Editorial

Sex, drugs and arrhythmia: are gender differences in risk of torsades de pointes simply a matter of testosterone?

Andrew F. James*, Jules C. Hancox

Department of Physiology and Cardiovascular Research Laboratories, School of Medical Sciences, University of Bristol, University Walk, Bristol, BS8 1TD, UK

Received 14 October 2002; accepted 21 October 2002


As highlighted by a recent ‘Spotlight’ issue of Cardiovascular Research [1], the existence of major differences between men and women in the function and pathophysiology of the cardiovascular system implicates the need for gender-specific optimisation of patient treatment. One key gender difference resides in the electrocardiogram: it has long been known that women have higher resting heart rates than men, but that the rate-corrected QT interval (QTc) is longer in women (by 2–6%) [2,3]. As will be discussed below, this difference is an important factor in sex-linked differences in pro-arrhythmic risk, and its basis is the subject of an article in this edition of the journal by Liu et al. [4].

Women are at significantly greater risk than men of developing the potentially lethal ventricular tachyarrhythmia torsades de pointes in response to certain drugs that prolong ventricular repolarisation [3,5–7]. Excessive prolongation of ventricular repolarisation, known as the long QT syndrome owing to the increase in duration of the QTc interval, is thought to favour the generation of early after depolarisations (EADs), cellular proarrrhythmic events that, with the appropriate dispersion of repolarisation, in turn may initiate torsades de pointes [8–10]. Long QT syndrome can be either inherited through mutations in ion channels or, as alluded to above, acquired through administration of drugs that block cardiac K+ channels (in particular channels responsible for the rapid delayed rectifier current, \(I_{Kr}\)) [8,9,11,12]. Female gender is also an independent risk factor for the incidence of syncope and sudden death in the inherited long QT syndrome [3].

The basis for the gender difference in risk of torsades de pointes is unclear, but is likely to reflect the influence of sex hormones on ventricular repolarisation. In addition to a longer QTc interval [2,3], women show a steeper rate-adaptation in QT interval than men [13,14]. There are also differences between men and women in the rising and descending slopes of the T-wave, suggestive of possible gender differences in the dispersion of repolarisation [15]. The association of gender differences in QTc interval with the onset of puberty strongly implicates the sex hormones in the differences between men and women in ventricular repolarisation [16]. In line with this idea, the QTc interval in men gradually increases from puberty until it becomes similar to that in women by the age 50. The shorter JT interval of virilised compared with normal women and the longer JT interval of orchiectomised men compared to normal men argue in particular for a role for testosterone in somehow shortening male ventricular repolarisation [17].

In order to understand the underlying mechanisms by which the sex hormones influence ventricular repolarisation, it is necessary to use appropriate animal models to determine how these hormones affect key repolarising ionic conductances. The rabbit has been of significant value in this respect (for an extensive review see [3]). Similar to humans, female rabbits show a greater cycle length-dependent increase in QT interval than males, so that the QT interval of female rabbits is longer than that of male rabbits at slow heart rates [18]. Importantly, the gender difference in QT interval in rabbits has been associated with corresponding differences in the density of two potassium currents critical to ventricular repolarisation: \(I_{Kr}\) and the outward component of \(I_{K1}\) (the inward rectifier K+ current) [18]. The identification of a role for \(I_{Kr}\) is of particular note, due to the underlying channel’s acknowledged pharmacological promiscuity and role in the acquired long QT syndrome. In this regard, it is notable that drug-induced QT-prolongation by quinidine and D-
sotalol (both of which block \(I_{Kr}\)) is greater in female than in male rabbits [5].

In the work presented in this issue of \textit{Cardiovascular Research}, Liu et al. again use a rabbit model to extend our understanding of sex-linked differences in the QT interval [4]. Specifically, they have examined the effect of administration of 5α-dihydrotestosterone (DHT) to ovariectomised bucks both on the QT interval and upon the repolarising currents \(I_{K1}\) and \(I_{Kr}\) [4]. The cycle length-dependent increase in QT interval of ovariectomised bucks was similar to that of females and this was normalised by subcutaneous administration of DHT. In addition, quinidine prolonged the QT interval to a lesser extent in DHT-treated than in placebo-treated ovariectomised bucks, which suggests that testosterone may provide some protection against the acquired long QT syndrome [4]. Consistent with their previous data regarding male/female differences [18], the maximum densities of \(I_{K1}\) and of outward (but not inward) \(I_{Kr}\) were increased in DHT-treated ovariectomised bucks. However, in contrast to the previous findings comparing currents between male and female ventricular myocytes [18], in the present study the voltage-dependent activation of \(I_{Kr}\) was also shifted by approximately \(-10\) mV by the administration of DHT. The alterations in \(I_{Kr}\) were not associated with a change in rabbit \(erg\) mRNA, implying a role for altered \(erg\) product trafficking, altered association with an accessory sub-unit, or other post-translational modification of the channel. The authors did not examine the expression of subunits underlying \(I_{K1}\) but, nevertheless, the changes in rectification of the current rather than in current density across the entire voltage range examined argue that changes other than expression of the pore-forming subunit contribute to modulation of this current by DHT. Collectively, the present findings of Liu et al. [4] suggest that testosterone confers a shorter QT interval and protects against QT prolongation in males through modulation of repolarising \(K^+\) currents, consistent with a previous suggestion by Drici et al. [19]. Independent, supportive evidence that testosterone may play a protective role comes from the observation that it can reduce the extent of blockade of HERG channels by neuroleptic drugs that can induce \textit{torsades de pointes} [20]. Hence, in addition to influencing the functional density of \(I_{Kr}\), as demonstrated by Liu et al. [4], testosterone may also act to reduce susceptibility to ventricular tachyarrhythmias by modulating drug binding to the \(I_{Kr}\) channel.

As there is clearly now ample evidence to suggest that high levels of testosterone shorten ventricular repolarisation and reduce drug-induced QT interval prolongation, the question arises as to whether or not this alone can account for the increased arrhythmogenic risk associated with female gender. There is evidence that it cannot. For example, Rosen’s group have examined the effect of sex hormone treatment in ovariectomised female rabbits on papillary muscle action potential duration at 30 and 90\% repolarisation (\(APD_{30}\) and \(APD_{90}\), respectively) [21]. Although DHT, but not 17\(\beta\)-oestradiol (EST), reduced the cycle-length dependent \(APD_{90}\) relative to placebo-treated control, the effects on \(APD_{90}\) were less pronounced [21]. Moreover, treatment with EST significantly prolonged \(APD_{90}\) and increased the incidence of early after depolarisations (EADs) in response to an \(I_{Kr}\) blocker (E-4031). These findings suggest that EST may play a role in increasing pro-arrhythmic risk [21]; however, critical measurements of plasma hormone levels were not reported in that study, so that it was not possible to relate the changes in APD to circulating hormone levels [3,21]. A more recent study of ovariectomised and ovariectomised rabbits by Pham et al. [22] provides evidence that testosterone does protect males against excessive prolongation of repolarisation by \(I_{Kr}\) blocking drugs, but that the risk of excessive prolongation of repolarisation in females involves sex-linked factors other than oestrogen. Very recently, Rosen’s group have reported differences in the L-type \(Ca^{2+}\) current (\(I_{Ca,L}\)) between myocytes from the epicardial and endocardial regions of the left ventricular free wall of female, but not male, rabbit hearts that may contribute to gender differences in ventricular repolarisation [23]. The transmural heterogeneity in \(I_{Ca,L}\) was lost in ovariectomised females and could be restored by administration of oestradiol or DHT [23]. Oestradiol and DHT have also been shown to reduce expression of Kv1.5 and KCNE1 \(K^+\) channel mRNAs in ovariectomised rabbit hearts [19].

Arguably, the relevance to humans of the consequences of oestradiol or DHT administration to ovariectomised rabbits can be questioned. The normal female rabbit is an induced ovulator with only a brief period of oestrous and with very low circulating levels of oestradiol and testosterone, which are little affected by ovariectomy [3,22]. Moreover, the circulating levels of oestradiol and DHT achieved by sub-cutaneous implantation of slow release pellets in ovariectomised rabbits are not physiological [23]. Nevertheless, the lack of correlation between plasma levels of either DHT or oestradiol and the drug-induced prolongation of \(APD_{90}\) in female rabbits suggests that factors in addition to these hormones are likely to contribute to the gender differences in susceptibility to arrhythmogenic events [22]. In humans, there is good evidence that factors in addition to testosterone contribute to the differences between men and women in susceptibility to ventricular arrhythmias. Women taking oral contraceptives are at increased risk of ventricular ectopy, suggesting a pro-arrhythmic action of either oestrogen or progesterone [24]. It has been suggested that it is actually the ratio of progesterone-to-oestradiol, rather than the absolute levels of these two hormones \textit{per se}, that are important in modulating the propensity of women to develop \textit{torsades de pointes} [3,25]. Very notably, in a recent study of ibutilide-induced QTc prolongation in women at different stages of the menstrual cycle, drug-induced QTc prolongation was greatest during menses and at the ovulatory stage of the cycle, as compared with the luteal phase [26]. Thus,
plasma levels of progesterone and the progesterone-to-oestriadiol ratio, but not oestriadiol or testosterone, inversely correlated with ibutilide-induced QTc prolongation, suggesting a key role for progesterone in control of susceptibility to ventricular arrhythmias in women [26]. The emerging picture then, to which the paper by Liu et al. [4] in this edition of Cardiovascular Research makes a very valuable and material contribution, is that testosterone does provide males with protection against excessive QT interval prolongation and susceptibility to drug-induced pro-arrhythmia. However, the situation for females appears to be more complex. Further information is therefore required regarding the mechanisms by which sex hormones influence female ventricular repolarisation and susceptibility to ventricular arrhythmias. One potential problem with the use of the rabbit as the sole or dominant animal model for such investigations is that the abbreviated oestrous cycle of female rabbits differs markedly from the situation in humans. Rats, cats and dogs are commonly used to investigate cardiac electrophysiology in the laboratory but are unlikely to be superior alternatives to the rabbit for this particular type of study, either because of the unrepresentative nature of their repolarising K+ currents (the rat), or the unusual nature of their oestrous cycles (cats have periods of anoestrus and dogs have a prolonged inter-oestrus period) [27]. On the other hand, laboratory guinea-pigs are polyoestrous all year around, have a conventional oestrous cycle of approximately 16 days, and circulating levels of oestriadiol that are reduced by ovarietomy [28,29]. Whilst (unlike rabbit and human) guinea-pig myocytes lack the transient outward potassium current, Ito1, involved in early repolarisation, both delayed rectifier subtypes and IK1, are functionally expressed. The guinea-pig may therefore be of value in elucidating further the effects of sex hormones on female ventricular repolarisation and these latter, key underlying conductances, particularly if it is used in concert with the existing rabbit model. Whichever model is chosen, it is essential that further information is obtained, in order to understand more clearly the sex-linked factors that place females at increased risk of serious ventricular arrhythmia. The unambiguous evidence for a protective role of testosterone in males [4,16–18,22] suggests that detailed cellular and molecular investigations into the underlying basis for this effect are now warranted. The information that this line of investigation would yield might ultimately aid the development of novel approaches to offset excessive QT interval prolongation and mitigate the risk of drug induced pro-arrhythmia.

References