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Review Article

Diagnosis of Malignancy and Other Pathologies from Bad Breath: Putative Molecules and Analysis of Oral Malodor, Using Gas Chromatography

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Abstract

Rapid diagnosis of pathologies, including oncology, is a major challenge in medical practice. Oral malodor is ubiquitously associated with local mouth pathologies but is rarely used for diagnosing remote pathologies or systemic disease. Oral malodors are not all the same. This appraisal re-affirms different types of oral and non-oral malodors as ozaena, ozostomia, halitosis, or stomatodysodia and.... indicates how using gas-chromatography (GC) on stomatodysodia evaluates common oral malodors and how by using GC to investigate exhaled breath is becoming a promising method for screening and diagnosing remote pathologies and/or associated co-morbidities, to provide a rapid, accurate, reliable and affordable diagnosis may facilitate rapid, and accurate diagnosis of disease, by identifying specific GC patterns of volatile organic compounds (VOC) derived from specific pathologies including cancers.

Keywords: *Breath; Olfaction; Exhaled; Oral-Malodor; Halitosis; Ozaena; Gas-Chromatography; Diagnosis; Stomatodysodia; Smell*

Abbreviations

GC: Gas Chromatography; MS: Mass Spectrometry; VOC: Volatile Organic Compounds; VSC: Volatile Sulfur Compounds

Introduction

Rapid diagnosis of pathologies, including oncology, is a major challenge in medical practice. Various direct examination methods are used for a provisional diagnosis to assess lumps or swellings and subsequent special methods for accurate specific diagnosis are indicated [1]. Corporeal malodors are sourced mainly from the mouth and other body organs and products. Bad breath can derive from oral and non-oral causes. Different pathologies give specific features to body smells, and characteristic molecules can indicate origins and/or derivation [1]. Volatile gas analytic chemistry technology (Gas Chromatography GC) provides accurate detection of specific molecules. Definitive histopathology diagnosis from biopsies remains the gold standard for diagnosis, but alternate indicators for biopsy as non-invasive methods are needed [3,4]. To hasten diagnosis with cost-reduction, avoid time delay, easier techniques are needed that facilitates use of odors as a clinical tool for accurate diagnosis. Animals have been suggested to detect ultra-diluted smells, as canines have a higher sensitivity to smells, with some claiming they smell odors originating from cancers [4]. Gas chromatography as a non-invasive clinical method can be a very useful tool for indicating if invasive biopsy is mandatory for trustworthy diagnoses [6-9].

Aim of the Study

This article evaluates common oral malodors and how by using gas chromatography (GC) to investigate exhaled breath, is becoming a promising method for screening and diagnosing remote pathologies and/or associated co-morbidities, to provide a rapid, accurate, reliable and affordable diagnosis.

Classification of oral malodors

Oral malodor is classified as halitosis, of oral and non-oral or psychogenic origin. Smells may be designated different nomenclature depending on their origin. Fetor-oris stems from oral causes [Dental/lingual biofilm]; ozaena and ozostomia derives from organs above the carina [Nose, pharynx, larynx and sinuses], stomatodysodia from organs below the carina [Bronchus, bronchioles, lungs, and pleura] [1-4]. Oral causes are termed halitosis mainly of bacterial origin from soft-tissue pathologies like gingivitis, necrotizing ulcero-membranous, gingivitis, periodontitis, or tooth decay. Non-oral causes are termed either as 'psychogenic', in which a subjective sense of oral malodor is falsely perceived because of central nervous system pathology, like the existence of a brain-tumor. Or malodor originating from the nose is often termed ozaena, deriving direct from the nasal passages or ozostomia when originating from any of the cranial sinuses, the pharynx, larynx, tonsils, adenoids above the carina [2-4]. And malodorous breath from below the carina is termed stomatodysodia, and it is deeply inhaled and willfully expelled exhaled breath. Often bad-breath is constituted from all the origins mentioned. Subjective human olfaction-detection depends mainly. on smelling volatile sulfur compounds (VSC's). Clinical apparatus with VSC detector-sensors exists to measure VSC's, but they do not detect other indicative diagnostic molecules or compounds [6,7].

Stomatodysodia as exhaled breath is a volatile complex mix of diverse atomized air-matrix augmented with many volatile metabolites - sometimes called volatile organic compounds (VOCs). These VOC's derive from both the physiological ongoing reactions throughout the body and from gases and particulates through inhalation from the environment [7,12,17]. Infection stimulates specific metabolic/catabolic pathological cascades in the body, with consequent induction of host immune responses that create various unique patterns of VOCs detectable in the breath. Microbial pathogens per-se also have their own specific metabolic processes - the metabolic products of which can be identified in the breath [8-10].

Using gas chromatography-mass spectrometry (GC-MS) analysis - is a technical-based method which separates volatile compounds in exhaled breath - and will render data from mass spectra constituting a retrievable anthology of patterned peaks that have various unique sizes, shapes and outlines depending on the concentration and chemical composition of the compounds. The current GC-MS apparatus is manufactured as a portable machine which can be used anywhere and requires minimal training for use. Reliable simple exhaled air collection removes the necessity for patients to visit a clinic or laboratory to take breath tests because breath can be collected anywhere and sent for analysis. GC-MS can determine existence of molecule at ultralow concentrations with unique liner patterns shown on graphs [11-13,36,37].

Instead of limiting identification of a single molecule, there are portable sensor-based breath testing devices that detect the pattern - or GC-MS "breath-prints" - of exhaled breath. Also, by identifying groups of specific volatile compounds it reliably helps linking potentially associated biomarkers in exhaled breath with underlying pathology. This is not the case with individual sensor-based techniques due to a lack of repeatable reliability deriving from technical issues like setting-drift and sensor faults [14,15].

An underused sample for infectious disease diagnosis, breath is a virtually inexhaustible resource that is produced constantly by the body. A very large volume can be collected quickly and easily and, with certain methods, the volatile compounds in breath can be concentrated for higher sensitivity.

For example, *Helicobacter pylori* infection of the stomach is found in nearly 50 percent of the global population's stomach. *H. pylori* causes chronic gastritis and considered a risk factor for developing gastric cancer. *H. pylori* is detected by ingesting a solution containing 13 Carbon Urea (^{13}C-Urea), and then collecting exhaled breath samples after 30 minutes. *H. pylori* uniquely metabolizes urea into ammonia and carbon dioxide, and consequently the presence of an *H. pylori* infection is indicated by increased levels of these compounds in the exhaled test-breath [19-23].

Unique characteristic changes in breath composition are linked to specific infections and may be detected before symptoms manifest. Changes in levels of volatile metabolites in exhaled breath with active infections can be identified for influenza A and B, parainfluenza 1, 2 and 3, respiratory syncytial virus, human metapneumovirus, human rhinoviruses, tuberculosis, aspergillosis, and neoplasia's among others [6,27-37]. Characteristic changes in the VOCs in breath, can be used for diagnosis of these pathologies [22-29]. In 2022, the FDA authorized InspectIR COVID-19 Breathalyzer that identifies diagnostic breath molecules derived from SARS-CoV-2 in two to three minutes. Typical unique easily identifiable GC-patterns on this monitor show "Breathprints" which are used for rapid and reliable diagnosis of Covid-19 [26].

Unique oral malodors have been positively identified to indicate the presence of cancers in various organs: lung cancer, ovarian cancer, late-stage breast, and melanomas, colorectal cancers and screwworms [6,27-35]. Portable gas-chromatography machines have been describes and have been successfully used to determine various types of drugs [36].

With insignificant false-positive and false-negative results being rare, (sensitivity and specificity) GC-MS is rapidly becoming a highly desirable 'Artificial Nose' for analyzing VOCs in exhaled breath. Because smelly breath samples are easy to collect and test GC-MS offers an accurate and accessible diagnostic modem for analysis.

Discussion

Oral malodor has both oral and non-oral causes but is a ubiquitous symptom of which patients complain. The non-oral cause includes physiological… like dehydration, menstruation, dietary, constipation and others… or pathological…. such as from kidney disease uremia, from pancreatic ketosis in diabetes mellitus, and others the musty odor from hepatitis, esophagitis, anorexia/bulimia, xerostomia or even from gastritis. Subsequently, when a metabolic and/or cellular oncological changes somewhere in the body, a unique cancer catabolic, metabolic and/or metabolite specific-cancer marker-molecule is created in small quantities and will emanate from the body. It is assumed that an oncological metabolic change in the body will give off singular smells from metabolism, which will be present in exhaled breath, and which may be identified with a detector sensitive enough to distinguish the derived molecules. Since humans have a relatively (to dogs and pigs) low threshold for subjective smells in parts per billion (ppb), and do not reach required levels of detection for these molecules, other methods are needed to detect oncology emanations through smell. Accordingly, some have suggested canines for this [5] but the practical reality of acquiring, training, sustaining and ensuring healthy dogs as a diagnostic tool, has indicated there is an imperative demand for a more controllable, easier, more accurate, reliable and less expensive method. Most reliable biopsy methods are invasive and are always associated with some risk of infection, or local damage to the surrounds. Collection of breath-samples is totally non-invasive and risk free. Invasive tests require expertise, manual-skill and often sterile surgical apparatus. Consequently, biopsies are more expensive and demanding than collecting breath samples. This is important in public health policies that impact budgets and offered services. However, he use of GS-MS should be used with discretion before anti-oncological drugs are administered, as trace amounts of drugs can possibly confuse the diagnosis of pathology.

Skills and technology available: Many clinicians have a well-developed subjective olfactory sense, yet interpretation of smells molecules is not reliable as chemical compositions vary. Modern theory includes both electron-vibratory and mechanical-fit theories of smell. For objective reliably accurate identification of organic smells, analytical chemistry methods are used. These embrace: Gaseous chromatography (GS); Atomic absorption spectrophotometry; Flame photometry, Griffin G510 (Flir Systems) and Torion T-9 (PerkinElmer) [37], Halimeter Volatile Sulfur Compounds Monitor** (Accurate numerical parts per billion); Tanita dot Breath-Checker* (less accurate); and artificial noses which may use metallo-porphyrin polymers. Oral malodor and body odors are usually sensed through smell, and bodily secretions often hold metabolic diagnostic clues with smells [4-7]. The exhaled odor of a patient's breath may detect ifa patient has lung cancer. Mass spectrometry sensors are capable of detecting numerous biological markers that reliably indicate the presence of lung cancer. Specific prints may be able to indicate the type and a need for a biopsy [36,37].

The ultimate 'gold standard' for definitive confirmatory diagnosis of cancer remains with histopathology biopsies or specimens, (from cellular harvests, partial incisional or total excisional) [5]. Should any cancer be suspected, proper special tests (like biopsies mentioned, or other biochemical markers in blood, urine or other human tissues) are needed. Oral malodor may be detected subjectively by an examiner; but MS of bad breath can be used as a clinical tool to accelerate facilitate and/or confirm the diagnosis of cancers.

Concluding Remarks

To date (2024) many 'Olfaction molecules', including an "Oncolfaction molecule" (As volatile organic compounds VOC's) have been identified, for existing pathologies in exhaled breath. An easy, non-invasive, affordable and reliable test remains desirable. A technological facility, like portable gas chromatography for VOCs, rapidly and reliably diagnoses smelly traces of infective, metabolic or neoplastic metabolites, and is most useful as an indicator for invasive and confirmatory diagnostic biopsy as needed.

Author's Statement

The author has no conflict-of-interest to declare.

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