

## ORIGINAL PAPER

# Domiciliary humidification improves lung mucociliary clearance in patients with bronchiectasis

A Hasani<sup>1</sup>, TH Chapman<sup>2</sup>, D McCool<sup>3</sup>, RE Smith<sup>1</sup>, JP Dilworth<sup>2</sup> and JE Agnew<sup>1</sup>

<sup>1</sup>Department of Medical Physics, Royal Free Hospital, London, UK; <sup>2</sup>Department of Thoracic Medicine, Royal Free Hospital, London, UK; and <sup>3</sup>Department of Nuclear Medicine, Royal Free Hospital, London, UK

Inspired air humidification has been reported to show some benefit in bronchiectatic patients. We have investigated the possibility that one effect might be to enhance mucociliary clearance. Such enhancement might, if it occurs, help to lessen the risks of recurrent infective episodes. Using a radioaerosol technique, we measured lung mucociliary clearance before and after 7 days of domiciliary humidification. Patients inhaled high flow saturated air at 37 °C via a patient-operated humidification nasal inhalation system for 3 h per day. We assessed tracheobronchial mucociliary clearance from the retention of <sup>99m</sup>Tc-labelled polystyrene tracer particles monitored for 6 h, with a follow-up 24-h reading. Ten out of 14 initially recruited patients (age 37–75 years; seven females) completed the study (two withdrew after their initial screening and two prior to the initial clearance test). Seven patients studied were non-smokers; three were ex-smokers (1–9 pack-years). Initial tracer radioaerosol distribution was closely similar between pre- and post-treatment. Following humidification, lung mucociliary clearance significantly improved, the area under the tracheobronchial retention curve decreased from 319 ± 50 to 271 ± 46%h ( $p < 0.007$ ). Warm air humidification treatment improved lung mucociliary clearance in our bronchiectatic patients. Given this finding plus increasing laboratory and clinical interest in humidification mechanisms and effects, we believe further clinical trials of humidification therapy are desirable, coupled with analysis of humidification effects on mucus properties and transport. *Chronic Respiratory Disease* 2008; 5: 81–86

**Key words:** bronchiectasis; humidification; mucociliary clearance; radioaerosol

## Introduction

Lung mucus retention is a prominent feature of bronchiectasis and an important pre-disposing factor to the vicious cycle of recurrent respiratory infection.<sup>1</sup> Stagnant mucus tends to become chronically colonized with bacteria capable of giving rise to overt recurrent episodes of infection.<sup>2</sup> The sensation of retained mucus and a concomitant high frequency of coughing and sputum production can furthermore be distressing to the patient.

The importance of mucociliary clearance as a first-line defense mechanism of the bronchial tree is well established.<sup>3</sup> Clearance by cough comes into play when mucociliary clearance is impaired.<sup>4</sup> Whether achieved by mucociliary clearance or by cough, active removal of microbial matter and host-derived inflammatory products is essential if a vicious cycle of microbial colonization is to be

avoided.<sup>5</sup> Clearly the role of water, as a main constituent of mucus, can be crucial to the composition of mucus and to its transportability.<sup>6</sup> Recent work has shown that airway surface liquid is controlled by airway epithelial cells via the reciprocal regulation of active Na<sup>+</sup> absorption and Cl<sup>-</sup> secretion and that mucus transport increases with increasing airway surface liquid volume.<sup>7</sup> Moreover, it seems likely that mucosal function may be optimal at 37 °C and 100% relative humidity.<sup>8</sup> A recent *in vitro* study strongly supports this proposition by showing that mucus transport and ciliary beat frequency both progressively diminished as experimental conditions deviated further from the 'optimum'.<sup>9</sup>

Our methodology has, in the past, been used to assess the efficacy in terms of enhancing mucus clearance both of cough<sup>4</sup> and of several physiotherapy regimes.<sup>10</sup> Undoubtedly, methods of enhancing mucus clearance in bronchiectasis remain a significant clinical concern.<sup>11</sup>

The only previous study on humidification in bronchiectasis utilized humidification from a cold

Correspondence to: Dr Amir Hasani, Department of Medical Physics, Royal Free Hospital, London NW3 2QG, UK.  
Email: amer.alhasani@royalfree.nhs.uk

water jet nebulizer along with chest physiotherapy exercises.<sup>12</sup> The authors found that cold water humidification gave a significant clearance increase relative to the clearance achieved by physiotherapy on its own.

Given the demonstrated roles of both temperature and humidification in optimizing mucosal function, we have investigated the clearance-effectiveness of a warm air humidification treatment system. We compared the humidification treatment to a control (baseline) assessment. Whilst a considerable variety of inhaled agents could be postulated to influence mucociliary transport, we considered that if 'optimal' humidification *per se* proved effective, then future work on inhaled agents should include consideration of the extent to which humidification and temperature factors might be contributory. Moreover, we hypothesized that if both an underlying mechanism and evidence of clinical effectiveness could be established for a patient-acceptable warm air humidification approach, then such an approach might prove helpful to the future care of patients with various mucociliary clearance disorders.

## Methods

### Patients

Volunteer patients with the diagnosis of idiopathic bronchiectasis, using high resolution computed tomography scanning,<sup>2</sup> were enrolled into the study. Patients were required to be between 18 and 75 years of age and with a smoking history of <10 pack-years. Patients with a history of cystic fibrosis, immotile cilia syndrome or Young's syndrome were excluded. Patients who had a significant disease other than bronchiectasis were also excluded. Patients attended an initial screening visit to check their eligibility for the investigation and to be given an explanation of the procedures involved. Patients were allowed to continue with their regular medication throughout the study period except that use of short- and long-acting  $\beta_2$  agonists was withheld for 6 h and 48 h, respectively, prior to each mucociliary clearance assessment and during the 6-h monitoring period. None of the patients were having airway physiotherapy clearance techniques.

### Study design

We carried out a prospective, single-center study. This was conducted as an 'open' study – the nature of the equipment itself clearly precluded either the

investigators or the patients being 'blind' to use, or not, of the treatment equipment. Our objective was simply to determine the potential impact of warm air humidification rather than to compare it to any other form of possible treatment for impaired mucociliary clearance. We, therefore, concentrated on a very simple before and after design<sup>13</sup>: baseline assessment, treatment period, second assessment. In order, within a small number of patients, to test whether a meaningful clearance enhancement could be achieved, we investigated a combined effect of an acute (lasting 3 h) treatment with a short-term (3 h per day for 6 days) treatment course. Power calculations based on the pairwise *t*-test and using an estimate of variability from similar work<sup>14</sup> suggested that 10 patients would suffice for achieving 80% power to detect a meaningful difference at the 5% level of significance in our chosen measure of tracheobronchial clearance (the area under the retention curve, as defined below).

The study was approved by the Ethics Committee of the Royal Free Hospital, London.

### Mucociliary clearance

This was measured, at the same time of day on each visit, by using a previously reported radioaerosol technique.<sup>15</sup> Polystyrene particles, 5  $\mu\text{m}$  in diameter, were firmly labelled with the radionuclide <sup>99m</sup>Tc and produced by a spinning top generator located inside an airtight tank.<sup>16</sup> Each patient inhaled the radioaerosol particles, under strictly controlled conditions, by taking discrete breaths of 0.45 L from the resting level of the lung, which was ascertained by using a pneumotachygraph linked to a dedicated computer<sup>17</sup> thus allowing the measurement of inhalation flow rate.

The initial radioaerosol lung deposition was measured and its subsequent clearance was monitored by two collimated scintillation detectors positioned posteriorly and anteriorly to the chest.<sup>18</sup> The detectors measured the radioactivity emitted by the inhaled particles from both the lungs. Measurements were commenced immediately following the radioaerosol inhalation and repeated at 30-min intervals up to 6 h and then at 24 h. The remaining activity of radioaerosol particles in the lungs at 24 h (corrected for radioactive decay) was used to estimate alveolar deposition (AD), which was taken to represent the amount of particles deposited in the non-ciliated airways and thus unavailable for mucociliary clearance.<sup>19</sup>

Tracheobronchial clearance was assessed by measuring the area under the tracheobronchial retention

curve (AUC), which was generated by subtracting the AD from the total lung burden, for the entire 6-h monitoring period.<sup>20</sup> The retention of radioaerosol particles at 6 h was also used as a measure of tracheobronchial clearance (TBC<sub>6</sub>). A high AUC or TBC<sub>6</sub> value indicates slow clearance. During the 6-h monitoring period, patients were encouraged to avoid coughing. However, any involuntary coughs were recorded and sputum samples (when produced) were collected and weighed over this period.

The initial distribution of the radioaerosol particles within the lungs was assessed by a gamma camera. This distribution was expressed in terms of a penetration index (PI), which is the ratio of the amount of radioaerosol particles in an outer to an inner region of the lungs divided by the same ratio of krypton gas (<sup>81m</sup>Kr).<sup>21</sup>

### *Humidification system*

One of the investigators personally took the system (MR880; Fisher & Paykel Healthcare, Auckland, New Zealand) to each patient's home and gave instruction for its daily use. Patients were asked to operate the system and use it for a short period of time to make sure that they were comfortable with it. The humidification system provides humidified air, fully saturated at 37 °C delivered via nasal interface at a flow rate between 20 and 25 l/min. Each patient was provided with a new nasal interface, heated breathing tube, humidification chamber, air delivering tube to connect the humidification chamber with a blower HC211 (Fisher & Paykel Healthcare) plus a bag of sterile water.

Compliance with the treatment regime was assessed electronically, as usage time of the blower, which provides air to the humidifier, is recorded automatically and can be retrieved.

### *Lung function*

Spirometry was performed immediately prior to each radioaerosol assessment. Lung function indices were measured using a MicroLab 3300 spirometer (Micro Medical, Kent, UK). The highest value for each lung function index was recorded out of three technically acceptable measurements.

### *Data analysis*

Statistical analysis used the Wilcoxon signed ranks test for pairwise differences. GB-STAT software (Dynamic Microsystems, Silver Spring, Maryland,

USA) was used for that purpose. The results are expressed as mean ± SE or median (range) and the level of significance was taken at *p*-value of <0.05.

## **Results**

### *Patient demographics*

Fourteen patients were enrolled into the study, of whom 10 completed the study. Two patients withdrew following the screening visit and two discontinued at the start of baseline mucociliary clearance assessment as they felt that they would be unable to comply with the radioaerosol inhalation maneuver.

The patients who completed the study had a mean ± SE age of 63 ± 4 years. Three patients were ex-smokers with tobacco consumption of 5.8 ± 2.5 pack years. All but one of the 10 patients who completed the study exceeded the planned 'target' of 21 h humidification. Median duration of humidification was 25.0 h (range 14.9–26.9). All patients used humidification during day time and found the procedure very acceptable. Data on the patients studied are summarized in Table 1.

### *Radioaerosol deposition and mucociliary clearance*

One of the measures of initial tracer aerosol deposition (PI) changed little between pre- and post-treatment. The other AD changed relatively more following humidification treatment. But in neither case was there any significant change (Table 2). There was, however, a significant change in AUC and tracheobronchial retention (Table 2). Humidification resulted in significant enhancement of clearance compared with baseline assessment. The enhancement of clearance was sustained at statistically significant levels throughout the 6-h monitoring period as seen in Figure 1. The AUC at baseline was 319 ± 50%/h and after treatment was 271 ± 46%/h. Although inter-patient variability was high (Figure 2a), intra-patient assessment showed a highly significant clearance difference (*p* = 0.0069). There was also a significant improvement in TBC<sub>6</sub> (*p* = 0.0166) following humidification (35 ± 10 vs. 27 ± 9), with only one patient not improving (Figure 2b).

After 7 days of treatment, the number of coughs was slightly (nonsignificantly) reduced. During both 6-h monitoring periods, three patients had no coughs. The median number of coughs in the other seven patients was five coughs (3–37) with sputum wet weight of 1.8 g (0.0–2.9) at the baseline assessment and four coughs (0–13) with sputum wet

**Table 1** Characteristics of the patients who completed the study

Patient	Age (years)	Gender	Height (cm)	Smoking (pack-year)	Duration of disease (years)	Medication
1	60	M	170	9.0	10	SIB, LIB, IS, OS, NA
2	52	M	171	0.0	28	SIB, LIB, IS
5	61	F	148	0.0	7	SIB, LIB, IS
6	73	F	159	0.0	1	SIB
7	70	F	161	7.5	10	None
8	63	F	162	0.0	10	None
9	75	F	151	0.0	1	IS
11	37	F	164	0.0	12	SIB, LIB, IS, NA
13	66	F	160	1.0	3	None
14	73	M	168	0.0	30	SIB, IS, OS

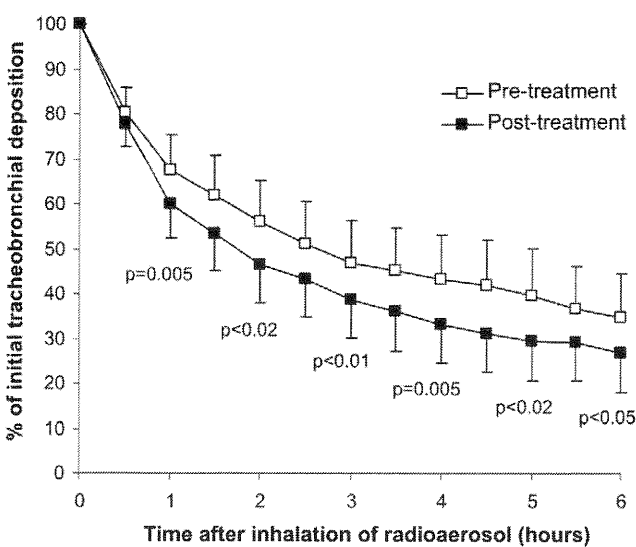
SIB, short-acting inhaled bronchodilators; LIB, long-acting inhaled bronchodilators; IS, inhaled steroids; OS, oral steroids; NA, nebulized antibiotics.

**Table 2** Lung clearance, radioaerosol distribution, and lung function indices for the 10 patients at baseline and following treatment

Variable	Baseline	Post-humidification	P-value
AUC (%h)	319 ± 50	271 ± 46	0.007
TBC <sub>6</sub> (%)	35 ± 10	27 ± 9	0.017
AD (%)	58 ± 6	63 ± 5	0.114
PI	0.78 ± 0.11	0.79 ± 0.10	0.759
AIFR (l/min)	27 ± 2	26 ± 3	0.859
FEV <sub>1</sub> (l)	1.69 ± 0.21	1.74 ± 0.22	0.092
FVC (l)	2.35 ± 0.26	2.46 ± 0.26	0.155
PEF (l/min)	323 ± 37	325 ± 40	0.838
FEF <sub>50</sub> (l/min)	1.88 ± 0.37	1.89 ± 0.35	0.236
FEF <sub>25</sub> (l/min)	0.62 ± 0.11	0.66 ± 0.12	0.721

AUC, area under the TBC curve over 6 h; TBC<sub>6</sub>, tracheobronchial clearance over 6 h; AD, alveolar deposition; PI, penetration index; AIFR, aerosol inhalation flow rate; FEV<sub>1</sub>, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow; FEF<sub>xx</sub>, forced expiratory flow at xx% of functional residual capacity.

Data were presented as mean ± SE values.



**Figure 1** Mean tracheobronchial retention curves at baseline and following humidification. Data were mean and standard error values.

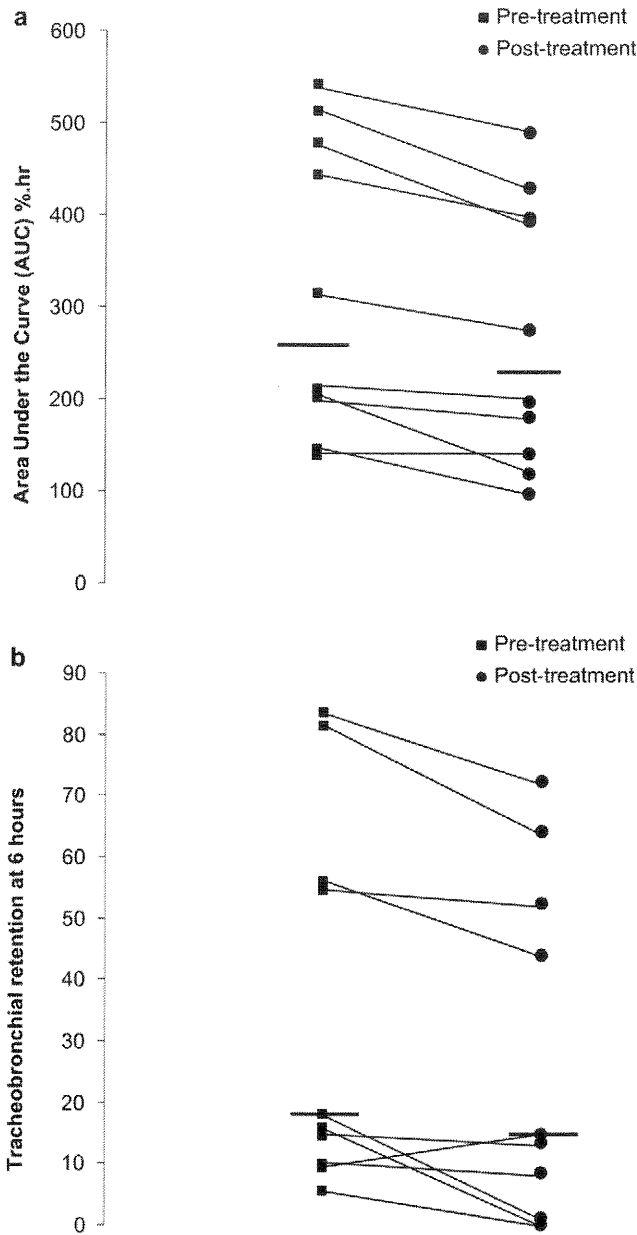
weight of 1.4 g (0.0–8.2) during the post-treatment assessment.

### Lung function

Although, differences were statistically nonsignificant, all lung function indices slightly improved following humidification compared with baseline assessment (Table 2). Forced expiratory volume in 1 s and forced vital capacity at baseline were 1.69 ± 0.20 l and 2.35 ± 0.25 l, after treatment were 1.74 ± 0.20 and 2.46 ± 0.24 l, respectively.

### Discussion

Maintenance of a sufficient airway surface liquid volume is crucial to preserving effective mucociliary defense of the airways.<sup>22,23</sup> In particular, a periciliary liquid layer of some 7 µm thickness is probably a prerequisite for an efficient ciliary beat – even if the mechanisms of regulating to this thickness are, as yet, unclear.<sup>23</sup> Hydration of the airways has for



**Figure 2** Area under tracheobronchial retention curve (AUC) over 6 h (a) and tracheobronchial retention (TBC<sub>6</sub>) at 6 h (b) for each patient at baseline and following humidification. Horizontal bars indicate median values.

some time been suggested as a step towards facilitating mucus clearance<sup>24</sup> and as a rational component of some therapeutic approaches.<sup>12,25,26</sup> Cell culture studies have shown that airway epithelia regulate both the periciliary and the mucus levels of airway surface liquid<sup>27,28</sup> and both layers tend to be transported together.<sup>29</sup> Current research findings highlight the complexity of the possible factors influencing airway surface liquid volume, but do place an

emphasis on Na<sup>+</sup> absorption and Cl<sup>-</sup> secretion.<sup>23</sup> Procedures adding extra liquid onto proximal airway surfaces may stimulate Na<sup>+</sup> absorption.<sup>23</sup>

The mucociliary clearance test, we have used – tracheobronchial aerosol retention – serves as an overall test of mucociliary function summing clearance from both bronchial and bronchiolar airways. It is potentially influenced by cough as well as by mucociliary transport. Cough has been shown to be a very important clearance mechanism in patients with chronic airways obstruction,<sup>30</sup> but the mean number of coughs over the 6-h monitoring period was lower in the present study than in other studies, we have conducted.<sup>15,17,20,31</sup> Given also that cough frequency decreases slightly (albeit not significantly) on treatment, we suggest that the change we measured in radioaerosol clearance was a reflection of improved mucociliary clearance.

Our inhaled tracer can only reach ventilated regions of the lung. Bronchiectasis patients may have a very heterogeneous distribution of ventilation such that some elements of lung volume are inaccessible to any inhaled agents. These regions are likely to have little or no effective mucus clearance whether by mucociliary transport or cough. Our data can obviously shed no light on the long-term effects humidification therapy might have on these regions. Nevertheless, an improvement in clearance for the ventilated regions can of itself be a mechanism underlying an improvement in patient well-being. Arguably (but beyond any present proof), it might offer conditions favorable to some eventual partial recovery in adjacent non-ventilated regions. In bronchiectasis recurrent exacerbations may well reflect an overwhelmed defense system. They also serve as landmarks in the vicious cycle<sup>5</sup> of infection and damage, and in so doing also provide evidence of stages in the patient's progression at which a clear need exists for an effective repair process.

Baseline mucociliary clearance in our patients (AUC 319%h) was closely similar to that in a much earlier study of bronchiectatic patients from our group (AUC 333%h).<sup>32</sup> In that earlier study, clearance in bronchiectatic patients was significantly impaired relative to that in a normal control group (AUC 210%h) indicating a marked abnormality of clearance. Clearly the post-treatment results in our present patients fall far short from a level that could be considered 'normal', a finding that can hardly be considered surprising in the context of a long history of disabling disease. The real question for the future is the extent to which suitable therapies – including, we would suggest, warm air

humidification – can slow down the patients' progressive rate of lung damage and lessen the likelihood of exacerbation episodes.

In conclusion, our results suggest a positive effect from humidification. Work in other laboratories has underlined the importance of fluid transport in the airways. Further clinical trials of humidification therapy should indicate whether short-term promise can be maintained in the longer term. This may then lead to the possibility of considering humidification therapy for other patients with disorders known adversely to affect the mucociliary transport process (such as cystic fibrosis), particularly where evidence exists of difficulty in maintaining an adequate airway surface liquid level.

## Acknowledgement

The present study was supported by a grant from Fisher & Paykel Healthcare (NZ).

## References

- 1 Cole, PJ. Inflammation: a two-edged sword – The model of bronchiectasis. *Eur J Respir Dis* 1986; **147**: 6–14.
- 2 Barker, AF. Medical progress: bronchiectasis. *N Engl J Med* 2002; **346**: 1383–1393.
- 3 Wanner, A, Salathe, M, O'Riordan, TG. Mucociliary clearance in the airways. *Am J Respir Crit Care Med* 1996; **154**: 1868–1902.
- 4 Hasani, A, Pavia, D. Cough as a clearance mechanism. In: Braga, PC, Allegra, L, (eds), *Cough*. New York: Raven Press; 1989. p. 37–52.
- 5 Cole, PJ, Wilson, R. Host-microbial relationships in respiratory infection. *Chest* 1989; **95**: 217S–221S.
- 6 Shibuya, Y, Wills, PJ, Cole, PJ. Effect of osmolality on mucociliary transportability and rheology of cystic fibrosis and bronchiectasis sputum. *Respirology* 2003; **8**: 181–185.
- 7 Tarran, R, Grubb, BR, Gatzky, JT, Davis, CW, Boucher, RC. The relative roles of passive surface forces and active ion transport in the modulation of airway surface liquid volume and composition. *J Gen Physiol* 2001; **118**: 223–236.
- 8 Williams, RW, Rankin, N, Smith, T, Galler, D, Seakins, P. Relationship between the humidity and temperature of inspired gas and the function of airway mucosa. *Crit Care Med* 1996; **24**: 1920–1929.
- 9 Kilgour, E, Rankin, N, Ryan, S, Pack, R. Mucociliary function deteriorates in the clinical range of inspired air temperature and humidity. *Intensive Care Med* 2004; **30**: 1491–1494.
- 10 Sutton, PP, Parker, RA, Webber, BA, Newman, SP, Garland, N, Lopez-Vidriero, MT, et al. Assessment of the forced expiration technique, postural drainage and directed coughing in chest physiotherapy. *Eur J Respir Dis* 1983; **64**: 62–68.
- 11 Eaton, T, Young, P, Zeng, I, Kolbe, J, Elborn, JS. A randomised evaluation of the acute efficacy, acceptability and tolerability of Flutter and active cycle of breathing with and without postural drainage in non-cystic fibrosis bronchiectasis. *Chron Respir Dis* 2007; **4**: 23–30.
- 12 Conway, JH, Fleming, JS, Perring, S, Holgate, ST. Humidification as an adjunct to chest physiotherapy in aiding tracheo-bronchial clearance in patients with bronchiectasis. *Respir Med* 1992; **86**: 109–114.
- 13 Smith, EP. BACI design. In: El-Shaarawi, AH, Piegorisch, WW, (eds), *Encyclopedia of environmetrics (ISBN 0471 899976)*, vol. 1. Chichester: John Wiley & Sons, 2002. p. 141–148.
- 14 Del Donno, M, Pavia, D, Agnew, JE, Lopez-Vidriero, MT, Clarke, SW. Variability and reproducibility in the measurement of tracheobronchial clearance in healthy subjects and patients with different obstructive lung diseases. *Eur Respir J* 1988; **1**: 613–620.
- 15 Hasani, A, Toms, N, O'Conner, J, Dilworth, JP, Agnew, JE. Effect of salmeterol xinafoate on lung mucociliary clearance in patients with asthma. *Respir Med* 2003; **97**: 667–671.
- 16 Hasani, A, Pavia, D, Toms, N, Dilworth, JP, Agnew, JE. Effect of aromatics on lung mucociliary clearance in patients with chronic airways obstruction. *J Altern Complement Med* 2003; **9**: 243–249.
- 17 Hasani, A, Toms, N, Agnew, JE, Lloyd, J, Dilworth, JP. Mucociliary clearance in COPD can be increased by both a D<sub>2</sub>/β<sub>2</sub> and a standard β<sub>2</sub> agonists. *Respir Med* 2005; **99**: 145–151.
- 18 Hasani, A, Pavia, D, Spiteri, MA, Yeo, CT, Agnew, JE, Clarke, SW, et al. Inhaled frusemide does not affect lung mucociliary clearance in healthy and asthmatic subjects. *Eur Respir J* 1994; **7**: 1497–1500.
- 19 Bennett, WD, Chapman, WF, Lay, JC, Gerrity, TR. Pulmonary clearance of inhaled particles 24 to 48 hours post deposition. *J Aerosol Med* 1993; **6**: 53–62.
- 20 Hasani, A, Pavia, D, Rotondetto, S, Clarke, SW, Spiteri, MA, Agnew, JE. Effect of oral antibiotics on lung mucociliary clearance during exacerbation of chronic obstructive pulmonary disease. *Respir Med* 1998; **92**: 442–447.
- 21 Agnew, JE. Characterising lung aerosol penetration. *J Aerosol Med* 1991; **4**: 237–249.
- 22 Puchelle, E, Zahm, JM, Tournier, JM, Coraux, C. Airway epithelial repair, regeneration, and remodelling after injury in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2006; **3**: 726–733.
- 23 Tarran, R, Trout, L, Donaldson, SH, Boucher, RC. Soluble mediators, not cilia, determine airway surface liquid volume in normal and cystic fibrosis superficial airway epithelia. *J Gen Physiol* 2006; **127**: 591–604.
- 24 Girod, S, Zahm, JM, Poltkowski, C, Beck, G, Puchelle, E. Role of the physicochemical properties of mucus in the protection of the respiratory epithelium. *Eur Respir J* 1992; **5**: 477–487.
- 25 Knowles, MR, Church, NL, Waltner, WE, Yankaskas, JR, Gilligan, P, King, M, et al. A pilot study of aerosolized amiloride for the treatment of lung disease in cystic fibrosis. *N Engl J Med* 1990; **322**: 1189–1194.
- 26 Kellett, F, Redfern, J, Niven, RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. *Respir Med* 2005; **99**: 27–31.
- 27 Matsui, H, Grubb, BR, Tarran, R, Randell, SH, Gatzky, JT, Davis, CW, et al. Evidence for periciliary liquid layer depletion, not abnormal ion composition, in the pathogenesis of cystic fibrosis airways disease. *Cell* 1998; **95**: 1005–1015.
- 28 Matsui, H, Davis, CW, Tarran, R, Boucher, RC. Osmotic water permeabilities of cultured, well-differentiated normal and cystic fibrosis airway epithelia. *J Clin Invest* 2000; **105**: 1419–1427.
- 29 Matsui, H, Randell, SH, Peretti, SW, William Davis, C, Boucher, RC. Coordinated clearance of periciliary liquid and mucus from airway surfaces. *J Clin Invest* 1998; **102**: 1125–1131.
- 30 Hasani, A, Agnew, JE. The role of cough on mucociliary clearance measurements. In: Salathe, M, (ed), *Cilia and mucus*. New York: Dekker; 2001. p. 399–405.
- 31 Hasani, A, Toms, N, Agnew, JE, Sarno, M, Harrison, AJ, Dilworth, JP. The effect of inhaled tiotropium bromide on lung mucociliary clearance in patients with COPD. *Chest* 2004; **125**: 1726–1734.
- 32 Currie, DC, Pavia, D, Agnew, JE, Lopez-Vidriero, MT, Diamond, PD, Cole, PJ. Impaired tracheobronchial clearance in bronchiectasis. *Thorax* 1987; **42**: 126–130.

Printed by SAGE Publications. [www.sagepub.co.uk](http://www.sagepub.co.uk)  
For more information about *Chronic Respiratory Disease*, please visit: <http://crd.sagepub.com>  
For further reprint information contact: [chloe.bond@sagepub.co.uk](mailto:chloe.bond@sagepub.co.uk)

Ref 185045297