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Original Research Article

Perspective of breathe analysis as the innovative diagnostic tool

Ranabir Pal[1] and Sanjay Dahal[2]*

[1]Department of Community Medicine and Family Medicine, All India Institute of Medical Sciences, Jodhpur, India
[2]Department of Chemistry, Sikkim Manipal Institute of Technology, Majitar, Sikkim, India
***Corresponding author e-mail:** dahal.sanjay@gmail.com*

A B S T R A C T

Globally breathe researchers are on the lookout for an inexpensive assessing tool and rapid point-of-care diagnostic methods of case finding in the new millennium. To assess the value of exhaled breath by different valid tools and methods. An extensive literature search was conducted in the course of data sources in the indexed literatures and website-based research reports. Sixty-six studies were identified from our exploration amongst 250 relevant articles. A broad standard was formulated in the dearth of a generally acknowledged methodology in the field of exhaled breathe research. Further, all available results were given due importance irrespective of the criteria for diagnosis used there. Wide differences in samples, primary outcome variables, lack of consistency in age category, ethnic variation, criteria for positive diagnosis, and study technologies confounded the outcome variables. All the approaches are essentially non-invasive and translating vital markers that need to be encouraged to conduct extensive field studies for precision of the methods. Further, we have to generate awareness about newer non-invasive diagnosis of different diseases to be embedded in the primary care levels among health care delivery personnel.: Enduring works on exhaled breathe has being considered with keen interest in this review. We have to walk on both feet by combining recent developments with the earlier gains in this field. The time has come to explore the unlimited worth of breath with sincerity as the successes of this cost-effective entrant will have a far reaching impact in self-care futuristic non-invasive models in health care.

Keywords

Exhaled breath analysis; disease; innovative diagnostic; disease; health.

Introduction

Researchers visualized breath as a physiological window of the body with expulsion of exhaled thousands of molecules at each moment as the metabolic outcomes enter the blood stream and are eventually metabolized or excreted via exhalation along with other outlets. Breath sampling is non-invasive and breath samples can be extracted as often as desired. The emancipation of modern breath testing was initiated in 1971 by Nobel Prize winner Linus Pauling who showed that breath contain more than 250 distinctive chemicals. With this driving force later on scientists have dared to think that human breath is a complex gas of outcomes from all organ-systems. So the exploration of potential biomarkers in exhaled breath is ongoing for the morbidities in pulmonary grid for example in asthma, lung cancer, pulmonary tuberculosis etc. Further, the widespread use of rapid, non-invasive, and inexpensive breath diagnosis promises a sea-change in the diagnosis and prognosis beyond lung diseases. Time has come when we can now dare to think of applicability in any problem in whole of the living human body in health and diseases like transplant rejection, *Helicobacter pylori* infectivity, breath alcohol concentration, during anesthesia and ventilation, in surgical interventions; even afford invaluable real-time information during situations of life style management or sleep as breath testing offers real-time results on spot at outreach and domiciliary infrastructure settings. On the top of everything, the nonintrusive nature that is embedded in the exhaled breath analysis offers unlimited replication of data in terms of collection of specimen in amount (unlike blood), timing (unlike urine), or frequency (unlike chest radiography) and overcome the age barrier(neonates to the elderly) FDA already has approved tools for detection of blood alcohol concentration, *Helicobacter pylori* infection, lactose intolerance, and airway monitoring by end-tidal carbon dioxide, and lately the fraction of exhaled nitric oxide (FENO) for asthma monitoring. (Paschke *et al.*, 2011; Breath gas analysis, 2013; Metabolomx, 2013; Bajtarevic *et al.*, 2012).

In this review, contemporary advances and prospective worth of exhaled breath analysis by effective methods were explored with their evolution and attainment.

Materials and Methods

Study design

A retrospective systematic review was conducted on the data collected through an extensive exploration from different sources in which exhaled breathe analysis were reported, as well as proceedings of conferences and employing personal connections,. Through an extensive website-scanned search in peer reviewed journal publications and study reports, sixty-six studies were identified from our exploration amongst 250 relevant articles from various institutional libraries of India, and websites on exhaled breathe analysis published since 1990. The studies were identified by searching Pubmed-entrez and abstracts from scientific meetings (1990 – 2012) also. Reviews of citations and reference lists were performed to identify additional studies by the search terms exhaled breathe analysis, biomarkers, diagnosis of airway disease etc. Manual searches were conducted from review articles, cross references and previous meta-analyses. Where possible, sources were contacted for additional research information unavailable in the public domain or for translations from languages other than English.

Selection criteria

We developed few criteria to select studies from among peer-reviewed articles. First, we used broad criteria to define breathe analysis. Second, we also sought to include all those studies that studied exhaled breathe other than using sensors. Finally, in the absence of universally acceptance of sensors as non-invasive diagnostic method, other methods of diagnosis of breath biomarkers were taken into consideration.

Main outcome variable: breathe analysis, disease, health, biomarkers

Results and Discussion

Data abstraction and analysis

The antiquity of studying exhaled breath as a diagnostic test is unquestionable as a non-invasive diagnosis. Excessive vascular structure and circulatory pattern in the human lungs has made it possible as surrogate excretory gateway for the metabolic end products. From the father of Medicine Hippocrates, the clinicians have perceived that in certain diseases like diabetes, hepatic and renal ailments and kidney failure, the odor of breath distinctly changes putting firm footstep in the new millennium. The encouraging results are finding out novel and reliable non-invasive clinical tools to extend the work on in the health and disease, covering the entire gamut of communicable and non-communicable diseases (Filipiak *et al.,* 2008; Dweik and Amann, 2008; Phillips *et al.,* 1999).

Biomarkers

In health and disease the composition of breath changes continuously with 3000 identifiable volatile compounds from inorganic gaseous compounds like hydrogen, nitric oxide (NO), and carbon monoxide to infinite number of organic compounds; also endogenously formed non-gaseous proteins are present that can be analyzed by breath condensate. Clinically worthwhile thought processes are edging prospectively for the rapid diagnostic methods from exhaled breath looking beyond the pulmonary diseases. (Dweik and Amann, 2008; Phillips *et al.,* 1999; Grob *et al.,* 2008; Grob and Dweik, 2013).

Scientists have noted compounds in exhaled breath like methanol, ethanol, acetone, acetaldehyde and isoprene. 2,2-diethyl-1,1-biphenyl or 2-methyl-1(1,1-dimethylethyl)-2-methyl-1,3-propanediyl propanoic acid ester. In cancer cell lines significant increase in the concentrations of 2,3,3-trimethylpentane, 2,3,5-trimethylhexane, 2,4-dimethylheptane and 4-methyloctane, acetaldehyde, 3-methylbutanal, butyl acetate, acetonitrile, acrolein, methacrolein, 2-methylpropanal, 2-butanone, 2-methoxy-2-methylpropane, 2-ethoxy-2methylpropane, and hexanal (Filipiak *et al.,* 2008).

Up to 130 attributable breath biomarkers have been identified that are selective to patients suffering from pulmonary tuberculosis like Monomethylated alkanes, viz. dimethylcyclohexane, methylheptane, methylcyclododecane, and tetramethylbenzene; others are naphthalene, 1-methyl-, 3-heptanone, methylcyclododecane, heptane, 2,2,4,6,6-pentamethyl-, benzene, 1-methyl-4-(1-methylethyl)-,and cyclohexane. Though researches on exhaled nitric oxide from tuberculosis patients had ambivalent results, different breath tests assay mycobacterial metabolism (exhaled antigen 85, mycobacterial urease activity, and detection by trained rats of disease-specific odor in sputum) have promise as early markers with prognostic value. [Phillips *et al.,* 1999; Mashir A, Dweik , 2009; Buszewski *et al.,* 2007; Phillips *et al.,* 2010; Bourzac, 2010; Marczin *et al.,* 2011; Volatile Markers of Pulmonary Tuberculosis in the Breath, 2011; Now

There's a Breath Test For Tuberculosis, 2011; Van Beek *et al.*, 2011).

Tools used

The initiation of chemiluminescence analyzers two decades back enabled us to detect NO per billion levels led us to evaluation of exhaled NO as a potential noninvasive method to diagnosis and prognosis of asthma with antiinflammatory therapy (Grob NM, Dweik, 2013). Breath analysts have attempted to find not only the semi-volatiles compound in gaseous phase. Yet recently exploration is moving on to the dissolved chemicals in exhaled breath condensate and in exhaled breath vapor for metabolic end products, proteins, cytokines, and chemokines.

The latter development not only allows augmented portability, training, sampling and analysis, but also provides additional outcome variables and sensitivity (Grob *et al.*, 2008; Horvath *et al.*, 2005; Cap *et al.*, 2008; Martin *et al.*, 2010).

Miscellaneous methods in breath research have been used in the past two decades like isotopic ratio mass spectrometer, ultraviolet absorbance spectrometer, gas chromatography/mass spectroscopy, Polymerase Chain Reaction (PCR) amplification, immunosensor, bio-optical technology etc. to identify thousands of unique substances in exhaled breath [Phillips *et al.*, 1999; Grob et al., 2008 Buszewski et al., 2007; Phillips et al., 2010; Bourzac, 2010; Marczin et al., 2011; Volatile Markers of Pulmonary Tuberculosis in the Breath, 2011; Now There's a Breath Test For Tuberculosis, 2011; Van Beek et al., 2011; Phillips et al., 2001; Lai et al., 2002; Mashir et al., 2013).

Later on with the emerging technologies have provided more precise yet point-of-care recognition of chemical in parts per trillion ranges using selected-ion flow-tube mass spectroscopy, multi-capillary column ion mobility mass spectroscopy and proton transfer reaction mass spectroscopy. (Ross, 2008; Perl *et al.*, 2009; Wehinger *et al.*, 2007; Chambers *et al.*, 2012).

On the other hand, in contrast to the customary quantitative breath biomarker analysis, the electronic nose can make out odor patterns using an array of gas sensors to detect lung cancer, pneumonia, and asthma with specificities and sensitivities up to 98 percent; can distinguish chronic obstructive pulmonary disease and asthma (Fens *et al.*, 2009; Taivans *et al.*, 2009; Machado *et al.*, 2005; Dragonieri *et al.*, 2009; Handique, 2013; Electronic Nose can sniff tuberculosis, 2012). Further, a respiratory monitoring system has been based on a quartz crystal microbalance (QCM) sensor with a functional film is under investigation in breath research. (Selyanchyn et al., 2011)

The basic macrocycle of porphyrin and their metal containing complexes have been methodically explored for their photochemical properties in search of newer sensors improvement over the past few decades as popular functional chromophores. In a diverse range of research fields, porphyrin and other chemical based colorimetric sensor arrays are being investigated based on cross-responsive sensor elements in the prototype of olfactory system of mammals to find biomarkers of cancer and other disease conditions capable of being applied clinically in the near future (Paolesse *et al.*, 2008; Hungerford *et al.*, 2000; Xie *et al.*, 2007; Tuberculosis

Applications Metabolomx, 2013; Rakow and Suslick, 2000; Pal *et al.,* 2013; Pal and Dahal, 2013).

Breath analysis in health and diseases

Exhaled breath analysis has spectrum of advantages including application womb to tomb, even at the intensive care settings with advantages of on-line sampling and analysis offers the possibility of providing real-time results in point-of-care or at-home testing, and it increases the potential for personalized life style promotive interventions in primary health care under a challenge (a test on an ergometer with varying pulse and heart rate, ingestion of food etc.) (Filipiak *et al.*, 2008; Mashir *et al.,* 2013).

Breath analysis may offer a relatively inexpensive, rapid, and non-invasive method for detecting a variety of circumstances in health and disease. In the land mark research the Bronchial asthma patients were noted with high levels of NO in their exhaled breath that decreased in response to treatment with corticosteroids that initiated the diagnosis as well as prognosis with anti-inflammatory therapy in asthma patients predictable (Grob and Dweik, 2013). Currently, NO in breath is being evaluated in the detection lung cancer and tuberculosis. Though NO has limited value in diagnosis, it has probability in screening of pulmonary tuberculosis (Mashir *et al.,* 2013; Costa *et al.,* 2011; Amann *et al.,* 2011).

The urease breath test can be employed to diagnose urease-producing microbial species, such as *Helicobacter pylori, Mycobacterium tuberculosis* (Maiga *et al.,* 2012) Breath testing with an electronic nose is promising for the diagnosis *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa* and *Aspergillus fumigatus*. (Chambers *et al.,* 2012) Breath biomarkers comprising oxidative stress products and volatile metabolites of *Mycobacterium tuberculosis* were identified, when sputum culture, microscopy, and chest radiography were either all positive or all negative with 85 percent accuracy in symptomatic high-risk subjects using GC/MS with a Monte Carlo analysis of time-slice alveolar gradients (Jain *et al.,* 2011). Metabolomx has developed, tested, and deployed a breath analysis instrument that uses the CSA technology to perform a rapid, inexpensive, and completely non-invasive diagnosis based on the molecular fingerprint of the disease signature in exhaled breath (Pal, 2013; Metabolomx. Applications, 2013).

Exhaled breath analysis is a promising supplement for confirmation in early stages of lung cancer as evidenced by numerous studies with specificities and sensitivities up to 94 percent. (Machado *et al.*, 2005; Gordon *et al.*, 1985; Phillips *et al.*, 1999; Di Natale *et al.*, 2003; Phillips *et al.*, 2003; Mazzone *et al.*, 2007; Phillips *et al.*, 2008). The combination of a positive Computed Tomography (CT) followed by a Metabolomx breath examination has lowered false positive rate Metabolomx, 2013). Even trained dogs has been tried in the breath diagnosis of both early and late stage lung cancers with sensitivities and specificities approaching 99 percent, providing promise for future lung cancer breath tests (McCulloch *et al.*, 2006). However, in order to be useful screening test for this types of high-risk populations, as a tool to evaluate pulmonary nodules, or as a diagnostic test for lung cancer, a breath test should be at least 90-95 percent sensitive and specific (ATS/ERS, 2005).

Ongoing Research methodologies

Globally, in the transitioning of exhaled breath analysis from 'bench side to bed side', this new entrant is a relatively poles apart in conceptual aspect. Contemporary breath analysis techniques have a resurrection of age-old method of smelling as the diagnostic option like the electronic noses based on specific stereochemical characteristics of odorant molecules with a combination of thousand of biomarkers and pathogens (Lai *et al.,* 2002; Costa *et al.,* 2011; Amann *et al.*, 2011; Munoz *et al.,* 1999; Pavlou *et al.,* 2000; Katiyar *et al.,* 2006).

Exhaled breathe analysis has conventionally taken two major mindsets. The conventional approaches have used spectroscopy based broad range of qualitative and quantitative estimations in search of individual volatile and non-volatile compounds (Phillips *et al.,* 2007; Probert *et al.,* 2009).

Later on researchers are engaged in attempting a pattern recognition in the entire assortment of analytes in the exhaled breathe and exhaled breathe condensate without qualitative or quantitative detection of individual chemical which are relatively more noninvasive and inexpensive. Exhaled breath analysis using a broad range of chemical-sensing interactions has been capable to identify unique chemical signature with high accuracy though desired outcome are yet to be achieved (Mazzone *et al.,* 2007; Mazzone *et al.,* 2012; James *et al.,* 2005).

Applied facets under scan

With ever expanding possibilities the concept of breath testing has developed rapidly over last 20 years. Investigators have visualized that similar to a fingerprint, all the individuals has a "breathprint" that can provide useful information about their physical condition comprising of innumerable molecules. New techniques that can identify fingerprints for specific diseases and specific markers have been applied with the recent advances in breath analysis for the diagnosis of bacterial and fungal lower respiratory tract infections; yet pre-concentration techniques are needed to analyze many target VOCs for most systems (Dweik and Amann, 2008; Chambers *et al.,* 2012).

Apart from being noninvasive character breath analysis can be repeated without sanction to time, place and person as real-time personalized medicine at point-of-care, and it increases the potential for even in the remote domiciliary settings of the developing countries. On the downside, there are multitude of possible confounders, from host diurnal and seasonal variations to even dietary patterns and environment. Lack of standardization is also a major problem; sampling and timing in relation to the respiratory cycle with control of flow, pressure, and ambient conditions are key issues. The researchers are facing problems of standardization of tests budding out from a range of variables viz. lifestyle factor variations like diet, addiction, and ambience of infrastructure including sampling methods. Historically, in the evidence based medicine physician acceptance of the nontraditional method of testing has been a major hurdle. With their blocked mindset exclusively to the microbiological and serological approaches lead to resistance oozing from unawareness and sincere approval of novel method of diagnosis and prognosis. Novel tools in sampling, design, standardization, and analytical model in breathe testing have unlimited potential to change the concept of primary level care. This is particularly interesting for critically ill persons, as well as for large scale screening, in the case of renal and liver diseases or for cancer. Careful attention needs to be paid to the sensitivity and specificity of any technique and probable confounders from the environment (Mashir *et al.,* 2013; Chambers *et al.,* 2012).

Researchers have uncovered the scientific and chemical basis for epidemiological link between clinical observations and biomarkers of breath that originates from a) endogenous outcomes, b) prescription elements and c) environmental chemicals. Further, special attention should be devoted to the examination of possible influence of other chemicals present in breath matrix known to contain wide range of compounds present at different concentrations along with some other non-endogenous confounders. Moreover, precision is required in the abstraction of experiences in all the promising methods prior to recommend as diagnostic tools with instructions to avoid the influence of environmental effects (Pal, 2013; Breathe analysis during artificial ventilation, 2013).

Aberrant thinking are pouring in with dynamic assessments of normal physiological function or pharmacodynamics like assessment of exogenous VOCs penetrating the body as a result of environmental exposure, ingestion of isotopically labeled precursors, producing isotopically labeled carbon dioxide and other metabolites. Bias in sampling frame to the complex physiological mechanisms underlying pulmonary gas exchange and cardiovascular circuit are additional problems in co-morbid conditions (Breath gas analysis, 2013).

Limitations of Study

With the best of our efforts, we had to limit our data published in peer-reviewed journals. Moreover, we have limited availability of printed full published articles. So, we had to depend on free publications with their on-line availability.

To sum up, the investigators critically reviewed the ongoing work in the field of exhaled breathe analysis as globally these have emerged as a new avenue of non-invasive tool. For the direct point-of-care diagnosis of diseases exhaled breath analysis may be worth developing and evaluating as a cost-effective competitor in clinical epidemiology algorithms that may facilitate individual care to enable greater understanding of the factors influencing prognosis for a futuristic model of non-invasive diagnostic procedure. The time has come to explore this to the fullest extent considering future public health research priority with the target of approval from the federal governments for use in the primary care level. Further, this kind of systematic review would be of immense impact if this activity could be replicated to bring out knowledge and positive change in attitude of scientific community with quantum leap in their thought processes and help optimum quality life for our future generations (Dahal and Pal, 2013).

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