

## Determinants of blood oxygenation during pregnancy in Andean and European residents of high altitude

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**Vargas M, Vargas E, Julian CG, Armaza JF, Rodriguez A, Tellez W, Niermeyer S, Wilson M, Parra E, Shriver M, Moore LG.** Determinants of blood oxygenation during pregnancy in Andean and European residents of high altitude. *Am J Physiol Regul Integr Comp Physiol* 293: R1303–R1312, 2007. First published July 3, 2007; doi:10.1152/ajpregu.00805.2006.—High altitude decreases birth weight, but this effect is diminished in long vs. short-resident, high-altitude populations. We asked whether women from long vs. short-resident, high-altitude populations had higher arterial oxygenation levels by comparing 42 Andean and 26 European residents of La Paz, Bolivia (3,600 m), serially during pregnancy (*weeks 20, 30, and 36*) and again 4 mo postpartum. Pregnancy raised hypoxic ventilatory sensitivity threefold, resting ventilation ( $\dot{V}_E$ ), and arterial O<sub>2</sub> saturation (SaO<sub>2</sub>) in both groups. Ancestry, as identified using 81 genetic markers, correlated with respiratory pattern, such that greater Andean ancestry was associated with higher respiratory frequency and lower tidal volume. Pregnancy increased total blood and plasma volume ~40% in both groups without changing red blood cell mass relative to body weight; hence, hemoglobin fell. The hemoglobin decline was compensated for by the rise in  $\dot{V}_E$  and SaO<sub>2</sub> with the result that arterial O<sub>2</sub> content (CaO<sub>2</sub>) was maintained near nonpregnant levels in both groups. Birth weights were similar for all Andean and European babies, but after adjusting for variation in gestational age, maternal height and parity, Andeans weighed 209 g more than Europeans. Babies with heavier birth weights and greater ponderal indices were born to Andean women with higher  $\dot{V}_E$  during pregnancy. We concluded that while maternal  $\dot{V}_E$  and arterial oxygenation were important, some factor other than higher CaO<sub>2</sub> was responsible for protecting Andeans from altitude-associated reductions in fetal growth.

hypoxia; ventilation; ventilatory control; infant birth weight; fetal growth; genetics of birth weight; human adaptation; respiratory pattern

RESIDENCE AT HIGH ALTITUDE (>8,000 ft, 2,500 m) exerts among the most powerful effects on birth weight with values falling, on average, 121 g per 1,000 m in Colorado high-altitude (>2,500 m, 8,000 ft) residents (15). This effect is due primarily to a slowing of fetal growth, not shortened gestation, and is greater than the effects of parity, the number of prenatal visits, or moderate maternal smoking on birth weight. Existing data indicate that the birth weight fall is not due to socioeconomic or other known risk factors (6, 15), but rather to the effects of hypoxia itself.

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Some 140 million persons live at high altitude, making them the largest single group at risk of low birth weight (16). While birth weight declines in all populations studied to date, the magnitude of fall varies, being least in long- and greatest in short-resident groups. For example, across a 2,700–4,700 m (8,900–15,500 ft) altitude range, birth weight decreases three times as much in Han (“Chinese”) compared with Tibetans (24). In La Paz, Bolivia, at 3,600 m (11,880 ft), women of indigenous (Aymara or Quechua) ancestry give birth to heavier weight infants than European women, regardless of whether the data are adjusted for differences in maternal body size, nutrition, or the mother’s own altitude of birth and development (9).

On the basis of our previous work indicating the importance of maternal physiological adjustments to pregnancy at high altitude (23, 25, 33, 34), we hypothesized that women with multigenerational high-altitude ancestry were able to deliver more oxygen to the uteroplacental circulation than those with shorter duration of residence. La Paz, Bolivia, was chosen as our study site since it is the highest capital city in the world and has both long-resident (Aymara or Quechua, termed “Andeans” here) and shorter-term (largely European) high-altitude populations. Since oxygen delivery to the uteroplacental circulation is the product of its concentration in the arterial blood and uteroplacental blood flow, we considered the possibilities that the Andean women either had higher levels of arterial oxygenation, greater uteroplacental blood flow, or both.

Here, we consider the first possibility, asking whether Andeans have higher levels of arterial oxygenation during pregnancy than women of European ancestry. We measured resting ventilation, arterial O<sub>2</sub> saturation, hemoglobin concentration, and arterial O<sub>2</sub> content serially during pregnancy and again postpartum for a measurement in the nonpregnant state. To identify the factors responsible for any differences observed, we also determined ventilatory sensitivity to hypoxia and hypercapnia, end-tidal gases, and total blood volume. In a companion paper (31), we address the possibility that differences in uteroplacental blood flow are responsible for the protection from altitude-associated reductions in fetal growth afforded by multigenerational high-altitude residence. We considered that these results would be informative for identifying the physiological and possibly genetic factors contributing to

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population differences in susceptibility to hypoxia-induced fetal growth reduction.

## MATERIALS AND METHODS

**Subjects.** Subjects were 57 women of Andean and 26 of non-Andean ancestry living in La Paz, Bolivia (elevation 3,600 m, 11,880 ft), or the neighboring city of El Alto (4,082 m, 14,470 ft). Women were contacted via their physicians or persons in the community. Criteria for accepting women into this study included being in good health, receiving prenatal care, willing to participate, and presenting no known risk for developing maternal preeclampsia or other complications during the current pregnancy. Subjects who withdrew from the study ( $n = 3$  Andeans) or in whom postpartum studies could not be completed ( $n = 12$  Andeans) were excluded, such that data concerning maternal oxygenation were available for a total of 42 Andeans and 26 Europeans. Six of the twenty-six European women left at weeks 32–34 to give birth at hospitals in the United States, all of which were located at low altitude. Six of the Andeans delivered at home such that birth weights were present for 36 of the 42 Andeans. Two of the Andeans and one European woman were diagnosed with mild preeclampsia following the week 36 study time; their study results did not differ from those of the other study subjects for any of the parameters measured, and hence their data are included here.

All studies were conducted at the Instituto Boliviano de Biología de Altura (Bolivian High-Altitude Biology Institute) or the nearby Clínica del Sur (Southern Clinic) at altitudes of 3,600 and 3,500 m, respectively. Studies were performed between October 2000 and November 2004 following procedures approved by the Colorado Multiple Institutional Review Board and the Colegio Médico, the equivalent ethical review group in Bolivia.

Andeans were self-identified as being of Aymára or Quechua descent with no known or minimal foreign parentage. Europeans were defined as persons whose ancestors were from Europe or European-derived populations residing in North, Central, or South America. Because the overwhelming majority of the non-Andeans (20 of 26) were of European ancestry and five were of mixed European and Central American descent, the group is referred to as “European” here. Ancestry was confirmed with the use of 81 ancestry informative genetic markers (AIMs), as described elsewhere (2, 27). Of these 81 AIMs, 51 show large (>30%) frequency differences between European and Native American populations, 65 show large-frequency differences between West African and Native American populations, and 53 show large-frequency differences between West African and European populations. Details of these markers, including allele frequencies in all parental populations, DNA sequences, exact positions of single-nucleotide polymorphisms (SNPs), and the PCR primers and amplification conditions used are available from the dbSNP database ([www.ncbi.nlm.nih.gov/SNP](http://www.ncbi.nlm.nih.gov/SNP)) under the submitter handle PSU-ANTH (1, 2, 27). The maximum likelihood method was used to estimate individual genomic ancestry (4).

**Variables and definitions.** Maternal characteristics were obtained by questionnaire and physical exam. None of the Andean or European women smoked cigarettes, as judged by self-report and measured carboxyhemoglobin level. Blood pressure was measured by arm cuff sphygmomanometer and averaged from measurements made on the right and left sides. Maternal heart rate was measured by auscultation and fetal heart rate using a fetal heart monitor (model AM66, Advanced Medical Systems, Hamden, CT). Maternal body weight and height were obtained while lightly clothed. A clean catch urine specimen was obtained at each visit using Albustix (Bayer, Elkhart, IN) and scored for protein content as negative, trace, 1+, 2+, 3+,  $\geq 4+$ . Triceps and subscapular skinfolds were summed as an index of body fat. Hematocrit was determined using the microcentrifuge technique and hemoglobin content using the cyanmethemoglobin technique, as described previously (25). Arterial O<sub>2</sub> content (CaO<sub>2</sub>) was calculated as  $1.36 \times \text{hemoglobin} \times \text{SaO}_2$ . Total blood volume was

determined using a carbon monoxide technique as previously described and validated (3, 7, 8).

Birth weight, gestational age, infant sex, length, head circumference, and Apgar scores were obtained from medical records completed by hospital personnel at the time of birth. Gestational age was calculated as weeks from the last menstrual period, which was equivalent in all cases to that estimated by fetal ultrasound at week 20. Preterm was considered as <37 wk and postterm as >42 wk gestation.

**Protocol.** Women were scheduled for study at weeks 20, 30, and 36 of gestation and at 4 mo postpartum for a measurement in the nonpregnant state. Actual times of study were  $21.7 \pm 0.3$ ,  $30.3 \pm 0.2$ ,  $36.1 \pm 0.1$  wk of pregnancy and  $3.8 \pm 0.3$  mo postpartum. At each visit, the physical exam (body weight, blood pressure, maternal and fetal heart rate, and urinalysis) was conducted, followed by the blood withdrawal from an antecubital vein, measurement of blood volume, and then the ventilatory measurements.

For measurement of blood volume, subjects breathed through a rebreathing circuit initially containing 100% O<sub>2</sub>, from which CO<sub>2</sub> was continuously removed and 100% O<sub>2</sub> periodically added. Briefly, a venous blood sample was withdrawn from an indwelling catheter after 5 min of quiet breathing. Then a known volume of 100% carbon monoxide (60 ml ATP) was added to the rebreathing circuit, and additional blood samples obtained after 10 and 15 min of rebreathing. The percent CO-Hb rose from ~2% to 6–8%, as measured in triplicate by OSM3 (Radiometer, Copenhagen, Denmark). Total blood volume was calculated using the equation  $[\text{CO added}/\Delta\text{CO content}] \times [1/\text{Hb}] \times 100$  where CO is the volume of CO added to the rebreathing circuit,  $\Delta\text{CO}$  content is the difference in CO content between the baseline and the average of the 10- and 15-min values, and Hb is the measured hemoglobin concentration using the cyanmethemoglobin technique. Red blood cell mass was calculated as total blood volume multiplied by hematocrit after correcting hematocrit for trapped plasma, using the constant 0.98 (3), and the remainder considered plasma volume.

All ventilatory studies were performed between 9:00 AM and noon after an at least 2-h fast. While resting quietly in the seated position and breathing room air through a bidirectional respiratory valve with a mouthpiece and nose clip in place, ventilation ( $\dot{V}_E$ ), expired gases, arterial O<sub>2</sub> saturation (SaO<sub>2</sub>), and heart rate were monitored for 5- to 8-min or until values became stable by monitoring flow by pneumotachograph through a bidirectional respiratory valve, while monitoring expired gas by O<sub>2</sub> and CO<sub>2</sub> analyzers and SaO<sub>2</sub> in a warmed digit, as described previously (25).

The isocapnic hypoxic ventilatory response (HVR) was measured in duplicate using a rebreathing technique as previously described (20). Fetal heart rate and variability were monitored throughout the HVR testing procedure in a subset of subjects; no changes occurred in either measure during the ~3 min of hypoxic (below room air P<sub>I,O<sub>2</sub></sub>) breathing. Isocapnia was maintained at the PETCO<sub>2</sub> measured during room air breathing by regulating the amount of expired gas shunted through a canister containing CO<sub>2</sub> absorber.  $\dot{V}_E$  was averaged over 8-breath intervals and coordinated with the corresponding average PETO<sub>2</sub>, SaO<sub>2</sub>, and PETCO<sub>2</sub> values. As has been previously described (29), curves relating  $\dot{V}_E$  and PETO<sub>2</sub> are hyperbolic and thus could be summarized for each test by the shape parameter A derived from the hyperbolic equation  $\dot{V}_E = V_o + A (\text{PETO}_2 - 32)$  where  $\dot{V}_E$  is in liters per minute BTPS,  $V_o$  is the ventilation asymptote, A is the shape parameter, and 32 is the PETO<sub>2</sub> asymptote. The relationship between  $\dot{V}_E$  and SaO<sub>2</sub> is linear and described by the slope  $\Delta\dot{V}_E/\Delta\text{SaO}_2$ . Two responses were obtained for each subject and averaged, with large A values and high negative slopes denoting brisk ventilatory responses.

Because ambient P<sub>I,O<sub>2</sub></sub> was hypoxic relative to sea level, we measured the ventilatory response to sea-level normoxia following the HVR test to avoid having brief exposure to hyperoxia influence the HVR. Subjects breathed a mixture of 100% O<sub>2</sub> and N<sub>2</sub> to achieve a P<sub>I,O<sub>2</sub></sub> of 160 mmHg for 10 min. The ventilatory response was expressed

as the  $\Delta\text{PET}_{\text{CO}_2}$ , or the room air  $\text{PET}_{\text{CO}_2}$  minus the sea-level normoxic  $\text{PET}_{\text{CO}_2}$  value.

The hypercapnic ventilatory response (HCVR) was measured using a modified rebreathing technique.  $\text{O}_2$  was added to the spirometer to obtain a gas mixture of  $\sim 55\%$   $\text{O}_2$  in  $\text{N}_2$  to maintain  $\text{PET}_{\text{CO}_2} > 250$  mmHg. As the subject rebreathed, a progressive 10–15 mmHg rise in  $\text{PET}_{\text{CO}_2}$  occurred over 7–10 min. Data were analyzed by calculating the slope of the linear portion of the curve by means of a simple linear equation  $\dot{V}_E = S + B$  where  $S$  is the slope  $\Delta\dot{V}_E/\Delta\text{PET}_{\text{CO}_2}$  and  $B$  is the  $x$ -intercept. One hypercapnic response was obtained in each subject.

**Statistics.** Values are expressed as means  $\pm$  SE, the 95% confidence interval for proportions, or the mode and range, as clarified in the text, tables, and figures. One or two-way ANOVA with repeated measurements and multiple comparisons were used to identify the effects of pregnancy and ancestry. After confirming that birth weight demonstrated a normal distribution, multiple linear regression was employed to identify those maternal and infant characteristics related to birth weight among our study subjects, with the criterion for inclusion and exclusion at  $P \leq 0.10$ . Significant covariates (gestational age, maternal height, and parity) were set to the average values for the two groups combined to isolate the effect of population ancestry on birth weight and ponderal index. The effects of ancestry on birth weight were examined by multiple linear regression. The final model was verified by examining residuals and other standard diagnostics, as well as with a stepwise approach that included all of the terms related to birth weight, as well as any interactions. Comparisons between groups at single time points were conducted using Student's  $t$ -tests for continuous variables and  $\chi^2$ -test for nominal variables using SPSS. Results were considered significant when the two-tailed  $P$  values of  $<0.05$ , unless the direction of the comparison was specified in advance, in which case, one-tailed tests were employed.

## RESULTS

**Maternal characteristics.** The Andeans had been born and raised at high altitude, whereas the Europeans had lived there an average of 4.4 yr (range = 0.4–20 yr) (Table 1). The Andeans lived  $\sim 700$  m higher than the Europeans ( $4,072 \pm 16$  vs.  $3,375 \pm 26$  m,  $P < 0.001$ ) since nearly all (91%) lived in El Alto (4,082 m or 13,470 ft), whereas most Europeans resided in the lower portions of La Paz (3,200 m or 10,500 ft).

The Andeans were younger, had higher gravidity or parity, lower educational status, and markedly lower monthly household incomes (Table 1). The Andeans were shorter than the Europeans but similar in nonpregnant body weight, body mass index, and weight gain from week 20 to 36 of pregnancy. The sum of the triceps and subscapular skinfolds, an index of body fat, was similar in the two groups during pregnancy (Table 1) and in the nonpregnant state (data not shown).

Mean blood pressures were lower in the Andean than European women when nonpregnant, as well as at week 30 or 36 of pregnancy (Table 1). Resting heart rate was similar when nonpregnant and rose with pregnancy in each group. At 30 and 36 wk of pregnancy, the European women had higher heart rates than the Andeans (Table 1). Approximately one-third of the women had moderate (1+) proteinuria during pregnancy, with only two cases demonstrating significant (2+) proteinuria, but no women in either group had moderate or greater proteinuria when nonpregnant.

**Ventilatory characteristics.** When nonpregnant, the Andeans hypoventilated relative to the European women, as demonstrated by lower  $\dot{V}_E$  and higher  $\text{PET}_{\text{CO}_2}$  values, but  $\text{PET}_{\text{CO}_2}$  and  $\text{SaO}_2$  values were similar (Table 2). The Andeans had smaller tidal volumes than the Europeans (Table 2) due partly to

Table 1. Maternal characteristics

Variable	Andeans	Europeans	P Value
Ancestry, %			
European	3.3 $\pm$ 1.1 (41)	72.8 $\pm$ 7.1 (19)	<0.0001
American Indian	95.6 $\pm$ 1.1 (41)	22.7 $\pm$ 6.7 (19)	<0.0001
West African	1.1 $\pm$ 0.4 (41)	4.6 $\pm$ 1.1 (19)	<0.0001
Age, yrs	27.2 $\pm$ 1.0 (42)	32.4 $\pm$ 0.8 (25)	<0.0001
Residence >3000 m, yr	21.3 $\pm$ 1.4 (42)	4.4 $\pm$ 0.9 (24)	<0.0001
Education, % $\geq$ secondary school	79 [64, 88] (42)	100 [86, 100] (26)	NS
Income, US\$/month	142 $\pm$ 24 (42)	2,338 $\pm$ 445 (18)	<0.0001
Gravidity, no. pregnancies	3.4 $\pm$ 0.3 (42)	2.3 $\pm$ 0.2 (25)	<0.05
Parity, no. live births	3.0 $\pm$ 0.3 (42)	2.1 $\pm$ 0.2 (25)	<0.05
Height, cm	150.0 $\pm$ 0.6 (42)	162 $\pm$ 1.3 (26)	<0.0001
Nonpregnant weight, kg	58.8 $\pm$ 1.5 (42)	63.5 $\pm$ 2.5 (17)	NS
Nonpregnant BMI, kg/cm <sup>2</sup>	26.1 $\pm$ 0.6 (42)	24.7 $\pm$ 1.2 (16)	NS
$\Delta$ weight week 20, >36, kg	6.2 $\pm$ 0.5 (42)	6.0 $\pm$ 1.9 (14)	NS
Skinfolds <sub>triceps+subscapular</sub> , mm	43.6 $\pm$ 2.6 (42)	37.8 $\pm$ 3.4 (18)	NS
Blood pressure, Nonpregnant, mmHg	72.5 $\pm$ 1.0 (42)	78.9 $\pm$ 2.6 (18)	<0.01
Week 20	76.1 $\pm$ 1.5 (38)	79.0 $\pm$ 2.2 (19)	NS
Week 30	72.5 $\pm$ 1.4 (41)	78.0 $\pm$ 1.9 (23)	<0.05
Week 36	75.1 $\pm$ 1.5 (41)	81.6 $\pm$ 1.8 (20)	<0.05
Heart rate, Nonpregnant, beats/min	75 $\pm$ 1 (41)	78 $\pm$ 3 (16)	NS
Week 20	79 $\pm$ 2 (32)	79 $\pm$ 5 (14)	NS
Week 30	82 $\pm$ 1 (40)	91 $\pm$ 2 (20)	<0.01
Week 36	81 $\pm$ 2 (35)	93 $\pm$ 2 (18)	<0.01
Proteinuria ( $\geq 1+$ ), %, Nonpregnant	0 [0, 0]	0 [0, 0]	NS
Week 20	33 [20, 50] (36)	28 [13, 51] (18)	NS
Week 30	24 [14, 39] (41)	26 [13, 47] (23)	NS
Week 36	39 [26, 54] (41)	32 [15, 54] (19)	NS

Data are expressed as means  $\pm$  SE or 95% confidence intervals in brackets. Sample sizes for each variable are indicated in parentheses.

Table 2. Resting maternal ventilation, heart rate, blood pressure, and ventilatory responsiveness to hypoxia and hypercapnia in Andean and European women when nonpregnant (4 mo postpartum) and at weeks 20, 30, and 36 of pregnancy

Variable	Group	Nonpregnant	Week 20	Week 30	Week 36	P Time
Ventilation, l·btps <sup>-1</sup> ·min <sup>-1</sup>	Andean	8.5±0.4 (36)	8.8±0.4 (29)	9.7±0.4 (35)	8.9±0.4 (35)	NS††
	European	10.6±0.8 (15)	9.7±0.8 (15)	10.1±0.7 (19)	12.1±0.7 (17)	NS
	P-ancestry	<0.05	NS	NS	<0.01	
Tidal volume, l·btps <sup>-1</sup> ·min <sup>-1</sup>	Andean	0.48±0.03 (40)‡	0.54±0.03 (29)	0.64±0.03 (36)*	0.58±0.03 (35)	<0.01
	European	0.69±0.05 (15)	0.76±0.05 (15)	0.79±0.04 (19)	0.77±0.05 (17)	NS
	P-ancestry	<0.01	<0.01	<0.05	<0.01	
Respiratory frequency, no. breaths/min	Andean	18.5±0.6 (40)	18.5±0.6 (32)	17.8±0.6 (39)	17.9±0.6 (38)	NS
	European	17.4±0.9 (16)	14.9±0.9 (15)	14.7±0.8 (20)	17.4±0.8 (18)	<0.05
	P-ancestry	NS	<0.01	<0.01	NS	
PET <sub>O<sub>2</sub></sub> room air, mmHg	Andean	68.6±1.0 (37)†‡§	77.2±1.2 (30)*	76.7±1.0 (39)*	75.9±1.0 (37)*	<0.01
	European	66.4±1.1 (16)†§	74.5±1.2 (15)*	69.6±1.0 (20)	73.0±1.1 (18)*	<0.01
	P-ancestry	NS	NS	<0.05	NS†	
PET <sub>O<sub>2</sub></sub> room air, mmHg	Andean	35.9±0.5 (41)†‡§	31.1±0.6 (30)*	30.7±0.5 (39)*	31.1±0.5 (38)*	<0.01
	European	33.5±0.7 (16)†‡§	29.1±0.7 (15)*	29.7±0.6 (20)*	28.9±0.7 (18)*	<0.01
	P-ancestry	<0.01	<0.05	NS	P < 0.05	
Sa <sub>O<sub>2</sub></sub> rm air, (%)	Andean	91.7±0.3 (41)†‡§	94.6±0.3 (33)*	94.3±0.3 (40)*	94.0±0.3 (38)*	<0.01
	European	91.0±0.6 (16)†‡§	94.3±0.6 (17)*	93.9±0.5 (20)*	93.8±0.5 (18)*	<0.01
	P-ancestry	NS	NS	NS	NS	
PETCO <sub>2</sub> , room air - HI <sub>O<sub>2</sub></sub> , mmHg	Andean	0.4±0.4 (39)	-0.2±0.4 (32)	0.04±0.4 (39)	-0.4±0.4 (38)	NS
	European	-1.8±0.5 (13)	-0.8±0.5 (15)	-1.0±0.4 (20)	-0.6±0.4 (19)	NS
	P-ancestry	<0.05	NS	NS†	NS	
HVR A value	Andean	46.6±8.0 (34)†‡	142.6±23.6 (27)*		116.1±15.0 (35)*	<0.01
	European	42.7±6.3 (8)†	205.7±54.0 (10)*		112.4±3.0 (8)	<0.05
	P-ancestry	NS	NS		NS††	
Δ $\dot{V}_E/\Delta S_{aO_2}$	Andean	-0.22±0.03 (36)	-0.54±0.08 (28)		-0.51±0.06 (37)	<0.01
	European	-0.30±0.17 (8)	-1.00±0.29 (10)		-0.72±0.25 (8)	NS
	P-ancestry	NS	NS		NS	
HCVR, S value	Andean	1.4±0.1 (37)‡	1.8±0.1 (31)		2.1±0.1 (36)*	<0.01
	European	1.0±0.2 (8)	1.7±0.3 (10)		1.8±0.3 (9)	NS
	P-ancestry	NS	NS		NS	

Data are expressed as means ± SE. Sample sizes for each variable are indicated in parentheses. HVR and HCVR tests were not performed at week 30. \*Significantly different from nonpregnant value. †Significantly different from week 20 value. §Significantly different from week 30 value. ‡Significantly different from week 36 value. ††0.05 < P < 0.10.

differences in body size, but the difference remained significant when tidal volume was normalized by height ( $0.322 \pm 0.015$  and  $0.430 \pm 0.028$  ml/mm ht, respectively;  $P < 0.001$ ). Variation in nonpregnant PETCO<sub>2</sub> tensions related to resting Sa<sub>O<sub>2</sub></sub> levels in Andean ( $R^2 = 0.33$ ,  $P < 0.01$ ) but not European women [ $R^2 = 0.05$ ,  $P =$  not significant (NS)]. Nonpregnant HVR and HCVR values were similar in the Andean and European subjects. Breathing sea-level normoxic gas mixtures reduced alveolar ventilation (rise in PETCO<sub>2</sub>) in the European women only, indicating that ambient hypoxia exerted a depressant effect on resting ventilation in the Andeans (Table 2).

Pregnancy increased  $\dot{V}_E$ , lowering PETCO<sub>2</sub> 4–5 mmHg and raising Sa<sub>O<sub>2</sub></sub> in both groups (Fig. 1). The Andeans had lower  $\dot{V}_E$  and higher PETCO<sub>2</sub> than the European women at several time points, but Sa<sub>O<sub>2</sub></sub> values were similar. Andean respiratory frequencies were higher than the Europeans, and tidal volumes were lower, both absolutely and when adjusted by maternal height ( $P < 0.05$ ). Genetic background correlated with respiratory pattern such that women with greater amounts of American Indian ancestry had higher respiratory frequencies and lower tidal volumes relative to maternal height (Fig. 2, bottom).

While Sa<sub>O<sub>2</sub></sub> values were similar throughout pregnancy, the Andeans attained higher PETCO<sub>2</sub> tensions than the Europeans at week 30 and tended to do so also at week 36. Among the Andeans, those with the highest alveolar ventilation (lowest PETO<sub>2</sub>) had the highest Sa<sub>O<sub>2</sub></sub> at week 20, but no such relationships were present among the Europeans (Fig. 3). Significant

correlations were also present among the Andeans at weeks 30 and 36 ( $R^2 = 0.14$  and  $0.15$  respectively, both  $P < 0.05$ ).

Pregnancy raised HVR two- to threefold to achieve similar values in both groups (Table 2). This rise was not due to higher PETCO<sub>2</sub> levels during the test since isocapnia was maintained at a lower, not higher, PETCO<sub>2</sub> in the pregnant compared with the nonpregnant state (data not shown). When both groups were combined, HVR was related to the level of alveolar  $\dot{V}_E$  as measured by PETCO<sub>2</sub> (Fig. 4). Pregnancy did not change the ventilatory response to sea-level normoxia, although most  $\Delta$ PETCO<sub>2</sub> values were negative, as would be expected given the higher HVRs. Pregnancy increased HCVR in the Andean but not European women (Table 2).

**Hematological characteristics.** Hemoglobin, hematocrit, red blood cell mass, plasma, and total blood volume were similar in the nonpregnant Andean and European women (Table 3). Arterial O<sub>2</sub> content (Ca<sub>O<sub>2</sub></sub>) was also similar in the two groups whether or not all hemoglobin or just that available for oxygen binding (i.e., the sum of oxy- and deoxyhemoglobin) was used in the calculation (data not shown).

Pregnancy increased red blood cell mass, plasma, and total blood volume, although red blood cell mass did not change relative to body weight (Table 3). Thus, hemoglobin concentration and hematocrit fell in both groups. Hemoglobin, hematocrit, red blood cell mass, plasma, and total blood volume were similar during pregnancy in the Andean and European women when calculated on a per kilogram body weight basis. How-

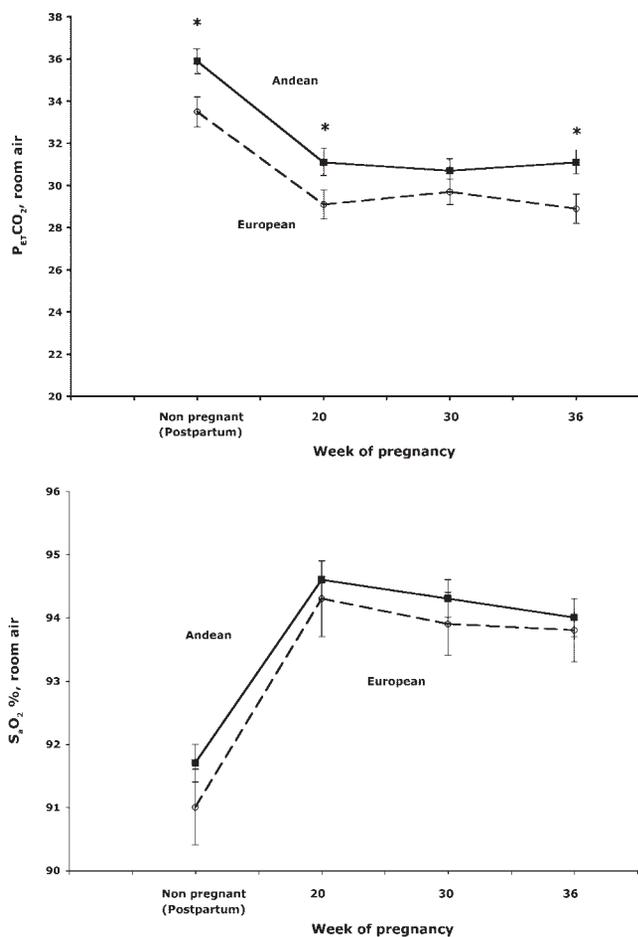


Fig. 1. *Top*: pregnancy decreases end-tidal  $PCO_2$  ( $P_{e}CO_2$ ), an index of alveolar  $\dot{V}_E$ , in Andean and European residents of 3,600 m (2-way ANOVA,  $P < 0.05$  in both groups).  $P_{e}CO_2$  is higher in the Andean than European women when nonpregnant ( $P < 0.05$ ) and at weeks 20 and 36, indicating relative hypoventilation in the Andeans. *Bottom*: arterial  $O_2$  saturation ( $S_aO_2$ ) is the same in both groups when nonpregnant and rises to attain similar values in the two groups during pregnancy. There is no interaction between the effects of ancestry and pregnancy on  $P_{e}CO_2$  or  $S_aO_2$ . Values shown are means  $\pm$  SE. \* $P < 0.05$  for group comparisons at the time points specified.

ever, Andeans had lower absolute total blood and plasma volumes at week 20 because of their smaller body size. The percent increases in total blood and plasma volume at week 36 of pregnancy relative to nonpregnant values were also similar in the Andean and European groups ( $\Delta$ total blood and plasma volume =  $31.5 \pm 3.2\%$  and  $40.3 \pm 3.5\%$  vs.  $37.9 \pm 12.9\%$  and  $45 \pm 12.2\%$ , respectively,  $P = NS$ ).

$CaO_2$  levels were similar in the Andean and European women throughout pregnancy (Table 3). In both groups, the pregnancy-associated rise in  $S_aO_2$  offset the hemoglobin fall so as to preserve  $CaO_2$  close to nonpregnant levels whether or not values were adjusted for the amount of hemoglobin available for oxygen binding (data not shown).

*Relationship of ventilatory characteristics to infant birth weight.* Comparing all babies, birth weights, ponderal indices, gestational ages, frequency of preterm delivery, sex distribution, and chest circumference were similar in the Andean and European groups (Table 4). The European babies' head circumference, length, and 1- and 5-min Apgar scores were marginally greater than the Andean values. Because multiple

factors influence birth weight, and several known determinants differed between the two groups, we used multiple linear regression to identify the variables related to birth weight in our study subjects. Among those characteristics listed in Tables 1 and 4, only maternal height, parity, and infant gestational age were related to birth weight (partial correlation coefficients = 0.47, 0.26, and 0.41,  $P = 0.000$ , 0.002, and 0.06, respectively). Considered together with ancestry and setting, gestational age, maternal height, and parity to the mean values for the two groups combined, the resultant multiple regression model was  $y = -209.4x_1 + 51.3x_2 + 103.9x_3 + 32.9x_4 - 5,992.0$  where

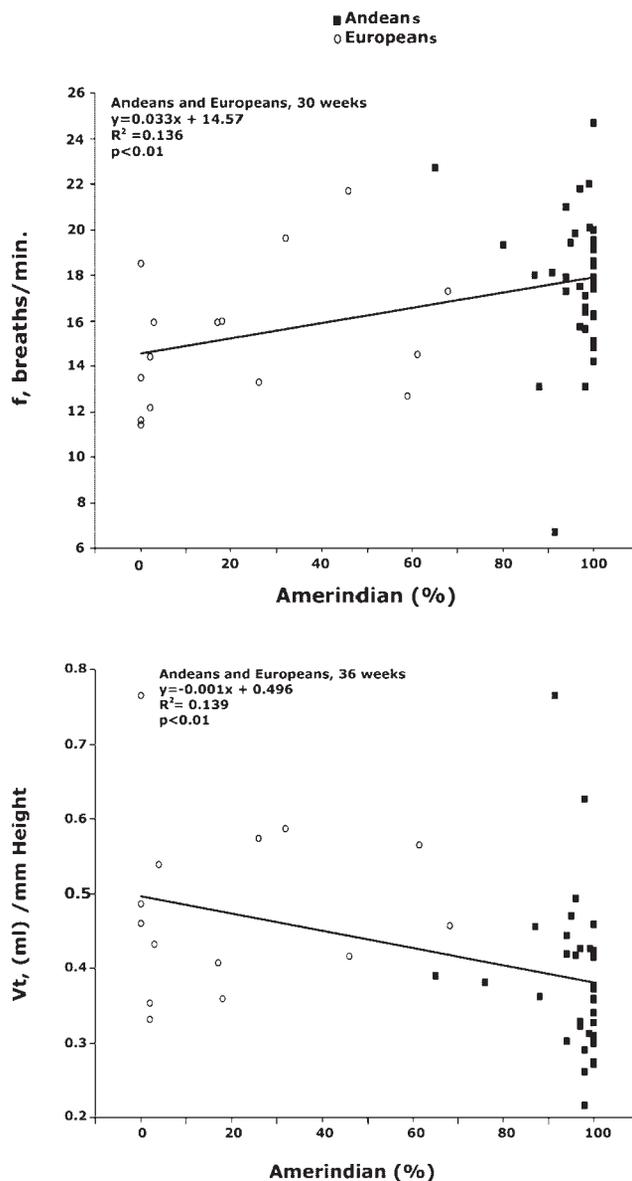


Fig. 2. Percent American Indian genetic ancestry correlates with respiratory pattern among all women such that those with greater American Indian ancestry have higher respiratory frequencies and lower tidal volumes relative to their height. *Top*: data for week 36 of pregnancy; similar correlations were present at the other time points (nonpregnant  $r = 0.34$ ,  $P < 0.01$ ; week 20,  $r = 0.26$ ,  $P < 0.06$ ; week 30,  $r = 0.26$ ,  $P < 0.05$ ). *Bottom*: respiratory frequency data at week 30. Similar associations were present at week 20 but not the other time points (nonpregnant  $r = 0.05$ ,  $P = NS$ ; week 20,  $r = 0.29$ ,  $P < 0.05$ ; week 36,  $r = 0.01$ ,  $P = NS$ ).

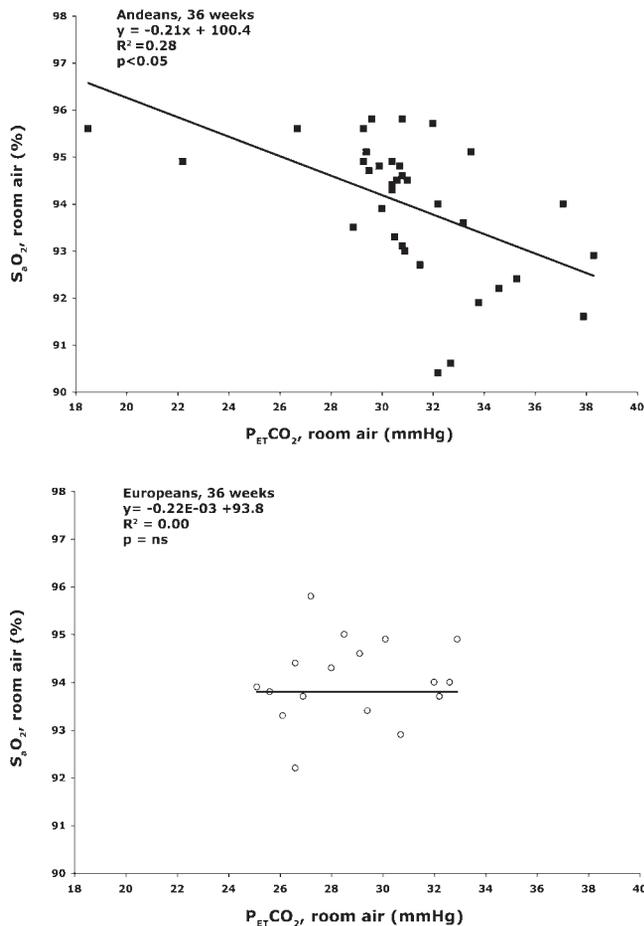


Fig. 3. *Top*: Andean women with higher alveolar  $\dot{V}_E$  (lower  $P_{ETCO_2}$ ) have higher arterial oxygen saturation ( $S_{aO_2}$ ) at 36 wk of pregnancy. Similar correlations were present at other pregnancy time points ( $R^2$  values at weeks 20 and 30 = 0.14 and 0.15, respectively, both  $P < 0.05$ ). *Bottom*: Lower  $P_{ETCO_2}$  is not associated with higher levels of  $S_{aO_2}$  in the European women at any time; shown are week 36 values.

$y$  was birth weight in grams,  $x_1$  represented European ancestry,  $x_2$  parity,  $x_3$  gestational age (wk), and  $x_4$  maternal height (cm). In other words, after adjusting birth weights for variation in gestational age, maternal height, and parity, the Andean babies weighed 209 g more than the European newborns (Table 4). Ponderal index tended to be greater as well in the Andean vs. European babies as well (one-tailed  $P = 0.06$ ).

The Andean women with higher  $\dot{V}_E$  at week 20 gave birth to heavier birth-weight babies (Fig. 5). This was also true for the two groups combined ( $y = 60.8x + 2,691.6$ ,  $R^2 = 0.15$ ,  $P < 0.05$ ) but was entirely due to the relationship present among the Andeans (European  $R^2 = 0.003$ ,  $P = NS$ ). In the Andeans, women with higher  $\dot{V}_E$  at weeks 20, 30, and 36 also gave birth to babies with greater ponderal indices ( $R^2$  values = 0.27, 0.30, and 0.25 respectively, all  $P < 0.05$ ) but again no such relationships existed among the Europeans (all  $P = NS$ ). After adjusting birth weight for the influences of maternal height, gestational age, and parity, variation in maternal  $\dot{V}_E$  at week 20 could account for 20% of the variation in birth weight in the Andeans alone ( $P < 0.05$ ). Similarly, Andean mothers with lower  $P_{ETCO_2}$  at week 36 also gave birth to babies with greater ponderal indices ( $R^2$  value = 0.25,  $P < 0.01$ ).

Neither infant birth weight nor ponderal index was associated with maternal  $CaO_2$  at any time during pregnancy, whether or not the influences of gestational age, parity, or maternal height were taken into account (all  $P = NS$ ). Thus despite the fact that higher  $\dot{V}_E$  raised  $S_{aO_2}$  and related positively to birth weight, there was no association between  $CaO_2$  and birth weight because  $CaO_2$  was also affected by the plasma volume-induced fall in hemoglobin concentration.

## DISCUSSION

Our primary findings were that Andean and European high-altitude residents raised their  $\dot{V}_E$  and  $S_{aO_2}$  equally during pregnancy which, in turn, offset the plasma volume-induced fall in hemoglobin so as to maintain  $CaO_2$  close to nonpregnant levels in both groups. Contrary to our hypothesis, the Andeans did not have higher levels of  $CaO_2$  than the Europeans during pregnancy. Nonetheless, after taking the influences of gestational age, parity, and maternal height and into account, Andean babies weighed 209 g more and tended to have greater ponderal indices as well, indicating that the Andeans' relative protection from hypoxia-associated reductions in birth weight was due to some factor(s) other than higher  $CaO_2$ .

Our data were subject to practical and ethical constraints. Given the limited access to health care in the high-altitude regions of Bolivia, it was impractical to identify women prior to pregnancy. We therefore used data obtained 4 mo postpartum as an index of the nonpregnant state. We reasoned that any alterations in hematological variables due to blood loss, fluid shifts, or other factor at delivery would no longer be present, as supported by finding no differences in hematological or ventilatory variables in never-pregnant vs. 4 mo postpartum women in a prior study in a similar setting (20). Another practical constraint was the number of European women available for study. Despite extending the sampling frame to nearly 4 years, the sample size for the Europeans was only about half that of the Andeans. However, the fact that not even trends were present toward lower  $CaO_2$  values in the European women

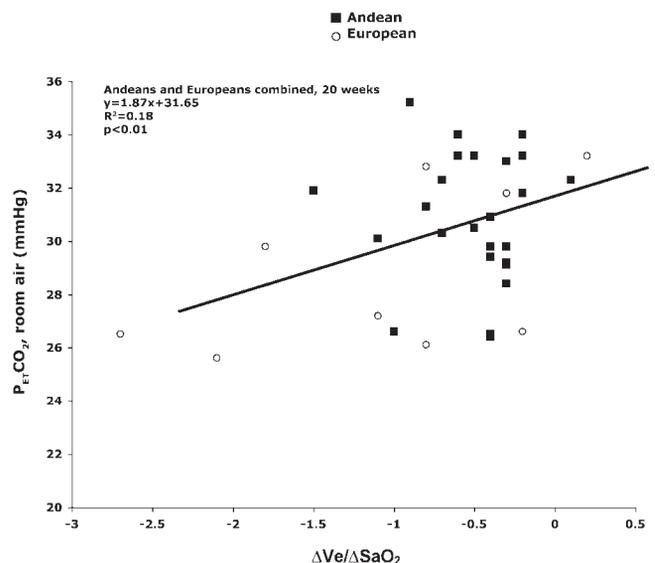


Fig. 4. For the Andean and European women combined, those with greater hypoxic ventilatory response (more negative  $\Delta\dot{V}_E/\Delta S_{aO_2}$  values) have higher levels of alveolar  $\dot{V}_E$  (lower  $P_{ETCO_2}$ ) at week 20 of pregnancy.

Table 3. Maternal hematological characteristics in Andean and European women when nonpregnant (4 mo postpartum) and at weeks 20 and 36 of pregnancy

Variable	Group	Nonpregnant	Week 20	Week 36	P-Time
Hemoglobin, g/dl	Andean	15.2±0.9 (39)†‡	13.3±0.2 (38)*	13.3±0.2 (40)*	<0.05
	European	14.5±0.3 (15) c	13.4±0.2 (17)*	13.5±0.2 (17) *	<0.01
	P-ancestry	NS	NS	NS	
Hematocrit, %	Andean	44.4±0.5 (40)†‡	40.2±0.4 (38)*	40.6±0.5 (40)*	<0.0001
	European	44.6±0.7 (15)†‡	40.1±1.1 (17)*	41.1±0.9 (16)*	<0.01
	P-ancestry	NS	NS	NS	
Red blood cell mass, ml	Andean	4396±134 (41)†‡	4991±141 (37)*	5597±138 (39)*	<0.01
	European	4637±276 (13)†‡	5868±242 (17)*	6125±266 (14)*	<0.01
	P-ancestry	NS	P < 0.01	NS	
Red blood cell mass, ml/kg	Andean	32.8±0.8 (41)	32.9±0.7 (37)	34.2±0.8 (39)	NS
	European	31.3±1.4 (13)	34.0±1.3 (17)	34.8±1.8 (14)	NS
	P-ancestry	NS	NS	NS	
Plasma volume, ml	Andean	2482±79 (41)†‡	3008±83 (40)*	3354±81 (39)*	<0.01
	European	2631±182 (13) †‡	3580±159 (17)*	3660±175 (14)*	<0.01
	P-ancestry	NS	P < 0.01	NS	
Plasma volume, ml/kg	Andean	42.8±1.2 (41)†‡	50.0±1.0 (37)*	51.4±1.1 (39)*	<0.0001
	European	41.1±2.1 (13)†‡	53.5±2.5 (17)*	51.4±2.5 (14)*	<0.01
	P-ancestry	NS	NS	NS	
Total blood volume, ml	Andean	4396±134 (41)†‡	4991±141 (37)*	5597±138 (39)*	<0.01
	European	4637±276 (13)†‡	5868±242 (17)*	6125±266 (14)*	<0.01
	P-ancestry	NS	P < 0.01	NS	
Total blood volume, ml/kg	Andean	75.8±2.3 (41)†‡	83.0±1.6 (37)*	85.5±1.7 (39)*	<0.01
	European	72.6±3.5 (13)†‡	87.5±3.2 (17)*	86.0±3.9 (14)*	<0.05
	P-ancestry	NS	NS	NS	
CaO <sub>2</sub> , ml/dl	Andean	17.9±0.2 (39) †‡	17.1±0.3 (33)*	17.1±0.2 (37)*	<0.05
	European	18.0±0.4 (13)	17.3±0.4 (14)	17.4±0.4 (15)	NS
	P-ancestry	NS	NS	NS	

Data are expressed as means ± SE. Sample sizes are indicated in parentheses. Results of multiple comparisons using Tukey's post hoc test. \*Significantly different from nonpregnant (postpartum) value. †Significantly different from week 20 value. ‡Significantly different from week 36 value.

made it unlikely that such differences would have appeared in larger-sized samples. We relied on noninvasively measured  $\dot{V}_E$ ,  $SaO_2$ ,  $PETCO_2$ , and  $PETO_2$  for assessing arterial oxygenation since we considered that arterial puncture for direct measurement was not ethically defensible in these healthy subjects.  $PETCO_2$  is a reliable index of  $PACO_2$  in healthy persons and provides an accurate measure of alveolar ventilation per unit  $CO_2$  production that is independent of body size. For assessing  $CaO_2$ , we used the measured  $SaO_2$ , hemoglobin concentration,

Table 4. Characteristics of infants born to study subjects at high altitude

Variable	Andeans	Europeans	P Value
Birth weight, g	3150±60 (36)	3265±88 (20)	NS
Length, cm	48.8±0.4 (34)	50.4±0.5 (17)	<0.05
Ponderal index, kg/m <sup>3</sup>	27.2±0.6 (34)	26.1±0.9 (17)	NS
Gestational age, wk	39.1±0.3 (35)	39.4±0.3 (20)	NS
Preterm, %	8.8 [2, 22] (35)	0 [0, 0] (20)	NS
Sex, %male	50 [34, 66] (36)	70.6 [47, 88] (17)	NS
Chest circumference, cm	33.9±0.3 (10)	34.3±0.3 (14)	NS
Head circumference, cm	34.1±0.2 (31)	35.1±0.3 (16)	<0.01
Apgar score, 1 min	8 [5, 9] (29)	9 [6, 9] (17)	<0.05
Apgar score, 5 min	9 [7, 10] (29)	9 [9, 10] (17)	<0.05
Birth weight, adjusted, g	3271±62 (34)	3062±90 (19)	<0.05‡
Ponderal index, adjusted, kg/m <sup>3</sup>	27.4±0.7 (32)	25.1±1.1 (16)	NS*†

Data are expressed as means ± SE, 95% confidence intervals within "[ ]," mode with range in "{ }" and sample sizes in "( )". \*0.10 > P > 0.05. †One-tailed P value. Adjusted birth weight and ponderal index values are those calculated using multiple linear regression after controlling for variation in gestational age, maternal height, and parity, as described in the MATERIALS AND METHODS.

and the well-validated constant 1.36 for the milliliters of oxygen that can be bound to each gram of hemoglobin. Hemoglobin was measured using both the cyanmethemoglobin technique, as well as by an OSM3 oximeter. To avoid overestimating  $CaO_2$ , we also calculated it using the sum of oxy- plus deoxyhemoglobin, as these are the forms of hemoglobin available for oxygen binding. Because at no time did the Andeans

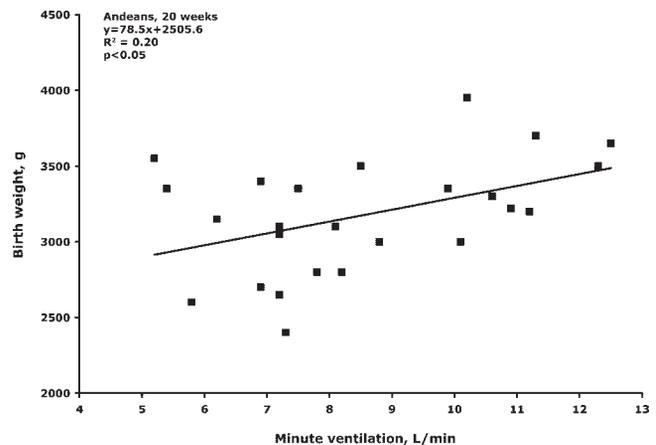


Fig. 5. Andean women with higher levels of  $\dot{V}_E$  at week 20 gave birth to heavier birth weight babies ( $y = 78.5x + 2,505.6$ ,  $R^2 = 0.20$ ,  $P < 0.05$ ). This was also true among all women ( $y = 60.8x + 2,691.6$ ,  $R^2 = 0.15$ ,  $P < 0.05$ ), but results obtained in the Andeans showed a greater correlation; no such correlation was present in the European women alone [ $R^2 = 0.03$ ,  $P =$  not significant (NS)]. Similar relationships were present at weeks 30 and 36 for the Andeans ( $R^2 = 0.13$  and  $0.13$ , both  $P < 0.05$ ) but not among the Europeans ( $R^2 = 0.05$  and  $0.00$ , both  $P =$  NS).

have higher  $\text{CaO}_2$  levels than the Europeans regardless of how the calculations were performed, we concluded that our study results, indicating similar levels of  $\text{SaO}_2$  and  $\text{CaO}_2$  in the Andean and European groups were valid.

A special feature of this study was our ability to confirm self-identified population ancestry using 81 AIMs that had been shown previously to discriminate accurately between persons of American Indian, European, and African parentage (1, 2, 27). The questionnaire data agreed well with that obtained from the panel of markers as demonstrated by the marked differences in %American Indian and European-specific gene markers. The extent of American Indian genetic ancestry was associated with a respiratory pattern characterized by high respiratory frequency and low tidal volume, both absolutely and relative to maternal height, but not with any of the other ventilatory variables ( $\dot{V}_E$ ,  $\text{SaO}_2$ , HVR, or HCVR). The significance of this association is unclear; such a respiratory pattern is generally considered inefficient, but, nonetheless, it has been observed repeatedly in long-resident, high-altitude populations, Tibetans and Andeans alike (5, 10). Perhaps such a pattern contributed to minimizing intersubject variability in  $\dot{V}_E$ ; of note, two of these variables— $\dot{V}_E$  and tidal volume—had reduced variance in the Andean than European group. Another possibility is that if the Andeans were breathing at a higher FRC, such a respiratory pattern could serve to maintain the lung in a relatively more inflated state. Further study is warranted to identify the functional consequences of a high-frequency, low-tidal volume respiratory pattern.

Our results agreed with prior studies showing that pregnancy has marked effects on  $\dot{V}_E$  and ventilatory control (14, 22). The rise in  $\dot{V}_E$  was greater than that which can be accounted for by increased  $\text{CO}_2$  production, as demonstrated by the fall in  $\text{PETCO}_2$ . We showed previously that about two-thirds of the  $\dot{V}_E$  rise can be attributed to elevated progesterone and estrogen hormones which act, in turn, to raise carotid body chemosensory sensitivity to hypoxia (20, 22), central translation, and thus respiratory drive (11, 12). The present study was consistent with these observations insofar as the women with the highest HVR had the highest alveolar  $\dot{V}_E$  (lowest  $\text{PETCO}_2$ ). Pregnancy also increased HCVR in the Andean but not the European women, likely because of the small number of Europeans studied and the more modest effects of pregnancy on hypercapnic than hypoxic drives. In short, even though lifelong high-altitude Andean residents hypoventilate relative to newcomers, pregnancy raises the hypoxic chemosensory response and thus  $\dot{V}_E$  to levels that are similar to those seen in acclimatized newcomers (20, 29). Our observation that mild proteinuria was common in both ancestry groups during pregnancy was consistent with our prior observations in Colorado (21) and other reports from high altitudes (13) but was not due to an increased incidence of preeclampsia since it occurred even among women whose blood pressures remained normal. That it was confined to the pregnant condition suggests that pregnancy-induced increases in renal blood flow likely exacerbated the known effects of chronic hypoxia on increasing capillary permeability and glomerular filtration (13).

The rise in  $\dot{V}_E$  seen in the Andean and European groups was important in three respects. First, it raised  $\text{PaO}_2$  and  $\text{SaO}_2$  to levels similar to what we have reported previously from high altitudes (20, 23, 25) but unlike those seen at sea level. This is because while pregnancy increases  $\dot{V}_E$  and  $\text{PaO}_2$  at sea level, it does not elevate  $\text{SaO}_2$  because values are already near maximal.

Second, the rise in  $\text{SaO}_2$  at high altitude compensates for the plasma volume-induced hemoglobin fall so as to preserve  $\text{CaO}_2$  close to nonpregnant levels, whereas  $\text{CaO}_2$  generally falls during pregnancy at low altitude. It was surprising that higher  $\dot{V}_E$  was only associated with greater  $\text{SaO}_2$  among the Andeans. This may have been due to the European group's smaller sample size, although their much smaller  $R^2$  values suggest that something else was involved. One factor may have been the larger functional residual capacities (FRC) reported previously in Andean women (19). A greater FRC increases the surface area for gas exchange and thus would be expected to lower the alveolar-arterial diffusion gradient and raise  $\text{SaO}_2$  for a given  $\text{PETO}_2$ . However, while somewhat higher in the Andeans, differences in  $\text{SaO}_2$  were not statistically significant between groups. It therefore appeared that the stronger relationship between  $\dot{V}_E$  and  $\text{SaO}_2$  within the Andean group was due to the greater consistency among subjects in the pregnancy-related changes rather than greater magnitude.

The third reason why we considered the  $\dot{V}_E$  increase to be important was that it related to infant birth weight. After taking into account the influences of gestational age, maternal height, and parity, 20% of the variation in birth weight or ponderal index among the Andeans could be attributed to maternal  $\dot{V}_E$  (Fig. 5). That birth-weight differences were only present after such statistical adjustment reflected the fact that Andean women were shorter, and somewhat more Andean babies were born prematurely. Removing such influences permitted us to evaluate the contribution of  $\dot{V}_E$  and other factors related to arterial oxygenation independent of other birth weight determinants. The relationship between birth weight and maternal  $\dot{V}_E$  was apparent by *week 20*, earlier than the *week 30–32* time points seen previously (17, 28). But again, no such relationship was present among Europeans (Fig. 5). While the Europeans' smaller sample size—reduced further by the fact that about one-fourth (23%) descended to lower altitudes to give birth—may have contributed, there was little evidence for such an association ( $R^2 = 0.03, 0.05, 0.0003$  at *weeks 20, 30, and 36*, all  $P = \text{NS}$ ). We concluded that while the European women's rise in  $\dot{V}_E$  may have helped defend arterial oxygenation and thus fetal growth, such relationships were overridden by their much lower uterine artery blood flows and hence uteroplacental  $\text{O}_2$  delivery (31).

The 86 ml/kg total blood volume and 51 ml/kg plasma volume values seen in the Andean and European women at 3,600 m are similar to previous reports [79 and 50 ml/kg at sea level (18), 83 and 54 ml/kg at 1,600 m (33)] but considerably greater than those seen previously at 3,100 m in Colorado [70 and 43 ml/kg (33)]. The reason for this difference is not clear. The same methods were used; even though a correction factor for trapped plasma was not employed in the previous report, differences between the studies remained when this correction factor was omitted. The duration and altitude of residence were similar, since the European women in the present study lived in the lower (~3,200 m) section of La Paz. Our values for red blood cell mass (31–35 ml/kg) were greater than those seen at sea level (28–29 ml/kg) or at moderate altitude (30 ml/kg), consistent with the Bolivian's higher hemoglobin levels. But the red blood cell mass values seen previously in the Colorado high-altitude study (27 ml/kg) seem surprisingly low, especially in light of the fact that the hemoglobin levels were only slightly (~1 g) higher. In any event, the higher red blood cell

mass did not lower plasma volume in the Andean subjects, as plasma volume was similar or greater than at low altitude. Likewise, the European women did not have lower plasma volume levels, which might have been expected given that the European women appeared to have increased sympathetic neural activity, as suggested by their higher heart rates and blood pressures. In summary, while the differences between the present and the previous Colorado high-altitude study remain unclear, the pregnancy-associated changes in blood volume were the same in the European and Andean women and were fully normal by sea level standards.

Haas was the first to report population-associated differences in the magnitude of birth weight reductions at high altitude, finding that Andean babies born in La Paz, Bolivia (3,600 m), weighed 127 g more than European babies, or 143 g more when the influences of maternal body size, parity, and skin-folds on birth weight were taken into account (9). Since Andeans are disproportionately represented in lower socioeconomic groups in Bolivia, Andean ancestry was likely responsible for the lower reduction in birth weight seen at high altitude in lower vs. upper socioeconomic status Bolivians (6). We observed even greater birth-weight differences between Tibetan vs. Han ("Chinese") residents of Lhasa (3,600 m) where Tibetan babies weighed 635 g more than Han newborns ( $3,280 \pm 78$  vs.  $2,645 \pm 96$  g,  $P < 0.01$ ) or 694 g more when birth weights were adjusted for maternal age, parity, height, and near-term body weight (25). This was not the result of Tibetans having heavier birth weights at any altitude since birth weights of Tibetans born at lower altitude (1,300 m) were the same as those at high altitude (32). Confirming this, we also found that living across a 2,700 to 4,800 m (8,900 to 15,800 ft) altitude gradient in northern and eastern Tibet, Tibetans had one-third the birth-weight decline seen in Han (24) (26).

Given the importance of birth weight for infant mortality and morbidity risk, we hypothesized that genetic adaptations may have occurred, which enabled women with multigenerational high-altitude ancestry to transport more oxygen to the uteroplacental circulation, and thereby to protect their infants from altitude-associated reductions in fetal growth. Since multiple factors influence birth weight, we first examined the possibility that the heavier birth weights were due to differences in maternal body size, nutrition, or use of health care. The present data indicated that this was unlikely since Andeans were disadvantaged, not advantaged, with respect to these characteristics. For example, the Andean women in the present study were shorter, poorer, began their prenatal health care later, and likely had less access to nutritional and other resources than did the Europeans. Tibetans too are socioeconomically disadvantaged compared with Han living in Tibet today, but similar in body size (25). We also considered the possibility that the mother's altitude of birth and development was important. As shown here, the European and Andean women differed not only in population ancestry but also in the altitudes at which they were born and raised. Previous studies based in Colorado and Bolivia do not indicate that the altitude at which a woman is born and raised influences her physiological adjustment to pregnancy or her infant's birth weight (9, 23, 30). Further investigation of this question is warranted, however, since the greater health care resources present in Colorado may have obscured influences of the duration of the mother's high-altitude exposure on her infant's birth weight. In addition, there

is some uncertainty about the extent to which population ancestry differed in the Andean and European women studied previously in Bolivia, since genetic markers were not available for confirming ancestry at an individual level at that time (9).

In summary, we undertook the present study to determine whether differences in ventilatory and/or blood volume adjustment to pregnancy permitted Andean women to achieve greater arterial oxygenation than Europeans living at the same, high altitudes. We found that pregnancy raised  $\dot{V}_E$ ,  $Sa_{O_2}$ , and plasma volume in both groups, with the result that  $Ca_{O_2}$  was preserved close to nonpregnant levels but that there were no differences in  $Ca_{O_2}$  at any time between the Andean and European groups. Although there were no differences in birth weight when all cases were considered, once birth weights were adjusted for the known influences of gestational age, parity, and maternal height, Andean babies weighed 209 g more than the Europeans and tended to have greater ponderal indices as well. While higher pregnancy  $\dot{V}_E$  correlated positively with birth weight in the Andeans, differences in arterial oxygenation could not account for their heavier adjusted birth weights. Hence, we concluded that some other factor was responsible for protecting Andeans from the chronic, asymmetric form of fetal growth restriction typical at high altitude. Because higher uteroplacental blood flow is the primary factor responsible for increasing oxygen delivery to the uteroplacental circulation, we considered it important to investigate the possibility that Andeans achieved higher levels of uteroplacental blood flow during pregnancy. As shown by the data in the accompanying paper, this appears to be the case (31).

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