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The relationship between serum potassium concentrations and electrocardiographic characteristics in 163,547 individuals from primary care

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ABSTRACT

Aims: Potassium disturbances are common and associated with increased morbidity and mortality, even in patients without prior cardiovascular disease. We examined six electrocardiographic (ECG) measures and their association to serum potassium levels.

Methods and results: From the Copenhagen General Practitioners' Laboratory, we identified 163,547 individuals aged ≥16 years with a first available ECG and a concomitant serum potassium measurement during 2001–2011. Restricted cubic splines curves showed a non-linear relationship between potassium and the Fridericia corrected QT (QTcF) interval, T-wave amplitude, morphology combination score (MCS), PR interval, P-wave amplitude and duration. Therefore, potassium was stratified in two intervals K: 2.0–4.1 mmol/L and 4.2–6.0 mmol/L for further analyses. Within the low potassium range, we observed: QTcF was 12.8 ms longer for each mmol/L decrease in potassium ($p < 0.0001$); T-wave amplitude was 43.1 μV lower for each mmol/L decrease in potassium ($p < 0.0001$); and MCS was 0.13 higher per mmol/L decrease in potassium ($p < 0.001$). Moreover, P-wave duration and PR interval were prolonged by 2.7 and 4.6 ms for each mmol/L decrease in potassium ($p < 0.0001$), respectively. Within the lowest potassium range (2.0–4.1 mmol/L) P-wave amplitude was 3.5 μV higher for each mmol/L decrease in potassium ($p < 0.0001$). Within the high potassium range associations with the above-mentioned ECG parameters were much weaker.

Introduction

The incidence of hypokalaemia is up to 21% in hospitalized patients and 2–3% in outpatient contacts [1–5], while hyperkalaemia is seen in approximately 10% of hospitalized patients and 1% of outpatient visits [5]. Both hypo- and hyperkalaemia are associated with increased morbidity and mortality [6–8], even in patients with no prior cardiovascular disease [1].

Potassium is very important for the myocardial action potential, and disruption of the potassium gradient across the cell membrane can lead to electrophysiological changes and occurrence of fatal arrhythmias [9–11]. The Multiple Risk Factor Intervention Trial demonstrated that a reduction in serum potassium of 1 mmol/L was associated with a 28% increase in ventricular arrhythmias in men [12]. The electrocardiogram (ECG) is commonly used as a diagnostic tool in both primary care and in more specialized settings, and the ECG may reveal changes indicating potassium disorders. Recognizing these changes is crucial to prevent adverse events, especially in high-risk patients [13,14].

ECG abnormalities related to hyperkalemia include peaked T-waves, P-wave widening and flattening, prolonged PR interval, prolonged QRS duration, conduction block and bradycardia [13,15,16]. Conversely, the

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most common ECG changes seen in individuals with hypokalemia are increased amplitude and width of the P-wave, prolonged PR interval, decreased T-wave amplitude, prolonged QT-interval, ST-segment depression and appearance of U-waves or bifid T-waves [15,17].

The great majority of previous studies have shown that these ECG characteristics are most commonly seen in individuals with moderate to severe potassium abnormalities, and that mild deviations are not reflected on the ECG [9,15,18]. However, one study of 12 hemodialysis patients showed that even small changes in potassium concentrations within the normal range cause significant ECG changes [14]. Moreover, Kanters et al. recently showed a linear relationship between serum potassium and the Fridericia corrected QT interval (QTcF) and T-wave amplitude in 6314 presumed healthy individuals [19]. Based on these studies, it is important to examine whether specific potassium concentrations, also within the normal range, can lead to significant ECG abnormalities. We investigated the relationship between different serum potassium levels and six ECG parameters (QTcF, T-wave amplitude, T-wave morphology (expressed as MCS), P-wave duration, P-wave amplitude and PR interval) using a large primary care study population with >160,000 patients who had an ECG recording and a concomitant potassium measurement between 2001 and 2011.

Methods

Our study is based on individuals from the Copenhagen ECG study, comprising a large cohort of primary care patients referred to a central core facility (Copenhagen General Practitioners' Laboratory, CGPL) for digital ECG recordings, from June 1st, 2001 to September 26th, 2011. Detailed characterization of the population has been described previously [20].

ECG analysis and interpretation

All ECGs were digitally recorded and stored in the MUSE Cardiology Information System (GE Healthcare, Wauwatosa, WI, USA) [21]. The ECGs were processed by the Marquette 12SL algorithm, version 21. All measurements were derived using median beats. This method has been validated extensively in both QT and MCS studies and this method is also frequently used in drug studies as a robust way of obtaining QT and MCS measurements. The ECGs were filtered using 0.05 to 150 Hz as suggested in the "Recommendations for the Standardization and Interpretation of the Electrocardiogram" [22].

We used the 12SL algorithm to identify atrial fibrillation, atrial flutter, LBBB, RBBB, and 12SL measurements to code the following composite ECG criteria: pathological Q waves, ST-T deviations, Sokolow-Lyon and Cornell voltage criteria for left ventricular hypertrophy and non-specific intraventricular block [23]. ECGs with non-specific intraventricular block were identified as ECGs with QRS duration >120 ms not fulfilling criteria for RBBB or LBBB. Significant ST-T deviations and pathologic Q waves (as a sign of prior myocardial infarction) were defined according to the Fourth Universal Myocardial Infarction Definition [24]. The definition of ST elevation was slightly modified as the measurement of the ST segment was performed at QRS offset +1/16 of the average RR interval known as the STM point measure in the 12SL algorithm (equivalent to about 80 ms after QRS offset in most cases). This measurement point was selected instead of the J-point because a notched or slurred appearance of the terminal QRS complex (also described as early repolarization) can make it difficult to define the J-point [20]. LBBB and non-specific intraventricular block are known to affect the repolarization of the heart causing ST-T deviations [25–27]. Consequently, when ST-T deviation was concomitantly present with LBBB or non-specific intraventricular block, we disregarded the finding. In patients with RBBB, ST-T deviations in V1-V3 are common [25]. When ST-T deviations in V1-V3 were present together with RBBB, the ST-T deviations were disregarded. Sokolow-Lyon and Cornell sex-specific voltage criteria were used to identify left ventricular hypertrophy [28,29]. The criteria for left ventricular hypertrophy has low predictive value when applied on an ECG with identified LBBB, RBBB [22]. According to the Fourth Universal Myocardial Infarction Definition, pathological Q waves, as a sign of prior myocardial infarction, were only defined when hypertrophy criteria or LBBB were absent [25].

Databases

All residents in Denmark have a personal, unique, and permanent civil registration number that enables individual linkage of administrative registries. The Danish National Patient Registry contains information about all hospital admissions since 1978. At discharge, each hospitalization is registered with one primary and, if applicable, one or more secondary diagnoses according to International Classification of Disease (ICD). Since 1994, the 10th revision (ICD-10) has been used. The National Register for Medicinal Statistics includes all dispensed prescriptions from Danish pharmacies since 1995 based on the Anatomical Therapeutic Chemical System (ATC). As the healthcare system is publicly financed and partly reimburses drug costs, all Danish pharmacies are legally required to register all dispensed drug prescriptions, providing a valid and accurate register [30]. Date of birth, date of death, and vital status were obtained from the Danish Register of Causes of Death and the Danish National Population Register.

Study population

During 2001–2011, we identified patients referred to CGPL who had digital ECG recordings accompanied by a serum potassium measurement within one day from the index ECG.

Before crosslinking of the ECGs with the blood samples, we excluded ECGs with pacemaker rhythms [31–35], ECGs with 12SL statements that can make analysis on continuous variables erroneous (e.g. 2nd or 3rd degree AV-block [31,36–38]), ECGs with left anterior or left posterior fascicular block, ECGs with RBBB or LBBB, ECGs with pathological Q waves, ECGs with ST elevation or ST depression, ECGs with left ventricular hypertrophy (according to Cornell and Sokolow-Lyon criteria), ECGs with voltage duration product >244 mV × ms, ECGs with T-wave peak amplitude in lead V5 ≤ 0 μV, ECGs with P-wave peak amplitude in lead II ≤ 0 μV, ECGs with PR-interval in lead II ≤ 0 ms, ECGs with non-specific intraventricular block or non-specific intraventricular delay, ECGs with pericarditis, ECGs not qualified for sufficient interpretation (poor quality), ECGs from patients with missing information regarding sex and age and patients younger than 16 years. A population flowchart with detailed information on the different exclusion criteria can be found in Supplementary Data Fig. S1.

The current guidelines provide a normal lower potassium limit from 3.5 to 3.8 mmol/L, while the upper normal limit is between 5.0 and 5.5 mmol/L [11,39,40]. One of the most commonly used formulae to calculate QTc is Fridericia's (QTcF). Current studies define QTcF prolongation as >480 ms in women and > 470 ms in men [41]. Individuals with a PR interval > 220 ms are categorized as having first degree atrioventricular block (AV-block) [42]. MCS was calculated based on T-wave asymmetry, flatness and notching using the following formula: MCS = Asymmetry + Notch +1.6 x Flatness [43]. An illustration of the asymmetry, flatness and notching is shown in Fig. 1. Healthy subjects have MCS values around 0.60 to 0.70 and patients with LQT2 syndrome have MCS values around 1.80 [36,37,44].

After crosslinking the first-ever available ECG with a corresponding potassium measurement, we further excluded: patients with pacemaker or implantable cardioverter defibrillator device prior to ECG, patients with congenital heart disease prior to ECG, patients with missing values on P-wave amplitude, P-wave duration, PR-interval, QRS-duration, T-wave amplitude or QTcF, patients who redeemed antidepressants or antipsychotics up to 90 days before or 10 days after ECG, patients who redeemed other drugs with QT-prolonging effect up to 30 days before or 5 days after ECG and patients with potassium

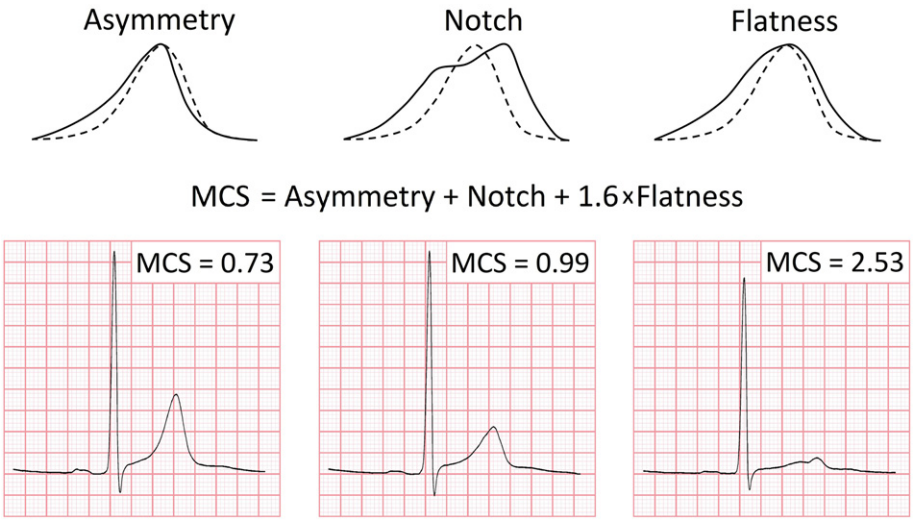

Fig. 1. Components of the Morphology Combination Score (MCS) quantifying the degree of asymmetry, flatness and notching of the T-wave. (Upper lane) Grey dashed line represents a normal T-wave. The full line represents a T-wave which from left to right is more asymmetric, notched or flat, respectively. (Lower lane) Three ECGs with a normal (left), moderately increased (middle) and strongly increased (right) Morphology Combination Score. Healthy individuals have MCS values around 0.7 with symmetric T-wave that do not appear flat. There is no notching of the T-wave. Borderline abnormal MCS values are close to 1.0. The T-waves in this range appear more asymmetric and flat but without notches. Notable abnormal MCS values are close to 2.0. In this range there is pronounced flattening and asymmetry of the T-wave with evident notching. Reproduced with permission from Hong et al. [53]

measurements >6.0 mmol/L. The population flowchart in Supplementary data Fig. 1 provides information on the ICD and ATC codes used to identify comorbidities and medication for exclusion.

Co-morbidities and medication

Besides age and gender, we identified if the following conditions were present before the index ECG recording: chronic obstructive pulmonary disease (ICD-10: J41–44), cerebrovascular disease (ICD-10: I60–69), malignancy (ICD-10: C00–97), arrhythmia (ICD-10: I44, I45, I48, I471, I495), valve disease (ICD-10: I34–37), acute myocardial infarction (ICD-10: I21–24), ischemic heart disease (ICD-10: I20, I25), cardiomyopathy (ICD-10: I119, I517, I42, I43), heart failure (ICD-10: I110, I50), thyroid disease (ICD-10: DE00-DE07), hypertension, and diabetes. No patients were diagnosed with severe arrhythmia (ICD-10: I472, I490) prior to ECG recording. Diabetes was defined as minimum two successive dispensed prescriptions of glucose-lowering drugs (ATC code A10A and A10B; insulin or oral hypoglycaemic agents) [45]. Hypertension was defined by the use of at least two concomitant antihypertensive drugs in two consecutive quarters. Patients were considered hypertensive in the second quarter [46,47]. Serum sodium and creatinine were obtained within one day from index ECG. Serum creatinine levels were used to calculate the estimated glomerular filtration rate (eGFR) of the patients [48]. Thereafter, we categorized the patients into five grades of renal function according to their eGFR level: normal and high (≥90 mL/min/1.73 m^2), mild reduction (60–89 mL/min/1.73 m^2), moderate reduction (30–59 mL/min/1.73 m2), severe reduction (15–29 mL/min/1.73 m^2) and kidney failure (<15 mL/min/1.73 m^2).

Statistical analysis

Dichotomous variables were reported as frequencies with corresponding percentages and continuous variables were reported as medians and 1st to 3rd quartiles (Q1-Q3). Differences between variables were compared using chi-square and Kruskal-Wallis tests, as appropriate. Statistical analyses were performed on each patient's first ECG and related potassium measurement.

Linear regression models were created to determine the relationship between serum potassium levels and QTcF, T-wave amplitude in lead V5, MCS, PR interval and P-wave amplitude, and P-wave duration in lead II, respectively. The assumption of linearity between serum potassium level and each of the six ECG parameters was not fulfilled. Therefore, we further investigated the relationship between serum potassium and each of the six ECG parameters using restricted cubic splines. The L-shaped splines curves shown in Fig. 2 and Fig. 3 indicated that the association of potassium on the six ECG parameters was not linear throughout all potassium levels. Based on these observations, serum potassium was stratified according to two intervals: 2.0–4.1 mmol/L, and 4.2–6.0 mmol/L. We tested also for interaction in the linear regression model and found interaction between QTcF and T-wave amplitude in lead V5 and gender. Only interaction terms with $p < 0.01$ were considered for inclusion in the multivariable model. For other analyses, $p < 0.05$ was considered significant. The multivariable model was adjusted for age, gender, serum sodium, kidney function, heart rate and comorbidities including chronic heart failure, ischemic heart disease, cardiomyopathy, hypertension and diabetes. Regression coefficients are presented with 95% confidence intervals (95% CIs).

Data management and analyses were performed with SAS (version 9.4, SAS Institute Inc., Cary, NC, USA) and R statistical software (version 3.5.0, R development core team,2018 R: A language and environment for statistical computing. R foundation for Statistical Computing, VIE, Austria. https://www.R-project.org/).

Results

Demographics

We identified 163,547 patients from the CGPL population who had a first recorded ECG and a serum potassium measurement within 1 day of the index ECG during 2001 and 2011. Population characteristics stratified by the two serum potassium groups are shown in Table 1. There was a majority of females in both groups. Approximately 31% of the patients had a potassium measurement within 2.0 and 4.1 mmol/L. The cohort consisted of 1444 patients with hypokalemia (K < 3.5 mmol/L) and 3531 patients had hyperkalemia (K > 5.0 mmol/L). T-wave peak amplitude in lead V5 was significantly lower among patients with lower compared to higher potassium ranges (292 vs 322 μV). For QTcF, we observed median values 4 ms higher among patients with lower compared to higher potassium ranges. Patients with diabetes and patients with hypertension tended to have potassium concentrations between 4.2 and 6.0 mmol/L (72.2% and 57.6% respectively). Of the patients

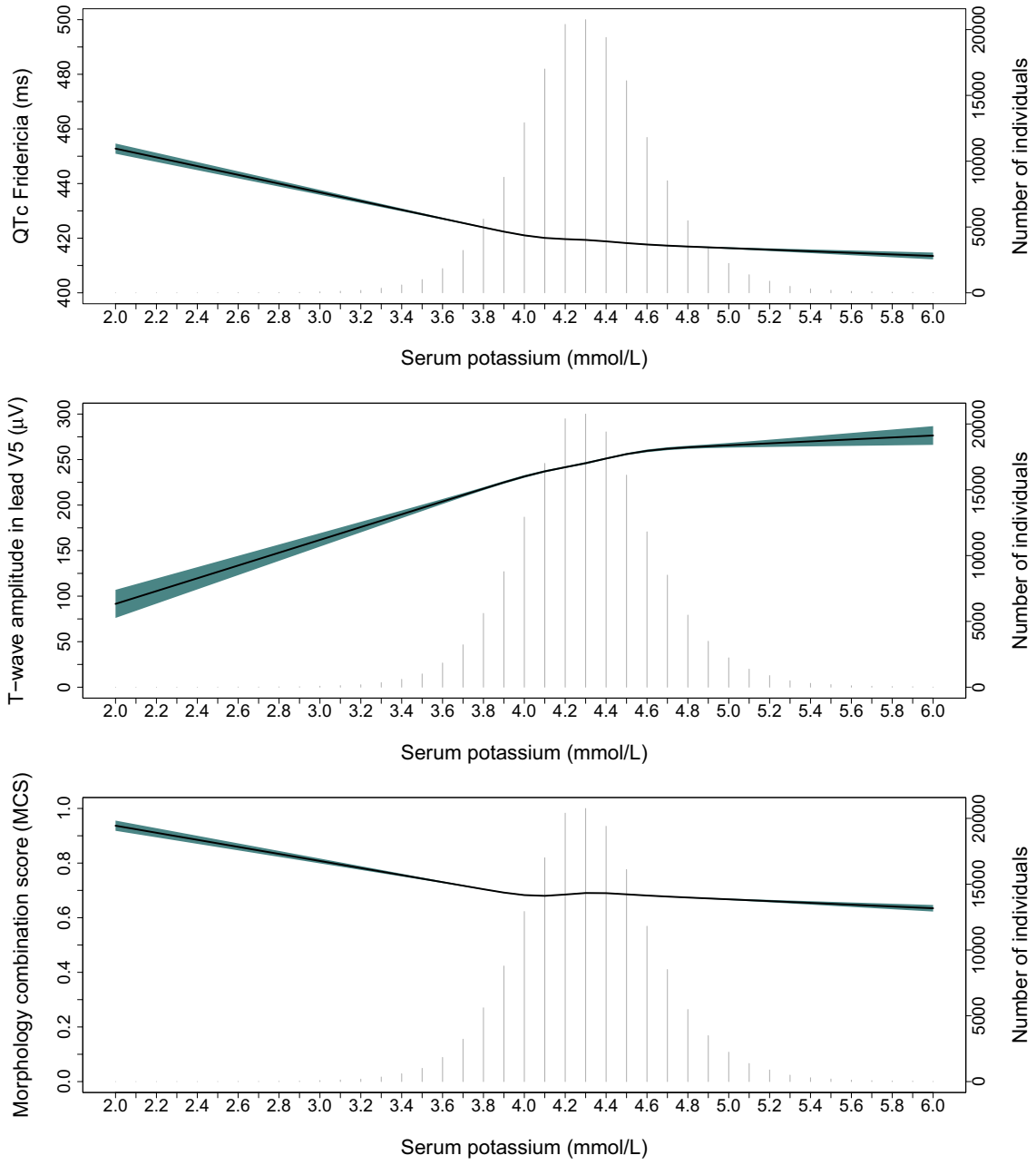

Fig. 2. Restricted cubic splines on adjusted linear regression model showing the relationship between serum potassium and QTcF, T-wave amplitude in lead V5 and MCS ($n = 163{,}547$). Adjusted for age, gender, serum sodium, kidney function, heart rate, past history chronic heart failure, ischemic heart disease, cardiomyopathy, hypertension and diabetes.

with severe reduction in renal function and kidney failure, 80.6% and 86.5% had potassium concentrations between 2.0 and 4.1 mmol/L, respectively.

Relationship between serum potassium and ECG measurements

The results of the univariable and multivariable linear regression analyses are shown in Table 2. Results are presented according to the two potassium intervals.

[K+] : 2.0–4.1 mmol/L

Overall, the association between potassium and each of the six ECG parameters was statistically significant ($p < 0.0001$) both in univariable and multivariable analyses. The following ECG parameters were strongly associated with potassium: QTcF was 17.4 ms longer per mmol/L decrease in serum potassium (95% CI -18.2; −16.5), while T-wave amplitude was 96.8 µV higher for each mmol/L increase in serum potassium (95% CI 90.06; 103.62).

The multivariable analyses showed similar results to the univariable analyses.

[K+] : 4.1–6.0 mmol/L

Within the high potassium range we noted only weak, albeit often statistically significant, associations with the six ECG parameters.

Spline curves

The spline curves shown in Figs. 2 and 3 indicated a non-linear relationship between potassium concentrations and the six ECG measurements.

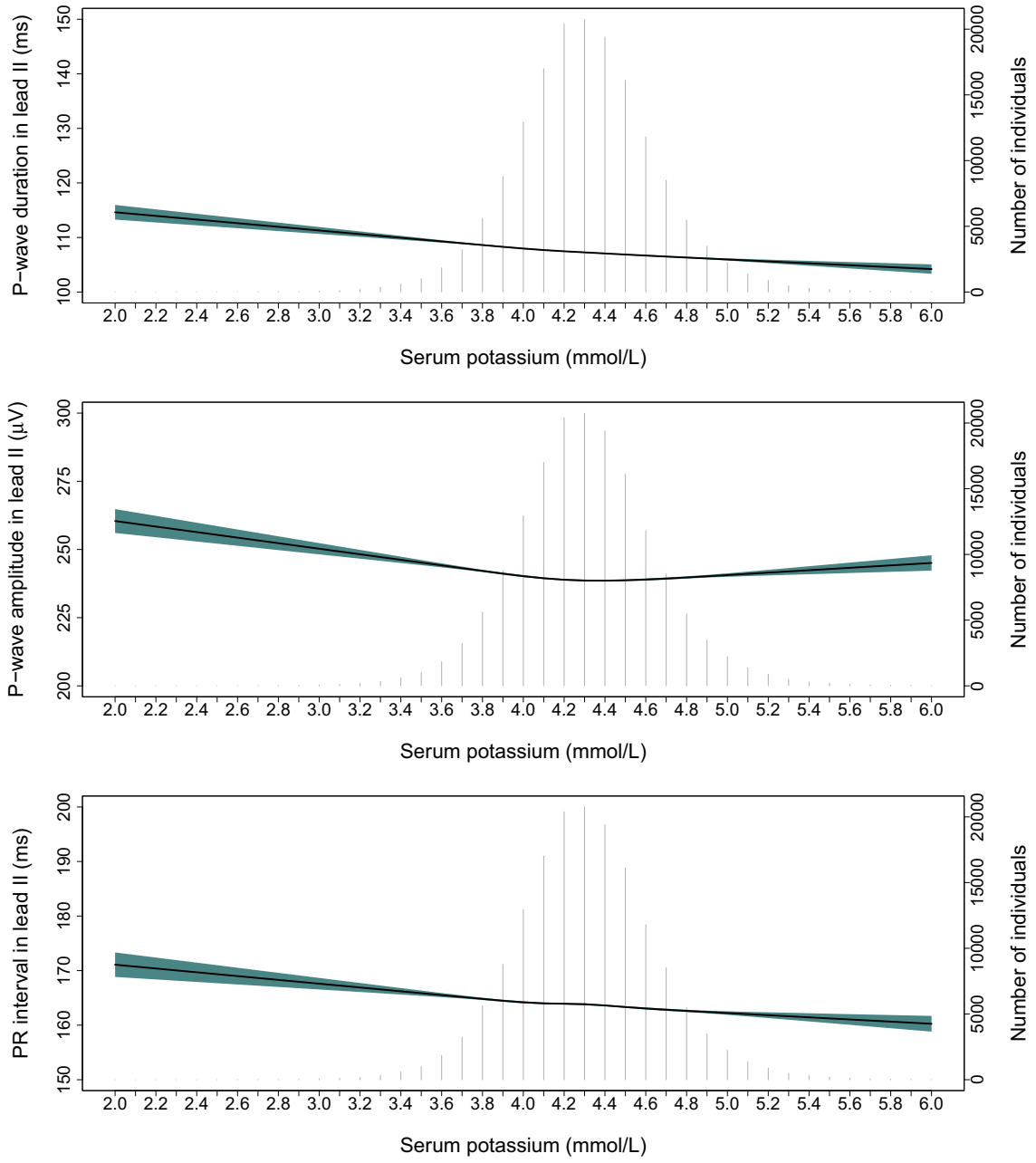

Fig. 3. Restricted cubic splines on adjusted linear regression model showing the relationship between serum potassium and P-wave duration, P-wave amplitude in lead II and PR-interval in lead II (n = 163,547). Adjusted for age, gender, serum sodium, kidney function, heart rate past history chronic heart failure, ischemic heart disease, cardiomyopathy, hypertension and diabetes.

Sensitivity analyses

To ensure that the results were not partly driven by specific morbidity, we performed linear regression analyses on individuals not having history with COPD, diabetes, hypertension, AMI, IHD, HF, malignancy, arrhythmia, cerebrovascular disease, cardiomyopathy, severe reduction of kidney function and kidney failure ($n = 133{,}231$). The results of these analyses were similar to the main analysis (Supplementary data Table S1).

Discussion

This study analyzed the association between serum potassium and QTcF, T-wave amplitude, MCS, PR interval, P-wave duration and P-wave amplitude. The major finding was that potassium values in the low range between 2.0 and 4.1 mmol/L had stronger association with each of the six ECG parameters compared to potassium values in the high range between 4.2 and 6.0 mmol/L.

Recently, Kanters et al. [19], analyzed the magnitude of repolarization changes during physiological variations of serum potassium in a cohort of 9914 patients of both healthy and unhealthy individuals. It is difficult to compare our study with the study by Kanters et al., as we had different approaches to analyses. Kanters et al. did not have many patients with low or higher potassium levels, only one patient had <3.0 mmol/L and five patients had potassium above 4.8 mmol/L, thus masking any non-linearity. In contrast, our data which was more complete in the lower and higher levels of potassium revealed a non-linear relationship between potassium and the six ECG parameters. Another important difference between the two studies is that we exclude

Table 1
Demographics ($n = 163,547$).

		K:2.0–4.1 mmol/L ($n = 51,834$)	K:4.2–6.0 mmol/L ($n = 111,713$)	Total (n = 163,547)	*p*-value
Gender	Female	32,007 (61.7)	60,387 (54.1)	92,394 (56.5)	
	Male	19,827 (38.3)	51,326 (45.9)	71,153 (43.5)	<0.0001
Age	Median [iqr]	53.6 [40.7, 65.4]	55.1 [43.9, 65.3]	54.7 [42.9, 65.4]	<0.0001
Atrial rate	Median [iqr]	70.0 [63.0, 79.0]	68.0 [61.0, 77.0]	69.0 [61.0, 78.0]	<0.0001
Ventricular rate	Median [iqr]	70.0 [63.0, 79.0]	68.0 [61.0, 77.0]	69.0 [61.0, 78.0]	<0.0001
P-wave peak amplitude in lead II (μV)	Median [iqr]	117.0 [87.0, 146.0]	117.0 [87.0, 146.0]	117.0 [87.0, 146.0]	<0.0001
P-wave duration in lead II (ms)	Median [iqr]	108.0 [100.0, 116.0]	108.0 [100.0, 116.0]	108.0 [100.0, 116.0]	<0.0001
PR interval in lead II (ms)	Median [iqr]	156.0 [142.0, 172.0]	156.0 [142.0, 172.0]	156.0 [142.0, 172.0]	0.15
QRS duration (ms)	Median [iqr]	92.0 [86.0, 98.0]	92.0 [84.0, 98.0]	92.0 [84.0, 98.0]	<0.0001
T-wave peak amplitude in lead V5 (μV)	Median [iqr]	292.0 [205.0, 400.0]	322.0 [229.0, 434.0]	312.0 [219.0, 424.0]	<0.0001
QTcF	Median [iqr]	418.0 [406.0, 431.0]	414.0 [402.0, 426.0]	415.0 [403.0, 428.0]	<0.0001
MCS	Median [iqr]	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.6 [0.5, 0.7]	0.57
Prolonged QTcF		266 (0.5)	229 (0.2)	495 (0.3)	<0.0001
Type I AV-block		719 (1.4)	1520 (1.4)	2239 (1.4)	0.69
Serum sodium (mmol/L)	Median [iqr]	141.0 [140.0, 143.0]	141.0 [139.0, 142.0]	141.0 [140.0, 143.0]	<0.0001
Kidney function	Normal and high	21,523 (19.3)	12,036 (23.2)	33,559 (20.5)	
	Mild reduction	72,079 (65.5)	32,362 (62.4)	104,441 (63.9)	
	Moderate reduction	17,640 (15.8)	7326 (14.1)	24,966 (15.3)	
	Severe reduction	426 (0.4)	103 (0.2)	529 (0.3)	
	Kidney failure	45 (0.0)	7 (0.0)	52 (0.0)	<0.001
Chronic obstructive pulmonary disease		777 (1.5)	1932 (1.7)	2709 (1.7)	0.0007
Diabetes		5018 (9.7)	12,432 (11.1)	17,450 (10.7)	<0.0001
	Insulin	1074 (2.1)	2974 (2.7)	4048 (2.5)	<0.0001
	Non-insulin	4762 (9.2)	11,777 (10.5)	16,539 (10.1)	<0.0001
Cancer		1703 (3.3)	3554 (3.2)	5257 (3.2)	0.27
Cerebrovascular disease		1046 (2.0)	2154 (1.9)	3200 (2.0)	0.23
Hypertension		4429 (8.5)	6008 (5.4)	10,437 (6.4)	<0.0001
Arrhythmia		743 (1.4)	1400 (1.3)	2143 (1.3)	0.0031
Cardiomyopathy		81 (0.2)	143 (0.1)	224 (0.1)	0.17
Heart failure		422 (0.8)	915 (0.8)	1337 (0.8)	0.94
Ischemic heart disease		1092 (2.1)	2653 (2.4)	3745 (2.3)	0.0008
Acute myocardial infarction		438 (0.8)	1139 (1.0)	1577 (1.0)	0.0008
Thyroid disease		890 (1.7)	1691 (1.5)	2581 (1.6)	0.0023

Table 2
Results of the linear regression model. The multivariable model was adjusted for: age, gender, sodium, creatinine, antidiabetic medication, history with hypertension, heart failure, ischemic heart disease and cardiomyopathy (n = 163,547). The results show differences in ECG parameters per 1 mmol/L increase/decrease in potassium.

	Variable	Univariable analysis	CI.95	p-Value	Multivariable analysis	CI.95	p-Value
		Coefficient			Coefficient		
QTcF (ms)							
K: 2.0–4.1 mmol/L							
	Serum potassium	−17.36	[−18.22; −16.49]	<0.0001	−12.8	[−13.82; −11.72]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	−4.07	[−4.50; −3.63]	<0.0001	−5.11	[−5.69;-4.54]	<0.0001
T-wave amplitude V5 (μV)							
K: 2.0–4.1 mmol/L							
	Serum potassium	96.84	[90.06; 103.62]	<0.0001	43.22	[35.35; 51.10]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	22.25	[18.43; 26.07]	<0.0001	38.15	[33.29; 43.01]	<0.0001
MCS							
K: 2.0–4.1 mmol/L							
	Serum potassium	−0.09	[−0.10; −0.08]	<0.0001	−0.13	[−0.14; −0.12]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	−0.02	[−0.03; −0.02]	<0.0001	−0.02	[−0.02; −0.02]	<0.0001
P-wave duration II (ms)							
K: 2.0–4.1 mmol/L							
	Serum potassium	−4.52	[−5.16; −3.87]	<0.0001	−2.66	[−3.28;−2.04]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	−0.42	[−0.74; −0.10]	0.0099	−1.76	[−2.07; −1.45]	<0.0001
P-wave amplitude II (μV)							
K: 2.0–4.1 mmol/L							
	Serum potassium	−10.01	[−11.99; −8.03]	<0.0001	−3.48	[−5.36; −1.60]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	0.56	[−0.46; 1.58]	0.2834	1.94	[0.96; 2.92]	<0.0001
PR-interval (ms)							
K: 2.0–4.1 mmol/L							
	Serum potassium	−6.37	[−7.43; −5.30]	<0.0001	−4.56	[−5.56; −3.55]	<0.0001
K: 4.2–6.0 mmol/L							
	Serum potassium	0.81	[0.26;1.36]	0.0041	−2.39	[−2.92; −1.87]	<0.0001

patients administered drugs with known or possible QTcF prolongation and/or TdP, whereas Kanters et al. excluded participants with self-reported myocardial infarction/angina pectoris, history of cerebrovascular incident, diabetes, Hba1c > 42, eGFR lower than age- and gender-adjusted 5% percentile and/or intake of any cardiac medication.

Another study by Dillon et al. from 2015 investigated whether ECG repolarization measures can be used to detect slight changes in serum potassium levels in 12 hemodialysis patients [13]. They looked at the slope of the terminal part of the T-wave, the amplitude of the T-wave, the center of gravity of the T-wave, the ratio of the amplitude of the T-wave to amplitude of the R-wave and the center of gravity of the last 25% of the area under the T-wave curve. Using linear mixed models, the authors found significant correlations with potassium levels for five of the six ECG parameters, not with the center of gravity of the last 25% of the area under the T-wave curve. Our study confirms that there is an association between deviations in potassium concentrations and changes in T-wave amplitude. Furthermore, our study shows that MCS is also correlated with potassium, which is in agreement with the findings by Dillon et al. [14], although the parameters included in the MCS formula and the repolarization parameters are not identical.

Numerous studies have analyzed ECG changes in patients with hypo-or hyperkalemia [1,13,16,17,49]. Having a linear relationship between lower potassium concentrations (2.0–4.1 mmol/L) and each of the six ECG parameters, our study showed that strong associations between the six ECG measurements not only can be observed in participants with hypokalemia (<3.5 mmol/L), but also in individuals with low normal potassium concentrations (3.5–4.1 mmol/L).

Strengths and limitations

The main strength of this study is the ability to combine information from recorded ECGs and blood test results with detailed information in registries about concomitant pharmacotherapy, and comorbidity. It is a strength that the vast majority of primary care patients who have blood withdrawn and ECGs taken in the Copenhagen area are referred to one core facility. Our population represents patients from primary care settings, which is relatively generalizable in western countries where patient follow-up of patients is quite common.

The observational nature of the study is a limitation. As such, our results should be interpreted only as associative and not causal relations to potassium. Additionally, the design precludes assurance that unmeasured potential confounders could have been present and biased the results.

For patients who were prescribed drugs, we have no precise information about the dose of the prescribed medication and we cannot be sure that patients took their medicine despite the drug redemptions. Furthermore, we did not have information about the quality of the blood samples at the time of analysis, fact that can lead to inclusion of samples with different degrees of hemolysis. This form of bias can results with misclassification of the patients. Thus, patients with hypokalemia could be classified as having normal potassium concentrations or patients with normal potassium levels could be classified as having hyperkalemia. However, studies have shown that hemolysis was most common in emergency departments [50,51] and that most laboratories had a hemolysis rate <3% [52].

The registry does not contain information about ECG referral indication at CGPL, therefor we cannot exclude selection bias. The filter settings used for pre-processing do not markedly affect the T-wave because of their relatively low frequency content compared to the QRS complex, nor do they distort the ST-segment. As such, the filtering does not affect QT or MCS measurements.

Finally, blood potassium analysis has been performed in plasma and not serum at the end of the study period, which represents a limitation for the current paper.

Conclusion

The association of potassium with six commonly measured ECG parameters was non-linear. Strong associations between ECG abnormalities and potassium were seen among individuals with lower potassium levels (≤4.1 mmol/L).

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Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jelectrocard.2019.09.005.

References

[1] Mattsson N, Sadjadieh G, Kumarathurai P, Nielsen OW, Kober L, Sajadieh A. Ambulatory cardiac arrhythmias in relation to mild hypokalaemia and prognosis in community dwelling middle-aged and elderly subjects *Europace* Department of Cardiology, Copenhagen University Hospital of Bispebjerg, Bispebjerg Bakke 23, 2400 Copenhagen NV, Denmark nickm@dadlnet.dk.; Department of Cardiology, Copenhagen University Hospital of Rigshospitalet, Copenhagen, Denmark.; Department of Car: For permissions please email: journalspermissions@oup.com , 18; 2016; 585–91.

[2] Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543–51 Department of Medicine University of Toronto, Toronto. dnj@ices.on.ca: Massachusetts Medical Society.

[3] Liamis G, Rodenburg EM, Hofman A, Zietse R, Stricker BH, Hoorn EJ. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med 2013;126:256–63.

[4] Paice BJ, Paterson KR, Onyanga-Omara F, Donnelly T, Gray JM, Lawson DH. Record linkage study of hypokalaemia in hospitalized patients. Postgrad Med J 1986;62:187–91.

[5] Viera AJ, Wouk N. Potassium disorders: Hypokalemia and hyperkalemia. Am Fam Physician 2015;92:487–95.

[6] Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, et al. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. Eur Heart J 2016;38:ehw129.

[7] Krogager ML, Eggers-Kaas L, Aasbjerg K, Mortensen RN, Køber L, Gislason G, et al. Short-term mortality risk of serum potassium levels in acute heart failure following myocardial infarction. Eur Hear journal Cardiovasc Pharmacother 2015;1:245–51.

[8] Aldahl M, Jensen A-SC, Davidsen L, Eriksen MA, Moller Hansen S, Nielsen BJ, et al. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* England 2017;38:2890–6.

[9] Podrid PJ. Potassium and ventricular arrhythmias. Am J Cardiol 1990;65:33E–44E Evans Memorial Research Division, Boston University School of Medicine, Massachusetts. [discussion 52E].

[10] Webster A, Brady W, Morris F. Recognising signs of danger: ECG changes resulting from an abnormal serum potassium concentration. Emerg Med J 2002;19:74–7 Addenbrooke's NHS Trust, Cambridge, UK.

[11] Kjeldsen K. Hypokalemia and sudden cardiac death. Exp Clin Cardiol 2010;15:e96–9 Laboratory for Molecular Cardiology, Medical Department B, The Heart Centre, Copenhagen University Hospital (Rigshospitalet) and Danish National Research Foundation Centre for Cardiac Arrhythmia, University of Copenhagen, Copenhagen, Denmark.

[12] Cohen JD, Neaton JD, Prineas RJ, Daniels KA. Diuretics, serum potassium and ventricular arrhythmias in the multiple risk factor intervention trial. Am J Cardiol 1987;60:548–54 United States.

[13] Levis JT. ECG diagnosis: hyperkalemia. Perm J 2013;17:69–88 Santa Clara Medical Center, CA, USA. joel.levis@kp.org.

[14] Dillon JJ, DeSimone CV, Sapir Y, Somers VK, Dugan JL, Bruce CJ, et al. Noninvasive potassium determination using a mathematically processed ECG: proof of concept for a novel 'blood-less, blood test'. J Electrocardiol 2015;48:12–8 Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA.; Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, USA.; Electrical and Computer Engineering, Ben-Gurion University of the Negev, Beer Sheva, Israel.; Division of Cardiovascular: Elsevier Inc.

[15] Slovis C, Jenkins R. ABC of clinical electrocardiography: conditions not primarily affecting the heart. BMJ 2002;324:1320–3 Vanderbilt University Medical Center in the Department of Emergency Medicine, Nashville, TN, USA.
[16] Levis JT. ECG diagnosis: Hyperacute T waves. Perm J 2015;19:79–243 Senior Emergency Physician at the Santa Clara Medical Center, and Clinical Assistant Professor of Emergency Medicine (Surgery) at Stanford University. He is the Medical Director for the Foothill College Paramedic Program in Los Altos, CA. joel.levis@kp.or.
[17] Levis JT. ECG diagnosis: hypokalemia. Perm J 2012;16:57 Santa Clara Medical Center, CA, USA. joel.levis@kp.org.
[18] Dittrich KL, Walls RM. Hyperkalemia: ECG manifestations and clinical considerations. J Emerg Med 1986;4:449–55 United States.
[19] Kanters Jørgen K, Graff Claus, Henriksen Lise, Petri Anne Sofie, Christiansen Michael, Nielsen Jimmi, et al. The QT interval increases with decreasing plasma potassium in the Danish general population. *Poster* annual conference of the International Society for Computerized Electrocardiology. San Francisco, USA: ISCE; 2015.
[20] Rasmussen PV, Nielsen JB, Pietersen A, Graff C, Lind B, Struijk JJ, et al. Electrocardiographic precordial ST-segment deviations and the risk of cardiovascular death: results from the Copenhagen ECG study. *J Am Heart Assoc* England 2014;e000549:3.
[21] No title. https://www.gehealthcare.com/en-GB/products/diagnostic-cardiology/marquette-12sl. [17 December 2018].
[22] Hancock EW, Deal BJ, Mirvis DM, Okin P, Kligfield P, Gettes LS, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part V: electrocardiogram changes associated with cardiac chamber hypertrophy: a scientific statement from the American Heart Association electrocardiography. Circulation 2009;119:e251–61 United States.
[23] Healthcare G. MarquetteTM 12SLTM. ECG Analysis Program - Statement of Validation and Accuracy 2008;416791-003:43–62 revisionB.
[24] Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). Circulation 2018;1.
[25] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35 United States.
[26] Deshpande A, Birnbaum Y. ST-segment elevation: distinguishing ST elevation myocardial infarction from ST elevation secondary to nonischemic etiologies. *World J Cardiol* United States 2014;6:1067–79.
[27] Wang K, Asinger RW, Marriott HJL. ST-segment elevation in conditions other than acute myocardial infarction. N Engl J Med 2003;349:2128–35 United States.
[28] SOKOLOW M, TP LYON. The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am Heart J* United States 1949;37:161–86.
[29] Casale PN, Devereux RB, Alonso DR, Campo E, Kligfield P. Improved sex-specific criteria of left ventricular hypertrophy for clinical and computer interpretation of electrocardiograms: validation with autopsy findings. *Circulation* United States 1987;75:565–72.
[30] Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. , 39Denmark: *Scand J Public Health* Center for Healthy Ageing, Department of Public Health, University of Copenhagen; 2011; 38–41 hewk@sund.ku.dk.
[31] Reddy BR, Taha B, Swiryn S, Silberman R, Childers R. Prospective evaluation of a microprocessor-assisted cardiac rhythm algorithm: results from one clinical center. J Electrocardiol 1998;30:28–33 United States. **Suppl**.
[32] Swiryn S, Arrhythmia diagnosis by computer JJ. The Marquette 12SL program. Computerized interpretation of the electrocardiogram. Proceedings of the Engineering Foundation Conference 1983:35–54.
[33] Nessmith Jr, M.G., T.W. Simmons and WKHJ. Computerized detection of paced rhythms in the resting 12-Lead electrocardiogram. Wake Forest University Medical Center; 2001.
[34] Kazi WM, RMSK. New algorithm improves detection accuracy of paced rhythms in the resting ECG. Division of Cardiology/Electrophysiology. Medical College of Wisconsin-Milwaukee; 2002.
[35] Guglin ME, Datwani N. Electrocardiograms with pacemakers: accuracy of computer reading. *J Electrocardiol* United States 2007;40:144–6.
[36] Farrell, R., J. Xue BY. Enhanced rhythm analysis for resting ECG using spectral and time-domain techniques. Comput Cardiol 2003;733–736.
[37] Poon K, Okin PM, Kligfield P. Diagnostic performance of a computer-based ECG rhythm algorithm. J Electrocardiol 2005;38:235–8 United States.
[38] Bossone E, Butera G, Bodini BD, Rubenfire M. The interpretation of the electrocardiogram in patients with pulmonary hypertension: the need for clinical correlation. *Ital Heart J* Italy 2003;4:850–4.
[39] Sica DA. Antihypertensive therapy and its effects on potassium homeostasis. J Clin Hypertens (Greenwich) 2006;8:67–73 Section of Clinical Pharmacology and Hypertension, Division of Nephrology, Medical College of Virginia of Virginia Commonwealth University, Richmond, VA 23298, USA. dsica@hsc.vcu.edu.
[40] Macdonald JE, Struthers AD. What is the optimal serum potassium level in cardiovascular patients? J Am Coll Cardiol 2004;43:155–61 Department of Clinical Pharmacology, Ninewells Hospital, Dundee, United Kingdom. macdonald_je@hotmail.com.
[41] Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. *Circulation* United States 2010;121:1047–60.
[42] Mymin D, Mathewson FA, Tate RB, Manfreda J. The natural history of primary first-degree atrioventricular heart block. *N Engl J Med* United States 1986;315:1183–7.
[43] Graff C, Matz J, Christensen EB, Andersen MP, Kanters JK, Toft E, et al. Quantitative analysis of T-wave morphology increases confidence in drug-induced cardiac repolarization abnormalities: evidence from the investigational IKr inhibitor Lu 35-138. J Clin Pharmacol 2009;49:1331–42 Department of Health Science and Technology, Center for Sensory Motor Interaction, Aalborg University, Aalborg, Denmark. cgraff@hst.aau.dk.
[44] Graff C, Andersen MP, Xue JQ, Hardahl TB, Kanters JK, Toft E, et al. Identifying drug-induced repolarization abnormalities from distinct ECG patterns in congenital long QT syndrome: a study of sotalol effects on T-wave morphology. *Drug Saf* New Zealand 2009;32:599–611.
[45] Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation 2008;117:1945–54 Department of Cardiology, Gentofte University Hospital, Niels Andersens Vej 65, DK-2900, Hellerup, Denmark. tks@heart.dk.
[46] Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. *Blood Press* Centro di Fisiologia Clinica e Ipertensione, Universita Milano-Bicocca; IRCSS, Istituto Auxologico Italiano, Milano, Italy 2014;23:3–16.
[47] Olesen JB, Lip GY, Hansen ML, Hansen PR, Tolstrup JS, Lindhardsen J, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. *BMJ* Department of Cardiology, Copenhagen University Hospital Gentofte, 2900 Hellerup. Denmark jo@heartdk 2011;d124:342.
[48] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–12.
[49] Montague BT, Ouellette JR, Buller GK. Retrospective review of the frequency of ECG changes in hyperkalemia. Clin J Am Soc Nephrol 2008;3:324–30 Department of Medicine, Saint Mary's Hospital, 56 Franklin Street, Waterbury, CT 06706, USA. brianmontaguedo@gmail.com.
[50] Lippi G, Plebani M, Di Somma S, Cervellin G. Hemolyzed specimens: a major challenge for emergency departments and clinical laboratories. Crit Rev Clin Lab Sci 2011;48:143–53 England.
[51] Phelan MP, Reineks EZ, Schold JD, Hustey FM, Chamberlin J, Procop GW. Preanalytic factors associated with hemolysis in emergency department blood samples. *Arch Pathol Lab Med* United States 2018;142:229–35.
[52] Howanitz PJ, Lehman CM, Jones BA, Meier FA, Horowitz GL. Practices for identifying and rejecting Hemolyzed specimens are highly variable in clinical laboratories. *Arch Pathol Lab Med* United States 2015;139:1014–9.
[53] Hong L, Andersen LJ, Graff C, Vedel-Larsen E, Wang F, Struijk JJ, et al. T-wave morphology analysis of competitive athletes. *J Electrocardiol* United States 2015;48:35–42.