ORIGINAL CONTRIBUTION

Reverse rate-dependent changes are determined by baseline action potential duration in mammalian and human ventricular preparations

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Abstract Class III antiarrhythmic agents exhibit reverse rate-dependent lengthening of the action potential duration (APD). In spite of the several theories developed so far to explain this reverse rate-dependency (RRD), its mechanism has not yet been clarified. The aim of the present work was to further elucidate the mechanisms responsible for RRD in mammalian ventricular myocardium. Action potentials were recorded using conventional sharp microelectrodes from human, canine, rabbit and guinea pig ventricular myocardium in a rate-dependent manner varying the cycle length (CL) between 0.3 and 5 s. Rate-dependent drug effects were studied using agents known to lengthen or shorten action potentials, and these drug-induced changes in APD were correlated with baseline APD values. Both drug-induced lengthening (by dofetilide, sotalol, E-4031, $BaCl_2$, veratrine, BAY K 8644) and shortening (by mexiletine, tetrodotoxin, lemakalim) of action potentials displayed RRD, i.e., changes in APD were greater at longer than at shorter CLs. In rabbit, where APD is a biphasic function of CL, the drug-induced APD changes were proportional to baseline APD values but not to CL. Similar results were obtained when repolarization was modified by injection of inward or outward current pulses in isolated canine cardiomyocytes. In each case the change in APD was proportional to baseline APD (i.e., that measured before the superfusion of drug or injection of current). Also, the net membrane current (I_{net}), determined from the action potential waveform at the middle of the plateau, was inversely proportional to APD and consequently with to CL. The results indicate that RRD is a common characteristic of all the drugs tested regardless of the modified ion current species. Thus, drug-induced RRD can be considered as an intrinsic property of cardiac membranes based on the inverse relationship between I_{net} and APD.

Keywords Ventricular repolarization · Action potential duration · Reverse rate dependence · Membrane current · Human myocardium · Mammalian cardiac cells

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Introduction

Class III antiarrhythmic agents are known to display a reverse rate-dependent lengthening of APD, called RRD [6, 9]. This RRD nature of the APD lengthening is undesirable because it minimizes drug effects on repolarization during tachyarrhythmias and enhances their proarrhythmic potential at normal rates [6, 11, 18]. Several hypotheses have been developed so far to explain the mechanism of RRD. Based on results obtained in guinea pig ventricular myocytes, it was first suggested that significant accumulation of I_{Ks} may occur due to the

incomplete deactivation of the current at fast heart rates, which would greatly attenuate the APD lengthening effect of I_{Kr} blockade [9]. According to another hypothesis the effect of I_{Kr} blockers is reduced, and consequently the drug-induced prolongation of APD becomes diminished, at fast heart rates due to the potassium accumulation in the sarcolemmal clefts. This theory was based on observations showing that I_{Kr} blockade by quinidine and dofetilide was attenuated when extracellular potassium concentration was elevated [19]. A third hypothesis, the modulated receptor theory, was based on the rate dependency of drug–channel interactions stating that drug binding and unbinding are strongly dependent on the state of the channel, which is dynamically changing during the cardiac cycle [4, 5]. Assuming that I_{Kr} blockers may be binding preferably during the diastole and unbinding during the action potential, RRD can be expected indeed. Finally, rate-dependent changes in action potential morphology were also claimed to contribute to the reverse rate dependency by controlling the kinetic properties of I_{Kr} and I_{K1} in guinea pig, dog, and human ventricular preparations [12, 16].

The multitude of theories suggested explaining RRD indicates that its exact mechanism is still unclear. In a recent study in dog myocardium [1], APD modulation by drugs with diverse mechanisms was invariably characterized by RRD. This was interpreted as RRD being an "intrinsic" property, resulting from the shape of the relationship between I_{net} and APD [1, 20]. Such an interpretation was based on the assumption that APD modulation depends on drug-induced changes in I_{net}, independently of the specific current affected. The interpretation also predicts that, instead of depending on heart rate (as suggested by the term RRD), the extent of drug-induced APD change may be a function of baseline APD, the latter being in turn a function of rate.

The aims of the present study were to test (1) whether RRD is a general property of APD modulation also in other species, including man; (2) the assumption and the predictions of the interpretation of RRD provided in our previous work [1, 20].

Methods

Animal tissue preparations

Adult mongrel dogs (10–15 kg), guinea pigs (0.3–0.5 kg), and New Zealand white rabbits (2–3 kg) of either sex were anesthetized using sodium pentobarbital. After opening the chest the hearts were rapidly removed and placed in Tyrode solution containing (in mM): NaCl 140, KCl 5.4, $CaCl_2$ 2.5, $MgCl_2$ 1.2, HEPES 5, glucose 10, at

pH 7.4. Papillary muscles, excised from both ventricles, were used for standard microelectrode measurements. A wedge-shaped section of the left ventricular wall of canine hearts, supplied by the left anterior descending coronary artery, was dissected and cannulated for isolation of single myocytes. All experiments were carried out in compliance with the *Guide for the Care and Use of Laboratory Animals* (USA NIH publication NO 86-23, revised 1985), and the protocols were approved by the local ethical committee (CAR I-74-66/2005). Chemicals used in the experiments were obtained from Sigma–Aldrich Co. (St. Louis, MO, USA).

Human tissue preparations

Papillary muscles were excised also from undiseased donor hearts. The hearts were obtained from general organ donors, their valves were utilized for pulmonary and aortic valve transplantation surgery. Before explantation of the hearts the patients did not receive any medication except for dobutamine, furosemide and plasma expanders. The experimental protocol complied with the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the Ethical Review Board of the Albert Szent-Györgyi Medical University (No. 51-57/1997 OEJ).

Action potential recording in multicellular muscle preparations

Papillary muscles were mounted in a plexiglass chamber, allowing continuous superfusion with oxygenized Tyrode solution at 37°C, and paced through a pair of platinum electrodes. The pacing cycle length was initially set to 1 s for at least 60 min allowing the preparations to equilibrate before starting the measurement. Following equilibration the cycle length was set to 5 s, then it was gradually reduced to 3, 2, 1.5, 1, 0.7, 0.5, 0.4, and 0.3 s at least for 5 min at each cycle length. This period of time was sufficient for stabilization of action potential parameters, including APD. After taking control records the preparations were superfused for 40 min with the drug tested and the measurement was repeated at each pacing cycle length. Glass microelectrodes, filled with 3 M KCl and having tip resistances of 5–20 MΩ, were used to record transmembrane potentials after amplification (Experimetria Ltd., Budapest, Hungary). Action potential duration at 90% of depolarization (APD_{90}) was determined automatically by a HSE-APES software running on an IBM compatible computer containing an ADA 3300 analogue-to-digital data acquisition board (Real Time Devices Inc., State College, PA, USA) with a

Fig. 1 a–f Cycle length-
dependent changes of action
potential duration (APD$_{90}$)
induced by 50 nM dofetilide
(**a**, $n = 5$), 30 µM sotalol
(**b**, $n = 4$), 1 µM E-4031
(**c**, $n = 6$), 10 µM BaCl$_2$
(**d**, $n = 5$), 10 µM mexiletine
(**e**, $n = 4$), and 2 µM
tetrodotoxin (**f**, $n = 3$) in human
papillary muscle preparations.
The pacing cycle length was
gradually decreased from 5 to
0.3 s before and 40 min after
administration of drugs.
g, **h** Drug-induced changes,
plotted against baseline
(pre-drug) APD values. APD
changes in panel **g** are displayed
as absolute magnitudes, while in
h in a percentage form. *Symbols*
and *bars* denote mean ± SEM
values
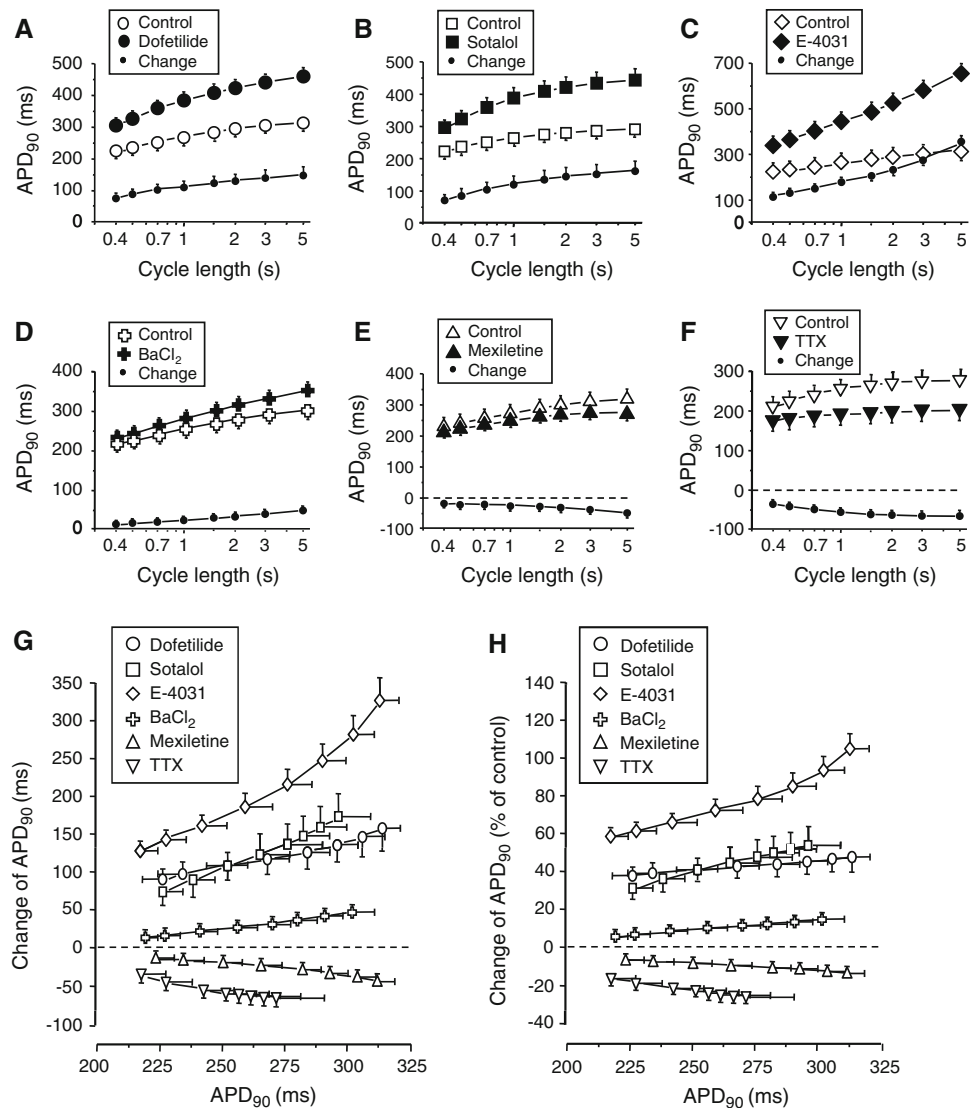
maximum sampling rate of 40 kHz. Efforts were made to maintain the same impalement throughout each experiment. When the impalement became dislodged, adjustment was attempted, and if the action potential characteristics of the re-established impalement deviated by less than 5% from the previous measurement the experiment continued.

Action potential recordings in isolated cardiomyocytes

Single canine ventricular myocytes were obtained by enzymatic dispersion using the segment perfusion technique [10]. The cells were sedimented in a plexiglass chamber and superfused with oxygenized Tyrode solution at 37°C. Only rod shaped cells with clear cross striations were used. Transmembrane potentials were recorded using

3 M KCl filled sharp glass microelectrodes having tip resistance between 20 and 40 MΩ. These electrodes were connected to the input of an Axopatch-200B amplifier (Axon Instruments, Foster City, CA, USA) under current clamp conditions, allowing for simultaneous recording of action potentials and injection of inward or outward current pulses. These current pulses (having amplitudes of either −30 or +60 pA, respectively, and durations longer than the expected APD) were injected from the upstroke of every 20th action potential at any cycle length tested (following the 5-min period of equilibration at the given cycle length, as described above). Thus, action potentials with current injections were separated from one another by 19 regular action potential waveforms. The cells were paced through the recording electrode using 1-ms-wide rectangular current pulses with twice threshold amplitude. The cycle

length was initially set to 5 s, and following stabilization of action potential configuration the cycle length was continuously varied to shorter values. Since the cytosol was not dialyzed, time-dependent changes in action potential duration were negligible for at least 60 min under these experimental conditions [7].

Estimation of net transmembrane current density

I_{net} (in pA/pF) was calculated from the first derivative of membrane potential changes during repolarization (I_{net} density $= -dV/dt$). I_{net} was obtained at half duration of the action potential by considering a 50-ms-long segment of repolarization (half AP duration $\pm$ 25 ms).

Statistics

Results are expressed as mean $\pm$ SEM values. Statistical differences were evaluated using ANOVA. Differences were considered significant when P was less than 0.05.

Fig. 2 a–d Cycle length-dependent changes in APD induced by 10 μM $BaCl_2$ (a, $n = 11$), 1 μM dofetilide (b, $n = 13$), 1 μM BAY K 8644 (c, $n = 6$), and 1 μg/ml veratrine (d, $n = 7$) in canine papillary muscles. The pacing cycle length was gradually decreased from 5 to 0.3 s) before and 40 min after administration of drugs. Drug-induced changes, plotted against baseline (pre-drug) APD values, are summarized in panel e. Symbols and bars denote means $\pm$ SEM
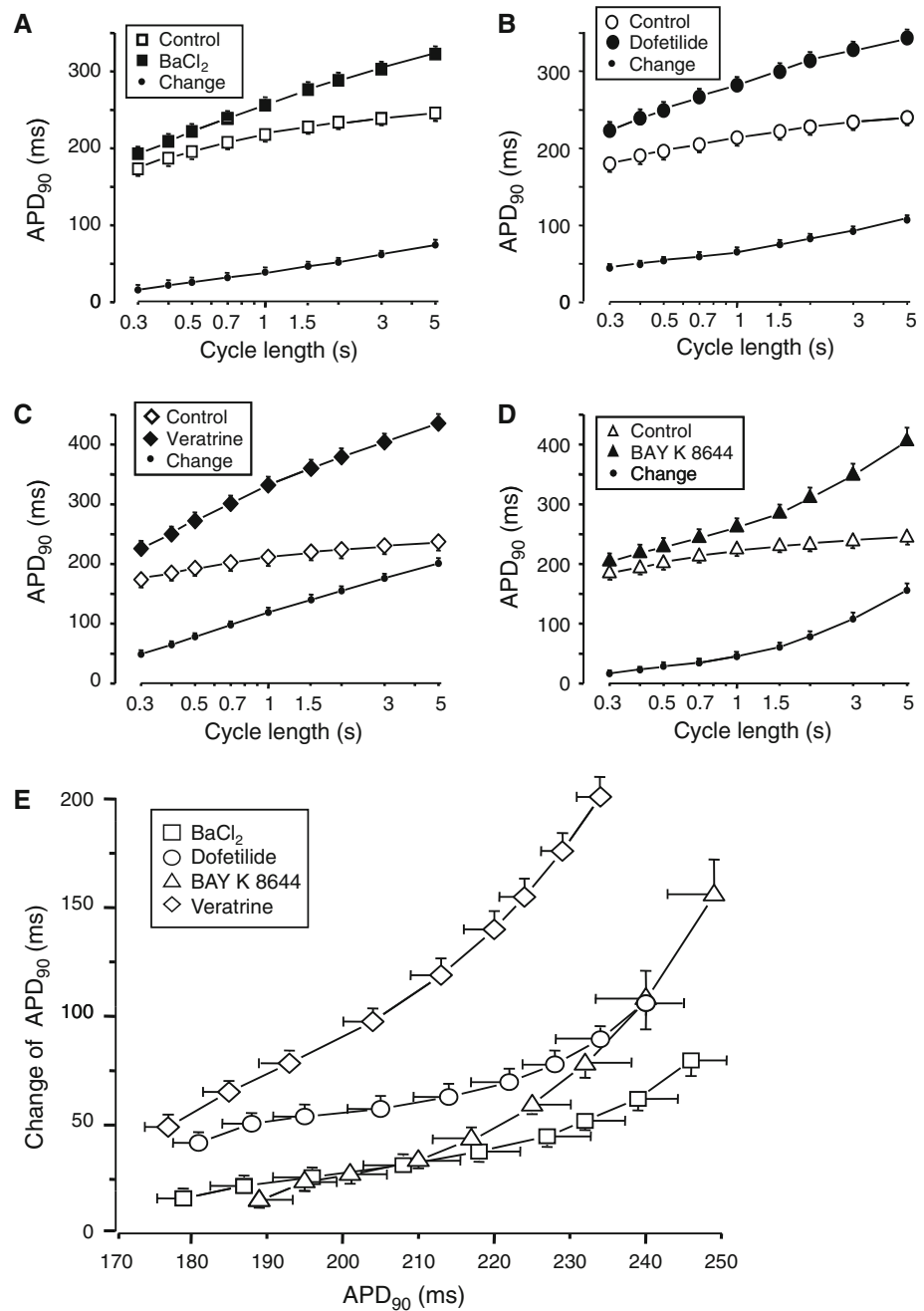
Table 1 Drugs used to modify action potential duration

Drug	Concentration	Action	Expected change in APD
Dofetilide	50 nM, 1 μM[a]	Block of I_{Kr}	Lengthening
Sotalol	20–40 μM[b]	Block of I_{Kr}	Lengthening
E-4031	1 μM	Block of I_{Kr}	Lengthening
BaCl$_2$	10 μM	Block of I_{K1}	Lengthening
Veratrine	1 μg/ml	Enhancement of I_{Na}	Lengthening
BAY K 8644	1 μM	Enhancement of I_{Ca}	Lengthening
Mexiletine	10 μM	Block of I_{Na}	Shortening
Tetrodotoxin	2 μM	Block of I_{Na}	Shortening
Lemakalim	15 μM	Enhancement of $I_{K(ATP)}$	Shortening

[a] 50 nM in human and 1 μM in canine papillary muscles

[b] 20, 30, and 40 μM in rabbit, human, and guinea pig papillary muscles, respectively

Results

RRD in human and canine myocardium

The rate-dependent effects of several cardioactive compounds were tested on APD in human (dofetilide, sotalol, E-4031, BaCl$_2$, mexiletine, and TTX) and canine (dofetilide, BaCl$_2$, veratrine, and Bay K 8644) multicellular ventricular preparations (Figs. 1, 2). The compounds used to modulate repolarization were chosen to either prolong or shorten APD based on modulation of different ion channels, as summarized in Table 1. Although the magnitude of APD changes varied with the applied compound, both the shortening and lengthening effects showed clear-cut RRD (i.e., the effects were larger at longer than at shorter CLs) with all the compounds tested (Figs. 1a–f, 2a–d).

Dependency of drug-induced APD changes on the pre-drug baseline APD is shown in Figs. 1g, h, 2e. In both species drug-induced changes of APD were proportional to baseline APD. The relationship tended to become steeper at larger APD values. This property was differently expressed with different drugs and was most obvious for BAY K 8644 (Fig. 2e).

RRD in guinea pig and rabbit myocardium

The coincidence observed between human and canine ventricular tissues is not surprising, because the electrophysiological properties of human and canine myocardium are believed to be quite similar [8, 13, 14]. In contrast, the type and density of ion channels underlying the action potential in guinea pig and rabbit hearts are markedly different from those found in dog and human [15]. Furthermore, as opposed to the other species tested, APD displayed a non-monotonic dependency on CL in rabbits,

maximum APD being achieved at an intermediate CL between 0.5 and 0.7 s. This provided a unique opportunity to discriminate between rate-dependency and APD-dependency of drug-induced APD changes. In this case, sotalol and lemakalim were used to prolong and shorten APD, respectively.

As expected, sotalol lengthened and lemakalim shortened APD in papillary muscles of both species (Fig. 3a–d). In guinea pig, similar to results obtained in canine and human preparations, both APD lengthening and shortening displayed monotonic RRD. In rabbit preparations the maximal drug-induced APD changes occurred at an intermediate CL between 0.5 and 0.7 s, at which baseline APD was the longest (Fig. 3e, f). This suggests that the magnitude of drug-effect depended on baseline APD, rather than on pacing rate. This interpretation was supported by the analysis presented in Fig. 4, which shows that the drug-induced APD changes were, in both species, related to baseline APD. Moreover, when the APD–CL relationship was non-monotonic in rabbit, similar APDs occurring at different CLs were associated with the same magnitude of APD changes. These observations lead us to conclude that longer action potentials are more sensitive to modulation than shorter ones, irrespective of the actual pacing rate.

APD modulation by current injection

Independency of RRD from the features (rate-dependency, profile, etc.) of the modulated current was tested by changing APD through the injection of a constant current. For technical reasons, these experiments were performed in single myocytes.

Inward (-30 pA) and outward ($+60$ pA) current pulses were injected throughout repolarization to lengthen and shorten APD, respectively, in isolated canine ventricular cells. As shown in Fig. 5a, b, the effect of current injection on APD was reversely rate-dependent. Furthermore, the changes in APD induced by the inward and outward current pulses were linearly proportional to the baseline APD values measured prior to current injection (Fig. 5c). In another series of experiments APD was lengthened or shortened by injections of current pulses of various amplitudes (ranging from -40 to $+100$ pA) and the lengthening effect of BaCl$_2$ was tested. BaCl$_2$ induced greater APD lengthening when the pre-drug APD was longer, in spite of the constant pacing CL of 1 s applied in these experiments (Fig. 6).

Constancy of the relationship between APD and I_{net}

The assumption that APD modulation reflects a change in I_{net}, independently of the specific current affected by the drug, was verified by testing whether modulation of

Fig. 3 Cycle length-dependent changes in APD induced by sotalol and lemakalim in guinea pig and rabbit ventricular preparations. **a, b** Effect of 40 μM sotalol 15 μM lemakalim in guinea pig papillary muscles ($n = 5$ and $n = 11$, respectively). **c, d** Effect of 20 μM sotalol 15 μM lemakalim in rabbit papillary muscles ($n = 5$ and $n = 13$, respectively). Drug-induced APD changes are presented in panels **e** and **f**. *Symbols* and *bars* denote means ± SEM
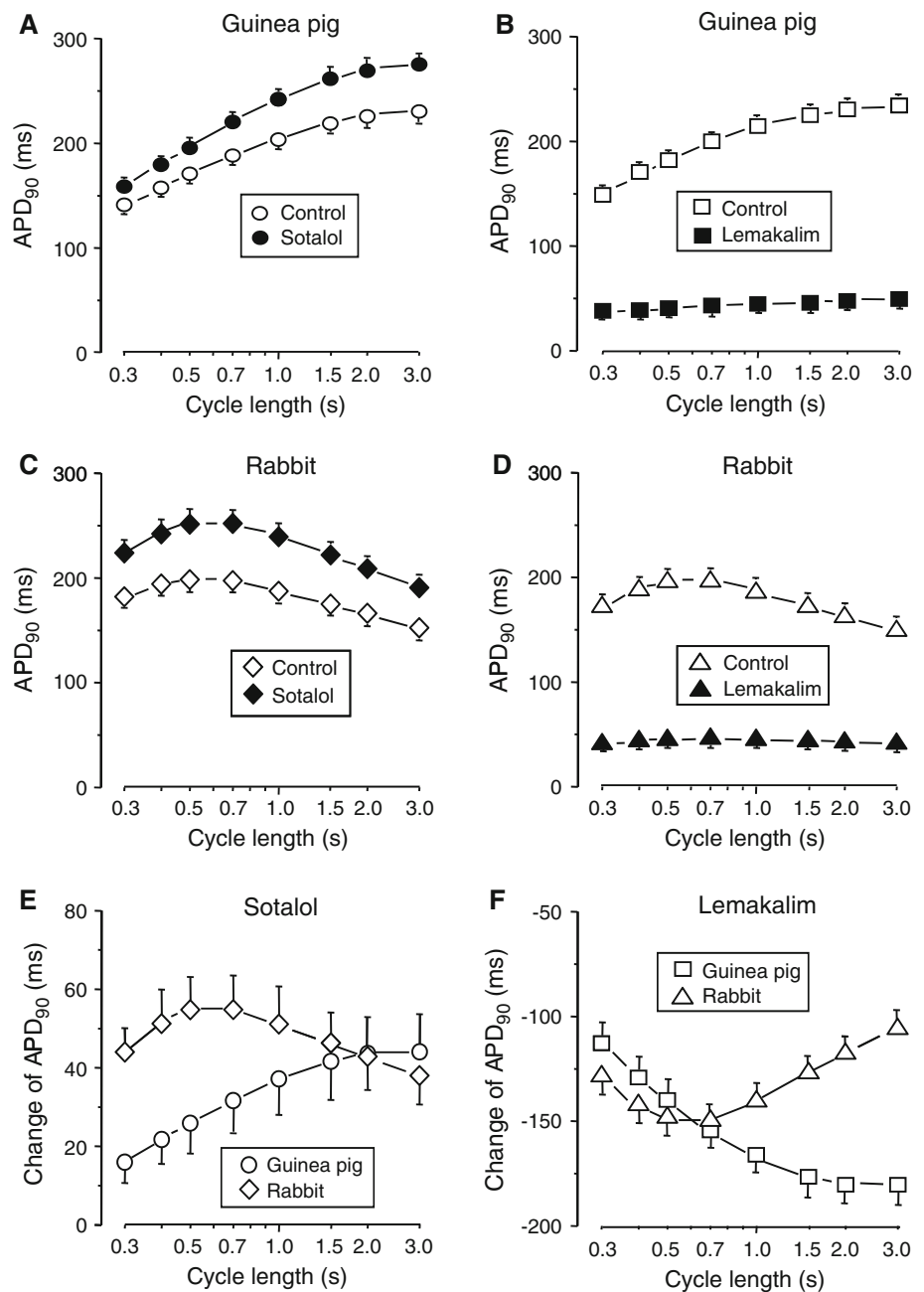
different currents led to changes in the relationship between APD and I_{net} of human papillary muscles. To this end, APD was plotted as a function of I_{net}, measured at mid repolarization (see "Methods") in control and in the presence of various drugs. As shown in Fig. 7, APD was a non-linear function of I_{net}, and the I_{net}–APD relationships obtained in the presence of different drugs closely overlapped.

Discussion

The findings of this study indicate that (1) RRD is a general property of APD modulation, equally represented in different species, including dog, rabbit, guinea pig, and man; (2) the extent of drug-induced APD change is a function of baseline APD, irrespective of pacing rate; (3) the shape of the function relating APD to I_{net}, measured at an arbitrary point during repolarization, was substantially independent of the drug used to modulate APD.

RRD was recently interpreted as the consequence of the numerical relationship between APD and I_{net} (proportional to repolarization velocity) [1, 20]. As such, RRD should be seen as the indirect consequence of an intrinsic property of APD modulation, conserved across different species and types of modulatory interventions. Such an interpretation was supported by numerical modeling, which was based on

Fig. 4 APD changes induced by sotalol (**a**, **b**) and lemakalim (**c**, **d**) in guinea pig (**a**, **c**) and rabbit (**b**, **d**) papillary muscles plotted against the respective baseline (pre-drug) APD values. Data are derived from experiments shown in Fig. 3. Symbols and bars denote means ± SEM
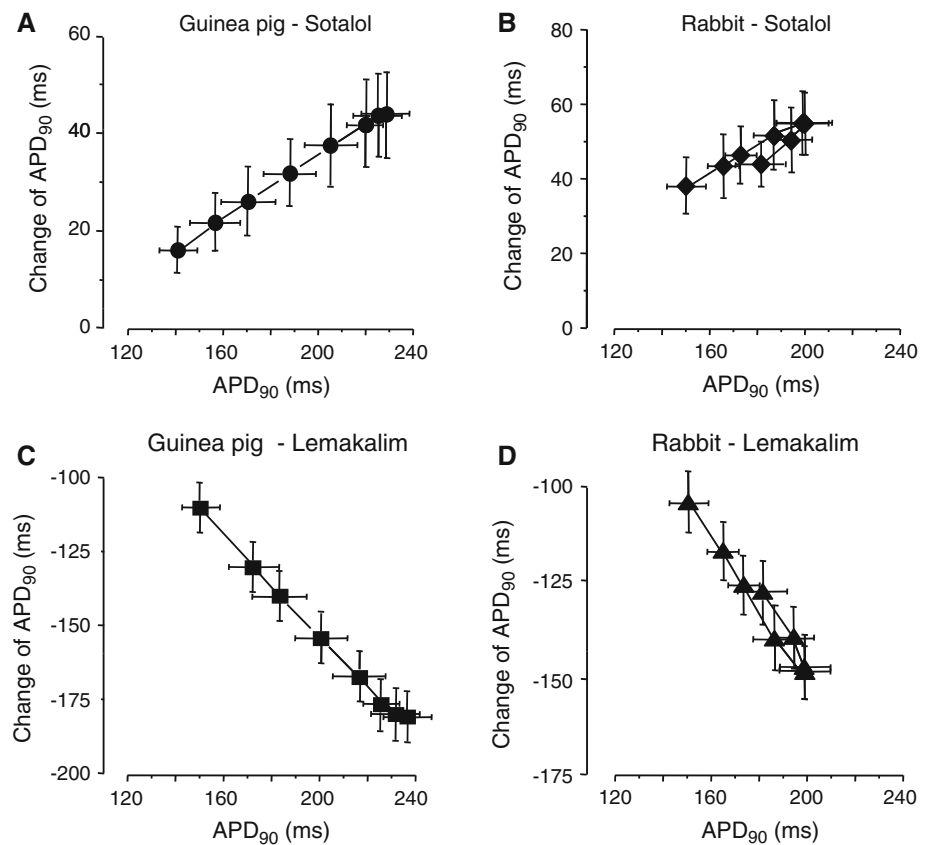
an assumption and led to the predictions tested in this study (see "Introduction"). In spite of a similar action potential contour, repolarization mechanisms significantly differ between larger mammals (dog, man) and smaller ones (rabbit, guinea pig). The observation that RRD is a general feature across these species supports the view that it may be accounted for by a general property of the system. If RRD depended on changes in the proportion of individual currents expressed at each cycle length, rather than on changes in I_{net}, the relationship between APD and I_{net} should differ among drugs acting on different ion channels. APD–I_{net} relationships obtained with different drugs largely overlapped instead, thus confirming that I_{net} determines APD, independently of which channel is modulated. This validates the assumption underlying our RRD interpretation.

Finally, drug-induced APD changes proved to be directly determined by baseline APD, instead of the pacing rate. This confirms the prediction that APD modulation by drugs is intrinsically more pronounced under conditions when action potentials are ab ovo longer, with pacing rate being just one factor causing baseline APD to change. Although the view that the mathematical relationship between APD and I_{net} may cause RRD is fully confirmed by the present results, several observations indicate that additional mechanisms may account for the extent to which

RRD is expressed. For instance, if the same mechanism accounted for RRD in all cases, we would expect the relationship between drug-induced APD changes and baseline APD to be identical in all cases. However, such a relationship was almost linear with some drugs (e.g. Fig. 4), but non-linear with others (e.g. Fig. 2e). This implies that even the dependency of APD modulation on baseline APD may include components that cannot be explained by a single mechanism. Furthermore, the existence of an intrinsic dependency of APD modulation on baseline APD does not rule out that other genuinely rate-dependent mechanisms, such as drug–ion channel interactions [5, 9, 19] and rate dependency of ion current kinetics [3, 12, 16], may contribute to determine the magnitude of RRD. Indeed, whereas the same extent of RRD would be expected if only the "intrinsic" mechanism was operative, the magnitude of RRD was different between the various drugs tested.

Good example for RRD resulting from rate dependency of ion current kinetics was observed in murine ventricular myocardium exposed to sotalol [3]. In that study 20 μM sotalol prolonged APD with reverse rate dependency. Since in the same preparation APD was not rate-dependent under baseline conditions within the relatively narrow range of the studied frequencies [3, 17], reverse rate-dependency cannot be accounted for the intrinsic mechanism described
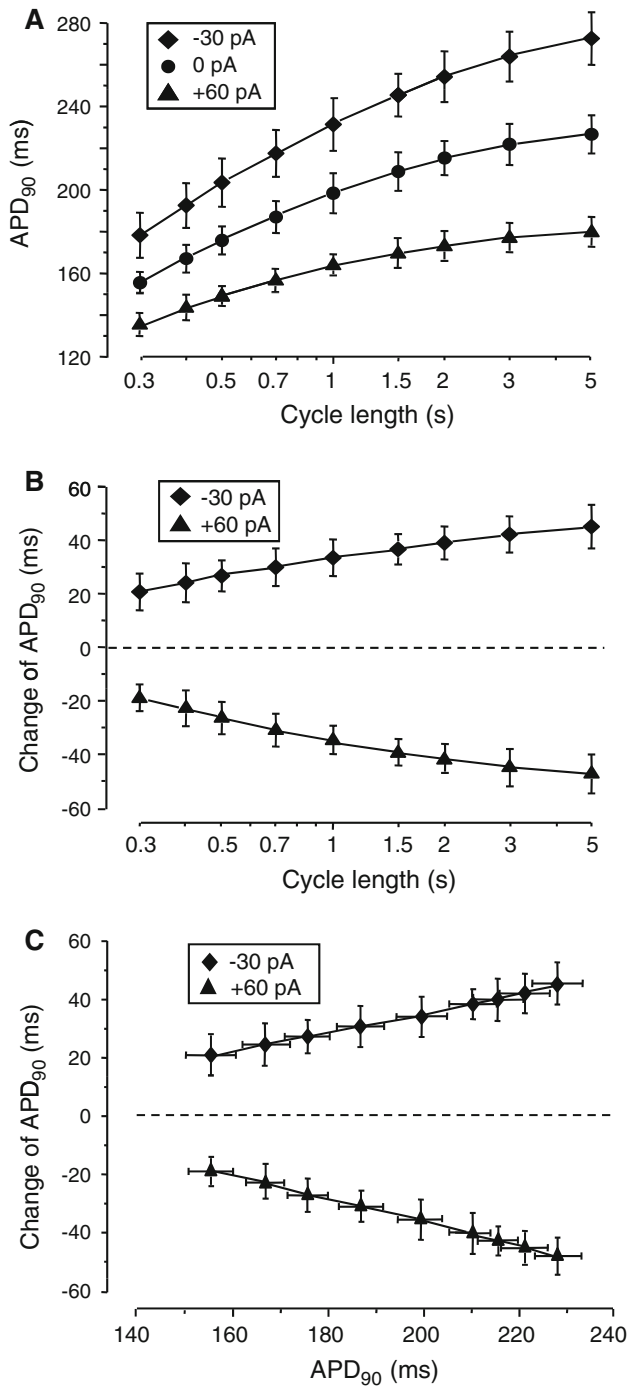
Fig. 5 Cycle length-dependent changes in APD induced by inward (−30 pA) and outward (+60 pA) current pulses, injected throughout the entire duration of the action potential, in single canine ventricular cells ($n = 10$). **a** Measured APD_{90} values. **b** Changes in APD induced by the current pulses. **c** APD changes plotted against the control (0 pA) APD values. *Symbols* and *bars* denote means ± SEM

Fig. 6 Effect of 3 μM $BaCl_2$ on isolated canine myocytes ($n = 7$) paced at a constant CL of 1 s. APD was lengthened or shortened by current pulses of various amplitudes (ranging from −40 to +100 pA) in the absence (*control*) and presence of $BaCl_2$. The APD lengthening effect of $BaCl_2$ was plotted as a function of the injected current (**a**) or against the control (pre-drug) APD values (**b**). *Symbols* and *bars* denote means ± SEM

above. Consequently, an additional mechanism, very likely an I_{to} blockade, must be responsible for the sotalol-induced RRD in mice. In sheep Purkinje fibers 10 μM sotalol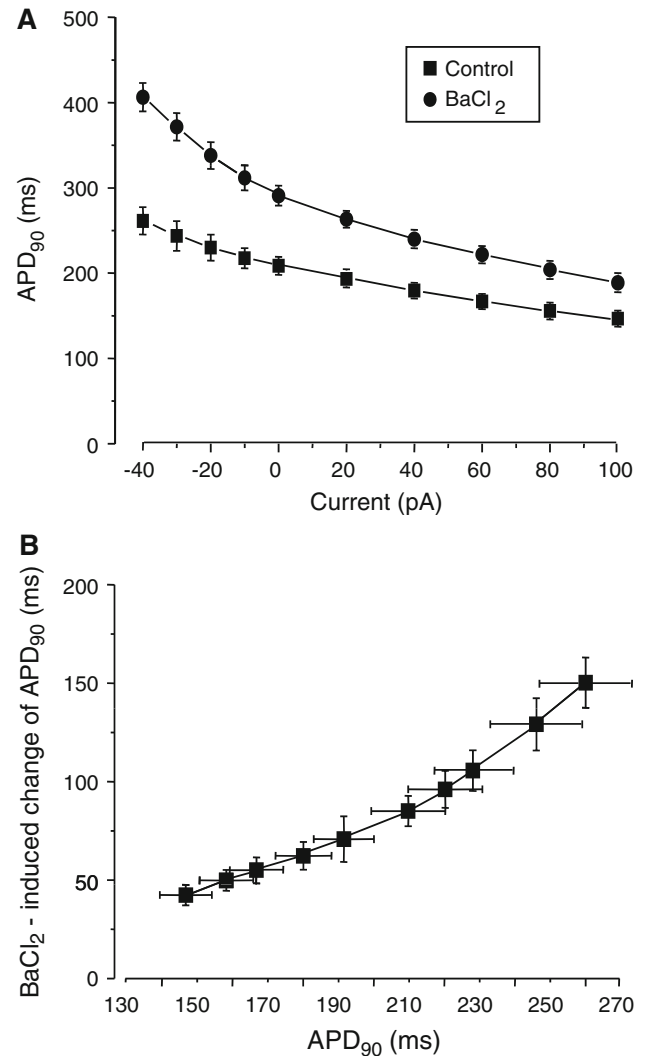 suppressed significantly (by 23%) I_{to}, a current whose amplitude is known to decrease at short CLs due to incomplete recovery from inactivation [2]. Since I_{to} is a strong repolarizing current in murine myocardium, and I_{to} is expectedly larger at longer CLs, its block can reduce I_{net} to a larger extent at slow rates.

Conclusions

The extent by which APD is changed by interventions depends on the initial APD, irrespective of rate. Since the initial APD is generally longer at lower rates, this may
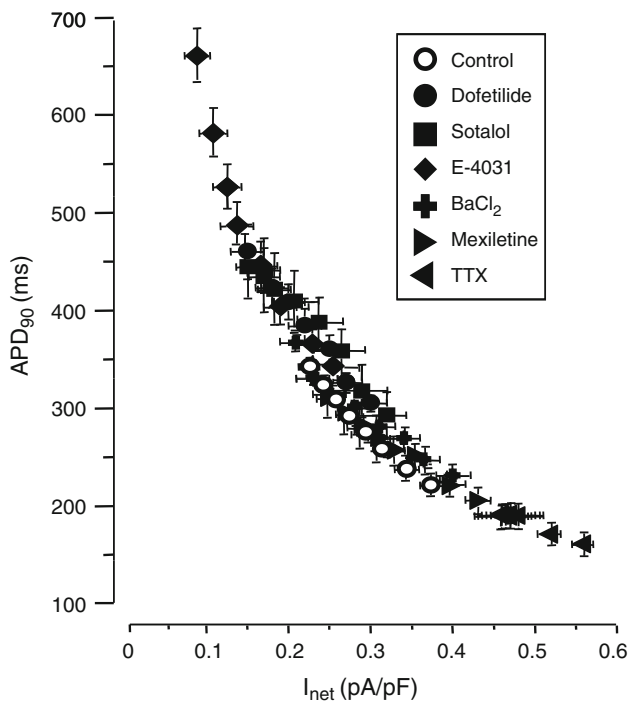
Fig. 7 Action potential duration (APD_{90}) plotted as a function of the net membrane current (I_{net}) measured at half duration of the action potential. I_{net} was determined from the slope of membrane potential changes (dV/dt). Data are obtained from experiments performed in human papillary muscles paced at CLs varying between 0.3 and 5 s, as shown in Fig. 1. *Symbols* and *bars* denote means ± SEM

explain why RRD is so common and supports its origin from an "intrinsic" property independent of the modulation mechanism [1, 17]. Nevertheless, properties of the affected current and genuinely rate-dependent changes in its kinetics may overlap with intrinsic RRD and modulate its magnitude in a drug-specific way.

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