The prognostic value of altitude in patients with heart failure with reduced ejection fraction

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ABSTRACT

Objective: It is well known that the altitude may affect the cardiovascular system. However, there were a few data related to the effect of altitude on the adverse outcome in patients with heart failure with reduced ejection fraction (HFREF). The aim of the present study was to investigate the role of intermediate high altitude on the major adverse cardiovascular outcome in patients with HFREF.

Methods: Patients with HFREF admitted to the outpatient clinics at the first center at sea level and the second center at 1890 m were prospectively enrolled in the study. HFREF was defined as symptoms/signs of heart failure and left ventricular ejection fraction <40%. The major adverse cardiac outcome (MACE) was defined as all-cause death, stroke, and re-hospitalization due to heart failure. The median follow-up period of the study population was 27 months.

Results: The study included 320 (58.55% male, mean age 65.7±11.2 years) patients. The incidence of all-cause death was 8.5%, stroke 6.1%, re-hospitalization due to decompensated heart failure 34.3%, and MACE 48.9%. In Kaplan-Meier analysis, patients with HFREF living at high altitude had more MACE (71.1% vs. 25.3%, log rank p=0.005) and presented with more stroke (11.3% vs. 2.1%, log rank p=0.001) and re-hospitalization due to heart failure (65.1% vs. 20.1%, log rank p<0.001) rates than those at low altitude in the follow-up; however, the rate of all-cause death was similar (9.4% vs. 8.1%, log rank p=0.245).

Conclusion: In the present study, we demonstrated that the intermediate high altitude is the independent predictor of MACE in patients with HFREF. High altitude may be considered as a risk factor in decompensating heart failure. *(Anatol J Cardiol 2019; 22: 300-8)*

Keywords: heart failure, altitude, cardiovascular outcome

Introduction

Currently, the number of individuals exposed to high altitude is increasing due to several reasons, such as increasing world population and interest in sports, including mountain climbing, aviation and winter sports (1, 2). Hypoxia occurring with the increased altitude causes several alterations in the cardiovascular and pulmonary systems by activating the chemoreceptors in the sympathoadrenergic system to provide sufficient oxygen to the organs. Barometric pressure decreases with the increase of altitude, resulting in a decrease in partial oxygen pressure and ability of tissues to use oxygen. As a result of the hypoxic setting, the human body tries to compensate this situation by increasing respiratory rate, blood flow, hemoglobin, and hemoconcentration (2, 3).

Heart is an endocrine organ that in addition to its pumping function plays a role in the regulation of body fluid volume and synthesizes peptide hormones, such as atrial natriuretic peptide and brain natriuretic peptide (BNP) (3). Heart failure with reduced ejection fraction (HFREF) is a clinical syndrome in which tissues remain incapable to meet their metabolic needs due to the impairment of heart muscle function neurohormonal order. HFREF is the most common disease in patients aged >65 years who are admitted to primary care with breathlessness (4). Given that even individuals with normal cardiac function may be affected by chronic hypoxia occurring in a high altitude, this effect

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can be expected to cause much more negative results in patients with systolic dysfunction.

Considering that high altitude causes different changes in the cardiovascular system, it may be beneficial to predict the outcomes that may result physiologically and pathologically which will occur especially in patients with known HFREF. Therefore, the aim of the present study was to evaluate the role of intermediate high attitude on the major adverse cardiovascular outcomes in patients with HFREF.

Methods

A total of 576 consecutive patients with HFREF who were admitted to the outpatient clinics at two different centers between January 2014 and July 2014 were prospectively enrolled in the study. The duration of the HFREF diagnosis of the patients was recorded. The first center was at sea level (group 1, n=374), and the second center was at intermediate high altitude (1890 m, group 2, n=202).

Patients with severe valvular disease (n=42), newly diagnosed heart failure (n=9), acute coronary syndrome (n=38), isolated pulmonary hypertension (n=5), and cor pulmonale (n=18) were excluded from the study. Patients who did not match according to propensity score matching (PSM) were also excluded. Finally, 360 patients were included in the study. The major adverse cardiac outcome (MACE) was defined as the composite of all-cause death, stroke, and re-hospitalization due to heart failure. The study was approved by the Local Ethics Committee. Written informed consent was obtained from all patients.

Definitions

HFREF was defined as symptoms/signs of heart failure and left ventricular ejection fraction (LVEF) <40%. Hypertension was defined as having at least two blood pressure measurements >140/90 mm Hg or using antihypertensive medications. Diabetes mellitus (DM) was defined as having at least two fasting blood sugar measurements >126 mg/dL or using antidiabetic agents. Chronic kidney disease (CKD) was defined as having an estimated glomerular filtration rate <60 mL/min/1.73.

Laboratory measurements

Blood samples were collected in anticoagulant-free gel tubes to measure fasting glucose, urea, creatinine, albumin, total cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and uric acid (UA). Blood samples were centrifuged at 1800 rpm for 15 min, and plasma and serum samples were obtained. Fasting glucose, total cholesterol, TG, high-density lipoprotein (HDL)-C, LDL-C, UA, urea, creatinine, and albumin levels were measured colorimetrically using an Abbott original reagent on Abbott Architect c8000 auto analyzer. They were measured by the method of HbA1c High Performance Liquid Chromatography using the

Automatic Glycohemoglobin Analyzer ADAMS A1c HA-8160 (Arkray) device. Renal function was estimated using the Modification of Diet in Renal Disease formula (5).

Venous blood is routinely collected in a tube containing Ethylenediaminetetraacetic Acid (EDTA) for the measurement of hemoglobin, total white blood cell, neutrophils, and lymphocytes that were determined using an automated blood cell counter by an Abbott Cell-Dyn 3700 Hematology in all patients.

Transthoracic echocardiography

Commercially available instruments (Philips IE33 xMatrix, USA) equipped with 2.25 to 7.5 MHz imaging transducers were used; the subjects were in the left decubitus position, and an experienced sonographer was blinded to all the clinical details of the patients. The end-diastolic and end-systolic left ventricle diameters, interventricular septum thickness, and posterior wall thickness were measured from the parasternal long-axis view. LVEF was calculated from the apical four-chamber and two-chamber views using Simpson's biplane method. Pulsed-wave Doppler of mitral, as well as tricuspid, inflow velocities, including early E and atrial A waves, were measured. Tissue Doppler imaging was used to measure averaged lateral and septal mitral annular systolic and early and late diastolic (Sm, E′, and A′) velocities, isovolumetric relaxation time, isovolumetric contraction time, and ejection time by placing a 1–2 mm sample volume in the septal and lateral mitral annulus, and these measurements were averaged. Pulmonary artery systolic pressure (PASP) was measured using the highest TR velocity recorded in any single view (PASP=4V2+estimated right atrial pressure).

Statistical analysis

Data were analyzed using SPSS version 20.0 package software (SPSS Inc., Chicago, IL, USA). Kolmogorov–Smirnov test was used to test the normal distribution of the groups. Descriptive statistics are expressed as mean±SD for continuous data and percentages for categorical characteristics. Student's t and Mann–Whitney U tests were used to study whether there was a statistically significant difference between the groups. Chi-square test was used for categorical comparison. A p value <0.05 was considered statistically significant. The basal demographic and clinical features of the patients were significantly different; thus, PSM was performed to decrease the bias rate. Taking the estimated propensity score of each patient, a 1:1 match analysis was performed using the nearest-neighbor matching with a caliper distance of 0.001 without replacement. The model fit was examined by the Hosmer–Lemeshow goodness-of-fit test and the C-statistic test. The postmatching balance was examined by mean standardized difference, in which <10% for a given covariate suggested adequate balance.

Kaplan–Meier survival curves were used to display MACE in patient subgroups, and log rank test was used to compare the groups. Stepwise multiple Cox regression analysis with stepwise prognostic variables selection was used to evaluate

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the relationship between variables and MACE. Variables with a p value <0.05 in univariate analysis were subjected in a stepwise multiple Cox regression analysis with stepwise prognostic variables selection to determine the independent prognostic factors of MACE. Results of regression analysis were presented as hazard ratio and 95% confidence interval. All variables showing significant values < 0.05 on univariate analysis (intermediate high altitude, hypertension, CKD, hyperlipidemia, history duration, digoxin, fasting blood sugar, white blood cell, left ventricle systolic diameter, right ventricle diastolic diameter, Sep-am, deceleration time, PASP, and BNP) were included in the Cox regression model.

Results

Baseline characteristics

The study included 320 patients who were matched with PSM analysis. The study comprised 58.55% male. The mean age of the patients was 65.7±11.2 years. The study flow diagram is shown in Figure 1. The baseline characteristics of group 1 (low altitude) and group 2 (intermediate high altitude) are presented

in Tables 1 and 2. In the demographic examination, intermediate high altitude, hyperlipidemia, hypertension, CKD, and the use of digoxin were higher in group 1 than in group 2. In the biochemical
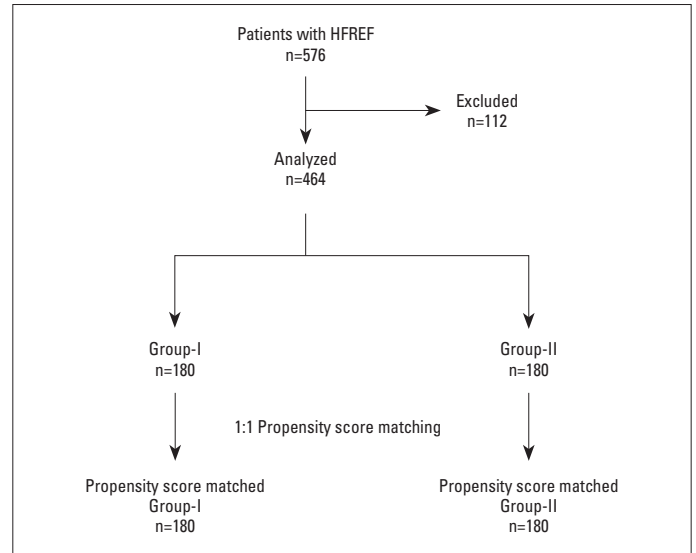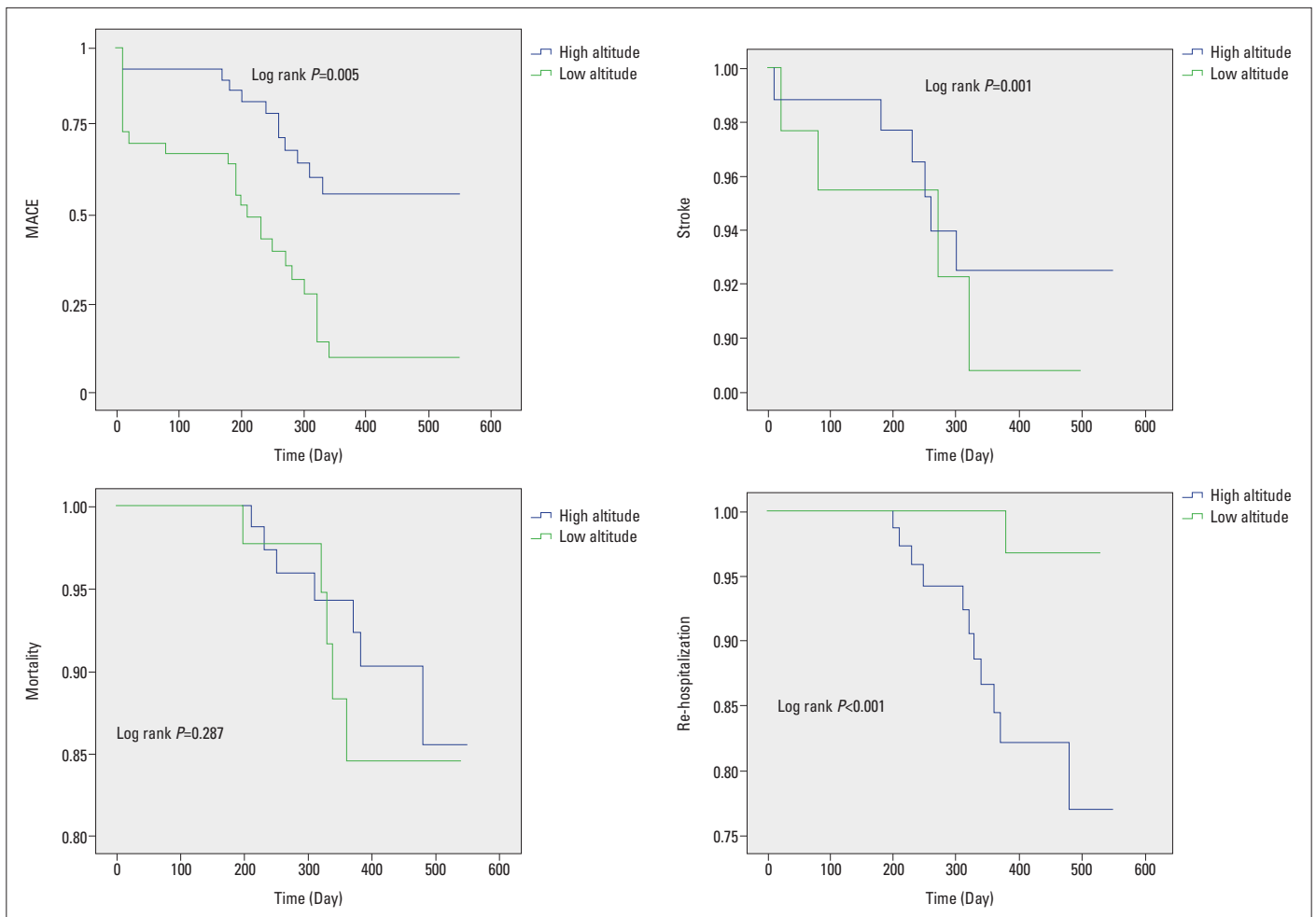

Figure 1. Study flow diagram

Figure 2. Kaplan–Meier analysis according to altitude status

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Table 1. Baseline characteristics of the study groups

Variables	Group 1 (n=180)	Group 2 (n=180)	*P* value
Age (year)	65.2±11.7	66.3±10.7	0.309
Gender (male, %)	57.0	60.1	**<0.001**
Heart rate (beats/min)	71.2±12.3	72.1±10.1	0.067
Height (cm)	168.4±8,1	168±7.1	0.161
Weight (kg)	76.3±10.5	77.1±11	0.716
Waist circumference (cm)	101.2±15	105±12	0.751
Diabetes mellitus (%)	31	32	0.437
Hypertension (%)	40	42	0.280
Chronic kidney disease (%)	5.3	6.1	**<0.001**
Hyperlipidemia (%)	9.7	18.1	**<0.001**
Smoking (%)	29.9	27.7	0.755
Heart failure type (ischemic, %)	50.5	49.4	0.921
Duration of heart failure (month)	18 (16-21)	21 (10-32)	0.112
Medications (%)			
ACEI	81.5	80.2	0.185
Beta blocker	77.2	76.1	0.490
Diuretic	90.1	90.6	0.224
ASA	82.1	84.4	0.090
Digoxin	16	17.2	0.046
MRA	54.4	50.5	0.120
Anticoagulants	25.3	24.6	0.249
NYHA (%)			
1	30.2	35.3	0.008
2	35.3	37.1	
3	28	25	
4	6.5	2.6	
Rhythm (sinus, %)	51.1	50.9	0.990
Systolic blood pressure (mm Hg)	111±11	112±12	0.670
Diastolic blood pressure (mm Hg)	81±6	80±7.5	0.381
Hgb (g/dL)	14.1 (8.6-16.8)	14.7 (12.7-17.1)	0.004
WBC (10^3/μL)	6.1 (5.3-9.2)	7.4 (6.3-10.8)	**<0.001**
Plt (10^3/μL)	218±70	231±75	0.891
Fasting glucose (mg/dL)	97 (91-106)	100 (93-102)	0.629
Creatinine (g/dL)	0.9 (0.7-1)	1 (0.8-1.5)	**<0.001**
AST (U/L)	22 (16-30)	22 (18-30)	0.182
ALT (U/L)	19 (14-28)	19 (15-33)	0.284
Cholesterol (mg/dL)	169 (152-200)	175 (158-210)	**<0.001**
HDL (mg/dL)	39 (32-46)	38 (29-47)	0.171
LDL (mg/dL)	116 (103-139)	112 (100-133)	0.07
TG (mg/dL)	134 (92-198)	129 (102-167)	0.006
UA (mg/dL)	5.7 (4.6-7.2)	5.6 (4.5-7.8)	0.631
BNP (pg/mL)	2441 (852-4177)	2582 (508-4360)	0.843
Troponin (ng/mL)	0.014 (0-0.037)	0.01 (0-0.08)	0.724
CRP (mg/L)	5 (3-9.7)	5.1 (3-9.7)	0.876

ACEI - angiotensin-converting enzyme inhibitor; ASA - acetylsalicylic acid; MRA - mineralocorticoid receptor antagonist; Hgb -hemoglobin; WBC - white blood cell; Plt - platelet; AST - aspartate aminotransferase; ALT - alanine aminotransferase; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TG - triglycerides; UA - uric acid; BNP - brain natriuretic peptide; CRP - C-reactive protein

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Table 2. Baseline echocardiography characteristics of the groups

Variables	Group 1	Group 2	*P* value
Left atrium	42.3±3.5	42.8±5.5	0.322
Septum	10.3±2.1	10.7±2.2	0.567
LVDD	59.2±9.3	60.5±8.1	0.061
LVSD	42.5±10.1	43.3±6.6	0.079
Ejection fraction	28.2±5.2	28.4±6.2	0.658
RVDD	30.7±3.5	35.7±5.1	**<0.001**
TAPSE	18.2±3.2	12.6±4.2	**0.025**
Right atrium	41.5±6.3	43.1±6.3	0.479
Septum SM	9.7±2.3	8.8±4.6	0.794
Septum EM	8.2±2.1	7.9±4.5	0.163
Septum AM	9.4±2.6	7.8±3.1	**0.005**
E	1.4 (0.9-2.1)	1.3 (1-1.8)	0.532
A	1.2 (0.8-2.6)	0.1.1 (0.8-1.8)	0.152
E/A	1.16 (0.9-2.2)	1.01 (0.7-1.9)	0.144
Deceleration time	259±37	222±43	**<0.001**
A time	179 (119-200)	166 (120-195)	0.980
IVRT	110±22	111±23	0.245
PASP	22 (15-35)	37 (26-55)	**<0.001**

LVDD - left ventricular diastolic diameter; LVSD - left ventricular diastolic diameter; TAPSE - tricuspid annular plane systolic excursion; RVDD - left ventricular diastolic diameter; IVRT - isovolumetric relaxation time; PASP - pulmonary artery systolic pressure

examination of the groups, blood sugar, cholesterol, creatinine, urea, and white blood cell values were markedly higher in group 1. In the echocardiographic examination of the groups, patients with intermediate high altitude (group 2) had more right ventricle dilation, impaired left ventricular (LV) diastolic function, hypertension, CKD, and bundle branch block and had a higher PASP than patients with low altitude.

Follow-up and outcomes

The basic characteristics of patients with MACE are given in Table 3. The median follow-up period of the study population was 27 months. In all groups, the incidence of all-cause death was 8.5%, stroke 6.1%, re-hospitalization due to decompensated heart failure 34.3%, and MACE 48.9%.

Significant parameters in univariate analysis were investigated to determine the effect of MACE by using Cox regression model (Table 4). In Cox regression analysis, PASP and intermediate high altitude were found as independent predictors of MACE development.

In Kaplan–Meier analysis (Fig. 2), patients with HFREF living at intermediate high altitude had more MACE (71.1% vs. 25.3%, log rank p=0.005) and presented with more stroke (11.3% vs. 2.1%, log rank p=0.001) and re-hospitalization due to heart failure (65.1% vs. 20.1%, log rank p<0.001) rates than those at low

altitude in the follow-up; however, the rate of all-cause death was similar (9.4% vs. 8.1%, log rank p=0.245).

Discussion

In the present study, we demonstrated that the incidence of adverse cardiovascular events, stroke, and re-hospitalization due to HFREF was higher in people living at an intermediate high altitude. In addition, it was observed that pulmonary pressures were higher, right ventricular dilatation was more, and LV diastolic functions were more impaired in patients with HFREF living at an intermediate high altitude.

The number of large volume studies evaluating the effect of altitude on HFREF is limited; thus, the impact of the high altitude in the follow-up of patients with HFREF has not been demonstrated clearly. A previous study has reported that the sympathetic system is activated in high altitudes. It was revealed that the plasma and urinary levels of catecholamine are increased after raising to high altitudes (6, 7). High altitude is associated with decreased maximal oxygen uptake and decreased barometric pressures and thus with decreased blood oxygenation (1). Owing to adaptation mechanisms, cardiac output, workload, and oxygen intake are not different from the sea level, but when oxygen pressure decreases too much, workload and heart rate increase. Alexander et al. (8) demonstrated that maximal oxygen intake is decreased by 25% in normal individuals who stayed at an altitude of 3100 m. Heart rate was increased during all exercise levels, but maximal heart rate did not change. Maximal cardiac output and beat volume were decreased in resting and during all exercise levels (8). In another study, heart rate was high, and beat volume was low in people who lived at high altitudes for a long time. However, in another study, resting cardiac output was found to be similar in individuals living at sea level (9, 10). In a study from Italy, it was found that there was no difference between patients living at a high altitude who had an LVEF of 35% and those living at sea level with respect to symptoms, such as arrhythmia, angina, or acute heart failure, but maximal exercise capacity was further decreased with altitude in individuals with a low exercise capacity (11). In our study, the rate of hospitalization due to cardiac failure was higher in patients living at a high altitude than those at sea level. It is known that disruption in right ventricular functions impairs effort capacity (12). In our study, we observed that right cardiac dimensions were wider, and that PASP was higher in patients with cardiac failure who lived at intermediate high altitudes. We believe that exacerbation of cardiac failure and further impaired exercise capacity in patients living at intermediate high altitudes may be attributed to that intraventricular septum shifts toward the left as a result of overloading of the right ventricle due to impaired right ventricular functions and effect of filling pressures, and its contribution to the LVEF is decreased (13), affecting LV filling pressure.

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Table 3. Baseline characteristics of MACE

Variables	MACE (−)	MACE (+)	*P* value
Age (year)	67.4±10.5	68.1±9.5	0.231
Gender (male, %)	58.9	60.5	0.346
Height (cm)	164.9±11.2	167.6±6.4	0.758
Weight (kg)	75.8±12.8	79±14.8	0.432
Intermediate high altitude (%)	12.2	67.4	**<0.001**
Waist circumference (cm)	96.7±12.1	100±14	0.476
Diabetes mellitus (%)	33.9	30.1	0.234
Hypertension (%)	40.1	42.5	0.252
Chronic kidney disease (%)	5.4	7.8	**<0.001**
Hyperlipidemia (%)	10.9	22.1	**<0.001**
Smoking (%)	25.1	28.9	0.823
Heart failure type (ischemic, %)	52.7	48.8	0.870
Duration of heart failure (month)	19.2±5.1	24.1±5.8	**0.001**
Medications (%)			
ACEI	78.6	86.8	0.658
Beta blocker	78.6	92.1	0.765
Diuretic	94.6	92.2	0.321
ASA	87.5	84.2	0.371
Digoxin	7.7	7.9	0.343
MRA	53.1	57.2	0.128
Anticoagulants	24.6	27.2	0.776
NYHA (%)			
1	34.5	34.2	0.167
2	27.3	26.3	
3	34.5	36.3	
4	3.6	3.2	
Rhythm (sinus, %)	55.4	48.4	**0.020**
Systolic blood pressure (mm Hg)	110±12	114±13	0.671
Diastolic blood pressure (mm Hg)	83±7	81±7.5	0.392
Hgb (g/dL)	13.1±2.3	13.8±2.6	0.603
WBC (10³/μL)	7.9±3.1	10.5±3.2	**<0.001**
Plt (10³/μL)	230±88	235±74	0.952
Fasting glucose (mg/dL)	112±40	118±32	**0.021**
Creatinine (g/dL)	0.9 (0.8-1.2)	1.2±0.9	**0.005**
AST (U/L)	20 (15-28)	21 (19-31)	0.873
ALT (U/L)	17 (13-24)	20 (18-34)	0.576
Cholesterol (mg/dL)	187 (161-199)	178 (170-205)	**0.035**
HDL (mg/dL)	41 (32-51)	38 (29-47)	0.061
LDL (mg/dL)	118±32	129.1±35	**0.028**
TG (mg/dL)	173.9±59	165±41	0.120
UA (mg/dL)	5.2 (4-7.1)	5.9 (4.3-7.8)	0.291
BNP (pg/mL)	2822 (952-4403)	2632 (482-4735)	0.753
Troponin (ng/mL)	0.15 (01-0.37)	0.1 (0.1-0.52)	0.466
CRP (mg/L)	5.1 (3-9.7)	3.8 (3-7.4)	0.247

ACEI - angiotensin-converting enzyme inhibitors; ASA - acetylsalicylic acid; MRA - mineralocorticoid receptor antagonist; Hgb - hemoglobin; WBC - white blood cell; Plt - platelet; AST - aspartate aminotransferase; ALT - alanine aminotransferase; HDL - high-density lipoprotein; LDL - low-density lipoprotein; TG - triglycerides; UA - uric acid; BNP - brain natriuretic peptide; CRP - C-reactive protein

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Table 4. Multiple Cox regression analysis for MACE

Variables	Univariate HR	95% CI	P value	Multivariate HR	95% CI	P value
Intermediate high altitude	14.9	9.75-22.7	<0.001	5.904	1.68-15.60	**0.027**
Duration of heart failure	1.035	1.038-1.052	0.001	0.96	0.91-1.2	0.216
Sinus rhythm	1.84	1.62-2.65	0.020	2.58	0.938-7.12	0.066
White blood cell	1.11	1.031-1.32	<0.001	1.01	0.883-1.16	0.589
Glucose	1.005	1.002-1.015	0.026	1.36	1.1-1.8	**0.042**
Creatinine (g/dL)	2.78	1.45-5.21	0.005	2.1	0.93-3.56	0.062
LDL	2.1	1.5-3.8	0.028	1.21	0.91-2.7	0.723
RVDD	1.1	1.06-1.14	<0.001	0.87	0.73-1.5	0.132
TAPSE	1.5	1.02-1.98	0.02	1.03	0.81-1.4	0.081
Septum AM	0.89	0.84-0.93	0.008	0.888	0.769-1.02	0.107
Deceleration time	0.99	0.985-0.994	<0.001	0.951	0.892-1.1	0.802
PASP	1.03	0.202-1.04	<0.001	2.65	1.67-4.63	**0.035**

HR - hazard ratio; CI - confidence interval; LDL - low-density lipoprotein; RVDD - right ventricular diastolic diameter; TAPSE - tricuspid annular plane systolic excursion; PASP - pulmonary artery systolic pressure

In a study conducted at high altitudes that evaluated LV diastolic functions, it was observed that pressure difference in the tricuspid valve and PASP was increased, and that E/A ratio was changed in favor of A (14). Among patients presenting with cardiac failure, diastolic heart failure alone was seen in 1/3, systolic heart failure alone in 1/3, and diastolic and systolic heart failure in the remaining 1/3 of these patients. Atrial contribution, synchronous contraction of the left ventricle, and the presence of a normal association between the left and right ventricles are known to have serious effects on symptoms in patients with low ejection fraction who have cardiac failure. Events, e.g., development of atrial fibrillation (AF), left affecting any of these may cause acute decompensation, conduction disorders, such as left bundle branch block, and cases imposing additional hemodynamic burden on the heart (15). In our study, impaired diastolic functions and pulmonary pressured were higher, as well as bundle branch was more in patients with cardiac failure who lived at an intermediate high altitude, suggesting that further impairment of symptoms caused a higher rate of hospitalization in these patients.

Decreased oxygen resulting in hypoxia at high altitudes affects myocardial tissue and negative inotropic effects hypoxia in the myocardial fibrils (8, 16-18). In addition, high altitudes influence coronary flow. Since oxygen use of the myocardium is very high even in normal conditions, coronary flow must increase for sufficient myocardial oxygenation in a hypoxia setting. Acute hypoxic conditions are associated with increased coronary flow rate (19, 20). Coronary flow has been shown to decrease in individuals who stayed at high altitudes for a long time (21). In a study from South America, conversely, coronary flow was shown to be protected in chronic hypoxic situation, and it was stated that sufficient oxygen distribution was probably provided by the increase in oxygen amount due to polycythemia rather than coronary flow (22). Although all this information indicates that normal myocar-

dium well tolerates hypoxia, when in our study increased cardiac events and re-hospitalization are evaluated together, it suggests that hypoxia increases the risk of patients with ejection fraction and HFREF to become decompensated at high altitudes.

Studies have shown that thrombogenic risk may increase due to the effects of various mechanisms at high altitudes. Moreover, although the mechanism is not clear, the risk of stroke has been reported to increase at high altitudes. In addition to classical risk factors, such as AF, dyskinetic myocardial segments and mural, hypertension, DM, and smoking, other factors, including increased hypercoagulopathy, hypoxic setting, and hyperviscosity secondary to polycythemia, have been reported to have an effect on stroke risk in individuals living at high altitudes (23, 24). An increase in blood viscosity induced by polycythemia damages vascular endothelium, activates platelets, and thus accelerates the thrombotic process (25). In our study, the incidence of stroke was higher in patients with cardiac failure who lived at an intermediate high altitude. These patients had a higher hypertension incidence and increased hemoglobin and hematocrit. Although studies have reported that the clear response of healthy individuals to altitude was increased blood pressure (26, 27), an increase in the incidence of major complications, such as retinopathy, intracranial hemorrhage, and stroke, occurred at high altitudes (27-29). In addition, in a prospective cohort study in the United States, CKD was confirmed to be associated with an increased risk of stroke (30). We think that the association of all these factors creates more risk for stroke in the case of neuroendocrine disorders, such as cardiac failure.

Study limitations

The limitation of the present study may include limited number of patients and heterogeneity of patients with HREF who lived in intermediate high and low altitudes, although they received

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standard medical treatment and follow-up duration. Furthermore, there were no patients in the present study who had heart failure with preserved ejection fraction. In addition, patients' diets could not be optimized due to cultural differences and different socio-economic status.

Conclusion

In conclusion, almost all altitude adaptation mechanisms, such as increased sympathetic activity and heart rate, increased myocardial oxygenation demand, hypoxia, polycythemia, increased afterload, and noncompliance between both ventricles due to increased pulmonary pressure, may cause exacerbation of the status of patients with HFREF living at intermediate high altitudes. Altitude may be considered as a risk factor in becoming decompensated, and patients with heart failure living at intermediate high altitudes should be followed up more closely. It would be useful to confirm this data with larger and multicenter studies.

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References

1. Simonson TS. Altitude Adaptation: A Glimpse Through Various Lenses. High Alt Med Biol 2015; 16: 125-37.
2. Rimoldi SF, Sartori C, Seiler C, Delacretaz E, Mattle HP, Scherrer U, et al. High-altitude exposure in patients with cardiovascular disease: risk assessment and practical recommendations. Prog Cardiovasc Dis 2010; 52: 512-24.
3. Webb JD, Coleman ML, Pugh CW. Hypoxia, hypoxia-inducible factors (HIF), HIF hydroxylases and oxygen sensing. Cell Mol Life Sci 2009; 66: 3539-54.
4. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al.; ESC Scientific Document Group. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37: 2129-200.
5. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006; 145: 247-54.
6. Bogaard HJ, Hopkins SR, Yamaya Y, Niizeki K, Ziegler MG, Wagner PD. Role of the autonomic nervous system in the reduced maximal cardiac output at altitude. J Appl Physiol (1985) 2002; 93: 271-9.
7. Cunningham WL, Becker EJ, Kreuzer F. Catecholamines in plasma and urine at high altitude. J Appl Physiol 1965; 20: 607-10.
8. Alexander JK, Hartley LH, Modelski M, Grover RF. Reduction of stroke volume during exercise in man following ascent to 3,100 m altitude. J Appl Physiol 1967; 23: 849-58.
9. Vogel JA, Hartley LH, Cruz JC. Cardiac output during exercise in altitude natives at sea level and high altitude. J Appl Physiol 1974; 36: 173-6.
10. Hartley LH, Alexander JK, Modelski M, Grover RF. Subnormal cardiac output at rest and during exercise in residents at 3,100 m altitude. J Appl Physiol 1967; 23: 839-48.
11. Agostoni P, Cattadori G, Guazzi M, Bussotti M, Conca C, Lomanto M, et al. Effects of simulated altitude-induced hypoxia on exercise capacity in patients with chronic heart failure. Am J Med 2000; 109: 450-5.
12. Kim J, Di Franco A, Seoane T, Srinivasan A, Kampaktsis PN, Geevarghese A, et al. Right Ventricular Dysfunction Impairs Effort Tolerance Independent of Left Ventricular Function Among Patients Undergoing Exercise Stress Myocardial Perfusion Imaging. Circ Cardiovasc Imaging 2016; 9. pii: e005115.
13. Mahmud E, Raisinghani A, Hassankhani A, Sadeghi HM, Strachan GM, Auger W, et al. Correlation of left ventricular diastolic filling characteristics with right ventricular overload and pulmonary artery pressure in chronic thromboembolic pulmonary hypertension. J Am Coll Cardiol 2002; 40: 318-24.
14. Allemann Y, Rotter M, Hutter D, Lipp E, Sartori C, Scherrer U, et al. Impact of acute hypoxic pulmonary hypertension on LV diastolic function in healthy mountaineers at high altitude. Am J Physiol Heart Circ Physiol 2004; 286: H856-62.
15. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. [ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012]. Turk Kardiyol Dern Ars 2012; 40 Suppl 3: 77-137.
16. Silverman HS, Wei S, Haigney MC, Ocampo CJ, Stern MD. Myocyte adaptation to chronic hypoxia and development of tolerance to subsequent acute severe hypoxia. Circ Res 1997; 80: 699-707.
17. Tucker CE, James WE, Berry MA, Johnstone CH, Grover RF. Depressed myocardial function in the goat at high altitude. J Appl Physiol 1976; 41: 356-61.
18. Noakes TD. Physiological models to understand exercise fatigue and the adaptations that predict or enhance athletic performance. Scand J Med Sci Sports 2000; 10: 123-45.
19. Hilton R, Eichholtz F. The influence of chemical factors on the coronary circulation. J Physiol 1925; 59: 413-25.
20. Wyss CA, Koepfli P, Fretz G, Seebaurer M, Schirlo C, Kaufmann PA. Influence of altitude exposure on coronary flow reserve. Circulation 2003; 108: 1202-7.
21. Moret PR. Coronary blood flow and myocardial metabolism in man at high altitude. In: High Altitude Physiology: Cardiac and. Respiratory Aspects. Edinburgh and London: Churchill-Livingstone 1971; pp.131-44.
22. Suarez J, Alexander JK, Houston CS. Enhanced left ventricular systolic performance at high altitude during Operation Everest II. Am J Cardiol 1987; 60: 137-42.
23. Isik T, Ayhan E, Tanboğa IH. Does intermediate high-altitude level affect major cardiovascular outcomes of patients with acute myocardial infarction treated by primary coronary angioplasty? Preliminary results of observational study. Anatol J Cardiol 2012; 12: 611.

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Anatol J Cardiol 2019; 22: 300-8
DOI:10.14744/AnatolJCardiol.2019.81535

24. Jha SK, Anand AC, Sharma V, Kumar N, Adya CM. Stroke at high altitude: Indian experience. High Alt Med Biol 2002; 3: 21-7.

25. Fujimaki T, Matsutani M, Asai A, Kohno T, Koike M. Cerebral venous thrombosis due to high-altitude polycythemia. Case report. J Neurosurg 1986; 64: 148-50.

26. Palatini P, Businaro R, Berton G, Mormino P, Rossi GP, Racioppa A, et al. Effects of low altitude exposure on 24-hour blood pressure and adrenergic activity. Am J Cardiol 1989; 64: 1379-82.

27. Ponchia A, Noventa D, Bertaglia M, Carretta R, Zaccaria M, Miraglia G, et al. Cardiovascular neural regulation during and after prolonged high altitude exposure. Eur Heart J 1994; 15: 1463-9.

28. Roach RC, Houston CS, Honigman B, Nicholas RA, Yaron M, Grissom CK, et al. How well do older persons tolerate moderate altitude? West J Med 1995; 162: 32-6.

29. Wu TY, Ding SQ, Liu JL, Yu MT, Jia JH, Chai ZC, et al. Who should not go high: chronic disease and work at altitude during construction of the Qinghai-Tibet railroad. High Alt Med Biol 2007; 8: 88-107.

30. Abramson JL, Jurkovitz CT, Vaccarino V, Weintraub WS, McClellan W. Chronic kidney disease, anemia, and incident stroke in a middle-aged, community-based population: the ARIC Study. Kidney Int 2003; 64: 610-5.