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Development of the Concept of a System for Registration of Biomarkers of Necrotic Changes and Lung Destruction in the Early Stages by Exhaled Air

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***Abstract*—The coronavirus-19 pandemic has shown that early diagnosis of structural changes in lung tissue is essential. However, many remote medical institutions lack the necessary equipment, such as a computed tomography scanner. In this work, we want to present the developed concept of a device that allows registering lung tissue abnormalities at early stages by detecting biomarkers in liquid droplets and human respiration.**

Keywords—exhaled air, expiratory markers, biomerkers of lung necrosis, biomarkers in expiratory air, early diagnosis, miniature laboratory equipment

I. Introduction

Necrotic changes and other structural changes are most often controlled using such methods of "expensive" or "large" medicine as magnetic resonance imaging and computed tomography, ultrasound machines, various X-ray equipment in our time. However, the current epidemiological situation associated with the spread of the Covid-19 pandemic has shown that monitoring the condition of patients in the absence of such equipment is difficult. This situation forced scientific teams around the world to look for analogues for methods of detecting structural changes in lung tissue. We want to consider some of the features of gas metabolism in the lungs, compare data for healthy patients and patients with diagnosed diseases, put forward a hypothesis about how to register lung disorders based on the analysis of the chemical and biomarker composition of the patient's exhaled air in this article.

II. Description of Respiratory Metabolism

In the ideal model of gas exchange, the exhalation of a person should contain only O_2, CO_2, N_2 and CO. However, in reality, human exhalation contains volatile organic compounds (VOCs) (alcohols associated with raising their stomach air masses; VOCs associated with gas exchange in the alveolar space; VOCs released from the blood). An example of such a substance is acetone - a reaction product of ketone metabolisms. Previously, scientists [1] described the mechanisms for assessing the content of ketone bodies in the blood by extrapolating the obtained data on the content of acetone in the exhaled air. However, some VOCs can be released during chemical reactions inside the lungs, so the presence of formaldehyde can indicate pathological processes associated with lung cancer [2].

Exhalation analysis is a non-invasive diagnostic method, therefore it is of great interest to scientists and developers. But, despite the significant advantage, this method has not received widespread use at the moment for two reasons:

1) lack of information about the set of markers-gases in exhaled air for many diseases and pathologies;

2) the complexity of using the available technical means for analysis both in laboratories and in hospitals.

There are the following methods of studying metabolic profiles: gas and liquid chromatography, mass spectrometric detection, nuclear magnetic resonance spectroscopy. Gas chromatography is universal for substances that evaporate without decay. When using this method, it is necessary to pre-prepare the sample, usually by solid-phase microextraction (deposition of components on a polymer-coated thread and subsequent evaporation of the components in a gas chromatograph). The final data are obtained using one of two methods: mass spectrometry (the disadvantages of the method - it is impossible to determine the amount of a biomarker, the signal intensity depends on the type of sample preparation, its advantage is high sensitivity) or nuclear magnetic resonance spectroscopy (the advantages of the method - it allows obtaining data not only on the presence, but also on the concentration of each biomarker, it is universal for the analysis of various biological fluids).

TABLE I. Biomarkers in Exhaled Air in Pathological Changes in the Lungs

Chemical Substance	Disease
Octadiene, nonanal, 1-chlorheptane	Covid-19
Acetic acid, formaldehyde	Lung cancer
Octane, acetic aldehyde	Acute Respiratory Distress Syndrome (ARDS)
Succinate, glutamine, sincaline, phosphorylcholine	Chronic obstructive pulmonary disease (COPD)

We will give several examples of biomarkers that were recently discovered [3-5] in the human body with various structural lung lesions, including those undergoing Covid-19 (table 1).

The data indicated in table one, this is only a small part of the described biomarkers, in reality there are many more of them, however, not all biomarkers have the revealed specificity, for example, a number of scientists associate the concentration of acetaldehyde in exhaled air with various diseases, formaldehyde also has a similar property. When analyzing such biomarkers, for a more accurate diagnosis, it is necessary to take into account the patient's history of illness.

In the near future, in our opinion, the main task for scientific and engineering teams is to create adequate small-sized means for detecting markers-gases in the exhalation of a person and calculating their concentration.

III. Proposed concept

One of the stages in the development of a portable device for monitoring the state of patients with chronic lung diseases by exhaled air is the development of a method that implements a quantitative assessment of a particular marker in gas. We propose to use chemical reactions with a change in the color of reagents for detection. Consider a few examples of hypothetically possible color-changing chemical reactions for the biomarkers described earlier.

Oxidation of nonanal with copper hydroxide to form nonanoic acid, copper oxide and water (chemical reaction equation 1):

$$C_9H_{18}O + 2Cu(OH)_2 \rightarrow C_9H_{18}O_2 + Cu_2O\downarrow + 2H_2O \quad (1)$$

A sign of this chemical reaction is the appearance of a red-brown copper oxide precipitate, which can be detected colorimetrically.

Another example is the mild oxidation of alkadienes, for example, the oxidation of methylene with potassium permanganate (chemical reaction equation 2):

$$3C_6H_{12}+2KMnO_4+4H2O\rightarrow 3C_6H_{14}O_2+2MnO_2+2KOH \quad (2)$$

In this case, the potassium permanganate solution is discolored with a 2-2-methylant. The reaction proceeds with the formation of 2-methylenediol-2,3 and manganese oxide.

The structure of the device being developed assumes that the air exhaled by the patient reacts with the reaction mixture (reagent). In the course of a chemical reaction, the color of the reagent changes or its discoloration occurs, which can be recorded using a spectrophotometric device.

In the process of working on a scientific project, a structural diagram of a hardware-software complex was developed, designed to assess the structure of the patient's exhaled air. Figure 1 shows a block diagram of the device being developed.

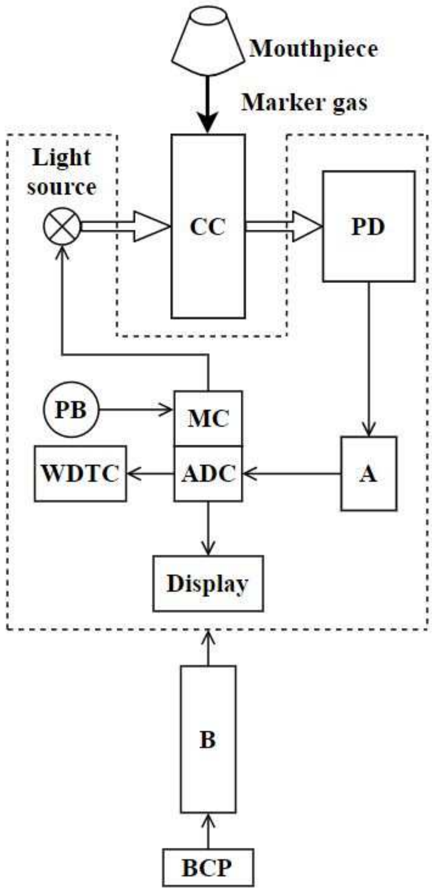

Fig. 1. Device block diagram

There is a power button (PB) on the device casing. Pressing this button closes the section of the electrical circuit that separates the battery (B) from the rest of the circuit, and power begins to flow to all electronic components. A microcontroller (MC) signal ignites the light source and spectrophotometric analysis begins.

A person breathes into a mouthpiece. The exhalation contains a certain marker gas that enters the capsule-cuvette (CC), where the photochromic reaction occurs. As a result, the solution in the cuvette changes its color. In this case, the capsule-cuvette can be replaced for ease of use with a solid test strip coated with the reagent necessary for the reaction. Radiation from the light source passes through the capsule-cuvette, is attenuated and recorded by a photodetector (PD). Since the signal is weak, it is amplified by an amplifier (A) and then fed to the analog-to-digital converter (ADC) as part of the control microcontroller (MC). The digitized data is transmitted over a wireless data transmission channel (WDTC) to the patient's smartphone, on which a special application is installed. The data is analyzed by the device itself, the results are calculated (thanks to the computing power of the microcontroller) and displayed on a small display. The battery of the small-sized gas analyzer is charged like a smartphone: from the socket using a wire that is inserted into a special charging connector (BCP).

A distinctive feature and advantage of the developed analyzer is its small dimensions, which determine its portability and ease of use both in the hospital and at home. Figure 2 shows an image of the device case concept.

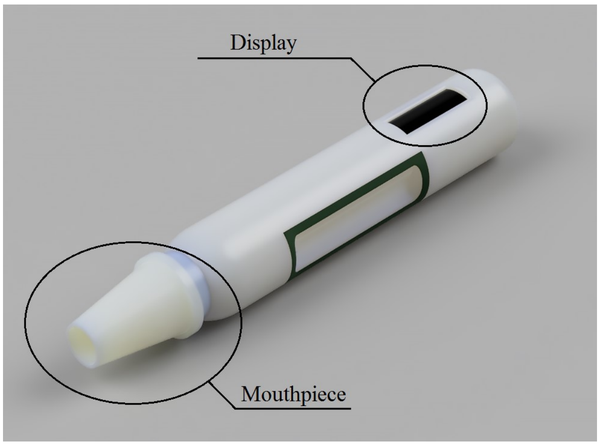

Fig. 2. Concept of the developed device

A removable mouthpiece ensures sterility of the study. The results obtained are briefly displayed on the device display for the user to get acquainted with, and the dynamics of changes in indicators are presented in a detailed form in the user application.

To implement continuous monitoring, which allows the doctor and the patient to constantly exchange data about the state of the body and adjusting the treatment, it is necessary to provide within the hardware-software complex for the presence of a telemedicine application paired with the patient's smartphone and medical device. Figure 3 shows the concept of the telemedicine system being developed.

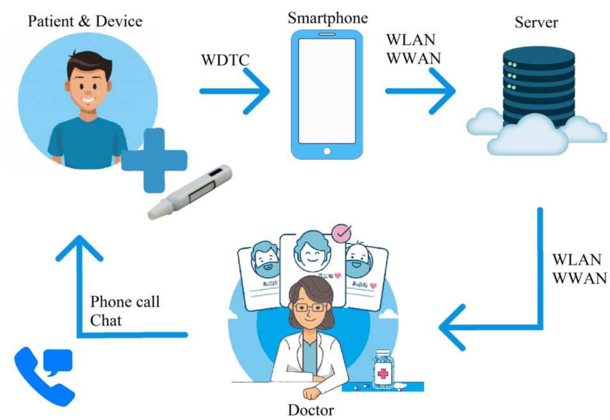

Fig. 3. Block diagram of the remote monitoring system

It is assumed that the data obtained as a result of spectrophotometry, implemented within the hardware complex, is transmitted wirelessly via Bluetooth to the patient's smartphone. Patient data is stored in the application database, can be displayed as individual measurements throughout the day, and the application must also be able to display statistics, graphs of changes in the indicator of interest.

Further, the data is transmitted via a global wireless channel to the server of the medical institution for storage and further transmission to the attending physician. Thus, the doctor will constantly have access to the patient's data. To ensure convenient contact between the doctor and the patient, the telemedicine application should provide for the possibility of making a call, text or video chat.

This multi-level system is the basis for building the architecture of a telemedicine application.

IV. Conclusions

We hope that the creation and use of a device of this type and design will allow not only early diagnosis of some pulmonary pathological diseases, but can also be used in home use as a means of diagnosing the course of rehabilitation after suffering Covid-19.

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