Sex differences in cardiac electrophysiology

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Sex differences in cardiac electrophysiology

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Abstract

Women have a longer QT-interval than men and this difference appears to evolve after puberty suggesting that sex hormones have an influence on cardiac electrophysiology. Sex hormones do in fact regulate cardiac ion channels via genomic and non-genomic pathways. Women are at greater risk for life threatening arrhythmias under conditions that prolong QT interval. In addition women exhibit greater sensitivity to QT interval prolonging drugs. Female sex has also an impact in propensity to cardiovascular disease, including atrial fibrillation. However, ex-vivo recorded atrial action potentials (APs) from female and male patients in atrial fibrillation did not exhibit significant differences in shape, except that APs from women had slower upstroke velocity. It is concluded, that sex-related differences should be taken into account not only in the clinics but also in basic research.

Key words

Sex differences in ECG – sex hormones – proarrhythmic potential - sensitivity to drugs - atrial fibrillation

Introduction

In the past decades, all disciplines in medicine have increasingly acknowledged that differences between men and women in manifestation of disease and in responses to therapy do in fact matter and should be taken into account in optimal patient care. In the cardiovascular field this is particularly true with respect to the greater risk of women for developing life-threatening arrhythmias

Based on my invited lecture held at the Annual Meeting of the International Academy for Cardiovascular Sciences, European Section in Pécs 2017, I shall briefly summarize physiological sex differences in the electrocardiogram (ECG) and their molecular basis. Next I have chosen atrial fibrillation as an example of differences between men and women in clinical presentation and outcome. I shall conclude with an analysis of sex differences in a data set collected for investigating electrophysiological remodelling in atrial fibrillation.

ECG differences between men and women

One of the first systematic ECG comparisons between the sexes detected longer intervals in women than in men between the beginning of the QRS complex and various points of the T wave, all corrected for heart rate (Lepeschkin 1956). This observation has since been repeatedly confirmed [for review see (Jonsson et al. 2010)].

The changes in electric field detected during the ECG at the surface of the human body represent a spatial-temporal integral of the electrical activity from all individual cardiomyocytes [for review, see (Nerbonne and Kass 2005)]. Therefore, the QT interval in the ECG represents the average ventricular action potential duration (APD) of all ventricular cardiomyocytes, and prolongations in APD are usually reflected as a prolonged QT interval. Since the cardiac AP obtains its characteristic shape by the concerted activity of selective ion channels that allow depolarising (inward) and repolarising (outward) current flow across the cell membrane, changes in action potential shape are due to altered expression or gating of these channels.

Action potentials and ion channels

At rest, the inward rectifier K^+ channels are open, whereas the other channels are closed. Thus the plasma membrane is permeable for K^+ but not for Na^+ and the cardiac resting membrane potential lies close to the K^+ equilibrium potential where net K^+ flow is zero, because K^+ efflux along the concentration is equal and opposite to K^+ influx due the negative potential inside the cell. During the course of an AP, Na^+ channels (SCN5A), L-type Ca^{2+} channels (CACNA1C) and various K^+ channels (KCNx) activate and inactivate in a voltage-dependent manner to allow current flow. The rapid upstroke is due to the fast activating and inactivating Na^+ current (I_{Na}), the plateau phase is maintained by $I_{Ca,L}$, and final repolarisation is due to multiple K^+ currents, providing some redundancy as 'repolarization reserve' (Roden 1998; Varro et al. 2000) and preventing excessive AP prolongation. Excessive prolongation in ventricular APD by conventional class III antiarrhythmic drugs, mainly human ether-a-go-go related gene (hERG or KCNH2) channel blockers, is associated with a high risk of life-threatening torsade de pointes (TdP) arrhythmias that may exacerbate into ventricular fibrillation (Sanguinetti and Mitcheson 2005).

Human ventricular cardiomyocytes isolated from failing hearts from female and male patients differ only in APD, but not in any other AP parameter. The longer APD in 'female' compared with 'male' cardiomyocytes appears to be due to less transient outward current and larger L-type Ca^{2+} current in females than males (Papp et al. 2017; Verkerk et al. 2005).

Any persisting depolarising current and any decrease in repolarising current will prolong APD and hence also QT interval, thereby causing a so-called 'long QT syndrome' (LQTS). This syndrome is characterized by an enhanced risk for polymorphic ventricular tachyarrhythmias (e.g. TdP) that may exacerbate into ventricular fibrillation causing sudden cardiac death (SCD). LQTS can be caused by mutations in ion channels or by drugs (even those used in non-cardiovascular indication) and is a major health concern. Though more than a dozen different genotypes for LQTS are presently known, approximately two thirds of LQTS patients host 3 major genetic defects, i.e. LQT1 and LQT2 exhibit loss of function mutations in the K^+ channel genes KCNQ1 and KCNH2, respectively, and LQT3 hosts a gain of

function mutation for in SCN5A encoding for the cardiac Na⁺ channel (Steinberg 2018). Because of their longer QT interval, women are at greater risk for SCD when harbouring LQTS-associated ion channel mutations or treated with APD-prolonging drugs (Roden 2006). The general consensus is that women have a reduced repolarization reserve (James et al. 2007). In a recent study of analysing predictors for SCD in a large cohort of LQT patients, males below 14 and females over 14 years of age had a markedly increased risk for cardiac events in LQT1 and LQT2, but not for LQT3, and β -receptor blockers that can prevent cardiac incidences in LQT1 and LQT2 of both men and women were effective in LQT3 only in females (Kutyifa et al. 2018).

Not only prolongation, but also shortening of QT interval in combination with ST segment elevation in the right precordial leads ('Brugada syndrome') is a risk factor for SCD (Brugada and Brugada 1992). The pathophysiology of Brugada syndrome is still not fully understood. Nevertheless, about 20% of the cases are accounted for by numerous different loss of function mutations in SCN5A and men have an almost 10-fold higher risk for SCD than women (Di Diego et al. 2002).

Effects of sex hormones on ion channels

Interestingly, hormonal status has an important impact on QTc duration. The prevalence in women with a heart-rate corrected QT interval (QTc) > than 440 ms in baseline ECG develops only after puberty (Locati et al. 1998) and there are no longer any differences observed in late adulthood/post menopause (Pham and Rosen 2002). Nevertheless, there is still some discussion, whether the difference in QTc between men and women is due to shortening of QT by testosterone in men or prolongation of QTC by estrogen/progesterone in women (Rautaharju et al. 1992). In addition, there is QTc variability during menstrual cycle and pregnancy, suggesting intrinsic hormonal regulation in female hearts. During pregnancy, for instance, QTc values were consistently shorter with higher estradiol plasma concentrations, whereas progesterone plasma concentrations had no impact (Anneken et al. 2016). This finding provides an explanation for the observation that carriers of LQTS mutations are less prone to develop TdP arrhythmia during pregnancy than in the post partum period where estrogen plasma concentrations normalise again.

Sex hormones do in fact influence cardiac ion channel activity, either by genomic or non-genomic pathways (**Figure 1**). For genomic effects, the sex hormones diffuse into the cytosol of their target cell where they activate specific receptors. Activated hormone receptors dimerise, bind to hormone-response elements of gene promoters and induce target gene transcription (Luo and Kim 2016). In the above-mentioned study of risk for TdP during pregnancy, estradiol shortened of APD by enhancing outward current I_{Kr} , an important repolarising current flowing through KCNH2 (hERG) channels. This increase in current amplitude was due to enhanced trafficking of hERG channels into the plasma membrane (Anneken et al. 2016). Other non-genomic effects of gonadal hormones include receptor binding but activation of specific pathways outside the nucleus which involve eNOS or MAP-kinase signalling. Last but not least, receptor-independent non-genomic effects of sex hormones on ion channels have also been reported [for review see (Kurokawa et al. 2016)]. To complicate the issue even further, acute and chronic effects or effects of physiological and excessive concentrations of sex hormones may counteract each other (Odening and Koren 2014).

Differences between men and women in susceptibility to drug effects

Women are generally at greater risk to develop arrhythmia (specifically TdP) in association with prolonged QT interval (Abi-Gerges et al. 2004; Locati et al. 1998). Approximately 65 – 75 % of all drug-induced LQTS occur in women (Kurokawa and Furukawa 2013; Makkar et al. 1993). The drugs involved are not only medications for treatment of cardiovascular diseases (e.g. antiarrhythmic drugs such as d,l-sotalol, ibutilide or dofetilide) but also include drugs for many different indications, e.g. antibiotics (erythromycin), antimycotics (fluconazole), antihistaminics (astemizole), antiemetics (cisapride), antimalarial agents (chloroquine), neuroleptic drugs (risperidone) and antidepressant drugs (fluoxetine) [for recent review see (Schwartz and Woosley 2016)]. Conversely, in Brugada syndrome, men are at higher risk of developing a fully-blown ECG phenotype and even cardiac events in response to drugs class-1 antiarrhythmic drugs (sodium channel blockers) but also following exposure to tricyclic antidepressants, fluoxetine, lithium, trifluoperazine, antihistamines, or cocaine (Konigstein et al. 2016; Yap et al. 2009).

The question whether the increased risk of drug-associated arrhythmia in women is due to the ~20-ms longer baseline QTc value (Kurokawa and Furukawa 2013) or is related to an intrinsic female property of the cardiovascular system has been addressed by investigating the response to a single oral dose of racemic sotalol (d,l-sotalol) in men and women (Darpo et al. 2014). In women, mean peak plasma concentration after a therapeutic dose of 160 mg was 128.5 % and the plasma concentration-time integral (area-under-the curve, AUC) was 117.1% of that in men. In both genders, d,l-sotalol reduced heart rate, and increased QT-interval as well as QTc-interval (multiple methods used to correct for heart-rate dependence). To account for baseline differences in QTc interval and for differences in d,l-sotalol concentration, the change in QTc interval at any time point during the test day was plotted against the d,l-sotalol plasma concentration at the same time point. The slope of this relationship was steeper in women than in men. The authors concluded that the intrinsic sensitivity for d,l-sotalol-induced QT prolongation is greater in women in comparison to men and that this may contribute to the greater pro-arrhythmic risk in women (Darpo et al. 2014).

Drug effects during the menstrual cycle

There is also some evidence in healthy humans that the responsiveness to QT prolongation may vary during the menstrual cycle. Rodriguez and coworkers studied women in 3 phases of their menstrual cycle (menses, ovulation and luteal phase) and compared them with men (Rodriguez et al. 2001). During baseline, women's QTc interval was ~20 ms longer than men's, but the differences between the 3 menstrual cycle phases were not statistically significant (**Figure 2A**). Moreover, the changes in QTc interval after 10 minutes of ibutilide infusion were also larger in women than in men (**Figure 2B**). But only when expressing the response to the drug as the integral of the change in QTc over time (i.e. area under the curve, AUC, expressed as ΔQTc over 60 min) could significant differences be detected between women during menses and ovulation on one side, and women during the luteal phase and men on the other side (**Figure 2C**). The authors concluded that the risk of women for developing drug-induced TdP arrhythmias varies during the menstrual cycle (Rodriguez et al. 2001).

Differences in atrial fibrillation between men and women

As an example of differences between men and women in manifestation of disease, I shall discuss atrial fibrillation (AF). This common arrhythmia affects more than 6 million Europeans (European Heart Rhythm et al. 2010) worsening their quality of life and increasing their mortality due to elevated risk of stroke and heart failure (Benjamin et al. 1998). Therefore, the two major treatment goals are prevention of stroke with novel oral anticoagulants and prevention of heart failure by normalizing heart rhythm or, if that is not feasible, by reducing heart rate (Kirchhof et al. 2016).

There is compelling epidemiological evidence for sex-specific differences in the epidemiology, pathophysiology, presentation, prognosis, and treatment of AF (Ko et al. 2016; Magnussen et al. 2017). Women with AF generally experience worse symptoms, poorer quality of life, and have higher risk of stroke, severe bleeding after treatment with anticoagulants and death than men with AF (Yarnoz and Curtis 2008). In the Gutenberg Health study, the incidence of AF increased with increasing age, and, per decade of age, was always higher in men than women. In fact, the AF incidence in women appeared to be shifted by one decade compared with men, i.e. older women experienced the same AF incidence as one-decade younger men (Schnabel et al. 2012). For optimised management of patients with chronic AF gender-specific differences must be taken into account (Ball et al. 2013).

Electrical remodelling in AF: Differences in human ex-vivo atrial AP between men and women?

The high frequency of electrical activity in AF leads to characteristic electrical and structural changes in the atrial tissue (electrical and structural “remodelling”), including changes in atrial APs and tissue morphology. The hallmark of electrical remodelling is the change of the action potential from a spike-and-dome to a typical triangular shape (**Figure 3**, inset) (Dobrev and Ravens 2003; Ravens 2017; Ravens et al. 2015).

In pharmacological experiments conducted in Dresden between 2006 to 2014, we have collected control APs recorded with microelectrodes from human right atrial trabeculae donated by patients undergoing open-heart surgery (Ravens et al. 2015).

Standard AP parameters (amplitude, resting membrane potential, duration at various levels of repolarisation, maximum upstroke velocity and plateau potential, see **Figure 3**) have been analysed, and histograms of these values (**Fig. 3**) illustrate that individual values for AP parameters displayed huge variability between preparations. Nevertheless, as published previously for smaller cohorts, significant differences between APs from patients in AF and SR were confirmed with exception for $dV/dt_{\max}$ (Ford et al. 2016; Loose et al. 2014; Skibsbye et al. 2014; Wettwer et al. 2013).

Here, the complete data set (659 APs from 520 patients), has been analysed in search for differences in AP parameters between preparations from female and male patients (**Figure 4**). All patients underwent scheduled open-heart surgery and gave informed consent for the electrophysiological study of their right atrial appendage. The project conformed to the principles outlined in the Declaration of Helsinki and had been reviewed and approved by relevant ethics committee (ethic committee approval number of TU Dresden: EK790799). The patient cohort consisted of 89 female and 231 male patients in SR, and 74 female and 126 male patients in AF at the time of surgery. In the SR group, female patients were significantly older than male (70.1 vs. 66.0 years), but not in the AF group (73.0 vs. 72.1 years). Though women weighed less and were shorter than men, there were no differences in body mass index between female and male patients neither in the SR nor in the AF group. Interestingly, QTc interval in female SR patients was on average 7.5 ms longer than in males, however, this difference did not reach the level of significance. In the AF group, uncorrected QT intervals were even 19 ms shorter in female than in male patients (and this was highly significant), but the QTc interval was no longer significantly different after correction for heart rate (on average 4 ms shorter in women than in men). **Figure 4** depicts the differences between female and male patients in the various action potential parameters separated for SR and AF. Gender differences were significant in the SR group for maximum upstroke velocity, APA and resting membrane potential (lower in women than men), but also for APD at 50% and 20% of repolarisation (longer in women than men) and for the plateau potential (higher in women than in men). In AF, only upstroke velocity was lower in women than in men, all other parameters were not significantly different. This suggests, that electrical remodelling during AF appeared to abolish gender differences observed in SR. It must be emphasized, however, that all patients, even those in SR, were

seriously ill, because they required cardiac surgery. Hence there are many factors that may confound possible sex differences in atrial (and ventricular) action potentials.

Although the differences in ex-vivo electrophysiological parameters of human atrial tissue were small or absent for the parameters studied, we suggest that sex-differences should be considered worth investigating at an early stage of planning investigations. This is important, both to collate more data from a highly heterogeneous biological sample population with the view of unmasking electrophysiologically relevant differences at the single cell level, and to identify electrophysiologically relevant mechanisms that may be present in native tissue or in-situ only.

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Legends to Figures

Figure 1.

Genomic and non-genomic effects of sex hormones on ion channels. See text for further explanation. Reproduced from (Jonsson et al. 2010), with kind permission of the publisher.

Figure 2.

QTc interval in women in 3 phases of the menstrual cycle and men, and responses to 10 min of infusion of ibutilide (0.003 mg/kg). **A:** Independent of the phases of the menstrual cycle QT-interval was ~20 ms longer in women than in men. **B:** Changes in QTc interval after ibutilide infusion over 4 hours women and over 2 hours in men. Means $\pm$ S.E.M. **C:** Change in QTc interval expressed as AUC over 60 min (Δ QTc, 0-60 min, ms $\cdot$ min). Note that the values for women in during their menses and ovulation were significantly larger than during the luteal phase of in men. [Redrawn after (Rodriguez et al. 2001) with kind permission of the Publisher.]

Figure 3.

Electrical remodelling in human right atrial trabeculae. Top: typical action potentials from patients in sinus rhythm (SR) and chronic atrial fibrillation (AF). Histograms of action potential parameters from SR (black) and AF (red) patients. APD₉₀ and APD₂₀, action potential duration at 90% and 20% of repolarisation, respectively, in ms; PLT₂₀, plateau potential in mV after 20% of APD₉₀; APA, action potential amplitude in mV; RMP, resting membrane potential in (-) mV; dV/dt_{max} upstroke velocity in V/s. (Ravens et al. 2015), with kind permission of the publisher.

Figure 4.

Box and whisker plots of action potential parameters of human atrial trabeculae from female and male patients in sinus rhythm (SR) and atrial fibrillation (AF). Numbers in parenthesis are the numbers of action potentials in each group. P values for unpaired t-test; ** P < 0.01. F, female; M, male; other abbreviations, see legend to Figure 3. (Ravens U, unpublished results).

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Figure 1

Figure 3

SR (n = 101 F; 270 M) **AF (n = 106 F; 182 M)**

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Figure 4