Review Article

EXHALED BREATH SEMICONDUCTOR SENSORS FOR DIAGNOSTICSOF RESPIRATORY DISEASES

Abstract

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, volatile organic compounds, carbon monoxide, hydrocarbons, and hydrogen peroxide. Breathomics from exhaled volatile organic compounds and oximeters are also shortly discussed.

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. Fractional exhaled nitric oxide biomarker

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).

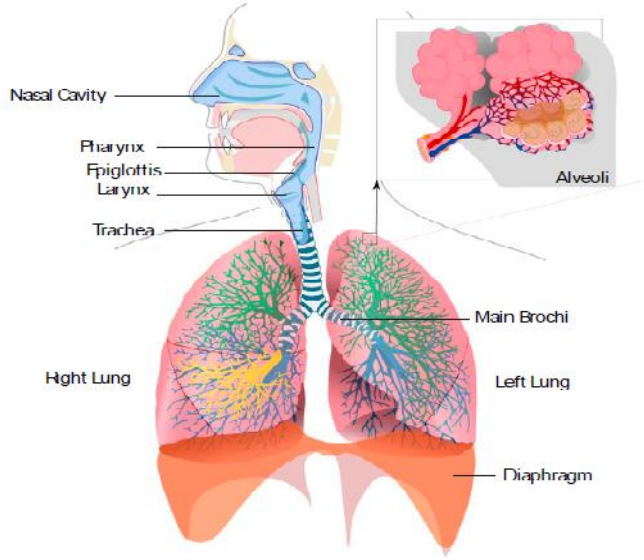

Figure 1. Basic picture of the respiratory system [9].

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. Siemens devicefor measuring the amount of nitrogen monoxide

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.small-size devices for measuring the amount of nitrogen monoxide

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.

Symptoms of asthma often begin in early childhood, and mostly improve, or even disappear, but can relapse later in life.Obstructive pulmonary disease (COPD) is characterized by oxidative stress and the production of VOCs secreted by the lungs [1]. Principle component analysis (PCA) of the sensing signals had 88% accuracy for distinguishing fixed asthma from COPD. Since both COPD and asthma patients have chronic airway inflammation, the results might include overlapping features, and COPD patients could be misdiagnosed as asthmatics and

vice versa. Hence, it is essential to clearly discriminate COPD from asthma, especially in elderly people who have a higher probability of adverse reactions to different classes of inhaled agents or systemiccorticosteroids [1]. The combined system consisting of an array of quartz crystal microbalance sensors coated with six derivatives of metalporphyrins found nine VOCs that were significantly correlated with COPD, of which two positively correlated with COPD and seven negatively correlated with COPD. Lung cancer is typically asymptomatic in its early stages and, thereforeis diagnosed in later stages when treatment is no longer effective [8, 24]. Numerous GC-MS and proton transfer reaction-MS studies have examined the profile of VOCs in lung cancer; more than1000 trace VOCs have been found in the exhaled breath of lung cancer patients at concentrations ranging from parts per million by volume to parts per trillion by volume [25-33]. Typical examples are isoprene, methanol, acetone and 2-propanol (appearing in all human breath samples), acetonitrile, furan, 2-methyl furan (primarily found in smokers), and many others [1]. Hence, efforts have been invested in analyzing exhaled breath as a simple noninvasive method of the early detection of lung cancer [35, 36]. DiNataleet al. [37] reported 100% classification of patients with lung cancer versus healthy subjects by using eight quartz crystal microbalance sensors coated with different metalporphyrins. Various VOCs in breath exhaled by patients with lung cancer were usually analyzed by both gas condenser-equipped gas chromatography-mass spectrometry (GC/MS) and semiconductor metal oxide sensors. For example, the Pt-, Pd-, and Au-loaded SnO2 sensor elements were recommended [38]. Pt (particle size: 2 nm), Pd (4 nm), and Au (3 nm) colloid suspensions were added to the SnO_2 powder (particle size <100 nm).The sensors' response was analyzed using PCA and discriminate analysis.

Using artificial neural network analysis of a SAW detectorcoated with a film of isobutylene**,**it is possible to correctly diagnose patients with lung cancer from exhaled breath with 80% sensitivity and specificity. All groups were examined by a colorimetric sensors array and compared with breath signatures of eight binary groups for the identification and characterization of lung cancer with high sensitivities and specificities. The disposable features of such sensors might be a limitation in real-world applications. Chemiresistorsmade from monolayer-coated metal nanoparticles have been used to detect and monitor lung at room temperature and sub-ppb concentration, lower operating voltage, a wider dynamic range, faster response and recovery times, higher tolerance to humidity and compatibility with standard microelectronic industry [39, 40]. Using this approach, the group of Haick and co-workers. [41–44] successfully discriminated early and late stages of lung cancer with 88% accuracy. Moreover, this sensors array could 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 after surgery, as well as monitor the response of patients to therapy with an accuracy of 59%. Discriminant factor analysis of the collective responses from the nanoarray could monitor changes in tumor response during therapy and also indicate lack of any further response to therapy with a success rate of 85% [45]. Using the same sensors array, these authors managed to detect lung cancer at early onset and monitor breath volatolomics after lung cancer resection. Moreover, patients with lung cancer and volunteers with benign nodules before and after surgery could clearly be differentiated. Ultimately, the nanomaterial-based sensors array distinguished between pre-surgery and post-surgery lung cancer states yielding an 80% classification accuracy [42]. A nanomaterial-based sensors array composed of 40 cross-reactive, chemically diverse chemiresistors based on organically stabilized spherical GNPs, and single-walled carbon nanotubes, were used to discriminate patients with lung. Nanoarray sensors also showed that patients with early lung cancer could be discriminated from patients with benign pulmonary nodules, with high sensitivity, specificity, and accuracy.

Pulmonary arterial hypertension (PAH)is a progressive cardiopulmonary disease characterized by the extensive occlusion of small to mid-sized pulmonary arterioles, as well as structural alterations in the vascular wall that eventually lead to right heart failure [46-48]. Although a wide range of therapeutic agents have been established for the management of PAH, it remains incurable, with lung transplantation continuing to be the main treatment in severe cases [49]. Exhaled breath of patients with 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. In contrast, there was no association between levels of ammonia in the breath and plasma (plasma levels of ammonia were similar in both groups) [50]. Ammonia is generated by the breakdown of nucleic acids, polyamines and amino acids, mainly glutamine.

Efforts continue to be made to develop nanoscale sensors for the rapid detection of VOCs in exhaled breath. For example, Cohen-Kaminsky et al. [51] have established that GNP-based sensors can successfully detect and classify PAH cases. Similarly, a colorimetric sensors array was used as a diagnostic method for the discrimination of patients with lung cancer from other common lung diseases [52]. The results showed that the breath signatures of patients with lung cancer differed from PAH, idiopathic pulmonary fibrosis, COPD and healthy controls. In the validation set of the nanoarray, the sensors could discriminate between the diseases with a sensitivity of 73.3% and a specificity of 72.4%. These results were not influenced by sex, and age of patients.

Diagnosis of tuberculosis (TB) remains a major global public health challenge, with its social burden increasing because many patients may also be infected with human immunodeficiency virus. The rates of multidrug-resistant TB are increasing [53]. In 2010, there was an estimated incident case count of 8.8 million active TB infections, resulting in 1.5 million deaths [54]. Current diagnostic methods rely on either insensitive smear microscopy or sensitive, but lengthy, microbiologic culture, unlikely to be used in poorly resourced centers [55, 56]. More recently, the Xpert MTB/RIF assay, a fully automated sample-to-answer nucleic acid amplification test, has significantly improved sensitivity compared with smear microscopy [54]. However, this assay requires a sputum sample or an invasive sample from patients that cannot expectorate. Its high cost also limits it use in poor and resource-limited countries where TB is rampant [1]. Hence, the development of a rapid, affordable, and noninvasive assay is needed for TB screening, especially in developing countries. Phillips et al. [56] analyzed the breath of 226 patients using GC-MS, pointing out several biomarkers of active pulmonary TB. They suggested biomarkers in oxidative stress products, such as alkanes and alkane derivatives, and volatile metabolites of mycobacterium tuberculosis, such as cyclohexane and benzene derivatives.

Nakhlen et al. [55] used arrays of molecularly modified GNP and molecularly modified single-walled carbon nanotubes for the detection of active TB. The two groups were age- and sex-matched, but differed in their smoking habits etc. Three single-walled carbon nanotubes sensors modified with a layer of polyaromatic hydrocarbon derivative showed >80% accuracy in the training set, whereas the other nine showed either <80% accuracy or a random classification. The chemiresistor based on dodecanethiol-capped GNPs correctly scored a sensitivity of 90%, a specificity of 93% and an accuracy of 92%. Another group used a sensors array composed of eight metalloporphyrin-coated QMB sensors to assess the exhaled breath of patients with TB during treatment. The sensors response was validated and correlated with clinical and microbiological measurements on sputum samples [54]. The sensors scored 93% accuracy in distinguishing TB cases from controls; additionally, serial measurements of VOCs also showed signal changes during TB treatment among patients.

Approximately 15% of lung diseases are attributed to a condition that is associated with occupational exposure leading to inhalation of dust, silica, asbestos or smoke [1]. The high-risk population includes shipyard workers, construction workers, asbestos textile workers and asbestos miners. Mortality due to asbestos exposure continues to increase in many developed countries. Lipid peroxidation occurs and hence screening for lipid peroxidation-related VOCs should be useful in diagnosing pneumoconiosis.

Obstructive sleep apnoea syndrome (OSAS) is a common disease associated with an increased risk for cardiovascular disorders [57]. Despite the introduction of several screening

tools, the diagnosis of OSAS still needs to be confirmed by polysomnography, and hence the use of expensive instruments by trained personnel is required limiting its large-scale application [58]. In an attempt to utilize sensors array technology for the detection of OSAS, the polymer composite-based sensors were utilized in the discrimination of OSAS between healthy controls. INCALZI et al. [59] used the same quartz-based sensors array to show that breath-prints of patients with OSAS significantly change after a single night of continuous positive airways pressure and it largely depends upon studied comorbidities like diabetes mellitus, metabolic syndrome and chronic heart failure.

Monitoring of airway inflammation and oxidative stress can be helpful in the diagnosis and monitoring of cystic fibrosis (CF), especially since inflammation arises before clinical symptoms appear [60]. The currently available techniques for measuring inflammation and oxidative stress in the airways are bronchoscopy, bronchoalveolar lavage and biopsy; however, these techniques are too invasive for repeated routine use, especially in children [61]. FeNO is the most extensively studied marker in exhaled breath in some pulmonary diseases, including CF [62]. Nevertheless, monitoring NO has several limitations, most noted in that FeNO is largely a marker of allergic inflammation, thereby limiting its use in non-allergic patients. Investigations indicated that it was impossible to detect any overall difference between chronically and non-chronically infected patients. It was also impossible to differentiate nonchronically 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

Carbon monoxide (CO) is a gas that exhaled in the body isfrom the degradation of hemoglobin [61]. There are several reasons to consider that the alveoli arethe predominant site of exhaled CO in normal subjects. CO has been measuredto identify current and passive smokers, to monitor bilirubinproduction, including hyperbilirubinemia in newborns, and inthe assessment of the lung diffusion capacity.CO can be quantified by a number of different techniques. Most of the measurements in humans have been made usingelectrochemical CO sensors. The sensor is selective, gives reproducible results [67], and is inexpensive. However, theseinstruments are susceptible to interference from a large number of substances, for example, hydrogen, which is present inexhaled breath and may be increased after glucose ingestion.

Exhaled CO can also be measured (at ppb level) by adjustable laser spectrophotometer [68], or by a near-infraredCO analyzer [69]. Sensitive and stable near-IR instruments are fairly used for continuous monitoring of atmospheric. However, they are larger than electrochemical CO sensors, sensitive to water and CO_2 concentrations,and require large sample volumes. This may explain the low CO levels detected by these instruments even after a prolonged breathhold time of 20s. Gas chromatography is a reference method for CO measurements, but its use is limitedto specialized laboratories.

Elevated levels of exhaled CO have been reported in stable asthma [70], [71] with normal levels in patients treated withinhaled corticosteroids. The difference in exhaled CO between normal and asthmatic subjects, however, is much lessthan in exhaled NO, and the effect of inhaled steroids on exhaled CO in patients with mild asthmais negligible. A major limitation of exhaled CO in COPD is the marked effects of cigarette smoking, which masks any increase that mayoccur because of the disease process. There is no difference in exhaled CO in patients with chronic bronchitis obstruction when compared with normal subjects. Exhaled CO levels are

elevated in patients with bronchiectasis, irrespective of whether they are treated with inhaled corticosteroids [72[.

In contrast to NO, exhaled CO levels were markedly elevated in patients with stable cystic fibrosis (CF)[73], and increased furtherduring exacerbations and reduced with antibacterial treatment. This suggests that exhaled CO is notonly a marker of oxidative stress / inflammation in CF, but is also a marker of disease severity. This is further confirmed bythe finding of lower CO levels in patients receiving oral corticosteroid treatment. Elevation of exhaled CO is related to lung function deterioration (74) and impaired gas transfer in patients.In patients with allergic rhinitis exhaled CO is increased during the pollen season and returns to normal values after the season [75]. The levels of exhaled CO are significantly higher in patients with symptoms than in those without.

4. Exhaled hydrocarbonsmarkers

Exhaled hydrocarbons have been measured in a variety of conditions.Hydrocarbons are non-specific markers of lipid peroxidation, which is one of the consequences of the constant and inevitable formation of oxygen radicals in the body. The main source of exhaled hydrocarbons in the body is the liver. The low molecular mass hydrocarbonsethane and pentane are end-products and have been extensively studied in exhaled breath. Hydrocarbons such as propane and butane are mainly derived from protein oxidation and their role as the markers of lipid peroxidation is doubtful. However, ethane and pentane excretion are increased during the first few daysof life in premature newborns when the gut is not colonized and, therefore, supporting that the bacterial flora is not themajor contributor of these exhaled hydrocarbons [76].

The measurements of two differentexhaled markers (NO and pentane), for example, might behelpful to distinguish asthma from obstructivesleep apnea [77]. Elevated levels of exhaled and nasalNO, but not pentane, have been found in patients with sleepapnea. Pentane and isoprene are increased in normal smokers, and ethane in patients with COPD who smoke.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 may be ofdiagnostic value in a variety of clinical conditions, as it hasbeen shown in patients with lung cancer [78]. In patientswho developed a pulmonary infection, pentane elimination wasincreased, but isoprene elimination was reduced, resulting in asignificant increase in their ratio when compared with patientswithout pulmonary infection. A significant increase of exhaledethane, which is related to a lower cardiac index and a highersystemic vascular resistance, has been demonstrated in patientsundergoing cardiopulmonary bypass operations,suggesting oxidative damage caused by reperfusion in thesepatients.

5. Hydrogen Peroxide markers

As $H_2O_2$is less reactive than other reactive oxygen species, it has the propensity to cross biologic membranes and enter other compartments. Exhaled H_2O_2 has the potential as a marker of oxidative stress in the lungs. H_2O_2 has been detected in exhaled condensate inhealthy adults and children with increased concentrations inasthma [79, 80].

Cigarette smoking causes an influx of neutrophilsand other inflammatory cells into the lower airways, and fivefold higher levels of H_2O_2 have been found in exhaled breath condensate of smokers than in nonsmokers. Levels of exhaled H_2O_2 are increased compared with those in normal subjectsin patients with stable COPD[81]. CF is characterized by marked oxidative stress in the airways [82], and elevated levels of 8-isoprostane have been detected in plasma [83]. Concentrations of 8-isoprostane in the breath condensate of patients with stable CFare increased about threefold compared with those in normal subjects.

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.

In order to diagnose and monitor complex and heterogeneous diseases, such as asthma, a combination of VOCs is needed, rather than using a singular VOC as a disease biomarker. Such a combination of VOCs can be considered as a “molecular fingerprint” of breath, similar to other metabolomics technologies providing fingerprints at the level metabolites in blood, sputum, urine, etc,theterms“breathome” as the fingerprint of VOCs in exhaled breath, and “breathomics” as the study of these fingerprints[90-92] are accepted.Breathomics may provide a key step towards personalized medicine, since the final clinical goal of these studies is to optimize treatment for patients by taking into account individual patients’ breath characteristics.

Asthma is the most common chronic disease in children, and is characterized by airway inflammation, bronchial hyper responsiveness, and airflow obstruction. The analysis of VOCs in exhaled by asthmatic breath could be an interesting non-invasive approach, but has not yet reached clinical practice. This review describes the current status of breath analysis in the diagnosis and monitoring of pediatric asthma.

Several spectrometry and spectroscopy techniques have been used to collect, detect and analyse exhaled VOCs of respiratory diseases [93–97]. Frequently used techniques include proton transfer reaction-mass spectrometry (MS), selected ion flow tube (SIFT)-MS, ion mobility spectrometry, laser spectroscopy and gas chromatography (GC). In GC techniques, the exhaled breath is collected and usually stored in inert bags or sorption tubes. While GC-MS-based techniques are powerful in detecting disease-related VOCs, they unfortunately require expensive equipment, high levels of expertise to operate the instruments, considerable time and effort for sampling and analysis, and a need for pre-concentration techniques [98]. These approaches have been used to identify the VOCs distinctive of many respiratory diseases. To overcome the challenges associated with spectroscopic and/or MS techniques for breath analysis of respiratory diseases, chemical sensors have been adopted. Chemiresistors change their electrical resistivity due to sorption of VOCs on the organic film, or by steric changes within the sensing layer affecting the charge transfer from/to the inorganic nanomaterial [100]. Surface acoustic wave (SAW) sensors were also used as a detector for the breath analysis. Acoustic sensors detect changes in the propagation (velocity and amplitude) of acoustic waves through or on the surface of the sensor's coating material due to sorption of VOCs [101]. Colorimetric sensors are based on indicators, specifically chemoresponsive dyes, which chemically react and change colour on exposure to VOCs, thereby identifying the exposed species [102].

7. OXYMETERS

The level of oxygen (or oxygen saturation) in the blood may be lower in the case of respiratory disease. It should always be above 95 percent. The blood's percentage of oxygen saturation can be measured using a pulse oximeter [103]. Pulse oximeter is a simple, cheap, and noninvasive device. A clip-like sensor device that is placed on body of patient. Oxygen is breathed into the lungs. The oxygen then passes into the blood where the majority of the oxygen attaches to hemoglobin. Hemoglobin is a protein located inside our red blood cells that transports the oxygen through the bloodstream to the rest of our body and tissues. In this way, our body is given the oxygen and nutrients it needs to function. Pulse oximetry is used to assess oxygen saturation in the blood for a variety of reasons. It is often used in surgeries and other procedures that involve sedation (such as a bronchoscopy) and to make any adjustments of supplemental oxygen. A pulse oximeter may also be used to assess whether an adjustment of supplemental oxygen is needed, whether lung medications are working effectively, and to determine patient tolerance to increased activity levels. Pulse oximetry may also recommend if patient uses a ventilator to support breathing, suffer from sleep apnea or has a serious medical condition, such as COPD, lung cancer, asthma, or pneumonia as well as heart attack, congestive heart failure,

anemia disease. Oximeters use the light absorptive characteristics of hemoglobin and the pulsating nature of blood flow in the arteries 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

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. This value is then assessed to determine the amount of oxygen being carried in the blood.Measurements of relative light absorption are made multiple times every second. These measurements are then processed by the machine to give a new reading 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. Portable pulse oximeters can be purchased from a wide array of drag stores, and even online. Most pulse oximeters are clip-like and look like a clothespin. There are also adhesive probes for children and infants that can be placed on your finger or forehead.

Conclusions

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, 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 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.

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