Validation of a Novel Method for Non-invasive Blood Potassium Quantification from the ECG

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Abstract

Blood potassium concentration [K^+] has a strong influence on ECG and particularly on T-wave morphology. We previously developed a method to quantify [K^+] from ECG analysis. The aims of the study were i) to test this method quantifying [K^+] on a larger group of hemodialysis (HD) patients ii) to give a mechanical interpretation of the link between [K^+] and ECG by testing the estimator on congenital LQT2 patients. The ECG-based potassium estimator (K_{ECG}), based on the ratio between the T-wave descending slope and the T-wave amplitude ($T_{S/A}$) was tested on 69 HD sessions (23 patients, 3 sessions each) and on 12 LQT2 patients. ECG recordings were acquired and [K^+] values were measured from blood samples (K_{LAB}). The agreement between K_{ECG} and K_{LAB} was satisfactory in the HD patients (absolute error: 0.43±0.28mM). The systematic error was very small (0.05mM) while the standard deviation was 0.5mM. As expected, in LQT2 patients our method significantly underestimated [K^+] (error: 1.15±0.68mM), thus pointing to the I_{Kr} dependence on extracellular potassium in determining the link between [K^+] and T-wave morphology. This method could be effectively applied to monitor patients at risk for hyper- and hypokalemia.

1. Introduction

Maintenance of physiological potassium homeostasis is an important limiting factor in the therapy of cardiovascular diseases. Many pharmacological agents that reduce morbidity and mortality in patients with complicated myocardial infarction and chronic heart failure (HF), including β-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, and aldosterone receptor antagonists, are also known to raise serum potassium and augment the risk of life-threatening hyperkalemia. Conversely, loop diuretics, a mainstay of heart failure treatment, tend to enhance the risk of hypokalemia and ventricular arrhythmias, which may in part account for their consistent dose-related association with increased mortality in observational studies. Because combination drug therapy may simultaneously improve clinical outcomes and enhance the risk of potassium-related adverse events, an appropriate balance of benefit and risk depends heavily on careful patient selection and adequate surveillance of serum potassium [1]. Therefore a noninvasive monitoring of serum potassium would be of great importance and useful especially in patients already undergoing specific monitoring, including home monitoring.

The only available measurement for blood potassium concentration [K^+] is laboratory-based through blood samples, but it is well known that [K^+] has a strong influence on ECG signal [2,3] and particularly on T-wave morphology. The earliest electrocardiographic manifestation of hyperkalemia is the appearance of narrow-based, peaked T waves. However, no quantitative relations between parameters derived from ECG analysis and potassium levels in the blood have been established for clinical use.

We previously developed a new automatic method to quantify [K^+] from ECG T-wave analysis [4,5] on data from dialysis patients, in which [K^+] varies significantly during the session.

The aims of the study were i) to test this method quantifying [K+] on a larger group of hemodialysis (HD) patients ii) to give a mechanical interpretation of the link between [K^+] and ECG by testing the estimator on congenital long QT type 2 (LQT2) patients, where such link is likely to be disrupted. Indeed, LQT2 patients carry "loss of function" mutations of the gene encoding for HERG (I_{Kr}) channels. Therefore, the potassium current is reduced in a way, at some extent, similar to that observed in hypokalemic conditions. Based on this observation we hypothesized that ECG based estimator should systematically underestimate blood potassium in this population.

2. Methods

An ECG-based potassium estimator (K_{ECG}) was previously defined [4,5] based on the hypothesis that the morphological changes in the T-wave due to changes in potassium could be captured by a combination of simple measurements reflecting at what extent the T-wave is "narrow and peaked". In other words, we looked for a way to describe an amplitude-invariant measurement of the sharpness of T-wave. In particular, we defined a direct, quadratic, relationship between the ratio of the T-wave descending slope to amplitude ($T_{S/A}$) and serum potassium.

The quadratic function of $T_{S/A}$ was identified on data from 39 HD sessions from 13 patients. Briefly: the two most significant eigenleads were used to calculate the down slope and the amplitude of the T-wave for each beat. The values of $T_{S/A}$ on which the potassium estimates had to be based were derived by considering a 2-minute window median value of the $T_{S/A}$ at 15 minute intervals. The ECG-based potassium estimator was then defined as $K_{ECG} = 0.17*T_{S/A}^2-0.48*T_{S/A}+$"patient bias". The "patient bias" was derived from a patient-specific calibration: K_{LAB} (first and last) measurements from first session were used to correct the bias for each patient in successive sessions.

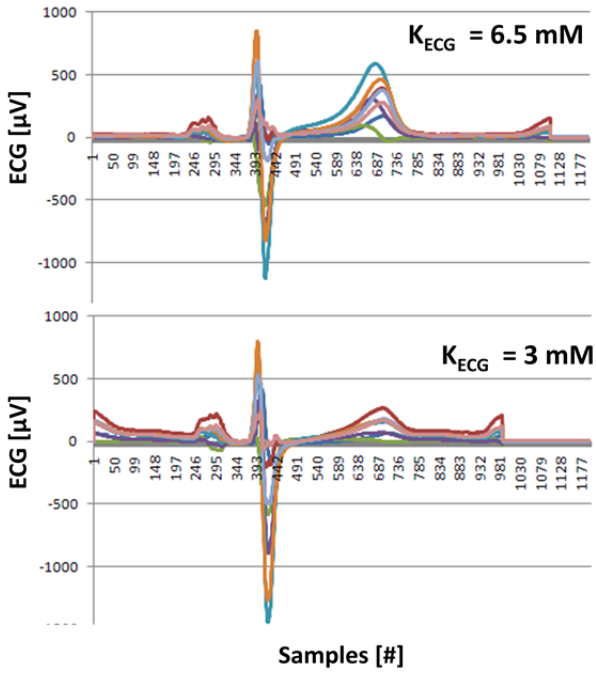

Figure 1. Example of ECGs with different T-wave morphology in a real patient during a dialysis session leading to different K_{ECG} estimates. Tracings from eight ECG leads during the same beat are superimposed.

An example of $[K^+]$ estimates derived from ECGs with different T-wave morphology in a real patient is shown in Fig. 1.

We tested the estimator on 69 HD sessions (23 consecutive patients, 67±13years, 14F, 3 sessions per patient for three weeks, the first session was used to assess the patient-specific bias and the other two to test the estimator). Eligible patients should have been at a metabolic steady state in dialysis treatment for at least 6 months with thrice-weekly and double-needle hemodialysis. Exclusion criteria were: diabetes mellitus, pacemaker holders, anemic patient, vascular access recirculation > 10%, history of miocardic ischemia, coronaric bypass, atrial fibrilation and ejection fraction < 50%.

Holter ECG recordings (H12+, Mortara Instrument Inc.) were acquired on these patients. ECG data were exported and analyzed by implementing a dynamic link library that interfaces to the post-processing software already available (SuperECG/Spectrum Mortara Instrument Inc.).

Reference values for $[K^+]$ (K_{LAB}) were obtained at the following times: 0, 30, 60, 120, 180, 240 minutes from the start of dialysis by blood samples (RapidLab 855, Bayer) taken from the extracorporeal circuit for each dialysis session.

The estimates based on T-wave analysis were then compared with the reference potassium measurements by Bland-Altman analysis.

We also analyzed the estimator on 12 patients (25±15years, 7F) with LQT syndrome type 2. One blood sample was taken immediately before the ECG recordings in these patients and data were analyzed as in the other group of patients.

3. Results

3.1. Hemodialysis patients

Some examples of the results obtained in HD patients are shown in Fig. 2. The agreement was satisfactory (absolute error: 0.43±0.28 mM) and the decreasing trend of $[K^+]$ during the session was captured by the estimator in almost all the sessions. Bland-Altman analysis showed that the mean overall systematic error was very small (0.05 mM) with standard deviation of 0.5 mM (Fig. 3). A slight polarization of the error is observable, denoting some underestimation of high $[K^+]$ values.

3.2. LQT2 patients

As expected in LQT2 patients, in which the potassium current I_{Kr} is reduced in a way similar to that observed in

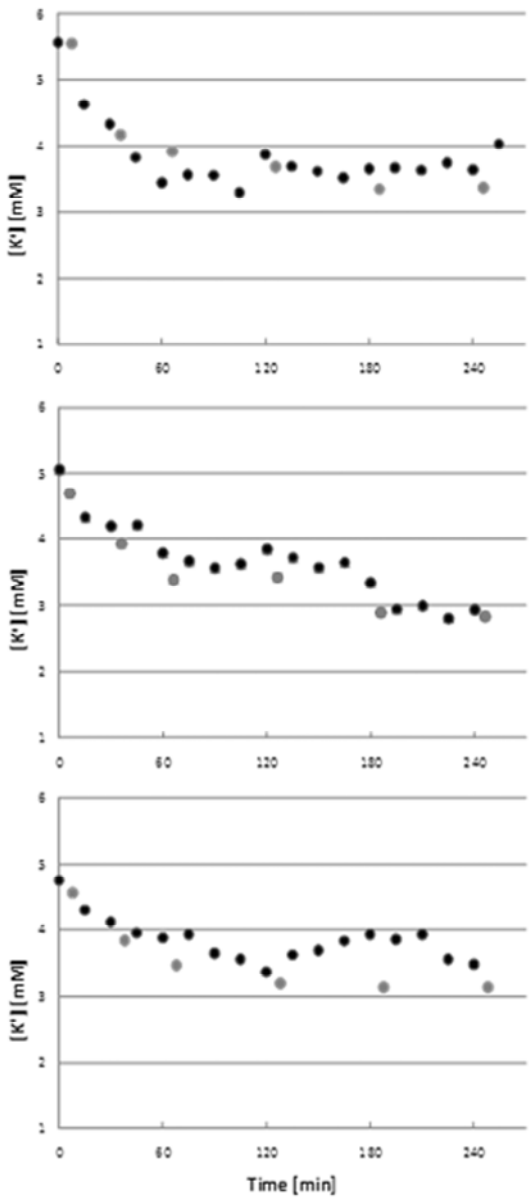

Figure 2. Example of the agreement between the K_{ECG} (dark points) and K_{LAB} (light points) measured and estimated during three hemodialysis sessions.

hypokalemic conditions, our method underestimated [K^+]. The measured K_{LAB} was 4.27±0.33 mM whereas the estimated K_{ECG} was 3.55±1.03 mM ($p<0.05$), with a mean systematic error of 0.71 mM.

4. Discussion and conclusions

We have tested a new automatic method for quantification of blood potassium concentration from the ECG.

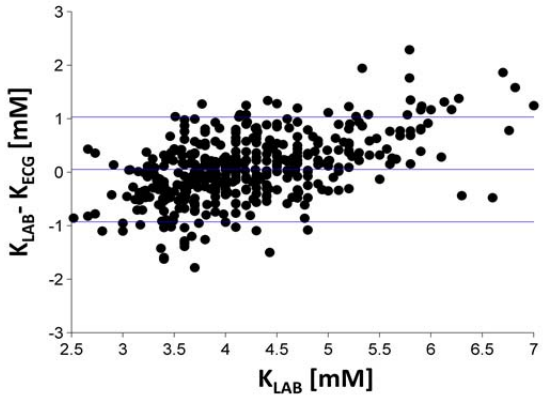

Figure 3. Bland-Altman plot of the estimated vs the reference values for [K^+].

The treatment of several classes of patients could benefit from a real-time and noninvasive measurement of [K_+]. Drug therapies administered to HF patients may improve clinical outcomes and, at the same time, increase the potassium-related adverse events risk. For this reason, an appropriate balance of benefit and risk depends heavily on an adequate surveillance of serum potassium [1]. Since [K^+] measurement is invasive and laboratory-based through blood tests, a continuous serum potassium monitoring is not available and a method allowing it, available also at patient's home, could be extremely useful.

The estimator was tested on data from dialysis patients (HD), since they experience wide fluctuations in blood composition and hemodynamic parameters including serum potassium pre- and post-dialysis. For this reason hemodialysis therapy is a unique "experimental model" for this testing. In addition, data acquisition is not particularly challenging in this population: the reference values for [K^+] measured through standard laboratory analysis are straightaway available through blood samples taken from the extracorporeal circuit and ECG signal can be easily recorded, without any additional invasive procedure or discomfort for the patient.

The results on HD patients are promising and show the K_{ECG} estimates can be an effective tool for hyper- hypo-kalemic risk patient monitoring, which are among the main risk factors for cardiac arrhythmias as well as being indicators for worsening of heart or kidney conditions. The accuracy of these results is clinically relevant since a mean error of 0.05±0.5 mM on a first-level estimate can be considered acceptable in many clinical conditions. In addition, [K^+] fluctuations are more clinically useful than single values and the [K^+] trend, even for sessions in which a bias is present, is correctly assessed. To achieve these results a patient-specific calibration was necessary since we could not find any reason explaining the bias in some of the sessions, further investigations on this

session-dependent bias carried out on the influence of other parameters such as calcium, magnesium, initial hydration status, pH, HR did not explain it. Obviously, this patient-specific calibration is possible on HD patients and the possibility of an initial blood test to calibrate the system should be investigated in additional patient populations.

We tested the hypothesis that reduction in I_{Kr} current with $[K^+]$ decrease (a well known physiological regulation process of cardiac cell electrophysiology) could be the crucial mechanism leading to the change in T-wave morphology we detected with our estimator. In fact, data from LQT2 patients, in which an I_{Kr} reduction is present due to a different pathological factor, show the same estimator reduction we found in hypokalemia condition, thus supporting the idea that the I_{Kr} dependence on extracellular potassium could be determinant for the link between $[K^+]$ and T-wave morphology.

In conclusion, to our knowledge, this is the first study to validate, and test in the clinical setting a new technique aimed at real time and accurate quantification of serum potassium concentration from ECG. This analysis holds promise for effective applications to monitor patients at risk for hyper- and hypokalemia for several diseases, both in a clinical environment and in the scenario of health monitoring at home.

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