Role of potassium channels in cycle length dependent regulation of action potential duration in mammalian cardiac Purkinje and ventricular muscle fibres

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This review examines the putative role played by three repolarising potassium currents, namely the transient outward current (\(i_o\)), the inward rectifying current (\(i_ki\)), and the late outward rectifying current (\(i_k\)), in the regulation of action potential duration in cardiac Purkinje and ventricular muscle fibres under normal physiological conditions. The role of other potassium currents, including the ATP activated current (\(i_{k,ATP}\)) under these conditions is uncertain. Personal experiences and work of others are reviewed to summarise: (1) regulation of normal cycle length dependent action potential duration; (2) the characteristics of \(i_o\), \(i_ki\), and \(i_k\) pertinent to repolarisation; and (3) the effects of potassium channel blockers and activators on cycle length dependent action potential duration.

The presence of \(i_o\) creates a notch after depolarisation and limits action potential duration at long cycles. Block of \(i_ki\) prolongs action potential duration predominantly by slowing phase 3 of the action potential. Block of \(i_k\) prolongs the duration predominantly by lengthening phase 2 of the action potential, and the lengthening becomes more pronounced at longer cycles. Activation of \(i_{k,ATP}\) shortens the duration, and the shortening becomes more pronounced at longer cycles. Each of the three major repolarising potassium currents appears to play a different role in modulating the action potential duration. \(i_o\) creates a notch which resets the early course of plateau, and also limits the duration at long cycles. \(i_ki\) contributes to maintenance of plateau and controls repolarisation course during phase 3 of the action potential. \(i_k\) plays major role in controlling action potential duration within a wide range of cycle lengths in Purkinje fibres, and when present, also in ventricular muscle fibres.

Control of action potential duration

Action potential duration in cardiac cells depends on the cycle length, defined as the interval between two successive depolarisations. Cycle length dependent changes are caused predominantly, and in some cases exclusively, by changes in plateau duration. However, their possible role in the control of cycle length dependent action potential duration in cardiac Purkinje and ventricular muscle fibres has not been studied, to my knowledge.
Figure 1 Relation between action potential duration during steady state (ordinate) and log of cycle length of stimulation (abscissa) in dog ventricular muscle and Purkinje fibres. Each point represents the mean, bars=SEM. Reproduced with permission from reference II.

The curve relating steady state action potential duration to cycle length (fig 1) has been expressed mathematically in many different ways depending on the range of cycle lengths, fibre type, species, and experimental conditions. The relation shown in fig 1 fits a hyperbolic curve that predicts an achievement of APDmax at long basic cycle length. APDmin is determined predominantly by the duration of terminal repolarisation which varies little with time. Action potential duration tends to be longer in larger than in smaller animals. My survey of published values in different species under normal physiological conditions at 35°C-37°C revealed the shortest APDmin of about 80 ms at a cycle length of 0.1 s in the rabbit and the longest APDmax of about 600 ms at a cycle length of 2.7 s in the human. Figure 1 shows that in the dog Purkinje fibre steady state action potential duration ranges from about 170 to about 500 ms and in the ventricular muscle fibres from about 150 to about 300 ms. In several species, including dog, sheep, cat, and human, APDmax is usually reached at cycles \( \approx 10 \) s. With further increase in cycle length APDmax does not change, or in some cases the duration of the action potential becomes shorter than the APDmax. In some species APDmax is achieved early. For instance, in rabbit ventricular fibres, action potential duration reaches maximum at about 0.3 s and then declines at longer cycle lengths.

Restitution controls the duration of premature action potential which becomes progressively longer at increasing diastolic intervals. In the Purkinje fibres, the restitution curve bisects the steady state curve at two points (fig 2). During the earliest portion of restitution, action potential duration is shorter than the steady state duration. Subsequently, the restitution curve crosses the steady state curve, and recrosses it again when the test cycle and the basic cycle become equal. After the second crossing the restitution curve runs below the steady state curve, and reaches a quasi-plateau. The difference between action potential duration during restitution and during steady state after the first crossing is caused by the effect of ‘memory.’ In ventricular muscle fibres the early portion of restitution before the first crossing is absent. This difference is probably caused by different kinetics of repolarising currents in the two fibre types. The kinetics of restitution were independent of basic action potential duration in Purkinje fibres and ventricular muscle fibres.

Memory describes gradual adjustment of action potential duration to a new steady state when the cycle length is changed. Transition from a longer to a shorter cycle results in gradual shortening of action potential duration, and transition from a shorter to a longer cycle in gradual lengthening of duration. In our study, memory dissipated in the canine Purkinje fibres within about three minutes, and in the ventricular muscle fibres within about 5-6 minutes (fig 3).

The number of beats required to achieve a new cycle length dependent steady state action potential duration differs depending on the direction of change, ie, whether the change proceeds from the previous to the new cycle length or returns from the new to the previous one. Such a hysteresis loop, observed in several fibre types, can be attributed to differences in the duration of memory dissipation.
Role of potassium currents in control of action potential duration

Repolarisation is controlled by a fine balance of inward and outward currents. The currents modulating repolarisation assure that action potential duration is neither too short (which may abort calcium inflow and produce a negative inotropic effect), nor too long (which may delay relaxation and also contribute to electrical instability and arrhythmias). The cycle length dependent relation is important because action potential duration controls the duration of refractory period and influences the duration of developed tension. Of the three potassium currents participating in repolarisation, referred to earlier, the \( i_{\text{K1}} \) is more ubiquitous than \( i_{\text{Ko}} \) and \( i_{\text{Kr}} \) in the ventricular muscle and Purkinje fibres since the latter two currents are not consistently present in all species. However, if present, they play a significant role in repolarisation.

The transient outward current is not equally expressed in all cardiac fibre types, and in some may be absent. The \( i_{\text{Ko}} \) is a time and voltage dependent predominantly potassium current\(^{20-25} \) which differs in different tissues and animal species. In various cardiac preparations (human, dog, rabbit, rat) \( i_{\text{Ko}} \) is larger than and more rapidly activated than \( i_{\text{Kr}} \). The current has two components, one of which is 4-aminopyridine sensitive and the other is modulated by intracellular calcium.\(^{26} \) The latter has been attributed to chloride rather than potassium.\(^{27} \) In ventricular muscle \( i_{\text{Ko}} \) has been found in the mouse,\(^{28} \) dog,\(^{29} \) and rabbit\(^{29} \) but the amplitude was small in cat\(^{30} \) or absent in guinea pig preparations.\(^{31} \) In dog the current was prominent only in the epicardial and not in the endocardial ventricular fibres.\(^{32} \) Also, in rabbit ventricular myocytes isolated from the endocardial region, \( i_{\text{Ko}} \) was several-fold bigger than in those from the papillary muscle.\(^{33} \)

The 4-aminopyridine sensitive component of \( i_{\text{Ko}} \) is activated in both Purkinje and ventricular muscle fibres at about \(-20 \text{ mV}\).\(^{34} \) with time constant (\( T \)) of 5-10 ms.\(^{35} \) In most studies the inactivation was voltage independent. In Purkinje fibres, the course was biexponential with \( T_1 \) ranging from 48-100 ms and \( T_2 \) from 250-400 ms.\(^{35-37} \) In ventricular fibres, both monoeponential (with \( T \) ranging from 20-30 ms\(^{38} \)) and double exponential inactivation kinetics (with \( T_1 \) of 17-19 ms and \( T_2 \) of 76-109 ms\(^{39} \)) were described. In mouse ventricular myocytes two single \( i_{\text{Kr}} \) channels were found, one of which remained open for 3.9 ms and the other for 34 ms.\(^{40} \) The kinetics of recovery from inactivation of \( i_{\text{Kr}} \) are voltage dependent and vary in different studies. In addition to rapid components, slow components lasting several hundred seconds were found in dog Purkinje fibres, sheep Purkinje fibres, and rabbit and dog ventricular myocytes.\(^{41} \)

The 4-aminopyridine insensitive component, present in both Purkinje fibres and ventricular muscle fibres, has been less accurately characterised than the 4-aminopyridine sensitive component, but in Purkinje fibres it appears to be smaller, more slowly activated, and more rapidly inactivated than the latter.\(^{24} \) The amplitude of this current was decreased in Purkinje fibres at fast stimulation rates\(^{42} \) but in rabbit ventricular myocytes it was enhanced with increased frequency of stimulation.\(^{43} \)

Rate dependent changes in the configuration of the initial repolarisation (notch) have been correlated with the kinetics of 4-aminopyridine sensitive current (\( i_{\text{Kr}} \)) in sheep Purkinje fibres.\(^{44} \) It has been reported that in dogs\(^{45} \) and rabbits\(^{46} \) the notch, attributed to \( i_{\text{Kr}} \) in the presence of an inward current, was recorded in the action potentials from the epicardial ventricular muscle layers but was either absent or less pronounced in those from the endocardial layers.

In addition to causing the notch of action potential, \( i_{\text{Kr}} \) has another interesting property, namely slow recovery from inactivation, i.e., a long repolarising time.\(^{24} \) This means that action potentials at cycle lengths shorter than the repolarising time will escape the shortening effect of \( i_{\text{Kr}} \). Accordingly, the cycle length dependent differences between the epicardial (presumably endowed with \( i_{\text{Kr}} \)) and the endocardial (presumably \( i_{\text{Kr}} \) deficient) fibres are such that at short cycles the action potential duration in epicardial fibres is either the same or slightly longer than in endocardial fibres, but at longer cycles the duration in the epicardial fibres is shorter than in the endocardial fibres (see fig 16.3 in\(^{40} \), fig 2 in\(^{42} \), and fig 3 in\(^{43} \)).

Inward rectifier \( (i_{\text{K1}}) \)

This current is believed to play an important role in stabilising the plateau, terminating repolarisation, and maintaining resting membrane potential. It is activated on hyperpolarisation, has very fast (less than 5-10 ms) voltage dependent activation and deactivation kinetics,\(^{40} \) and is blocked by intracellular calcium\(^{46} \) and Mg\(^{46} \). Single channel conductance is proportional to square root of (K\(^+\))\(^{48} \). In sheep Purkinje fibres, time dependent changes in the conductance of the inward rectifier were observed\(^{49} \) in potassium free solution. However, it appears unlikely that under normal conditions the kinetics of inward rectifier directly affect cycle length dependent changes in action potential duration. Nevertheless an indirect effect cannot be ruled out because the current is altered by changes in intracellular Ca\(^{2+}\)\(^{50} \) and K\(^+\).\(^{51} \) Time dependent changes in the intracellular concentrations of these ions may alter the level and/or duration of the plateau which may in turn influence the kinetics of other plateau currents.

Another rapidly activated plateau potassium current has been found in guinea pig ventricular myocytes.\(^{52} \) The slope conductance of this current was insensitive to (K\(^+\)). No detectable inactivation of this current was found in the
plateau, and the current was not observed upon return to the level of −100 mV. This current is not expected to play role in time dependent changes of action potential duration.

**Delayed rectifier**

i\(K\) in general, i\(K\) appears to be more prevalent and better represented in Purkinje fibres than in ventricular muscle fibres but there are marked species differences. The delayed rectifier (i\(K\)), formerly i\(K_a\) is mainly a potassium current (54-56) which has been recorded in the Purkinje fibres of sheep, calf, guinea pig, cat, and dog (57-60). The current appears to be larger in Purkinje fibres than in ventricular muscle fibres and there are marked species variations. For instance, in rabbit ventricular myocytes the current is very small or absent (61). Similarly, the current is small in ventricular muscle of calf and sheep (62). Also, in some preparations of guinea pig myocytes the current was too small to be detected in the absence of isoprenaline and it was reported recently that i\(K\) is significantly greater in epicardial than in endocardial cells (63). The delayed rectifier is modulated by intracellular Ca\(^{2+}\), Mg\(^{2+}\), the adrenergic system, and c-AMP dependent phosphorylation (64).

The i\(K\) is activated at plateau potentials with T of 300-700 ms in Purkinje fibres (52-54) and 100-700 ms in ventricular muscle, depending on experimental conditions (55-56). In Purkinje fibres the deactivation at potentials negative to −50 mV followed a double exponential course with \(T_1\), ranging from 100-800 ms and \(T_2\) from 0.5-3.5 s. In the ventricular muscle the deactivation was monoeponential with reported T of 100-390 ms at potentials more negative than −30 mV. The slow kinetics of activation and deactivation suggest that the shortening effect of i\(K\) on action potential duration extends over a wide range of cycle lengths (57-59).

Recently, a rapid component of i\(K\) was detected in guinea pig ventricular muscle. This current is activated with T of 15 ms at +20 mV and deactivated with T of 50 ms at −70 mV. The amplitude of this current was about 10% of the total i\(K\) current.

**i\(K_{ATP}\)**

This time and voltage independent current (except for rectification at extremely high voltages) is activated when intracellular ATP concentration falls below 1 mM (72) or when intracellular lactate concentration increases (71). The i\(K_{ATP}\) is blocked by barium, caesium, tetraethylammonium ions (54, 72), glibenclamide, quinidine, verapamil, and amiodarone, as well as by intracellular Mg\(^{2+}\) and Na\(^{+}\). Activators of i\(K_{ATP}\) include pinacidil, nicorandil, and cromakalim derivatives.

The i\(K_{ATP}\) is not expected to play a role in the control of action potential duration when the intracellular ATP concentration is normal. However, shortening of action potential may not require a large fall in intracellular ATP concentration because the shortening was more than 50% when only a small fraction of ATP sensitive channels was stimulated by a channel opener, SR 4486 (73).

**Effect of potassium channel blocking agents on cycle length dependent action potential duration**

A component of i\(K\) can be blocked by 4-aminopyridine, and another component by changes in intracellular calcium concentration. The effect of i\(K\) blocking agents has been studied on the restitution of the amplitude of phase 1 but has not been studied systematically on cycle length dependent action potential duration. However, the probable effect of i\(K\) block can be deduced from changes in this variable in the endocardial ventricular muscle fibres devoid of i\(K\) discussed earlier.

The effect of i\(K\) block can be deduced from repolarisation changes associated with low g\(K\) and suppression of anomalous rectification at low extracellular potassium concentrations (74, 75). In both Purkinje and ventricular muscle fibres, lowering of extracellular potassium concentration results in slower course of repolarisation and lengthening of action potential, even though the plateau becomes shorter (76, 77). However, these effects may not be due exclusively to low g\(K\) because low potassium may inhibit the electrogenic sodium/potassium pump current.

Blocking potassium channels by applying barium, caesium, tetraethylammonium salts, and class III antiarrhythmic agents such as sotalol prolongs action potential duration. Caesium blocks predominantly i\(K_c\), and the illustrated lengthening of action potential duration in sheep Purkinje fibres is caused predominantly by lengthening of phase 3 of action potential (fig 3B in (78)). In dog Purkinje fibres application of 5 mM Cs prolonged action potential duration, and the difference between the values in control Cs treated fibres increased progressively with increasing cycle length so that the maximum duration at a cycle length of 3 s was about 600 ms compared to the control value of about 300 ms (fig 1 in (79)).

Tetraethylammonium (TEA) salts predominantly block the late rectifier (74, 75). Injection of TEA into the axoplasm of the giant squid axon prolonged action potential duration several hundred-fold without change in the resting membrane potential, thus making a nerve action potential similar to a cardiac action potential. In the ventricular myocardial fibres, 20 mM extracellular TEA concentration had no appreciable effect on action potential duration but the action potential became longer when TEA diffused intracellularly through the cut end. However, in guinea pig papillary muscles, action potential duration was prolonged within 60 minutes after superfusion with 5-10 mM TEA solution (77).

Ito and Surawicz (77) applied 20 mM TEA chloride intracellularly using modified method of Ochi and Nishiyama (78). In this study TEA had no effect on dV/dt\(_{max}\), overshoot, slope of diastolic depolarisation, and maximum diastolic potential; the latter displayed normal sensitivity to increasing extracellular potassium concentration changes. Intracellularly applied TEA increased action potential duration predominantly by lengthening the plateau. Duration increased with increasing cycle length, thus reversing the normal relation between increments of cycle length and action potential duration by augmenting the increments in the latter within the range of 1.0 to 0.1 Hz more than within the range of 3.0 to 1.0 Hz (fig 4). Figure 4 shows that at a stimulation rate of 0.1 Hz action potential duration in TEA loaded fibres increases from 610 to 4600 ms, and that the increase is caused predominantly by lengthening of plateau.

Figure 5 shows the effect of TEA on "memory" and hysteresis (in this study we measured the new action potential duration when it was within 10% of the new steady state value). The number of beats required to reach the new steady state increased with increasing interval between stimuli. Although the number of beats required to reach a new steady state tended to be significantly smaller with decreasing than with increasing interval, the two curves were
Figure 4  Representative example of steady state action potential duration at different rates of stimulation before (A) and after (B) tetraethylammonium chloride (TEA) loading in dog Purkinje fibre. Superimposed action potentials are retraced from oscilloscopic images. TEA loaded fibres failed to respond at rates faster than 2 Hz. Note that at a stimulation rate of 0.1 Hz, action potential duration increases after TEA loading from 610 to 4600 ms.

Figure 5  Average and SD (vertical bars) of number of beats (ordinate) required to achieve new steady state action potential duration after change in stimulus interval (abscissa) in 10 dog Purkinje fibres. Filled circles represent values before and empty circles values after tetraethylammonium chloride (TEA) loading. Broken lines connect values obtained following stepwise increase, solid lines connect values following stepwise decrease in stimulus interval. In experiments in which stimulus interval was progressively decreased, initial value on the far right was obtained after change from quiescence to 10 s stimulus interval (0.1 Hz). In experiments in which stimulus interval was progressively increased, initial value on far left was obtained after change from stimulation at 2.5-3 Hz (interval of 0.33 s). Statistical significance between consecutive steps: *p<0.02. **p<0.01. Statistical significance between ascending step (increasing stimulus interval) and analogous descending step (decreasing stimulus interval); †p<0.05. ††p<0.01. Reproduced with permission from reference 21.

Figure 6  (A) Effect of intracellular loading with tetraethylammonium chloride (TEA) on restitution of action potential duration (APDₜ) in dog Purkinje fibre. Ordinate: duration of test action potential (APDₜ); abscissa: diastolic intervals preceding test action potentials. Each interval between vertical bars equals 1000 ms with the first bar set at 0. (B) Effect of intracellular loading with TEA on normalised restitution curves. Data from panel (A) were normalised for action potential duration during the plateau of restitution (APDₜₐₘₜ) (ordinate); abscissa: diastolic intervals preceding test action potentials. Each interval between vertical bars equals 1000 ms with the first bar set at 0. Reproduced with permission from reference 89.

K channels and action potential duration

approximately parallel to each other during most of their course. The curves in TEA loaded fibres (open circles) maintained a course similar to that of control curves but shifted upward. This suggests that TEA did not change the kinetics of “memory” dissipation and the hysteresis appreciably. In another study, we established that intracellular loading with TEA increased action potential duration during restitution (fig 6A) but did not change restitution kinetics in canine Purkinje fibres (fig 6B) and ventricular muscle fibres.

Sotalol is a widely studied representative of antiarrhythmic drugs with class III properties. At concentrations between 10⁻⁶ and 10⁻¹³ M the drug prolonged action potential duration in guinea pig papillary muscle and rabbit Purkinje fibres by increasing plateau duration (figs 1 and 3 in "). These changes correlated with a substantial reduction of iₚ and a slight reduction of potassium background current. However, in sheep Purkinje fibres sotalol predominantly blocked iₚ and iₖ; without affecting iₚ and prolonged action potential duration predominantly by lengthening phase 3 (fig 1 in "). Recently the cardiac delayed rectifier was separated into two components, of which sotalol blocked only one, activated more rapidly between −50 and 0 mV." Varro et al" studied the effect of sotalol on cycle length dependent action potential duration in dog Purkinje and guinea pig ventricle muscle fibres. Figure
7 shows that sotalol prolonged action potential duration, and that the difference between the control value and that in sotalol treated fibres increased with increasing cycle length. Similar effects were produced by bretylium (fig 7) but not by several class IA and IB antiarrhythmic drugs tested in the same study.93

Effect of potassium channel activators on cycle length dependent action potential duration

The potassium channel activator nicorandil (SG 75, Chugai Co) shortens action potential duration in cardiac fibres.64,66 In the study of Elharrar et al66 nicorandil shortened action potential duration at all cycle lengths, and the difference between the values before and after nicorandil application increased with increasing cycle length; this means that the greatest relative shortening occurred at the longest cycles (fig 8). Nicorandil did not alter the kinetics of restitution in canine Purkinje and ventricular muscle fibres.89

Earlier studies suggested that nicorandil activates background K+ conductance and the delayed outward K+ current. However, Hiraoka and Fan67 found that in guinea pig and rabbit ventricular myocytes nicorandil increased the probability of opening the ATP sensitive single channel current at low intracellular ATP concentrations, and that this effect was antagonised by increased intracellular ATP concentration. This could explain the shortening of the action potential duration because nicorandil did not change resting membrane potential, had no effect on delayed outward current, and did not increase the Ca2+ sensitive and Ca2+ insensitive transient outward current.

Another potassium channel activator, BRL 3915,68 also produced concentration dependent shortening of action potential duration99 and the difference between the values before and after drug application increased with increasing cycle length (fig 3 in 9). As with nicorandil, BRL 3915 activated iK,ATP.

Discussion

Cycle length dependent action potential duration is controlled by a fine balance of inward and outward currents. Each of the three major outward potassium currents appears to play a different role in modulating action potential duration: iKo creates a notch which resets the early course of plateau, and also limits action potential duration at long cycles; iK1 contributes to maintenance of plateau and controls repolarisation course during phase 3 of the action potential; iK plays a major role in controlling action potential duration within a wide range of cycle lengths in Purkinje fibres and, when present, also in ventricular muscle fibres. A caveat needs to be inserted that the consequence of activities of any given cardiac channel may not be limited to the specific immediate effects, because transmembrane ion fluxes change intracellular ion concentrations, which in turn may alter activities of other channels, as well as those of ion pumps and exchangers.

Judging from the cycle length dependent differences in action potential duration between ventricular muscle fibres endowed with iKo and those deprived of iKo, this current plays a more limited role in modulating the duration of the action potential than iK. However, it appears to serve the same purpose, namely to prevent excessive lengthening of the duration at long cycles. In support of this hypothesis are observations in rabbit ventricular muscle fibres where iKo is more strongly expressed than iK.41 In this tissue, action potential duration reaches a maximum at a cycle of 0.3 s, and then declines with increasing cycle length.47,100 The presence of iKo in the epicardial but not in the endocardial layers of ventricular muscle fibres in dog,37 rabbit,42 and perhaps in

![Figure 7](image7.png) Effect of cycle length (abscissa, logarithmic scale) on the action potential duration (APD) (ordinate) in control (empty symbols), and in the presence of bretylium and sotalol (filled symbols) in dog Purkinje fibre. Bars=SEM. Reproduced with permission from reference 93.

![Figure 8](image8.png) Effect of two nicorandil concentrations on action potentials at various stimulation frequencies in guinea pig papillary muscles. In each panel, the upper, middle, and lower traces represent zero potential, action potential, and dV/dt, respectively (the peak excursion of dV/dt gives dV/dtmax). All recordings were made from the same cell. Reproduced with permission from reference 96.
hypokalaemia and hyperkalaemia, respectively, presumably by blocking iK. Several other sodium channel blocking drugs prolong terminal repolarisation with or lengthening the plateau, presumably due to block of iK. The atrial myocytes obtained from surgically excised specimens. distributed in all muscle layers.

The transient outward current has been recorded in human ventricular muscle fibres and QT interval in humans, cause its own shortening. This type of feedback mechanism by the same mechanisms as the steady state APD.

The effect of TEA on action potential duration in Purkinje fibres suggests that the current blocked by TEA controls APDmax. Assuming that the observed effects of TEA are due exclusively or predominantly to the reduction of iK, we can make certain deductions that would help us explain the mechanism of control of action potential duration at slow rates of stimulation. Any realistic model of control must postulate the existence of a hypothetical lengthening factor responsible for increasing action potential duration with increasing cycle length. In TEA loaded fibres, cycle length dependent lengthening was very pronounced and rose with increasing duration of diastolic intervals. This can be taken as evidence that the decreasing influence of iK unmasks the effect of lengthening factor on action potential duration and that normally the iK is responsible for the suppression of lengthening factor at slow heart rates. This can be attributed to the kinetics of iK, which increases with increasing duration of depolarisation.

Thus the longer the duration of a given action potential the more iK would be activated to cause its own shortening. This type of feedback mechanism would explain the normal conditions where an action potential, after reaching a certain critical duration, responds to a further increase in cycle length either by a very slight lengthening or no change in duration. The absence of TEA and niconandil effects on the kinetics of "memory" dissipation, hysteresis, and restitution of action potential duration suggests that these processes may not be controlled by the same mechanisms as the steady state APDmax.

Clinical relevance

The transient outward current has been recorded in human atrial myocytes obtained from surgically excised specimens. The kinetic properties and the effect on the shape and duration of the human atrial action potential resembled those in other species and tissue types. At this time it is not known whether iK is present in human ventricular myocardium, and if present, whether it is uniformly distributed in all muscle layers.

The effects of decreased and increased gK caused by hypokalaemia and hyperkalaemia, respectively, on the course of repolarisation in the electrocardiogram are well known. Quindine prolongs terminal repolarisation in ventricular muscle fibres and QT interval in humans, presumably by blocking iK. Several other sodium channel blocking drugs prolong terminal repolarisation with or without lengthening of action potential duration.

Class III antiarrhythmic drugs such as sotalol prolong action potential duration and QT interval mainly by lengthening the plateau, presumably due to block of iK. The effect of sotalol on cycle length dependent action potential duration is similar to that of TEA, as the difference between control values and values in sotalol treated fibres increased with increasing cycle length (fig 7).

Kleiman and Houser found that in the cat myocytes from hypertrophied ventricles iK was smaller and more rapidly deactivated than in myocytes from normal ventricles, a finding that could explain longer action potential duration in the cells from hypertrophied ventricles in their study. Prolonged action potential duration has been found in ventricular muscle tissues of patients with hypertrophic cardiomyopathy, as well as ischaemic or dilated cardiomyopathy, but the mechanism is not known. Future studies of cycle length dependent changes of transmembrane action potential duration in vitro and monophasic action potential duration and QT interval in vivo may be helpful in understanding the mechanism of QT lengthening in various clinical conditions. For instance, two recent studies have shown that in patients with congenital long QT syndrome action potential duration lengthens more at long than at short or intermediate cycle lengths. Figure 9 shows this relation in one of these studies. The similarity of these effects on QT interval to those of TEA and sotalol on action potential duration in vitro invites a speculation that congenital malfunction of iK or of a similar potassium channel may be responsible for the congenital lengthening of QT interval.

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Figure 9 Relation between QT interval and heart rate. The QT interval in the group without torsades de pointes [TdP(-)] increased linearly when the heart rate was decreased. The QT interval in the group with torsades de pointes [TdP(+)] increased almost linearly from 100 to 70 beats-min⁻¹. However, when the heart rate was decreased to 60 beats-min⁻¹, the QT interval was markedly increased and became significantly longer than that in the TdP(-) group. QT prolongation was more prominent at 50 beats-min⁻¹. Reproduced with permission from reference 112.

*p<0.05, t<0.01 v TdP(-)

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