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Effect of ubiquinol on electrophysiology during high-altitude acclimatization and de-acclimatization: A substudy of the Shigatse CARdiorespiratory fitness (SCARF) randomized clinical trial

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ABSTRACT

Background: High-altitude exposure changes the electrical conduction of the heart. However, reports on electrocardiogram (ECG) characteristics and potent prophylactic agents during high-altitude acclimatization and de-acclimatization are inadequate. This study aimed to investigate the effects of ubiquinol on electrophysiology after high-altitude hypoxia and reoxygenation.

Methods: The study was a prospective, randomized, double-blind, placebo-controlled trial. Forty-one participants were randomly divided into two groups receiving ubiquinol 200 mg daily or placebo orally 14 days before flying to high altitude (3900 m) until the end of the study. Cardiopulmonary exercise testing was performed at baseline (300 m), on the third day after reaching high altitude, and on the seventh day after returning to baseline.

Results: Acute high-altitude exposure prolonged resting ventricular repolarization, represented by increased corrected QT interval (455.9 ± 23.4 vs. 427.1 ± 19.1 ms, $P < 0.001$) and corrected T_{peak}-T_{end} interval (155.5 ± 27.4 vs. 125.3 ± 21.1 ms, $P < 0.001$), which recovered after returning to low altitude. Ubiquinol supplementation shortened the hypoxia-induced extended T_{peak}-T_{end} interval (−7.7 ms, [95% confidence interval (CI), −13.8 to −1.6], $P = 0.014$), T_{peak}-T_{end} /QT interval (−0.014 [95% CI, −0.027 to −0.002], $P = 0.028$), and reserved maximal heart rate (11.9 bpm [95% CI, 3.2 to 20.6], $P = 0.013$) during exercise at high altitude. Furthermore, the decreased resting amplitude of the ST-segment in the V3 lead was correlated with decreased peak oxygen pulse ($R = 0.713$, $P < 0.001$) and maximum oxygen consumption ($R = 0.595$, $P < 0.001$).

Conclusions: Our results illustrated the electrophysiology changes during high-altitude acclimatization and de-acclimatization. Similarly, ubiquinol supplementation shortened the prolonged T_{peak}-T_{end} interval and reserved maximal heart rate during exercise at high altitude.

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1. Introduction

Hypoxia and hyperoxia are potent activators of autonomic nerve activity, which can stimulate the cardiopulmonary response and reduce cardiac functional reserve [1–3]. When combined with physical activity, increased body oxygen demand further stimulates the carotid body,

Abbreviations: ATP, adenosine triphosphate; CoQ10, coenzyme Q10; CPET, cardiopulmonary exercise testing; ECG, electrocardiogram; HR, heart rate; KATP, ATP-sensitive potassium; O_2-pulse, oxygen pulse; QRS, QRS complex duration; QT, QT interval; QTc, Corrected QT interval; SpO_2, oxygen saturation; VO_{2max}, maximum oxygen consumption.

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activating the adrenergic system and increasing circulating catecholamine levels and heart rate (HR) [1]. However, evidence showed that maximum HR decreased gradually with altitude, with a loss of 1 bpm for every 130 m of altitude gain above 3100 m [4]. Since cardiac perfusion mostly occurs during diastole, the risk of cardiac ischemia could increase with altitude owing to the reduced cardiac perfusion connected to increased myocardial oxygen consumption. These physiological responses correspond with electrocardiogram (ECG) changes in individuals exposed to simulated or real high altitudes over generations [5].

Furthermore, 30% of sudden cardiac deaths occurred over 8 years in the Austrian Alps during high-altitude mountain exercise [6]. Moreover, supraventricular, ventricular extrasystoles, and atrial fibrillation could worsen with a rapid ascent from sea level and were commonly associated with stroke at high altitudes [7]. However, a few reports have focused on preventing ECG changes after acute hypoxic exposure and whether these were reversible after returning to lowland. Given the impact of hypoxia on cardiac electrophysiology, a strategy is urgently required to improve acute acclimatization to high altitudes.

Our recent findings suggest that improving cardiac metabolism could be a novel approach to preventing altitude-induced cardiopulmonary functional injury [8]. Thus, sustaining cardiorespiratory function by supplementing the intermediates or enzymes involved in energy metabolism could be feasible. Coenzyme Q10 (CoQ10), also known as ubiquinol, is an electron carrier abundantly distributed in tissues with high energy demands, such as the heart and muscles [9]. Clinical studies in patients with post-myocardial infarction, cardiac arrhythmias and dilated cardiomyopathy have demonstrated that CoQ10 reduced prolongation of the QT-interval, premature ventricular contractions and shortened ventricular depolarization [10–12]. In addition, some experiments on rats have shown that treatment with CoQ10 improved doxorubicin-induced myocardial damage and reduce ECG abnormalities, whereas CoQ10 did not affect ECG parameters in healthy groups [13,14]. These results suggest that CoQ10 may affect the electrophysiology of the heart in pathological states.

Thus, in this study, we 1) evaluated the resting and exercise ECGs using the cardiopulmonary exercise test (CPET), 2) explored independent predictors of physical exercise capacity under hypoxic conditions using the ECG changes observed, and 3) conducted a double-blind, placebo-controlled, clinical trial to determine whether ubiquinol supplementation could improve impaired cardiovascular function during high-altitude acclimatization and de-acclimatization.

2. Material and methods

2.1. Setting

The Shigatse CARdiopulmonary Fitness (SCARF) study was a prospective observational, randomized, double-blind, placebo-controlled cohort clinical trial conducted in 2022 at Chongqing was registered at www.chictr.org.cn (ChiCTR2200059900). Healthy Han participants were included in the study and randomly assigned to the ubiquinol or placebo group at a 1:1 ratio by two physicians blinded to the study through a random code generator software (www.randomization.com). Participants were enrolled between June 1 and June 15, 2022, and basic data were recorded for all participants. Healthy Chinese Han volunteers aged between 18 and 55 years who had lived at low altitudes (<500 m) for at least 10 years and had no recent (last 6 months) exposure to high altitudes (>2500 m) fit the inclusion criteria. In addition, candidates who had a recent history of administering diuretics, acetaminophen, nonsteroidal anti-inflammatory drugs, or other drugs for preventing or treating acute mountain sickness were excluded. The allocation was not disclosed until the conclusion of the statistical data analysis or in the event of any adverse occurrences, such as severe diarrhea. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, and ethical approval was obtained from the Medical Ethics Committee of Xinqiao Hospital of the Army Medical University, Chongqing, China (approval number: 2022–060-01). All participants provided written informed consent. The protocol conforms with the Consolidated Standards of Reporting Trials (CONSORT) [15].

2.2. Experimental design

This study protocol has been described previously [16]. Each participant was instructed to take two capsules per day containing 200 mg of ubiquinol (provided by the Qunol, USA) or the placebo throughout the study. The tests were conducted in a temperature-controlled laboratory (20–25 °C) by a physician and technician blinded to treatment allocation and other study outcome assessments. Each participant underwent CPET to evaluate ECG at baseline (Chongqing, China, 300 m, Visit-1). After a 3-day rest, all participants traveled to Shigatse (China, 3900 m) via a 3-h flight. Furthermore, 3 days after arrival, a second CPET was performed (Visit-2). After 1 week of high-altitude exposure, all participants returned to a low altitude (Chongqing, 300 m). After 1 week of returning, the final CPET was conducted (Visit-3). Two participants were excluded from the sample because they did not reach their best efforts according to the CPET guidelines [17]; one from the placebo group reported precordial discomfort and displayed exercise-induced frequent ventricular premature beats, and the other from the ubiquinol group chose to stopped early at a high altitude (Fig. 1). There were no critical harms or unintended effects in each group.

2.3. Cardiopulmonary exercise test

As previously described [16], CPET was performed using an electronically braked cycle ergometer (EC3000e, Custo Med, GmbH, Ottobrunn, Germany) in an upright position and monitored using a spiroergometry system with breath-by-breath technology (Metalyzer 3B, Cortex, Leipzig, Germany). The maximum effort incremental ramp protocol comprises four stages: 3 min of rest, 3 min of unloaded exercise, a maximum incremental ramp (20 or 25 W/min), and 3 min of unloaded cycling for recovery. Participants continued CPET until they experienced symptoms of angina, dyspnea, or muscular fatigue, or at the physician's discretion if certain pre-specified stoppage criteria were met, such as hemodynamic abnormalities, arrhythmia, or neurological impairment, in adherence to the American Heart Association guidelines [17]. Maximum oxygen consumption (VO_{2max}) was defined and asserted as the plateau when there were no further increases in VO_2 despite further increases in work rate [16]. Standard 12-lead ECG, blood pressure, and oxygen saturation (SpO_2) were obtained throughout the procedure using a 12-lead connection (Custo-Cardio 300BT-A, Cortex, Leipzig, Germany) in real-time, blood pressure cuffs (Suntech Tango M2, Cortex, Leipzig, Germany) on the upper arm, and a portable finger clip oximeter (Nonin WristOx2 3150, Nonin, United States), respectively. All CPET parameters were obtained as direct outputs from the CPET system.

2.4. Electrocardiographic measurements

Standard 12-lead ECGs were recorded at 25 mm/s and 10 mm/mV. The ECG data measurements at resting and exercise were retrospectively extracted. The average resting voltages and durations of the ECG segments were automatically obtained using software (Custo Diagnostic 5.5.9 Build 214, Custo Med GmbH, Ottobrunn, Germany). Similarly, the same HR over 10 s (130 ± 5 bpm, minimum 10 QRS complexes) was manually analyzed in standard and precordial leads on a high-resolution computer screen by two trained physicians who were blinded to this study. Average values were obtained when measurements differed.

The P-wave duration was derived from the longest duration in the extremity lead groups throughout the P-wave. QT intervals were measured from the onset of the QRS complex to the end of the T-wave. QT interval (QTc) was corrected using the Bazett formula, where the

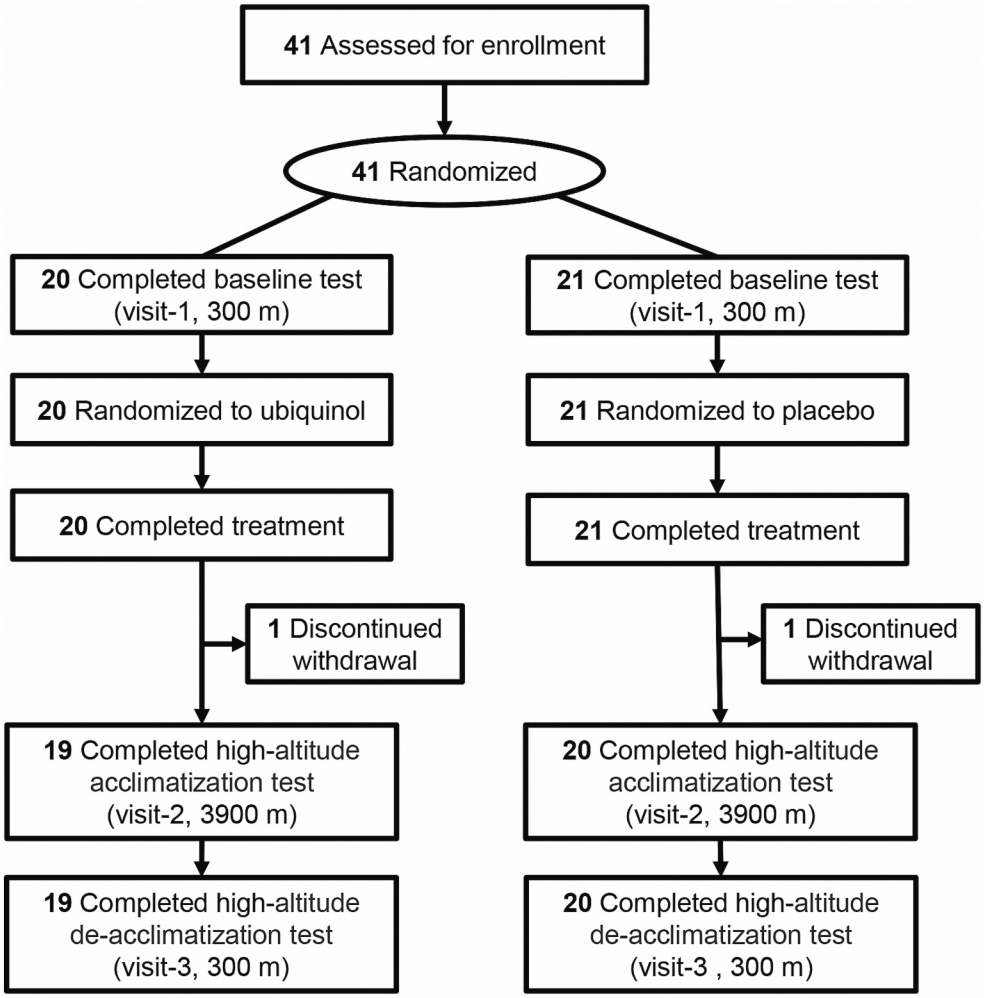

Fig. 1. Flow chart.

T_{peak}-T_{end} interval is defined as the interval between the peak and the end of the T-wave [18]. If T_{peak} was not clearly definable, that is, when the T-wave was not flattened or had a notch, the midpoint of the flattened top or the nadir of the notch was taken as the T-value, according to Antzelevitch et al. [19]. The end of the T-wave was determined using the tail method [19]. The reference level for measuring the P-, QRS-, J-, T-, and ST-segment amplitudes was the PR-segment at the beginning of QRS [20]. The ST-segment changes were measured 60 ms after the J-point.

All ECG data and abnormal ECG findings, such as incomplete right bundle branch block, right atrial abnormality, supraventricular premature beat, and premature ventricular contractions, were analyzed in blindness of clinical data, according to the European Society of Cardiology criteria [21].

2.5. Outcomes

The primary outcomes were the characteristics and effects of ubiquinol on resting and exercise ECG during high-altitude acclimatization and de-acclimatization. The secondary outcomes included the association between submaximal exercise and ECG parameters according to CPET.

2.6. Sample size

To determine the sample size required for statistically significant results, prior and post-hoc power analyses were performed using computer software (G-Power, version 3.1.9.2, Dusseldorf, Germany). The chosen α error probability was 0.05, with power (1-β) set at 0.9. Considering that the correlation between repeated measures was 0.5, a sample size of 39 was required to determine the effects of ubiquinol. After accounting for a 5% dropout rate, the final required sample size was 41. To calculate the sample size within the two groups (ubiquinol and placebo) and the within-altitude interactions, a non-sphericity correction (ε) of 1 was used, resulting in a required sample size of 36. Setting the α error probability at 0.05 with 39 participants, a power of 0.9 was obtained for the statistical significance of treatment, altitude, and the treatment-altitude interaction.

2.7. Statistical analyses

Baseline characteristics of continuously scaled variables were assessed using the *t*-test after testing for normality using the Shapiro–Wilk test. Continuous variables were expressed as the mean ± standard deviation, and categorical variables were expressed as n (%). To account for the longitudinal setting and the possibility of varying the number of participants per phase, the models were estimated using generalized estimating equations with an exchangeable working correlation [2]. In the mixed models, treatment, altitude, and the treatment–altitude interaction were considered independent variables. A comparative analysis was performed between the two groups at each altitude, and the least significant difference test was used to adjust for within-altitude differences for multiple comparisons. Pearson's correlation tests were used to analyze the correlations between continuous variables, whereas Spearman's rank tests were used for categorical

variables. Two-sided tests with *P*-values OF <0.05 were considered statistically significant. All statistical analyses were conducted using SPSS software (version 26, IBM Corp., Armonk, NY, USA).

3. Results

3.1. Population characteristics

In total, ECG data from 39 healthy participants (20 and 19 in the placebo and ubiquinol groups, respectively) who completed CPET in 3-visits were included in the analysis. At baseline, the ubiquinol and placebo groups differed slightly in age, sex, body mass index, smoking status, or alcohol consumption (Table 1). Individuals in the ubiquinol group had higher serum ubiquinol levels than those in the placebo group (201.4 ± 49.2 vs. 102.8 ± 45.8 nmol/L, $P < 0.001$) after administering ubiquinol.

3.2. Characteristics of resting ECG

The resting ECG characteristics of the overall population at baseline, acclimatization, and de-acclimatization are presented in Table S1 and Fig. 2A. After acute high-altitude exposure, the essential ECG indicators representing ventricular repolarization, QTc Bazett (427.1 ± 19.1 vs. 455.9 ± 23.4 ms, $P < 0.001$), JTc (321.0 ± 20.2 vs. 339.0 ± 24.3 ms, P < 0.001), and corrected T_{peak}-T_{end} (125.3 ± 21.1 vs. 155.4 ± 27.4 ms, P < 0.001), showed a marked extension. Under hypoxic conditions, the P-wave had a general tendency to increase in 12-lead, and the amplitudes of the J-point and ST-segment in the inferior and precordial leads were significantly lower during acclimatization than those at baseline (Table S1). Similarly, the R- and T-waves were lower but not statistically significant. The marked effect of ubiquinol on the resting ECG after acute hypoxia exposure was insignificant. Moreover, most of the above parameters recovered to baseline levels during de-acclimatization, and they differed insignificantly before and after acute high-altitude exposure.

3.3. Characteristics of exercise ECG with an HR of 130 bpm

When exercising at high altitudes, the further increase of oxygen requirement causes different hypoxia ECG characteristics. The corrected T_{peak}-T_{end} interval prolonged in the placebo group (−6.8 ms [95% confidence interval, −11.5 to −2.2], $P = 0.004$) and was significantly prevented in the ubiquinol group (2.2 ms [95% CI, −2.0 to 6.3], $P = 0.304$, Table 2), which was similar to the T_{peak}-T_{end}/QT in the placebo group (−1.3% [95% CI, −2.3 to −0.2], $P = 0.016$) than that in the ubiquinol group (0.6% [95% CI, −0.2 to 1.4], $P = 0.124$, Table 2). However, ubiquinol did not have a distinct effect on QTc duration during exercise. In addition, the amplitudes of the P-wave, R-wave, ST slope, ST-segment, and T-waves showed a declining trend in II, V1, V5, and V6 under hypoxic conditions (Table S2 and Fig. 2B). The amplitude of the negative S-wave in V1 was diminished (−0.557 ± 0.298 vs. -0.460 ± 0.273 mV, $P = 0.002$, Table S2), and the Sokolow index significantly decreased (RV5 + SV1, 1.683 ± 0.561 vs. 1.511 ± 0.518 mV, $P < 0.001$, Table S2). Notably, when exercising under hypoxic conditions, the amplitudes of RV1 + SV5 were significantly lower in the ubiquinol group (−0.119 mV [95% CI, −0.212 to −0.025], $P = 0.013$, Table 2). During de-acclimatization, there was also a slight difference with baseline exercise ECG (Table S2).

Table 1
Baseline characteristics of participants.

Variables	Placebo ($n = 20$)	Ubiquinol ($n = 19$)
Age, years (Mean ± SD)	32.3 ± 6.2	31.0 ± 6.9
BMI, kg/m^2 (Mean ± SD)	21.9 ± 2.3	21.7 ± 3.3
Female	12 (60)	13 (68)
Male	8 (40)	6 (32)
Alcohol	7 (35)	2 (11)
Tobacco	1 (5)	4 (21)
Supraventricular premature beat	1 (5)	0 (0)
Premature ventricular contractions	1 (5)	0 (0)
Right bundle-branch block, incomplete	0 (0)	1 (5)
Right bundle-branch block, complete	1 (5)	0 (0)
Right atrial abnormality*	2 (10)	2 (11)
Ubiquinol* (nmol/L, Mean ± SD)	102.8 ± 45.8	201.4 ± 49.2

Values are presented as n (%). (*) indicates a measurement at high-altitude acclimatization.

3.4. Associations between ECG and CPET parameters

To explore independent predictors of physical exercise capacity under hypoxic conditions, we further analyzed the associations between changed ECG and CPET parameters. As presented in Table S3, under hypoxic conditions, VO_{2max}, maximum oxygen pulse (O_2-pulse), and maximal heart rate (HRmax) decreased during exercise, whereas systolic and diastolic blood pressure increased. The ST-segment amplitudes in the precordial and limb leads at rest were generally positively correlated with VO_{2max} ($R = 0.595$, $P < 0.001$) and O_2-pulse ($R = 0.713$, P < 0.001; Fig. 2C and Fig. S1, S2), particularly in the V3 lead. However, during maximal exercise, the HRmax was better maintained in the ubiquinol group (11.9 bpm [95% CI, 3.2 to 20.6], $P = 0.007$, Fig. 2D). Given the effect of ubiquinol on exercise T_{peak}-T_{end} interval and HRmax, the correlation of the corrected T_{peak}-T_{end} interval and HR at rest was found at baseline ($R = 0.449$, $P = 0.004$), acclimatization ($R = 0.504$, $P = 0.001$), and de-acclimatization ($R = 0.576$, $P < 0.001$). Owing to the noise on ECG produced by body muscles during maximal exercise, particularly at HRmax, determining the association between T_{peak}-T_{end} interval at peak exercise and HRmax to further verify their relationship is challenging.

4. Discussion

This study explored the effect of ubiquinol on ECG combined with CPET after acute high-altitude hypoxia exposure and subsequent reoxygenation. In our cohort, participants exhibited longer ventricular repolarization parameters and lower amplitudes of the R-wave, J-point, ST-segment, and T-wave after hypoxia. Participants who received preventive ubiquinol treatment had a shorter T_{peak}-T_{end} interval and a higher peak HR, indicating its benefit on electrophysiology during exercising at high-altitude acclimatization. In addition, a higher normal ST-segment level at rest could be predictive of a larger O_2-pulse and VO_{2max}.

Consistent with a previous report by Coustet et al. [4], we observed a distinct and systematic decrease in the amplitudes of the R-wave, J-point, ST-segment and T-wave at rest and during exercise under hypoxic conditions; however, these changes remained within the normal physiological range [5]. The differences were that the P-wave amplitude tended to increase at rest [22,23] and decrease during exercise [4], and the Sokolow index was significantly lower during exercise at high altitudes. These ECG changes were likely due to the low intracellular oxygen availability and a decrease in oxygen-dependent ion channel activity, as well as hypoxia-induced alterations in adenosine triphosphate (ATP)-dependent channels, which have been reported during anemia [24]. During cardiac ischemia, decreased ATP levels caused the opening of ATP-sensitive potassium (KATP) channels, which helped to prevent excessive depolarization [25]. This shortened the duration of the action potential, maintained excitability, and protected the metabolism of myocardial cells from ischemia-induced damage [26], which was consistent with the hypoxia-induced ECG changes observed in our study.

Moreover, CoQ10 reportedly had no effects on ECG variable parameters [27,28], consistent with the results at rest in this study. However, we discovered the benefits of ubiquinol treatment during exercise. In hypoxic conditions, the ECG indicators representing ventricular repolarization (QTc, JTc, and corrected T_{peak}-T_{end}) were

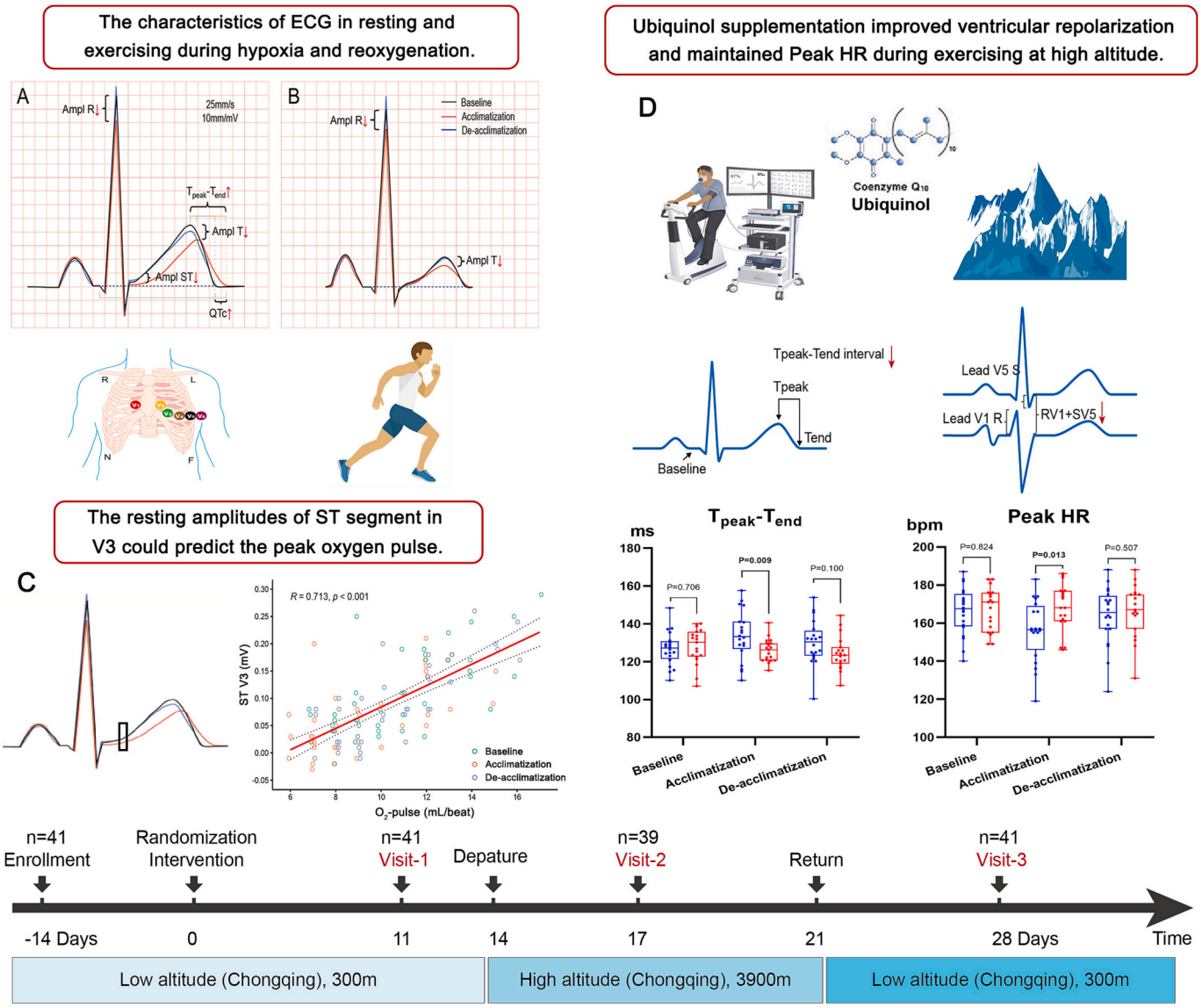

Fig. 2. Schematic figure of Shigatse CARdiorespiratory Fitness-electrocardiogram (SCARF-ECG) trial.
This randomized, double-blind, placebo-controlled clinical trial was conducted at Chongqing Xinqiao Hospital and Shigatse Branch Hospital (Shigatse CARdiorespiratory Fitness [SCARF] study). The study focuses on the ubiquinol-induced ECG changes and the ECG parameters, which can be used to predict cardiac function and physical exercise capacity during acclimatization. The diagrams demonstrate the average rest (A) and exercise (B) ECG changes among participants at 25 mm/s and 10 mm/mV. (C) The correlation between resting ST V3 amplitude and peak O_2 pulse. (D) The benefits of taking ubiquinol supplements before ascending to high altitude.
ECG, electrocardiogram. Ampl, amplitude.

significantly longer [29–31], which was prevented in the ubiquinol group. The QT interval includes depolarization and repolarization, and the T_{peak}-T_{end} symbolizes the total spatial distribution of repolarization. It has been reported that an extended T_{peak}-T_{end} interval or a higher T_{peak}-T_{end} /QT ratio is linked to the risk of arrhythmic phenotypes, such as long QT syndrome, Brugada syndrome and early repolarization patterns [19,29,32]. Treatment with CoQ10 and trimetazidine has been shown to improve myocardial energy metabolism, which can prevent QT interval prolongation and shorten the T_{peak}-T_{end} interval in patients with chronic heart failure and doxorubicin-treated rats [13,33,34].

Furthermore, diastole is an energy-consuming process requiring mitochondrial ATP synthesis [35]. At the end of ventricular repolarization, Na^+/Ca^{2+} exchange and Ca^{2+} pump activity constantly reduce cytoplasmic Ca^{2+} and induce ventricular diastole. In this process, CoQ10 plays an vital role in enhancing ATP synthesis and reducing oxidative stress, which stabilizes Ca^{2+}-dependent ion channels in the myocardium [35]. Similarly, the statin-induced impairment of left ventricular diastolic function in previously healthy individuals could be improved after CoQ10 treatment by mediating electron transfer in the electron transport chain [36]. Therefore, we suggest that the ubiquinol-induced shortened T_{peak}-T_{end} during exercise under hypoxia was likely related to the membrane-ATPase stabilization [10], improved diastolic function, and decreased total spatial distribution of repolarization.

The reduced VO_{2max} in hypobaric hypoxia could be partially explained by a decline in maximal cardiac output during exercise [2,37], which was caused by a significant decline in the peak O_2 pulse and lower HRmax. Consistent with previous results, we observed that HR increased during rest and submaximal exercise, while HRmax decreased at high altitudes due to altered parasympathetic function [38]. In our study, the decreased HRmax was prevented by ubiquinol. The potential mechanism of decreased HRmax could be explained by the ubiquinol-mediated improved corrected T_{peak}-T_{end} interval during exercise at high altitudes.

Table 2
Effects of ubiquinol on the exercise electrocardiogram (ECG) with a heart rate (HR) of 130 bpm during altitude acclimatization and de-acclimatization.

Variables	Baseline			Acclimatization			De-acclimatization						
	Placebo (n = 20)	Ubiquinol (n = 19)	P-value	Placebo (n = 20)	Ubiquinol (n = 19)	P-value	Placebo (n = 20)	Ubiquinol (n = 19)	P-value	P1	P2	P3	Interaction effect P
Corrected T_{peak}-T_{end} (ms)	126.8 ± 8.9	128.1 ± 9.4	0.656	133.6 ± 13.0	125.9 ± 6.1	0.014	130.2 ± 11.8	124.4 ± 8.8	0.076	0.141	0.933	0.133	0.018
T_{peak}-T_{end} /QT (%)	27.5 ± 1.8	27.9 ± 2.0	0.448	28.8 ± 2.6	27.3 ± 1.5	0.028	28.3 ± 2.7	27.2 ± 2.0	0.126	0.334	0.971	0.349	0.017
Corrected QT (ms)	461.5 ± 13.9	458.7 ± 15.0	0.537	464.9 ± 19.2	461.5 ± 13.2	0.502	460.6 ± 14.5	458.2 ± 14.6	0.600	0.130	0.733	0.055	0.964
RV1 + SV5 (mV)	0.383 ± 0.213	0.318 ± 0.163	0.272	0.372 ± 0.188	0.254 ± 0.109	0.013	0.366 ± 0.228	0.275 ± 0.138	0.116	0.062	0.324	0.763	0.387
VO_{2max}* (mL/min/kg)	30.2 ± 5.4	30.9 ± 4.9	0.440	24.3 ± 6.3	27.5 ± 5.1	0.030	29.5 ± 5.8	30.2 ± 6.1	0.483	<0.001	0.130	<0.001	0.003
Peak HR* (bpm)	166.2 ± 12.5	167.1 ± 11.3	0.818	156.3 ± 15.9	168.2 ± 12.3	0.007	163.8 ± 15.3	166.4 ± 13.8	0.555	0.044	0.398	0.252	0.041
Peak O_2 pulse* (ml)	11.0 ± 2.8	10.7 ± 2.7	0.758	9.2 ± 2.7	9.4 ± 2.5	0.736	10.6 ± 2.3	10.6 ± 2.8	0.979	<0.001	0.167	<0.001	0.491

Values are presented as the mean ± SD. P1, the difference between baseline and acclimatization; P2, the difference between baseline and de-acclimatization; P3, the difference between acclimatization and de-acclimatization. HR, heart rate; $VO_{2max,}$ maximum oxygen uptake; VE/VO_2, oxygen ventilation equivalents; VE/VCO_2, carbon dioxide ventilation equivalents; AT, anaerobic threshold. (*) indicates a measurement at the peak exercise.

Nowadays, it has been established that some athletes have a benign variation characterized by a higher amplitude of ST-segment elevation [21,39]. However, the specific correlation between ST segment and athletic ability remains unclear. Our study illustrated that the peak O_2-pulse and VO_{2max} were significantly positively correlated with the normal ST-segment amplitudes in the precordial and limb leads, particularly in V3 at rest during the whole process of hypoxia and reoxygenation. This ST-segment elevation in healthy athletes have been reported to associate with a 30% reduced risk of coronary heart disease-related mortality compared with individuals with normal ST segments [40]. The benign variation might be induced by administering KATP channel openers and modulated by autonomic nerves and HR changes [21,41].

4.1. Limitations

Our study had some limitations. First, the manual analysis of the ECG signal at 130 bpm limited the result accuracy. Second, the low incidence of rhythmic or conductive disturbances in our participants was given the relatively short exposure to hypoxic conditions. Lastly, the effects mentioned above were limited to observation on a 12-derivation standard ECG and CPET, which were done only after 3 days at high altitude and not repeated. Thus, more precise tools, such as echocardiography, cardiac magnetic resonance imaging, and electrophysiology, could have been used repeatedly to further analyze the effects of hypoxia on the cardiovascular system.

5. Conclusion

This study was conducted in a field cohort of participants performing an exercise test before, during, and after exposure to an altitude of 3900 m, and it illustrated hypoxia-induced changes in resting and exercise ECG during the high-altitude acclimatization and de-acclimatization. The prophylactic administration of ubiquinol was beneficial to ventricular repolarization, which was manifested by shortening the prolonged T_{peak}-T_{end} interval, and it also reserved maximal heart rate during exercise at high altitude. In the absence of a cardiopulmonary exercise test, the resting ST-segment amplitude in the V3 lead could be used to predict physical exercise capacity under hypoxic conditions.

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CRediT authorship contribution statement

Zhen Liu: Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jie Yang:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Bingjie Yang:** Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation. **Mengjia Sun:** Validation, Investigation, Formal analysis, Data curation. **Xiaowei Ye:** Validation, Investigation, Formal analysis, Data curation. **Shiyong Yu:** Validation, Investigation, Formal analysis, Data curation. **Hu Tan:** Validation, Investigation, Formal analysis, Data curation. **Mingdong Hu:** Validation, Investigation, Formal analysis, Data curation. **Hailin Lv:** Validation, Investigation, Formal analysis, Data curation. **Boji Wu:** Validation, Investigation, Formal analysis, Data curation. **Xubin Gao:** Writing – review & editing, Supervision, Project administration, Funding acquisition. **Lan Huang:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors report no relationships that could be construed as a conflict of interest.

Data availability

The datasets generated in this study are available upon request to the corresponding author.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2024.131817.

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