# Brainstem auditory evoked potentials in newborn infants born in a high-altitude area

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## ABSTRACT

***Introduction.*** A non-invasive and safe way to assess neurophysiological parameters in newborn infants is the evaluation of brainstem auditory evoked potentials (BAEPs).

***Objective.*** To assess the latencies and wave intervals of BAEPs in healthy newborn infants born in a high-altitude area (Cusco, 3399 MASL).

***Population and methods.*** Cross-sectional and prospective study. Newborn infants younger than 14 days of age, discharged less than 7 days after birth, were assessed to determine BAEP values at intensities of 70 dB, 80 dB, and 90 dB. The study variables were gestational age, birth weight, and type of delivery. The median differences in wave latencies and intervals were estimated according to gestational age and birth weight.

***Results.*** A total of 96 newborn infants (17 preterm infants) were assessed. The median latencies of waves I–V at 90 dB were for wave I: 1.56 ms, wave II: 2,74 ms, wave III: 4.37 ms, wave IV: 5.62 ms, and wave V: 6.63 ms. The latency of wave I for 80 dB was 1.71 ms and for 70 dB, 1.88 ms. Wave intervals (I–III, III–V, I–V) were 2.8 ms, 2.2 ms, and 5.0 ms, respectively, without differences among intensities ($p > 0.05$). Prematurity and low birth weight were associated with a longer wave I latency ($p < 0.05$).

***Conclusions.*** Here we describe adjusted BAEP latency and interval values for newborn infants born at high altitude. At different sound intensities, we identified differences in wave latencies, but not in interwave intervals.

***Keywords:*** *preterm newborn infant; low birth weight newborn infant; auditory evoked potentials; altitude.*

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## INTRODUCTION

The Andes extend through several countries in South America, where people have acclimatized to chronic hypoxia. Several studies have been conducted on this topic;[1–3] however, there is less information about the effects of such chronic exposure on fetal development and its consequences on newborn infants born at high altitude. These infants are known to have lower oxygen saturation at birth and lower Apgar scores compared to those born at sea level;[4] because of this, it has been suggested that cognitive and behavioral impairment occurs due to an incomplete adaptation to hypoxia,[5] which continues even in adulthood.[6] However, the consequences on the neonatal central nervous system are very difficult to assess by means of accessible, rapid, and non-invasive methods. An option is to use neurophysiological techniques, such as brainstem auditory evoked auditory potentials (BAEPs).

BAEPs are the result of the neuroelectric response to sound stimuli in the auditory system—from the cochlear nerve to the brainstem at the level of the inferior colliculi—; they manifest as waves at each station where one neuron relays another, forming a sequence of waves that reflect the integrity of that part of the nervous system.[7] Five waves (I to V) are usually formed, and latencies (time from stimulus to wave peak) and interwave intervals are measured. Although each facility is expected to assess the normal values for its population, it is considered that in newborn infants born at 36–37 weeks of gestation and under a stimulus of 70 dB, wave I has a latency of 1.80 ms, and the interval of waves I–III is 3 ms; waves III–V, 2.2 ms; and waves I–V, 5.2 ms.[8]

By comparing them with the waves produced in a "normal population," we may identify deviations that may require further hearing diagnosis. Prolonged latencies or longer intervals suggest problems related to physiological maturation. Several studies have reported changes in BAEPs associated with hypoxia,[9–11] including rapid ascent to high altitudes in healthy adults[12] or in children aged 5 to 15 years living at high altitudes.[13] However, there is no information on values for newborn infants born at high altitude or on whether such data deviate from normal values at other altitudes. Therefore, the objective of this study was to determine BAEP values in a population of newborn infants born in a high-altitude area (Cusco, 3399 MASL).

## POPULATION AND METHODS

### Design and population

This was a cross-sectional, prospective study carried out in newborn infants born in Cusco, a city located at 3399 meters above sea level. The sample population was made up of newborn infants seen at Hospital Nacional Adolfo Guevara Velasco (HNAGV), in Cusco, between October 2019 and January 2020. HNAGV is a national referral hospital that provides tertiary care, with specialized neurology and neonatology services and caters to preterm and healthy newborn infants, with or without complications.

### Sample and selection criteria

The sample size was estimated based on information from the study by Jiang ZD,[14] where a population of term newborn infants had an average wave I latency of 2.3 ms, with a standard deviation of 0.16 ms, because there are no parameters available on Peruvian neonates. We estimated a mean sample size of n = 160, considering a 95% confidence level and a 2.5% accuracy. Considering that 2 independent measurements were obtained for each participant (1 for each ear) and that the test might not be performed in 10% of patients, the minimum estimated sample size was 86 participants. The PASS 11 software was used.

The inclusion criteria were newborn infants up to 14 days of age discharged from the hospital during the first week of age, who attended the well-baby clinic for an assessment, whose growth and development records had complete data and whose mothers gave their informed consent for the performance of the BAEP test. Patients receiving anticonvulsant therapy, with identifiable syndromic conditions, or with visible ear malformations were excluded.

To obtain the sample, we attended the well-child clinic 3 times a week and 1 out of 4 eligible mothers of newborn infants was systematically selected, considering that approximately 12 mothers were identified each day. It was estimated that approximately 10 weeks would be required to complete the sample size.

### BAEP protocol

The tests were performed with the newborn infants in natural sleep or while breastfeeding on their mother's lap, for approximately 45 min, in an isolated environment designed for conducting neurophysiological examinations.

BAEPs were obtained with Nihon Kohden

Neuropack equipment, using the MEB 08 software.[11] The BAEP protocol starts by cleaning the retroauricular area, the forehead, and the scalp with an abrasive cleaning paste (Nuprep) and placing the electrodes with conductive paste on Cz (active), A1, A2 (reference), and Fpz (ground).

Then, clicking sounds are used as stimuli, starting with stimuli in the right ear at an intensity of 70 dB and masking of 30 dB in the left ear, and then performing the same procedure reversing the order (70 dB in the left ear and 30 dB in the right ear). The right ear was then re-stimulated at 80 dB with masking of 40 dB in the left ear, and the procedure was repeated in the reverse order; and then at 90 dB.

For each stimulation, 2000 repetitions at 10 Hz were done. If waves were replicable and showed similar characteristics at different decibel stimulations, BAEPs were considered adequately obtained. Thresholds were established at 70 dB to 90 dB because previous studies had demonstrated a poor wave formation with 60 dB or less.[15]

### Data analysis plan

Quantitative variables were described as median with their corresponding interquartile ranges, whereas categorical variables were presented as absolute and relative frequencies (percentage).

BAEPs provide information on latencies of waves I to V and interwave intervals, which were processed as continuous quantitative ratio variables. The following data were also assessed: gestational age (preterm [36–37 weeks of gestational age at birth] and term [38 weeks or more]), type of delivery (eutocic, C-section), Apgar score at 1 minute and 5 minutes, birth weight (≤ 3000 g, 3001–3500 g, > 3500 g), length (< 50 cm, 50 cm or more), and head circumference at birth (< 35 cm, 35 cm or more). The median differences of latencies and wave intervals were estimated based on the category of these variables; the Mann-Whitney U test was used for 2 median differences, while the Kruskal-Wallis test was used for multiple median differences. A value of $p < 0.05$ was considered significant. Data were processed using the STATA statistical software, version 16.0.

### Ethical aspects

This study was approved by the Ethics and Research Committee of HNAGV. The informed consent was obtained from all mothers, who received their newborn infants' results and, when necessary, received other health care services to complement tests. Due to the COVID-19 pandemic alert, outpatient tests were interrupted, and the study was permanently terminated in February 2020.

## RESULTS

A total of 120 newborn infants were invited to participate; the parents of 24 of these refused to participate, so 96 newborn infants whose parents gave their consent were finally included. Their median gestational age was 39 weeks, with a birth weight of 3270 g, a height of 49 cm, and an Apgar score of 8/9. Of these, 17 (17.7%) were preterm infants. The population characteristics are described in *Table 1*.

Out of the 192 wave sequences assessed (left-right ear), the normal distribution of each wave (I to V) and interwave intervals were assessed. Given the biased distribution towards the left, median values are described.

Wave I latencies for 90 dB, 80 dB, and 70 dB, with a median of 1.6 ms, 1.7 ms, and 1.9 ms were obtained. The other values are shown in *Table 2*. Also, wave intervals (I–III, III–V, I–V) were 2.7 ms, 2.2 ms, and 5.0 ms, respectively, without differences among 90 dB, 80 dB, and 70 dB ($p > 0.05$). The graphic representation of waves and intervals is shown in *Figure 1*.

*Table 3* shows the values of waves, intervals, and sequences by type of delivery, Apgar score at 1 min, head circumference, or age at the time of test, which did not show significant differences ($p > 0.05$). Differences were observed in preterm infants, whose wave I latency was prolonged by 0.09 ms ($p = 0.03$). Differences were also observed in terms of length ($p = 0.01$) and birth weight ($p = 0.04$).

A stratified analysis by gestational age showed that differences in length were not sustained. Instead, in terms of weight, newborn infants with a birth weight ≤ 3000 g had prolonged latencies, regardless of their prematurity status.

## DISCUSSION

This study is an initial assessment to establish values of latencies and intervals in BAEPs in newborn infants born at high altitude, and this is its main strength. Both BAEPs and otoacoustic emissions are alternative hearing tests for children and are part of several regional screening programs.[16–18] In a study conducted

**Table 1. Characteristics of the population of clinically healthy newborn infants (n = 96) born in a high-altitude area (Cusco, 3399 MASL)**

| | Median | IQR |
|---|---|---|
| Weight (g) | 3270 | [2985–3590] |
| Height (cm) | 49 | [48–50] |
| Head circumference (cm) | 35 | [33.5–35.5] |
| Apgar score at 1 m | 8 | [8–9] |
| Apgar score at 5 m | 9 | [8–9] |
| Type of delivery (n, %) | | |
| Eutocic | 61 | 63.5% |
| C-section | 35 | 36.5% |
| Gestational age (weeks) at birth | 39 | [38–40] |
| Weight (n, %) | | |
| ≤ 2500 g | 4 | 4.2% |
| 2501–3000 g | 20 | 21.0% |
| 3001–3500 g | 43 | 44.8% |
| 3501–4000 g | 23 | 23.9% |
| > 4000 g | 6 | 6.3% |
| Preterm infants (n, %) | 17 | 17.7% |
| Age at the time of test (days) | 8 | [6–10] |

*IQR: interquartile range in square brackets; MASL: meters above sea level.*

**Table 2. Latencies of waves I–V, by sound intensity (70 dB, 80 dB, and 90 dB) in clinically healthy newborn infants (n = 96) born in a high-altitude area (Cusco, 3399 MASL)**

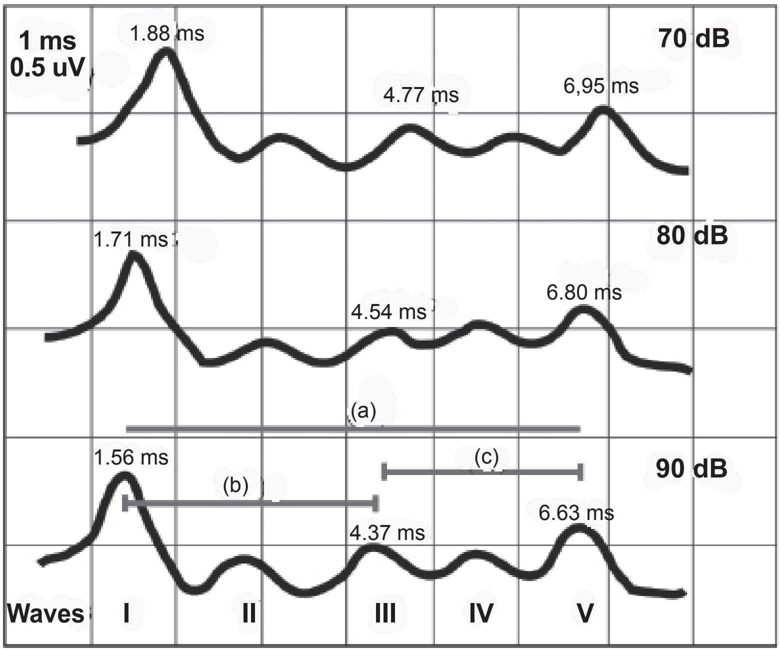
| | Wave I | Wave II | Wave III | Wave IV | Wave V | I–III interval | III–V interval | I–V interval |
|---|---|---|---|---|---|---|---|---|
| **70 dB** | 1.88 [1.79–2.12] | 3.0 [2.83–3.21] | 4.77 [4.55–4.88] | 5.78 [5.59–6.01] | 6.95 [6.71–7.21] | 2.76 [2.60–2.98] | 2.18 [2.04–2.32] | 5.03 [4.75–5.24] |
| **80 dB** | 1.71 [1.61–1.82] | 2.81 [2.64–2.93] | 4.54 [4.39–4.75] | 5.68 [5.56–5.86] | 6.80 [6.65–7.03] | 2.81 [2.61–2.93] | 2.21 [2.11–2.40] | 5.04 [4.86–5.22] |
| **90 dB** | 1.56 [1.47–1.68] | 2.74 [2.56–2.94] | 4.37 [4.22–4.54] | 5.62 [5.44–5.83] | 6.63 [6.46–6.89] | 2.79 [2.61–2.96] | 2.25 [2.10–2.40] | 5.05 [4.83–5.24] |

*Values are expressed in milliseconds (median and interquartile range); MASL: meters above sea level.*

in Peru in children aged 0 to 4 years, it was concluded that the sensitivity and specificity of otoacoustic emissions were lower compared to BAEPs.[19] However, the choice between BAEPs and otoacoustic emissions is based on available resources and patient characteristics, so the normal values for each test in the population analyzed should be known.

Compared to our values for latencies and interwave intervals, in a study in newborn infants born at 36–37 weeks of gestation and at 70 dB, wave I showed a 1.80 ms latency and the wave I–III interval was 2.99 ms; wave III–V interval, 2.27 ms; and wave I–V interval, 5.27 ms.[8] In a study conducted in term newborn infants at 65 dB,[20] the wave I latency was 1.86 ms and the wave I–III interval was 2.76 ms. In another study in Brazilian term infants at 80 dB,[21] the wave I latency was 1.79 ms, the wave I–III interval was 2.75 ms, and the wave I–V interval was 4.97 ms. The values observed in those studies were similar to ours; the small differences in the measures of central tendency may be due to the sample size of each study and do not seem to be clinically relevant. This suggests that BAEP values are similar between newborn infants conceived at sea level or at high altitude; therefore, regardless of the region or altitude where the baby is born, they should meet similar parameters of neurophysiological maturity. Early interventions may be performed if they deviate from previously established parameters (e.g., prolonged latencies or broader interwave intervals). The evidence suggests that early interventions in newborn infants with deviations in hearing screening tests, especially associated with prematurity,

**Figure 1. Brainstem auditory evoked potentials in healthy newborn infants (preterm and term infants, n = 96) born in Cusco. Representation of waves I–V and interwave intervals by sound intensity**




*(a) Wave I–V interval = 2.8 ms; (b) wave I–III interval = 2.2 ms; (c) wave III–V interval = 5.0 ms. Intervals are statistically similar among the 3 sound intensities (dB).*

**Table 3. Wave I latencies as per the characteristics of the population of clinically healthy newborn infants (n = 96) born in a high-altitude area (Cusco, 3399 MASL)**

| | n (%) | Wave I latency at 90 dB | *p* |
|---|---|---|---|
| Gestational age | | | 0.03 |
| Preterm infants | 17 (17.7%) | 1.63 [1.52–1.97] | |
| Term infants | 79 (82.3%) | 1.54 [1.45–1.68] | |
| Type of delivery | | | 0.54 |
| Eutocic | 35 (36.5%) | 1.56 [1.47–1.68] | |
| C-section | 61 (63.5%) | 1.55 [1.47–1.82] | |
| Apgar score at 1 m | | | 0.53 |
| 8 or less | 32 (33.3%) | 1.56 [1.47–1.78] | |
| 9 | 64 (66.7%) | 1.54 [1.48–1.67] | |
| Height | | 0.01 | |
| < 50 cm | 51 (53.1%) | 1.60 [1.50–1.74] | |
| 50 cm or more | 45 (46.9%) | 1.49 [1.43–1.67] | |
| Head circumference | | | 0.80 |
| < 35 cm | 46 (47.9%) | 1.57 [1.48–1.72] | |
| 35 cm or more | 50 (52.1%) | 1.56 [1.47–1.67] | |
| Age | | 0.68 | |
| 7 or less days | 45 (46.9%) | 1.57 [1.48–1.68] | |
| 8 or more days | 51 (53.1%) | 1.53 [1.44–1.73] | |
| Birth weight | | | 0.04 |
| ≤ 3000 g | 24 (25.0%) | 1.63 [1.51–1.85] | |
| 3001–3500 g | 43 (44.8%) | 1.53 [1.47–1.66] | |
| > 3500 g | 29 (30.2%) | 1.55 [1.44–1.66] | |

*Values are expressed in milliseconds (median and interquartile range); MASL: meters above sea level.*

may prevent difficulties in learning and language development and predict neurodevelopmental disorders.[22–26]

Contrary to our results, another study conducted in 12 children aged 5 to 15 years living at 3000 MASL showed a prolonged mean latency of wave I at 80 dB (1.75 ms) and, when compared with 22 other children living at sea level (1.60), the differences were significant;[13] however, their central conduction times (I–V interval) were shorter (4.02 ms) than in our study. Although the sample size is small and does not allow drawing further conclusions, we have not found other studies supporting changes in BAEPs in newborn infants or children born at high altitude, so their effects require further investigations. Given that hypoxia is strongly associated with changes in BAEPs,[9–12] differences are likely to be observed during neonatal or infant development, as supported by Counter et al.,[13] probably due to adaptations associated with changes in middle or inner ear pressure[27,28] which may affect hearing sensitivity. Given that our population was made up of newborn infants, such adaptive changes would not yet be installed as they would be in children.

We also identified that, at different decibels (70 dB, 80 dB, or 90 dB), there were no differences in the wave I–V intervals and they were distinguished based on wave I latency values. This differs from the findings of a study by Stockard and Westmoreland,[8] who identified that the lower the intensity, the greater the interval between waves I to V, although this difference may be due to the fact that, in their study, they worked with intensities between 30 dB and 70 dB. In our study, this consideration allowed us to propose studies at a single sound intensity, which could be 80 dB, because fewer artifacts are found than at 70 dB,[15] and they allow the newborn infant to remain calm, unlike at 90 dB.

Prematurity and low birth weight were associated with a prolonged latency, which makes our results consistent when compared to other studies. In the study by Jiang ZD et al.,[29] a difference of 0.2 ms was found in favor of newborn infants with a very low birth weight (< 1500 g) when compared to those with a birth weight of > 2500 g. In our study, those with a birth weight of less than 3000 g showed significant differences (0.1 ms), regardless of whether or not they were born preterm. Our differences were small because the sample included only 17 near-term preterm infants, unlike other studies with extremely preterm infants or patients in the neonatal intensive care unit in whom wave I latencies may be greater than 2 ms.[30–32]

The pandemic limited the possibility of enlarging the sample size beyond the estimation described here, which would have allowed for a more complex data analysis, including standardization by gestational age. Even so, the sample size shows differences compatible with other studies. Also, the population comes from low-risk pregnancies, but we do not have more data on the mothers, such as their nutritional levels during pregnancy, which could have an effect on the development of the fetal central nervous system. We have no data on population genetics. Cusco and much of the South American Andes have a high level of miscegenation, and physiological adaptation is lower compared to native Tibetans.[33] Finally, other aspects of the neurophysiological assessment of BAEPs, such as amplitudes, have not been analyzed in this study.

## CONCLUSIONS

Here we describe BAEP values in newborn infants born at a high altitude; the values are similar to those reported in same-age populations living at sea level. Only differences attributable to prematurity and low birth weight were found, within the parameters already indicated in the existing bibliography. ■

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