Feasibility of Critical Congenital Heart Disease Newborn Screening at Moderate Altitude

WHAT’S KNOWN ON THIS SUBJECT: The American Academy of Pediatrics (AAP) and other organizations have recommended critical congenital heart disease (CCHD) pulse oximetry screening. Small studies have revealed lower saturations at higher altitude, but this effect on CCHD screening is unknown. The AAP requested additional studies at altitude to help clarify the dilemma.

WHAT THIS STUDY ADDS: The AAP has endorsed higher-altitude studies of CCHD screening. This observational prospective study revealed a higher positive screen rate at moderate altitude than at sea level. These findings suggest that current national recommendations may result in increased screening failures at moderate altitude.

BACKGROUND AND OBJECTIVE: Consensus guidelines have recommended newborn pulse oximetry screening for critical congenital heart disease (CCHD). Given that newborn oxygen saturations are generally lower at higher altitudes, the American Academy of Pediatrics and others recommend additional evaluation of the screening algorithm at altitude. Our objective was to evaluate the feasibility of newborn pulse-oximetry CCHD screening at moderate altitude (Aurora, CO; 1694 m). We hypothesized the overall failure rate would be significantly higher compared with published controls.

METHODS: We enrolled 1003 consecutive infants at ≥35 weeks’ gestation in a prospective observational study. The nationally recommended protocol for CCHD screening was adhered to with the exceptions of no reflex echocardiograms being performed and providers being informed of results only if saturations were less than predefined critical values.

RESULTS: There were 1003 infants enrolled, and 988 completed the screen. The overall failure rate for completed screenings was 1.1% (95% confidence interval: 0.6–2.0%). The first 500 infants had 1.6% fail, and the last 503 infants had 0.6% fail. Among infants who failed screening, 73% failed secondary to saturations <90%, whereas saturations between 90% and 94%, persistently >3% difference, and multiple criteria were each responsible for 9% of failures. Overall, 1.6% of all infants had incomplete screening and had not passed at the time the test was stopped.

CONCLUSIONS: Pulse oximetry screening failure rates at moderate altitude are significantly higher than at sea level. Larger studies with alternative algorithms are warranted at moderate altitudes. Pediatrics 2014;133:e561–e569
Congenital heart disease is among the most common birth defects and the leading cause of birth defect–related deaths. It occurs worldwide with an incidence of ~8 to 12 per 1000 live births. Critical congenital heart disease (CCHD) has been defined as structural heart defects that are usually associated with hypoxia in the newborn period and have potential for significant morbidity and mortality early in life. CCHD has been estimated to be present in ~4 in 1000 live births. Prenatal ultrasound currently identifies <50% of all congenital heart disease in utero. Even with the addition of standard newborn physical examination, between 13% and 55% of patients with CCHD may leave the hospital undiagnosed. Failure to diagnose CCHD in the first several days after birth can result in high morbidity and mortality rates, and 1 California study found >50% of patients with a missed CCHD diagnosis died at home or in the hospital emergency department.

Screening with pulse-oximetry has been identified as a low-cost, painless, non-invasive test that increases the ability to identify CCHD in newborns with a 15-fold greater positive predictive value than physical examination alone. Pooled studies of oximetry performed in 229421 newborn infants showed sensitivity for detecting CCHD of 76.5% and a specificity of 99.9% with a false-positive rate on screens performed after 24 hours of only 0.05%. The US Secretary of Health and Human Services, in collaboration with the American Academy of Pediatrics (AAP), the American College of Cardiology Foundation, and the American Heart Association, have targeted 7 specific lesions for a pulse oximetry screening protocol: truncus arteriosus, transposition of the great arteries, tricuspid atresia, tetralogy of Fallot, total anomalous pulmonary venous return, hypoplastic left heart syndrome, and pulmonary atresia.

Newborn oxygen saturations have been well established and are consistent at sea level, but newborn studies at higher altitude suggest lower corresponding saturations and wider SDs. As a result of the paucity of available data, The US Secretary of Health and Human Services, the Colorado Newborn Screening Advisory Committee, and the AAP requested that additional studies of newborn populations at higher altitude be performed.

METHODS

We endeavored to determine the failure rate of infants at a moderate altitude of 5557 feet (1694 m) for the CCHD screening protocol endorsed by the AAP, American College of Cardiology Foundation, and the American Heart Association. We hypothesized the total screening failure rate would be at least 3.2% or an absolute difference of 3 percentage points from previously published data. We hypothesized that a 3% difference such as this would be near 2 SD from previously published data at similar altitude. We also sought to establish normative oxygen saturation data at moderate altitude for a large population of well, late preterm and term newborns at 24 to 48 hours after birth.

Study Design

We prospectively enlisted infants at 350/7 weeks’ gestation and above in the newborn nursery without known congenital heart disease or conditions known to predispose to hypoxia. Screenings were conducted at ≥24 hours after birth (near time of first newborn screen) or as near to hospital discharge as possible for those discharged before 24 hours. The screenings were performed similarly to the national recommendations (Fig 1) except that infants were not subject to study protocol echocardiograms, and providers were informed only if saturations were <90% after 3 screenings, saturations had a persistently >3% difference by the end of testing, or if saturations were <85% at any time (Fig 2). These criteria were agreed on based on standard saturation practice at this altitude, national recommendations for differential saturations, and >2 SD from the mean of previous saturation studies at similar altitude. We structured our study to achieve >98% power to detect a 3% absolute difference in failure rate (where 0.2% failure rate was used as a sea level baseline).

We conducted the study at the University of Colorado Hospital in Aurora, Colorado, from July to October 2012. The Colorado Multiple Institutional Review Board gave approval to the study with a waiver of consent and full waiver of Health Insurance Portability and Accountability Act authorization. Parents were given a fact sheet describing the study as well as potential risks. Trained nursing staff placed Rad-87 Pulse Oximeter and LN0P Neo-L sensors (Masimo Corporation, Irvine, CA) on the right hand or wrist and in close succession on a single foot. Both the Masimo Rad-87 pulse oximeter and the LN0P Neo-L sensors were currently in use in the well-infant unit and NICU at the study location. The study was designed to occur around the time of the first newborn screen: between 24 and 48 hours after birth or just before discharge if hospital stay was <24 hours. Whenever possible, we attempted to screen infants awake, quiet, and without pacifier, bottle, or concurrent feeding. All data were analyzed by using the sea level screening protocol suggested by Kemper et al (Fig 1); however, for the purposes of this study, modifications were made to the lower saturation limits for the first and second screenings in an attempt to reduce the number of early screening failures. Infants with saturations of ≥95% and
3% difference in saturations or <85% at any screening were assigned pass or fail screen status respectively and exited the study. Infants with saturations of 85% to 94% or >3% differential in saturations between the right upper extremity and the lower extremity were referred to repeat testing in 1 hour’s time. Infants not achieving a pass screen status but with saturations ≥85% on the second attempt were tested again 1 hour after the second test, for a total of up to 3 screening attempts. Infants with saturations <95%, saturation difference >3% persisting through the third round of testing, or infants at any time with saturations <90% constituted a positive screen as per national standards. Additional items noted at the time of screening were the infant’s behavior, including sleeping, wakefulness, agitation, pacifier use, and feeding. Also recorded were gestation, gravida and para status, ethnicity, risk factors for CCHD and screen failure, birth weight, age in hours for each.

FIGURE 1
saturation measurement, and difference in saturation between right upper extremity and lower extremity. Study data were collected and managed by using REDCap electronic data capture tools hosted at the University of Colorado.18

Statistical Analysis
Before the study, a power analysis was done to determine appropriate sample size. To detect a 3% absolute difference in failure rates with a 98% power the sample size required 500 infants. In an effort to accumulate a large volume of data for pulse oximetry averages, 1003 infants were tested.

Failure rates based on the Kemper model12 were assessed with a t test. Correlations to failure were assessed with $\chi^2$, Fisher exact, and Wilcoxon testing.

RESULTS
Of 1233 deliveries during the study period, we enrolled 1003 consecutively born infants and 988 completed the protocol (Fig 3). The mean time of initial screen was 23.8 hours with an SD of 2.3 hours. Among those who completed the protocol, we found a mean preductal saturation of 97.2% (±1.9%) and postductal saturations of 97.2% (±2.1%). The screening failure rate was 1.1%, which was statistically different from sea level baseline control10 rate of 0.2% ($P = .0221$). Additionally, 1.6% (16 of 1003) who had incomplete screening were not passing at the time the test was stopped. Eight of 11 (73%) failed secondary to saturations <90%, in 3 of whom the value was <90% in the right hand and 5 of whom had postductal values <90%. We found 1 of 11 (9%) failed secondary to saturations between 90% to 95% who had both failing right hand and foot saturations. We found 1 of 16 (9%) infants failed for a persistently >3% difference in saturations. The remaining 1 of 11 (9%) failed >1 of these criteria (Fig 4). None of the infants had unreadable saturations due to poor waveforms or signal strength.

The nonpassing rate on the first screen was 57 of 987 (5.8%). The second screen resulted in a nonpassing rate of 14 of 39 (35.9%). Third screen nonpassing and therefore failure rate occurred in 3 of 9 (33.3%). The difference in nonpassing rates nominator and the next screens denominator were the total of incomplete screening and failed screenings. Some infants had multiple reasons for not passing during each screening. Three infants failed screening in the last 503 screens (failure rate = 0.6%; 95% confidence interval: 0.1%–1.7%) compared with 8 in the first 500 screens (failure rate = 1.7%; 95% confidence interval: 0.7%–3.2%). Reasons for not passing the first, second, and third screens are outlined in Fig 5. Our study protocol allowed for continued testing of infants if saturations were 84%. We found 4 of the 11 infants failing the screening would have gone on to passing if allowed to have a second or third screen. There were 2 infants in each 500 infant testing group who
would pass from additional testing after failures.

Sixteen patients did not complete testing. Among these patients, 15 should have had a second screen and did not. One infant had a nonpassing second screen and was not retested. Infants with saturations in the 90% to 94% range comprise the largest group who should have had additional rounds of screening and did not, although smaller numbers did not have full testing because of a 3% difference in saturations and missing saturation values (Fig 5).

We evaluated gestation, gravid and para status, ethnicity, risk factors for CCHD and screen failure, and birth weight. We found that gestational diabetes and infant weight were the only maternal/infant factors associated with failed screens among 13 possible factors (Table 1). All other factors were nonsignificant.

DISCUSSION

Our study represents the largest single-center report of saturation data in late preterm and term newborns at moderate altitude and is the first study to assess the feasibility of the national CCHD screening guidelines at altitude. We found that using the currently recommended sea level CCHD screening protocol resulted in a failure rate of 1.1% at a moderate altitude of 5557 feet (1694 m). This failure rate was significantly higher than previous studies performed at lower elevations; however, the failure rate was lower than we had anticipated. We hypothesized the failure rate would be at least 3.2%, or an absolute difference of 3% points from previously published sea level data.10 This assumption was based on the value 2 SD below the mean from previously published sea level data.14

Altitude is believed to affect newborn saturations via 2 main physiologic mechanisms. The first is through delayed transition from fetal to neonatal circulation. The lower partial pressure of oxygen results in limited pulmonary vasodilation. The resulting pulmonary artery to aortic artery shunting via the ductus arteriosus causes postductal desaturation. Additionally, there can be atrial-level shunting from the right to left atrium, resulting in equivalent but decreased pre- and postductal saturations.19 Furthermore, limited respirations after birth can result in extra cardiac shunting with V/Q mismatch directly in the lungs.20 As a result, before this study, infants at our institution found to be desaturated to ~88% or above would routinely be discharged without supplemental oxygen or further workup. Those <88% would likely have undergone evaluation for respiratory causes for desaturation, including infection, before proceeding toward echocardiogram.

Previous studies of normal infants at moderate altitude found much lower mean oxygen saturations and wider ranges or SDs than has been observed at sea level (Fig 6). Samuel21 found average preductal functional saturations of 97.86% to 98.49% with a 2 SD range encompassing 94.7% to 100% from 2559 feet (780 m). Thilo et al16 found term postductal saturations of 92% to 93% with a range of 80% to 98% and a 2 SD value of 85% in Denver (5280 feet/1610 m); however, they used fractional saturation technology, and saturation results in their study are likely lower secondary to this.22,23 Bakr and colleagues15 reported functional mean preductal saturations of 95.4% at 24 hours after birth at 5300 feet (1640 m) and 2 SD of 88.7% to 100%. Ravert14 reported 12 to 48 hours after birth mean preductal and postductal saturations of 96.67% and 96.29% (range 88%–100%) at 4498 feet (1371 m) and 93.39% and 94.58% (range 76–100) at 6800 feet (2073 m). We found oxygen saturation means during CCHD screening of 97.2% for both right hand and lower extremity near 24 hours after birth at 5557 feet (1694 m). Our saturation data are consistent with the more recent

FIGURE 3
Deliveries during the study period.
FIGURE 4
Screening failures.

FIGURE 5
Incomplete screenings. F, foot; RH, right hand.
previous studies\textsuperscript{14,15,21} and add strength to this data pool by including such a large sampling of infants.

On the basis of the previously available saturation data at moderate altitude, we were surprised to see a screening failure of only 1.1%. If all the incomplete screenings had gone on to screening failures, our failure rate may have been as high as 2.7%, which would have been closer to our anticipated value. Because nearly all of our incomplete screenings occurred after the first round of screening and because the majority of completed screenings who failed the first round went on to pass in the second and third rounds of screening, we feel that our overall screening rate of 1.1\% is an accurate representation for this infant population at this altitude.

Variation was found, however, between the first 500 infants and the latter 503 infants. In the first 500 infants, 8 of 500 (1.6\%) failed with 18 of 500 (3.6\%) either failing or having incomplete screening. The last 503 infants had only 3 of 503 infants (0.6\%) fail and 9 of 503 (1.8\%) either failed or had incomplete screening. We were encouraged by our incomplete testing rate of 1.6\% for a novel protocol. Confusion about the protocol was estimated to be the major contributor to incomplete testing, and as the protocol became routine, incomplete results were reduced. The significantly lower incomplete screening rate and screening failure rate in the last 503 infants of the study compared with the first 500 suggests a training effect. One possible explanation for this reduction in the failure rate is due to more accurate nursing assessment as proficiency using the pulse oximetry equipment improved over time. It is also possible that nursing staff monitored infants for a longer period of time to achieve passing saturations as the study progressed. This could result in more time spent in the screening process but could also provide more accurate results.

The only association with various maternal and infant parameters that appeared to increase the likelihood of failing CCHD screening in our sample was gestational diabetes and infant weight (higher weights corresponding to greater risk). It is possible that these findings were associated with mildly inadequate alveolar surfactant production and resultant desaturation.\textsuperscript{24} No other risk factor in our population was statistically significant for predicting CCHD screening failure. This was mildly surprising because previous studies have noted lower saturations when infants were sleeping, taking a pacifier or bottle, or agitated.\textsuperscript{25}

Our study was limited by not having echocardiographic evidence of CCHD status for those infants who failed the screening or had incomplete screening. In our effort to obtain feasibility data, we wished to conduct screening in a manner most like other institutions that already use routine blood-derived screening tests. We strove to achieve screening without parental signed consent to achieve this goal. Colorado has not mandated CCHD screening, and there were limited Colorado institutions in which screening was performed before the study. The ability to conduct a large study required waiver of consent, and therefore follow-up echocardiograms were not part of the study protocol.

<table>
<thead>
<tr>
<th>TABLE 1 Associations With Screening Failure</th>
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<tbody>
<tr>
<td>Failed (n = 11)</td>
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<tr>
<td>-----------------</td>
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<tr>
<td>Gender, male</td>
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<td>Birth weight, mean</td>
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<td>Gestational age (wk), median</td>
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<tr>
<td>Multiple gestation</td>
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<td>Assisted reproduction</td>
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<td>Gestational diabetes</td>
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<td>Family history of CHD</td>
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<td>Concerning prenatal studies</td>
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<td>Other risk factors for CHD</td>
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<tr>
<td>Para status, median</td>
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<td>Gravida status, median</td>
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FIGURE 6
All studies used mean saturations ± SD with the exception of Ravert’s study\textsuperscript{15} who used a mean saturation and saturation range.
Similarly, because patient-specific identifiers were not recorded (allowing for waiver of consent and full waiver of Health Insurance Portability and Accountability Act authorization), follow-up after discharge was not possible.

CONCLUSIONS

Pulse oximetry has been shown to be a safe and effective screening tool for CCHD in newborns at sea level. Moderate and high altitude locations have several barriers to implementing the national criteria for CCHD screening, however, including potentially lower saturations and wider variation in saturation range. Our study revealed a correspondingly higher failure rate for CCHD screening at altitude when using sea level guidelines. Secondary to this, implementing the national screening for CCHD at moderate altitude is feasible but may result in increased economic, emotional, and logistical burdens on families, communities, and health resources. Alternative screening protocols should be evaluated in an attempt to optimize sensitivity while limiting the false-positive rates at higher elevations. Studies adjusting for the special relationship between saturations and moderate or high altitudes may lead to the way forward in screening for these disorders at all elevations.

ACKNOWLEDGMENTS

The authors would like to thank the nurses at the University of Colorado, Suchunya Aungkulanon, and Marci Sontag, PhD, for their invaluable contributions to this study.

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Pediatrics 2014;133;e561; originally published online February 24, 2014;
DOI: 10.1542/peds.2013-3284
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