

Factors Related to Ventricular Size and Valvular Regurgitation in Healthy Tibetans in Lhasa

Ying Yang¹, Yun-Dai Chen¹, Bin Feng¹, Zha-Xi-Duo Ji², Wei Mao³, Guang Zhi¹

¹Department of Cardiology, Chinese PLA General Hospital, Beijing 100853, China

²Department of Ultrasound Diagnosis, Tibet Second People's Hospital, Lhasa, Tibet 850000, China

³Department of Internal Medicine, People's Hospital of Doilungdeqen County, Lhasa, Tibet 850000, China

Abstract

Background: Lhasa is the main residence of Tibetans and one of the highest cities in the world. Its unique geography and ethnic population provide the chance to investigate the interactions among high altitude, ethnicity, and cardiac adaptation. Meanwhile, echocardiographic data about healthy Tibetans on a large scale are not available. This study aimed to analyze physiological factors related to ventricular size and valvular function in healthy Tibetans in Lhasa.

Methods: A representative sample of residents in Tibet was recruited using a multistage cluster random sampling method. Two-dimensional echocardiographic measurements and Doppler evaluation for valvular function were performed. Healthy Tibetans in Lhasa constituted the study population. Associations between physiological parameters and ventricular dimensions in healthy Tibetans were analyzed by canonical correlation analysis. Factors related to valvular regurgitations were determined by logistic regression analysis.

Results: The 454 healthy Tibetans (340 females and 114 male) in Lhasa were included in the final analysis. Canonical correlation analysis revealed that weight was positively correlated with the proximal right ventricular outflow diameter and the basal left ventricular linear dimension in both genders. Weight and pulse were negatively related to mild tricuspid regurgitation. Age was a positive factor for pulmonary and aortic regurgitations. The same was found between systolic blood pressure and mitral regurgitation.

Conclusions: Weight is associated with ventricular size and valvular regurgitation in healthy Tibetans. It should be of more concern in research of high altitude population.

Key words: Altitude; Echocardiography; Healthy Tibetans; Ventricular Regurgitation; Ventricular Size

INTRODUCTION

Lhasa is the administrative capital of the Tibet Autonomous Region of China. It is the main residence of Tibetans and has a population of 527,300.^[1] Lhasa is also one of the highest cities in the world, at an altitude of 3650 m. Compared to other parts of China, it is unique in ethnicity and geography.

Echocardiography is currently widely used in clinical practice for determination of cardiac size and function. Studies designed to analyze the interaction of high altitude and the heart by echocardiography have increased in Tibet. However, the target population for the identification of the prevalence of congenital heart diseases is frequently children and juveniles, and the information about adults is rare.^[2,3] Some studies have been carried out in hospitals for specific diseases, such as pulmonary hypertension, but they did not adequately represent the real world.^[4] To the best of our knowledge,

echocardiographic data about healthy Tibetans on a large scale are not available. An epidemiological study was carried out in Tibet for 3 years to identify the prevalence of chronic cardiac and pulmonary diseases. The study in Lhasa was the first to be completed. It provided the chance to analyze factors related to ventricular size and valvular function in healthy Tibetans.

METHODS

Ethical approval

The study was conducted in accordance with the

Address for correspondence: Dr. Guang Zhi,
Department of Cardiology, Chinese PLA General Hospital,
Beijing 100853, China
E-Mail: 13910994856@163.com

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2017 Chinese Medical Journal | Produced by Wolters Kluwer - Medknow

Received: 04-05-2017 **Edited by:** Xin Chen

How to cite this article: Yang Y, Chen YD, Feng B, Ji ZX, Mao W, Zhi G. Factors Related to Ventricular Size and Valvular Regurgitation in Healthy Tibetans in Lhasa. Chin Med J 2017;130:2316-20.

Access this article online

Quick Response Code:



Website:
www.cmj.org

DOI:
10.4103/0366-6999.215327

Declaration of Helsinki and was approved by the Local Ethics Committee of Fuwai Hospital. Informed written consent was obtained from all participants prior to their enrollment in this study.

Study population

This study was a part of a cross-sectional study in Tibet to identify the prevalence of chronic cardiac and pulmonary diseases. To include a sample cohort that is representative of the general population, we used multistage, cluster randomization and sampling methods. First, districts and counties in Tibet were divided into urban and rural areas. Two districts and four counties were drawn by the probability proportional to size method. Second, we selected two subdistricts from each district and two townships from each county using the simple random sampling (SRS) method. Third, we selected three communities from each subdistrict and three villages from each township by the SRS method. Finally, individuals aged 15 years or older, who have been living in the selected communities/villages for more than 0.6 years, were selected as candidates. It was estimated that the required sample size was approximately 1000 in each district/county. The total number was divided into seven age groups (15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years, 65–74 years, and ≥ 75 years), and included an equal number of males and females. The number of participants in each age group was calculated from the percentage of population of the same age living in Tibet. Then, the number was divided among the six chosen communities/villages proportional to the number of candidates of this age. The final participants of each age group in a community/village were randomly chosen by SRS from the corresponding candidates.

Participants aged between 15 and 91 years were enrolled in the study. The data of basic information, physical examination, chest X-ray, electrocardiogram, echocardiography, and blood tests were collected from each participant.

Healthy Tibetans were recruited from the whole sample. The inclusion criteria required that participants should be aged 15 years or older, be of Tibetan ethnicity, and have normal results from the physical examination. The exclusion criteria were as follows: any self-reported and verified histories of coronary artery disease, structural heart disease, heart failure, stroke, endocrine diseases, acute or chronic respiratory diseases, anemia, connective tissue disease, or abnormal liver function. Participants with abnormal physical examinations and test results were also excluded, including hypertension (systolic blood pressure [SBP] ≥ 140 mmHg, or diastolic blood pressure [DBP] ≥ 90 mmHg or taking relevant drugs), obesity (body mass index [BMI] ≥ 28.0 kg/m²), hyperlipidemia (serum total cholesterol ≥ 6.22 mmol/L, triglyceride ≥ 2.26 mmol/L, or taking relevant drugs), diabetes mellitus (fasting blood glucose >7.0 mmol/L or taking relevant drugs), abnormal renal function (serum creatinine ≥ 110 μ mol/L), abnormal electrocardiography (Q wave, arrhythmia, or bundle block), valvular stenosis (any degree), more than mild valvular regurgitation, wall motion abnormalities and pericardial

effusion on echocardiographic recordings, Assessment Test Score of chronic obstructive pulmonary disease >20 , forced expiratory volume in 1 s/forced vital capacity ratio from pulmonary function test <0.7 , emphysema, pulmonary heart disease, pneumonia, bronchiectasis, tuberculosis, and pleural effusion on chest X-ray. Professional athletes, pregnant or lactating women, participants addicted to alcohol, and participants with inadequate echocardiographic images were excluded from the study.

Acquisition of echocardiographic information

Echocardiography was performed by two certified physicians using two Vivid-Q portable machines (Vingmed-Ultrasound General Electric, Horten, Norway). The two-dimensional images were acquired and measured in the parasternal (standard long- and short-axis images) and apical 4-chamber views, according to the guidelines of the American Society of Echocardiography (ASE).^[5] Right ventricular (RV) linear dimensions were estimated from an RV-focused apical 4-chamber view. The basal RV linear dimension (RVbd) was defined as the maximal transverse dimension in the basal one-third of the RV inflow at end diastole. The proximal RV outflow diameter (RVOTprox) was defined as the linear dimension measured from the anterior RV wall to the interventricular septal-aortic junction in the parasternal long-axis view at end diastole. The pulmonary artery (PA) dimension was measured between the valve and the bifurcation point at end diastole.^[6] The basal left ventricular linear dimension (LVbd) was defined as the maximal transverse dimension in the basal one-third of the LV inflow at end diastole. M-mode was used to measure the diameters of the left ventricle at end diastole (LVEDD) and at end systole (LVESD). The cursor was perpendicular to the LV long axis and located at the level of the mitral valve leaflet tips. Electronic calipers were positioned at the interface between the myocardial wall and cavity. The assessment of valvular stenosis and regurgitation by Doppler was carried out as recommended by the ASE.^[7,8] LVEF was derived from M-mode using the Teichholz formula, except for the regional abnormality of wall motion. At least 3 cardiac cycles were recorded for each view, and the optimal view was selected for measurement.

Statistical analysis

Qualitative data were expressed as percentages (%). The normality distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Data with normal distribution were presented as the mean \pm standard deviation (SD) and compared by independent sample *t*-test. Data with skewed distribution were presented as the median (Q₁, Q₃) and compared by the Wilcoxon rank-sum test. Comparison between skewed data and normal data was performed by the Wilcoxon rank-sum test. Associations between physiological parameters and ventricular dimensions were analyzed by canonical correlation analysis. Factors related to valvular regurgitation were analyzed using a multivariate unconditional logistic regression (method: forward: LR). Two-tailed *P* < 0.05 was considered statistically significant.

Statistical analyses were performed using the SPSS software version 19.0 (IBM SPSS, Armonk, NY, USA).

RESULTS

Demographic features and cardiac measurements

Individuals in the Chengguan district and Doilungdeqen county in Lhasa were recruited for the epidemiological study. The 894 participants (571 females and 323 males) from the Chengguan district and 570 participants (371 females and 199 males) from the Doilungdeqen county were initially screened. The 454 healthy Tibetans (340 females and 114 male) in Lhasa met the inclusion and exclusion criteria and were included in the final analysis. Demographic features of the study sample are summarized in Table 1.

The study revealed that the values of height, weight, and blood pressure were higher in males than those of females (all $P < 0.01$), whereas no significant differences in age, pulse, and blood oxygen saturation (SpO_2) were found between males and females (all $P > 0.05$). The parameters of ventricular measurements (including RVbd, LVbd, LVEDD, and LVESD) were larger in males than those of females (all $P < 0.01$).

Factors related to ventricular size

In healthy Tibetans, the canonical correlation analysis method was used to analyze the relationship between physiological parameters ($U1 =$ age, height, weight, pulse, SBP, DBP, and SpO_2) and right/left ventricular dimensions ($Vr =$ PA, RVOTprox and $RVbd/VI =$ LVbd, LVEDD, and LVESD).

Table 1: Demographic features and cardiac measurements of healthy Tibetans in Lhasa ($n = 454$)

Items	Males ($n = 114$)	Females ($n = 340$)	Statistical values	P
Age (years)	44.0 (20.8, 57.0)	39.5 (30.0, 51.0)	-0.70*	0.49
Height (cm)	165.4 \pm 7.4	156.7 \pm 5.5	-10.50 [†]	<0.01
Weight (kg)	62.3 \pm 8.8	56.4 \pm 7.5	-6.95 [†]	<0.01
Pulse (beat/min)	76.0 (68.8, 87.3)	77.0 (70.0, 85.0)	-0.48*	0.63
SBP (mmHg)	122.0 (114.0, 130.0)	119.0 (110.0, 127.0)	-3.13*	<0.01
DBP (mmHg)	75.0 (69.0, 83.0)	73.0 (67.0, 80.0)	-2.62*	<0.01
SpO_2 (%)	88.0 (85.0, 91.3)	89.0 (85.0, 91.8)	-0.86*	0.39
PA (mm)	18.0 (16.0, 19.0)	17.0 (16.0, 19.0)	-0.49*	0.63
RVOTprox (mm)	25.0 (23.0, 26.3)	23.0 (21.0, 26.0)	-3.38*	<0.01
RVbd (mm)	29.3 \pm 5.2	27.5 (25.0, 30.0)	-3.87*	<0.01
LVbd (mm)	41.0 (38.0, 45.0)	38.0 (36.0, 41.0)	-5.97*	<0.01
LVEDD (mm)	43.0 (40.0, 45.0)	39.0 (36.0, 42.0)	-6.42*	<0.01
LVESD (mm)	28.0 (26.0, 30.0)	26.0 (24.0, 28.0)	-4.79*	<0.01
TR	22 (19.3)	57 (16.8)	-	-
PR	2 (1.8)	7 (2.1)	-	-
MR	2 (1.8)	4 (1.2)	-	-
AR	4 (3.5)	5 (1.5)	-	-

Data are presented as median (Q_1 , Q_3), mean \pm SD, or n (%). *Z values; [†]t values. SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SpO_2 : Blood oxygen saturation; PA: Pulmonary artery; RVOTprox: Proximal right ventricular outflow diameter; RVbd: Basal right ventricular linear dimension; LVbd: Basal left ventricular linear dimension; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular end-systolic diameter; SD: Standard deviation; TR: Tricuspid regurgitation; PR: Pulmonary regurgitation; MR: Mitral regurgitation; AR: Aortic regurgitation; -: Not applicable.

Table 2: Canonical correlation coefficients and hypothesis testing between physiological parameters and right ventricular dimensions in healthy Tibetans

Canonical correlation	Males					Females				
	Coefficients	Wilk's	χ^2	df	P	Coefficients	Wilk's	χ^2	df	P
First	0.46	0.73	56.14	21.00	<0.01	0.40	0.82	78.57	21.00	<0.01
Second	0.22	0.87	25.69	12.00	0.01	0.16	0.97	12.99	12.00	0.37
Third	0.14	0.95	9.05	5.00	0.11	0.09	0.99	3.15	5.00	0.68

Table 3: Canonical correlation coefficients and hypothesis testing between physiological parameters and left ventricular dimensions in healthy Tibetans

Canonical correlation	Males					Females				
	Coefficients	Wilk's	χ^2	df	P	Coefficients	Wilk's	χ^2	df	P
First	0.53	0.68	70.45	21.00	<0.01	0.34	0.83	73.27	21.00	<0.01
Second	0.20	0.93	13.21	12.00	0.35	0.15	0.94	24.78	12.00	0.02
Third	0.18	0.97	5.84	5.00	0.32	0.11	0.98	9.92	5.00	0.08

in males and females. In these cases, the first (and the second) canonical correlation was statistically significant, as summarized in Tables 2 and 3. However, the second canonical correlations were usually omitted in conventional way because of their small coefficients compared to the first ones.

According to the calculation of standardized canonical coefficients, the first canonical relationship between U1 and Vr can be presented as the following equations:

for men:

$$U1 = -0.57 \text{ age} + 0.32 \text{ height} - 0.56 \text{ weight} + 0.14 \text{ pulse} - 0.25 \text{ SBP} + 0.02 \text{ DBP} + 0.28 \text{ SpO}_2,$$

$$Vr = 0.11PA - 1.07 \text{ RVOTprox} + 0.32 \text{ RVbd}$$

for women:

$$U1 = -0.29 \text{ age} - 0.09 \text{ height} - 0.77 \text{ weight} + 0.23 \text{ pulse} - 0.12 \text{ SBP} + 0.03 \text{ DBP} + 0.14 \text{ SpO}_2,$$

$$Vr = -0.47 \text{ PA} - 0.60 \text{ RVOTprox} - 0.35 \text{ RVbd}.$$

The first canonical relationship between U1 and V1 can be presented as the following equations:

for men:

$$U1 = 0.23 \text{ age} - 0.07 \text{ height} - 0.59 \text{ weight} + 0.76 \text{ pulse} + 0.08 \text{ SBP} - 0.16 \text{ DBP} - 0.04 \text{ SpO}_2,$$

$$V1 = -0.59 \text{ LVbd} - 0.47 \text{ LVEDD} - 0.10 \text{ LVESD}$$

for women:

$$U1 = -0.29 \text{ age} + 0.04 \text{ height} + 0.72 \text{ weight} - 0.27 \text{ pulse} + 0.54 \text{ SBP} - 0.25 \text{ DBP} - 0.01 \text{ SpO}_2,$$

$$V1 = 0.83 \text{ LVbd} + 0.15 \text{ LVEDD} + 0.15 \text{ LVESD}.$$

In those equations, larger standardized canonical coefficients indicated a closer relationship between physiological parameters and ventricular sizes. Parameter and dimension with the same tokens (both are plus signs or minus signs) exhibited a positive relationship with each other. Similarly, opposite tokens represented an inverse relationship. Canonical correlation analysis revealed that weight was positively correlated with RVOTprox for the right ventricle and LVbd for the left ventricle in both genders. In addition, age was positively correlated with RVOTprox and pulse was negatively correlated with LVbd in men. SBP was positively correlated with LVbd in women.

Table 4: Factors related to mild valvular regurgitation calculated by logistic regression

Valvular regurgitation	Factors	β	P	EXP (β)	95% CI
Mild TR	Weight (kg)	-0.05	<0.01	0.95	0.92–0.98
	Pulse (beat/min)	-0.03	0.02	0.97	0.95–0.99
Mild PR	Age (years)	0.04	0.03	1.04	1.00–1.09
Mild MR	SBP (mmHg)	0.06	0.04	1.06	1.00–1.12
Mild AR	Age (years)	0.09	<0.01	1.10	1.05–1.14

TR: Tricuspid regurgitation; PR: Pulmonary regurgitation; MR: Mitral regurgitation; AR: Aortic regurgitation; SBP: Systolic blood pressure; CI: Confidential interval.

Factors related to valvular regurgitations

Participants with valvular stenosis (any degree) and more than mild valvular regurgitation were excluded from the study population. The unconditional logistic regression model was used to evaluate whether gender, age, height, weight, pulse, SBP, DBP, or SpO₂ were related to mild valvular regurgitation. Table 4 summarizes the independent factors for mild valvular regurgitation. Weight and pulse were negatively related to mild tricuspid regurgitation (TR). Age was a positive factor for pulmonary regurgitation (PR) and aortic regurgitation (AR). The same was found for SBP and mitral regurgitation (MR).

DISCUSSION

The effect of age on cardiac size has been long studied. Recently, a nationwide, population-based study of healthy Han Chinese adults revealed that values of RV anterior wall thickness and RV anteroposterior dimension gradually increase with age in both genders, while values of the RV outflow tract, RV middle dimension, and RV basal dimension did not vary with age in either gender.^[9] The article partly supports the results of our study. In our study, the RVOTprox was measured in the same view as that used to acquire the RV anteroposterior dimension. Therefore, their changes were positively correlated with age. In addition, the RVbd did not vary with age in both genders. The aforementioned study also revealed that there were no significant differences in the LV outflow tract among the six age groups in both genders. This result was similar with the little relationship between age and the LV dimensions in our study. Age was a risk factor for PR and AR. A study of autopsy specimens of normal hearts concluded that, in both genders, all indexed mean valve circumferences progressively increased throughout adult life, and this trend was greater for the semilunar valves than the atrioventricular valves.^[10] Additionally, aortic root dilatation is one of most common causes of AR.^[11] A study assessing clinical determinants of valvular regurgitation from the Framingham Heart Study revealed that the clinical determinants of MR were age, hypertension, and BMI. The determinants of AR were age and male gender.^[12] The relationship between blood pressure and MR might enhance at high altitude though SBP is in normal range.

Weight is neglected in most studies. In fact, the study of autopsy specimens of normal hearts reported that body weight was a better predictor of normal heart weight than body surface area or height, and its mean values per decade was significantly increased in women.^[10] High altitude presents a hypoxic environment that adversely affects human physiology and metabolism. A study reported that body weight decreased following exposure to high altitude.^[13] Tibetan women give birth to larger babies than Han Chinese women, which is one of the physiological adaptations to high altitude-related hypoxia.^[14] It is postulated that weight might be one of the indicators of adaptation, development, and nourishment at high altitudes. Therefore, it is positively related to cardiac size.

Hypoxia at high altitudes causes pulmonary vasoconstriction, which improves the matching of perfusion to alveolar ventilation. On the other hand, hypoxic vasoconstriction induces pulmonary hypertension and increases RV afterload.^[15] TR is related to pulmonary hypertension and RV enlargement at high altitudes.^[16] However, it was found that SpO₂ was not related to mild TR in our study. It was the weight negative for TR. This meant that mild TR at high altitudes might be related to physiological development rather than hypoxia.

The limitations of the current study included the following: only two-dimensional measurements were reported in the present study, short of Doppler data and volumes of chambers. In the future, more advanced and accurate echocardiographic technologies will be applied in Tibet and produce more valuable information for high altitudes.

In conclusion, this study indicated that weight is associated with ventricular size and valvular regurgitation in healthy Tibetans. It should be of more concern in research of high altitude population.

Financial support and sponsorship

The study was supported by a grant from Healthcare Scientific Research in the Public Interest of the China National Health and Family Planning Commission (No. 201402002).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Annual by Selected Cities. NBS: National Bureau of Statistics of China; 2014. Available from: <http://www.data.stats.gov.cn/English/easyquery.htm?cn=E0105>. [Last accessed on 2016 Aug 20].
2. Hou HJ, Liu WX, Meng RY, Qin J, Su JL, Jing RF, *et al*. Prevalence of Congenital Heart Diseases of Rural Tibetan Pupils in Suo Country in Naqu Area. The National Echocardiographic Academic Conference (in Chinese). Beijing: Chinese Association of Ultrasound in Medicine and Engineering; 2014. p. 234-5.
3. Wang J, Wang ZN, Li SZ, Wang LJ, Chen ZD, Wang HY, *et al*. An investigation of congenital heart diseases of 6500 pupils in Lhasa (in Chinese). *Tibet Sci Technol* 2002;1:12-4. doi: 10.3969/j.issn.1004-3403.2002.01.005.
4. Li JM, Cen WJ. The value of pulse Doppler for estimating pulmonary hypertension in highland (in Chinese). *Tibet Med* 1991;3:5-7.
5. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L,

et al. Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39.e14. doi: 10.1016/j.echo.2014.10.003.

6. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, *et al*. Guidelines for the echocardiographic assessment of the right heart in adults: A report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr* 2010;23:685-713. doi: 10.1016/j.echo.2010.05.010.
7. Zoghbi WA, Enriquez-Sarano M, Foster E, Grayburn PA, Kraft CD, Levine RA, *et al*. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiogr* 2003;16:777-802. doi: 10.1016/S0894-7317(03)00335-3.
8. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, *et al*. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1-23. doi: 10.1016/j.echo.2008.11.029.
9. Yao GH, Deng Y, Liu Y, Xu MJ, Zhang C, Deng YB, *et al*. Echocardiographic measurements in normal Chinese adults focusing on cardiac chambers and great arteries: A prospective, nationwide, and multicenter study. *J Am Soc Echocardiogr* 2015;28:570-9. doi: 10.1016/j.echo.2015.01.022.
10. Kitzman DW, Scholz DG, Hagen PT, Ilstrup DM, Edwards WD. Age-related changes in normal human hearts during the first 10 decades of life. Part II (Maturity): A quantitative anatomic study of 765 specimens from subjects 20 to 99 years old. *Mayo Clin Proc* 1988;63:137-46. doi: 10.1016/S0025-6196(12)64946-5.
11. Olson LJ, Subramanian R, Edwards WD. Surgical pathology of pure aortic insufficiency: A study of 225 cases. *Mayo Clin Proc* 1984;59:835-41. doi: 10.1016/S0025-6196(12)65618-3.
12. Singh JP, Evans JC, Levy D, Larson MG, Freed LA, Fuller DL, *et al*. Prevalence and clinical determinants of mitral, tricuspid, and aortic regurgitation (the Framingham Heart Study). *Am J Cardiol* 1999;83:897-902. doi: 10.1016/S0002-9149(98)01064-9.
13. Chen KT, Chen YY, Wu HJ, Chang CK, Lee WT, Lu YY, *et al*. Decreased anaerobic performance and hormone adaptation after expedition to Peak Lenin. *Chin Med J* 2008;121:2229-33.
14. Bigham AW. Genetics of human origin and evolution: High-altitude adaptations. *Curr Opin Genet Dev* 2016;41:8-13. doi: 10.1016/j.gde.2016.06.018.
15. Naeije R, Dedobbeleer C. Pulmonary hypertension and the right ventricle in hypoxia. *Exp Physiol* 2013;98:1247-56. doi: 10.1113/expphysiol.2012.069112.
16. Po JR, Meeran T, Davey R, Benza R, Raina A. Tricuspid regurgitation is associated with pulmonary hemodynamics and right ventricular dysfunction in pulmonary arterial hypertension but does not alter the geometry of right ventricular contraction. *J Am Coll Cardiol* 2016;67:2056. doi: 10.1016/S0735-1097(16)32057-5.