CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Increased leukotriene B4 and 8-isoprostane in exhaled breath condensate of patients with exacerbations of COPD

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Background: Exacerbations are an important feature of chronic obstructive pulmonary disease (COPD), accounting for a large proportion of health care costs. They are associated with increased airway inflammation and oxidative stress.
Methods: Concentrations of leukotriene B4 (LTB4), a marker of inflammation, and 8-isoprostane, a marker of oxidative stress, were measured in the exhaled breath condensate of 21 patients (11 M) with COPD during an exacerbation and 2 weeks after treatment with antibiotics. In 12 patients who had no further exacerbations these markers were also measured after 2 months.
Results: LTB4 concentrations were raised during the COPD exacerbation (mean (SE) 15.8 (1.1) pg/ml and fell after treatment with antibiotics to 9.9 (0.9) pg/ml ($p<0.0001$). In 12 patients the level of LTB4 fell further from 10.6 (1.1) pg/ml to 8.5 (0.8) pg/ml ($p<0.005$) after 2 months. In 12 normal age matched subjects the LTB4 levels were 7.7 (0.5) pg/ml. Concentrations of 8-isoprostane were also increased during the exacerbation (13.0 (0.9) pg/ml) and fell after antibiotic treatment to 9.0 (0.6) pg/ml ($p<0.0001$). In 12 patients there was a further fall from 9.3 (0.7) pg/ml to 6.0 (0.7) pg/ml ($p<0.001$) after 2 months compared with normal subjects (6.2 (0.4) pg/ml).
Conclusions: Non-invasive markers of inflammation and oxidative stress are increased during an infective exacerbation of COPD and only slowly recover after treatment with antibiotics.

Chronic obstructive pulmonary disease (COPD) is a progressive disease characterised by reduced expiratory flow that is relatively stable over several months.[1] Patients with COPD are prone to periods of exacerbation of their illness,[2] and frequent exacerbations of COPD may contribute to the decline in lung function.[3] Little is known about the mechanisms of acute exacerbations of COPD. Infections account for most,[4] and there is a significant benefit associated with antibiotics.[5] Recent studies indicate that recurrent exacerbations of COPD may be associated with increased airway inflammation, which may contribute to disease progression.[6] It is therefore important to quantify and monitor inflammatory changes in patients with COPD.

Neutrophils are an important component of airway inflammation in COPD and have been found in bronchial biopsy specimens and bronchoalveolar lavage fluid.[7 8] However, these methods are relatively invasive, so in recent years more research has been focused on developing less invasive techniques to assess markers of inflammation. Induced sputum samples show an increase in neutrophils in patients with COPD,[9] together with increased concentrations of interleukin 8 (IL-8) and tumour necrosis factor α (TNF-α).[10 11] The sputum concentrations of these cytokines are found to increase further during acute exacerbations.[11] During bacterial exacerbations the concentrations of neutrophil products (myeloperoxidase and elastase) and neutrophil chemoattractants (IL-8 and leukotriene B4 (LTB4)) are increased and subsequently fall after treatment with antibiotics.[12–14] Sputum concentrations of IL-8 appear to be closely associated with the degree of airflow obstruction and have been suggested as a useful marker for evaluating the severity of airway inflammation.[10] Ongoing airway inflammation increases lung oxidative stress in patients with COPD.[15] Several non-invasive markers of oxidative stress—including hydrogen peroxide and 8-isoprostane— are increased in exhaled condensate during exacerbations of COPD and decrease during recovery.[16–19]

A study was undertaken to assess markers of inflammation (LTB4) and oxidative stress (8-isoprostane) in exhaled breath condensate in patients with exacerbations of COPD and after treatment with antibiotics. The study was conducted in a general practice clinic as most exacerbations of COPD are managed out of hospital.

METHODS

Thirty patients (19 men) with exacerbations of COPD were recruited from general practice clinics. COPD was defined as forced expiratory volume in 1 second (FEV_1) of <80% predicted for age and height and a ratio of FEV_1 to forced vital capacity (FVC) of <70%. In all patients the spirometric bronchodilator response to 500 µg nebulised salbutamol was <15% of the baseline when clinically stable.

All patients were current or ex-smokers; all smokers refrained from smoking for at least 12 hours before collection of breath condensate. This was confirmed by normal values of exhaled carbon monoxide levels. An exacerbation of COPD was diagnosed according to the criteria of Anthonisen and colleagues.[20] All patients had to have the following three major symptoms: increased breathlessness, sputum volume, and purulence. We deliberately used symptoms to define exacerbations since these criteria apply in clinical practice. Patients were asked to contact practice nurses as soon as the symptoms appeared and all tests were performed within 12–16 hours.

Twelve control subjects (8 men) were recruited from the staff working in the practices. All were non-smokers and had no significant past medical history.

Study design

Patients completed a short questionnaire about their symptoms and colour of the sputum. Spirometric tests were then performed and expired breath condensate was collected. All these measurements were taken during an exacerbation,

Table 1 Characteristics of study subjects

	COPD (n=21)	Normal (n=12)
Mean (SD) age (years)	66 (8)	56 (4)
M/F	11/10	8/4
Pack years smoking	38 (27)	0
FEV_1 (% predicted)	51 (13)	91 (5)
FVC (% predicted)	67 (21)	103 (11)
FEV_1/FVC%	52 (5)	90 (6)

FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity.

before starting a course of a broad spectrum antibiotic (amoxycillin or erythromycin), and then repeated after 2 weeks and also after 2 months when in a stable condition. All the patients were allowed to increase the use of inhaled β_2 agonist and/or ipratropium bromide as required. However, if there was no clinical improvement after 3 days of treatment with the antibiotic they were asked to contact the doctor again.

Expired condensate was collected by an Eco Screen condenser (Jaeger, Hoechberg, Germany). Patients were required to breathe tidally through the mouthpiece connected to the condenser for 10 minutes while wearing a nose clip. Approximately 2 ml of condensate was immediately stored at –20°C, transferred on dry ice within a few days, and stored in the laboratory at –70°C.

Assays of LTB4 and 8-isoprostane were performed by a specific immunoassay (EIA) kit (Cayman Chemical Company, Ann Arbor, Michigan, USA) as previously described.[21] The specificity of LTB4 and 8-isoprostane assays was 100%. The detection limit for LTB4 was 5 pg/ml and for 8-isoprostane was 4 pg/ml. The intra-assay and inter-assay variabilities were <10%. Assays were directly validated by gas chromatography/spectrometry.

Spirometric tests were performed using a Vitalograph 2120 hand held storage spirometer (Vitalograph Ltd, Buckingham, UK). All patients were treated for 7 days with a course of a broad spectrum antibiotic (amoxycillin 500 mg tds or erythromycin 500 mg qds if they were allergic to penicillin).

The study was approved by the local West Kent ethical committee and all patients gave informed consent.

Statistical analysis

All data are presented as mean (SE). Demographic data are expressed as mean (SD). For parametric data the Student's paired *t* test was used to compare groups. Differences between patients at the start and after the exacerbation were compared with the control patients using the Mann-Whitney U test. Correlation analysis was used to assess the relationship between LTB4 and FEV_1 and also between 8-isoprostane and FEV_1. A p value of <0.05 was considered significant.

RESULTS

Patient selection

Thirty patients were originally recruited. However, nine patients who did not respond clinically within 3 days to antibiotics (three major symptoms unchanged) were also given oral corticosteroids and were excluded from the analysis as we wanted to assess purely the effect of antibiotics in patients with clinical symptoms of an infective exacerbation of COPD. In those patients we did not repeat measurements of markers in exhaled breath condensate and we did not include the initial measurements. However, these patients had a similar degree of airways obstruction (FEV_1 49 (18)% predicted) and similar levels of markers in initial samples of expired breath condensate (LTB4 16.1 (2.0) pg/ml; 8-isoprostane 14 (0.8) pg/ml).

The baseline characteristics of the 21 patients included in the analysis are summarised in table 1. Patients with COPD had a wide range of airways obstruction as shown by FEV_1. Only four patients were allergic to penicillin and they were treated with erythromycin. Since this subgroup was very small, it was impossible to make any comparison with the patients treated with amoxycillin.

All patients were on inhaled corticosteroids, the dose of which remained constant during the exacerbation, but none of those patients included in the final analysis was treated with oral steroids. All the patients were allowed to increase inhaled β_2 agonist and/or ipratropium bromide as required. In all patients included in the study all three major symptoms had improved after treatment with antibiotics. We deliberately did not start oral steroids at the initial visit since, in our clinical opinion, the exacerbation was not severe enough.

All control subjects were lifelong non-smokers and they were only slightly younger than the patients with COPD (table

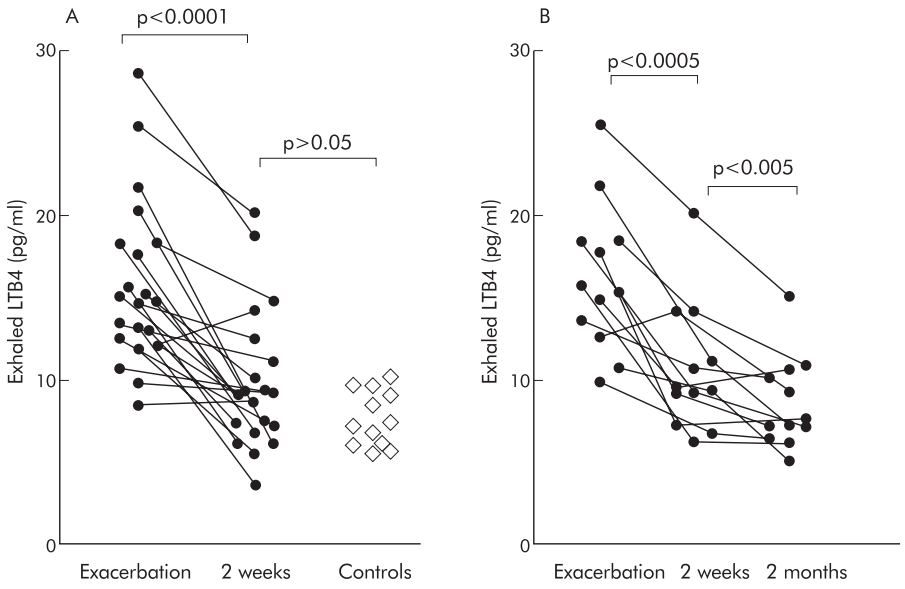

Figure 1 (A) Concentrations of exhaled leukotriene B4 (LTB4) during an exacerbation of COPD (n=21) and after 2 weeks compared with normal non-smoking subjects (n=12). (B) Concentrations of exhaled LTB4 in 12 patients with COPD during an exacerbation, after 2 weeks, and after 2 months.

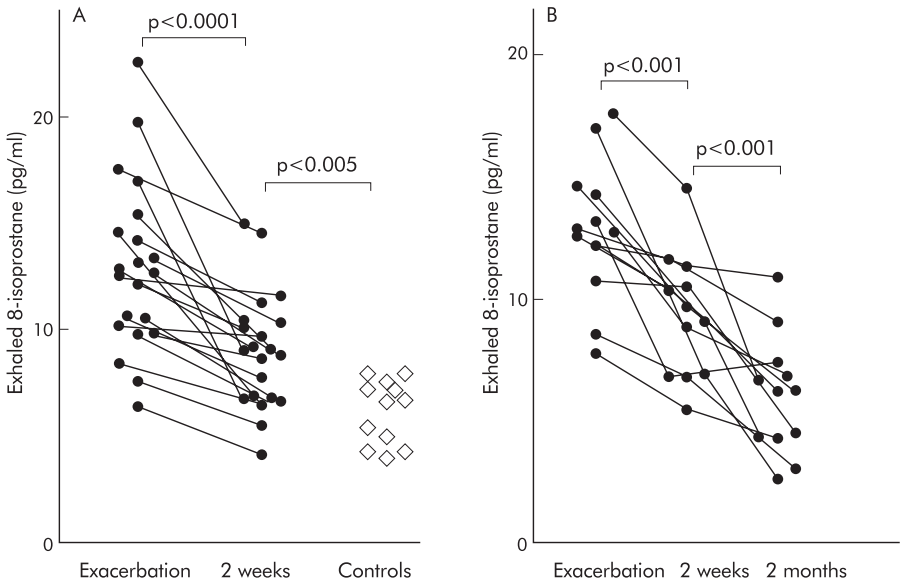

Figure 2 (A) Concentrations of exhaled 8-isoprostane during an exacerbation of COPD (n=21) and after 2 weeks compared with normal non-smoking subjects (n=12). (B) Concentrations of exhaled 8-isoprostane in 12 patients with COPD during an exacerbation, after 2 weeks, and after 2 months.

1). None had a significant medical history, they were not taking any medication, and they had normal spirometric values. All control subjects were living in the same area as the study patients.

LTB4

LTB4 levels were increased during the exacerbation periods (15.8 (1.1) pg/ml) and fell after treatment with antibiotics to 9.9 (0.9) pg/ml ($p<0.0001$) which was similar to the level in normal non-smoking subjects (7.7 (0.5) pg/ml; fig 1A). In 12 patients who agreed to participate further in the study the tests were repeated after 2 months when in a stable condition and LTB4 levels were found to decrease further from 10.6 (1.1) pg/ml to 8.5 (0.8) pg/ml ($p<0.005$, fig 1B).

8-isoprostane

Levels of 8-isoprostane were increased during the exacerbation periods (13.0 (0.9) pg/ml) and fell to 9.0 (0.6) pg/ml ($p<0.0001$, fig 2A) after treatment with antibiotics, although the level was still significantly higher than in normal subjects (6.2 (0.4) pg/ml; $p<0.005$). In the 12 patients who agreed to have repeat tests after 2 months and who had no further exacerbations there was a further fall in 8-isoprostane levels from 9.3 (0.7) pg/ml to 6.0 (0.7) pg/ml ($p<0.001$, fig 2B).

Spirometric parameters

There was no significant change in FEV_1 after treatment with antibiotics (initial measurement 1.15 (0.08) l, after treatment 1.25 (0.08) l, $p>0.05$). Furthermore, in 12 patients who were followed up for 2 months there were no significant changes in FEV_1 (initial FEV_1 1.23 (0.11) l, after 2 weeks 1.14 (0.14) l, after 2 months 1.26 (0.18) l). There was no significant correlation between the degree of airways obstruction as shown by FEV_1 and the levels of LTB4 or 8-isoprostane in exhaled condensate either during the exacerbation or after treatment with antibiotics.

DISCUSSION

All the study patients had exacerbations of COPD as defined by Anthonisen *et al*[20] with the three major criteria present. It was therefore assumed that all patients had a bacterial exacerbation of COPD. We have shown that patients with exacerbations of COPD have increased concentrations of LTB4 and 8-isoprostane in the exhaled condensate which return to normal during the recovery period. LTB4 is a potent and selective chemoattractant of neutrophils[22] and may be released from macrophages and epithelial cells as well as from activated neutrophils.[23 24] The increase in LTB4 may contribute to the increase in neutrophil influx during an exacerbation.[11] LTB4 levels fell after antibiotic treatment and became similar to the levels in normal non-smoking subjects. This may reflect a fall in neutrophil markers in the airways during the recovery period. Furthermore, LTB4 levels fell further after 2 months in patients who had no further exacerbations, which suggests that exhaled LTB4 may be useful in the non-invasive assessment and monitoring of inflammation in patients with COPD. Our results are consistent with a recent report that LTB4 levels are increased in the sputum of patients with bacterial exacerbations of COPD and fall rapidly after antibiotic treatment.[14] In another study, which included larger numbers of patients with exacerbations of COPD, the LTB4 level was increased but fell after treatment and remained stable for 56 days.[25] The increased concentration of LTB4 in patients with COPD is correlated with myeloperoxidase activity, indicating activation of neutrophils.[13] This relationship may reflect increased numbers of bronchial neutrophils in these patients. A similar increase in LTB4 is also seen in patients with bronchiectasis.[26] Infection may also increase the production of other inflammatory mediators—for example, IL-8, IL-6, and TNF-α levels in induced sputum are increased during exacerbations of COPD—and these measurements can be used to evaluate the severity of airway inflammation.[10 12] Endothelin-1 (ET-1) has also been shown to increase in the sputum during COPD exacerbations.[27]

Infection is the most common cause of exacerbations of COPD and may be responsible for an increase in inflammation in the airways.[6] Indeed, in a recent study an increased airway bacterial load was strongly related to several markers of inflammation in the sputum including IL-8 and LTB4.[28] Sputum levels of IL-8 and TNF-α were reported to increase significantly during exacerbations of COPD and to return to baseline after recovery.[10]

Our study also showed that exhaled 8-isoprostane levels were increased during exacerbations. This may reflect increased oxidative stress. Indeed, an infection may contribute to oxidative stress, which is a major component of airways

inflammation in patients with COPD.[29] Increased levels of 8-isoprostane have also been found in the urine of patients with COPD during exacerbations and declined as the acute exacerbation resolved.[17] In our patients the levels of 8-isoprostane in exhaled condensate fell after antibiotic treatment, with a further reduction after 2 months in patients who had no further exacerbations. Our findings are in agreement with those of other studies which have also shown increased oxidative stress in patients during exacerbations of COPD using other markers such as exhaled ethane, 8-isoprostane in urine, and hydrogen peroxide in exhaled breath condensate.[16–18]

We did not perform sputum culture in our patients as they all had clinical symptoms of bacterial exacerbations of COPD with increased amounts of purulent (yellow or green) sputum. Sputum colour has been shown to be an important identifier of bacterial exacerbations of COPD and a marker of individuals who may benefit from antibiotic treatment.[28] In all our patients the sputum became clear after antibiotic treatment, which suggests that bacterial infection played an important role in these exacerbations. Indeed, in the clinical phenotype described by Anthonisen *et al*,[20] antibiotics were effective in patients with worsening dyspnoea, cough, and increased sputum volume and purulence. This has been confirmed in a recent study by Woolhouse *et al*[30] based on patient diary cards which showed rapid improvement in symptoms in patients with bacterial exacerbations after treatment with antibiotics.

In our study there was no significant difference in the degree of airways obstruction as shown by FEV_1 during exacerbations compared with the stable state. This could be because our patients had largely irreversible airways obstruction and the exacerbation was not severe enough to cause further deterioration. Other studies have also shown that spirometric changes associated with exacerbations may be very small, so lung function tests are not very useful in detecting exacerbations.[31] Bhowmik *et al*[12] found no relationship between peak expiratory flow recovery times and symptoms and cytokine levels during exacerbations. However, increased baseline levels of sputum cytokines have been reported in patients with more frequent exacerbations of COPD. In our study exhaled inflammatory markers were raised during the exacerbations, and this could be a be more sensitive measurement than respiratory function.

We measured exhaled condensate levels of LTB4 and 8-isoprostane and believe that this method allows us to assess inflammation and oxidative stress accurately in the whole airway. Inflammation in COPD is mainly present in peripheral airways rather than the central airway, and this can be assessed by exhaled condensate. On the other hand, sputum samples are more likely to measure inflammation in the central airway and this has been confirmed in a recent study using radiolabelled markers.[32] Collection of exhaled condensate is safe and can be performed repeatedly, even in patients with severe airways obstruction. Exhaled condensates contain fluid from two sources—pure exhaled water vapour and droplets generated from the secretions lining the pulmonary surface. The collection of the samples was identical so it is likely that the dilution was similar. Although there was considerable variability in the initial levels of expired biomarkers between patients, the changes in several samples are more important. The level of inflammatory markers during the stable state may be used in the future as a reference value for early detection of an exacerbation. There is currently no standardised method for collecting breath condensate, but Van Beurden and collegues[33] have shown that the measurement of hydrogen peroxide in exhaled condensate was reproducible. However, more data are needed regarding the reproducibility of measurements of the other markers in exhaled breath condensate. Our study was conducted in a family practice setting, demonstrating the feasibility of these measurements in the community.

This study confirms the important role of LTB4 in inflammation in patients with exacerbations of COPD. LTB4 in exhaled condensate is increased during a COPD exacerbation and may play a part in mediating airway inflammatory changes. Oxidative stress, as assessed by the level of 8-isoprostane in exhaled condensate, is also increased during exacerbations of COPD, but appears to take longer to return to normal after antibiotic treatment. Measurements of LTB4 and 8-isoprostane in exhaled condensate may provide another useful diagnostic tool for detecting and monitoring inflammation and oxidative stress in patients with COPD. They can be performed repeatedly even in patients with severe airways obstruction and may be helpful in detecting exacerbations of COPD.

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LUNG ALERT

The cost of helical CT lung cancer screening is high

▲ Mahadevia PJ, Fleisher LA, Frick KD, *et al*. Lung cancer screening with helical computed tomography in older adult smokers: a decision and cost-effectiveness analysis. *JAMA* 2003;**289**:313–22

In this study a computer simulated model of a hypothetical cohort of 100 000 60 year old current, quitting, and former smokers was used to assess the cost effectiveness of helical CT lung cancer screening. Using the best available data on outcomes associated with lung cancer screening, the costs of diagnosis, treatment and long term outcomes, the efficacy of changing the clinical stage distribution of lung cancer so that the screened group would have fewer advanced staged cancers and more localised stage cancers was assessed. Biases such as lead time (from earlier onset of costs as a result of earlier diagnosis), length (due to long latency periods), and overdiagnosis (for example, of subclinical disease) were incorporated. Over 20 years there were 553 fewer lung cancer deaths and 1186 false positive invasive tests in the screened group. The incremental cost for current, quitting, and former smokers was $116 300, $558 600, and $2 322 700 per quality-adjusted life year (QALY) gained, respectively. Even the most favourable parameters estimated the most cost effective outcome for current smokers to be $42 500 per QALY.

The debate on the usefulness of helical CT scanning to screen for lung cancer rages on. The National Cancer Institute has recently initiated a large randomised trial to assess the efficacy of helical CT screening for detection of early lung cancer. While the results of this trial are awaited, commercially available cancer screening programmes are being widely promoted in the US. Mahadevia and colleagues have used complex analysis techniques to suggest that screening is not cost effective with current methods.

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