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Noninvasive Potassium Determination Using a Mathematically Processed ECG: Proof of Concept for a Novel “Blood-less, Blood Test”

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Abstract

Objective—To determine if ECG repolarization measures can be used to detect small changes in serum potassium levels in hemodialysis patients.

Patients and Methods—Signal-averaged ECGs were obtained from standard ECG leads in 12 patients before, during, and after dialysis. Based on physiological considerations, five repolarization-related ECG measures were chosen and automatically extracted for analysis: the slope of the T wave downstroke (T right slope), the amplitude of the T wave (T amplitude), the center of gravity (COG) of the T wave (T COG), the ratio of the amplitude of the T wave to amplitude of the R wave (T/R amplitude), and the center of gravity of the last 25% of the area under the T wave curve (T4 COG) (Figure 1).

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Results—The correlations with potassium were statistically significant for T right slope ($P < 0.0001$), T COG ($P=0.007$), T amplitude ($P=0.0006$) and T/R amplitude ($P=0.03$), but not T4 COG ($p=0.13$). Potassium changes as small as 0.2 mmol/L were detectable.

Conclusion—Small changes in blood potassium concentrations, within the normal range, resulted in quantifiable changes in the processed, signal-averaged ECG. This indicates that non-invasive, ECG-based potassium measurement is feasible and suggests that continuous or remote monitoring systems could be developed to detect early potassium deviations among high-risk patients, such as those with cardiovascular and renal diseases. The results of this feasibility study will need to be further confirmed in a larger cohort of patients.

Keywords

potassium; ECG; signal processing; T-wave; dialysis; hyperkalemia

Introduction

Potassium homeostasis is impaired in patients with cardiovascular diseases due to advanced age, diabetes, and renal dysfunction.¹ Evidence-based therapies including renin-angiotensin blockade, beta adrenergic blockade, and potassium sparing diuretics promote hyperkalemia. Diuretic-induced hypokalemia may promote arrhythmogenesis. There is compelling evidence that even modest potassium changes in patients with cardiovascular or renal disease may increase the risk of hospitalization and death.^{1–3} In patients undergoing three times weekly hemodialysis, the sudden death rate triples in the 12 hours prior to scheduled dialysis following a two day, weekend hiatus, the time at which hyperkalemia is most likely.^{4–6} Importantly, no method of non-invasively detecting hyperkalemia exists currently.

A tool to permit non-invasive, unobtrusive potassium assessment that integrates with current remote monitoring platforms may shorten hospitalizations, facilitate remote outpatient care, foster independent living, and ease transitions of care. Currently, all tests to assess potassium require access to blood. A bloodless test to assess potassium would be an important advance. Significant abnormalities in potassium are accompanied by marked derangements on the surface electrocardiogram (ECG).^{7–10} However, while dramatic ECG abnormalities in association with often life-threatening alterations in potassium have been well described, subtle ECG changes may occur from physiologic increases or decreases in potassium levels, including changes within the normal range of 3.5 to 5.5 mmol/L. These subtle ECG changes are not routinely appreciated on the surface electrocardiogram due to their small amplitude relative to background ECG noise (from skeletal muscle or skin galvanic current, often in the range of 8–10 microVolts (mV)), resulting in a poor signal-to-noise ratio. Additionally, confounding factors may influence the ECG, including heart rate, body position, individual variations in body habitus and ECG, and other metabolic or cardiovascular conditions. We have developed algorithms for acquisition, processing and analysis of ECG signals that augment the signal-to-noise ratio, correct for confounders, create an individualized template and permit determination of potassium values within the normal range.

We hypothesized that: 1) Small changes in plasma potassium are accompanied by quantifiable changes in the processed surface ECG; 2) Once an *individualized* baseline ECG is obtained for a known potassium value, subsequent changes in potassium can be determined noninvasively by measuring changes in the processed ECG; 3) Potassium related ECG changes can be used to track changes in potassium levels in the clinical context. To test these hypotheses we performed a pilot, feasibility study in patients undergoing hemodialysis.

Methods

Patient Cohort

Patients 18 years old or older, undergoing hemodialysis at Mayo Clinic Rochester, were eligible for study enrollment under an IRB approved protocol (IRB# 10-008249; #13-006127). Both inpatient and outpatient hemodialysis patients were enrolled.

Data acquisition

An ECG was recorded with electrodes in standard clinical positions using a Siesta 802 system (Compumedics, Charlotte, NC) with a sampling at a rate of 1024 bps. ECG acquisition commenced 15 minutes before the start of hemodialysis, and continued until its conclusion. Blood was drawn from the arterial tubing at three time points during the study: i) pre-dialysis, ii) at the mid-time point of the dialysis run after temporarily clamping the heparin line (if in use), stopping dialysate flow and decreasing the blood flow rate to 100 mL/min for at least 15 seconds and iii) post-dialysis after stopping dialysate flow and decreasing the blood flow rate to 100 mL/min for at least 15 seconds.

ECG processing

For analysis purposes the ECG recordings were “batched” into three 15 minute segments corresponding to signals acquired: i) immediately before dialysis, ii) at the time of the mid-dialysis blood sample and iii) immediately following dialysis. Analysis of the data was then performed programmatically in a numerical computing environment (Matlab, R2009b, Beer Sheva, Israel). QRS complexes were excluded from analysis based on R-R interval and amplitude deviations, and using template matching and covariance filtering to eliminate artifact and repolarization changes due to ectopy. Following these steps, the filtered complexes were signal averaged to eliminate noise. The processed signals underwent feature extraction and predictive analysis for potassium assessment.

Based on initial data and physiologic significance, we chose five ECG features for in-depth analysis: the right slope of the T wave (T right slope), the amplitude of the T wave (T amplitude), the center of gravity (COG) of the T wave (T COG), the ratio of the amplitude of the T wave to amplitude of the R wave (T/R amplitude), and the center of gravity of the last 25% of the area under the T wave curve (T4 COG) (Figure 1). T right slope was calculated as the mean first derivative of the T wave from the beginning to the end of the TpTe interval. We defined the center of gravity as the mean amplitude (mV)/mean duration (ms). Automatic algorithms to extract these features were created.

Principal Component Analysis and Unsupervised Optimal Fuzzy Clustering

Principle component analysis and clustering processes were performed on ECG sampled records to observe changes in the samples' patterns. The ECG data set included records constructed from one minute of filtered and averaged ECG data. The records were represented by P dimensions of samples in the time domain, where P is the number of samples in each heart beat ($P \approx 800$, but is heart-rate dependent). Each session included 15 records that represented a measured potassium level. The clustering procedure included two major steps: principal component analysis of the records in the set and unsupervised optimal fuzzy clustering (UOFC).

A set of basis waveforms (principal components) common to all the records were computed using a covariance matrix ($P \times P$) of the ECG matrix that was defined as $cov = E\{(V - \mu_v)(V - \mu_v)^T\}$, where: μ_v is the averaged ECG vector of all 60 records. G ($P \times P$ dimensional matrix) and λ_i , ($i = 1, 2, \dots, 800$) were the eigenvectors and the corresponding eigenvalues of the covariance matrix. We then reduced the records to a small number of coefficients. These coefficients were used to divide the records into clusters. Utilizing principle component analysis with a mean standard error (MSE) of 1% we were able approximate the data with 10 coefficients; by increasing the MSE to 5% we can reduce the number of the eigenvectors to $F=4$. The coefficients matrix $Y_{F=10}$ was then used as the features vectors for unsupervised optimal fuzzy clustering. Data were clustered without a priori assumptions about the characteristic features of the clusters. The clustering procedure ran in two iterative steps: 1. All records were assigned to a single cluster, and the memberships in this cluster were calculated; 2. A second cluster was created to include records with the lowest memberships in the first cluster. This sequence was repeated until two validity criteria were met that were based on: a) sum of memberships within each cluster, b) standard deviation of members within the cluster.

Statistical Analysis

In order to test for association of each parameter with measured potassium values, a linear mixed model was used. Potassium values were used as the dependent variable and each individual parameter was tested one at a time for evidence of association. A random per subject intercept with a freely estimated correlation structure was used to properly account for the correlation between repeated measurements within subjects. A fixed effect corresponding to the ECG parameter was included in each model as the main effect and tested. The fit of the model generated for each parameter and lead combination was determined using the Akaike Information Criterion (AIC).¹¹ Lower AICs denote a better fit of the data. The AICs for all parameters across the 12 ECG leads were given a ranking from lowest to highest. Average rankings by lead and parameter were calculated and summarized. The ranks were compared for differences between parameters in order to determine the best parameter. This was done via one way analysis of variance on the ranks and corrected for multiple comparisons using the Turkey HSD test. A second analysis was also conducted within the mixed model framework that included a patient by ECG parameter interaction term. This term was used to test for evidence of different slopes by subject. Pearson correlation coefficients were calculated to summarize correlation between measurements of potassium and individual ECG parameters within subject. Heart rates were compared among

time periods using repeated measures analysis of variance. All analyses were conducted using SAS version 9.3, Cary, NC. Two-sided p-values <0.05 were considered to be statistically significant.

Results

Twelve dialysis patients (58% men, 42% women) with a mean age of 55 ± 15 years were enrolled. Ten were Caucasian, one was Native American and one was Asian. All patients were in normal sinus rhythm at the time of the study. The mean heart rates (beats per minute) were 74 ± 12 before dialysis, 78 ± 13 mid-dialysis and 78 ± 13 following dialysis. The heart rates did not differ statistically among time periods ($P=0.06$). Figure 2A depicts the tracings acquired from a single patient showing the raw original vs. the filter, processed tracing. Figure 2B shows a signal averaged ECG from a single patient at different levels of potassium. The lead with the lowest average AIC rank was precordial lead V4, however, the leads did not differ statistically. ECG parameters were also evaluated by AIC ranks across all leads (Table 1). The parameter with the lowest average AIC rank was T right slope. T right slope was not statistically different from either T COG ($P=0.99$) or T4 COG ($P=0.82$). The average AIC ranks for T Right slope, T COG, and T4 COG were superior to both T amplitude and T/R amplitude ($P<0.001$).

The correlations between potassium and each ECG parameter, in precordial lead V4, are shown in Table 2. The correlations with potassium were statistically significant for T right slope ($P < 0.0001$), T COG ($P=0.007$), T amplitude ($P=0.0006$) and T/R amplitude ($P=0.03$), but not T4 COG ($p=0.13$). To determine whether there was significant individual variability in the rate of ECG feature response to potassium changes, we tested whether there was evidence for individual patient slopes. Differences among the slopes of the individual-patient regression lines for potassium versus each parameter in V4 were statistically significant only for T amplitude ($P=0.05$) and T/R amplitude ($P=0.0005$), suggesting that the other parameters may be more universal in response slopes. Table 3 shows the AIC and statistical significance for T right slope (the preferred parameter) across leads. The presence of statistically significant correlations in leads V2-V6 and in the inferior leads indicates that the T right slope parameter is relatively insensitive to lead position across the precordium as well as in the inferior leads. Figures 3A and 3B show the individual patient values and individual patient regression lines for the parameters with the greatest statistical significance in lead V4, T right slope and T amplitude. For T right slope, a negative correlation with potassium was present (meaning that the downslope became steeper with increasing potassium) for 10 of the 12 patients, with correlation coefficients between -0.86 and -0.99 . The single, positive correlation ($R=0.75$) occurred in a patient in whom the potassium range was small ($4.2-4.3$). The second patient with aberrant correlation had no variability in the T right slope measurements and a correlation could not be calculated. For T amplitude, a positive correlation with potassium was present for 9 of the 12 patients, with correlation coefficients between 0.77 and 0.99 . The three, aberrant, negative correlations ($R=-0.84$, -0.71 , -0.03) also occurred patients in whom the potassium ranges were small ($4.2-4.3$, $3.6-4.1$, $3.6-4.2$).

Principle component analysis and unsupervised optimal fuzzy clustering were used to define the magnitude of potassium change that resulted in automated segregation of ECG changes. With this approach changes in the ECG morphology were detected (clustered) when the potassium measure changed by as little as 0.2 mmol/L.

Discussion

In this feasibility study we demonstrate the proof of a novel concept: identifying changes in an individual's potassium level by recording the body's physiologic response those changes, rather than by extracting blood and subjecting it to chemical processes. The availability of chronically wearable and subcutaneously injectable ECG recording systems that transmit wirelessly and securely to the internet opens the door to ambulatory, non-obtrusive, frequent assessment of potassium as a clinical reality.¹² A key aspect of this strategy is the use of *personalization* to acquire an individual's physiologic template at a known potassium value, and detect changes from the personalized template to register potassium changes – a form of *individualized medicine*. A second important aspect was advanced signal processing and filtering to eliminate noise, ectopy, and other potential confounders. Moreover, by using principal component analysis we were able to compress the data to facilitate its use in mobile platforms, and through unsupervised optimal fuzzy clustering demonstrated that even very small changes in blood potassium levels (down to 0.2 mmol/L) result in algorithmically identifiable changes in the surface ECG. The ability to detect small changes is important – trends can be identified and interventions taken before life-threatening hyperkalemia or hypokalemia develops. With this technology integrated into a remote-monitoring system, patient alerts ranging from dietary and medication reminders to instruction to seek care could be generated automatically.

A large body of evidence supports the clinical significance of detecting abnormalities of blood potassium. First, mild hyperkalemia, usually under-detected due to an absence of signs and symptoms, increases the one-day odds of death.² Second, following the RALES study, potassium-sparing diuretic use increased hospitalization for hyperkalemia by 3 to 5 fold and doubled hyperkalemia-related deaths.³ Third, in ambulatory patients with cardiovascular disease and chronic kidney disease (eGFR < 60 ml/min/1.73 m²), the occurrence of a single hyperkalemic event (potassium > 5.0 mEq/L) doubles all-cause mortality.¹³ As noted above, the risk for sudden death among hemodialysis patients triples during the 12 hours each week that hyperkalemia is most likely.^{4–6} After a single episode of hyperkalemia, 50% of patients will have a second episode within one year². Hyperkalemia usually lacks signs and symptoms, a noninvasive means of identifying it is currently lacking.

We chose to study hemodialysis patients since: they have predictable potassium level changes that decrease during treatment and increase in-between dialysis runs, we could easily obtain several potassium levels for validation, and we could record the ECG at multiple potassium levels in a relatively short time span. Additionally, patients receiving dialysis may benefit most from integration of our refined ECG algorithm into remote monitoring systems. However, we anticipate this form of monitoring would have applicability in wide range of patients with cardiovascular and renal disease. For example, the ability to monitor potassium would facilitate life prolonging renin-angiotensin system

antagonist therapies in heart failure patients at risk for hyperkalemia,^{14–18} in whom it is currently withheld.

While we found that all ECG leads provide useful information for potassium prediction, we focused on V4 and a small number of ECG parameters for both physiological and practical purposes. In order to monitor potassium remotely, a small unobtrusive recording device—one with a limited number of recording channels—is necessary to ensure adherence. The fact that findings were robust in multiple precordial leads (Table 3) suggests an insensitivity to lead position across the chest. The fact that V4 and surrounding leads had the best AIC score for location, and that T right slope did for feature, is consistent with the mechanisms by which potassium changes affect the surface ECG. As elegantly demonstrated by Antzelevitch et al in a wedge preparation,¹⁹ extracellular potassium differentially affects the action potential duration in mid-myocardial as compared to endocardial and epicardial myocytes (Figure 4). This is reflected predominantly on the surface ECG as the T wave. T wave characteristics are significantly affected by potassium flow through voltage gated ion channels, and these channels themselves are exquisitely sensitive to extracellular potassium concentrations. This makes T wave parameters ideal “micro-sensors” of potassium levels. The finding that the best performing ECG parameter was “T right slope” supports the concept that we are detecting the sum of potassium changes at the cellular level, accounting for our unique fidelity in detecting subtle changes.

Our results are best interpreted in the context of their limitations. During hemodialysis, the concentrations of analytes other than potassium (e.g. magnesium, calcium, phosphorus) change, as well as fluid status, change. We focused initially on potassium because of its importance to morbidity and mortality, and its known impact on the ECG. Since other analytes exert known and different changes in the ECG, it may be possible to process recordings to determine which ECG changes are attributable to which analyte, recognizing that some overlap will exist and that sophisticated analysis will be required. In this preliminary study, we have only compared potassium at three time points peri-dialysis, and as such, our results may not be applicable to other circumstances. We are performing animal studies to permit modulation of single analytes to better define these issues. Additionally, this was an exploratory feasibility study involving a small number of patients, and will thus require confirmation in a larger cohort of patients. Further validation of these algorithms in a larger cohort could provide the ability to make this a wearable technology that can be adapted to any recording device, implantable recorder, or any web-based platform in an automated, user-friendly fashion.

In conclusion, we found that small changes in blood potassium concentrations, in or near the normal potassium range, result in quantifiable and measurable changes in the processed, signal-averaged ECG. Additionally, the processing can be performed in a computationally efficient manner to permit a mobile, non-obtrusive monitoring system to be developed. These findings will support the development of “bloodless blood-tests,” that is, acquiring biological information that in the past has required access to blood, with potentially large implications for patients with cardiovascular and renal diseases.

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Highlights

- Serum potassium can be reliably estimated using mathematical algorithms for processing signal-averaged ECGs
- Potassium changes as small as 0.2 mmol/L were detectable
- Potassium could be measured within and near the normal range
- Initial, individual correlation of potassium with the ECG is required

Figure 1. ECG parameters analyzed for correlation with potassium changes

Large image: All measurable ECG parameters that were tested for sensitivity to potassium changes while recording ECG in dialysis patients at various potassium concentrations. Inset: Close-up view of parameters that had best correlation to changes in potassium: T center of gravity (T Cog), T amp- Amplitude of T wave, T wave area, T right slope. T/R amplitude is calculated based on the corresponding values of the T wave area and R wave area shown in figure. T4 Cog is the latter 25% of the area under the T wave.

Figure 2. Mathematical Processing of ECG Signals

Panel A) Depicts the averaged raw original versus processed ECG averaged signal for a given patient. The green tracing shows difference between a raw and a processed signal; this is the pre-processed signal. The red tracing is the averaged ECG signal after ECG processing algorithm was performed by exclusion based on R-R interval and amplitude deviations, template matching, and covariance filtering to eliminate artifact and noise. Inset- zoomed in view of the T wave of both unfiltered and filtered tracings. Panel B) Depicts multiple ECG averaged signals from a single patient at various potassium concentrations. Three examples are shown that display time-aligned, rectified, and processed ECG signals at various times during dialysis in at various potassium concentrations (red, blue, green). Note that the dotted S wave is a positive transposition of the negative solid S wave in order to calculate from an absolute positive value. Inset- zoomed in version of T wave segment of all three ECG tracings. T-wave changes are clearly visible after processing, despite relatively minor potassium changes.

Figure 3. Changes in Potassium Concentration Correlate with Subtle Changes in Processed ECG
 Panel A) shows subtle how ECG changes in response to changes in potassium concentration, as its correlation with T-right slope. Individual patient values and individual patient regression lines for the T right slope are shown using processed T-right slope values in each of the individual dialysis patients. Each color represents data from a single patient. The lines are the individual-patient, linear regression lines. ($P < 0.0001$ for correlation between T right slope and potassium). Panel B) shows subtle changes in potassium concentration correlates with changes in T Amp. Individual patient values and individual patient regression lines for the T Amp are shown using processed T Amp slope values in each of the individual dialysis patients. Each color represents data from a single patient. The lines are the individual-patient, linear regression lines. ($P = 0.0006$ for correlation between T amplitude and potassium)

Yan G, and Antzelevitch C *Circulation*. 1998;98:1928-1936

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Figure 4. ECG signature of T wave changes are due to underlying cellular electrophysiologic changes in potassium channels in the presence of various potassium concentrations

Reproduced with permission from Antzelevitch et al. Yan GX, Antzelevitch C. Cellular basis for the normal T wave and the electrocardiographic manifestations of the long-QT syndrome. Circulation. 1998;98:1928–1936. Alterations in Action potential and T wave morphology are shown, and are dependent on potassium concentration. These signals are dependent on specific cardiac tissue layer; mid-myocardium (M cells) or epicardial layer. The resultant surface ECG recorded reflects a transmural repolarization change between the tissues.

Table 1

Mean AIC ranks across all leads, by parameter (N = 12 patients)

Parameter	Mean Rank
T right slope	17.3 *
T COG (mv/ms)	18.5 *
T4 COG (mv/ms)	21.7 *
T amplitude	41.5 #
T/R amplitude	53.5

Akaike Information Criterion (AIC); center of gravity (COG); mean amplitude (mV); mean duration (ms)

* P < 0.001 vs. T amplitude and T/R amplitude

P = 0.04 vs. T/R amplitude

Table 2

Correlations between potassium and each parameter in lead V4 (N = 12 patients)

Parameter	Slope estimate	AIC	P
T right slope (mv/ms)	−198	55	< 0.0001
T COG (mv/ms)	3117	64	0.007
T4 COG (mv/ms)	2850	69	0.13
T amplitude (mv)	1.8	74	0.0006
T/R amplitude	0.74	87	0.03

Center of gravity (COG); mean amplitude (mV); mean duration (ms)

Table 3

Correlations between potassium and T right slope parameter across all leads (N = 12 patients)

Lead	Slope Estimate (meq/L/mv)	AIC	P
V3	-243	52	<0.0001
V4	-198	55	<0.0001
III	-184	61	<0.0001
aVF	-185	61	<0.0001
II	-166	63	0.0002
V5	-180	63	0.0003
V6	-210	65	0.0005
V2	-185	72	0.002
aVL	225	74	0.14
aVR	132	75	0.11
I	-159	75	0.17
V1	32	77	0.70