BREATHOMICS OF RESPIRATORY DISEASES

Respiratory diseases are common in humans. Rapid, risk-free and potentially inexpensive diagnostics of respiratory diseases observed in the patient's exhaled air is extremely importanttoday. The following exhaled biomarkers are discussed: fractional exhaled nitric oxide(FENO),volatile organic compounds, carbon monoxide, hydrocarbons, and hydrogen peroxide. Breathomics from exhaled volatile organic compounds and oximeters are also shortly discussed.FENO monitors made of WO_3 are discussed. They large-scale produced and widely used in medical centers and clinics for diagnostics of respiratory diseases. Promising semiconductor sensors are manufactured from SnO_2, doped with Pd, Au, or Pt or multi walls carbon nanotubes, gold nanoparticle with single wall carbon nanotubes, quartz microbalance devices with porphyrin, ITO –Zno-Pt films, and surface acoustic wave devices with isobutylene. A combination of VOCs is considered as a “molecular fingerprint” of breath. The electronic nose on metal oxide detectors allows investigating lung cancer and tuberculous.

Introduction

Respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), lung cancer, pulmonary arterial hypertension, tuberculosis, cystic fibrosis, bronchiectasis, rhinitis, interstitial lung disease, chronic cough, lung transplant rejection, adult respiratory distress syndrome, diffuse panbronchioliti, obstructive sleep apnea syndrome and pneumoconiosis. Rapid, risk-free and potentially inexpensive diagnostics of respiratory diseases observed in the patient's exhaled air is very important today [1, 2]. It is impossible within the frames of this article to provide detailed information on the achievements in the field of respiratory diseases ,and series of tests, including chemical, imaging, endoscopic, immunological and genomic procedures for the detection of all these diseases [1-3]. Detection of respiratory diseases at an early stage can significantly reduce the consequences of the disease and mortality [1, 4], as this allows for surgical intervention/treatment with the prospect of achieving the best possible therapeutic outcome for the patient. The development of new tests and biomarkers is necessary because current sputum, radiography, and computed tomography (CT) tests are expensive, invasive (endoscopy, pulmonary catheterization, biopsy, and bone marrow tests), and do not rule out complications and/or require special equipment (for example, CT), and highly qualified medical workers for its operation [1, 5]. An ideal respiratory disease test should be highly accurate, low cost, non-invasive and easily reproducible.

1. Fractionalexhalednitricoxidebiomarker

Much attention has been paid recently to metal oxide gas sensors, which are promising for use in medicine (see, e.g., [6-8]).The most popular biomarker for the respiratory disease today is fractional exhaled nitric oxide NO (FENO).The potential of tungsten trioxide (WO_3) gassensorsfor breath analysis is discussed in [9].WO_3 is an oxygen-deficient n-type semiconductor. Itis one of the most commonly used materials for the manufacture of semiconductor gas sensors. They are small, reliable, inexpensive, and highly sensitive, which make them promising for portable medical diagnostic detectors. WO_3 responds to several biomarkers found in exhaled air (nitric oxide, acetone, ammonia, carbon monoxide, hydrogen sulfide, toluene etc.) and allows comparison of probing results with those obtained using much more expensive analytical methods. Analyzing a patient's breathing is an extremely interesting field of application for gas sensors. Such small-sized instruments allow real-time measurements.

Righettoni et al. reported the detection of acetone in human breath using a sensor made of Si-doped WO_3 [8]. Breath analysis of asthma using nitric oxide was reportedtodayusing WO_3-based sensors in [30–32]. Its resistance decreases when exposed to reducing gas and increases in the presence of oxidizing gases [39].Some basic research exists on the interaction of the WO_3 surface with gases. For example, it is known that COreduces the WO_3 lattice [40].Akamatsu et al. investigated the surface reaction of $WO_3$with $NO_2$and NO. Oxidation of the surface was visible during exposure to NO_2 [9]. A slight reduction was visible with NO.

During inhalation air enters through the mouth and nostrils into the pharynx, then passesthe epiglottis into the trachea, and finally enters the bronchi which branch into bronchioles that endin clusters of alveoli (see Fig.1). The exchange of air with the bloodstream takes place in the alveoli [9]. The total exhaled breath contains a combination of the alveolar air and the air originatingfrom the physiological dead space (air originating from the nasal/oral cavity, pharynx, larynx, tracheaand bronchi).

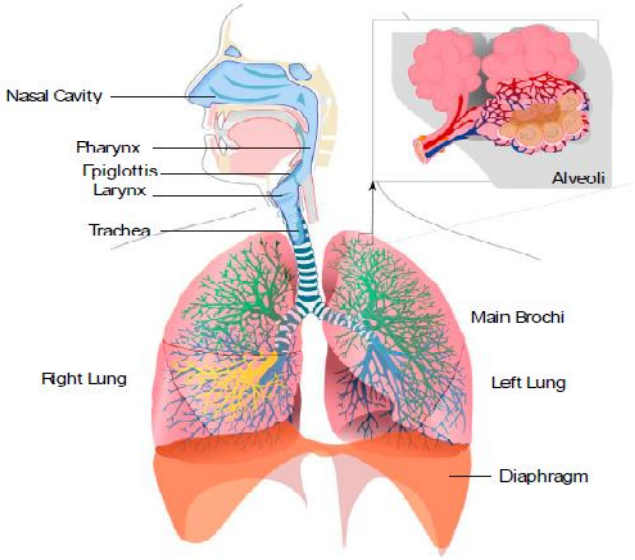

Figure 1. Basic picture of the respiratory system [9].

Asthmatic patients exhale between 20 and 25 ppb >30 ppbof NO, whereas a healthy population exhales lower concentrations [17]. Portable NO-selective sensors are already used to detect asthma, generally being sensitive to NO levels of <1 ppb, with a rapid response time [68]. Sensors array have given a higher degree of diagnostic accuracy for asthma than exhaled NO [14, 44].

Most popular detectors for measuring the amount of nitrogen monoxide (NO) are producedby the Siemens and Bosch companies (Figs. 2 and 3) [21, 22]. The Siemens device is the size of a mobile phone and works by analyzing a patient's breath and measuring the amount of nitrogen monoxide (NO). The Siemens device will be help asthma sufferers predict attacks. It is so sensitive it can measure amounts as small as one ppb (part per billion). Heightened levels signal that an asthma

Fig. 2 [21, 22].

sufferer's air passages are about to become inflamed. This latent inflammation generally spreads hours before a patient becomes aware that anything is wrong. The prototype device will allow patients to analyze their breath themselves and take the minimum amount of preventive medication when necessary.

Fig. 3.BedfontNObreathFeNO Monitor [23].

Specification of the monitor: Concentration range: 5-300ppb nitric oxide, Sensor sensitivity: 5ppb,Breath test time: Adult 12 seconds, Child 10 seconds, Operating temperature range: 10-30°C (ambient), Maximum ambient operating level: 350ppb NO.

Bosch Healthcare Solutions (USA) also developed small-size devices formeasuring the amount of nitrogen monoxide (NO) (see Fig. 4).

Fig. 4.[21, 22].

2. Volatile organic compounds biomarkers for respiratory diseases and their specific

Volatile organic compounds (VOCs)are also known as biomarkers for respiratory diseases. The monitoring of them by breath analysis is noninvasive. Specific of respiratory diseases are discussed below.

Obstructive pulmonary disease (COPD) is characterized by oxidative stress and the production of VOCs secreted by the lungs [1]. Since both COPD and asthma patients have

chronic airway inflammation, COPD patients could be misdiagnosed as asthmatics and vice versa. It is essential to clearly differ COPD from asthma in the caseof elderly people who have systemiccorticosteroids [1]. Is proposed to use an array of quartz crystal microbalance sensors coated with metalporphyrins in order to solve this problem. VOCs have been found in the exhaled breath of lung cancer patients [8, 24-33], and efforts have been realized the early detection of lung cancer using exhaled breath [34???35, 36]. DiNataleet al. reportedin [37] how it is possible to differ patients with lung cancer versus healthy subjects by using the same quartz crystal microbalance sensors coated withporphyrins. The Pt-, Pd-, and Au-loaded SnO_2 sensors wereused for PCA and discriminate analysis [38]. A SAW detectorcoated with a film of isobutylenecorrectly diagnosed patients with lung cancerat room temperature and sub-ppb concentration[39, 40]. Haick and co-workers. [41–44] successfully discriminated early and late stages of lung cancer, distinguish between small cell lung carcinoma and non-small cell carcinoma, as well as in differentiating between adenocarcinoma and squamous cell carcinoma with high accuracy, respectively. One gold nanoparticle (GNP) sensor could differentiate patients with lung cancer before and after surgery. Single-walled carbon nanotubes-based sensors array also was used to discriminate patients with lung[42, 45].

Exhaled breath of patients with pulmonary arterial hypertension (PAH) had raised concentrations of 2-nonene, 2-propanol, acetaldehyde, ammonia, ethanol and pentane compared with control subjects, whereas 1-decene and 1-octene were significantly lower [46-50]. Cohen-Kaminskyet al. [51] have established that GNP-based sensors can successfully detect and classify PAH. The results showed that the breath signatures of patients with lung cancer differed from PAH[52].All results were not influenced by sex, and age of patients.

The development of a rapid, affordable, and noninvasive assay is needed for tuberculosis TB screening [53, 54]. New devices for diagnosis of (TB)were proposed (the Xpert MTB/RIF assayetc)[55]. Phillips et al. [56] suggested biomarkers in oxidative stress products, such as alkanes and alkane derivatives, and volatile metabolites of mycobacterium tuberculosis, such as cyclohexane and benzene derivatives.GNP and molecularly modified single-walled CNTswere proposed by Nakhlen et al. [55] for the detection of active TB. Another group used a sensors array composed of eight metalloporphyrin-coated QMB sensors to assess the exhaled breath of patients with TB during treatment [54].

Obstructive sleep apnoea syndrome (OSAS)is a common disease associated with an increased risk for cardiovascular disorders [57]. The polymer composite-based sensors were utilized in the discrimination of OSAS between healthy controls[58]. Incalziet al. [59] used the quartz-based sensors array to show that breath-prints of patients with OSAS largely depends upon diabetes mellitus, metabolic syndrome and chronic heart failure.

Incalzi et al. [59] used the quartz-based sensors array to show that breath-prints of patients with obstructive sleep apnoea syndrome. Significantly change after a single night is largely depends upon studied comorbidities like diabetes mellitus, metabolic syndrome and chronic heart failure. Inflammation during monitoring of cystic fibrosis arises before clinical symptoms appear [60, 61]. FeNO is the most extensively studied marker in exhaled breath in some pulmonary diseases, including cystic fibrosis [62]. It was also impossible to differentiate non-chronically infected patients with CF from patients with CF having other chronic pulmonary infections with other pathogens [1].

Sensor arrays are potentially becoming convenient devices for physicians in the detection and monitoring of therapy of patients with respiratory diseases. Improvement in sensor technologies, machine-learning methods, disease-specific reference libraries and databases, in addition to the identification of respiratory disease biomarkers, have all contributed to the advance in diagnostic methods based on exhaled breath [63, 64]. Note in discussing of some future perspectives and concluding remarks that the relative humidity of exhaled breath may vary and influence measurements; water absorption reduces the sensitivity of metal oxide sensors by preventing electron donation to the surface charge layer. Alternatively, gold or platinum metal monolayer-capped nanoparticle chemiresistors have low sensitivity to water. One of the most crucial aspects of nanomaterial-based sensor technology is data analysis; the digital outputs generated by the sensors have to be analyzed and interpreted in order to provide useful information. The choice of method depends on the type of available input data acquired from the sensors and the type of information that is sought [65]. Sensor response to VOCs can be analyzed by pattern recognition algorithms to classify different cases individually, in which the principal component reduction and subsequent pattern recognition by discriminant analysis are the most frequently used types of raw-data analysis for their responses [66]. Other techniques are also used for data analysis, such as machine-learning algorithms and neural networks. These techniques mimic the cognitive process of the human brain, containing interconnected data processing algorithms that work in parallel [65]. The results of the artificial neural network data analysis are usually in the form of a percentage match of identification elements in a given breath sample with those of VOC patterns seen in a training set-up. The diversity of analytical techniques that are available may hinder the standardization of sensors array technologies, and consequently, special care must be given to avoid overfitting the training data and validation sets.

3. Exhaled carbon monoxide biomarkers

Degradation of hemoglobin leads to exhalation of carbon monoxide (CO)viathe alveoli [61]. CO can be quantified by a number of different techniques. The measurements of CO in humans gives reproducible results [67]by adjustable laser spectrophotometer [68], or by a near-infrared CO

analyzer [69]. Sensitive and stable near-IR instruments are used for continuous monitoring of stable asthma [70], [71] and patients treated with inhaled corticosteroids, but the effect of inhaled steroids on exhaled CO in patients with mild asthma is negligible.The cigarette smokingmasks influence of CO when the COPD,chronic bronchitis,and bronchiectasisdiseases are investigated[72[.

In contrast to NO, exhaled CO levels were markedly increased in patients with stable cystic fibrosis (CF)and allergic rhinitis[73-75], and reduced with antibacterial andcorticosteroid treatment, which is related to lung function deterioration [74, 75].

4. Exhaled hydrocarbonsmarkers

The main source of exhaled hydrocarbons in the body is the liver.Studiesof ethane and pentane in exhaled breath were carried out for newborns[76].Pentane and isoprene are increased in normal smokers, and ethane in patients with COPD who smoke.To distinguish asthma from obstructive sleep apnea,two different exhaled markers (NO and pentane) are used [77]. Elevated levels of exhaled and nasalNO, but not pentane, have been found in patients with sleepapnea. Patients with CF have elevated levels of exhaled ethane, whichis significantly correlated with exhaled CO and airway obstruction[73].Exhaled breath profile of different hydrocarbons hasbeen shown in patients with lung cancer [78].Pentane elimination was increased, but isoprene elimination was reduced in the case of pulmonary infection in comparison with patientswithout pulmonary infection. A significant increase of exhaledethane was observed in patientsundergoing cardiopulmonary bypass operations.

5. Hydrogen Peroxide markers

Exhaled $H_2O_2$is a marker of oxidative stress in the lungs. H_2O_2 has been detected in exhaled condensate inpatients with increased concentrations inasthma [79, 80]. Fivefold higher levelof H_2O_2 have been found in exhaled breath condensate of smokers with stable COPD [81]than in nonsmokers. Concentrations of 8-isoprostane in the breath condensate of patients with stable CFare increased about threefold compared with those in normal subjects[83].

Many different sensors were developed-fuel cell aldehyde sensor[84], sensor prepared using ITO (Indium Tin Oxide) substrate spin-coated with ZnO layer, that was prepared by sol-gel technique and thermal evaporation [85]. Platinum were placed over the ZnO. An electronic nose is used in the discrimination of patients with non-small cell lung cancer and COPD [86, 87]. Exhaled breath analysis using electronic nose was carried out for non-invasive diagnosis of chronic kidney disease, and diabetes mellitus [88]. Our patent [89] is suggested for detection of respiratory diseases.

6. Breathomics from exhaled volatile organic compounds.

Asthma is a complex disease and for its monitoring a combination of VOCs is needed, that can be considered as a “molecular fingerprint” of exhaled breath.A“breathome” termin is proposed for such fingerprint, and “breathomics” describing for its [90-92]. The analysis of VOCs in exhaled by asthmatic breath isan non-invasive approach, that has not yet reached clinical practice.

Several spectrometry and spectroscopy techniques have been used to collect, detect and analyses exhaled VOCs of respiratory diseases [93–97]. Techniques including proton transfer reaction-mass spectrometry (MS), selected ion flow tube (SIFT)-MS, ion mobility spectrometry, laser spectroscopy and gas chromatography (GC) are commonly used. But this equipment is powerful but rather expensive[98]. Therefore, chemical sensors are proposed, that, as usually, changed their electrical resistivity due to contact with VOCs [100]. Surface acoustic wave (SAW) sensors were used as a detector for the breath analysis, as well as acoustic and colorimetric sensors [101, 102].

7. Oxymeters

The level of oxygen (or oxygen saturation) in the blood can be measured using a pulse oximeter [103] in the case of respiratory disease. A clip-like sensor device that is placed on body of patient. Pulse oximetry is used to assess oxygen saturation in the blood, and often used in surgeries and bronchoscopy) and assess whether an adjustment of supplemental oxygen is needed, whether lung medications are working effectively, and to determine patient tolerance to make any adjustments of supplemental oxygen. Pulse oximetry may also recommend if patient uses a ventilator to support breathing, suffer from sleep apnea, COPD, lung cancer, asthma, or pneumonia as well as heart attack, congestive heart failure, anemia disease. Oximeters use in all cases when it is necessary to measure the level of oxygen in the body.

A device contains a light source, light detector, and microprocessor, which compares and calculates the differences in oxygen-rich versus oxygen-poor hemoglobin. One side of the probe contains a light source with two different types of light: infrared and red. These two types of light are transmitted through the body's tissues to the light detector on the other side of the probe.

Fig. 5. Pulse oximeter[103].

Hemoglobin that is more saturated with oxygen absorbs more of the infrared light, while hemoglobin without oxygen absorbs more of the red light. The microprocessor in the probe calculates the differences and converts the information to a digital value. Measurements of relative light absorption are made multiple times every 0.5-1 second. The readings of the last 3 seconds are then averaged out. Several different types of pulse oximeters are available. The most popular are portable handheld and fingertip pulse oximeters. That can be purchased in drag stores.

Conclusions

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