

## CLINICAL SCIENCE

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### SLEEP IN INFANTS WITH CONGENITAL HEART DISEASE

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**OBJECTIVES:** To investigate hypoxia and sleep disordered breathing in infants with congenital heart disease.

**METHODS:** Prospective study. In-hospital full polysomnography was performed on 14 infants with congenital heart disease, age  $7 \pm 1$  months, and in 7 normal infants, age  $10 \pm 2$  months. Congenital heart disease infants were classified as acyanotic (n=7) or cyanotic (n=7).

**RESULTS:** Nutritional status, assessed by the Gomez classification and expressed as % weight for age, was  $70 \pm 7$ ,  $59 \pm 11$  and  $94 \pm 16$  in the acyanotic, cyanotic congenital heart disease and control infants, respectively (p<0.001). The respiratory disturbance index (AHI, events per hour) was [median (25-75%)]: 2.5 (1.0-3.4), 2.4 (1.5-3.1) and 0.7 (0.7-0.9) in acyanotic, cyanotic CHD infants and controls, respectively (p=0.013). Almost all congenital heart disease infants (11 out of 14) and only one control infant had an AHI >1 event/hour. The minimum oxygen saturation was 79% (74-82), 73% (57-74) and 90% (90-91) in the acyanotic, cyanotic congenital heart disease infants and controls, respectively (p<0.001). The arousal index (events/hour) was similar among the three groups at  $8.4 \pm 2.4$ ,  $10.3 \pm 8.7$  and  $6.5 \pm 3$ , respectively (p=0.451).

**CONCLUSIONS:** Infants with congenital heart disease frequently present with sleep-disordered breathing associated with oxygen desaturations but not arousals. Therefore, sleep may represent a significant burden to infants with congenital heart disease.

**KEYWORDS:** Sleep disorders; Sleep apnea syndromes; Infant; Congenital heart defects; Polysomnography.

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#### INTRODUCTION

The incidence of congenital heart disease (CHD) among live-born infants averages from 4 to 9 per thousand (0.4-0.9%). There are approximately 1.5 million new cases per year worldwide<sup>1</sup>. Recent advances allow accurate anatomical and physiological cardiac diagnoses that are important for reparative surgery.<sup>1</sup> Because of its impact on survival, there is a growing interest in the many clinical features of infants with CHD.

The central fetal circulation changes dramatically at birth. Two distinct circulations in series replace the inefficient separation of the oxygen uptake and delivery circulations of the fetus after birth. CHD may cause decreased cardiac output and heart failure. Moreover, systemic hypoxia and cyanosis, resulting from the mixture of oxygenated (pulmonary venous) and desaturated (system venous) blood shunting through the systemic circulation, is common in CHD patients. Although there is some controversy about nomenclature in pediatric cardiology, infants with congenital heart disease are classified as acyanotic or cyanotic on the basis of their aortic SaO<sub>2</sub> levels at the time of cardiac catheterization (greater or less than 90% SaO<sub>2</sub>, respectively).<sup>2</sup>

Infants spend a significant amount of time sleeping, a period in which respiratory instability and oxygen desaturation may occur.<sup>3</sup> Sleep apnea occurs in children of all ages, from neonates to adolescents. It is more frequent in the preschool age group due to adenotonsillar hypertrophy. The prevalence of obstructive sleep apnea in toddlers and

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preschoolers is conservatively estimated to be 1-3%.<sup>4</sup> Sleep apnea can result in serious morbidity, and complications such as failure to thrive and asymptomatic degree of pulmonary hypertension may be common.<sup>5</sup> There is evidence that patients with CHD frequently present oxygen desaturation during sleep;<sup>5</sup> however, there are no systematic data regarding sleep in these infants. Adults with congestive heart disease frequently present central sleep apnea<sup>6</sup>, raising the possibility that infants with congenital heart disease may also present central sleep apnea. There is also evidence for interaction of obstructive sleep apnea with other cardiovascular pathologies<sup>7</sup> and it is known that pharyngeal dimensions are critical with regard to airway obstruction.<sup>8</sup>

The objective of our study was to investigate sleep-disordered breathing as well as the characteristics of sleep architecture in infants with CHD. To this end, we performed in-hospital full polysomnography on infants with CHD, who were grouped according to the presence or absence of hypoxia while they were awake. In addition, a control group of healthy infants was also studied.

## METHODS

We studied a total of 21 infants (age 6-12 months), including 14 infants with CHD and 7 normal controls. The CHD infants were classified as acyanotic (n=7) or cyanotic (n=7). The CHD infants were recruited from the Pediatric Heart Unit of our hospital (Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo) during admission for surgical evaluation. Patients who had undergone previous cardiac surgery, those who had neurological or infectious diseases, those requiring oxygen, premature infants and those with associated syndromes (such as Down syndrome) were excluded. Healthy control infants were recruited from a nursery school associated with our institution. These healthy infants were born at term and had no history of lower respiratory tract illness. The infants' nutritional status was assessed by the Gomez classification<sup>9</sup>, using weight for age. Briefly, values of 90-110%, 75-89%, 60-74% and <60% are considered normal, mild, moderate and severe malnutrition, respectively. The protocol was approved by the ethics committee of our institution, and informed consent was obtained from each parent or relative in charge of the care of the patient.

### Sleep study

All participants were submitted to full hospital-based overnight polysomnography using an EMBLA digital system (16 channels, Flaga hf. Medical Devices). No sedation or sleep deprivation was used to induce sleep. The

following variables were monitored: electroencephalogram (EEG) four channels: C3-A2, C4-A1, O1-A2 and O2-A1; electrooculogram (EOG) two channels: LOC-A1 and ROC-A1; electromyogram (EMG) two channels: submental and anterior tibial muscles using surface electrodes; electrocardiogram (ECG) one channel; and snoring and body position were detected with EMBLA sensors. A thermocouple transducer was used to detect airflow. Chest and abdominal piezo sensors monitored respiratory effort. Oxygen saturation (SaO<sub>2</sub>) and pulse were recorded with a pulse oximeter (EMBLA). All polysomnograms were recorded and scored based on guidelines for sleep studies (Rechtschaffen & Kales). Arousals were defined as shifts to increased EEG frequencies for 3 seconds. Apneas were defined as at least two respiratory cycles in length and associated with oxygen desaturation >4% from baseline or an arousal; hypopnea was defined as two missed breaths, ≥ 50% fall in amplitude and >3% desaturation associated or not associated with arousal (AASM Manual, 2007).<sup>10</sup> Obstructive apnea was defined as an absence of oronasal airflow despite continued out-of-phase chest and abdominal movements. Mixed apnea was defined as absence of oronasal airflow associated with central followed by obstructive components. The number of apneas and hypopneas per hour of sleep defined the apnea-hypopnea index (AHI). Periodic breathing was characterized by the presence of three or more consecutive respiratory pauses of three seconds or longer, interposed with periods of ventilation of less than 20 seconds.

### Statistical analysis

Due to the small sample size, all parameters were assumed to have non-parametric distributions. The descriptive data are given as medians (25-75% range), and comparisons were made using a Kruskal-Wallis one-way analysis of variance on ranks with a Tukey post-hoc test. P-values of <0.05 were considered statistically significant.

## RESULTS

The origins of the 14 CHD infants studied are presented in Table 1. In general, the cyanotic CHD infants presented complex CHD defects. The demographic characteristics as well as the resting cardiac and respiratory rates of the entire study population are described in Table 2. Despite the relatively narrow age range adopted as an entry criterion, CHD patients were younger than controls (p = 0.017) and were significantly so in the group of cyanotic infants. The CHD infants presented moderate-to-severe malnutrition (Table 2).

**Table 1** - Diagnoses in congenital heart defects, according to SaO<sub>2</sub> above (Acyanotic) and below (Cyanotic) 90%

	Number of cases
<b>Acyanotic</b>	
VSD	2
VSD + Atrial septal defect	1
Patent ductus arteriosus	2
Aortic coarctation + Atrial septal defect	1
Corrected transposition of the great arteries + VSD	1
<b>Cyanotic</b>	
Transposition of the great arteries + VSD	3
Tricuspid atresia Type I C	1
Persistent truncus arteriosus	2
Double-outlet right ventricle + VSD	1

VSD, ventricular septal defect.

All CHD patients were stable when the sleep study was performed and slept for at least six hours. The main results derived from polysomnography studies are presented in Table 3.

Cyanotic CHD infants had increased wakefulness times with consequent decreased sleep efficiencies. However, there were no significant differences in sleep architecture or arousals between groups. As expected, the mean oxygen saturation during sleep (SaO<sub>2</sub>) and the minimum oxygen saturation were lower in cyanotic infants. Almost all CHD infants (11 of 14) demonstrated an AHI >1 event/hour. By contrast, only one healthy infant had an AHI >1 event/hour. This particular infant had no obstructive apnea but exhibited 13 hypopneas and 5 central apneas with minimal SaO<sub>2</sub> of 90%, which was in the normal range. The majority of respiratory events among CHD infants were represented by central apnea or hypopnea. Only one CHD infant had more than one obstructive apnea (10 out of a total of 43

events). The durations of the central apneas in CHD and control infants were similar ( $6.99 \pm 1.24$  s and  $7.70 \pm 0.62$  s, respectively;  $p=0.253$ ) and varied from 5 to 13 s and from 6 to 18 s, respectively. No infants had obstructive apneas >10 s in duration (range: 4–9 s) or periodic breathing. The respiratory hypopneas occurred predominantly during Rapid Eye Movement (REM) sleep. In our study, we observed that CHD patients frequently experienced central apneas during sleep, which were associated with hypoxia and oscillations in cardiac frequency.

## DISCUSSION

The present study was designed to investigate the pattern of sleep in patients with CHD. We found that CHD infants frequently presented central hypopneas and apneas during sleep. These respiratory events were associated with significant oxygen desaturation, particularly in cyanotic CHD infants. However, as expected for this age range, the respiratory events were not associated with arousals.<sup>11</sup>

Our results confirm those of a previous study using limited respiratory monitoring without EEG, which also showed frequent oxygen desaturation during sleep in CHD infants.<sup>5</sup> Our study extends these findings by showing that increased wakefulness time after sleep onset resulted in decreased sleep efficiency in cyanotic CHD infants, which was intermediate in acyanotic CHD infants compared to normal controls. The decreased sleep efficiency in cyanotic CHD infants could be related to persistent hypoxia or a more severe underlying cardiac disease, which is characteristic of cyanotic CHD infants (Table 2). Our study also showed that despite an increased AHI in CHD infants, the respiratory events were not associated with increased arousals. The lack of difference in arousal indices among the three groups is not surprising, considering that the lower spontaneous arousal indices are usually not altered among children with SDB.<sup>12</sup>

**Table 2** - Demographic and physiological characteristics of the population studied. Data are presented as mean  $\pm$  SD or median (25-75% inter-quartile range)

	CHD Acyanotic (n=7)	CHD Cyanotic (n=7)	Control (n=7)	P
Age, months	7.8 $\pm$ 1.9	6.9 $\pm$ 1.5 *	10.0 $\pm$ 1.5	0.011
Height, cm	66 $\pm$ 4	60 $\pm$ 6*	72 $\pm$ 5	0.001
Weight, Kg	6.9 $\pm$ 0.7*	4.7 $\pm$ 0.9*	8.7 $\pm$ 0.1	<0.001
Goméz, %	70 $\pm$ 7*	59 $\pm$ 11*	94 $\pm$ 16	<0.001
SaO <sub>2</sub> , %	95 (94-96)	85 (78-86)	97 (96-98)	<0.001
Cardiac rate, cycles/min	130 $\pm$ 11	140 $\pm$ 9*	124 $\pm$ 8	0.020
Respiratory rate, breaths/min	49 $\pm$ 6* <sup>p</sup>	66 $\pm$ 13*	25 $\pm$ 2	<0.001

CHD, congenital heart defects. \*Different from control, \*\*Different between cyanotic and acyanotic CHD groups, Goméz = weight X 100/ideal weight. The p-value corresponds to the comparison of the three groups; n corresponds to the number of infants studied in each group.

**Table 3** - Polysomnography data of the population studied. Data are presented as mean  $\pm$  SD or median (25-75% interquartile range)

	CHD Acyanotic (n=7)	CHD Cyanotic (n=7)	Control (n=7)	P
Total sleep time, minutes	424 $\pm$ 57	395 $\pm$ 43	449 $\pm$ 37	0.127
Wakefulness time, min	95 $\pm$ 42	116 $\pm$ 47*	60 $\pm$ 15	0.038
Sleep efficiency, %	82 $\pm$ 7	77 $\pm$ 8*	88 $\pm$ 3	0.022
Arousal Index, events/hr	8.4 $\pm$ 2.4	10.3 $\pm$ 8.7	6.5 $\pm$ 3.1	0.451
S1 + S2, %	46 $\pm$ 9	44 $\pm$ 10	42 $\pm$ 10	0.547
S3 + S4, %	36 $\pm$ 12	39 $\pm$ 6	39 $\pm$ 3	0.371
REM, %	15 $\pm$ 6	16 $\pm$ 10	19 $\pm$ 7	0.699
AHI, events/hr	2.5 (1.0-3.4)*	2.4 (1.5-3.1)*	0.7 (0.7-0.9)	0.013
Obstructive apneas	0 (0 - 1)	0 (0-0)	0 (0-1)	0.191
Central apneas	5 (1 - 7)	5 (0-8)	3 (1-4)	0.975
Hypopneas	17 (6-25)*	14 (5-16)*	3 (1-5)	0.023
SaO <sub>2</sub> Mean, %	94 $\pm$ 2**	85 $\pm$ 5*	96 $\pm$ 2	<0.001
SaO <sub>2</sub> Minimum, %	79 (74-82) **	73 (57-74)*	90 (90-91)	<0.001
AHI REM	1.3 $\pm$ 1.4	0.7 $\pm$ 1.2	0.5 $\pm$ 0.3	0.345
AHI nREM	1.0 (0.5-2.3)	0.3 (0.05-2.3)	0.2 (0.02-0.5)	0.076
SaO <sub>2</sub> min REM	83 $\pm$ 4**	75 $\pm$ 7*	89 $\pm$ 1	<0.001
SaO <sub>2</sub> min nREM	81 $\pm$ 5	76 $\pm$ 5*	91 $\pm$ 1	<0.001

\*Different from control group, \*\*Different between acyanotic and cyanotic groups. SaO<sub>2</sub> mean and minimum oxygen saturation during sleep, respectively. S1, S2, S3 and S4 correspond to Stage 1, Stage 2, Stage 3 and Stage 4 of sleep, respectively. The p-value corresponds to the comparison of the three groups. Significant differences between groups (p <0.05) are indicated with symbols.

The arousal index in the control group was similar to what has been previously reported in this age range (6.5/h and 7-9/h)<sup>4</sup> and was not significantly different from the CHD infants (approx. 9/h, Table 2). The low level of arousals in children with SDB<sup>4</sup> contrasts with what is found in adults. This may reflect the inability of children to awaken when faced with potentially life-threatening respiratory events.

The role of hypoxemia during sleep in infants with CHD and its effects on the development of pulmonary hypertension have not been investigated<sup>5</sup>. However, sustained hypoxia and hyperflow may contribute to the development of pulmonary hypertension in infants with CHD.<sup>13,14</sup> Therefore, our data showing intermittent hypoxia over and above sustained hypoxia in cyanotic CHD raise the possibility that recurrent central apneas may contribute to the development of pulmonary hypertension. The oxygen desaturations that occurred in the absence of arousals in our study may also be relevant. The main cause of death in children under one year of age is sudden infant death syndrome (SIDS),<sup>15</sup> in which the cause of death remains unexplained after a thorough post-mortem examination. Notably, a significant proportion of sudden infant death is associated with CHD, including isolated ventricular septal defects<sup>16</sup> and ductus-dependent, complex and cyanotic CHD.<sup>17</sup> Malignant arrhythmias triggered by sleep-related hypoxemia may be an important

mechanism leading to death. For instance, Dancea et al. found in a case series of sudden infant death that a large proportion of the infants were stable at home and died unexpectedly during sleep.<sup>16</sup> Delayed resetting of peripheral chemoreceptors has been demonstrated in chronically hypoxic kittens and preterm infants with bronchopulmonary dysplasia.<sup>5</sup> Because peripheral chemoreceptors play a key role in initiating ventilatory, cardiovascular and arousal responses to hypoxia, we speculate that this delay may be among the factors that place cyanotic CHD infants at greater risk for SIDS. The observation of bradycardia and tachycardia associated with central apneas could represent a sympatho-vagal imbalance, a mechanism potentially involved in the genesis of arrhythmias.<sup>17</sup>

There are multiple reasons for oxygen desaturation during sleep in infants with CHD. Compared to adults, healthy infants have a greater chest wall compliance, which predisposes them to breathing at a lower relative lung volume than adults, resulting in airway closure, more lung units with a low ventilation/perfusion ratio and more intrapulmonary shunting<sup>18</sup>. These differences may become more pronounced during sleep and may predispose infants to greater ventilation-perfusion mismatching and greater oxygen desaturation than adults. Infants with CHD have decreased respiratory compliance (associated with

decreased tidal volume and increased respiratory rate), findings that are consistent with restrictive pulmonary disease.<sup>5</sup> Adult patients with restrictive pulmonary disease of various causes experience oxygen desaturation during sleep.<sup>19</sup> The restrictive pulmonary disease in CHD infants may be a result of increased pulmonary artery pressure, which may be associated with congestive heart failure and pulmonary edema. CHD infants typically demonstrate a high resting respiratory rate (Table 2), which may result in a disproportionate increase in dead space ventilation during sleep. In addition to these mechanisms, the increased AHI observed in CHD infants may also contribute to oxygen desaturation during sleep.

The reasons for increased central apneas and hypopneas in CHD infants were not explored in this work. Whereas ventilation is under the influence of several factors during wakefulness, during sleep, ventilation is under chemical-metabolic control. For ventilation to be maintained, it is necessary that PaCO<sub>2</sub> stay above the apnea threshold; therefore, hyperventilation and the resultant hypocapnia are thought to be the major abnormalities contributing to ventilatory control instability.<sup>20</sup> In adults with congestive heart failure, central apneas in association with Cheyne-Stokes respiration are common. In adults, Cheyne-Stokes respiration is also associated with hyperventilation and hypocapnia.<sup>6</sup> In our study, CHD infants demonstrated tachypnea, but unfortunately, we did not monitor arterial CO<sub>2</sub> levels. Of note, no CHD infants exhibited either Cheyne-Stokes respiration or periodic breathing in association

with central apneas or hypopneas. The absence of a typical Cheyne-Stokes pattern of breathing may be related to a different pattern of cardiovascular and pulmonary involvement in these infants.

Our study has some limitations. First, we studied a small number of subjects, making it difficult to draw definitive conclusions. Second, we studied infants in different age ranges; that variation, however, does not affect the respiratory findings. CHD infants were also malnourished. Because malnourished infants have shorter bouts of sustained sleep,<sup>21</sup> the increased wakefulness found in CHD infants could be related to nutritional status rather than to central apneas. Finally, although infants using medications that potentially affect the CNS were excluded, the use of cardiovascular drugs could also have affected sleep.

In conclusion, CHD patients are prone to sleep-related oxygen desaturations, central apneas and hypopneas that are not associated with arousals. Although sleep may represent an additional burden to these infants, it has rarely been studied. Therefore, this study provides a strong rationale for investigating sleep disordered breathing in CHD infants.

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