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Newborns physiological differences in low- and high-altitude settings of Ecuador

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Abstract

Newborns show physiological differences in low- and high-altitude settings of Ecuador; those differences are especially relevant because most important cities in Ecuador are located at high altitude, above 2500 m. This study is an epidemiological, observational, and cross-sectional research performed at San Francisco Hospital in Quito (at 2850 m) and General Hospital in Manta (at 6 m) in the Manabí province. We studied 204 full-term newborns, healthy without any prenatal comorbidities, singleton pregnancy, mestizos, and born of healthy parents born. We found significant differences between the values of red blood cells (RBC), leucocytes, hematocrit, and hemoglobin. There was a difference of 27% more in RBC, 3% at hematocrit, and 0.4 g at hemoglobin in the high-altitude cohort. The leucocyte difference is 1270 cells/μl, which means a difference of 6%. At high-altitude settings, the mean pH was lower than normal values and pO_2, pCO_2, and HCO_3. High-altitude newborns showed RBC of > 4,500,000 cells/μl; leukocytes > 19,000; $pO_2 \leq 72$ mm Hg; hemoglobin > 17.50 g/dl; and hematocrit > 54%. Both cohorts showed physiological changes of transition to extrauterine life. We observed higher polycythemia, respiratory acidosis, and hypoxemia among high-altitude newborns. High-altitude setting intensifies the physiological changes in hematological and arterial blood gases parameters.

Introduction

At least 139 million persons live above 2500 m in 24 countries worldwide.[1] Ecuador is one of these countries and is located in the northwest of South America. The most important cities in the highland's regions are located above 2500 m, especially the capitals of the provinces. This location makes our country interesting for altitude-related studies.[2] The Andean altiplano extends nearly 4800 km along almost the whole of South America, averaging 200 km wide and encompassing almost 100 million hectares.[1] Current residents of the Andes, Native Amerindians, and Mestizos are likely to be descendants of north and central Asian populations who migrated in several waves over the Beringian land bridge and most likely came to Ecuador between 7000 and 9000 years ago.[3] The implication is that natural selection over thousands of years results in some populations being genetically more suited to high altitude life.

Indeed, the current Ecuadorian population mostly lives in urban cities in capitals of provinces, being urban the 60% of the total population. In this study, we compare two cities, Quito, the capital located at 2850 m, and Manta, a coastal town at 6 m of altitude. We believe that there are significant physiological differences in individuals of these two locations, especially at birth.

Altitude is defined on the following scale high altitude between 2500 and 3500 m, very high between 3500 and 5500 m, and extremely high above 5500 m. Physiological and pathological changes vary between them, but of course, at higher altitudes, more significant changes. Between 2500 and 3000 m, the physiological changes are not so severe and could even be imperceptible in some individuals.[4] Most of the Ecuadorian highland's population lives at this altitude.

On the other hand, the oxygen concentration at sea level is about 21%, and the barometric pressure averages 760 mm Hg. As altitude increases, the concentration remains the same, but the number of oxygen molecules per breath is reduced. However, the air pressure is 30% lower at the higher altitude because the atmosphere is less dense. At sea level, the atmospheric pressure of about 1.04 kg/cm^2 (14.7 pounds per square inch) causes oxygen to pass through selectively permeable lung membranes into the blood efficiently. The lower air pressure makes it more difficult for oxygen to enter our vascular systems at high altitudes. The result is hypoxia pronounced or oxygen deprivation.

In newborns, the perinatal high altitude chronic adaptation starts in the transition process to extrauterine life.[5] In a high-altitude zone, significant environmental changes could be seen, especially atmospheric pressure, temperature, and barometric pressure of oxygen. Consequently, a state known as hypobaric hypoxia occurs in individuals.[6] Acute exposure to hypobaric hypoxia is known to cause sleep disturbances, hypophagia, oxidative stress, and alterations of

acetylcholine neurotransmitters.[7] Chronic exposure also causes genetic modifications and neuroplasticity changes in response to hypoxia.[8] Body adaptations in the hematological, lymphatic system, and the acid–base balance compensate for oxygen deficiency due to high altitude, which causes a greater diffusion of oxygen in peripheral areas and a higher affinity of hemoglobin for available oxygen.[9]

However, the embryo requires red blood cells (RBC) for maternal oxygen transportation to allow its growth and development. Birth brings dramatic changes in circulation and oxygenation, affecting hematopoiesis.[10] During embryogenesis, hematopoiesis occurs at different sites, including the additional embryonic yolk sac, the fetal liver, and the premature bone marrow.[11] Usually, the transition from intrauterine to extrauterine life is accompanied by more or less pronounced hypoxia that carries the risk of brain damage. Still, it is remarkably well tolerated by the newborn.[12] The underlying mechanisms that increase hypoxia tolerance in newborns are still not fully understood.[13] Fetal hemoglobin is another mechanism used by the fetus to compensate for the relative hypoxemic environment. This unique hemoglobin has a high affinity for oxygen, increasing oxygen absorption in the lower oxygenated placental vascular bed.[14] Hypoxia is essential in embryonic and fetal development. It causes a physiological adaptation response in the fetus, depending on the degree of hypoxemia, the duration of exposure, and the stage of development in which it is found.[15] There is enough evidence to confirm that newborns at high geographic altitudes have improved hematopoiesis, showing more hypoxia than newborns born at sea level.[16]

Besides, high altitude causes several metabolic responses to increasing the affinity of hemoglobin for oxygen.[17] These changes occur due to the acid–base imbalance that accompanies hypoxemia, which stimulates the production of 2,3-DPG in the RBC, which releases oxygen to the tissues as an adaptation mechanism. This situation causes a displacement of the dissociation curve of hemoglobin to the right, increasing the affinity of hemoglobin for available oxygen, which at high altitudes is scarce.[18]

This study aims to compare the physiological changes in newborns born at high altitude versus those born at sea level, considering that there are not enough data to confirm substantive differences in the chronic hypoxia of the inhabitants at high altitude.

Subjects and methods

Research design: It is an epidemiological, cross-sectional, observational study, with two cohorts of newborns born at high-altitude and low-altitude settings.

Settings: We performed this study at San Francisco Hospital in Quito, at 2850 m, and Manta General Hospital at 6 m, at Manabí province, from December 2019 to March 2020.

Participants: To avoid confounding variables, we studied two cohorts of full-term individuals born at high altitude and sea level, from mothers without any prenatal comorbidities, singleton pregnancy, children of healthy parents, also born and residing at the exact location. We selected children with normal birth weight within the inclusion criteria, delivered by vaginal delivery, single deliveries, without comorbidities, with an APGAR at the birth of 9 and 10 points. Only mestizos ethnic group.

N = 204 individuals.

Variables: Hematological values, hematocrit, arterial blood gases (ABG), and glycemic value; related to altitude.

Data sources: Secondary sources such as neonatal clinical history.

Bias avoidance: The same person always collected the information. For the collection of information, we used a standardized data collection sheet.

Study size: The study population was 204 full-term newborns, 102 infants born at high-altitude settings, and 102 newborns at sea level.

Statistical methods: we analyzed data with the SPSS© software version 22.0. We used descriptive and inferential statistics; for comparing the differences of variables. We calculated Chi-square with an accepted significance of *P* less than 0.05. Finally, we also performed multivariate analysis.

Exposure: The authors considered altitude as the primary variable.

Ethical approval: Institutional Review Board (Committee on Research Ethics in Human Beings, CEISH) of the Universidad San Francisco de Quito approved this research with the code P2019-173TPG, expedient IR-EXP144-2019. All procedures performed in studies involving human participants were following the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Table 1 shows the distribution of hematological parameters comparing high-altitude and low-altitude settings. We found differences in RBC, leucocytes, hematocrit, and hemoglobin. There was a difference of 27% more in RBC, 3% at hematocrit, 0.4 g at hemoglobin in high-altitude cohort. The leucocyte difference was 1270 cells/µl, which means a difference of 6%. Considering that the normal range for hemoglobin is, for men, 13.5−17.5 g/dl, and for women, 12.0−15.5 g/dl, it exists an increase of at least 0.3 g in those samples. Similarly, the normal hematocrit for men is 40%−54%; for women, it is 36%−48%, being the highest value 56% in this study, showing a mean difference of 2%. The mean of RBC was 5,357,843 cells/µl for high altitude compared to 3,913,725 cells/µl for low altitude setting. The mean RBC count was 20,685 cells/mm^3 for high altitude versus 19,415 for low altitude setting. Hematocrit values were 56.04% for high altitude versus 52.97% for low altitude setting. Finally, the mean hemoglobin was 17.81 g/dl for high altitude compared to 17.40 g/dl for low altitude setting.

Table 1 also shows the distribution of ABG parameters comparing high-altitude and low-altitude settings. Typical values of ABG at sea level are pH of 7.38−7.42; partial pressure of oxygen (PaO_2) from 75 to 100 mm Hg; partial pressure of carbon dioxide ($PaCO_2$) from 38 to 42 mm Hg and; bicarbonate (HCO_3) from 22 to 28 mEq/l. The mean pH was lower than typical values, similarly in pO_2, pCO_2, and HCO_3. There was a statistical difference in pH, pO_2, and pCO_2. The pH showed a mean of 7.28 for high altitude vs. 7.31 for low altitude setting. pO_2 a means of 69.66 mm Hg for high altitude vs. 77.31 mm Hg for low altitude. The pCO_2 showed a mean of 39.31 mm Hg for high-altitude vs. 38.04 mm Hg for low-altitude setting.

Table 2 shows a comparison of cut-off points of hematological and ABG parameters comparing high altitude and low altitude settings. The cut-off points based on the mean value were determined to characterize the zones; we observed an inversely proportional relationship between individuals born at high altitudes and individuals born at low altitudes. In individuals born at high altitude, RBC of > 4,500,000 cells/µl was present in 76.47% of all individuals, leucocytes of > 19,000 in 58.82%, hematocrit of > 54% in 55.88%; hemoglobin of > 17.50 g/dl in 56.86%; pH of ≤ 7.32 in

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Table 1. Distribution of hematologic and ABG parameters comparing high-altitude and low-altitude settings

	Value (mean (SD))	Group		*P*-value (<0.05)
		High altitude	Low altitude	
Hematologic parameters				
RBC cells/μl	4,635,784 (998,147)	5,357,843 (780,382)	3,913,725 (583,441)	0.000
Leucocytes cells/μl	20,049 (2019)	20,685 (1919)	19,415 (1923)	0.000
Hct %	54.5 (2.96)	56.04 (3.03)	52.97 (1.39)	0.000
Hemoglobin g/dl	17.61 (0.68)	17.81 (0.72)	17.40 (0.57)	0.000
Blood gases parameters				
pH	7.29 (0.05)	7.28 (0.05)	7.31 (0.04)	0.001
pO_2 mm Hg	73.49 (6.70)	69.66 (4.32)	77.31 (6.48)	0.000
pCO_2 mm Hg	38.68 (2.93)	39.31 (2.50)	38.04 (3.18)	0.006
HCO_3 mmol/l	21.23 (1.84)	21.26 (1.86)	21.20 (1.84)	0.757

ABG, arterial blood gases; Hct, hematocrit; mm Hg, millimeters of mercury; mmol/l, millimols per liter; RBC, red blood cells; SD, standard deviation.
Source: Research data. Elaboration: authors.

Table 2. Comparison of cut-off points of hematologic and ABG parameters comparing high altitude and low altitude settings

Cut-off points*	Group		*P*-value (<0.05)
	High altitude (n = %)	Low altitude (n = %)	
RBC			
≤4,500,000 cells/μl	24 (23.53)	100 (98.04)	0.000
>4,500,000 cells/μl	78 (76.47)	2 (1.96)	
Leucocytes			
≤19,000	42 (41.18)	68 (66.67)	0.000
>19,000	60 (58.82)	34 (33.33)	
Hct			
≤54%	45 (44.12)	91 (89.22)	0.000
>54%	57 (55.88)	11 (10.78)	
Hemoglobin			
≤17.5 g/dl	44 (43.14)	67 (65.69)	0.001
>17.5 g/dl	58 (56.86)	35 (34.31)	
pH			
≤7.32	66 (64.71)	44 (43.14)	0.002
>7.32	36 (35.29)	58 (56.86)	
pO_2			
≤72 mm Hg	75 (73.53)	29 (28.43)	0.000
>72 mm Hg	27 (26.47)	73 (71.57)	
pCO_2			
≤38 mm Hg	47 (46.08)	62 (60.78)	0.035
>38 mm Hg	55 (53.92)	40 (39.22)	

μl, microliter; ABG, arterial blood gases; Hct, hematocrit; mm Hg, millimeters of mercury; RBC, red blood cells.
*Based on the test of homogeneity of the Chi-square statistic.
Source: Research data. Elaboration: authors.

64.71%; pO_2 of ≤ 72 mm Hg in 73.53%; pCO_2 of > 38 mm Hg in 53.92%. We found opposite values in individuals born at low altitudes.

Figure 1 shows the multivariate relationship between high-altitude and low-altitude settings concerning hematological and ABG parameters, based on categorical principal component multivariate analysis. Dimension 1 discriminates between high-altitude and low-altitude settings and the cutoff points for the hematological and ABG parameters. We observed the following associations: in quadrants I and IV, it associates newborns born in high altitude setting with RBC > 4,500,000 cells/μl; leukocytes > 19,000; pO_2 ≤ 72 mm Hg; hemoglobin > 17.50 g/dl; and hematocrit > 54%. There was also a relationship between pH ≤ 7.32 and pCO_2 > 38 mm Hg. In quadrants II and III, low-altitude newborns showed RBC ≤ 4,500,000 cells/μl, leukocytes ≤ 19,000, pO_2 > 72 mm Hg, hemoglobin ≤ 17.50 g/dl, and Hct ≤ 54%. There was also a relationship with pH > 7.32 and pCO_2 ≤ 38 mm Hg.

Discussion

Chronic adaptation to high altitude is an evolutionary process that has taken many years, at least 9000–7000 years, with the arrival of the first inhabitants to Ecuador. We use the adaptation concept to refer to a structure feature, function, or behavior that enables an organism to live and reproduce in a given environment.[19] One of the best-documented effects of high altitude is a progressive reduction in birth weight about intrauterine growth and pregnancy duration. Birth weights decline an average of 100 g per 1000 m altitude gain in studies conducted over several years. The reduction in birth weight is due to direct effects of high altitude and not interactive effects with other risk factors such as maternal age, parity, body size, or prenatal care access.[20] The primary cause of reducing birth weight is the retardation of intrauterine growth rather than shortened gestation.[21] Nutritional, behavioral, and other pregnancy-specific characteristics are likely important in each location. Maternal hypoxemia is also a risk factor for low birth weight in offspring.

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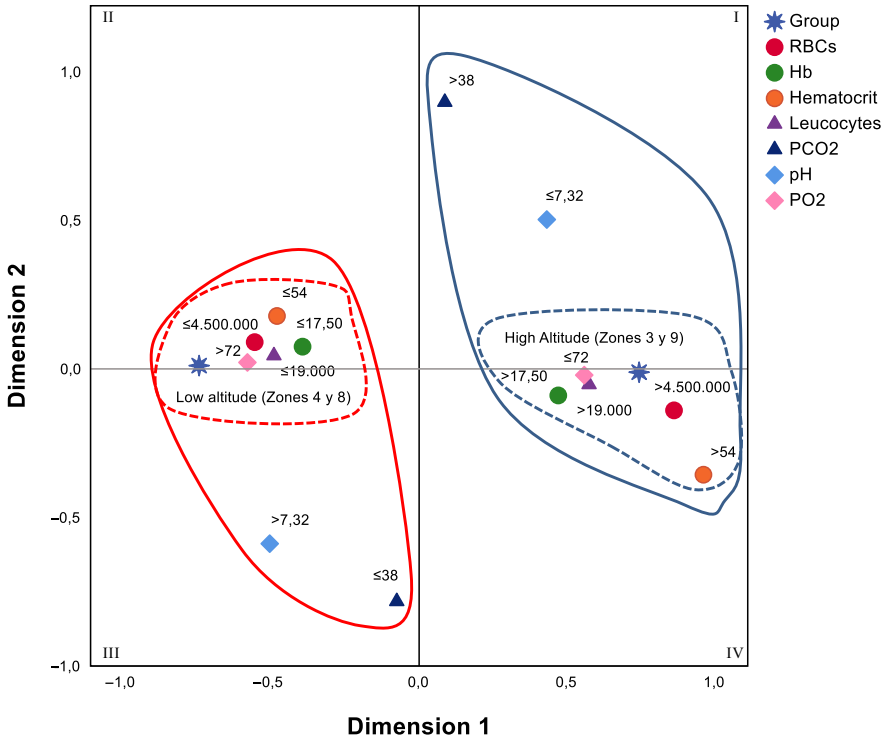

Fig. 1. Multivariate relationship between high-altitude and low-altitude settings concerning hematic and arterial blood gases parameters in newborns. Based on categorical principal components multivariate analysis. Source: Research data. Elaboration: authors.

However, lifelong residents of the Andes, compared with acclimatized new residents, mainly due to their chronic adaptation, have less intrauterine growth retardation, better neonatal oxygenation, a better neonatal cardiopulmonary transition, enlarged lung volumes, decreased alveolar-arterial oxygen diffusion gradients, and higher maximal exercise capacity.[1]

Newborns born at high altitude have polycythemia and leukocytosis and lower levels of oxygenation and blood pH, in general. This factor is explained by the effect of altitude-associated chronic hypoxemia on the production and regulation of fetal erythropoietin as an adaptive response to the low levels of oxygenation detected at high altitude.[22] During intrauterine life, erythropoietin levels in umbilical fluid and amniotic fluid are inversely correlated with umbilical artery levels, pH, excess base, and pO_2. Similarly, it is directly related to the level of pCO_2 and lactate in cases of chronic fetal hypoxia. Plasma erythropoietin levels begin to increase exponentially when the arterial oxygen content falls below 60% of normal. This approach is reinforced by determining that the cutoff point for the number of RBC was higher among newborns born at high altitudes than those born at sea level.

Geographical altitude is also related to a decrease in the diameter of the umbilical cord artery and the flow through it, which conditions fetal growth in conditions of chronic hypoxemia, with low levels also of nitric oxide and endothelin 1, which reflects the chronic stress in which the product of conception is developing.[23] The measure of cord blood hemoglobin levels, rather than maternal hemoglobin levels, may provide important diagnostic information about utero fetal adaptation to suboptimal placental function and neonatal health.

Neonatal hemoglobin and hematocrit were other parameters, which turned out to have statistically significant differences in both cohorts. Both were significantly superior among high-altitude-born infants. This factor indicates that high-altitude infants had a higher concentration of RBC and hemoglobin. This variable is considering normal in all full-term newborns who are born with a tendency to polycythemia. This issue also presupposes a certain degree of hypoxia. However, hypoxia is also produced by an active mechanism among those born at high altitude, which increases erythropoiesis.[24]

On the other hand, it also observed statistically significant differences concerning the value of total leukocytes, which turned out to be greater among newborns at high altitude, which could be related to spinal stimulation of chronic hypoxemia. In effect, when establishing the cutoff point for the total number of leukocytes in both cohorts of newborns, among those born at high altitude, leukocytosis predominated, while in those born at sea level, they were below the cut. At this point, it is valid to point out that for both cohorts, the values obtained are within the normal range for newborns.

When analyzing the behavior of ABG parameters, it observed that the high-altitude infant cohort had lower pH levels more frequently, indicating that it was acidemia. The reduction of the pH of the blood is other of the adaptation mechanisms of the fetus to the low concentrations of oxygen available at high altitudes; therefore, respiratory acidosis, through its inhibitory effects on global enzyme activity, central thermoregulatory mechanisms, and the responsiveness of brown fat to noradrenergic stimulation, plays a supporting role in the metabolic reduction.

Indeed, it found that in high altitude newborns, a significantly lower pO_2 was more frequent than in those born at sea level. However, it remained within the accepted range of normality, although with a tendency to hypoxemia, since the cases that were below the established cutoff point ($pO_2 \leq 72$ mm Hg) predominated in this group. This variable means that, among these patients, the physiological mechanisms of adaptation to extrauterine life

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have not yet been established, with low availability of oxygen in the extrauterine environment. Therefore, these are high concentrations of circulating hemoglobin with a high affinity for oxygen, which results in the low partial pressure of oxygen in the peripheral blood or hypoxemia.

On the other hand pCO_2 levels were also higher in high-altitude infants, although, in both study cohorts, they remained within the accepted range of normality; however, it means that in those born in the area with the highest geographical altitude, there was a greater tendency to hypercapnia. This variable, together with the reduction in pH and pO_2 concentrations, indicates adaptation mechanisms to extrauterine life at altitude, with a lower barometric pressure of oxygen and, therefore, a lower saturation level. The findings obtained in this investigation infer that the geographic altitude had a statistically significant impact on blood count parameters. However, the observed physiological changes are within the normal range for newborns; there were substantial differences in both study groups. This factor indicates that to survive and develop properly in conditions of high geographic altitude, the fetus and newborn use mechanisms that include optimized gas exchange across a large respiratory surface area, such as the placenta, and improve oxygen transport by hematological adaptations and metabolic adjustments at the tissue level. The differences in the Hct and Hb values are smaller between low and high altitudes, so they might seem of the same magnitude, which is not valid.

Rightward shifts of the O_2-hemoglobin association curve occur when there is a decrease in the affinity of hemoglobin for O_2. An affinity decreasing shows an increase in P_{50}, which means that saturation of 50% is achieved at a higher-than-normal value of PO_2. Hypoxemia caused by high altitude stimulates the production of 2,3-DPG in RBCs, which facilitates the release of oxygen to the tissues as an adaptation mechanism.

There is a difference of 27% more in RBC, 3% at hematocrit, 0.4 g at hemoglobin in high altitude cohort. These changes do not start at birth but begin from embryonic development, during intrauterine hematopoiesis, in fetuses of high geographic altitude, which is due to a rise in RBC concentration and a subtle increase in the size of RBC. The decrease in the partial pressure of oxygen, associated with a reduction in the barometric pressure, stimulates erythropoiesis, which causes physiological polycythemia and increases hemoglobin.

We compared our results, carried out in newborns, with another published research,[25] carried out in adults, and it observed a 3% deviation in hematocrit at high altitude. In contrast, in hemoglobin values, the results are similar. It could say that when growing an individual, there is an adaptation to altitude, which could be due in part to the adaptation of hemoglobin within the erythrocyte.

There may be some possible limitations in this study. We found some methodological limitations in the sample and selection of patients because we use only two hospital data. The patients were limited to some geographic areas of the country. We analyzed 204 patients, and we think it was a sufficient sample size for statistical measurement. Probably, in future studies, it will be necessary to get a vast number of participants. However, another limitation is there a lack of previous research studies, specifically in Ecuadorian populations. Another significant limitation was the limited access to data because medical records did not always have enough data, mainly due to the archiving system. Despite this, our findings are still reliable and valid. We can extrapolate our results to other similar populations, especially in countries with similar conditions. Further studies are needed.

Conclusion

Both cohorts of healthy full-term newborns showed physiological changes of transition to extrauterine life. We observed higher polycythemia, respiratory acidosis, and hypoxemia among newborns born at high altitudes, indicating that geographic altitude intensifies the physiological changes seen in hematological biometry and ABG in full-term infants. There was a difference of 3% more at hematocrit, 0.4 g at hemoglobin, and 6% in leukocytes in the high altitude cohort. Newborns born in high altitude areas associates with RBC > 4,500,000 cells/μl; leukocytes > 19,000; $pO_2 \leq$ 72 mm Hg; hemoglobin > 17.50 g/dl; and hematocrit > 54%.

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Contribution of the Authors. The authors carried out the research protocol and its design, data collection, statistical analysis, evaluation, interpretation of the data, critical analysis, discussion, writing, and final manuscript approval.

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