

Acute effect of inhaled bradykinin on tracheobronchial clearance in normal humans

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Abstract

Background Bradykinin, a nonapeptide that contributes as a mediator to the pathogenesis of asthma, may affect lung mucociliary clearance, as it has been shown to be a potent secretagogue in canine airways and in human nasal mucosa *in vivo*. To evaluate this possibility the effect of inhaled bradykinin on mucociliary clearance has been studied in 10 healthy volunteers.

Methods Subjects attended the laboratory on two occasions to take part in tracheobronchial clearance studies using a non-invasive radioisotopic technique. Inhalation of radioaerosol was followed 30 minutes later by inhalation of either bradykinin (8 mg/ml) or vehicle placebo in a randomised, double blind fashion. After each inhalation the number of coughs was recorded. Whole lung radioactivity was measured every half hour for six hours with two collimated scintillation counters, and a tracheobronchial clearance curve was plotted for each subject on each occasion.

Results Mucociliary clearance, expressed as the area under the tracheobronchial radioaerosol retention curve calculated for the first six hours (AUC_{0-6h}), was greater in nine out of 10 subjects after inhalation of bradykinin than after placebo. The median values (range) for AUC_{0-6h} were significantly reduced from 126% (78-232%)/h with placebo to 87% (51-133%)/h with bradykinin.

Conclusion It is concluded that acute exposure to inhaled bradykinin accelerates tracheobronchial clearance in normal human airways.

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Bradykinin is a nonapeptide that may be an important mediator in the pathogenesis of airway inflammation by interacting with specific receptors, mainly of the B_2 type.¹⁻³ The observation that kinin like activity is recovered in increased amounts from lavage fluid following provocation by allergen of the nasal⁴ and bronchial mucosa⁵ of atopic subjects indicates that this pathway is activated in human allergic disease. Inhaled bradykinin elicits many of the features of asthma, including bronchoconstriction,⁶⁻⁸ cough,⁷ plasma exudation,^{9,10} and mucus secretion.¹¹

The impairment of mucociliary function, which has been recently found in patients with

both symptomatic and asymptomatic asthma,^{12,13} may be related to local release of chemical mediators of anaphylaxis, including bradykinin. In support of this, it has been reported that the allergen provoked early asthmatic reaction is accompanied by a decrease in tracheal mucus transport in asthmatic patients, which could be reversed by pretreatment with sodium cromoglycate,^{14,15} a drug that has a potent inhibitory activity on bradykinin responses in the airways.⁷

Animal and *in vitro* studies suggest that bradykinin may have various effects on different components of the mucociliary transport system. Bradykinin may be directly responsible for the impaired mucociliary clearance in asthma as it has been shown to be a potent mucus secretagogue in canine airways *in vivo*¹¹ and in human nasal mucosa *in vitro*.¹⁶ It also stimulates chloride secretion by canine airway epithelial cells,¹⁷ leading to an increase in the water content within the periciliary fluid. Altered mucus transport may result not only from abnormalities of the rheological properties of airway secretions but also from impairment of ciliary function. Recently Tamaoki *et al*¹⁸ have shown that bradykinin stimulates ciliary motility in isolated rabbit tracheal epithelium. From these studies an alteration in mucociliary clearance by bradykinin could be predicted.

To our knowledge the effect of bradykinin on bronchial mucociliary clearance in man has not been previously studied. Owing to the complexity of studying the mucociliary clearance response to inhaled bradykinin in asthmatic subjects because of its potent bronchoconstrictor effect,⁶⁻⁸ we decided to investigate the effect of inhaled bradykinin on mucociliary clearance using a radioaerosol technique in a group of healthy volunteers.

SUBJECTS

Ten healthy subjects (eight of them male), ranging in age from 19 to 53 years, with no history of respiratory disease and with baseline values of forced expiratory volume in one second (FEV_1) above 80% of their maximum predicted values, took part in the study (table 1). Seven subjects (subjects 1, 4, 5, 7, 8, 9, and 10) were atopic, as defined by positive responses to skin prick tests (weals over 2 mm in diameter) with two or more common aeroallergens: house dust, *Dermatophagoides pteronyssinus*, *D farinae*, mixed grass pollen, cat fur, dog hair (Bencard, Brentford, Middlesex). Two subjects (subjects 8 and 9) were smokers. Smoking was not allowed for at least 12 hours

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Table 1 Area under the time-course curve (AUC_{0-6h} , %·h) and 95% tracheobronchial clearance time (95% TBCT, min) on the placebo and the bradykinin study days

Subject No	Sex	Age (y)	FEV ₁ (% pred)	Placebo study day		Bradykinin study day	
				AUC_{0-6h}	95% TBCT (min)	AUC_{0-6h}	95% TBCT (min)
1	M	19	99	232	348	93	124
2	M	23	94	123	310	80	85
3	F	53	101	148	240	133	150
4	M	34	78	78	168	69	78
5	M	27	118	97	175	74	82
6	M	43	89	175	360	109	115
7	M	25	91	129	156	128	160
8	F	20	105	83	115	51	72
9	M	28	87	104	180	76	86
10	M	22	86	152	266	109	198
Mean or median		29.4*	94.8*	126	210	87	101
SE or range		3.5*	3.6*	78-232	115-360	51-133	72-198

*Mean (SE).

before radioaerosol inhalation or in the subsequent 24 hours' observation period. They took no medication and were free from respiratory tract infections for at least four weeks before and throughout the investigation. Subjects were allowed a light breakfast on the day of the study but could not have caffeine containing substances for the previous 12 hours. The study was approved by the Royal Free Hospital's ethical subcommittee and written informed consent was obtained from each subject.

MEASUREMENTS

Airways function was measured both as the FEV₁ and forced vital capacity (FVC)—by dry bellows spirometer (Vitalograph, Buckingham)—and as the peak expiratory flow (PEF)—by peak flow meter (Wright, London)—10–20 minutes before each radioaerosol inhalation. The highest value of three technically acceptable readings was recorded and all values were corrected to body temperature and ambient pressure.

Tracheobronchial clearance was measured by a non-invasive radioisotopic method.¹⁹ Polystyrene particles 5 µm in diameter were firmly tagged with the gamma emitting radionuclide technetium-99m ($t_{1/2}$ 6 hours) and inhaled via a mouthpiece under strictly controlled conditions. The initial topographical distribution of the radioaerosol within the lungs was monitored with a gamma camera (International General Electric, Berkshire), linked to a computer (Nodecrest, Byfleet, Surrey). Posterior views were obtained to derive a penetration index for the ^{99m}Tc labelled particles (ratio of counts recorded over the peripheral lung to those recorded over central lung).²⁰ This index estimates the degree of penetration into the lungs of this radioaerosol relative to that of krypton gas, ^{81m}Kr ($t_{1/2}$ 13 seconds), which was subsequently inhaled.

Radioaerosol clearance was monitored with two suitably collimated scintillation counters, axially opposed anteroposteriorly over the mid sternum. An immediate radioaerosol count was made to ascertain the initial lung burden. Thereafter counts were made at half hourly intervals for six hours and a final one at 24

hours to estimate radioaerosol deposition on non-ciliated airways ("alveolar deposition"). To overcome unavoidable differences in the amount of radioactivity initially measured in the lung, all counts were expressed as a percentage of the initial count after correction for the natural decay of the radioisotope and background radioactivity. Alveolar deposition for each subject was expressed as the percentage of the initial lung activity remaining in the lungs at 24 hours and was subtracted from all readings of the whole lung clearance curve to give a tracheobronchial clearance curve. Throughout the first six hours after radioaerosol inhalation all coughs were recorded.

BRADYKININ ADMINISTRATION

On each occasion bradykinin triacetic acid (Nova Biochem Ltd, Nottingham) was freshly prepared in 10% ethanol in normal saline to produce 3 ml of solution containing 24 mg. To avoid loss of bradykinin through adherence to plastic surfaces and oxidation, the solution was kept stored at 4°C before use and administered within 20 minutes of reconstitution. The control vehicle solution (placebo) consisted of the 10% ethanol-saline diluent used for dissolving the bradykinin. Both the placebo and the bradykinin solutions were administered as aerosols generated from a starting volume of 3 ml in a disposable Inspiron Mini-neb nebuliser (CR Bard International, Sunderland) connected to a dosimeter driven by compressed air at a pressure of 138 kPa (25 lb/in²). The dosimeter setting was adjusted so that this procedure generated 80–100 µl of an aerosol with a mass median particle diameter of 4.7 µm at the mouth.²¹ Subjects, wearing nose clips, were instructed to take five consecutive breaths from end tidal volume to total lung capacity via a mouthpiece as described by Chai *et al.*²²

STUDY DESIGN

Each subject attended the laboratory on two occasions separated by at least two weeks to undertake tracheobronchial clearance studies. Before radioaerosol inhalation baseline values of FEV₁, FVC, and PEF were obtained. On each occasion subjects inhaled either bradykinin (8 mg/ml) or vehicle placebo 30 minutes after inhalation of the radioaerosol in a

Table 2 Baseline spirometric values, inspiratory flow rates, penetration indices, and alveolar deposition on the two study days*

	Placebo	Bradykinin
FEV ₁ (l)†	4.1 (0.3)	4.0 (0.3)
FVC (l)†	4.7 (0.4)	4.7 (0.3)
PEF (l/min)†	576 (25)	562 (26)
Alveolar deposition (%)‡	49 (32–72)	55 (23–70)
Inspiratory flow rate (l/min)‡	41.9 (28.9–47.1)	38.6 (26.2–47.5)
Penetration index (units)‡	0.62 (0.48–0.78)	0.71 (0.41–0.80)

*All differences are non-significant.

†Mean (SE).

‡Median (range).

FVC—forced vital capacity; PEF—peak expiratory flow.

randomised and double blind manner. The inhalation procedure with both bradykinin and vehicle placebo was repeated on a further three occasions at half hourly intervals. After each inhalation of bradykinin and placebo solutions, the number of coughs was counted and recorded by an independent observer. Although subjects were not told which was the active solution, the pharyngeal irritation with bradykinin made it difficult to maintain blindness. The investigators responsible for analysing the data (AH and DP) were not, however, aware of the subjective sensations of the subjects studied, who were blind to the rationale of the study. Regular whole lung counts were obtained as described above and a tracheobronchial clearance curve was plotted for each subject on each occasion.

DATA ANALYSIS

All figures are means and standard errors unless otherwise stated and $p < 0.05$ was accepted as the level of significance. Baseline values of FEV₁, FVC, and PEF on the two study days were compared by paired Student's *t* test. Topographical distributions of the radioaerosol within the lungs on the two study days were compared by the Wilcoxon signed rank test on penetration indices, alveolar deposition, and inspiratory flow rates. The Wilcoxon signed rank test was also used to compare the number of coughs after bradykinin and placebo. The relation between the number of coughs after bradykinin inhalations

and the degree of acceleration of mucociliary transport was investigated by the Kendall correlation test. To quantify tracheobronchial clearance, areas under the curves for tracheobronchial retention of the ^{99m}Tc polystyrene particles (AUC) were calculated by trapezoid integration between time points 0 and 6 hours (AUC_{0-6h}) and between time points 0 and 3 hours (AUC_{0-3h}). The efficiency of the mucociliary transport in the subjects studied was also expressed as 95% tracheobronchial clearance time, which represents the time needed to clear 95% of the initial radioaerosol deposition within the lung. The values of AUC_{0-6h} and AUC_{0-3h} and the 95% tracheobronchial clearance time for the two study days were compared by Wilcoxon signed rank test.

Results

There were no significant differences in the baseline spirometric values between the two study days (table 2). Similarly, inspiratory flow rates, penetration indices, and alveolar depositions were not significantly different on bradykinin and placebo study days (table 2).

All subjects noticed pharyngeal irritation after inhaling bradykinin; this was most noticeable with the first inhalation but rapidly diminished during subsequent inhalations. In addition, four subjects (subjects 7, 8, 9, 10) had a dry cough with bradykinin. Although the median (range) number of coughs recorded after bradykinin inhalations (2.0 (0–18)) was significantly higher than the 0.5 (0–2) after placebo ($p < 0.05$), no significant correlation was found between acceleration of tracheobronchial clearance and number of coughs recorded throughout the first six hours after radioaerosol inhalation.

Mucociliary clearance, expressed as AUC_{0-6h} and AUC_{0-3h}, was greater in nine out of 10 subjects after inhalation of bradykinin than after placebo (figure). The medians (range) for AUC_{0-6h} and AUC_{0-3h} were reduced from 126 (78–232) to 87 (51–133)%·h ($p < 0.001$) after placebo and from 121 (78–192) to 86 (51–133)%·h ($p < 0.01$) after bradykinin (figure,

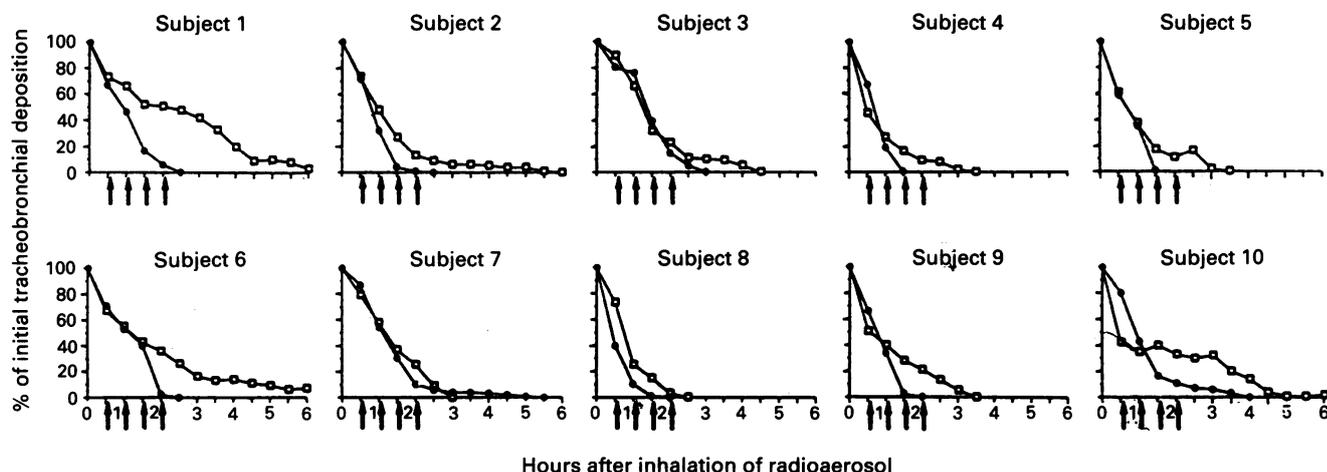


Figure Individual tracheobronchial retention curves for 10 normal subjects after inhalations of bradykinin (solid circles) and vehicle placebo (open squares). ↑↑↑ Bradykinin or placebo inhalations.

table 1). Inhaled bradykinin reduced 95% tracheobronchial clearance time in all but one subject (No 7), the median (range) 95% tracheobronchial clearance time decreasing from 210 (115–360) to 101 (72–198) minutes after administration of placebo and bradykinin respectively (table 1).

Discussion

In the present study we have shown that repeated inhalations of bradykinin greatly enhance tracheobronchial clearance in normal human airways. Because the deposition pattern of the inhaled radioaerosol was the same on the two study days, as clearly shown by the reproducibility of penetration indices and alveolar deposition values, the speeding of mucociliary clearance is likely to indicate the true result of bradykinin stimulation and not different deposition of the radioaerosol on the two study days. With the nebulisation procedure used, about 10% of the dose administered to the mouth (80 µg) would be delivered to the airways of our subjects. This dose produces a concentration of the same magnitude as the concentration of kinin like activity in bronchoalveolar lavage fluid from subjects with asthma,^{5,23} indicating that bradykinin released into the airways as a component of the inflammatory response in asthma might serve to influence the mucociliary transport.

The tracheobronchial retention curves in our subjects closely resemble those previously reported in normal human subjects.²⁴ The low concentration of alcohol used in the vehicle solution is therefore unlikely to have altered clearance as such. The technique of measuring tracheobronchial clearance used in this study is highly repeatable, with an intersubject coefficient of variation for healthy non-smokers of 13%, the intrasubject coefficient being half of the intersubject coefficient.²⁴

In view of the profound effects on mucosal inflammation^{3,25} and mucus hypersecretion^{16,26} reported in several studies performed on animal models in vitro and in vivo after exposure to bradykinin, it is not surprising that this nonapeptide has a potent action on mucociliary clearance in human airways. Bradykinin may stimulate mucociliary clearance by several mechanisms. One possibility is that this and related peptides alter the rheological properties of tracheobronchial secretions, rendering them less viscous and more easily transportable. Leikauf *et al*¹⁷ have shown that in canine trachea bradykinin may affect ion transport and water flux across the epithelium. Such water flux redistribution may in turn alter the rheological properties of the periciliary layer. In addition, topical application of bradykinin to mucosal surfaces causes vasodilation³ and plasma extravasation.^{3,27} More recently we have shown that topical application of bradykinin to human airway mucosa provokes plasma leakage into the nasal fluid,¹⁰ thus confirming results of animal studies. Possibly therefore an increase in plasma exudate at the level of the bronchial mucosa modifies the rheological properties of the tracheobronchial secretions. Bradykinin

could also accelerate mucociliary clearance by its effect on mucus secretion. In anaesthetised dogs bradykinin stimulates tracheal gland secretion.¹¹ Moreover, Baraniuk *et al*¹⁶ have shown that human nasal fragments release increased amounts of secretory products (glycoconjugate) in response to bradykinin. A similar finding has been reported for explants of ferret trachea.¹⁶

Efficient mucociliary clearance depends not only on the composition and consistency of the periciliary layer and the amount and viscoelastic properties of the epiphase but also on the beat frequency and coordination of the cilia.²⁸ Lindberg and Mercke²⁹ found that bradykinin increases mucociliary activity in the rabbit maxillary sinus, probably through activation of neural reflexes. Recent evidence from in vitro studies confirm the potent ciliostimulatory action of bradykinin in the rabbit¹⁸ and dog trachea.³⁰ In these preparations the authors could not elicit any failure of ciliary coordination. The effect of bradykinin on ciliary motility in human airway epithelium, however, remains to be investigated.

Although our results suggest that bradykinin may have a direct effect on mucociliary clearance, its ability to release various prostanoids in the guinea pig in vitro^{3,31} and humans in vivo³² and to degranulate mast cells in vitro^{33,34} may enable it to influence this airway function by modulating the generation of chemical mediators within the airways. Prostaglandins, leukotrienes, and histamine accelerate the beating frequency of cilia in airway epithelial cells in vitro.^{35,36} In addition, the effect of inhaled histamine on bronchial mucociliary clearance investigated with a radioaerosol technique in six healthy subjects has clearly shown an enhancing effect of the same magnitude as that seen in our investigation.³⁷ At least in humans in vivo, however, the contribution of intermediate inflammatory products to the overall response to bradykinin stimulation seems to be small. For example, the mode of action of bradykinin in provoking bronchoconstriction in asthmatic subjects does not seem to depend on the release of histamine³⁸ or prostanoids.^{7,38} Similarly, bradykinin induced weal and flare in humans are not altered by pretreatment with an antihistamine or cyclooxygenase inhibitor.³⁹ That bradykinin may have indirect effects on mucociliary clearance is a possibility that remains to be investigated.

As healthy volunteers were studied in the present investigation, it is difficult to extrapolate these data to patients with bronchial asthma, whose clearance rate is already reduced.^{12,13} Nevertheless, although the airways response to inhaled bradykinin differs strikingly in asthmatic and non-asthmatic subjects,^{6,8} mucociliary clearance may not differ in the same way. Indeed, histamine, another well known mediator of bronchoconstriction in asthma, when inhaled enhanced the mucociliary transport to a similar degree in healthy volunteers and in asthmatic subjects.^{37,40}

Mucociliary clearance has been reported to be slower in subjects with asthma, even during

clinical remission, than in normal subjects.¹²⁻¹⁵ These findings are at variance with the results of the present study, which show a speeding of the mucociliary clearance by acute exposure to bradykinin, a putative mediator in the pathophysiology of asthma. It has been recently reported, however, that acute exacerbations of asthma sharply accelerated mucociliary transport from baseline in eight asthmatic patients, even though two weeks after an asthma attack their mucociliary clearance was significantly less than the baseline level.⁴¹ Acute exposure to bradykinin may initially cause a transient increase in mucociliary function, whereas chronic exposure to this kinin may be followed by prolonged depression of mucociliary transport.

Although our findings clearly indicate that inhaled bradykinin stimulates tracheobronchial clearance in normal human airways, further experiments are required to confirm whether it is directly responsible for the impaired mucociliary transport seen in bronchial asthma. Only when suitable antagonists become available will it be possible to establish the importance of this mediator in modulating mucociliary transport.

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