Effect of Developmental Exposure to Hypobaric Hypoxia in Aerobic Capacity and Ventilatory Efficiency during Maximal Exercise in Young Admixed Andean Residents

Manuel A. Cardenas-Romero [1], Julio C. Bermudez-Muñoz [2], Sebastian C. Cortes-Rosero [1], Ana M. Beltran-Cortes [3], Juan C. Cardenas-Arciniegas [1]

manuel.cardenas@javeriana.edu.co

Exercise Prescription Research Group

1 Physiological Sciences Department - Faculty of Medicine, Pontificia Universidad Javeriana 2 Psychological and Health Counseling Center, Pontificia Universidad Javeriana 3 Department of Industrial Engineering, Pontificia Universidad Javeriana

Pontificia Universidad JAVERIANA Bogotá

INTRODUCTION

Bogota (2600 m, barometric pressure 560 mmHg, 28% reduction in inspired oxygen pressure) is the most populated city above 2500 m, with roughly 8 million people from diverse and admixed genetic background and high immigration levels from lower altitudes.

Ancestral Andean high-altitude natives (Quechua and Aymara) exhibit specific genetic adaptations at rest and during exercise when compared to lowlanders acclimatized to the same altitude [1, 2]: higher hemoglobin concentration (Hb), lower hypoxic ventilatory drive, lower resting and exercise total ventilation (V_E) and higher alveolar-capillary diffusing capacity. Some studies propose early developmental adaptations in Andean high-altitude residents lacking altitude ancestry [3].

It is not clear for admixed Andean population, born and raised at moderate altitude, if early developmental hypoxic exposure confers beneficial effects during exercise in hypoxic conditions.

We hypothesized that differential chronic altitude exposure in prenatal and postnatal development affects aerobic capacity and ventilatory response in young healthy admixed Andean residents at moderate altitude.

OBJECTIVE

To determine the effect of duration and time of exposure to hypobaric hypoxia on aerobic capacity and ventilatory efficiency during maximal cardiopulmonary exercise test (CPET) on cycle ergometer in young Andean residents at moderate altitude.

METHODS

Study subjects

We used a cross-sectional study design to recruit and enroll 407 healthy, non-athlete, non-smoking, young residents (18 – 25.9 yr) in Bogota with normal body mass index (BMI: 18.5 – 24.9 kg/m²); study protocol was approved by Institutional Ethics Committee. Study subjects recruitment, enrollment and cardiorespiratory and metabolic data acquisition were supported by REDCap® web application; **figure 1** summarizes the study phases.

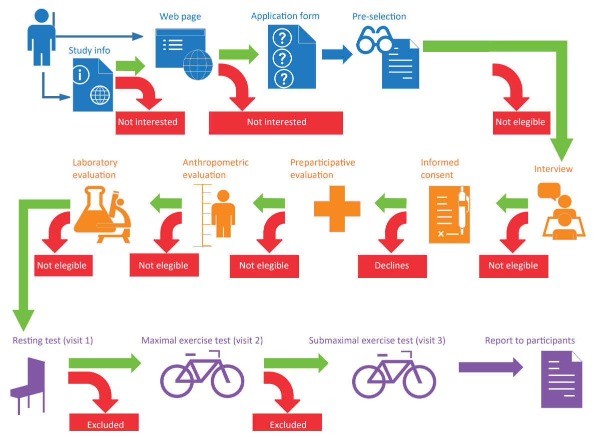


Figure 1. Recruitment phase (blue), enrollment phase (orange) and cardiorespiratory / metabolic data acquisition phase on separate days (purple).

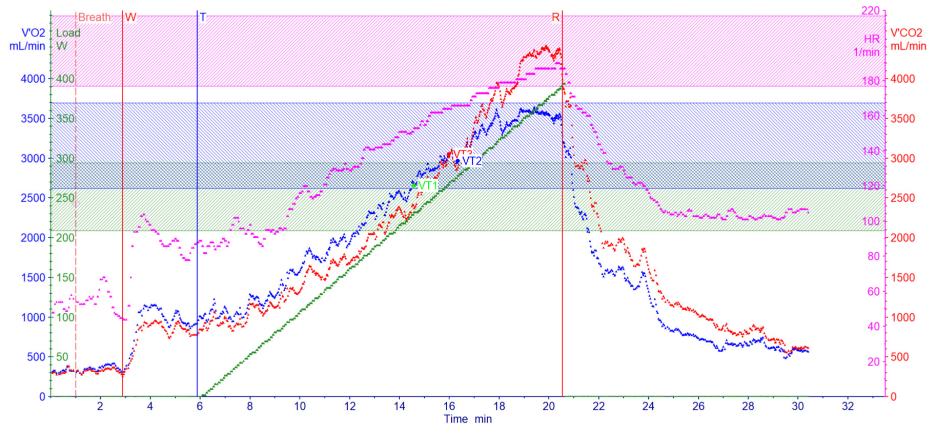


Figure 2. Maximal cycle ergometer cardiopulmonary exercise test protocol: Rest (3 min), unloaded warm-up (3 min), ramp exercise (male 27 W / min, female 15 W / min), unloaded cool-down (3 min), recovery (7 min).

Eight subjects were excluded from this analysis for technical reasons (not achieving maximal effort or poor-quality tests). 399 subjects were included in the final analysis and assigned to four groups according to sex and altitude exposure.

Native groups were born and raised at altitudes between 2500 m and 2800 m:

Native male: n = 167
Native female: n = 155

Acclimatized groups were born and raised, at least their first 14 years of age, at altitudes below 500 m in Colombia, and should have permanently lived at 2600 m at least for 10 weeks before enrollment:

Acclimatized male: n = 39
Acclimatized female: n = 38

Resting measurements

Forced vital capacity (FVC), forced expiratoy volume in first second (FEV_1) and 12-second maximal voluntary ventilation (MVV_{12}) were measured; in sitting position, continuous 12-minute breath by breath gas analysis (Vyntus CPX, Vyaire®), 12-lead electrocardiography (Cardiosoft, GE®) and forehead reflectance pulse oximetry (SpO_2 - 8000R sensor, Nonin®) were recorded.

Laboratory and genetic ancestry analysis

Venous blood sample was drawn for main hematologic parameters and tri-ethnic genetic ancestry proportion analysis (Native American NAAP, African AAP, and European EAP) trough ancestry-informative insertion deletion multiplexing [4].

REFERENCES: 1. Brutsaert TD, Parra EJ, Shriver MD, Gamboa A, Rivera-Ch M, León-Velarde F. Ancestry explains the blunted ventilatory response to sustained hypoxia and lower exercise ventilation of Quechua altitude natives. Am J Physiol Integr Comp Physiol. 2005 Jul;289(1):R225–34. 2. Beall CM. Two routes to functional adaptation: Tibetan and Andean high-altitude natives. Proc Natl Acad Sci U S A. 2007 May 15;104 Suppl(Supplement 1):8655–60. 3. Frisancho AR. Developmental Functional Adaptation to High Altitude: Review. Am J Hum Biol. 2013 Mar;25(2):151–68. 4. Pereira R, Phillips C, Pinto N, Santos C, Santos SEB dos, Amorim A, et al. Straightforward Inference of Ancestry and Admixture Proportions through Ancestry-Informative Insertion Deletion Multiplexing. Kayser M, editor. PLoS One. 2012 Jan 17;7(1):e29684. 5. Midgley AW, McNaughton LR, Polman R, Marchant D. Criteria for Determination of Maximal Oxygen Uptake. Sport Med. 2007;37(12):1019–28. 6.Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001 Jan;37(1):153–6.

Exercise test

On a different day, subjects performed an incremental ramp (male 27 W / min, female 15 W / min) cardiopulmonary exercise test until exhaustion in an electronically braked cycle ergometer (Excalibur Sport, Lode®) with continuous breath by breath gasanalysis, 12-lead electrocardiography and forehead pulse oximetry recording, earlobe capillary lactic acid concentration was sampled every 2.5 min (Biosen C line, EKF®). Cardiopulmonary exercise test protocol and subject monitoring are illustrated in **figures 2** and **3**, respectively.

Subjects included in this analysis complied with at least two of the following maximal effort criteria [5]:

Respiratory exchange ratio at maximal exercise (RER_{pk}) > 1.1.

Maximal heart rate (HR_{pk}) > 85% of predicted maximal heart rate (HR_{pred}) by Tanaka equation [6].

Maximal capillary lactate concentration (Lac_{pk}) > 8 mMol /L in recovery phase.

Figure 3. Subject monitoring during maximal CPET.

Data treatment and test interpretation

Raw breath by breath data were fitted using Kernel regression, values farther than three interquartile ranges were removed; final values were displayed as 5-breath average. Peak oxygen uptake ($VO_{2\,pk}$) was identified as the highest 20-seconds average during the last 2 minutes of the exercise phase.

Two independently investigators identified ventilatory threshold 1 (VT1) using both, ventilatory equivalent (EqO_2) and end-tidal pressure for oxygen ($PetO_2$), as well as ventilatory threshold 2 (VT2) using both, ventilatory equivalent (EqO_2) and end-tidal pressure for carbon dioxide ($PetCO_2$). Each ventilatory threshold was calculated as the mean from four lectures, two from each investigator.

Statistical analysis

Main cardiopulmonary resting and exercise variables were compared (Wilcoxon Rank Sum test) between altitude groups by sex at rest, VT1, VT2 and maximal exercise; α error was set at 0.05 level. R statistical software® v 4.0.3 was used for data treatment and analysis.

RESULTS

Groups were similar in key parameters that influence exercise performance. **Table 1** summarizes main characteristics of study subjects. **Table 2** shows maximal exercise results.

Table 1. Main characteristics of study subjects by sex and altitude subgroup: median (interquartile range).

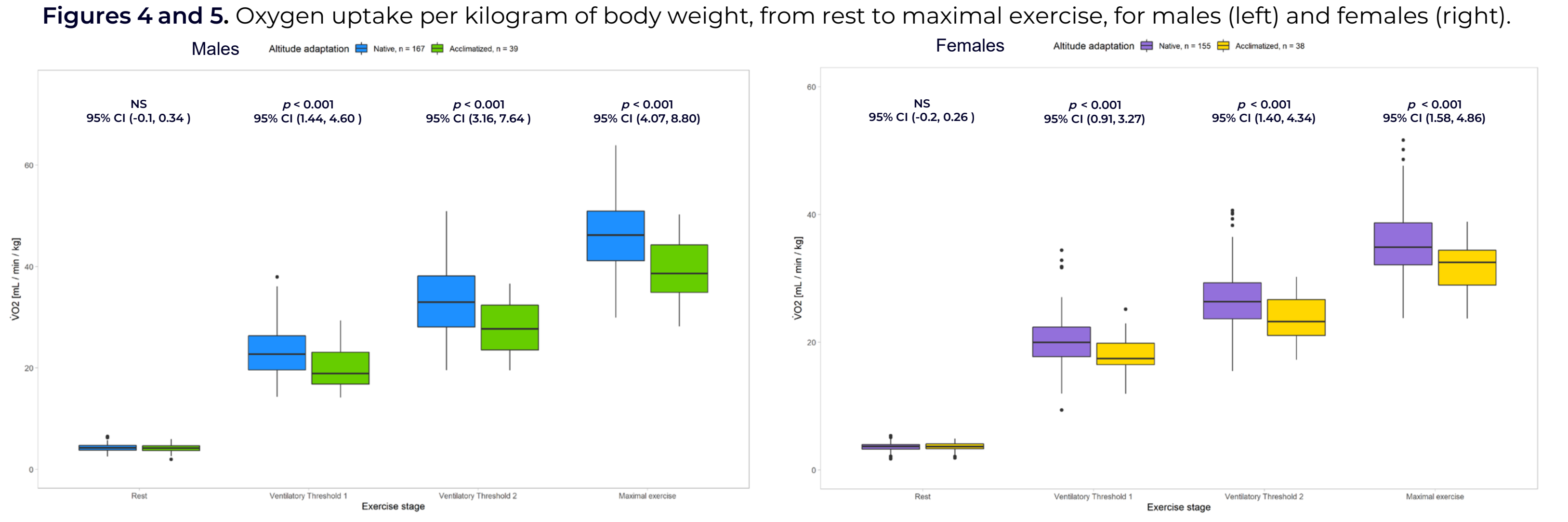
	Male			Female		
	Native	Acclimatized	p value	Native	Acclimatized	p value
Demographics						
n	170	39		156	38	
Age [yr]	22.5 (3.02)	20.2 (2.84)	< 0.001	21.4 (3.19)	20.7 (3.17)	NS
Weight [kg]	63.3 (9.65)	66.1 (8.5)	NS	55.2 (7.7)	55.1 (7.42)	NS
Height [cm]	171.3 (7.22)	172 (8.69)	NS	159.3 (7.92)	158.5 (8.87)	NS
BMI (kg/m^2)	21.8 (3.09)	21.6 (2.14)	NS	21.5 (2.75)	21.3 (2.49)	NS
Body fat (%)	13.0 (5.55)	12.7 (3.55)	NS	23.5 (6.1)	23.0 (5.87)	NS
Pulmonary function						
FEV1 [L]	4.37 (0.73)	4.25 (0.75)	NS	3.23 (0.56)	3.2 (0.60)	NS
FVC [L]	5.09 (0.81)	4.93 (1.06)	NS	3.75 (0.62)	3.49 (0.74)	< 0.05
FEV/FVC	0.84 (0.08)	0.87 (0.08)	NS	0.86 (0.07)	0.90 (0.07)	< 0.01
MVV_{12} [L/min]	190. (38.0)	187. (38.2)	NS	130. (25.5)	135. (18.3)	NS
Blood markers						
Hb [g/dL]	16.6 (0.90)	16.9 (1.09)	NS	14.7 (1.1)	14.7 (0.95)	NS
EAP (%)	50 (18.6)	43.7 (18.4)	< 0.01	51.0 (23.4)	49.9 (16.4)	NS
AAP (%)	10 (8.5)	13.3 (10.6)	< 0.05	10.3 (7.55)	13.2 (12)	NS
NAAP (%)	38.1 (19.9)	38.9 (16)	NS	37.6 (20.4)	33.2 (18.5)	NS

Table 2. Main parameters at maximal exercise by sex and altitude subgroup: median (interquartile range).

	Male			Female		
	Native	Acclimatized	p value	Native	Acclimatized	p value
General						
Exercise time [s]	603 (61.5)	529 (76.5)	< 0.01	660.5 (39)	591.5 (25.2)	< 0.01
WR_{pk} [W]	272 (61.5)	234 (76.5)	< 0.001	165 (39)	147.5 (25.2)	< 0.01
WR_{pk-kg} [W/kg]	4.3 (1.0)	3.6 (0.9)	< 0.001	2.9 (0.7)	2.7 (0.4)	< 0.01
Metabolic						
$VO2_{pk}$ [mL/min]	2918.4 (653.8)	2599.1 (626.8)	< 0.001	1937.2 (448.2)	1723.5 (315.0)	< 0.001
$VO2_{pk-kg}$ [mL/min/kg]	46.1 (9.76)	38.6 (9.40)	< 0.001	34.7 (6.58)	32.4 (5.46)	< 0.001
RER_{pk}	1.21 (0.09)	1.22 (0.09)	NS	1.16 (0.08)	1.18 (0.08)	NS
La_{pk} [mmol/L]	13.4 (3.14)	13.7 (3.71)	NS	10.9 (2.51)	10.3 (1.54)	< 0.05
Respiratory						
V_{Tpk} [L]	2.53 (0.47)	2.47 (0.76)	NS	1.79 (0.39)	1.75 (0.32)	< 0.05
fB_{pk} [breaths/min]	58.7 (12.0)	53.7 (14.8)	NS	52.0 (11.2)	55.7 (12.2)	< 0.05
V_{Epk} [L/min]	144. (34.0)	133. (35.4)	< 0.05	93.6 (22.5)	93.4 (17.6)	NS
$V_{Epk-BSA}$ [L/m^2]	84.8 (19.2)	78.2 (16.9)	< 0.01	59.6 (11.5)	60.4 (11.9)	NS
$EqO2_{pk}$	45.1 (10.2)	49.6 (10.6)	< 0.05	45.3 (6.98)	49.6 (7.21)	< 0.001
$EqCO2_{pk}$	37.7 (6.48)	40.7 (7.78)	< 0.05	38.5 (5.66)	41.5 (6.46)	< 0.001
$pO2_{ET-pk}$ [mmHg]	83.2 (5.00)	85.5 (3.86)	< 0.05	84.1 (3.04)	85.5 (2.79)	< 0.001
$pCO2_{ET-pk}$ [mmHg]	28.7 (5.16)	26.5 (4.09)	< 0.05	27.0 (3.48)	25.5 (3.64)	< 0.001
SpO2 [%]	93 (6.37)	94.0 (4.77)	NS	93.5 (4.52)	95.0 (3.79)	< 0.05
Cardiovascular						
HR_{pk} [beats/min]	190 (10.5)	196 (10)	NS	190 (12)	193 (11.25)	NS
HR_{pred} [%]	99.4 (5.7)	100. (6.1)	NS	98.6 (6.2)	99.6 (5.1)	NS
O2 $pulse_{pk}$ [mL/beat]	15.6 (3.33)	13.5 (3.63)	< 0.001	10.3 (2.29)	9.26 (1.34)	< 0.001
Slopes						
VO2 - WR slope	8.42 (1.19)	7.50 (1.29)	< 0.001	7.64 (1.89)	7.28 (1.13)	NS
V_E - VCO2 slope	32.27 (6.07)	36.18 (6.82)	< 0.001	33.66 (6.52)	37.17 (6.79)	< 0.001
OUES	1327.0 (324.2)	1147.4 (306.5)	< 0.001	927.25 (247.9)	763.65 (154.0)	< 0.001
HR - VO2 slope	0.032 (0.01)	0.032 (0.00)	NS	0.043 (0.01)	0.043 (0.01)	NS

For both sexes across all exercise stages (VT1, VT2, maximal exercise), work rate (WR_{pk}) and $VO_{2\,pk}$ per kilogram of body weight ($VO_{2\,pk\text{-}kg}$) were higher in native groups, **table 2** and **figures 4** and **5**. VO_2 - WR slope was higher only for native males, **figures 10** and **11**.

Figures 4 and 5. Oxygen uptake per kilogram of body weight, from rest to maximal exercise, for males (left) and females (right).



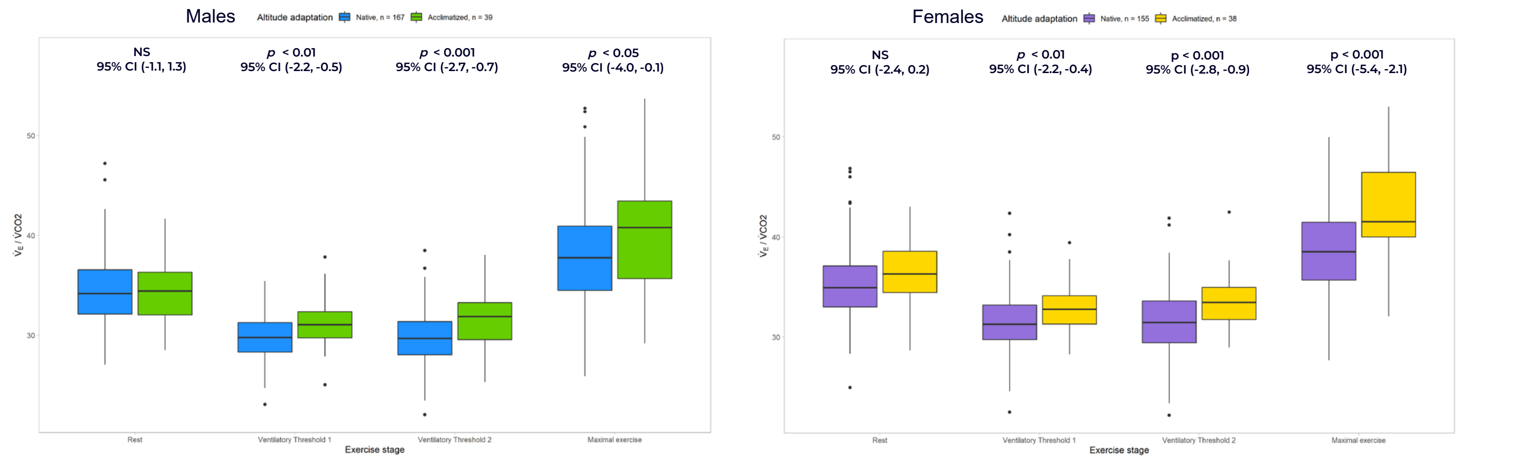
For both sexes, relative oxygen uptake at both ventilatory thresholds: VT1 ($VO_{2\,VT1}$), VT2 ($VO_{2\,VT2}$) were similar between groups:

$VO_{2\,VT1}$: native male 49.5% vs acclimatized male 49.8%, p NS; native female 57.1% vs acclimatized female 55.9%, p NS.

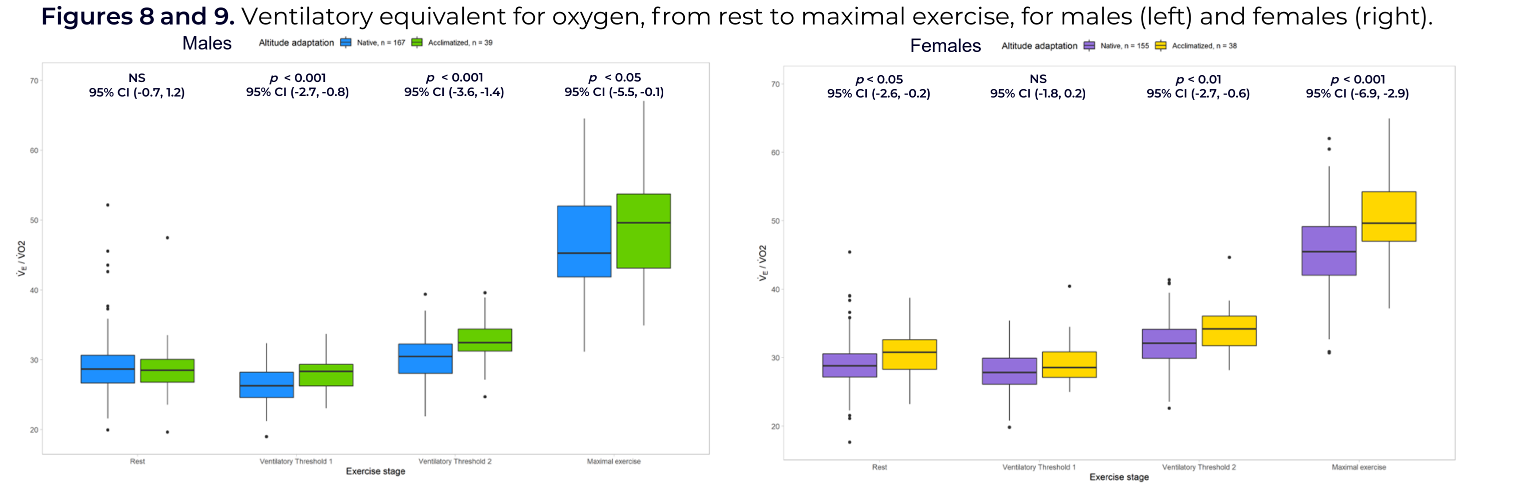
$VO_{2\,VT2}$: native male 71.5% vs acclimatized male 70.9%, p NS; native female 76.5% vs acclimatized female 75.1%, p NS.

$PetCO_2$ and $EqCO_2$ were lower in native groups in both sexes across all exercise stages, **table 2** and **figures 6** and **7**; similarly, for both sexes, native groups also had lower $PetO_2$ across all exercise stages and higher EqO_2 at VT2 and at maximal exercise, **table 2** and **figures 8** and **9**.

Figures 6 and 7. Ventilatory equivalent for carbon dioxide, from rest to maximal exercise, for males (left) and females (right).



Figures 8 and 9. Ventilatory equivalent for oxygen, from rest to maximal exercise, for males (left) and females (right).

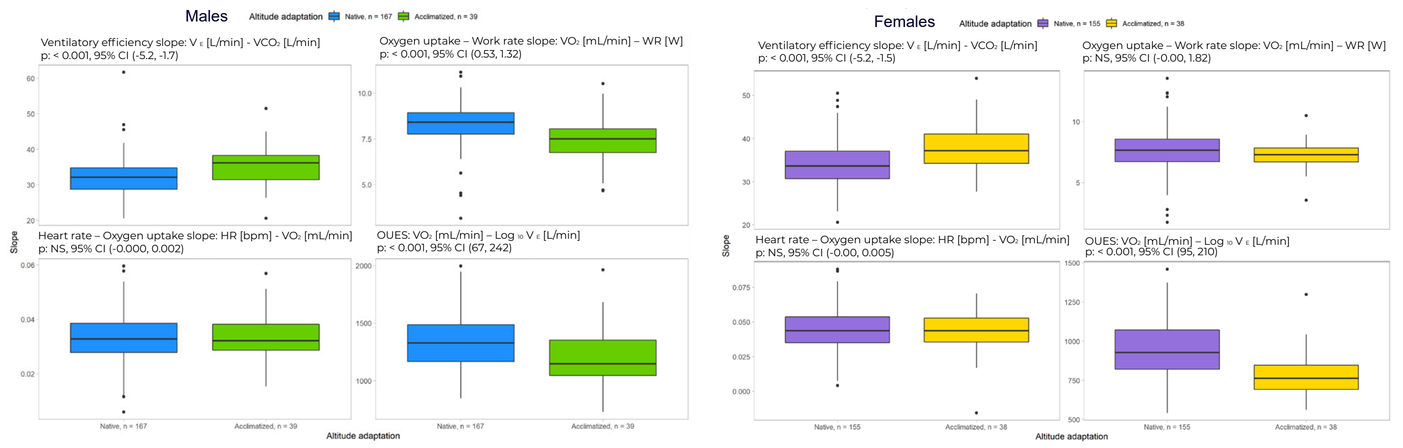


For native female across all exercise stages, tidal volume (V_T) was higher and respiratory frequency (f_B) was lower, f_B was lower also at rest; for native male V_T was higher only at VT1 and VT2; for both sexes total ventilation (V_E) was similar at most exercise stages, **table 2**.

For native groups in both sexes, exercise ventilatory efficiency slope (V_E - carbon dioxide production: VCO_2) was lower and oxygen uptake efficiency slope (OUES: VO_2 - $\log_{10} V_E$) was higher, **figures 10** and **11**.

For both sexes across all exercise stages, oxygen pulse (O_2 pulse) was higher for natives but HR was similar between groups, **table 2**; exercise HR – VO_2 slope was similar between groups, **figure 10** and **11**.

Figures 10 and 11. Incremental exercise slopes analysis, for males (left) and females (right).



CONCLUSIONS

For healthy young admixed Andean residents, prenatal and continuous postnatal developmental exposure to hypobaric hypoxia have a favorable effect in aerobic capacity and ventilatory efficiency during maximal incremental exercise at moderate altitude. These findings supports the hypothesis of developmental adaptation to altitude.

Further research is needed to establish the relative contribution of oxygen transport and utilization systems to developmental altitude adaptation in Andean admixed populations.

Supported by COLCIENCIAS grant number 120356934972, 713-2013.

El conocimiento es de todos — Minciencias