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Original Article

Circadian Variability of Pulse Oximetry in Healthy Children Under the Age of 7☆

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ABSTRACT

Background: Peripheral oxygen saturation (SpO_2) measured by pulse oximetry is widely used in clinical practice, but its fluctuations over the course of the 24 h of a day have not been explored at length. Recently, we reported that children hospitalized due to non-cardiopulmonary causes had a circadian variation in SpO_2. This finding needed to be corroborated in healthy children, which is the objective of the present study.
Patients and methods: Healthy children residing in a state foster home were studied with pulse oximetry every 2 h for 24 h.
Results: Eighty-two children were included in the study, ranging in age from 1 month to 6.5 years (average±standard error of 3.06±0.16 years), with a weight-for-length/height percentile of 65.5±2.9. In 65 (79.3%) children, the SpO_2 levels followed a sinusoidal curve suggesting circadian rhythm. The total group of sinusoidal curves in this population had a mesor of 95.10±0.08%SpO_2, period of 21.05±0.54 h (in 53.8% of these children, the period was between 20 and 28 h). The maximum SpO_2 was reached at 3:14 pm±16 min, and the minimum at 5:16 am±48 min. When the 24 h were divided into four periods, it was demonstrated that the highest SpO_2 levels were reached between 2 pm and 8 pm.
Conclusions: In this population of clinically healthy children, there was a circadian variation in pulse oximetry, with maximum values in the late afternoon and minimal values in the early morning.

Variabilidad circadiana de la oximetría de pulso en niños sanos menores de 7 años

Palabras clave:
Ritmo circadiano
Saturación de hemoglobina
Función pulmonar

RESUMEN

Antecedentes: La saturación periférica de oxígeno (SpO_2) medida por oximetría de pulso es ampliamente usada en la práctica clínica, pero sus fluctuaciones durante las 24 h del día han sido poco exploradas. Recientemente describimos que niños hospitalizados por causas no cardiopulmonares tenían una variación circadiana de la SpO_2. Este hallazgo necesitaba ser corroborado en niños sanos, lo que constituyó la finalidad del presente estudio.
Población y método: Niños sanos residentes en una casa cuna gubernamental se estudiaron mediante oximetría de pulso cada 2 h a lo largo de 24 h.
Resultados: Se incluyeron 82 niños de un mes a 6,5 años de edad (media ± error estándar: 3,06 ± 0,16 años), con peso para la talla en el percentil 65,5 ± 2,9. En 65 (79,3%) niños los valores de SpO_2 siguieron una curva sinusoidal sugestiva de un ritmo circadiano. El conjunto de curvas sinusoidales en esta población tuvo un mesor de 95,10 ± 0,08%SpO_2 y un período de 21,05 ± 0,54 h (en el 53,8% de estos niños el período estuvo entre 20 y 28 h). El valor máximo de SpO_2 se alcanzó a las 3:14 PM ± 16 min, y el más bajo a las 5:16 AM ± 48 min. Al dividir las 24 h en 4 períodos se demostró que los valores más altos de SpO_2 se alcanzaban entre las 2 PM y las 8 PM.
Conclusiones: En esta población de niños clínicamente sanos existió una variación circadiana en la oximetría de pulso, con valores máximos a media tarde y mínimos en la madrugada.

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Introduction

Pulse oximetry is a widespread procedure used in clinical and surgical settings, and it is an essential tool in intensive care units.[1] This technique is usually done by placing a sensor on a finger or toe of one of the extremities or in other places such as an earlobe. The device emits a ray of light at 2 different wavelengths (~660 and ~940 nm, alternatively), which are partially absorbed by hemoglobin.[2] The quantity of absorption will depend on whether the hemoglobin is bound with oxygen or not. By calculating the quantity of light absorbed at each of the wavelengths, an index is determined that is automatically compared with a table or equation of references values, thus obtaining the percentage of hemoglobin saturation in the peripheral blood (SpO_2).[3]

Several studies have published references values for SpO_2 in children[4–9] as well as in adults.[10,11] However, these studies are usually done with nighttime polysomnography or with tracings that are relatively short; therefore, they do not make a complete 24-h analysis. The studies aimed at evaluating possible circadian changes in oxygenation are very scarce. In 1972, Reinberg and Gervais[12] reported that PaO_2 was lower during the night in healthy adults or in patients with chronic airway obstruction. In 1985, Updike et al.[13] studied 6 pre-term newborns and they concluded that in half of the babies transcutaneous oxygen pressure ($tcPO_2$) followed a circadian rhythm, reaching minimal levels during the early hours of the morning. Contrarily, in 1985 Postma et al.[14] could not demonstrate a circadian rhythm in PaO_2 or SpO_2 in 8 healthy adults although said rhythm was evident in 8 patients with chronic airway obstruction. In a recent study, we assessed SpO_2 values in 131 children aged between 23 days and 16 years who were hospitalized at the *Hospital de Pediatría del Centro Médico Nacional Siglo XXI* due to different diseases, but with no acute or chronic cardiorespiratory alterations.[15] Each child underwent pulse oximetry approximately every 2 h for 24 h, and we found that in most of them (85%) SpO_2 measurements followed a sinusoidal circadian rhythm, with maximal values in the late afternoon (~5:00 pm) and minimal levels in the early morning (~3:00 am). Clearly, the main disadvantage of this study was that it was done in children with some sort of disease. Thus, it was essential to explore whether this circadian rhythm phenomenon was likewise present in clinically healthy children, which is the objective of this present paper.

Patients and Methods

Ours is a prospective, longitudinal and observational study carried out between June and November 2009 in a government-run orphanage located in Mexico City (*Centro Nacional Modelo de Atención, Investigación y Capacitación Casa Cuna Tlalpan, Sistema Nacional para el Desarrollo Integral de la Familia* [*DIF*]). Children are admitted to the orphanage between the ages of 0 and 6, and upon admittance a medical file is opened for each child. The children undergo complete physical examinations as well as complete blood count, blood chemistry and parasitology. The children's vaccinations are reviewed and any necessary vaccines are administered. The facilities have a nurse and physician on duty for each shift who supervise the children's daily state of health. In addition, after admittance the children are included in a health-care program of periodical check-ups (at least every 3 months) that include dental, vision and orthopedic check-ups. Outside of the programmed activities for each age group (bathing, eating, schooling, etc.), the children spend free time with the other children.

We selected for participation in the study those children who, according to their medical history and physical examination, were clinically healthy and had no history of frequent snoring or any respiratory tract infection in the previous 30 days. After informed consent was given by their legal guardian, the children included in the study underwent SpO_2 measurements approximately every 2 h for a period of 24 h. In order to do so, a portable pulse-oximeter was used (model 513, Novametrix Medical Systems Inc., Wallingford, CT, USA) with a non-disposable, pediatric, rigid clip sensor (model DB-9). According to the manufacturer's instructions, the precision of this oximeter is ±2% in SpO_2 values between 80 and 100%. The sensor was placed on either a finger or toe, choosing one that best fit inside its concave shape. After a stabilization period of between 10 and 15 s, SpO_2 was read for 1 min. The final value selected was the most constant value during the measurement. When the children were asleep, oximetry was done without waking them. When the children were awake, they were made to rest for at least 5 min before the measurements were taken. All measurements were taken by the two physicians who participated in the study (IRG and JAG). These values and other variables (pulse, tympanic temperature, conditions, etc.) were registered on the data collection sheet.

The sinusoidal function was determined for each child (Levenberg–Marquardt method) with a 12-point system (referring to the 12 SpO_2 values taken over the course of the 24 h cycle) using a computer program (CurveExpert v1.38, Daniel Hyams, USA). This same procedure was done to obtain a global equation, using all the SpO_2 values of all the children. The presence of a sinusoidal function with a cycle that was close to 24 h (between 20 and 28 h) corroborated the existence of circadian variability of SpO_2. A sinusoidal function, such as that illustrated in Fig. 1, generally adheres to the formula:

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

where y is the SpO_2 value from the fraction of the day selected (x), the constant a is the mesor (*midline estimating statistic of rhythm*, whose value is very similar to the average of the SpO_2 measurements from a complete cycle), b is the amplitude (distance from the mesor to the either the highest or lowest point of the curve), c is 2π/period (the period is the duration of a complete cycle, which in this case is expected to be close to 24 h) and d is the phase (moment of the period in which maximal SpO_2 is reached). Therefore, once the sinusoidal function formula is obtained, it is possible to know the time at which the maximal and minimal SpO_2 values occur as well as the degree of variation (maximum–minimum). The possible circadian rhythm was also evaluated by dividing the 24 h cycle into 4 periods of 6 h each (2–8, 8–14, 14–20 and 20–2 h).

The majority of the variables followed a normal distribution according to the Kolmogorov–Smirnov test; therefore, parametric statistics were used, including regression and correlation analysis and the Student's t-test. The only variable that did not follow a normal distribution was the measurement of SpO_2 in 4 periods of 6 h each, and for this we used non-parametric statistics by means

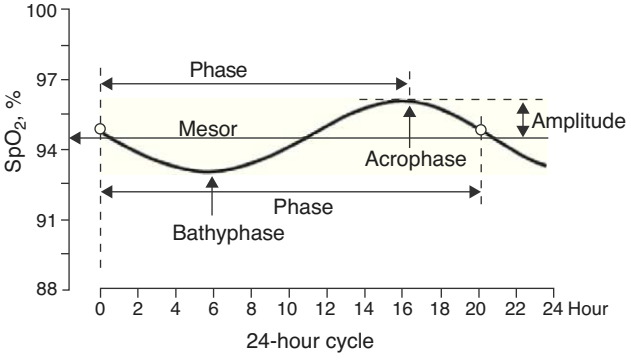

Fig. 1. Elements of a sinusoidal curve. For the description of each element, see the "Patients and Methods" section.

of the Kruskal–Wallis test, followed by the Dunn test for multiple comparisons.

The protocol was approved by the *Comisión Nacional de Investigación en Salud del IMSS* (2008-785-040), as well as by the *Dirección General de Rehabilitación y Asistencia Social del DIF* (221 000 00/668/09).

Results

We studied 82 children aged between 1 month and 6.5 years (mean 3.06±0.16 years [standard deviation]), 43 of whom (52.4%) were girls. Mean weight was 12.9±0.39 kg and mean height was 87.8±1.55 cm. According to the WHO reference values, the weight-for-length/height indicator was in percentile 65.5±2.9; none of the children were below the 5th percentile and only 9 were above the 95th percentile.

In 65 (79.3%) children, the SpO_2 values taken during the 24 h period were able to be adjusted to a sinusoidal curve. Fig. 2 shows some examples of these registers. There were no statistically significant differences in the anthropometric characteristics of these children or in the 17 children in whom it was not possible to obtain a sinusoidal curve. Nor were there any differences in mean SpO_2 or in the minimal and maximal values. When we grouped all the sinusoidal curves, the average mesor was 95.10±0.08%SpO_2 and the amplitude was 1.39±0.07%SpO_2. The period had an average duration of 21.05±0.54 h, and in 35 (53.8%) of these children the period was between 20 and 28 h. Peak SpO_2 was reached (acrophase) at 3:14 pm±16 min, while the lowest value (bathyphase) was at 5:16 am±48 min. At the same time, the highest and lowest SpO_2 values had averages of 96.49±0.07 and 93.71±0.14%SpO_2, respectively, and the maximal differences reached an average of 2.77±0.14%SpO_2.

When we grouped all the SpO_2 measurements from all the children who had circadian changes, we found that they were adjusted to a single sinusoidal curve with the correlation coefficient r=0.47 (Table 1 and Fig. 3A). This coefficient was greater when, instead of using the original SpO_2 values, we used the differences of each value compared with its respective mesor. Thus, with this latter approach, the resulting sinusoidal curve had an r=0.51, with the formula y=0.022+1.032 cos(6.192x−3.671) (Table 1 and Fig. 3B). According to this equation, the period had a duration of 24 h 21 min and the acrophase was reached in the afternoon (2:14 pm), while the bathyphase occurred in the early morning (2:03 am). The difference between the highest and lowest SpO_2 value was 2.06 percentage points.

Regarding heart rate and body temperature, we also obtained sinusoidal patterns when we grouped all the measurements of the children (Table 1). In the case of heart rate, the sinusoidal function equation was y=101.13+10.51 cos(6.59x−3.70), the period was 22 h 54 min and the acrophase and bathyphase occurred at 1:28 pm and 2:01 am, respectively. For body temperature, the function was y=36.24+0.30 cos(7.59x−3.95), with a period of 19 h 52 min, acrophase at 12:30 pm and bathyphase at 2:34 am.

Upon dividing the SpO_2 of the 82 children into 4 intervals of 6 h each, there was an observed progressive modification in their values, reaching the maximum between 2:00 pm and 8:00 pm (Fig. 4).

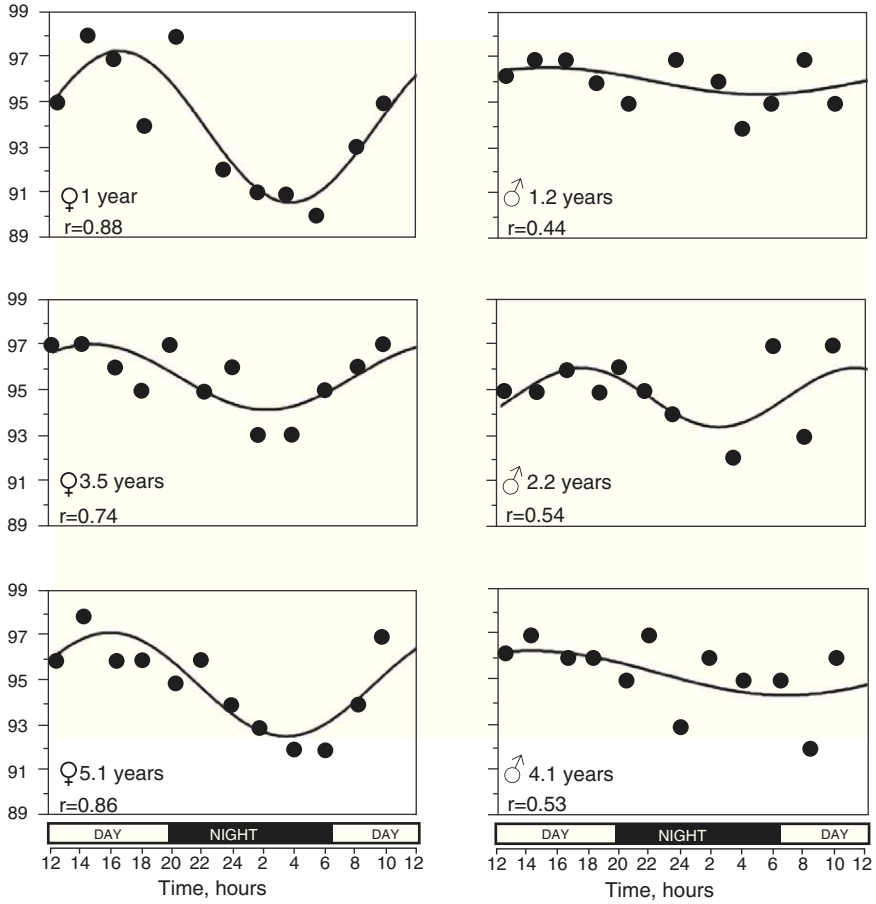

Fig. 2. Examples of the distribution of the SpO_2 values during the 24 h period and the associated sinusoidal function. Each panel shows the age and sex of the child, as well as the correlation coefficient of the curve (r).

Table 1
Characteristics of the Curves for SpO_2, ΔSpO_2, Heart Rate and Tympanic Temperature, Calculated After Grouping the Data for All the Children and Calculating a Single Sinusoidal Function for Each Variable.

Characteristic	Curve Using Actual %SpO_2	Curve Using Δ %SpO_2 (Actual – Mesor)	Heart Rate Curve, beats/min	Temperature Curve (°C)
Mesor, %SpO_2, °C	95.11	0.02	101.13	36.24
Maximum, %SpO_2	96.13	01/05/12	111.64	36.54
Minimum, %SpO_2	94.09	−1.01	90.62	35.93
Period, h	24.93	24.35	22.89	19.86
Acrophase, h	14:19	14:14	13:28	12:30
Bathyphase, h	01:51	02:03	02:01	02:34
Correlation coefficient	0.47	0.51	0.48	0.37

Acrophase: time of day at which the maximum value was reached; bathyphase: time at night when the minimal value was reached.

Discussion

Living organisms frequently present changes at the biochemical, cell and/or functional level during the 24 h cycle, and the presence of this biological clock is an important advantage for adapting to an environment.[16] The cardiovascular system and the respiratory tract present this type of circadian variation.[17,18] Nevertheless, one of the possible consequences, which is the circadian modification of SpO_2, has not been fully explored. In a previous study done in children who were hospitalized due to non-cardiopulmonary diseases, it was found that SpO_2 had a circadian variation.[15] In the present study, we have evaluated whether this phenomenon is also present in clinically healthy children. Our results corroborate the fact that there is a circadian variation in SpO_2 and that it reaches maximal values in mid-afternoon and minimal values in the early hours of the morning. The present study, however, shows some differences compared with the previous study: the hospitalized children had a slightly lower mesor (mean 94.2%SpO_2), a greater amplitude in the circadian rhythm (mean 1.6%SpO_2) and the acrophase was reached later (mean 4:53 pm). Although part of these differences could be due to the fact that the age range was greater (23 days to 16 years; mean, 6.9 years), there is also the possibility that the hospital setting could have been an influence.

Although in the study we did not research the causes of this daytime–nighttime variation in SpO_2, it is possibly due to changes in the two main factors that determine the degree of oxygenation in blood: ventilation (V') and pulmonary circulation (Q') in the so-called V'/Q' ratio. As for the ventilation, it is known that the caliber of the airways reaches their maximum aperture at around 4 pm, and the minimum at 4 am.[19,20] Some of the neurohormonal factors that influence pulmonary circulation also follow a circadian pattern. For example, it is known that vagal tone and plasma concentration of histamine, capable of producing vasodilation of the lung microcirculation, are higher in the early morning and lower in mid-afternoon.[21] Conversely, the sympathetic tone and plasma concentrations of adrenalin and suprarenal steroids, which are factors that promote vasoconstriction, are lower in the early morning and higher in the mid-afternoon.[22,23] Therefore, the fluctuations in alveolar ventilation and pulmonary circulation over the course of a 24-h day can lead to progressive changes in the V'/Q' ratio and, consequently, in SpO_2.[15] The maximal imbalance of this relation (meaning lower ventilation with higher perfusion) would translate into a decrease in SpO_2 which would theoretically be reached during the early morning.

The results found in this study could have implications in clinical practice. In our study, the difference between the peak and low SpO_2 was an average of 2.77 percentage points, which seems a relatively small difference. However, there were children who reached differences of up to 6%SpO_2, and a fall of that magnitude could be clinically relevant in patients with cardiopulmonary affectations. On the other hand, its has recently been proposed that if all

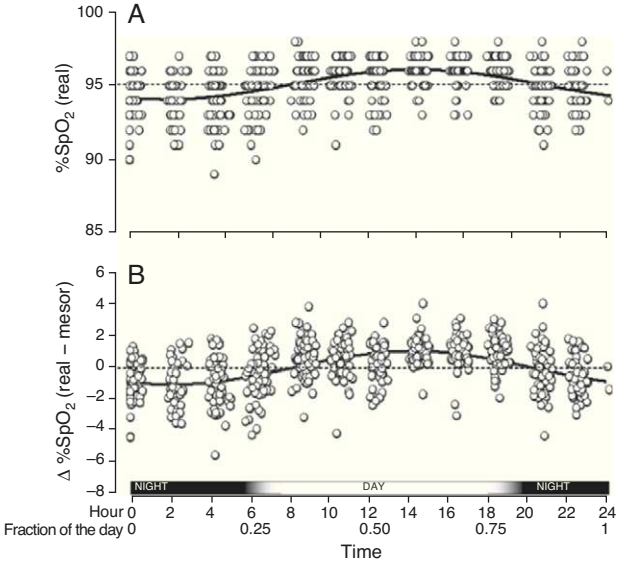

Fig. 3. Global SpO_2 values obtained from the 65 children who had a sinusoidal pattern. (A) Each circle corresponds to the actual value of each SpO_2 measurement. (B) As the individual curves of each child could be situated at different SpO_2 levels (meaning higher or lower than the *Y* axis), the actual SpO_2 values for each child were adjusted to the mesor of the same child, and so the position of the curves is homogenized and the circadian variability is better illustrated.

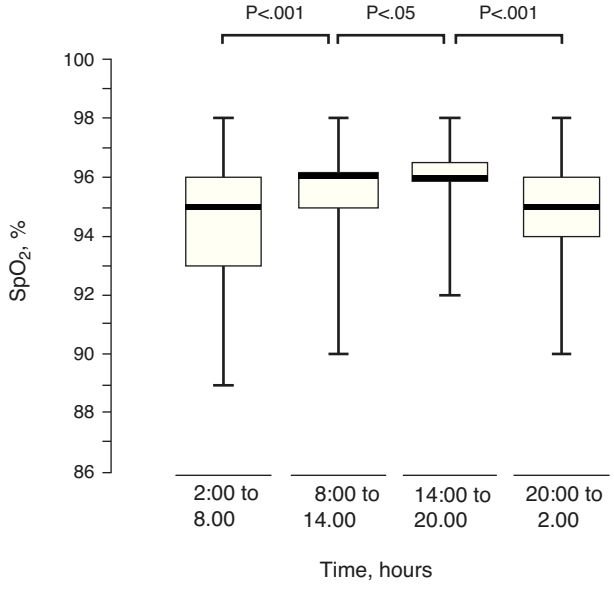

Fig. 4. Distribution of the SpO_2 values of the total population of children according to measurement times. The thick line represents the mean; the lower and upper edges of the rectangle represent the first and third quartiles, while the ends represent the minimal and maximal values.

newborns undergo pulse oximetry 24 h after birth and before leaving the hospital, potentially severe congenital heart disease could be detected among those who present SpO_2 values less than or equal to 90%–95%, which would help prevent higher morbidity and mortality in these children.[24–26] Obviously, the limit that is set should take into account the circadian variation of SpO_2.

Altitude above sea level is the main determinant of absolute oxygen pressure in inhaled air and, therefore, of the quantity of alveolar oxygen available for diffusion toward the bloodstream. Due to this, it has been widely confirmed that SpO_2 values slowly decrease from ~97% at sea level to ~87% at an altitude of 4000 m.[27] The present study was done in Mexico City, located at 2240 m above sea level, therefore the absolute values of SpO_2 could be different at other altitudes. Nevertheless, we consider it very likely that the circadian variability of SpO_2 will continue to be present, regardless of altitude and atmospheric oxygen pressure.

There are oximeters on the market that can store the SpO_2 determinations continuously for 24 h or more. However, their use in the circadian analysis of SpO_2 is still uncertain as there would be no way of knowing the conditions of the child (whether he/she was playing, coughing, eating, sleeping, crying, etc.).

In conclusion, in the present study of clinically healthy children, we found a circadian variation in the oximetry values of healthy subjects, with an average period of close to 21 h and higher values of SpO_2 in the afternoon (~3:14 pm) and lower values in the early morning (~5:16 am).

Conflict of Interests

The authors declare that they have no conflict of interests.

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