LETTERS TO THE EDITOR

Combined pulmonary fibrosis and emphysema syndrome associated with familial SFTPC mutation

The syndrome of combined pulmonary fibrosis and emphysema (CPFE) in adults has not been previously associated with mutations of the surfactant protein-C (SFTPC) gene.

A 32-year-old woman, never smoker, presented with dyspnoea and dry cough, 3 days after a caesarean delivery. Physical examination revealed finger clubbing and bilateral basal crackles. There was no manifestation indicative of connective tissue disease. High-resolution computed tomography (HRCT) of the chest showed conspicuous centrilobular emphysema in the upper zones of the lungs, and diffuse, infiltrative lung disease in the lower zones (figure 1). Emphysema was apparent even in areas devoid of infiltrative foci. The bronchoalveolar lavage differential cell count was 57% neutrophils, 40% macrophages and 3% lymphocytes. Pulmonary function test results 3 months later were forced vital capacity, 62% of predicted value; total lung capacity, 77%; forced expiratory volume in 1 s, 60%; forced expiratory volume in 1 s/vital capacity, 83%; residual volume, 108%; carbon monoxide diffusing factor, 33%; PaO2 on room air, 11.3 kPa; PaO2 after 10-min exercise of 35 W, 7.3 kPa. Video-assisted lung biopsy (see online material) demonstrated disseminated fibrotic thickening of the interalveolar septa, numerous fibroblastic foci, with areas of dense collagen deposition of peribronchial predominance, and peribronchial emphysema, especially in the upper zones. Echocardiography showed normal heart cavities, with estimated systolic pulmonary arterial pressure of 40 mm Hg. Anti-nuclear antibodies with a nucleolar pattern were further characterised as anti-brillarin antibodies. Alpha-1 antitrypsin level was normal. The patient received oral prednisone for 3 months with no improvement. Two years after presentation, chest HRCT and pulmonary function tests had worsened. The patient declined treatment.

A girl born to this patient was diagnosed to have interstitial lung disease 3 months later (see online material). Her condition improved with oxygen and corticosteroid therapy. (see online material). Her condition improved with oxygen and corticosteroid therapy. HRCT and pulmonary function tests had worsened. The patient declined treatment.

The putative pathophysiology of SP-C-associated disease involves the dysfunction of surfactant homeostasis, causing injury or death of alveolar epithelial type II cells and myofibroblast proliferation. A process of genetically mediated alveolar injury may conceivably contribute to emphysema in addition to inflammation and fibrosis, and thus to the CPFE phenotype. As an autoantibody was detected, a forme fruste of connective tissue disease may also have contributed to the lung disease.

Adults with CPFE syndrome may have an underlying genetic predisposition. This hypothesis needs confirmation in further studies.

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Additional materials are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

Funding Hospices Civils de Lyon.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

Accepted 9 December 2010

Published Online First 19 January 2011


REFERENCES

Influence of respiratory variables on the on-line detection of exhaled trace gases by PTR-MS

Background
Modern gas analysis techniques permit real time and on-line quantification of multiple volatile trace gases within a single exhalation. However, the influence of various respiratory manoeuvres affecting exhalation flow and the kinetics of metabolite release to the gas-phase remain largely unknown.

Methods
We examined variation in the concentrations of selected trace gases over a range of expiratory flows (50, 100, 250 ml/s) and after 30 second periods of breathhold and paced hyperventilation. On-line measurement of breath samples from healthy volunteers (n=10) was performed by proton transfer mass spectrometry.

Results
Exhaled acetone increased with higher expiratory flow rate (205, 328, 398 ppb, p=0.02). Levels of methanol (206 vs 179 ppb, p<0.01), acetaldehyde (26 vs 22 ppb, p<0.01), ethanol (410 vs 208 ppb, p<0.01), isoprene (348 vs 390 ppb, p=0.02) and dimethyl sulphide (113 vs 136 nCps, p=0.01) fell significantly following 30s hyperventilation. After 30 second breathhold levels of methanol (206 vs 179 ppb, p<0.01), dimethyl sulphide (113 vs 136 nCps, p<0.01), acetaldehyde (26 vs 22 ppb, p<0.01) and ethanol (410 vs 208 ppb, p<0.01) fell significantly following the 30-s hyperventilation (figure 1). Variation in respiratory parameters did not significantly alter the levels of acetonitrile, propanol and butyric acid (table 2 in online supplement).

Conclusions
These findings demonstrate that respiratory manoeuvres significantly influence the measured concentration of a number of exhaled VOCs that are of potential importance within the clinical setting. Our results support the adoption of standardised practices for breath gas analysis by on-line and real time mass spectrometry methods.

Analysis of volatile trace gases within exhaled breath, for the purpose of non-invasive disease detection and monitoring, is a rapidly emerging field of research.\(^1\)\(^2\) Recent technological developments such as proton transfer reaction-mass spectrometry (PTR-MS) have allowed on-line and real-time detection of multiple trace gases in breath, leading to novel discoveries in cancer, infectious disease and metabolism.\(^2\)\(^3\)

One of the greatest lessons on clinical applicability of breath analysis has been the recognition that multiple physiological variables can influence the quantification of exhaled nitric oxide (NO), necessitating international consensus guidelines for its standardised measurement.\(^4\)\(^5\) There remains however limited experimental evidence defining the impact of confounding factors which may influence the quantification of other exhaled volatile trace gases.\(^5\)\(^6\) Herein we present the finding of a study investigating the influence of respiratory variables on the on-line detection and quantification of a judiciously selected and potentially clinically relevant panel of exhalation trace gases.

We examined the variation in the concentrations of selected trace gases (methanol, acetaldehyde, ethanol, acetonitrile, propanol, dimethyl sulphide and butyric acid) over a range of expiratory flows (50, 100, 250 ml/s) and after the 30-s periods of breath hold and paced hyperventilation. These volatiles were compared to exhaled NO and carbon dioxide. On-line measurement of breath samples from healthy volunteers (n=10) was performed by combining PTR-MS (Ionimed Analytik GmbH, Innsbruck, Austria) with the LR2500 multiple-gas analyser (Logan Research Ltd, Rochester, UK). Quantification of trace gases by PTR-MS was achieved by calibration experiments using accurately known gas standards and a purpose built gas calibration unit (Ionimed). (Further details of methodology are provided as supplementary digital content).

In contrast to NO, exhibiting an inverse relationship with expiratory flow rate, exhaled acetone increased with higher flows (805 vs 838, 898 ppb, p=0.02) (figure 1). After a 30-s breath hold, levels of acetone (805 vs 869 ppb, p=0.01), methanol (206 vs 217 ppb, p=0.02), isoprene (348 vs 390 ppb, p=0.02) and dimethyl sulphide (113 vs 136 nCps, p=0.02) increased significantly. Levels of methanol (206 vs 179 ppb, p<0.01), dimethyl sulphide (113 vs 136 nCps, p<0.01), acetaldehyde (26 vs 22 ppb, p<0.01) and ethanol (410 vs 208 ppb, p<0.01) fell significantly following the 30-s hyperventilation (figure 1). Variation in respiratory parameters did not significantly alter the levels of acetonitrile, propanol and butyric acid (table 2 in online supplement).

This work constitutes the first concerted attempt to discern the effect of ventilatory variables on breath analysis by an on-line

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Figure 1 Influence of respiratory physiological variables on the concentrations of selected trace gases measured within the exhaled breath of healthy volunteers. Trace gas level are presented as the ratio of the difference in breath manoeuvres versus their respective control breath measures at a flow rate of 50 ml/s.