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Original Article

Cardiac systolic function in Greek children with obstructive sleep-disordered breathing

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ABSTRACT

Background: Obstructive sleep-disordered breathing (SDB) in children has been associated with increased ventricular strain and decreased left ventricle (LV) diastolic function. The aim of this study was to assess systolic myocardial function in children with SDB of variable severity.
Methods: Children who were referred for polysomnography during the study period underwent echocardiography (two-dimensional, Doppler and tissue Doppler imaging).
Results: A total of 46 subjects (age 6.4 ± 2.6 years) were recruited. Fourteen of them had moderate-to-severe SDB (obstructive apnea-hypopnea index (OAHI): 16.6 ± 11.6 episodes/h), 13 children had mild SDB (OAHI: 3.1 ± 0.7 episodes/h) and 19 subjects had primary snoring (OAHI: 1.2 ± 0.6 episodes/h). Children with moderate-to-severe SDB had significantly lower LV shortening fraction (SF) and ejection fraction (EF) than subjects with primary snoring ($p < 0.05$). SF in moderate-to-severe SDB, mild SDB and primary snoring groups was: 34.3 ± 5.5%, 36.9 ± 3.2% and 37.7 ± 4.4%, respectively, and EF: 66.9 ± 7.9%, 71.7 ± 6.4% and 72.3 ± 5.9%, respectively. OAHI, age, and systolic blood pressure were significant predictors of SF and EF ($p < 0.01$).
Conclusions: In children with obstructive SDB, LV systolic function is inversely associated with severity of intermittent upper airway obstruction during sleep.

1. Introduction

Accumulating evidence indicates that severity of obstructive sleep-disordered breathing (SDB) in childhood correlates with surrogate measures of future cardiovascular morbidity [1–10]. Elevated serum concentrations of C-reactive protein (CRP) have been demonstrated in subgroups of children with sleep apnea [2,11], and increased fasting insulin levels have been found mostly in obese children with SDB [12–14]. Moreover, a significant association has been identified between the metabolic syndrome and sleep apnea in children and adolescents [3,9]. Treatment of intermittent upper airway obstruction during sleep with adenotonsillectomy is accompanied by improved lipid profile and endothelial function and reduced CRP levels [1,4].

In addition, several studies have revealed that obstructive SDB is associated with blood pressure elevation [5,10,15] and changes in myocardial structure and function [7,8,16,17]. Children with snoring and apnea-hypopnea index > 5 episodes/h have significantly higher wake systolic and wake and sleep diastolic blood pressure compared to healthy controls [5], and successful treatment of upper airway obstruction by adenotonsillectomy seems to decrease mainly the diastolic component of blood pressure [2,6,18]. Subjects with severe sleep apnea can present with pulmonary hypertension [19] and decreased right ventricle systolic function [16,17]. A recent echocardiography study has identified increased right ventricle end-diastolic dimension and left ventricle mass index [7]. Finally, a negative correlation has been reported between severity of obstructive SDB and left ventricle (LV) diastolic function [8], which improves after surgical removal of adenoids and tonsils [20].

In contrast to older reports [16,17], recent echocardiography studies have not detected a negative impact of sleep apnea on systolic myocardial function [8,20]. Children with obstructive SDB, however, have increased blood and urine norepinephrine levels [21,22], and, at least in adults with sleep apnea, increased release of catecholamines has been associated with decreased sensitivity of β-adrenergic receptors [23]. Desensitization of the β-adrenergic receptors may conceivably lead to isolated reduced systolic

Abbreviations: EF, ejection fraction; LV, left ventricle; OAHI, obstructive apnea-hypopnea index; SDB, sleep-disordered breathing; SF, shortening fraction; SpO_2, oxygen saturation of hemoglobin by pulse oximetry.

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function even without the presence of diastolic dysfunction or cardiac structure abnormalities. Therefore, we performed an exploratory study to assess cardiac systolic function in children with moderate-to-severe SDB in comparison to subjects with mild SDB or with primary snoring.

2. Patients and methods

2.1. Participants

The study protocol was approved by the University of Thessaly Ethics Committee. Informed consent was obtained from parents of participants and child's assent from subjects older than 6 years. Consecutive children with snoring (>3 nights/week) who were referred to the Sleep Disorders Laboratory for polysomnography were offered the chance to participate in the study if they did not have (1) symptoms of upper respiratory tract infection; (2) history of cardiovascular, neuromuscular or genetic disorders; or 3) history of adenoidectomy or tonsillectomy. Subjects were finally recruited to the study if (1) parental informed consent and children's assent were obtained and (2) an appointment for echocardiography was available in the morning after polysomnography. The cardiologist performing the study was completely blinded to results of polysomnography and the only "selection" criterion was availability of echocardiography appointments.

Information on symptoms of SDB was collected and a physical examination was performed. Somatometrics were recorded and body mass index (BMI) z-score was calculated [24]. Z-score indicates how many standard deviations the calculated BMI value is above or below the mean BMI value for age and gender; mean BMI is obtained from reference growth curves [25]. About 30 min after completion of polysomnography, blood pressure was measured three times using the right arm, and the average value of the three measurements was used in statistical analysis [26]. To control for the effect of age, gender, and height on blood pressure, an index was calculated: (average measured value-95th percentile value) $\times$ 100/95th percentile value [26,27].

2.2. Polysomnography

All participants underwent overnight polysomnography and the following parameters were recorded: electroencephalogram, right and left oculogram, submental and tibial electromyogram, body position, electrocardiogram, thoracic and abdominal wall motion (piezoelectric transducers), oronasal airflow (three-pronged thermistor), and oxygen saturation of hemoglobin (SpO_2). Polysomnography methods have been presented in detail elsewhere [28].

2.3. Echocardiography

Complete transthoracic echocardiography was carried out the morning after completion of the sleep study by one experienced cardiologist who was blinded to polysomnography results, using commercially available equipment (Vivid 3/1.5–3.6 MHz transducer, GE Medical Systems, Milwaukee, WI). The study was completed while children were awake. Measurements were performed over three cardiac cycles by standard M-mode; two-dimensional, Doppler and tissue Doppler imaging (TDI) echocardiography were averaged and used for analysis in order to minimize beat-to-beat variability.

LV shortening fraction (SF) and ejection fraction (EF; Simpson's rule) were determined. The coefficient of variation for the measurement of LV SF ranged from 1.6% to 6.6% and for LV EF from 1.2% to 5.7%. Reported normal values for LV SF are 28–40% and for EF 54–75% [29]. Right ventricular systolic function was evaluated by the EF area in four-chamber view:

(right ventricle area in end-diastole- right ventricle area in end-systole/area in end-diastole) $\times$ 100. For evaluation of diastolic function the following indices were measured by Doppler: early (E) and late (A) wave of mitral and tricuspid valves peak inflow velocities and E/A ratios, mitral valve inflow deceleration time of the E wave and isovolumic relaxation time of LV [30]. The coefficient of variation for the measurement of E wave and P wave mitral valve peak inflow velocities ranged from 1.7% to 5.6% and from 2% to 5.8%, respectively. TDI was used to obtain interventricular septum, tricuspid annular (lateral corner) and mitral annular (lateral corner and at interventicular septum) systolic tissue Doppler velocities (Sm), peak early (Em) and late (Am) diastolic myocardial velocity and their ratio (Em/Am). E/Em for both ventricles was estimated; this ratio correlates well with diastolic filling pressures [30].

Peak tricuspid regurgitant velocity and transtricuspid pressure gradient were calculated by continuous wave Doppler, even when minimal regurgitation was detected and suboptimal signals were enhanced by agitated saline [31]. Right atrial pressure was obtained according to respiratory variation of the inferior vena cava diameter and it was added to the transtricuspid gradient in order to estimate systolic pulmonary artery pressure [32]. End-diastolic pulmonary valve pressure gradient that corresponds to diastolic pulmonary artery pressure was measured when pulmonary regurgitant flow was detected. The ratio of acceleration time to ejection time of right ventricle outflow, also reflecting pulmonary artery pressure, was estimated.

Left atrium maximum area was assessed by planimetry at the time of mitral valve opening. Relative wall thickness of LV was calculated as the sum of interventricular septum and posterior wall thickness divided by LV end-diastolic dimension. LV mass was estimated according to the formula of Devereux and Reichek [33], and it was divided by standing height raised to the power of 2.7 to obtain an index adjusted for body size [34].

2.4. Data analysis

Three study groups were formed: (1) children with obstructive apnea-hypopnea index (OAHI) > 5 episodes/h (moderate-to-severe SDB); (2) subjects with OAHI $\leqslant$ 5 episodes/h and OAHI > 2 episodes/h (mild SDB); and (3) children with OAHI $\leqslant$ 2 episodes/h (primary snoring) [35]. Study groups were compared in terms of participants' characteristics, polysomnography parameters and outcome measures. LV systolic function was the *primary outcome measure* and indices of diastolic ventricular function, pulmonary artery pressure and cardiac structure were *secondary outcome variables*.

Chi-squared test (Yates correction) was applied for categorical variables and one-way analysis of variance (followed by post hoc tests) for continuous characteristics. Values of LV SF and EF were compared to published reference pediatric data [29]. Multiple linear regression was applied to detect independent predictors of echocardiography indices. Age, gender, BMI z-score, morning systolic or diastolic blood pressure index, and OAHI were entered as independent variables in the regression analysis models. Multivariable analysis was repeated using oxygen desaturation of hemoglobin index or respiratory arousal index in the place of OAHI.

2.5. Sample size calculation

When children with symptoms of SDB underwent adenotonsillectomy, LV EF increased at least 10% compared to the pretreatment value [17]. This increase can be attributed to the effect of SDB on cardiac systolic function that was reversed by surgical treatment. The required sample size in order to detect a difference