Sex differences in the mechanisms underlying long QT syndrome

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Salama G, Bett GC. Sex differences in the mechanisms underlying long QT syndrome. Am J Physiol Heart Circ Physiol 307: H640–H648, 2014. First published June 27, 2014; doi:10.1152/ajpheart.00864.2013.—Sexual dimorphism is a well-established phenomenon, but its degree varies tremendously among species. Since the early days of Einthoven’s development of the three-lead galvanometer ECG, we have known there are marked differences in QT intervals of men and women. It required over a century to appreciate the profound implications of sex-based electrophysiological differences in QT interval on the panoply of sex differences with respect to arrhythmia risk, drug sensitivity, and treatment modalities. Little is known about the fundamental mechanism responsible for sex differences in electrical substrate of the human heart, in large part due to the lack of tissue availability. Animal models are an important research tool, but species differences in the sexual dimorphism of the QT interval, the ionic currents underlying the cardiac repolarization, and effects of sex steroids make it difficult to interpolate animal to human sex differences. In addition, in some species, different strains of the same animal model yield conflicting data. Each model has its strengths, such as ease of genetic manipulation in mice or size in dogs. However, many animals do not reproduce the sexual dimorphism of QT seen in humans. To match sex linked prolongation of QT interval and arrhythmogenic phenotype, the current data suggest that the rabbit may be best suited to provide insight into sex differences in humans. In the future, emerging technologies such as induced pluripotent stem cell derived cardiac myocyte systems may offer the opportunity to study sex differences in a controlled hormonal situation in the context of a sex specific human model system.

action potential; arrhythmia; estradiol; hormones; ion channels

OUTSTANDING progress has been made in understanding structure-function relationships of cardiac ion channels and how changes in ion channel expression and gating alter the electrical substrate. In addition, ion channel properties are significantly modified by subunit assembly and environmental conditions (pH, ionic concentrations, and hormones), which in turn have substantial effects on electrical activity. Profound changes in the ECG have helped in the discovery of mutations in ion channels and diseases caused by subunit mutations are known as “channelopathies.” Despite this revolution in our understanding of ion channel biophysics, there is a significant gap in translating the behavior of ion channels at the level of the single myocyte to alterations in the ECG because of heterogeneities in ion channel expression among ventricular cells and among the various cell types that comprise the heart. This is particularly true when considering sex differences in the
human ECG because of incomplete and controversial information on sex differences in the expression and properties of ion channels and their regulation by sex hormones.

This review examines some of the recent advances in the study of sex differences in cardiac electrophysiology, specifically focusing on new hypotheses derived from novel data. A detailed appreciation of the molecular basis for the profoundly different electrical and arrhythmogenic substrate between men and women will require an integrated systems approach that incorporates several diverse factors, including developmental differences, hormonal effects on ion channels (steroid and nonsteroidal hormones), and an understanding of differences in coupling between membrane potential ($V_m$) and intracellular $\text{Ca}^{2+}$ ($\text{Ca}_i$), $V_m \rightarrow \text{Ca}_i$, and the reverse coupling $\text{Ca}_i \rightarrow V_m$.

The ECG. The major source for information on sex differences in electrical activity of the human heart is somewhat indirect, as it largely comes from the ECG. In the absence of cardiac disease, there are several significant differences in the ECG from adult men and women. The ECG is commonly used as a simple and convenient noninvasive diagnostic tool, and the exercise ECG is the recommended and most frequently performed diagnostic evaluation of coronary artery disease. However, this test has significantly lower diagnostic accuracy in predicting heart disease in women than in men (75). Knowledge of the underlying molecular basis for sex differences in the ECG and of differences in the physiology and pathophysiology of cardiac electrical activity will profoundly improve diagnosis and treatment, particularly for women.

The major quantitative components of the ECG are the RR interval (a measure of the time between successive ventricular depolarizations and thus heart rate), the QT interval (typically measured from the initial Q-wave deflection to the end of the T wave), and the width and shape of the T wave. The QT interval is in part a function of heart rate (or RR interval), and several formulae have been used to calculate a corrected QT interval (QTc) that is a QT interval independent of heart rate. Several sex differences are well recognized in the human ECG. Most notably, women have longer QTc than men (5, 26, 54), which increases the likelihood of polymorphic ventricular tachycardia, known as Torsade de Pointes (TdP). TdP is an arrhythmia that occurs in the absence of structural deformities and can lead to ventricular fibrillation (VF) and sudden cardiac death. In addition to QTc differences, the timing, dispersion, and morphology of the T wave is sex dependent (8, 54, 62, 77, 92). Women have shorter resting RR intervals, reflecting a higher resting heart rate. The higher heart rate likely reflects an intrinsic difference, as women have higher vagal tone and lower heart rate variability than men (6, 18). The QT-to-RR ratio is steeper in women than in men (37, 78), with the result that at slower heart rates, sex differences are more pronounced and the QRS complex shorter in women than men (80).

The underlying molecular mechanisms for these fundamental sex differences in the electrical profile of the healthy human are largely unknown. Sex differences in ECGs cannot be explained by sex differences in body weight, left ventricular mass, or height (61). Sex differences in QTc interval are not present at birth (78), but postpubertal women have longer baseline QTc than men (26, 54). This change may be due to shortening of the male QT interval (66, 79). The transition of electrical properties postpuberty (at ~14 yr) may be due to the surge of sex steroids. Although women have the potentially proarrhythmic longer QTc than men, women are actually less likely than men to suffer sudden cardiac death in their reproductive years (35). Furthermore, the QTc interval in women is prolonged during pregnancy, presumably as a protective event (40). Thus, for sex differences in arrhythmia susceptibility, QT prolongation alone is not a satisfactory indicator.

There are few, yet conflicting, reports on the effect of the menstrual cycle on QTc. Some studies have reported changes in QTc with menstrual cycle (23, 58), and others have reported no changes (11, 31). A few studies linked the phase of the menstrual cycle to arrhythmia vulnerability (57, 70) and to the ability of drugs to prolong QTc (69). These findings are consistent with several studies that show no linear correlation between numerical change in QTc and the risk of total mortal-
ity or sudden cardiac death (26, 29, 68). In other words, the absolute QTc interval is not an accurate predictor of arrhythmia risk. This should not be surprising because the QTc interval is not particularly sensitive to changes in the profile of ionic currents that can cause profound changes in Ca\textsubscript{i} handling and in the arrhythmogenic substrate.

**Sex differences in electrical diseases: the long QT syndromes.** Although QTc prolongation in premenopausal women is not associated with a higher incidence of sudden cardiac death than in men, it does predispose women to greater problems with diseases associated with further QT prolongation. Sex-based differences in cardiac electrical activity, long noted but little understood, have gained new notoriety and interest with the identification of channelopathies that cause long QT syndromes (LQTS). LQTS is a family of disparate conditions that can be congenital or drug induced, which result in QT prolongation and increases the risk to TdP, VF, and sudden death (68, 74, 86, 87) and where postpubertal women are at higher risk for both congenital and acquired forms of LQT and TdP than men (16, 46, 51, 89, 95). The diagnosis of LQTS is sex specific and defined as QTc > 440 ms for adult males and > 460 ms for adult females (12).

LQTS is considered to be an electrical disease, as it occurs in structurally normal hearts and arises from a diverse range of mutations or drugs that alter ionic current during the AP with a common outcome of AP and QTc prolongation. Genetic LQTS is the result of mutations in the main or ancillary subunits of cardiac ion channels causing an increase or decrease of their associated currents, referred to as a “loss” or “gain” of function mutations. Although mutations in 13 genes have been associated with LQTS, mutations in three ion channels account for most of the LQTS (56). Women are at higher risk than men of TdP with LQT type 1 and type 2 (LQT1 and LQT2) (46), but both sexes are equally vulnerable to LQT3 (95). Sex differences in human electrophysiological data are summarized in Table 1.

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Protein Product</th>
<th>Affected Current</th>
<th>LQT Penetration, %</th>
<th>Overall Frequency, %</th>
<th>Sex Differences in Human EP Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>LQT1</td>
<td>KCNQ1</td>
<td>I\textsubscript{Ks}</td>
<td>25–100 (59)</td>
<td>30–50 (59)</td>
<td>Males younger at first cardiac event (17, 46, 73)</td>
</tr>
<tr>
<td>Jervell and Lange-Nielsen Syndrome; Romano Ward Syndrome</td>
<td>KvLQT1</td>
<td>I\textsubscript{Ks}</td>
<td></td>
<td></td>
<td>Prepubertal males at higher risk of cardiac event (95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Romano Ward Syndrome</td>
</tr>
<tr>
<td></td>
<td>Kv</td>
<td>I\textsubscript{Ks}</td>
<td>50–70 (59)</td>
<td>25–40 (59)</td>
<td>Females more likely to have cardiac events than males (46, 55, 95)</td>
</tr>
<tr>
<td>LQT2</td>
<td>HERG</td>
<td>I\textsubscript{Ks}</td>
<td></td>
<td></td>
<td>Females have longer baseline QT, than males (55)</td>
</tr>
<tr>
<td>Romano Ward Syndrome</td>
<td>KCNH2</td>
<td>I\textsubscript{Ks}</td>
<td></td>
<td></td>
<td>Females more likely than males to have events postpuberty (55, 95)</td>
</tr>
</tbody>
</table>

See main text for definitions of abbreviations.

**Table 1. Sex differences in electrophysiological characteristics of long QT syndromes**

**Review**

*SEX DIFFERENCES IN MECHANISMS UNDERLYING LONG QT SYNDROME*

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LQT1 is the result of mutations in KCNQ1 ion channel. In the heart, KCNQ1 combines with KCNE1 to produce \( I_{Ks} \), the slow delayed rectifier current. \( I_{Ks} \) activates relatively slowly and accelerates AP repolarization during adrenergic stimulation. Mutations in this channel reduce the net K\(^+\) efflux that prolongs the AP during exercise compared with normal individuals. The incidence of LQT1 events is highest in prepubertal males (17), despite the fact that there is no difference between the QT interval between boys and girls with LQT1 at \( \sim <14 \) yr old. Following puberty, the male QT interval is reduced and the female QTc is significantly longer than the adult male. Adult women are more at risk to TdP (46) or at the same risk (17) as adult males. The penetrance of LQT1 in genetically affected individuals is only 55\% (59). Recently, exciting evidence points to the importance sex differences in the effects of basic biophysical structure-function properties of the LQT1 mutations. LQT1 mutations are distributed throughout the LQT1 gene, and the distribution of the mutations in the different locations was reported to be similar for both men and women (17). For men, the location of the mutation did not matter, but women with mutations in the cytoplasmic loop region were much more likely to have an aborted cardiac event or sudden cardiac death than for women with mutations outside this region (17). These cytoplasmic regions are the site of interaction of \( \alpha \)-channel subunit with regulatory \( \beta \)-subunits. Ancillary subunits change the level of expression but can also profoundly affect kinetics and drug sensitivity (7). Thus these new data strongly suggest that sex-dependent ancillary subunit modification of ion channel function may play a significant role in the sex differences of arrhythmogenic substrate and pharmacological sensitivity.

LQT2 is caused by mutations in the human ether-à-go-go-related gene (hERG) KCNH2 channel, which encodes for the rapid component of the delayed rectifier current (\( I_{Kr} \)). Similar to \( I_{Ks} \), this delayed rectifier current turns on with a 100–200 ms delay after the AP upstroke to drive the rapid AP downstroke. Reduction in \( I_{Kr} \) density through reduced surface expression or alteration in gating of hERG can delay repolarization. Penetrance of LQT in genetically affected individuals is 70\% (59). Women with LQT2 are more likely than men to suffer a life-threatening cardiac event (55, 95). Men with LQT2 arising from a pore loop mutation were more likely to suffer an event than men with no pore loop mutations. In contrast, women had no dependence on the location of the mutation (55). This disparity in mutation location again points to sex differences being important at the level of ion channel structure-function.

LQT3 arises from mutations in the Na\(^+\) channel, which is responsible for the rapid initiation of excitation in the ventricle and underlies the QRS complex in the ECG. There are no reported sex differences in the cardiac events of LQT3, either pre- or postpubertally (95). Penetrance of LQT3 in genetically affected individuals is 79\% (59).

There is substantial overlap of QTc among genetically affected individuals compared with family members without the mutation (59), see Fig. 2. The penetrance of LQT1–3 genes ranges from 55–70\% (59), which points to the importance of studying the mutated channel in human myocytes and in considering other factors beyond the primary defect, such as sex differences, hormonal status, etc.

Although congenital LQTS remains a rare disease, drug-induced LQTS remains a major public health problem resulting from drugs that interact with cardiac ion channels. Healthy individuals can develop acquired or drug-induced LQTSs in response to a wide variety of drugs where women are at much greater risk than men of suffering drug-induced LQTSs and developing the potentially fatal TdP (22, 41, 45, 50, 88). Drug-induced TdP can arise from diverse drugs (67, 68) (e.g., antiarrhythmics, antidepressants, antihistamines, antipsychotics, antiemetics). Currently, this susceptibility is attributed to drug interactions with the hERG channel, in combination with the longer female AP, reduced repolarization reserve compared with that in males and the effects of sex steroids (primarily estrogen and testosterone). Although these broad concepts may be correct, Na\(^+\) channel mutation prolongs the AP, but LQT3-related TdP is relatively insensitive to sex differences, suggesting that factors other than repolarization reserve may contribute to overall sex differences in TdP risk in LQT1 and 2. Postpubertal women are at higher risk for both congenital and acquired forms of TdP than men (16, 46, 51, 89, 95).

Sex differences in ventricular AP. The ECG is the vectorial sum of current flow across the membranes of single cells (~10\(^9\) cells) that comprise the human heart. The question is what combination of cellular ionic channel changes underlies sex differences in the ECG. Direct extrapolation from the ECG to the individual cellular currents is not possible. Clearly, the information that can be gathered from ECG signals is limited, but there is a tight correlation between the QT interval and ventricular AP durations (APDs). Hence, the longer QTc duration in women should be correlated with longer APDs in females compared with males. The channel proteins and the ionic currents of the human ventricular AP can be generally classified as depolarizing and repolarizing currents where an increase in depolarizing current and a decrease in repolarizing current result in APD prolongation. The main depolarizing currents are the rapidly activating and inactivating voltage-gated Na\(^+\) current (\( I_{Na} \) that produces the AP upstroke and the voltage-gated L-type Ca\(^{2+}\) current (\( I_{Ca,L} \)), which provides the Ca\(^{2+}\) influx that triggers further Ca\(^{2+}\) release from the sarcoplasmic reticulum to initiate contractions and helps maintain the AP plateau phase (Fig. 1B). The entry of Ca\(^{2+}\) during each
beat is balanced by Ca\(^{2+}\) efflux via the electrogenic Na\(^{+}/Ca\(^{2+}\) exchanger (NCX), which is a depolarizing current, \(I_\text{NCX}\) in the forward mode where the influx of three Na\(^{+}\) ions drives the efflux of one Ca\(^{2+}\). The main repolarizing currents are the rapid and slow components of delayed rectifying K\(^{+}\) outward currents \(I_\text{K}_\text{a1}\) and \(I_\text{K}_\text{c}\), which turn on the AP downstroke. \(I_\text{K}_\text{c}\) is a major determinant of APD and QT-interval. The voltage-dependent transient outward K\(^{+}\) current \(I_\text{to}\) is a rapidly activating and inactivating current that is primarily expressed in the epicardium. Paradoxically, \(I_\text{to}\) prolongs rather than shortens APD because it contributes to a very early repolarization, immediately after the AP upstroke that delays the AP time course. Human ventricular APs, like most nonrodent APs, have a high plateau phase, which is the result of battling depolarizing \(I_\text{Ca,L}\) and repolarizing \(I_\text{K}_\text{a1}\) mediated a K\(^{+}\) channel responsible for the resting \(V_\text{m}\) currents.

One study addressed sex differences in human APs through measurements on midmyocardial left ventricular myocytes from explanted hearts in end-stage heart failure (85). Despite concerns regarding the health of these hearts, APs from female myocytes were significantly longer than in males, consistent with longer QT intervals in women. There was also a trend toward larger \(I_\text{Ca.L}\) and smaller \(I_\text{to}\) in female compared with male myocytes, which did not reach statistical significance because of cell-to-cell variability.

The lack of voltage clamp data, the gold standard for determining functional ion channels, from freshly isolated human myocytes means that inferences have to be made from relative expression of mRNA and protein. These studies have so far proved inconclusive, with some demonstrating sex differences in channel expression, and others not, depending on the region of the heart studied (2, 25).

The paucity of human data and the fact that most studies on human tissue are not sufficiently powered to detect sex-dependent differences mean that alternative analysis is required. Computer modeling, based on the combination of disparate data sets, has helped to test potential hypotheses (15, 27, 93). The lack of primary data from healthy, age-matched human tissue has the result that most of what is commonly accepted about our understanding of sex-dependent mechanisms in the heart is inferred from animal studies. The degree of correlation between electrophysiological behavior in the animal and human heart is dependent on the ion channel under investigation, as well as species.

Animal models for sex differences in the heart. The majority of our understanding of the molecular basis of sex differences in the cellular cardiac AP comes from animal studies. A wide range of animal models have been used to this furnish information, as freshly isolated human cardiac myocytes from healthy men and women are rarely available for electrophysiological analysis. This electrophysiological work on the cellular basis of sex differences has been performed on isolated ventricular myocytes from various animal models, and it is not always clear how good a correlation there is between these species and the human heart. At many levels, including the heart, there are marked species and strain differences in the nature and the degree of sexual dimorphism. Consequently, animal experiments have produced conflicting results, leading to a need to carefully consider the merits of animal models of human sex differences.

Mouse models of human diseases have received a lot of traction, because mice can be molecularly engineered to study the effects of specific human genetic abnormalities. However, marked differences between human and murine electrophysiology (72) make it difficult to gain new insights regarding the molecular basis of human sex differences. For instance, mouse ventricular AP are >10 times shorter than humans, lack a plateau phase, and express a different combination of ion channels (72). In addition, mice have considerably faster heart rates (>600 beats/min) and an ECG that is substantially different from the human ECG. Human data indicate that sex differences are particularly noticeable at lower heart rates, so perhaps unsurprisingly, data on sex differences in mice are difficult to interpret. Some report no sex differences in mouse ECGs (10, 49), others report changes (9), and another report detected sex differences in arrhythmia risk but only in the presence of drugs or anesthesia (20) or in distinct phases of the estrus cycle (71).

Reports on sex differences in ionic channels in mice are inconsistent and summarized in Table 2. The basis for these inconsistencies is unclear, but strain differences most likely account for these divergent findings. In other mammals, sex differences in cellular properties may be due to regional heterogeneities of ion channel expression in the heart (76).

The dog, with a heart size and AP characteristics similar to humans, has been used extensively as a model for heart failure and sudden cardiac death. However, sex differences have not been observed in the QTc interval or other ECG parameters (24, 28, 53, 81). Despite a lack of sex differences in QTc, significant differences were reported in individual current densities, and APDs (20%) are longer in female dogs than in males in Purkinje fibers and midmyocardium (1, 91). In addition, the dispersion of \(I_\text{to}\) (4) and the density of \(I_\text{Ca,L}\) (30–40%) are greater in females, whereas the density of \(I_\text{K}_\text{a1}\) is lower (40%) in the endocardium and \(I_\text{K}_\text{c}\) is greater (60%) in the epicardium and endocardium but not the midmyocardium (91). The interpretation of these data may be limited because of strain differences, intrinsic regional differences in current densities between the base and apex of the heart, and insufficient controls regarding the estrus cycle of the females. Still, substantial differences in the electrical substrate can occur with no apparent changes in QTc (91).

The lagomorph or, more precisely, the New Zealand white rabbit is a frequently used strain of animals. It exhibits similar sex differences in LQT2-related arrhythmias as in humans, for both adult and prepubertal rabbits and approximately the same combination of ionic currents underlie rabbit and human APs. At rapid pacing rates, there are no sex differences in the rabbit ECG, but sex differences are revealed at longer cycle lengths (21, 33, 44, 96). The rabbit exhibits significant sex differences in response to drugs (48) and has longer ventricular APDs in females than in males (65, 84, 96). An important difference between humans and rabbits is that rabbits are inducible ovulators and they lack a menstrual cycle that is often considered to be a valuable advantage in studies of female hearts with constant levels of sex steroids. For these reasons, sex differences have been extensively studied in rabbits as the most appropriate animal model to study sex differences in cardiac electrical activity.

The marked difference in the propensity to TdP in women is readily observed in adult female compared with male rabbits.
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Table 2. A selection of conflicting data from sex differences in individual ionic currents in adult animal models

<table>
<thead>
<tr>
<th>Current</th>
<th>F &lt; M</th>
<th>No Change</th>
<th>F &gt; M</th>
</tr>
</thead>
<tbody>
<tr>
<td>I_{Na}</td>
<td>Mouse (82)</td>
<td>Mouse (82)</td>
<td>Mouse RV (10)</td>
</tr>
<tr>
<td>I_{Ca,L}</td>
<td>Guinea pig (32)</td>
<td>Rabbit LV apex (76)</td>
<td>Dog (91)</td>
</tr>
<tr>
<td>I_{K_{Ca}}</td>
<td>Mouse (82)</td>
<td>Mouse LV apex (10)</td>
<td>Dog epi (91)</td>
</tr>
<tr>
<td>I_{K_{Ca}}</td>
<td>Mouse septum (10)</td>
<td>Mouse LV apex (10) mouse (82)</td>
<td>Dog mid (91)</td>
</tr>
<tr>
<td>I_{K_{s}}</td>
<td>Mouse (82)</td>
<td>Mouse RV (10)</td>
<td>Mouse RV (10)</td>
</tr>
<tr>
<td>I_{K_{1}}</td>
<td>Guinea pig Day 4 estrus cycle (32)</td>
<td>Guinea pig day 0 estrus cycle (32)</td>
<td>LV dog, epi (91)</td>
</tr>
<tr>
<td>I_{K_{1}}</td>
<td>Outward I_{K_{1}} rabbit (44)</td>
<td>Mouse RV (10)</td>
<td>LV dog, mid (91)</td>
</tr>
<tr>
<td>I_{inward K_{1}} guinea pig (32)</td>
<td>Mouse LV apex (10) Mouse septum (10)</td>
<td>Mouse LV apex (10)</td>
<td></td>
</tr>
<tr>
<td>I_{K_{1}}</td>
<td>Mouse RV (10) Mouse septum (10)</td>
<td>Mouse LV apex (10)</td>
<td></td>
</tr>
</tbody>
</table>

See main text for definitions of abbreviations.

Moreover, the TdP risk is reversed in prepubertal rabbits (43), in agreement with subsequent analysis of human data (42). Optical mapping of APs and Ca^{2+} transients revealed that TdP was initiated by early afterdepolarizations (EADs) at the base but not the apex of the ventricles in female rabbits with drug-induced LQT2 (76). EADs that triggered TdP were elicited by large secondary release of Ca^{2+} by 

...
mia (76). In contrast, heterogeneous $I_{Ca,L}$ expression, higher at the base than apex, accounts for the greater arrhythmia risk by promoting EADs and ectopic activity at the base of the heart (13, 76, 94) and by enhancing dispersion of repolarization and the amplitude of T waves to help sustain arrhythmias (36). These findings challenge the significance of the concept of repolarization reserve, advancing $Ca^{2+}$ homeostasis as an underlying mechanism that can predict arrhythmia risk.

Future directions. Although sex differences in the human heart are clearly apparent at the level of the ECG, determining the molecular basis for these differences has proved difficult. Animal models have played a vital role in investigating the molecular bases for sex differences in ventricular repolarization and arrhythmogenesis. Despite some limitations, the rabbit appears to generally parallel the overall electrophysiological sex differences reported in the human. However, other animal models may be equally or more suitable for a specific condition or ion channel. What is clear is that sex differences in the electrical substrate are not the result of a simple change in expression of a single or even a few ionic currents. There are likely to be multiple changes in several ion channels, as well as their regulatory subunits. In addition, these changes are subtle and are not readily detectable by microarray techniques, and care must be taken to test for ion channel distribution across regions of the heart. The recent evidence pointing to sex differences at the level of fundamental structure-function relationships in ion channel biophysics adds another exciting new direction.

The paucity of data on sex differences in cellular electrophysiology from freshly isolated human preparations has severely hampered determination of the key components contributing to sex differences in human myocytes. The recent development of human cardiac myocytes derived from induced pluripotent stem cells offers the potential to have a significant impact on this field, as sex differences, in normal hearts as well as in the presence of known human channelopathies, can be studied in the context of male and female human myocytes and well-defined hormonal treatment, as they are grown in culture. Furthermore, cardiac myocytes derived from induced pluripotent stem cells are plentiful and are sufficiently robust to withstand the long protocols required to determine the effects of sex steroids on ion channel biophysics; a key component of sex differences in the electrical substrate.

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AUTHOR CONTRIBUTIONS

G.S. and G.C.L.B. conception and design of research; G.S. and G.C.L.B. drafted manuscript; G.S. and G.C.L.B. edited and revised manuscript; G.S. and G.C.L.B. approved final version of manuscript; G.C.L.B. prepared figures.

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