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 changes. 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%; PaO_2 on room air, 11.3 kPa; PaO_2 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 peribronchiolar predominance, and peribronchiolar 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-fibrillarin 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.

After informed consent was obtained, sequencing of the five translated exons of the *SFTPC* gene[1] from blood samples demonstrated the same heterozygous I73T substitution in both the child and the mother; neither of them had mutation of the *SFTPB* and *ABCA3* genes.

This is the first report of a phenotype of CPFE syndrome in an adult patient carrying a mutation of the *SFTPC* gene. The patient had fibrosing interstitial pneumonia, with HRCT pattern suggestive of nonspecific interstitial pneumonia, and unclassifiable pathology. Emphysematous lesions were remarkably apparent on imaging and pathologically in the vicinity of peribronchiolar fibrosis. The clinical presentation of the infant was comparable to that described previously.[1 2] Interestingly, multiple lung cysts associated with septal thickening and ground glass opacities have been reported in subjects with familial pulmonary fibrosis carrying *SFTPC* mutations.[3 4]

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.[5]

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

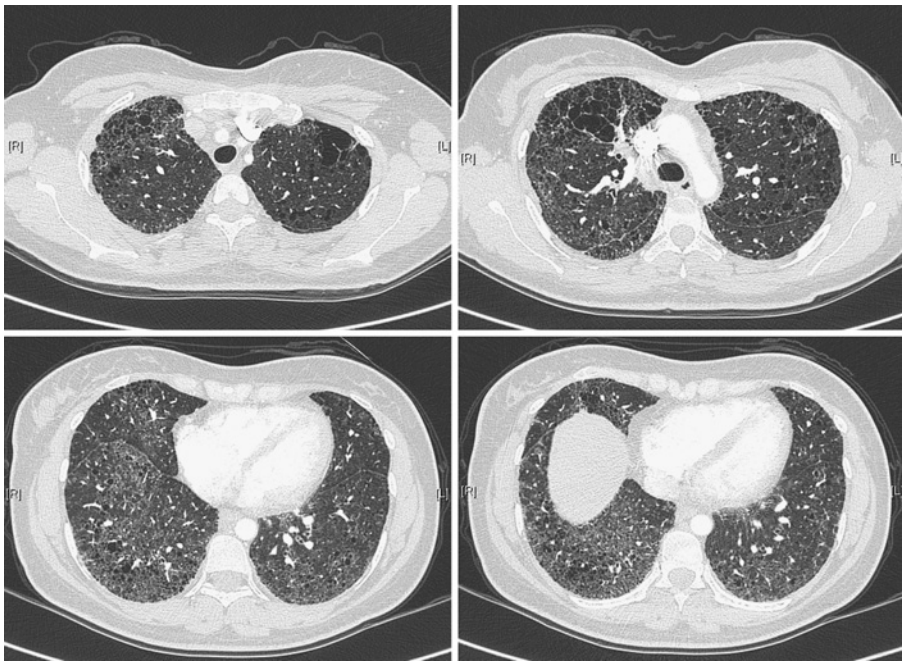

Figure 1 High-resolution computed tomography of the chest of adult non-smoking patient demonstrating centrilobular emphysema in the upper zones of the lungs, and diffuse, infiltrative lung disease in the lower zones, including bilateral reticulation without subpleural predominance, traction bronchiectasis, architectural distortion and ground glass attenuation.

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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 breathold 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 (805, 838, 898 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) and dimethyl sulphide (113 vs 103 ncps, p<0.01) fell significantly following 30s hyperventilation. After 30 second breathold levels of methanol (206 vs 217 ppb, p=0.02), acetone (805 vs 869 ppb, p<0.01), isoprene (348 vs 390 ppb, p=0.02) and dimethyl sulphide (113 vs 136 ncps, p=0.02) increased significantly. Variation in respiratory parameters did not significantly alters the level of acetonitrile, propanol and butyric acid within the breath of healthy subjects.

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] There remains however limited experimental evidence defining the impact of confounding factors which may influence the quantification of other exhaled volatile trace gases.[5] 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 expiratory trace gases.

We examined the variation in the concentrations of selected trace gases (methanol, acetaldehyde, ethanol, acetone, isoprene, 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 103 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

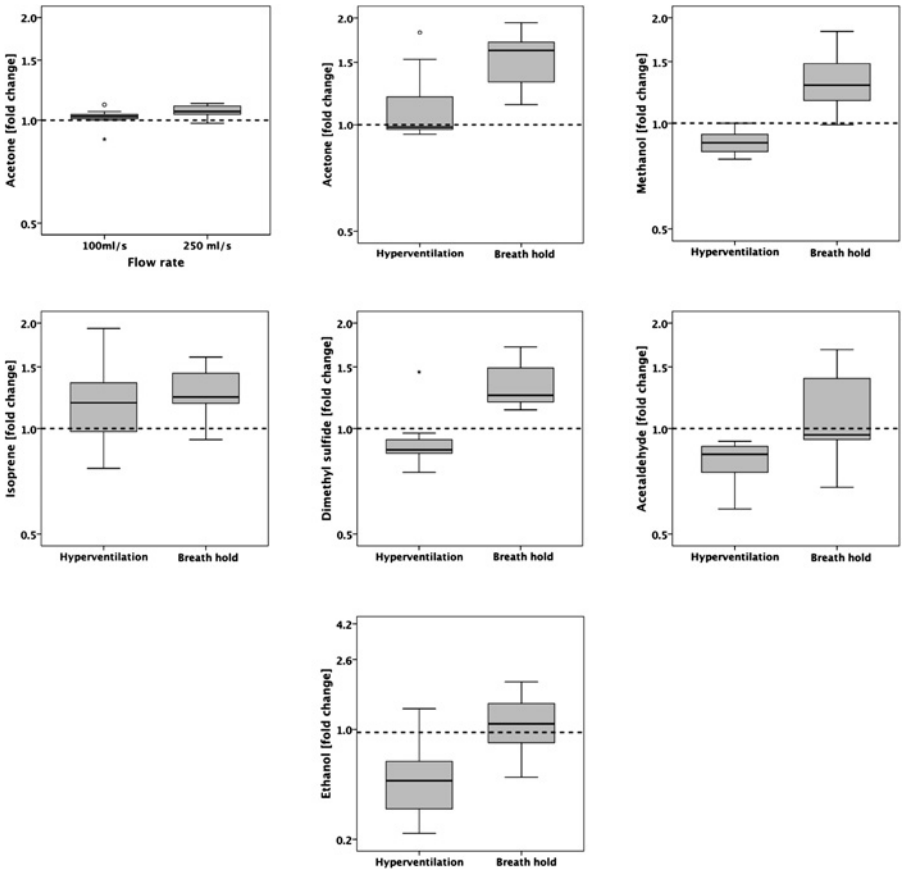

Figure 1 Influence of respiratory physiological variables on the concentrations of selected trace gases measured within the exhaled breath of healthy volunteers. Trace gas level are presented as the ratio of the difference in breath manoeuvres versus their respective control breath measures at a flow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