Personalized Evaluation of Life-threatening Conditions in Chronic Kidney Disease Patients: The Concept of Wearable Technology and Case Analysis

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Abstract: The progressive aging of society results in a one-third increase in mortality rates of chronic kidney disease (CKD) patients over the past decade. In the end stage of CKD, 40% of deaths are sudden deaths due to cardiac arrhythmias precipitated by electrolyte imbalance. Unfortunately, there is a lack of technology for unobtrusive long-term monitoring of life-threatening conditions, leading to limited knowledge on arrhythmia characteristics and their relationship with complications. This paper presents a wearable technology prototype to monitor CKD patients between subsequent dialysis procedures. The proposed technology enables at-home monitoring of electrolyte fluctuations and detection of cardiac arrhythmias, such as ventricular tachycardia and extreme bradycardia. A patient uses a wearable wrist-worn device to record continuous photoplethysmogram and intermittent electrocardiogram signals together with a smart device, such as a tablet or a smartphone, to enter meals and medications that may alter electrolyte levels. The application of the proposed wearable technology is demonstrated in a case analysis. The developed wearable technology for monitoring CKD patients in a home environment can be valuable for identifying patients susceptible to dangerous arrhythmias due to electrolyte imbalance.

1 INTRODUCTION

Chronic kidney disease (CKD) affects 13.4% of the population and is especially common among older individuals (>65 years), leading to a one-third increase in mortality rates over the past decade (Wang et al., 2016). In the end stage of CKD, 40% of all deaths are sudden deaths due to cardiac arrhythmias, namely, ventricular tachycardia and extreme bradycardia (Kalra et al., 2018; Saran et al., 2019). While ventricular tachycardia that eventually progresses to more advanced stages (ventricular flutter, ventricular fibrillation) often precedes sudden cardiac death, recent research has shown that extreme bradycardia leading to asystole is also a common cause in CKD patients (Wong et al., 2015b; Yamaguchi et al., 2020). Thus, it is crucial to detect initial life-threatening arrhythmia episodes as soon as possible to avoid a fatal outcome. Unfortunately, the existing devices for long-term continuous arrhythmia monitoring are either invasive (implanted devices) or inconvenient for the patient (Holter monitors, ECG patches). Furthermore, it is often unclear what factors contribute most to arrhythmia initiation in a particular CKD patient.

The end-stage CKD is often treated with thrice-weekly hemodialysis (HD), increasing the interval between the procedures 1.5 times during the weekend. About 50% of life-threatening arrhythmias occur on the last day of the long interval, linked to increased volume of bodily fluids and electrolyte imbalance (Wong et al., 2015a), with potassium being the most suspected arrhythmogenic electrolyte (El-Sherif and Turitto, 2011). Electrolyte imbalance is common and often asymptomatic in CKD patients (Brunelli et al., 2017), therefore gathering information on elec-

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trolyte fluctuations between HD procedures is of importance for restoring the normal balance before the onset of arrhythmias. Unfortunately, the only clinically accepted method for evaluating electrolyte balance is an invasive blood test, which cannot be performed at home.

Noninvasive assessment of electrolyte imbalance spawns scientific research and technological innovation. Electrolyte imbalance affects cardiac electrical function and can be reflected in the electrocardiogram (ECG). Based on this property, researchers at Mayo Clinic (USA) are developing an ECG analysis-based algorithm for the assessment of serum potassium levels (Attia et al., 2016), whereas Medtronic (USA) has patented the method for use in implantable devices (Soykan et al., 2016).

An implantable cardioverter-defibrillator is the primary treatment against sudden death due to ventricular tachycardia, while a pacemaker is prescribed for bradycardia management. However, the usage of implantable devices for sudden death prevention is restricted by various factors, mainly the significant cost of the invasive device itself and implantation procedures, unclear criteria for selection of CKD patients for implantation, and their predisposition to infection (Boriani et al., 2014). Since implantable devices are the only technology providing convenient long-term monitoring of arrhythmias, such restriction vastly limits the knowledge of arrhythmia characteristics and their relationship with complications.

The growing interest in wearable biosensors inspires scientists to search for more convenient means of arrhythmia monitoring. Detection of atrial fibrillation in a photoplethysmogram (PPG) has already demonstrated promising results (Bonomi et al., 2018; Sološenko et al., 2019; Perez et al., 2019; Pereira et al., 2020). The potential of wrist-worn devices capable of detecting atrial fibrillation will likely encourage the development of detectors for different arrhythmia types. Nevertheless, thus far, only a few attempts to detect life-threatening arrhythmias in PPG have been published (Bonomi et al., 2017; Paliakaitė et al., 2021).

This paper presents the concept of wearable technology for a personalized evaluation of life-threatening conditions in CKD patients undergoing HD. Electrolyte balance is usually altered prior to HD and normalizes after the procedure. Accordingly, we hypothesize that the corresponding differences in ECG morphology parameters are related to the patient's electrolyte balance before and after HD. We also hypothesize that electrolyte fluctuations may cause life-threatening arrhythmias in some patients. The application of the proposed wearable technology is illustrated with a case study involving a CKD patient with electrolyte fluctuations and ventricular arrhythmias.

2 METHODS

2.1 The Components of Wearable Technology

Figure 1 shows a prototype of a wearable technology for CKD patient monitoring. A patient uses a wearable device for recording continuous PPG and intermittent ECG signals. Also, the patient can enter meals and medications, which may alter electrolyte levels, using a smart device (tablet or smartphone) with a dedicated software.

The technology ensures wearing comfort since biosignal sensors are integrated into a wrist-worn device. By using the proposed technology, electrolyte fluctuations are monitored relying on a single-lead short-term (1-min) ECG. The use of wires is avoided by integrating the ECG electrodes into the device – one at the bottom, in contact with the skin, and the other on the top. The ECG is recorded by touching the top electrode with a finger of the opposite hand. Meanwhile, extreme bradycardia and ventricular tachycardia are detected by analyzing a PPG signal, acquired using the same device. In case life-threatening arrhythmia is detected, the patient is informed by the device (e.g., by vibration) to touch the integrated biopotential electrode. The recorded short-term ECG can be sent to the physician for arrhythmia type confirmation.

After the recording period, e.g., interdialytic interval, the patient connects the wearable device to the smart device where the app automatically opens the most recent GDF (general data format) file and sends it via HTTPS to a web API hosted on the server. The web API is implemented in the Haskell programming language using the Servant framework. The database (PostgreSQL) stores data about meals and medications together with timestamps and performs synchronization to the signal files. After each data file is received, the MATLAB-based processing server, situated in a high-performance computing workstation equipped with a GPU, processes the file and creates a report that includes electrolyte estimates in relation to detected extreme bradycardia and tachycardia episodes. Then the report is saved in the database and emailed to the physician responsible for the patient. Each of the components are described in more detail below.

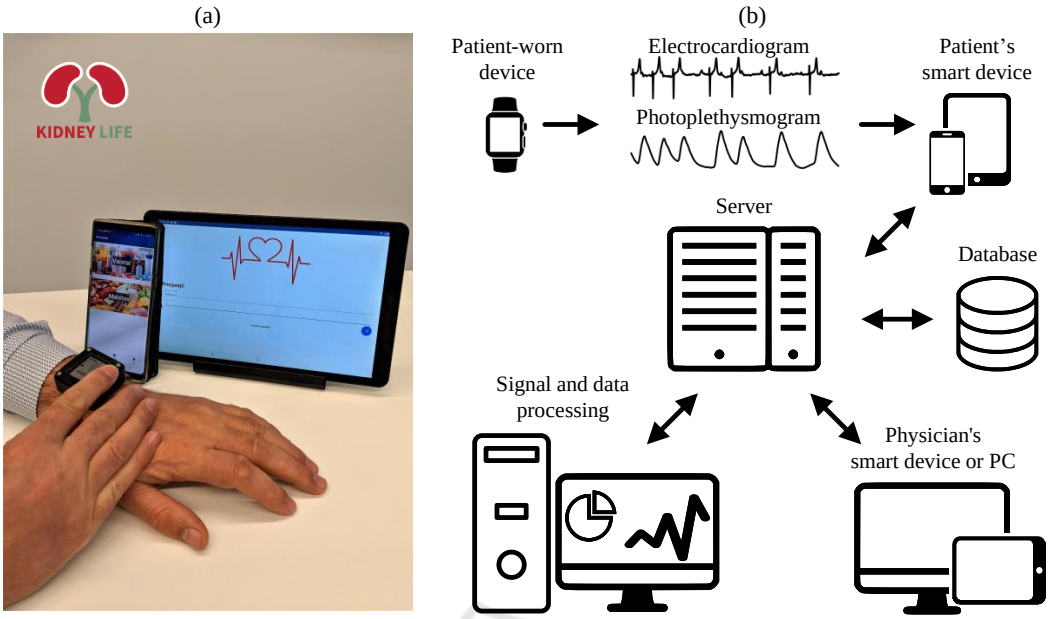

Figure 1: (a) A prototype of a wrist-worn device for arrhythmia detection and monitoring of electrolyte fluctuations together with a smartphone and a tablet for entering meals and medications. Note Lithuanian interface of an application adapted for local patients. (b) A basic system architecture of a technology for CKD patient monitoring. Icons used from www.onlinewebfonts.com/icon, licensed by CC BY 3.0.

2.2 Monitoring of Electrolyte Fluctuations

Electrolyte fluctuations can be recognized in ECG since anomalous electrolyte levels affect the cardiac electrical conduction. For instance, potassium fluctuations usually alter the T-wave morphology, whereas calcium precipitates changes in the ST-segment duration (Surawicz, 1967). To evaluate potassium-induced T-wave morphology changes in HD patients, we developed a model-based parameter, θ_δ, that evaluates global changes in T-wave morphology (Rodrigues et al., 2020). The T-wave, composed of two slopes—upward and downward—is parameterized using a composite model comprising one Gaussian and one lognormal functions to characterize each individual slope. θ_δ combines two parameters: *(i)* the angle θ (in °) between the gradients of upward and downward slopes (Figure 2a-b); and *(ii)* the temporal displacement δ (in s) between the modes of the lognormal and Gaussian functions (Figure 2c-d). The principle of θ_δ is as follows. As potassium level rises above the normal level, the T-wave tends to become more peaked and decreases in duration. The angle θ quantifies variations in T-wave peakedness, whereas δ measures changes in T-wave elongation. θ_δ amplifies the response of θ and δ to potassium fluctuations and is estimated as:

$$\theta_\delta = -\log_{10}(\theta \cdot \delta). \quad (1)$$

The logarithm expands the dynamic range and ensures a positive correlation of θ_δ with potassium fluctuations. θ_δ is estimated from an averaged heartbeat representative of a defined short period. For this paper, we used a sliding window of 90 s with a 20 s overlap to segment a single-lead ECG. The ECG signal is preprocessed similarly to our previous study (Rodrigues et al., 2020).

2.3 Detection of Life-threatening Arrhythmias

Extreme bradycardia is defined as at least 5 consecutive beats at a heart rate lower than 40 bpm, and ventricular tachycardia is defined as at least 5 consecutive ventricular beats at a heart rate higher than 120 bpm. Following these definitions, life-threatening arrhythmias are detected in pulse rate series, obtained from the peak-to-peak intervals where the occurrence times of the PPG pulses are determined using a peak detector similar to the one described in (Aboy et al., 2005). To avoid false alarms, the threshold-based life-threatening arrhythmia detector (Paliakaitė et al., 2021) is supplemented with a signal quality index proposed in (Sološenko et al., 2019). A PPG pulse is considered to be of high quality if maximum correlation coefficient between the pulse and a template pulse exceeds 0.8. Hence, an episode of a life-threatening arrhythmia is detected only if at least 5 consecu-

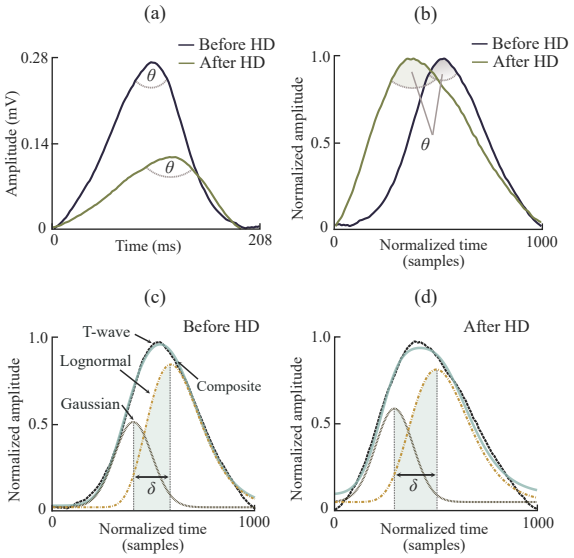

Figure 2: Concept of θ_δ calculation: (a) original T-waves before and after HD; (b) variation of θ in amplitude normalized T-waves before and after HD. Variation of δ: (c) before and (d) after HD. Potassium decreased from 5.5 mmol/L to 3.2 mmol/L.

tive high-quality pulses satisfies one of the above-described criteria for the pulse rate. In the case described in this paper, a reference synchronously acquired continuous ECG signal was used to confirm the arrhythmia episodes detected in the PPG signal.

3 CASE ANALYSIS

3.1 Patient Description

Signals were recorded at the hospital of Lithuanian University of Health Sciences Kaunas Clinics from a 79-year-old male patient, with a body-mass index 30.1 kg/m^2, hospitalized due to arteriovenous fistula thrombosis. Chronic kidney inflammation (pyelonephritis) is a suspected unconfirmed cause of CKD in this patient. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Kaunas Region Biomedical Research Ethics Committee (No. BE-2-43). The patient gave written informed consent to participate in the study.

3.2 Data Analysis

Figure 3 shows the variation of θ_δ and blood pressure throughout the monitoring period. Nine extreme bradycardia episodes lasting for 6–10 heartbeats were detected in the continuous PPG signal; however, three could not be verified due to the loss of reference ECG signal. The PPG-based algorithm also produced three false-positive arrhythmia episodes, verified by simultaneously acquired ECG: one of extreme bradycardia and two of ventricular tachycardia.

Throughout the monitoring period, systolic and diastolic blood pressures were 121.8 ± 14.3 mmHg and 77.6 ± 10.0 mmHg during the day, and 131.3 ± 18.5 mmHg and 79.5 ± 8.6 mmHg during the night. Curiously, blood pressure was elevated during bradycardia episodes, and there was no clear indication of nocturnal dipping.

Parameter θ_δ increased during HD, suggesting an unlikely increment of potassium level, which cannot be confirmed since no blood samples were acquired. Compared to other periods, the ECG signal quality decreased during HD, which can disturb T-wave morphology, leading to estimation errors of θ_δ. We also verified that the patient displayed unusual T-waves throughout HD upon further inspection. As electrolyte levels get corrected, T-waves tend to flatten. Instead, the patient exhibited peaked and symmetrical T-waves, typical of hyperkalemia and, perhaps, with concomitant metabolic acidosis. Prolonged ST segments are also visible throughout the recording, hinting at possible hypocalcemia.

θ_δ varies coincidently with the expected potassium circadian variation, decreasing from 09:00 to 11:00 and from 15:00 to 21:00 and rising from 00:00 to 09:00. Although θ_δ decreased during the night, θ_δ likely reacted to altered T-wave morphology due to body position changes.

4 DISCUSSION

The proposed technology for in-home use is beneficial for investigating electrolyte fluctuations as possible instigators of life-threatening arrhythmias. The technology has both scientific and clinical significance. The acquired knowledge of arrhythmia occurrence, progression, temporal distribution, and causal relationship with electrolyte fluctuations could be used to predict the course of the disease, personalize medication, and assess the risk of sudden death for individual patients.

Despite the recently spurred scientific interest in non-invasive monitoring of electrolyte fluctuations, most research focuses predominantly on the development of potassium biomarkers (Rodrigues et al., 2020; Palmieri et al., 2021; Attia et al., 2016; Corsi et al., 2017), neglecting, thus far, calcium, bicarbonate, and magnesium. While potassium is a well-

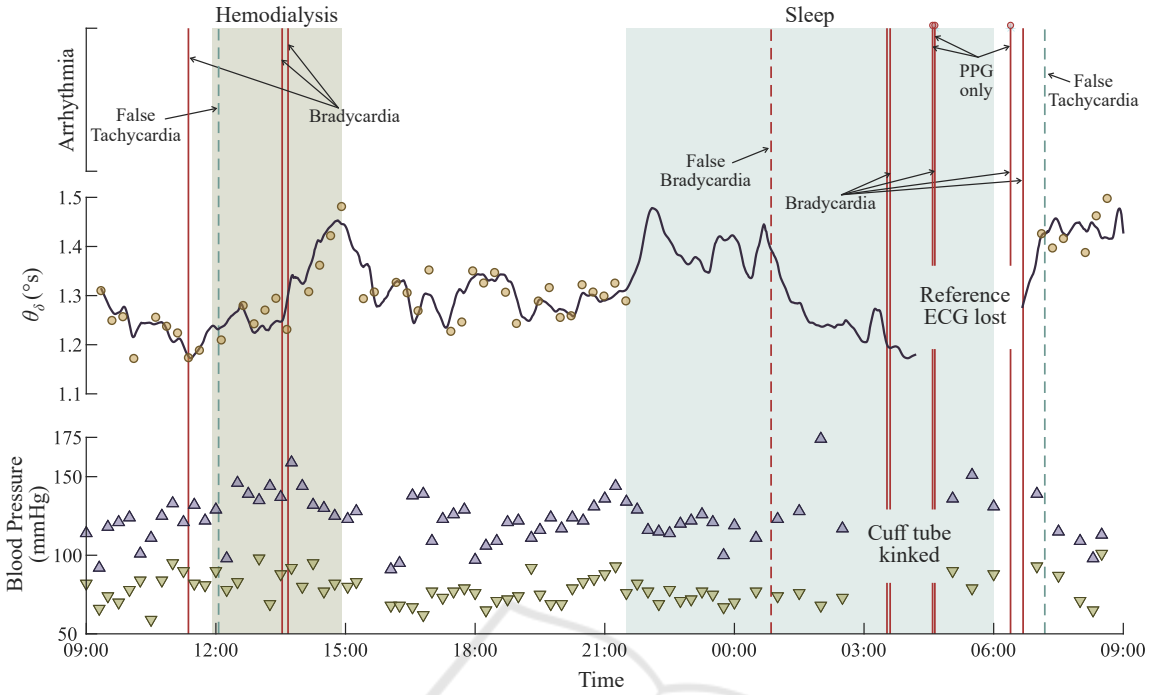

Figure 3: Variation of θ_δ and blood pressure throughout the monitoring period. Vertical lines indicate detected arrhythmia episodes: solid red – true bradycardia, dashed red – false bradycardia, dashed blue – false tachycardia. A solid black curve is a moving average of θ_δ estimated from all 90 s segments in a single-lead continuous ECG, and dots are the estimated values of θ_δ every 15 min. Upward- and downward-pointing triangles indicate systolic and diastolic blood pressure values from an ambulatory monitor, respectively.

known arrhythmogenic agent in CKD patients, the entire panel of blood electrolyte levels is necessary to understand what electrolyte combinations provoke life-threatening arrhythmias. Even from a technological point of view, any algorithm for assessing blood potassium level needs to consider the remaining electrolytes. Concomitant electrolyte imbalance (e.g., hyperkalemia and metabolic acidosis) can alter the T-wave morphology differently than isolated potassium abnormalities (Severi et al., 2002), thus influencing the results of any developed biomarker (Rodrigues et al., 2020).

Albeit unconfirmed with blood tests, the presented case study illustrates the necessity of monitoring all electrolytes instead of solely potassium. In our previous study, unexpected variations of θ_δ were found in patients with severe hypocalcemia and pH imbalance (Rodrigues et al., 2020), which we suspect the patient of this case study may have had due to a prolonged ST-segment and peaked T-waves. Hypocalcemia decreases cardiac contractility and is a likely trigger of bradycardia (Loewe et al., 2019; Yamaguchi et al., 2020). The unanticipated variation of θ_δ observed in this case study challenges us to question our knowledge regarding the arrhythmogenic potential of different electrolyte fluctuations. It further substantiates the need to continue developing technologies for ambulatory assessment of electrolyte fluctuations that take into account various electrolytes.

The rapid development of electronics opened the possibility to acquire a short-term ECG by employing a wrist-worn device with two integrated biopotential electrodes. Thus far, such technological principle is used only for personal purposes, such as obtaining an instantaneous heart rate, without analyzing ECG morphology which is unsurprising since comprehensive ECG analysis requires good signal quality and computational resources. In principle, the ECG signal quality can be assessed in real-time with an indication for the patient to make some contact adjustments. However, real-time morphology analysis is more challenging and still demands offline processing, as preferred in the presented case study. Signal quality issues are also particularly common in PPG acquisition. While overlooked noise and artifacts may produce false arrhythmia alarms, especially tachycardia, eliminated poor-quality segments of PPG signal may result in missed arrhythmia episodes (Paliakaitė et al., 2021). This issue should not be overlooked when evaluating the relationship between electrolyte fluctuations and life-threatening arrhythmias.

5 FUTURE WORK

The proposed wearable technology could serve for obtaining knowledge regarding causal relationships of electrolyte fluctuations with arrhythmia development and sudden cardiac death. Algorithms for identification of the causal direction, coupling delay, and causal chain relations from time series could be applied (Huang et al., 2020).

Information on the occurrence of life-threatening conditions is valuable for developing a system for personalized decision support, for instance, implemented as a deep recurrent neural network based on long short-term memory, such as described in (Kwon et al., 2018). The neural network can consist of three time series inputs involving information on signal quality, electrolyte fluctuations, and temporal distribution of arrhythmia episodes. Temporal distribution that carries important information about arrhythmia progression can be characterized using a model-based approach (Henriksson et al., 2021). The output of the personalized decision support system may be a sudden cardiac death risk score.

The proposed framework for personalized decision support can potentially be adapted for other groups with an increased risk of electrolyte fluctuations and life-threatening arrhythmias, e.g., those with heart failure or receiving chemotherapy treatment.

6 CONCLUSION

An unobtrusive noninvasive technology for monitoring electrolyte fluctuations and detecting ventricular tachycardia and extreme bradycardia in a home environment can be of value for identifying patients susceptible to dangerous arrhythmias precipitated by electrolyte imbalance.

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