Sex differences in subinterval measurements in intervention-free, fasted ECGs from seven intensive QT studies

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Introduction

Differences in the electrical activity in the heart between males and females are well recognised [1, 2]. Females have longer QTc intervals than males and are associated with a higher risk of Torsades de Pointes [1].

This difference is apparent only after puberty; suggesting that sex hormones play a role [1]. There is an observed hormonal influence on ion-channel density, where oestrogen likely counteracts the progesterone-led enhancement of IK [2].

There are also sex differences in drug-induced changes in cardiac electrophysiology [3]. Specifically, women are at greater risk of drug-induced Torsades de Pointes [2].

The importance of sex differences in cardiac electrical activity has not been fully appreciated in the context of drug sensitivity and the design of intensive cardiac studies.

This study examines differences in the length of ECG intervals and subintervals (QTcF, QRS, J-T_{peak}, J-T_{peak}cJ, $T_{peak}T_{end}$ to elucidate more precisely the differences between cardiac electrical activity in males and females.

Methods

Fasted and intervention-free data were collected from healthy volunteers participating in 7 different intensive QT studies. Where these data were from cross-over studies, Period 1 pre-dose data were used. Placebo treatment was considered to be an intervention; therefore placebo data were not included.

ECG Analysis: Standard 10s ECGs were recorded in triplicate and processed using the GE Healthcare Marquette 12SL ECG machine. Because of known differences between processing algorithms, data processed using the AMPS Bravo and the QT Guard Plus algorithms are presented separately. Four studies were processed using only the QT Guard Plus algorithm, and 2 were studied using the AMPS Bravo algorithm. One study presented here has been analysed using both algorithms separately. A total of 333 individuals were examined, 117 were female, 216 were male. A total of 2736 ECGs were recorded, making 916 averaged triplicates.

All fasted and intervention-free ECG recordings were averaged by individual ID and by algorithm, and individual ID averages were averaged again in order to have each unique person contributing the same weight.

Conclusions

The data from this study suggest that future studies investigating QT prolonging drugs should take into account sex differences.

This study agrees with previously published studies in finding that females had a mean QTcF longer than males, entirely due to longer J-T_{peak}. This was mitigated by the slightly longer QRS and $T_{peak}T_{end}$ in males, but this still was not enough to offset longer female J-T_{peak}.

Both algorithms show the same trend but they do return different values.

Differences in subinterval lengths between the sexes were proportional, however differences became disproportional when subinterval durations were had correction formulae applied. Care should be taken when comparing corrected subinterval data between sexes. Uncorrected data may be more reliable or other correction methods, such as different correction methods for each sex [4] could be explored.

Differences in J-T_{peak} suggest that females may be more at risk of Torsades and arrythmias following administration of predominant hERG blockers, which prolong J-T_{peak} [5] and not "balanced blockers" which do not [5], though further investigation is needed.

The limitations of this study are: (i) known QT prolonging drugs and/or the meal effect were not used to explore sex differences when prolonging QT, and (ii) this was an assessment of normal cardiac electrophysiology, therefore populations of men and women at greater risk of long QT (e.g. patient groups) were not studied.

Results

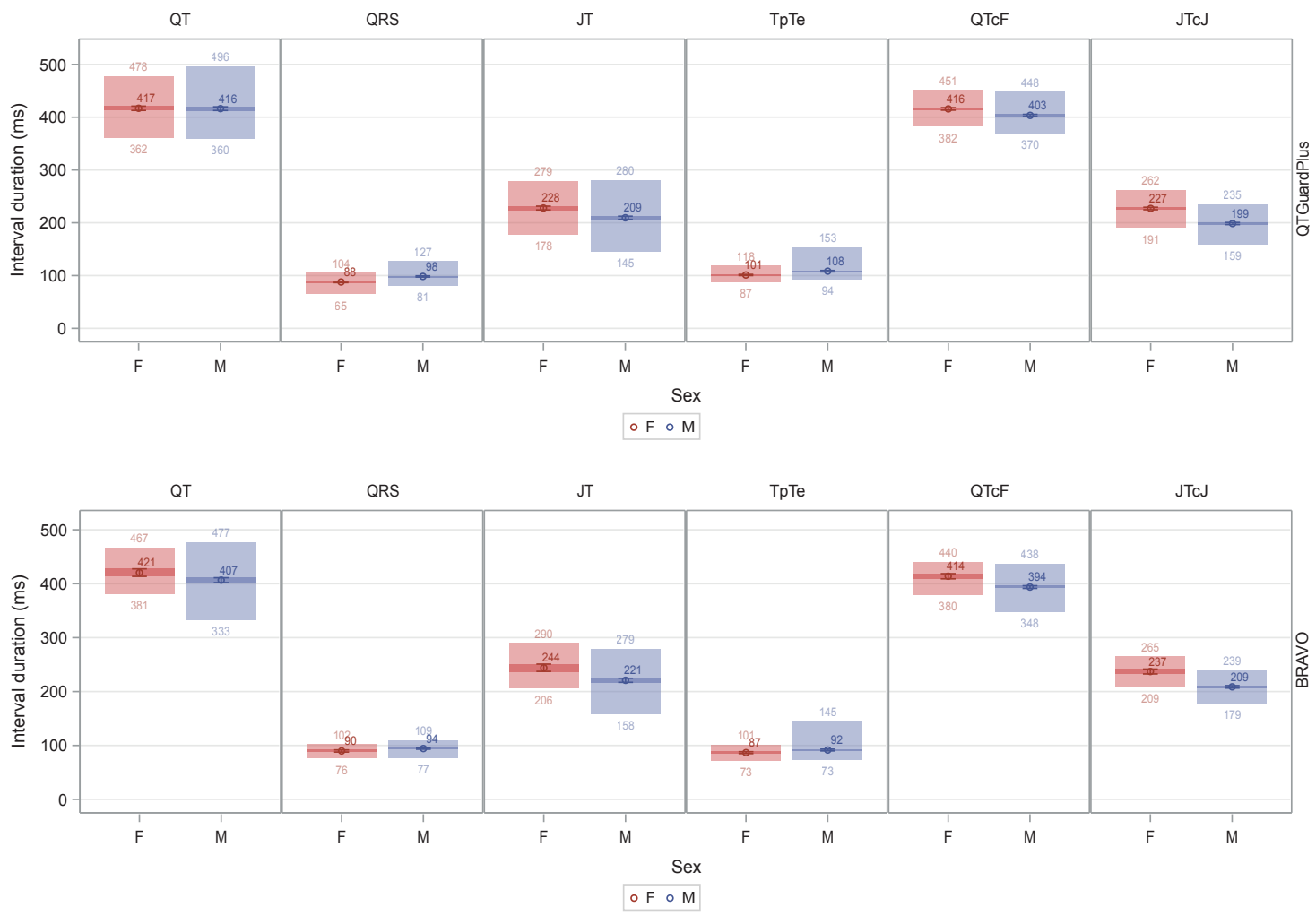

Figure 1. ECG subintervals calculated using (A) Bravo and (B) QT guard plus. Numbers denote the mean, minimum and maximum values.

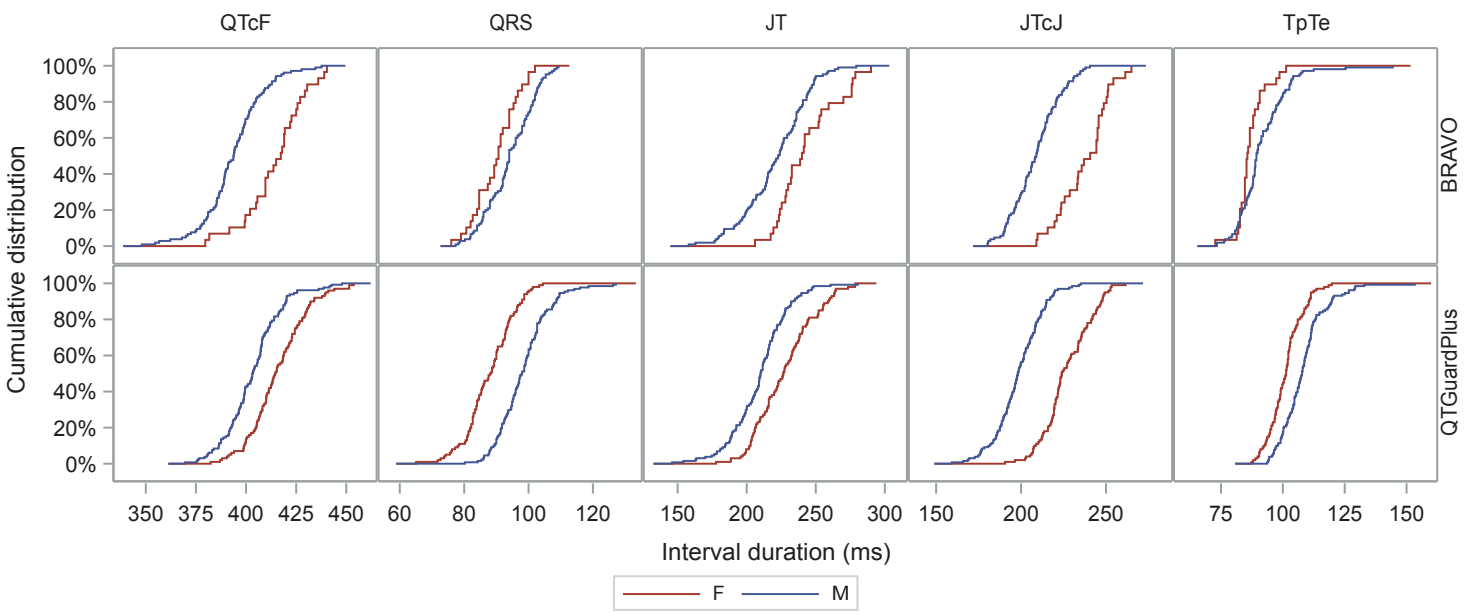

Figure 2. Empirical cumulative distribution plots of ECG subintervals calculated using Bravo and QT Guard Plus algorithms

The results shown in **Figure 1** showed QT was longer in females (20 ms in Bravo and 13 ms in QT Guard Plus). The source of this difference was the J-T_{peak} which was significantly longer in females (uncorrected J-T_{peak} 23 ms in Bravo and 19 ms in QT Guard Plus).

Conversely QRS and $T_{peak}T_{end}$ were both longer in males (QRS: 4 ms in Bravo and 10 ms in QT Guard Plus; $T_{peak}T_{end}$: 5 ms in Bravo and 7 ms in QT Guard Plus), however these were not sufficiently long in males to offset the greater J-T_{peak} in females. The net result was a longer QT in females.

The difference in QT between males and females was magnified by rate correction. J-T_{peak}cJ was 28ms longer in females in both algorithms (5 ms and 9 ms longer tan uncorrected J-T_{peak} respectively) which led to females having a greater QTcF than males (20 ms in Bravo, 13ms in QTGuard Plus).

Subintervals had similar distribution patterns in each sex. Differences in mean subinterval durations between males and females were consistent, rather than due to outlier individuals (**Figure 2**). TpTe was reported to have a larger variance in males when calculated by Bravo.

References

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