

EDITORIAL FOCUS

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Beyond the QT interval: how QT/RR hysteresis may reveal a sex-dependent hidden risk for cardiac arrhythmias

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Cardiac arrhythmia is a life-threatening condition in which disturbances in the electrical signals that control the heart cause an irregular heart rate (HR) or rhythm that may lead to a sudden cessation of cardiac activity and potentiate sudden cardiac death (SCD) (1). Cardiac arrhythmia can be categorized into two subtypes: supraventricular arrhythmias (atrial fibrillation, atrial flutter, and paroxysmal supraventricular tachycardia) and ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) (1). Ventricular arrhythmias are the more serious form that occur most frequently in the context of heart disease, although the incidence is increasing in apparently healthy individuals (2). The age- and sex-adjusted rates of idiopathic ventricular arrhythmias increased from 45 to 62 per 100,000 individuals from 2005–2007 to 2011–2013, with an overall incidence increasing with age (2). Thus, identification of potential prognostic biomarkers is important clinically and may aid in the risk stratification and prevention of cardiac arrhythmias and SCD in the general population, regardless of heart disease.

QT/RR hysteresis represents a clinically promising biomarker that provides insight into the temporal relation between changes in HR and the delayed adaptation of the QT interval (ventricular repolarization). In general, longer RR intervals are followed by longer QT intervals, and shorter RR intervals are followed by shorter QT intervals. The QT adjustment is not instantaneous, and the lag in QT adaptation creates the hysteresis effect, which is associated with an elevated risk of arrhythmias and SCD in healthy and clinical populations. QT/RR hysteresis is more pronounced during situations that induce an abrupt autonomic transition and HR oscillations, such as exercise onset and recovery (3), and in clinical conditions afflicted with autonomic derangements, such as long QT syndrome and coronary artery disease (4). Concerning biological sex, females typically present with longer QT intervals compared to males, despite comparable HR, and have more pronounced alterations in QT interval with changes in HR

after puberty (5). Such sex-related differences in cardiac electrophysiology suggest that QT/RR hysteresis may manifest differentially between males and females during abrupt autonomic changes, although evidence in this area is limited.

In this journal, Araújo et al. (6) sought to address this knowledge gap by exploring sex differences in QT/RR hysteresis in thirty-four young, healthy adults (17 females) in response to trigeminal nerve stimulation (TGS) induced by 2-min facial cooling (Fig. 1). QT hysteresis, which was evaluated as the relation between TGS-induced changes in HR and QT intervals, was stronger in females ($r = 0.868$, $P < 0.001$) than males ($r = 0.481$, $P = 0.051$) and remained significant in females (partial $r = -0.625$, $P = 0.01$) but not males (partial $r = -0.373$, $P = 0.155$) after adjustment for the degree of HR fluctuations (tertiles). On average, TGS-induced reductions in HR and increases in RR and QT intervals were similar between sexes. However, sex differences were evident after TGS onset (initiation) and offset (recovery). An increase in QT interval was evident at 15 s for both sexes after TGS onset, but continued to increase throughout the 30-s onset window only in females, despite similar reductions in HR and increases in RR interval. During the TGS offset, only females exhibited reductions in QT interval at 20 s that persisted throughout the 30-s offset window despite comparable increases in HR and reductions in RR interval. Despite evidence for sex differences in the QT interval in response to TGS, both sexes exhibited comparable changes in blood pressure and pain ratings, suggesting a relatively similar physiological stimulus between sexes. In addition, the root mean square of successive differences in RR intervals (RMSSD), a time-domain index of heart rate variability (HRV) that represents cardiac parasympathetic modulation, was similarly increased in both sexes. Together, these findings indicate females exhibit a more integrated QT–RR relation during TGS, whereas it was disassociated in males, highlighting



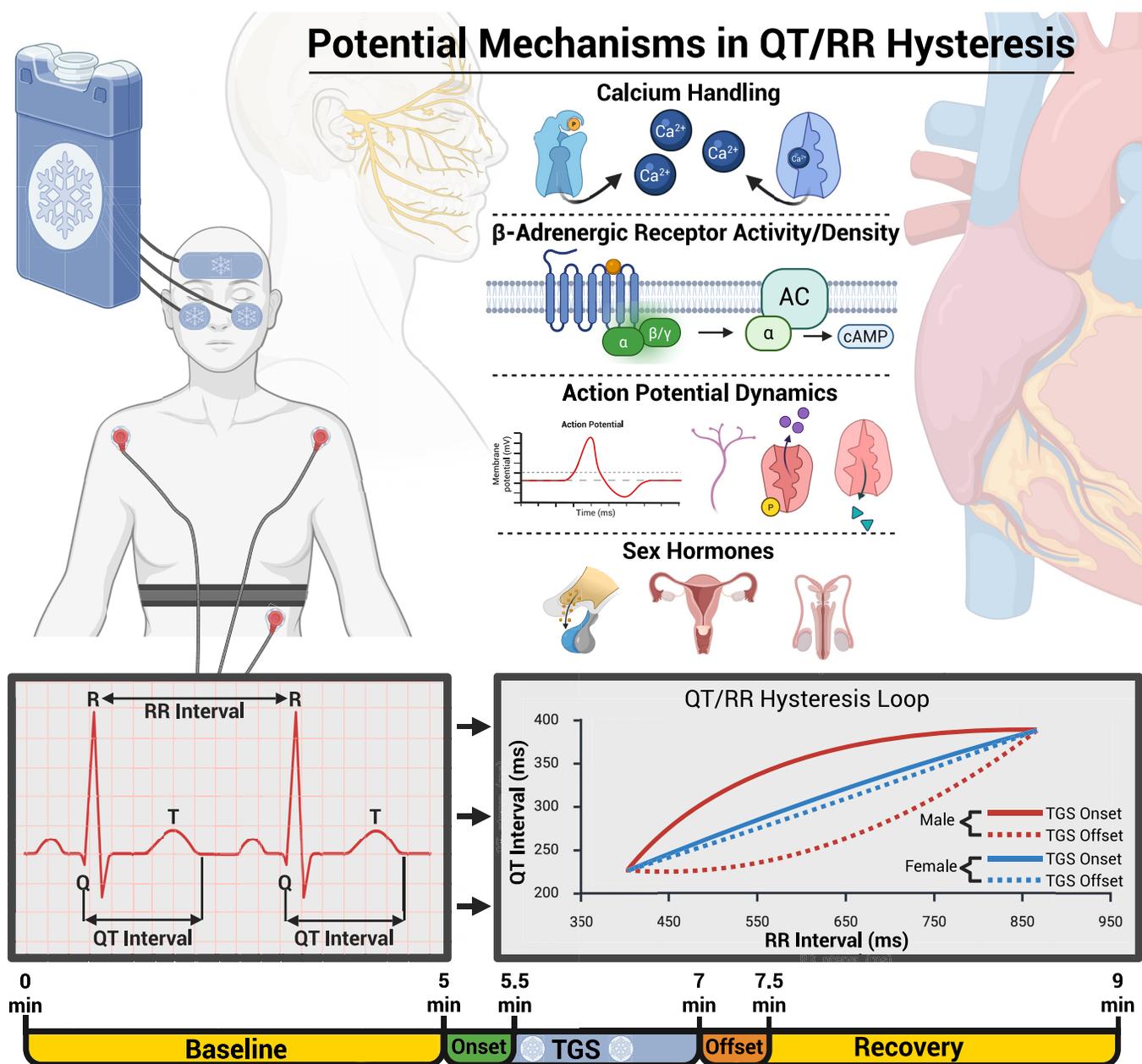


Figure 1. Potential Mechanisms in QT/RR Hysteresis. The trigeminal nerve stimulation (TGS) used in recent work by Araújo et al. (6) involved a 2-min facial cooling protocol (timeline displayed at the bottom). Specifically, an ice pack was placed on the forehead and cheeks to stimulate the ophthalmic and maxillary divisions of the trigeminal nerve while beat-to-beat electrocardiography (ECG), blood pressure, and respiratory rate were collected (top and middle left). Ultimately, during the onset and offset of TGS, males exhibited a disassociation of their QT and RR intervals (QT/RR hysteresis), whereas females did not. Hypothetical data displaying this response are depicted in the middle right, and proposed mechanisms driving this result are listed on the top right. Figure created with a licensed version of Biorender.com.

sex differences in dynamic ventricular repolarization. The more adaptive repolarization response in females may be cardioprotective and could help explain the lower incidence of SCD in females (1).

Using facial cooling for TGS represents a controlled and unique experimental tool for examining neural and cardiovascular responses to partial activation of the so-called “diving reflex.” In addition, TGS elicits concurrent activation of the parasympathetic and sympathetic nervous systems, or “autonomic conflict,” which can create sympathovagal antagonism and thereby increase arrhythmogenic risk. One notable

observation from the recent work by Araújo et al. (6) was that despite comparable HR and RMSSD responses, females exhibited a more integrated and responsive alteration in QT intervals compared to males, highlighting sex differences in ventricular repolarization and QT/RR hysteresis that may be inherent to the heart per se (5). Compared with males, females have proportionally smaller septal and posterior wall thickness and left ventricular mass as well as exhibit differences in the dispersion of ventricular repolarization and overall electrocardiogram (ECG) patterns, suggesting that biological sex may influence cardiac

structure and neural innervation to produce disparities in cardiac electrophysiology (5). Furthermore, preclinical data have demonstrated sex differences in excitation-contraction coupling, intracellular calcium handling, action potential dynamics, ion channel activity, and beta-adrenergic sensitivity that may be attributed, in part, to sex hormones as well as age (5). Collectively, sex-related differences in structural, cardiac electrophysiological, and cellular signaling cascades governing ventricular repolarization (5) possibly drive sex-specific differences in QT/RR hysteresis seen during TGS in an integrative manner (6).

Although autonomic conflicts contribute to cardiac arrhythmias, a direct assessment of real-time cardiac autonomic efferent nerve activity in humans is challenging. HRV somewhat circumvents these limitations as a noninvasive tool for estimating cardiac parasympathetic modulation in humans. Using HRV, Araújo et al. (6) documented similar increases in RMSSD between males and females despite sex differences in QT/RR hysteresis, suggesting that TGS-induced changes in cardiac parasympathetic modulation were not different between sexes and may not explain QT/RR hysteresis. To confirm these findings, additional studies utilizing pharmacological inhibition of cardiac muscarinic and/or beta-adrenergic receptors are needed. For instance, Pelchovitz et al. (7) evaluated whether QT/RR hysteresis was caused by differential autonomic states during exercise and recovery, which was accomplished by cardiac parasympathetic blockade via intravenous infusion of atropine. Cardiac parasympathetic blockade ultimately reversed QT/RR hysteresis that was present during exercise in both healthy adults and those with coronary artery disease and diabetes; however, sex differences in QT/RR hysteresis were not explored (7). Krahn et al. (4) documented that beta-adrenergic receptor blockade via a 1-mo treatment with either atenolol or nadolol normalized QT/RR hysteresis in patients with long QT syndrome during exercise and recovery, suggesting that derangements in the cardiac sympathetic nervous system play an important role in the arrhythmogenic risk in this patient group. Future studies may consider incorporating pharmacological manipulation of cardiac muscarinic and/or beta-adrenergic receptors in conjunction with non-invasive tools such as HRV, cardiac sympathetic imaging with meta-iodobenzylguanidine, or concurrent muscle sympathetic nerve activity (MSNA) recordings to provide insight into sex-related disparities in QT/RR hysteresis in response to TGS.

Araújo et al. (6) quantified QT/RR dynamics using a single-lead ECG, but did not specify the placement of ECG electrodes or the choice of leads (leads I, II, or III), which is crucial for obtaining an accurate and consistent reading of cardiac electrical activity. While the use of a one-lead ECG is not uncommon in research settings, a 12-lead ECG is a standard diagnostic tool for assessing cardiac electrical activity, but may not be easily accessible across all clinical and nonclinical settings. Given the prognostic value of the QT interval and QT/RR hysteresis, validation of data generated from a one-lead ECG against a clinical 12-lead ECG is needed. Recently, Beers et al. (8) conducted simultaneous recording of a smartphone-operated single-lead ECG and a standard 12-lead ECG in a primary care setting and found excellent agreement between the two methods for evaluating ventricular repolarization with corrected QT

(QTc) intervals (8). This important finding not only enhances the utility of this smartphone-operated single-lead ECG in clinical practice but also potentially changes how technological advances can be more integrated in daily life for the general population to provide clinical information as well as to allow for a quick intervention in case of a medical emergency.

The use of QT/RR hysteresis is promising in the context of risk assessment as well as the prevention and treatment of adverse cardiac events. Nevertheless, no universally agreed-upon guidelines exist regarding the implementation of this method to better quantify risk. To evaluate QT/RR hysteresis, Araújo et al. (6) used a linear regression between changes in HR and QT intervals and adjustment for the degree of HR fluctuations (tertiles) to account for variability in the HR response. However, the speed at which the QT interval adapts to changes in HR is highly heterogeneous, with intra-subject stability and intersubject variability (9). Because QT/RR hysteresis is independent of the static QT/RR relationship, there is a need for combining HR correction with individual hysteresis correction of the QT interval (9). However, several QT correction formulae exist that account for different time points and HRs as part of the QTc intervals, with each QT correction formula potentially influencing the clinical interpretation and related mortality risk (9). These findings highlight the importance of incorporating multiple methods for evaluating ventricular repolarization and QT/RR hysteresis.

Beyond the heart, TGS raises blood pressure due to sympathetic activation and peripheral vasoconstriction as determined via MSNA and femoral vascular conductance, respectively (3). Specifically, TGS increases MSNA total activity and mean arterial pressure and reduces femoral vascular conductance (3). Araújo et al. (6) also observed comparable blood pressure responses between males and females. Still, it remains unclear if there are sex differences in MSNA, femoral vascular conductance, and other determinants of blood pressure (stroke volume and cardiac output) in response to TGS. In this regard, there is evidence for sex differences in sympathetic and hemodynamic responses to sympathetic stimulation via the cold pressor test (10). In this study, females exhibited lower baseline mean arterial pressure and greater femoral vascular resistance compared to males, despite comparable MSNA (10). Upon sympathetic activation, females exhibited smaller increases in mean arterial pressure and vascular resistance, but comparable increases in MSNA when compared to males (10). Importantly, cold pressor test-induced increases in MSNA predicted corresponding increases in mean arterial pressure and vascular resistance in males but not in females, suggesting that changes in neurovascular coupling during sympathetic activation may be sex-dependent (10). These interesting findings do not provide a mechanistic explanation for the recent work by Araújo et al. (6) but rather highlight an important knowledge gap that future studies may explore in the context of sex differences in neurovascular and hemodynamic responses to TGS.

In conclusion, recent work by Araújo et al. (6) provides important insight that may advance our understanding of sex-related differences in QT/RR hysteresis in young healthy adults. TGS via facial cooling represents an easily

implementable protocol that could be applied in research and clinical settings to evaluate QT interval dynamics in response to autonomic conflicts, which may improve our ability to assess future arrhythmic and SCD-related risks. The finding that males are more susceptible to QT/RR hysteresis during TGS aligns with recent data reporting a six-fold higher risk for sudden cardiac arrest and SCD in male competitive athletes compared to female counterparts (1). Future studies may consider incorporating this clinically relevant evaluation in conjunction with pharmacological interventions and/or experimental conditions such as TGS when examining sex-related disparities and health and disease to advance both mechanistic and translational knowledge and therapeutic approaches.

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DISCLAIMER

The content and any opinions expressed in this article are those of the authors and do not necessarily represent the views of the American Physiological Society.

DISCLOSURES

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AUTHOR CONTRIBUTIONS

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