

Impact of Sex and Gonadal Steroids on Prolongation of Ventricular Repolarization and Arrhythmias Induced by I_{K} -Blocking Drugs

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Background—Mechanisms for longer rate-corrected QT intervals and higher incidences of drug-induced torsade de pointes in women than in men are incompletely defined, although gonadal steroids are assumed to be important determinants of these differences.

Methods and Results—We used microelectrode techniques to study isolated rabbit right ventricular endocardium from control male and female and castrated male (ORCH) and female (OVX) rabbits. Action potential duration to 30% repolarization (APD_{30}) was significantly shorter in male than female and in ORCH than OVX at a cycle length of 500 ms. The I_{Ks} blocker chromanol 293B had no effect on APD in males or females. The I_{Kr} blocker dofetilide prolonged APD in female and ORCH more than in male and OVX. At 10^{-6} mol/L dofetilide (cycle length=1 second), the incidence of early afterdepolarizations was: female, 67%; ORCH, 56%; male, 40%; and OVX, 28%. Serum 17β -estradiol levels were unrelated to the effects of dofetilide, but as testosterone levels increased, the dofetilide effect to increase APD diminished, as did early afterdepolarization incidence.

Conclusions—Sex-related differences in basal right ventricular endocardial AP configuration persist in castrated rabbits, suggesting that extragonadal factors contribute to the differences in ventricular repolarization. In this model, drugs that block I_{Kr} but not I_{Ks} prolong repolarization in a way that suggests that protection from excess prolongation in males is attributable to testosterone, whereas the risk of excess prolongation of repolarization in females is related to sex-determined factors in addition to estrogen. (*Circulation*. 2001;103:2207-2212.)

Key Words: sex ■ steroids ■ arrhythmias ■ ion channels ■ drugs

Repolarization-prolonging drugs induce torsade de pointes (TdP) more frequently in women than men.^{1,2} Similarly, in the congenital long-QT syndrome, female sex is an independent risk factor.³ The higher propensity toward arrhythmia in women is associated with differences in normal cardiac repolarization such that rate-corrected QT intervals are longer in women than in men and T waves in men have steeper ascending and descending slopes than in women.⁴⁻⁶

Experimental data concerning sex differences in electrophysiological properties are derived largely from experiments on oophorectomized female rabbits treated long-term with gonadal steroids as surrogates for sex-based effects. Surface electrogram QT intervals were longer and QT prolongation induced by quinidine was greater in isolated hearts from estrogen-treated than testosterone-treated oophorectomized rabbits.⁷ Similarly, ventricular endocardial action potential duration (APD) of oophorectomized 17β -estradiol-treated rabbits was longer and early afterdepolarizations (EADs)

induced by the I_{Kr} blocker E4031 were more frequent than with 5α -dihydrotestosterone treatment.⁸ In the only report in normal males and females, isolated female rabbit hearts had longer QT intervals than males at a cycle length (CL) of 2.3 seconds.⁹

It remains unclear whether sex-based differences in repolarization and responsiveness to I_K blockers are due entirely to gonadal steroids or are associated with other sex-related factors. In this study we asked: Are there sex-related differences in (1) the ventricular AP at physiological CLs and (2) occurrence of EAD induced by drugs that block I_{Kr} and I_{Ks} ? Are gonadal steroids the unique determinants of sex-related differences in ventricular repolarization and EAD?

Methods

This investigation conforms to the *Guide for the Care and Use of Laboratory Animals* published by the US Public Health Service, NIH publication No. 85-23, 1996.

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Five female and 11 male New Zealand White rabbits (Hare Marland, Hewitt, NJ) (50 to 60 days old, 1.8 to 2.5 kg) were anesthetized with 2% isoflurane and O₂ and underwent gonadectomy under sterile techniques. Animals were fed water and Rabbit Diet HF 5326 (Laboratory diet, Purina Mills), which contains phytoestrogen. This has estrogenic effects¹⁰ but was a constant in all experiments. Two weeks after surgery, oophorectomized (OVX) females were implanted with 60-day sustained-release pellets (Innovative Research of America) of vehicle. Orchiectomized (ORCH) males were treated with pellets of vehicle, 17 β -estradiol (EST), or 5 α -dihydroxytestosterone (DHT). Rabbits were treated with hormones for 4 to 5 weeks before experimental studies. Another 5 females and 5 males were raised to the same age and studied as controls.

Before euthanasia, 2 mL of blood was obtained and serum was stored at -20°C for analysis. EST was measured by a solid-phase chemiluminescence immunoassay (Immulite, Diagnostic Products Co, DPC; sensitivity 20 pg/mL). DHT was measured by radioimmunoassay (Diagnostic Systems Laboratories) coupled with an oxidation/extraction procedure to remove testosterone (sensitivity 4 pg/mL).

All rabbits (3.0 to 3.5 kg at the time of terminal experiment) were anesthetized with sodium pentobarbital (30 mg/kg IV), and the hearts were excised and immersed in Tyrode's solution equilibrated at 37°C with 95% O₂/5% CO₂. The solution contained (mmol/L) NaCl 131, NaHCO₃ 18, KCl 4, CaCl₂ 1.2, MgCl₂ 0.5, NaH₂PO₄ 1.8, and dextrose 5.5. Right ventricular (RV) papillary muscles (3 to 5 mm long, 0.3 to 1 mm in diameter) were dissected and placed in a 4-mL chamber perfused with Tyrode's solution (37°C , pH 7.4) at 12 mL/min. Right epicardial preparations isolated from the midbasal RV were studied in males and females only. Stimulation and recording techniques have been described.⁸

Selection of tissue for microelectrode study was based on preliminary experiments demonstrating no differences in repolarization duration between left ventricular (LV) and RV sites in OVX females. LV and RV epicardial monophasic action potential (MAP) durations to 90% repolarization (MAPD₉₀) did not differ (133 ± 3 and 141 ± 3 ; $n=26$ and 17 , respectively). Moreover, percent prolongation of repolarization induced by 2 and 5 $\mu\text{mol/L}$ azimilide (a nonspecific I_{K} blocker, provided by Procter and Gamble) was similar in the LV and RV (2 $\mu\text{mol/L}$ azimilide: $14\pm 4\%$ and $23\pm 5\%$, $n=26$ and 17 ; 5 $\mu\text{mol/L}$ azimilide: $35\pm 3\%$ and $42\pm 7\%$, $n=25$ and 13 , respectively). Because no interventricular difference in repolarization or effects of I_{K} blockade on MAP prolongation were found, we did all transmembrane AP recordings in isolated RV.

To compare transmural APD dispersion, APs were recorded from RV endocardial (papillary muscle) and epicardial preparations obtained from the same animal. We did not prepare transmural RV slab preparations, because the RV wall is very thin in rabbits of this age. Thus, we compared transmural APD dispersion as APD differences between epicardial and papillary muscle.

Predrug measurements of AP were made at CLs=1000, 500, and 330 ms, with 3 minutes allowed to achieve steady state at each CL. Each drug concentration was superfused for 30 minutes before measurements were made.

A 0.2 mol/L stock solution of the I_{Ks} blocker chromanol 239B¹¹ (a gift from Hoechst Marion Roussel, Frankfurt, Germany) was prepared in DMSO. DMSO 1% induces prolongation of APD by 4%.¹² In our experiments, 10^{-5} mol/L chromanol Tyrode's solution contained 0.005% DMSO. Thus, the effect of DMSO on APD was negligible. The I_{Kr} blocker dofetilide^{13,14} (a gift from Helopharm, Berlin, Germany) was dissolved in water to obtain a 10^{-3} mol/L stock solution before every experiment.

Because of discrepancies in the literature regarding I_{Ks} in rabbits,^{13,14} we did preliminary voltage-clamp experiments in female RV myocytes. I_{Kr} was present and sensitive to dofetilide in 4 of 4 cells, and I_{Ks} was present and sensitive to chromanol 293B in 3 of 3 cells (Figure 1).

Data are reported as mean \pm SEM. Student's *t* test was used to compare single parameters between independent pairs. Dose-response relationships were analyzed by ANOVA for multiple comparisons and Bonferroni's or Dunnett's test when appropriate.

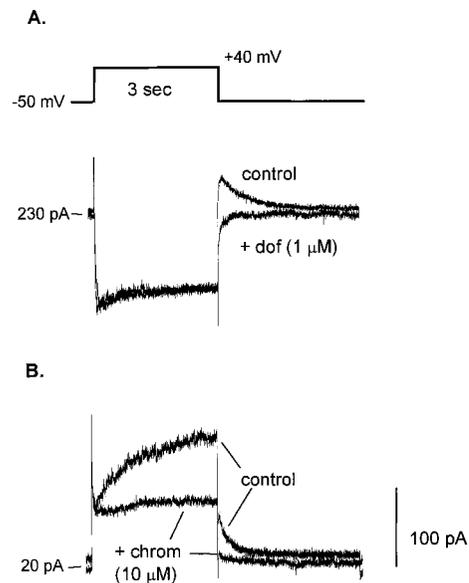


Figure 1. Recordings of I_{Kr} and I_{Ks} . A single-step voltage-clamp protocol (as shown) was applied in absence or presence of drug. Internal pipette solution contained (in mmol/L): aspartic acid 140, KOH 146, NaCl 10, EGTA 5, CaCl₂ 2, Mg-ATP 2, and HEPES 10 (pH adjusted to 7.2 with KOH). A, I_{Kr} in Tyrode's solution containing (in mmol/L): NaCl 140, KCl 5.4, CaCl₂ 1.8, MgCl₂ 1, HEPES 5, and glucose 10 (pH adjusted to 7.4 with NaOH). Tail current, predominantly I_{Kr} , was completely blocked by dofetilide (Dof). B, I_{Ks} in Na⁺, K⁺, and Ca²⁺-free external solution containing (in mmol/L): *N*-methyl-D-glutamine 144, MgCl₂ 1, HEPES 5, and glucose 10 (pH adjusted to 7.4 with HCl). Dofetilide (1 $\mu\text{mol/L}$) was added to block I_{Kr} . chrom indicates chromanol 293B.

Fisher's exact test was used to analyze EAD incidence. A value of $P<0.05$ was considered significant.

Results

Sex-Related Differences in Endocardial Action Potentials

At all CLs, maximum diastolic potential (range -82 to -85 mV), AP amplitude (107 to 113 mV), and V_{max} (161 to 181 V/s) of phase 0 did not differ significantly among groups. Control and OVX females had longer APD₃₀ than control and ORCH males ($P<0.05$), but there was no significant difference in APD₉₀ (Figure 2). After gonadectomy, sex-related differences in APD₃₀ persisted. No EADs or delayed afterdepolarizations occurred.

Effects of Chromanol and Dofetilide

Chromanol 293B had no effect on female and male AP parameters. For example, at CL=1000 ms and 10^{-5} mol/L chromanol, APD₉₀ (female: 153 ± 14 ms, $n=8$; male: 170 ± 7 ms, $n=13$) did not differ from control (female: 157 ± 17 ms, $n=8$; male: 155 ± 8 ms, $n=13$). Hence, castrated groups were not studied. Dofetilide had no effect on maximum diastolic potential, AP amplitude, or V_{max} (data not shown), but it prolonged APD₉₀ in all groups (Figure 3). Dofetilide 10^{-8} mol/L induced greater APD₉₀ prolongation (ΔAPD_{90}) in control females and ORCH males than control males and OVX females ($P<0.05$). Higher concentrations induced EADs in all groups, making it difficult to measure APD

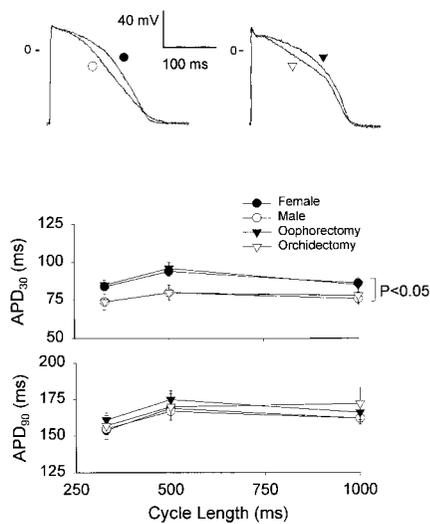


Figure 2. Sex- and gonadectomy-related differences in endocardial AP. Top, Papillary muscle AP of female, male, OVX female, and ORCH male at CL=500 ms. Middle and bottom, APD₃₀ and APD₉₀, respectively, in all 4 groups. n=51, 56, 14, and 17 for females, males, OVX females, and ORCH males, respectively.

accurately. EAD incidence was greatest in normal females and ORCH males (Figure 3).

Effects of Gonadal Steroids

EST levels were similar among all groups except ORCH males treated with EST (ORCH-EST), whose levels were higher (Table). DHT levels were greater in males and ORCH males treated with DHT (ORCH-DHT) than other groups.

Dofetilide induced a smaller Δ APD₉₀ in OVX than control females and larger Δ APD₉₀ in ORCH than control males

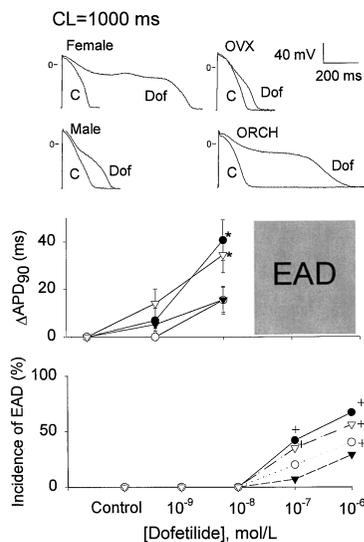


Figure 3. Effects of dofetilide on APD and EAD incidence at CL=1000 ms. Top, Representative AP; C indicates control; Dof, 10^{-6} mol/L dofetilide. Middle, Relationship of Δ APD₉₀ to increasing dofetilide concentrations. For control values see Figure 2. Bottom, Incidence of EADs induced by dofetilide. n=12, 10, 13, and 16 for female (●), male (○), OVX (▼), and ORCH (▽), respectively. * $P < 0.05$ vs OVX and control male; + $P < 0.05$ vs respective predrug control.

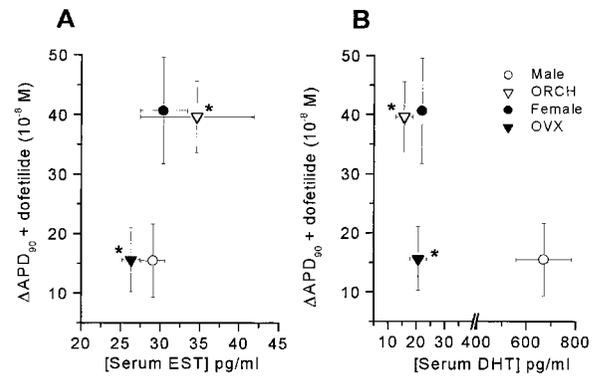


Figure 4. Relationship between serum EST and DHT levels and changes in APD₉₀ (vs baseline) induced by dofetilide (10^{-8} mol/L) at CL=1000 ms. A, Lack of relationship of EST levels to Δ APD₉₀. B, Relationship between DHT levels and Δ APD₉₀ in males. n and Δ APD₉₀ values are as in Figure 3. * $P < 0.05$ vs respective controls.

(Figure 4A). Because EST levels were similar in all groups, we infer that EST is not a necessary determinant of the effects of dofetilide on APD. In contrast, ORCH males had lower DHT levels and a greater Δ APD₉₀ induced by dofetilide than control males (Figure 4B), suggesting that DHT may protect males against dofetilide-induced APD prolongation. Therefore, we prepared additional ORCH male rabbits treated with EST (ORCH-EST) or DHT (ORCH-DHT) to assess hormonal impact on dofetilide responsiveness (hormone levels in the Table). DHT replacement in ORCH males diminished the effects of dofetilide on APD (Figure 5A). Whereas ORCH and ORCH-EST males had a significant EAD incidence in the presence of dofetilide (10^{-6} mol/L), normal males and ORCH-DHT males did not (Figure 5B).

Epicardial AP

APD₃₀ and APD₉₀ were similar in female and male epicardium at all CLs (Figure 6). Dofetilide prolonged epicardial APD equivalently in females and males (Figure 6). There were no EADs. Chromanol 293B had no effect on epicardial APD. At CL=1000 ms, predrug control APD₉₀ (female: 165 ± 4 ms, n=14; male: 171 ± 7 ms, n=12) did not differ from APD₉₀ in the presence of 10^{-5} mol/L chromanol 293B (female: 159 ± 6 ms, n=14; male: 161 ± 7 ms, n=12, $P > 0.05$). Because there were no sex-related differences in APD and effects of I_K blockade in epicardium, we did not

Serum Hormone Levels

	n	17 β -Estradiol, pg/mL	n	5 α -Dihydrotestosterone, pg/mL
Female	19	30 \pm 3	7	22 \pm 1
OVX	29	26 \pm 1	14	21 \pm 3
Male	11	29 \pm 2	9	671 \pm 112*
ORCH	4	35 \pm 7	4	16 \pm 3
ORCH-EST	5	560 \pm 57*	5	19 \pm 2
ORCH-DHT	3	22 \pm 1	3	633 \pm 252*

n indicates number of rabbits per group. Results are from larger groups of rabbits, of which those in the present study were a subset.

* $P < 0.05$ vs hormone levels of respective placebo groups.

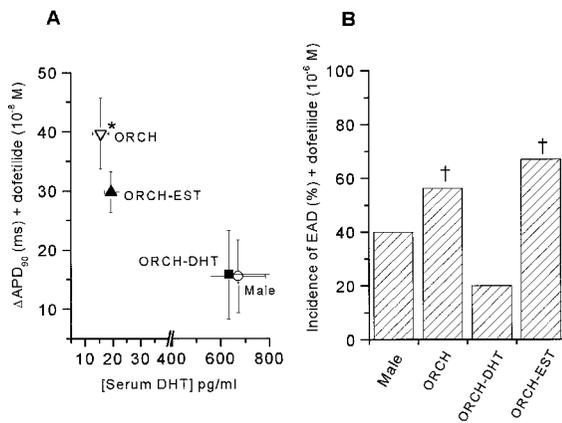


Figure 5. Effects of hormone replacement on ΔAPD_{90} (A) and EAD incidence (B) in dofetilide. $n=10, 16, 6,$ and 10 for male, ORCH, ORCH-DHT, and ORCH-EST, respectively. $*P<0.05$ vs control males; $\dagger P<0.05$ vs respective predrug control.

determine the influence of gonadectomy on epicardial APD and response to drugs.

Endocardium Versus Epicardium

There are sex-related differences in transmural dispersion of APD₃₀ but not APD₉₀ in control female compared with male rabbits (Figure 7, A and B). Transmural APD₉₀ dispersion became apparent in the presence of dofetilide, which also induced EADs in male and female endocardium but not epicardium.

Discussion

Sex and AP

APD₃₀ is longer in papillary muscles of female than male rabbits, and females manifest greater transmural dispersion of

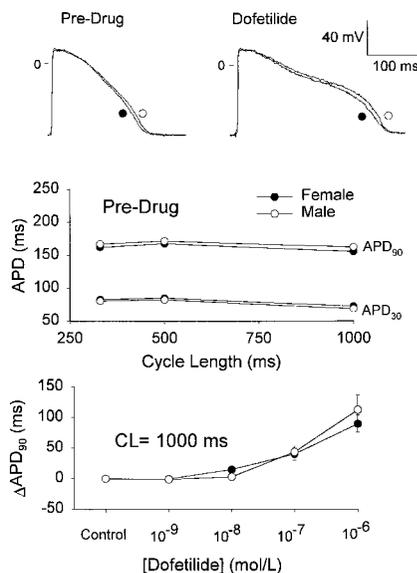


Figure 6. Normal female and male epicardial AP in control and in dofetilide. Top, Control and 10^{-6} mol/L dofetilide recordings from female and male preparations at CL=1000 ms. Middle, Dependence of APD₃₀ and APD₉₀ on CL in control Tyrode's solution. $n=42$ (females) and 41 (males). Bottom, Dofetilide-induced APD₉₀ prolongation at CL=1000 ms. $n=8$ (females) and 10 (males).

APD₃₀. These disparities may contribute to sex-related differences in the slopes of the ascending and descending limbs of the T wave.⁶ These findings imply not only sex-related differences in ionic currents responsible for early repolarization but also greater transmural dispersion of currents contributing to repolarization in females. In the only report of sex (as opposed to hormonal) differences, ion currents, and repolarization, I_{Kr} density was smaller in female than male rabbit ventricle.⁹ These results may explain the longer APD₃₀ in females but not the equal APD₉₀.

Although we found no significant difference in APD₉₀, females and OVX females had $\approx 3\%$ longer APD₉₀ than males and ORCH males. This small difference is consistent with the 2% to 6% differences in QTc reported between men and women.^{4,5} Furthermore, in some series, baseline QTc differences were not even demonstrable between men and women (for example, see Reference 1).

Sex Differences in Drug Response

Dofetilide induced greater APD₉₀ prolongation, EAD incidence, and dispersion of repolarization in females than males. These conditions put females at greater risk for TdP.^{15,16} Interestingly, we found no effect of chromanol 293B on APD in epicardium or endocardium, although we did demonstrate I_{Ks} and chromanol blockade in isolated myocytes. It is possible that in intact tissue, I_{Ks} does not contribute significantly to the normal rabbit ventricular AP, an interpretation consistent with findings in dogs.¹⁷

Transmural dispersion resulting from I_{Kr} blockade suggests epicardial-endocardial differences in I_{Kr} or other currents contributing to repolarization. Whereas I_K density is greater in subepicardial than subendocardial guinea pig myocytes,¹⁸ no transmural gradient in I_{Kr} density was seen in dogs, although I_{Ks} density was lower in midmyocardium than endocardium and epicardium.¹⁹ These data illustrate species-dependent differences in transmural I_K expression. Although there are no reports of epicardial-endocardial gradients of I_K in rabbits, I_{to} density is greater in epicardium than papillary muscle in rabbit²⁰ and other species.^{21,22} A larger epicardial I_{to} could sufficiently repolarize the epicardium in the presence of dofetilide as opposed to the endocardium. Moreover, we have demonstrated a transmural gradient for $I_{Ca,L}$ in female but not male hearts (unpublished data). Such a gradient could contribute to transmural dispersion of repolarization and differences in occurrence of EADs.

Effects of Gonadectomy and Hormone Replacement

Serum EST levels in control females and DHT levels in control males (Table) are consistent with reported values.^{23,24} That extragonadal or nonestrogenic factors may contribute to sex differences in repolarization is suggested by the persistence of sex-related differences in AP after gonadectomy. Consistent with other reports,^{7,8} however, our results demonstrate that gonadal steroids modulate proarrhythmic responses to I_{Kr} blockers.

Gonadectomy dramatically affected the response of papillary muscles to dofetilide (Figure 4). In males, orchietomy resulted in decreased DHT levels and increased dofetilide-

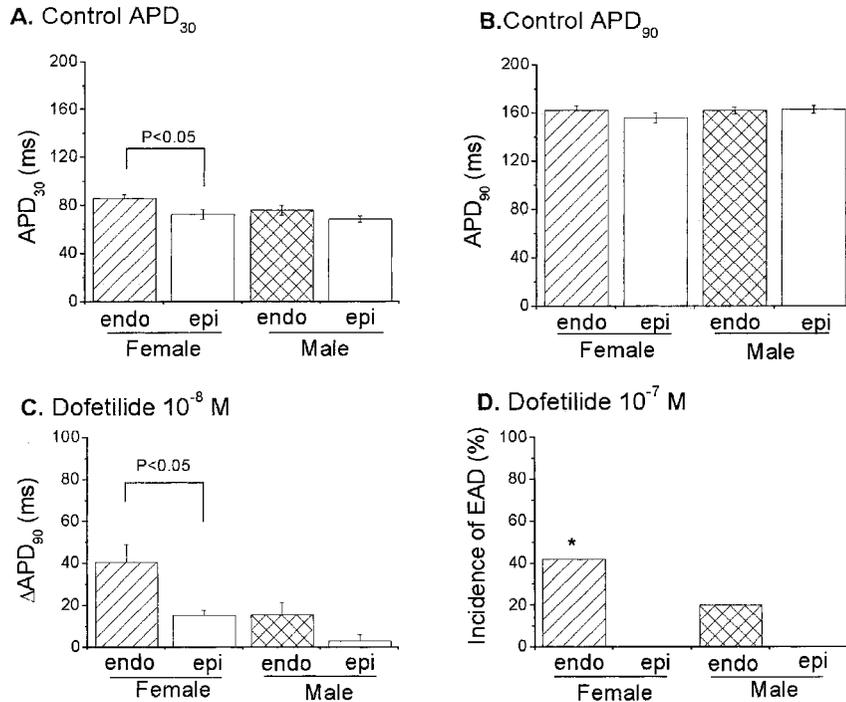


Figure 7. Sex-related differences in and effects of dofetilide on transmural dispersion of APD at CL=1000 ms. A, Endocardial-epicardial (endo-epi) differences in control APD₃₀ were significant in females but not males. B, No endocardial-epicardial differences were seen in control APD₉₀. C, Dofetilide-induced transmural dispersion of Δ APD₉₀ was greater in females than in males. D, Transmural differences in EAD incidence induced by 10⁻⁷ mol/L dofetilide. n as in Figures 3 and 6. *P<0.05 vs predrug control.

induced EADs. This is consistent with the hypothesis of the protective role of testosterone.^{7,8} Earlier studies,^{7,8} however, did not measure DHT levels and hence could not test whether DHT protects against the effects of I_{Kr} blockade.

In females, oophorectomy reduced the risk of dofetilide-induced APD prolongation and EAD. The consistently low serum EST levels argue against a unique estrogenic basis for the greater risk for females of proarrhythmic effects of I_{Kr} blockade. Given the effect of oophorectomy to blunt the actions of dofetilide, it is probable that nonestrogenic ovarian or pituitary-hypothalamic factors are important to proarrhythmia. These factors may be influenced by progesterone or gonadotropins (eg, luteinizing hormone, follicle-stimulating hormone) whose levels could be altered by gonadectomy.

Clinical Implications

Virilized women have shorter JT intervals than castrated men.²⁵ Moreover, males have longer JT intervals after orchectomy.²⁵ These results suggest that testosterone influences normal ventricular repolarization. In view of this, our demonstration of the action of testosterone may explain why in men the QTc interval shortens at puberty.²⁶ Similarly, testosterone might account for the tendency toward age-dependent reduction in the numbers of male long-QT syndrome patients manifesting QT intervals >440 ms.²⁷

The similar propensity for drug-induced TdP in premenopausal and postmenopausal women² and lack of significant effects of hormone replacement therapy on QTc intervals in postmenopausal women²⁸ argue that factors additional to those of estrogen contribute to sex-based differences in ventricular repolarization. The results of our study support this supposition.

The possibility that factors other than estrogen may contribute does not detract from the important role of estrogen in the proarrhythmic response to I_{Kr} blockers. For example, EST

replacement in OVX rabbits excessively prolongs repolarization and increases incidence of EAD induced by I_{Kr} blockade,⁸ and EST (and DHT) downregulate HK2 and I_{sk} mRNA expression.⁷ These results suggest that EST modulates ion channels, thus affecting the AP in a manner resembling the influence of sex. Moreover, this and earlier studies⁸ demonstrate the potential for deleterious effects of chronic EST treatment. Although these observations might suggest that women receiving hormone replacement therapy would be at increased risk for drug-induced TdP, there are insufficient data concerning this matter.

In closing, testosterone appears to protect against the proarrhythmic effects of I_{Kr} blockade in males. In females, the situation is more complicated, implicating estrogen and other factors. It is important to learn more about EST and DHT modulation of ion channel function and how this modulation influences the response to cardiac and noncardiac I_{Kr} -blocking drugs, many of which induce arrhythmias.²⁹ Given the wide spectrum of drugs that block I_{Kr} , the risk of administering such drugs to women must be carefully considered. Finally, the possible roles of progesterone and other hormones in sex-related differences in ventricular repolarization should receive greater attention.

Limitations

Female rabbits do not have menstrual cycles. Their serum estradiol levels remain constant and low (<100 pg/mL) and are unchanged by oophorectomy.²³ In women, normal estradiol levels range from 130 to 400 pg/mL.³⁰ Thus, the oophorectomized rabbit model fails to replicate the differences in estradiol levels between normal premenopausal and postmenopausal women. This could limit the interpretation and extrapolation of data referring to estradiol in females and restrict our ability to infer the possible role of physiological

estradiol concentrations in modulating ventricular repolarization in women.

We recorded action potentials from isolated RV endocardium and epicardium based on preliminary data from isolated rabbit hearts demonstrating no interventricular differences in epicardial MAPDs. These data are consistent with other data for rabbits.³¹ Nonetheless, regional disparities not taken into account might contribute clinically to male-female differences in repolarization.

Acknowledgments

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