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Commentary

A Breath of Fresh Air for Clinical Diagnoses

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The use of blood as a diagnostic medium is routine and widespread medical practice, not only in providing indications of general health status, but also in delivering information on individual diseases via specific constituent biomarkers. Established diagnostic clinical chemistry assessments on blood serum target non-volatile markers – many disease-specific – that include enzymes, proteins, peptides, hormones or metabolites to aid in the diagnosis of organ dysfunction or systemic illnesses, from hepatic, pancreatic, renal and heart conditions, to cardiovascular and bone diseases, amongst others (Neumann, 2015). Besides the patient's presenting symptoms, such blood tests often provide the first clues of ill-health and trigger further probative measures such as biopsies. Despite the utility of blood-based biomarkers in disease diagnosis – notwithstanding its current indispensability in most cases – it is invasive (painful, to a degree) and requires considerable effort for the preparation and analysis of a sample, often offsite. A prospective alternative to this approach with the potential to provide point-of-care analysis and instant results – as well as being non-invasive – is offered in the form of exhaled breath gas analysis (Dweik and Amann, 2008).

Breath analysis is based on the hypothesis that the biochemical perturbations associated with an imbalance in the body generate by-products that enter the systemic circulation, are volatilised when they encounter the liquid–gas interface of the alveoli in the lungs, and consequently are expelled from the body during exhalation (Beauchamp and Pleil, 2015). Unlike most diagnostic target compounds in blood (or urine), breath biomarkers are necessarily volatile in nature – with some minor exceptions – in that they must transition from the liquid-phase of the blood to the gas-phase of breath in order to be observed in the latter. Despite the growing number of developments and discoveries in the field in recent years, advancements in breath analysis are largely hampered by the vast number (>800) of volatile organic compounds (VOCs) found to be present in breath (de Lacy Costello et al., 2014), notably with a high degree of commonality between illnesses and conditions such that unique, disease-specific markers seem unattainable. Indeed, potential breath biomarkers awaiting discovery inevitably will be endogenous compounds that are merely generated and excreted at sufficiently high concentrations to allow for their 'unique' detection (when typical levels are below instrumental detection limits) or their significant discrimination from steady-state (healthy) levels (Spacek and Risby, 2013).

The following paper by Fernández del Río et al. (2015) reports on breath analysis to detect liver cirrhosis, which is an advanced stage of hepatic fibrosis that is caused by several conditions, primarily viral hepatitis and chronic alcohol abuse (Byass, 2014). Presently, the detection of liver disease is commonly made by blood tests targeting liver function enzymes, with subsequent biopsy if test results indicate high levels. Symptoms are often presented late in the course of the disease, which considerably reduces the chances of survival. In terms of prevalence and mortality rates, worldwide liver cirrhosis mortality was estimated at just over one million in 2010 (~2% of the global total) (Mokdad et al., 2014), it was listed as the twelfth leading cause of death in the USA (almost 32,000 deaths, or 1.3% of total deaths) (Murphy et al., 2013) and is on the rise in countries such as the UK, where its prevalence in terms of premature mortality increased substantially (by 65%) between 1990 and 2010 (Murray et al.). Thus the need for diagnostic tools that offer an *early* and individualised detection of liver cirrhosis is clearly evident.

The exhaled breath of liver cirrhosis sufferers was investigated in the ensuing study via a two-stage approach, with an initial discovery phase to seek potential breath biomarkers associated with the disease that was supplemented by a targeted phase to follow the identified markers during recovery progression after hepatic transplantation. Three compounds, namely methanol, 2-pentanone and limonene, correlated with liver disease and function, with elevated levels in the exhaled breath of cirrhotic patients compared to a healthy control group and a decreasing post-surgery trend that corresponded to the functional commencement of the transplanted organ. The data revealed a high diagnostic accuracy based on the area under the receiver operator characteristic (ROC) curve, with a sensitivity of 97% and a specificity of 70%.

The study is unique, not only due to its complementary (two-stage) approach, but because the cirrhosis-related breath volatiles discovered are, contradictorily, by no means unique, yet appear to reflect the functionality of the liver to a high degree. Most breath research focusses on searching for biomarkers generated by the illness, but rather than attributing these compounds to a production in the diseased liver, the authors hypothesise that their elevated concentrations in the breath of cirrhotic patients represent an accumulation in the body due to a lack of metabolic breakdown by the impaired liver. This very plausible explanation, which is supported by considerations on the biochemistry and physicochemical properties of these biomarkers, makes for a strong and compelling case on the potential utility of breath analysis in diagnosing liver cirrhosis and monitoring organ function after transplantation via these markers.

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Moreover, the authors propose a prospective pharmacokinetic-based test for assessing liver function, whereby known quantities of limonene are administered to a patient and its subsequent wash-out from the body is monitored in breath. This latter approach has a realistic potential in joining the handful of approved breath screening tests that have found their way to routine clinical use, offering a positive outlook in tackling this chronic disease. I, for one, will follow the developments with bated breath.

Disclosure

The author declared no conflicts of interest.

References

Beauchamp, J.D., Pleil, J.D., 2015. Breath: an often overlooked medium in biomarker discovery. In: Seitz, H., Schumacher, S. (Eds.), Biomarker Validation Technological, Clinical and Commercial Aspects. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, pp. 75–93.

Byass, P., 2014. The global burden of liver disease: a challenge for methods and for public health. BMC Med. 12, 159.

de Lacy Costello, B., Amann, A., Al-Kateb, H., Flynn, C., Filipiak, W., Khalid, T., Osborne, D., Ratcliffe, N.M., 2014. A review of the volatiles from the healthy human body. J. Breath Res. 8 (1), 014001.

Dweik, R.A., Amann, A., 2008. Exhaled breath analysis: the new frontier in medical testing. J. Breath Res. 2 (3), 030301.

Fernández del Río, R., O'Hara, M.E., Holt, A., Pemberton, P., Shah, T., Whitehouse, T., Mayhew, C.A., 2015. Volatile biomarkers in breath associated with liver cirrhosis — comparisons of pre- and post-liver transplant breath samples. EBioMedicine 2 (9), 1243–1250.

Mokdad, A.A., Lopez, A.D., Shahraz, S., Rafael, Lozano, Mokdad, A.H., Stanaway, J., Murray, C.J., Naghavi, M., 2014. Liver cirrhosis mortality in 187 countries between 1980 and 2010: a systematic analysis. BMC Med. 12, 145.

Murphy, S.L., Xu, J., Kochanek, K.D., 2013. Deaths: final data for 2010. Natl. Vital Stat. Rep. 61 (4), 1–118.

Murray, C J L, Richards, M A, Newton, J N, Fenton, K A, Anderson, H R, Atkinson, C, Bennett, D, Bernabé, E, Blencowe, H, Bourne, R, Braithwaite, T, Brayne, C, Bruce, N G, Brugha, T S, Burney, P, Dherani, M, Dolk, H, Edmond, K, Ezzati, M, Flaxman, A D, Fleming, T D, Freedman, G, Gunnell, D, Hay, R J, Hutchings, S J, Ohno, S L, Lozano, R, Lyons, R A, Marcenes, W, Naghavi, M, Newton, C R, Pearce, N, Pope, D, Rushton, L, Salomon, J A, Shibuya, K, Vos, T, Wang, H, Williams, H C, Woolf, A D, Lopez, A D, & Davis, A. UK health performance: findings of the Global Burden of Disease Study 2010. Lancet, 381(9871), 997–1020.

Neumann, S., 2015. Biomarkers — past and future. In: Seitz, H., Schumacher, S. (Eds.), Biomarker Validation Technological, Clinical and Commercial Aspects. Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, pp. 1–22.

Spacek, L., Risby, T., 2013. Breath analysis for disease diagnosis. Anal. Sci. (0613), 402.