Anti-arrhythmic effects of hypercalcemia in hyperkalemic, Langendorff-perfused mouse hearts

GARY TSE[1*], BING SUN[2*], SHEUNG TING WONG[3], VIVIAN TSE[4] and JIE MING YEO[3]

[1]School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, SAR; [2]Department of Cardiology, Tongji University Affiliated Tongji Hospital, Shanghai 200065, P.R. China; [3]School of Medicine, Imperial College London, London SW7 2AZ, UK; [4]Department of Physiology, McGill University, Montreal, Quebec H3G 1Y6, Canada

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Abstract. The present study examined the ventricular arrhythmic and electrophysiological properties during hyperkalemia (6.3 mM $[K^+]$ vs. 4 mM in normokalemia) and anti-arrhythmic effects of hypercalcemia (2.2 mM $[Ca^{2+}]$) in Langendorff-perfused mouse hearts. Monophasic action potential recordings were obtained from the left ventricle during right ventricular pacing. Hyperkalemia increased the proportion of hearts showing provoked ventricular tachycardia (VT) from 0 to 6 of 7 hearts during programmed electrical stimulation (Fisher's exact test, $P<0.05$). It shortened the epicardial action potential durations (APD_x) at 90, 70, 50 and 30% repolarization and ventricular effective refractory periods (VERPs) (analysis of variance, $P<0.05$) without altering activation latencies. Endocardial APD_x and VERPs were unaltered. Consequently, ΔAPD_x (endocardial APD_x-epicardial APD_x) was increased, VERP/latency ratio was decreased and critical intervals for reexcitation (APD_{90}-VERP) were unchanged. Hypercalcemia treatment exerted anti-arrhythmic effects during hyperkalemia, reducing the proportion of hearts showing VT to 1 of 7 hearts. It increased epicardial VERPs without further altering the remaining parameters, returning VERP/latency ratio to normokalemic values and also decreased the critical intervals. In conclusion, hyperkalemia exerted pro-arrhythmic effects by shortening APDs and VERPs. Hypercalcemia exerted anti-arrhythmic effects by reversing VERP changes, which scaled the VERP/latency ratio and critical intervals.

Correspondence to: Dr Gary Tse, School of Biomedical Sciences, Li Ka Shing Faculty of Medicine, University of Hong Kong, 3/F Laboratory Block, 21 Sassoon Road, Hong Kong, SAR, P.R. China
E-mail: gary.tse@doctors.org.uk

*Contributed equally

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Introduction

The extracellular potassium concentration ($[K^+]_o$) is normally maintained between 3.5 and 5 mM. Hyperkalemia and hypokalemia are defined as a serum potassium concentration above and below this range, respectively (1). The two are important clinical conditions (2), predisposing patients to life-threatening ventricular arrhythmias (3,4). Of these, hyperkalemia exerts a wide range of effects on cardiac conduction and repolarization properties, depending on the degree of high $[K^+]_o$. Its most common electrocardiographic manifestations are flattened or loss of the P-wave (5), prolonged PR and QRS intervals (6), and T-wave abnormalities, particularly peaked T-waves (7). A sine-wave appearance can be observed at the most severely elevated levels of $[K^+]_o$ (8). Calcium gluconate or 10% calcium chloride are used acutely to suppress ventricular arrhythmias in hyperkalemic patients (9,10), despite the fact that hypercalcemia alone has pro-arrhythmic effects (11,12). There have been certain previous studies on the electrophysiological changes during hyperkalemia (13,14), but not on the mechanism underlying the anti-arrhythmic action of calcium in this situation, apart from its 'membrane-stabilizing effect' (15). This notion has been disputed and the protective action of high $[Ca^{2+}]_o$ has instead been attributed to restoration of conduction velocities (CVs) back to normal values (16).

Mouse systems have been extensively used for the study of arrhythmogenesis, as they permit the use of genetic and pharmacological manipulation to produce ion channel abnormalities with great translational potential (17-26). This has resulted in demonstrations of the following mechanisms (27,28). Firstly, the early-after depolarization phenomena and triggered activity observed during hypokalemia have been attributed to prolonged action potential durations (APDs) (29). Secondly, several reentrant substrates during hypokalemia have been identified: Prolonged epicardial but unaltered endocardial APDs leading to negative ΔAPD_{90} given by endocardial APD_{90}-epicardial APD_{90} (30). Reduced ventricular effective refractory periods (VERPs) leading to increased critical intervals given by APD_{90}-VERP (29). By contrast, reduced CVs were shown to induce ventricular arrhythmias following treatment with the gap junction and sodium channel inhibitor heptanol through

a reduction in excitation wavelengths despite unaltered APDs and even with increased VERPs (31,32). However, to the best of our knowledge, there have been no investigations of the arrhythmogenic effects of hyperkalemia in the mouse system.

Therefore, in the present study, the ventricular arrhythmogenic properties of hyperkalemia were characterized in Langendorff-perfused mouse hearts for the first time. An increased external calcium concentration is known to reduce membrane excitability at the cellular level (33), but exerts pro-arrhythmic effects in the whole heart level under normokalemic conditions (34). However, as a decrease in membrane excitability would lead to an increase in refractoriness, it was hypothesized that hypercalcemia would abolish arrhythmic properties of hyperkalemia by increasing VERPs.

Materials and methods

Solutions. Krebs-Henseleit solution [119 mM NaCl, 25 mM $NaHCO_3$, 4 mM KCl, 1.2 mM KH_2PO_4, 1 mM $MgCl_2$, 1.8 mM $CaCl_2$, 10 mM glucose and 2 mM sodium pyruvate (pH 7.4)] that had been bicarbonate-buffered and bubbled with 95% O_2-5% CO_2 (35) was used in the experiments. Hyperkalemic solution was prepared by increasing the amount of KCl added to produce a [K^+] of 6.3 mM, whereas hypercalcemic solution was prepared by increasing the amount of $CaCl_2$ added to produce a [Ca^{2+}] of 2.2 mM.

Preparation of Langendorff-perfused mouse hearts. Wild-type mice of the 129 genetic background between 5 and 7 months of age were used in the study. These mice were housed in an animal facility at room temperature (21±1˚C), subject to a 12:12 h light:dark cycle and had free access to sterile rodent chow and water. All the experiments described complied with the UK Animals (Scientific Procedures) Act 1986. The procedures for the preparation of Langendorff-perfused mouse hearts have been described previously (36). Mice were sacrificed by cervical dislocation in accordance with Sections 1(c) and 2 of Schedule 1 of the UK Animals (Scientific Procedures) Act 1986. The hearts were quickly excised and immediately submerged in ice-cold Krebs-Henseleit solution. The aorta was cannulated using a tailor-made 21-gauge cannula that had been prefilled with ice-cold buffer, secured using a micro-aneurysm clip (Harvard Apparatus, Cambridge, UK) and attached to the perfusion system. Retrograde perfusion was started at a rate of 2-2.5 ml min^{-1} using a peristaltic pump (Watson-Marlow Bredel pumps model 505S; Falmouth, Cornwall, UK) with the perfusate passing through 200- and 5-μm filters successively and heated to 37˚C using a water jacket and circulator prior to reaching the aorta. Approximately 90% of the hearts that regained their pink colour and spontaneous rhythmic activity were studied further. The remaining 10% did not and were therefore discarded. Perfusion continued for a further 20 min to minimise any residual effects of endogenous catecholamine release prior to examination of the electrophysiology of the perfused hearts.

Stimulation protocols. Electrical stimulation was achieved using paired platinum electrodes (1 mm interpole distance) placed at the basal right ventricular epicardium. Pacing occurred at 8 Hz, using square wave pulses 2 msec in duration, with a stimulation voltage set to three times the diastolic threshold (Grass S48 Stimulator; Grass-Telefactor, Slough, UK) immediately after the start of perfusion. This allowed direct comparisons with previous mouse studies of arrhythmogenesis (29-32). Programmed electrical stimulation (PES) was used to assess for arrhythmogenicity and thereby for reentrant substrates. This procedure consisted of a drive train of eight regularly paced S1 stimuli at a 125 msec baseline cycle length (BCL), followed by premature S2 extra-stimuli every ninth stimulus. S1S2 intervals first equalled the pacing interval and were successively reduced by 1 msec with each nine stimulus cycle until arrhythmic activity was initiated or refractoriness was reached, whereupon the S2 stimulus elicited no response.

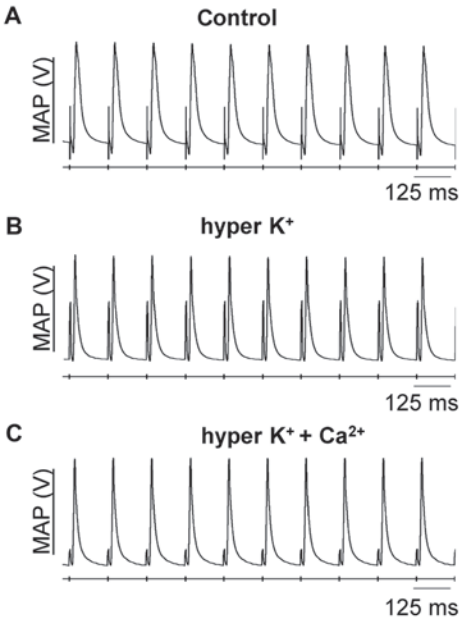

Figure 1. Representative epicardial MAP recordings obtained under (A) control conditions, (B) hyperkalemia alone or (C) following hypercalcemia treatment during regular 8 Hz pacing. Typical regular rhythms can be observed, with each MAP occurring directly following its preceding stimulus. MAP, monophasic action potential.

Recording procedures. Monophasic action potentials (MAPs) recordings were obtained from the left ventricular epicardium using an MAP electrode (Linton Instruments, Harvard Apparatus). They were also obtained from the left endocardium using a custom-made MAP electrode that was made from two strands of 0.25-mm Teflon-coated silver wire (99.99% purity; Advent Research Materials, Witney, UK). The tips of the electrode had previously undergone galvanic treatment with chloride to eliminate DC offset. The endocardial electrode was introduced through a small access window made in the inter-ventricular septum and subsequently positioned on the lateral aspect of the left ventricular cavity. All the recordings were performed using a BCL of 125 msec (8 Hz) to exclude rate-dependent differences in APDs. MAPs were pre-amplified using an NL100AK head stage, amplified with an NL104A amplifier and band-pass filtered between 0.5 Hz and 1 kHz using an NL125/6 filter (Neurolog, Hertfordshire, UK) and subsequently digitized (1401plus MKII; Cambridge

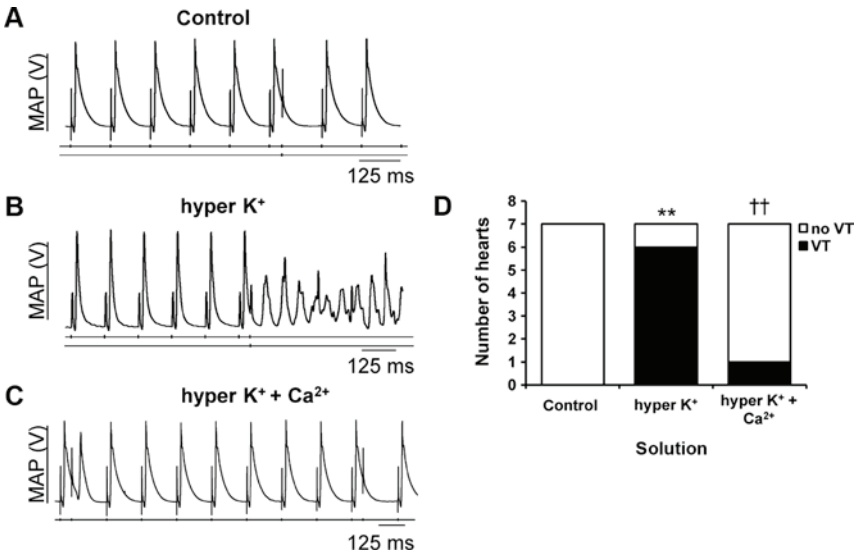

Figure 2. Representative epicardial MAP recordings from programmed electrical stimulation (PES) under (A) control conditions, and (B) hyperkalemia alone and (C) following hypercalcemia treatment. (D) The incidences of provoked ventricular tachycardia (VT) demonstrate the pro-arrhythmic effects of hyperkalemia (Fisher's exact test, **P<0.01) and the subsequent anti-arrhythmic effects of hypercalcemia treatment (Fisher's exact test, ††P<0.01). MAP, monophasic action potential.

Electronic Design, Cambridge, UK) at 5 kHz. Following this, they were analyzed using Spike2 software (Cambridge Electronic Design). MAP waveforms that did not match the previously established stringent criteria for MAP signals (37) were rejected. The MAPs must have stable baselines, fast upstrokes, with no inflections or negative spikes, and a rapid first phase of repolarization. The peak of the MAP was used to measure 0% repolarization and 100% repolarization was measured at the point of return of the potential to baseline (37-39). The following parameters were measured: Activation latency, defined as the time difference between the stimulus and the peak of the MAP; APD_x, defined as the time difference between the peak of the MAP and x% repolarization; and VERP.

Statistical analysis. All the values are expressed as mean ± standard error of the mean. Different experimental groups were compared by one-way analysis of variance (ANOVA) and Student's t-test was used as appropriate. P<0.05 was considered to indicate a statistically significant difference. Categorical data were compared with Fisher's exact test (one-tailed).

Results

Ventricular arrhythmogenicity and action potential characteristics. Ventricular arrhythmogenicity and its associations to action potential characteristics were examined under normokalemia (5.2 mM [K^+]), normocalcemia (1.8 mM [Ca^{2+}]), hyperkalemia alone (6.3 mM [K^+]) and hyperkalemia with hypercalcemia treatment (2.2 mM [Ca^{2+}]).

Hyperkalemia exerts pro-arrhythmic effects that are abolished by hypercalcemia. The initial experiments were performed on hearts extrinsically paced at 8 Hz, which is close to the heart rate observed in vivo under normokalemic, hyperkalemic and combined hyperkalemic and hypercalcemic conditions. Fig. 1 shows representative traces of epicardial MAP recordings under these pharmacological conditions, in which stable MAPs occurring directly following its preceding stimulus, with consistent waveforms, can be observed.

PES delivering progressively premature stimuli was used to examine the arrhythmic tendency. It consistently failed to provoke any arrhythmia under the control conditions (Fig. 2A; S2 extrastimulus indicated by an arrow). By contrast, provoked ventricular tachycardia (VT) was observed under hyperkalemic conditions alone (Fig. 2B). This was prevented by further hypercalcemia treatment (Fig. 2C). The incidences of provoked VT observed are summarized in Fig. 2D, demonstrating that hyperkalemia was significantly arrhythmogenic (Fisher's exact test, P<0.01), whereas hypercalcemia treatment was anti-arrhythmic under hyperkalemic conditions (Fisher's exact test, P<0.01).

Shortenings in the QT interval were observed in electrocardiograms (ECGs) obtained from patients suffering from hyperkalemia (6). This may reflect alterations in APD either locally or transmurally across the myocardial wall. APDs at x=30, 50, 70 and 90% repolarization (APD_x) were therefore assessed in the epicardium and endocardium, allowing calculation of ΔAPD_{90} given by endocardial APD_{90}-epicardial APD_{90}, thereby providing an indication of the transmural repolarization gradient. Epicardial APD_{90} was decreased from 42.2±2.6 to 24.5±1.6 msec by hyperkalemia (P<0.001; Fig. 3A), as were APD_{70} (P<0.001; Fig. 3B), APD_{50} (P<0.01; Fig. 3C) and APD_{30} (P<0.05; Fig. 3D). However, the corresponding endocardial APD_x values were not altered (P>0.05; Fig. 3E-H). These changes corresponded to increases in ΔAPD_{90} (Student's t-test, P<0.05; Fig. 4A), ΔAPD_{70} (P<0.01; Fig. 4B), ΔAPD_{50} (P<0.01; Fig. 4C) and ΔAPD_{30} (P<0.05; Fig. 4D). None of the epicardial or endocardial APD_x and ΔAPD_x values were further altered upon hypercalcemia treatment (P>0.05 in all cases).

Epicardial VERPs were decreased from 45.9±1.7 to 33.7±2.6 msec during hyperkalemia (ANOVA, P<0.001; Fig. 5A)

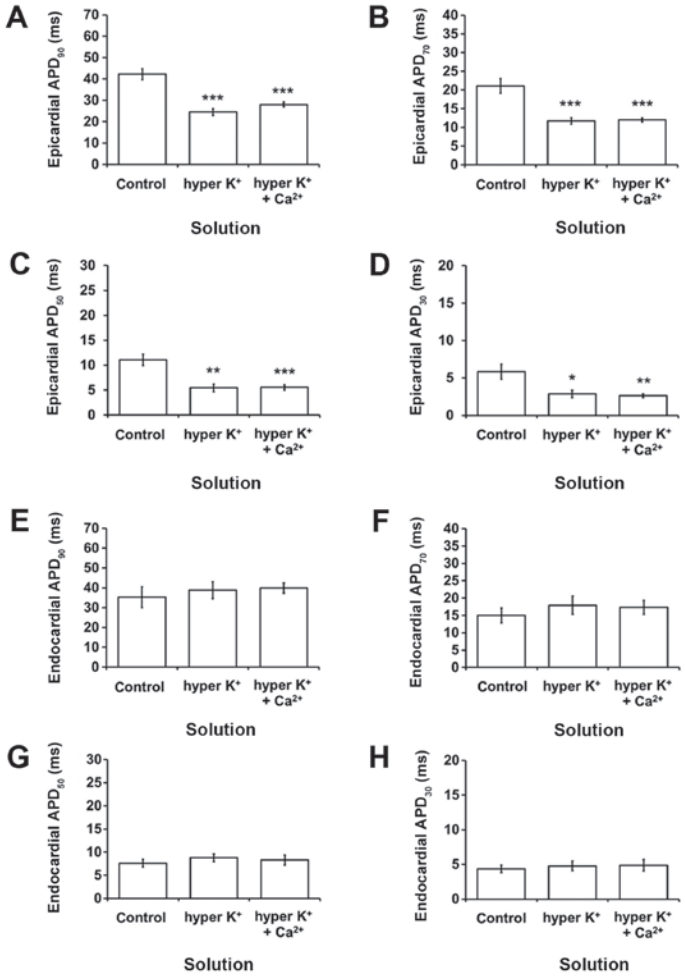

Figure 3. Epicardial action potential durations (APD_x) at x=(A) 90, (B) 70, (C) 50 and (D) 30% repolarization (msec) (mean ± SEM) (C) under control conditions, hyperkalemia alone or following hypercalcemia treatment during 8 Hz pacing (n=7). All APD_x values were shortened by hyperkalemia (ANOVA, $^{***}P<0.001$, $^{***}P<0.001$, $^{**}P<0.01$, $^{*}P<0.05$, respectively), which were not further altered by hypercalcemia treatment (ANOVA, P>0.05). Endocardial APD_x at x=(E) 90, (F) 70, (G) 50 and (H) 30% repolarization (msec) (mean ± SEM) obtained under the same experimental conditions. None of these values was altered by hyperkalemia alone or following hypercalcemia treatment (ANOVA, P>0.05). APD, action potential duration; SEM, standard error of the mean; ANOVA, analysis of variance.

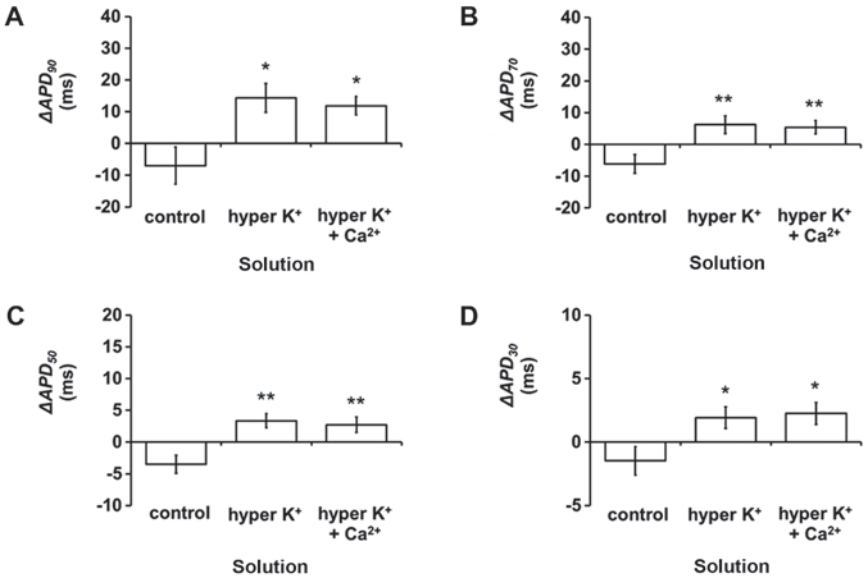

Figure 4. ΔAPD_x (endocardial APD_x-epicardial APD_x) at x=(A) 90, (B) 70, (C) 50 and (D) 30% repolarization (msec) (mean ± standard error of the mean) under control conditions, hyperkalemia alone or after hypercalcemia treatment during 8 Hz pacing (n=7). ΔAPD_{90}, ΔAPD_{70}, ΔAPD_{50} and ΔAPD_{30} were increased by hyperkalemia (Student's t-test, $^{*}P<0.05$, $^{**}P<0.01$, $^{**}P<0.01$ and $^{*}P<0.05$, respectively) and were not further altered by hypercalcemia treatment (P>0.05). APD, action potential duration.

and reversed by hypercalcemia treatment (P>0.05). By contrast, endocardial VERPs had a mean value of 36.7±2.1 msec under control conditions and this was not altered by hyperkalemia alone or following hypercalcemia treatment (P>0.05; Fig. 5B). Epicardial VERPs were significantly shorter compared to the corresponding endocardial VERPs under hyperkalemic conditions alone (P<0.05) but not under control conditions or hyperkalemic conditions following hypercalcemia treatment (P>0.05).

Hyperkalemia is known to cause prolongations in QRS durations, reflecting slowed ventricular conduction in humans (6). Reduced CVs have been shown to be an important factor in producing ventricular arrhythmogenesis following heptanol treatment (31). Therefore, in the studythe activation latencies, which provide an indication of the CVs, were quantified to determine whether changes in these values contribute to the arrhythmogenic substrate. Epicardial and endocardial activation latencies had values of 16.7±0.8 (Fig. 6A) and 17.0±1.1 msec (Fig. 6B), respectively, under normokalemic conditions. These values were not altered by hyperkalemia alone or following hypercalcemia treatment (ANOVA, P>0.05). Epicardial activation latencies were not significantly different from their corresponding endocardial activation latencies under any of the aforementioned pharmacological conditions studied (P>0.05).

Increased critical intervals for reexcitation have previously been associated with increased arrhythmogenicity in hypokalemic mouse hearts (40). To determine their possible roles in hyperkalemia-induced arrhythmogenesis, these values were accordingly calculated for all the pharmacological conditions studied. The local critical interval for the epicardium was -7.0±4.1 msec under control conditions (n=7; Fig. 7A). The interval was not altered by hyperkalemia alone but was reduced by hypercalcemia treatment to -23.1±4.5 msec (ANOVA, P<0.05). By contrast, the local critical interval for the endocardium had a value of -1.4±3.5 msec (n=7; Fig. 7B) but this was not altered by either hyperkalemia alone or following further hypercalcemia treatment (P>0.05). The transmural critical interval for reexcitation of the endocardium by the epicardium had a value of 5.3±3.5 msec (n=7; Fig. 7C). This was reduced by hyperkalemia to -16.2±4.2 msec (Student's t-test, P<0.01) and not further altered by hypercalcemia treatment (P>0.05). By contrast, the critical interval for reexcitation of the epicardium by the endocardium had a value of -10.3±5.7 msec, and was not altered by either hyperkalemia alone or following hypercalcemia treatment (Fig. 7D; P>0.05).

Reductions in the wavelength of excitation, defined as the product of VERP and CV, increase the likelihood of arrhythmogenesis (41). The VERP/latency can be used as a surrogate marker of wavelength (42). VERP/latency was decreased by hyperkalemia from 2.8±0.2 to 1.9±0.2 mm (n=8; ANOVA, P<0.01; Fig. 7E) and subsequently restored to 2.8±0.2 mm by hypercalcemia treatment, a value that was not statistically different from the control value (ANOVA, P>0.05).

Such reexcitation criteria employing the concept of the critical interval therefore correlated poorly with arrhythmogenicity in this hyperkalemia model, unlike the case of hypokalemia described previously. This would suggest arrhythmogenesis may not be due to APD exceeding VERP, but may arise from reductions in VERP/latency ratios.

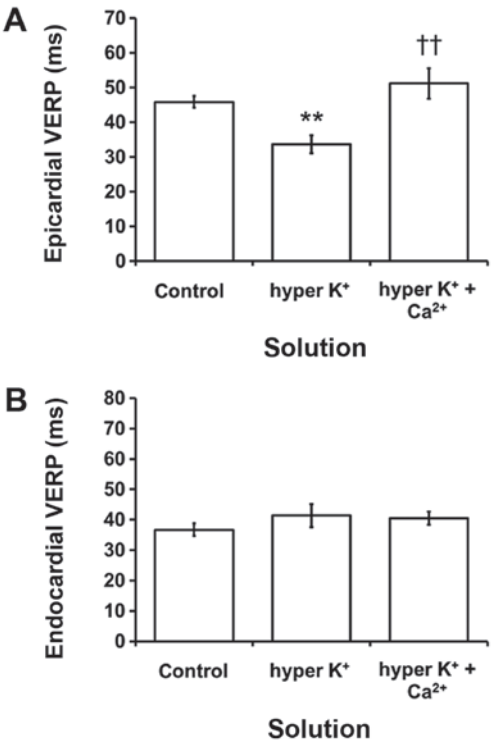

Figure 5. (A) Epicardial and (B) endocardial VERPs obtained under control conditions, hyperkalemia alone or after hypercalcemia treatment (n=7). Hyperkalemia alone reduced epicardial VERP (**P<0.01), which was reversed following hypercalcemia treatment (††P<0.01). Endocardial VERP was not affected by hyperkalemia alone or following hypercalcemia treatment (analysis of variance, P>0.05). Epicardial VERPs were significantly shorter compared to the corresponding endocardial VERPs during hyperkalemia alone (P<0.05) but not under control conditions or hyperkalemic conditions following hypercalcemia treatment (P>0.05). VERP, ventricular effective refractory periods.

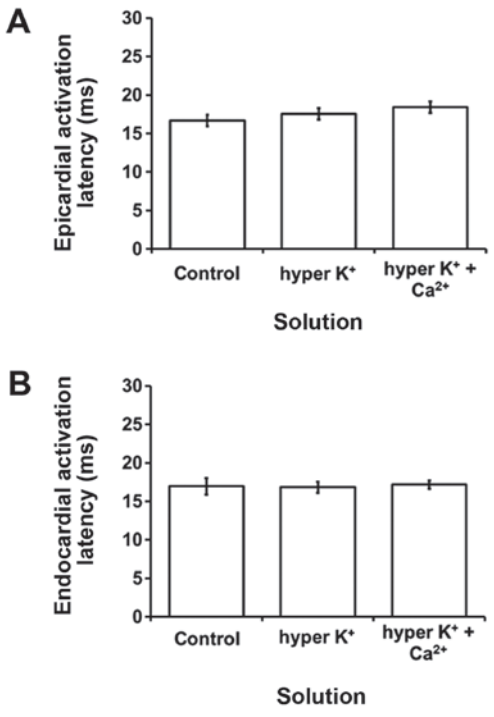

Figure 6. (A) Epicardial and (B) endocardial activation latency obtained under control conditions, hyperkalemia alone or following hypercalcemia treatment (n=7). These values were not altered by hyperkalemia alone or following hypercalcemia treatment (analysis of variance, P>0.05).

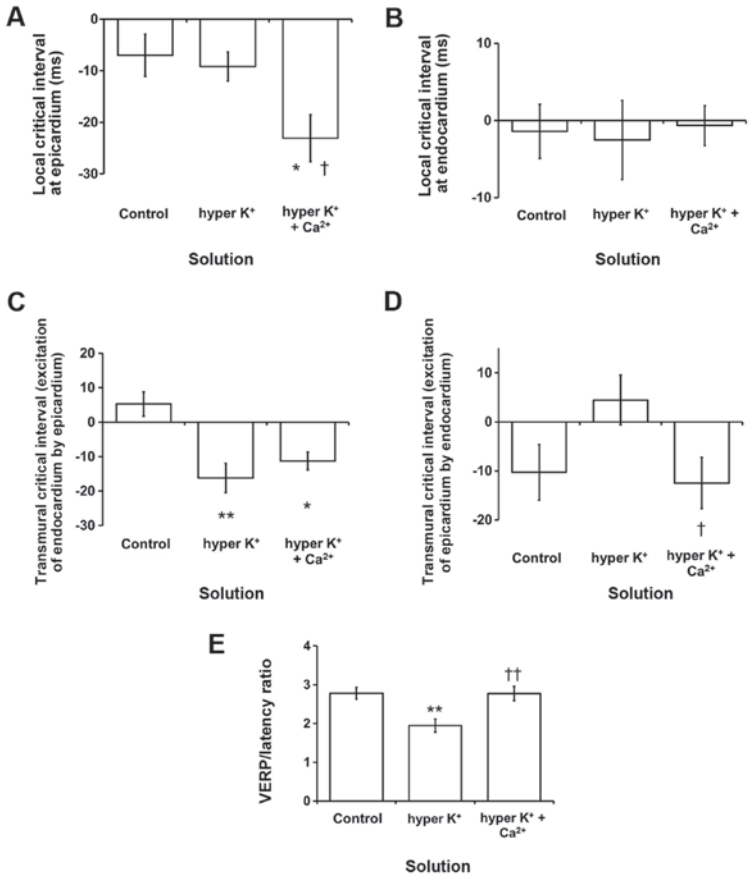

Figure 7. (A-D) Critical intervals (APD_{90}-VERP) and (E) VERP/latency ratio. * and ** indicate significant differences from control values, and † indicates significant differences from values obtained during hyperkalemia alone. Local critical intervals obtained from the (A) epicardium were not significantly affected by hyperkalemia alone but were reduced by hypercalcemia treatment (ANOVA, *,†P<0.05). The local critical interval obtained from the (B) endocardium was not altered by either hyperkalemia alone or following hypercalcemia treatment (P>0.05). The transmural critical interval for reexcitation of the endocardium by the (C) epicardium was reduced (Student's t-test, *P<0.05 and **P<0.01) and not further altered by hypercalcemia treatment (P>0.05). (D) The transmural critical interval for reexcitation of the epicardium by the endocardium was not altered by either hyperkalemia alone or following hypercalcemia treatment (P>0.05; but there was a difference between K^+ and $K^+ + Ca^{2+}$, †P<0.05). (E) VERP/latency was decreased by hyperkalemia from 2.8±0.2 to 1.9±0.2 mm (n=8; ANOVA, **P<0.01; K^+ vs. $K^+ + Ca^{2+}$, ††P<0.01) and subsequently restored to 2.8±0.2 mm by hypercalcemia treatment, a value that was not statistically different when compared to the control value (ANOVA, P>0.05). APD, action potential duration; VERP, ventricular effective refractory periods; ANOVA, analysis of variance.

Discussion

Hyperkalemia is one of the most common electrolyte abnormalities observed in hospitalized patients, predisposing them to life-threatening ventricular arrhythmias (43). The mechanisms of arrhythmogenesis have been studied using animal models as they permit the use of genetic or pharmacological manipulation to study the consequences of ion channel abnormalities (19,20,22,23,44-46). In the present study, arrhythmogenic effects of hyperkalemia were examined in Langendorff-perfused mouse hearts. The potential anti-arrhythmic effects of hypercalcemia were also examined under this condition, mimicking 10% calcium chloride administration used clinically to suppress ventricular arrhythmias in patients suffering from hyperkalemia (10). In the present experiments, epicardial and endocardial MAPs were recorded from the left ventricle during electrical stimulation at the right ventricular epicardium. This led to several new conclusions.

Stable epicardial and endocardial MAP recordings were demonstrated under control conditions, hyperkalemia alone and following hypercalcemia treatment during regular pacing. There was no evidence of spontaneous arrhythmias under these conditions. This subsequently permitted the use of PES to assess arrhythmogenicity and detect the presence of reentrant substrates. No inducible arrhythmias were observed under the control conditions. By contrast, episodes of provoked VT was observed during hyperkalemia, recapitulating clinical findings of increased arrhythmogenicity in humans (9). These arrhythmogenic effects were associated with reductions in the epicardial APD_{90} and VERP in an absence of alterations in activation latencies, which is inversely proportional to CV. Endocardial APD_{90} and VERP were not altered. These findings are consistent with the shortened QT intervals observed in ECGs of patients suffering from hyperkalemia (6). The QT interval is a reflection of ventricular repolarization time that is determined by the balance between influx and efflux of ions across the cell membrane (47). Initially, increased $[K^+]_o$ would produce hyperpolarization of the myocardial membrane, but upon reaching a steady state, there is a depolarizing shift in the resting membrane potential (RMP), as described by the Goldman field relationship (48). This has been shown to increase the conductance of the I_{Kr} channel (49,50), which would accelerate repolarization durations. As well as affecting action potential repolarization, it also influences its initiation

and subsequent propagation through the myocardium. Thus, hyperkalemia produces a positive shift in the threshold potential (TP) to a smaller extent than the depolarizing shift in RMP, thereby increasing myocardial excitability given by 1/(TP-RMP) (48,51). This could explain why mild hyperkalemia increases CV. However, hyperkalemia also increases the proportion of inactivated sodium channels, reducing dV/dt_{max}, and therefore the CV, of the propagating cardiac excitation (51,52). Activation latency was not altered by the hyperkalemia in the present study ($[K^+]_o$ of 6.3 mM), suggestive of little conduction abnormalities. This may be due to a balance between increased myocardial excitability and reduced proportion of sodium channels available for activation. This is consistent with previous findings that QRS duration was increased or CV was reduced when $[K^+]_o$ was >6.5-7.5 mM (53).

The differing effects of hyperkalemia upon endocardial and epicardial APD_{90} led to increased ΔAPD_{90} given by their difference, which is a measure of the transmural repolarization gradient (54). Under normokalemic conditions, the time courses of repolarization are longer in the endocardium compared to the epicardium, giving rise to a positive ΔAPD_{90}. This ensures a normal unidirectional spread of the excitation through the heart (28,55), preventing the epicardium from reexciting the endocardium by phase 2 reentry. It is also responsible for the upright electrocardiographic T-waves in the right precordial leads (56,57). ΔAPD_{90} remained positive during exposure to hyperkalemia, suggesting the increased arrhythmogenicity here was not due to reversal of such gradients, as was the case in hypokalemia (29). Instead, the arrhythmogenesis observed can be explained by decreases in the VERP through shortening in the action potential, which would reduce VERP/latency ratios and therefore predispose to reentry (58). However, the critical intervals for reexcitation given by the difference between APD_{90} and VERP (40) were either unchanged or decreased, which would be expected to have no effect on or decrease, rather than increase, arrhythmogenicity.

Hypercalcemia treatment exerted anti-arrhythmic effects during experimental hyperkalemia, complementing clinical findings that calcium chloride administration is effective in suppressing arrhythmia episodes in hyperkalemic patients (10). It reversed VERP changes without correcting for the shortenings in APDs, and left activation latencies unaltered. Consequently, the VERP/latency ratio returned to control values and the critical intervals were either unchanged or decreased. High $[Ca^{2+}]_o$ causes a positive shift in the TP without significant effects on the RMP (59). This effect can be explained by adsorption of calcium ions to the outer surface of the cell membrane, generating an electric field that shifts the threshold of I_{Na} activation to more depolarized potentials (60). It also has a positively inotropic effect in the context of hyperkalemia in a rabbit model (15). Although ventricular tachyarrhythmias attributable to hypercalcemia has been reported in humans (61) and mouse studies (34) under normokalemic conditions, they are nevertheless rare occurrences (62). Due to these protective effects of calcium on the heart, it has been used clinically to treat patients with hyperkalemia acutely prior to correcting for the plasma levels of potassium through the use of insulin and glucose infusion with nebulized salbutamol (63). Notably, no further APD shortening was found in the presence of hypercalcemia. Although hypercalcemia has been shown to cause QT shortening, in certain instances it may be associated with a normal QT interval (64,65). The QT interval may therefore be an unreliable indicator of the level of hypercalcemia (66). In addition to the effects of $[Ca^{2+}]_o$ on the RMP and TP, it is possible that the calcium-dependent potassium currents or calcium currents are also altered, and this remains to be studied in the future.

There are several limitations of the present study. First, whilst the mouse is a common animal model for studying cardiac arrhythmias, certain caution must be taken when attempting to extrapolate the results to human findings. In mouse hearts, cardiac action potentials are triangular with the transient outward current (I_{to}) being the major repolarizing current (67). By contrast, the human action potential shows a characteristic plateau phase (68). Repolarization is initially mediated by I_{to}, followed by a delayed plateau phase mediated by a balance between the inward calcium current (I_{Ca}) and outward delayed rectifier potassium currents (I_{Kr} and I_{Ks}). Guinea pig and rabbit hearts have the same action potential morphology with similar ionic contributions, and may therefore provide better translational results when used as model systems for studying human arrhythmic syndromes (69-80).

Secondly, the MAP technique was chosen for studying electrophysiology in the present study, which allows electrical recordings to be made from intact, isolated, perfused hearts. This has the advantage of preserving intercellular coupling, meaning that the experimental system would be more physiological. MAP recordings close recapitulate the intracellular action potential obtained from single cells (37,81,82). Previous studies have shown that the MAP technique is sufficiently sensitive for detecting alterations in activation latencies, APD and VERP from atrial and ventricular tissue under a variety of experimental conditions (29-32). Furthermore, parameters derived from MAP recordings only show small variations on repeated measurements and between different hearts, suggesting that this technique is sufficiently reliable for studying cardiac electrophysiology. However, certain limitations of the MAP technique must be noted, as recently reviewed (83). One major disadvantage is that MAPs, unlike microelectrode recordings, do not provide information on the upstroke velocity of the cellular action potential. Although the CV of the propagating excitation wave could not be determined, activation latency could be measured instead. This also permitted the calculation of VERP/latency ratios that are used clinically for approximating the excitation wavelength. Future studies can investigate further by using optical mapping, which would allow simultaneous measurements of cellular activation from numerous recording sites, and CVs as well as excitation wavelength to be calculated. Measurement of magnetic signals, such as cardiac magnetic resonance imaging, has been used for the characterization of structural properties (84-86), and future studies could utilize magnetocardiography to detect electrical abnormalities and predict arrhythmic risk (87-92).

Finally, why epicardial APDs are altered by hyperkalemia whereas endocardial APDs are not remains to be elucidated. Such differences were also observed in experimental

hypokalemia, where it was noted that epicardial APDs were prolonged but endocardial APDs remained unaltered (40). This may be due to differences in ion channel types or their levels of expression between these regions, but these issues remain to be clarified in future studies.

Taken together, the present study produced an arrhythmia model of hyperkalemia for the first time in the mouse, in which ventricular tachyarrhythmias were associated with shortenings in APD and VERP. Hypercalcemia treatment was able to prevent this arrhythmogenesis through correction of VERP alone without influencing APD, thereby scaling the VERP/latency ratio. Therefore, excitation wavelength appears to be a central determinant of arrhythmogenesis in this system, as has been demonstrated for other models (93).

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