Inflammation and Heart Rate–corrected QT Interval: Evidence for a Potentially Reversible Cause of Sudden Death in Patients with Rheumatoid Arthritis?

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Editorial

Inflammation and Heart Rate–corrected QT Interval: Evidence for a Potentially Reversible Cause of Sudden Death in Patients with Rheumatoid Arthritis?

Rheumatoid arthritis (RA) is associated with an increased cardiovascular (CV) mortality risk; however, evidence to date suggests that the presence of traditional CV risk factors, prevalent in patients with RA, only partially accounts for the increased cardiac mortality risk[1]. In an effort to reduce the CV morbidity and mortality associated with RA, numerous novel risk factors have been sought and implicated, including myocardial repolarization abnormalities[2], autonomic dysfunction[3], and inflammation[4]. Given that RA is associated with a doubled risk of sudden cardiac death[1], an arrhythmic mechanism would seem plausible. The QT interval marks the time from onset of ventricular depolarization to the completion of repolarization and can be measured using a 12-lead electrocardiogram (ECG) from the beginning of the Q wave to the end of the T wave. Prolongation of ventricular repolarization duration increases the risk of torsade de pointes, which can lead to ventricular fibrillation and sudden death. Prolongation of heart rate-corrected QT interval (QTc) independently predicts sudden death in the general population[5] and more strongly in patients with RA[6]. In fact, several studies have demonstrated associations between inflammation and QTc interval in RA[2,6,7]. Lazzerini, *et al* reported normalization of the QTc interval following 52 weeks of treatment with the interleukin 6 (IL-6) inhibitor tocilizumab (TCZ) in 17 patients with RA[2]. In this issue of *The Journal*, Kobayashi and colleagues[8] have provided further evidence that inflammation in RA is associated with QTc prolongation, which can be reversed with the use of antiinflammatory agents.

Kobayashi, *et al*[8] performed a cross-sectional case control study comparing QTc interval between 94 patients with RA and 42 age- and sex-matched controls. They report that QTc interval was higher in patients with RA compared to controls. In their study, patients underwent 24 weeks of treatment with TCZ, which resulted in a significant reduction in QTc interval. This well-conducted study provides direct evidence that controlling inflammation in patients with RA through IL-6 inhibition can reduce arrhythmia risk, possibly reducing sudden death risk. Further, they demonstrated that the change in inflammation [as measured by C-reactive protein (CRP)] independently predicted the change in QTc interval. Interestingly, the association between CRP and QTc was strongest in patients who had prolonged QTc at baseline. There are a number of plausible mechanisms for the observed reduction in QTc following IL-6 inhibition. Animal studies have demonstrated that the inflammatory cytokines tumor necrosis factor-α (TNF-α) and IL-1 can delay cardiomyocyte action potential through effects on cardiac potassium channels[9] and calcium channels[10], respectively. IL-6 inhibition reduces inflammation and results in lower concentrations of circulating TNF-α and IL-1. The effect of IL-6 on cardiomyocyte potential is not known and requires further study. Another potential mechanism is the effect of inflammation on autonomic function. The QTc interval can be influenced by the autonomic nervous system; surgical sympathetic denervation[11] and cholinergic stimulation[12] can reduce QTc interval. Observational data show that patients with RA have reduced parasympathetic activity[13,14] and heightened sympathetic activity[3,15], independent of the presence of hypertension[3,13]. One interesting mechanism is the effect of IL-6 inhibition on cardiac remodeling. In an earlier study, Kobayashi, *et al* demonstrated that TCZ treatment promoted positive cardiac remodeling in patients with RA[16]. Cardiac magnetic resonance imaging demonstrated increases in left ventricular ejection fraction and reductions in left ventricular mass index in 20 female patients with RA after 52 weeks of IL-6 inhibition. In the current article[8], the authors comment that this may not explain their present findings, given that patients demonstrated reductions in QTc interval after 24 weeks of IL-6 inhibition therapy, and only 12 weeks in an earlier study by Lazzerini, *et al*[2], supporting a process of electrical rather than structural remodeling.

This study by Kobayashi, *et al*[8] provides mechanistic

See QTc treated with TCZ, *page 1620*

insight into the potential etiology of sudden death in patients with RA and provides further evidence for the link between inflammation and arrhythmia risk. Further, this work provides a number of clinical implications at the bedside for rheumatologists, cardiologists, and general physicians. First, should all patients with RA undergo routine ECG screening to assess QTc interval? What constitutes a normal QTc interval in patients with RA? While normal range values of QTc interval exist for the general population, these are lacking in the RA population and require further quantification. Can QTc interval be used as an additional criterion to support the use of biologic agents in patients with RA who fail to meet standard criteria? Given that β blockers can reduce QTc interval in patients with long QT syndrome[17] and their proven mortality benefit in patients with chronic heart failure[18] and myocardial infarction[19], is there a role for β blocker use in patients with RA?

The results of this study support the hypothesis that inflammation is a potentially reversible cause of QTc prolongation, and controlling inflammation may thereby reduce the risk of sudden death. Further, in patients with prolonged QTc the presence of chronic inflammatory diseases should be sought and inflammation controlled at the earliest opportunity.

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