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

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 sympathtoadrenergic 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

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
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 altitude 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 (Arkay) 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 sepal 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
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](image)

![Figure 2. Kaplan–Meier analysis according to altitude status](image)
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 (10^9/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 (0.0-0.037)| 0.01 (0.0-0.08) | 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
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.

| 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 (1.1-1.8)| 0.532   |
| A                  | 1.2 (0.8-2.6)| 0.1 (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 systolic diameter; TAPSE - tricuspid annular plane systolic excursion; RVDD - left ventricular diastolic diameter; IVRT - isovolumetric relaxation time; PASP - pulmonary artery systolic pressure.
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 (%)                          | 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 (10^3/µL)                     | 7.9±3.1    | 10.5±3.2   | <0.001  |
| Plt (10^3/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±135    | 0.028   |
| TG (mg/dL)                        | 173.9±59   | 165±41     | 0.120   |
| UA (mg/dL)                        | 5.2 (4.7-7.1) | 5.9 (4.3-7.8) | 0.291   |
| BNP (pg/mL)                       | 2822 (952-4403) | 2632 (482-4735) | 0.753   |
| Troponin (ng/mL)                  | 0.15 (0.1-0.37) | 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
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 myocardium 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, dysskinetic 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...
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 socioeconomic 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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