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Exhaled breath analysis in the differentiation of pneumonia from acute pulmonary oedema

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Abstract

Introduction: Community-acquired pneumonia (CAP) and acute cardiogenic pulmonary oedema (ACPO) are common clinical conditions requiring hospital admission, but require different treatment. To assess whether exhaled breath analysis can distinguish between these, we measured exhaled breath condensate biomarkers and fractional exhaled nitric oxide (F_ENO) in 14 patients with CAP and 12 patients with ACPO admitted acutely to hospital via the Emergency Department, comparing profiles with 15 control subjects.

Methods: F_ENO was measured using a NO Breath analyser and exhaled breath condensate (EBC) was collected for analysis of EBC biomarkers. EBC pH was measured with pH meter. The EBC biomarkers C-reactive protein (CRP), neopterin and 5N-terminal pro-brain natriuretic peptide (5NT-proBNP) were quantified using enzyme linked immunosorbent assays.

Results: EBC 5NT-proBNP was raised in ACPO, while EBC CRP was raised in CAP. However, neopterin and pH showed no differences between groups. F_ENO levels were significantly higher in CAP than in ACPO ($p=0.03$).

Conclusions: This study demonstrates that exhaled breath analysis may be useful in assessing the acutely breathless patient, but that even this easy non-invasive technique is difficult for sick patients. More rapid measurements, application of novel biomarkers and combined assessment of several EBC biomarkers are likely to improve diagnostic differentiation in the future.

Keywords: Community-acquired pneumonia, acute cardiogenic pulmonary oedema, exhaled breath condensate, exhaled nitric oxide, biomarkers

Introduction

Pneumonia and acute cardiogenic pulmonary oedema (ACPO) are common acute clinical conditions. Despite their distinct pathophysiology, both may present with similar non-specific symptoms and can be difficult to distinguish radiologically, resulting in misdiagnosis and inappropriate treatment [1]. Methods for distinguishing between these conditions include blood but not exhaled breath biomarkers [2-4]. Exhaled breath analysis is being increasingly used for the clinical diagnosis of conditions ranging from lung cancers to tuberculosis [5-7], and offers the potential of a rapid, easily-performed method for triage and clinical management in the emergency setting.

The advantage of exhaled breath analysis is that it is totally non-invasive and relatively easy to perform even in sick and elderly patients. Exhaled breath condensate (EBC) biomarkers have been assessed in an increasing number of respiratory conditions [8,9] including pneumonia [10] and fractional exhaled nitric oxide (F_ENO) is now accepted as a valuable clinical tool in the management of respiratory disorders. Several studies have also indicated that exhaled breath biomarkers may also be useful in assessing cardiac conditions such as cardiac failure [11] and pulmonary hypertension [12].

Community-acquired pneumonia (CAP) is still a common worldwide problem and a common cause of hospital admission. CAP defined is an acute infection of the lung parenchyma by bacteria, viruses or both, manifesting as crackles on auscultation

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and as an infiltrate on radiological imaging; however, these features may not occur in all patients, particularly the elderly or immunosuppressed. In contrast, ACPO occurs when fluid leaks from the pulmonary capillary network into the lung interstitium and alveoli. In ACPO, cardiac dysfunction causes increased pulmonary capillary hydrostatic pressure, forcing fluid into the alveolar and interstitial spaces [13]. Auscultatory crackles and opacities on the chest x-ray occur. Differentiation between ACPO and pneumonia relies upon a careful history, clinical examination and radiographic findings. The latter have poor discriminative value [1,14].

Exhaled breath contains a mixture of volatile and non-volatile biomarkers. The condensate formed from exhaled breath, EBC, contains a large number of ions, metabolites, and other molecules [15], while the gaseous phase contains volatile organic compounds, a diverse group of carbon-based chemicals [7]. Exhaled breath condensate can be collected using a hand held, simple device which is portable and usable at the bedside; EBC is then snap frozen and later analysed for a wide variety of biomarkers. However, it is possible using modern methodologies to immediately assess potential biomarkers at the bedside, although no studies have currently assessed this.

In this preliminary clinical study, we examined candidate breath biomarkers including CRP and neopterin, measured in EBC and fractional exhaled nitric oxide in a group of patients acutely admitted to hospital. We hypothesised that some breath biomarkers would be raised in CAP but not in ACPO or in a matched control group, while EBC pH would be decreased [16-19]. We also measured EBC 5N-terminal pro-brain natriuretic peptide (5NT-proBNP), a marker of cardiac myocyte injury, which is raised in the peripheral blood in heart failure [20,21].

Methods

Study design and subjects

Institutional ethics approval (REF SVH H02/004) and written informed consent were obtained. This prospective cross-sectional study compared three subject groups: CAP, ACPO and control subjects. Subjects completed a standardised questionnaire, provided EBC and breath for F_ENO analysis.

Participants were admitted to Hospital acutely via the Emergency Department at St Vincent's hospital and selected on the basis of a clinical diagnosis of either CAP or ACPO, made by the admitting doctor in the Department. Patients had to be diagnosed with either disease alone and to have no other respiratory disorder; allocation was made using current international guidelines [22,23] and exclusions were strictly applied to ensure no overlap between groups. Subjects were recruited, as far as possible, within 24 hrs of admission and patients admitted to Intensive Care were excluded. CAP was diagnosed according to the British Thoracic Society's definition: i.e., symptoms and signs consistent with an acute lower respiratory tract infection associated with new chest radiographic shadowing that has no other explanation [22]. ACPO was diagnosed based on characteristic clinical signs as described by the European Society of Cardiology, including orthopnoea, severe respiratory distress, basal fine inspiratory crackles, the presence of radiological opacities and decreased oxygen saturation on room air [23].

The diagnosis was substantiated by retrospective review of hospital case notes after admission, to ensure it had remained unaltered. Exhaled breath analysis was performed as soon as the patient was stable enough, usually within 24 hrs of admission. Control participants were selected on the basis of lack of any known underlying pulmonary or cardiac disease and were matched for age, gender and smoking status. All subjects who had factors recognised to affect exhaled breath biomarkers were excluded, including other lung diseases such as asthma, COPD, bronchiectasis or idiopathic pulmonary fibrosis, and other systemic diseases which could theoretically affect exhaled biomarkers such as connective tissue disorders, uncontrolled hypertension. Smoking habits were documented and for the purposes of the study ex-smokers were defined as those who had not smoked cigarettes for more than 1 year.

Exhaled breath condensate

EBC collection

EBC was collected using a validated custom-made glass tube apparatus according to published recommendations [15]. Subjects rinsed their mouths with water before breathing tidally for 10-12 minutes into a disposable one-way valve mouthpiece (Vitalograph, Buckingham, England). EBC was collected into a glass tube placed on ice and after collection immediately de-aerated with argon gas to displace CO_2 and to stabilise the sample.

EBC pH

EBC pH for each subject was measured using a hand-held pH meter (Hach, Colorado, USA) at three different time points: immediately prior to de-aeration, immediately following de-aeration and after a freeze-thaw cycle to ensure that the effects of EBC processing and storage were taken into account [24].

EBC biomarker analysis

EBC biomarker analysis was undertaken using enzyme linked immunosorbent assays. Neopterin was measured using an enzyme linked immunosorbent assay (ELISA, GenWay Biotech, San Diego, USA) with a lower limit of detection (LLOD) of 0.7nmol/l. NT-proBNP was measured using an enzyme immunoassay (EIA, Alpco Diagnostics, Salem, USA) with a LLOD of 5 fmol/ml. CRP was measured by ELISA (Invitrogen, Camarillo, USA) with a LLOD of 1.84pg/ml following optimisation of the standard curve by the addition of more standard points. Absorption levels were determined spectrophotometrically (Molecular Devices, Surrey, UK) using the specified wavelengths.

EBC data analysis

A D'Agostino& Pearson omnibus normality test was followed by

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either one way analysis of variance (ANOVA) with Bonferroni's multiple comparison post-hoc test or the Kruskal-Wallis test with Dunn's post-hoc test. Data were expressed as means ±standard errors (SE) for parametric data and as median (interquartile range) for nonparametric data. Significance was set at $p<0.05$. A value of one-half of the LLOD was assigned to all undetectable values.

Fractional exhaled nitric oxide

F_ENO was measured in accordance with published guidelines [25]. Subjects exhaled into the NO breath analyser (Bedfont Scientific Ltd, Kent, UK) for 15 seconds at a pressure of 15cm H_2O, to close the soft palate and thus avoid nasal NO contamination. An average was taken of 3 sequential readings if they were within a 10% range. A flow rate of 0.05 L/second was used.

Results

Subject characteristics

Fourteen subjects with CAP, twelve subjects with ACPO and fifteen healthy controls were able to provide EBC samples, and clinical characteristics are shown in **Table 1**. All subjects provided EBC and also had their F_ENO measured, except for one subject with CAP.

Patients with concomitant diseases had been excluded from the study, so none had any evidence of respiratory disorders such as asthma or bronchiectasis. Subjects were younger than the usual patient with CAP, probably reflecting the above exclusion factor. No significant differences were found between study groups, including smoking habits.

Exhaled breath condensate

Although 20 subjects were recruited in both disease groups, not all were able to complete EBC collection and F_ENO analysis.

Table 1. Characteristics of the cohort providing EBC.

	CAP	ACPO	Controls	Statistical difference
Subjects (n)	**14**	**12**	**15**	
Age (years) mean±SE	59.43±5.689	54.50±5.804	56.33±5.414	ANOVA p=0.83
BMI (kg/m^2) mean±SE	24.87±1.311	28.41±1.817	27.05±1.158	ANOVA p=0.24
Gender (male/female)	12/2	7/5	11/4	Fisher's exact test p=0.31
Smoking status (non/ex/ current)	6/4/4	5/4/3	10/3/2	Fisher's exact test p=0.60

ACPO: Acute cardiogenic pulmonary oedema; CAP: Community acquired pneumonia; BMI: Body mass index; n: Number of subjects; SE: Standard error. Smoking status was defined as non-smoking when subject had never smoked, ex-smoker when subject had not smoked for twelve months and a current smoker if subject was still smoking or had quit within the preceding eleven months.

This was primarily due to breathlessness in the acutely ill patients. Patients found it difficult to complete the EBC collection, which requires at least 10 minutes breathing into the simple collection device, and asked to terminate the procedure early before sufficient EBC had been collected.

EBC pH

EBC was available in 14 subjects with CAP, 12 with ACPO and 15 healthy controls (n=41). No significant differences in mean EBC pH were found between the three groups. This applied before de-aeration (p=0.24), after de-aeration (p=0.51), and after a freeze-thaw cycle (p=0.17) of EBC (**Figure 1**). In 2 CAP subjects, EBC pH could not be accurately measured after de-aeration due to technical problems.

EBC biomarkers

EBC CRP was detected in more subjects with CAP (7/14; 50%), than in those with ACPO (4/12; 30%) and controls (1/15; 6.6%; p=0.03 for differences between groups). The remaining subjects had levels below the LLOD. Median (interquartile range) CRP values were: CAP 1.188 (0.920-2.565) pg/ml; ACPO 0.920 (0.920-11.340) pg/ml; controls 0.920 (0.920-0.920) pg/ml (p=0.07, **Figure 2a**). On clinical review after recovery, the four ACPO subjects who had high CRP levels also had other clinical conditions (renal failure, Pseudomonas infection, chronic sinusitis) which may have affected CRP levels other than their clinical presenting problem. After removing these four subjects from the analysis there was a significant difference in CRP levels between subjects with CAP and other groups (p=0.009). To assess if EBC CRP reflects the severity of pneumonia, EBC CRP levels were correlated with total white blood cell count. We found no significant positive correlation between total white blood cell count and EBC CRP levels in the pneumonia group (r=0.08, p=0.78). Ten subjects with ACPO and 14 subjects with CAP had serum CRP levels measured by the hospital laboratory. There was no correlation between serum CRP and EBC CRP (r=-0.1, p=0.63).

Neopterin was detectable in all groups but there were no significant differences between groups (11/14 CAP subjects (78.6%), 11/12 ACPO (91.7%) and 11/15 controls (73.3%, p=0.54). Median (interquartile range) neopterin values were: CAP 2.478 (1.279-3.721) nmol/L; ACPO 2.338 (1.939-3.311) nmol/L; controls 1.644 (0.350-3.421) nmol/L (p=0.64, **Figure 2b**).

5NT-proBNP was detected in 6/12 ACPO subjects (50%), 4/14 CAP subjects (28.6%) and 12/15 controls (80%, p=0.02). Median (interquartile range) 5NT-proBNP values were: CAP 2.5 (2.5-17.71) fmol/ml; ACPO12.85 (2.5-976.2) fmol/ml; controls 30.18 (3.467-184.7) fmol/ml (p=0.04, **Figure 2c**) and post-hoc test analysis showed a significant difference between the controls and CAP group, with levels higher in the controls.

Exhaled nitric oxide

F_ENO was measured in CAP (n=13), ACPO (n=12) and control (n=15) subjects and mean values were: CAP 19.36±3.662

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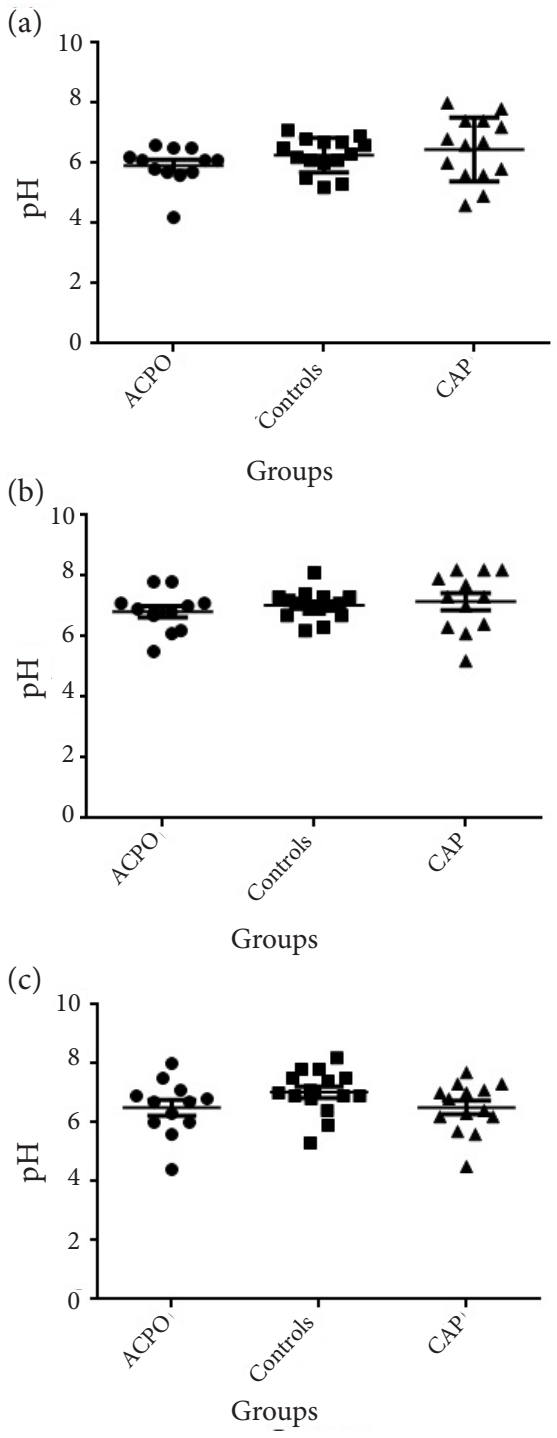

Figure 1. **EBC pH was measured in ACPO (n=12), control (n=15) and CAP subjects (n=14) at three different time points.**
(**a**) before de-aeration; (**b**) after de-aeration and (**c**) after a freeze-thaw cycle. Two CAP subjects did not have their EBC pH measured after de-aeration due to technical problems. No significant differences in mean EBC pH were found between the three groups; before de-aeration (p=0.24), after de-aeration (p=0.51), or after a freeze-thaw cycle (p=0.17). (Bars=mean±SE).

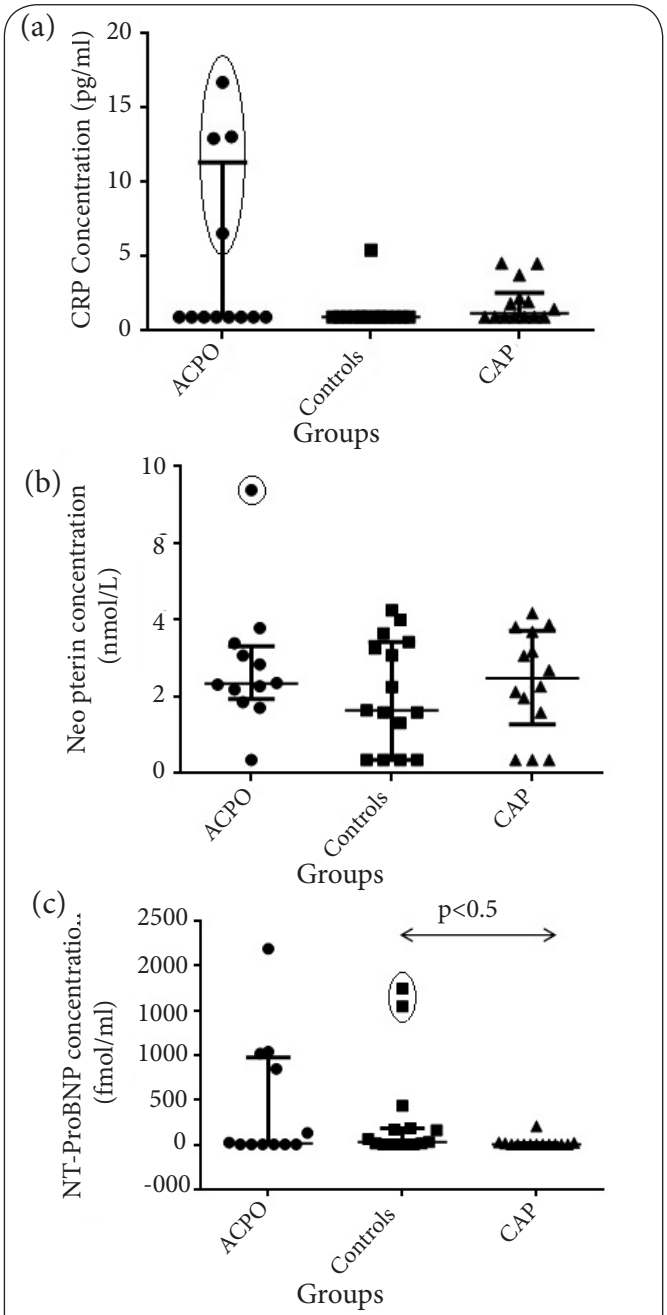

Figure 2. EBC levels of CRP (pg/ml) (**a**), neopterin (nmol/L) (**b**) and NT-proBNP (fmol/ml) (**c**) were measured in ACPO (n=12), control (n=15) and CAP (n=14) subjects. (**a**) There was no significant difference in EBC levels of CRP between the groups (p=0.07). After removing four outliers from the ACPO group (circled) from the analysis there was a significant difference in CRP levels between subjects with CAP and other groups (p=0.009, Kruskal-Wallis test). (**b**) There was no significant difference in EBC levels of neopterinbetween the groups (p=0.64). Reanalysing data after removing the outlier (circled) from the ACPO group did not alter the results. (**c**) There was a significant difference in EBC levels of NT-proBNP (p=0.04, Kruskal-Wallis test) and post-hoc test analysis showed a significant difference between the control and CAP group. Reanalysing data after removing the outliers (circled) from the control group did not alter the results. (Bars=median±interquartile range).

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parts per billion (ppb); ACPO 11.51±1.737 ppb; controls 13.88±1.783ppb. The data have been logarithmically transformed. Exhaled NO levels were significantly higher in the CAP group compared to the ACPO group (p=0.03). No significant difference was found between the ACPO group and controls (**Figure 3**).

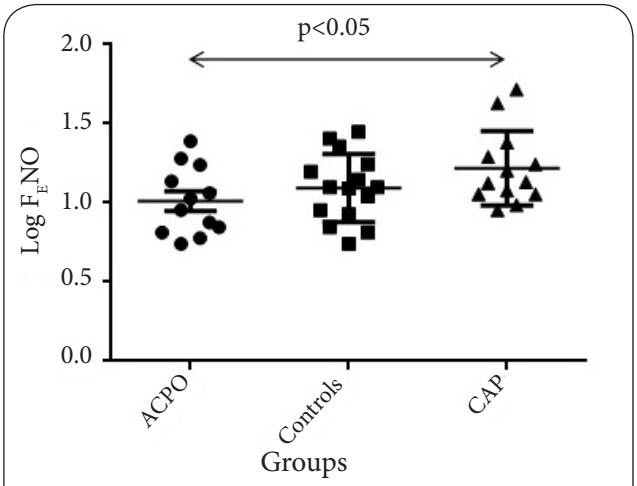

Figure 3. Log transformed levels of fractional exhaled nitric oxide (F_ENO) in ACPO, control and CAP subjects. F_ENO was measured in ACPO (n=12), control (n=15) and CAP (n=13) subjects. F_ENO levels were significantly in the CAP group compared to the ACPO group (p=0.03) but no significant difference was found when compared to control group. (Bars=mean±SE).

Discussion

This study is the first to attempt to distinguish between CAP and ACPO using exhaled breath analysis in acutely ill patients. These patients are difficult to study and there is very limited research in this area. Until now, research has focussed upon serum biomarkers, particularly CRP, derived from blood samples. If exhaled breath samples were feasible and accurate, this procedure would be much less invasive and easier for the patient. If these could be collected during an acute attack of dyspnoea by using, for example, a common clinical device e.g., a respiratory mask, and at the bedside, these might provide very valuable clinical information and could possibly be used in situations where blood collection is difficult. However, preliminary data on EBC in this situation is first required, and thus we aimed initially to collect data on EBC in the acute situation using the standard collection methods before embarking on a larger study. In practice, even when breath collection was delayed by up to 24 hours to facilitate patient participation, we found that patients were too breathless to willingly complete breath collection for research purposes, but that once samples were collected, several useful biomarkers could be identified.

We measured several well known blood biomarkers in order to define an EBC profile which might distinguish accurately between ACPO and pneumonia in these patients, including EBC pH, CRP, neopterin, and 5NT-proBNP. We also measured fractional exhaled nitric oxide, which is known to be raised in acute inflammatory conditions such as pneumonia in the acute setting.

5NT-proBNP is a product of the pro-hormone brain natriuretic peptide which is released by cardiac myocytes when the ventricles are subject to haemodynamic stress [**26**] and is the current serological diagnostic marker of heart failure [**21**]. There is now a large literature on 5NT-proBNP in heart failure, which has clearly demonstrated that a normal blood 5NT-proBNP excludes cardiac failure in 99% of cases [**20**,**21**]. We measured EBC 5NT-proBNP in EBC in acutely dyspnoeic patients, and found that ACPO group had the highest numerical mean value, as expected. Levels were also statistically different between the control and CAP groups, with a clear difference between the groups with CAP and ACPO. However, levels in our controls were higher than expected, with two outliers with values clearly above the others. We are unsure as to why these levels were raised in these two volunteers; review of co-morbidities in these cases found none other than one patient with controlled hypertension, which is not thought to affect basal levels of serum NT-proBNP [**27**]. Unfortunately, we were not able to collect blood 5NT-proBNP in controls which would have been of interest; it is possible that the raised EBC levels in the controls were due to laboratory factors or storage, or else that these subjects have some unrecognised condition. The normal limits for EBC 5NT-proBNP have not yet been assessed. Thus, EBC 5NT-proBNP may have potential clinical applicability in this diagnostic setting but requires further evaluation. Other exhaled breath biomarkers of heart failure such as EBC acetone [**28**] have been described and dual measurement might increase specificity in future studies.

There are a number of studies now which confirm that F_ENO is increased in CAP [**25**], probably due to inflammatory cytokines acting on inducible NO synthase [**29**]. F_ENO is high in ventilator-acquired pneumonia (VAP) [**18**] and eosinophilic pneumonia [**30**]; however, not all studies have had similarly high F_ENO levels [**31**]. In our study, F_ENO was higher in CAP compared to ACPO, and adequately distinguished between the conditions. However, the difference between CAP and control subjects fell just short of statistical significance; it is possible that this reflects differences in severity of pneumonia, or else a treatment effect because antibiotics are given intravenously early *(*within 2 hours) in CAP in our Emergency Department. *M*ean levels in control subjects were within the published normal range (8-14ppb) [**29**], but levels in CAP (19.4 ppb) were not as high as in previous studies of VAP (56 ppb) [**32**] and eosinophilic pneumonia (48 ppb) [**30**], which may account for the lack of statistical significance.

We anticipated that CRP, an acute phase protein synthesised in the liver in response to pro-inflammatory cytokines, might be raised in CAP but not in ACPO. EBC CRP has been

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previously measured although not in pneumonia [33]. We found that EBC CRP was detectable in a larger number of cases with CAP compared to ACPO and control groups (p=0.03). Differences between groups did not reach statistical significance. The lack of significance was contributed towards by unexpectedly increased levels in the ACPO group. Several of these subjects were overweight, and three had other clinical conditions (mild renal failure, Pseudomonas infection, chronic sinusitis). Serum CRP have been shown to be increased in obesity [34], but should not increase to high levels with bacterial colonisation rather than pneumonia. CRP could be increased in EBC in obesity, but this has not been examined. EBC CRP remains a potentially useful biomarker but as always in the acute clinical situation, multiple pathologies can co-exist and individual patient factors may alter results.

Neopterin is a non-specific marker of cell-mediated immunity and cytotoxic T lymphocyte activity [35]. Serum neopterin has been previously studied in CAP [36], and EBC neopterin can be detected in patients with infective exacerbations of asthma and COPD [8]. We detected neopterin in most EBC samples but the levels did not differ between the groups. The only other study evaluating EBC neopterin compared patients with acute and stable obstructive lung disease, and also failed to find a difference in EBC levels, but suggested that sputum neopterin might be more useful [8]. It is possible that EBC neopterin levels are too low for a useful clinical measurement. EBC pH levels are usually a robust discriminator between acute and stable respiratory disease [8], and reflect inflammation in obstructive lung diseases [19,37]. We found however that EBC pH did not differentiate between groups in our study.

There are several possible confounding factors in our study, which relate to real clinical issues and are therefore valuable to identify for future clinical research. One factor was the delay between initial presentation of these acutely ill breathless patients and EBC collection. This was included as part of the research plan for both ethical and practical reasons. Both CAP and ACPO require emergency treatment, which was given within hours of presentation. EBC was therefore collected after treatment had commenced, usually within 24hrs, and once the patient had been stabilised. Serum CRP levels fall rapidly (within 24 hrs) with commencement of appropriate antibiotic therapy [1]; this may also apply to EBC CRP and neopterin and pH, but no data are yet available. Similarly, EBC NT-proBNP would also be expected to change rapidly, but has not been previously assessed. Clinical treatment must take priority over research procedures but immediate collection and comparison with serum values would be of interest.

Our study was probably also limited by the small sample size, which we acknowledge. It was, however, only planned as a preliminary study. Power calculations in future studies need to be based on individual biomarker reproducibility, which has not yet been assessed in EBC for the biomarkers we studied. A number of samples had levels below the LLOD of the assays, which were actually designed for serum not for EBC. This aspect could also possibly be improved by concentrating EBC through lyophilisation, which has proved successful in other studies [38], or by new assays.

Conclusions

In summary, our study has shown that exhaled breath analysis in the acute emergency setting is promising, but not yet currently sufficiently sensitive or specific to fulfil clinical needs. Many patients are simply too unwell to be studied acutely, at least for research purposes. EBC CRP, NT-proBNP and F_ENO seem promising markers, but differences in breath levels between diseases do not seem large enough to allow good discrimination when measured at 24 hours after acute presentation. Currently, most biomarker assays are not available acutely other than CRP, which is available as a bedside test (QuickRead CRP), and biomarkers also need further evaluation in EBC. Development of rapid accurate assays would be potentially useful. In practice, clinical diagnosis relies on the assimilation of multiple types of information and thus in the future, analysis of combinations of biomarkers as well as novel biomarkers may be required to allow diagnostic accuracy and to achieve the aim of giving a patient an immediate bedside diagnosis without invasive methods.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	SP	NE	PST	DHY
Research concept and design	--	--	✓	✓
Collection and/or assembly of data	✓	✓	--	--
Data analysis and interpretation	✓	✓	✓	✓
Writing the article	✓	✓	--	--
Critical revision of the article	--	--	✓	✓
Final approval of article	✓	✓	✓	✓
Statistical analysis	✓	✓	--	--

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