Gender disparities in torsade de pointes ventricular tachycardia

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Background. **Gender disparities in the incidence of torsade de pointes (TdP) ventricular tachycardia exist, but the mechanisms in humans are unresolved. We addressed this issue using a mathematical model of a human ventricular cell.**
Methods. **We implemented gender differences in the Priebe-Beuckelmann model cell by modifying the amplitudes of the L-type Ca^{2+} current ($I_{Ca,L}$), transient outward K^+ current (I_{to}), and rapid component of the delayed rectifier K^+ current (I_{Kr}), according to experimental data from animal male and female hearts. Gender disparities in electrical heterogeneity between transmural layers (subepicardium, midmyocardium, subendocardium) were implemented by modifying various ion currents according to experimental data.**
Results. **Action potentials in female cells have longer durations and steeper duration versus frequency relationships than male cells. In the female cells, electrical heterogeneity between transmural layers is larger and the susceptibility to early afterdepolarisations is higher than in male cells.**
Conclusion. **Gender-related differences in $I_{Ca,L}$, I_{to}, and I_{Kr} may explain the gender disparities in human cardiac electrophysiology. Female cells have an increased susceptibility to early afterdepolarisations following mild reductions in net repolarising forces. Combined with their greater electrical heterogeneity, this renders them more vulnerable to TdP.**
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Gender differences in the incidence of cardiac arrhythmias exist (for a review, see James et al.)[1] Most notably, women are more likely to sustain torsade de pointes (TdP) ventricular tachycardia than men in inherited[2,3] and acquired (e.g., secondary to drug use) long-QT syndrome (LQTS).[4] Clinical observations suggest that the gender disparity in the incidence of TdP is largely due to male sex hormones. While boys and girls under the age of 15 years have similar incidences of TdP in inherited LQTS, from puberty through to adulthood, men have a lower incidence of TdP.[2]

Clinical[5] and experimental[6-8] studies have produced two theories regarding the electrophysiological basis of TdP. One theory holds that TdP arises from triggered activity in competing ventricular foci. Evidence for this hypothesis stems from experimental observations[6,7] and computer models[9] which demonstrate an enhanced susceptibility of cardiac myocytes to early afterdepolarisations (EADs) in response to factors that prolong action potential duration (APD). The other theory emphasises transmural dispersion of repolarisation, suggesting an involvement of reentrant excitation.[7,8]

To date, data in healthy subjects about sex-dependent differences in the occurrence of EADs or transmural dispersion, which may explain gender differences in TdP, are not available. We aimed to investigate whether gender disparities in the density of sarcolemmal ion currents may account for the gender difference in the incidence of TdP. Accordingly, we modified ion current conductances in the Priebe and Beuckelmann (PB) human ventricular cell model,[10] based on experimental data obtained from healthy male and female hearts of various species. We studied action potential characteristics, transmural electro-

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Table 1. Relative magnitude of sarcolemmal ion currents in models of male and female myocytes.

	Male			Female		
	Epi	Mid	Endo	Epi	Mid	Endo
I_{Na}	1	1	1	1	1	1
$I_{Ca,L}$	1	1	1	1.32	1.32	1
I_{to}	1	1	0.5	0.75	0.75	0.375
I_{Kr}	1	1	1	0.83	0.83	0.83
I_{Ks}	1.42	1	1.42	1.42	1	1.42
I_{K1}	1	1	1	1	1	1
$I_{Na,b}$	1	1	1	1	1	1
$I_{Ca,b}$	1	1	1	1	1	1
I_{NaK}	1	1	1	1	1	1
I_{NaCa}	1	1	0.69	1	1	0.69

Values for subepicardial (epi), midmyocardial (mid), and subendocardial (endo) myocytes are relative to the current magnitude in the original Priebe-Beuckelmann model of a human ventricular myocyte.[10]
I_{Na}=fast sodium current, $I_{Ca,L}$=L-type calcium current, I_{to}=transient outward current, I_{Kr}=rapid delayed rectifier potassium current, I_{Ks}=slow delayed rectifier potassium current, I_{K1}=inward rectifier potassium current, $I_{Na,b}$=background sodium current, $I_{Ca,b}$=background calcium current, I_{NaK}=sodium-potassium pump current, I_{NaCa}=sodium-calcium exchange current.

physiological heterogeneity, and susceptibility to EAD development.

Methods

Priebe-Beuckelmann model

The PB mathematical model of a human ventricular cell[10] is based on the Luo and Rudy guinea pig ventricular cell model[11] with modified time constants of Ca^{2+} release and new equations for L-type Ca^{2+} current ($I_{Ca,L}$), inward rectifier K^+ current (I_{K1}), rapid (I_{Kr}) and slow (I_{Ks}) components of the delayed rectifier K^+ current, and transient outward K^+ current (I_{to}). These new equations in the PB model were based on experimental data obtained from single ventricular cells isolated from explanted human hearts. As these cells were generally isolated from midmyocardial areas of the left ventricle of male patients (see Priebe & Beuckelmann,[10] and the primary references cited therein), the PB model is one of a typical male midmyocardial ventricular cell.

To study gender disparities in action potential properties, transmural electrophysiological heterogeneity, and susceptibility to EAD development, we incorporated the disparities in ion current densities between genders and myocardial layers, as reported in experimental studies, into the PB model. These changes are discussed below and summarised in table 1. All values are expressed as conductance relative to the conductance of the PB model. All figures show action potential properties determined in steady-state conditions, two minutes after the onset of stimulation (stimulus pulse: 2 ms, 3 nA).

Gender disparities in ion current densities

We reviewed all studies into gender disparities in ion current densities, conducted in single ventricular myocytes. These cells were obtained from dog, rabbit, guinea pig, and mouse hearts, but not from human hearts. $I_{Ca,L}$ in female subepicardium and midmyocardium is 1.32 times that of males.[12] I_{to} in females is 0.75 times that of males in all cell layers,[13,14] although this is not a consistent finding.[15,16] I_{Kr} in females is 0.83 times that of males.[17] These gender disparities were incorporated into the PB model.

Although the ultrarapid component of the delayed rectifier K^+ current (I_{Kur}) and the ATP-regulated K^+ current ($I_{K,ATP}$) also exhibit gender disparities (57% larger[15] and 60% smaller[18] in males than in females, respectively), these disparities were not incorporated into the PB model, because I_{Kur} is not present in human ventricular cells,[19] while $I_{K,ATP}$ is not functional under normal conditions. Similarly, the Na^+ current (I_{Na}),[15] I_{Ks},[20] and I_{K1}[15-17] were left unchanged, because they are similar in male and female hearts, as are the intracellular concentrations of Na^+ and Ca^{2+} at baseline.[18,21]

Transmural heterogeneities in ion current densities

To study gender disparity in transmural heterogeneity, we incorporated the differences in ion current densities between subepicardium, midmyocardium, and subendocardium according to quantitative measurements in isolated ventricular myocytes. Data from dog hearts were used, because those from human hearts are limited. $I_{Ca,L}$ in subepicardium and midmyocardium is 1.32 times that in subendocardium in females, but not in males.[12] In both genders, I_{to} in subepicardium and midmyocardium is twice that in subendocardium,[20,22] while I_{Ks} in subepicardium and subendocardium is 1.42 times that in midmyocardium.[20] The Na^+-Ca^{2+} exchange current (I_{NaCa}) in subendocardium is 0.69 times that in the other layers.[23] Although a late component of I_{Na} ($I_{Na,late}$) is 27% smaller in subepicardium and

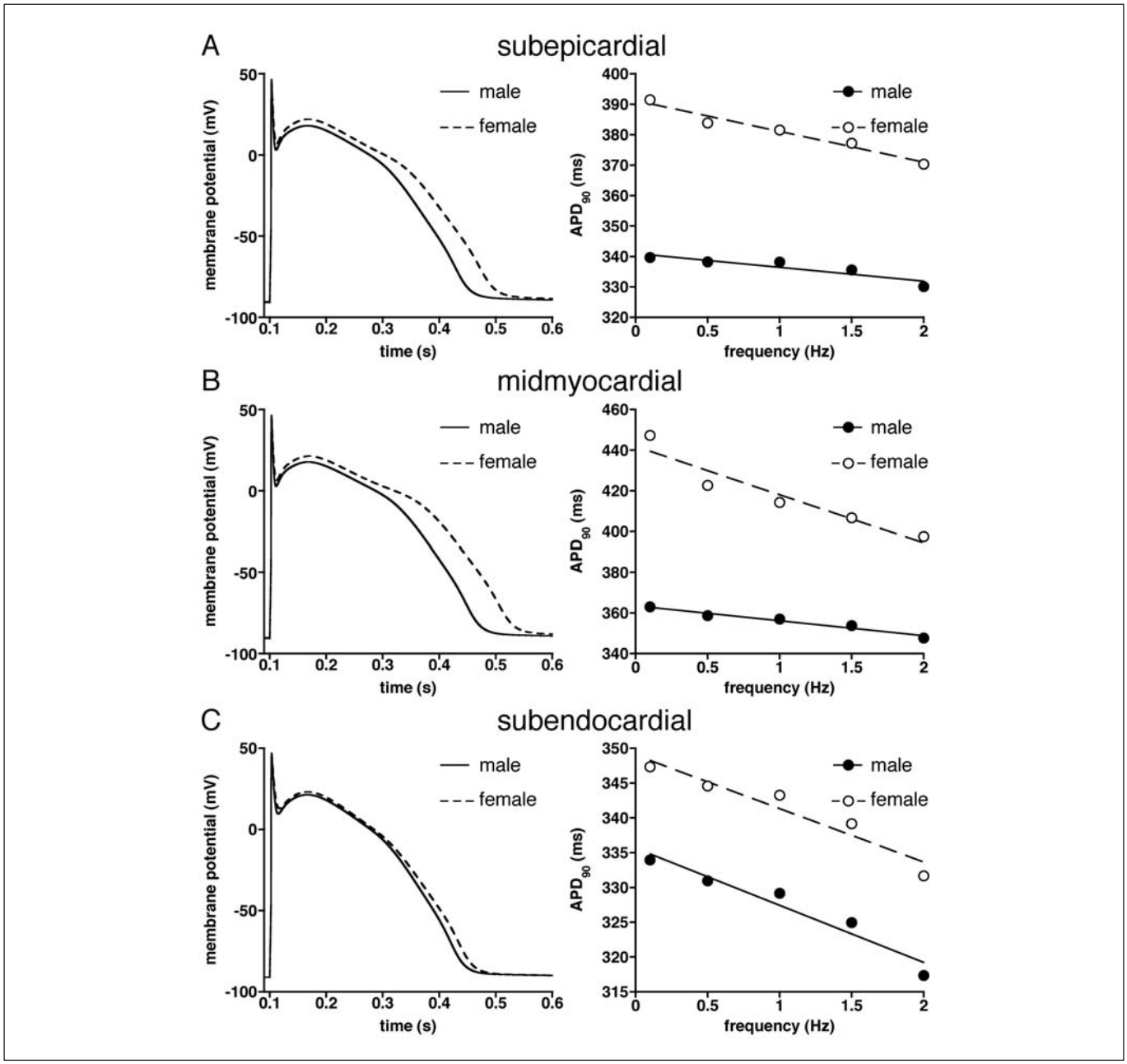

Figure 1. Superimposed action potentials elicited at 1 Hz (left) and action potential duration at 90% repolarisation (APD_{90}) vs. stimulus frequency (right) of (A) subepicardial, (B) midmyocardial, and (C) subendocardial model cells of male and female.

subendocardium than in midmyocardium,[24] this transmural heterogeneity was not incorporated, because $I_{Na,late}$ is not present in the original PB model. Similarly, no transmural heterogeneities in I_{Na}, I_{Kr}, and I_{K1} were reported.[20,22,24]

Results

We used our 'male' and 'female' models of subepicardial, midmyocardial, and subendocardial cells to assess gender disparities in APD restitution, transmural dispersion in APD, and susceptibility to EADs.

Effects of gender on action potential duration

Simulations at different stimulation frequencies (0.1 to 2 Hz) revealed significant APD differences between both genders. Figure 1, left panels, shows superimposed action potentials at 1 Hz in the female and male model of subepicardial (figure 1A), midmyocardial (figure 1B), and subendocardial (figure 1C) cells. In all cell types, the action potentials were significantly longer in females than males. Figure 1, right panels, summarises the APD at 90% repolarisation (APD_{90}) of males and females at various stimulation frequencies.

At all frequencies, APD_{90} of subepicardial (figure 1A), midmyocardial (figure 1B), and subendocardial (figure 1C) model cells were longer in females than males. Moreover, APD_{90} was longest at low stimulus frequencies and decreased at higher frequencies in all cell types. This APD-frequency relationship was steeper in females than in males. Linear fits[25] of the APD-frequency relationships (restitution curves, fitting correlation coefficients >0.92) indicated that APD-frequency relationships were steeper in females, except in subendocardium (figures 1A-C).

Effects of gender on transmural electrical heterogeneity

There were significant differences in APD_{90} between subepicardial, midmyocardial, and subendocardial cells in both genders at all stimulation frequencies (0.1 to 2 Hz). This is illustrated in figure 2, which shows superimposed action potentials at 0.5 Hz in male (A) and female (B) subepicardial, midmyocardial, and subendocardial model cells. In both genders, action potential was shortest in subepicardial cells and longest in midmyocardial cells, but with a considerably larger difference between shortest and longest action potential in the female. This APD_{90} heterogeneity (ΔAPD_{90}) was larger in females than in males at all frequencies, as summarised in figures 2C and 2D. Of note, ΔAPD_{90} in females was particularly large at slow stimulation frequencies.

Effects of gender on early afterdepolarisations

EADs typically occur at slow heart rates (for a review, see Tan et al.[26]). In isolated ventricular myocytes, EADs may result from moderately enhanced $I_{Ca,L}$ or reduced I_{Kr}.[27,28] Simulations with 25% increased $I_{Ca,L}$ or 50% decreased I_{Kr} densities revealed significant gender differences in the incidence of EADs. Figure 3 shows superimposed action potentials at 0.1 Hz in the female and male midmyocardial model cells resulting from increased $I_{Ca,L}$ (A, top panel) or reduced I_{Kr} (B, top panel). In both genders, the applied changes in $I_{Ca,L}$ and I_{Kr} conductances resulted in action potential prolongation. The excessive prolongation that was observed in females (top panels, arrows), but not in males, appeared to be due to reactivation of $I_{Ca,L}$ (bottom panels, arrows), consistent with previous findings.[29]

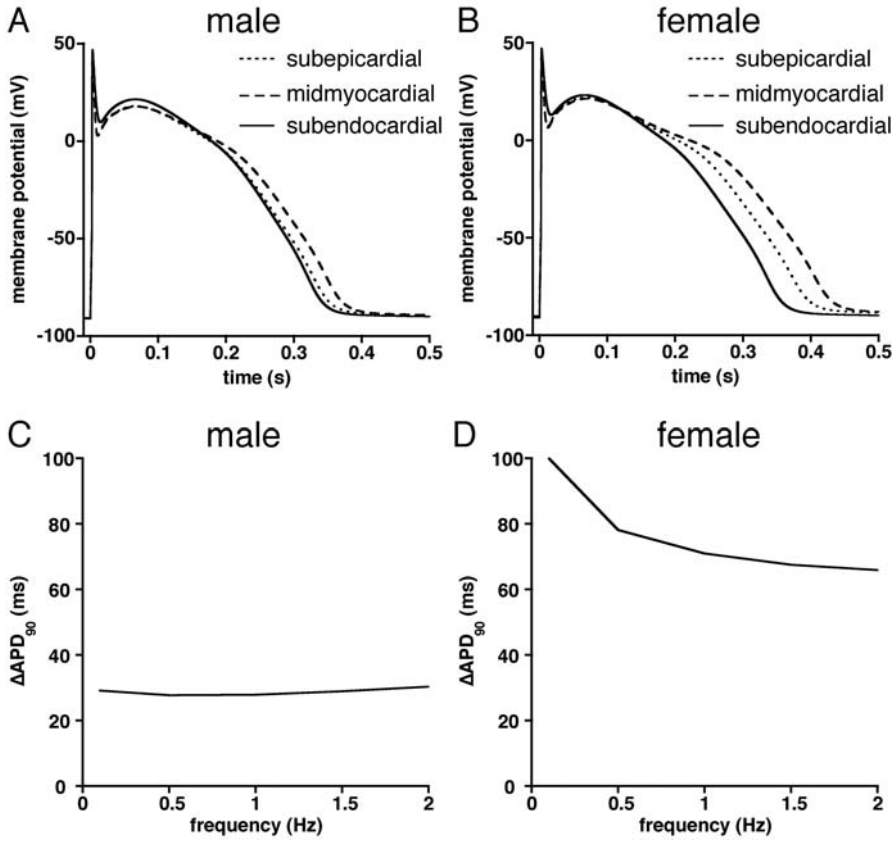

Figure 2. (A,B) Superimposed action potentials (0.5 Hz) of subepicardial, midmyocardial, and subendocardial model cells of male (A) and female (B). (C,D) Differences between longest (midmyocardial) and shortest (subendocardial) action potentials (ΔAPD_{90}) at various stimulus frequencies in male (C) and female (D) model cells.

This prolongation prolongs the plateau phase of the action potential and thus increases the susceptibility to EADs.

Discussion

We studied whether gender disparities in the densities of sarcolemmal ion currents may explain the gender disparity in the incidence of TdP in humans. We incorporated gender differences in a human ventricular model cell by modifying $I_{Ca,L}$, I_{to}, and I_{Kr} conductances, according to experimental data obtained from animal studies. We demonstrated that human cardiac electrophysiology exhibits clear gender disparities in action potential repolarisation, transmural dispersion, and susceptibility to EADs.

Gender effects on action potential characteristics

We found that female model cells had longer action potentials than their male counterparts (figure 1). This agrees with experimental findings of gender disparity in APD in left ventricular midmyocardial myocytes isolated from explanted hearts of patients with end-stage heart failure who underwent cardiac transplantation.[30] In addition, our results are in agreement with experimental findings in animal studies. In mouse subepicardial myocytes[13,15] and rabbit subendocardial myocytes,[31] action potentials were significantly longer in females than in males. Our results are also in agreement with the clinical observations in healthy subjects that women have longer QTc intervals.[32]

The female model cells had steeper APD-frequency relationships than their male counterparts (figure 1). Although not studied in detail, experimental findings in animals provide supportive results. In rabbits, APD at 20, 50 and 90% repolarisation (APD_{20}, APD_{50}, and APD_{90}, respectively) are similar in male and female at a cycle length of 300 ms, but different at longer cycle lengths.[31] Our results are in keeping with previously reported ECG observations that women have a steeper QT-heart rate relationship than men.[25]

Gender effects on transmural heterogeneity and incidence of EADs

We found that the female model cells exhibit greater differences in APD_{90} between subendocardium, midmyocardium, and subepicardium, i.e., greater trans-

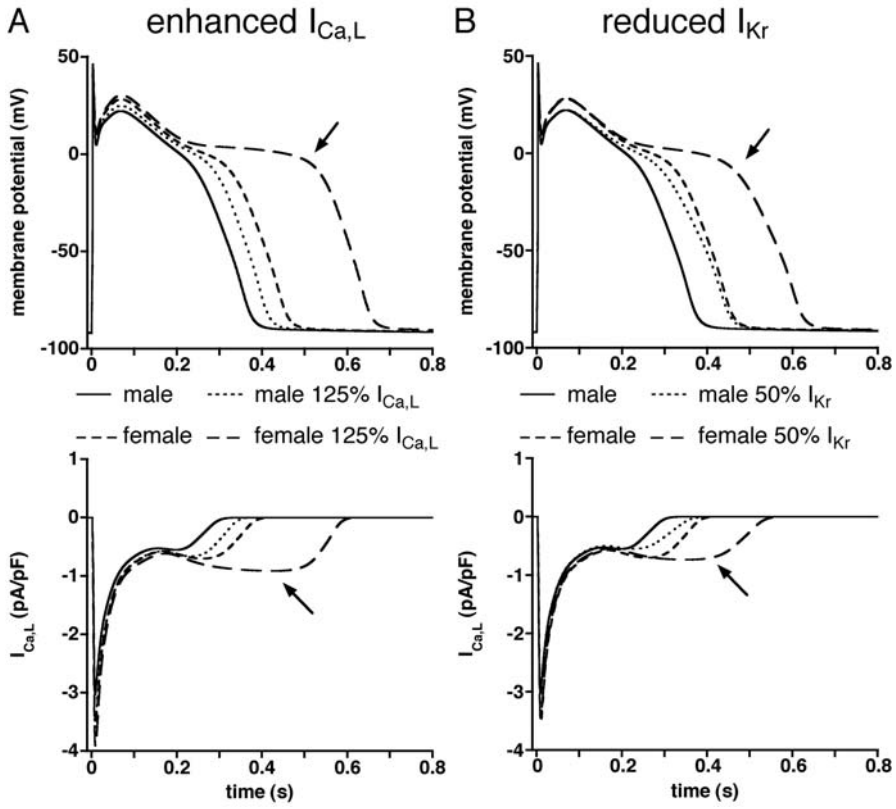

Figure 3. (A) Action potentials (top) and L-type calcium current ($I_{Ca,L}$, bottom) of midmyocardial cells at 0.1 Hz under control conditions and enhanced $I_{Ca,L}$ (125% of control). (B) Action potentials (top) and $I_{Ca,L}$ (bottom) of midmyocardial cells at 0.1 Hz under control conditions and reduced rapid delayed rectifier potassium current (I_{Kr}, 50% of control). Arrows indicate excessive action potential prolongation (top) due to reactivation of $I_{Ca,L}$ (bottom).

mural dispersion, particularly at slow heart rates (figure 2). This agrees with findings in left ventricular myocytes of dog which also demonstrated a greater transmural APD heterogeneity in females.[33] These observed gender disparities may contribute to the clinically observed sex-related differences in the slopes of the ascending and descending limbs of the T wave,[34,35] suggesting larger transmural heterogeneity in the final repolarisation phase. We also found that increasing $I_{Ca,L}$ or reducing I_{Kr} prolonged action potentials in both genders (figure 3), but significantly more so in females than in males. Furthermore, these interventions resulted in excessive action potential prolongation, thus favouring EAD formation, in the female, but not the male, model cell. These findings are in agreement with experimental findings in rabbits.[28]

Two theories regarding the electrophysiological basis of TdP exist, i.e., triggered activity in competing ventricular foci and dispersion of transmural repolarisation. Either way, female cells have an increased susceptibility to EADs following mild reductions in net repolarising forces. Combined with their greater electrical heterogeneity, particularly at slow heart rates, this renders them more vulnerable to TdP.

Limitations

While the clear differences in action potential properties between models of subepicardial, midmyocardial, and subendocardial cells, as reported here, may explain clinical observations, it is conceivable that normal cell-to-cell coupling in the intact heart would attenuate these inherent differences.[36,37] This has been demonstrated in various studies (see Akar et al. and the primary references cited therein).[8] Nevertheless, it has been found that the specific electrophysiological properties of M cells, in conjunction with their topographical distribution (midmyocardium), may create spatial gradients of repolarisation of sufficient magnitude to cause unidirectional block and reentrant excitation underlying TdP in LQTS type 2.[8]

Conclusion

We provide insights into the cellular and ionic basis for the sex-related distinction in the incidence of TdP. Gender disparities in I_{to}, I_{Kr}, and I_{Ks} conductance result in an increased susceptibility to EADs in females. Combined with a larger electrical transmural heterogeneity in female, this renders females more vulnerable to TdP.

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