CARDIOPULMONARY TRANSITION IN THE NEONATE AND INFANT AT HIGH ALTITUDE

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RESUMEN: Transición Cardiopulmonar en la Altura: el Neonato y el Lactante

Objetivo: En la altura , ocurren alteraciones relacionadas con el nivel de altitud en la saturacidn arterial de oxígeno (S_aO_2), tanto en el neonato como en el lactante.

Diseño: La evidencia tomada de investigación original y de la literatura publicada permite la comparación de varios grupos poblacionales residentes en altura, tanto en América del Norte y del Sur como en Asia.

Material y Métodos: Datos de oximetria de pulso, pletismografia respiratoria, ecocardiografía, cateterización cardíaca y examen histológico de neonatos y lactantes ilustran alteraciones en la función, ejemplos de adaptación exitosa, y ejemplos de morbilidad y mortalidad relacionados con el nacimiento o la residencia en altura.

Resultados: La S_aO_2 cae al aumentar la altura; sin embargo, este efecto no tiene relación lineal con la altura o la presión barométrica. La S_aO_2 varia marcadamente con el estado conductual. En contraste con los patrones observados a nivel del mar, la S_aO_2 disminuye luego de una semana de vida en ciertas poblaciones de altura. La prevalencia y la duracidn de la respiración periódica de los lactantes aumenta en la altura en comparacidn con los del nivel del mar. La respiración periódica ocurre más comúnmente durante el sueño activo y tranquilo y se asocia con un patrón cíclico de saturación de oxígeno. La presión de la arteria pulmonar cae lentamente luego del nacimiento en altura extrema. En altura moderada, las presiones de la arteria pulmonar pueden normalizarse, pero el lecho vascular pulmonar sigue siendo susceptible al desarrollo de hiperntensión pulmonar sintomática durante un periodo prolongado de transición. El sindrome de mal de montaña subagudo infantil y la persistencia de cortocircuítos de derecha a izquierda por el foramen oval y el conducto arterioso reflejan una presión de arteria pulmonar y una resistencia vascular elevadas en la infancia.

Conclusión: El recién nacido de la altura experimenta una transición más lenta de patrones fetales a patrones maduros de función cardiopulmonar. Ocurren effectos diferenciales al aumentar la altura y se observan diferencias en respuesta entre varios grupos poblacionales a alturas similares.

Palabras claves: Adaptación fisiológica; Altura; Hipoxia; Oximetria de pulso; Hipertensión pulmonar; Mal de montaña subagudo infantil; Perú; Tibet; China.

RÉSUMÉ: Transition cardiorespiratoire à grande altitude : le nouveau-né et le nourrisson.

Objectif : Des altérations de la saturation artérielle d'oxygène (S_aO_2) liées au niveau d'altitude se produisent aussi bien chez le nouveau-né que chez le nourrisson.

Plan : L'évidence obtenue de l'investigation originale et de la littérature publiée permet la comparaison entre plusieurs groupes humains habitant des régions de grande altitude en Amérique du Nord, Amérique du Sud et Asie.

Matériel et méthodes : Des données d'oxymétrie de pouls, de pléthysmographie respiratoire, d'échocardiographie, de cathétérisation cardiaque ainsi que l'examen histologique de nouveau-nés et de nourrissons illustrent les altérations de la fonction, les exemples d'adaptation réussie et les exemples de morbidité et de mortalité liées à la naissance ou à la résidence en altitude.

Résultats : Bien que la S_aO_2 diminue quand augmente l'altitude, cet effet n'est pas lié linéairement à l'altitude ou à la pression barométrique. La S_aO_2 varie très nettement en fonction de l'état comportemental. Contrairement aux modèles observés au niveau de la mer, chez certaines populations vivant à grande altitude la S_aO_2 diminue au bout d'une semaine de vie et la prévalence et la durée de la respiration périodique du nourrisson sont en augmentation. La respiration périodique se produit le plus souvent pendant le sommeil actif et paisible et elle est associée à un *pattern* cyclique de saturation d'oxygène. A très grande altitude la pression de l'artère pulmonaire diminue lentement après la naissance. A une altitude modérée, les pressions de l'artère pulmonaire peuvent se normaliser mais le lit vasculaire pulmonaire reste susceptible au développement d'une hypertension pulmonaire symptomatique pendant une période prolongée de transition. Le syndrome du mal des montagnes subaigu infantile et la persistance de courts-circuits de droite à gauche par l'orifice ovale et le conduit artériel reflètent une pression de l'artère pulmonaire et une résistance vasculaire élevées pendant l'enfance.

Conclusion : Chez l'enfant nouveau-né de grande altitude, la transition des *patterns* foetaux aux *patterns* matures de la fonction respiratoire se fait plus lentement. Des effets différentiels se produisent quand l'altitude augmente et l'on observe des différences dans les réponses de plusieurs groupes de population vivant à des altitudes similaires.

Mots-clés : Adaptation physiologique, Altitude, Hypoxie, Oxymétrie de pouls, Hypertension pulmonaire, Mal des montagnes subaigu infantile, Pérou, Tibet, Chine.

SUMMARY:

Objective: Altitude-related alterations in arterial oxygen saturation (S_aO_2), ventilation, and the pulmonary circulation occur during cardiopulmonary transition in the neonate and infant at high altitude. Design: Evidence gathered from original research and the published literature allows comparison of various population groups resident at high altitude in North and South America and Asia.

Material and Methods: Data from pulse oximetry, respiratory plethysmography, echocardiography, cardiac catheterization and histologic examination of neonates and infants illustrate alterations in function, instances of successful adaptation, and examples of morbidity and mortality related to birth or residence at high altitude.

Results: S_aO_2 falls with increasing altitude; however, this effect is not linearly related to altitude or barometric pressure. S_aO_2 varies markedly with behavioral state. In contrast to patterns observed at sea level, S_aO_2 decreases after 1 week of life in certain populations at high altitude. Periodic breathing in infancy increases in prevalence and duration at high altitude as compared to sea level. Periodic breathing occurs most commonly in active and quiet sleep and is associated with a cyclic pattern of oxygen saturation. Pulmonary artery pressure falls slowly after birth at extreme high altitude. At moderate high altitude, pulmonary artery pressures may normalize, but the pulmonary vascular bed remains susceptible to development of symptomatic pulmonary hypertension during a prolonged transition period. The syndrome of subacute infantile mountain sickness and persistence of right-to-left shunts at the foramen ovale and ductus arteriosus reflect elevated pulmonary artery pressure and pulmonary vascular resistance in infancy.

Conclusion: The newborn infant at high altitude experiences a slower transition from fetal to mature patterns of cardiopulmonary function. Differential effects occur with increasing altitude and differences in response are observed among various population groups at similar altitudes.

Key Words: Adaptation, Physiologic; Altitude, Hypoxia, Pulse oximetry, Pulmonary hypertension, Subacute infantile mountain sickness, Peru, Tibet, China

Background

Altitude-related alterations in arterial oxygen saturation (S_aO_2), ventilation, and the pulmonary circulation occur during the cardiopulmonary transition after birth and during infancy at high altitude. A comparative approach using data from various population groups resident at high altitude in North America, South America, and Asia illustrates the effect of increasing altitude and the differences observed among certain population groups at similar altitudes. Arnong these examples exist instances of successful adaptation, altitude-related alterations in function, and increased morbidity and mortality due to birth or residence at high altitude.

A vignette from the history of Spanish settlement of the Andes in in the mid- 16th century points out the hazards of birth at high altitude. Antonio de la Calancha wrote that in the first years of the settlement of Potosi, a silver-mining community at an altitude of 4000 m, no Spanish infants born there survived the neonatal period (1). Women of European descent chose to descend to nearby valleys, where their infants remained during infancy. Only after more than half a century is there record of a Spanish infant surviving after delivery in Potosi.

Arterial Oxygen Saturation

Oxygenation is the critical function assumed by the lungs at the moment of birth. The transition from fluid-filled to air-filled lungs not only effects oxygen transfer across the alveolar-capillary membrane, but the physical inflation of the lungs and the increased alveolar oxygen serve to dilate the pulmonary vascular bed and facilitate increased pulmonary blood flow, the other key component in raising the P_aO_2 after birth. At sea level, S_aO_2 rises from 47 to 61% immediately after birth to more than 80% by 7 minutes of life (2). In the first week, S_aO_2 remains in the low-to-mid 90% range and reaches adult levels of 94 to 98% by the end of the first month of life (3).

At 1610 m in Denver, Colorado, mean S_aO_2 during infancy ranged from 92 to 94% (4). After the first month of life, S_aO_2 varied with infant activity; S_aO_2 was higher while awake and feeding as compared to active and quiet sleep (Figure 1). At 2800 m in Summit County, Colorado the mean S_aO_2 for healthy awake infants was 92% (5).

At 3100 m in Leadville, Colorado, mean S_aO_2 ranged from 81 to 91% (Figure 1) in the first 4 months of infancy (6). Arterial oxygen saturations were initially at the upper limits of this range; S_aO_2 fell by one week after birth to a mean of 81% in quiet sleep, at the lower end of the range. Infant activity had notable effect on saturations at and after one week of life, when values were higher during wakefulness than during sleep. S_aO_2 during feeding was intermediate between saturations while awake and asleep. Values in quiet sleep rose to 86% by 2 and 4 months; the highest saturations were achieved in the awake state at 4 months. Although all infants in the study cohort remained healthy, the drop in SaO2 at one week of age coincided with the reported onset of symptoms in other babies who developed clinical signs of hypoxemia (e.g. cyanosis, irritability, poor feeding, failure to thrive).

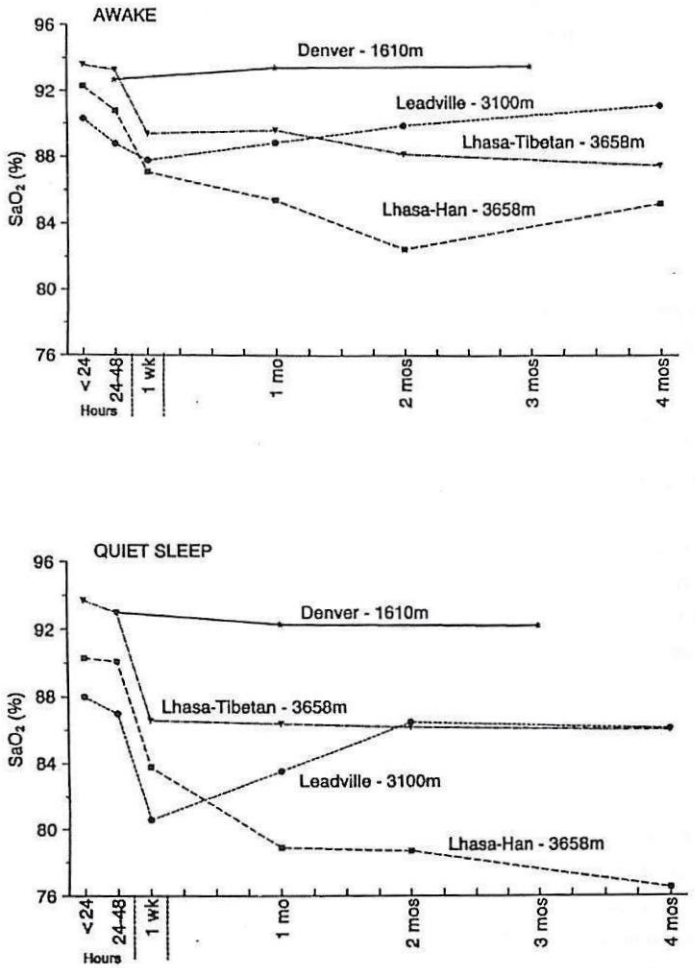

Figure 1. Arterial oxygen saturation in awake (upper panel) and quietly sleeping (lower panel) infants decreased with increasing altitude. At altitudes above 3000 m, S_aO_2 fell by one week of life from initial values at the upper end of the observed ranges. In Tibetans at 3658 m and residents of Leadville, CO at 3100 m, arterial oxygen saturations then stabilized through 4 months of age. Han infants in Lhasa, Tibet at 3658 m showed a progressive decline in saturations, most marked in quiet sleep, through 4 months.

At 3658 m in Lhasa, Tibet mean S_aO_2 for Tibetan infants ranged between 86 and 94% (7). The highest S_aO_2 occurred in the first two days after birth while awake. A fall in saturations occurred by one week of life. Thereafter, saturations stabilized in the Tibetans, with S_aO_2 only slightly greater while awake than in active or quiet sleep. Han infants born in Lhasa to mothers of low-altitude ancestry showed lower S_aO_2 than the Tibetans from birth through 4 months of age (Figure 1). Again, the highest saturations occurred in the first two days after birth (91 to 92%); a fall in S_aO_2 occurred by one week to 87%. However, mean S_aO_2 declined progressively in the Han to 76% by 4 months, while the Tibetans' values remained stable during this period.

At an altitude of 3750 m in La Oroya, Peru the mean S_aO_2 value was 88% in native Quechua infants from 2- to 5-months old (8). At extreme high altitude in Morococha, Peru (4540 m), directly measured arterial saturations ranged from 57% to 75% in newborns from 1/2 hour to 72 hours of age (9). Arterial saturations remined in the range of 74 to 80% throughout infancy (10).

The decrement in S_aO_2 observed with increasing altitude is not simply linear. This is due, at least in part, to varying degrees of hyperventilation, resulting in smaller drops in alveolar oxygen. Hyperventilation also increases pH and thereby shifts the oxyhemoglobin dissociation curve to the left, at least temporarily; metabolic compensation for respiratory alkalosis and intermittent

hypoventilation may decrease pH, resulting in a lower saturation for a given P_aO_2 (11). The prominent differences in SaO2 between sleep and wakefulness and the fall in S_aO_2 at one week likely relate to respiratory pattern. However, the dramatic differences between saturations in the Tibetan and Han infants cannot be explained on the basis of respiratory rate and pattern alone. Tibetans are unique in their length of settlement at high altitude, the lack of admixture with other populations, and the absence of migratory patterns to low-altitude regions. While the native populations in the Andes are analogous to the Tibetans with respect to long ancestry at high altitude, there has been much greater opportunity for admixture with lowland populations and migration to low altitude. North Americans and the Han are both newcomers to high altitude in the genetic sense. The Tibetan-Han differences which exist at the same altitude illustrate the probable role of genetic adaptation to high altitude.

Respiratory Patterns

Periodic breathing is a recognized feature of infancy at sea level, where it occurs in up to 78% of full-term neonates in the first two weeks of life (12). Periodicity in the respiratory pattern declines with postnatal age, from one month through 5-6 months (13).

Early studies in Denver (14) suggested that periodic breathing occurred more frequently and for a greater duration at 1610 m than previously reported from sea level. At 3100 m (Leadville, CO) the reported incidence of periodic breathing was 100% in neonates (15). The pattern of periodicity exhibited was a cycle of 4 to 6 breaths over 6-7 seconds with a subsequent pause of 6-7 seconds.

Periodic breathing likely represents an exaggeration of normal oscillations in respiratory frequency and tidal volume; as such it may be a normal phase in the development of respiratory control (16, 17). Peripheral chemoreceptor reflexes and the interaction of central with peripheral chemoreceptors may be important in the genesis of periodic breathing in newborns (13). The functional inactivity ofthe carotid chemoreceptor in the first 48 hours of life may account for the virtual absence of periodic breathing during this period (18, 19, 20).

Pulmonary Circulation

In normal postnatal transition, the fall in pulmonary vascular resistance and pulmonary artery pressure (P_{pa}) is the cornerstone to achieving higher P_aO_2 and effecting functional, then anatomic closure of the fetal atrial and ductal shunts. At sea level, pulmonary artery pressure falls to adult levels within the first 3 days of life, with the steepest decline in the first 24 hours (21).

At 3100 m in Leadville, CO the the ratio of right ventricular pressure to left ventricular pressure (RVP/LVP) fell within the normal to moderately elevated range during the first week of life. All 2 and 4 -month infants had values in the normal range, using the echocardiographic technique of LVSCI (left ventricular systolic circular index) (6). However, all infants born in Leadville routinely received supplemental oxygen at delivery and during postnatal transition. From the era before routine oxygen supplementation, 5 infants and 6 older children from Leadville were reported with a syndrome of pulmonary hypertension. Cardiac catheterizaton in three infants confirmed the clinical diagnosis. One infant who died exhibited medial hypertrophy and intimal thickening of pulmonary arterioles and disruption of the internal elastic lamina on autopsy (22).

In Lhasa at 3658 m, fifteen infants and children aged 3 to 16 months at death defined the syndrome of subacute infantile mountain sickness, characterized by pulmonary hypertension and right heart failure (23). All children were Han with the exception of one Tibetan boy; 13 of 15 were born at low altitude and brought to Lhasa an average of two months prior to onset of illness. Clinical signs which characterized the syndrome included: dyspnea, cough, cyanosis, sleeplessness and irritability, facial edema, hepatomegaly, and oliguria. Histology was characterized by medial hypertrophy of small pulmonary arteries, muscularization of pulmonary arterioles, and severe right ventricular hypertrophy and dilation.

The most striking data in support of a prolonged postnatal fall in pulmonary artery pressure come from extreme high altitude. Newborns at 4540 m in Peru had nearsystemic pulmonary artery pressures for several days following birth (9). Administration of 100% oxygen to 3 infants at 72 hours age resulted in normalization of P_{pa} values to levels near those of infants at sea level.

Other evidence supporting delayed fall in P_{pa} at

extreme high altitude comes from cardiac catheterization studies and pulmonary histology. Right heart catheterization of children under 5 years living at 4330 m and 4540 m in Peru confirmed instances of elevated PPA and increased pulmonary vascular resistance (10). In healthy children who died of non-pulmonary causes, there was evidence of slow regression of pulmonary arteriolar muscularization and thickening of the muscular layer of small pulmonary arteries. Delay in regression of the fetal pulmonary vascular pattern was so pronounced in some cases that a fully adult pattern was never achieved (24).

Delayed functional closure of fetal shunts gives further clinical evidence of the prolonged decrease in pulmonary vascular resistance and pulmonary artery pressure. The incidence of patent ductus arteriosus in Peruvian children at 4330 m (Cerro de Pasco) was 0.74%, in contrast to 0.05% at sea level (25). In Qinghai Province, PRC, the prevalence of atrial septal defect and patient ductus arteriosus increased from zero at sea level to > 5% at 4500 m (26). Hypoxemia is presurned to be the stimulus contributing to the increased prevalence of patent ductus arteriosus at high altitude (25-27).

CONCLUSION

The newborn at high altitude experiences a slower transition from fetal to mature patterns of cardiopulmonary function. Arterial oxygen saturation remains lower than corresponding adult values through early infancy. S_aO_2 declines in the first week and remains lower in sleep than the awake state. Extreme high altitude results in persistently low saturations, and certain populations show an exaggerated and prolonged fall in S_aO_2 associated with clinical signs of hypoxemia or right heart failure in infancy. Periodic breathing patterns are common to all neonates at high altitude. Periodic breathing in sleep is associated with cyclic changes in S_aO_2. Pulmonary artery pressure falls very slowly with persistence of fetal pulmonary vascular patterns and a higher prevalence of persistent right-to-left shunts. Symptomatic pulmonary hypertension may develop in susceptible infants at high altitude.

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