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Electrocardiographic Changes During Exercise in Acute Hypoxia and Susceptibility to Severe High-Altitude Illnesses

Baptiste Coustet, MD; François J. Lhuissier, MD, PhD; Renaud Vincent, MD; Jean-Paul Richalet, MD, PhD

Background—The goals of this study were to compare ECG at moderate exercise in normoxia and hypoxia at the same heart rate, to provide evidence of independent predictors of hypoxia-induced ECG changes, and to evaluate ECG risk factors of severe high-altitude illness.

Methods and Results—A total of 456 subjects performed a 20-minute hypoxia exercise test with continuous recording of ECG and physiological measurements before a sojourn above 4000 m. Hypoxia did not induce any conduction disorder, arrhythmias, or change in QRS axis. The amplitude of the P wave in V_1 was lower in hypoxia than in normoxia. The amplitudes of the R, S, and T waves and the Sokolow index decreased in hypoxia. Under hypoxia, the amplitude of the ST segment decreased in II and V_6 and increased in V_1, the ST slope rose in V_5 and V_6, and the J point was lower in II, V_5, and V_6. Multivariate regression of hypoxic/normoxic ratios of electrophysiological parameters and clinical characteristics showed a correlation between the decrease in Sokolow index and T-wave amplitude in V_5 with desaturation at exercise. Trained status and low body mass index were associated with a smaller decrease in T-wave amplitude in V_5 and V_6. Comparison of ECG between subjects suffering or not suffering from severe high-altitude illness failed to show any difference.

Conclusions—During a hypoxia exercise test, a dose-dependent hypoxia-induced decrease in the amplitude of the P/QRS/T waves was observed. No standard ECG characteristic predicted the risk of developing severe high-altitude illness. Further studies are required to clarify the cause of these electric changes and their potential predictive role in cardiac events. **(*Circulation*. 2015;131:786-794. DOI: 10.1161/CIRCULATIONAHA.114.013144.)**

Key Words: altitude sickness ■ anoxia ■ brain edema ■ electrocardiography ■ exercise test ■ pulmonary edema of mountaineers

The evidence for myocardial ischemia/hypoxia at high altitude and its possible consequence on a limitation of cardiac function in normal subjects have been debated for a long time. Despite very low arterial Po_2 values (24.6–30 mm Hg at the summit of Mt. Everest[1,2]), no clinical or electric signs of ischemia have been reported in normal well-trained subjects, suggesting physiological adaptation to protect cardiac myocytes from severe hypoxia.

Clinical Perspective on p 794

The normal cardiac response to acute hypoxia is mediated through the stimulation of the carotid bodies, leading to an activation of the adrenergic system and an increased level of circulating catecholamines.[3] This activation results in tachycardia at rest and at a given level of exercise intensity.[3–5] In prolonged hypoxia, a desensitization of the adrenergic system, through a complex interaction of hypoxia with the G-protein–coupled cardiac receptors, leads to a decrease in resting and maximal heart rate (HR).[6] Contractile function, evaluated by echocardiography, is not altered up to the simulated altitude of 8000 m, at least at rest.[7] ECG changes at simulated or real high altitude have been reported in numerous studies since the 1950s.[8] Despite a small number of participants, these studies showed consistent findings, most linked to both activation of sympathetic activity and transient pulmonary arterial hypertension. The width of the QRS complex is unchanged under hypoxic conditions, but its pattern is more often modified, exhibiting a right bundle-branch block.[9–12] A 1-mm increase in P-wave amplitude represents another widespread modification of ECG at rest and exercise in hypoxia in leads II, III, and aVF.[10–14] In addition, the amplitude of T waves decreases or even reverses in precordial leads, mainly in V_1 and V_2 at rest.[15–19]

However, the effects of exercise on ECG under hypoxia have been less documented, with most data coming from Operation Everest II in 1986. Maximum HR decreases gradually with altitude,[20,21] with a loss of 1 bpm for every 130 m of altitude gained above 3100 m.[22] Ventricular arrhythmias with ventricular ectopic beats or short ventricular tachycardia can be observed during exercise at high altitude.[12,14,16,19,21,23]

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From the Université Paris 13, Sorbonne Paris Cité, Laboratoire "Hypoxie et Poumon," EA2363 and Assistance Publique-Hôpitaux de Paris, Hôpital Avicenne, Service de Physiologie, Explorations Fonctionnelles et Médecine du Sport, Bobigny, France.

Correspondence to Jean-Paul Richalet, MD, PhD, Laboratoire "Hypoxie et Poumon," EA2363, 74 Rue Marcel Cachin, 93017 Bobigny Cedex, France. E-mail richalet@univ-paris13.fr

Ischemic changes are exceptionally reported in healthy mountaineers, the majority of studies showing no change in QRS, ST, or T-wave components.[12,14,15] Concerning the incidence of cardiac diseases in the general population exposed to moderate or high altitude for sports or leisure activities, conflicting data are reported. In the mountains, 10% to 30% of deaths are sudden deaths.[24,25] The rate of sudden death increases with altitude, in part because of the absence of medical facilities.[24–27] In addition, another cardiac morbidity, atrial fibrillation, can be worsened by rapid ascent to altitude[28] and is more often involved in strokes in patients living at high altitude.[29] Nevertheless, coronary artery disease remains the main cause of sudden cardiac death[30] as a result of reduced coronary vasodilatory reserve and increased cardiac work.[31] However, patients asymptomatic after conventional treatment perfectly tolerate altitude exposure,[32,33] even 6 months after revascularization.[34]

To date, no relation has been found between acute mountain sickness (AMS), high-altitude pulmonary (HAPE) or cerebral (HACE) edema, and alteration in cardiac function.

In addition, our group recently demonstrated that cardiac response to hypoxia during exercise independently contributes to the prediction of severe high-altitude illness (SHAI), an entity that includes severe AMS, HAPE, and HACE.[35,36]

Then the question arises, Does acute hypoxia actually induce ECG changes at exercise in healthy individuals, and, if any, what would be the causes and consequences of these changes?

We took the opportunity to study the cohort of patients who came to our mountain medicine consultation at Avicenne Hospital in Bobigny, analyzing the ECGs recorded at moderate exercise in normoxia and acute hypoxia. HR is an important parameter in qualitative and quantitative ECG interpretation. Assuming that afterload (arterial blood pressure) is not substantially modified in hypoxia, HR is an indirect marker of cardiac work. Because HR is higher in hypoxia, it is important to compare the ECG during exercise at a similar HR (thus for a similar cardiac work) in both normoxic and hypoxic conditions to exclude the component of sympathetic stimulation in the comparison of ECG characteristics between conditions.

The aims of the present study were to compare ECGs at moderate exercise in normoxia and hypoxia at the same HR, to provide evidence of independent predictors of these ECG changes, and to evaluate whether these changes, if any, are risk factors of SHAI.

Methods

Subjects

During a 3-year period from 2010 to 2012, 456 subjects who underwent an outpatient mountain medicine consultation before a sojourn of at least 3 days at an altitude above 4000 m with overnight sleeping above 3500 m were included in this study. Individual informed consent was obtained. Subjects were asked to complete a daily self-questionnaire during their sojourn at high altitude to determine daily altitude level and gain, symptoms of AMS and SHAI, and medication use. This group of subjects was extracted from a larger group of 1326 people who came to the consultation from 1992 to 2012 and were included in a prospective study to determine risk factors of SHAI.[35,36] This noninterventional retrospective study was performed by using data from a clinical test that has been done routinely since 1992 at the

Table 1. Interpretation Criteria of the ECG

Abnormal ECG Finding	Definition
T-wave inversion	>1 mm in depth from baseline in ≥2 adjacent leads not including aVR or V_1
ST-segment depression	≥1 mm in depth in ≥2 adjacent leads
Pathological Q waves	>3 mm in depth or >0.04 s in duration in ≥2 leads
Complete left bundle-branch block	QRS >0.12 s, predominantly negative QRS complex in lead V_1 (QS or rS), and upright monophasic R wave in leads I and V_6
Complete right bundle-branch block	QRS >0.12 s, terminal R wave in lead V_1 (rsR′), and wide terminal S wave in leads I and V_6
Left atrial enlargement	Prolonged P-wave duration of >0.12 s in leads I or II with negative portion of the P wave ≥1 mm in depth and ≥0.04 s in duration in lead V_1
Left axis deviation	−30° to −90°
Right atrial abnormality	High/pointed P wave ≥2.5 mm in leads II and III or V_1
Right ventricular hypertrophy	Right axis deviation ≥120°, tall R wave in V_1 plus persistent precordial S waves ($R\text{-}V_1+S\text{–}V_5$>10.5 mm)
Mobitz type II second-degree atrioventricular block	Intermittently nonconducted P waves not preceded by PR prolongation and not followed by PR shortening
Third-degree atrioventricular block	Complete heart block
Long QT interval	QTc ≥0.44 s
Short QT interval	QTc ≤0.34 s
Profound sinus bradycardia	<30 bpm or sinus pauses ≥3 s
Atrial tachyarrhythmias	Supraventricular tachycardia, atrioventricular nodal reentrant tachycardia, atrial fibrillation, and atrial flutter
Premature ventricular contractions	≥2 per tracing
Ventricular arrhythmias	Couplets, triplets, and nonsustained ventricular tachycardia

Table 2. Anthropometrical, Clinical, and Physiological Characteristics of the Subjects: Total Group and Subgroup Exposed to High Altitude

		Subgroup Exposed to High Altitude (n=113)		
	Total (n=456)	SHAI+ (n=22)	SHAI– (n=91)	*P**
Female sex, n (%)	194 (42.5)	15 (68)	36 (40)	0.020†
Age, y	47.5±14.5	52.2±14.2	48.6±14.8	0.30
Body weight, kg	69.0±12.5	61.6±10.5	68.3±12.2	0.020†
Height, cm	171±9	168±7	171±9	0.22
History of coronary disease, n (%)	4 (0.9)	0	0	1
History of arrhythmia, n (%)	15 (3.3)	0	5	0.58
Hypertension, n (%)	44 (10.7)	2	9	1
Pulmonary hypertension, n (%)	0 (0.0)	0	0	1
Hypercholesterolemia, n (%)	53 (11.6)	2	13	0.12
History of vascular disease, n (%)	6 (1.3)	0	3	1
Familial history of cardiovascular disease, n (%)	96 (21)	5	23	1
Asthma, n (%)	23 (5)	0	3	1
History of bronchopulmonary disease, n (%)	20 (4.4)	2	4	0.33
Allergies, n (%)	148 (32.5)	9	36	1
History of migraine, n (%)	65 (14.3)	5	9	0.14
History of head trauma plus loss consciousness, n (%)	28 (6.1)	4	1	0.005†
History of vagal malaise, n (%)	62 (13.6)	4	11	0.49
Menopause, n (%)	93 (48)	10/15	20/36	0.54
Raynaud syndrome, n (%)	31 (6.8)	4	**5**	0.07
Smoking, n (%)	63 (13.8)	0	12	0.12
Insomnia, n (%)	43 (9.4)	5	3	0.007†
Snoring, n (%)	112 (24.6)	5	21	1
Regular use of aspirin, n (%)	30 (6.6)	2	2	0.17
Regular use of calcium blockers, n (%)	11 (2.4)	0	1	1
Regular use of β-blockers, n (%)	24 (5.3)	1	6	1
Regular use of sleeping pills, n (%)	14 (3)	2	1	0.1
Regular use of psychotropes, n (%)	12 (2.6)	1	2	0.48
Regular mountaineering, n (%)	16 (3.5)	0	4	1
Regular endurance training, n (%)	167 (37)	5	32	0.32
Day maximum altitude, m	3940±1112	4227±1004	3900±1092	0.20
Sleep maximum altitude, m	3042±1190	3377±1060	2933±1173	0.11
History of severe AMS, n (%)	56 (12.3)	6	4	0.004†
History of peripheral edema, n (%)	22 (4.8)	2	1	0.10
History of HAPE, n (%)	4 (0.9)	1	0	0.19
History of HACE, n (%)	3 (0.7)	1	0	0.19
SHAI susceptible, n (%)	60 (13.2)	7	4	0.026†
Trekking, n (%)	285 (62.5)	15	57	0.8
Expedition, n (%)	32 (7)	1	11	0.45
Tourism, n (%)	67 (14.7)	1	10	0.69
Work, n (%)	71 (15.6)	3	13	1
Planned altitude, m	5148±985	5191±909	5296±971	0.65
ΔSaR, %	9.3±2.9	9.2±2.7	9.0±3.2	0.71
ΔSaE, %	20.9±4.6	22.7±4.4	20.1±5.0	0.028†
HCR rest, bpm/%	1.13±0.66	0.93±0.53	1.16±0.69	0.16
HVR rest, $L \cdot min^{-1} \cdot kg^{-1} \times 100$	0.64±0.49	0.53±0.46	0.74+0.55	0.11
HCR exercise, bpm/%	0.76±0.32	0.55±0.28	0.76±0.32	0.006†
HVR exercise, $L \cdot min^{-1} \cdot kg^{-1} \times 100$	0.86±0.38	0.58±0.24	0.93±0.41	0.001†
SHAI score‡	4.3±1.9	6.3±1.7	3.8±1.5	0.001†

Values are mean±SD when appropriate. AMS indicates acute mountain sickness; ΔSaE, desaturation at exercise; ΔSaR, desaturation at rest; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; HCR, cardiac response to hypoxia at exercise; HVR, ventilatory response to hypoxia at exercise; and SHAI, severe high-altitude illness.

*Student *t* test for unpaired variables for quantitative variables; Pearson χ^2 test or Fisher exact test (when <5 subjects in any condition) for qualitative variables.

†Significant ($P<0.05$).

‡Composite score established following Canouï-Poitrine et al.[36]

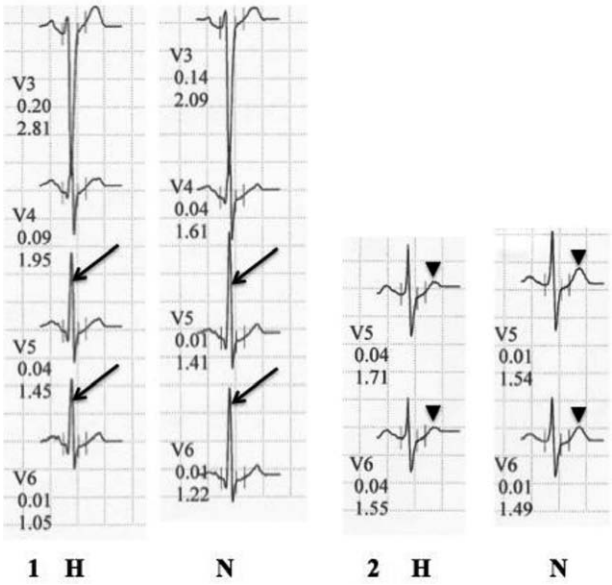

Figure. Examples of main ECG changes during the hypoxia test. Subject 1 had decreased R waves in V_5 and V_6 (arrows) under hypoxia (H) that normalized in normoxia (N). Subject 2 had decreased T waves in V_5 and V_6 under hypoxia (black arrowheads).

hospital for patients who intend to go to high altitude. The test was initially submitted to the Ethics Committee of Paris Ile de France II in its development phase, but it now is submitted only to informed consent, signed by each patient.

Methods

All subjects performed physiological measurements during a 20-minute routine submaximal exercise test consisting of 5 successive 4-minute phases as previously described: rest in normoxia, rest in hypoxia (fraction of inspired oxygen 0.115 equivalent to 4800-m altitude), exercise in hypoxia at 30% of maximal normoxic power output, exercise in normoxia with the same power output as in exercise in hypoxia, and exercise in normoxia with the same HR achieved during exercise in hypoxia (reached by slightly increasing power output). Room air temperature was maintained at 22°C throughout the test by air conditioning. Exercise was performed on an electrically braked cycloergometer (ER 900, Jaeger, Wuerzburg, Germany). A continuously recording 12-lead ECG was performed.

ECGs at the same HR from both exercise in hypoxia and exercise in normoxia with a slightly increased power output were retrospectively extracted. Voltages and duration of the ECG segments (amplitudes of P, Q, R, S and T waves with the PQ segment as the zero line; PR interval; QRS duration; and QT interval) were manually analyzed in standard and precordial derivations by a trained physician with an accuracy of 0.5 mm and 0.03 second, respectively. The QRS axis was determined with a previously reported[37] plotting method with manual checking in case of aberrant values. In addition to the measured QT value, corrected QT was assessed with the following formula: $QTc=QT/\sqrt{(60/HR)}$. The J point, amplitude, and slope of the ST segment were determined by software (Cardiosoft version 6.5, GE Healthcare, Milwaukee, WI) with an accuracy of 0.01 second. All ECG data were analyzed by researchers blinded to clinical data, according to European Society of Cardiology criteria.[38,39]

The interpretation criteria are presented in Table 1.

Statistical Analysis

Baseline characteristics of the overall population and of subjects who did or did not develop SHAI were analyzed as described previously.[35] The Student *t* test for unpaired variables for quantitative variables and the Pearson χ^2 test for qualitative variables were used to compare the SHAI+ and SHAI– groups. ECG parameters during exercise in normoxia with a slightly increased power output and exercise in hypoxia phases were compared by use of the Student *t* test for paired variables for quantitative variables and McNemar χ^2 test for paired qualitative variables. Quantitative variables are reported as mean±SD. Qualitative variables are reported as number (percent). A multivariable analysis of clinical characteristics, physiological values, and ECG parameters was performed by logistic regression. Values of $P<0.05$ were considered significant. Statistical analysis was performed with Stata 11.0 (College Station, TX).

Results

A total of 456 subjects (42.5% women) were included. Participants' mean age was 47.5 years. The maximum altitude achieved was 3940±1112 m. Among the participants, 12.3% reported a history of AMS, 0.9% reported a history of HAPE, and 0.7% reported a history of HACE. Of the 456 subjects,

Table 3. Anthropometrical, Clinical, and Physiological Characteristics of the Subjects: Data From the Stay at High Altitude

	Whole Group (n=113)	SHAI+ (n=22)	SHAI– (n=91)	*P**
Severe AMS, n (%)	22 (19.5)	22	0	0.001†
Peripheral edema, n (%)	6 (5.3)	5	1	0.001†
HAPE, n (%)	2 (1.8)	2	0	0.037†
HACE, n (%)	1 (0.9)	1	0	0.19
Use of aspirin, n (%)	16 (14.2)	6 (27)	10 (11)	0.049†
Use of acetazolamide, n (%)	47 (41.6)	8 (36)	39 (43)	0.58
Use of paracetamol, n (%)	28 (24.8)	7 (32)	21 (23)	0.39
Use of ibuprofen, n (%)	4 (3.5)	1 (5)	3 (3)	1
Altitude reached, m	4849±738	4849±738	5244±708	0.022†
Speed of ascent >400 m/d, n (%)	43 (38)	8 (36)	35 (38)	0.65

Values are mean±SD when appropriate. AMS indicates acute mountain sickness; HACE, high-altitude cerebral edema; HAPE, high-altitude pulmonary edema; and SHAI severe high-altitude illness.

*Student *t* test for unpaired variables for quantitative variables; Pearson χ^2 test or Fisher exact test (when <5 subjects in any condition) for qualitative variables.

†Significant ($P<0.05$).

Table 4. Electrophysiological Characteristics of the Subjects at Exercise in Normoxic and Hypoxic Conditions for the Same HR (n=456)

	Normoxia	Hypoxia	*P**
HR, bpm	130±15	130±15	0.40
Supraventricular premature beats/4 s, n	0.02±0.20	0.03±0.29	0.018†
PR, s	0.144±0.02	0.143±0.02	0.098
Short PR (<0.12 s), n	17	14	0.37
Atrioventricular block 1	2	2	1
Atrioventricular block 2 or 3	0	0	1
Amplitude P DII, mm	1.58±0.87	1.56±0.87	0.59
Amplitude P DIII, mm	1.62±0.55	1.60±0.55	0.34
Amplitude P V_1, mm	1.52±0.55	1.44±0.54	0.001†
Right atrial abnormality, n	49	53	0.13
Left atrial hypertrophy, n	49	51	0.48
Amplitude R R′ V_1, mm	2.14±1.27	2.10±1.24	0.076
Right ventricular hypertrophy, n	5	3	0.48
Amplitude S V_1, mm	8.41±3.58	7.83±3.44	0.001†
Amplitude R V_5, mm	15.26±5.97	14.26±5.63	0.001†
Amplitude R V_6, mm	13.22±4.60	12.23±4.37	0.001†
Sokolow index	24.18±7.74	22.51±7.39	0.001†
Left ventricular hypertrophy, n	79	55	0.48
Duration QRS, s	0.076±0.01	0.076±0.01	0.36
Right bundle-branch block, incomplete, n	182	184	0.48
Right bundle-branch block, complete, n	4	3	1
Left bundle-branch block, n	1	2	1
QRS axis, degrees	57±47	57±48	0.51
QRS axis >120°, n	35	39	0.13
QRS axis < 30°, n	37	42	0.07
Abnormal Q wave, n	6	6	1
Amplitude ST DII, mV	0.004±0.051	−0.010±0.053	0.001†
Slope ST DII, mV/s	0.69±0.64	0.70±0.59	0.39
Amplitude ST V_1, mV	0.029±0.045	0.032±0.043	0.001†
Slope ST V_1, mV/s	−0.77±0.66	−0.75±0.61	0.21
Amplitude ST V_2, mV	0.053±0.058	0.053±0.053	0.98
Slope ST V_2, mV/s	0.08±0.84	0.09±0.81	0.58
Amplitude ST V_5, mV	0.022±0.080	0.020±0.083	0.41
Slope ST V_5, mV/s	1.46±1.02	1.57±0.95	0.001†
Amplitude ST V_6, mV	0.003±0.063	−0.000±0.067	0.026†
Slope ST V_6, mV/s	1.05±0.78	1.14±0.70	0.001†
Amplitude T DII, mm	1.27±1.00	1.14±0.98	0.001†
Amplitude T V_1, mm	−0.58±1.15	−0.51±1.08	0.040†
Amplitude T V_2, mm	1.07±1.64	0.95±1.45	0.001†
Amplitude T V_5, mm	3.01±1.75	2.77±1.66	0.001†
Amplitude T V_6, mm	2.34±1.36	2.13±1.27	0.001†
Anomaly of repolarization, n	218	229	0.08
QTcB	0.42±0.02	0.41±0.02	0.066
Long QTc >0.44 s, n	48	45	0.37
Short QTc, n	0	0	1
J-point DII, mV	−0.045±0.050	−0.052±0.054	0.001†
J-point V_1, mV	0.075±0.043	0.077±0.039	0.089
J-point V_2, mV	0.047±0.041	0.047±0.039	0.55
J-point V_5, mV	−0.065±0.053	−0.074±0.066	0.001†
J-point V_6, mV	−0.060±0.044	−0.068±0.056	0.001†

Values are mean±SD when appropriate. HR indicates heart rate.

*Student *t* test for paired variables for quantitative variables; McNemar χ^2 test for paired qualitative variables.

†Significant ($P<0.05$).

113 returned the questionnaire after their trip to high altitude, allowing us to determine 2 groups: subjects who suffered from SHAI (HACE, HAPE, or severe AMS; SHAI+; n=22) and subjects without SHAI (SHAI−; n=91).

Anthropometric characteristics, level of physical activity (>3 or <3 hours of moderate to intense aerobic training per week), cardiovascular history, and treatment with β-blockers and calcium channel blockers are presented in Tables 2 and 3.

The ECGs analyzed showed a mean HR of 130±15 bpm in both hypoxic and normoxic conditions (*P*=NS). ECG characteristics in the overall population (n=456) in normoxic and hypoxic conditions are presented in Table 4.

There were no hypoxia-induced conduction disorders, arrhythmias, or changes in QRS axis.

The amplitude of the P wave in V_1, but not in II or III, was lower in hypoxia than in normoxia. In addition, the amplitudes of R, S, and T waves decreased significantly in hypoxia (example shown in the Figure). The Sokolow index was lower under hypoxia, with a trend of decreased prevalence of left ventricular hypertrophy that did not reach statistical significance (Figure). Under hypoxic conditions, the amplitude of the ST segment decreased significantly in II and V_6 and increased in V_1, the ST slope rose in V_5 and V_6, and the J point was lower in II, V_5, and V_6. Because ST-segment depression and elevation do not have the same significance, we compared for each subject the ST displacement between normoxia and hypoxia. We found a significantly greater number of subjects showing ST depression in II, V_5, and V_6 in hypoxic versus normoxic conditions (data not shown), which is similar to the quantitative ST measurements shown in Table 4 for II and V_6. There was no difference in QT and QTc duration or in repolarization parameters.

The magnitude of these hypoxia-induced electric changes was directly correlated to the baseline amplitude of studied parameters. To avoid bias and to explain the hypoxia-induced changes, we conducted a multivariate regression of hypoxic/normoxic ratios of main electrophysiological parameters and clinical characteristics. Results are shown in Table 5. The decrease in the Sokolow index and T-wave amplitude in V_5 and V_6 in hypoxic conditions was correlated with desaturation at exercise. Moreover, trained status and low body mass index were correlated with a smaller hypoxia-induced

Table 5. Multivariable Regression Explaining the Hypoxia-Induced Changes in Main Electrophysiological Parameters (n=456)

Dependent Variable	Independent Variables	Estimated β	*P*	95% Confidence Interval
Sokolow ratio H/N	Saeh	0.138	0.025	0.017 to 0.258
Amplitude T V_5 ratio H/N	Saeh	1.075	0.001	0.547 to 1.603
	Training	0.0606	0.027	0.0068 to 0.1144
	BMI	−1.049	0.015	−1.900 to −0.201
Amplitude T V_6 ratio H/N	Saeh	1.032	0.001	0.465 to 1.600
	Training	0.0911	0.002	0.033 to 0.149
	BMI	−1.282	0.006	−2.19 to −0.370
Amplitude ST V_6 ratio H/N			NS	
Amplitude ST V_5 ratio H/N			NS	

BMI indicates body mass index (in kg/m^2/100); H/N, hypoxia/normoxia; and Saeh, arterial O_2 saturation at exercise and hypoxia (in %/100).

decrease in T-wave amplitude in V_5 and V_6. No significant association was found for ST-segment amplitude ratio in V_5 and V_6.

The comparison of ECG characteristics between the SHAI+ and SHAI− groups for the subset of 113 patients is presented in Tables 6 and 7. No ECG parameter showed any significant association with the susceptibility of developing SHAI. As expected, risk factors associated with the occurrence of SHAI previously described by our group (desaturation at exercise, cardiac and ventilatory response to hypoxia at exercise, history of SHAI) were found to be significantly different between the SHAI+ and SHAI− groups (Tables 2 and 3).

Discussion

Our study is the first to describe ECG changes during a standardized hypoxic exercise test able to predict risk factors of SHAI in a large cohort of 456 subjects. We aimed to describe variations of standard ECG parameters during submaximal exercise at a simulated altitude of 4800 m and to correlate these changes with the occurrence of SHAI.

Our study has several limitations. First, the manual analysis of ECG lowers the accuracy of the results, although precise results were available by computerized measurement of ST amplitude and slope. The weak prevalence of rhythm or conductive disturbances in the population and during this short exposure to hypoxia diminishes the probability of showing any effect of hypoxia in generating these abnormalities. In addition, only a quarter of subjects returned their questionnaires, allowing us to determine their SHAI status retrospectively. The quality of the information in this self-questionnaire is highly dependent on the subject's compliance and accuracy.

Our results are consistent with previous reports. As demonstrated by our group and others, history of AMS and its complications, desaturation at exercise and hypoxic cardiac and ventilatory response to hypoxia at exercise, were confirmed as well-known risk factors of SHAI.[35,40,41] We observed a very clear and systematic decrease in the amplitude of P/QRS/T waves in hypoxic conditions, even though these amplitudes remained in the normal physiological range. These results are in line with previous studies, although the present study is the only one allowing a comparison of ECG characteristics for the same level of HR (and supposedly the same level of adrenergic activation and cardiac work) in normoxic and hypoxic conditions at exercise. In addition, independently of basal values, we demonstrated that the magnitude of decrease was correlated with the intensity of desaturation at exercise, untrained status, and body mass index. This is in line with our recent report finding an influence of aging on improving respiratory response to hypoxia and blood oxygenation in men, whereas cardiac response is blunted with aging in both sexes. Furthermore, training improved the ventilatory response to hypoxia and limited the aging-induced blunting of cardiac response to hypoxia.[42] Thus, variations in ECG parameters could be linked to a variable cardiac response to hypoxia, depending on age and training status but not mediated by sympathetic activity.

No difference in right axis deviation or right bundle-branch block was noticed in our study. We assume that the short duration of our hypoxic test does not allow the induction of pulmonary arterial hypertension and right ventricular dilatation or hypertrophy, as demonstrated by a previous report showing a right axis deviation after 45 minutes of altitude exposure worsening gradually with altitude gain.[18]

No ECG parameter achieved statistic significance to predict the occurrence of SHAI. This result confirms that none of the altitude illnesses (AMS, HAPE, and HACE) is linked to an alteration of cardiac function. However, this conclusion can be drawn confidently from the present study for AMS but not for HAPE or HACE because the number of corresponding subjects is limited (2 with HAPE and 1 with HACE). Explaining how a low cardiac response to hypoxia during exercise is one of the physiological risk factors of SHAI remains challenging. However, the present study confirms that low sensitivity of the chemoreceptors, rather than intrinsic cardiac electric changes, might be responsible for this observation. The effect of hypoxia at the medullar level on the sympathetic/parasympathetic balance could also be involved. The correlation of ECG changes such as a greater decrease in the amplitude of P/QRS/T waves with the severity of hypoxemia at exercise suggests that the observed changes in electric activity (although remaining in the normal range) might

Table 6. Electrophysiological Changes Induced By Hypoxia in SHAI + and SHAI– Subjects for the Same HR at Moderate Exercise

	Difference (Value in Hypoxia–Value in Normoxia)		
	SHAI+ (n=22)	SHAI– (n=91)	*P**
HR, bpm	–0.3±1.2	–0.1±0.9	0.33
PR, mm	–0.1±0.3	–0.0±0.3	0.47
Amplitude P DII, mm	–0.05±0.47	–0.02±0.34	0.71
Amplitude P DIII, mm	–0.06±0.52	0.01±0.36	0.49
Amplitude P V_1, mm	–0.14±0.32	–0.08±0.34	0.50
Amplitude R R′ V_1, mm	0.05±0.26	–0.05±0.35	0.20
Amplitude S V_1, mm	–0.5±0.6	–0.6±0.7	0.56
Amplitude R V_5, mm	–0.6±1.1	–1.0±1.4	0.30
Amplitude R V_6, mm	–0.6±1.0	–1.0±1.1	0.23
Sokolow index, mm	–1.1±1.3	–1.7±1.5	0.12
Duration QRS, s	–0.002±0.008	0.0004±0.007	0.24
QRS axis, degrees	1±12	0±9	0.64
Amplitude ST DII, mV	–0.01±0.03	0.00±0.03	0.13
Slope ST DII, mV/s	–0.06±0.45	0.01±0.40	0.44
Amplitude ST V_1, mV	–0.00±0.02	–0.00±0.02	0.85
Slope ST V_1, mV/s	–0.01±0.37	0.06±0.36	0.44
Amplitude ST V_2, mV	0.00±0.02	0.00±0.02	0.22
Slope ST V_2, mV/s	0.09±0.42	0.04±0.32	0.60
Amplitude ST V_5, mV	–0.01±0.05	0.00±0.04	0.26
Slope ST V_5, mV/s	0.02±0.43	0.16±0.51	0.56
Amplitude ST V_6, mV	0.00±0.04	0.00±0.02	0.42
Slope ST V_6, mV/s	–0.02±0.40	0.18±0.42	0.049†
Amplitude T DII, mm	–0.25±0.57	–0.09±0.56	0.23
Amplitude T V_1, mm	0.30±0.68	0.08±0.65	0.16
Amplitude T V_2, mm	–0.27±0.84	–0.12±0.69	0.38
Amplitude T V_5, mm	–0.39±0.58	–0.21±0.77	0.40
Amplitude T V_6, mm	–0.20±0.50	–0.21±0.60	0.83
QT, s	0.00±0.01	0.00±0.01	0.30
QTcB	–0.01±0.02	0.00±0.02	0.29
J-point DII, mV	–0.01±0.03	–0.01±0.03	0.32
J-point V_1, mV	0.00±0.02	0.00±0.03	0.67
J-point V_2, mV	–0.01±0.04	0.00±0.02	0.35
J-point V_5, mV	–0.01±0.05	–0.01±0.03	0.75
J-point V_6, mV	0.00±0.05	–0.01±0.03	0.25

Values are mean±SD. HR indicates heart rate; and SHAI, severe high-altitude illness.

*Unpaired Student *t* test between SHAI+ and SHAI–.

†Significant ($P<0.05$).

Table 7. Electrophysiological Changes Induced by Hypoxia in SHAI + and SHAI– Subjects for the Same HR at Moderate Exercise

	Ratio (Value in Hypoxia/Value in Normoxia)		
	SHAI+ (n=22)	SHAI– (n=91)	*P**
Amplitude S V_1, mm	0.93±0.08	0.93±0.10	0.56
Amplitude R V_5, mm	0.96±0.11	0.93±0.10	0.57
Amplitude R V_6, mm	0.92±0.07	0.92±0.09	0.39
Sokolow index, mm	0.94±0.06	0.93±0.07	0.19
Amplitude ST V_5, mV	1.12±0.88	1.01±0.85	0.60
Amplitude ST V_6, mV	1.30±1.66	1.03±1.22	0.070
Amplitude T V_5, mm	0.88±0.33	0.89±0.35	0.35
Amplitude T V_6, mm	0.95±0.29	0.84±0.57	0.86

Values are mean±SD. HR indicates heart rate; and SHAI, severe high-altitude illness.

*Unpaired Student *t* test between SHAI+ and SHAI–.

be attributable to low intracellular O_2 availability and a reduction in the O_2-dependent activity of the ion channels. Thus, this decrease in amplitude of QRS and T waves has been reported during anemia.[43] The observed changes in ECG could be linked to hypoxia-induced changes in ATP-dependent channels. During cardiac ischemia, ATP levels drop and then K_{ATP} channels are opened to reduce ADP and to prevent excessive depolarization,[44] shortening the action potential duration, maintaining excitability, and protecting the metabolism of myocytes from the injuries caused by ischemia.[45] Thus, during ischemia, the ECG shows peak T waves and ST depression, which contrast with the decrease in T-wave amplitude observed in our study during hypoxia. Anatomically, it could correspond to the differentiated suffering of epicardium and endocardium, hypoxia being a diffuse process. However, such effects are difficult to prove on a 12-derivation standard ECG. More precise tools could resolve these technical limitations.

The observed ECG changes induced by hypoxia for a given cardiac workload, although kept in the normal range, might be predictive of future cardiac events such as coronary disease[46] or arrhythmias. Similarly, a hypoxic test (at rest) was developed in the late 1930s to detect patients with coronary artery disease or to evaluate the efficacy of therapeutics.[47] Subjects were exposed to an inhalation of 10% O_2 for 20 minutes or until the appearance of ischemic signs. Compared with a standard exercise test, this test had a good sensitivity but with false negatives.[48,49] In our study, no hypoxia test led to the diagnosis of coronary artery disease. This could be attributable to several factors such as a population bias with limited cardiovascular risk factors, low cardiac workload, and short exposure to hypoxia. Four participants had a history of coronary artery disease, from 16 months to 16 years previously. These subjects benefited from myocardial revascularization by angioplasty or implantation; 3 of them had a negative exercise stress test in the year preceding the hypoxia test. Thus, none of them had significant abnormalities of repolarization during exercise in normoxia or during exercise in hypoxia.

Conclusions

Our study, conducted in a large cohort of subjects performing a hypoxic exercise test before a sojourn above an altitude of 4000 m, evidenced a hypoxia-induced decrease in

P/QRS/T-wave amplitude. No ECG standard characteristic predicted the risk of developing SHAI. Further studies are required to clarify the mechanisms responsible for these electric changes and their potential role in the prediction of future cardiac events. This approach could lead to the development of a new hypoxic exercise test for the evaluation of coronary risk.

Disclosures

None.

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CLINICAL PERSPECTIVE

The purposes of the study were to compare ECG at moderate exercise in normoxia and hypoxia at the same heart rate, to provide evidence of independent predictors of these ECG changes, and to evaluate the risk factors of acute mountain sickness. The study, conducted in a large cohort of subjects performing a hypoxic exercise test before a sojourn above 4000 m, provided evidence of a hypoxia-induced decrease in the amplitude of P/QRS/T waves. No ECG standard characteristic predicted the risk of developing acute mountain sickness. The best physiological predictor of acute mountain sickness remains the ventilatory response to hypoxia at exercise. Any cardiac patient planning a stay above 4000 m could benefit from a hypoxic exercise test with ECG recording to evaluate the impact of acute hypoxia on cardiac electrophysiological characteristics.

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Electrocardiographic Changes During Exercise in Acute Hypoxia and Susceptibility to Severe High-Altitude Illnesses

Baptiste Coustet, François J. Lhuissier, Renaud Vincent and Jean-Paul Richalet

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