Analysis of Nonlinear T wave Dynamics by Lyapunov Exponents for Serum Potassium Monitoring in End-Stage Renal Disease Patients

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Abstract

Non-invasive estimation of serum potassium, $[K^+]$, is of major importance to prevent associated risks, but current ambulatory estimation methods are limited. We investigated changes in maximum Lyapunov exponent (λ_{max}) of T waves in electrocardiograms (ECGs) from 15 end-stage renal disease (ESRD) patients undergoing hemodialysis (HD) and assessed the relationship with $[K^+]$. ECGs from 22 simulated transmural ventricular fibers were additionally calculated. In ESRD patients, λ_{max} took the largest values at the beginning and end of the HD session, corresponding to the highest and lowest $[K^+]$ values. The median correlation coefficient over patients between the change in λ_{max} and $[K^+]$ was 0.92 and decreased to 0.74 after controlling for the effects of $[Ca^{2+}]$ and heart rate. These associations were, however, highly patient-dependent. Both the strength and variability of the λ_{max}-$[K^+]$ relationship was reproduced in the simulations, with the variability explained by differences in transmural heterogeneities: 10% variations in the proportion of epicardial and midmyocardial cells lead to more than 10% and 8% changes in λ_{max}, respectively. In conclusion, changes in the nonlinear dynamics of the ECG T waves can be related to $[K^+]$ variations in ESRD patients, despite the high inter-individual variability.

1. Introduction

Around 10% of the worldwide population are affected by chronic kidney disease. The economic cost, increased mortality risk and decreased quality of life associated with this disease are remarkably high [1]. At the final stage, so called end-stage renal disease (ESRD), patients present an increasingly impaired ability to maintain potassium homeostasis. Serum potassium levels ($[K^+]$) outside normal ranges, in the form of hypokalemia or hyperkalemia, increase the risk for life-threatening arrhythmias and sudden cardiac death [2].

Investigating the effects of $[K^+]$ variations on the electrical activity of the heart could allow deriving electrocardiogram (ECG)-based markers for continuous monitoring of $[K^+]$, which would facilitate the delivery of more timely therapies for ESRD patients. Variations in $[K^+]$ levels have been indeed shown to affect depolarization and repolarization features of the ECG [2]. Most of the investigated ECG markers in the literature are aimed at characterizing T wave properties [3]. However, such properties commonly refer to a specific time point or small portion of the T wave and are, thus, not necessarily representative of the whole T wave morphology changes in response to varying $[K^+]$.

In previous studies, we characterized changes in the T wave shape at varying $[K^+]$ by using time-warping techniques over clinical and simulated ECGs [4, 5]. The linear but also the nonlinear components of the measured warping markers showed a strong relationship with $[K^+]$. Based on those results, we hypothesized that evaluation of nonlinear dynamics of the T wave, as measured by other techniques like the maximum Lyapunov exponent (λ_{max}), could provide relevant information for $[K^+]$ estimation. We quantified λ_{max} over ECGs of ESRD patients during a hemodialysis (HD) session, where large $[K^+]$ changes are expected to occur. Also, we simulated a set of ventricular fibers covering a wide range of transmural heterogeneities and we calculated pseudo-ECGs (pECGs) at different $[K^+]$ levels. After confirming that simulated λ_{max} reproduced the evidences from clinical ECGs, we performed a sensitivity analysis to assess the contribution of transmural heterogeneities to inter-individual differences in nonlinear T wave dynamics, particularly for $[K^+]$ values out of normal ranges.

2. Methods

2.1. Processing of ECG signals

48-hour 12-lead ECGs were recorded from 15 ESRD patients at Hospital Clínico Universitario de Zaragoza (HCUZ). ECG acquisition started 5 minutes before the HD treatment onset and lasted for 48 hours, as shown in Figure 1 [4,5]. Concurrently, six blood samples were taken at the HD onset, at every hour during the HD session, at the HD end (minute 215 or 245, depending on the patient) and after 48 hours, immediately before the next HD session (Figure 1, K1 to K6). Extracellular potassium and calcium concentrations, $[K^+]$ and $[Ca^{2+}]$, as well as heart rate were measured at those time points. The ethical committee approved the study protocol and all patients provided signed informed consent (CEICA ref. PI18/003).
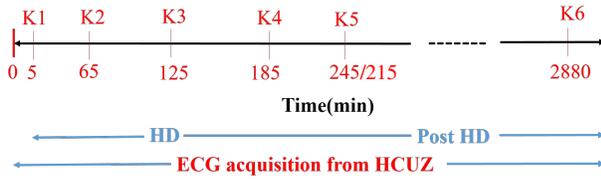

Figure 1. Diagram of the study protocol. K1 to K6 are the time points (in minutes) for blood sample extraction.

ECG pre-processing included baseline wander removal, muscle and electric noise removal as well as single-lead delineation using a wavelet-based automatic algorithm [6]. To enhance the T wave energy and allow more precise delineation, spatial principal components (PCs) were obtained by computing the inter-lead auto-correlation matrix of T waves in a stable ECG segment at the end of the HD session. The ECG recording was subsequently projected onto the direction of the 1st PC and the corresponding T waves were again delineated with [6] to determine the locations of their onset, peak and end.

Mean warped T waves (MWTWs), representing optimal averages in the time and amplitude domains [7], were calculated at each of the analyzed time points when blood samples were extracted. For this calculation, T waves in two-minute windows before the blood extraction time point were aligned, iteratively warped and averaged to compute the MWTW, as fully described in [4,5].

2.2. Computational modeling and simulation

Transmural electrical propagation from ventricular endocardium to epicardium was simulated using one-dimensional fibers of 1.65 cm in length. The action potential (AP) model of Ten Tusscher and Panfilov [8], with the updates by Severi et al. [9], was used to represent human ventricular cell electrophysiology. Transmural heterogeneities were simulated for a total of 22 combinations with variations in the proportions of endocardial (from 10% to 50%), midmyocardial (from 10% to 50%) and epicardial cells (from 20% to 80%) [5].

A series of 10 stimuli was applied to the endocardial end of the fiber every 1000 ms with an amplitude equal to 1.5 times the diastolic threshold. A finite element method based software [10] was used to compute electrical propagation with a time step of 0.01 ms and space discretization of 0.01 cm. pECGs were computed as in [11] and the T waves were also delineated with [6].

Simulations were run for the reference physiological level in the Ten Tusscher−Panfilov model, i.e. $[K^+]$ = 5.4 mM, as well as two different levels below and above it: $[K^+] = 3, 4, 5.4, 6.2, 7$ mM.

2.3. Maximum Lyapunov exponent

The T wave dynamical content was described by evaluation of Lyapunov exponents. The maximum Lyapunov exponent (λ_{max}) was calculated for the patients' ECGs and the simulated ECGs by the Rosenstein method [12]. Let a given MWTW be denoted by $\boldsymbol{x} = [x(t_0), x(t_1), ..., x(t_n)]$. The so-called reconstructed trajectory for a time delay τ is represented by $\boldsymbol{x}' = [x(t_0 + \tau), x(t_1 + \tau), ..., x(t_n + \tau)]$. Here, τ is an arbitrary constant with a value chosen according to Takens theorem [13], which in this study was set to 15 ms.

From the two trajectories $\boldsymbol{x}$ and $\boldsymbol{x}'$, λ_{max} was computed as:

$$\lambda_{max} = \frac{1}{n} \sum_{i=1}^{n} d_i, \qquad (1)$$

where $d_i = \ln\left(\frac{|L_i|}{|L_0|}\right)$, with $L_i = x(t_i) - x(t_i + \tau)$, $i \in \{0, ..., n\}$. Please note that the last samples of the MWTW within τ time units were not included in $\boldsymbol{x}$ so that the reconstructed trajectory could be fully evaluated. In the above equations, d_i represents the divergence/convergence of the trajectory $\boldsymbol{x}$ calculated for each value of i, with the mean of d_i providing the maximum Lyapunov exponent λ_{max}, as described in equation (1).

Figure 2 illustrates λ_{max} for MWTWs from a patient at different HD time points (H1-H3) as well as the corresponding divergence/convergence d_i for i varying from 0 to n.

In each patient and simulated fiber, $[K^+]^*$ and λ_{max}^* were used to denote the values of $[K^+]$ and λ_{max} associated with minimum λ_{max}. We denoted $\Delta[K^+]=[K^+]$ - $[K^+]^*$ and $\Delta\lambda_{max}=\lambda_{max}$- λ_{max}^*. Pearson correlation coefficients were computed to assess the strength of the linear relationship between λ_{max} and $[K^+]$. Linear partial
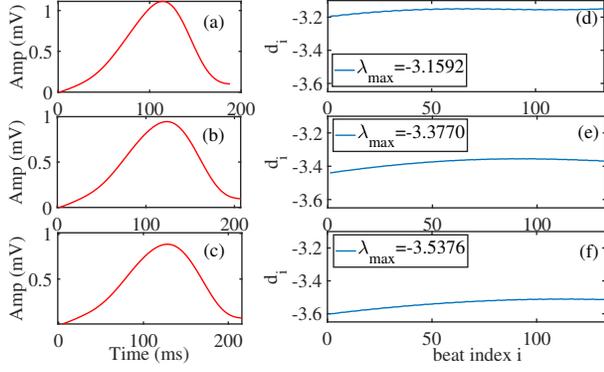
Figure 2. Panels a-c: MWTWs from a particular patient at different HD time points. Panels d-f: d_i versus beat index i varying from 0 to n as described in the text. $\lambda_{\max}$ values obtained as the average of d_i for all values of i are shown for each MWTW.
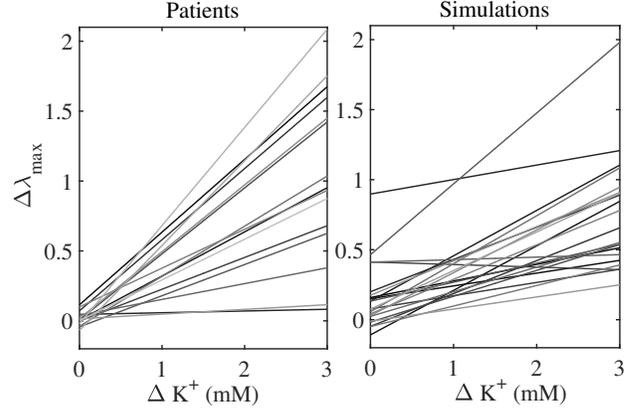

Figure 3. Fitted linear regression models to the relationships between $\Delta\lambda_{\max}$ and $\Delta[K^+]$ for the analyzed patients (left panel) and simulated fibers (right panel).
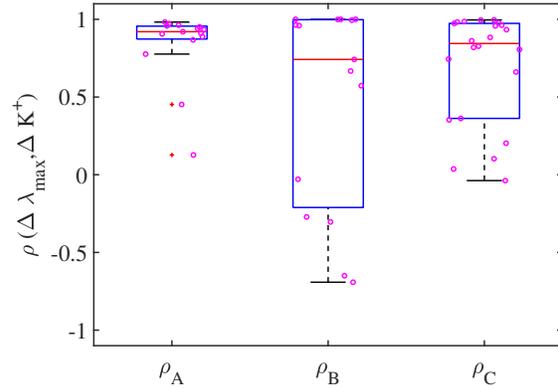
correlation coefficients were computed while controlling for the effects of $[Ca^{2+}]$ and heart rate.

2.4. Sensitivity Analysis

To assess how transmural heterogeneities modulated $\lambda_{\max}$ at different $[K^+]$ concentrations, a sensitivity analysis was performed. The percentage of change and the sensitivity of $\lambda_{\max}$ ($S_{\lambda_{max}}$) to variations in the proportion of endo-, mid- and epicardial cells were calculated as described in [5, 14].

3. Results and Discussion

Figure 3 shows the regression lines obtained from linear fitting $\Delta\lambda_{\max}$ vs $\Delta[K^+]$ for each of the analyzed ESRD patients (left panel) and each of the simulated ventricular fibers (right panel). The range of $[K^+]$ values in the simulations corresponds to the range calculated from the patients' data. As can be observed from the figure, the simulated results reproduce the behavior observed from the clinical ECGs, including the high inter-individual variability. In the patients, $\Delta\lambda_{\max}$ took the largest values at the beginning of the HD session, corresponding to the highest $[K^+]$ values. Similarly, in the simulated fibers, the highest $\Delta\lambda_{\max}$ values were found under hyperkalemia.

Results presented in Figure 4 illustrate the strong linear correlation between $\Delta\lambda_{\max}$ and $\Delta[K^+]$ in the patients (ρ_A, with a median value of 0.92) and in the simulated fibers (ρ_C, median of 0.84). Also, the figure shows that, even after controlling for additional effects, the partial correlation between $\lambda_{\max}$ and $[K^+]$ in the patients is still high in median: median ρ_B of 0.74 after accounting for both heart rate and $[Ca^{2+}]$ variations.

Figure 5 shows the results from the sensitivity analysis

Figure 4. Boxplots of Pearson correlation coefficients between $\Delta\lambda_{\max}$ and $\Delta[K^+]$ for the analyzed patients (ρ_A) and simulated fibers (ρ_C) as well as boxplots of linear partial correlation coefficients for the patients after controlling for the effects of both $[Ca^{2+}]$ and heart rate (ρ_B). Each dot represents a patient or a simulated fiber.

for $\lambda_{\max}$. As can be observed, the largest sensitivity of $\lambda_{\max}$ was found to variations in the proportion of epi- and midmyocardial cells within the ventricular wall. This was particularly more prominent when $[K^+]$ became elevated above physiological levels. For $[K^+]$ = 7 mM, sensitivity values above 100% and 80% were found for epi- and midmyocardial proportions, which means that 10% variations in the epi- and midmyocardial proportions led to changes larger than 10% and 8% in $\lambda_{\max}$.

4. Conclusions

The maximum Lyapunov exponent $\lambda_{\max}$, as a descriptor of the nonlinear dynamics of the T wave, presents
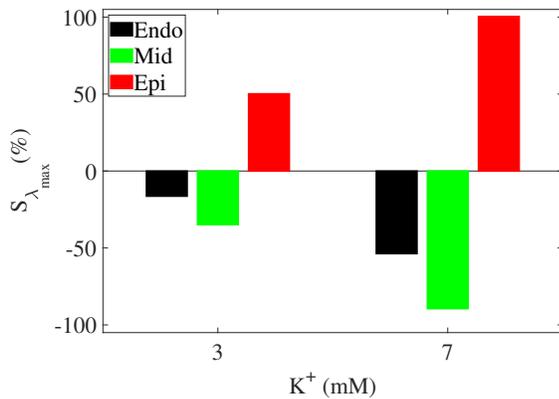
Figure 5. Sensitivity of $\lambda_{\max}$ to variations in the proportion of endo-, mid- and epicardial layers of the simulated ventricular fibers at two different $[K^+]$ levels.

remarkable changes with varying $[K^+]$ in ESRD patients, although high inter-individual variability in the $\lambda_{\max}$-$[K^+]$ relationship is observed. The wide range of strengths and patterns of such relationship in the patients are well reproduced *in silico*. Transmural heterogeneities in simulated human ventricular fibers are shown to play a relevant role in determining the patient-specific response of the T wave to hypo/hyperkalemia.

Acknowledgements

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