Sex- and Menopause-Specific ECG Repolarization Patterns

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Abstract

Sex- and menopause-specific hormonal patterns are known to influence the risk of ventricular tachycardia and may be reflected in electrocardiogram (ECG) markers of ventricular repolarization. This study aims to identify ECG features that capture these differences by analyzing key ventricular repolarization indices: the corrected QT (QT_c) and T-peak-to-T-end (Tpe_c) intervals and the mean spatial QRS-T angle ($QRS-Ta$). Using data from the UK Biobank, we assessed these markers in males and females, with the female cohort further stratified into premenopausal and postmenopausal groups. Group comparisons and multiple linear regression models were employed to quantify differences and evaluate the relative contribution of a broad set of baseline and demographic factors. In sex-specific analyses, all three indices, as well as the overall ECG morphology showed significant differences, primarily influenced by variables such as height, body mass index or pulse rate. In menopause-specific comparisons, significant differences were observed for Tpe_c and $QRS-Ta$, but morphological changes were more subtle. Notably, left ventricular wall thickness and left ventricular ejection fraction were associated with variations in Tpe_c in both female subgroups. These findings highlight the importance of accounting for sex and menopausal status in assessing susceptibility to ventricular arrhythmias and support the need for more personalized diagnostic approaches.

1. Introduction

Sex plays a critical role in the electrophysiological substrate of the heart, particularly in ventricular repolarization, which influences susceptibility to ventricular arrhythmias. Moreover, female-specific factors, such as menopause, significantly impact negatively the arrhythmogenic risk profile of women due to hormonal changes that occur during this transition [1]. Sex-related differences in electrocardiogram (ECG) repolarization indices have been previously reported, such as longer QT interval durations or a narrower $QRS-T$ angle in women [2].

In addition, previous studies have demonstrated the capacity of deep learning models to accurately predict biological sex based on ECG signals. Importantly, misclassifications of sex by these models have been reported to carry prognostic significance [3]. Specifically, in populations with low cardiovascular (CV) risk , a higher sex discordance score, indicating divergence between predicted and actual sex, has been linked to adverse CV outcomes in females, but not in males, suggesting potential sex-specific vulnerabilities in CV risk stratification as well as sex-related hormonal changes that obscure sex-specific ECG features. This highlights the important role of hormones in mediating arrhythmogenic risk and suggests that their effects can be measured on the ECG. In fact, the influence of circulating sex hormones on ECG parameters has been substantiated by physiological studies [4].

Hormonal imbalances, especially an increased testosterone-to-estrogen ratio, have been associated with a higher risk of CV disease (CVD) in postmenopausal women [5]. While the cardioprotective effects of female hormones during the reproductive years are well recognized, how menopause and the associated hormonal decline impact ECG patterns remains largely unknown.

In this study, we hypothesize that sex- and menopause-related hormonal influences are reflected on the ECG signal. Our first aim is to identify ECG markers of ventricular repolarization that differ between males and females, and between females before and after menopause in a large cohort from the general population. Our second aim is to investigate the underlying mechanisms explaining these differences.

2. Materials and Methods

2.1. Study Population

Our study population consisted of 55,730 individuals without known prevalent CVD from the Imaging cohort in the UK Biobank study. Information available from individuals in this cohort included collections of 10 second 12-lead ECGs recorded at rest, as well as electronic health records and a wealth of baseline and demographic data. The UK Biobank study received approval from the North West Multi-Centre Research Ethics Committee [6], and this work was conducted under application number 8256. The definition of CVD is described in [7].

The study population was first stratified by sex into males and females, with the female cohort subsequently subdivided into premenopausal (F-NoMP) and postmenopausal (F-MP) groups based on menopausal status to assess their effects on ventricular repolarization markers. Postmenopausal females having hormone replacement therapy (HRT) were excluded from the analysis. Figure 1 shows the flowchart of the study population and Table 1 describes the characteristics of the population.

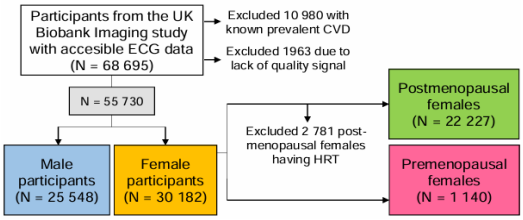

Figure 1: Flow diagram showing the recruitment process of participants. HRT: Hormone replacement therapy.

2.2. ECG Pre-Processing

To remove high frequency noise, the ECG signals were low-pass filtered at 40 Hz, followed by removal of baseline wander using cubic splines interpolation. Using only sinus rhythm beats, a median heartbeat was calculated and a wavelet based delineator [8] was used to locate the ECG wave onsets, peaks and end timings. For each lead, three repolarization ECG indices were derived: the corrected QT (QT_c) [9] and T-peak-to-T-end (Tpe_c) intervals (using the Bazett formula)[10] and the mean spatial QRS-T angle ($QRS-Ta$) [11]. The mean spatial $QRS-Ta$ angle was defined as the angle between the mean QRS vector and the mean T-wave vector.

Additionally, we performed principal component analysis [12] using the 8 independent ECG leads to maximise the energy in the T-wave by deriving the eigenvectors and eigenvalues using samples from the T-wave exclusively. All subsequent measurements and representations were based on the first principal component (PC_1), which captures the direction of maximal variance and dominant signal energy within the T-wave.

2.3. Statistical Analyses

One-tailed Mann–Whitney U tests were employed to assess the associations of QT_c, Tpe_c, and $QRS-Ta$ with sex and menopausal status. Specifically, comparisons were made between males and females, as well as between F-NoMP and F-MP groups. In the comparison between males and females, left-tailed Mann–Whitney U test was used for QT_c and a right-tailed test was used for Tpe_c and $QRS-Ta$. In the comparison between F-NoMP and F-MP, a right-tailed test was used for QT_c and a left-tailed test was used for Tpe_c and $QRS-Ta$. Only those ECG indices where we found a significant difference between males and females, or between F-NoMP and F-MP, were taken forward into the subsequent analyses. All statistical analyses were conducted using RStudio (version 2024.12.0).

We next investigated the potential mechanisms underlying the differences observed between males and females, or between F-NoMP and F-MP through multiple linear regression. First, to address potential multicollinearity, we performed a correlation analysis prior to model fitting and excluded variables with a pairwise correlation coefficient greater than 0.8. All continuous predictors were standardized using their respective standard deviations prior to inclusion in the models. After that, we constructed the models within each of the four study groups by regressing the corresponding ECG index on demographic, functional, lifestyle, clinical, anatomical and cardiac factors, as detailed in Table 1. In cases where the ECG index was QT_c or Tpe_c, lead PC_1 was used. To account for multiple comparisons, the p-value was corrected for the number of ECG indices and the number of groups included in the analysis, so a p-value < 0.00416 was considered statistically significant.

3. Results

After exclusion criteria, the final population for sex-specific groups consisted on 25,548 males (45.85%) and 30,182 females (54.15%) and for menopause-specific groups, 22,227 F-MP (73.6%) and 1,140 F-NoMP (3.8%) (Table 1).

Figure 2 (A) illustrates the distribution of QT_c and Tpe_c intervals across the 8 independent leads and PC_1 for males and female groups and of $QRS-Ta$. Statistically significant differences were found for the three ECG indices, being QT_c lower and Tpe_c and $QRS-Ta$ higher in males. Figure 2 (B) highlights the morphological differences in PC_1, showing clear differences with the males

Table 1: Baseline characteristics of study participants in the UK Biobank

	Overall population N = 55 730	Males N = 25 548	Females-MP N = 22 227	Females-NoMP N = 1 140
Age (years)	65 (12)	66 (12)	65 (10)	51 (3)
Height (cm)	168 (14)	176 (9)	162.6 (8.6)	165 (8.5)
BMI (kg/m^2)	25.8 (5.4)	26.3 (4.8)	25.1 (5.7)	25.6 (5.8)
Fat free mass (kg)	49.5 (18.1)	59.7 (11.6)	43.4 (7.5)	44.9 (7.2)
Hand grip strength (kg)	29 (16)	38 (12)	23 (8)	28 (8)
Smoking status (current)	1 906 (3.5%)	1 048 (4.2%)	621 (2.8%)	41 (3.6%)
Alcohol drinker (current)	51 079 (93.3%)	23 701 (94.5%)	20 513 (92.3%)	1 061 (93.1%)
Physical activity (active)	38 742 (89.2%)	18 412 (88.9%)	15 384 (90.3%)	856 (86.3%)
Diabetes (yes)	2 574 (4.7%)	1 565 (6.2%)	752 (3.4%)	21 (1.84%)
LV myocardial mass (g)	81.3 (31.9)	93.8 (29.6)	72.8 (22.7)	72.2 (18.3)
LV wall thickness (mm)	5.5 (1.0)	5.9 (0.9)	5.3 (0.8)	5.1 (0.7)
LV ejection fraction (%)	56 (7)	56 (7)	57 (7)	57.5 (7)
DBP (mmHg)	79 (14)	80.5 (13)	77.5 (13.5)	76 (12.5)
SBP (mmHg)	139 (25.5)	141.5 (24)	137.5 (26.5)	126.5 (23.6)
Pulse Rate (bpm)	67 (14.5)	65.5 (15)	68.5 (14)	69 (15)

[1]Data are presented as absolute frequencies and percentages and median with interquartile range. MP: Menopause; N: number of cases; BMI: Body Mass Index; LV: Left Ventricle; DBP: Diastolic Blood Pressure; SBP: Systolic Blood Pressure

group showing higher R and T-wave amplitudes and prolonged repolarization duration compared to females. Figure 4 (A) shows the factors with significant p-values in the multiple linear regression analyses. In males, height, alcohol drinker and systolic blood pressure were the strongest contributors to variation in ECG indices, whereas in females were menopause status, diastolic blood pressure and pulse rate. Notably, functional and clinical variables played a major role in $QRS-Ta$ differences.

Figure 3 (A) shows the distribution of of QT_c and Tpe_c intervals across the 8 independent leads and PC_1 and of $QRS-Ta$ for F-NoMP and F-MP groups. Only Tpe_c and $QRS-Ta$ ECG indices showed statistical differences, with the F-MP group exhibiting higher Tpe_c and $QRS-Ta$ values. No significant differences were observed in QT_c values. Figure 3 (B) shows less pronounced morphological differences between F-NoMP and F-MP groups, with the F-MP group showing slightly higher R and T-wave amplitudes and slower repolarization duration compared to F-NoMP. Figure 4 (B) in the menopause-specific groups shows that only left ventricle (LV) wall thickness and LV ejection fraction, were associated with the Tpe_c index in both F-NoMP and F-MP groups. In F-MP, age, body mass index (BMI) and LV wall thickness played a predominant role.

4. Discussion and Conclusions

The first main finding of this study is that males have shorter QT_c and longer Tpe_c and wider $QRST-a$ compared to females, along with distinct morphological differences in the ECG waveform. These differences were mainly influenced by height or alcohol consumption in males and menopause, DBP and pulse rate in females.

The second main finding is that F-MP exhibited a pattern analogous to that of males, with longer Tpe_c and $QRST$-a compared to F-NoMP. These patterns align with hormonal changes during menopause, characterized by a decline in estrogen levels and a shift toward a more male-like hormonal profile, which is reflected in the emergence of a slightly more male-like ECG phenotype in F-MP compared to F-NoMP [5]. This trend is also evident in the comparison of the median ECG morphology, where F-MP exhibited higher energy features compared to F-NoMP, mirroring the pattern observed between males and females. Additionally, in menopausal status, age, BMI, diabetes, pulse rate, LV mass and LV ejection fraction were key contributors influencing the ECG markers of ventricular repolarization, compared to F-NoMP.

Overall, using the largest available cohort with both ECG and extensive phenotypic data, our results confirm sex-specific differences on ECG markers of ventricular repolarization and identify, for the first time, differences in F-NoMP and F-MP, as well as the potential mechanisms underlying them. Future work should validate our findings, as well as explore the effects of HRT on these ECG indices.

Acknowledgments

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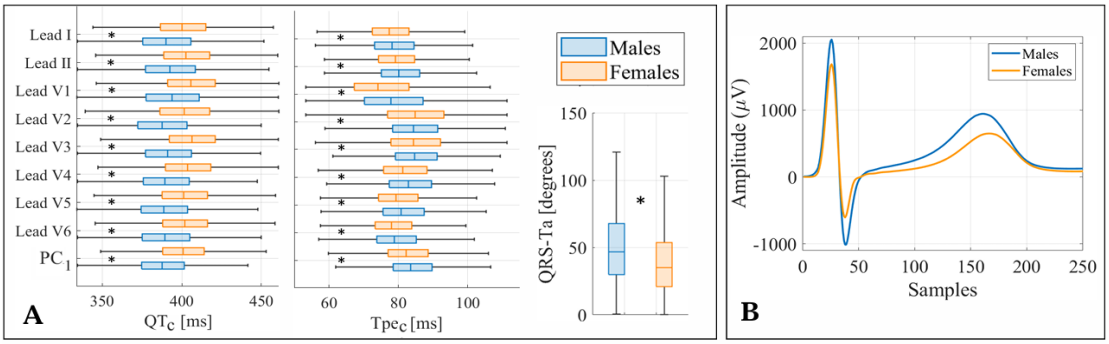

Figure 2: (A) Distribution of QT_c and Tpe_c intervals, and $QRS - Ta$ in males and females. * indicates statistically significant differences between groups. (B) Morphology of PC_1 in males and females.

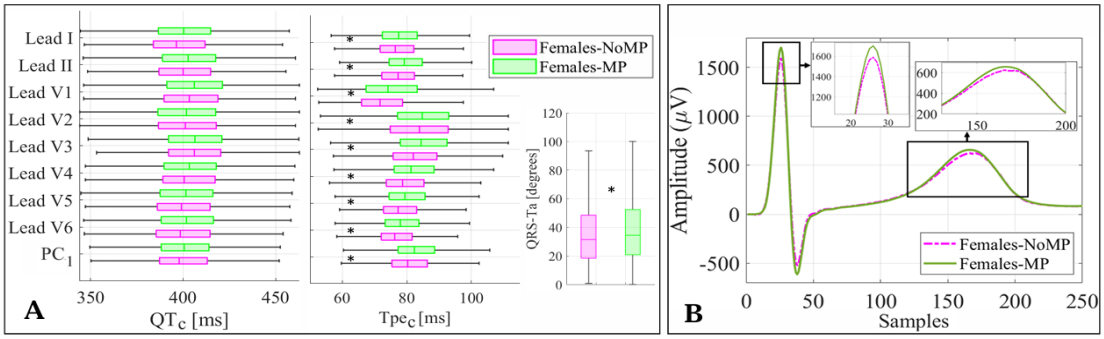

Figure 3: (A) Distribution of QT_c and Tpe_c intervals, and $QRS-Ta$ in F-NoMP and F-MP groups. * indicates statistically significant differences between groups. (B) Morphology of PC_1 in F-NoMP and F-MP. MP: Menopause

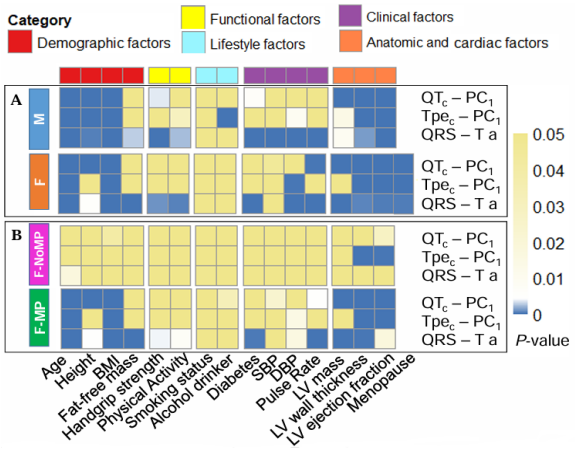

Figure 4: (A) Contribution of factors to ECG parameters in males (M) and females (F) and (B) in F-NoMP and F-MP. Significant p-values are displayed in a gradient of blue.

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