Growing up in the highest city in the world: cardiac remodeling in children born and living at high altitude

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Presentation

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I am resident in cardiology, between my 10th and my 11th (and final) year of study. I have made all my studies in Grenoble. I'm passionate about sport cardiology and globally, cardiovascular and pulmonary physiology. Outdoor activities in (high)-mountain are my main extra-professional hobbies. Logically, I've been attracted by HP2's research thematic, particularly human adaptation to hypoxia. For the future, I would like to continue this process of understanding these mechanisms in a shared project between hospital and laboratory.

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Abstract

Introduction

More than 80 million humans permanently live at high altitude (above 2500 m) [1], mainly in South America, Central Asia and East Africa. Crossed by the Altiplano, Peru is one of the countries gathering the highest percentage of its population living at high altitude. This is where the highest city in the world, La Rinconada, is located, spreading between 5000 and 5300 meters above sea level (meters asl).

Living permanently at high altitude constitutes a constant challenge for the organism. Barometric pressure, thus partial pressure of oxygen, decreases progressively with altitude to reach approximately 50% of sea-level values around 5000 meters asl. This reduced availability of inspired oxygen requires several adaptive mechanisms to optimize oxygen delivery to peripheral tissues.

Physiological responses to chronic hypoxia differ from those encountered in acute hypoxia but also between high-altitude populations. Indeed, distinct physiological and biological traits have been observed in Sherpa populations, in Central Asia and Andean populations, even though they have a similar exposure to hypoxia [2].

Cardiovascular adaptations in adults permanently living at high altitude are extensively documented. Chronic exposure to hypoxia leads to an altitude-dependent increase in pulmonary artery pressure, enlarged right cavities [11][40], left ventricle hypertrophy, and mild diastolic dysfunction [11].

Previous missions at La Rinconada focused on male adults who lived here only for few years but who were born at lower altitudes [11]. More recently families permanently live in this extreme environment, confronting children with severe hypoxia during crucial steps of their growth – from their conception to adulthood.

As opposed to sea level, where PVR quickly fall after birth to near-adulthood level in a few days, the drop in PVR is more gradual at high altitude because of the persistent hypoxic stimulus. This was confirmed invasively, by right-heart catheterization, in 32 children from 1 to 14 years old in Morococha and Cerro de Pasco in Peru [30], or more recently, by echocardiography, in 257 Tibetan children from 15 days to 14 years living at 3700 m [32].

In adults living at high altitude, chronic hypoxia induces hemodynamical, haematological and hemorheological changes and determine cardiac remodeling [11]. However, lesser is known about how these factors influence cardiac development in children.

Therefore, this study aims to describe the heart of middle-aged children living at various altitudes, ranging from sea level (Lima) to 5300 meters asl (La Rinconada) and the determinants of cardiac remodeling.

Materials and Methods

Study population

This study is part of a larger research program - *Expedition 5300* – which describes the pathophysiological effects of high-altitude living since 2018, particularly in La Rinconada.

For this study, we included 350 healthy children (183 boys, 167 girls) in 3 different missions (from October 2023 to October 2024): 81 at Lima (sea level), 56 at Cuzco (3300 meters asl), 121 at Juliaca (3800 meters asl) and 92 at La Rinconada (5000-5300 meters asl). Children living at Lima were defined as lowlanders, other children as highlanders. Ages ranged from 7 years and 3 months to 12 years and 11 months.

All children underwent a preliminary clinical examination by a pediatrist, a blood sample, a measure of haemoglobin mass and intravascular volume and a resting echocardiography.

Body surface area was calculated using Dubois formula ($BSA = 0.007184 * Height^{0.725} * Weight^{0.425}$) [42] and Haycock formula for comparisons with echocardiographic norms ($BSA = 0.024265 \times height\ (cm)^{0.3964} \times weight\ (kg)^{0.5378}$) [43].

Subject's parents provided written informed consent – also sought in children themselves. The study was approved by XXXX, conformed to the standards set by the Declaration of Helsinki.

Study variables

Echocardiography

Images were obtained by 2 successive trained operators (S.D. for the 1st mission, A.C. for the 2nd and 3rd) using a portable ultrasound system (Vivid-IQ Portable Cardiac Ultrasound, GE Healthcare, Little Chalfont, UK during the 1st and the 2nd mission, Philips CX 50 during the 3rd mission), with a 1–3 MHz cardiac transducer. Recordings were stored for offline analysis (EchoPac system, GE Healthcare, Little Chalfont, UK). Cardiac dimensions and functions were assessed using ASE (American Society of Echocardiography) standards. Left ventricle dimension was determined using TM mode, LV systolic function using both LV ejection fraction (Simpson's biplane method) and Global Longitudinal Strain (GLS). Right ventricle dimension was assessed by contouring the end-systolic and end-diastolic RV area. RV systolic function was evaluated with RV Fractional Area Change (RV FAC), calculated by the formula $(RV\ end\ diastolic\ area - RV\ end\ systolic\ area)/(RV\ end\ diastolic\ area)$, TAPSE (tricuspid annular plane systolic excursion), lateral tricuspid annulus peak systolic velocity (S' tric) and RV strain of RV free wall from an apical 4-chamber view. LV and RV diastolic function were assessed by transmitral and transtricuspid peak velocity wave ratios (early, "E", and late, "A"). Left atrium volume was calculated using the biplane method, right atrium volume was estimated from RA contouring in 2D. Z-scores for right atrium area relative to BSA were calculated ; RA was

considered dilated if Z-score were superior to 2 [41]. Cardiac output and stroke volume were estimated from LVOT pulse wave doppler. Systolic pulmonary artery pressure was calculated from the maximal tricuspid regurgitation velocity using the simplified Bernoulli equation; mean pulmonary artery pressure was then determined as follows: $mPAP = 0.61 * sPAP + 2\ mmHg$. Pulmonary Vascular Resistances (PVR) was estimated by the ratio of mPAP to cardiac output (in Wood Units, WU).

Comparisons of echocardiographic data with reference values

Echocardiographic data were compared with paediatric reference values, notably LV mass [43], mitral E/A ratio [44], left atrium volume [45], right ventricle end-diastolic area, left ventricle end-diastolic diameter [46] and right atrium surface [47]. Z-score were calculated for each parameter. A z-score inferior to -2 or superior to +2 SD was considered as significantly different from the norms.

Haemoglobin concentration, haematocrit, haemoglobin mass and blood volume measurement

Haemoglobin concentration ([Hb]) was measured *in situ* with a HemoCue system (HemoCue Hb201+, HemoCue AB, Ängelholm, Sweden) and haematocrit (Ht) by microcentrifugation (Hemata STAT – II, Separation Technology Inc., Sandford, USA). Haemoglobin mass (Hbmass) and intravascular volumes were measured in a supine position, using the CO rebreathing technique with an automated system (OpCO; Detalo Health, Denmark). As haematocrit increases with altitude, PVR was normalized to an haematocrit of 45% following this formula: $PVR45\% = PVR/e[2(measured\ haematocrit — 45\%)]$.

Blood viscosity

Blood viscosity was measured at native Ht and at several shear rates using a cone-plate viscometer (Brookfield DVII with CPE40 spindle, Ametek Brookfield, Middleborough, USA).

Statistical analysis

Qualitative variables were described by using frequencies and percentages, and quantitative ones by means and standard deviations. As all our different groups (corresponding to each altitude) were composed of more than 50 children, we hypothesised that measured parameters followed normal distribution. Comparisons between groups were performed using one-way ANOVA analysis. In case of significant results ($p < 0.05$), *post-hoc* Tukey tests were performed for between-group comparisons. Pearson correlations were used to assess correlations between parameters. Multivariate linear regression models were performed for selected parameters (right heart cavities dimension and pulmonary artery pressure) with adjustment for age, haematocrit, Hbmass/kg and blood viscosity. Variance inflation factor (VIF) was measured for each variable to estimate multicollinearity. All of the variables retained had a VIF inferior to 5. In case of significant global Fisher test, a bidirectional step-wise regression was applied to

select the most pertinent variables. Statistical analyses were performed by using R 4.4.3 (R-project). A p-value threshold of 0.05 was considered to be significant.

Results

Clinical, hematological and hemorheological characteristics

Clinical and biological characteristics are detailed in Table 1.

Children's mean age and height were similar along altitudes whereas weight significantly decrease from Lima (40.0 ± 11.0 kg) to Cuzco (34.3 ± 10.8 kg, p=0.011) and La Rinconada (32.5 ± 9.6 kg, $p < 10^{-3}$).

Resting heart rate slightly decreased from Lima to Juliaca (80 ± 12 vs 75 ± 12 bpm, p= 0.029), then increased at La Rinconada (84 ± 13 bpm, $p < 10^{-3}$). On the contrary, mean arterial pressure gradually and significantly decreased from Lima (78 ± 9 mmHg) to La Rinconada (61 ± 14 mmHg, $p < 10^{-3}$).

As expected, **SpO_2** significantly decreased with altitude (from 98 % in Lima to 80 % in La Rinconada; $p<10^{-3}$ for all comparisons). Conversely, haemoglobin level, haematocrit and Hb mass significantly increased with altitude (see table 1). **Hct, Hb, viscosity and Hb mass/kg** were highly correlated to SpO2 ($p<10^{-3}$, r^2 adjusted = 0.64, 0.56, 0.51 and 0.41 respectively). **RBCV** increased with altitude and was significantly higher in La Rinconada ($p<10^{-3}$), whereas **PV** decreased, resulting in a similar **total blood volume** among groups (ANOVA: p=0,147). **RBCV and PV** were significantly correlated with SpO2 ($p<10^{-3}$, r^2 adjusted = 0.13 and 0.10 respectively). BV was not significantly correlated with SpO2

	Lima	Cuzco	Juliaca	La Rinconada	ANOVA	Lima vs Cuzco	Lima vs Juliaca	Lima vs La Rinconada	Cuzco vs Juliaca	Cuzco vs La Rinconada	Juliaca vs La Rinconada
Sex H/F (%)	61,7 % / 38,3 %	33,9 % / 66,1 %	51,2 % / 48,8 %	56,5 % / 43,5 %							
Age (months)	122,0 ± 17.7	117,8 ± 15,7	122,2 ± 16,1	124,3 ± 17,2	0.175						
Weight (kg)	40,0 ± 11,0	34,3 ± 10,8	36,9 ± 10,6	32,5 ± 9.6	$< 10^{-4}$	0.011	0.17	$< 10^{-3}$	0.42	0.72	0.013
Height (cm)	140,7 ± 10,9	136,5 ± 9.0	137,8 ± 9,4	136,9 ± 11.0	0.038	0.078	0.18	0.053	0.87	0.99	0.90
Body surface area (m^2)	1,24 ± 0,19	1,13 ± 0,19	1,18 ± 0,19	1,11 ± 0,19	$< 10^{-4}$	0.010	0.13	$< 10^{-3}$	0.49	0.90	0.063
SpO2 (%)	98 ± 1	91 ± 2	88 ± 2	80 ± 3	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$
Heart rate (bpm)	80 ± 12	79± 12	75 ± 12	84± 13	$< 10^{-4}$	0.96	0.029	0.13	0.21	0.069	$< 10^{-3}$
Systolic blood pressure (mmHg)	100 ± 10	85 ± 11	94 ± 12	83 ± 13	$< 10^{-4}$	$< 10^{-3}$	0.0027	$< 10^{-3}$	$< 10^{-3}$	0.70	$< 10^{-3}$
Diastolic blood pressure (mmHg)	67 ± 10	54 ± 12	60 ± 13	52 ± 13	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.010	0.70	$< 10^{-3}$
Mean systemic blood pressure (mmHg)	78 ± 9	64 ± 10	71 ± 12	61 ± 14	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.0012	0.45	$< 10^{-3}$
Haemoglobin (g/L)	132,6 ± 10,5	147,5 ± 8,0	153.8 ± 8,6	176,4 ± 16,7	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.0069	$< 10^{-3}$	$< 10^{-3}$
Hematocrit (%)	39 ± 3	42 ± 2	45 ± 3	52 ± 4	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$
Hb mass (g)	317, 5 ± 79,0	333.3 ± 92,0	365.19 ± 92,0	435,5 ± 132,8	$< 10^{-4}$	0.84	0.0091	$< 10^{-3}$	0.29	$< 10^{-3}$	$< 10^{-3}$
Hb mass (g/kg)	8.0 ± 1.2	9.3 ± 1.5	9.8 ± 1.8	12.8 ± 2.6	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.47	$< 10^{-3}$	$< 10^{-3}$
Red blood cell volume (mL)	992,4 ± 250.6	985.1 ± 267.7	1103.6 ± 279.0	1323,6 ± 402,7	$< 10^{-4}$	0.99	0.074	$< 10^{-3}$	0.13	$< 10^{-3}$	$< 10^{-3}$
Plasma volume (mL)	1533,4 ± 360,4	1323.0 ± 317.8	1300.4 ± 310.6	1199.4 ± 269,1	$< 10^{-4}$	0.0028	$< 10^{-3}$	$< 10^{-3}$	0.98	0.15	0.12
Blood volume (mL)	2526,3 ± 585,5	2308.1 ± 573.2	2404.3 ± 577.5	2519,3± 640,0	0.147						
Viscosity (cP)	7,39 ± 1,19	8,62 ± 1,53	10,59 ± 1,81	14,02 ± 3,05	$< 10^{-4}$	0.0059	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$

Table 1: clinical, haematological and hemorheological data. Data are expressed as means ± standard deviations.

Finally, blood **viscosity** ($6\ s^{-1}$) progressively increased with altitude ($p<10^{-3}$ for all comparisons, except between Lima and Cusco, p = 0,0059).

Right heart remodeling and function (Table 2; Fig 1)

Both right ventricle and auricle significantly dilated with altitude in La Rinconada ($p<10^{-3}$ for all comparisons, Fig 1A and 1B) with a slight but significant decrease in systolic ventricular function as determined by **RV FAC** and **free wall RV strain** (p<0.01 and 0.024 respectively).

RA area relative to BSA exceeded 2 standard-deviations in 1/81 children in Lima, 1/56 in Cuzco, 7/121 in Juliaca and 25/92 in La Rinconada. RV end-diastolic area was under 2 S.D in 9/81, 4/56, 7/121 and 5/92 children respectively in Lima, Cuzco, Juliaca and La Rinconada,

whereas it exceeded 2 S.D only in 1/121 and 3/92 children, respectively in Juliaca and La Rinconada.

Curiously, **Et/At ratio** progressively increased and was higher in La Rinconada vs Lima ($p<10^{-3}$), **Peak Et** was reduced in La Rinconada vs Lima, Cuzco and Juliaca (p=0.006, 0.01 and 0.001). **Peak At** decreased from Lima to Juliaca (Lima vs Juliaca: $p<10^{-3}$, Cuzco vs Juliaca: p=0.01) then increased from Juliaca to La Rinconada (p=0.012), nevertheless at a lesser level relative to Lima (p = 0.005).

Mean pulmonary artery pressure could be assessed in 91 % of our children (except for 20 children in Juliaca and 14 in La Rinconada). As expected, **mean pulmonary artery pressure** as well as **Pulmonary Vascular Resistances** (PVR) gradually and significantly increased with altitude ($p<10^{-3}$ for all comparisons, Fig. 1C and Fig. 1D). 6 children, all living in La Rinconada, exhibited mPAP > 30 mmHg, usual threshold considered as criteria for High Altitude Pulmonary Hypertension.Interestingly, **normalising with an haematocrit of 45%, PVR** were still increasing from Lima to all the cities of high altitude (Cusco, Juliaca, La Rinconada). Detailed data are reported in Table 2.

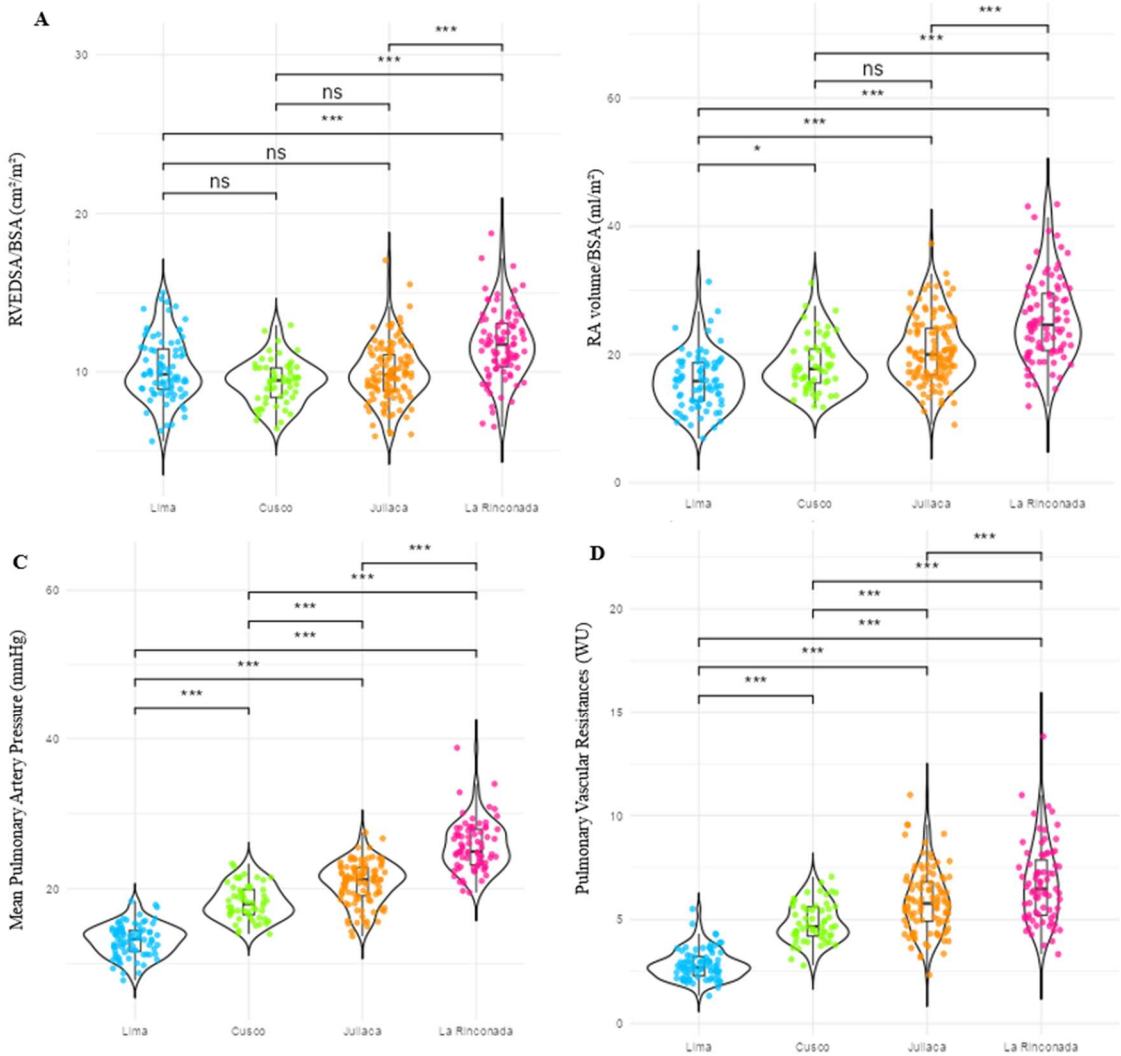

Figure 1: Right ventricular end-diastolic area relative to BSA (A), right atrium volume relative to BSA (B), mean pulmonary artery pressure (C) and pulmonary vascular resistances (PVR). ***: p < 0.001 ; **: p < 0.01 ; *: p < 0.05 ; ns: non significant

	Lima (n=81)	Cuzco (n=56)	Juliaca (n=121)	La Rinconada (n=92)	ANOVA	Lima vs Cuzco	Lima vs Juliaca	Lima vs La Rinconada	Cuzco vs Juliaca	Cuzco vs La Rinconada	Juliaca vs La Rinconada
RVED area/BSA	10,2 ±2,0	9,4 ± 1,4	10.0 ± 1,9	11,7 ± 2,2	$< 10^{-4}$	0.08	0.86	$< 10^{-3}$	0.24	$< 10^{-3}$	$< 10^{-3}$
RA volume/BSA	15,8 ±4,4	18,5 ± 4,2	20,6 ± 5,1	25,5 ± 6.6	$< 10^{-4}$	0.017	$< 10^{-3}$	$< 10^{-3}$	0.06	$< 10^{-3}$	$< 10^{-3}$
RV FAC	49,3 ±6,6	51,3 ± 5,0	47,4 ± 6,5	46,4 ± 6,1	$< 10^{-4}$	0.27	0.14	0.01	$< 10^{-3}$	$< 10^{-3}$	0.68
Free wall RV strain	-24,2 ±3,3	-22,7 ± 3,1	-23,5 ± 3,6	-22,7 ± 3,4	0.015	0.059	0.57	0.024	0.40	0.99	0.28
RV S'	12,9 ±1,7	11,9 ± 1,4	12,1 ± 1,5	12,6 ± 1,6	$< 10^{-4}$	0.0014	0.0014	0.56	0.94	0.057	0.092
Peak Et	0,60 ± 0,08	0,61 ± 0,09	0,60 ± 0,10	0,56 ± 0,10	0.001	0.99	0.99	0.0055	0.99	0.011	0.0016
Peak At	0,42 ± 0,09	0,37 ± 0,09	0,32 ± 0,08	0,36 ± 0,15	$< 10^{-4}$	0.046	$< 10^{-3}$	0.0038	0.010	0.98	0.011
Et/At ratio	1,49 ± 0,29	1,71± 0,40	2,01 ± 0,52	1,73 ± 0,61	$< 10^{-4}$	0.046	$< 10^{-3}$	0.011	$< 10^{-3}$	0.99	$< 10^{-3}$
mPAP	13,1 ± 2,1	18,2 ± 2,3	20,7 ± 2,8	25,7 ± 3,3	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$
PVR	2,8 ± 0,7	4,9 ± 0,9	5,9 ± 1,5	6,7 ± 1,9	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$
PVR 45%	3,2 ± 0,8	5,3 ± 1,5	5,7 ± 1,5	5,8 ± 1,7	$< 10^{-4}$	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.40	0.25	0.96
Pulmonary acceleration time	139,3 ± 19,3	148,1±17.0	132,4 ± 19,0	127,9± 19,7	$< 10^{-4}$	0.041	0.06	$< 10^{-3}$	$< 10^{-3}$	$< 10^{-3}$	0.33

Table 2: Echocardiographic data of the right heart in lowlanders and highlanders. Data are expressed as means ± standard deviations. RVED area: Right-Ventricular End-Diastolic Area. BSA: Body Surface Area. RA volume: Right Atrium volume. RV S': Lateral tricuspid annulus peak systolic velocity. mPAP: mean pulmonary artery pressure. PVR: Pulmonary Vascular Resistances. PVT 45%: PVR corrected to an haematocrit of 45%.

RVED/BSA was significantly – but modestly correlated with RA volume/BSA ($p < 10^{-3}$, $r^2=0.13$).

RA volume/BSA, RVED area/BSA and mean PAP were significantly correlated with SpO2 (Fig. 2A, 2B and 2C), haematocrit, Hb mass (absolute and indexed to BSA). PVR was significantly correlated with SpO2, haematocrit and Hb mass indexed to BSA. RV FAC and RV strain were both correlated with SpO2 and haematocrit (Fig 2D); RV FAC was also significantly correlated with Hbmass, whereas RV strain was correlated with Hb mass indexed to BSA. Finally, Et/At ratio was significantly correlated with SpO2, haematocrit and Hb mass indexed to BSA. Correlations are detailed in Supplementary materials 1.

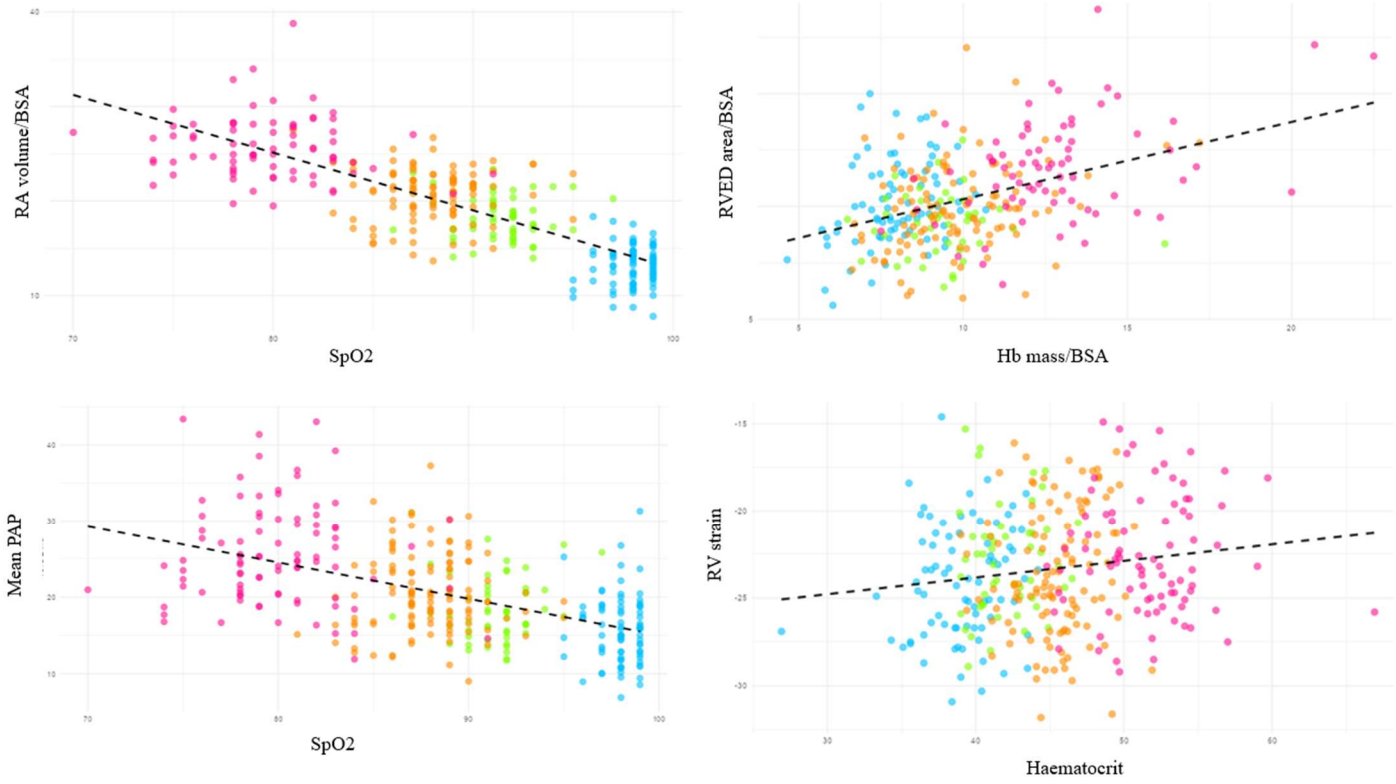

Figure 2: Correlation of right atrium volume relative to BSA with SpO2 ($p < 10^{-4}$, $R^2 = 0.27$), RVED area relative to BSA with Hb mass relative to BSA ($p < 10^{-4}$, $R^2 = 0.17$), mean pulmonary artery pressure with SpO2 ($p < 10^{-4}$, $R^2 = 0.66$) and RV strain with haematocrit ($p=0.0017$, $R^2 = 0.019$).

Left heart remodeling and function (Table 3)

Left ventricle dimensions and thickening (indexed to BSA) were similar between all groups. LV mass exceeded 2 S.D in 22/81, 13/56, 14/121 and 26/92 children respectively in Lima, Cuzco, Juliaca and La Rinconada.

There were no significant changes in **LVEF** along altitudes. **LV longitudinal strain** was slightly lower in Lima relative to Cuzco and Juliaca ($p<10^{-3}$), and at La Rinconada vs Juliaca ($p=0.049$).

The LV diastolic pattern was modified with altitude: **E/A ratio** was significantly lower in La Rinconada vs Cuzco and Juliaca ($p<10^{-3}$), because of a significant decrease in **E mit velocity** ($p< 10^{-3}$, 10^{-2} and 10^{-3} in comparison with Lima, Cusco and Juliaca). **Mitral A velocity** was slightly decreased in Juliaca vs Lima ($p=0.02$) and La Rinconada ($p=0.03$). On the contrary, **E/E' ratio** was similar along different altitudes.

E/A ratio was under 2 S.D in 6/81, 2/56, 2/121 and 12/92 children respectively in Lima, Cuzco, Juliaca and La Rinconada, whereas no children exhibited higher than 2 S.D E/A ratio value.

LA vol/BSA decreased with altitude (-9.2% in Juliaca and –9.6% in La Rinconada relative to Cuzco, p=0.029 and 0.030 respectively). LA vol was under 2 S.D. in 11/81, 5/56, 32/121 and 19/92 children respectively in Lima, Cuzco, Juliaca and La Rinconada.

Stroke volume relative to BSA decreased with altitude (Lima vs all other cities: $p<10^{-3}$). Then, **cardiac output** and **cardiac index** dropped with altitude (the latter diminished by 12.8% at Cuzco, 20.5% at Juliaca and 7.6% at La Rinconada relative to Lima, respectively $p<10^{-3}$, $<10^{-3}$ and 0.010).

All parameters are detailed in Table 3.

Correlations ?? à déterminer

Figure 3: left cavities

	Lima (n=81)	Cuzco (n=56)	Juliaca (n=121)	La Rinconada (n=92)	ANOVA	Lima vs Cuzco	Lima vs Juliaca	Lima vs La Rinconada	Cuzco vs Juliaca	Cuzco vs La Rinconada	Juliaca vs La Rinconada
S thickness (mm)	7,1± 1,2	7,4± 1,0	7,0± 1,1	6,9± 1,2	0.07						
LV EDD (mm)	39,7± 3,7	37,3± 3,7	38,3± 3,4	37,4± 3,9	$< 10^{-4}$	0.0011	0.032	$<10^{-3}$	0.38	0.99	0.31
LV EDD /BSA (mm/m²)	32,6± 4,1	33,5± 4,1	33,0± 4,1	34,2± 4,3	0.059						
P thickness (mm)	7,5± 1,2	6,8± 1,1	6,9± 1,0	7,0± 1,1	$< 10^{-4}$	0.0017	0.0010	0.010	0.94	0.79	0.96
RWT	0,38± 0,07	0,37± 0,06	0,36± 0,05	0,38± 0,06	0.144						
LA vol/BSA (ml/m²)	24,0± 5,1	24,9± 4,4	22,6± 5,6	22,5± 4,9	0.011	0.72	0.25	0.24	0.029	0.030	0.99
LV mass (g)	83,7± 21,3	72,6± 21,0	73,6± 20,5	71,3± 20,8	0.001	0.013	0.005	$<10^{-3}$	0.99	0.98	0.85
LV mass/BSA (g/m²)	67,4± 12,5	63,5± 11,4	62.0± 10,8	63,5± 12,8	0.017	0.24	0.0089	0.14	0.85	0.99	0.79
EF (Teicholz, %)	66 ± 6	69± 5	69± 7	67± 6	0.007	0.096	0.015	0.90	0.99	0.31	0.092
LV longitudinal strain (%)	-17,7± 1,7	-19,9± 2,0	-19,2± 2,4	-18,4± 2,2	$< 10^{-4}$	$<10^{-3}$	$<10^{-3}$	0.14	0.23	$<10^{-3}$	0.049
Cardiac output (l/min)	4,8± 0,9	3,9± 0,9	3,7± 0,9	4.0± 1,1	$< 10^{-4}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.66	0.93	0.16
Cardiac index (l/min/m²)	3,9± 0,7	3,4± 0,6	3,1± 0,6	3,6± 0,8	$< 10^{-4}$	$<10^{-3}$	$<10^{-3}$	0.010	0.037	0.61	$<10^{-3}$
SV (Teicholz, ml)	45,9± 10,8	41,5± 11,5	44,4± 10,5	41.0± 11,9	0.012	0.098	0.77	0.020	0.37	0.99	0.12
SV/BSA (Teicholz, ml/m²)	37, 3 ± 7,9	36,6 ± 7,2	37,22 +/8,56	35,97 ± 9,84	$< 10^{-4}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.58	0.66	0.99
SV (PW, ml)	60,3± 10.0	49,5± 12,4	49,4± 12,3	47,7± 12,7	$< 10^{-4}$	$<10^{-3}$	$<10^{-3}$	$<10^{-3}$	0.99	0.81	0.75
SV/BSA (PW, ml/m²)	49,2 ± 7,6	43,6 ± 7,4	41,9 ± 7,2	42.0 ± 10,7	$< 10^{-4}$	0.0016	0.0010	0.010	0.94	0.78	0.96
Peak E (m/s)	0,95± 0,13	0,94± 0,12	0,93± 0,14	0,87± 0,15	$< 10^{-4}$	0.97	0.92	$<10^{-3}$	0.99	0.016	0.0029
Peak A (m/s)	0,54± 0,12	0,50± 0,11	0,49± 0,10	0,54± 0,12	0.003	0.27	0.022	0.99	0.93	0.18	0.0085
E/A ratio	1,84± 0,41	1,95± 0,45	1,96± 0,42	1,66± 0,35	$< 10^{-4}$	0.36	0.15	0.024	0.99	$<10^{-3}$	$<10^{-3}$
E/E' ratio	5.0± 0,9	5,3± 0,9	5,3± 0,9	5,2± 1.0	0.11						

Table 3: Echocardiographic data of the left heart in lowlanders and highlanders. Data are expressed as means ± standard deviations. LV EDD: Left Ventricle End-Diastolic Diameter. RWT: Relative Wall Thickness. LA vol: Left Atrium Volume. EF: Ejection Fraction. SV: Stroke Volume.

Multivariate analyses

To better understand the relation between altitude and cardiac remodeling, we performed multivariate analysis including age but also crucial haematological and hemorheological indicators which are known to vary with altitude: Hb mass relative to body weight, haematocrit, and blood viscosity. Analyses were focused on right cavities.

The model was significant for RA volume relative to BSA (p-value: 4.47^{-20}, $R^2 = 0.276$); only Hct and Hb mass/kg were independently associated with this parameter (respectively $\beta 1 = 0.43$; $\beta 2 = 0.53$). Similarly, it was also significant for RVEDSA relative to BSA (p-value: 1.47^{-11}, $R^2 = 0.17$) with only Hb mass/kg independently associated ($\beta = 0.335$). Finally, this model was significant for PVR (p-value: 2.57^{-30}, $R^2 = 0.42$): age, Hct, Hb mass/kg and blood viscosity were all independently associated with PVR (respectively $\beta 1 = -0.028$; $\beta 2 = 0.14$; $\beta 3 = 0.11$ and $\beta 4 = 0.10$).

Discussion

Main results

This study describes cardiac remodeling in middle-aged children permanently living at high altitude (0, 3300, 3800 and 5300 meters asl), in relation to haematological and hemorheological data. Main observations are: 1) an increase in mPAP with altitude, correlated with SpO2, Hb and Hb mass ; 2) right cavities dilation with slightly altered RV systolic function in altitude ; 3) the absence of major LV remodeling neither LV systolic function alteration ; 4) a modified LV diastolic pattern ; 5) a decreased cardiac index, in relation with plasma volume contraction.

Pulmonary haemodynamics

As expected, **mPAP and PVR increased with altitude** and were inversely correlated with SpO2. Our values were similar to those previously reported and measured invasively [8] or by echocardiography [36] in children living permanently at high altitude. As observed in adults, this rise in pulmonary artery pressure was positively correlated with [Hb], Hbmass, Hct and RBCV [8][11] in relation with the fall in SpO2 [14]. In 2005, the Consensus Statement on Chronic and Subacute High Altitude Diseases described an entity called “High Altitude Pulmonary Hypertension” or HAPH, corresponding to a clinical syndrome occurring in children or adults living above 2500 m who exhibit an elevation of mPAP > 30 mmHg or sPAP > 50 mmHg, in absence of excessive erythrocytosis ([Hb] < 19 g/l in females, < 21 g/l in males), associated with RV hypertrophy, heart failure and moderate hypoxemia [31]. In our population, only 6 children exhibited mPAP value above this value, all living at La Rinconada. We didn’t find any sign or symptom of right heart failure in these children, whose echocardiography differed from other children of La Rinconada only by a slightly higher RVED area (+12.8%) and RA volume relative to BSA (+4.7%).

This high level of pulmonary pressure in children could be related to different factors: haematological, haemorrheological and vascular. Chronic exposure to hypoxia increases the erythropoietic drive and consequently, considerably rises haemoglobin levels, haematocrit, Hbmass and RBCV. Pulmonary vascular resistance increases exponentially with haematocrit [15]. However, on the contrary to adults evaluated in a previous study (who mainly grew up at lower altitude and later went to La Rinconada to work) [11], this increase in pulmonary vascular resistances persisted after correcting haematocrit to 45% (sea-level value), highlighting the importance of pulmonary vasculature changes with hypoxia.

Hypoxic pulmonary vasoconstriction (HPV), a physiological mechanism aiming at matching ventilation with lung perfusion, is widely activated at altitude, causing a rise in PVR. HPV may be greater in children than in adults, as demonstrated by previous work in acute hypoxia [38]. If the hypoxic stimulus persists, arterial remodeling can occur, notably a muscularization of

little arteries and arterioles [8]. Therefore, thickening of arterial walls and narrowing of their lumens (previously described as a “foetal pattern”) provokes an irreversible rise in pulmonary artery pressure [8]. Then, this rise of PVR has 2 components : dynamic, because of the HPV, and structural, because of the arterial remodeling. Previous study showed that, after 2 years spent at sea level, resting PVR of highlanders (born at 4540m) normalized. However, during an effort, PVR considerably and abnormally rose in comparison to lowlanders, demonstrating that arterial remodeling persisted in time [32].

We observed a wide range of mPAP a same altitude: from 19.6 to 35 mmHg at Cuzco, 19.1 to 41.8 mmHg at Juliaca, and 28.6 to 60.3 mmHg at La Rinconada. Then, a similar hypoxic stimulus had different pulmonary haemodynamics consequences. Previous study described an important inter-species [34] and inter-individual [30] variability in the pulmonary vasopressive response to hypoxia, suggesting that some subjects could be “hypo” and other “hyper” reactive to hypoxia. https://journals.physiology.org/doi/epdf/10.1152/japplphysiol.00394.2016 (méta analyse)

It could have been supposed that, for each city, mPAP was the highest in the more hypoxemic children. Nevertheless, multivariate analysis did not find, at each altitude, significant correlation between mPAP and SaO2. Similarly, a large meta-analysis in adults living in high altitude did not demonstrate a significant relationship between arterial O2 saturation and pulmonary pressure [39].

Moreover, previous invasive studies found that mPAP of children living at high altitude decreased with growth. Again, we didn’t find significant correlation between age and mPAP at each altitude [8]. However, the age difference between our oldest and our youngest children could have been to small to find a significant effect of this parameter.

Pulmonary vascular reactivity may also vary with ethnicity. Previous work demonstrated that systolic pulmonary artery pressure was 33% lower in Aymara children (age 9.5 +/- 3.6 years) asl relative to children of European ancestry, both living between 3600 and 4000 meters asl [36]. Another study performed in Lhasa (3658 m) in 5 young Tibetan highlanders found that their resting mean PAP was similar to those encountered at sea level [37].

Other factors can modulate the rise in pulmonary pressure in response to chronic hypoxia.

- Pregnancy

Usually, mothers descend to a lower altitude (around 4000 meters asl) during the peri-partum period, but some of them stay at La Rinconada. Pregnancy at high altitude exposes the mother to several complications, notably, hypertensive disorders. For the foetus, the main risks are prematurity, reduced birth weight and, in the most extreme situations, intrauterine death [12].

The prevalence of these disorders is higher in non-acclimatized populations experimenting with pregnancy at high altitude [13]. Later during childhood and adulthood, there's a close relationship between the severity of hypoxia during pregnancy and pulmonary vascular dysfunction, leading to pulmonary hypertension [12].

- Iron

Specifically, iron deficiency is actually considered a major health challenge in Peru, considering the close relationships between iron metabolism and (mal)adaptation to high altitude. Moreover, environmental pollution, notably by heavy metals, could modulate children's growth.

- Mercury

Right heart remodeling

Right heart cavities dilated with altitude, notably RA volume, well correlated with pulmonary artery pressure. Similar remodeling was observed in adults [11]. However, whereas this right heart remodeling correlated with Hb mass and total blood volume in adults (the latter 2-fold increased in highlanders vs lowlanders), we found that BV remained constant with altitude in children. Indeed, we found that red blood cell expansion with altitude was accurately compensated by plasma volume contraction in children. Rôle du volume plasmatique dans CMS

Right ventricular predominance over the left ventricle is physiological after birth but usually regresses in few months at sea level. On the contrary, this RV predominance was found up to 10 years in children living at high altitude [15]. We found similar constatations in our oldest children, between 12 and 13 years old, without differences of right heart remodeling with age.

In a similar way to adults, **RV systolic function was significantly reduced** in children living at high altitude, although remaining within standard values [11]. Importantly, no children had signs or symptoms of right heart failure.

A previous study in adults showed a decreased Et/At ratio, however nonsignificant after controlling for age [11]. In our population of young children, no right diastolic dysfunction was observed - Et/At ratio was even slightly increased in La Rinconada.

Left heart remodeling

On the contrary to adults [11], **we didn't observe significant LV remodeling in children:** parietal thickness and LV mass were slightly higher in Lima, mainly explained by a higher BSA in the children evaluated in this city. LV EDD was a little bit increased in La Rinconada.

There **weren't major modifications in LV systolic function with altitude,** as previously described in adults [11]. Nevertheless, **LV diastolic function markers were slightly altered**. Indeed, a significant drop in mitral E velocity was observed, probably related to this reduction in plasma volume. Another explanation could be the influence of the higher pressure in right cavities leading to reduced early LV filling due to LV/RV interdependence as previously described in chronic thromboembolic pulmonary hypertension [22]. However, diastolic function markers as mitral E/A ratio weren't correlated with pulmonary arterial pressure levels.

Systemic hemodynamic

Stroke volume diminished with altitude, only partially compensated by a rise in heart rate. Consequently, **cardiac index was significantly lowered** at high altitude. This could be explained by a significantly lowered total blood volume due to plasma volume contraction. This observation contrasts with what has been described in adults, whose plasma volume reduction was over-counterbalanced by the rise in RBCV, leading to a greater total blood volume in highlanders [11]. A discuter +++ et à articuler avec paragraphe « right heaart remodeling ».

As demonstrated by Simonson et Al. [24], a negative relationship exists between [Hb] and cardiac output. We found a similar negative correlation between [Hb] and Hct and cardiac output in children.

Future directions

While high-altitude dwellers exhibit significant physiological adaptations (ventilatory, cardio-circulatory, haematological, hemorheological and metabolic [3]), a substantial number of them develop an intolerance to high altitude – a condition known as "Chronic Mountain Sickness" (CMS) or Monge's disease (1928). Its prevalence vary widely among regions and ethnic groups: only 1.2% in Tibetans [25], 5.6% [25] to 17.8% [26] in Chinese Han males, from 5 to 33% in Andeans [27]. CMS prevalence increases with altitude of residence and aging [28].

CMS is characterized by excessive erythrocytosis (haemoglobin ≥ 210 g/L in men, ≥ 190 g/L in women) and a wide spectrum of symptoms (headache, tinnitus, cyanosis, palpitations, dyspnea, paresthesia, venous dilation, sleep disorders) evaluated by the Qinghai score [4]. CMS may be associated with abnormally high pulmonary artery pressure [29], which could lead to right heart failure in the absence of adequate treatment (first of all, descend to a lower altitude).

Cardiovascular changes are more pronounced in individuals suffering from CMS [11].

Classically, CMS is not described in children. First, time of exposition to hypoxia, previously identified as an important risk factor of CMS [ ] , may not be long enough to develop deleterious effects of living at high-altitude. Then, CMS is often interwined with various chronic pulmonary diseases (pulmonary emphysema, chronic bronchitis) or other hypoxemic diseases (severe obesity), rarely found in children. Patients suffering from CMS are more likely to have a blunted respiratory response to hypoxia, notably during night. Sleep-disordered breathing are more frequent in CMS patients [25] and may exacerbate cardiovascular consequences of hypoxia []. Nearly all children had a nocturnal oximetry, whom analysis will help us to better understand the link between night hypoxic burden, erythropoietic response and cardiac remodelling.

Hypoxic Pulmonary Vasoconstriction (HPV) plays a key role in the rise in PAP in acute hypoxia as well as in chronic hypoxia. However, various factors modulate HPV. Children with a medical history of transient perinatal hypoxia exhibit an enhanced pulmonary vascular reactivity [17]. Hypertensive disorders like preeclampsia are also more prevalent during pregnancy at high altitude. A previous study showed an association of vascular disorders of pregnancy and neonatal pulmonary hypertension [18] as well as a lifelong-persistent higher susceptibility to pulmonary hypertension [19]. Then, iron deficiency can also be responsible for an increased HPV [20]. Iron deficiency, and consequent anaemia, are major health preoccupations in Peru. Future works will explore these relationships in our population.

Moreover, we found an important variability in cardiac remodeling in children exposed to the same physiological stimulus – chronic hypoxia. Whether children whom cardiac remodeling is the most pronounced will be more susceptible to develop CMS in their future life still unanswered. Thus, longitudinal works are necessary to identify physiological, biological and imaging traits that could lead to a particular follow-up and/or preventive interventions.

Study limitations

Our study has several limitations. Our different groups were slightly different – with a similar age but a higher body surface area in Lima, and a different sex ratio. Moreover, children could have grown up and lived in different socio-economic situations among altitude, although our evaluation places were chosen to recruit similar family profiles. Because child recruitment was based on volunteership and often with “word-of-mouth” between families, they could not have been exactly representative of other children of their cities. However, our different samples – cumulating 350 children – constitute one of the most important databases ever constituted on this topic, ensuring a certain degree of representativity.

We cannot rule out a “survival bias”, as all the children evaluated were in apparent good health. A significant number of children who suffered from various diseases may have descended to

lower altitude. Consequently, we could imagine that children living permanently at these extreme altitudes are those who adapted the best.

Echocardiographies were performed by two different cardiologists (S.D. during the first mission, A.C. during the second and the third). Nevertheless, A.C. was formed by S.D. years before this study, and all images were secondly re-analysed and post-treated by A.C. We evaluated inter-observator bias

We should have used a different echocardiograph during the 3rd mission. However, as all images were post-treated with the same software by the same person, risk of erroneous measurement was relatively low.

Because our evaluation were non-invasive, we should assume a certain degree of uncertainty relative to the echocardiography measurements. However, our values, notably relative to right heart pressures, were in a similar range to what has been described earlier invasively. Finally, the number of missing data was low, less than 5%.

Conclusion

Children born and living at high altitude exhibit notable cardiac remodeling, largely predominant on right heart cavities, in relation with rise in pulmonary artery pressure. This remodeling was gradually more important as altitude rose and was similar to those encountered in adults. However, no left cardiac remodeling was observed. This remodeling is multifactorial, partly predetermined (notably with pregnancy and early-life significant events), partly in relation with acquired non modifiable factors (pulmonary arteria remodeling), modulated by various factors that life in high altitude implies: chronic hypoxia and subsequent erythropoietic response, rise in blood viscosity in relation with rise in haematocrit, malnutrition and dietary deficiencies and its consequences (notably on iron metabolism).

The large variability in cardiac remodeling signs observed in this population in response to chronic hypoxia, only modestly explained by our current models, incites us to find other key determinants of this cardiac remodeling. Moreover, longitudinal works are required to identify decisive factors which could be identified during childhood that could predispose in latter life to maladaptation to altitude.

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Supplementary materials

	SpO2		Haematocrit		Hbmass		Hb mass/kg	
	p-value	R^2	p-value	R^2	p-value	R^2	p-value	R^2
RA volume/BSA	$<10^{-4}$	0.27	$<10^{-4}$	0.257	$<10^{-4}$	0.173	$<10^{-4}$	0.213
RVED area /BSA	$<10^{-4}$	0.079	$<10^{-4}$	0.051	0.004	0.027	$<10^{-4}$	0.172
mPAP	$<10^{-4}$	0.661	$<10^{-4}$	0.516	$<10^{-4}$	0.155	$<10^{-4}$	0.269
PVR	$<10^{-4}$	0.408	$<10^{-4}$	0.354	0.481	0.002	$<10^{-4}$	0.244
RV S’	0.398	0.002	0.477	0.002	0.459	0.002	0.152	0.007
RV FAC	0.0012	0.03	0.0008	0.03	0.64	0.001	0.01	0.02
RV strain	0.0017	0.029	0.0017	0.029	0.00133	0.034	0.688	0.001
Et/At ratio	0.011	0.019	0.0126	0.018	0.934	0	$<10^{-4}$	0.052

Supplementary material 1: Correlation between right heart echocardiography parameters and SpO2, haematocrit, Hb mass and Hb mass indexed to body weight.