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Nonlinear analysis of beat-to-beat variability of action potential time series data identifies dynamic re-entrant substrates in a hypokalaemic mouse model of acquired long QT syndrome

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Abstract

Background Previous studies have quantified repolarization variability using time-domain, frequency-domain and nonlinear analysis in mouse hearts. Here, we investigated the relationship between these parameters and ventricular arrhythmogenicity in a hypokalaemia model of acquired long QT syndrome.

Methods Left ventricular monophasic action potentials (MAPs) were recorded during right ventricular regular 8 Hz pacing during normokalaemia (5.2 mM [K^+]), hypokalaemia modeling LQTS (3 mM [K^+]) or hypokalaemia with 0.1 mM heptanol in Langendorff-perfused mouse hearts.

Results During normokalaemia, mean APD was 33.5 ± 3.7 ms. Standard deviation (SD) of APDs was 0.63 ± 0.33 ms, coefficient of variation was 1.9 ± 1.0% and the root mean square (RMS) of successive differences in APDs was 0.3 ± 0.1 ms. Low- and high-frequency peaks were 0.6 ± 0.5 and 2.3 ± 0.7 Hz, respectively, with percentage powers of 38 ± 22 and 61 ± 23%. Poincaré plots of APD_{n+1} against APD_n revealed ellipsoid morphologies with SD along the line-of-identity (SD2) to SD perpendicular to the line-of-identity (SD1) ratio of 4.6 ± 1.1. Approximate and sample entropy were 0.49 ± 0.12 and 0.64 ± 0.29, respectively. Detrended fluctuation analysis revealed short- and long-term fluctuation slopes of 1.62 ± 0.27 and 0.60 ± 0.18, respectively. Hypokalaemia provoked ventricular tachycardia in six of seven hearts, prolonged APDs (51.2 ± 7.9 ms), decreased SD2/SD1 ratio (3.1 ± 1.0), increased approximate and sample entropy (0.68 ± 0.08 and 1.02 ± 0.33) and decreased short-term fluctuation slope (1.23 ± 0.20) (ANOVA, $P < 0.05$). Heptanol prevented VT in all hearts studied without further altering the above repolarization parameters observed during hypokalaemia.

Conclusion Reduced SD2/SD1, increased entropy and decreased short-term fluctuation slope may reflect arrhythmic risk in hypokalaemia. Heptanol exerts anti-arrhythmic effects without affecting repolarization variability.

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Keywords Repolarization variability, Beat-to-beat, Entropy, Delayed repolarization, Long QT

Introduction

Long QT syndrome (LQTS) is an important clinical condition predisposing to the occurrence of ventricular tachyarrhythmias, which can lead to sudden cardiac death. It can have congenital or acquired causes, the latter reflected by electrolyte disturbances such as hypokalemia or certain drugs that block potassium channels. Of these, hypokalaemia is the commonest electrolyte abnormality observed in patients who are admitted to the hospital [1] and is an important cause of arrhythmias and associated mortality clinically [2]. It is frequently observed in patients with pre-existing heart conditions [3–5]. Previously, several important re-entrant substrates of hypokalaemia have been identified using pre-clinical models [6–9]. These include repolarization abnormalities in the form of action potential prolongation, increased transmural dispersion of repolarization, reduced refractoriness, steep restitution gradients and increased amplitude of repolarization alternans [10, 11].

Moreover, altered beat-to-beat variations in the repolarization time-course have been associated with arrhythmogenesis in other pharmacological or disease models [12, 13]. For example, higher degrees of short-term repolarization variability using Poincaré plot analysis were associated with the development of ventricular arrhythmias in dogs [14]. Moreover, a combined experimental and computational approach associated higher repolarization variability with pro-arrhythmic abnormalities [15]. Finally, high entropy was shown to predict arrhythmic outcomes following gap junction and sodium channel inhibition in a mouse model [16]. However, whether variability or complexity of beat-to-beat repolarization variability plays a role in hypokalaemia modeling LQTS has never been studied. We hypothesized that increased repolarization variability contributes to arrhythmic substrate in an experimental mouse model of LQTS using hypokalaemia.

Materials and methods

This study received approval from the University of Cambridge (Approval Number: BB/G017565/1). The methodology used in this study has previously been described by us in detail. The reader is directed to this publication for further details [16]. Langendorff-perfused mouse hearts were used for the experiments, as described previously [17–19]. Monophasic action potential (MAP) waveforms were obtained from the left ventricular epicardium during right ventricular stimulation. MAP waveforms must have met established criteria for MAP signals and those that did not were rejected [20, 21]. They must have stable baselines, fast upstrokes, with no inflections or negative spikes, and a rapid first phase of repolarization. 0% repolarization was measured at the peak of the MAP and 100% repolarization was measured at the point of return of the potential to baseline [20, 22, 23].

Results

Action potential duration variability determined using time-domain methods

Our previous work has reported the pro-arrhythmic effects of hypokalaemia and anti-arrhythmic effects of 0.1 mM heptanol under hypokalaemic conditions [24] and also the time- and dose-dependent effects of heptanol between 0.1 and 2 mM [25, 26]. This is an extension of the previously work by examining the beat-to-beat variability in repolarization durations of monophasic action potential (MAP) time series data over 20-s periods. Typical examples of MAP waveforms, time series and histograms of action potential durations (APDs) at 90% repolarization for normokalaemia, hypokalemia alone or in the presence of 0.1 mM heptanol are shown in Fig. 1A–C, respectively. Time-domain analysis demonstrated a mean APD_{90} of 33.5 ± 3.7 ms (Fig. 2A), standard deviation (SD) of APDs of 0.63 ± 0.33 ms (Fig. 2B), coefficient of variation (CoV) of 1.9 ± 1.0% (Fig. 2C), and root mean square (RMS) of successive differences in APDs of 0.3 ± 0.1 ms (Fig. 2D). Hypokalemia prolonged APD_{90} to 51.2 ± 7.9 ms without significantly altering the remaining parameters (ANOVA, $P > 0.05$). After further treatment with heptanol, all of the above parameters remained unaltered (ANOVA, $P > 0.05$).

Action potential duration variability determined using frequency-domain methods

Fast Fourier Transform was used to generate frequency spectra, with examples obtained during normokalaemia, hypokalemia alone or in the presence of 0.1 mM heptanol are shown in Fig. 3A–C. Frequency-domain analysis revealed that the peaks for very low-, low- and high-frequency were 0.03 ± 0.01, 0.58 ± 0.46 and 2.30 ± 0.74 Hz, respectively (Fig. 4A–C). Their corresponding powers took values of 0.00 ± 0.01, 0.22 ± 0.28 and 0.23 ± 0.18 ms^2, respectively (Fig. 4D–F). The low-frequency to high-frequency ratio was 0.95 ± 0.98 (Fig. 4G) and total power (in log units) was -1.25 ± 1.11 (Fig. 4H). Their percentage powers were 1.2 ± 2.0, 38.3 ± 22.4 and 60.5 ± 23.5% (Fig. 4I–K). None of these parameters was altered by

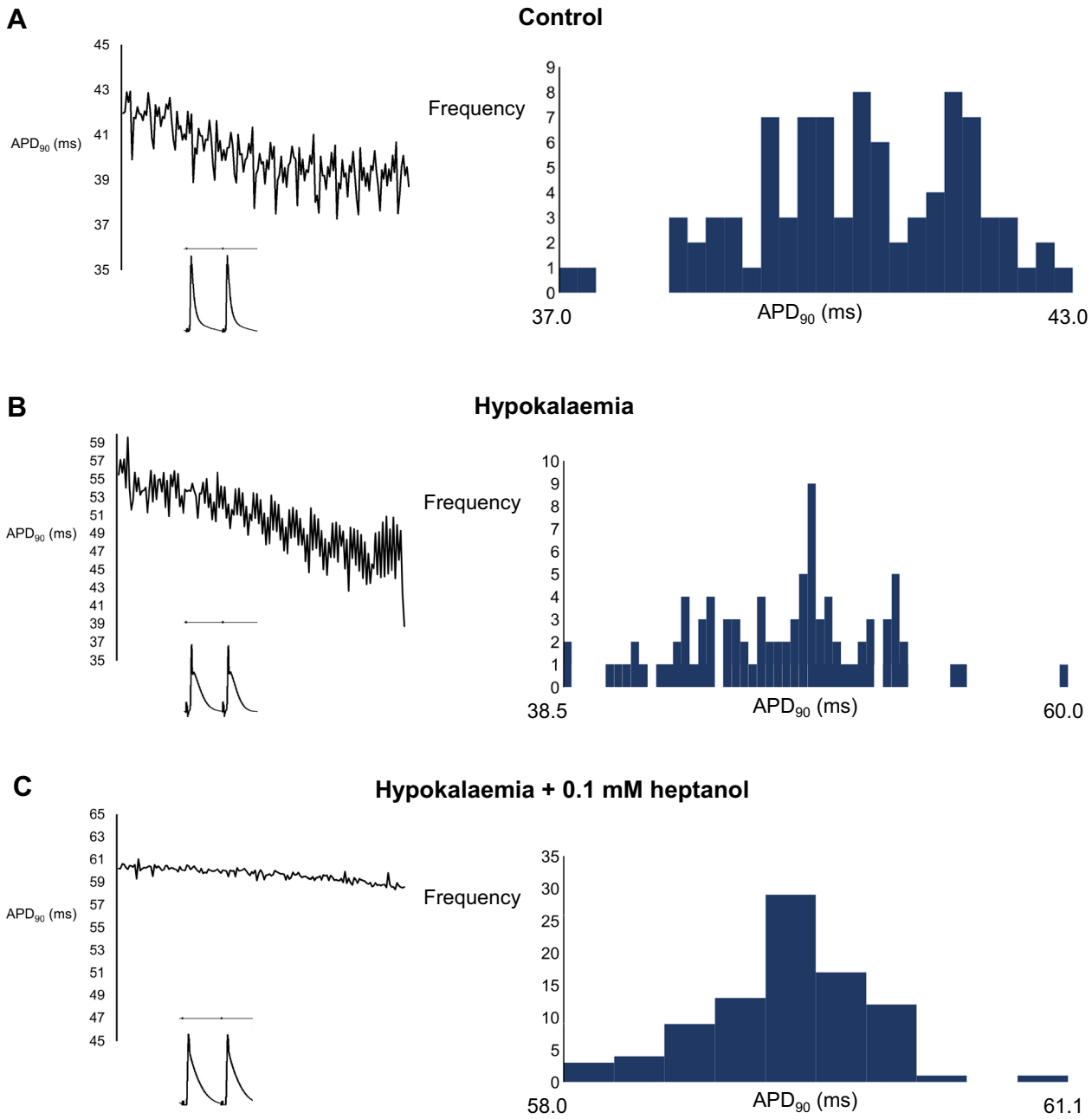

Fig. 1 MAP traces, time series and histograms of APDs from a representative heart before (**A**) or after the application of experimental hypokalaemia (**B**) and hypokalaemia with 0.1 mM heptanol (**C**)

hypokalemia alone or in the presence of 0.1 mM heptanol (ANOVA, $P > 0.05$).

Action potential duration variability determined using nonlinear methods

Poincaré plots, which plotted APD_{n+1} against APD_n, were generated (Fig. 5A–C). Ellipsoid shapes of the data points were observed for the different hearts studied. The SD1 (SD perpendicular to the line-of-identity), SD2 (SD along the line-of-identity) and SD2/SD1 ratio are shown in Fig. 6A–C, taking values of 0.19 ± 0.08, 0.87 ± 0.46 and 4.60 ± 1.07, respectively. Approximate and sample entropy were 0.49 ± 0.12 (Fig. 6D) and 0.64 ± 0.29, respectively (Fig. 6E). Detrended fluctuation analysis, which expressed the detrended fluctuations F(n) as a function of n in a logarithmic-logarithmic scale was

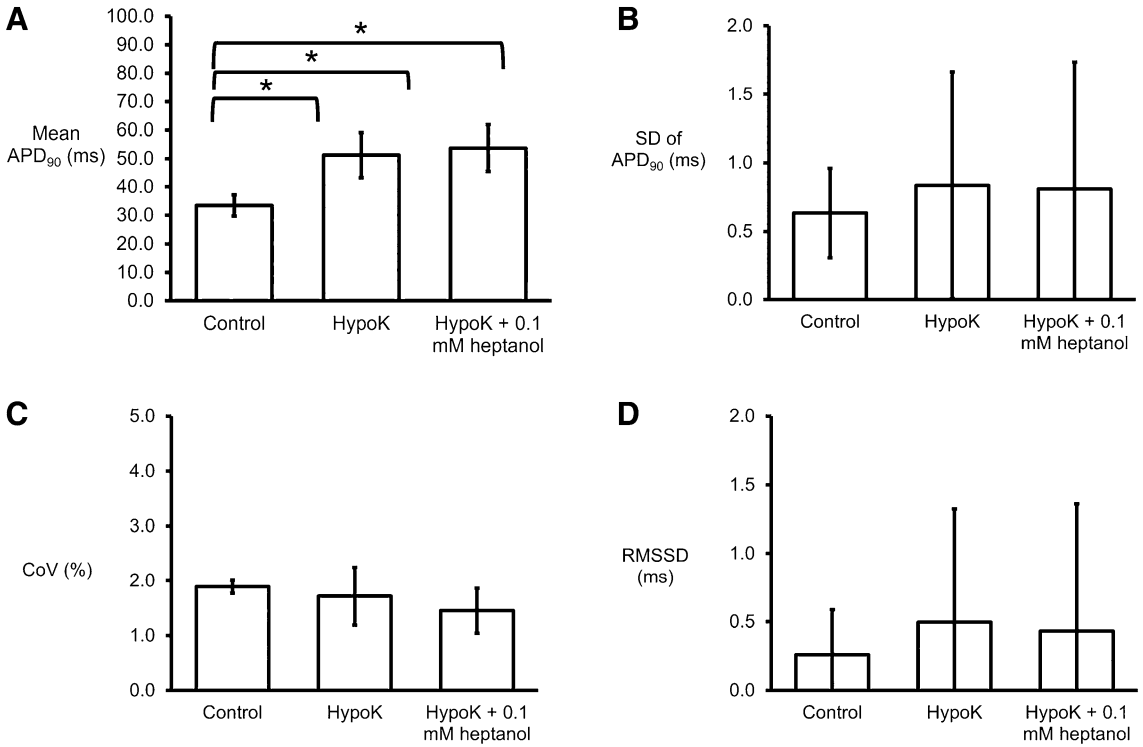

Fig. 2 Time-domain analysis yielding mean APD (**A**), standard deviation (SD) of APDs (**B**), coefficient of variation (CoV) (**C**), and root mean square (RMS) of successive differences of APDs (D) ($n=6$) ($n=7$ hearts)

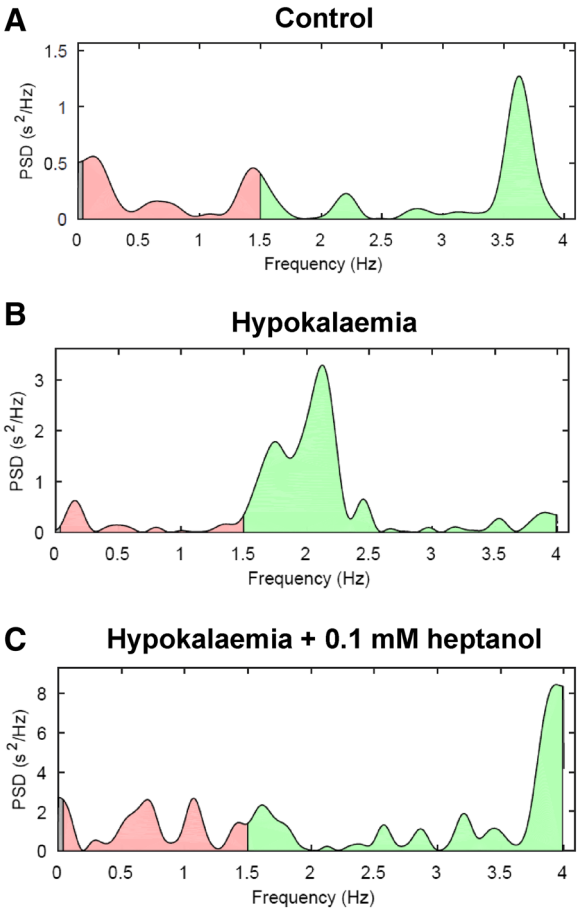

Fig. 3 Examples of frequency spectra using the Fast Fourier Transform method from a representative heart before (**A**) or after the application of experimental hypokalaemia (**B**) and hypokalaemia with 0.1 mM heptanol (**C**)

conducted (Fig. 7A–C). This revealed short- and long-term fluctuation slopes of 1.62 ± 0.27 (Fig. 7D) and 0.60 ± 0.18 (Fig. 7E), respectively. Hypokalemia significantly decreased SD2/SD1 ratio to 3.1 ± 1.0, increased approximate and sample entropy to 0.68 ± 0.08 and 1.02 ± 0.33 and decreased short-term fluctuation slope to 1.23 ± 0.20 (ANOVA, $P < 0.05$). After treatment with heptanol, no further changes in the above parameters were observed (ANOVA, $P > 0.05$).

Discussion

In this study, we examined the effects of experimental hypokalemia modeling acquired long QT syndrome on beat-to-beat variability in APD using time-domain, frequency-domain and nonlinear analyses. Our main findings are that 1) increased arrhythmogenicity in hypokalemia was associated with prolonged APD, decreased SD2/SD1 ratio, increased approximate and sample entropy, and a decrease in short-term fluctuation slope; 2) heptanol exerted anti-arrhythmic effects despite leaving the hypokalemia-induced repolarization abnormalities unaltered.

Beat-to-beat variability in repolarization time-courses is a normal physiological phenomenon reflecting stochastic fluctuations in ion channel gating. Previous reports demonstrate that this variability is altered in pro-arrhythmic states. For example, higher degree of short-term variability determined using the Poincaré method was detected before the occurrence of *torsade de pointes* with reduced intercellular coupling in a canine model [14]. Secondly, computational modeling efforts complemented by experimental data suggested that higher variability was associated with pro-arrhythmic abnormalities using similar Poincaré plots [15]. Such a temporal variability in repolarization provide incremental value for arrhythmic risk stratification in human subjects with non-ischemic heart failure [27]. Recently, our group reported the use of time-domain, frequency-domain and fractal complexity analysis for assessing repolarization variability of action potential waveforms recorded from mouse hearts [28].

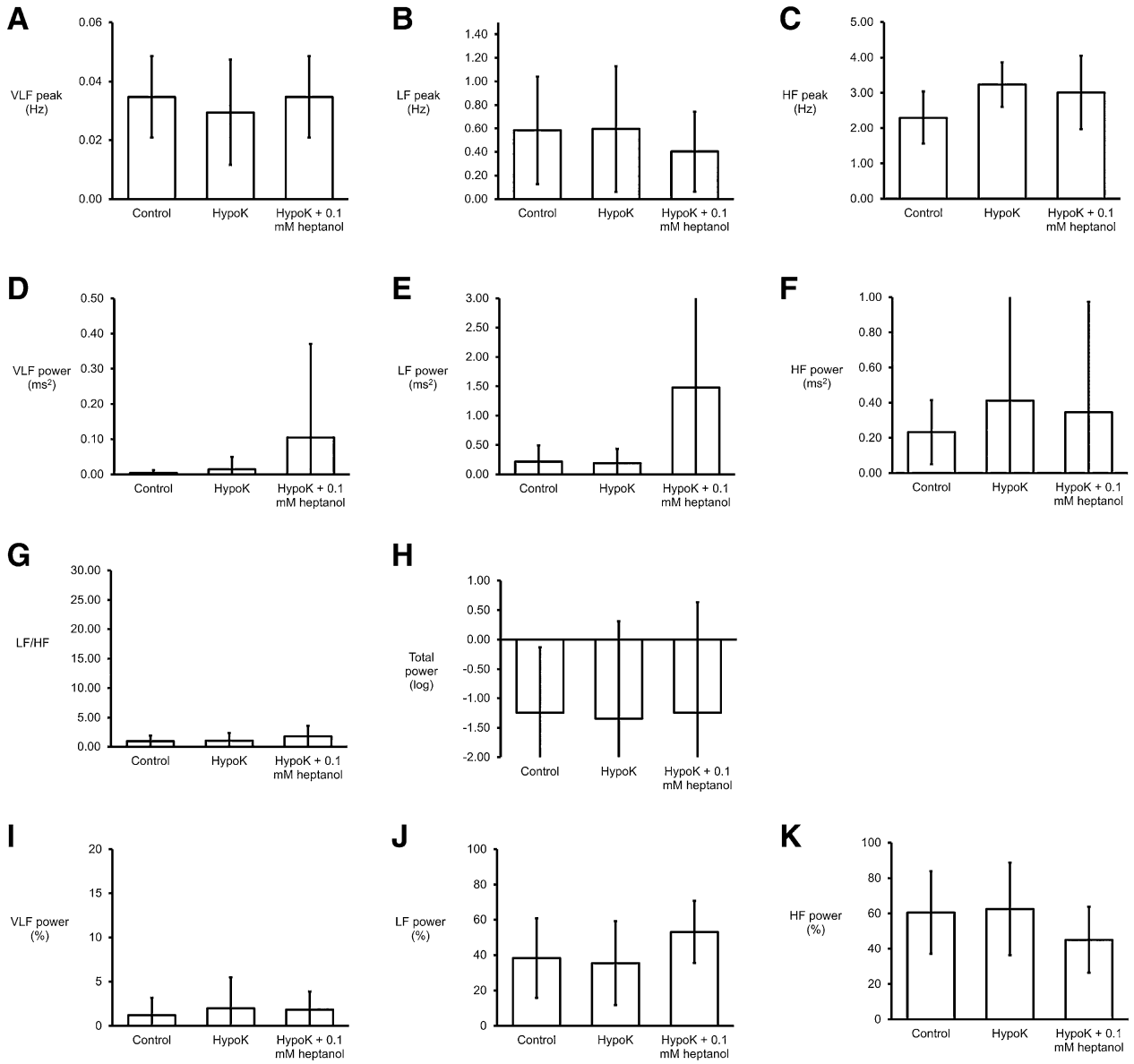

Fig. 4 Peaks for very low- (**A**), low- (**B**) and high-frequency (**C**), their corresponding powers (**D**–**F**), low-frequency to high-frequency ratio (**G**) and total power (**H**). The percentage powers for very low- (**I**), low- (**J**) and high-frequency (**K**) bands ($n = 7$ hearts)

This was subsequently extended to demonstrations that nonlinear measures of repolarization variability, such as SD2/SD1, entropy, and fluctuation slope can predict ventricular arrhythmogenesis in mouse hearts using the gap junction and sodium channel blocker, heptanol [16]. The present work extends these findings by demonstrating that such measures of repolarization variability can similarly reveal re-entrant substrate in the context of acquired LQTS and represent biomarkers that can improve risk stratification. These findings have clinical implications given recent demonstrations of the association between increased beat-to-beat variability in the electrocardiographic T-wave with sudden cardiac death [29], but it remains to be elucidated whether the nonlinear measures would predict ventricular arrhythmias or sudden cardiac death in the clinical setting [30].

Previous studies have reported alterations in beat-to-beat repolarization variability with differing degrees of gap junction coupling using time-domain methods. Thus, single ventricular cardiomyocytes isolated from canine hearts showed a baseline level of APD variability [31]. When two cardiomyocytes were electrically coupled, this variability was attenuated [31]. These experimental findings were supported of those from computational

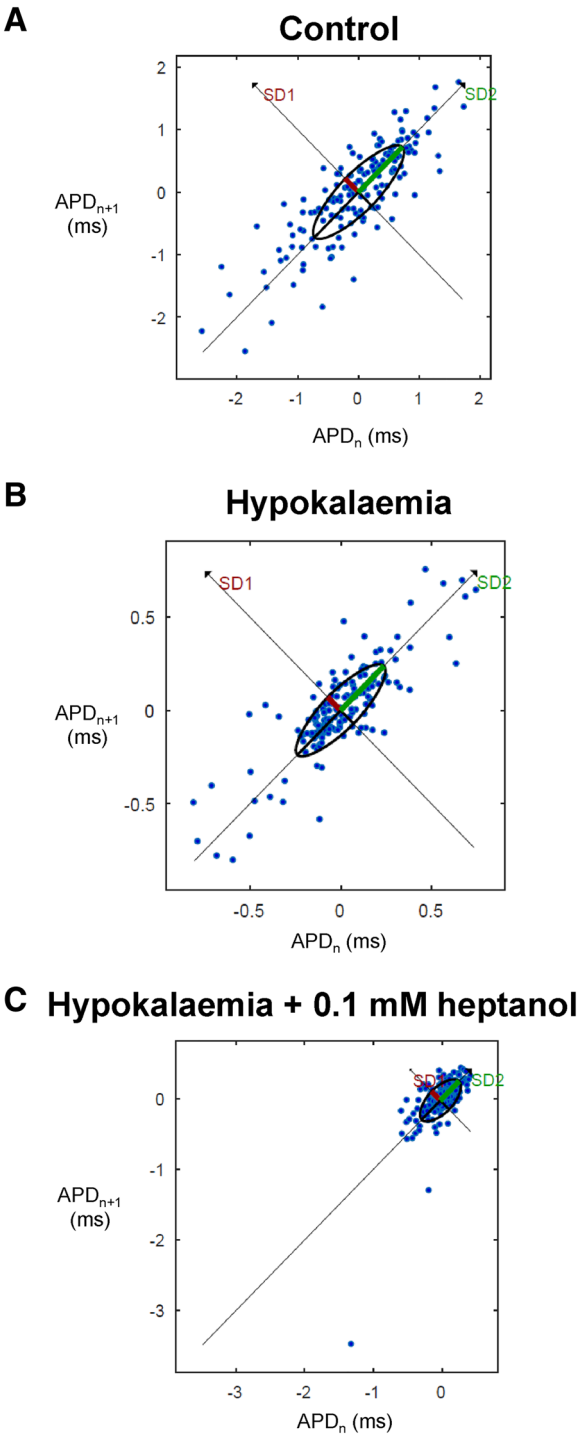

Fig. 5 Representative Poincaré plots of APD_{n+1} against APD_n with SD along the line-of-identity (SD1) and SD perpendicular to the line-of-identity (SD2) before (**A**) or after the application of experimental hypokalaemia (**B**) and hypokalaemia with 0.1 mM heptanol (**C**) ($n = 7$ hearts)

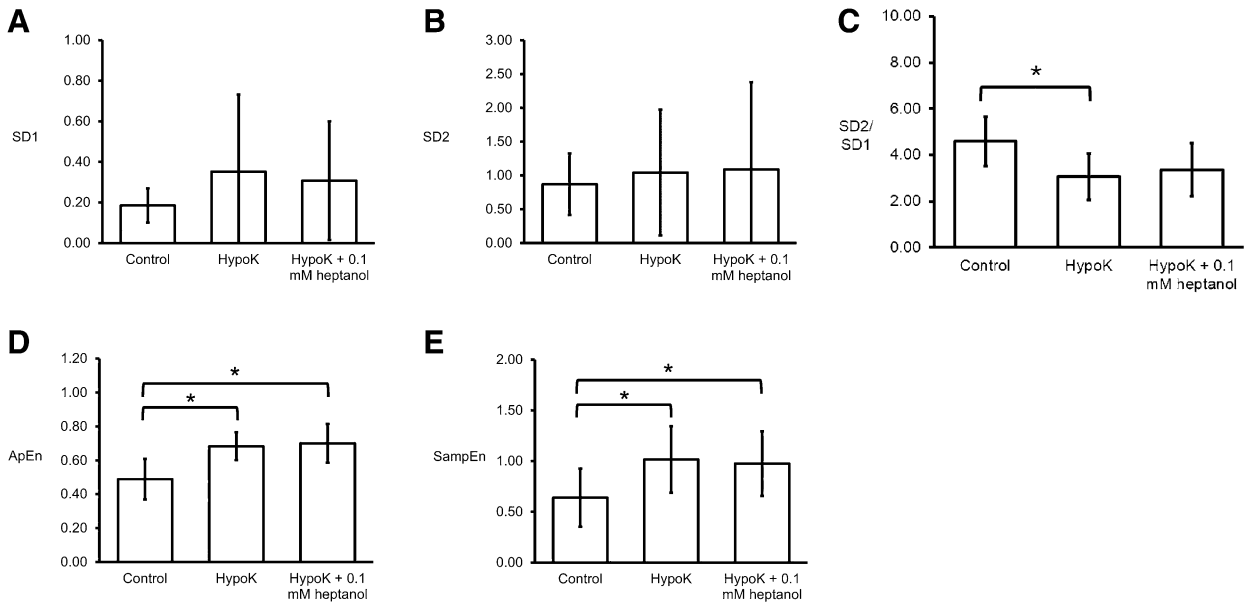

Fig. 6 Bar charts plotting SD perpendicular to the line-of-identity (SD1) (**A**), SD along the line-of-identity (SD2) (**B**), SD2/SD1 ratio (**C**), the approximate entropy (**D**) and the sample entropy (**E**) ($n = 7$ hearts)

modeling studies, reporting higher repolarization variability with lower level of intercellular coupling [32]. In the present work, APD variability was not significantly higher after introduction of heptanol. Some possible reasons could explain the present findings. For example, heptanol has multiple targets, such as potassium and calcium channels [13]. It was previously demonstrated that beat-to-beat variability is affected by not only the mean APD but also the pacing rate [33]. Therefore, pacing rate was fixed in this study to exclude its possible effects on variability. Future studies should systematically explore the relationship between pacing rate and different measures of variability. The anti-arrhythmic effects of heptanol can be attributed to its actions in prolonging the ventricular effective refractory period, which would lead to increase in the excitation wavelength [24].

Our findings in the mouse are in keeping with those from clinical studies. In heart failure patients, higher approximate entropy of the interval between R_{peak} and T_{peak} were predictive of appropriate ICD shocks and death [34]. Moreover, in patients who have implantable cardioverter-defibrillator for primary prevention, high entropy of QT intervals also predicted ventricular arrhythmogenesis and mortality [35]. This study extends these findings by quantifying entropy using action potential time series data recorded from isolated hearts that are free from autonomic influence and associated increased entropy with ventricular arrhythmogenesis under hypokalaemic conditions. Interestingly, our study found that it was possible to reduce arrhythmogenicity in the presence of high variability in beat-to-beat repolarization. Instead, the anti-arrhythmic effects are instead attributed to increases in tissue refractoriness, which was initially reduced by hypokalemia [24]. These findings are in keeping with known effects of different anti-arrhythmic agents. For example, class III and class IV anti-arrhythmic agents inhibit potassium and calcium channels, respectively, yet they increase beat-to-beat variability for two reasons. Firstly, the inward calcium current has the highest amplitude at the beginning of the plateau phase of cardiac repolarization, and this is a powerful modulator of subsequent potassium channel activation [36]. Secondly, the membrane resistance is high during the late phase of repolarization [31], and any small increase in the net inward current (e.g., produced by potassium channel block) can lead to larger variation in APD [37, 38]. Together, these findings would suggest multiple interacting mechanisms that are important determinants of arrhythmogenesis. The implications are that patients who are suffering from hypokalaemia at an inpatient setting could benefit from not only continuous monitoring but its real-time quantification of repolarization variability and the QT intervals. This could theoretically provide warning messages for patients at immediate risks of developing ventricular arrhythmias [39]. A limitation is that the possible modifying effects of age on hypokalaemia-related electrophysiology and arrhythmogenicity were not explored. Given that there is an age-dependent

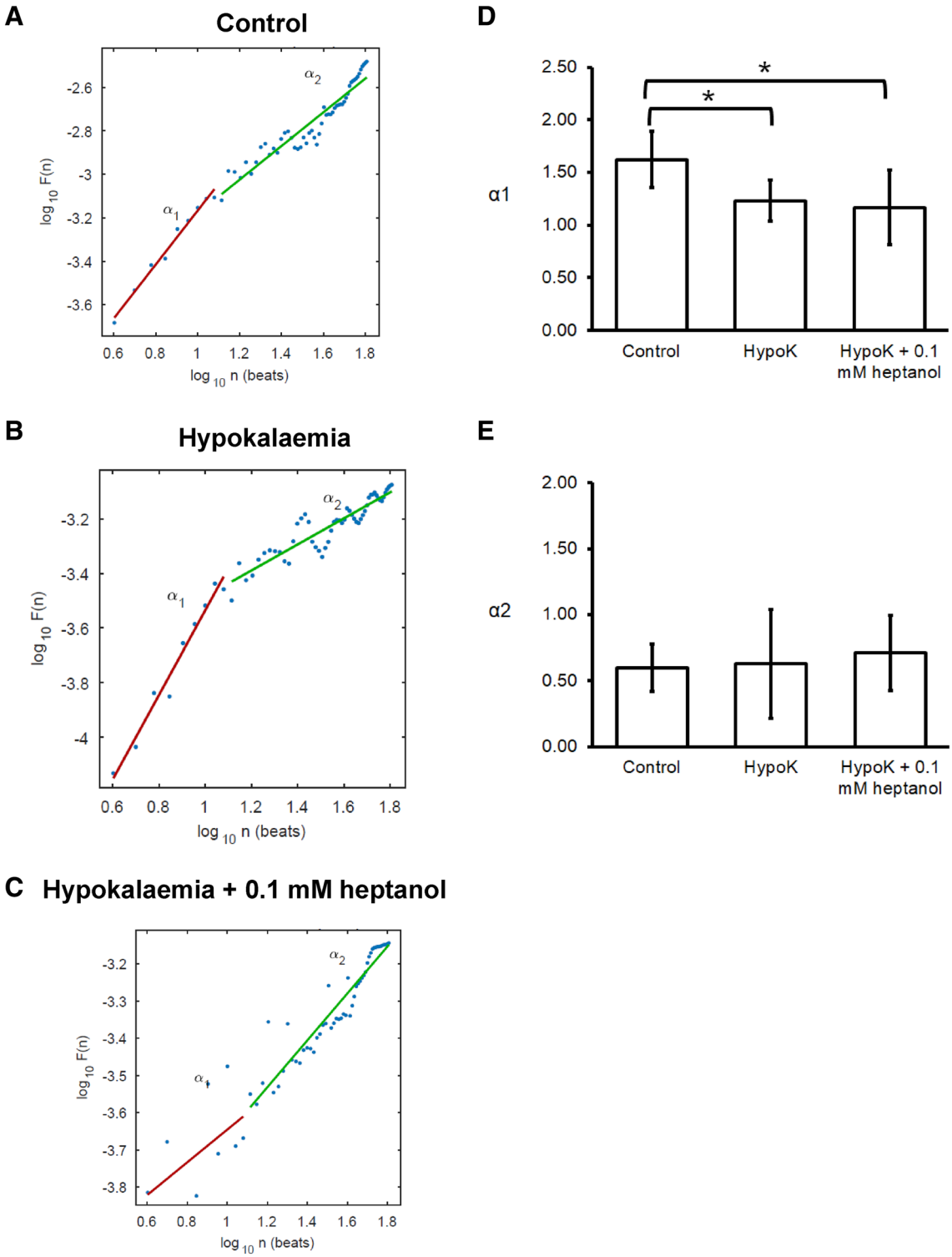

Fig. 7 Detrended fluctuation analysis plots expressing detrended fluctuations *F*(*n*) as a function of *n* in a log–log scale before (**A**) or after the application of experimental hypokalaemia (**B**) and hypokalaemia with 0.1 mM heptanol (**C**). Short-term (**D**) and long-term (**E**) fluctuation slopes ($n = 7$ hearts)

increase in QT intervals [40], whether increasing age would interact with hypokalaemia to exacerbate arrhythmogenic or electrophysiological abnormalities remain to be elucidated. Finally, wild-type mice from the 129 genetic background were used. Previously studies have reported the differing effects of genetic background on electrophysiology [41, 42]. Future studies should therefore be conducted to explore the effects of hypokalaemia in different genetic strains.

Conclusions

Reduced SD2/SD1 and increased entropy and decreased short-term fluctuation slope may reflect arrhythmic risk in hypokalaemia. Heptanol exerts anti-arrhythmic effects without significantly influencing repolarization variability.

Abbreviations

APD	Action potential duration
ICD	Implantable cardioverter-defibrillator
LQTS	Long QT syndrome
VT	Ventricular tachycardia

Acknowledgments

None.

Author contributions

GT contributed to data acquisition, statistical analysis, manuscript drafting, critical revision of manuscript. JZ contributed to statistical analysis, data interpretation, critical revision of manuscript. XD contributed to statistical analysis, data interpretation, manuscript drafting, critical revision of manuscript. GH contributed to statistical analysis, data interpretation, manuscript drafting, critical revision of manuscript. SL contributed to statistical analysis, data interpretation, manuscript drafting, critical revision of manuscript. KSKL contributed to statistical analysis, data interpretation, manuscript drafting, critical revision of manuscript. TL contributed to data interpretation, critical revision of manuscript, study supervision. YD contributed to data interpretation, critical revision of manuscript, study supervision. SHC contributed to data interpretation, critical revision of manuscript, study supervision. WTW contributed to data interpretation, critical revision of manuscript, study supervision.

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Availability of data and materials

Raw data are available from the corresponding author without restriction.

Declarations

Ethics approval and consent to participate

This study was approved by the University's Animal Ethics Committee.

Consent for publication

All authors consent to publication.

Competing interests

The authors declare that they have no competing interests.

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