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Plasma potassium concentration and cardiac repolarisation markers, T_{peak}-T_{end} and T_{peak}-T_{end}/QT,during and after exercise in healthy participants and in end-stage renal disease.

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Abstract

Purpose

The cardiac T-wave peak-to-end interval (T_{pe}) is thought to reflect dispersion in ventricular repolarisation, with abnormalities in T_{pe} associated with increased risk of arrhythmia. Extracellular K^+ modulates cardiac repolarisation and since arterial plasma K^+ concentration ($[K^+]$) rapidly increases during and declines following exercise, we investigated the relationship between $[K^+]$ and T_{pe} with exercise.

Methods

Serial ECGs (T_{pe}, T_{pe}/QT ratio) and $[K^+]$ were obtained from 8 healthy, normokalaemic volunteers and 22 patients with end-stage renal disease (ESRD), at rest, during and after exhaustive exercise.

Results

Post-exercise $[K^+]$ nadir was 3.1 ±0.1, 5.0 ±0.2 and 4.0 ±0.1 $mmol.L^{-1}$ (mean ± SEM) for healthy participants and ESRD patients before and after HD, respectively. In healthy participants, compared to pre-exercise, recovery-induced low $[K^+]$ was associated with a prolongation of T_{pe} (110 ±8 vs. 87 ±5 ms, respectively, p=0.03) and an increase in T_{pe}/QT ratio (0.28 ±0.01 vs. 0.23 ±0.01, respectively, p=0.01). Analyses of serial data revealed $[K^+]$ as a predictor of T_{pe} in healthy participants (β = -0.54 ±0.11, p=0.0007), in ESRD patients (β = -0.72 ±0.1, p < 0.0001) and for all data pooled (β = -0.64 ±0.52, p = 0.0007). The $[K^+]$ was also a predictor of T_{pe}/QT ratio in healthy participants and ESRD patients.

Conclusions

T_{pe} and T_{pe}/QT ratio are predicted by $[K^+]$ during exercise. Low $[K^+]$ during recovery from exercise was associated with increased T_{pe} and T_{pe}/QT, indicating accentuated dispersion of ventricular repolarisation. The findings suggest that variations in $[K^+]$ with physical exertion may unmask electrophysiological vulnerabilities to arrhythmia.

Keywords: Potassium, exercise, Tpeak-Tend, QT, ECG, arrhythmia, sudden cardiac death, hypokalaemia, hyperkalaemia

Abbreviations

ANOVA	Analysis of variance
ECG	Electrocardiogram
ESRD	End-stage renal disease
HD	Haemodialysis
$[K^+]$	plasma potassium concentration
PVC	premature ventricular contraction
QT Interval	ECG interval between Q and T waves
SEM	Standard error of the mean
T_{pe}	T wave peak-to-end interval
T_{pe}/QT ratio	Ratio of Tpe interval divided by QT interval

Declarations

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Conflicts of interest/Competing interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material (data transparency)

The datasets generated during and/or analysed during the current study are not publicly available due to regulations/agreements with the Danish Data Protection Authority, but are available from the corresponding author on reasonable request.

Authors' contributions

CTT, KPK, and MJM conceived and designed the research. CTT, TA, KPK and MJM conducted the experiments. CTT, TA, CG, JM, JKK, CTT, TA, KPK, and MJM analysed data. CTT, and MJM performed the statistical analyses. CTT wrote the initial manuscript draft. All authors read and approved the manuscript.

Ethics approval

The studies were approved by the respective ethics committees governing the institutions involved (Copenhagen Regional Committee for Health Research Ethics: *KF 01 319759*; and Human Research Ethics Committee at Victory University). The study conforms to the principles outlined in the Declaration of Helsinki.

Consent to participate

All participants gave written informed consent to participate in the study.

Introduction

Exercise is associated with large K^+ shifts from contracting skeletal muscle cells into the muscle interstitium, venous and then arterial plasma, such that the arterial plasma K^+ concentration ($[K^+]$) can reach 6-8 $mmol.l^{-1}$ during intense exercise (Sejersted and Sjøgaard 2000; Lindinger and Cairns 2021). Plasma $[K^+]$ then falls precipitously during recovery after intense exercise and can fall to below resting values, with lows of around 3 – 3.5 $mmol.l^{-1}$ (Lindinger et al. 1990; Atanasovska et al. 2014; Medbo and Sejersted 1990; Atanasovska et al. 2018). Therefore, intense exercise can expose the heart to both hyper- and hypokalaemia over a timeframe of minutes. Furthermore, myocardial interstitial and coronary sinus $[K^+]$ exceed left atrial $[K^+]$ with increased heart rate, with this gradient reversed during early recovery (Sejersted and Sjøgaard 2000), suggesting that the myocardial cells may be bathed in even higher extracellular $[K^+]$ during intense exercise. The extracellular $[K^+]$ is an important modulator of cardiac repolarisation, with high extracellular $[K^+]$ increasing conductivity of the rapid delayed rectifier (I_{Kr}) and inward rectifier (I_{Kir}) repolarising potassium currents (Ackerman and Clapham 1997; Yellen 2002). Conversely, low extracellular $[K^+]$ is associated with prolonged cardiac repolarisation, which on the surface electrocardiogram (ECG) is associated with a longer QT interval (Choy et al. 1997).

The cardiac T wave peak-to-end interval (T_{pe}) has been used as an index for the dispersion of cardiac repolarisation times (Prenner et al. 2016). The underlying electrophysiological basis for the variations in the duration of the cardiac action potential and repolarisation is in part due to topographical differences in the expression of the components of the delayed rectifier rapid I_{Kr} and slow (I_{Ks}) repolarising potassium currents. Increased dispersion of repolarisation, as reflected by prolonged T_{pe}, has been shown with inhibition of the I_{Kr} current (Bhuiyan et al. 2015) and moderate hypokalemia (Yan and Antzelevitch 1998). Clinically, increased dispersion of repolarisation as reflected in prolonged T_{pe} has been associated with increased risk of cardiac arrhythmia. The T_{pe} expressed relative to the QT interval, the T_{pe}/QT ratio, has been suggested as a marker of arrhythmia and been shown to be relatively stable across different animal species and as a function of heart rate (Gupta et al. 2008). In the LQT-1 subtype of long QT syndrome, T_{pe} increases during exercise due to the defect in I_{Ks} current, which under normal circumstances augment the repolarisation current at higher heart rates (Takenaka et al. 2003; Zumhagen et al. 2016). In Brugada syndrome, T_{pe} prolongation and T_{pe}/QT ratio have been found to be predictors for ventricular arrhythmia inducibility (Letsas et al.

2010) and arrhythmic events (Maury et al. 2015; Zumhagen et al. 2016). In population studies, prolonged T_{pe} has been associated with increased risk of cardiovascular death (Bachmann et al. 2015; Porthan et al. 2013).

The dramatic fluctuations in $[K^+]$ during and after intense exercise may modulate repolarising K^+ currents and contribute to changes in T_{pe}. In particular, the large and rapid decline in $[K^+]$ during early recovery may augment the dispersion of repolarisation, thus increasing the susceptibility to the triggering of arrhythmia. We previously reported that the post-exercise decline in $[K^+]$ was a determinant of the QT hysteresis (Tran et al. 2013; Atanasovska et al. 2018), suggesting that the heart is sensitive to exercise-induced $[K^+]$ variations. However, the effects of $[K^+]$ during and following exercise on the repolarisation dispersion reflected in T_{pe} and T_{pe}/QT ratio have not previously been examined. In this study, we therefore investigated whether $[K^+]$ affected the T_{pe} and the T_{pe}/QT ratio during exercise and recovery. We included both healthy participants and end-stage renal failure (ESRD) patients to assess the relationships in participants with normokalaemia and also with chronic hyperkalaemia. We further investigated in the ESRD patients the effects of K^+ reduction in the extracellular fluid phase by haemodialysis (HD) on the T_{pe} and the T_{pe}/QT ratio. We hypothesised that post-exercise reductions in $[K^+]$ in healthy participants and by haemodialysis in ESRD would be associated with prolongation of T_{pe} and increase in T_{pe}/ratio.

Methods

Participants

Eight healthy adult volunteers and 22 adult patients with ESRD participated in the study. The healthy participants were recreationally active, age 31.8 ± 6.8 years (mean ± SD, range 19 - 40 years), height 181.8 ± 5.7, cm, body mass 87.7 ± 10.9 kg and were recruited at Victoria University, Australia as part of a previously described study (Atanasovska et al. 2018). The ESRD patients were recruited among patients undergoing HD thrice-weekly at the Department of Nephrology, Copenhagen University Hospital (Rigshospitalet), Denmark and were part of a previously described study (Tran et al. 2013). The ESRD patients' age was 47.2 ± 17.1 years (range 23 - 86 years) with body mass at pre-HD 72.1 ±12.5 kg and at post-HD 70.4 ±12.6 kg. The studies were approved by the respective ethics committees governing the institutions involved (Copenhagen Regional Committee for Health Research Ethics, KF 01 319759; and Human Research Ethics Committee at Victory University,

HRETH 11/249). The study conforms to the principles outlined in the Declaration of Helsinki. All participants gave written informed consent to participate in the study.

Exercise, blood sampling protocols, K^+ measurements and calculations

Both study cohorts exercised until exhaustion followed by a recovery period, with protocols fully described elsewhere (Atanasovska et al. 2018; Tran et al. 2013). Twelve-lead electrocardiogram (ECG) electrodes were attached. Vascular access was established in all participants at the beginning of the day of the study session. In healthy participants, a cannula was inserted into the radial artery whilst in ESRD patients, catheters were inserted into an arterio-venous fistula in 12 patients and a central venous access in 10 patients, as per routine preparation for HD. The difference between arterial [K+] and mixed venous [K+] has previously been found to be small (Sejersted and Sjøgaard 2000). An extension tube with a stopcock was connected to facilitate blood sampling in both study groups. The healthy participants underwent a maximal exertion exercise bout for 3 minutes on a rowing ergometer and then recovered for 60 minutes, being seated on the ergometer for the initial 5 min and thereafter supine recovery. Rowing power output was 1698 ± 944 W during the initial 30 s, declining to 881± 356 W by 3 minutes, whilst heart rate reached ~160 beats.min^{-1} excluding the first 30 s of exercise, with peak of 165.4 ±12.7 beats.min^{-1} (Atanasovska et al. 2018). The rowing ergometer was used to induce large [K^+] increases during exercise, and substantial post-exercise decline in [K^+], due to intense contractions of a large musculature (Atanasovska et al. 2018). Arterial blood samples were drawn 2 min and immediately prior to exercise, every 30 s during exercise and during recovery at 1, 2, 3, 5, 10, 20, 30, 40, 50 and 60 minutes. The ESRD patients underwent incremental exercise on an electromagnetically braked cycle ergometer, commencing at 25 W and increasing by 25 W every 2 min until exhaustion; patients then recovered whilst seated for 10 minutes and then underwent routine HD (Tran et al. 2013). The incremental cycle ergometer exercise protocol was more suitable for ESRD patients with variations in physical activity levels. The peak exercise work rate and heart rate were 116 ± 41 W and 144 ± 24 beats.min^{-1}, respectively (Tran et al. 2013). After 20 min of rest following HD, all patients then underwent a second exercise session using already established vascular access and connected ECG electrodes. In ESRD patients, blood was sampled immediately before exercise, every 2 min during exercise, at exhaustion and at 2, 5 and 10 minutes during recovery. After initial aspiration to clear the dead space in the tubing system, blood was collected for both cohorts in heparinized blood sample containers and analysed for [K^+] using an

automated blood gas analyser (ABL 625 blood analyser (Radiometer, Ballerup, Copenhagen) (Tran et al. 2013) and Rapid Point 405 (Siemens Medical Solutions and Diagnostics, Tarrytown, NY) (Atanasovska et al. 2018). The [K^+] obtained immediately before exercise was used for the pre-exercise baseline. Values at exercise half-time were extracted, or if occurred between two observations for ESRD, were derived by calculating a weighted means from adjacent values. The [K^+] nadir was defined as the lowest measured [K^+] during recovery for each individual. All [K^+] data from 2 min pre-exercise up to 60 min recovery were included in relevant statistical analyses. Plasma [K^+] are reported here only at times analysed in relation to Tpe. All [K^+] were compared statistically against 0 min pre-exercise. Per technical reference manuals, for the Radiometer ABL 625, the precision (average difference) between [K^+] measurements is 0.05 mmol/L. For the Siemens RapidPoint 405, the precision between [K^+] measurements is 0.03 mmol/L.

Electrocardiogram Measurement and Calculations

All participants had 12-lead ECGs (GE MAC 5000 (GE Healthcare, Milwaukee, WI, US) and Model X-Scribe Stress Test System (Mortara Instrument, Milwaukee, WI, US) extracted at time within 10 s of each [K^+] measurement. ECG data were extracted from the 8 healthy participants and 22 ESRD patients, although in one patient only the post-HD session ECG was extractable with the exception of the QT intervals, and in another patient some ECGs during exercise following haemodialysis could not be extracted. All extractable ECG data were included in the analyses. The 10 s ECGs were stored in the MUSE® Cardiology Information System (GE healthcare, Wauwatosa, WI, USA) and subsequently used for analyses. Heart rate and QT intervals were measured automatically using version 21 of the Marquette 12SL algorithm. The algorithm uses the vector magnitude signal of all 12 leads to determine the onset of the QRS complex, the peak of the T-wave, and the offset of the T-wave. The QT interval measured from the QRS-onset to T-offset by the 12SL algorithm essentially corresponds to the distance between the earliest detection of depolarization in any lead (QRS onset) and the latest detection of repolarisation in any lead (T-offset). QT are indicated at times analysed in relation to T_{pe} The T_{pe} interval was measured from the peak of the T-wave to T-offset on the vector magnitude ECG because it has been shown previously with cell-to-ECG modelling that T_{pe} based on vector magnitude ECG from 12 leads has the highest correlation to dispersion among other ECG parameters, which include T_{pe} from individual leads (V3 or V5) and principal component analysis (Xue et al. 2008). The T_{pe}/QT ratio was calculated by dividing the T_{pe} by the QT interval. Although

measurements of QT intervals using the 12SL algorithm have previously been validated extensively (Fosser et al. 2009; Hnatkova et al. 2006), all QT intervals were manually assessed with digital calipers at 10 times magnification by an experienced reader blinded (JKK) to $[K^+]$ values and the protocol stage. Calipers were then adjusted as needed by the reader. A similar procedure was used for over-reading of RR-intervals and T_{pe}-intervals.

Statistical analyses

Testing of serial data means for $[K^+]$, T_{pe}, QT, and T_{pe}/QT ratio were performed with repeated measurement ANOVA with post-test comparisons against pre-exercise values with Dunnett's correction for multiple comparisons. Student's t-tests were used for non-repeated means for $[K^+]$, T_{pe}, QT, T_{pe}/QT ratio and time. Simple linear regression using the method of least squares was used for modelling continuous outcome data for $[K^+]$, T_{pe} and T_{pe}/QT ratio. Linear mixed model regression analysis was used to evaluate serial for $[K^+]$, T_{pe} and T_{pe}/QT ratio data from exercise and recovery. Compound symmetry co-variance structure was selected for the analysis. To obtain comparable data structures, for ESRD patients, mid-exercise and end-exercise values were used to represent during-exercise data in the analyses. For linear regression analyses, model assumption testing was performed to verify linearity, homoscedasticity, and normality. Transformation of $[K^+]$ and T_{pe} was performed as needed to meet these assumptions. For logarithmic transformations, the base number of 2 was used due to the relatively narrow variable range and for ease of interpretation. Regression coefficients estimates are given as β-values, where $y = \beta x + c$. Values are means ± SEM. Two-tailed p-values are given. $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the SAS 9.2 (SAS Institute Inc., Cary, NC, US).

Results

Potassium, QT and T wave measurements

$[K^+]$

In healthy participants, $[K^+]$ increased above pre-exercise during exercise ($p < 0.0001$); post-exercise, $[K^+]$ fell but remained elevated at 1 min, did not differ from pre-exercise at 2 min post-exercise, declined below pre-exercise at 3, 5 and 10 min post-exercise ($p < 0.01$), returning to pre-exercise

levels thereafter (20-60 min) (Table 1). The $[K^+]$ nadir of 3.1 ± 0.1 mmol.L^{-1} occurred at 6.9 ± 0.9 min post-exercise.

In ESRD, before HD, $[K^+]$ increased above pre-exercise during exercise and post-exercise declined to return to pre-exercise; similar responses were found following HD during exercise ($p < 0.0001$), however, $[K^+]$ remained higher than pre-exercise at 2, 5 and 10 min recovery ($p < 0.0001$, $p = 0.02$, and $p = 0.006$, respectively). The $[K^+]$ nadir was 5.0.± 0.2 mmol.L^{-1} at 2.7 ± 0.3 min post-exercise before HD and 4.0 ± 0.1 mmol.L^{-1} at 4.7 ± 0.5 min post-exercise following HD ($p = 0.002$).

QT

In healthy participants, the QT interval decreased during ($p < 0.0001$) and 2 min post-exercise ($p = 0.0001$), returning to pre-exercise levels at 5 min and subsequently (Table 1).

In ESRD, QT decreased at during exercise both before HD ($p < 0.0001$) and following HD ($p < 0.0001$); after 10 min post-exercise, QT remained shorter than pre-exercise before HD ($p = 0.007$) and following HD ($p < 0.0001$).

***Tpeak-Tend interval* (T_{pe})**

In healthy participants, T_{pe} shortened from pre-exercise to mid-exercise ($p = 0.02$) and increased again during early post-exercise, being longest at 10 min post-exercise ($p = 0.01$, Table 1). The T_{pe} at the $[K^+]$ nadir of each participant during post-exercise (108.8 ± 9.7 ms) was longer than pre-exercise ($p = 0.03$). The $[K^+]$ nadir coincided temporally with the T_{pe} prolongation during recovery.

In ESRD, the T_{pe} was also shortened from pre-, to mid- and end-exercise, before HD ($p = 0.008$ and $p < 0.0001$) and following HD ($p = 0.009$ and $p <0.0001$), with prolongation during post-exercise that did not exceed pre-exercise values (Table 1).

The T_{pe} at the $[K^+]$ nadir of each participant during post-exercise did not differ from pre-exercise before HD (73.2 ± 2.5 ms, $p = 0.79$), but was shorter following HD (83.3 ± 4.5 ms, $p = 0.03$).

Comparing ESRD patients before versus following HD, T_{pe} was shorter before HD than after HD at each of pre- ($p = 0.002$), mid- ($p = 0.0007$) and end- exercise ($p = 0.04$) and at the $[K^+]$ nadir post-exercise ($p = 0.002$). Following HD, T_{pe} was shorter at pre-, mid- and end-exercise, and at $[K^+]$ nadir ($p = 0.001$, .$p = 0.0007$, $p = 0.04$, and 0.002, respectively).

Comparing ESRD with healthy participants, before HD, T_{pe} tended to be shorter at pre-exercise ($p = 0.06$) and was shorter at $[K^+]$ nadir ($p < 0.0001$); following HD, T_{pe} was shorter at $[K^+]$ nadir post-exercise ($p = 0.01$).

T_{pe}/QT ratio

In healthy participants, the T_{pe}/QT ratio did not change significantly during exercise but increased from 2 min post-exercise (p = 0.02, Table 1). The T_{pe}/QT ratio at the [K^+] nadir was higher than pre-exercise (0.285 ± 0.016, p = 0.01).

In ESRD patients before HD, the T_{pe}/QT ratio did not change significantly during exercise (Table 1), but was increased from 2 min of recovery (p = 0.0006) and at the [K^+] nadir (0.220 ± 0.009 ms, p < 0.0001). In ESRD patients following HD, the T_{pe}/QT ratio did not change significantly during exercise and early post-exercise, but decreased after 10 min post-exercise (p = 0.009). The T_{pe}/QT ratio was not significantly different at the [K^+] nadir (0.243 ± 0.010, p = 0.50). The T_{pe}/QT ratio was higher at pre-exercise following HD compared to before HD (p = 0.001).

Comparing healthy participants with ESRD patients, the T_{pe}/QT ratio was not significantly different at pre-exercise, whereas post-exercise, the T_{pe}/QT ratio was shorter before HD at the [K^+] nadir (p = 0.001) and following HD (p = 0.04).

Relationships between T_{pe} and plasma [K^+] a

Strong negative curvilinear relationships were evident between T_{pe} and [K^+] for linear regressions between T_{pe} and [K^+], analysed for pooled data from all healthy participants plus ESRD patients (p < 0.0001, Figure 1), as well as separately for the two groups. Log-log transformation was performed to achieve linearity and homoscedasticity in order to perform linear regression for T_{pe} and [K^+].

Between subject relationship was assessed for pre-exercise, end-exercise and at [K^+] nadir, due to the markedly different and diverging values exhibited in both T_{pe} and [K^+] during exercise and post-exercise. Negative log-log relationships were found between T_{pe} and [K^+] at both pre-exercise and at [K^+] nadir, but not at end-exercise, when data was pooled from healthy participants and ESRD before and following HD; as well as in ESRD only, before and following HD (Table 2). The equivalent analyses with only healthy participants did not reach statistical significance (data not shown). The mean T_{pe} at each given time and the corresponding [K^+] are shown in Figure 2 and demonstrated that T_{pe} exhibited a negative log-log relationship with [K^+]. Due to interdependence between repeated measurements, the serial data were analysed with mixed model regression. In a pooled analyses with all participants, logT_{pe} was linearly (negatively) associated with log[K^+] (β = -0.61 ± 0.04, c = 7.58 ± 0.09, p <0.0001). In separate analyses for healthy participants and ESRD patients, logT_{pe} was linearly (negatively) associated with log[K^+] for healthy participants (β = -0.54 ± 0.05, c = 7.53 ± 0.14, p <

0.0001) and for ESRD patients (β = -0.75 ± 0.06, c = 7.85 ± 0.14, p < 0.0001). The relationship remained statistically significant after adjusting for heart rate, before HD state, and post-exercise state (Table 3). Also, the relationship remained significant (p < 0.0001) after stratifying for mixed venous sampling in a subset of ESRD patients. To evaluate the effect of $[K^+]$ in the individual patients during exercise and post-exercise, analyses were additionally made for changes in T_{pe} (ΔT_{pe}) and $[K^+]$ ($\Delta [K^+]$) in relation to pre-exercise values. The ΔT_{pe} was negatively linearly associated with $\Delta[K^+]$ (β = -8.68 ± 0.84 ms.L.mmol^{-1}, c =– 4.05 ± 2.18 ms, p < 0.0001) for all participants pooled, for healthy participants (β = -7.75 ± 0.78 ms.L.mmol^{-1}. c = 2.83 ± 2.88, p < 0.0001) and ESRD patients (β =-15.96 ± 2.41 ms.L.mmol^{-1} , c = 4.67 ± 2.54 ms, p <0.0001)

Relationship between T_{pe}/QT ratio and $[K^+]$

The T_{pe}/QT ratio was linearly (negatively) associated with $[K^+]$ at pre-exercise including healthy participants and ESRD before HD (β = -0.05 ± 0.01 L.mmol^{-1}, R^2 = 0.51, p < 0.0001) and following HD (β = -0.12 ± 0.04 L.mmol^{-1}, R^2 = 0.24, p = 0.007). At the $[K^+]$ nadir, T_{pe}/QT ratio was linearly (negatively) associated with $[K^+]$ including healthy participants and ESRD following HD (β = -0.06 ± 0.02 L*mmol^{-1}, R^2= 0.25, p = 0.006), but only tended to be associated with $[K^+]$ including ESRD patients before HD. With analysis of serial data for all participants pooled, the T_{pe}/QT ratio was negatively linearly associated with $[K^+]$(β = -0.01 ± 0.002 L*mmol^{-1}, c = 0.28 ± 0.011, p < 0.0001). The mean T_{pe}/QT at each given time and the corresponding $[K^+]$ are shown in Figure 3 and demonstrated that T_{pe}/QT exhibited a linear (negative) relationship with [K+]. The relationship was significant for both the healthy participants (β = -0.006 ± 0.002 L*mmol^{-1}, c =0.38 ± 0.014, p = 0.007) for ESRD patients (β = 0.025 ± 0.003 L*mmol^{-1}, c = 0.34 ± 0.017, p < 0.0001). The relationship remained statistically significant after adjusting for heart rate, before HD state, and post-exercise state (p <0.0001). Also, the relationship remained significant (p < 0.0001) after stratifying for mixed venous sampling in a subset of ESRD patients.

Discussion

The major findings in the present study include prolongations of the T_{pe} and of the T_{pe}/QT ratio during recovery from exercise in healthy participants, and associations between T_{pe} and $[K^+]$, as well as the Tpe/QT ratio during exercise and post-exercise. These relationships were consistent for individuals at rest, during recovery, and serially during $[K^+]$ variations with exercise and recovery, and in healthy participants as well as in patients with ESRD. This reflects increased dispersion of cardiac repolarisation, which may be an important factor that augments susceptibility to arrhythmia following exercise.

Increased T wave dispersion and reduced $[K^+]$ during recovery from exercise

The negative linear relationship between $[K^+]$ and T_{pe} after logarithmic transformation is consistent with the expected effects of $[K^+]$ on the heart. An elevated $[K^+]$ augments I_{Kr} and I_{Kir} currents (Ackerman and Clapham 1997; Yellen 2002) and in addition, augments the repolarizing contribution from the electrogenic Na^+,K^+-ATPase, which is sensitive to the extracellular $[K^+]$ (Glitsch 2001). Low $[K^+]$ decreases K^+-sensitive repolarising currents, which may unmask more heterogeneously distributed depolarizing and repolarizing currents, leading increased dispersion in repolarisation (Bhuiyan et al. 2015; Shimizu and Antzelevitch 2000). Accordingly, the longest T_{pe} was found during recovery in healthy participants, who exhibited a pronounced post-exercise hypokalemia. The effect of $[K^+]$ on the dispersion of repolarisation was also reflected in the effect on T_{pe}/QT ratio, which largely mirrored the findings for T_{pe}. Furthermore, in ESRD patients, the lowering effect on $[K^+]$ by HD was associated with a longer T_{pe}, whilst the lack of a major undershoot in $[K^+]$ during early recovery was associated with an absence of prolongation of T_{pe}. The likely equilibration-related $[K^+]$ increase, through the exercise session following HD was also associated with a shortening of T_{pe}. Overall, the parameter estimates from regression analyses indicate that a decrease in $[K^+]$ from 6 to 3 mmol $.L^{-1}$, such as seen during and after intense exercise in healthy participants, is associated with an approximate 50% increase in T_{pe}. This reflects a major increase in dispersion of repolarisation.
The relationship between T_{pe} and $[K^+]$ was consistent across healthy participants and patients with ESRD, despite major differences between the two groups including age, exercise protocol and physical activity levels. Also, ESRD patients have marked abnormalities in $[K^+]$ changes with exercise and recovery (Sangkabutra et al. 2003) and deficits in muscle Na^+,K^+-ATPase activity and muscle function (Petersen et al. 2012). Furthermore, HD induces a state of fluid and electrolyte disequilibrium

as well as sympathetic activation (Santoro et al. 2008; Bleyer et al. 2006). Despite these differences, there was a high degree of overlap in the absolute values of T_{pe} and T_{pe}/QT ratio. There was a smaller absolute variation of T_{pe} in ESRD patients, that may reflect their impaired exercise capacity (Petersen et al. 2012) and the ceiling effect of high pre-exercise [K^+] that limits the absolute increase in [K^+] (Tran et al. 2013).

Hypokalaemia occurred following intense rowing exercise in the healthy participants, but not following incremental cycling exercise to fatigue in patients with ESRD. To understand these differences it is important to consider mechanisms responsible for changes in [K^+] both during and after exercise. Rowing requires intense contractions of a large muscle mass, sustained over several minutes; the underlying cellular excitation causes marked K^+ shifts from intra-to extracellular spaces in muscle, with a consequent large rise also in [K^+] (Atanasovska et al. 2018; Atanasovska et al. 2014; McKenna et al. 2008; Lindinger and Cairns 2021). Intense contractions also simultaneously induce pronounced activation of Na^+,K^+-ATPase in muscle (Clausen 2003); in isolated rat muscles, high frequency activation for only 10 s increased Na^+,K^+-ATPase activity to 80% of theoretical maximal levels (McKenna et al. 2003) and elevated Na^+,K^+-ATPase activity persisted for 30 minutes post-contraction (Nielsen and Clausen 1997). Thus, the observed rapid decline in [K^+] and hypokalaemia following rowing most likely reflects a pronounced Na^+,K^+-ATPase activity being sustained post-exercise, coincident with the end-exercise cessation of excitation-induced K^+ exit from muscle cells. Post-exercise hypokalaemia has been found following maximal exercise involving rowing, treadmill running as well as very intense cycling (Medbo and Sejersted 1994, 1990; Lindinger et al. 1990; Atanasovska et al. 2014; Atanasovska et al. 2018). In contrast, in ESRD, [K^+] did not decline to hypokalaemic levels after cycling exercise, consistent with our previous findings in ESRD (Sangkabutra et al. 2003; Petersen et al. 2012; McMahon et al. 1999; Petersen et al. 2009). In healthy participants, the early post-exercise decline in [K^+] was proportional with exercise intensity (Vollestad et al. 1994; Medbo and Sejersted 1990) and was also less after incremental cycling than after rowing (Sangkabutra et al. 2003; Atanasovska et al. 2014). Thus, key factors influencing the lack of hypokalaemia with cycling were a lesser exercise intensity and contracting muscle mass. However, an additional important factor in ESRD, may be a lower muscle Na^+,K^+-ATPase activity found in patients with ESRD on haemodialysis (Petersen et al. 2012).

Clinical Implications of increased T_{pe} and T_{pe}/QT ratio

The relative and absolute changes in T_{pe} and in the T_{pe}/QT ratio and the demonstrated statistical associated effect of [K^+] variations found here are of a magnitude of clinical relevance. The pronounced increase in T_{pe} to above 110 ms in healthy participants and of T_{pe}/QT ratio to ~0.29 units during recovery-associated hypokalemia approximate previously described values in patients with associated risk of arrhythmia. The T_{pe} reported in different patient groups included 89 ms in patients with Brugada syndrome with inducible ventricular tachyarrhythmia (Maury et al. 2015), 88 ms in patients with sudden cardiac arrest (Chua et al. 2016), 132 ms in long QT syndrome type 1 patients (Takenaka et al. 2003) and 149 ms in patients with ST-elevation myocardial infarction with arrhythmic events (Mugnai et al. 2016). Similarly, the increase in T_{pe}/QT ratio to 0.29 in healthy participants during recovery-associated hypokalemia is consistent with T_{pe}/QT ratio of 0.23 in patients with Brugada syndrome with inducible ventricular tachyarrhythmia (Letsas et al. 2010), although less than the 0.38 reported in patients with ST-elevation myocardial infarction with arrhythmic event (27). The high T_{pe} in recovery in healthy participants was extremely high as compared against a population study, where the mean T_{pe} was 94 ms, the 5^{th} and 95^{th} percentile limits were 77 and 116 ms, respectively (Bachmann et al. 2015). Both extremes were associated with increased risk of cardiovascular death (Bachmann et al. 2015). Clinically significant arrhythmia and sudden cardiac death related to exercise are rare occurrences in healthy individuals (Kim et al. 2012), indicating that these variations in [K^+], Tpe and the Tpe/QT ratio in normal circumstances are well tolerated. Despite the low absolute risk, the incidence of sudden cardiac death around the time of exercise has been found to be 17 times higher than during rest (Albert et al. 2000). A part of this increased mortality may be due to arrhythmia. The recovery phase following exercise has been identified as a particularly vulnerable period due to high level of adrenergic stimulation, low [K^+], increased intracellular calcium load and elevated blood pressure (Paterson 1996; Sutherland 2017; Wu et al. 1999). In this setting, the greater T_{pe} and T_{pe}/QT ratio reflecting increased dispersion of repolarisation may be an additional factor that augments susceptibility to arrhythmia in some individuals. Our findings suggest that low [K^+] post-exercise may play a pivotal role in this increased dispersion of repolarisation. Frequent premature ventricular contractions (PVCs) during recovery from exercise was a predictor for risk of death, whilst frequent PVCs during exercise was not (Frolkis et al. 2003). It is conceivable that a trigger such as a PVC may initiate an arrhythmia in the setting of increased dispersion of

repolarisation. Exercise-associated increase in dispersion of repolarisation, although tolerated in normal individuals, may be superimposed on underlying electro-anatomical abnormalities, including perfusion heterogeneities in coronary artery disease, electrical remodelling in left ventricular hypertrophy (Laukkanen et al. 2014), repolarisation abnormalities in inherited heart diseases (Prenner et al. 2016) and from I_{Kr} blocking medications (Yang and Roden 1996). It is notable that athletes participating in basketball, American football, and soccer, which have frequent cycles of intense exertion and recovery, have the highest incidence of sudden cardiac death (Harmon et al. 2015)..

The ESRD patients with high [K^+] before HD had a relatively short T_{pe} and low T_{pe}/QT ratio both before exercise and post-exercise; removal of K^+ from the extracellular phase by HD led to a significant increase in both T_{pe} and T_{pe}/QT ratio, which was mitigated by the subsequent equilibration from the efflux of K^+ from the intracellular phase. These findings suggest a potential protection against a significant increase in repolarisation dispersion post-recovery when K^+ stores are well-repleted. This may mitigate the previously found increased risk of sudden death around the time of HD from low [K^+] and other electrolyte and fluid perturbations (Bleyer et al. 2006). Furthermore, sudden cardiac death in ESRD patients involves ventricular tachycardia and ventricular fibrillation less frequently than asystole and pulseless electrical activity (Makar and Pun 2017), indicating that high [K^+] may protect against ventricular tachyarrhythmias but increase risk of sudden cardiac death from non-tachyarrhythmia. This may contribute to the finding that T_{pe} has not been found to be a significant predictor for sudden cardiac death in ESRD patients (Saour et al. 2019). In contrast, K^+ depletion is associated with lower baseline [K^+] (Tran and Kjeldsen 2011), and hypokalemia is a known risk factor for the development of arrhythmia in patients with myocardial infarction (Goyal et al. 2012). The role of K^+ depletion for exercise-related risk of cardiac arrhythmia is less well-investigated due to methodological challenges, as exercise-associated sudden cardiac death is generally a rare occurrence (Kim et al. 2012) and pre-exercise [K^+] has only been available in limited settings (Modesto et al. 2006).

The transient [K^+] variations may be modulated by sympathetic stimulation. Thus, beta-adrenoceptor antagonists, which among other effects, decrease sympathetic system-mediated [K^+] decrease (Sejersted and Sjogaard 2000) and reduce the risk of cardiac arrhythmia (Priori et al. 2015; Ackerman and Clapham 1997). The beta-adrenoceptor agonist salbutamol also modulated changes in arterial [K^+] during and after intense exercise (Altarawneh et al. 2016). Taken together, the dynamic nature of

[K^+] with intense exercise may be under-appreciated and could through a number of synergistic interactions with cardiac electrophysiological mechanisms be of clinical importance for the risk of cardiac arrhythmia.

Although the multiple statistical associations between [K^+] and T_{pe} in conjunction with a plausible mechanism of interaction suggest a causal relationship, we cannot claim causality due to our study design, which does not allow control of other variables. It is, however, interesting that the association persisted across healthy and clinical cohorts, between subjects and within subjects. Sympathetic stimulation may be a confounder, but the persistent relationship after adjustment for heart rate and stratification for exercise vs. recovery suggest that differences in sympathetic activity cannot sufficiently explain the overall effect. Furthermore, the parameter estimates indicated the effects of these were minor and cannot explain the prolonged T_{pe} during recovery. Also, it is interesting that [K^+] predicted the T_{pe} most consistently during the recovery from exercise, despite the variable response in [K^+] between groups and smaller variations in heart rate. Other limitations include the lack of HD in the healthy participants and differences in the exercise capacity, exercise protocol, and other underlying factors between the healthy participants and ESRD patients. These differences may limit the conclusion when comparing differences between groups, although this was not a primary objective of the study.

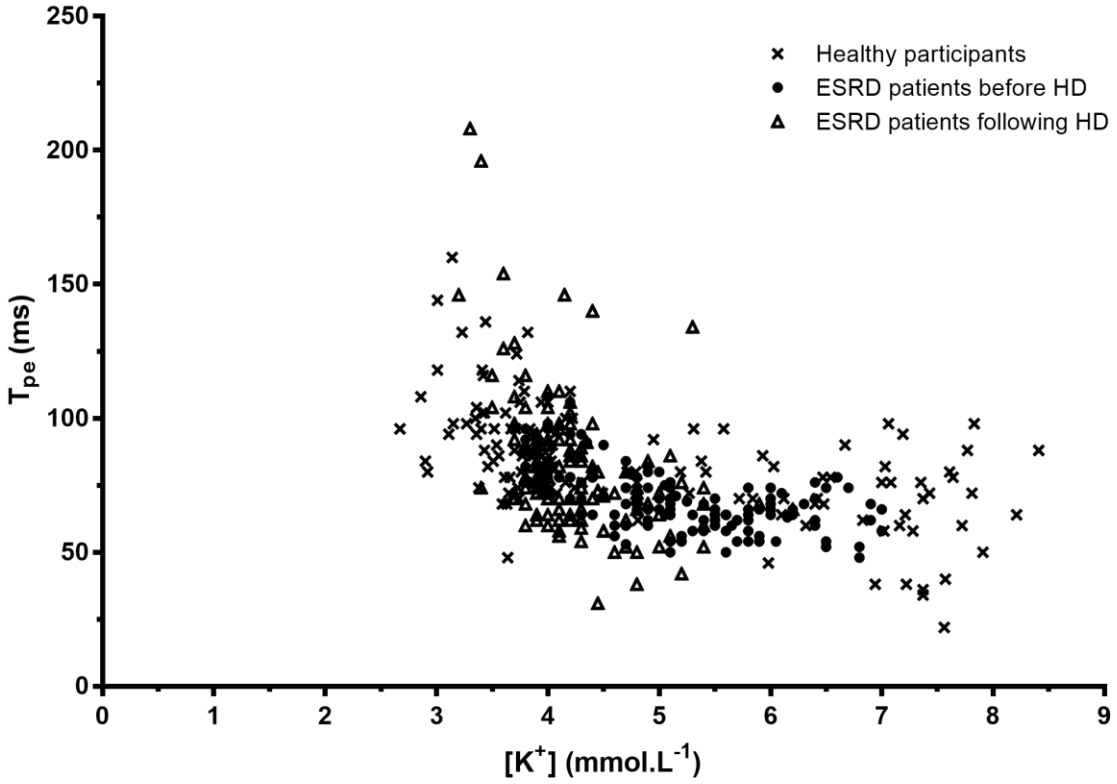
In conclusion, T_{pe} and T_{pe}/QT ratio were statistically predicted by [K^+], both during exercise-induced variations and between participants. In healthy participants, both T_{pe} and the T_{pe}/QT ratio increased significantly during recovery from exercise with an associated hypokalemia, indicating accentuated dispersion of repolarisation. In a K^+ loaded condition, as represented by ESRD patients, a blunted -K^+-decrease during recovery mitigated the effect of HD-induced reduction in [K^+] on T_{pe}. These findings suggest that the heart may be sensitive to variations in [K^+] during and especially after physical exertion, which may unmask electrophysiological vulnerabilities to arrhythmia. Whether [K^+] perturbations induced by chronic or acute K^+ depletion due to diarrhea, diuretics, or other medications that disturb K^+ homeostasis may also increase repolarisation dispersion variations and promote the triggering of cardiac arrhythmia in susceptible individuals remains to be determined.

Figure Legends

Figure 1.

The relationship between the Tpeak-Tend interval (T_{pe}) and plasma potassium concentration ($[K^+]$) at rest, during exercise and post-exercise, with data pooled from healthy participants and from end-stage renal failure (ESRD) patients before and after haemodialysis. Data are presented in absolute units (A) and log-log units (B). T_{pe} were determined from electrocardiogram (ECG) by an automated algorithm in 8 healthy participants and 22 ESRD patients before and following haemodialysis. In 1 ESRD patient, the T_{pe} was extractable only for the post-haemodialysis session. Although T_{pe} was negatively linearly related to $[K^+]$ (Figure 1A, $T_{pe} = -9.25 \pm 0.66 ([K^+]) + 123.3 \pm 3.18$, $R^2 = 0.24$, $P<0.0001$; β and c expressed as mean ± SEM), it is more correct to report the regression for the log T_{pe} log$[K^+]$ relationship (Figure 1B, with regression shown in the solid line (log $(T_{pe}) = -0.61$ (log$[K^+]$)+ 7.58, $p <0.0001$).

A



B

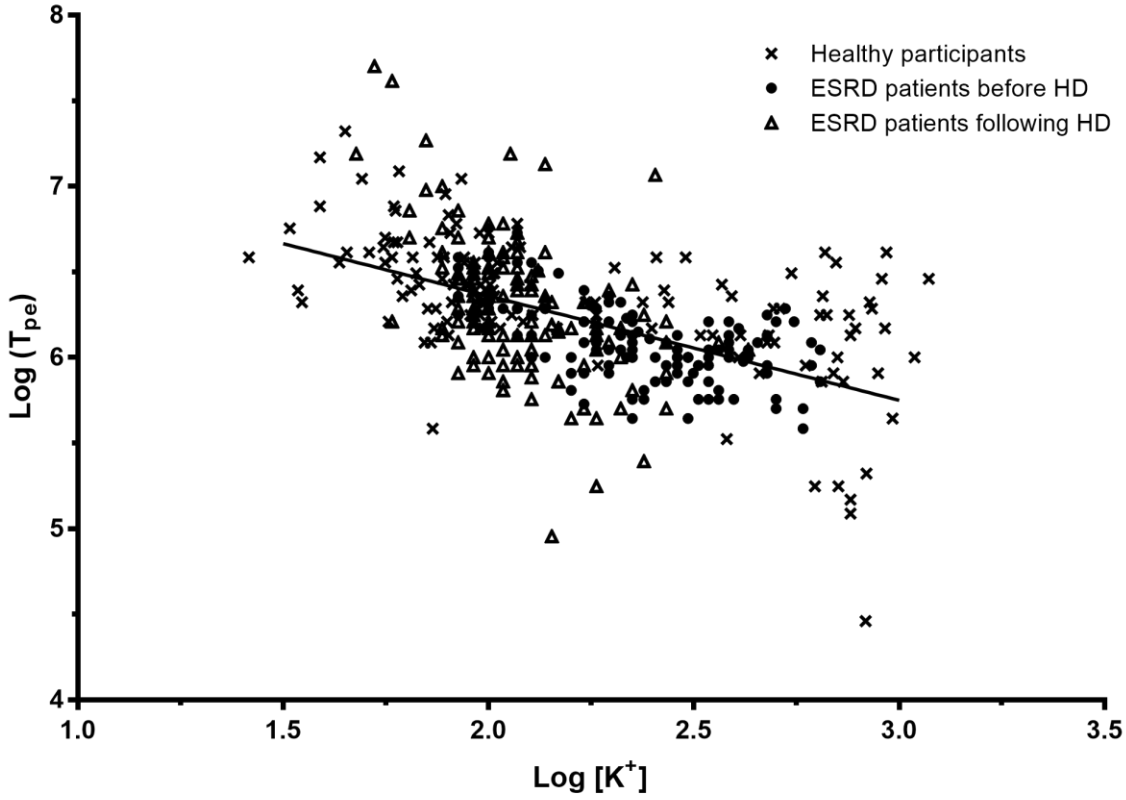


Figure 2.

The relationship between T_{pe} and plasma [K^+] during rest, exercise and . T_{pe} was determined from ECG by an automated algorithm in 8 healthy participants and 22 end-stage renal failure (ESRD) patients (n=21 following haemodialysis). Each symbol represents mean values of T_{pe} (ms) as a function of [K^+] (mmol.L^{-1}) for each patient group at one particular sampling time during pre-exercise, exercise and post-exercise for up to 10 min (ESRD patients) and 60 minutes (healthy participants). Data are plotted using logarithmic axes, due to the log-log relationship between the variables. Regression is shown in the solid line (log (T_{pe}) = -0.61 (log[K^+]) + 7.58, p <0.0001).

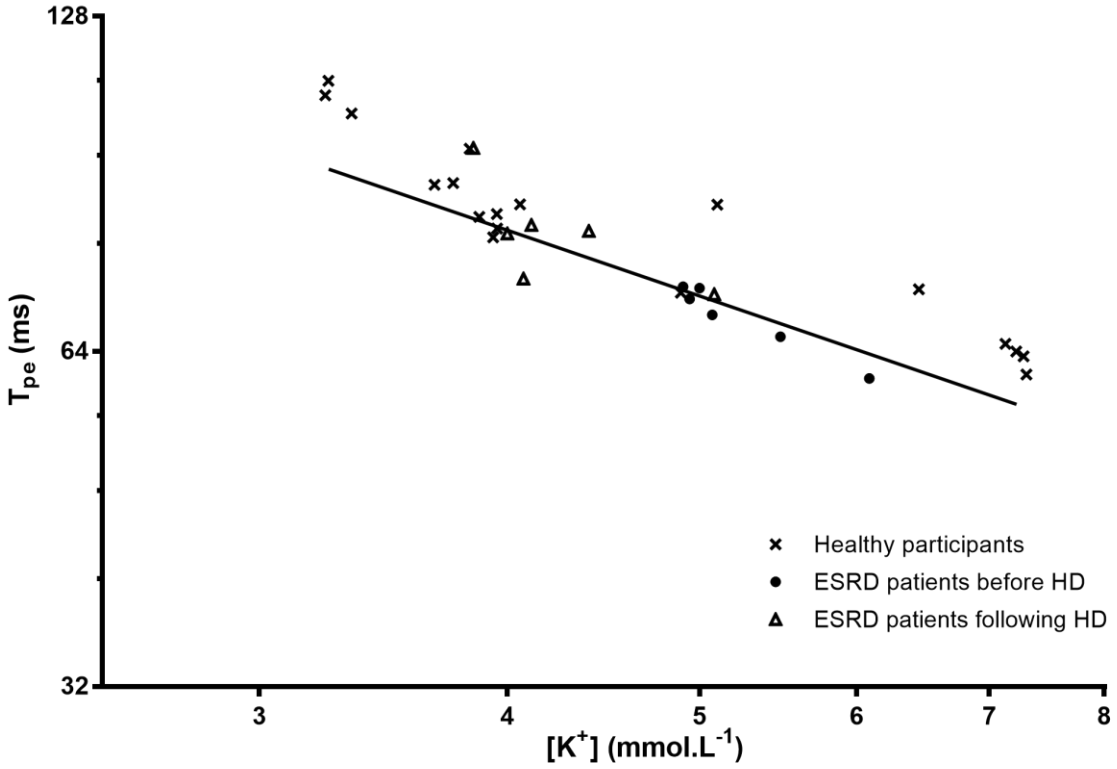


Figure 3.

The relationship between T_{pe}/QT and plasma [K^+] during rest, exercise and post-exercise. T_{pe} /QT was determined from ECG by an automated algorithm in 8 healthy participants and 22 end-stage renal failure (ESRD) patients (n=21 following haemodialysis). Each symbol represents mean values of T_{pe}/QT as a function of [K^+] (mmol.L^{-1}) for each patient group at one particular sampling time during pre-exercise, exercise and post-exercise for up to 10 min (ESRD patients) and 60 minutes (healthy participants). Regression is shown in the solid line T_{pe}/QT = -0.01 [K^+] + 0.28, p <0.0001).

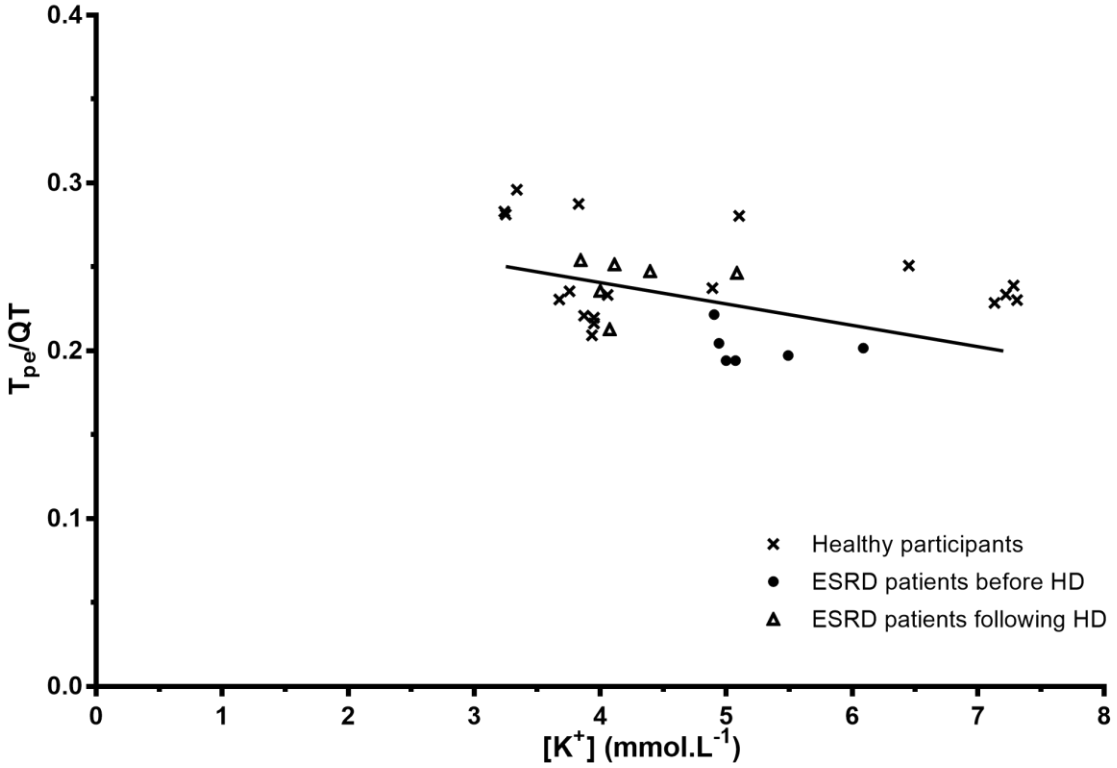


Table 1. Potassium and ECG T-wave variables reflecting cardiac repolarisation dispersion, at rest, during and following intense exercise in healthy participants and in patients with end-stage renal failure (ESRD). The $[K^+]$, QT interval, T_{pe} and T_{pe}/QT ratio data are presented at pre-, mid- and end-exercise and post-exercise at 2, 5 and 10 minutes. Variables for ESRD patients were measured both before and following haemodialysis (HD).

	Pre-exercise	**Exercise**		Post-exercise **(min)**		
		Half-time	**End**	**2**	**5**	**10**
healthy participants						
$[K^+]$ (mmol.L^{-1})	4.1 ±0.1	7.1 ±0.3 §	7.3 ±0.1 §	3.8 ±0.1	3.2 ±0.1 **	3.2 ±0.1 **
QT (ms)	371.5 ±11.8	278.8 ±10.4 §	283.0 ±8.6 §	324.0 ±7.7 **	371.8 ±11.8	389.3 ±11.5
T_{pe} (ms)	86.8 ±4.7	64.8 ±7.3 *	68.8 ±8.4	93.3 ±4.1	106.0 ±8.3	110.3 ±7.8 *
T_{pe}/QT ratio	0.23 ±0.01	0.23 ±0.02	0.24 ±0.02	0.29 ±0.01 *	0.28 ±0.01 *	0.28 ±0.01
ESRD patients before HD						
$[K^+]$ (mmol.L^{-1})	5.1 ±0.2	5.5 ±0.2 §	6.1 ±0.2 §	5.0 ±0.2	5.0 ±0.2	5.2 ±0.2
QT (ms)	378.0 ±7.0	338.2 ± 8.4 §	304.9 ± 9.4 §	333.6 ±6.9 §	352.8 ±8.5 **	358.8 ±8.0 **
T_{pe} (ms)	73.0 ±2.7	66.0 ±2.2 **	60.5 ±1.6 §	73.1 ±2.5	71.3 ±2.7	69.0 ±2.5
T_{pe}/QT ratio	0.19±0.01	0.20±0.01	0.20±0.01	0.22±0.01 **	0.20±0.01	0.19±0.01
ESRD patients following HD						
$[K^+]$ (mmol.L^{-1})	3.8 ±0.1	4.4 ±0.1 §	5.1 ±0.1 §	4.1 ±0.1 §	4.0 ±0.1 *	4.1 ±0.1 **
QT (ms)	389.3 ±12.0	337.1 ± 6.1 §	296.7 ± 8.4 §	336.1 ±10.6 §	351.9 ±9.9 §	354.3 ±7.1 §
T_{pe} (ms)	97.5 ±8.5	82.1 ±4.8 **	72.0 ±5.1 §	83.1 ±4.7 *	81.6 ±4.5 **	74.4 ±3.5 §
T_{pe}/QT ratio	0.25±0.02	0.25±0.02	0.25±0.02	0.24±0.01	0.24±0.01	0.21±0.01 **

Data mean ±SEM, n=8 for healthy participants and 22 for ESRD. * $P < 0.05$ compared with pre-exercise, ** $p < 0.01$ compared to pre-exercise, § $p < 0.0001$ compared to pre-exercise.

Table 2. Log-log relationships between T_{pe} and $[K^+]$ at specified time points for pooled data in combined and separate cohorts.

Time Points and Group(s)	β	R^2	p
Pre-exercise			
Pooled healthy participants plus ESRD patients before and following HD	-1.07 ±0.2	0.41	<0.0001
Pooled healthy participants plus ESRD patients before HD	-0.71 ± 0.2	0.44	p < 0.0001
Pooled healthy participants plus ESRD patients following HD	-2.5 ± 0.5	0.46	p < 0.0001
ESRD patients before HD	-0.68 ± 0.2	0.44	p = 0.001
ESRD patients following HD	-0.95 ± 0.4	0.22	p = 0.03
$[K^+]$ nadir			
Pooled healthy participants plus ESRD patients before and following HD	-0.77 ± 0.15	0.36	< 0.0001
Pooled healthy participants plus ESRD patients before HD	-0.82 ± 0.1	0.56	p < 0.0001
Pooled healthy participants plus ESRD partients following HD	-1.22 ± 0.3	0.37	p = 0.0003
ESRD patients before HD	-0.52 ± 0.2	0.22	p = 0.04
ESRD patients following HD	-1.47 ± 0.6	0.23	p = 0.02

ESRD, end-stage renal disease, HD, haemodialysis. All data from negative log-log relationships between T_{pe} and $[K^+]$ at identified time points, $\log T_{pe} = \beta (\log[K^+]) + c$, with β and c expressed as mean ± SEM, n=8 for healthy participants and 22 for ESRD patients.

Table 3.

Fixed effects for regression models predicting the T_{pe} in healthy participants and ESRD patients on serial data analysed with linear mixed model. Logarithmic transformations with base number of 2 of T_{pe} and $[K^+]$ were performed to ensure linearity. Parameters estimates for fixed effects and P values for each parameter are presented for each model.

	Parameter estimate	**p**
Pooled		
Log $[K^+]$	-0.64 ± 0.52	< 0.0001
Heart rate	0.0004 ± 0.0005	0.91
Post-exercise state	-0.039 ± 0.028	0.17
Intercept	7.68 ± 0.10	< 0.0001
Healthy participants		
Log $[K^+]$	-0.54 ± 0.11	<0.0001
Heart rate	0.0013± 0.001	0.28
Post-exercise state	0.11± 0.07	0.011
Intercept	7.32 ± 0.17	<0.0001
ESRD patients		
Log $[K^+]$	-0.72 ± 0.1	<0.0001
Heart rate	-0.002 ± 0.0008	0.02
Post-exercise state	-0.09 ± 0.03	0.03
Pre-HD state	-0.023± 0.05	0.61
Intercept	8.06 ± 0.20	<0.0001

$[K^+]$ = plasma K^+ concentration, Log = logarithm. ESRD, end-stage renal disease, HD, haemodialysis. Parameter estimates were expressed as value ± SEM, n=8 for healthy participants and 22= ESRD patients.

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