BRONCHIECTASIS

Comparison of exhaled and nasal nitric oxide and exhaled carbon monoxide levels in bronchiectatic patients with and without primary ciliary dyskinesia

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Background: Primary ciliary dyskinesia (PCD) is associated with chronic airway inflammation resulting in bronchiectasis.
Methods: The levels of exhaled nitric oxide (eNO), carbon monoxide (eCO) and nasal NO (nNO) from bronchiectatic patients with PCD (n=14) were compared with those from patients with non-PCD bronchiectasis without (n=31) and with cystic fibrosis (CF) (n=20) and from normal subjects (n=37) to assess the clinical usefulness of these measurements in discriminating between PCD and other causes of bronchiectasis.
Results: Exhaled NO levels were lower in patients with PCD than in patients with non-PCD non-CF bronchiectasis or healthy subjects (median (range) 2.1 (1.3–3.5) ppb *v* 8.7 (4.5–26.0) ppb, p<0.001; 6.7 (2.6–11.9) ppb, p<0.001, respectively) but not lower than bronchiectatic patients with CF (3.0 (1.5–7.5) ppb, p>0.05). Nasal levels of nNO were significantly lower in PCD patients than in any other subjects (PCD: 54.5 (5.0–269) ppb, non-PCD bronchiectasis without CF: 680 (310–1000) ppb, non-PCD bronchiectasis with CF: 343 (30–997) ppb, control: 663 (322–1343) ppb). In contrast, eCO levels were higher in all patient groups than in control subjects (PCD: 4.5 (3.0–24.0) ppm, p<0.01, other bronchiectasis without CF: 5.0 (3.0–15.0) ppm, p<0.001; CF: 5.3 (2.0–23.0) ppm, p<0.001 *v* 3.0 (0.5–5.0) ppm). Low values in both eNO and nNO readings (<2.4 ppb and <187 ppb, respectively) identified PCD patients from other bronchiectatic patients with a specificity of 98% and a positive predictive value of 92%.
Conclusion: The simultaneous measurement of eNO and nNO is a useful screening tool for PCD.

Primary ciliary dyskinesia (PCD) is a genetic disease characterised by defective motility of cilia resulting in impaired mucociliary clearance and infertility in most cases.[1 2]

Decreased ciliary motility with secondary microbial colonisation in the airways leads to chronic airway inflammation and bronchiectasis. Oxidants and inflammatory mediators released from activated inflammatory cells in airways may lead to the induction of inducible nitric oxide synthase (iNOS) producing nitric oxide (NO) and inducible heme oxygenase (HO-1) releasing carbon monoxide (CO). In pulmonary diseases associated with chronic airway inflammation, such as asthma, expression of iNOS and HO-1 is increased in the airways and levels of NO and CO are raised in exhaled breath.[3–5] Increased levels of exhaled NO (eNO) and CO (eCO) correlate with other markers of airway inflammation in asthma.[5–7] Concentrations of eNO and eCO are also increased in patients with bronchiectasis, which may reflect iNOS and HO-1 expression in macrophages and neutrophils in the airways of these patients.[8 9]

Patients with PCD may represent a unique group of subjects, however, as eNO and nasal NO (nNO) levels are abnormally low in patients with PCD with documented bronchiectasis.[10 11] Nasal NO is also lower in children with Kartagener's syndrome (a condition in which PCD is associated with situs inversus) compared with healthy control children,[2 12] suggesting a defect in the function and/or expression of NO synthases. The level of eNO and nNO in patients with PCD may not reflect the chronic inflammatory process in the airways and might not be used as a non-invasive inflammatory marker, but it may be useful in diagnosing PCD as a cause of bronchiectasis in these patients. Expression and/or function of HO-1, however, may not be defective in patients with PCD and the level of eCO may reflect the chronic inflammatory process in these subjects.

We have therefore measured eNO, eCO, and nNO levels simultaneously in bronchiectatic patients with PCD and compared these values with those obtained from age matched healthy subjects, and patients with non-PCD bronchiectasis, with and without cystic fibrosis (CF). We included bronchiectatic patients with CF because CF may present with symptoms of chronic inflammation of the upper and/or lower airways, similar to PCD. Furthermore, eNO and nNO levels are lower than normal not only in PCD, but also in CF.[13]

METHODS

Subject characteristics

Four groups of subjects participated in the study (tables 1 and 2). Patients with bronchiectasis (PCD and non-PCD without CF) were recruited from the Host Defence Unit at the Royal Brompton Hospital and control subjects were recruited from staff members and examined at the Asthma Laboratory at the Royal Brompton Hospital, London. Bronchiectatic patients with CF were recruited from those attending an outpatient clinic for a scheduled visit at the National Koranyi Institute for Pulmonology, Budapest and examined at the Department of Pathophysiology at the same institute. Patients had no evidence of exacerbations for at least 4 weeks before the study. PCD was proved clinically and confirmed functionally (saccharin test >60 min and abnormal ciliary beat frequency/dyskinetic beat pattern) and morphologically at the PCD clinic of the Royal Brompton Hospital. Patients with PCD had ciliary defects (dynein arm abnormalities, n=6; microtubular transposition, n=1, documented by electron microscopy of ciliary nasal epithelium obtained either by nasal brushing or biopsy)

Table 1 Mean (SD) subject characteristics

		Bronchiectasis		
		PCD (n=14)	Non-PCD	
	Control (n=37)		Without CF (n=31)	With CF (n=20)
Age (years)	33 (2.8)	35 (4.6)*	45 (5.1)*	25.7 (2.4)
Sex (M/F)	20/17	8/6	16/15	12/8
FEV_1 (% predicted)	94 (0.8)	51 (5.1)†	58 (6.1)†	53 (5.9)†
FVC (% predicted)	99 (0.4)	72 (4.2)†	77 (3.1)†	74 (3.3)†
FEV_1/FVC	0.81 (0.001)	0.62 (0.04)†	0.65 (0.02)†	0.62 (0.04)†
Treatment	None	7 IS	19 IS; 2 OS	8 IS

PCD= primary ciliary dyskinesia; CF= cystic fibrosis; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; IS=inhaled steroids; OS=oral steroids.
*p<0.05 *v* CF group; †p<0.05 *v* healthy control group.

Table 2 Clinical characteristics of patients with bronchiectasis

		Non-PCD	
	PCD	Without CF	With CF
Neonatal respiratory symptoms	6 (43)	2 (6)	7 (35)
Chronic sputum production	12 (86)	23 (74)	14 (70)
Rhinosinusitis	13 (93)	3 (10)	11 (56)
Otitis media	11 (79)	2 (6)	4 (20)
Situs inversus	6 (43)	0 (0)	0 (0)
Infertility/subfertility	11 (79)	0 (0)	1 (5)

Data are given as number (%) of patients.

or primary ciliary disorientation (n=7, verified using a computerised improvision image analysis system).[14] Bronchiectasis was diagnosed clinically and confirmed by high resolution computed tomographic (CT) scanning of the thorax in all patients. CF was confirmed by genetic analysis and a positive sweat test (chloride values >60 mM). Patients with atopy, asthma, or reversible (>12%) airway obstruction were excluded from the study. Normal control subjects had no history of chronic disease, were not receiving any regular medication, and had been free of respiratory infections for at least 6 weeks before the study. None of the subjects reported being current cigarette smokers or being exposed to smoke for more than 0.5 hours/day; this was confirmed by testing their urinary cotinine level with NicCheck I (DynaGen Inc, Cambridge, MA, USA).[15]

The study protocol was approved by the research ethics committees of both institutions and informed consent was obtained from all subjects.

Study design

Exhaled NO, eCO, and nNO were measured and spirometric tests were then performed. Forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) were measured using a dry spirometer (Vitalograph, Buckingham, UK) and the best of three manoeuvres was expressed as a percentage of the predicted normal value.

Measurement of eNO, eCO and nNO

Exhaled NO and CO were measured simultaneously and nNO was then determined. Exhaled NO was measured using a chemiluminescence analyser (Model LR2000, Logan Research, UK) sensitive to NO from 1 to 5000 ppb by volume with a resolution of 0.3 ppb. Exhaled CO was determined with an electrochemical sensor connected to the NO analyser. The analyser was designed for online recording of exhaled NO and CO concentrations. Measurement of eNO and eCO were made by slow exhalation (5–6 l/min) from total lung capacity for 20–30 s against a resistance (3 (0.4) mm Hg) to prevent nasal contamination. An end expiratory plateau of at least 3 s was the end point of the measurement and values of eNO and eCO were read at this plateau. Participants repeated the manoeuvre until two acceptable tests were performed (difference between readings <5%).

Levels of nNO were measured using a Teflon tube which was inserted just inside one nostril while the contralateral nostril was left open. Air was sampled at 250 ml/min continuously from one nostril via the other nostril during a breath hold maintained as long as possible. NO concentration was recorded when the value reached the plateau. Nasal CO_2 was also monitored to ensure exhalation was not taking place. This test was repeated twice and the mean value calculated.

The same model of analyser was used in both laboratories and measurements were performed by the same investigator to avoid any possible error arising from measurements taken at different sites. Both analysers were calibrated daily with certified NO mixtures (100 ppb) in nitrogen (BOC Special Gases, Guildford, UK). Two successive recordings were made and mean values were used in all calculations.

Statistical analysis

Age, FEV_1, and FVC values are given as mean (SE). Mediator values are expressed as median (range). Differences between groups were analysed non-parametrically using the Kruskal-Wallis test (p values of <0.0001 were considered significant). Pairwise comparisons using the Dunn's multiple comparison test were then carried out.

Spearman's rank correlation was used to determine the relationship between variables. Mean – 2SD values were calculated for nNO to obtain a cut off value for determining the specificity and sensitivity of the measurements. A p value of <0.05 was considered significant.

RESULTS

Exhaled NO

The concentration of eNO in patients with PCD and CF was significantly lower than that in healthy subjects (median (range) 2.1 (1.3–3.5) ppb; p<0.001 and 3.0 (1.5–7.5) ppb;

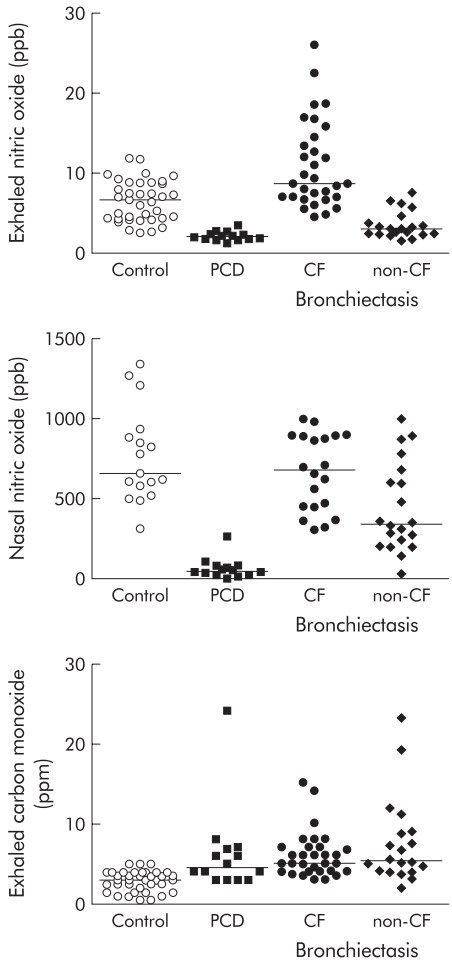

Figure 1 Exhaled nitric oxide, nasal nitric oxide, and exhaled carbon monoxide concentrations in normal subjects, patients with primary ciliary dyskinesia (PCD) with documented bronchiectasis, and patients with non-PCD bronchiectasis with and without cystic fibrosis (CF). The Kruskal-Wallis test showed significant differences between mediator levels ($p<0.0001$).

$p<0.001$, respectively, *v* 6.7 (2.6–11.9) ppb). The level of eNO was significantly higher than normal in patients with non-PCD bronchiectasis without CF (8.7 (4.5–26.0) ppb; $p<0.05$). There was a significant difference in eNO values between non-CF bronchiectatic patients with and without PCD ($p<0.001$). However, eNO values did not differ significantly between patients with PCD and those with CF ($p>0.05$; fig 1). There was no significant difference in eNO levels in patients treated with and without inhaled and/or oral steroids in any of the studied groups. When only data in patients without steroid treatment were compared between the different groups, similar differences were found as described for the pooled data (data not shown).

Nasal NO

Nasal NO measurements were obtained in all patients with PCD and CF, in 20 non-PCD, non-CF bronchiectatic patients, and in 17 healthy subjects. The nNO level was markedly reduced in bronchiectatic patients with PCD (median (range) 54.5 (5–269) ppb) compared with normal controls (663 (322–1343) ppb; $p<0.001$). Bronchiectatic patients with CF also had lower than normal levels of nNO (343 (30–997) ppb; $p<0.05$), but their nNO level was significantly higher than that of PCD patients ($p<0.01$). Nasal NO values of patients with non-PCD, non-CF bronchiectasis (680 (310–1000) ppb) were not significantly different from those in normal subjects. Patients with PCD had significantly lower nNO levels than non-PCD, non-CF bronchiectatic patients ($p<0.001$, fig 1). None of the patients was using nasal steroids and, when data were analysed without nNO values from patients on treatment with oral steroids ($n=2$), similar differences were found between the groups.

Exhaled CO

Levels of eCO were significantly higher than normal in all patient groups (bronchiectasis with PCD: 4.5 (3–24) ppm, $p<0.01$; non-PCD, non-CF bronchiectasis: 5 (3–15) ppm, $p<0.001$; CF: 5.3 (2–23) ppm, $p<0.001$; controls: 3 (0.5–5) ppm). No differences in eCO values were seen between the different groups of patients (fig 1). There were a few outliers in eCO data (24 ppm in the PCD group, 19 and 23 ppm in the CF group) so the results were also analysed without these values, giving the following results: PCD patients: 4 (3–8) ppm, CF patients: 5 (2–11) ppm; the values in both groups were significantly higher than those of the normal control group ($p<0.01$ and $p<0.001$, respectively). No significant difference was detected between patients with and without steroid treatment.

Sensitivity and specificity of the measurement of eNO and nNO

The sensitivity of eNO measurement in selecting PCD patients (number of PCD patients with low eNO reading/number of all patients with PCD in the population) was 79% when a cut off value of 2.4 ppb was chosen. The specificity of eNO measurement (number of non-PCD bronchiectatic patients with negative test/number of all non-PCD bronchiectatic patients) at this cut off value was 85%. The predictive value of a positive test (PPV; percentage of PCD patients with a positive result) was 69% and the predictive value of a negative test (NPV; percentage of patients with a negative test result from those patients who did not have PCD) was 94%.

The sensitivity of nNO measurement was 93% and the specificity was 95% when the mean – 2SD of the nNO level in healthy subjects (187 ppb) was used as a cut off value (only two patients with CF had a value below the cut off level). The PPV of nNO measurement was 87% and its NPV was 97% in discriminating between PCD and non-PCD bronchiectatic patients.

If a positive result was described as low values in both eNO and nNO readings together in the same patient (eNO <2.4 ppb + nNO <187 ppb), this identified PCD patients with a specificity of 98%, PPV of 92%, and NPV of 93%.

Correlations between variables

There was no correlation between lung function and eNO, nNO, or eCO values either when data were pooled or when data from steroid treated and non-treated subgroups were analysed separately or different subject groups were analysed separately (data not shown). Similarly, no relation was found between eNO and nNO readings or between eNO, nNO, eCO values and the age of subjects.

DISCUSSION

We have assessed the clinical usefulness of the simultaneous measurement of eNO and nNO in discriminating between PCD and other types of bronchiectasis. The reported specificity and sensitivity of the simultaneous measurements suggest that their combined use can be a valuable non-invasive screening tool for PCD. The measurement of nNO by itself has good diagnostic value. However, if a low nNO value is observed, determination of eNO and the combined evaluation of the two test results improves the diagnostic value by increasing its specificity and PPV. The measurement of eNO, however, cannot be used by itself for this purpose because of its low sensitivity and PPV. This study shows for the first time

that patients with PCD have lower nNO values than those with any other types of bronchiectasis. It also shows that eNO values are lower in patients with PCD than in those with non-PCD, non-CF bronchiectasis, although there is no difference in eNO values between patients with PCD and CF bronchiectasis. In addition, we have shown that the eCO concentration is increased in patients with PCD to a similar extent to that in other types of bronchiectasis.

There was a significant difference in the mean age of the patients with CF and the other groups. This difference, however, probably did not influence our results because eNO and eCO values have been found not to be age related in adults.[16 17] Furthermore, there was no evidence of any relation between age and nNO values.

We found a modest increase in eNO levels in non-PCD, non-CF bronchiectatic patients compared with healthy subjects, with some overlap between the two groups. This increase was smaller than we had observed in patients with atopic asthma.[18] This fits well with the notion that production of NO is linked to eosinophilic inflammation and that eNO levels are not as high in patients with airway inflammation dominated by neutrophils as in those with allergic asthma.

Some of our patients were treated with inhaled and/or oral steroids, but we could not detect any difference in eNO and eCO levels between patients with or without this treatment. Corticosteroids have been shown to reduce eNO levels profoundly in asthmatic patients[19] and to decrease nNO levels in patients with allergic rhinitis.[20] However, in patients with chronic suppurative upper and/or lower airway inflammation the results are somewhat contradictory. No difference was found in the eNO level between steroid treated and non-treated patients with CF,[13] while in patients with bronchiectasis one study showed a difference in the eNO level[8] but another did not.[21] Differences between the results of these studies can be explained by differences in the techniques used for eNO measurement and by the fact that all of these studies (including the present one) were cross sectional. Prospective follow up studies are required to investigate the possible influence of steroid treatment on eNO values in bronchiectatic patients.

Because nasal symptoms (nasal polyps, sinusitis, persistent serous otitis media) are the main presenting features of PCD, it is important to consider the diagnosis of PCD in these cases. Could the measurement of nNO and eNO help to exclude PCD as an underlying cause of chronic upper airway symptoms? Nasal NO levels are extremely low in PCD. However, low nNO levels are also found in patients with chronic rhinosinusitis[22 23] which may therefore influence the diagnostic value of nNO measurement in discriminating between patients with PCD and those with rhinosinusitis from other causes. Although not specifically investigated in the present study, subjects with non-PCD, non-CF upper airway and sinus diseases had normal NO levels in the lower airways.[22] The use of the combination of eNO and nNO measurements would therefore still have good specificity in identifying PCD.

In contrast to the results on NO levels, we found that eCO levels were raised in all patient groups studied compared with controls, with no difference between different conditions. In chronic airway infections increased HO-1 protein expression may result from the induction of the enzyme by inflammatory mediators such as interleukin-1β, tumour necrosis factor-α, interferon-γ and hydrogen peroxide (H_2O_2) present in the inflamed airways.[23–26] HO-1 may be induced in various cells in the respiratory tract, including airway macrophages,[4] epithelial cells,[27] and infiltrating inflammatory cells such as neutrophils. In the present study there was no correlation between eCO levels and FEV_1. This is not surprising as the decrease in FEV_1 may be the result of structural changes due to repeated inflammation while increased eCO levels are more closely linked with the ongoing inflammatory process. Increased CO production may have multiple functions in the airways including antioxidant, pro-inflammatory, and anti-inflammatory effects.[25]

The finding that eCO is increased equally in different inflammatory airway diseases including asthma,[4 5] bronchiectasis,[9] and CF[28] suggests that CO production has a profound link with inflammatory processes regardless of their atopic or non-atopic nature.

In conclusion, this study has shown that combined measurement of eNO and nNO levels discriminates between bronchiectatic patients with PCD and those with bronchiectasis from other causes, which suggests that this measurement can be used as a non-invasive screening tool for PCD. On the other hand, increased levels of eCO found in all patient groups indicate that the activation of CO production is generally involved in these airway conditions.

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LUNG ALERT

Thrombolysis for submassive pulmonary embolism

▲ Konstantinides S, Geibel A, Heusel G, *et al*. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl Med J* 2002;**347**:1143–50

This was a randomised placebo controlled trial of alteplase (100 mg over 2 hours) with heparin *v* placebo with heparin in 256 patients with submassive pulmonary embolism (PE) defined as echocardiographically detected PE; pulmonary artery hypertension with confirmation of PE by spiral computed tomography (CT); precapillary pulmonary hypertension with confirmation by CT; or new electrocardiographic signs of right ventricular strain followed by CT. Exclusion criteria included age >80 years, haemodynamic instability, and presentation more than 96 hours after onset of symptoms. In the alteplase group there was less escalation of treatment (p=0.004) and a greater chance of 30 day event free survival (p=0.005). There was no difference in mortality or adverse events between the two groups.

This is the largest trial of thrombolysis in PE ever conducted, and it looks at the controversial group of patients with submassive PE showing significant benefit of alteplase. The absence of haemorrhagic complications was surprising.

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