

Iron deficiency is a possible risk factor causing right heart failure in Tibetan children living in high altitude area

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Abstract

The aim of the study is to discuss the risk factor of right heart failure (RHF) especially the association of iron deficiency with RHF in Tibetan children who live in high altitude area. In this retrospective study, we collected the data of Tibetan children from January 2011 to December 2018 in our hospital. The patients included in the study had the following data: age, gender, ferritin, echocardiography, hemoglobin, C-reaction protein, and altitude of residence. According to whether RHF was diagnosed, the patients were divided into RHF group and non-RHF group. Totally 133 patients were included with 59 in RHF group and 74 in non-RHF group. In single factor analysis, age ($P = .008$), altitude of residence ($P < .001$), ferritin ($P < .001$), and pulmonary arterial systolic pressure ($P < .001$) showed significant difference between the 2 groups. Binary logistic regression was performed to further identify the association of the clinical factors with RHF. Higher pulmonary arterial systolic pressure (odds ratio: 29.303, 95% confidence interval: 5.249–163.589, $P < .001$) and lower ferritin level (odds ratio: 5.849, 95% confidence interval: 1.585–21.593, $P = .008$) were independent risk factors associated with RHF. In receiver-operating characteristic curve, the optimal cutoff value of ferritin level was 14.6 $\mu\text{g/L}$ with the sensitivity of 81.4% and specificity of 89.2%. As continuous variable, the correlation between ferritin and RHF was not certain ($P = .281$). Due to the possibility that iron deficiency be a risk factor of RHF in Tibetan children, prevention and treatment of iron deficiency might be a potential way in reducing the incidence of RHF in this high altitude area.

Abbreviations: AUC = area under the curve, CI = confidence interval, CRP = C-reaction protein, Hb = hemoglobin, HIF = hypoxia-induced factor, NHF = nonright heart failure, PASP = pulmonary arterial systolic pressure, RHF = right heart failure, SE = standard error.

Keywords: high altitude, iron deficiency, pulmonary hypertension, right heart failure

1. Introduction

There are over 140 million people who live at a high altitude (>2500 m) area globally.^[1] Besides, approximately 35 million

people travel to altitudes above 3000 meters each year.^[2] Long time exposure to hypoxic environment on highland induces pulmonary vascular remodeling which further results in pulmonary hypertension (PH) with some severe cases of right heart failure (RHF).^[3]

Previous study suggested that Tibetan population, with a long history of highland residence, might have more time to adapt to chronic hypoxia than other high altitude human populations and nonhighlanders.^[4] In genomic study, variants in EPAS1 and EGLN1, which are upstream genes of hypoxia-induced factor (HIF), were identified in Tibetan highlanders.^[5,6] These 2 genomic variants are considered to be associated with low hemoglobin (Hb) in Tibetans compared with Han Chinese migrants to high altitude or highlanders in other areas.^[7,8] Since increase in Hb concentration is believed to increase pulmonary pressures and resistance,^[9] relatively low Hb in Tibetans might be helpful in maintaining normal hemodynamics in pulmonary circulation. Due to the adaptation mechanisms above, PH in Tibetan highlanders is not as prevalent as Han Chinese migrants. However, in our clinical observation, some Tibetan children were found to have PH and even RHF with severe PH. In most of the cases, the age of the children was between 6 months and 3 years, which overlapped with the common age of alimentary iron-deficiency anemia.

Due to local custom, especially in rural area, some Tibetan children younger than 2 years are fed by parents with breast milk and “zanba” (a kind of local food made from highland barley), while little meat or other food being taken. The improper feeding could cause alimentary iron deficiency. It has been established that iron could affect pulmonary vascular response to hypoxia

Editor: Uddyalok Banerjee.

This work was supported by grants from Sichuan Province Science and Technology Support Program, China (no: 2018SZ0180).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Yu J, Yu L, Li Y, Hu F. Iron deficiency is a possible risk factor causing right heart failure in Tibetan children living in high altitude area. *Medicine* 2020;99:29(e21133).

Received: 21 April 2019 / Received in final form: 8 April 2020 / Accepted: 4 June 2020

<http://dx.doi.org/10.1097/MD.00000000000021133>

via HIF family.^[10,11] Reducing iron availability results in increased pulmonary artery pressure.^[12] In animal model, rats fed with low iron food appeared to have pulmonary vascular remodeling, increased pulmonary vascular resistance, and elevated pulmonary artery pressure.^[13] Besides, iron also takes part in multiple cellular activities in heart and iron deficiency seems to reduce systolic function of heart.^[14] As is proved that increased PH could result in RHF, is it possible that iron deficiency when participates in increased PH and decreased systolic function is an important risk factor of RHF?

Based on the studies above, we hypothesize that iron deficiency which attenuates adaptation to hypoxia might be an important factor which participates in RHF due to PH in Tibetan children who live in high altitude area.

2. Methods

2.1. Population

We retrospectively studied the Tibetan children from January 2011 to December 2018 in our hospital. The patients included in the study had the following data: age, gender, ferritin, echocardiography, Hb, C-reaction protein (CRP), and altitude of residence. The patients without any of the data above were excluded in the study. Patients with basic heart disease, for example, congenital heart diseases, were also excluded. According to whether RHF was diagnosed, the patients were divided into RHF group and non-RHF (NHF) group. RHF is recognized based on the clinical manifestations including dyspnea, swelling, oliguria, distension of jugular veins, hepatomegaly, and enlarged right ventricle and right atrium in echocardiogram. The diagnosis of RHF was made by at least 2 experienced doctors.

All the patients in this study have given the written informed consent including permission of using clinical data.

The study was approved by the ethic committee of West China Second University Hospital of Sichuan University.

2.2. Clinical data

Except for age and gender, the other clinical data collected were

1. Ferritin: iron deficiency was defined as ferritin level $<15 \mu\text{g/L}$.^[15] Since ferritin increases in inflammatory disease, patients with elevated CRP were excluded.
2. Pulmonary arterial systolic pressure (PASP): PASP was measured by tricuspid regurgitant jet velocity by echocardiography. PASP $>60 \text{ mm Hg}$, which represented sever PH was chose as the cutoff value.^[16]
3. Hb: in early stage of iron deficiency, Hb could remain normal, so we also studied whether anemia was associated with RHF.
4. Altitude: very high altitude was defined as height above sea level between 3500 and 5800 m above sea level, while high altitude being defined as -3500 m .^[17]

2.3. Statistical analysis

Data were tested by SPSS 23.0 software. The difference of the measurement data between 2 groups was tested by *t* test. Categorical variables were tested by Chi-squared test or Fisher exact test. For multivariate analysis, binary logistic regression test was used to study the risk factors for RHF and 95% confidence interval (CI) was computed. *P* value $<.05$ was considered statistically significant. To study the ferritin level distinguishing

RHF patients from NHF patients, receiver-operating characteristic curve was constructed for ferritin levels of the patients. The optimal cutoff value was decided with maximum Youden index with the formula below: Youden index = (sensitivity + specificity) - 1.

3. Results

3.1. Patient derivation

We totally reviewed 219 cases of Tibetan patients, among which 36 were excluded with lack of ferritin, while 21 excluded with lack of echocardiography, 18 excluded with lack of CRP or elevated CRP, 11 excluded with lack of altitude of residence. Finally, 133 patients were included in the study.

3.2. Clinical characteristics of patients

There were 59 patients with the diagnosis of RHF (RHF group) and the other 74 patients showed no evidence of RHF (NHF group). Patients in RHF group were admitted due to RHF and 13 of them had bronchopneumonia. Patients in NHF group were admitted due to the following causes: 52 with bronchopneumonia, 12 with diarrhea, 3 with anemia, and 7 with PH. None of the patients of bronchopneumonia developed to severe pneumonia. In single factor analysis, age ($P=.008$), altitude of residence ($P<.001$), ferritin ($P<.001$), and PASP ($P<.001$) showed significant difference between the 2 groups. Furthermore, we used ferritin $<15 \mu\text{g/L}$ as the diagnostic criteria to compare the number of iron deficiency patients in the 2 groups. The result indicated that there were 50 iron deficiency patients and 9 normal ferritin patients in RHF group, compared with 8 iron deficiency patients and 66 normal ferritin patients in NHF group ($P<.001$). However, the difference of gender and Hb was not significant (Table 1). To further clarify the effect of PASP and Hb on RHF, subgroup analysis was made to evaluate the difference of PASP or Hb in RHF and NHF groups at different ferritin levels. Either in ferritin ≥ 15 patients or in ferritin <15 patients, PASP showed a higher level in RHF patients. In ferritin ≥ 15 patients, the Hb level in RHF and NHF groups showed no significant difference. However, in ferritin <15 patients, the Hb level in NHF group was significantly lower than RHF group (see Table, Supplemental Content, which illustrates the PASP and Hb level in patients with different ferritin level, <http://links.lww.com/MD/E511>).

Table 1

Clinical characteristics of the 2 groups.

	RHF	NHF	<i>P</i>
Number of patients	59	74	
Age, mo	16.9 ± 5.4	21.7 ± 12.8	.008*
Gender			.338
Male	31	45	
Female	28	29	
Altitude, m	3443.1 ± 364.2	2953.8 ± 329.7	<.001*
Ferritin, $\mu\text{g/L}$	10.7 ± 6.5	21.7 ± 20.0	<.001*
<15	50	8	
≥ 15	9	66	
Hb, g/L	103.7 ± 19.6	109.7 ± 15.9	.59
PASP, mmHg	89.5 ± 12.1	43.9 ± 13.5	<.001*

Hb = hemoglobin, NHF = nonright heart failure, PASP = pulmonary artery systolic pressure, RHF = right heart failure.

* $P < .05$.

Table 2
Variables grouping and single risk factor analysis of right heart failure.

Variables	Group		P
	RHF	NHF	
Age, mo			.02*
≤36	58	59	
>36	1	14	
Altitude, m			<.001*
>3500	26	3	
2500–3500	33	71	
Ferritin, μg/L			<.001*
<15	50	8	
≥15	9	66	
PASP, mm Hg			<.001*
>60	57	16	
≤60	2	58	

NHF = nonright heart failure, PASP = pulmonary artery systolic pressure, RHF = right heart failure.
* P < .05.

3.3. Risk factors for RHF patients

Binary logistic regression was performed with single variables including age, ferritin, altitude, and PASP, which showed significant difference in single factor analysis. The variables were grouped as follows (Table 2): age: ≤36 and >36 months; altitude: 2500 to 3500 and >3500 m; ferritin: <15 and ≥15 μg/L; PASP: ≤60 and >60 mm Hg.

In binary logistic regression, higher PASP (odds ratio: 29.303, 95% CI: 5.249–163.589, P < .001), lower ferritin level (odds ratio: 5.849, 95% CI: 1.585–21.593, P = .008) were independent risk factors associated with RHF (Table 3), whereas altitude and age showed no significance. In receiver-operating characteristic curve (Fig. 1) between ferritin level and RHF, the area under the curve was 0.869. The optimal cutoff value of ferritin level was 14.6 μg/L with the sensitivity of 81.4% and specificity of 89.2%.

Furthermore, we tested the correlations of the continuous variables including age, ferritin, PASP, and altitude with RHF (Table 4). The result suggested that there was correlation between PASP and RHF (P < .001). However, the correlation between ferritin and RHF showed no significance (P = .281).

4. Discussion

The RHF induced by hypoxic environment is a life-threatening disease.^[9] In early study, only 1% of previous healthy individuals are at risk of RHF in high altitude.^[18] The reason of RHF is attributed to severe hypoxic PH caused by hyperactivity to hypoxia. Whereas, in clinical observation, it is difficult to distinguish which patients are in high risk of RHF.

Table 3
Binary logistic regression for multivariate analysis of risk factors in right heart failure.

Variables	SE	OR (95% CI)	P
Age	1.190	7.173 (0.696–73.956)	.098
Altitude	1.529	4.612 (0.879–24.210)	.071
Ferritin	1.766	5.849 (1.585–21.593)	.008*
PASP	3.378	29.303 (5.249–163.589)	<.001*

CI = confidence interval, OR = odds ratio, PASP = pulmonary artery systolic pressure, SE = standard error.
* P < .05.

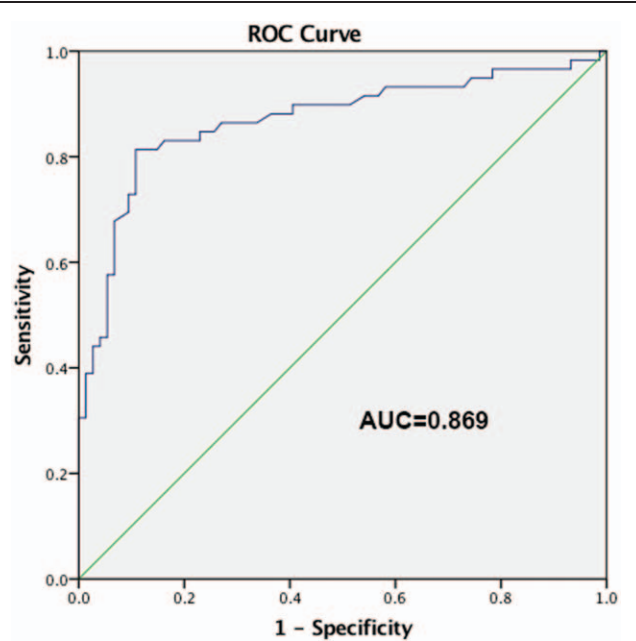


Figure 1. Receiver-operating characteristic (ROC) curve on the correlation between ferritin level and right heart failure. The optimal cutoff value of ferritin level was 14.6 μg/L with the sensitivity of 81.4% and specificity of 89.2%. AUC = area under the curve.

Iron is proved to affect tolerance to hypoxic environment. In a clinical trial, with exposure to hypoxic environment for 6 hours, the elevation of PASP in iron deficiency group was more obvious than iron-replete group. Besides, intravenous iron attenuated PASP in both groups with greater effect in iron deficiency group.^[19] In another study, infusion of iron reversed 40% of the PH caused by hypoxia and progressive iron deficiency was associated with 25% increase in PASP in chronic mountain sickness patients.^[20] The possible mechanisms of iron deficiency affecting response to hypoxia may be associated with increased HIF activity and expression of erythropoietin which result in elevated PASP.^[21–24] Moreover, iron is associated with multiple cellular activities such as generation of energy in myocardial cells, synthesis of lipids and carbohydrates and oxygen storage.^[25] It has been established that reduced iron in myocardium is associated with reduced systolic function and affects heart function directly.^[14] The studies above proved that iron could affect right heart function via multiple aspects except for effect on PH. In our study, ferritin when taken as a categorical variable showed that iron deficiency (with ferritin level <15 μg/L) was a risk factor of RHF. However, as a continuous variable, it did not show such a certain correlation.

Table 4
Binary logistic regression for risk factors as continuous variables in right heart failure.

Variables	SE	OR (95% CI)	P
Age	0.064	0.961 (0.848–1.089)	.532
Altitude	0.001	1.000 (0.998–1.003)	.773
Ferritin	0.065	0.932 (0.820–1.059)	.281
PASP	0.057	1.235 (1.105–1.381)	<.001*

CI = confidence interval, OR = odds ratio, PASP = pulmonary artery systolic pressure, SE = standard error.
* P < .05.

There are very limited studies on response to hypoxia in children. In acute hypoxia, children showed higher pulmonary artery pressure than adults, but the mechanism is not clear.^[26] In this study, when we chose the age 36 months as the cutoff value, the result suggested age was not associated with RHF. Although alimentary iron deficiency is more common in children under 3 years, there may be some other mechanisms affecting tolerance to hypoxia in children.

All the patients in this study lived in an altitude >2500 m. When we used 3500 m as the cutoff value, altitude was not considered as the risk factor of RHF. However, in single factor analysis, RHF group showed higher altitude than NHF group. It has been established that PASP is not in proportion to altitude because response to hypoxia relates to multiple mechanisms.^[11]

In summary, more patient data are needed to further prove the correlation between iron deficiency and RHF in Tibetan children. Due to the possibility that iron deficiency be a risk factor of RHF in Tibetan children, prevention and treatment of iron deficiency might be a potential way in reducing the incidence of RHF in this high altitude area.

4.1. Limitations

The study has some limitations. First, the sample size was limited because RHF is not a common symptom in Tibetan children. Second, the study is based on Tibetan residence only. More studies are needed to prove whether the result is applicable in other highlanders.

Author contributions

Conceptualization: Fan Hu.

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