Short QT Interval Linked to Androgen Misuse: Wider Significance and Possible Basis

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To the Editor:

We read with great interest the recent report by Dr. Bigi and colleagues¹ showing significantly shortened rate-corrected QT (QT_C) intervals in professional male bodybuilders taking anabolic androgenic steroids (AAS) compared to drug-free bodybuilders and age-matched sedentary controls. Not only are the findings of this study important in terms of providing a potential predictive measure of AAS misuse in strength athletes (QT_C interval values of ≤ 380 ms in a bodybuilder may provide 83% sensitivity and 88% specificity in predicting AAS abuse),¹ but they also contribute toward growing evidence (reviewed in reference 2) for an important role for androgens in cardiac repolarization.

Women exhibit QT_C intervals that are significantly longer than those from men, with male-female differences commencing at puberty.² Data from animal studies indicate that orchietomized male rabbits exhibit abbreviated ventricular repolarization that is more reminiscent of females and that is restored by androgen administration, implicating testosterone in observed repolarization differences.^{2,3} Studies comparing women with virilization syndrome (due to polycystic ovary syndrome or adrenal hyperplasia) with healthy age-matched controls report markedly shortened repolarization phases of the electrocardiogram (ECG) from the virilized group, with the duration of repolarization in virilized subjects being inversely associated with testosterone level.^{4,5} Thus, it appears that raised androgen levels can impact significantly

on QT_C interval duration in both sexes. In this regard, it would be of clear interest now to determine the relative extent to which sustained AAS use impacts on QT_C interval among female bodybuilders who misuse AAS.

Bigi and colleagues highlight a possible role for increased "I_{K1}" potassium channel current in mediating androgen-induced QT and QT_C interval shortening¹ and we agree with this possibility. We would suggest an additional candidate: the human ether-à-go-go-related gene (hERG)-mediated "I_{Kr}" current. The same experimental study that reported increased I_{K1} in androgen-treated orchietomized rabbits also reported an increase in I_{Kr}, though without any change in rabbit-*erg* message, suggestive of a posttranscriptional or posttranslational androgen effect.³ Recent data support nongenomic stimulation of hERG channels by testosterone via PI-3 kinase.⁶ Thus, increases to I_{K1} and I_{Kr} might both contribute to QT_C interval shortening induced by AAS use. At least in principle, the use of I_{Kr}-blocking drugs such as dofetilide and quinidine could discriminate between the two; although the established association between I_{Kr} blockade and drug-induced long QT syndrome and torsades de pointes arrhythmia warrants caution for in vivo investigational use. On the other hand, one might hypothesize that if AAS-induced QT_C interval shortening is mediated to a significant extent by nongenomic androgen actions, the short- and long-term users of AAS should manifest similarly shortened QT_C intervals. In this regard, it is

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perhaps notable that intramuscular administrations of testosterone to hypogonadal men have been reported to result in concentration-dependent QT interval shortening.^{5,7}

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