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Exhaled breath analysis: the new frontier in medical testing

Raed A Dweik [Guest editor] and

Departments of Pulmonary and Critical Care Medicine/Respiratory Institute, and Pathobiology/
Lerner Research Institute, Cleveland Clinic, Cleveland, OH 44195, USA

Anton Amann

Department of Operative Medicine, Innsbruck Medical University, A-6020 Innsbruck, Austria and
Breath Research Unit of the Austrian Academy of Sciences, Dammstrasse 22, A-6850 Dornbirn,
Austria

Raed A Dweik: dweikr@ccf.org

With each breath we exhale, thousands of molecules are expelled in our breath and each one of us has a 'breathprint' that can tell a lot about his or her state of health. While this may be news to some, it should not be to people in medicine. For one can argue that the field of breath analysis is as old as the field of medicine itself. Hippocrates described *fetor oris* and *fetor hepaticus* in his treatise on breath aroma and disease, Lavoisier and Laplace in 1784 showed that respiration consumes oxygen and eliminates carbon dioxide [1], Nebelthau in the mid 1800s showed that diabetics emit breath acetone [2], and Anstie in 1874 isolated ethanol from breath (which is the basis of breath alcohol testing today) [3].

The end of the 20th century and the beginning of the 21st century, however, have arguably witnessed a revolution in our understanding of the constituents of exhaled breath and the development of the field of breath analysis and testing. A major breakthrough in the scientific study of breath started in the 1970s when Linus Pauling demonstrated that there is more to exhaled breath than the classic gases of nitrogen, oxygen, carbon dioxide and water vapor, a lot more. Based on gas-liquid partition chromatography analysis, Linus Pauling reported the presence of 250 substances in exhaled breath [4]. With modern mass spectrometry (MS) and gas chromatography mass spectrometry (GC-MS) instruments, we can now identify more than 1000 unique substances in exhaled breath. These substances include elemental gases like nitric oxide and carbon monoxide and a multitude of volatile organic compounds. Exhaled breath also carries aerosolized droplets collected as 'exhaled breath condensate' that have non-volatile compounds like proteins dissolved in them as well.

We now have the technology to test for any and all of these components. Thanks to major breakthroughs in new technologies (infrared, electrochemical, chemiluminescence, and others) and the availability of very sensitive mass spectrometers, the field of breath analysis has made considerable advances in the 21st century. Several methods are now in clinical use or about ready to enter that arena.

There are currently commercially available analyzers that can measure NO levels in exhaled breath to the parts per billion (ppb) range and carbon monoxide to the parts per million (ppm) range [5]. Sensitive mass spectrometers can measure volatile compounds on breath down to the parts per trillion (ppt) range. Aerosolized droplets in exhaled breath can be

captured by a variety of methods and analyzed for a wide range of biomarkers from metabolic end products to proteins to a variety of cytokines and chemokines, and the possibilities continue to expand [6]. A major hurdle that faced this field as it transitions from the laboratory to clinical testing has been the standardization of sample collection methods. To advance in this area, there had to be a close collaboration between technical experts who typically have a device looking for clinical indication, the medical experts who have the clinical problem looking for a test/biomarker that can be helpful in diagnosis or monitoring, and industry/commercial experts who can build and commercialize the final product.

One great example of how the collaboration between technical, medical, and commercial professionals has resulted in a clinically useful tool is the measurement of exhaled nitric oxide (NO) in exhaled breath for monitoring airway inflammation. The advent of chemiluminescence analyzers in the early 1990s allowed the detection of low (ppb) levels of NO in exhaled breath [7]. This was quickly followed by the observation that patients with asthma had higher than normal levels of NO in their exhaled breath that was later linked to eosinophilic airway inflammation [8, 9]. Standardization of the gas collection methods and measurement techniques allowed the industry to build the next generation of analyzers suitable for use in the clinical setting [10, 11]. In 2003 the FDA approved the first desktop NO analyzer for monitoring airway inflammation in asthma [5]. The use of exhaled NO in monitoring asthma is useful for several reasons. It is non-invasive, it can be performed repeatedly, and it can be used in children and patients with severe airflow obstruction where other techniques are difficult or not possible to perform. Exhaled NO may also be more sensitive than currently available tests in detecting airway inflammation, which may allow more optimum therapy [12–19].

As breath analysis offers a window on lung physiology and disease, exhaled breath testing is becoming an increasingly important non-invasive diagnostic method that can be used in the evaluation of health and disease states in the lung and beyond. A few years ago the new International Association of Breath Research (IABR) was established to have a platform for researchers in the field. The association holds an annual meeting and the newly established *Journal of Breath Research (JBR)* is the official publication of the IABR.

In November 2007, the First Breath Analysis Summit/3rd annual meeting of IABR was held on the Cleveland Clinic Campus in Cleveland, Ohio, USA. The Summit brought together industry executives and entrepreneurs with scientists and clinicians to discuss key trends, future directions, and upcoming technologies in breath analysis and medicine. The major focus of the Summit was on medical applications. Topics included exhaled nitric oxide, exhaled breath condensate, electronic nose and sensor arrays, mass spectrometry and bench-top instrumentation, and cutting edge sensor technologies. Medical applications that were covered included asthma, COPD, pulmonary hypertension, other respiratory diseases, gastrointestinal diseases, occupational diseases, critical illness, and cancer. This special issue of *JBR* contains peer-reviewed, full articles of work presented at the Summit and represents the proceedings of this Summit.

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Figure 1.