Electrocardiographic Manifestations and Clinical Outcomes of Severe Hyperkalemia: Can the Electrocardiogram Risk Stratify for Short Term Adverse Events?

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Introduction

Background

Severe hyperkalemia is a potentially life threatening patient presentation to the emergency department. Without any preceding signs or symptoms, severe hyperkalemia may lead to lethal cardiac dysrhythmias.[1,2] Immediate and aggressive treatment of severe hyperkalemia has been demonstrated to improve patient survival.[2]

Hyperkalemia produces cardiotoxicity through early depolarization of the cell membrane, slowing of ventricular conduction and decreased duration of the action potential.[3] As a patient's potassium rises, standard teaching describes the sequential appearance of classic electrocardiographic (ECG) abnormalities.[3,4] Initially peaked T waves are observed. Next, the PR interval prolongs, followed by QRS prolongation. Then, there is loss of the P wave and escape rhythms are seen. Finally, the ECG develops a "sine wave" configuration, leading to ventricular fibrillation, pulseless electrical activity or asystole.[3,4]

However this classic teaching has been challenged by the finding that a significant proportion of patients with hyperkalemia do not have these expected ECG abnormalities. Small studies have demonstrated that ECGs without any findings consistent with hyperkalemia are seen in 50-64% of patients with potassium (K^+) ≥ 6.5 mEq/L.[5-7] Cases of patients with extreme hyperkalemia (10.1-10.3 mEq/L) and normal ECGs have also been reported.[8,9] While the insensitivity of the ECG for detecting hyperkalemia has been described, the relationship between the ECG and the development of adverse events is not as clear.[1,3,10,11]

Importance:

The presence or absence of ECG manifestations of hyperkalemia is frequently used to determine how aggressively a hyperkalemic patient is treated.[5,7,12] This practice is based on the presumption that ECG changes reliably occur prior to hyperkalemic

dysrhythmia or cardiac arrest. To our knowledge, there have been no previous studies examining the association between specific hyperkalemic ECG abnormalities and the development of short-term adverse events. This information would be beneficial to determine the appropriate use of the ECG in risk stratification of hyperkalemic patients.

Goals of this investigation:

ECGs and clinical outcomes of patients with severe hyperkalemia ($K^+ \geq 6.5$ mEq/L) are analyzed. The frequency and characteristics of hyperkalemic ECG abnormalities in patients with severe hyperkalemia are described. The short-term (6 hour) adverse event rate in patients with severe hyperkalemia is reported. The study aims to identify whether or not hyperkalemic ECG abnormalities are associated with short-term adverse events.

Methods

Study Design and Setting

We performed a retrospective cohort study of emergency department and hospitalized patients with severe hyperkalemia ($K^+ \geq 6.5$ mEq/L). The presence or absence of ECG findings of hyperkalemia and adverse clinical outcomes were reported. The study received institutional review board approval from Kent Hospital, with a waiver of informed consent.

The study was performed at Kent Hospital, a suburban 350-bed community hospital in Warwick, Rhode Island with an academic affiliation with the New England College of Osteopathic Medicine. The annual emergency department (ED) census is approximately 72,000 patients. Patients are primarily adults (90%); approximately 90% are White, 4% are Hispanic, and 2% are Black.

Selection of Participants

A list of medical record numbers for all adult patients (age ≥ 18 years) with $K^+ \geq 6.5$ mEq/L from August 15, 2010 through January 30, 2015 was electronically generated from the hospital laboratory database. This database contains all laboratory data for emergency department and admitted patients, which ensures that all hyperkalemia values were captured.

Inclusion and exclusion criteria were developed prior to data collection. Cases selected for inclusion were required to have a documented serum or plasma K^+ of ≥6.5 mEq/L and an ECG performed within one hour of the laboratory draw. The ECG could be performed either during the 60 minutes prior to the acquisition of the potassium sample, or during the 60 minutes after the laboratory draw. When a serum and plasma K^+ level were both obtained, the plasma level (also known as a heparinized K+) was used. The

plasma K^+ level was preferred because the serum K^+ level is generally higher than the plasma level, believed to be due to the release of K^+ from platelets during clotting. Only one episode of hyperkalemia per patient was included in the study. Recurrent episodes of hyperkalemia in the same patient (regardless of time frame between episodes) were excluded.

Exclusion criteria included laboratory notation of a hemolyzed sample, platelet count ≥ 500 x 10^9 platelets/L, paced rhythm on ECG, and treatment for hyperkalemia prior to obtaining the ECG and laboratory sample. Hemolyzed samples were excluded because the release of K^+ from red blood cells during hemolysis can lead to false elevation of the serum potassium. Similarly, patients with platelet count ≥ 500 x 10^9 platelets/L were excluded because this degree of thrombocytosis can cause pseudohyperkalemia. Treatment for hyperkalemia was defined as the administration of any of the following prior to the time the ECG was obtained and the laboratory sample was collected: calcium chloride, calcium gluconate, sodium bicarbonate, albuterol, insulin, dextrose, sodium polystyrene sulfonate, and/or hemodialysis. Patients who received prior treatment for hyperkalemia were excluded so that the measured potassium level more accurately reflected the potassium value at the time of the ECG. Patients were also excluded if they received atropine, dopamine, epinephrine, norepinephrine, or vasopressin prior to the time the ECG was obtained. These patients were excluded because of the potential of these medications to alter the ECG, such as precipitating ventricular tachycardia or masking hyperkalemic bradycardia.

Methods and Measurements

Data was abstracted from the electronic medical record, including emergency department record, admission history & physical, daily progress notes, discharge summary, and electronic medication administration record. A standardized, closed-ended electronic data collection form was used. All reviewers (AB, SD, BL, JV) were trained in the data collection rules and definitions using sample medical records. The electronic medical records and data collection forms of the final study group (n=188) were reviewed for accuracy by a second reviewer (ND).

The following information was abstracted from each record: (1) demographics (age, sex, race); (2) serum and plasma potassium levels and time obtained; (3) patient location at time of hyperkalemia (emergency department vs inpatient); (4) ECG and time obtained; (5) medications administered prior to obtaining ECG (including medications administered by Emergency Medical Services in the prehospital setting) and in the 6 hours after the ECG; (6) laboratory values (sodium, calcium, glucose, creatinine, CO_2, platelets) obtained on the same lab draw as the potassium level; (7) whether the patient was an established dialysis patient at the time of the episode of hyperkalemia; and (8)

occurrence of a study defined adverse event in the 6 hours after the ECG. All charts were reviewed by 2 reviewers for the presence or absence of an adverse event. The 2 reviewers disagreed for 6 charts. These 6 charts were reviewed by 2 additional reviewers and a final decision was made for the data analysis (AB,ND,BL,JV).

A copy of the ECG performed within one hour of laboratory draw, and prior to treatment, was obtained. When available, a copy of the most recent previous ECG was also obtained to serve as a baseline. Potassium level was confirmed to be <5.0 mEq/L at time of previous ECG.

A separate document containing only the initial ECG, previous ECG (when available) and an event identifier was created. A second standardized, closed-ended electronic data collection form was used to review all ECGs. All ECGs were reviewed by two experienced board- certified emergency physicians (VL, ES). Both reviewers were blinded to the objectives and methods of the study, the potassium value, associated medical history, clinical information, and all other data collected for the patient. The ECG reviewers were also blinded to the formal interpretation documented by the attending cardiologist, as well as each other's readings. The reviewers independently examined each ECG for rate, rhythm, peaked T wave, PR interval duration, QRS wave duration, and type of intraventricular conduction delay (if present). If the reviewer agreed with the computer-generated values of PR interval and QRS wave duration (in milliseconds), then the computer-generated values were used. In order to keep the ECG reviewers blinded to the study objective, additional data that did not pertain to the objective of the study (left ventricular hypertrophy, ST elevation, ST depression and/or T wave inversion) were included in the data collection form.

The ECG was categorized as "PR prolongation" if the PR interval was >200ms, and either there was no previous ECG for comparison or the PR interval was <200ms on the previous ECG. If the previous ECG had a PR interval >200ms, then the ECG was categorized as "PR prolongation" if the current PR interval was longer than the previous PR interval. Similarly, the ECG was categorized as "QRS prolongation" if the QRS duration was >110ms, and either there was no previous ECG for comparison or the QRS duration was <110ms on the previous ECG. If the previous ECG had a QRS duration of >110ms, then the ECG was categorized as "QRS prolongation" if the current QRS duration was longer than the previous QRS duration. In the scenario where the ECG reviewers disagreed on the rhythm, type of intraventricular conduction delay, or whether T waves were peaked or not, then the attending cardiologist reading was used.

Outcomes

The primary outcome was the presence or absence of hyperkalemic ECG abnormalities in patients with potassium ≥6.5 mEq/L. ECGs were categorized as having "any abnormality suggestive of hyperkalemia" if one or more of the following were present, (1) peaked T waves, (2) PR prolongation, (3) QRS prolongation, (4) bradycardia (HR<50bpm); (5) 2nd or 3rd degree heart block; (6) junctional rhythm; (7) ventricular escape rhythm; or (8) ventricular tachycardia.

The secondary outcome was the presence or absence of an adverse event within 6 hours of the laboratory measurement of a potassium ≥6.5 mEq/L. An adverse event was defined as symptomatic bradycardia, ventricular tachycardia, ventricular fibrillation, cardiopulmonary resuscitation and/or death. Symptomatic bradycardia was defined as bradycardia requiring treatment with calcium chloride, calcium gluconate, atropine, epinephrine, dopamine and/or pacing for symptoms of hypotension, syncope, chest pain, dyspnea and/or altered mental status. Calcium chloride or calcium gluconate administered solely for an abnormal ECG or high potassium value was not recorded as an adverse event.

Data Analysis

The Kappa statistic was calculated to evaluate the level of agreement between ECG reviewers for ECG variables, as well as for the level of agreement between reviewers for adverse events. For the association of clinical variables with ECG categorized as "any abnormality suggestive of hyperkalemia", and the association of ECG abnormalities with short-term adverse events, the Pearson Chi-Square statistic was used. Each variable was analyzed separately and an odds ratio was calculated. Univariate logistic regression was used to predict ECG abnormalities suggestive of hyperkalemia by potassium value. Potassium was included as a continuous variable in this model. Tests were run with SPSS (version 22; IBM Corp, Armonk, NY).

Results

Characteristics of study subjects:

A total of 1378 episodes of a serum or plasma potassium level greater than or equal to 6.5 mEq/L were identified (Figure 1). Over half (n=776, 56%) of these episodes were excluded due to laboratory notation of a hemolyzed sample. Recurrent episodes of hyperkalemia in the same patient were also excluded (n=129, 9%). Another common reason for exclusion was the lack of an ECG performed within 60 minutes of laboratory draw (n=209, 15%). Episodes were also excluded for concurrent plasma potassium of <6.5 mEq/L (n=29, 2%), platelets >500x10^{9}/L (n=8, 1%), and/or an ECG demonstrating paced rhythm (n=11, 1%). Twenty-eight episodes (2%) were excluded because the patient received medications for the treatment of hyperkalemia and/or vasoactive medications prior to the performance of the ECG and/or laboratory draw.

Consequently, no patients who experienced a cardiopulmonary arrest prior to the ECG and/or laboratory draw were included in the final study group.

The final study group included 188 episodes of severe hyperkalemia. A plasma potassium level was obtained on the same laboratory draw as the serum potassium level in 96 episodes (51%). The mean time between the ECG and potassium lab draw was 18 minutes (SD=14 minutes). Previous ECGs were available for comparison in 123 episodes (65%). The majority of episodes (n=176, 94%) occurred in the emergency department.

Baseline patient characteristics are presented in Table 1; mean age was 68 years, 54% were male, and 94% were white. All patients had abnormal kidney function. Half of the patients had an estimated glomerular filtration rate of less than 15 mL/min/1.73m^2. Established hemodialysis patients represented 32 (17%) of the 188 patients.

The mean serum potassium level was 7.1 mEq/L (SD=0.6mEq/L). The distribution of potassium values is presented in Figure 2. Potassium levels ranged from 6.5-9.3 mEq/L. The largest proportion of patients had a potassium level of 6.5-6.9 mEq/L (n=93, 49%).

Concurrent metabolic disturbances are detailed in Table 1. Severe sodium and/or calcium derangements were uncommon. The mean sodium level (corrected for glucose concentration) was 135 mEq/L (SD=6mEq/L); the mean calcium level was 9.0 mg/dL (SD=1.0 mg/dL). Blood gas analysis was generally not performed at the time of the potassium measurement; therefore, serum bicarbonate was used as a marker for acidosis. The mean bicarbonate level was 19 mEq/L (SD=9 mEq/L), with the majority of patients demonstrating an abnormally low bicarbonate level (below 23 mEq/L in 126 patients, 67%).

Main Results

A total of 134 episodes (71%, 95% CI: 64.4%-77.3%) had “any ECG abnormality suggestive of hyperkalemia”, as characterized in Table 2. The two most common findings were QRS prolongation (43%, 95% CI: 36.7%-50.8%) and peaked T waves (30%, 95% CI: 24.1%-37.2%). PR prolongation (15%, 95% CI:10.5%-20.7%) and bradycardia of less than 50 bpm (11%, 95% CI:7.4%-16.5%) were also noted. Additional abnormal rhythms (junctional rhythm, ventricular escape rhythm, ventricular tachycardia and 2nd degree heart block) were seen in less than 10% of the episodes. No 3rd degree heart blocks were identified.

Of the 82 patients with QRS prolongation ≥110 msec, the majority had a QRS duration of ≥120 msec (n=67; 82%). Nonspecific intraventricular conduction delay was seen

most commonly (n=29), followed by right bundle branch block (n=27) and left bundle branch block (n=11). Approximately half of the patients with QRS prolongation had a prior ECG available (n=40, 49%), of which the majority demonstrated a normal QRS duration of <110 msec (n=28, 70%). In the 13 patients with a prior ECG demonstrating previous QRS prolongation ≥110 msec , the current QRS duration was an average of 29 msec longer.

Of the 134 patients with hyperkalemic ECG abnormalities, more than half (n=77, 57%) had only a single finding of hyperkalemia. The most common isolated finding of hyperkalemia was QRS prolongation (n=33). There were also episodes whose only finding of hyperkalemia was peaked T waves (n=26), PR prolongation (n=10), bradycardia less than 50 bpm (n=5), or junctional rhythm (n=3).

There was no statistical difference between the frequency of hyperkalemic ECG abnormalities in established hemodialysis patients and nondialysis patients (OR 1.09, 95%CI 0.47-2.53). There was no statistically significant difference in the frequency of hyperkalemic ECG abnormalities between episodes who had a previous ECG available and episodes who did not have a previous ECG available (OR 0.73, 95%CI 0.37-1.44). Based on univariate logistic regression, potassium level was predictive of having “any ECG abnormality suggestive of hyperkalemia” (OR 2.71, 95%CI 1.32-5.59).

The effect of concurrent metabolic disturbances on the frequency of hyperkalemic ECG abnormalities was examined. Patients with hyponatremia (Na<135) were more likely to have hyperkalemic ECG abnormalities than patients without hyponatremia (OR 2.24, 95%CI=1.13-4.44). Patients with acidosis (CO2<23) were also more likely to have hyperkalemic ECG abnormalities than patients without acidosis (OR 2.26, 95%CI=1.17-4.35). In contrast, no statistically significant difference was seen in patients with hypernatremia (Na>145; OR 1.01, 95%CI=0.19-5.36) or hypocalcemia (Ca<8.5; OR 0.98, 95%CI=0.43-2.23). Analysis of hypercalcemia and its effect on the ECG is limited due to small sample size (n=3). All hypercalcemic patients in this study (Ca > 10.2 mmol/L) had hyperkalemic ECG abnormalities.

The interrater reliability was calculated with a kappa value of 1.0 for PR prolongation and QRS prolongation; 0.662 for peaked T waves, 0.716 for rhythm analysis, 0.870 for type of block, and 0.822 for “any abnormality suggestive of hyperkalemia”. The interrater reliability for the presence or absence of a short-term adverse event was strong (kappa 0.870).

Patients who received treatment prior to the ECG were excluded from the study. Almost all of the patients in the study (n=177, 95%) received treatment after the ECG was performed. The median time from ECG to treatment with calcium (calcium gluconate or calcium chloride) was 86 minutes. The median time from ECG to

treatment with potassium lowering intervention (insulin, sodium bicarbonate, albuterol, sodium polystyrene sulfonate, and/or hemodialysis) was 84 minutes. Thirty-six (19%) of patients were treated prior to laboratory notification of hyperkalemia. In patients treated after laboratory notification (n=141), the median time to treatment of any type was 30 minutes. When the time to treatment was examined for each particular ECG finding, there were no significant differences in time to treatment observed (Table 3).

Twenty-eight patients (15%, 95%CI: 10.4%-20.7%) were identified to have an adverse event within 6 hours of the measurement of hyperkalemia. The mean potassium value in patients with an adverse event was 7.5mEq/L (SD=0.7; range 6.5-8.9). The median time from the ECG to the adverse event was 47 minutes. Adverse events included symptomatic bradycardia (n=22, 12%), ventricular tachycardia (n=2, 1%), cardiopulmonary resuscitation (n=2, 1%) and death (n=4, 2%).

No patients had an adverse event after treatment with calcium (0%; 95%CI: 0-4%). Only one patient had an adverse event after potassium lowering intervention (0.6%; 95%CI: <0.01%-3.5%). This patient was treated with insulin and glucose at 130 minutes and developed symptomatic bradycardia at 290 minutes from the time of the ECG. All other adverse events occurred prior to the administration of any medications for the treatment of hyperkalemia. There was no significant difference in time from ECG to treatment with calcium or potassium lowering intervention between patients with an adverse event and without adverse event (Table 3).

The most common adverse event was symptomatic bradycardia. Of the 28 patients who experienced an adverse event(s), 22 patients had symptomatic bradycardia. One patient with symptomatic bradycardia was not treated because he was “comfort measures only”. All of the other patients with symptomatic bradycardia (n=21) were treated with calcium chloride or calcium gluconate. Treatments also included atropine (n=8), dopamine (n=2), epinephrine (n=1), and cardiac pacing (n=2). All the patients with symptomatic bradycardia that received treatment (n=21) improved with the interventions.

Ventricular tachycardia occurred as an adverse event in two patients. Both patients demonstrated ventricular tachycardia on their initial ECG. The first patient had a potassium level of 7.5 mEq/L associated with ventricular tachycardia and hypotension. Her ventricular tachycardia and hypotension resolved with the administration of calcium chloride. The second patient had a potassium level of 8.2 mEq. Seven minutes after the ECG was obtained, the patient developed pulseless ventricular tachycardia. She survived to discharge after being treated with cardiopulmonary resuscitation, defibrillation, and calcium chloride.

Cardiopulmonary resuscitation was also performed in an intubated dialysis patient hospitalized for 22 days for pneumonia and acute respiratory distress syndrome. This patient was newly hyperkalemic (7.7 mEq/L) on morning labs, and ECG demonstrated atrial fibrillation with a heart rate of approximately 52 bpm and new QRS prolongation (182msec, prior ECG QRS duration 88msec). One minute after the ECG the patient developed pulseless electrical activity; cardiopulmonary resuscitation was initiated, and subsequently the patient died.

Three additional deaths occurred in patients who were “comfort measures only”. These three patients had severe concurrent acute medical illness (one patient with bowel perforation, one patient with large anterior wall myocardial infarction, and one patient with hemorrhagic shock in the setting of DIC and retroperitoneal bleed). While these three patients are included in the adverse events analysis, it is unclear whether their deaths were due to hyperkalemia, their associated acute medical illness, or a combination of both.

All of the 28 patients with an adverse event within six hours had an ECG with evidence of at least one hyperkalemic abnormality (Table 2). QRS prolongation (n=22) and bradycardia of less than 50 bpm (n=17) were the most common ECG abnormalities identified. Of the patients with QRS prolongation, the average QRS duration was 152 msec (SD 35 msec, range 116-266 msec). The majority of the hyperkalemic patients with an adverse event had more than one hyperkalemic ECG abnormality (n=24, 86%). Two patients had isolated bradycardia (HR<50), one patient had isolated junctional rhythm, and one patient had isolated QRS prolongation (122msec, previous ECG QRS duration 96msec). No short-term adverse events occurred among patients with peaked T waves or PR prolongation as their only ECG manifestation of hyperkalemia.

QRS prolongation had a statistically significant association with short-term adverse events (OR 6.11, 95%CI 2.35-15.92), as did the presence of junctional rhythm (OR 25.24, 95%CI 7.24-88). Additionally, bradycardia (HR<50 bpm) had a strong positive association with short-term adverse event (OR 60.27, 95%CI 17.28-210.18). All patients with a ventricular escape rhythm (n=4) developed a short-term adverse event. There was no statistically significant correlation between peaked T waves and short-term adverse events (OR 0.73, 95%CI: 0.29-1.84). Analysis of the association of PR prolongation and adverse events was limited because the majority of the patients who had a short-term adverse event were in a nonsinus rhythm (junctional rhythm n=11, ventricular escape rhythm n=6, atrial fibrillation n=4, 2nd degree heart block n=1). Of the six patients with short-term adverse events who could have a PR interval measured, three patients had PR prolongation.

Limitations

Myocardial ischemia, metabolic acidosis, stroke and LVH have been associated with T wave changes that mimic hyperkalemia.[1,13,14] Consequently, peaked T waves may have been attributed to hyperkalemia when rather the T wave abnormalities were due to another underlying condition. In addition, atypical changes of hyperkalemia have been described (such as ST segment elevation or depression, pseudonormalization of T-wave inversions) and were not examined in this study.[9]

Some patients had additional metabolic abnormalities. Concurrent metabolic disturbances are thought to either lessen (hypercalcemia, hypernatremia, alkalemia) or worsen (hypocalcemia, hyponatremia, acidemia) the ECG manifestations of hyperkalemia.[3] Patients with hypercalcemia (2%), hypernatremia (4%) and/or alkalemia (10%) were less common in our study than patients with hypocalcemia (21%), hyponatremia (41%), and/or acidosis (67%). Accordingly, the low sensitivity of the ECG for hyperkalemia seen in our study is more remarkable in light of the concurrent metabolic disturbances present in our patients.

Our definition of symptomatic bradycardia required both treatment and symptoms. Symptomatic bradycardia may have been underestimated because symptoms may have been present but not recorded. Fortunately, the number of potential missed patients is low (n=4). All patients treated with atropine, epinephrine, dopamine and/or pacing had recorded symptoms and were classified as symptomatic bradycardia. Four patients were identified who were treated with calcium and had a documented HR of <50bpm within 6 hours, but were asymptomatic and therefore not classified as an adverse event. All 4 of these patients had an ECG with hyperkalemic abnormalities.

Almost all of the patients in the study (n=177, 95%) received treatment after the ECG was performed. Timing and type of treatment was not standardized. Treatment differences had the potential to confound the associations between specific ECG abnormalities and adverse events. However, this was not observed to have occurred. All adverse events occurred prior to treatment with calcium. All but one adverse event occurred prior to potassium lowering intervention. There was no significant difference in time to treatment between patients with or without adverse event. There was also no significant difference in time to treatment for each particular ECG finding.

Discussion

This paper is the largest study to date that reports the frequency of specific ECG abnormalities and their relationship to short term adverse events in patients with severe hyperkalemia (K≥6.5 mEq/L). The sensitivity of the ECG to demonstrate hyperkalemic changes was low (71%, 95% CI: 64.4%-77.3%). Short-term adverse events were uncommon (15%, 95%CI: 10.4%-20.7%). All patients who experienced a short-term

adverse event had a preceding ECG that demonstrated at least one hyperkalemic abnormality. An increased likelihood of short-term adverse event was found for hyperkalemic patients whose ECG demonstrated QRS prolongation, bradycardia (HR<50), and/or junctional rhythm.

Our finding that more than one quarter (29%, 95%CI: 22.7-35.6%) of patients with severe hyperkalemia have an ECG without hyperkalemic ECG abnormalities is consistent with previous research. Studies of patients with hyperkalemia (defined as either ≥6.0 or ≥ 6.5 mEq/L) have reported the absence of hyperkalemic ECG abnormalities in 36-54% of patients.[1,5-7,13,16] One potential explanation for the lack of ECG findings in previous studies could be the small magnitude of potassium elevation (mean 6.4-6.6 mEq/L). However, the insensitivity of the ECG for hyperkalemia persists in our study, despite a higher mean serum potassium level (7.1 mEq/L, SD=0.6mEq/L).

The reason for a normal ECG in the setting of severe hyperkalemia is not definitively known. Current theory is that the rate of change of potassium is more important in the development of cardiotoxicity than the absolute potassium value.[3,4,8] In patients with a slow rate of rise of potassium, the potassium channels are thought to be able to adjust to higher concentrations of extracellular and intracellular potassium and thus avoid cardiotoxicity.[4] This theory has been supported by previous reports that ECG findings typically occur in patients with chronic kidney disease at higher serum potassium levels than those with more preserved renal function.[4,8,9] We are unable to comment on this phenomenon, as all of our episodes occurred in patients with impaired renal function (Table 1). Our study design also did not allow for the determination of the rate of the rise of potassium in our patients.

The most common ECG findings of hyperkalemia in our study were new QRS prolongation >110ms (43%, 95% CI: 36.7%-50.8%) and peaked T waves (30%, 95% CI: 24.1%-37.2%). Four previous studies identified peaked T waves as the most common ECG finding of hyperkalemia, noted 28-52% of the time.[1,5-7] In contrast, our rate of QRS prolongation is higher than previously reported. The four previous studies reported that 7-17% of patients with hyperkalemia had QRS prolongation of >120ms. For comparison, more than one third of our patients had new QRS prolongation >120ms (36%, 95%CI: 29.1-42.7%). This may be due to the higher degree of hyperkalemia in our study (mean 7.1 mEq/L vs 6.1-6.6 mEq/L). PR prolongation, bradycardia (HR<50), junctional rhythm, ventricular escape rhythm and ventricular tachycardia were identified less frequently in our study, consistent with previously reported results.

Our clinical experience leads us to believe that many physicians overemphasize the ECG finding of peaked T waves, at the expense of recognition of other ECG findings of hyperkalemia. In contrast, our study demonstrates that the appearance of peaked T waves in hyperkalemia is inconsistent. Only 30% of ECGs demonstrated peaked T waves (95% CI: 24.1%-37.2%). In addition, more than half of the ECGs found to have hyperkalemic ECG abnormalities (such as QRS prolongation, PR prolongation, bradycardia and/or junctional rhythm) did not have peaked T waves (57%). For

example, of the 82 episodes in our study with QRS prolongation, 57 episodes (71%) did not have peaked T waves. Patients with short-term adverse events also frequently had ECGs without peaked T waves (75%). Finally, there was no statistically significant correlation between the presence of peaked T waves and the development of a short-term adverse event.

To our knowledge, only two other studies have reported the relationship between ECG findings of hyperkalemia and the development of adverse events. In An's study of patients with K≥6.5 mEq/L, ECG findings were correlated with survival to hospital discharge. [2] Unfortunately, significant limitations prevent An's findings from being applied to the risk stratification of hyperkalemic patients. The most common ECG finding of hyperkalemia was "asystole or pulseless electrical activity", a reflection of the fact that 20% of the hyperkalemic patients were diagnosed at time of cardiac arrest. In addition, the time from ECG to death was not reported. A significant lapse of time between the ECG and death is suggested by the report that almost half (47%) of patients were not hyperkalemic at the time of their death.

In Montague's study of 90 patients with K≥6.0 mEq/L, 14 patients experienced arrhythmia or cardiac arrest. Fewer than half of the patients with arrhythmia or cardiac arrest were noted to have new T-wave peaking or symmetry.[1] Montague's finding is consistent with our observation that only 25% of patients with short-term adverse events had peaked T waves. However, the presence or absence of other ECG manifestations of hyperkalemia in these patients (such as bradycardia, junctional rhythm, PR prolongation, QRS prolongation) are not commented upon. In addition, the time between the ECG and the adverse event is not reported. It is unknown whether or not serial ECGs would have detected hyperkalemic abnormalities prior to the adverse event.

Our study methods were designed to minimize the limitations noted above. No patients experienced a cardiac arrest prior to or during the performance of the ECG. Multiple ECG manifestations of hyperkalemia were examined. All adverse events occurred within six hours of the ECG, with a median time from ECG to adverse event of 47 minutes.

We report an overall short-term (6 hour) adverse event rate of 15% (95%CI: 10.4%-20.7%), consistent with previous research of hyperkalemic patients[1,12,16]. All of the adverse events occurred prior to treatment with calcium. All but one of the adverse events occurred prior to potassium lowering intervention. There was no significant difference in time to treatment between patients with or without adverse events. Adverse events occurred either prior to the laboratory notification of hyperkalemia

(n=16, 59%) or shortly after the laboratory notification of hyperkalemia (mean 36 min; SD 19 min). The very low rate of adverse events after treatment (0.6%; 95%CI: <0.01%-4%) suggests that the treatment regimens used were successful in preventing adverse events.

Our study suggests that one approach to decreasing adverse events in hyperkalemia would be to focus on the early identification of patients who are at higher risk of adverse events. These patients could then be prioritized to rapid treatment (either empirically if clinical suspicion for hyperkalemia is high or after laboratory notification if hyperkalemia was not clinically suspected). In our study, an increased likelihood of adverse events was found for hyperkalemic patients whose ECG demonstrated QRS prolongation, bradycardia (HR<50), and/or junctional rhythm. Future research is needed to evaluate whether earlier treatment in hyperkalemic patients with these ECG findings decreases adverse events.

Conversely, could the ECG also be used to identify patients who are unlikely to have an adverse event? In our study, all patients who experienced a short-term adverse event had a preceding ECG that demonstrated hyperkalemic abnormality (100%, 95%CI 85.7-100%). In fact, the majority of the hyperkalemic patients with a short-term adverse event had more than one hyperkalemic ECG abnormality (86%). While the small number of adverse events in our study resulted in confidence intervals that are too broad to conclude that hyperkalemia patients without ECG abnormalities do not have short term adverse events, they are likely uncommon.

In conclusion, our results agree with previous studies that the ECG is insensitive for the diagnosis of hyperkalemia. The absence of hyperkalemic ECG abnormalities does not exclude severe hyperkalemia. However, our study also demonstrates that the ECG continues to be a valuable tool in the risk stratification and management of hyperkalemia patients. Individual patients have different levels of hyperkalemia that can be tolerated without an adverse event. In our study, all patients with an adverse event had a preceding ECG that demonstrated hyperkalemic abnormalities. An increased likelihood of adverse events was found for hyperkalemic patients whose ECG demonstrated QRS prolongation, bradycardia (HR<50), and/or junctional rhythm. Accordingly, patients with these hyperkalemic ECG abnormalities warrant an aggressive monitoring and treatment plan.

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Tables

Table 1. Demographics and laboratory results of patients with severe hyperkalemia (K≥6.5 mEq/L)

Patient Characteristics	**N=188**
Age, mean (SD), y	68 (16)
Gender, n (%) male	102 (54)
Race, n (%)	
White	177 (94)
Black	4 (2)
Hispanic	1 (0.5)
Other	6 (3)
Established Hemodialysis, n (%)	32 (17)
Potassium level, mean (SD), mEq/L	7.1 (0.6)
Sodium	
Sodium level, mean (SD), mEq/L	135 (6)
Mild hyponatremia: 130-134 (%) mEq/L	51 (27)
Moderate hyponatremia: 121-129 (%) mEq/L	24 (13)
Severe hyponatremia: <121 (%) mEq/L	2 (1)
Hypernatremia: >145 (%) mEq/L	7 (4)
Calcium*	
Calcium level, mean (SD) mEq/L	9.0 (1.0)
Mild hypocalcemia: 7.6-8.4 (%) mg/dL	30 (16)
Severe hypocalcemia: <7.6 (%) mg/dL	9 (5)
Hypercalcemia: >10.2 (%), mg/dL	3 (2)
Bicarbonate	
Bicarbonate level, mean (SD), mEq/L	19 (9)
Mild acidosis: bicarbonate 15-22 (%), mEq/L	76 (40)
Severe acidosis: bicarbonate <15 (%), mEq/L	50 (27)
Alkalosis: bicarbonate >29 (%) mEq/L	18 (10)
Estimated glomerular filtration rate, mean (SD), mL/min/1.73 m^2	
<15 mL/min/1.73 m^2, n, (%)	94 (50)
15-29 mL/min/1.73 m^2, n, (%)	64 (34)
30-59 mL/min/1.73 m^2, n, (%)	28 (15)
60-89 mL/min/1.73 m^2, n, (%)	2 (1)
≥90 mL/min/1.73 m^2, n, (%)	0

Calcium level was not measured in 26 events (14%). Estimated glomerular filtration rate was calculated using the MDRD study equation.

Table 2. Electrocardiographic Findings in Patients with Severe Hyperkalemia (K^+≥6.5mEq/L)

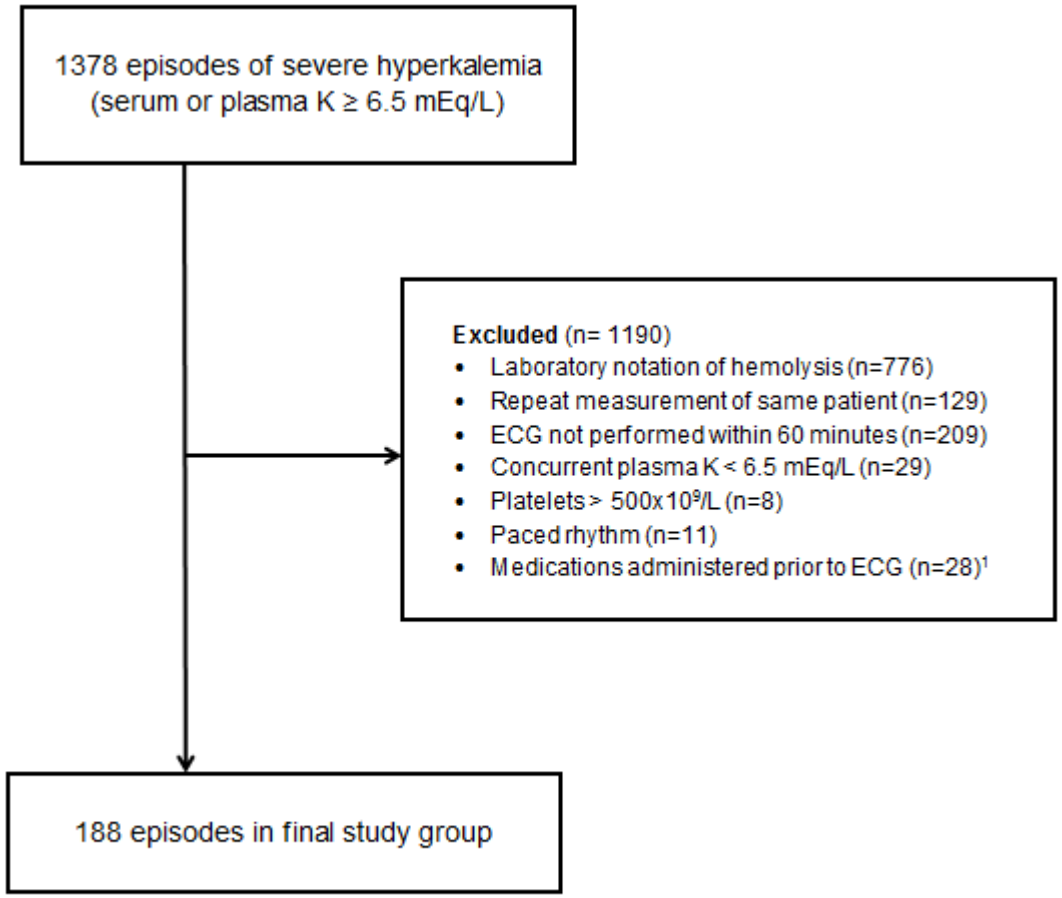
	All Patients		Patients with Adverse Event		Patients without Adverse Event		Odds Ratio for Adverse Event	
Characteristic	**N=188**	**Frequency (95% CI)**	**N=28**	**Frequency (95% CI)**	**N=160**	**Frequency (95% CI)**	**95% CI**	
Any ECG abnormality suggestive of hyperkalemia	134	71% (64.4-77.3)	28	100% (85.7-100)	106	66% (58.6-73.1)		
Peaked T waves	57	30% (24.1-37.2)	7	25% (12.4-43.6)	50	31% (24.6-38.9)	0.73	0.29-1.84
PR prolongation*	28	15% (10.5-20.7)	3	50% (18.8-81.2)	25	16% (10.8-22.1)	4.48	0.85-23.51
QRS prolongation	82	43% (36.7-50.8)	22	79% (60.1-90.1)	60	38% (30.4-45.2)	6.11	2.35-15.92
Mild QRS prolongation (111-119 msec)	15	8% (4.8-12.8)	2	7% (0.9-23.7)	13	8% (4.7-13.5)		
Left Bundle Branch Block	11	6% (3.2-10.3)	3	11% (2.9-28)	8	5% (2.4-9.7)		
Right Bundle Branch Block	27	14% (10-20.1)	10	36% (20.1-54.2)	17	11% (6.7-16.4)		
Nonspecific Intraventricular Conduction Delay	29	15% (10.9-21.3)	7	25% (12.4-43.6)	22	14% (9.2-20)		
Bradycardia (HR<50 bpm)	21	11% (7.4-16.5)	17	61% (42.3-76.5)	4	3% (0.8-6.5)	60.27	17.28-210.18
Junctional Rhythm	15	8% (4.8-12.8)	11	39% (23.5-57.6)	4	3% (0.8-6.5)	25.24	7.24-88
Ventricular Escape Rhythm	4	2% (0.6-5.5)	4	14% (5.1-32.1)	0	0% (0-2.8)		
Ventricular Tachycardia	2	1% (0-4)	2	7% (0.9-23.7)	NA			
2nd Degree Heart Block	1	0.5% (0-3.3)	1	4% (0-19.2)	0	0% (0-2.8)		

Patients may have had more than one hyperkalemic ECG abnormality.
*PR interval measured in 143 episodes. PR interval was unable to be measured in 45 episodes due to nonsinus rhythm.

Table 3. Frequency and timing of treatment in hyperkalemic patients with specific ECG characteristics

	Calcium Treatment N (%)	Odds Ratio for Calcium Treatment	Mean Time to Calcium Treatment	Difference in Mean Time to Calcium Treatment	Potassium Lowering Intervention N (%)	Odds Ratio for Potassium Lowering Intervention	Mean Time to Potassium Lowering Intervention	Difference in Mean Time to Potassium Lowering Intervention
Adverse Event								
Yes	25 (89)	OR 7.353 (2.13-25.34)	84	-13 (-40 to 14)	24 (86)	OR 0.32 (0.09-1.13)	77	-14 (-38 to 10)
No	85 (53)		97		152 (95)		91	
Peaked T Waves								
Yes	42 (74)	OR 2.59 (1.31-5.13)	93	-2 (-26 to 22)	56 (98)	OR 5.13 (0.65-40.74)	79	-15 (-32 to 2)
No	68 (52)		95		120 (92)		94	
Wide QRS								
Yes	58 (71)	OR 2.51 (1.36-4.62)	83	-11 (-32 to 10)	75 (91)	OR 0.53 (0.16-1.74)	91	-7 (-25 to 11)
No	52 (49)		94		101 (95)		98	
Bradycardia								
Yes	18 (86)	OR 4.89 (1.39-17.24)	88	-7 (-39 to 24)	20 (95)	OR 1.41 (0.17-11.51)	86	-3 (-29 to 23)
No	92 (55)		95		156 (93)		89	
Junctional								
Yes	12 (80)	OR 3.06 (0.83-11.24)	92	-3 (-40 to 34)	13 (87)	OR 0.4 (0.08-2.01)	85	-4 (-35 to 27)
No	98 (57)		95		163 (94)		89	
PR prolonged								
Yes	16 (57)	OR 1.22 (0.53-2.81)	91	-5 (-38 to 28)	26 (93)	OR 0.59 (0.11-3.22)	94	7 (-15 to 29)
No	60 (52)		96		110 (96)		87	

Figures



[1] Atropine, dopamine, epinephrine, norepinephrine, vasopressin, calcium chloride, calcium gluconate, sodium bicarbonate, albuterol, insulin, and/or sodium polystyrene sulfonate

Figure 1. Flow diagram for study inclusion.

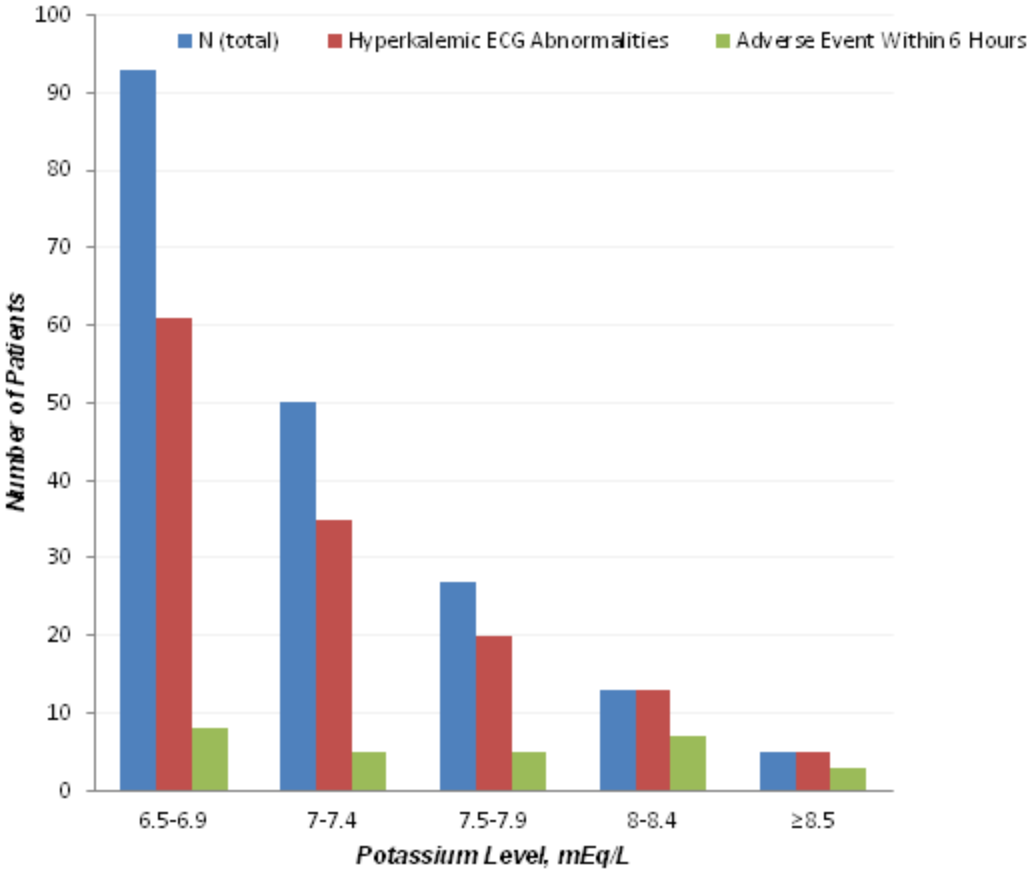


Figure 2. Hyperkalemic ECG abnormalities and 6-hour adverse events in patients with severe hyperkalemia (K^+≥6.5 mEq/L).