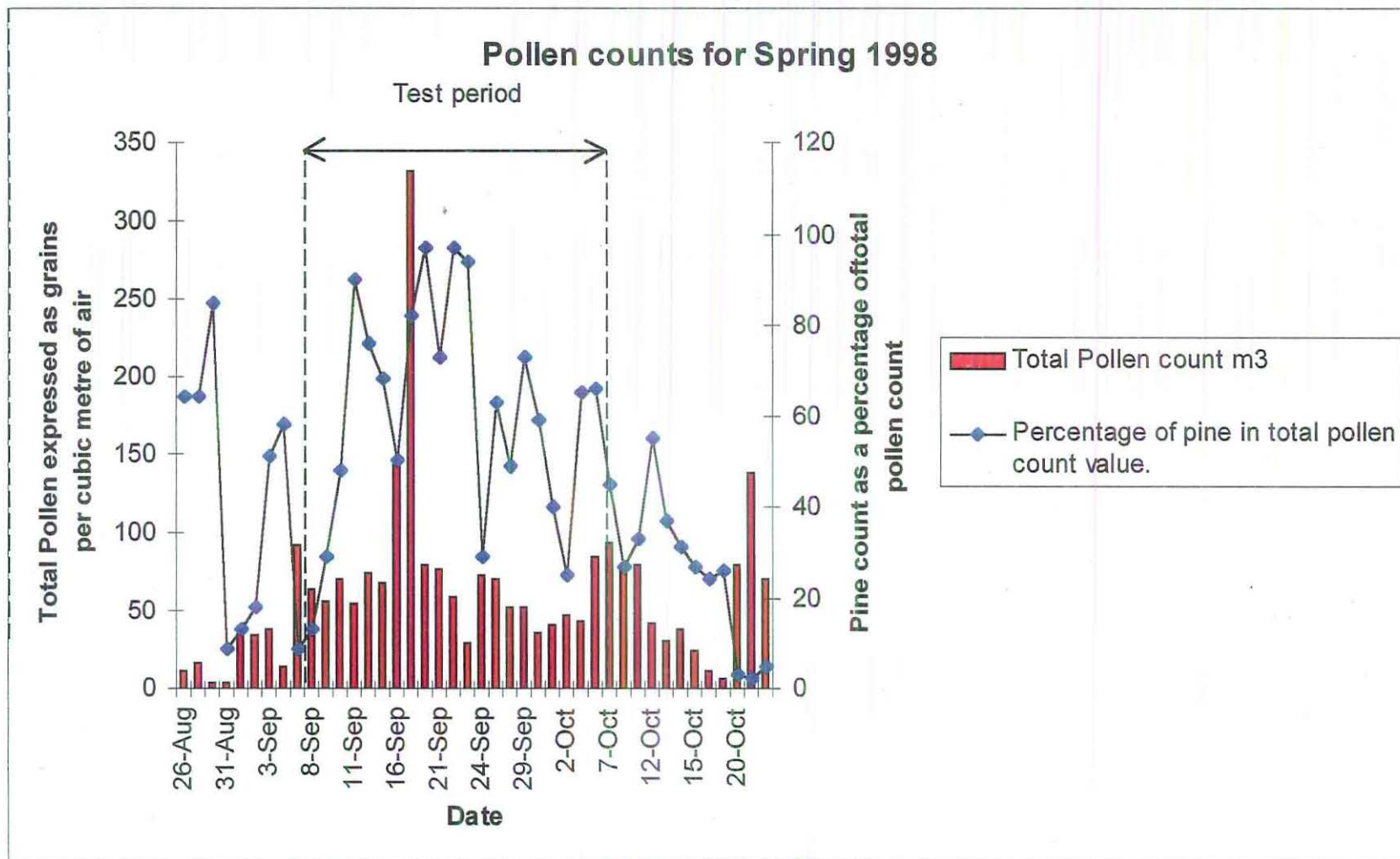
| | | | | | |
|---|-------------|----|----------|-------|-------|
| Test of within subjects Effects | | | | | |
| MEF50 | | | | | |
| Test | 828.314 | 2 | 414.157 | 0.846 | 0.453 |
| | | | | | |
| | Sum of sqrs | df | Mean sqr | F | sig p |
| Test of within subjects Effects | | | | | |
| Decrement | | | | | |
| FEV1 | | | | | |
| Test | 1481 | 2 | 740.5 | 2.876 | 0.095 |
| | | | | | |
| Test of within subjects Effects | | | | | |
| FVC | | | | | |
| Test | 975.253 | 2 | 487.627 | 2.909 | 0.093 |
| | | | | | |
| Test of within subjects Effects | | | | | |
| FEV1% | | | | | |
| Test | 147.448 | 2 | 73.724 | 0.917 | 0.426 |
| | | | | | |
| Test of within subjects Effects | | | | | |
| FEF25-75 | | | | | |
| Test | 2637.635 | 2 | 1318.818 | 3.387 | 0.068 |
| | | | | | |
| Test of within subjects Effects | | | | | |
| PEFR | | | | | |
| Test | 593.573 | 2 | 296.786 | 0.648 | 0.54 |
| | | | | | |
| Test of within subjects Effects | | | | | |
| MEF50 | | | | | |
| Test | 2679.497 | 2 | 1339.749 | 3.098 | 0.082 |
| | | | | | |
| T x T x s ANOVA time/test/subject. | | | | | |
| FEV1 | | | | | |
| | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | 15370.13 | 2 | 7685.064 | 2.983 | 0.089 |
| Lung*Test | 1385.377 | 12 | 115.448 | 2.514 | 0.008 |
| | | | | | |
| FEV1% | | | | | |
| | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | 2046.677 | 2 | 1023.338 | 2.142 | 0.16 |
| Lung*Test | 219.366 | 12 | 18.28 | 0.68 | 0.765 |
| | | | | | |
| MEF50 | | | | | |
| | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | 55367.474 | 2 | 27683.74 | 4.062 | 0.045 |
| Lung*Test | 2758.573 | 12 | 229.881 | 1.522 | 0.136 |
| | | | | | |
| Test of within subjects Contrasts | | | | | |
| MEF50 | | | | | |

| | | | | | | |
|----------------------------------|--------|-------------|----|----------|--------|-------|
| Test C | Test A | 4679.262 | 1 | 4679.262 | 1.298 | 0.298 |
| Test C | Test B | 108231.1 | 1 | 108231.1 | 7.226 | 0.036 |
| | | | | | | |
| MEF50 3 minutes | | 9153.638 | 2 | 4576.819 | 4.082 | 0.044 |
| Contrast | | | | | | |
| Test C | Test A | 3546.572 | 1 | 3546.572 | 2.552 | 0.161 |
| Test C | Test B | 8223.144 | 1 | 8223.144 | 7.853 | 0.031 |
| | | | | | | |
| MEF50 7 minutes | | 12179.778 | 2 | 6089.889 | 5.476 | 0.02 |
| Contrast | | | | | | |
| Test C | Test A | 5624.055 | 1 | 5624.055 | 2.556 | 0.161 |
| Test C | Test B | 24347.358 | 1 | 24347.36 | 9.792 | 0.02 |
| | | | | | | |
| MEF50 10 minutes | | 9013.128 | 2 | 4506.564 | 6.58 | 0.012 |
| Contrast | | | | | | |
| Test C | Test A | 3662.076 | 1 | 3662.076 | 2.855 | 0.142 |
| Test C | Test B | 7969.74 | 1 | 7969.74 | 13.308 | 0.011 |
| | | | | | | |
| MEF50 20 minutes | | 6481.977 | 2 | 3240.988 | 5.157 | 0.024 |
| Contrast | | | | | | |
| Test C | Test A | 2681.373 | 1 | 2681.373 | 2.349 | 0.176 |
| Test C | Test B | 2929.649 | 1 | 2929.649 | 10.794 | 0.017 |
| | | | | | | |
| PEFR | | | | | | |
| | | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | | 13869.76 | 2 | 6934.881 | 0.92 | 425 |
| Lung*Test | | 1802.642 | 12 | 150.22 | 1.762 | 0.071 |
| | | | | | | |
| FVC | | | | | | |
| | | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | | 6159.009 | 2 | 3079.504 | 2.793 | 0.101 |
| Lung*Test | | 1134.551 | 12 | 94.546 | 4.483 | 0.001 |
| T-TEST USED.FOR post hoc | | | | | | |
| FEF25-75 | | | | | | |
| | | Sum of sqrs | df | Mean sqr | F | sig p |
| Test | | 43314.18 | 2 | 21657.09 | 3.992 | 0.047 |
| Lung*Test | | 1766.161 | 12 | 147.18 | 1.057 | 0.408 |
| | | | | | | |
| Test of within-subjects contrast | | | | | | |
| FEF25-75 | | | | | | |
| Test C | Test A | 15124.6 | 1 | 15124.6 | 1.576 | 0.256 |
| Test C | Test B | 85888.77 | 1 | 85888.77 | 6.911 | 0.039 |
| | | | | | | |
| FEF25-75 3 minutes | | 7422.077 | 2 | 3711.039 | 4.563 | 0.034 |
| Contrast | | | | | | |
| Test C | Test A | 2442.197 | 1 | 2442.197 | 2.179 | 0.19 |
| Test C | Test B | 14678.15 | 1 | 14678.15 | 7.442 | 0.034 |
| | | | | | | |
| FEF25-75 7 minutes | | 9101.516 | 2 | 4550.758 | 5.61 | 0.019 |
| Contrast | | | | | | |
| Test C | Test A | 4515.646 | 1 | 4515.646 | 2.638 | 0.155 |

| | | | | | | |
|-----------------|-------------------|-----------|---|----------|--------|-------|
| Test C | Test B | 18202.94 | 1 | 18202.94 | 9.397 | 0.022 |
| | | | | | | |
| FEF25-75 | 10 minutes | 5700.919 | 2 | 2850.459 | 4.224 | 0.041 |
| Contrast | | | | | | |
| Test C | Test A | 3109.169 | 1 | 3109.169 | 2.877 | 0.141 |
| Test C | Test B | 11394.234 | 1 | 11394.23 | 7.193 | 0.036 |
| | | | | | | |
| FEF25-75 | 20 minutes | 6496.145 | 2 | 3248.073 | 6.549 | 0.012 |
| Contrast | | | | | | |
| Test C | Test A | 897.996 | 1 | 897.996 | 1.832 | 0.225 |
| Test C | Test B | 5598.149 | 1 | 5598.149 | 11.157 | 0.016 |
| | | | | | | |
| | | | | | | |

APPENDIX J

Pollen Count Graph and Data.



1998 Pollen Counts

Data collected by K.G. Maybury

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| Date | Pollen/m3 | % Pine | % Eucalypt | % Grass | % Compositae | % Callitris | %Unclassified |
|----------|-----------|--------|------------|---------|--------------|-------------|---------------|
| 26/08/98 | 12 | 64 | 4 | 9 | 1 | 19 | 2 |
| 27/08/98 | 17 | 64 | 4 | 14 | 2 | 15 | 1 |
| 28/08/98 | 4 | 85 | 0 | 0 | 0 | 15 | 0 |
| 31/08/98 | 4 | 9 | 12 | 0 | 0 | 79 | 0 |
| 1/09/98 | 37 | 13 | 27 | 4 | 0 | 52 | 4 |
| 2/09/98 | 34 | 18 | 24 | 0 | 0 | 53 | 5 |
| 3/09/98 | 39 | 51 | 4 | 0 | 0 | 43 | 1 |
| 4/09/98 | 14 | 58 | 11 | 4 | 0 | 22 | 4 |
| 7/09/98 | 92 | 9 | 3 | 8 | 7 | 63 | 10 |
| 8/09/98 | 64 | 13 | 3 | 8 | 13 | 44 | 19 |
| 9/09/98 | 56 | 29 | 2 | 10 | 3 | 34 | 22 |
| 10/09/98 | 71 | 48 | 1 | 4 | 1 | 33 | 13 |
| 11/09/98 | 55 | 90 | 1 | 0 | 0 | 7 | 2 |
| 14/09/98 | 75 | 76 | 5 | 2 | 1 | 11 | 5 |
| 15/09/98 | 68 | 68 | 4 | 5 | 5 | 13 | 4 |
| 16/09/98 | 144 | 50 | 2 | 14 | 2 | 27 | 6 |
| 17/09/98 | 332 | 82 | 0 | 1 | 1 | 14 | 2 |
| 18/09/98 | 79 | 97 | 1 | 0 | 1 | 0 | 0 |
| 21/09/98 | 77 | 73 | 2 | 2 | 0 | 13 | 9 |
| 22/09/98 | 59 | 97 | 1 | 0 | 2 | 0 | 0 |
| 23/09/98 | 29 | 94 | 1 | 0 | 1 | 2 | 2 |
| 24/09/98 | 73 | 29 | 1 | 13 | 5 | 37 | 15 |
| 25/09/98 | 71 | 63 | 9 | 7 | 0 | 14 | 7 |
| 28/09/98 | 53 | 49 | 1 | 1 | 0 | 42 | 6 |
| 29/09/98 | 53 | 73 | 1 | 2 | 0 | 19 | 5 |
| 30/09/98 | 36 | 59 | 3 | 5 | 0 | 21 | 11 |
| 1/10/98 | 41 | 40 | 1 | 4 | 0 | 46 | 9 |
| 2/10/98 | 47 | 25 | 2 | 48 | 0 | 18 | 6 |
| 5/10/98 | 43 | 65 | 2 | 15 | 3 | 10 | 5 |
| 6/10/98 | 85 | 66 | 1 | 5 | 2 | 22 | 4 |
| 7/10/98 | 94 | 45 | 3 | 20 | 5 | 19 | 8 |
| 8/10/98 | 80 | 27 | 2 | 21 | 0 | 41 | 8 |
| 9/10/98 | 79 | 33 | 1 | 22 | 0 | 39 | 4 |
| 12/10/98 | 42 | 55 | 1 | 18 | 0 | 16 | 10 |
| 13/10/98 | 31 | 37 | 10 | 14 | 0 | 26 | 13 |
| 14/10/98 | 39 | 31 | 0 | 35 | 1 | 26 | 7 |
| 15/10/98 | 25 | 27 | 2 | 21 | 0 | 26 | 24 |
| 16/10/98 | 11 | 24 | 18 | 15 | 0 | 24 | 18 |
| 19/10/98 | 7 | 26 | 15 | 23 | 0 | 21 | 15 |
| 20/10/98 | 79 | 3 | 1 | 56 | 4 | 21 | 14 |
| 21/10/98 | 139 | 2 | 2 | 62 | 4 | 16 | 13 |
| 22/10/98 | 70 | 5 | 4 | 45 | 5 | 15 | 26 |