Research Journal of Medical Sciences 9 (1): 8-12, 2015
ISSN: 1815-9346

Suggesting a Portable Biosensor for Personal Monitoring and Early Detection of Cardiovascular Diseases Based on Cardiac Markers Measuring in Human Saliva

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Abstract: Many people die every day because of heart attack as they have not timely received the medical help. Some suggestions to develop a miniature device implanted in human mouth for day and night monitoring of patient's saliva structure are represented in this study. The main requirements to the device are indicated. A sensor (for example, implanted in a tooth) periodically takes samples of saliva and analyzes it for the presence of biological markers indicating exacerbation of cardiovascular diseases. The device automatically informs a patient or medical stuff about possible risk. Developing technologies can be used for non-invasive diagnostics of diseases and dysfunctions based on data about biomarkers in the human saliva and provision of early medical intervention.

Key words: Biological markers (biomarkers), cardiac markers, cardiovascular system, biosensor, myocardial infarction, saliva, implant

INTRODUCTION

Nowadays the monitoring of cardiac markers in human blood is an effective mean for acute heart failure detection and prediction of the disease development (Chan and Ng, 2010). In the last years, methods for predicting the development of myocardial infarction are actively developed and some candidate cardiac markers are suggested. They have shown the diagnostic significance (Gluba *et al*., 2012; Park *et al*., 2011). However, all these methods are invasive which is not convenient.

Thus, it is very important to get timely information about the impending heart attack and provide emergency assistance. Moreover, it allows dynamically controlling the patient's state during the course of treatment measures and analysis of treatment effectiveness for further pharmacological correction. One of the most perspective ways is the development of new principles and methods for implanted/unimplanted biosensors functioning. These biosensors allow controlling the parameters of cardiovascular system with the help of biological markers in different biological liquids.

The saliva as a biological liquid is the reach source of information. In the last century, function of the salivary glands and saliva's structure were widely studied. However, for the last 10 years, thanks to high technologies, the saliva has been used for drug and hormone monitoring as an indicator of many diseases and infectious agents.

Metabolism in blood plasma is the main reason for using the saliva as material for somatic pathology diagnostics. A thin layer of epithelial cells (it shares ducts of the salivary glands and systemic bloodstream) provides fast transfer of substances to the saliva through active transportation, diffusion through the cell membrane, passive diffusion in accordance with concentration gradient.

Development of technologies based on polymer chain reactions allows detecting hundreds of biomarkers and dynamics of their concentration. It indicates character and degree of physiological and pathophysiological processes. Thus, information in the saliva becomes very useful and important for scientists (Saiki *et al*., 1985). What is more, the saliva can include proteins and other substances for diagnosis of various diseases (Alekseeva, 1992; Novichikhina, 2002).

This study proposes a device which will provide permanent monitoring of person's saliva to detect biomarkers pointing at approaching heart attack. Control of cardiac markers in the saliva will provide an opportunity of mass monitoring and effective preventive

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measures to reduce risks of vascular diseases without additional work for doctors (Floriano *et al*., 2009; Foley *et al*., 2012). Moreover, biochemical analytical methods together with modern means of information processing will allow considering individual features of a patient, identifying the most significant risk factors and evaluating the effectiveness of preventive and therapeutic measures (Pedrotty *et al*., 2012; Madanieh *et al*., 2013; Volzke *et al*., 2013). Realization of these approaches will be the next step to personalized medicine.

MATERIALS AND METHODS

The diagnosis and prognosis of cardiovascular events is demonstrated in many documents. Some of them described below are the closest analogues of the proposed device.

Mcdevitt *et al*. (2008) suggests some methods for cardiovascular biomarkers detection (Index-Cardiobioindex (CBI) each biomar; combination of biomarkers) to evaluate risks, cardiovascular diseases diagnosis and prognosis. Technical device for diagnostics works as lab-on-chip. The 3 years later (Mcdevitt *et al*. 2012) have patented the new method for express diagnostics of acute myocardial infarction based on the saliva.

Struck and Cleland (2013) suggest the invention for diagnosis and prognosis of chronic heart failure by the way of procalcitonin level detection in biological liquids (blood, serum, plasma, cerebrospinal fluid, saliva, sputum and urine).

In early works (Starikovsky *et al*., 2012; Igor *et al*., 2012; Ivanov *et al*., 2014; Panfilov, 2014), researchers of this study suggested solutions for heart diseases detection and prediction based on saliva analysis. A miniature detector is placed in human mouth as a tooth-implant which can get access to the saliva through small tubes. The feature of a salivary sensor, suggested in these studies is combination with RFID (Radio Frequency Identification) chip, i.e., data from the detector are transmitted to a reader with the help of radio frequency electromagnetic field.

RFID-system consists of two main components: RFID-tag and RFID-reader. RFID-tag is a small device which can have different shape (from a sticker to small grains).

The readers are active elementsused for reading the information from tags (detectors). The tag includes a battery, a metal ring (works as antenna), a microchip (stores the information and controls saliva and saliva sensor analysis) and a box for drugs (Fig. 1). The reader radiates a wave and all tags in the range of this wave

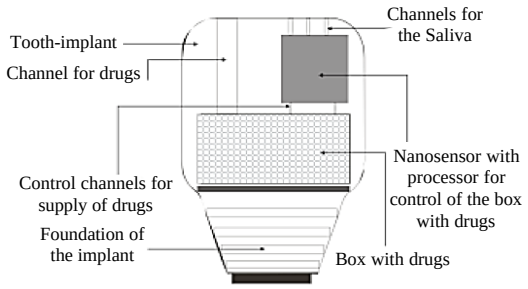

Fig. 1: Tooth-implant scheme

transmit information. RFID-device has a shape of a bracelet with microprocessor. If there is a risk of myocardial infarction, a special signal will be activated and a box with drags will be opened automatically (Igor *et al*., 2012).

The main disadvantage of this technology is limitation of battery power (not >1 month) and cartridge. The cartridge inside the implant should be recharged with new reagents for further analysis forcing the patient go to a dentist every month. The box for drugs is limited. Moreover, there is no opportunity of remote monitoring.

Therefore, it is necessary to do complex research to create the effective means of cardiac markers monitoring. The following tasks should be decided:

- Choice and substantiation a panel of cardiac markers for the most informative diagnostic information, taking into account the individual patient features
- Development of biosensor system for periodic multiparametric monitoring of cardiac markers, including a block for the saliva selection, cassettes for specific detection of cardiac markers on the basis of selective immune interactions and a portable system for registration and analog-to-digital conversion of the test results
- Development of software for transmitting test results, processing these results, detecting levels of cardiac markers, creating and analyzing of databases as a result of massive and periodic examinations

In this study, a miniature device for implanting in human mouth is suggested. The device will detect the concentration of proteins-markers which are specific for myocardial infarct: high-sensitivity troponin, fatty-acid-binding protein, myoglobin, Troponin T for a long period by the way of immunochemiluminescent saliva analysis and will inform a patient and a preventive clinic about the effectiveness of treatment and possible risks.

The developed technical solution suggests independent periodic monitoring of cardiac markers by patients or doctors. It allows timely detecting dangerous risks in the early stage or evaluating the effectiveness of therapy (if it is necessary, the therapy can be changed).

The analysis of study written by different research groups (Novichikhina, 2002; Alekseeva, 1992; Floriano *et al*., 2009; Kazuei *et al*., 2012) on the subject of correlation between different biomarkers in saliva and cardiovascular diseases shows the most informative biomarkers for personalized reliable diagnostics of cardiovascular system:

- Specific cardiac markers (cardiac troponin I, creatine kinase-MB, myoglobin)
- Nonspecific early markers of aseptic inflammation (predictive markers), i.e., C-reactive protein, soluble molecular protein of intracellular adhesion-1, interleukin 1β, fatty-acid-binding protein

Myeloperoxidase, B-natriuretic peptide, MMP-9, IL-6, e-Selectin will be considered as potential candidate markers. Researchers plan to choose optimal combination of cardiac markers for diagnostics and algorithms for making personalized decisions.

RESULTS

The proposed device will operate in the following way. Micro pumps integrated in the implant take the saliva penetrating for further analysis into •microscopic tubes• under pressure. Antibodies with fluorescent marks cover these •microscopic tubes•. The saliva can be taken for analysis with different periodicity every 10 min, once a month and so on. Duringthe interaction with protein markers, these marks produce luminescence with different wavelength which is registered. Obtained information is recorded in RFID-tag and can be read on request.

Detection of biomarkers in the saliva will be implemented based on chemical reactions by the way of immunochemiluminescent analysis. The reaction takes place in different cells of the detector:

- 1: the marker is detected
- 0: the marker is not detected

The further analysis will be implemented by the reader which can be constantly with a patient (for example in a bracelet) or it can be located in special medical equipment in hospitals (in this case, information is transmitted by GPS, Wi-Fi/GPRS).

The scheme of such system includes the tag with integrated sensor, the reader and the analyzer (Fig. 2). The

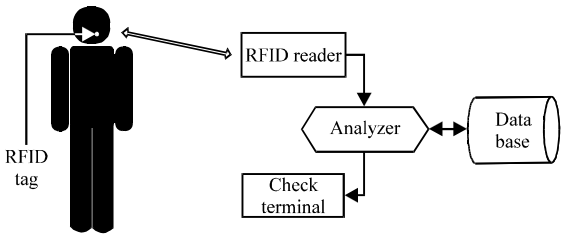

Fig. 2: Scheme of the system using information from miniature sensors

analyzer evaluates a consistence of the saliva based on data about possible protein combinations. Further, the system informs a patient or medical staff about possible risks. Note that the remote system has access to constantly updatable database. Medical staff can detect all possible diseases.

The algorithm of system functioning in both cases (patient has the reader/information is remotely transmitted to the hospitals) is quite simple. RFID-reader sends a request to the mark and receives a response which is converted to PML (programming language) message. Description of the parameters in binary form is stored in Data-tag. A program module analyzes this information and converts data from the sensor to specific protein specifications.

If the device detects certain concentration of biological markers, a patient or medical staff will be informed about risks bythe bracelet. The bracelet displays important information about necessary actions for a patient. Let us designate the main technical characteristics for developing sensory device:

- Volume of reagent should be sufficient for not <500 measurements for each protein-markers
- Frequency of measurements should be in the range of 1 h to 1 week or more (minimal step 1 h)
- Micro pumps should take the saliva (saliva channel should exceed the limits of patient tissues no >0.1 mm)
- Boxes cleaning system should be provided (it is possible not to use cleaning system if boxes for different proteins are separated)
- Necessary to provide the autonomous alarm system (if the allowable level of proteins is exceeded)

DISCUSSION

The device is easy to use, so it can be used out of laboratories or in special medical institutions. Thus, the developed system will rise the effectiveness and timeliness of medical care for patients with cardiovascular comorbidity. Moreover, this system will increase the

quality and rate of cardiovascular diseases diagnostics. That will result in prevention of these diseases and decreasing risks for human life.

The project is aimed at development of original portable detectors for registration of membranous immunochromatographic analysis results. These detectors can be used for various tasks in medical diagnostics, food security and quality monitoring, environmental monitoring.

CONCLUSION

Examination data, systematized with the help of developed software will allow drawing conclusions for different population groups, evaluating the effectiveness of therapeutic measures. The planned complex of measures forms scientific and methodological foundations of a scalable technology for production of portable biosensor system. This system is produced for mass using in order to monitor the state of the cardiovascular system.

In the future, implemented and tested technologies will be used for solving problems in non-invasive diagnostics of diseases and dysfunctions based on data about biomarkers in the human saliva.

ACKNOWLEDGEMENTS

Publication prepared based on the results of scientific research project No. 13-04-12092 "Development of technology for the prediction and early detection of disease based on the analysis of the composition of saliva of a person through implantable bio-sensing means supported by the Russian Foundation for Basic Research (RFBR)".

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