HEARTEN: An integrated mHealth platform for holistic HF management

Georgia S. Karanasiou, Evanthia E. Tripoliti, Member IEEE, Yorgos Goletsis, Member IEEE, Fanis G. Kalatzis, Katerina K. Naka, Roger Fuoco, Wolfram Miekisch, Kostis E. Tzannetis, Stefanos G.Zervos, Joan R. Bausells, Senior Member, IEEE, Abdelhamid Errachid, Dimitrios I. Fotiadis, Senior Member IEEE

***Abstract*— Heart Failure (HF) is a chronic disease with a continuously increasing incidence and prevalence. HF patients need to cope with often re-admissions and advert events. Patient adherence in medication, nutrition and physical activity guidelines becomes a critical factor that can significantly reduce or even prevent re-hospitalizations and improve quality of life. HEARTEN, an integrated mHealth platform for holistic HF management can significantly contribute to effective and efficient (self-) management of the HF patients, through the integration of novel breath and saliva biosensors, sensors and machine learning and knowledge management techniques.**

I. Introduction

Heart Failure (HF) is a chronic disease with a continuously increasing incidence and prevalence. This cardiovascular syndrome is expected to increase the next 25 years, double the incidence rates and increase its prevalence 10 fold from age 60 to age 80 [1]. Currently, 15 million people are living with HF in Europe [2].

In the current clinical practice, the management of HF patients involves different experts. The latter examine the patients in a frequent basis and provide a variety of treatment suggestions and recommendations. Current guidelines of the European Society of Cardiology for HF management call for optimal management in medication, hypertension control, nutrition, weight, physical activity, and adoption of individualized education and counseling that emphasizes self-care [3]. In this framework, patient adherence becomes a critical factor that can significantly reduce or even prevent re-hospitalizations and improve quality of life.

The identification of patients who could be decompensate is valuable in terms of expected hospitalization reduction. Several attempts have been made to recognize the HF patients being at risk by using telemonitoring programs or patient home visits. Some of these programs have been partially effective, however the latter were of excessive cost and were difficult to be implemented in high number of patients [5], [6]. An efficient self-management system, that avoids hospital visits, allows home monitoring and can therefore significantly increase patient adherence and reduce adverse events and re-hospitalities, is essential. Such a system should efficiently integrate and orchestrate all disease management actors, including the patient himself/herself, the doctors, the caregivers, the experts on nutrition, on physical activity, etc.

This is the goal of the HEARTEN platform, an integrated mHealth platform for holistic HF management. In contrast to the previously proposed systems, HEARTEN targets the management of the patients suffering from HF, the empowerment of a healthy lifestyle and the adherence to the medical prescriptions to avoid critical situations. This is achieved by employing novel breath and saliva sensors, that can detect HF related biomarkers without the need for lab tests, and vital sensor monitoring into an intelligent co-operative platform.

II. Material And Methods

HEARTEN platform is an mHealth system which enables the active involvement of several actors in the management of HF patients (healthcare professionals, caregivers, physical activity experts, nutritionists, psychologists). The key actions and components that this integrated platform relies on are: (i) specific biomarkers related to the HF, (ii) a non-invasive approach for detecting the specific HF biomarkers, (iii) development of saliva/breath biosensors and biosensor measurement unit (BMU), (iv) utilization of sensors for monitoring the blood pressure, the body temperature, the physical activity, the heart and respiratory rate, the electrocardiogram activity and the weight, (v) development of communication tools (mobile application, web application) for the involved ecosystem actors, (vi) creation of a software tool (Knowledge Management System) for the data analysis and decision support, based on artificial intelligence and data mining techniques, (vii) development of a Dynamic Patient

G.S. Karanasiou, E.E Tripoliti, and F.G. Kalatzis are with the Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, GR 45110, Ioannina, Greece, (email: etripoliti@gmail.com, g.karanasiou@gmail.com, tkalatz@gmail.com).

Y. Goletsis is with the Dept of Economics, University of Ioannina, GR45110 Ioannina, Greece (e-mail: goletsis@cc.uoi.gr)

K.K. Naka is with the 2nd Department of Cardiology, University of Ioannina, GR 45110, Ioannina, Greece, (email: drkknaka@gmail.com)

R. Fuoco is with the Department of Chemistry and Indurstrial Chemistry, University of Pisa, Pisa, Italy (email: roger.fuoco@unipi.it, fabio.difrancesco@unipi.it)

W. Miekisch is with the Department of Anaesthesia and Intensive Care Medicine, University Medical Center Rostock, Rostock, Germany (email: jochen.schubert@uni-rostock.de, wolfram.miekisch@uni-rostock.de)

K. E. Tzaxettis is with AppART SA, GR 15343, Athens, Greece (email: k.tzanettis@app-art.gr)

S. G. Zervos is with BIOAXIS healthcare, Athens, Greece (email: szervos@bioaxis.com)

J.R. Bausells is with the Instituto de Microelectrónica de Barcelona, IMB-CNM (CSIC), Campus UAB, 08193 Bellaterra, Spain (email: joan.bausells@imb-cnm.csic.es)

A. Errachid. is with the Université de Lyon, Institut de Sciences Analytiques (ISA) – UMR 5280, 5 rue de la Doua, 69100 Villeurbanne, France (e-mail: abdelhamid.errachid@univ-lyon1.fr)

D.I. Fotiadis is with the Department of Biomedical Research, Institute of Molecular Biology and Biotechnology, FORTH, Ioannina, Greece and Department of Materials Science, Unit of Medical Technology and Intelligent Information Systems, Ioannina, Greece (e-mail: fotiadis@cc.uoi.gr)

Communication Protocol (DynPCP) for providing real-time monitoring, notifications and reminders, overcoming the barrier of non-personalized patient management and treatment.

A. *Identification of /breath/saliva biomarkers*

The clinical status of a HF patient can be evaluated by biomarkers determination in biological specimens [7]. Non-conventional fluids, such as breath and saliva, represent easy, painless and non-invasive ways of mirroring physiological and pathophysiological conditions in the whole body [8]. Volatile organic compounds (VOCs) are produced during biochemical pathways in cells, transported via the bloodstream to the lung and exhaled within minutes after their generation [9]. Saliva contains numerous biological molecules which are directly related to the major physiological systems or are products of their activity [10]. The possibility to exploit such fluids to obtain significant information using easy, reliable and cost effective measurements at the point of care, can be a useful and effective tool for monitoring HF status. Based on the available data from previous studies reported in literature [11], a set of potential biomarker compounds have been selected and evaluated during the HEARTEN project.

For the breath biomarkers analysis, a three step process was followed: (i) setup and quality control of adequate analytical methods for the reliable identification and quantitation of the selected VOCs in trace (nmol/L) concentrations, (ii) in depth analysis on potential confounding variables onto marker concentrations in the patient cohort, (iii) definition of concentration ranges and variations of selected biomarkers in patients with HF in comparison to normal/ healthy patient cohorts.

Regarding the saliva biomarker analysis, a standard operating procedure was followed. Briefly, saliva was collected by asking the patient to roll a Salivette polyester swab in mouth for 2 minutes. After collection, salivary pH was measured by two independent observers using a Pehanon narrow range (6.0<pH<8.1) pH paper strips (Macherey Nagel, Germany) with a resolution of 0.3 pH units. The salivary flow rate (grams per minute) was calculated from the ratio between the weight difference of the sampling device before and after sampling and the collection time. The collection procedure and pH measurements were always completed in less than 10 minutes. The saliva was recovered by centrifugation of the swabs at 3000 rpm for 5 minutes at room temperature and then stored in a PCR tubes at –80°C until use.

A large number of sensitive and selective analytical techniques: (i) immunoassay and spectrophotometric methods, liquid chromatography with spectrophotometric, fluorescence or mass spectrometric detector, and (ii) thermal desorption, gas chromatography coupled with mass spectrometry have been used for the analysis of saliva and breath biomarkers, respectively. The results highlighted the potential role of acetone in breath, as well as cortisol and Tumor Necrosis Factor-alpha in saliva for monitoring the health conditions of HF patients (Table I).

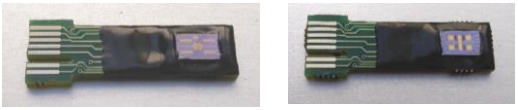
TABLE I. BREATH AND SALIVA BIOMARKERS INDICATIVE OF HF CLINICAL STATUS.

Biomarkers	***Saliva***	***Breath***
	TNF-a, Cortisol	Acetone

B. *Saliva/breath biosensors*

The developed biosensors can quantitatively measure the concentration of biomarkers in breath and saliva (Fig. 1).

Figure 1 Packaged breath (left) and saliva (right) biosensors.



i. Breath Biosensor

The operational principle is the measurement of conductance changes in a sensitive layer due to the presence of VOCs in breath. The conductance changes are measured by a transducer consisting on interdigitated metal microelectrodes on a silicon chip. The specifications for the silicon chips were: (i) silicon chip size: 7300 x 4100 μm, (ii) packaging of the biosensor chips: the silicon chips are bonded to a standard printed circuit board (PCB). Electrical connections are made by standard wire bonding between the pads on the chip and the PCB. A protective epoxy resist is added to protect the wire bonding interconnects. The size of the PCBs is around 3 cm x 1 cm, with a thickness of 1-2 mm. The biosensor chips are fabricated in 100 mm diameter silicon wafers. The sequence of process steps includes one oxidation, three metal depositions and four photolithography and etching processes. The breath biosensor has been successfully fabricated and packaged, reaching good detectability that can be performed measuring directly in breath. The evaluation of the cross-reactivity with the other gases has been demonstrated, showing low cross-reaction between them.

ii. Saliva Biosensors

The objective of the saliva biosensors is the quantitative measurement of the concentration of HF biomarkers in saliva. The operational principle is the measurement of electrochemical parameters on metal microelectrodes. The working electrode has specific receptors immobilized on its surface to detect a biomarker. The specifications for the silicon chips are the same as for the breath biosensor, while the structure of the chips is different. The saliva biosensor includes a metal working microelectrode, a counter electrode and a pseudo-reference electrode. The process for the fabrication of the saliva biosensor is essentially identical to that of the breath biosensor, however the latter has different device designs.

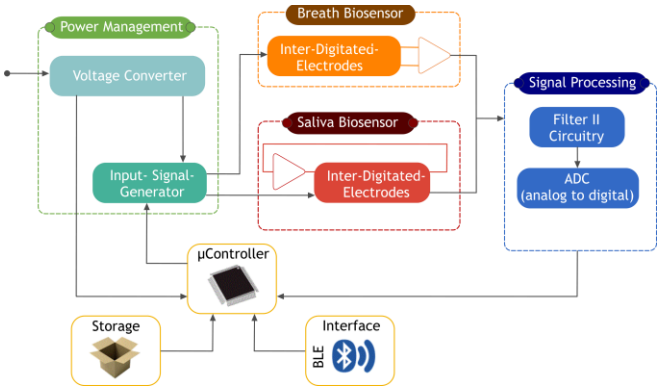
Electrochemical characterisation of the individual cytokines based on gold microelectrodes were analysed by electrochemical impedance spectroscopy (EIS). The inflammatory response of recombinant human proteins TNF-α and cortisol were measured in Phosphate buffered saline (PBS). Fabrication of the biosensor firstly ensures that a working prototype can be assembled, and demonstrated that the BioMEMs based on silicon is achievable. Secondly with EIS measurements made in PBS, it is proven that the microelectrodes can detect before analysis with real samples. The saliva biosensors were highly sensitive to the corresponding cytokines and no interference with others

cytokines was observed and satisfied recoveries were obtained by using standard addition method.

C. Biosensors measurement unit

The biosensors are connected to the Biosensor Measurement Unit (BMU), which provides the following functions: (i) electrical power to operate the biosensors, (ii) interface circuits for the readout of the output signal of the biosensors (analog-to-digital signal conversion), (iii) digital interface with the smartphones running the HEARTEN mHealth apps, which also controls the unit. Data is transferred between the BMU and the smartphones. The communication is based on the Bluetooth Low Energy (BLE) standard. The diagram of the hardware of the complete BMU is presented in Fig. 2.

Figure 2 BMU overall architecture.



D. Sensors and their integration

Apart from the biosensors, specific commercial, medical certified sensors have been integrated to monitor: (i) the blood pressure, (ii) the heart rate and possible arrhythmias along with the respiratory rate, (iii) body temperature, (iv) the body weight and other related features (body fat percentage, skeletal muscle percentage, body mass index, resting metabolism, body age), etc. and, (v) the physical activity. The measurements are pushed from the sensors to the HEARTEN application through the respective APIs and from there they are pushed automatically to the Cloud platform for storage.

E. Mobile Application and Communication Tools

The communication between the HEARTEN ecosystems actors is enabled through the mobile application (Android and iOS platforms are supported). Data coming from the sensors and biosensors through the bluetooth channel are collected by the mobile phone, aggregated and sent for storage to the cloud platform. For the communication layer, the Bluetooth Health API is used, which implements the Bluetooth Heath Profile. This profile is a wireless interface specification, which is designed to facilitate transmission and reception of Medical Device Data, using the ISO/IEEE 11073-20601 Data Exchange Specification protocol.

F. Knowledge Management System

The HEARTEN Knowledge Management System (KMS) provides multiple functionalities to the ecosystem actors. It is a valuable tool that includes advanced data-driven techniques incorporated with expert-knowledge techniques towards effectively assessing the HF patient condition and enhancing patient adherence. The KMS enables users with advanced expert-knowledge techniques to effectively assess and exploit real patient data [12], [13].

The set of the different modules of the KMS were identified by studying the nature of the HF disease, the requirements of the users and the multi-disciplinary data that are available by the clinical sides. The development of each module is accomplished as a separate subsystem of the KMS with its own interface and RESTfull webservices. The KMS modules are using their own computational or algorithmic data processing to provide: (i) measurable results and, (ii) knowledge to the expert users. Knowledge extraction is performed by applying data mining methods on the collected data of the pilot phases.

The HEARTEN KMS consists of the following modules: (i) NYHA class module, which detects the change of patient condition, (ii) Association module, which provides the experts the ability to perform profound analysis and research, originated from patient data and to discover hidden associations, (iii) Statistics module, which allows the experts to apply tools for finding and explaining dependencies that are observed frequently within the collected data and perform hypotheses testing, (iv) Adherence risk module, which estimates the adherence profile of the patient and allows the experts to identify patients risking to be non-adherent (v) Treatment adherence module, which evaluates whether the patient is adherent or not to the guidelines provided by the experts with regard to the medication, the diet and the physical activity, (vi) Score module, which calculates several acknowledged risk scores (vii) Event prediction module, which notifies the experts in case of expected potential onset of adverse events (relapses and mortality), (ix) Alerting mechanism module, which delivers critical alerts and messages regarding the patients' condition when needed.

The KMS was evaluated using a dataset of 72 patients collected by the clinical center of the Universita Di Pisa (UNIPI), the Servicio Andaluz de Salud (SAS) and the 2nd Department of Cardiology, University Hospital of Ioannina (UHI). The features collected for each patient can be grouped to the following categories: (i) General Information, (ii) Allergies, (iii) Medical Condition, (iv) Drugs, (v) Clinical Examinations, (vi) Adherence, (vii) Score, (viii) Sensor data, (ix) Biomarkers.

For the NYHA Class, the Adherence Risk, the Event prediction and the Treatment Adherence (Medication adherence sub-module), a three stage approach was followed; preprocessing, feature selection and classification. In the first stage, features with more than 60% of missing values are excluded, since imputation of missing values cannot be applied due to the nature of the data. In addition, features with minor distribution of values are removed. In the second stage, the Wrapper approach is used in combination with the classifiers that are applied in the third stage. For the classification, nine classifiers are tested [12]: (i) Random Forests, (ii) Logistic Model Trees, (iii) J48, (iv) Rotation Forest, (v) Support Vector Machines, (vi) Radial Basis Function Network, (vii) Bayesian Network, (viii) Naïve Bayes, (ix) Simple CART. The classifiers are combined with resampling techniques, when the number of classes is unbalanced. Resampling is performed only during the training of the model and not during the test for avoiding bias

of classification results. The results of the aforementioned classification models, in terms of accuracy, are presented in Table II.

TABLE II. RESULTS OF THE KMS MODULES

Module	*Accuracy*	*Classifier*
NYHA Class	96%	J48
Adherence risk	84%	Bayes
Event prediction	77%	Rotation Forest
Treatment adherence	75%	J48

H. Dynamic Patient Communication Protocol

The DynPCP uses predefined Patient Communication Protocols (PCPs), the outcomes of KMS and the patient's data, and generates patient specific messages and notifications which are provided to the corresponding actors of the HEARTEN platform. The messages and notifications are sent either as PUSH notifications to the HEARTEN mobile application (via the Google Firebase platform) or as SMS texts to the recipients' mobile phone. DynPCP monitors the delivery and read status of each message, notification and alert. The DynPCP is developed on PHP framework Symfony version 3 and it is installed on an Nginx web server running on the dedicated Virtual Machine for DynPCP. DynPCP MySQL database is installed on HEARTEN's Database Server. Due to Symfony PHP framework development process, DynPCP is consisted by bundles, which can be treated as system modules. Each module is connected with a specific context that most of the times is related to one or more database tables which allows DynPCP to abstract the needs to interact with the database in a specific context.

I. Cloud infrastructure and Databases

The HEARTEN platform is hosted in a cloud infrastructure. The technology that was selected for the development of all systems and services can be hosted in any cloud infrastructure. Each server of the HEARTEN platform resides in a Virtual Machine (VM) thus the final system architecture is composed of 6 VMs as follows: (i) the KMS server, (ii) the Web Application server, (iii) the DynPCP server, (iv) the MySQL database server, (v) the MongoDB server and (vi) the REST server. Communication between the VMs is private and only the KMS, the DynPCP, the Web Application and the REST services can be publicly accessed through secure SSL/TLS protocol.

J. Platform evaluation

In the context of HEARTEN project, an ongoing pilot study is performed, following a specific clinical protocol. The objective of the pilot study is to assess the impact of the HEARTEN platform on the HF patients by evaluating life quality indicators and health-behavioral changes. The estimated number of patients to be enrolled is 160; half of the patients are included in the intervention group and half in the control group. The pilot study will estimate improvements in patient's health, improvements in term of re-hospitalizations, in overall patient quality of live and in hospital care costs.

III. CONCLUSIONS

HEARTEN platform approaches the issue of HF management and adherence by detecting saliva and breath biomarkers indicative of HF progress, developing and validating non-invasive breath/saliva biosensors, monitoring vital signals and measurements, creating an mHealth application for the patient and the ecosystem actors, towards identifying trends and patterns of non-adherence through the utilisation of a KMS.

HEARTEN platform is a supportive and interactive ecosystem for holistic HF management. The creation of this collaborative environment enables the HF patients to become co-producers of their disease management from their home and the ecosystem actors to develop a co-production of a treatment model targeting non-adherent HF patients.

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