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The association between body temperature and electrocardiographic parameters in normothermic healthy volunteers

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Abstract

Background: Previous studies reported that hypo- and hyperthermia are associated with several atrial and ventricular electrocardiographical parameters, including corrected QT (QTc) interval. Enhanced characterization of variations in QTc interval and normothermic body temperature aids in better understanding the underlying mechanism behind drug induced QTc interval effects. The analysis' objective was to investigate associations between body temperature and electrocardiographical parameters in normothermic healthy volunteers.

Methods: Data from 3023 volunteers collected at our center were retrospectively analyzed. Subjects were considered healthy after review of collected data by a physician, including a normal tympanic body temperature (35.5-37.5°C) and in sinus rhythm. A linear multivariate model with body temperature as a continuous was performed. Another multivariate analysis was performed with only the QT subintervals as independent variables and body temperature as dependent variable.

Results: Mean age was 33.8 ± 17.5 years and mean body temperature was 36.6 ± 0.4°C. Body temperature was independently associated with age (standardized coefficient [SC] = −0.255, $P < .001$), female gender (SC = +0.209, $P < .001$), heart rate (SC = +0.231, $P < .001$), P-wave axis (SC = −0.051, $P < .001$), J-point elevation in lead V4 (SC = −0.121, $P < .001$), and QTcF duration (SC = −0.061, $P = .002$). In contrast,

other atrial and atrioventricular (AV) nodal parameters were not independently associated with body temperature. QT subinterval analysis revealed that only QRS duration (SC = −0.121, $P < .001$) was independently associated with body temperature.
Conclusion: Body temperature in normothermic healthy volunteers was associated with heart rate, P-wave axis, J-point amplitude in lead V4, and ventricular conductivity, the latter primarily through prolongation of the QRS duration.

KEYWORDS
body temperature, ECG, electrophysiology, healthy adults, normothermic

1 | INTRODUCTION

Normal body temperature is defined as 35.5-37.5°C in healthy volunteers, although different ranges have been described depending on the site where the body temperature is measured.[1] Body temperature values outside the normal range have been reported to result in substantial changes to the surface electrocardiographs (ECGs), such as heart rate,[2–5] QRS duration,[4–7] J-wave prevalence,[4,8–12] and QT interval duration.[4,6,13–15] Even within the normal range, body temperature has been reported to have an effect on the corrected QT interval (QTc interval).[4–6,15] Preclinical studies reported atrioventricular conduction, and QTc interval duration changes for each increase or decrease of a degree in body temperature of 5.3-14 milliseconds and 6.1-14 milliseconds, respectively.[2,16,17] These findings are further supported by in vitro human tissue studies.[18–20]

However, the effect of body temperature on the surface ECG in healthy volunteers with a normal body temperature has been underreported. An increased characterization of the association between the QTc interval, including QT subinterval analysis,[21] and body temperature aids a better differentiation between the direct effects of pharmacological agents on the ECG or indirect effects on the ECG through body temperature modulating pharmacological agents such as opioids or 5-HT_{1A} serotonin receptor modulators.[22,23]

Therefore, the aim of the present analysis was to investigate the association between body temperature and selected surface ECG parameters in healthy volunteers with a normal body temperature.

2 | METHODS

Data from 3023 male and female volunteers, aged 18 years or older with body temperatures between 35.5°C and 37.5°C were included in the retrospective analysis. All data were collected at the Centre for Human Drug Research in Leiden, the Netherlands, a clinical research organization specialized in early phase drug development studies. Data collected during the mandatory medical screening to verify study eligibility for enrolment in the early phase drug development studies as a volunteer between 2010 and 2016 were included in the present analysis. Ethical approvals from the Medical Ethical Review Committee for the intended studies were acquired, and informed consent documents were signed by the volunteers prior to any data collection. The present study was performed in accordance to local regulations. All activities were performed in accordance with applicable standard operating procedures.

2.1 | Medical screening

In this analysis, only subjects considered healthy were eligible for inclusion. Healthy was defined as the absence of clinically significant abnormalities on a large selection of tests with no evident history of diseases. This battery of tests consisted of a single visit to the clinical unit during office hours (between 09:00 and 17:00 o'clock) where a detailed medical history, a physical examination, vital signs including blood pressure, body temperature, weight and height measurement, body mass index calculation, and a twelve-lead ECG were recorded. Subjects were instructed not to eat or drink at least 3 hours prior to the medical screening. Additionally, hematologic and chemistry blood panel, urine dipstick, and a urine drug test were recorded. Only subjects with a normal body temperature (35.5-37.5°C) and considered healthy after review of collected data by a physician were included in the present analysis.

2.2 | Temperature measurement

Body temperature was measured tympanically using a BRAUN ThermoScan ear thermometer (Kronberg im Taunus, Germany) by a trained medical assistant following the standardized operating procedure. The subject was placed in a supine position with his/her head stabilized on a pillow. A disposable Braun Thermoscan lens filter (Kronberg im Taunus) was placed prior to the measurement. The ear canal was straightened by gently pulling the outer ear, with the thermometer probe pointing toward the eardrum. The measured body temperature was entered immediately into the database system (Promasys, Fort Lauderdale, FL).

2.3 | ECG measurements

The 12-lead ECGs were recorded with the volunteer in a resting supine position and after a 5-minute resting period. The twelve-lead ECGs

TABLE 1 Methods of determination or calculation of the electrocardiographic variables used in healthy volunteers aged 18 years or older with a tympanically measured body temperature between 35.5°C and 37.5°C

Variable	Description
Maximum P-wave duration (ms)	Longest P-wave duration sampled from all leads.
P-wave dispersion (ms)	Difference between the longest minus the shortest P-wave duration from all leads.
Total P-wave area in lead V1 (mm × ms)	Sum of the total area under and above the isoelectric line from onset to termination of the P-wave.[44]
P-wave axis (degrees)	Net vector of the P-wave axis based on the extremity leads.
PR-interval (ms)	Beginning of the P-wave until the beginning of the QRS complex.
QRS duration (ms)	Mean first deflection from the isoelectric line following the P-wave until the J-point.
R-amplitude in lead I (μV)	Amplitude of the first upward deflection of the QRS complex (R-wave) in lead I.
R-amplitude in lead aVL (μV)	Amplitude of the first upward deflection of the QRS complex (R-wave) in lead aVL.
R-amplitude in lead V1-V6 (μV)	Amplitude of the first upward deflection of the QRS complex (R-wave) in lead V1 through V6.
Heart axis (degrees)	Net vector of the R-wave axis based on the extremity leads.
Cornell product (ms × mm)	Product of the QRS duration and the Cornell voltage.[45] Cornell voltage is the sum of the amplitude of the R-wave in lead aVL and the amplitude of the S-wave in lead V3.[45]
J-point amplitude lead V4 (mm)	Deflection of the downward deflection of the QRS complex at the R-ST junction measured in lead V4.[9]
J-point – T-peak interval correct for heart rate (ms)	Duration of QRS complex offset to peak of the T-wave/RR-interval as measured in lead II to the power of 0.58 as proposed by Johannesen.[21] RR-interval is the interval between the onset of one QRS complex to the onset of the next QRS complex, measured in seconds, derived from the heart rate (HR) as 60/HR.
T-peak – T-wave interval (ms)	Duration of peak of the T-wave to end of the T-wave as measured in lead II.[21]
Maximum T-wave duration (ms)	Longest T-wave duration sampled from all leads
Minimum T-wave duration (ms)	Shortest T-wave duration sampled from all leads
T-wave dispersion (ms)	Difference between the longest and shortest T-wave duration selected from all leads
T-wave axis (degrees)	Net vector of the T-wave axis based on the extremity leads.
QTcF duration (ms)	QTcF duration is calculated using the Fridericia formula, which divides the QT-interval by the cube-root of RR-interval. QT-interval is the interval between the start of the Q-wave and the end of the T-wave.

were recorded using an ECG (Marquette 800/5500/2000; General Electric Healthcare, Milwaukee, WI), and 10 disposable electrodes were placed in the standard anatomical position. The ECG data were then uploaded into the ECG warehouse (Muse Cardiology Data Management System v7, General Electric Healthcare, Chicago, IL). The Marquette Cubic Spline and Finite Residual Filter filters were used for artefact and noise management. In addition, a physician manually reviewed all ECGs for quality, legibility, and abnormalities. The ECG warehouse automatically assesses interval and amplitude data from the digital ECGs with the Marquette 12SL algorithm, which provides a variety of validated ECG measurements on median beats and have been used in previous studies.[24,25] The ECG measurements were performed only by the Marquette 12SL algorithm, there were no manual adjustments or manual measurements. Independent evaluation showed that the Marquette 12SL algorithm passed all of the amplitude measurement requirements (maximum of 10 milliseconds deviation) as defined in International Electrotechnical Commission, as described in the GE Physician's Guide (version 2036070-006). Description, methods of determination and calculation, and units of the ECG parameters are described in Table 1.

2.4 | Statistical analysis

Only subjects who were considered healthy by a physician after review of all the collected data, including an ECG with sinus rhythm were included in the current analysis. Male and female subjects were analyzed collectively as a group. A separate analysis where male and female subjects were analyzed separately is provided as Supporting Information Data. Data are reported as mean ± SD, or median with interquartile range, or percentage where appropriate. Subjects were divided into quartiles based on their body temperature (35.5-36.3°C, 36.4-36.6°C, 36.7-36.9°C, and 37.0-37.4°C). Because of the large number of data samples, normality was tested through visual confirmation of graphical plots. Variances were compared using the analysis of variance (ANOVA) test with a post-hoc Tukey analysis. A linear univariate analysis and a backward linear multivariate regression model analysis were performed with body temperature as the dependent variable. Probabilities of less than 0.10 in the linear univariate regression model were added to the backward linear multivariate regression model. In the case that variables reversed in association between the univariate and multivariate analysis, they were excluded from the

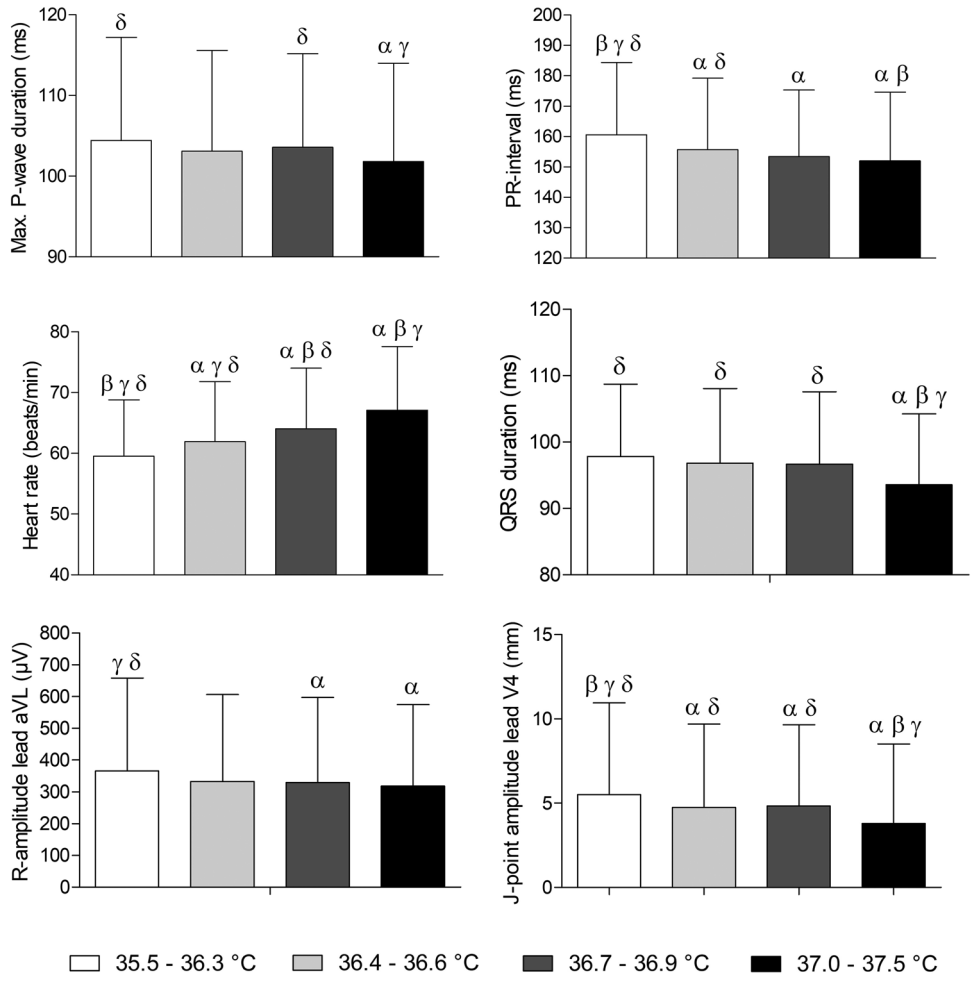

FIGURE 1 Overview of significant changes of electrographic parameters to body temperature in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5°C and 37.5°C. Results were based on analysis of variance (ANOVA) test between body temperature groups, and expressed as difference in the electrocardiographic parameter (with 95% confidence interval) per body temperature groups using a post-hoc Tukey analysis

multivariate analysis. Results are reported as unstandardized coefficient (USC) and SC with the corresponding *P*-value. Statistical analyses were performed using IBM SPSS version 20 (IBM corporation, Armonk, NY).

3 | RESULTS

In total, 3023 subjects were included in the present analysis. Average age was 33.8 ± 17.5 years, 74.4% were male and the mean body temperature was 36.63 ± 0.38°C. Subject characteristics are shown in Table 2. Incrementally with body temperature, the percentage of male gender, systolic and diastolic blood pressure, serum sodium and serum potassium decreased between the groups as can be presented in Table 2. Additionally, heart rate increased incrementally between the groups as can also be presented in Table 2, and Figures 1 and 2. Other baseline characteristics were not significantly different among body temperature groups.

3.1 | Body temperature and ECG parameters

Table 2 displays the association between the body temperature groups and the evaluated ECG parameters. Maximum P-wave duration, PR-interval, QRS duration, R-amplitude in lead aVL, heart axis, J-point elevation in lead V4, and the JpTpc interval were significantly different between the body temperature groups, as also displayed in Figure 1. Differences in these electrocardiographical parameters in lead V4 between body temperature groups are depicted in Figure 2.

3.2 | Linear regression analysis body temperature

In the univariate analysis, body temperature was associated with age (SC = −0.198, $P < .001$), female gender (SC = +0.222, $P < .001$), systolic blood pressure (SC = −0.096, $P < .001$), diastolic blood pressure (SC = −0.059, $P = .003$), heart rate (SC = +0.277, $P < .001$), serum sodium concentration (SC = −0.065, $P < .001$) and serum potassium

TABLE 2 Relation between patient characteristics and electrocardiographic parameters to body temperature in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5 and 37.5°C

	Body temperature (°C)			
	35.5-36.3 (n = 742)	36.4-36.6 (n = 783)	36.7-36.9 (n = 837)	37.0-37.5 (n = 661)
Corresponding groups	α	ß	γ	δ
Age (years)	28.0 (22-54)$^{\alpha,ß,\gamma,\delta}$	26.0 (22-47)$^{\alpha,\gamma,\delta}$	24.0 (21-39)$^{\alpha,ß,\delta}$	23.0 (21-29)$^{\alpha,ß,\gamma}$
Gender male (% male)	85.8	78.6	74.1	57.6
Body mass index (kg/m^2)	23.7	23.7	23.7	23.7
Systolic blood pressure (mm Hg)	125.0 ± 14.1$^{ß,\gamma,\delta}$	123.6 ± 12.9$^{\alpha}$	122.6 ± 12.6$^{\alpha}$	121.9 ± 12.8$^{\alpha}$
Diastolic blood pressure (mm Hg)	73.0 ± 9.6$^{\gamma,\delta}$	72.2 ± 9.6	71.5 ± 9.5$^{\alpha}$	71.3 ± 9.0$^{\alpha}$
Heart rate (beats/min)	59.5 ± 9.3$^{ß,\gamma,\delta}$	61.9 ± 9.9$^{\alpha,\gamma,\delta}$	64.1 ± 9.9$^{\alpha,ß,\delta}$	67.1 ± 10.5$^{\alpha,ß,\gamma}$
Serum sodium (mmol/L)	141.7 ± 1.9$^{\delta}$	141.6 ± 2.0$^{\delta}$	141.6 ± 1.9$^{\delta}$	141.4 ± 1.8$^{\alpha,ß,\gamma}$
Serum potassium (mmol/L)	4.37 ± 0.31$^{\delta}$	4.36 ± 0.31$^{\delta}$	4.34 ± 0.34$^{\delta}$	4.29 ± 0.29$^{\alpha,ß,\gamma}$
Serum calcium (mmol/L)	2.40 ± 0.09	2.41 ± 0.09	2.42 ± 0.09	2.41 ± 0.10
Maximum P-wave duration (ms)	104.4 ± 12.8$^{\delta}$	103.1 ± 12.5	103.6 ± 11.6$^{\delta}$	101.8 ± 12.2$^{\alpha,\gamma}$
P-wave dispersion (ms)	60.1 ± 15.5$^{\delta}$	58.8 ± 15.3	58.3 ± 14.5	57.7 ± 14.3$^{\alpha}$
Total P-wave area in lead V1 (mm × ms)	49.31 ± 81.39	49.32 ± 80.90	52.64 ± 81.64	50.55 ± 84.28
P-wave axis (degrees)	47.85 ± 20.05	46.67 ± 19.85	47.14 ± 19.99	45.74 ± 19.59
PR-interval (ms)	160.6 ± 23.8$^{ß,\gamma,\delta}$	155.6 ± 23.6$^{\alpha,\delta}$	153.4 ± 22.0$^{\alpha}$	152.0 ± 22.6$^{\alpha,ß}$
QRS duration (ms)	97.85 ± 10.87$^{\delta}$	96.83 ± 11.21$^{\delta}$	96.69 ± 10.88$^{\delta}$	93.58 ± 10.68$^{\alpha,ß,\gamma}$
R-amplitude lead I (μV)	700.3 ± 309.2	674.1 ± 283.2	682.4 ± 296.3	671.5 ± 296.6
R-amplitude lead aVL (μV)	365.4 ± 293.0$^{\gamma,\delta}$	332.1 ± 275.0	329.4 ± 268.3$^{\alpha}$	318.6 ± 256.3$^{\alpha}$
R-amplitude lead V1 (μV)	285.3 ± 196.5	291.8 ± 196.2	276.4 ± 180.1	274.4 ± 188.9
R-amplitude lead V2 (μV)	664.1 ± 355.1	701.3 ± 363.2$^{\delta}$	671.9 ± 363.2	648.5 ± 366.3^{ß}
R-amplitude lead V3 (μV)	1111.9 ± 596.4	1166.7 ± 600.2$^{\delta}$	1166.2 ± 649.5$^{\delta}$	1034.2 ± 610.9$^{ß,\gamma}$
R-amplitude lead V4 (μV)	1812.9 ± 684.2$^{\delta}$	1793.1 ± 670.5$^{\delta}$	1819.3 ± 704.6$^{\delta}$	1678.3 ± 708.0$^{\alpha,ß,\gamma}$
R-amplitude lead V5 (μV)	1672.7 ± 550.6$^{ß,\delta}$	1594.1 ± 520.8$^{\alpha}$	1623.4 ± 530.3	1557.9 ± 520.2$^{\alpha}$
R-amplitude lead V6 (μV)	1269.7 ± 427.3$^{ß,\delta}$	1206.8 ± 397.3$^{\alpha}$	1228.7 ± 394.9	1206.8 ± 383.5$^{\alpha}$
Heart axis (degrees)	45.7 ± 34.2$^{\delta}$	48.7 ± 33.2	49.8 ± 33.5	52.7 ± 32.8$^{\alpha}$
Cornell product (ms × mm)	128.8 ± 63.9$^{\delta}$	124.9 ± 60.7$^{\delta}$	123.7 ± 60.1$^{\delta}$	113.8 ± 59.7$^{\alpha,ß,\gamma}$
J-point amplitude lead V4 (mm)	5.50 ± 5.45$^{ß,\gamma,\delta}$	4.74 ± 4.96$^{\alpha,\delta}$	4.85 ± 4.79$^{\alpha,\delta}$	3.79 ± 4.71$^{\alpha,ß,\gamma}$
J-point - T-peak duration (corrected for heart rate) (ms)	217.9 ± 22.8	217.0 ± 22.9$^{\delta}$	217.9 ± 23.6	220.3 ± 24.0^{ß}
T-peak – T-end duration (ms)	95.7 ± 12.0	95.1 ± 12.4	94.7 ± 11.4	94.1 ± 12.0
Maximum T-wave duration (ms)	188.7 ± 23.1	187.1 ± 21.0	187.8 ± 21.3	189.2 ± 21.3
Minimum T-wave duration (ms)	120.4 ± 46.7	120.7 ± 48.5	121.1 ± 48.8	120.7 ± 46.6
T-wave dispersion (ms)	77.7 ± 56.8	77.3 ± 58.9	74.8 ± 57.5	75.5 ± 55.5
T-wave axis (degrees)	38.74 ± 18.30	39.12 ± 16.46	39.68 ± 17.02	37.94 ± 16.17
QTcF duration (ms)	411.3 ± 20.2	409.3 ± 19.1	409.2 ± 18.5	409.2 ± 18.5

Categorical variables were compared using chi-square test, while variances were compared using the analysis of variance test with a post-hoc Tukey analysis. Results are reported as median (25-75%), mean ± standard deviation, or as percentage. The symbols α, ß, γ, and δ represent a significant difference ($P < .05$) compared to that group. If no symbols are present, no significance was found between the groups.
Abbreviation: QTcF, corrected QT interval with Fridericia's method.

concentration (SC = −0.080, $P < .001$). Electrocardiographically, maximum P-wave duration (SC = −0.058, $P = .002$), P-wave dispersion (SC = −0.060, $P = .002$), PR-interval duration (SC = −0.130, $P < .001$), QRS duration (SC = −0.125, $P < .001$), R-wave amplitude in lead I (SC = −0.032, $P = .082$), R-wave amplitude in lead aVL (SC = −0.061, $P = .001$), R-wave amplitude in lead V1 (SC = −0.034, $P = .064$), R-wave amplitude in lead V3 (SC = −0.041, $P = .023$), R-wave amplitude in lead V4 (SC = −0.061, $P = .001$), R-wave amplitude in lead V5

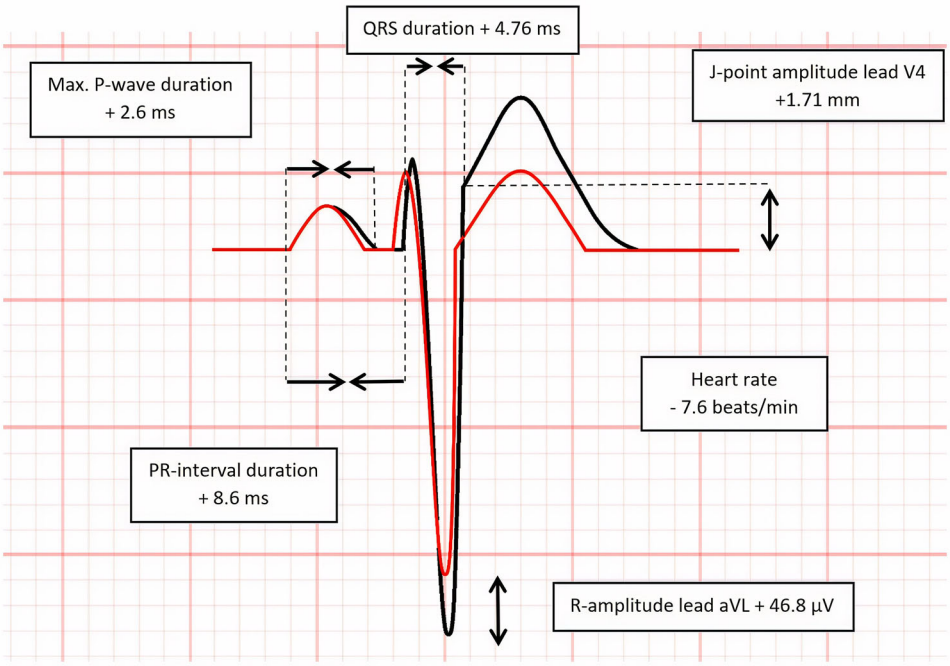

FIGURE 2 Overview of significant changes of electrographic parameters to body temperature in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5-36.3°C (black line) and 37.0-37.5°C (red line). Results were based on Analysis of Variance (ANOVA) test between body temperature groups, and expressed as difference in the electrocardiographic parameter per body temperature groups using a post-hoc Tukey analysis [Color figure can be viewed at wileyonlinelibrary.com]

(SC = −0.070, $P < .001$), R-wave amplitude in lead V6 (SC = −0.053, $P = .004$), heart axis (SC = +0.070, $P < .001$), J-point elevation in lead V4 (SC = −0.110, $P < .001$) and QTcF duration (SC = −0.036, $P = .050$) were associated with body temperature, as shown in Table 3. Diastolic blood pressure, maximum P-wave duration, R-amplitude in lead V4, R-amplitude in lead V5, JpTp, and TpTe were excluded from the multivariate analysis, because these variables reversed in association between the univariate and multivariate analysis. No collinearity was found in the final multivariate analysis model with no parameter displaying a variance inflation factor of >3. In the multivariate analysis, age (SC = −0.255, $P < .001$), female gender (SC = +0.209, $P < .001$), heart rate (SC = +0.231, $P < .001$), P-wave axis (SC = −0.051, $P < .001$), J-point elevation in lead V4 (SC = −0.121, $P < .001$), and QTcF duration (SC = −0.061, $P = .002$) were significantly associated with body temperature, as shown in Table 4. The *R*-square value of the multivariate analysis was 0.182. Gender-specific regression models were also made and are presented in the Supporting Information Materials.

3.3 | QT subintervals

In the multivariate analysis of the QT subintervals, JpTpc was excluded from the analysis because of reversing in association from positive in the univariate analysis to negative in the multivariate analysis. Body temperature showed the strongest association with the QRS interval duration (SC = −0.121, $P < .001$), with the TpTe interval nearly reaching statistical significance (SC = −0.035, $P = .054$), as can be observed from Table 5. The *R*-square of the second backward multivariate model was 0.017.

4 | DISCUSSION

In the present analysis of 3032 normothermic healthy volunteers, body temperature was found to be independently associated with heart rate, P-wave axis, J-point amplitude in lead V4, and ventricular conductivity. QT subinterval analysis revealed that the association was primarily mediated through prolongation of the QRS duration and not through repolarization prolongation. In contrast, other atrial and atrioventricular nodal ECG parameters were not independently associated with body temperature. These findings suggest that body temperature induces ventricular electrocardiographical changes that can be observed in a healthy population with a normal body temperature.

Previous studies already evaluated the cellular mechanism of the association between body temperature and the cardiac electrophysiological characteristics.[6,19,20,26–29] These studies showed that electrophysiological characteristics were predominantly caused by the effects of temperature on late current Na^+ influx channels.[6,19,20,26–29] Animal and in vitro studies showed Na^+ channels are temperature sensitive, with increased rates at higher temperatures of Na^+ channel activation, deactivation, fast and slow inactivation.[13,18,30–32] These Na^+ channel kinetics were also apparent in physiological body temperature conditions,[19] and appear to be reflected in our electrocardiographic findings in normothermic healthy individuals.

TABLE 3 Linear univariate regression model analysis in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5°C and 37.5°C

	Univariate analysis			
Variable	**USC**	**SC**	***R*-square**	***P*-value**
Age (years)	−0.004	−0.198	0.039	<.001
Female gender	0.192	0.222	0.049	<.001
Body mass index (kg/m^2)	0.002	0.017	<0.001	.337
Systolic blood pressure (mm Hg)	−0.003	−0.096	0.009	<.001
Diastolic blood pressure (mm Hg)	−0.002	−0.059	0.003	.003
Heart rate (beats/min)	0.010	0.277	0.076	<.001
Serum sodium (mmol/L)	−0.013	−0.065	0.004	<.001
Serum potassium (mmol/L)	−0.095	−0.080	0.006	<.001
Serum calcium (mmol/L)	0.092	0.023	<0.001	.222
Maximum P-wave duration (ms)	−0.002	−0.058	0.003	.002
P-wave dispersion (ms)	−0.002	−0.060	0.004	.002
Total P-wave area in lead V1 (mm × ms)	4.77×10^{-5}	0.010	<0.001	.571
P-wave axis (degrees)	−0.001	−0.031	0.001	.087
PR-interval (ms)	−0.002	−0.130	0.017	<.001
QRS duration (ms)	−0.004	−0.125	0.015	<.001
R-amplitude lead I (μV)	-4.04×10^{-5}	−0.032	0.001	.082
R-amplitude lead aVL (μV)	-8.39×10^{-5}	−0.061	0.003	.001
R-amplitude lead V1 (μV)	-6.70×10^{-5}	−0.034	0.001	.064
R-amplitude lead V2 (μV)	-2.63×10^{-5}	−0.025	0.001	.168
R-amplitude lead V3 (μV)	-2.53×10^{-5}	−0.041	0.002	.023
R-amplitude lead V4 (μV)	-3.34×10^{-5}	−0.061	0.004	.001
R-amplitude lead V5 (μV)	-4.98×10^{-5}	−0.070	0.005	<.001
R-amplitude lead V6 (μV)	-4.99×10^{-5}	−0.053	0.003	.004
Heart axis (degrees)	0.001	0.070	0.005	<.001
Cornell product (ms × mm)	-5.05×10^{-7}	−0.082	0.007	<.001
J-point amplitude lead V4 (mm)	−0.001	−0.110	0.012	<.001
J-point - T-peak duration (corrected for heart rate) (ms)	0.001	0.034	0.001	.064
T-peak – T-end duration (ms)	−0.002	−0.049	0.002	.007
Maximum T-wave duration (ms)	9.52×10^{-5}	0.005	<0.001	.765
Minimum T-wave duration (ms)	3.17×10^{-5}	0.004	<0.001	.833
T-wave dispersion (ms)	-9.25×10^{-5}	−0.014	<0.001	.443
T-wave axis (degrees)	0.000	−0.011	<0.001	.529
QTcF duration (ms)	−0.001	−0.036	0.001	.050

Results are reported as unstandardized coefficient (USC) and standardized coefficient (SC) with the corresponding *P*-value and the *R*-square value in the linear univariate regression model.
Abbreviation: QTcF, corrected QT interval with Fridericia's method.

Furthermore, an association between body temperature and heart rate has previously been reported. Hyperthermia in humans increases heart rate independently from age and gender, and is associated with increased incidences of ventricular arrhythmias in Brugada syndrome and long QT-syndrome patients.[3,13,27,29] Conversely, hypothermia is associated with sinus bradycardia, although not always observed in moderately hypothermic patients,[3–5] possibly because of a stress-induced sympathetically mediated increased heart rate secondary to initial cooling.[33] In our analysis, heart was independently associated with body temperature in normothermic healthy adults. Heart rate increased incrementally with body temperature, which is in line with previous findings in both hypo- and hyperthermia studies.

In the present analysis, we also observed an independent association between the J-point elevation in lead V4 and body temperature,

TABLE 4 Backward linear multivariate regression model analysis in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5°C and 37.5°C

	Multivariate analysis		
Variable	USC	SC	*P*-value
Age (years)	−0.005	−0.255	<.001
Female gender	0.183	0.209	<.001
Systolic blood pressure (mm Hg)	Dropped		
Diastolic blood pressure (mm Hg)	Excluded		
Heart rate (beats/min)	0.009	0.231	<.001
Serum sodium (mmol/L)	Dropped		
Serum Potassium (mmol/L)	Dropped		
Maximum P-wave duration (ms)	Excluded		
P-wave dispersion (ms)	Excluded		
P-wave axis (degrees)	−0.001	−0.051	<.001
PR-interval (ms)	Excluded		
QRS duration (ms)	Dropped		
R-amplitude lead I (μV)	Dropped		
R-amplitude lead aVL (μV)	Dropped		
R-amplitude lead V1 (μV)	Dropped		
R-amplitude lead V3 (μV)	Dropped		
R-amplitude lead V4 (μV)	Excluded		
R-amplitude lead V5 (μV)	Excluded		
R-amplitude lead V6 (μV)	Dropped		
Heart axis (degrees)	Dropped		
Cornell product (ms × mm)	Dropped		
J-point amplitude lead V4 (mm)	−0.001	−0.121	*P* <.001
T-peak – T-end duration (ms)	Excluded		
QTcF (ms)	−0.001	−0.061	.002

Probabilities of less than 0.10 in the linear univariate regression model were added to the backward linear multivariate regression model. Results are reported as unstandardized coefficient (USC) and standardized coefficient (SC) with the corresponding *P*-value. The *R*-square of the backward linear multivariate regression model was 0.182.
Abbreviation: QTcF, corrected QT interval with Fridericia's method.

TABLE 5 Backward linear multivariate regression model analysis with body temperature as dependent variable to identify which subintervals of the QT-interval were dependent on body temperature in normothermic healthy volunteers aged 18 years or older (n = 3023) with a tympanically measured body temperature between 35.5°C and 37.5°C

	Multivariate analysis		
Variable	USC	SC	*P*-value
QRS duration (ms)	−0.004	−0.121	<.001
J-point - T-peak duration (corrected for heart rate) (ms)	Excluded		
T-peak – T-end duration (ms)	−0.001	−0.035	.054

Results are reported as unstandardized coefficient (USC) and standardized coefficient (SC) with the corresponding *P*-value. The *R*-square of the backward linear multivariate regression model was 0.017.

although this was only observed in males in the multivariate analysis and not in females, presumable due to the increased amount of tissue between the heart and the electrodes in female subjects. Osborn waves, characterized by J-point elevation and being most apparent in precordial lead V4 are a well-recognized effect of hypothermia.[9,11,12] Hypothermia-induced accelerated Na+ channel inactivation leads a reduced amplitude of the action potential duration primarily in the epicardium but not in the endocardium.[27] This difference leads to a transmural voltage gradient, materializing as J-point elevation on the ECG.[12] The independent association found between body temperature and J-point elevation in lead V4 in the present analysis suggests that the gradient between epicardium and endocardium exists even in healthy volunteers with a normal body temperature and is modulated by body temperature within the normal range.

There are ample human and animal studies on the effects of hypo- and hyperthermia on the ventricular action potential.[2,16,17,33] Preclinically, for each degree centigrade that the body temperature was reduced below 38°C, the ventricular action potential was prolonged by 6.1 to 14 milliseconds, and for each degree of body temperature increase above 38°C, the ventricular action potential was shortened by 5.3 to 14 milliseconds.[2,16,17,33] A prolongation of the QTc interval occurred in about 73% of hypothermia patients[34] and in 100% of patients treated with targeted temperature management after cardiac arrest, which normalized after the body temperature was restored to the normal range.[2,4,34] In the current analysis in normothermic healthy volunteers, we also observed the inverse association between body temperature and the QTcF duration. These findings provide confirmation that the effects observed in hypo- and hyperthermia also occur within the clinically more common body temperature range.

However, QT subinterval analysis revealed that the main driver for QTc prolongation was prolongation of the QRS duration and not the duration of repolarization (JpTpc and TpTe). The effect of body temperature on the QTc interval is thereby substantially different from QTc interval prolongation induced by drug effects on the human ether-a-go-go-related gene (hERG/Kv11.1), which is a K^+ channel, where no effect on the QRS interval was observed, but rather a comparable prolongation of the JpTpc and TpTe intervals.[21] These data also appear to support the observation that hypothermia was not found to be associated with increased ventricular arrhythmias or mortality.[4,6,7,14,35] In summary, body temperature-related QTc interval prolongation is presumably mediated through reduced Na^+ channel activation materializing as QRS duration prolongation on the surface ECG and thereby

distinguishable from hERG channel mediated QTc interval prolongation. Our analysis supports this notion and may contribute an additional method to differentiate between direct pharmacological effects on hERG channels or through indirect effects by fluctuations in body temperature.

Finally, previous studies also reported on an association between body temperature and atrial and AV conduction time, such as P-wave amplitude and width and the PR-interval.[7,33,36] Although these associations were also observed in our univariate analysis, only P-wave axis remained independently associated with body temperature. Compared with the ventricular action potential, the atrial action potential has a less negative resting potential, an abbreviated plateau phase, and slower terminal repolarisation, which are predominantly induced by altered potassium currents.[20,37] Preclinically, significant decreases in body temperature of 18-27°C in rats were required to induce AV pathology.[33,38] However, in humans, severe AV-pathology, for example a total AV-block, was only observed in severe hypothermia cases (<28°C) and may explain the loss of significance in our multivariate analysis in normothermic healthy adults.[5,7,34]

4.1 | Limitations

In the present analysis, body temperature was measured peripherally with a tympanic thermometer, while the golden standard for the core body temperature measurement is pulmonary artery temperature.[39] Each peripheral body temperature measurement method has their own estimated error, but can be reduced to a minimum when considering method-specific factors prior to the measurements.[39,40] Comparative studies found that tympanic body temperature measurements had the highest accuracy compared to other peripheral temperature measurements and had a mean difference between the gold standard and tympanic measurements of 0.02°C with a 0.99 correlation.[39–41] Moreover, the present retrospective study design with the lack of paired data limits the sensitivity of our analysis to find true associations between body temperature and the measured ECG parameters. Finally, additional factors which may potentially influence both body temperature and ECG parameters through autonomic nerves system separately, such as menstrual cycle[42] or time of day,[43] were not included in this analysis. However, we believe that both menstrual cycle and the body temperature fluctuations during office hours and their potential influences are rather limited within the time-span of a screening and are partially corrected through the large sample size. Moreover, we provided a separate univariate analysis and a multivariate analysis for both genders as a supplement of this manuscript.

5 | CONCLUSION

Body temperature in normothermic healthy volunteers was associated with heart rate, P-wave axis, J-point amplitude in lead V4, and ventricular conductivity, primarily through prolongation of the QRS duration. In contrast, other atrial and AV nodal ECG parameters were not independently associated with body temperature.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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