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# Nomograms from 44647 Oxygen Saturations from Neonates Screened for Congenital Heart Disease in Northeast Brazil

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**Abstract**

**Background:** Pulse oxygen saturation (POS) is a great strategy for screening critical congenital heart disease. Nomograms for pre-ductal and post-ductal POS have been described, but several factors like skin color, ambient temperature, altitude, presence of anemia, and others can modify them. Therefore, the analysis of nomograms in a developing country can be useful to optimize the screening for critical congenital heart disease (CCHD).

**Objectives:** to describe and analyze results of nomograms derived from pulse oximetry saturations from newborns screened for critical congenital heart disease in a state in Northeast Brazil.

**Methods:** Asymptomatic newborns with gestational age equal or above 34 weeks were screened for critical congenital heart disease through physical examination and pulse oximetry. We divided them according to gender, Apgar, the time when the pulse oximetry was performed and gestational age. The results of pre and post ductal saturations were compared among these groups with non-parametric tests. Twenty health centers were included.

**Results:** 44647 newborns screened for critical congenital heart disease were analyzed. The mean for preductal saturation was 97.37% and for post-ductal saturation was 97.44%. Statistical differences were encountered between pre and postducal saturations in almost all groups. Preterm neonates had lower saturations when compared with term neonates ($p<0.001$).

**Conclusion:** Nomograms for pre and post-ductal saturations, and differences between them, were described in 44647 neonates from Northeast Brazil. These nomograms can be utilized to optimize screening criteria for critical congenital heart disease.

*Keywords:* Critical congenital heart disease, Oxygen saturation nomogram, Pulse oximetry screening universal screening

## 1. Background

Congenital heart disease (CHD) affects 8 in 1000 newborn babies (1), being one of the main causes of neonatal morbidity and mortality (2). Close to 30% of them will need surgical intervention in the first year of life and some as early as the first few days. The latter has the, so-called, critical congenital heart defects (CCHD).

Delayed diagnosis of CCHD leads to high mortality and morbidity as well as increasing hospital costs per patient (3). However, physical examination alone fails to identify 30 to 50% of CCHD before neonatal discharge (4). Thus, since 2011, arterial pulse oximetry (APO) has been proposed as an additional screening method for CCHD (5,6). But different APO screening methodologies have been described (7-10). Some include measurements of both pre and post-ductal oxygen saturations (O2-sat) while others use only post-ductal measurements (11). They also differ in proposed performance timing (varying between 4 to 72 hours) (9,12–15) and O2-sat cut-off points (from 92% to 96%). These methodological differences may explain different sensitivity (50% to 100%) and false-positive results (0.01% to 5.6%) reported with APO screening for congenital heart disease (7).

Within this scenario, reporting on normal O2-sat values from large datasets of children screened for CCHD can be of great value (7). Some studies have already shown that the majority of healthy newborn babies present saturations higher than ≥ 95%. However, there have been differences regarding which presents higher value (7). Until now, no O2-sat normogram for CCHD screening in developing regions has been reported. Therefore, the present study aims to describe nomograms of healthy neonates from a Brazilian Northeastern State screened for congenital heart disease with APO.

## 2. Methods

Screening program: A screening program for CCHD with APO was established in 2012 in 13 units in a Northeastern Brazilian State. In 2014, the program was expanded to 20 units. Local teams were trained to perform APO by skilled nurses. Neonates with suspected CCHD were further evaluated and managed with the support of pediatric cardiologists, via telemedicine, as reported elsewhere (16,17).

### *Population undergoing APO screening*

Asymptomatic neonates with gestational age ≥ 34 weeks were admitted to general neonatal wards.

### *Screening method*

All neonates underwent screening with APO and

a focused cardiovascular examination. Both were performed after 24h of life. Trained nurses obtained pre and post-ductal O2-sat in a sequential manner. Values were recorded on specific sheets and then uploaded to an online computer system. The equipment used had specific re-usable neonatal sensors (PM60, Mindray, Shenzhen, China). Sensors were placed on a right-hand finger for pre-ductal O2-sat and on a foot toe for post-ductal O2-sat. Screening was considered negative for CCHD when pre and post ductal saturations were ≥ 95% or the difference between them were ≤ 2%. Physical examination was performed by neonatologists and was considered positive in the presence of cyanosis, murmur or pulse alterations. All positive cases (physical exam and APO) were submitted to a screening echocardiogram by neonatologists under cardiology supervision, via telemedicine (17), and those with abnormal or inconclusive studies were referred to full evaluation by a pediatric cardiologist.

### *Data used*

O2-sat from all centers between Jan 2013 and 2014. The year 2012 was excluded from the analysis due to the elevated number of false positive APO tests, which reflected not only the learning curve of local teams but also the fact that the initial APO equipment was inadequate for the small neonatal fingers. Throughout that year, re-training sessions and equipment changes occurred in all Units. Also, cases missing one of the following information were excluded from the analysis: pre-ductal O2-sat, post-ductal O2-sat, first minute Apgar score, fifth minute Apgar score, gestational age, gender and time of APO test performance. Finally, all neonates with abnormal physical examination were excluded.

### *Data analysis*

Pre-ductal O2-sat distribution, post-ductal O2-sat distribution and their differences were summarized in means and medians. The mean, medians and percentiles for first and fifth minute Apgar scores, gender, gestational age and moment of APO test were calculated. As O2-sat do not follow a normal distribution, non-parametric tests were used. Pre and post ductal O2-sat were compared in different groups using the Mann-Whitney test. Within each group, the pre and post ductal O2-sat were compared using the Wilcoxon test; and the Kriskal-Walis was used for multiple groups. The statistical analysis was performed with the MedCalc Statistical Software version 15.2.1 (MedCalc Software bvba, Ostend, Belgium). A p-value <0.05 was considered statistically significant.

## 3. Results

From 53,680 neonates, 44,647 fulfilled all enrollment criteria. They were included in the study. The mean pre and post ductal O2-sat were respectively 97.37 % (CI: 97.36% to 97.39%) and 97.44% (CI: 97.42% to 97.45%). Pre-ductal O2-sats were lower (p<0.0001) than post-ductal ones. The median for both tests was 97%. At least 99.5% of the screened neonates presented O2-sat ≥96 %. The mean difference between pre and post ductal O2-sat was -0.062 (IC: -0.072 to -0.051), with at least 99.5% of all neonates presenting a difference of ≤4% and median of 0. Figures 1A and 1B summarize these results. Figure 2 shows the pre and post ductal O2-sat percentiles for gestational age. Table 1 shows pre and post ductal O2-sat values and the differences between them divided by age groups. There were no statistically significant differences between groups according to gender or first and fifth minute Apgar

**Table 1.** Distribution of pre and post ductal saturations per group

| | N | PRE-DUCTAL | POST-DUCTAL | DIFFERENCE | INSIDE THE GROUP |
|---|---|---|---|---|---|
| | | Mean (Median, 2.5-97.5 percentiles) | Mean (Median, 2.5-97.5 percentiles) | Mean | *P*a |
| **ALL** | 44647 | 97.375 (97, 95-100) | 97.436 (97, 95-100) | -0.062 | <0.0001 |
| **MALE** | 22914 | 97.369 (97, 95-100) | 97.438 (97, 95-100) | -0.069 | <0.0001 |
| **FEMALE** | 21733 | 97.380 (97, 95-100) | 97.415 (97, 95-100) | -0.054 | <0.0001 |
| ***P*B BETWEEN GROUPS** | - | 0.1961 | 0.6821 | 0.1637 | - |
| **TERM** | 42356 | 97.384 (97, 95-100) | 97.444 (97, 95-100) | -0.060 | <0.0001 |
| **PRE-TERM** | 2291 | 97.135 (97, 95-100) | 97.292 (97, 95-100) | -0.091 | 0.0008 |
| ***P*B BETWEEN GROUPS** | - | <0.0001 | <0.0001 | 0.3480 | - |
| **APGAR IN THE FIRST MINUTE ≥ 8** | 40375 | 97.376 (97, 95-100) | 97.437 (97, 95-100) | -0.061 | <0.0001 |
| **4 ≤ APGAR IN THE FIRST MINUTE ≤ 7** | 4014 | 97.3585 (97, 95-100) | 97.424 (97, 95-100) | -0.065 | 0.0001 |
| **APGAR IN THE FIRST MINUTE ≤ 3** | 258 | 97.368 (97, 95-99) | 97.461 (98, 95-100) | -0.093 | 0.3007 |
| **PC BETWEEN GROUPS** | - | 0.7314 | 0.5023 | 0.8282 | - |
| **APGAR IN THE FIFTH MINUTE ≥ 8** | 44034 | 97.374 (97, 95-100) | 97.436 (97, 95-100) | -0.062 | <0.0001 |
| **4 ≤ APGAR IN THE FIFTH MINUTE ≤ 7** | 590 | 97.398 (97, 95-100) | 97.461 (98, 95-100) | -0.063 | 0.4556 |
| **APGAR IN THE FIFTH MINUTE ≤ 3** | 23 | 97.478 (97, 96-100) | 97.304 (97, 95-100) | 0.1739 | 0.6304 |
| ***P*CBETWEEN GROUPS** | - | 0.6489 | 0.5675 | 0.6336 | - |

-, not applicable,
a P for Wilcoxon test
b P for Mann-Whitney test
c P for Kruskal-Wallis test

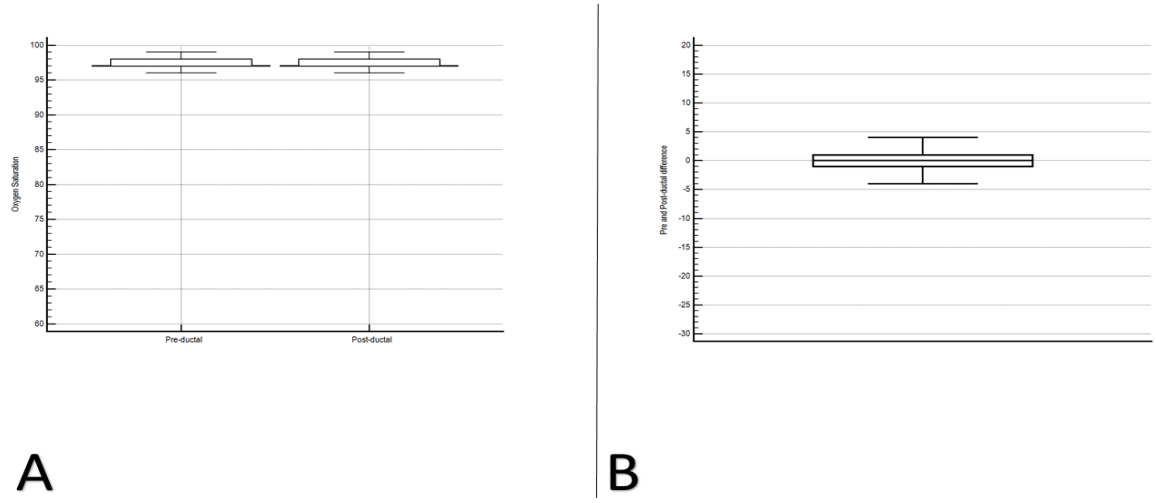


**Figure 1.** A- Nomograms of pre and post-ductal oxygen saturation in asymptomatic neonates. B- Nomogram of the pre and post-ductal saturation difference. The boxes represent the interquartile range of the percentiles 25 and 75. The lines that cross the boxes represent the median. The dots represent measurements of outliers (collection or typo). The "mustache wires" represent the values 1.5 times the interquartile range

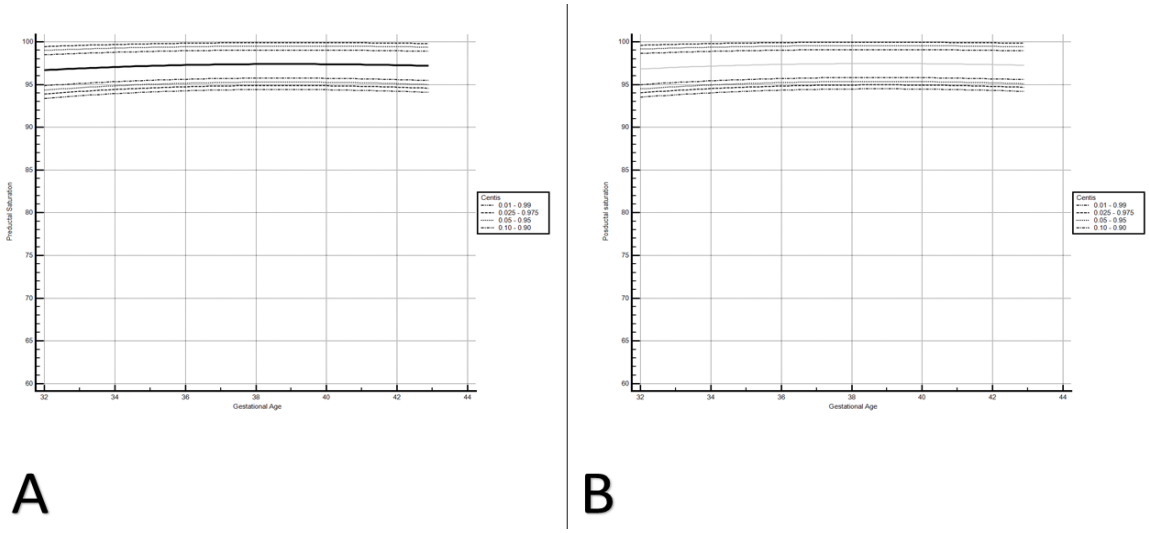


**Figure 2.** Percentiles of pre and post-ductal saturations by gestational age

**Table 2.** Pre and post ductal saturations by the time of screening

| TIME OF SCREENING | N | PRE-DUCTAL | POST-DUCTAL | DIFFERENCE | *P*A |
|---|---|---|---|---|---|
| | | Mean (Median, percentiles 2.5-97.5) | Mean (Median, percentiles 2.5-97.5) | Mean | |
| ≤24 HOURS | 3466 | 97.140 (97, 95-100) | 97.274 (97, 95-100) | -0.135 | <0.0001 |
| 25-48 HOURS | 29260 | 97.440 (97, 95-100) | 97.494 (98, 95-100) | -0.054 | <0.0001 |
| >48 HOURS | 11921 | 97.283 (97, 95-100) | 97.342 (97, 95-100) | -0.060 | <0.0001 |
| *P*B BETWEEN GROUPS | - | <0.0001 | <0.0001 | <0.0001 | - |

-. Not applicable
a *P* for Wilcoxon test
b *P* for Kruskal-Wallis test

scores. Preterm babies had lower pre and post ductal O2-sat than term ones (p<0.0001). In the majority of the cases, there were always statistically significant pre and post ductal O2-sat differences, with the exception of some Apgar groups. Nonetheless, this fact can be explained by the small size of the sample in these groups. The majority of neonates were screened after 24 hours of birth (65.54%), with

26.70% having the tests performed after 48 hours and 7.76% before the recommended 24 hours. Table 2 demonstrates the comparison between O2-sat and the timing of performance. There were significant pre and post ductal O2-sat differences within each group, similar to what is shown in table 1. Besides that, the analysis of multiple groups demonstrated significant differences in all cases. Three neonates were screened with age less than 34 weeks.

## 4. Discussion

This large neonatal dataset from a developing region demonstrated pre and post ductal O2-sat means, 97.37% (CI: 97.36% to 97.39%) and 97.44% (CI: 97.42% to 97.47%) respectively. These values are in accordance with some previous studies and slightly lower than others (7,18,19). Despite of some methodological differences among studies, this report supports the findings that the majority of neonates, born in different parts of the World, present with O2-sat ≥ 95% after 24 hours of birth.

As for pre and post ductal O2-sat differences, the present study demonstrated a mean of -0.062 (CI: -0.072 a -0.051), with at least 99.5% of all neonates showing ≤4% differences. These findings go against some APO screening protocols (9,10), which consider a 3% difference as an abnormal result. If other studies confirm our findings, changes in screening parameters could enhance test accuracy and diminish the number of unnecessary re-testing (20). The post-ductal O2-sats were only slightly higher, but with statistically significant differences ($p<0.001$) in nearly all groups. It had been previously demonstrated that in the first few hours after birth (18,21,22), pre-ductal O2-sat is higher than post-ductal one; however, these differences were not demonstrated after 24 hours.

Higher post-ductal O2-sat after 24 hours has been demonstrated in another study (7). In that study, pre and post-ductal APO tests were done simultaneously. In our methodology, however, the test was done sequentially; but we did find similar results. We believe that in the face of the expressive number of cases in our sample, this is a true finding, which may be harder to detect in smaller groups. As previously suggested by others (7), we feel that further discussions about these findings are important to better understand the underlying physiology and optimize the screening for CCHD. In regard to gestational age, we found that preterm neonates had lower pre and post ductal O2-sat. Other studies confirm these findings both at the first five minutes afterlife (23) as well as at approximately 24h later (7). In spite of the significant statistical differences encountered, the saturation levels are very close, making it improbable that such findings will have any impact on the establishment of screening cut-off points for CCHD.

The Apgar score was initially described in 1953 and since then, it has been one of the most utilized methods to evaluate neonates immediately after birth. In summary, it consists of the evaluation of 10 neonatal parameters, each receiving a score of 0 to 2, to a maximal score of 10. The evaluation is performed at one and five minutes after birth. The score serves, mainly, to identify those neonates who require immediate special care and low scores have been largely associated to increased neonatal mortality (24). Because of that, we hypothesized that the Apgar score could be related to APO O2-sat. However, as demonstrated by the results, there were no significant differences among groups. We could find no other study correlating Apgar scores with APO tests.

The timing of APO screening also influences the level of obtained O2-sat and the number of false-positive results (5). In the present study, it was demonstrated that besides differences between pre and post ductal saturations, there are differences between O2-sat obtained at different times.

The presentation of O2-sat normograms, obtained from large datasets, is important to further refine the methodology and results obtained from APO screening for CCHD. This study generated nomograms of neonates screened in a developing country, an exclusive data in the medical literature until now. A right-upper to lower limb difference in O2-sat ≤ 4% was observed in over 95% of healthy neonates. It also demonstrated, for the first time, that there is no correlation between Apgar scores and O2-sat.

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None.

## Conflicts of interest

None.

## Financial Disclosure

None

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