Influence of gender on drug-acquired long QT syndrome

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Numerous drugs from diverse classes, such as antiarrhythmics, antihistamines, gastrokinetics, antipsychotics and antibiotics, share the potential to induce a prolongation of the QT interval on the electrocardiogram and torsade de pointes ventricular arrhythmias. The underlying mechanism of these side-effects is the blocking of voltage-gated potassium channels, particularly the rapid component $I_{Kr}$, of the delayed rectifier $I_K$. The risk of such drug-induced arrhythmias is far greater in women than in men. Clinical data as well as experimental studies show that, in comparison to men, the feminine gender is associated with a longer baseline QT interval, a greater response to drugs that block $I_{Kr}$, and a greater propensity to drug-induced torsade de pointes. This is most likely the result of a specific regulation of channel expression by — and perhaps a direct non genomic effect of — sex steroids.

Key Words: Gender difference, potassium channel blockers, long QT syndrome, $I_{Kr}$, ventricular arrhythmia, sudden death.

Introduction

By reflecting the summation of all the action potentials of the ventricular cardiomyocytes, the QT interval as measured on an electrocardiogram is a relevant marker of the ventricular repolarization[1,2,3]. The spatial heterogeneity of the ventricular repolarization is witnessed by measuring the dispersion of the QT interval. The QT interval duration and dispersion are both positively associated with a worsened prognosis in post-myocardial infarction patients[4] and in patients with congenital[5] or acquired long QT syndrome[5].

The cardiac action potential results from a spatial and dynamic phenomenon due to the fine tuning of voltage gated channels. The delayed rectifier current $I_K$ plays a particularly important role with its outward repolarizing $K^+$ conductance. The pharmacology of $I_K$, and particularly its rapid component $I_{Kr}$, is now well explored. The remarkable role of this latter during the repolarization phase of the action potential, is subsequent to its recovery from fast inactivation that occurs during the plateau phase[6]. Most drugs responsible for the drug-acquired long QT syndrome and which are associated with polymorphic ventricular tachycardia and sudden death are, intentionally or not, $I_{Kr}$ blockers and mimic the congenital long QT2 in human[7]. Drugs that block $I_{Kr}$, augment the action potential duration (APD) and enable inward currents to reactivate. The prolongation of the APD usually results in an increase of the QT interval on the ECG. That not all cells have the same density of channels probably reflects the changes also observed in the QT dispersion[8]. The occurrence of early after-depolarizations (EADs) is thought to trigger polymorphic ventricular tachycardia such as torsade de pointes in such a setting of spatial and temporal heterogeneity of refractoriness[9]. However, several elements may imbalance the fine tuning of the voltage-gated channels. By infringing the security of these channels, drugs may change the actual proportion of channels and facilitate the occurrence of arrhythmias. Besides these factors, the pharmacology (efficacy, potency, etc.) of the drug itself is of importance. The factors influencing the cardiac response include the autonomic nervous system, the heart rate, electrolyte disturbances[10], circadian patterns and physical conditions of the myocardium itself[11-13]. Most of the clinical conditions associated with a prolongation of the QT interval on the electrocardiogram are well known[13,14]. They include heart insufficiency, left ventricular hypertrophy, myocardial ischaemia, hypothyroidism, obesity, old age and genetic defects in voltage-gated channels[15]. Feminine gender is also an independent factor that is now recognized as facilitating the occurrence of arrhythmias in a setting of drug-acquired long QT syndrome.
Clinical evidence for a female propensity to drug-acquired long QT syndrome and related polymorphic ventricular tachycardia

The fact that female gender has been associated with a longer QT interval on the ECG has been known since Bazett described it in 1920[3]. It seems that women may have a similar uncorrected QT interval to men, but a slightly faster heart rate, thus explaining their longer corrected QT interval[16,17]. Apparently, no gender differences in QTc affect the newborn[18], even if female neonates may have a faster heart rate[19]. It is only around puberty, when sex hormones impregnate the body, that gender influences the QT interval[20]. Then, the QT shortens in males and later returns to previous levels in the fifth to sixth decade[20]. This fact has raised the hypothesis that sex steroid, and particularly androgens, might be the source of such differences.

Not only is the QTc longer in women at baseline[21], but the QT interval prolongation relative to the administration of I_K blockers is greater and accompanied by a propensity of drug-induced polymorphic ventricular arrhythmia[22]. This reflects profound intrinsic differences of cardiac sensitivity according to the gender that have since been supported by several clinical and experimental studies.

Feminine gender and antiarrhythmic drug-acquired long QT syndrome

This link was first underlined in 1993, by a meta-analysis of pro-arrhythmogenic side-effects of antiarrhythmic drugs, mainly quinidine[23]. Out of the 332 cases of torsade de points retrieved from 93 articles, women formed 70%[23], whereas 50% was expected at most. These elements were later confirmed when it was found that women were more prone than men (about two-thirds of the cases) to dose-dependently develop torsade de points when treated with d, l-sotalol[24].

Women also had a bigger increase of their QT interval in response to I_K blockers[22]. Thus, it seemed evident that the female gender was associated with a worsened prognosis of cardiac patients treated with antiarrhythmic drugs.

The female gender was associated with (1) a longer baseline QT interval, (2) a greater response to drugs and (3) a greater propensity to drug-induced torsades.

Non-antiarrhythmic drugs and gender-related ventricular tachycardia

A similar ratio of cardiac side-effects (female two thirds of the cases) was found with a totally different class of drug in a non-cardiovascular domain of prescription: macrolide antibiotics. Cardiac-related side-effects, polymorphic ventricular tachycardia and sudden deaths were over-represented in women treated with erythromycin lactobionate, compared to men[25]. The prescription (over one million) was well balanced according to gender and the patients that were concerned were comparable to the general population with no special cardiac condition. The same finding was reported with another non-cardiovascular drug, the antimalarial halo-fangrine[26], among the cardiovascualr events reported to the FDA, about two-thirds occurred in women. The obvious common factor between these drugs is their efficacy in blocking the delayed rectifier current I_K even though they do not, at least in the case of erythromycin, profoundly prolong the QT interval on the electrocardiogram. Other reports have since implicated new classes of drug such as antipsychotics and antihistamines (see http://Torsades.org). One can therefore reasonably extend the notion of a ‘risk factor’ associated with feminine gender to most of the drugs that block I_K and/or prolong the QT duration.

Rationale for a feminine predisposition to drug induced long QT syndrome and/or ventricular arrhythmia

Pharmacological specificity associated with feminine gender

Several reasons may render women prone to such cardiac side effects (Fig. 1). It is possible that gender may affect the pharmacology and thus the resulting plasma levels of a drug for a standardized dose[27,28]. At present, several inferences on the influence of gender in the handling of drugs in the body and in drug response can be drawn form a limited database. It appears that drug pharmacokinetics are little affected by gender in general. However, in some cases of drugs with a small therapeutic index or bearing I_K blocking potentialities, small variations may hypothetically be relevant such as for antidepressants or antipsychotics[27,28] which block I_K. Hence, the pharmacokinetics of drugs that have shown to be protective against arrhythmia, such as beta-blockers in congenital long QT syndrome, may significantly vary according to gender[31,32]. This helps to explain the relative protection against sudden death that benefit women treated with beta-blockers[33]. But more than the pharmacokinetics of the drug it is important to consider the intrinsic sensitivity of the heart according to gender (Fig. 1). As an example, the concentration-effect relationship between quinidine plasma levels and QTc is much steeper in female than in male volunteers[34], even though the baseline QTc of the female volunteers is longer than that of their male counterpart.

Mechanism of the gender influence on drug-acquired long QT syndrome

Even if the propensity of female gender to influence the clinical outcome of long QT syndrome has been clearly
assessed little is known about which hormones and precise targets are implicated.

In the case of congenital long QT syndrome, as well as in the case of erythromycin-associated cardiac adverse events, the strong under-representation of males of sexual maturity (15–60 years of age) draws attention to the peculiar role that androgens may play. Furthermore, hormonal treatment of postmenopausal women does not seem to profoundly change their cardiac repolarization.

Role of androgens in blunting QT response to $I_K$ blockers

Conclusive experiments have been performed with female rabbits ovariectomized and implanted with sustained-release pellets of either 17β-oestradiol, 5-dihydrotestosterone or placebo, to maintain physiological levels of hormones for three weeks. Langendorff experiments with the hearts isolated from those rabbits have led to the conclusion that the female hearts that had been treated with androgens had a blunted QT response when challenged with quinidine compared to either placebo or oestradiol-treated rabbit hearts. This has been confirmed more recently in a similar model exploring the action potential duration of rabbit papillary muscle. Such an influence of gender is also highly perceptible on PK/PD of $I_K$ blockers, as well as resulting arrhythmias in humans. Star symbols represent the level where the influence of gender and/or sex steroids have been shown.

Figure 1  Gender influences drug-acquired long QT syndrome. By modulating drug pharmacokinetics, the resulting plasma levels of $I_K$ blockers may differ in males and females or with hormonal treatment. The blocking of $I_K$ is responsible for the prolongation of the action potential duration that is reflected by an increase of the QT interval. Feminine gender is associated with a greater magnitude of change (and/or male gender with a blunted response) of these parameters during $I_K$ blockade. The prolongation of the action potential facilitates early after-depolarizations (EADs) which are held accountable for triggering torsade de pointes ventricular arrhythmias (TdP). Both are experimentally potentiated by 17β-oestradiol. Such an influence of gender is also highly perceptible on PK/PD of $I_K$ blockers, as well as resulting arrhythmias in humans. Star symbols represent the level where the influence of gender and/or sex steroids have been shown.

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Table 1  Normal untreated animal display gender differences in cardiac repolarization process[41,43,44,66]

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Molecular targets of sex-steroids

A salient feature associated with gender differences in cardiac repolarization process, at least in the rabbit, is the comparative density of potassium channels in isolated cardiomyocytes, which differ according to the gender. Thus, a longer QT interval in female rabbit hearts is associated with a smaller density of I_{Ks}, the inward rectifier current I_{Kr} [43] and the transient outward K+ current I_{to} [43]. Furthermore, in cardiac papillary muscle of ovariectomized female rabbits treated with androgens, the APD_{90}, which strongly relies on calcium influx, is shortened compared to placebo and oestradiol[40]. More outward K+ and less inward Ca++ conductances in male hearts may be held accountable for the shorter QT duration observed in males. A smaller density of potassium current in females may be responsible for the greater QT prolongation resulting from I_{Ks} blockade (Table 1). So far, I_{Ks} does not appear to be critical for explaining gender differences [44,45] but the native current is quite difficult to discriminate in physiological conditions in other species than guinea-pigs.

By which mechanisms do androgens and oestrogens influence the channel regulation? The few experimental studies available on the cardiac effects of sex-steroids support a genomic effect. When administered at physiological concentrations, they induce changes in channel subunit mRNAs [39]. Such an effect can be quite rapid, as in the case of uteri of ovariectomized rats [46]. In that model, a single administration of oestradiol induces the synthesis, within 3 h, of the mRNAs of KCNE1, which encodes a regulatory subunit and component of the I_{Ks} channel. However, if the identification of sex-steroid non-genomic pathways acutely modulating K+ currents has largely remained elusive, some experimental evidence raises such a possibility. Besides influencing the direct inhibition of I_{Ks} by injected supraphysiological concentrations of 17β-oestradiol [47] (from 1 to 10 μM) in Xenopus oocytes, oestrogens may exert an effect within a much more rapid time frame than necessary for genomic effects. Thus an injection of 17β-oestradiol precipitates ventricular arrhythmia in dogs when co-administered with cisapride [48]. Likewise, oestradiol potentiates the lidocaine-induced depression of cardiac excitability [49] and the anti-oestrogen/partial agonist drug tamoxifen blocks native I_{Ks} current at a range of concentrations that is therapeutically relevant [49]. The rapid response in those cases suggest a non-genomic effect on voltage-gated channels. However this could be species-dependent since no effect can be seen on the QT interval when 17β-oestradiol is directly perfused in isolated rabbit hearts [50].

The role of other hormones (e.g. progesterone [51], other currents [e.g. voltage-dependent Na+ current (I_{Na}) or L type voltage-dependent Ca++ current (I_{Ca})] has yet to be thoroughly explored [52,53]. Little is known about a possible influence of sex steroids on K+ channel regulatory subunit/components such as KCNE2 or KCNE3, which modulate both human ether-a-go-go-related gene (HERG) and KCNQ1 currents.

**Does the QT-RR relationship reflect gender-induced QTc changes?**

The higher incidence of polymorphic ventricular tachycardia in women with drug-acquired long QT syndrome...
is somehow related to a longer QTc interval. This parameter, highly influenced by its correction factor\textsuperscript{[42]}, should not be seen as a static value but as a dynamic parameter under the influence not only of heart rate, but also of the autonomic nervous system\textsuperscript{[37,11]}. If a longer QTc interval in women is solely a result of a correction factor in the presence of a faster heart rate\textsuperscript{[12,17]}, a more global approach than QTc measurement, such as the QT-RR relationship, may be more relevant. It has been suggested that an abnormal adaptation of the QT interval to heart rate may be related to an increased risk of cardiac events in patients with a congenital long QT syndrome\textsuperscript{[11,59]}. In these patients, the QT-RR relationship is steeper than in controls\textsuperscript{[56–59]}. Curiously, this is also the case when patients are treated with drugs that prolong the QT interval, such as dofetilide\textsuperscript{[59]} or sotalol\textsuperscript{[60]}. That may simply reflect the reverse-use dependence usually encountered with such drugs. However, a similar exacerbated QT-RR adaptation has already been noticed in women as compared to men\textsuperscript{[61]}, and their adaptation of QT interval to heart rate drastically differs. This has been confirmed by Stramba-Badiale et al., who found steeper slopes of the linear regressions of QT values against the corresponding RR interval in young female volunteers devoid of any cardiac disease\textsuperscript{[62]}. Murine models also display such a gender difference in QT-RR relationship\textsuperscript{[64]}.

A greater slope of the QT-RR relationship means that the QT interval lengthens to a greater extent during bradycardia. This could explain that a pause almost systematically precedes a typical torsade de pointes\textsuperscript{[63]}. A subsequent greater APD may facilitate the emergence of EADs and precipitate arrhythmias. These elements have shed a new light on the QT-RR adaptation as possibly reflecting a diminution of the ‘repolarization reserve’ whether in females or when drugs blocking IKr are administered. Even if the QT-RR slope appears of interest in drug-induced QT prolongation (since it does not require any correction formula and can be adapted at different heart rates), further studies are needed to confirm its clinical relevance.

**Conclusion**

Since Bazett’s pioneering work\textsuperscript{[1]}, a longer duration of the QT interval corrected for the heart rate (QTc) has constantly been reported in women\textsuperscript{[1,20,64]}. Women are at increased risk for severe cardiac adverse events such as torsade de pointes in drug-acquired\textsuperscript{[24,25]} and congenital long QT syndrome\textsuperscript{[37]}. Even though a lower population-based incidence of sudden death in women may relate to a difference in the prevalence of coronary artery disease in men\textsuperscript{[65]}, gender differences affect the incidence of arrhythmias and sudden death for women treated with IKr blockers. Therefore, not only should caution be exercised when administering such drugs in women at risk of developing cardiac arrhythmias (hypokalemia, bradyarrhythmia, etc.) but studies of gender specificity should also be a goal in pre-clinical as well as clinical development of drugs prolonging the QT interval.

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