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Enhanced delivery of nebulised salbutamol during non-invasive ventilation

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Abstract

Non-invasive ventilation (NIV) is used to treat acute respiratory failure. Nebulised drugs can be delivered concurrently with NIV or during breaks from ventilatory support. We hypothesised that the amount of nebulised salbutamol inhaled when delivered via bi-level ventilation would be no different to the amount available directly from the same nebuliser. A standard bi-level ventilation circuit was attached to a lung model simulating adult respiration. Drug delivery was compared when salbutamol (5 mg) was nebulised at different positions in the circuit and separately, with no ventilator. The amount of salbutamol contained in various particle size fractions was also determined. Nebuliser position within the NIV circuit was critically important for drug delivery. Optimal delivery of salbutamol occurred with the expiration port between the facemask and nebuliser ($647 \pm 67\ \mu g$). This was significantly better than nebulisation without the ventilator ($424 \pm 61\ \mu g$; $P < 0.01$). Delivery when the nebuliser was positioned between the facemask and expiration port was $544 \pm 85\ \mu g$. The amount of salbutamol contained in particles $< 5\ \mu m$ was significantly increased when the nebuliser was used in conjunction with bi-level ventilation ($576 \pm 60\ \mu g$ vs $300 \pm 43\ \mu g$, $P < 0.001$). We conclude that nebulised bronchodilator therapy, using a Cirrus jet nebuliser, during bi-level ventilation increases respirable particles likely to be inhaled when the nebuliser is optimally positioned within the circuit.

Introduction

Regular inhaled bronchodilators are an important component of the medical management of acute exacerbations of chronic obstructive airways disease (COPD). They can significantly reduce airway obstruction and hyperinflation, and mechanical load on respiratory muscles. Inhaled bronchodilators are delivered either by nebulised solution or metered dose inhaler, but are usually administered in the nebulised form during acute exacerbations, as frequently as every 4 h initially (British Thoracic Society Nebuliser Project Group 1997). COPD patients developing acute hypercapnic respiratory failure are often commenced on non-invasive ventilation (NIV) using a bi-level positive airway pressure ventilator and the efficacy of this treatment is now well established (British Thoracic Society Standards of Care Committee 2002). NIV is used to reduce inspiratory muscle effort and respiratory rate, increase tidal volumes and improve arterial blood gases (Diaz et al 1997; Girault et al 1997). During treatment with NIV, it is important that inhaled bronchodilator therapy is continued. Traditionally, patients are taken off the ventilator to receive their nebulised bronchodilator, which can take 5–10 min to deliver. However, there are a number of advantages in remaining on the ventilator, particularly during the first 24 h, as the beneficial effects of NIV on respiratory dynamics are rapidly lost when it is stopped. It is therefore highly desirable for bronchodilator therapy to be given concurrently with NIV.

Although significant data exist in the current literature on the administration of inhaled bronchodilator therapy during invasive mechanical ventilation in patients with COPD (Mouloudi 2001; Duarte 2004), little data is available on delivery of bronchodilators during NIV. Two studies in patients with stable asthma (Parkes & Bersten 1997) and COPD (Nava et al 2001) have confirmed that aerosol delivery during NIV is feasible and can be effective, and data from a bench model study (Chatmongkolchart et al 2002) shows a nebuliser placed in the NIV circuit does not affect ventilator function. However, it is not known if delivery of nebulised salbutamol via a bi-level ventilator results in the same delivery of drug to the patient compared with

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inhalation directly from the nebuliser, and the effect of the bi-level ventilation on the amount of salbutamol contained in various particle size fractions has not been studied. Such information is essential as the particle size of a drug aerosol may have a significant effect on where the drug deposits.

We performed an in-vitro study using a bench model of adult respiration, to evaluate the effects of bi-level ventilation on the total amount of the bronchodilator salbutamol likely to be inhaled and the amount of salbutamol contained in various particle size fractions. We hypothesised that the amount of nebulised salbutamol that would be inhaled when delivered via bi-level ventilation would be no different to the amount available directly from the same nebuliser. The study also aimed to assess if the position of the nebuliser in the NIV circuit affected the total dose of salbutamol likely to be inhaled.

Materials and Methods

Study one

A Pari COMPAS breath simulator (Pari GmbH, Starnberg, Germany), set to produce a sinusoidal breath pattern, was connected to a bi-level ventilator (Knightstar 335, Mallincroft, UK) and circuit by means of a facemask pressed tightly against the faceplate of the breathing simulator (Figure 1). The NIV circuit consisted of a 187-cm length of disposable corrugated tubing (diameter of 25 mm) and a fixed leak expiration port. Spontaneous breathing was simulated to represent that of a typical adult and provided a tidal volume of 600 mL, breathing rate of 12 breaths/min and inspiratory phase of 40% (Barry & O'Callaghan 1998). The bi-level ventilator was set in spontaneous mode at an inspiratory pressure (IPAP) of 20 cmH_2O and expiratory pressure (EPAP) of 5 cmH_2O. Ventilator pressures were chosen as typical levels used for COPD patients when bi-level ventilation is initiated during acute exacerbations in clinical practice (British Thoracic Society Standards of Care Committee 2002).

Salbutamol 5 mg in 2.5 mL normal saline (Salamol; Ivax Pharmaceuticals, Runcorn, UK), was nebulised for 5 min using a Cirrus jet nebuliser (Intersurgical Ltd, Wokingham, UK) driven by a Medix Econoneb compressor (Clement Clarke, Harlow, Essex, UK) at a flow rate of 7 L min^{-1}. This nebuliser was chosen as it is used clinically in our department. The nebuliser position was varied within the ventilator circuit (Figure 1). The distances between the nebuliser and the breathing simulator faceplate were 10 cm, 19 cm and 204 cm for positions A, B and C, respectively. In a control study the nebuliser was attached directly to the facemask via a T-piece independent of the NIV circuit. An electrostatic filter pad (Pari GmbH, Starnberg, Germany) in a low dead-space filter holder (the inspiratory filter) was placed between the breathing simulator and the faceplate to trap the drug that would have been inhaled. At each nebuliser position in the NIV circuit the experiment was repeated five times, and for control conditions three times. The amount of salbutamol collected on the inspiratory filters was quantified using reverse-phase high-performance liquid chromatography (HPLC) (Barry & O'Callaghan 1999). A 10-cm Spherisorb ODS1 column (4.6 mm i.d.; Fisher Scientific, Loughborough, UK) was used with methanol–0.25% ammonium acetate as the mobile phase. The internal standard was benzyl biphenyl and ultraviolet detection was used at a wavelength of 276 nm. The limit of detection of the assay for salbutamol was $< 0.05\ \mu g\ mL^{-1}$. The system response was linear over a range of salbutamol concentrations (0.3–10 $\mu g\ mL^{-1}$). The coefficient of variation of the assay was 6% (at a concentration of 0.5 $\mu g\ mL^{-1}$).

Study two

A Next Generation Impactor (NGI) (Copley Scientific Ltd, Nottingham, UK) was used to determine the particle size distribution of the aerosolised drug delivered to the inspiratory filter. The experimental set-up was the same as for study one, using the nebuliser in position B, which gave the highest filter deposition of salbutamol during study one. The induction port of the NGI was connected into the circuit between the faceplate and inspiratory filter and a sample of aerosolised salbutamol was drawn through the NGI at a flow of 15 L min^{-1} using a vacuum pump. To minimise evaporation of the aerosol droplets, and resultant underestimation of their size, the NGI was cooled to 6–8°C (Berg & Asking 2004) and removed from the fridge

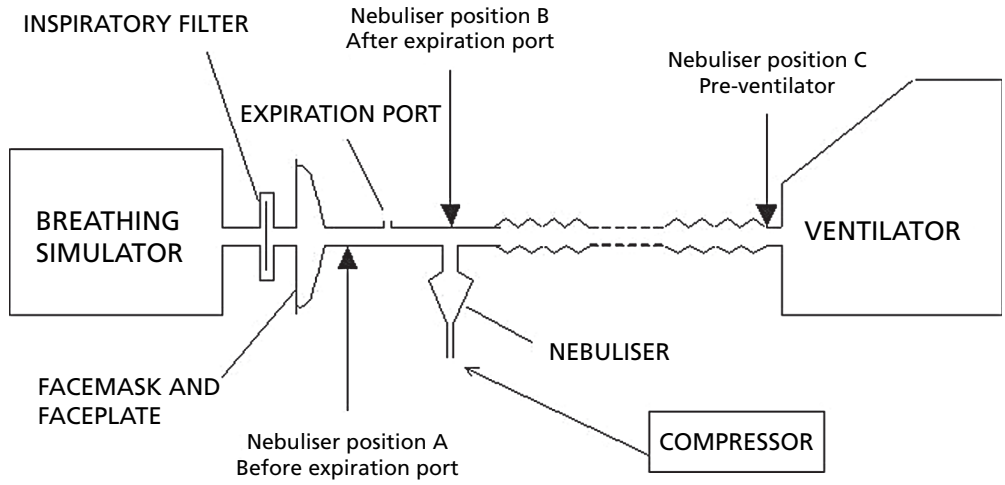

Figure 1 Bench model apparatus: breathing simulator and bi-level ventilator circuit. Nebuliser positions within the circuit are indicated.

immediately before each use. Particle size was measured 5 times with the ventilator on, 3 times with the ventilator switched off and 3 times with the nebuliser used independent of the NIV circuit (nebuliser and t-piece connected directly to the NGI). NGI cut-offs were: Stage 1, 14.1; Stage 2, 8.6; Stage 3, 5.4; Stage 4, 3.3; Stage 5, 2.1; Stage 6, 1.4; and Stage 7, 0.98 microns. The amount of drug deposited on each stage of the impactor was quantified by HPLC.

Data analysis

All data are expressed as mean±standard deviation. A one-way analysis of variance followed by Bonferroni post tests was used to determine whether the nebuliser position in the NIV circuit affected drug output and if using the nebuliser in the ventilator circuit resulted in a similar output to when it was used independently. For each particle sizing experiment, the total mass of drug deposited in the NGI and the percentage in each stage of the impactor was calculated. Cumulative percentages of drug in particles less than the effective cut-off size of each stage were calculated and a log probability plot prepared. This plot was used to predict the percentages of drug contained in particles with an aerodynamic diameter less than 5 μm and 3 μm. A one-way analysis of variance was used to determine whether the ventilator or circuitry affected the small particle fraction of the aerosolised salbutamol. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) of the aerosolised salbutamol were also calculated.

Results

Study one

Figure 2 shows the amount of salbutamol deposited on the inspiratory filter when the nebuliser was placed in 3 different positions in the NIV circuit and when used independently. Placing the nebuliser at position B in the circuit resulted in the highest output of salbutamol to the filter, slightly more ($P > 0.05$) than position A (544 ± 85 μg) and significantly more ($P < 0.001$) than position C (267 ± 26 μg). The 647 ± 67 μg of salbutamol deposited when the nebuliser was at position B in the circuit equates to 13% of the nominal dose of salbutamol and was significantly more ($P < 0.01$) than the 424 ± 61 μg (8.5% nominal dose) deposited when the nebuliser was used without the circuit.

Study two

Table 1 summarises the particle sizing data. The percentages of aerosolised salbutamol in particles < 5 μm and < 3 μm in diameter were significantly higher ($P < 0.001$) when the nebuliser was incorporated into the NIV circuit with the ventilator on, compared with when it was used without the circuit. Using the nebuliser without the NIV circuit, or in the circuit with the ventilator off, produced aerosols with a similar particle fraction. Assuming that particles smaller than 5 μm are likely to be deposited in the lower airways, the total amount of drug available for inhalation contained in particles < 5 μm was estimated by multiplying the total drug deposition on the inspiratory filters in study one by the appropriate mean percentage of drug in particles < 5 μm calculated in study two. The amount of salbutamol calculated to be contained in particles < 5 μm was significantly more ($P < 0.001$) when the nebuliser was used in conjunction with ventilation (576 ± 60 μg) than without (300 ± 43 μg).

Discussion

Using a bench model of spontaneous adult breathing, we have demonstrated that the total amount of salbutamol that would

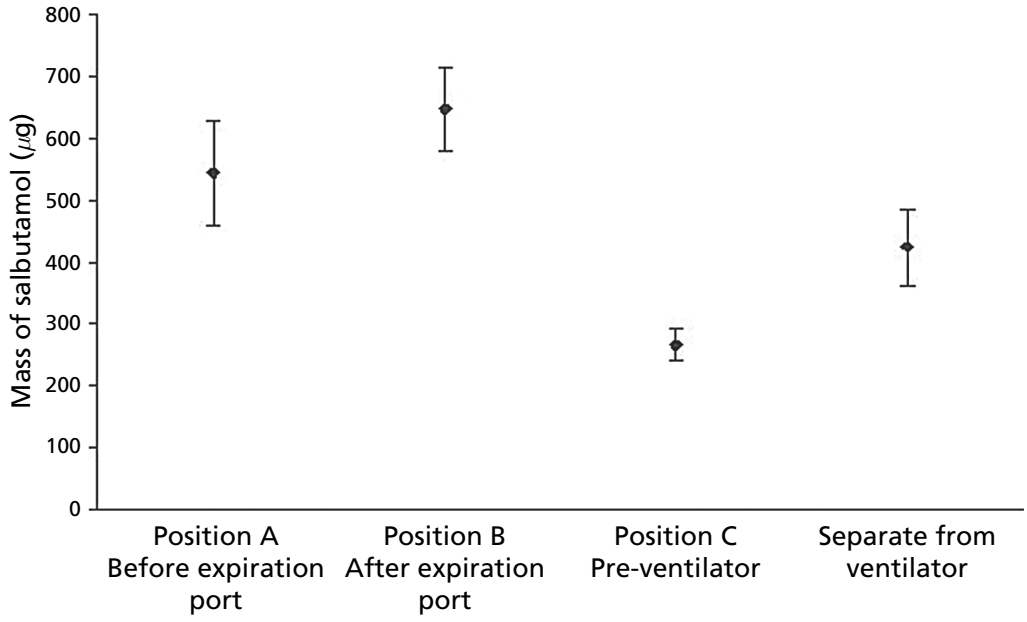

Figure 2 Mean (±standard deviation) weight of salbutamol recovered from inspiratory filter after 5 min nebulisation.

Table 1 Particle sizing data for aerosolised salbutamol when the nebuliser was used in the NIV circuit, with and without the ventilator switched on, and independent of the NIV circuit

	% Salbutamol in particles < 5 μm	% Salbutamol in particles < 3 μm	MMAD (μm)	GSD
Ventilator ON	89.12 (3.63)	70.93 (6.44)	2.21 (0.36)	2.15 (0.18)
Ventilator OFF	74.83 (1.65)	52.17 (1.88)	2.99 (0.12)	2.08 (0.02)
No NIV circuit	70.08 (3.14)	47.57 (3.04)	3.12 (0.21)	2.28 (0.07)

Data are presented as means (standard deviation). MMAD, mass median aerodynamic diameter; GSD, geometric standard deviation.

have been inhaled is significantly increased when nebulised via bi-level ventilation (IPAP 20 cmH_2O, EPAP 5 cmH_2O) with the Cirrus nebuliser run by a Medix Econeb compressor placed in the optimal position in the circuit as opposed to directly to the patient separate from the ventilator. Our results also show that the position of the nebuliser in the NIV circuit has a significant effect on the total dose of nebulised salbutamol patients are likely to inhale. The nebuliser can be positioned either side of the fixed leak expiration port for effective delivery, but the optimal position appears to be immediately after the expiration port (i.e. starting from the facemask, the expiration port is positioned before the nebuliser). As nebuliser designs vary, it is important each different type of nebuliser used in such a system is individually assessed. The most likely reason for increased drug availability, when the nebuliser is used optimally in the NIV circuit, is that the tubing acts as a spacer device. During inspiration, drug aerosol that does not deposit on the tubing walls or other parts of the circuitry will be captured on the inspiratory filter. The nebuliser will continue to deliver aerosol to the circuit during expiration, some of which will deposit on the tubing and some of which will exit the circuit via the expiratory port. However, some of the drug will still remain in aerosol particles within the tubing and will be inhaled during the next breath. A higher concentration of aerosol is available for inhalation in position B (starting from the facemask, the expiration port is positioned before the nebuliser) over position A (starting from the facemask, the nebuliser is positioned before the port). The most likely explanation is that more aerosol leaves the circuit via the expiration leak port when the nebuliser is in position A. In contrast, when the nebuliser is used independent of the circuit, aerosol produced during expiration will be lost.

If the nebuliser is placed away from the facemask, adjacent to the ventilator, the amount of salbutamol available for inhalation is significantly reduced compared with when the nebuliser is placed close to the facemask. These findings differ from invasive mechanical ventilation where a distance of at least 30 cm from the endotracheal tube has been identified as the ideal position of a nebuliser (Coleman et al 1996). There are two possible explanations. Firstly, there is likely to be enhanced deposition of drug as it passes along the ventilator tubing towards the patient. Secondly, during the inspiratory cycle of the ventilator aerosol in tubing close to the ventilator will be sucked into it.

Bosco et al (2005) have shown that breath simulation can provide an accurate in-vitro tool for estimating in-vivo aerosol delivery but cannot yet replace in-vivo measurements due to limitations in simulator operation. Breath simulation was an inaccurate tool for estimating the time to nebuliser dryness (Bosco et al 2005). Ideally, further studies using patients would be required to determine the effect of having a patient in the circuit. In our next study, we intend to use pharmacokinetic methods to estimate lung deposition of salbutamol.

Chatmongkolchart et al (2002) recently investigated bronchodilator therapy during NIV and found that salbutamol delivery was greatest with the nebuliser placed nearer the patient. Our data confirms this but gives additional information on the optimal position in relation to the expiration port and compares this with conventional nebulisation without the ventilator. Chatmongkolchart also found that drug delivery increased with increasing inspiratory pressure and decreased as expiratory pressure levels were increased, and that nebuliser flow had no effect on ventilator function. The settings used in our study were chosen as typical of those used widely in clinical practice when initiating NIV.

There is a strong evidence base for the use of NIV in the management of acute hypercapnic respiratory failure in COPD (British Thoracic Society Standards of Care Committee 2002). A further attraction of NIV is the avoidance of intubation, with its associated high morbidity and mortality (Hudson 1989). Regular inhaled bronchodilator therapy is an important component of the medical management of acute exacerbations of COPD and should be continued alongside NIV whenever it is instigated. Current clinical practice when patients are receiving NIV is to deliver nebulised bronchodilators during breaks from the ventilator. However, the effects on respiratory dynamics are rapidly lost when NIV is stopped (Martin et al 1982). Patients may not tolerate even short periods of time off the ventilator during this critical period. There are therefore a number of practical advantages to delivering nebulised therapy concurrently with NIV. However, the effectiveness of nebulisation during NIV has received little attention from the literature (Ceriana et al 2003), and it remains unclear whether the concurrent delivery of NIV interferes with the drug likely to be inhaled. The amount of drug delivered to the airways may be reduced by impaction on apparatus and changes in airflow rate (Phipps & Gonda 1990; Brand et al 1999). Particle size may be altered and consequently distribution of the drug within the airways will change. All these factors will have a potential effect on the therapeutic response to nebulised bronchodilator. Measuring aerosol properties and clinical effect in acutely unwell COPD patients with respiratory failure poses a number of difficulties but this study gives useful information on aerosol characteristics that can be used to help predict likely efficacy in-vivo.

Our study confirms that patients on bi-level ventilation may receive a substantially greater amount of nebulised salbutamol compared with inhaling salbutamol directly from the nebuliser, and that bi-level ventilation appears to increase the proportion of respirable particles (< 5 μm) within the aerosol produced. The reduction in particle size is most likely to be due to evaporation from particles in the circuit during nebulisation. However, this study does not predict how drug is likely to be distributed within the lungs of COPD patients, which may be dependent on factors such as inspiratory flow. França et al (2006) have shown reduced radioisotope lung distribution for nebulisation associated with NIV in healthy young subjects, which they attributed to higher flow rates achieved with NIV. However, in patients with airflow obstruction, NIV is likely to be more beneficial for drug distribution. Of interest, Fauroux and colleagues demonstrated an increase of 30% in total aerosol lung deposition, without increased particle impaction in the proximal airways, with the use of pressure support ventilation in children with cystic fibrosis (Fauroux et al 2000).

In conclusion, this study confirms that when using bi-level ventilation set at pressures commonly used in clinical practice, NIV enhances the amount of nebulised bronchodilator therapy that would be inhaled when a Cirrus nebuliser run by a Medix Econeb compressor is positioned optimally within the circuit. Furthermore, we have shown that aerosol characteristics are maintained and may even be improved when the nebuliser is given concurrently with bi-level ventilation. NIV is increasingly used in patients with COPD and acute respiratory failure, and there are a number of benefits to keeping patients on NIV while delivering nebulised therapy. Demonstration of the efficacy of this method of delivery therefore represents an important finding and further studies are now indicated to evaluate further whether clinical benefit in COPD subjects during the stable and acute setting is also seen.

References

Barry P. W., O'Callaghan C. (1998) Drug output from nebulisers is dependent on the method of measurement. *Eur. Respir. J*. **12**: 463–466

Barry, P. W., O'Callaghan, C. (1999) An in-vitro analysis of the output of salbutamol from different nebulisers. *Eur. Respir. J*. **13**: 1164–1169

Berg, E., Asking, L. (2004) Nebuliser droplet size distribution-refrigerated NGI at 15L/min. *Respir. Drug Deliv*. **IX**: 315–317

Bosco, A. P., Rhem, R. G., Dolovich, M. B. (2005) In vitro estimations of in vivo jet nebulizer efficiency using actual and simulated tidal breathing patterns. *J. Aerosol. Med*. **18**: 427–438

Brand, P., Haussinger, K., Meyer, T., Scheuch, G., Schulz, H., Selzer, T., Heyder, J. (1999) Intrapulmonary distribution of deposited particles. *J. Aerosol. Med*. **12**: 275–284

British Thoracic Society Nebuliser Project Group (1997) Nebuliser therapy. Guidelines. *Thorax*. **52** (Suppl. 2): S1–S24

British Thoracic Society Standards of Care Committee: Baudouin, S., Blumenthal, S., Cooper, B., Davidson, C., Davison, A., Elliot, M., Kinnear, W. (Chairman), Paton, R., Sawicka, E., Turner, L. (Secretary) (2002) Non-invasive ventilation in acute respiratory failure. *Thorax* **57**: 192–211

Ceriana, P., Navalesi, P., Rampulla, C., Prinianakis, G., Nava, S. (2003) Use of bronchodilators during non-invasive mechanical ventilation. *Monaldi Arch. Chest Dis*. **59**: 123–127

Chatmongkolchart, S., Schettino, G. P., Dillman, C., Kacmarek, R. M., Hess, D. R. (2002) In vitro evaluation of aerosol bronchodilator delivery during non-invasive positive pressure ventilation: effect of ventilator settings and nebuliser position. *Crit. Care Med*. **30**: 2515–2519

Coleman, D. M., Kelly, H. W., McWilliams, B. C. (1996) Therapeutic aerosol delivery during mechanical ventilation. *Ann. Pharmacother*. **30**: 644–655

Diaz, O., Iglesia, R., Ferrer, M., Zavala, E., Santos, C., Wagner, P. D., Roca, J., Rodriguez-Roisin, R. (1997) Effects of non-invasive ventilation on pulmonary gas exchange and hemodynamics during acute hypercapnic exacerbations of chronic obstructive airways disease. *Am. J. Respir. Crit. Care Med*. **156**: 1840–1845

Duarte, A. G. (2004) Inhaled bronchodilator administration during mechanical ventilation. *Respir. Care* **49**: 623–634

Fauroux, B., Itti, E., Pigeot, J., Isabey, D., Meignan, M., Ferry, G., Lofaso, F., Willemot, J. M., Clément, A., Harf, A. (2000) Optimization of aerosol deposition by pressure support in children with cystic fibrosis: an experimental and clinical study. *Am. J. Respir. Crit. Care Med*. **162**: 2265–2271

França, E. E. T., Dornelas de Andrade, A. F., Cabral, G., Filho, P. A., Silva, K. C., Filho, V. C. G., Marinho, P. E. M., Lemos, A., Parreira, V. F. (2006) Nebulization associated with bi-level noninvasive ventilation: analysis of pulmonary radioaerosol deposition. *Respir. Med*. **100**: 721–728

Girault, C., Richard, J., Chevron, V., Tamion, F., Pasquis, P., Leroy, J., Bonmarchand, G. (1997) Comparative physiologic effects of non-invasive assist-control and pressure support ventilation in acute hypercapnic respiratory failure. *Chest* **111**: 1639–1648

Hudson, L. D. (1989) Survival data in patients with acute and chronic lung disease requiring mechanical ventilation. *Am. Rev. Respir. Dis*. **140**: S19–S24

Martin, J. G., Shore, S., Engel, L. A. (1982) Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am. Rev. Respir. Dis*. **126**: 812–817

Mouloudi, E., Maliotakis, C., Kondili, E., Kafetzakis, A., Georgopoulos, D. (2001) Duration of salbutamol-induced bronchodilation delivered by metered-dose inhaler in mechanically ventilated COPD patients. *Monaldi Arch. Chest Dis*. **56**: 189–194

Nava, S., Karakurt, S., Rampulla, C., Braschi, A., Fanfulla, F. (2001) Salbutamol delivery during non-invasive mechanical ventilation in patients with chronic obstructive pulmonary disease: a randomised, controlled study. *Intensive Care Med*. **27**: 1627–1635

Parkes, S. N., Bersten, A. D. (1997) Aerosol kinetics and bronchodilator efficacy during continuous positive airway pressure delivered by facemask. *Thorax* **52**: 171–175

Phipps, P. R., Gonda, I. (1990) Droplets produced by medical nebulisers. Some factors affecting their size and solute concentration. *Chest* **97**: 1327–1332