EXPERIMENTAL SETUP BASED ON INFRARED QUANTUM-CASCADE LASER SPECTROSCOPY FOR ANALYSIS OF MICRO COMPONENTS IN HUMAN EXHALED BREATH

OLGA NEBRITOVA, PAVEL DEMKIN, IGOR FUFURIN, AND ANDREY MOROZOV

Bauman Moscow State Technical University, Moscow, Russia

ABSTARCT

According to the International Diabetes Federation about 537 million people in the world suffer from a chronic autoimmune disease of the endocrine system - diabetes mellitus. According to statistics, the number of patients will increase to 643 million by 2030 and 783 million worldwide by 2045. Non-invasive diagnostics allows to determine the disease at an early stage. This paper describes a method for diagnosing type 1 diabetes by human exhaled breath based on infrared spectroscopy using a quantum cascade laser in the range of 5.3-12.8 microns (150 mW peak power) and a multi-channel Herriot gas cell with an optical path length of 76m. An analysis of exhaled breath spectra of healthy volunteers and patients with type 1 diabetes was conducted. A method of early noninvasive diagnosis based on the combination of several microcomponents (acetone and ethanol) is shown, which allows to classify diseases with high accuracy both in a wide spectral range and by concentrations of individual biomarker molecules in human exhaled breath.

Diabetes mellitus is a disorder of metabolic homeostasis controlled by insulin, leading to a disruption of carbohydrate and lipid metabolism. According to the International Diabetes Federation, about 537 million people worldwide suffer from the chronic autoimmune disease of the endocrine system - mellitus diabetes. According to statistics, by 2030 the number of patients will increase to 643 million, and by 2045 - 783 million people in the world [1]. Type 1 diabetes mellitus accounts for only about 10% of diabetes cases worldwide but is increasingly common at a young age. The disease occurs as a result of the autoimmune destruction of pancreatic β-cells [2]. Thus, there is a need to develop methods of early noninvasive diagnostics by human excreted biomaterials, such as saliva, human exhaled breath, etc. Human exhaled breath consists of more than 1000 volatile organic compounds [3]. Some volatile organic compounds are biomarker molecules for certain diseases. For example, in a healthy volunteer, the average concentration of acetone is in the range of 290-870 ppb; in patients with a confirmed diagnosis of diabetes, it exceeds 1800 ppb [4, 5]. Average isopropanol concentrations are 500ppb and over 2000ppb, respectively [6]. In addition to the existing "gold standard" of gas chromatography with mass spectrometry, there is interest in spectral analysis of multicomponent gas mixtures in the infrared range [7].

The experimental setup is based on the method of infrared laser spectroscopy and is intended for high-sensitivity spectral analysis of multicomponent gas mixtures, including the composition of a human exhaled breath (Fig. 1). The setup consists of two main modules: a module of radiation analysis and a module of sample preparation and conveying module.

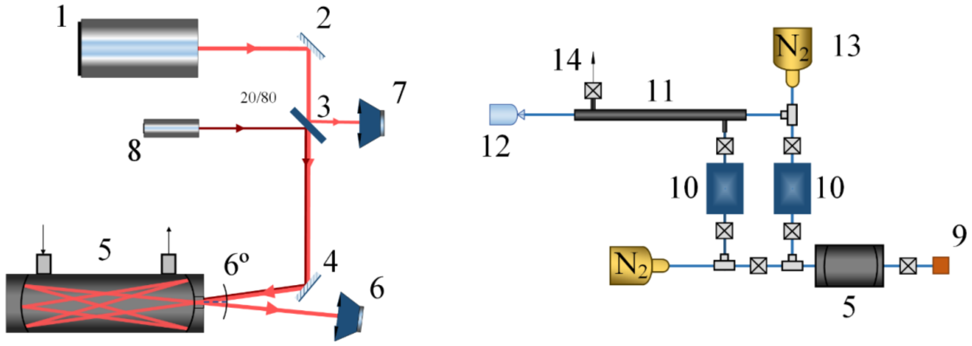

Figure 1: Schematic diagram of the experimental setup: a) module of radiation analysis; b) module of sample preparation and coveying. 1 - Infrared quantum-cascade laser; 2 - Gold-coated parabolic mirror; 3 - Light-separating plate 20/80; 4 - Mirror; 5 - Multipass cuvette; 6 - Signal photodetector; 7 - Reference photodetector; 8 - Laser of visible radiation; 9 - Vacuum pump of gas cuvette; 10 - Gas flow regulator; 11 - Membrane (naphion) dryer; 12. Tedlar bag for sampling; 13 - Bottle with pure nitrogen; 14 - Outlet valve of an external contour of membrane dryer

The radiation analysis module consists of both an infrared quantum-cascade laser 1 and a cadmium-mercury-tellurium (CdHgTe) photodetector 6 cooled by a cascade of Peltier cells. The quantum-cascade laser (LaserTune, Block Engineering) emits in a wide spectral tuning range of 5.3-12.8 μm in pulsed mode with a peak power up to 150 mW. The CdHgTe photodetector has a detecting capability of D*~6-8x10^9 cm*Hz$^{1/2}$/W. The radiation from the infrared quantum cascade laser hits the beam splitter 3 and is divided in 20/80 ratio so that 20% hits the reference photodetector 7 and 80% hits the multi-pass gas cell 5. To achieve a maximum optical path of 76 meters, the radiation is directed into the entrance pupil of the gas cell at an angle of 3° to the gas cell normal. Adjustment of the maximum optical path in multi-pass gas cell 5 is carried out by a pattern of over-reflections of visible laser radiation 8 adjusted coaxially with the quantum cascade laser 1. After passing through the optical path in the gas cell, the laser radiation (approximately 20% of the incoming flow) exits the exit pupil also at 3° and enters the signal photodetector 6 (Fig.1, a) [8].

The analyzed human exhaled breath sample is pre-collected in a Tedlar bag 12, which can be hermetically sealed, and is designed for short-term transportation of the analyzed breath sample. The bag 12 is directly connected to a membrane (Nafion) dryer 11, which uses a dual-circuit nitrogen N_2 13 pumping to dry the analyzed sample. The gas cell is vacuumized using vacuum pump 9. The analyzed sample is conveyed by two Mass Flow Controllers 10 while the pressure in the gas cell is constantly monitored (Fig. 1, b) [9].

In this study, exhaled air samples from two groups were examined: healthy volunteers and patients diagnosed with type 1 diabetes. The study was conducted at the Bauman Moscow State Technical University and the Morozovskaya City Children's Clinical Hospital of the DZM. The study protocol was approved by the ethical committee of the State Budget Health Institution "Morozov Children's Clinical Hospital," Department of Health Care of the City of Moscow (Moscow, Russia), № 174, dated January 18, 2022. Each study participant provided consent to process personal data and completed an anamnesis questionnaire.

Human exhaled breath contains more than 1000 volatile biomarker molecules. The reliability of a correct diagnosis of diseases at an early stage is increased in case a sample is analyzed by a set of biomarker molecules. In this study, two biomarkers of type 1 diabetes were examined: acetone and ethanol (Fig. 2).

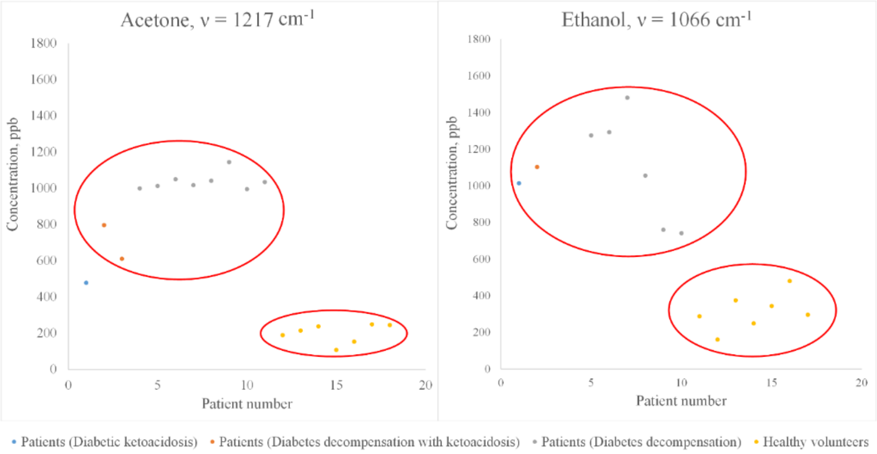

Figure 2: Diagram of concentrations of biomarker substances in healthy volunteers and patients with type 1 diabetes.

It is seen that the concentration of biomarker substances is higher in patients in contrast to healthy volunteers. This indicates the possibility of using the approach for early noninvasive diagnosis of this disease. Modern methods of machine and deep learning allow to classify diseases with high accuracy both by a wide spectral range of the whole and by concentrations of substances-biomarkers [10, 11].

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