Continuous positive airway pressure improves work of breathing in pediatric chronic heart failure

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Original Article

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Abstract

Background: Sleep disordered breathing (SDB) is common in adults with chronic heart failure (CHF), but its prevalence in children remains unclear. Continuous positive airway pressure (CPAP) is the treatment of SDB but deleterious hemodynamic effects have been reported.

Methods: We prospectively analyzed SDB in children with CHF and the effect of CPAP on work of breathing (WOB) and cardiac index (CI). Children aged 6 months to 18 years old with CHF due to: 1) dilated cardiomyopathy (DM) with an ejection fraction < 45%, 2) functional single ventricle (SV) or 3) aortic or mitral valve disease awaiting surgery (VD) were eligible for the study. A polysomnography (PSG), measurement of WOB and CI during spontaneous breathing (SB) and CPAP (6, 8 and 10 cmH2O) were performed.

Results: Thirty patients with mean age of 6.4 ± 5 years were included (16 DM 16, 10 SV, 4 LV). Twenty (73%) patients had a normal sleep efficiency. Median apnoeas hypopnea index (IAH) was within normal range at 1.6 events/h (0, 14) events/hour. Only one patient had central sleep apnoea, none had Cheyne-Stokes respiration, and 3 patients had an obstructive AHI between 5 and 10 events/hour. Optimal CPAP level decreased WOB (p = 0.05) and respiratory rate (p = 0.01).

Conclusions: Severe SDB was uncommon in children with CHF. However, CPAP may be beneficial by decreasing WOB and respiratory rate without deleterious effects on CI.
Many treatments of paediatric CHF are based on extrapolation of data from studies on adults. The prevalence, prognostic value and effect of treatment of SDB is largely unknown in the paediatric population. Data on WOB in children with CHF are missing, however this information seems important for the potential benefit of CPAP in children with CHF.

The aim of our study was therefore to determine if children with various causes of CHF have SBD and if CPAP therapy can improve their WOB.

2. Material and methods

2.1. Patients

Children aged 6 months to 18 years old, followed at the paediatric cardiology department of Necker university Hospital between October 2015 to September 2017, were considered eligible for the study if they had a:

1. Dilated cardiomyopathy (DM) with an EF of less than 45%.
2. Functional single ventricle (SV) in stage 2 or 3 of palliation.
3. Aortic or mitral valve disease (VD) awaiting surgery.

Exclusion criteria were an episode of acute heart failure requiring inotropes during the previous 30 days or a contraindication to CPAP (acute otitis, acute or chronic sinusitis, epistaxis). Anthropometric and clinical data were collected. Written informed consent was obtained for all parents or legal guardians and for all children older than 6 years. The study was conducted in agreement with the French regulations and received appropriate legal and ethical approval from the ethical committee (CPP Ile de France 2, n° P141003 accepted on the 5th October 2015).

2.2. Patient and public involvement

Patients were not involved in the design and recruitment of the study.

2.3. Polysomnography

An in-hospital polysomnography (PSG, Alice 6 LDxS, Philips Respironics, Carquefou, France) was performed during the first night. Sleep quality, sleep stages and cardiorespiratory parameters were scored manually using the criteria of the American Academy of Sleep Medicine (AASM) [14]. Full methods are available online.

2.4. Measurement of the work of breathing

The measurement of WOB by means of the measurement of oesophageal (Pes) and gastric (Pgas) pressures during spontaneous breathing (SB) and CPAP was performed on the following morning as described elsewhere [15]. Full methods for WOB measurement are available online.

2.5. Echocardiographic evaluation

Standardized complete transthoracic echocardiographic examinations were performed at baseline according to established guidelines [16] using a Vivid 9 system (GE Healthcare, Norway). Left ventricle ejection fraction was assessed by biplane Simpson’s rule. Cardiac output was assessed using the Doppler VTI method [17]. Cardiac output was measured at baseline and for each level of CPAP pressure, and cardiac index (CI) was calculated.

2.6. Effect of CPAP

After 20 min of calm and stable breathing in room air in the half-seated position, respiratory and echocardiographic parameters were recorded during 5 min. Afterwards, the patient received CPAP (BiPAP A40, Philips Respironics, Murrysville, PA, USA) at a starting pressure of 6 cmH2O with an appropriate nasal or nasobuccal mask. When a calm and stable breathing was obtained for at least 15 min with CPAP, the same cardiorespiratory parameters were recorded during 5 min. The same recordings were then made with a CPAP pressure of 8 and 10 cmH2O. “Optimal CPAP” was defined as the CPAP pressure associated with the greatest reduction in WOB.

2.7. Collection and analysis of data

An alphanumerical code was attributed to each patient (initials of name and surname and consecutive number of enrolment). Data regarding PSG, transthoracic echocardiographic and WOB were inserted in a Microsoft Excel® file. An investigator blinded to patients’ identity and type of CHF analysed the WOB tracings and determined the “optimal CPAP”. Only WOB data regarding “optimal CPAP” were used for statistical analysis.

3. Statistical analysis

Sample size estimation was based on the hypothesis of a mean reduction of 30% of the WOB (delta Pes), with a significant level of 0.05% and a power of 80%. Forty-five patients were expected to be included in the study (15 patients per group).
Data are reported as mean and standard deviation for continuous variables and as total number and percentage for categorical variables. Comparisons between the baseline and the “optimal CPAP” level were made using paired Student t-tests for continuous data and McNemar’s chi-squared tests with continuity correction for qualitative ones. All computations were performed with the R statistical environment V3.6.0 (https://www.R-project.org/). P-values less than 0.05 were considered as statistically significant.

4. Results

4.1. Patients

Two families refused to participate to the study, which left 30 included patients: 16 patients with a DM, 10 with a SV and 4 with a VD. Median age was 4.8 (0.7–17.0) years (Table 1). Two patients with VD had mitral stenosis, one mitral insufficiency and one aortic insufficiency. Regarding comorbidities, one patient with DM had also ectodermal dysplasia and one with VD had also a Down syndrome.

4.2. Polysomnographic data

PSG data are shown in Table 2. One patient refused the EEG recording but respiratory parameters were included for analysis. Median sleep efficiency (SE) was 87% (56, 97), with 21 children (72%) having a SE > 80%. Median percentage of wake after sleep onset (WASO) was 13% (3, 44). Sleep stages were normal for patients’ age.

Median AHI was normal 1.6 events/h (0, 14), with a median central apnoea index (CAI) of 0.2 events/h (0, 7). No patient...
presented Cheyne-Stokes respiration. Two patients had an AHI between 5 and 10 events/h: one patient with DM had an obstructive AHI (OAHI) of 7.1 events/h with a CAI of 0.2 events/h and one patient with LV had an OAHI of 2.5 events/h with a CAI of 2.7 events/h. Only 2 patients had an AHI >10 events/h; one with DM (with an OAHI of 10 events/h and a CAI of 0 events/h) who was referred for ENT surgery because of adenotonsillar hypertrophy and one with SV (with an OAHI of 7.1 events/h and CAI of 7.3 events/h).

4.3. WOB during SB and during CPAP

Three patients refused the oesogastric catheter and for 3 other patients, oesogastric tracings were not analysable due to the agitation of the child. One patient did not tolerate CPAP and therefore only WOB during SB was retained for analysis. Median WOB during SB was moderately increased (Table 3 and Fig. 1). The median “optimal CPAP” level was 8 cmH2O. For the DM group, “optimal CPAP” was associated with a significant decrease in WOB (assessed on delta Pdi, and PTPdi/min) and respiratory rate, with no significant change in CI (Table 3 and Fig. 1). For the SV group, “optimal CPAP” was also associated with a significant decrease in WOB (assessed on delta Pes, delta Pdi, and PTPes/min) (Table 3 and Fig. 1). No significant results were observed in the VD group.

4.4. Follow-up and clinical outcome

One patient with DM was started on long term CPAP because of a very significant improvement of WOB and subjective dyspnoea with CPAP. CPAP was continued until successful heart transplantation 22 months later. Four other patients, 3 with DM and one with SV, had successful heart transplantation between 3 months and 3 years after the study. Three patients with DM died within the two years following the study. All other patients were alive after two years.

5. Discussion

Our study is the first to analyze sleep quality, sleep architecture, and SDB in children with different types of CHF and to measure WOB during SB and CPAP. Sleep architecture was preserved, and sleep quality was moderately reduced, with only 3 patients having OSA and/or CSA and no patient having Cheyne-Stokes respiration. WOB was moderately increased during SB and improved significantly with CPAP therapy without a deleterious effect on CI.

In contrary to adult patients with CHF, SE was globally preserved in these children with only 9 (23%) children having a SE less than 80%. This percentage is much lower than observed in adults with CHF who reported 63%–81% poor subjective sleep quality via self-administered questionnaires [18,19]. A treatment with β-blockers has shown to be associated with sleep disturbance in adult patients [20] which may be explained by the inhibition of melatonin release via interaction with adrenergic beta1-receptors [21]. Fourteen of our patients were treated with beta-blockers. However, among the 8 patients having a SE below 80%, only two patients with DM were treated with beta-blockers at the time of the PSG. Their use does thus not seem to be associated with a low SE in our patients. A more plausible hypothesis is that the moderate reduction in % of N3 and REM sleep observed in the present study is related to a well-known first night in hospital effect [22].

In contrary to adult patients with CHF, the prevalence of severe SDB in our population was low with no patient having Cheyne-Stokes respiration. Among the 16 patients who had SDB in our study; 15 had OSA defined as an AHI >1.5/h, 9 in the CM group, 3 in the SV and the VD group, respectively. Three patients had an OAHI between 5 and 10 events/hour and only one patient had CSA. One patient with DM had an AHI of 7.3 events/h with a low CAI (0.2 events/h), not explained by tonsillar hypertrophy: she died from CHF 18 months after the study. Another patient with DM had an AHI of 10 events/h with tonsillar hypertrophy and was referred for ENT surgery. Finally, one patient with SV had a global AHI of 14.3 events/h, with a CAI of 7.3 events/h and an obstructive AHI of 7.3 events/h. This was also the only patient with a CI >5/h which is considered as the cut-off defining CSA in children [23]. A CSA prevalence of 19% has been reported in a series of 37 children with CHF but the cut-off used to define CSA was 1 event/h which is lower than the recommended cut-off of >5 events/h [24]. Three (8%) patients had Cheyne-Stokes respiration but all these patients were older than 12 years of age with two who had a heart transplant in the following two years. Two other cases of Cheyne-Stokes respiration have been reported in a 5-month-old girl with left ventricular non-compaction and an EF of less than 10% who was placed on Berlin EXCOR LV assist device [25], and a 13 year-old boy with DM and progressive deterioration of EF who had a heart transplant with complete resolution of Cheyne-Stokes respiration [26].

Data from literature confirms the higher prevalence of SDB in children with HF, but with an overall tendency to mild or moderate OSA. A higher prevalence of SDB has been reported in patients with severe HF undergoing heart transplantation. In a group of 50

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<td>Work of breathing during spontaneous breathing and optimal CPAP.</td>
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<td>SB</td>
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<td>SpO2 (%)</td>
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<td>PtcCO2 (mmHg)</td>
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<td>Delta Pdi (cmH2O)</td>
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<td>Delta Pdi (cmH2O/min)</td>
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<td>CI (L/min/m²)</td>
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Data are given as median and range. Bold and italic are statistically significant p values.

DM = dilated cardiomyopathy, SV = single ventricle, VD = valve disease, SB = spontaneous breathing, CPAP = continuous positive airway pressure, SpO2 = pulse oximetry, PtcCO2 = transcutaneous carbon dioxide, RR = respiratory rate, HR = heart rate, Pes = esophageal pressure, Pgas = gastric pressure, PTPes: esophageal pressure-time product, PTPdi: diaphragmatic pressure-time product, CI = cardiac index.
Fig. 1. Cardiac index, respiratory rate, Pes and PTPdi for each CPAP level in the DM group (n = 12) A and in the SV group (n = 6) B. Grey lines represent each patient, black line and error bars represents mean with their 95% confidence interval. Abbreviations: CPAP = continuous positive airway pressure, DM = dilated cardiomyopathy, CI = cardiac index, RR = respiratory rate, Pes = esophageal pressure, PTPdi: diaphragmatic pressure-time.
children who had a PSG pre or post heart transplantation, 14 had severe OSA and two older patients with severe DM had Cheyne-Stokes respiration, however these patients were older and had more severe HF compared to the patients in our study [27]. Another study on 30 children with CHD found an increased prevalence of OSA (57%), which was associated with cognitive impairment [28]. However, as in our study, OSA was generally mild (88%) or moderate (12%). Similar results were observed in 21 children with congenital cardiomyopathy, with an overall prevalence of SDB of 24% but only one patient had severe OSA and another presented Cheyne-Stokes respiration [29]. Finally, a large cross-sectional retrospective cohort study in infants younger than 1 year with congenital heart disease included in a national database, identified central sleep apnea as a risk factor for in hospital mortality [30]. However due to difference in population characteristics, these data are difficult to compare to our cohort of patients.

Our study is the first to measure the WOB in children with CHF and showed that WOB was moderately increased. Interestingly, CPAP was associated with a significant decrease in WOB and respiratory rate in children with DM. Similar levels of WOB have been observed in 11 adult patients with CHF with also a significant beneficial effect of noninvasive ventilation [31]. Interestingly, the decrease in WOB correlated with the improvement in dyspnoea. Unfortunately, most of our patients were too young for the subjective assessment of dyspnoea but it is noteworthy that at least 5 children felt asleep during CPAP, which may be an indirect marker of dyspnoea relief. As children with CHF have an increase in total energy expenditure (TBE) [32], one may hypothesize that CPAP may decrease the respiratory component of TBE. CPAP therapy thus represents an interesting treatment that may be proposed to improve thriving failure and quality of life in children with CHF, and to reduce morbidity and mortality while awaiting heart transplantation.

Importantly, CPAP was not associated with a significant change in CI in the present study. Different results have been observed in adult patients. In 22 adult patients with CHF, those with a high pulmonary capillary wedge pressure (PCWP) had an increase in CI whereas a decrease was observed in those with a low PCWP [9], suggesting that the patients who are most likely to benefit from CPAP are those with an elevated baseline left ventricular pressure. In another study of 7 adults with stable CHF, a significant global decrease in CI was observed after 2 h of CPAP at 5 cmH2O [10]. Finally, in 10 adult patients with CHF and CSA, large variations in CI were observed for different levels of CPAP, underlining the value of an individual CPAP titration [33]. In conclusion, even if the results concerning the CI were reassuring during the short duration of the study, the checking of CI after a longer CPAP use seems recommended. CPAP should be used with caution in patients with SV, since reducing cardiac preload may lead to a decrease of CO as reported in adult patients with SDB and Fontan circulation [34,35]. Interestingly, in patients with SV we did not observe a deleterious effect of the best CPAP pressure level on CI. One could argue that our patients had different types of palliative surgery (some patients had a Norwood stage 1, others a stage 2 and others a Fontan procedure), with various impacts of intrathoracic pressures changes on pulmonary circulation. Moreover, adult patients presented often with obesity and a reduced lung capacity. On the contrary in our cohort children had normal or low BMI with normal lung function, thus pressure changes may have different effects on pulmonary vascular compliance and cardiac preload.

Our study has several limitations. We planned to recruit 15 patients for each group but this number was only obtained for the group of DM, due to the smaller than expected number of patients with SV and VD. Most of the patients had a moderately severe CHF on the NYHA classification with only 2 patients having a NYHA IV and 11 having a NYHA III. However, the patients in the present study had a poor prognosis with 7 patients who died or were transplanted within the two years of follow up. The effect of CPAP on WOB was assessed after only 15–20 min of calm breathing. Even if the effect of CPAP on WOB is immediate, the hemodynamic effects may take longer to appear. There was a large variability of the effect of CPAP on WOB and CI between the CHF groups and also among patients of the same group. The patients were evaluated during daytime, preferentially during their usual nap time, and even if some patients fell asleep, this does not correspond to during their usual overnight sleep.

6. Conclusion

In conclusion, severe SDB is uncommon in children with CHF with the preservation of an acceptable sleep quality despite beta-blockers therapy, with only one patient having CSA and none Cheyne-Stokes respiration. WOB was moderately increased. CPAP was associated with a significant decrease in WOB and respiratory rate without a deleterious effect on CO. CPAP could thus be proposed in these children, not to correct SDB but to decrease WOB and respiratory rate. The long-term beneficial effect of CPAP seems worth to be evaluated in larger prospective studies in children with CHF, in particular to improve thriving failure and as a bridge to heart transplantation.

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Authorship statement

Prof Brigitte Fauroux and Damien Bonnet participated to the design of the study. Alessandro Amaddeo, Sonia Khirani, Diala Khraiche, Mathilde Meot and Prof Brigitte Fauroux contributed to data collection and analysis of the data. Jean Philippe Jais performed statistical analysis. All the authors contributed equally to the writing of the manuscript and approved the final version.

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Josephine Okoronkwo participated as clinical research assistant to the collection of the data.

Conflict of interest

No financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.04.003.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sleep.2021.04.003.