

# Day-night fluctuation of pulse oximetry: An exploratory study in pediatric inpatients

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## ABSTRACT

**Background.** Pulse oximetry is a simple and non-invasive procedure widely used nowadays in the clinical practice. However, it is unclear if SpO<sub>2</sub> values are constant throughout the 24 hours of the day or have periodic fluctuations. In the present study we evaluated if progressive day-night variations of SpO<sub>2</sub> values occur in children. **Material and methods.** Pulse oximetry (Nonin 2500) was carried out approximately every 2 hours during a 24-hours period in pediatric patients hospitalized due to different diseases but without acute or chronic respiratory diseases. Measurements were analyzed through the cosinor method (sinusoidal curve fitting). **Results.** A total of 131 patients (23 days to 16 years old) were studied. A sinusoidal fitting of the SpO<sub>2</sub> values was accomplished in 84.7% of children. According to these curves, maximal SpO<sub>2</sub> values occurred in the late afternoon [4:53 PM (3:49-5:32 PM), median (quartile 1-quartile 3)], while minimal values appeared in the first hours of the day [3:06 AM (2:12-4:08 AM)]. This pattern was the same in sleeping or awake children. More than half of these sinusoidal curves had a period near to 24 hours (between 20 and 28 hours). An additional finding was that maximal and minimal SpO<sub>2</sub> values diminished with age (~0.15 and ~0.13% SpO<sub>2</sub> per year, respectively). In children less than six years old 5<sup>th</sup> percentile of SpO<sub>2</sub> values were 93.8% in the late afternoon and 89.8% in the early hours of the day, while corresponding figures for older children were 91.0% and 88.5%, respectively. **Conclusions.** Our results suggested that, regardless of the sleep influence, in most children the SpO<sub>2</sub> follows a progressive fluctuation during a 24-hours cycle, a pattern which is suggestive of a circadian rhythm. A prospective study in healthy children is warranted.

**Key words.** Pulse oximetry. Oxygen saturation. Circadian rhythm. Hypoxemia. Lung function. Gas exchange. Reference values.

## Fluctuación diurna-nocturna de la oximetría de pulso. Estudio exploratorio en pacientes pediátricos hospitalizados

### RESUMEN

**Antecedentes.** La oximetría de pulso es un procedimiento simple y no invasivo que se usa muy frecuentemente en la práctica clínica. Sin embargo, no está bien descrito si los valores de SpO<sub>2</sub> son constantes durante las 24 horas del día o presentan fluctuaciones periódicas. En el presente estudio evaluamos si existen cambios progresivos diurnos y nocturnos de la SpO<sub>2</sub> en niños. **Material y métodos.** Se efectuó oximetría de pulso (Nonin 2500) aproximadamente cada dos horas durante un periodo de 24 horas en pacientes pediátricos hospitalizados por diversas enfermedades pero sin afección respiratoria aguda o crónica. Las mediciones se analizaron por el método de cosinor (ajuste de curva sinusoidal). **Resultados.** Se estudiaron 131 pacientes (23 días a 16 años de edad). En 84.7% de los niños se pudo ajustar una curva sinusoidal a los valores de la SpO<sub>2</sub>. De acuerdo con estas curvas, los valores máximos de SpO<sub>2</sub> ocurrieron por la tarde [4:53 PM (3:49-5:32 PM), mediana (cuartil 1-cuartil 3)], mientras que los valores mínimos se presentaron en la madrugada [3:06 AM (2:12-4:08 AM)]. Este patrón fue el mismo tanto en niños dormidos como despiertos. Más de la mitad de las curvas sinusoidales tuvieron un periodo cercano a las 24 horas (entre 20 y 28 horas). Un hallazgo adicional fue que la SpO<sub>2</sub> máxima y mínima disminuyó conforme avanzaba la edad (~0.15 y ~0.13% SpO<sub>2</sub> por año). En niños menores de seis años de edad el percentil 5 de los valores de SpO<sub>2</sub> fue de 93.8% por la tarde y 89.8% en la madrugada, mientras que en niños mayores fue de 91.0% y 88.5%, respectivamente. **Conclusiones.** Nuestros resultados sugieren que, independientemente de la influencia del sueño, en la mayoría de los niños la SpO<sub>2</sub> sigue una fluctuación progresiva durante un ciclo de 24 horas, lo cual es sugestivo de un ritmo circadiano. Es conveniente realizar estudios adicionales en niños sanos.

**Palabras clave.** Oximetría de pulso. Saturación de oxígeno. Ritmo circadiano. Hipoxemia. Función pulmonar. Intercambio gaseoso. Valores de referencia.

## INTRODUCTION

Arterial oxygen saturation ( $\text{SaO}_2$ ) is a valuable measurement for monitoring the patient's cardiopulmonary status, but it has the disadvantage that is an invasive procedure that requires an arterial blood sample. Peripheral blood oxygen saturation ( $\text{SpO}_2$ ) measured by pulse oximetry has to a great extent replaced this measurement. Pulse oximeters measure the percentage of oxyhemoglobin in relation to the sum of oxyhemoglobin plus reduced hemoglobin, but do not include the other two hemoglobin species that may be present, methemoglobin and carboxyhemoglobin. Thus,  $\text{SpO}_2$  slightly differ from  $\text{SaO}_2$  measured in blood gas analyzers, since these last equipments take into account the four hemoglobin species. Nevertheless, in spite of these and other limitations, pulse oximetry has been a major contribution to patient monitoring, and is currently widely used in many clinical settings.<sup>1,2</sup>

Reference values for  $\text{SpO}_2$  have been published by several studies in healthy children<sup>3-6</sup> and adults,<sup>7-9</sup> most of them concluding that  $\text{SpO}_2$  values lower than 90% or 92% should be considered abnormal. However, these studies have been usually accomplished through overnight polysomnography, and hence an analysis of the  $\text{SpO}_2$  values during the full 24-h period is lacking. This limitation precludes the recognition of potential day-night  $\text{SpO}_2$  fluctuations. Studies aimed at investigating whether a progressive circadian fluctuation of  $\text{SpO}_2$  is present in healthy or sick individuals are surprisingly scarce.<sup>10-12</sup> Thus, the objective of the present work was to explore  $\text{SpO}_2$  fluctuations during a 24-h period in children without respiratory diseases.

## MATERIAL AND METHODS

This was a prospective study carried out at the Hospital de Pediatría, Centro Medico Nacional Siglo XXI, Instituto Mexicano del Seguro Social, which is a tertiary level, 175-bed pediatrics hospital located in Mexico City (2,240 m above sea level, 19° 26' N latitude, 99° 07' W longitude). The study was conducted from January to July, when duration of daylight progressively increases from ~ 11 h (January) to a peak of ~ 13.3 h (June) and then diminishes to ~ 13 h (July). The protocol was approved by the institutional Scientific and Bioethics Committee.

Patients in any clinical ward, excepting the intensive and post-operative care units, and without an established diagnosis of acute or chronic respiratory diseases were considered for participation in the stu-

dy. By self or parental reports we corroborated that children were free of acute or chronic respiratory complaints. After a signed letter of consent was obtained from patients' parents or guardians, a physical examination was performed to corroborate the absence of respiratory signs and exclusion criteria. Afterward,  $\text{SpO}_2$  was measured approximately every two hours during a 24-h period (i.e., a total of twelve measurements were obtained from each patient). For practical reasons, this measurement period was nearly always assigned for Saturday morning through Sunday morning. The official local time (clock-hour) was always used even during the summer daylight saving time, which in Mexico City is applied from the first Sunday of April through the last Sunday of October. The most recent hemoglobin concentration value measured within the past 30 days was obtained from the patient's clinical chart. Exclusion criteria included administration of sedatives, anticonvulsants, or anesthetics in the last 72 h, history of frequent snoring (to avoid inclusion of children with sleep apnea syndrome), history or ancillary studies suggestive of gastroesophageal reflux, delayed capillary filling ( $> 3$  s), total arrhythmia, and fever ( $> 37.5$  °C). A pulse oximeter (model 2500, Nonin Medical Inc., Plymouth, MN, USA) equipped with a non-disposable, rigid, articulated finger clip pediatric sensor was put in a finger of either hand, selecting the finger that best fitted the sensor probe. After a stabilization period of approximately 15-30 sec,  $\text{SpO}_2$  values were read during 1 min to obtain the modal value. All  $\text{SpO}_2$  measurements were performed while the child was calmed. Accuracy of pulse oximeters has been considered to be between  $\pm 2\%$  and  $\pm 4\%$  for readings above 70%,<sup>13</sup> and a good correlation between cooximetry and  $\text{SpO}_2$ , as measured with a more portable oximeter of the same manufacturer, was observed at the same altitude than in our study.<sup>14</sup>

Circadian rhythmicity was assessed through the cosinor method.<sup>15</sup> Thus, for every subject, a sinusoidal curve fitting (Levenberg-Marquardt method) was applied to the  $\text{SpO}_2$  measurements performed during the 24-h cycle by using the CurveExpert version 1.38 computer software (Daniel Hyams, USA). The general equation to describe a sinusoidal function is as follows:

$$y = a + b \cdot \cos(cx + d)$$

**Where:** **y:** Is the resulting  $\text{SpO}_2$  at the selected time variable (*x*). **a:** Is the mesor (the midline estimating statistic of rhythm, which is close to the arithmetic average of  $\text{SpO}_2$  values in one pe-

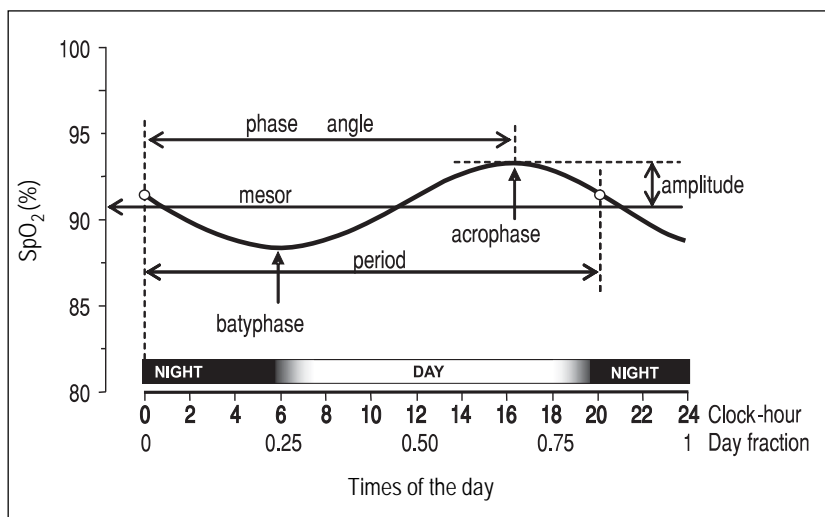


Figure 1. Variables of day-night rhythmicity obtained through the sinusoidal curve fitting (see the text).

riod). **b**: Is the amplitude (one half the difference between peak and trough SpO<sub>2</sub> values). **c**: Is 2 $\pi$ /period of the circadian rhythm (the period is the duration of a full cycle of the curve). **d**: Is the phase angle (Figure 1).

From these parameters, acrophase and bathyphase (time at which the highest and lowest SpO<sub>2</sub> values, respectively, are achieved) could also be derived. A global sinusoidal curve was also obtained after pooling SpO<sub>2</sub> values from all patients in whom an individual sinusoidal curve fitting could be demonstrated. With the aim of homogenizing day-night changes among children, the delta SpO<sub>2</sub> values (i.e., the actual SpO<sub>2</sub> value minus the mesor value) were calculated before the global sinusoidal curve fitting was applied.

The potential influence of sleep on the day-night SpO<sub>2</sub> fluctuation was assessed by separately analyzing the SpO<sub>2</sub> values obtained during the awake state and those obtained during sleep.

Due to the lack of normal distribution in most variables, a non-parametric approach was used. Thus, Mann-Whitney U test and Fisher exact test were used to evaluate differences in several variables between children with and without sinusoidal fitting. Kruskal-Wallis test followed by Dunn's test for multiple comparisons were used to evaluate SpO<sub>2</sub> values from awoken and sleeping children. Spearman's correlation coefficient ( $r_s$ ) was utilized to assess the possible influence of age on maximal and minimal SpO<sub>2</sub> values. Finally, multiple linear regression (stepwise approach) was performed to simultaneously evaluate the influence of sleep and hour of the day (as fraction of 24 h, starting at 9:00 AM) in the va-

riability of SpO<sub>2</sub> values during the 24 h cycle. This same analysis was also performed to evaluate the influence of gender, age, body mass index and hemoglobin concentration on the sinusoidal curve mesor. Data in the text and illustrations correspond to frequencies or median and quartile 1-quartile 3. Statistical significance was set at two-tailed  $p < 0.05$ .

## RESULTS

A total of 131 patients (53 females) from 23 days to 16 years of age (median, 6.9 years) were included in the study. The majority of these children had neoplastic (28.2%), gastroenterological (24.4%) or nephrologic (10.7%) diseases. A sinusoidal curve fitting of the SpO<sub>2</sub> measurements could be accomplished in 111 (84.7%) patients (in some of these patients, one SpO<sub>2</sub> value was replicated or eliminated to make the sinusoidal fitting evident). Examples of such sinusoidal curves can be observed in figure 2. There were no statistically significant differences regarding gender, age, weight, height, and hemoglobin concentration between these children and those without a clear SpO<sub>2</sub> circadian pattern (Table 1).

According to the individual sinusoidal curves, acrophases, i.e., maximal SpO<sub>2</sub> values, occurred in the late afternoon, at a median (quartile 1-quartile 3) clock-hour of 4:53 PM (3:49-5:32 PM), while bathyphases, i.e., minimal SpO<sub>2</sub> values, took place in the first hours of the day, at 3:06 AM (2:12-4:08 AM). At these time points, the calculated maximal SpO<sub>2</sub> values reached 95.9% (94.7-97.3%), while minimal values were 92.5% (91.1-93.8%), respectively. Difference between maximal and minimal SpO<sub>2</sub> values was 3.1 %SpO<sub>2</sub> (2.4-4.4 %SpO<sub>2</sub>). Finally, the length of the

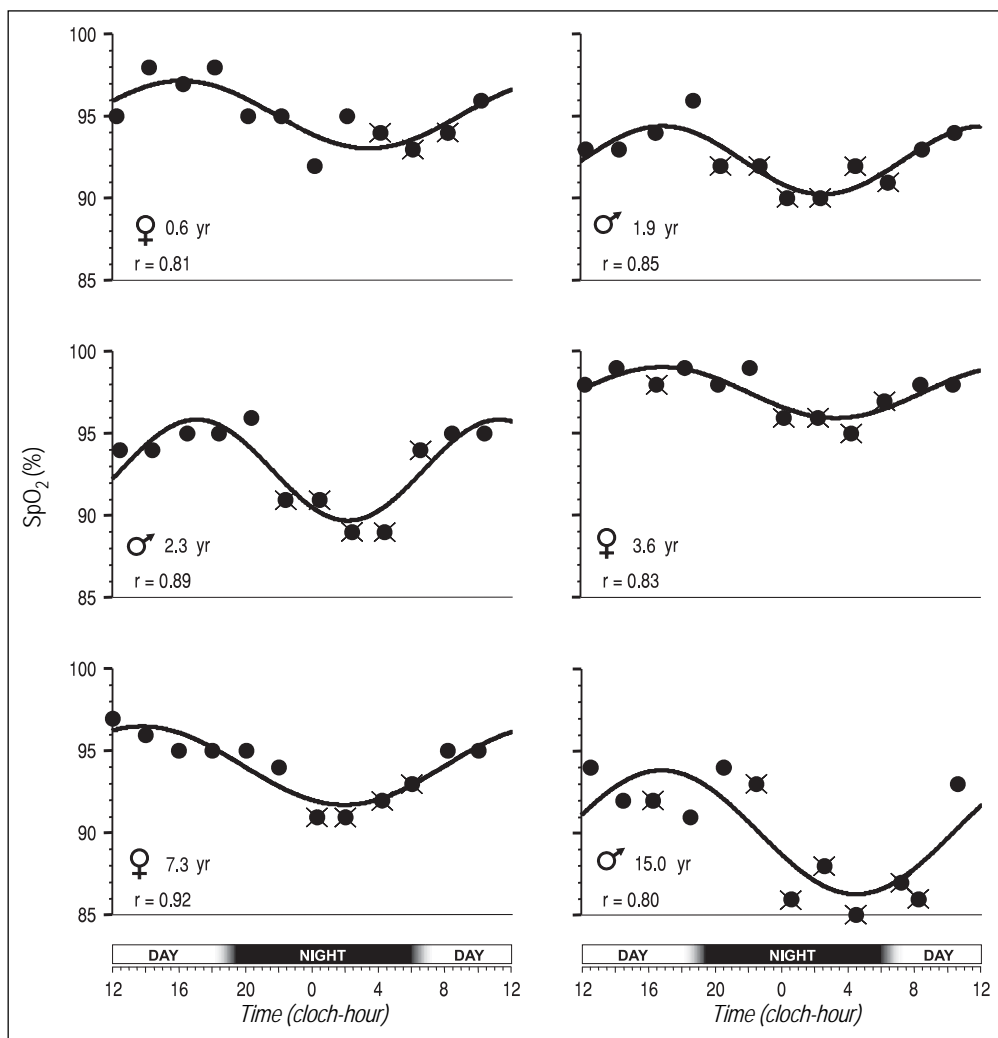


Figure 2. Examples of the sinusoidal curve fitting of day-night SpO<sub>2</sub> values in children. Subject's gender and age, as well as the correlation coefficient (*r*) are shown for each curve. Cross-marked circles correspond to SpO<sub>2</sub> values obtained when the child was sleeping.

Table 1. Characteristics of children with or without a sinusoidal curve fitting of SpO<sub>2</sub> values.

Characteristic	With sinusoidal curve (n = 111)	Without sinusoidal curve (n = 20)	p
Gender (F:M)	43:68	10:10	0.45
Age (years)	6.8 (0.063 to 16.6)	3.2 (0.139 to 15.7)	0.31
Weight (kg)	20.5 (2.1 to 90.7)	14.1 (3.0 to 59.6)	0.20
Height (cm)	108.0 (45.0 to 178.0)	90.5 (52.0 to 152.0)	0.18
Hemoglobin (g/dL)	13.3 (7.0 to 16.4)	11.7 (8.4 to 14.5)	0.05

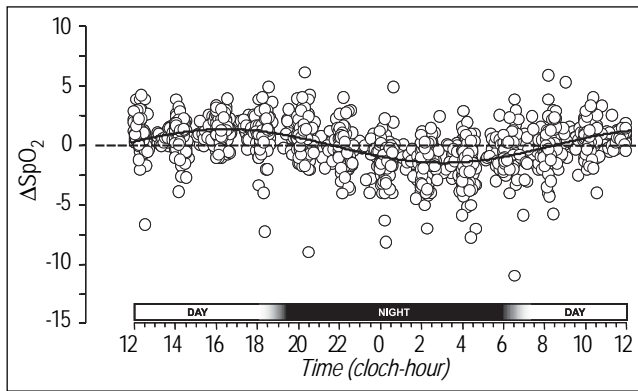
Values correspond to frequencies or median (range).

periods was 20:55 h (18:08-22:57 h). More than half (54.1%) of these periods were between 20 and 28 h in length, whereas 42.3% of them were shorter than 20 h, and 3.6% were larger than 28 h.

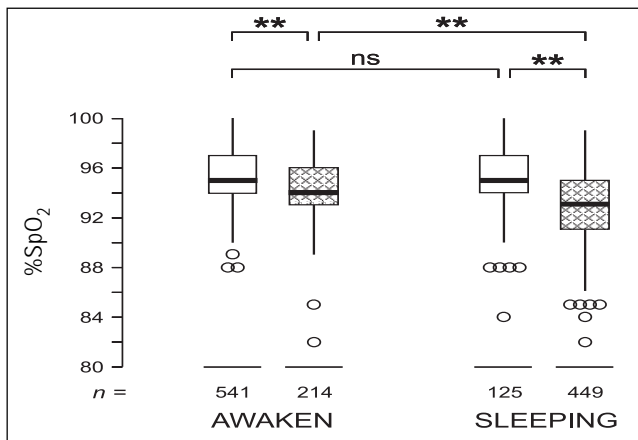
When SpO<sub>2</sub> measurements from all children with day-night rhythmicity were pooled, the single global sinusoidal curve showed values close to those obtained

by means of individual curves, i.e., acrophase at 4:26 PM, bathyphase at 3:02 AM, difference between peak and trough SpO<sub>2</sub> values (i.e., twice the amplitude) of 2.8 %SpO<sub>2</sub>, and the length of the period was 21:12 h (Figure 3).

We corroborated that a global sinusoidal curve fitting could be achieved even when only SpO<sub>2</sub> va-



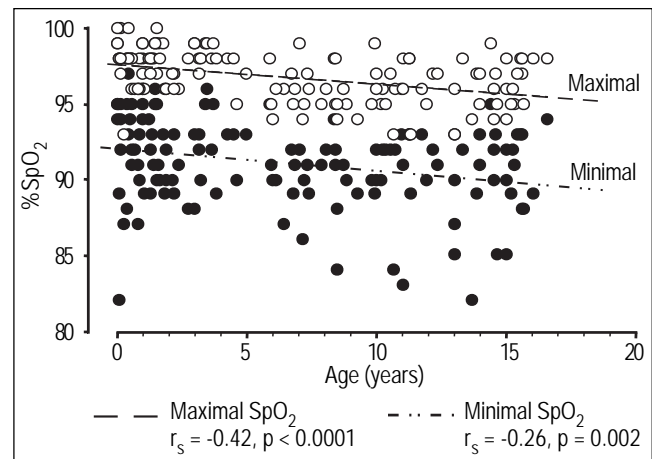
**Figure 3.** Day-night fluctuation of SpO<sub>2</sub> values in 111 children. A total of twelve SpO<sub>2</sub> measurements were performed in each subject throughout the 24-h cycle. Continuous line corresponds to the sinusoidal fitting, with formula  $y = 0.006 + 1.4 \cdot \cos(7.11x - 1.31)$ , and the horizontal broken line corresponds to its mesor. Symbols represent the difference between the actual SpO<sub>2</sub> measurement and the mesor of the individual's curve fitting.



**Figure 4.** Boxplots of the day-night differences of SpO<sub>2</sub> values in awoken and sleeping children. A significant decrease of SpO<sub>2</sub> values was observed at nighttime (from 9:00 PM to 9:00 AM, cross-hatched bars), as compared with daytime (from 9:00 AM to 9:00 PM, open bars), in both awoken and sleeping children. The number (n) of SpO<sub>2</sub> measurement in each condition is shown at the bottom of the figure. \*\*p < 0.001, ns = non-significant

lues from awoken children were taken into account, and the same occurred with SpO<sub>2</sub> measurements from sleeping children (data not shown). Moreover, SpO<sub>2</sub> attained lower values at night regardless of the condition (sleeping or awoken) in which oximetry was carried out (Figure 4). In the multivariate analysis we corroborated that both sleeping state and hour of the day were associated to lower SpO<sub>2</sub> values (standardized  $\beta$ -coefficients: 0.213 and -0.204, respectively,  $p < 0.001$ ).

On the other hand, both maximal and minimal SpO<sub>2</sub> values from each of the 131 children, at whatever hour of the day or night they occurred, diminished as age increased (Figure 5). These trends had an  $r_s = -0.42$  ( $p < 0.0001$ ) and  $r_s = -0.26$  ( $p = 0.0024$ ), respectively, and represent a decline of about 0.15 and 0.13%SpO<sub>2</sub> each year. A similar trend was observed in children with sinusoidal fitting in the multivariate analysis, since age was the only variable in the final model, discarding the influence of gender, body mass index and hemoglobin concentration.



**Figure 5.** Modifications of extreme SpO<sub>2</sub> values according to age. The scatter graph shows both maximal (open symbols) and minimal (closed symbols) SpO<sub>2</sub> values observed during a 24-h period in 131 children.

**Table 2.** Percentile values of %SpO<sub>2</sub> found in children according to age and clock hour.\*

Percentile	Children 0 to < 6 years old (n = 51)		Children 6 to < 17 years old (n = 60)	
	Late afternoon	Early morning	Late afternoon	Early morning
3	92.8	89.3	90.7	87.7
5	93.8	89.8	91.0	88.5
<b>50 (median)</b>	<b>97.0</b>	<b>94.5</b>	<b>95.0</b>	<b>92.0</b>
95	99.3	96.8	97.5	94.0
97	99.5	97.0	97.6	94.7

\* Late afternoon values correspond to the average of SpO<sub>2</sub> measurements obtained from 3 PM to 7 PM, while early morning values are those obtained from 1 AM to 5 AM. The majority of late afternoon measurements were obtained while children were awake, while nearly all early morning values were from children asleep.

Some percentile values of SpO<sub>2</sub> in younger (0 to < 6 years old) and older (6 to < 17 years old) children are shown in table 2.

## DISCUSSION

In the present study we found that SpO<sub>2</sub> values progressively changed during the day and night in most children, with maximal values occurring in the evening and minimal at early hours of the day. In more than half of these children such day-night fluctuations took place regardless of the sleep influence and their sinusoidal pattern had a period length close to 24 h (from 20 to 28 h), which is highly suggestive that a circadian rhythm was present.<sup>16</sup>

Although a great number of publications have described sudden nocturnal SpO<sub>2</sub> drops related to apneas/hypopnoeas (within the disorder known as obstructive sleep apnea syndrome<sup>17</sup>), a circadian fluctuation of arterial hemoglobin saturation or oxygen pressure has been scarcely mentioned in the medical literature. In 1972, Reinberg and Gervais<sup>10</sup> found that arterial oxygen pressure (PaO<sub>2</sub>) was lower during the night in adults with or without chronic airway obstruction. In 1985, Uptide, *et al.*<sup>11</sup> studied six preterm newborns and found that transcutaneous oxygen pressure (tcPO<sub>2</sub>) followed a circadian rhythm, with minimal values during the early hours of the day, though this only occurred in one half of patients. By contrast, in 1985 Postma, *et al.*<sup>12</sup> were unable to demonstrate a circadian variability of PaO<sub>2</sub> or SpO<sub>2</sub> in eight healthy adult male subjects, although such a rhythm was evident in eight patients with chronic airway obstruction.

It is well known that living organisms are often subjected to progressive changes at the biochemical, cellular, and/or functional levels during 24-h cycles, being a sinusoidal function the mathematical equation that often describes this circadian fluctuation.<sup>18</sup> In the present study we found that in general this was the case for SpO<sub>2</sub> values. A possible explanation for this diurnal-nocturnal variation of SpO<sub>2</sub> probably relies on the fact that ventilation and perfusion, the two most important factors determining blood oxygenation, likely follow a circadian pattern. Airway patency possesses a well-demonstrated circadian variability, with the lowest caliber occurring at approximately 4:00 AM and the highest at approximately 4:00 PM.<sup>19,20</sup> In turn, pulmonary blood flow is under neurohormonal influences that are subjected to a circadian pattern. For example, both vagal tone and plasma histamine concentration, which produce

vasodilation of the pulmonary microcirculation, are higher at early hours of the day and lower in the late afternoon.<sup>21</sup> Conversely, sympathetic tone and plasma concentrations of adrenaline and glucocorticoids, which promote vasoconstriction, are lower in the early hours of the day and higher in the late afternoon.<sup>22,23</sup> Therefore, fluctuations in alveolar ventilation and pulmonary circulation throughout the 24-h cycle might well explain progressive changes in the ventilation/perfusion ratio. The maximal imbalance of this ratio (i.e., lowest ventilation, highest perfusion) leading to a diminished SpO<sub>2</sub>, would be theoretically reached at the early hours of the day.

Independently of any influence of circadian rhythms, the sleeping state *per se* can modify a number of bodily functions, including the respiratory and cardiovascular patterns, and some research groups have described that sleep may cause a mild decrement of the SpO<sub>2</sub> value.<sup>24</sup> Thus, we were interested in assessing the possible role of sleep in the decrease of SpO<sub>2</sub> frequently observed at night in the study subjects. Our results could indeed show that sleep lowered SpO<sub>2</sub> values, but they also demonstrated that SpO<sub>2</sub> attained lower values at night in spite of the awaken or sleeping state, supporting the presence of a circadian rhythm.

By definition, a circadian rhythm should approximate 24 h in length, though it may range from 20 to 28 h. Obviously, it would be expected that those rhythms that do not exactly measure 24 h in length experience a progressive phase drift in the course of several days, i.e., the time at which acrophase occurs will progressively change day by day. To avoid such phase drift, the rhythm is "reset" every 24 h by an external synchronizer (also named *zeitgeber*) such as daylight. In this context, and due to the large variability of phase position between individuals, it is often recommended to make an adjustment of the results according to a marker of the endogenous circadian rhythm, such as the core body temperature or levels of melatonin or cortisol.<sup>25</sup> We were unable to measure these markers, and this could partially explain the variability in the time at which acrophases and batyphases were achieved.

Although the main objective of the present study was to explore a poorly described physiological phenomenon, namely the circadian rhythmicity of pulse oximetry, it might also yield a clue about reference values for SpO<sub>2</sub>. Thus, according to our results, clinicians should be aware that normal values of pulse oximetry might fluctuate during the 24 h of the day, reaching highest values during the late afternoon and lowest during the early hours of the

day. In children less than six years old the lower limit of normal (5<sup>th</sup> percentile) would be 93.8% in the late afternoon and 89.8% in the early hours of the day. Corresponding figures for older children would be 91.0% and 88.5%, respectively. Nevertheless, our study was made in Mexico City, which is located at an altitude of 2,240 m over the sea level. Although Mexico City is at a moderate altitude, ventilation and oxygenation better resemble those physiological responses observed at higher altitude, more than at lower altitude.<sup>26,27</sup> It is well known that altitude is a key determinant of the partial pressure of oxygen in inspired air, and thus of the amount of alveolar oxygen available to diffuse to the pulmonary bloodstream. Due to this reason, a number of studies have shown that SpO<sub>2</sub> values steadily fall from about 97% at sea level to approximately 87% at an altitude of 4,000 m (reviewed by Beall<sup>28</sup>). Therefore, normal values observed in our study might be different in other locations, and hence further studies in children and adults at different altitudes are warranted.<sup>29</sup>

A potential limitation of our study is that results were drawn from sick individuals, and might not be representative of what occurs in healthy children. Thus, although we were cautious to only include children free of respiratory diseases or other conditions that could potentially affect our results, the main conclusions must be validated with further studies in healthy populations. On the other hand, the oximeter used in the study did not possess the new technology that avoids spuriously low values due to unaware motion, as in the new-generation oximeters. However, all SpO<sub>2</sub> readings were directly made by one pediatrician involved in the study, thus ensuring that motion-artifacts, if any, were negligible. In addition, if circadian fluctuation of SpO<sub>2</sub> was apparent while using the Nonin 2500 oximeter, it is reasonable to assume that such a rhythm should be even more evident on employing oximeters with more sophisticated technology.

## CONCLUSION

In conclusion, our results suggested that in most children SpO<sub>2</sub> progressively fluctuates in a 24-h cycle, which is suggestive of a circadian rhythm, with highest values occurring in the evening and lowest values at the early hours of the day. Such variations should be kept in mind by clinicians when interpreting pulse oximetry. In addition, we found that both maximal and minimal SpO<sub>2</sub> values decrea-

se with age. Nevertheless, further studies must be replicated in healthy populations to validate these findings.

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