Oxygen Saturation Nomogram in Newborns Screened for Critical Congenital Heart Disease

WHAT’S KNOWN ON THIS SUBJECT: Universal oxygen saturation screening by pulse oximetry is now recommended for early detection of critical congenital heart disease. The distribution of saturations in asymptomatic newborns in a large population has not been described.

WHAT THIS STUDY ADDS: Our study is the largest to date to establish simultaneous pre- and postductal oxygen saturation nomograms in asymptomatic newborns at ~24 hours after birth. The mean postductal saturation is higher than preductal during this time.

OBJECTIVE: To establish simultaneous pre- and postductal oxygen saturation nomograms in asymptomatic newborns when screening for critical congenital heart disease (CCHD) at ~24 hours after birth.

METHODS: Asymptomatic term and late preterm newborns admitted to the newborn nursery were screened with simultaneous pre- and post-ductal oxygen saturation measurements at ~24 hours after birth. The screening program was implemented in a stepwise fashion in 3 different affiliated institutions. Data were collected prospectively from July 2009 to March 2012 in all 3 centers.

RESULTS: We screened 13,714 healthy newborns at a median age of 25 hours. The mean preductal saturation was 98.29% (95% confidence interval [CI]: 98.27–98.31), median 98%, and mean postductal saturation was 98.57% (95% CI: 98.55–98.60), median 99%. The mean difference between the pre- and postductal saturation was −0.29% (95% CI: −0.31 to −0.27) with P < .00005. Its clinical relevance to CCHD screening remains to be determined. The postductal saturation was equal to preductal saturation in 38% and greater than preductal in 40% of the screens.

CONCLUSIONS: We have established simultaneous pre- and postductal oxygen saturation nomograms at ~24 hours after birth based on >13,000 asymptomatic newborns. Such nomograms are important to optimize screening thresholds and methodology for detecting CCHD.
Critical congenital heart disease (CCHD) is defined as congenital heart disease that requires surgical intervention during infancy for survival. This occurs in 1 to 2/1000 live births, and fewer than 50% of these conditions are diagnosed prenatally. Some newborns with CCHD remain asymptomatic in the first few days after birth. Physical examination fails to identify 30% to 50% of CCHD before discharge.\(^2\) Delay in identification of CCHD leads to severe morbidity or mortality as many of these undiagnosed newborns become critically ill with cardiovascular collapse. Pulse oximetry screening can be used to identify CCHD in asymptomatic newborns to lessen the burden of undiagnosed CCHD.\(^5, 6\) Multiple studies have evaluated different screening methodologies including postductal oxygen saturation measurements alone,\(^6, 9\) or both pre- and postductal\(^14, 11\) saturations. There are also considerable differences in both the timing of screening (from 4 to 24–72 hours after birth)\(^15, 10\) and the threshold values (from \(\geq 92\%\) to \(\leq 96\%\)). This has led to widely varying sensitivity from 50% to 100% and false-positives from 0.01% to 5.6%. Increasing the sensitivity and reducing the false-positive rate requires optimizing the screening methodology. Accuracy and efficacy of CCHD screening programs depend on understanding oxygen saturation distribution in newborns in the first few days after birth. Oxygen saturation in newborns in the first week after birth was described in an early physiology study\(^11\) wherein blood gas oxygen saturation was measured by cooximetry. Subsequent studies have used noninvasive pulse oximetry to measure oxygen saturation. Our current knowledge of oxygen saturation in newborns comes from studies done immediately after birth\(^12, 14–16\) and in the first 24 hours after birth.\(^12, 17–20\) Some studies have assessed oxygen saturation from single sites alone and others from both pre- and postductal sites. The pre- and postductal saturations were obtained by sequential measurements\(^15, 18, 19\) in some studies and by simultaneous measurements in others.\(^12, 16\) Rosvik et al\(^20\) described postductal saturation in the first 6 hours in \(>6800\) newborns screened for CCHD, but there has been no similar study using both pre- and postductal oxygen saturation.

We implemented a pulse oximetry screening program in our institution in August 2009, following the de-Wahl Granelli method, which included pre- and postductal saturation screening\(^10\) and the Koppel method of screening after 24 hours.\(^8\) In addition, we measured pre- and postductal saturations simultaneously instead of consecutively. Evaluating pre- and postductal oxygen saturation in large numbers of asymptomatic newborns is essential in defining threshold values for CCHD screening. The objective of this study was to describe the distribution of simultaneous pre- and postductal oxygen saturation in asymptomatic newborns who undergo screening for CCHD at \(\sim 24\) hours after birth.

## METHODS

### Program Sites

We implemented the pulse oximetry screening program in a stepwise manner in 3 institutions. A pilot program was implemented in August 2009 at our primary site, center 1 (Santa Clara Valley Medical Center, San Jose, CA, a public hospital with \(\sim 5000\) deliveries annually with a regional level 3 NICU). We subsequently expanded to universal screening in January 2010. Universal screening was implemented in July 2011 at center 2 (O’Connor Hospital, San Jose, CA, a nonprofit hospital with \(\sim 4000\) deliveries annually with a community level 3 NICU), and in January 2012 at center 3 (St. Francis Medical Center, Lynwood, CA, a nonprofit hospital with \(\sim 6000\) deliveries annually with a community level 3 NICU). All 3 centers are at sea level (<100 ft elevation).

### Subjects

Asymptomatic newborns born at \(\geq 34\) weeks’ gestation admitted to the newborn nursery were screened utilizing pulse oximetry for CCHD at \(\sim 24\) hours after birth.

### Screening Method

Simultaneous pre- and postductal oxygen saturations of all asymptomatic newborns were recorded by nursing staff at \(\sim 24\) hours after birth. We used reusable probes with disposable wrap ($1.4–$1.9/disposable wrap; Masimo Corporation, Irvine, CA). The probes were placed on the right palm or wrist for prudential and on either foot for postductal saturation. The oxygen saturation values were recorded when both pre- and postductal pulse oximetry had stable waveforms and their heart rates were correlating. The equipment and pulse oximetry technology used in all 3 institutions were newer-generation, motion-tolerant devices (Table 1) with 8 to 10 seconds averaging time. The pulse oximetry screen was considered “pass” if either the

### TABLE 1 Pulse Oximetry Screening Equipment

<table>
<thead>
<tr>
<th>Center</th>
<th>Pulse Oximetry Equipment/Technology</th>
<th>Probes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center 1</td>
<td>*Masimo Rad-87/SET</td>
<td>Reusable</td>
</tr>
<tr>
<td>Center 2</td>
<td>Masimo Rad-5/SET and Philips/FAST</td>
<td>Reusable</td>
</tr>
<tr>
<td>Center 3</td>
<td>Masimo Rad-87/SET</td>
<td>Reusable</td>
</tr>
</tbody>
</table>

FAST, Fourier artifact suppression technology; SET, signal extraction technology.

* Masimo (Masimo Corporation, Irvine, CA).
* Philips (Philips Healthcare, Andover, MA).
pre- or postductal saturation was ≥95% and the difference between the 2 was ≤3%. The screen was considered a “fail” if either the pre- or postductal saturation was <90%. A fail triggered a prompt clinical evaluation by a pediatric provider and transfer to the NICU if indicated. The screen was repeated if either the pre- and postductal saturations were 90% to 94%, or there was a >3% difference. If the repeat screen within 4 hours remained the same, then it was considered a fail. Failed screens were followed with an echocardiogram before discharge.

Data Collection
The oxygen saturation values of all screens from August 2009 to March 2012 were documented by nursing staff and entered into study data set by a research assistant. The number of repeat screens was also collected. Those screens that had either pre- or postductal values missing were removed from the data set. Additional variables collected in a subset of newborns included the following: gestational age, birth weight, gender, and delivery type.

Data Analysis
The distribution of simultaneous pre- and postductal oxygen saturations and their differences is presented in a box plot and summarized as means with 95% confidence intervals (CIs) and medians with percentiles. The mean, median, and percentile values for the subgroups based on center, gender, gestational age (preterm versus term), and age of screening (<20 hours, 21–28 hours, 29–36 hours, 37–48 hours, and >48 hours) were calculated. As the oxygen saturations were not normally distributed but were skewed to the left, nonparametric tests were used for comparisons. Pre- and postductal saturations and their differences were compared between groups by using the Wilcoxon Mann-Whitney rank sum test and the Kruskal-Wallis test (for multiple groups). The paired pre- and postductal oxygen saturation differences were compared by using the Wilcoxon signed rank test. Statistical data analysis software Stata 10.0 (Stata Corp, College Station, TX) was used for the analysis.

The number of screens that needed to be repeated per protocol, number of fails per protocol, and the number of protocol violations per center were collected and summarized. Protocol violations were defined as failure to repeat a screen in newborns who met criteria for rescreening and failure to perform an echocardiogram in those who failed the screen.

RESULTS
Oxygen Saturation Nomograms
A total of 13 714 newborns were screened. The mean preductal saturation was 98.29% (95% CI: 98.27–98.31), and the median was 98%. The mean postductal saturation was 98.57% (95% CI: 98.55–98.60), and the median was 99% (Fig 1A). Of screened asymptomatic newborns, 99.5% had pre- or postductal saturations ≥95%. Figure 1B reveals the percentile distribution of the pre and postductal oxygen saturations.

Pre- and Postductal Saturation Difference
In our study, 99.5% of asymptomatic newborns had a pre- and postductal
saturation difference of $\leq 3\%$ (Fig 2). Pre- and postductal saturations were the same in 38%; preductal was greater in 22%, and postductal was greater in 40% of the screens. The mean difference between pre- and postductal saturation was $-0.29\%$ (95% CI: $-0.31$ to $-0.27$), which was statistically significant ($P < .00005$), and the median was 0.

**Subgroups**

The mean, median, and the percentile values of the pre- and postductal oxygen saturation in the different subgroups is shown in Table 2. There was no difference between the pre- and postductal saturation in boys versus girls. Preaductal values in the cesarean delivery group were higher than those delivered vaginally, but their postductal saturations were not different. Postductal saturation in preterm newborns was lower than term newborns, but their preductal saturations were not different. Center 2 had a higher preductal saturation compared with the others but not the postductal.

The mean difference between the pre- and postductal saturation ranged from $-0.12$ to $-0.33$, which was statistically significant in all subgroups. There was no significant difference between boys and girls, term versus preterms, or cesarean delivery versus vaginal delivery. However, center 2 had a lower difference of $-0.13$ compared with $-0.3$ in the other 2 centers.

**Age of Screening**

The age of screening data were available in 13,287 newborns. The median age of screening was 25 hours. Ninety-seven percent of screening was done between 21 and 36 hours. There was no significant difference in preductal or between pre- and postductal saturations between the age categories (Table 3). Although postductal saturation between the groups was statistically different, it did not remain significant when individual groups were compared. The pre- and postductal oxygen saturation differences ranged from $-0.21$ to $-0.49$ for all ages and are statistically significant.

**Screening Program**

In our study, on the first screening, 13,615 (99.3%) passed, 8 failed, and 91 (0.66%) required a repeat (Fig 3). Of the 91, only 55 screens were repeated; 5 failed the repeat screen. There were a total of 42 (0.3%) protocol violations; 35 due to failure to repeat a screen, 1 due to obtaining an echo before repeat, and 6 due to failure to obtain an echo for oxygen saturation <90%. The number of repeats, protocol violations, and failed screens by center is shown in Table 4. In total, 8 echocardiograms were done as a result of the CCHD screen, and 2 of those...
newborns had CCHD (Tetralogy of Fallot and Ebstein anomaly).

**DISCUSSION**

Our study is the first to establish simultaneous pre- and postductal oxygen saturation nomograms, at sea level, at \(~\)24 hours after birth, using a large sample of \(\geq 13\ 000\) asymptomatic newborns. We show that 99\% of the newborns have both pre- and postductal saturations \(\geq 95\%\) and that the preductal oxygen saturation is often less than postductal at the time of screening. This finding has not been previously reported.

We show that the mean (\(\pm\) SD) pre- and postductal oxygen saturations are 98.3 \(\pm\) 1.4 and 98.6 \(\pm\) 1.3, respectively. These values appear to be slightly higher than those described in earlier studies.\(^11,12,18,21\) In 1968, Koch et al\(^\text{11}\) used cooximetry from umbilical artery blood gases in 17 newborns and reported a mean (\(\pm\) SD) postductal oxygen saturation of 96.8 \(\pm\) 1.7 at 24 hours after birth. Dimich et al\(^\text{12}\) reported mean (\(\pm\) SD) pre- and postductal saturations of 95.7 \(\pm\) 2.2 and 95.2 \(\pm\) 2.3 at 24 hours in 100 newborns by using Ohmeda pulse oximetry. Fractional oxygen saturation measured this way may be up to 2\% lower than the pulse oximeters used in our study, as it approximates the average carboxyhemoglobin and methemoglobin levels present in healthy nonsmoking adults.\(^\text{22}\) A recent study with newer generation pulse oximetry describes the mean pre- and postductal saturation at 24 hours as 97.2 \(\pm\) 1.6.\(^\text{18}\) Despite these discrepancies, all these studies are consistent in revealing that a majority of newborns have oxygen saturation \(\geq 95\%\) at 24 hours after birth.

The difference between pre- and postductal saturation has been described in the first few days after birth. Studies done immediately after birth\(^\text{12,16}\) and within 4 hours after birth\(^\text{15,18}\) have revealed that the preductal is greater than the postductal saturation. Levine et al\(^\text{18}\) described pre- and postductal saturations measured consecutively by using Novametrix pulse oximetry on admission to the nursery, at 24 hours and at discharge in 718 normal newborns. They reported that there was a tendency for the preductal to be higher by 0.3\% than postductal at 2.7 hours after birth, but this difference was not observed at 24 hours. Dimich et al\(^\text{12}\) measured pre- and postductal saturations simultaneously at 24 hours in 100 newborns with a different pulse oximetry device (Ohmeda Biox 3700) and showed that the mean preductal saturation was higher than postductal saturation (although it did not attain statistical significance). Our observation that the mean preductal is lower than the postductal saturation has not been described previously. This difference is very small (\(-0.29\%) and within the inherent margin of error.

**TABLE 3** Pre and Postductal Oxygen Saturation Based on Age of Screening

<table>
<thead>
<tr>
<th>Age of Screening, h</th>
<th>n</th>
<th>Preductal Mean (Median, 1st–99th Percentile)</th>
<th>Postductal Mean (Median, 1st–99th Percentile)</th>
<th>Difference Mean</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>(&lt;\leq 20)</td>
<td>71</td>
<td>98.4 (99, 94–100)</td>
<td>98.9 (99, 96–100)</td>
<td>0.49</td>
<td>.001</td>
</tr>
<tr>
<td>21–28 h</td>
<td>1040</td>
<td>98.3 (98, 95–100)</td>
<td>98.6 (99, 95–100)</td>
<td>0.3</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>29–36 h</td>
<td>1983</td>
<td>98.3 (98, 95–100)</td>
<td>98.5 (98, 96–100)</td>
<td>0.21</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>37–48 h</td>
<td>234</td>
<td>98.2 (98, 95–100)</td>
<td>98.5 (98, 96–100)</td>
<td>0.23</td>
<td>.0039</td>
</tr>
<tr>
<td>(&gt;48) h</td>
<td>159</td>
<td>98.4 (99, 94–100)</td>
<td>98.8 (99, 96–100)</td>
<td>0.4</td>
<td>.0001</td>
</tr>
<tr>
<td>Between groups (\text{P}^b)</td>
<td></td>
<td>.6</td>
<td>.0015</td>
<td>.06</td>
<td></td>
</tr>
</tbody>
</table>

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**TABLE 4** Screening Program

<table>
<thead>
<tr>
<th>Center</th>
<th>Total Screened</th>
<th>Repeat Screens</th>
<th>Protocol Violations</th>
<th>Failed Screens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Center 1</td>
<td>10 290</td>
<td>62</td>
<td>29</td>
<td>4</td>
</tr>
<tr>
<td>Center 2</td>
<td>2081</td>
<td>11</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Center 3</td>
<td>1343</td>
<td>18</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>13 714</td>
<td>91 (0.7%)</td>
<td>42 (0.3%)</td>
<td>13 (0.1%)</td>
</tr>
</tbody>
</table>

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**FIGURE 3**

Screening program flow diagram.

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**TABLE 3** Pre and Postductal Oxygen Saturation Based on Age of Screening

* Data not applicable.
*\(P\) is from Wilcoxon signed rank test.
*\(P\) is from Kruskal-Wallis multiple group comparisons.
infants born by cesarean delivery.\textsuperscript{20} The study also revealed higher postductal saturations at 5 minutes after birth.\textsuperscript{13,16,24,25} In our study, the preductal saturation was lower than or equal to the postductal saturation in most cases. This observation is unlikely to be due to random chance because the same discrepancy was observed in all 3 centers despite the use of different devices. Although this finding is of unclear clinical significance, it may be relevant to the discussion of the optimal screening methodology to detect CCHD and requires further validation. Delivery room studies have revealed that infants born via cesarean delivery have lower oxygen saturation immediately after birth and that it increases within few minutes after birth.\textsuperscript{13,16,24,25} Interestingly, we found that both pre- and postductal saturations at 24 hours after birth were slightly higher in those born via cesarean delivery compared with those delivered vaginally, although only the preductal saturation was statistically significant. Another recent large study also revealed higher postductal saturation between 2 and 24 hours in infants born by cesarean delivery.\textsuperscript{20} Again, the reason for this observation is unclear. Multiple studies have revealed that preterm newborns have lower saturations at 5 minutes after birth.\textsuperscript{14,25} We found that this persists even at 24 hours. Even though these differences in cesarean delivery versus vaginal deliveries and term versus preterm newborns are statistically significant, they are too small to indicate a different threshold for CCHD screening.

Pulse oximetry has been used in multiple CCHD screening studies since the early 2000s with different methods. The variability of published false-positive rates is most related to age at screening. Mahle et al.\textsuperscript{26} summarized that the false-positive rate was 0.035% when the screening was done after 24 hours compared with 0.9% for all studies including early screening at 4 to 6 hours. Our experience reveals that very few newborns (0.09%) fail the screen when done at 24 hours. There is still controversy regarding whether to do both pre- and postductal screens or only postductal for CCHD screening. There were 2 cases in the 39 821 screened by de Wahl Granelli et al.\textsuperscript{19} that were detected only by the difference between pre- and postductal difference. In our experience, the nursing time for the total screen was <5 minutes, which led to minimal increase in cost. We used the reusable probe to do our screening that led to an added cost of <$1.5 per screen. We followed the de-Wahl Granelli method of screening both pre- and postductal saturations to increase the detection of CCHD cases and justified the minimal added cost.\textsuperscript{4,19} In our study, 91 newborns required a repeat screen, 75% of which were triggered by a >3% difference; 90% passed the repeat screen. The number of CCHD cases in our study is too small to make any argument regarding single post ductal versus pre- and post ductal screens. In fact, the cumulative published saturation experience to date may still be insufficient to make conclusions about the optimal methodology for CCHD screening. Regardless of what methodology is used, ongoing oxygen saturation data collection in large numbers is essential to better refine the thresholds for CCHD screening in the future. Furthermore, cost-effectiveness analysis need to be performed to address whether the added cost of both pre and post ductal screening justify the benefit of increase in sensitivity to detect CCHD.

Our study protocol is identical to the recent national recommendation put out by the work group for the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children, which strategized implementation of screening for CCHD\textsuperscript{27}; therefore, it is important to evaluate our protocol adherence. We had successful protocol adherence in 99.7% of the newborns from all 3 centers, demonstrating the feasibility of this protocol. There were 42 (0.3%) protocol violations in our study: 35 due to failure to repeat a screen, 1 due to obtaining an echo before repeat screening, and 6 due to failure to obtain an echocardiogram for oxygen saturation <90%. Eight newborns who failed the first screen with saturation <90% should have undergone an echocardiogram per protocol, but 6 out of the 8 had a repeat screen and passed. This suggests a role for repeating the screen even when 1 saturation is <90% in asymptomatic newborns. This would further decrease the number of unnecessary echocardiograms done due to failed screens. As universal screening becomes more widespread, it is critical that protocol adherence be monitored carefully.

One of the important limitations of our study is that we do not have the outcomes of all screened newborns, especially those with protocol violations who did not get a repeat screen. We did have follow-up data from readmissions with CCHD, outpatient echocardiograms in the first year, and deaths due to CCHD in the birthing county to identify missed cases. However, linkage of the birth hospital data to the Society of Thoracic Surgeons national database (STS) and interventional cardiology, Improving Pediatric And Adult Congenital Treatment (IMPACT) data sets and deaths due to undiagnosed CCHD is unavailable for accurate identification of all missed CCHD cases. We used only 2 types of pulse oximetry devices in our study in all 3 centers. The finding that mean
postductal saturation is higher than preductal saturation should be validated in other study settings with other devices and technology. The saturation data were recorded manually by the nurses who performed the screen, leaving room for human error during transcription, and systematic bias of picking the highest number with an intention to pass. A more accurate method would be to download the pulse oximetry data electronically.

CONCLUSIONS
Pre- and postductal oxygen saturation nomograms from large numbers are essential to further refine methodology for CCHD screening. Hence ongoing data collection and review of newborn populations screened for CCHD is essential. Linkage of the birth hospital data to cardiothoracic surgery data sets such as STS and IMPACT and to vital statistics are essential to accurately identify all CCHD cases missed by screening.

ACKNOWLEDGMENTS
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