

Nocturnal breathing in cyanotic congenital heart disease

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Abstract

Background: Sleep disordered breathing is frequently observed in patients with cardiovascular disease. Even in the absence of heart disease, acute and chronic hypoxia have been shown to promote sleep-related periodic breathing with central apnea characterized by a repetitive reduction or lack of respiratory activity. Cyanotic congenital heart disease (CCHD) is associated with chronic hypoxia, regardless of whether an increase in pulmonary artery pressures coexists. Sleep aggravated hypoxia has been observed in many such patients, but it remains to be determined whether sleep disordered breathing is contributory. We, therefore, sought to assess sleep-related breathing pattern in patients with CCHD.

Methods: Adults with CCHD, resting arterial oxygen saturation <90%, and systemic ejection fraction >40% were prospectively enrolled in a cross-sectional study. To assess sleep and respiratory indices, subjects underwent a standardized clinical appraisal that included arterial blood gas analysis and a comprehensive sleep study with an ambulatory device. An apnea–hypopnea index (AHI) ≥ 5 /h was considered to indicate sleep apnea.

Results: Ten adults with CCHD, aged 38 ± 11 years, completed the study. Seven patients had elevated pulmonary artery pressures, with a mean systolic pressure of 86.3 ± 18.1 mm Hg. All patients demonstrated normal sleep parameters. Oxygen saturation further declined in 5 patients during sleep. However, no associated alteration in respiratory parameters was observed and no significant arrhythmia. The mean AHI was 1.1 ± 1.0 /h. No subject met the pre-defined criterion for sleep apnea.

Conclusion: Although further oxygen desaturation may be observed during sleep in patients with CCHD, it occurs in the absence of sleep disordered breathing.

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1. Introduction

Sleep disordered breathing (SDB), whether obstructive or central in origin, is frequently observed in patients with cardiovascular disease and is characterized by the presence of frequent and repetitive respiratory pauses leading to profound oxygen desaturations and sleep disruption [1]. Central sleep apnea (CSA) is seen in up to 45% of patients with stable congestive heart failure [2] and is associated with excess morbidity and mortality [3]. It has also been reported in up to

55% of patients with asymptomatic left ventricular dysfunction [4] and appears to be associated with impaired cardiac autonomic control and arrhythmias. Finally, periodic breathing with central apneas has been described in athletes training under hypoxic conditions and during acute and chronic exposure to hypobaric hypoxia [5,6] and in otherwise healthy individuals living at high altitude [7].

Cyanotic congenital heart disease (CCHD) is associated with chronic hypoxia, regardless of whether an increase in pulmonary artery pressures coexists. In these subjects, sleep has been reported to further aggravate hypoxia [8]. It is not clear, however, whether sleep disordered breathing may be a contributing factor. The purpose of this study was to

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Table 1
Patient characteristics

Patient	Sex	Age	Type of malformation	NYHA class	Systolic pulmonary pressure (mm Hg)	Resting O ₂ saturation (%)	Hemoglobin (g/dL)	Hematocrit	Arterial pH	pO ₂ (mm Hg)	pCO ₂ (mm Hg)	HCO ₃ (mmol/L)	BMI
1	F	33	Truncus arteriosus	3	75	73	181	0.568	7.44	40	37	25.7	24
2	M	43	L-Transposition	1	65	84	168	0.522	7.44	49	43	29.6	24
3	F	46	Pulmonary atresia	2	70	75	190	0.561	7.44	40	44	30	23
4	M	21	Pulmonary atresia	1	N/A	87	207	0.610	7.48	82	32	27	20
5	F	24	Pulmonary atresia	3	104	80	222	0.696	7.41	42	44	28.2	51
6	M	30	Single ventricle	2	100	78	223	0.670	7.44	45	39	27	21
7	F	48	Tricuspid atresia	3	80	80	178	0.545	7.47	40	34	24.8	22
8	M	45	Single atrium	2	37	89	203	0.604	7.43	51	37	25.2	28
9	F	44	L-Transposition	2	N/A	76	139	0.454	7.46	41	40	28.9	19
10	F	55	Pulmonary atresia	3	110	81	154	0.462	7.47	43	45	33.1	18
		38±11				80.3±0.5	186.5±28	0.57±0.07	7.44±0.02	47.3±12.3	39.5±4.2	28.1±2.7	25±9.5

N/A=not available.

assess sleep breathing pattern in patients with CCHD and determine whether sleep apnea contributes to the pathophysiology of the hypoxemia further observed during sleep.

2. Methods

Contingent upon providing written informed consent, ambulatory patients with CCHD were recruited from the Adult Congenital Heart Disease Center of the Montreal Heart Institute. Eligible candidates were required to be 18 years or older, have a systemic ventricular ejection fraction >40%, and a resting arterial oxygen saturation <90%. A stable medical regimen was mandated, with no change in therapy or hospitalization in the preceding 3 months. Patients were excluded if previously diagnosed with obstructive sleep apnea or other conditions associated with sleep dysfunction, including genetic disorders (e.g. trisomy 21, William's syndrome), prior stroke, or untreated hypothyroidism. The protocol was approved by the institutional research and ethics committees.

At the first visit, functional class was assessed according to the NYHA classification system and a physical examination was performed. Venous blood was sampled for hemoglobin and hematocrit levels and an arterial blood gas was drawn at room air after 10 min of rest. One night full polysomnography was conducted at the patient's home by means of an ambulatory device (Siesta, Compumedics). Sleep recording included four electroencephalogram leads (C3, C4, O1 and O2), two bilateral electro-oculograms (EOG) and one chin electromyogram (EMG). Leg movements were assessed by bilateral tibialis EMG. Respiration was assessed by nasal cannula, thoraco-abdominal strain gauges and finger pulse oxymetry. One lead ECG (lead I) was also used. Sleep was scored according to standard methods [9]. The variables considered in the analysis were: sleep latency, sleep efficiency, the percent of sleep stages, SaO₂ saturation, respiratory events (apneas and hypopneas), microarousals, periodic legs move-

ments (PLMS). Apnea was defined as cessation of airflow lasting 10 s or more. Central apnea was defined as the absence of flow with a concordant lack of thoracoabdominal movement. Hypopnea was defined as >50% reduction in the sum of thoracoabdominal movements for at least 10 s, followed by a reduction in SaO₂ by 4% or more [4]. An apnea-hypopnea index (AHI) ≥5/h was considered to indicate sleep apnea. Microarousals (MA) were scored according to standard ASDA criteria (1992) [10]. MA was defined as an abrupt shift in EEG frequency lasting at least 3 s, which could include theta, alpha and/or frequencies greater than 16 Hz. PLMS were scored according to Coleman's criteria [11].

2.1. Statistical analysis

Continuous variables are expressed as mean±SD. Categorical variables are represented as frequency and percentage.

3. Results

3.1. Patient characteristics

Ten ambulatory patients with CCHD (6 females), mean age 38±11 years (range 21–55 years), participated in the study.

Table 2
Sleep parameters

	Mean±SD
Sleep duration min	438.1±95.2
Sleep efficiency %	84.0±5.2
Apnea-hypopnea index (n/h)	1.1±1.0
Microarousal index (n/h)	10.4±3.5
PLMS ^a index (n/h)	1.5±1.8
Mean SaO ₂ (%)	80.6±4.6
SaO ₂ min (%)	71.1±10.5
% of the night with SaO ₂ <80%.	39.4±42.5

^a PLMS=Periodic legs movements.

Table 3
Baseline and sleep saturations

Patient	Baseline sat O ₂ (%)	Sat O ₂ mean (%)	Sat O ₂ min (%)	Sat O ₂ max (%)
1	73	74	47	79
2	84	84	67	89
3	75	80	69	85
4	87	86	81	89
5	80	78	70	83
6	78	68	58	74
7	80	77	65	83
8	89	85	78	90
9	76	74	71	80
10	81	85	83	92
Mean	80	79	69	84

Sat = saturation.

Baseline characteristics are reported in Table 1. The pulmonary systolic pressure was elevated in 7 patients (86.3 ± 18.1 mm Hg), normal in 1 and unknown in 2. All patients had severe hypoxemia, with a mean PaO₂ of 43.4 ± 4.1 mm Hg and secondary erythrocytosis. Marked hypoxemia was noted on blood gases, with arterial pH, pCO₂, and HCO₃ remaining within normal limits.

3.2. Sleep data

Sleep recordings were well tolerated in 8 patients. Two patients reported that the electrodes contributed to disturbing their sleep. Sleep study results are depicted in Table 2. Subjects showed a normal architecture of sleep, without pathological indices of microarousals or PLMS. Mean AHI was 1.1 ± 1.0 /h, with no subject meeting the criterion for sleep apnea. During sleep, mean oxygen saturation was only slightly lower compared to daytime (Table 3). Five subjects had >40% of the night with O₂ sat <80%. Six patients experienced nocturnal desaturation (1 to 10%, mean 3.7%), with 3 patients exhibiting a mild increase in their baseline saturation (1 to 5%) and one patient remaining stable. No patients presented significant arrhythmia during sleep.

4. Discussion

In this study we documented that sleep apnea is not a common feature associated with CCDH, despite nocturnal desaturation.

4.1. Hypoxia in cyanotic congenital heart disease

Hypoxia and cyanosis are prominent features of many types of congenital heart disease. Chronic hypoxia triggers adaptive mechanisms including erythrocytosis, with hematocrit levels that may reach 0.65 to 0.70. These mechanisms are usually inadequate to restore normal oxygen saturation, with levels that commonly hover around 80% on room air. In patients with Eisenmenger physiology, further desaturation has been observed during sleep [9]. This

phenomenon was thought to be related to the supine position and attributed to ventilation-perfusion abnormalities and/or to a diffusion limitation rather than exaggerated right to left shunting associated with the increase in venous return. Baseline saturation levels could be restored with nasal oxygen supplementation. Disappointingly, no survival benefit was noted in a prior study assessing long-term nocturnal oxygen therapy in Eisenmenger patients [12].

We hypothesized that profound nocturnal desaturation observed in patients with CCHD, many of whom have Eisenmenger physiology, may result from central sleep apnea, a potentially treatable condition. Our results did not, however, support this notion as no significant periodic breathing was observed in any patient.

4.2. Physiologic response to acute and chronic hypoxia

Acclimatization to low pO₂ has been studied in mountain climbers and athletes training at high altitudes. In such situations, the normal ventilatory response to acute oxygen desaturation without a concomitant increase in pCO₂ is linear. With several days of exposure, most normal individuals will further increase their ventilation 3 to 6-fold when arterial pO₂ reaches 40 mm Hg, which generally corresponds to a hemoglobin saturation of 75%. After initial inhibition of the respiratory center by the associated decrease in pCO₂ and increase in pH, the inhibition response dissipates, allowing the respiratory center to respond to hypoxic chemoreceptor stimuli. The hypoxic ventilatory response is notoriously variable and characteristically depressed during sleep.

Within the span of a few weeks, hypoxia will increase red cell production and blood volume. A rise in pulmonary capillary blood volume will increase capillary surface and diffusing capacity. Chronic hypoxia can eventually result in sustained elevation of pulmonary artery pressure due to vasoconstriction caused by a low alveolar oxygen concentration. In natives of the Andes and Himalayas living at altitudes above 13,000 feet, other mechanisms are recruited since infancy, including increased chest size coupled with decreased body size resulting in a high ratio of ventilatory capacity to body mass. These adaptive mechanisms result in a greater quantity of oxygen in the blood despite arterial pO₂ levels as low as 40 mm Hg.

4.3. Altered sleep patterns in acute and chronic hypoxia

The pathophysiological mechanisms responsible for sleep related periodic breathing are still unclear. The most widely accepted theory explains periodic breathing as a self-sustaining oscillation due to the loss of stability in the closed-loop chemical control of ventilation [13]. The consequent hypoxia and hypercapnia elicit chemoreflex activation and subsequent hyperventilation. In the presence of “instability” in the control loop, this event can initiate periodic breathing, with oscillations of pCO₂ below and above the apnea threshold [14]. Hypocapnia and low PaCO₂ threshold are

believed to be essential for the generation of periodicity and instability. Periodic breathing with central apnea is a common feature of sleep in healthy people acutely exposed to the hypobaric hypoxic environment created by high altitude as well as by a normobaric hypoxic environment (the “live high, train low” approach used in elite athletes) [6].

Our patients with CCHD did not experience periodic breathing. One possible explanation is that the permanent and chronic nature of hypoxia in CCHD leads to a blunted or absent reflex hyperventilation in response to hypoxia. It might also be that even when these subjects hyperventilate, PaCO₂ remains above the apnea threshold because of the mixing with venous return and the hypocapnic triggering mechanism for periodic breathing is absent.

4.4. Nocturnal arterial saturation

Six of our patients experienced further nocturnal desaturation with 4 patients exhibiting a mild increase in their baseline saturation. Rafanan et al [15] also reported episodes of nocturnal desaturation in 13 patients with primary pulmonary hypertension. In 10 (77%) patients, they occurred independently of apnea or hypopnea. Nocturnal desaturation was seen more frequently in patients with lower resting PaO₂ (61.8±16.1 vs 90.3±2.3 mm Hg, $p=0.001$) and SpO₂ (91.6±5.4% vs 98.7±2.3%, $P=0.038$). In our small group of patients, baseline saturation was similar whether nocturnal desaturation was present or not. In patients where a mild increase in saturation was observed during sleep (1 to 5%), we hypothesize that this difference may reflect a limitation engendered by comparing one day time saturation with multiple nocturnal samples.

5. Limitations

Our study was limited by a small sample size, a common and unavoidable problem in investigations involving adults with congenital heart disease. Nevertheless, the consistent absence of sleep disordered breathing is unlikely to have been reversed by a larger sample size. Secondly, sleep studies were conducted on only one night and no control patients were studied. Subjects did not get a chance to get accustomed to the equipment used for the polysomnography study. It is, therefore, possible that our results are not representative of usual sleep patterns for these subjects. Again, considering the lack of abnormal results or suggestive trends, an adjustment period or comparison group is unlikely to substantially modify our findings.

6. Conclusion

Although further oxygen desaturation may be observed during sleep in patients with CCHD, it occurs without alterations in sleep patterns. Given the absence of sleep disordered breathing, we found no rationale to support the use of nocturnal positive airway pressure ventilation in patients with CCHD.

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