# 6 Age, Sex and Racial Differences in Cardiac Repolarization and Arrhythmogenesis

Arja Suzanne Vink, Sally-Ann B. Clur, Pieter G. Postema, Nico A. Blom, and Arthur A. M. Wilde

## Introduction

Willem Einthoven recorded the first electrocardiogram (ECG) in a healthy man in 1905, long before the understanding of the role of ion channels and the cardiac action potential. Over the last decades, extensive progress has been made in our understanding of the relationship between structure and function of the cardiac ion channels and the effects of changes in expression and gating of these channels on the electrical substrate and the ECG. The function of ion channels is significantly modified by the subunit assembly and environmental conditions (i.e. hormones, electrolyte concentrations and pH), which have substantial effects on the cardiac depolarization and repolarization. Profound ECG changes in individuals with primary arrhythmia syndromes have helped to discover the role of subunits of ion channels in causing different types of cardiac channelopathies. Indeed, pathogenic mutations in the genes encoding these subunits are causal to some of these rare arrhythmia syndromes. However, despite this improved understanding of the physiology of the cardiac ion channels, there is still a lack of knowledge on age, sex and racial differences seen in the human ECG especially regarding the QTc-interval. This is due to incomplete and controversial information on age, sex and racial differences in the expression and properties of ion channels and the regulation of ion channels, i.e. by sex hormones.

This chapter outlines the recent developments in the study of age, sex and racial differences in QTc-interval in healthy individuals.

A. S. Vink (✉)
Department of Clinical and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Heart Center, Amsterdam, The Netherlands

Department of Pediatric Cardiology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
e-mail: a.s.vink@amsterdamumc.nl

S.-A. B. Clur
Department of Pediatric Cardiology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands
e-mail: s.a.clur@amsterdamumc.nl

P. G. Postema · A. A. M. Wilde
Department of Clinical and Experimental Cardiology, Amsterdam UMC, University of Amsterdam, Heart Center, Amsterdam, The Netherlands
e-mail: p.g.postema@amsterdamumc.nl; a.a.wilde@amsterdamumc.nl

N. A. Blom
Department of Pediatric Cardiology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands

Department of Paediatric Cardiology, Willem-Alexander Children's Hospital, Leiden University Medical Centre, Leiden, The Netherlands
e-mail: n.a.blom@amsterdamumc.nl

## General Aspects of Cardiac Repolarization

The role of cardiac ion channels in the generation of the ventricular cardiac action potential is


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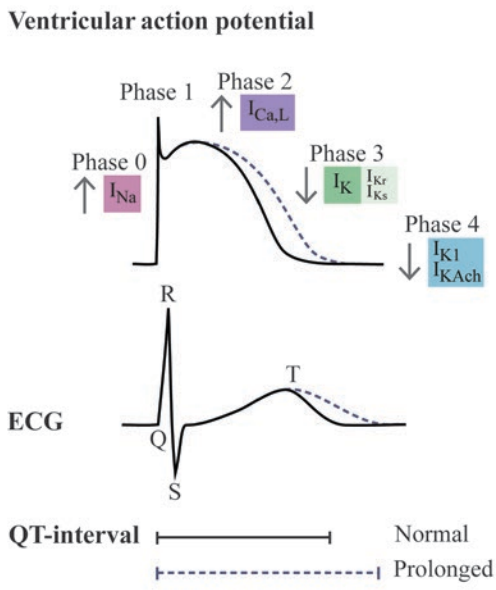


**Fig. 6.1** Electrophysiological basis of the ventricular action potential and prolongation of the QT-interval. See text for explanation

outlined in depth in Chap. 1. In short, the rapid depolarization (phase 0) is caused by the influx of sodium ions into the cell through voltage-gated sodium channels ($I_{Na}$) (Fig. 6.1). Phase 1 repolarization is mainly caused by activation of the transient outward potassium currents ($I_{to}$) together with a corresponding rapid decay of the sodium current, which is followed by phase 2. In this plateau phase, continued L-type late calcium ($I_{Ca,L}$) and a small amplitude late sodium current into the cell balance the effect of potassium currents out of the cell. The decay of the calcium current and the increase in delayed rectifier potassium current ($I_{Ks}$), in the rapid activation component of the delayed rectifier potassium current ($I_{Kr}$), and particularly the late activation of the inward rectifier potassium current ($I_{K1}$), are together responsible for the repolarization (phase 3) with ultimate return to the resting potential (phase 4).

The vectorial sum of the complex interactions of these different electrical currents in all the cardiomyocytes results in the physical manifestation of the cardiac waveform morphologies on the ECG that consist of a QRS complex and a T-wave. The QT-interval is measured from the beginning of the QRS complex to the end of the T-wave and represents the duration of activation and recovery of the ventricular myocardium. The QT-interval is most affected by alterations in phase 2 and phase 3 of the ventricular action potential [1]. Upregulation of the $I_{Ca,L}$ channel currents prolongs the QT-interval, whereas downregulation shortens the QT-interval. During phases 2 and 3, upregulation of $I_{Ks}$, $I_{Kr}$ and $I_{K1}$ channel currents shorten the QT-interval, and downregulation prolong the QT-interval. Finally, an increased amplitude of the late sodium current lengthens the action potential and thus the QT-interval.

In the normal heart, the QT-interval shortens with an increase in heart rate and lengthens with a decrease in heart rate. Since the QT-interval adapts to the heart rate, the QT-interval should be corrected for heart rate using the preceding RR-interval (QTc-interval), which can be done using several formulas [2]. None of these formulas gives an optimal correction, but the Bazett correction formula is most frequently used in daily practice [3]. A prolonged QTc-interval is a marker for an increased risk of torsades de pointes (TdP), a malignant polymorphic ventricular tachyarrhythmia that precipitates syncope, sudden cardiac arrest (SCA) or sudden cardiac death (SCD) [4, 5].

## Age-Related QTc-Interval Changes in Healthy Individuals

The QTc-interval is remarkably long after birth, in both males and females [6–8]. The QTc-interval then decreases during the first weeks after birth in both sexes [6–8] and then remains relatively consistent over the years until the age of approximately 16 years [6, 8–14]. However, when individual age trends are taking into account, both males and females have longer QTc-intervals at the age of 12 years compared to the ages of 6 and 15 years [15, 16]. After puberty, the QTc-interval shortens in males but not in females [6, 17–21]. During adulthood, the QTc-interval gradually increases with age [11, 22–33]

in both sexes [17–20, 22, 34–45]. In contradiction, there is one study that showed QTc-interval shortening in older age groups (>60 years) [46].

## Sex Differences in QTc-Interval in Healthy Individuals

Nearly 100 years ago in the early ECG recordings by Bazett [3], differences in QTc-interval were described between healthy adult males and females. Decades later, it became clear that these sex differences are not present during the first month of life [6, 8, 47, 48] but arise at a later age. At the age of 1–3 months, females have a slightly longer QTc-interval compared to males [6, 13, 14]. Thereafter, no sex difference is seen until approximately the onset of puberty [6, 9, 10, 12–14, 16, 18, 20, 49, 50]. Fukushige et al. [15] described a shorter QTc-interval in 6-year-old females compared to males, but this difference was very small (384 ms versus 386 ms; $P < 0.05$). After puberty, females have a longer QTc-interval compared to males [6, 9, 14–17, 20, 21, 50–59]. This difference has also been reported in adulthood by several studies [3, 15, 17, 19, 20, 22–27, 29–33, 35–46, 57, 60–74], although some other studies found no difference [34, 66] or even a longer QTc-interval in males [75]. The difference in QTc-interval between males and females decreases with age [25] because the QTc-interval increases more in time in males compared to females [37]. As a result, no clear sex differences are present in the highest age groups of approximately >60 years [19, 20, 27, 34, 37].

## Racial Differences in QTc-Interval in Healthy Individuals

The presence of racial differences in QTc-interval still requires clarification as the effect of race has been looked at in only a limited number of studies. Most studies report no clear racial differences [29, 48, 70, 76], although some small differences may be present. Blacks tend to have slightly shorter QTc-intervals compared to Caucasians [8, 31, 32, 74], and Asians, especially females [31, 62, 72, 73, 77], have slightly longer QTc-intervals compared to Caucasians [30, 48, 72, 78]. In addition, collective consideration of available pharmacogenetic and clinical information suggests that there may be inter-race differences in QT-prolonging effects of drugs and that Caucasians may be more sensitive than other populations [79]. These possible differences are most likely the result of the presence of considerable heterogeneity among race/ethnicity for multiple genetic loci that have an impact on the QT-interval. Some of these loci show a striking difference (i.e. order of magnitude 40–50%) between the highest and lowest frequencies between ethnicities [80]. Unfortunately, there is no data on racial-specific age-related sex differences.

## Possible Role of Sex Hormones on the QTc-Interval and Arrhythmogenesis

The age- and sex-related differences in QTc-interval, especially the change post-puberty, most likely are due to changes in sex hormones levels. The mechanisms underlying the influence of sex hormones on the repolarization are complex and still unresolved; however, mechanistic studies suggest that sex hormone has varying effects on the $I_{Ca,L}$, $I_{Kr}$, $I_{Ks}$ and $I_{K1}$ channel currents. Testosterone decreases the $I_{Ca,L}$ current and increases the potassium channel currents, resulting in a shorter QTc-interval observed in both animal and human studies [81]. Progesterone decreases the $I_{Ca,L}$ current and increases the $I_{Ks}$ current and may therefore shorten the QTc-interval [81]. Conflicting results of endogenous oestrogen on the QTc-interval have been described. Oestrogen lengthens the QTc-interval in animals; however, this has not been supported by human studies. In animal studies, oestrogen decreases the potassium channel currents and may lengthen the QT-interval through this mechanism [81].

In children, concentrations of sex hormones are influenced by the activity of the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis is active during the (I) mid-gestational period in the

foetus, (II) first months of life and (III) pubertal period [82], and therefore higher concentrations of testosterone and oestrogen are found during these periods. As a consequence, during periods of sudden changes in sex hormone concentrations (i.e. the first months of life and the onset of puberty), a marked QTc-interval shortening in males would be expected based on the higher level of testosterone compared to females. This could explain the shorter QTc-intervals in males between 1 and 3 months and after the onset of puberty compared to females.

In adulthood, the level of testosterone gradually decreases with age in males [83], potentially explaining why with ageing, the QTc-interval in males gradually lengthens and approximates that of females. Changes in sex hormone levels in females are more complex due to the influence of the menstrual cycle, pregnancy and the menopause.

## Menstrual Cycle

Oestrogen and progesterone levels fluctuate during the menstrual cycle and are lowest at the onset of menses (menstrual phase). After the cessation of the menstrual flow, there is a gradual increase in oestrogen (follicular phase). Oestrogen levels peak in the middle of the menstrual phase during the ovulation (ovulation phase), and after the ovulation, the oestrogen levels gradually decrease during the luteal phase. Progesterone levels, in contrast, are low during the menstrual and follicular phase and increase after the ovulation through the luteal phase (Fig. 6.2).

In females, there are no clear QTc-interval differences between the different phases of the menstrual cycle [84–89]. In addition, there are also no distinct differences in heart rate [86, 87, 89–92], so there is probably no effect of the method chosen to correct the QT-interval for the heart rate. Hulot et al. [84] found no relationship between the level of oestrogen and the length of the QTc-interval ($P = 0.92$). In the study by Nakagawa et al. [85], the uncorrected QT-interval was shorter in the luteal phase compared to the follicular phase, although no difference in QTc-interval was seen. They found no statistically significant difference in oestrogen level between the luteal and follicular phase, while progesterone ($P < 0.001$) and noradrenaline levels ($P < 0.05$) were higher in the luteal phase suggesting the role of progesterone and/or autonomic tone on the uncorrected QT-interval. When double autonomic blockade was given, e.g. atropine and propranolol administration, QTc-interval differences between the phases of the menstrual cycle were seen. Under these circumstances, Burke et al. [86] found a shorter QTc-interval in the luteal phase compared to the menstrual and follicular phase, whereas Endres et al. [87] observed a significantly longer QTc-interval during the follicular phase compared to the menstrual and luteal phase. Both studies indicate the important role of autonomic tone in alternations in the QTc-interval during the menstrual cycle. Rodriguez et al. [88] showed that ibutilide infusion, a known $I_{Kr}$ blocker mimicking long QT syndrome (LQTS), causes differences in QTc-interval between the phases of the menstrual cycle, whereas the luteal phase seemed to be protective against the drug-induced QTc-interval prolongation. Hence, since there is an effect of the menstrual cycle on the QTc-interval during administration of QTc-interval prolonging medication, it could be argued that this effect is also present in patients with LQTS.

Despite the unclear changes in the QTc-interval between the phases of the menstrual cycle in the normal situation, there seems to be a cyclic variation in the occurrence of episodes of arrhythmia with the menstrual cycle. During the luteal phase, an increase in the number and duration of paroxysmal supraventricular tachycardia (SVT) has been reported compared to other phases of the menstrual cycle [93, 94], with a correlation with plasma concentrations of progesterone and an inverse correlation with plasma concentrations of oestradiol [93]. Also ventricular ectopic beats seems to be more frequent during the luteal phase of the menstrual cycle [93]. So it seems that there can be significant changes in the arrhythmogenic substrate of the heart throughout the menstrual cycle without dramatic changes in the QTc-interval. As we know, there is no simple relationship between absolute QTc-

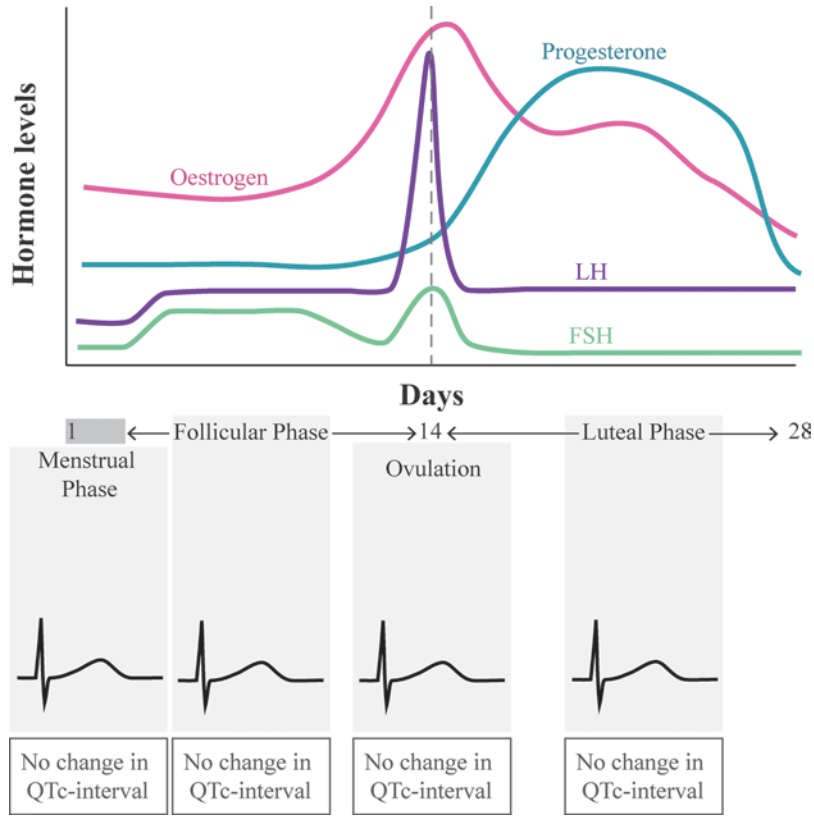


**Fig. 6.2** Oestrogen, progesterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels over a single menstrual cycle in females together with a schematic representation of the QTc-intervals during the phases of the menstrual cycle (i.e. menstrual phase, follicular phase, ovulation and luteal phase). See text for explanation. (Derived from data in: Sedlak et al. [81])

interval and arrhythmogenic potential or SCD [63, 88, 95], so perhaps the autonomic tone also plays an important role which is influenced by sex hormones [85, 96].

The fluctuations of oestrogen and progesterone levels during the menstrual cycle are controlled by the gonadotropin hormones, e.g. luteinizing hormone (LH) and follicle-stimulating hormone (FSH). A peak in LH and FSH is seen prior to ovulation in the normal menstrual cycle which is recognizable by an increase in body temperature (Fig. 6.2). Abehsira et al. [97] showed recently that the QTc-interval is probably influenced by a complex interaction between sex hormones and gonadotropins. In both males and females, FSH was positively correlated to QTc-interval ($r = 0.39$ and $r = 0.38$, respectively, in males and females), while free testosterone in males ($r = -0.34$) and progesterone/oestrogen ratio in women ($r = -0.38$) were negatively correlated. LH was only correlated in females to the QTc-interval ($r = 0.30$).

## Pregnancy

During gestation, there is a complex and varying combination of sex hormones. Oestrogen and progesterone levels gradually increase during pregnancy until labour when the levels drop sharply reaching pregravid levels by the fifth postpartum day (Fig. 6.3) [98–102].

Studies regarding changes in QT/QTc-interval during pregnancy used either longitudinal data during pregnancy [103], the postpartum state as a control [104] or a control group of non-pregnant women [105, 106]. There is a longer QTc-interval during the first trimester and late pregnancy, with a shortening of the QTc-interval after delivery [104–106]. The QTc-interval just after delivery is however longer compared to the postpartum period [104]. The heart rate is, on the contrary, higher during pregnancy and delivery compared to the control group [104–106] and seems to increase with gestation [103]. Due to these changes in heart rate, it is not unlikely that the

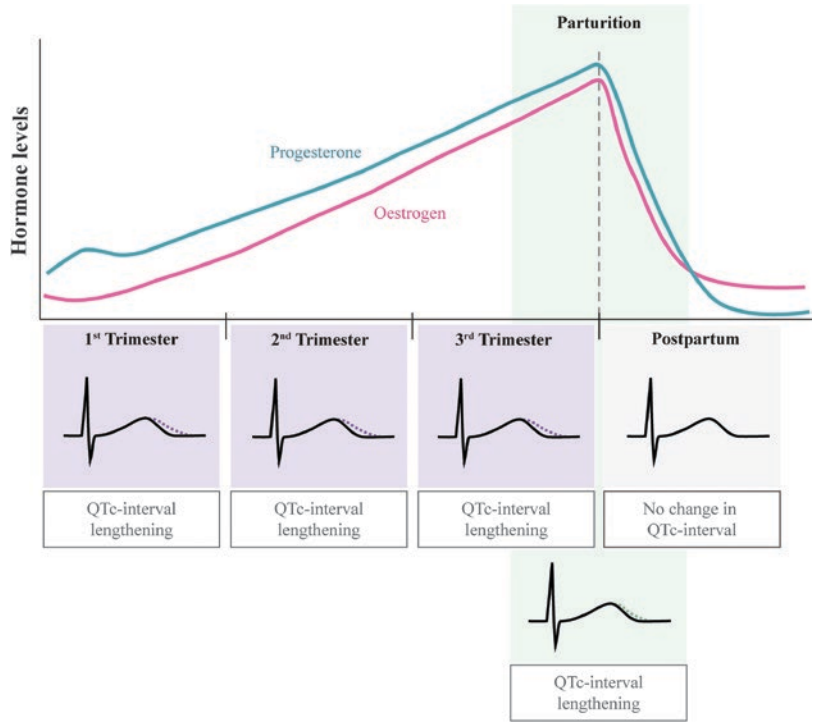


**Fig. 6.3** Oestrogen and progesterone levels during pregnancy and after parturition together with a schematic representation of the QTc-intervals during the trimesters, parturition and the postpartum period. See text for explanation. (Derived from data in: Bett [115])

observed differences in the QTc-interval are influenced by the correction method used to correct the QT-interval for the heart rate [107]. Anneken et al. [108] recently studied five healthy women who became pregnant after stimulation by clomiphene citrate therapy for infertility, observing shorter QTc-intervals during higher oestrogen levels. Progesterone did not affect the QTc-interval significantly in that study.

The gestational prolongation of the QTc-interval does not precipitate widespread fatal cardiac arrhythmias in pregnant women. However, there is a slight increase in arrhythmias during pregnancy regarding SVTs and even ventricular tachycardia (VT) compared to the postpartum period or non-pregnant controls [109, 110]. Although the occurrence of VT is usually uncommon, there presence should raise a suspicion of underlying cardiovascular disease.

## Menopausal Period

The menopause is defined as the permanent cessation of menstrual periods, determined retrospectively after a woman has experienced 12 months of amenorrhoea without any other obvious pathological or physiological cause. The menopause is a reflection of complete, or near-complete, ovarian follicular depletion resulting in very low levels of oestrogen and progesterone and high levels of FSH concentrations (Fig. 6.4). The menopausal transition, or perimenopause, occurs after the reproductive years and before the menopause. This period is characterized by irregular menstrual cycles and significant hormonal variability [111, 112].

Two studies comparing premenopausal females to postmenopausal females showed no differences in QTc-interval and heart rate [113, 114]. One of the studies also measured the hormone levels and found no difference in oestrogen levels but a lower level of progesterone in the postmenopausal phase compared to the premenopausal phase [114].

The data regarding postmenopausal arrhythmogenesis is lacking; however the autonomic tone may also play a role in the peri-/postmenopausal period. Hence, the QTc-interval is shorter in women with hot flushes compared to those without, and the absence of menopausal hot flushes is associated with an elevated activity of the sympathetic nervous system.

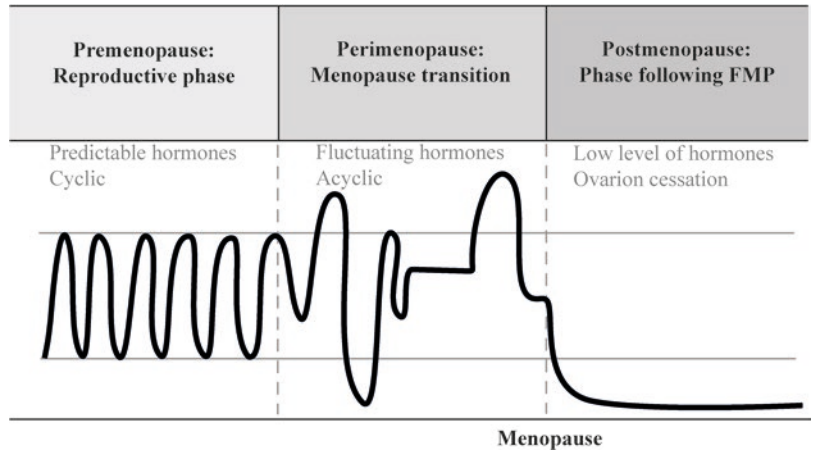


**Fig. 6.4** Menstrual cycle patterns during menopause. FMP = Final menstrual period. See text for explanation. (Reprinted by permission from Springer Nature: Deecher and Dorries [116])

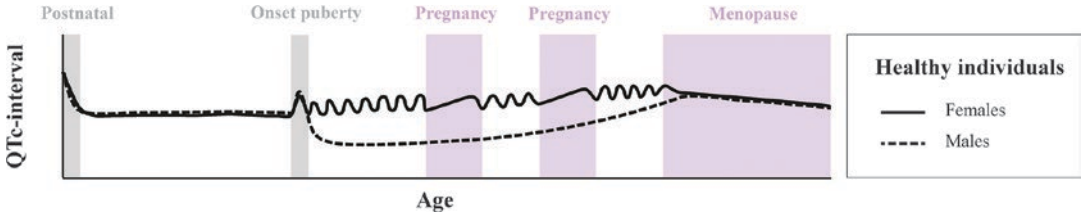


**Fig. 6.5** Schematic representation of hypothetical changes in QTc-interval in healthy individuals

## Conclusion

Age, sex and race have an influence on the QTc-interval. Although data regarding racial differences is lacking, the small differences seen are probably the result of the presence of considerable heterogeneity among race/ethnicity for multiple genetic loci that influence the QT-interval. Age- and sex-related differences in QTc-interval (Fig. 6.5) are most likely the result of changes in sex-specific hormones. Although the exact mechanisms and pathophysiology of the effect of sex hormones on the QTc-interval and the arrhythmogenesis are not known, testosterone appears to shorten the QTc-interval in males. In females, however, there is a more complex interaction between progesterone and oestrogen. In addition, the autonomic nervous system and gonadotropins may play an important part in this complex interaction.

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