



Application of laser spectroscopy for measurement of exhaled ethane in patients with lung cancer

K.D. Skeldon^{a,*}, L.C. McMillan^b, C.A. Wyse^c, S.D. Monk^a, G. Gibson^a,
C. Patterson^a, T. France^d, C. Longbottom^b, M.J. Padgett^a

^aDepartment of Physics and Astronomy, Kelvin Building, University of Glasgow, Glasgow, G12 8QQ, UK

^bDental Health Services Research Unit, 9th Floor, Dental School, University of Dundee, Park Place, Dundee, DD1 4HR, UK

^cInstitute of Comparative Medicine, University of Glasgow Veterinary School, Bearsden, Glasgow, G61 1QH, UK

^dNinewells Hospital, East Block Level 4, Dundee, DD1 9SY, UK

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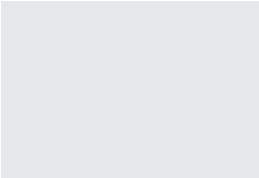
KEYWORDS

Breath test;
Ethane;
Lung cancer;
Oxidative stress;
Lipid peroxidation;
Laser spectroscopy

Summary There is increasing interest in ethane (C₂H₆) in exhaled breath as a non-invasive marker of oxidative stress (OS) and thereby a potential indicator of disease. However, the lack of real-time measurement techniques has limited progress in the field. Here we report on a novel Tunable Diode Laser Spectrometer (TDLS) applied to the analysis of exhaled ethane in patients with lung cancer. The patient group ($n = 52$) comprised randomly selected patients presenting at a respiratory clinic. Of these, a sub-group ($n = 12$) was subsequently diagnosed with lung cancer. An age-matched group ($n = 12$) corresponding to the lung cancer group was taken from a larger control group of healthy adults ($n = 58$). The concentration of ethane in a single exhaled breath sample collected from all subjects was later measured using the TDLS. This technique is capable of real-time analysis of samples with accuracy 0.1 parts per billion (ppb), over 10 times less than typical ambient levels in the northern hemisphere.

After correcting for ambient background, ethane in the control group (26% smokers) ranged from 0 to 10.54 ppb (median of 1.9 ppb) while ethane in the lung cancer patients (42% smokers) ranged from 0 to 7.6 ppb (median of 0.7 ppb). Ethane among the non-lung cancer patients presenting for investigation of respiratory disease ranged from 0 to 25 ppb (median 1.45 ppb).

*Corresponding author. Tel.: +44 141 330 2047; fax: +44 141 330 2893.
E-mail address: kskeldon@physics.gla.ac.uk (K.D. Skeldon).



We conclude that, while the TDLS proved effective for accurate and rapid sample analysis, there was no significant difference in exhaled ethane among any of the subject groups. Comments are made on the suitability of the technique for monitoring applications.

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Introduction

Exhaled ethane is produced *in vivo* by the oxidation of cell membrane lipids¹ which occurs as a consequence of free-radical-mediated attack.² Antioxidant defences counter free-radical attack resulting in a state of equilibrium in healthy individuals. Oxidative stress (OS) was defined in 1985 as 'a disturbance in the pro-oxidant/antioxidant balance in favour of the former'.³ While the precise role of OS in the pathogenesis of disease is unclear, it has been widely recognised as a contributory factor⁴ with extreme levels of OS being associated with critical illness⁵ and eventually contributing to organ failure.⁶ Considerable evidence supports the hypothesis that an increased level of OS is associated with lung cancer. Zieba demonstrated increased concentrations of markers of OS (conjugated dienes, thiobarbituric acid reacting substances, Schiff bases, and lipid hydroperoxides) in tumour tissue homogenates compared to lung parenchyma, in patients with lung cancer.^{7,8} Tumour tissue samples taken from patients with pulmonary adenocarcinoma and squamous cell carcinoma showed striking alterations in antioxidant capacity consistent with increased levels of OS, compared with tumour-free lung parenchymal tissues from the same individuals.⁹

Given that ethane is believed to be produced *in vivo* solely by the process of lipid peroxidation, it is metabolised slowly¹⁰ and it is poorly soluble in body fat,¹¹ it makes an ideal breath biomarker for OS.¹² Previous studies have demonstrated increased ethane exhalation in human patients with respiratory disease, airway inflammation and other conditions.^{13–15} However, the study of volatile organic compounds (VOCs) in the exhaled breath of lung cancer patients has focussed on the hydrocarbons in the range C4–C20^{16,17} possibly due to the difficulties in trapping and measuring ethane (C2) at the parts per billion (ppb) level. Having said this, the majority of groups studying exhaled ethane employ variants of gas chromatography (GC) sometimes coupled with mass spectrometry. This is undeniably the accepted gold standard for VOC measurement in breath analysis, and a technique we have employed in some of our own studies in the past.¹⁸ However, where ethane is concerned at ppb

levels the GC-based technique requires pre-concentration of the breath exhalate and the time taken to measure a single sample is typically more than half-an-hour, even in an automated system. In contrast (and an important advantage in the present study) is that our spectroscopy technique offers baseline sensitivity of 0.1 ppb and, moreover, this accuracy is achieved essentially in real-time, making for swift measurement of breath samples. The recent availability of such optical spectroscopy systems for gas concentration analysis promises to open up new opportunities for the application of the ethane breath test for assessment of OS in medicine.^{19–23}

The aims of this study were: (i) to investigate the feasibility of applying a novel laser spectrometer (Tunable Diode Laser Spectrometer (TDLS)) shown in Fig. 1 to the analysis of clinical breath samples; and (ii) to investigate the association between exhaled ethane and lung cancer. This study was approved by the NHS Tayside Regional Ethics Committee.

Materials and methods

Participants

Patients

Fifty-two patients (age 66 ± 13 years, mean $\pm$ sd), newly referred to Ninewells Hospital for evaluation of respiratory disease were prospectively included in this study (Group 1). Being newly referred, patients had not received any medication prior to providing breath samples. Other inclusion criteria were: aged 18 or older, comprehension of the breath-collection procedure and signed informed consent. Otherwise, patients were essentially selected at random, being those who happened to have appointments on the days set aside for sample collection. Consequently, males and females were included and both smokers and non-smokers.

Twelve of the patients (age 70 ± 10 years, mean $\pm$ sd) were subsequently confirmed to have lung cancer (Group 2) diagnosed by biopsy of bronchus or cytology of bronchial brushings supported by clinical features of lung cancer.

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