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ORIGINAL ARTICLE

Early cardiac abnormalities and increased C-reactive protein levels in a cohort of children with sleep disordered breathing

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Abstract
Background This study aims to evaluate left ventricular (LV) structure and function and inflammation in a paediatric population with sleep disordered breathing (SDB) and in control subjects.
Methods Forty-nine children with SDB and 21 healthy, age-matched subjects were enrolled. The diagnosis of obstructive sleep apnoea syndrome (OSAS) was confirmed by the laboratory polysomnography, showing an obstructive apnoea/hypopnoea index of more than one per hour, according to the criteria of the American Academy of Sleep Medicine and modified for paediatric population. Fasting blood samples for the biochemical evaluation (including high-sensitivity C-reactive protein (hsCRP) were drawn in the morning, after the polysomnographic examination in all patients with SDB and in the control group. All children underwent a two-dimensional colour Doppler cardiac examination with LV mass assessment and systolic and diastolic function evaluation.
Results Higher hsCRP levels were observed in subjects with OSAS than in children with primary snoring and in controls (0.8±0.7 vs 0.3±0.1 ng/dl, p=0.001, and 0.4±0.2 ng/dl, p=0.01, respectively). The LV diastolic dysfunction was significantly more frequent in patients with severe OSAS and higher hsCRP levels than in control group.
Conclusions This study shows that OSAS in children is associated with higher LV mass, early LV diastolic dysfunction and a pro-inflammatory state (high CRP levels). These findings might help to explain the higher incidence of cardiovascular morbidity in patients with OSAS.

Keywords Children · Sleep disordered breathing · Sleep apnoea syndrome · Systemic inflammation · C-Reactive protein · Diastolic dysfunction

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a complex clinical condition, characterized by repeated events of partial and/or complete upper airway obstructions that occur during sleep and result in the disruption of normal ventilation, hypoxaemia and sleep fragmentation [1, 2].

Cardiovascular (CV) diseases have frequently been reported in patients with moderate to severe OSAS [3]. These abnormalities may include systemic hypertension [3–5], pulmonary hypertension with cor pulmonale [6], left ventricular (LV) hypertrophy or dysfunction [7, 8], cardiac arrhythmias [9], atherosclerosis and coronary artery disease [10]. The pathogenesis of CV complications in patients with OSAS is most likely to be a complex process that involves a range of factors, such as abnormal sympathetic nervous system activation [11, 12], endothelial dysfunction [13], systemic inflammation [14], insulin resistance [15] and intermittent hypoxia–reoxygenation episodes during sleep [16, 17].

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A common pathophysiological aspect of these alterations is the presence of a condition of oxidative stress and increased reactive oxygen species generation, which directly or indirectly promotes the development and progression of LV dysfunction or hypertrophy and vascular remodelling [7]. Oxidative stress and asymptomatic (subclinical) pro-inflammatory state, as demonstrated by the higher serum levels of high-sensitivity C-reactive protein (hsCRP), have been observed in adults and children with OSAS and have been interpreted as pathogenetic factors that promote cardiac remodelling and LV structural and functional adaptations in these patients [18].

Previous studies have demonstrated the presence of both left and right ventricular hypertrophies as well as diastolic abnormalities, detected by means of conventional Doppler examination of LV filling patterns, in children with severe OSAS, hypertension or obesity [7, 19].

Recently, tissue Doppler imaging (TDI) has emerged as a more sensitive and predictive tool for detecting early abnormalities in LV systolic and diastolic functions compared with the conventional Doppler examination [20–22]. The relationship between inflammatory response and cardiac structural and functional abnormalities, detected by both conventional echocardiography and TDI analysis, has not previously been investigated in children with OSAS.

On the basis of these considerations, the primary aim of this study was to evaluate LV mass and LV systolic and diastolic functions by means of both conventional echocardiography and TDI analysis and to investigate a possible correlation with hsCRP, a well-known marker of systemic inflammation, in a paediatric population with sleep disordered breathing (SDB).

Methods

Study population

We enrolled consecutive outpatients (age range of 2–16 years) with presumed SDB, who had been referred to our Paediatric Sleep Centre, at the II Faculty of Medicine, "La Sapienza" University, Sant'Andrea Hospital, Rome, between March and June 2007. The control group (age range of 3–16 years) included healthy age- and gender-matched children recruited from the same urban area, with no symptoms or signs of SDB and acute or chronic respiratory and cardiac disease.

After a detailed personal and family history had been obtained, all the subjects included in the present study underwent a complete physical examination in order to exclude the presence of any acute inflammatory disease, according to the study protocol. Additional exclusion criteria included the presence of genetic disorders, cerebral palsy, neuromuscular diseases, any systemic disease, acute infective processes and any cardiac or non-cardiac disease that may have affected the clinical parameters considered in the present analysis.

Written informed consent was obtained from the parents of each child, and assent was obtained from children over the age of 6 years. The study protocol was approved by the local ethics committee.

Study design

In children with SDB, the diagnosis of OSAS was confirmed by the laboratory polysomnography (PSG), showing an obstructive apnoea/hypopnoea index of more than one per hour [23, 24]. Primary snoring (PS) was diagnosed in children with habitual snoring, an apnoea/hypopnoea index of <1, and snoring detected by microphone [24]. The duration of the disease was established by standardized questionnaires. [25]

Healthy subjects did not undergo the polysomnographic evaluation in order to increase the compliance with the subsequent examinations. Nevertheless, we excluded the presence of SDB by obtaining a detailed personal and family history and performing a complete physical examination in this group of subjects.

Fasting blood samples for the biochemical evaluation (including hsCRP) were drawn in the morning, after the polysomnographic examination in all patients with SDB and in the control group.

All the children underwent a two-dimensional colour Doppler cardiac examination with LV mass assessment and systolic and diastolic function evaluation at the Echo Laboratory, Hypertension Unit, Division of Cardiology at our hospital. Echocardiographic examinations were performed in the morning (between 08:00 and 10:00 a.m.), following polysomnographic examinations and blood samples drawing. After 5 min of rest in a quiet room, all subjects were invited to assume the left lateral position; then, echocardiograms were performed according to the recommendations of the International Echocardiographic Committee. Clinical blood pressure was measured in all children included in our analysis, and normotension was defined according to the recent European guidelines' recommendations [26].

Assessment of high-sensitivity C-reactive protein levels

Serum levels of hsCRP were measured with Vitros reagents, which are based on a particle-enhanced, turbidimetric, immunoassay technique. At our site, hsCRP normal serum levels ranged between 0.0 and 0.5 mg/dl.

Polysomnography parameters

Children with SDB underwent standard overnight PSG recordings, obtained with a Grass Heritage polygraph. The variables recorded included at least an eight-channel electroencephalogram (bilateral frontal, central temporal and occipital, bipolar and mono-polar montages referred to the contralateral mastoid), electro-oculogram (electrodes placed 1 cm above the right outer cantus and 1 cm below the left outer cantus and referred to as A1), submental electromyogram and electrocardiogram (one lead). Sleep was subdivided into 30-s epochs, and sleep stages were scored according to the standard criteria by the American Academy of Sleep Medicine [23].

Central, obstructive and mixed apnoea events were counted according to the criteria established by the American Academy of Sleep Medicine [23]. An obstructive apnoea was scored when there is a >90% drop in the signal amplitude of airflow for >90% of the entire event, compared with the pre-event baseline amplitude, with continued chest wall and abdominal movement, for a duration of at least two breaths. A central apnoea was defined as the absence of airflow, with the cessation of respiratory effort, lasting more than 20 s or an event lasting at least two missed breaths (or the duration of two baseline breaths) and is associated with an arousal, an awakening or a >3% desaturation; central apnoea occurring after gross body movements or after sighs was not considered as a pathologic finding. A mixed apnoea was defined as an apnoea that usually began as central and ended in obstruction, according to changes in the chest, abdominal and flow traces. An event may be scored as a hypopnoea if there is a >50% drop in airflow signal amplitude compared with the pre-event baseline amplitude for at least 90% of the duration of the event; the event must last at least two missed breaths and should be associated with an arousal, awakening or a >3% desaturation. Chest and abdomen movements were measured by strain gauges, and sleep respiratory effort was detected by intercostal electromyogram. Oronasal airflow was recorded with a thermocouple. Arterial oxygen saturation was monitored with a pulse oximeter. The apnoea–hypopnoea index was defined as the average number of apnoeas and hypopnoeas per hour of sleep. All recordings started at the patients' usual bedtime and continued until spontaneous awakening.

Echocardiographic examination

The echocardiographic investigations were performed with a phased array sector scan (Acuson Sequoia, Mountain View, California, USA) using a multifrequency probe at 2.5, 3.5 or 5 MHz and an S-VHS tape recorder. Two-dimensionally guided M-mode echocardiography was performed on each subject by two expert sonographers (GMC and GT) and blindly revised for accuracy. Sonographers were also blinded for polysomnographic results. End-diastolic and end-systolic LV diameters, interventricular septum thickness in diastole and systole and posterior wall thickness in diastole and systole were measured according to recommendations from the American Society of Echocardiography [27]. Thus, LV mass was calculated using Devereux's formula [28] and normalized by height and by height$^{2.7}$ [29, 30]. The following indexes of LV systolic function were considered: fractional shortening, ejection fraction, TDI systolic myocardial peak flow velocity (Sm) wave amplitude, isovolumetric contraction time and myocardial performance index. The indexes of diastolic function were as follows: (1) conventional Doppler analysis, early diastolic peak flow velocity (E), late diastolic peak flow velocity (A) and the ratio of early to late peak (E/A ratio); (2) TDI analysis of the lateral wall of the left ventricle, early diastolic myocardial peak flow velocity (Em), late diastolic myocardial peak flow velocity (Am), the ratio of early to late myocardial peak Em/Am ratio and isovolumetric relaxation time [22, 31].

Statistical analysis

All values are expressed as mean ± SD for continuous variables and as number and percentages for categorical variables. The comparisons between sleep parameters and CV parameters obtained in PS, OSAS and normal controls were conducted using the non-parametric Kruskal–Wallis analysis of variance (ANOVA) followed by the Mann–Whitney *U* test between the different groups used as a post hoc comparison when ANOVA results were significant or using Mann–Whitney *U* test when appropriate; multiple linear regression analysis (stepwise regression model) was performed using the Em/Am ratio as a dependent variable and age, body mass index, apnoea–hypopnoea index, hsCRP, mean diastolic and systolic blood pressure and mean overnight oxygen saturation (SaO_2) as independent variables. Statistical analysis was performed using the SPSS system (version 12.0; SPSS Inc., Chicago, Illinois, USA). *p* values of less than 0.05 were considered statistically significant.

We performed a statistical comparison of clinical, laboratory and CV parameters between controls and a subgroup of children with SDB, without overweight (body mass index (BMI) values between 85th and 95th percentiles).

Results

Study population selection and general characteristics

Out a total of 67 subjects who fulfilled the inclusion criteria, nine were excluded because their parents did not wish to

participate in the study, and nine were excluded because data regarding their hsCRP levels or echocardiographic parameters were incomplete. Thus, the study analysis was thus conducted on an overall population sample of 49 non-hypertensive, non-obese children with SDB (38 males (M), mean age 8.2±3.2 years, body mass index 20.2±4.9 kg/m^2), comprising 18 children with PS (14 males, mean age 7.5±3.5 years, body mass index 19.8±5.1 kg/m^2, range of apnoea–hypopnoea index 0–1 per hour, mean oxygen saturation 98.2±1.2%, minimal oxygen saturation 93.6±3.3), and 31 children with OSAS (24 M, mean age 7.1±3.7 years, body mass index 19.6±5.2 kg/m^2, range of apnoea–hypopnoea index 1.2–24.0 per hour, mean oxygen saturation 96.9±1.6%, minimal oxygen saturation 87.5±5.7%). The control group included 21 healthy subjects (15 M, mean age 7.3±3.6 years, body mass index 18.3±4.6 kg/m^2).

The anthropometric, clinical and PSG parameters in the different subgroups are shown in Table 1. No significant difference in these variables was found between the SDB children and the control group. Patients with PS were approximately 1 year older than those in the other groups, though the difference was not statistically significant. As expected, the apnoea–hypopnoea index was significantly higher (p=0.001) and the mean SaO_2 values were significantly lower (p=0.001) in OSAS patients than in PS patients with a comparable disease duration.

High-sensitivity C-reactive protein serum levels

Significantly higher hsCRP serum levels were found in patients with OSAS than in patients with PS or in the control group (p=0.001 and p=0.01, respectively, Table 1).

Echocardiographic parameters

The mono-dimensional parameters are shown in Table 2. No significant difference was found in the mono-dimensional parameters between the various subgroups. An increasing trend in absolute LV mass values and in values indexed by height$^{2.7}$ was observed from the control group toward patients with PS and OSAS, though this did not achieve statistical significance; LV mass indexed by height was generally higher in SDB patients than in the control group, though there was no statistical significance in this case either.

Parameters related to LV systolic and diastolic function are shown in Table 3. With regard to the systolic indexes, significantly higher left ventricular ejection fraction values were observed in patients with OSAS than in patients with PS (p=0.02). In addition, an increasing trend in left ventricular fractional shortening was observed from control subjects toward patients with PS and OSAS, i.e. according to the severity of the disease, though statistical significance was not reached.

Table 1 Anthropometric data, PSG parameters and serum levels of hsCRP in children with primary snoring (group 1), in children with obstructive sleep apnoea syndrome (group 2) and in control subjects

	Control group (n=21)	Group 1 PS (n=18)	Group 2 OSAS (n=31)	Kruskal–Wallis p	Mann–Whitney p
Clinical and laboratory parameters					
Gender (M/F)	15/6	14/4	24/7	NS	
Age (years)	7.3±3.6	8.2±3.2	7.1±3.7	NS	
Height (cm)	126.8±22.2	133.4±22.3	126.4±23.2	NS	
Weight (kg)	31.9±18.2	39.5±23.2	34.3±21.3	NS	
BMI (kg/m^2)	18.3±4.6	20.2±4.9	19.6±5.2	NS	
Systolic BP levels (mmHg)	99.0±9.4	98.6±11.8	98.6±10.6	NS	
Diastolic BP levels (mmHg)	66.9±9.0	69.8±9.6	66.6±8.9	NS	
hsCRP (ng/dl)	0.4±0.2	0.3±0.1	0.8±0.7	0.001	C vs G2 p=0.01 G1; C vs G2 p=0.001
Duration of SBD (years)	–	3.4±2.3	2.5±1.8	–	
PSG parameters					
Apnoea–hypopnoea index (event/hour)	–	0.3±0.3	8.1±7.1	–	G1 vs G2 p=0.001
Mean SaO_2 (%)	–	98.2±1.2	96.9±1.6	–	G1 vs G2 p=0.007
Minimal SaO_2 (%)	–	93.6±3.6	87.5±5.7	–	G1vs G2, p=0.0001

BMI body mass index, *BP* blood pressure, *SBD* sleep disordered breathing, *SaO_2* blood oxygen saturation, *PSG* polysomnography, *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome, *M* male, *F* female, *BP* blood pressure, *hsCRP* high-sensitivity C-reactive protein, *C* control, *G1* group 1, *G2* group 2

Table 2 Mono-dimensional parameters and LV mass indexes in patients with primary snoring (group 1), in patients with obstructive sleep apnoea (group 2) and in control subjects

Variables	Control group (n=21)	Group 1 PS (n=18)	Group 2 OSAS (n=31)	Kruskal–Wallis p
LV diameter				
IVSd (mm)	5.9±1.8	6.5±1.5	6.3±1.2	NS
IVSs (mm)	9.1±2.1	9.6±3.3	10.3±2.2	NS
PWd (mm)	5.7±1.5	6.3±0.9	6.3±1.1	NS
PWs (mm)	9.4±2.2	10.0±2.3	10.3±2.2	NS
LVEDd (mm)	40.2±6.1	40.1±7.4	38.1±5.6	NS
LVESd (mm)	25.0±3.5	25.2±5.3	23.4±3.8	NS
LA (mm)	25.4±4.5	25.7±5.1	25.0±5.2	NS
LV mass				
LV mass (g)	35.6±7.8	37.3±8.2	37.6±8.0	NS
LV mass H (g/h)	46.0±14.7	50.6±17.8	47.9±15.6	NS
LV mass $H^{2.7}$($g/h^{2.7}$)	30.3±7.1	30.7±6.0	33.6±9.4	NS

IVSd interventricular septal thickness at diastole, *IVSs* interventricular septal thickness at systole, *PWd* posterior wall thickness at diastole, *PWs* posterior wall thickness at systole, *LVEDd* LV end-diastolic diameter, *LVEDs* LV end-systolic diameter, *LA* left atrium, *LV* left ventricle, *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome, *NS* not significant

No significant differences were found between the different subgroups with regard to the TDI analysis of LV systolic function, although lower Sm wave amplitude values and a trend toward a reduction in isovolumetric contraction time were observed in SBD patients compared with those in the control group.

The conventional Doppler analysis revealed an increase in the A wave amplitude (p=0.02), paralleled by a reduction in the E/A ratio (p=0.01), in SDB patients compared with that in control subjects, though this difference was statistically significant in patients with PS alone.

Table 3 Systolic and diastolic parameters at both conventional and tissue Doppler analysis in patients with primary snoring (group 1), in patients with obstructive sleep apnoea (group 2) and in control subjects

Variables	Control group (n=21)	Group 1 PS (n=18)	Group 2 OSAS (n=31)	Kruskal–Wallis p	Mann–Whitney p
LV systolic parameters					
EF (%)	66.8±4.7	66.5±5.0	70.2±5.1	0.03	G1 vs G2 p=0.02
FS (%)	34.6±5.5	37.0±5.6	38.6±6.1	NS	
Tissue Doppler analysis for LV systolic function					
Sm wave (cm/s)	2.0±0.2	1.4±0.4	1.5±0.5	NS	
IVCT (ms)	63.2±11.6	62.3±9.7	61.5±11.9	NS	
Conventional Doppler analysis for LV diastolic function					
E wave (cm/s)	92.8±12.8	91.5±15.8	92.0±11.7	NS	
A wave (cm/s)	42.8±12.3	52.5±10.5	47.2±12.1	NS	C vs G1 p=0.02
Ratio E/A	2.3±0.45	1.7±0.4	2.0±0.5	0.02	C vs G1 p=0.01
Tissue Doppler analysis for LV diastolic function					
Em wave (cm/s)	2.4±0.4	2.7±0.7	2.5±0.5	NS	
Am wave (cm/s)	0.9±0.2	1.2±0.4	1.2±0.3	0.004	C vs G1 p=0.006; C vs G2 p=0.003
Ratio of Em/Am	2.7±0.6	2.3±0.7	2.2±0.5	0.03	C vs G1 p=0.01; C vs G2 p=0.01
IVRT (ms)	58.8±23.7	74.8±17.8	75.1±25.5	0.014	C vs G1 p=0.004; C vs G2 p=0.02

LV left ventricle, *EF* ejection fraction, *FS* fractional shortening, *E wave* early diastolic peak flow velocity, *A wave* late diastolic peak flow velocity, *Ratio E/A* ratio of early to late peak, *IVRT* isovolumetric relaxation time, *IVCT* isovolumetric contraction time, *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome, *C* control, *G1* group 1, *G2* group 2, *NS* not significant

The TDI analysis revealed a more evident, statistically significant increase in the Am wave amplitude and a concomitant reduction in the Em/Am ratio in children with SDB compared with those in control subjects. In particular, in the presence of a comparable Em amplitude value (as an index of intrinsic myocardial distensibility), OSAS patients yielded a significantly lower Em/Am ratio at the TDI analysis than control subjects (Fig. 1). In addition, children with SDB displayed significantly higher isovolumetric relaxation time values than those observed in the control group (Fig. 2).

Table 4 showed the results at both conventional and TDI analyses in controls and in children with SDB, excluding those with overweight (11 subjects). The conventional Doppler analysis revealed an increase in the A wave amplitude (p=0.05), paralleled by a reduction in the E/A ratio (p=0.02), in SDB patients compared with that in control subjects, though this difference was statistically significant in patients with PS alone. The TDI analysis revealed the same statistical differences found in all patients, excluding overweight as described above (Table 4).

After excluding overweight subjects (n=11), no significant differences were found among snoring, OSAS and control groups with respect to gender distribution (10/2 M/females (F), 19/7 M/F and 15/6 M/F, respectively), age (6.7±2.5, 6.1±2.9 and 7.3±3.6 years, respectively) and BMI (17.2±1.8, 17.9±3.3 and 18.3±4.6 kg/m2, respectively), with the only exception of hsCRP levels (0.3±0.1, 0.9±0.8 and 0.4±0.2 ng/dl, respectively), which were significantly higher in patients with OSAS than in patients with PS or in the control group (C vs G2 p=0.02, G1 vs G2 p=0.002, respectively). Lastly, multiple regression analysis showed that hsCRP serum levels and mean SaO_2 were independent predictors of the Em/Am ratio at the TDI analysis (Table 5).

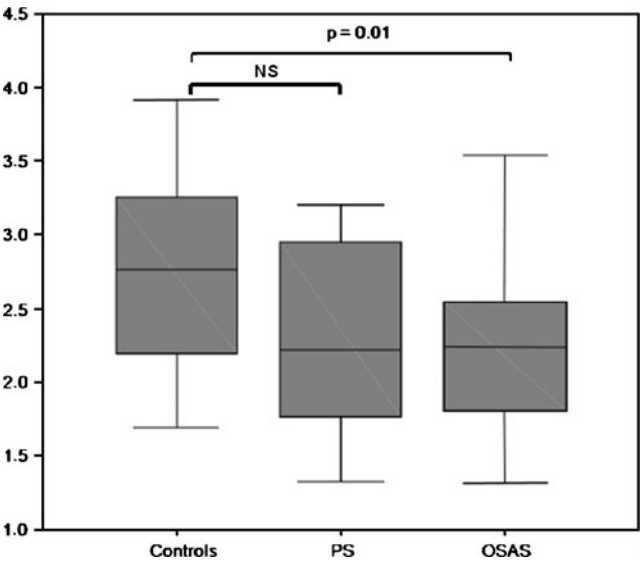

Fig. 1 The ratio of early to late myocardial peak Em/Am ratio obtained by tissue Doppler imaging analysis in children with primary snoring, in children with obstructive sleep apnoea syndrome and in the control group. Abbreviations used in figure: *NS* not significant, *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome

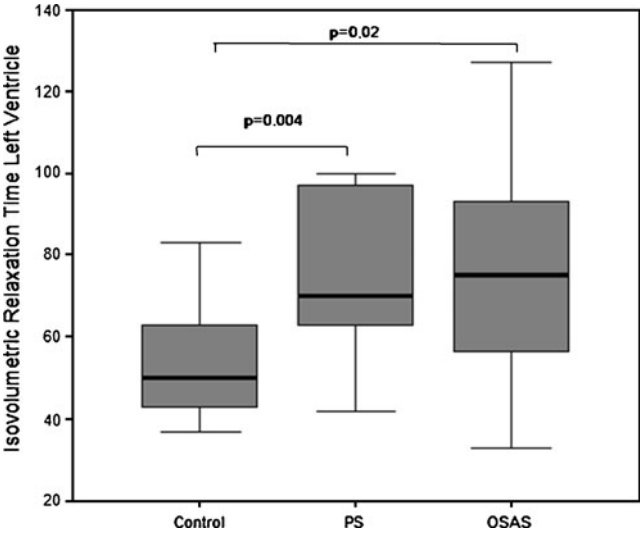

Fig. 2 Left ventricle isovolumetric relaxation time in children with primary snoring and with obstructive sleep apnoea syndrome and in the control group. Abbreviations used in figure: *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome

Discussion

This paper demonstrates the presence of early asymptomatic LV myocardial dysfunction and signs of subclinical inflammation in children with SDB, studied for the first time to our knowledge, by means of both conventional echocardiography and TDI analysis. The cardiac functional impairment observed in our study was characterized by an alteration in the late phase of LV diastolic function (increased A wave amplitude, paralleled by reduced E/A ratio and prolonged isovolumetric relaxation time) and was more evident in children with a severe OSAS and higher hsCRP serum levels. We found the same results in the subgroup of children without overweight, demonstrating that BMI did not seem to influence the CV abnormalities, as it has also been confirmed by the multiple regression analysis.

All subjects included in the present analysis were fully compliant to polysomnographic procedures and echocardiographic examinations, thus providing us the opportunity to analyse a high-quality database of young subjects with OSAS and early asymptomatic cardiac abnormalities. Previous studies have primarily demonstrated the presence of right ventricle alterations in paediatric populations with severe OSAS [32, 33]. More recently, Amin et al. [7] reported the presence of cardiac hypertrophy involving both ventricular chambers as well as an increased LV mass in

Table 4 Systolic and diastolic parameters at both conventional and tissue Doppler analysis in patients with primary snoring (group 1), in patients with obstructive sleep apnoea (group 2) and in control subjects, without 11 overweight children

Variables	Control group (n=21)	Group 1 PS (n=12)	Group 2 OSAS (n=26)	Kruskal–Wallis p	Mann–Whitney p
LV systolic parameters					
EF (%)	66.8±4.7	66.8±5.2	69.5±5.02	NS	
FS (%)	34.6±5.5	37.0±6.8	38.2±5.7	NS	
Tissue Doppler analysis for LV systolic function					
Sm wave (cm/s)	2.0±0.2	1.4±0.5	1.4±0.4	NS	
IVCT (ms)	63.2±11.6	65.0±9.7	63.0±12.2	NS	
Conventional Doppler analysis for LV diastolic function					
E wave (cm/s)	92.8±12.8	87.6±13.9	91.0±11.4	NS	
A wave (cm/s)	42.8±12.3	49.8±6.8	45.8±11.7	NS	
Ratio E/A	2.3±0.45	1.8±0.3	2.1±0.5	NS	C vs G1 p=0.05
Tissue Doppler Analysis for LV diastolic function					
Em wave (cm/s)	2.4±0.4	2.7±0.8	2.4±0.5	NS	
Am wave (cm/s)	0.9±0.2	1.2±0.4	1.12±0.3	0.01	C vs G1 p=0.01; C vs G2 p=0.01
Ratio of Em/Am	2.7±0.6	2.3±0.7	2.2±0.6	0.04	C vs G2 p=0.02
IVRT (ms)	58.8±23.7	79.4±16.8	78.8±25.2	0.005	C vs G1 p=0.003; C vs G2 p=0.02

LV left ventricle, *EF* ejection fraction, *FS* fractional shortening, *E wave* early diastolic peak flow velocity, *A wave* late diastolic peak flow velocity, *Ratio E/A* ratio of early to late peak, *IVRT* isovolumetric relaxation time, *IVCT* isovolumetric contraction time, *PS* primary snoring, *OSAS* obstructive sleep apnoea syndrome, *C* control, *G1* group 1, *G2* group 2, *NS* not significant

children with OSAS. In that study, which was performed by indexing LV mass to body surface area according to Devereux's formula [28–30], all cardiac abnormalities correlated with the severity of the disease: the higher is the apnoea–hypopnoea index and the lower is the SaO_2, the higher is the LV mass. The authors thus suggested that the presence of LV hypertrophy might be considered an independent risk factor for future CV disease in children with OSAS [7]. The results of our study, in which we found an increased LV mass, confirm previous observations and lend further support to recent evidence by showing an increased LV mass indexed by height$^{2.7}$ in OSAS children [28]. The lack of statistical significance, observed in our study, might be related to the size of the population sample, though it is more likely due to the fact that we included younger SDB patients in whom disease severity was consequently less severe than in other populations [7, 32–34].

Table 5 Stepwise multiple linear regression analysis

Variables	Multivariate (beta ln)	p value
Age	−0.139	NS
BMI	−0.164	NS
hsCRP	−0.240	0.04
AHI	0.086	NS
Mean SaO_2	0.289	0.014
Minimal SaO_2	0.153	NS
DBP	−0.051	NS
SBP	−0.072	NS

Model 1 (mean SaO_2) excluded variables: age, BMI, hsCRP, AHI, minimal overnight oxygen saturation percent, DBP and SDB. Model 2 (mean SaO_2 and CRP) excluded variables: age, BMI, AHI, min SaO_2, DBP and SDB

BMI body mass index, *hsCRP* high-sensitivity C-reactive protein, *AHI* apnoea–hypopnoea index, *mean SaO_2* mean blood oxygen saturation, *min SaO_2* minimal blood oxygen saturation, *DBP* diastolic blood pressure, *SDB* systolic blood pressure, *NS* not significant

Our findings extend the observations reported in previous studies [7] by showing early asymptomatic cardiac abnormalities in children with OSAS by means of TDI analysis. In addition, these alterations were found to be correlated with increased serum levels of hsCRP, a well-known marker of systemic inflammation.

Previous evidence suggests that conventional Doppler analysis is not a fully reliable means of detecting early cardiac abnormalities in patients with normal left ventricular ejection fraction [35]. In our study, in which LV size, mass and systolic function were comparable in both patients and controls, children with SDB showed early LV diastolic functional impairment, as demonstrated by a significantly higher Am wave amplitude, lower Em/Am ratio and longer isovolumetric relaxation time. These abnormalities may indicate the presence of an early asymptomatic cardiac adaptation to higher end-diastolic LV pressure in young patients with SDB compared with those in the control group.

Considering that one parameter (i.e. ejection fraction) showed a difference between the PS and OSAS groups, this abnormality demonstrated that early cardiac dysfunction could be also related to the severity of SDB.

It should also be borne in mind that conventional Doppler analysis may not reliably detect early cardiac alterations, which instead significantly and independently correlated with markers of systemic inflammation (high hsCRP serum levels) and SDB severity in our sample.

In this regard, Kawanishi and colleagues demonstrated that Em wave amplitude at the TDI analysis directly and positively correlated with the severity of OSAS in adults [35–38]. Our data did not reveal a significant difference in the early phase of the LV diastole at either the conventional or TDI analyses, but we did observe a negative correlation between oxygen overnight saturation and the Em/Am ratio in OSAS patients compared with that in the control group. The results of both our study and previous studies thus suggest that impaired diastolic function and sleep disorder characteristics, such as apnoea–hypopnoea index and hypoxia, are correlated.

A recent study performed by Sciarretta et al. on an adult population of hypertensive patients demonstrated a strong correlation between higher LV mass indexed by height$^{2.7}$, higher early diastolic peak flow velocity/early myocardial diastolic velocity ratio (E/Em ratio), lower Sm wave amplitude and higher hsCRP serum levels and other pro-inflammatory cytokines (including tumour necrosis factor alpha and transforming growth factor beta) in patients with than in those without metabolic syndrome [39]. Interestingly, conventional Doppler analysis in that study did not reveal a significant difference between the various subgroups of patients either, while LV adaptations detected by means of TDI analysis significantly correlated with both cardiac and renal organ damage in that hypertensive population [39]. It should also be mentioned that, in this study, LV mass was indexed by height$^{2.7}$, which has been recently proposed as a "gold standard" for evaluating LV geometry in both obese and normal-weight subjects [30, 39].

Lastly, the multivariate regression analysis performed in our study showed that increased serum hsCRP levels and decreased average overnight saturation were independent predictors of LV functional impairment in children with SDB, while age, body mass index, blood pressure and duration of disease did not seem to be predictive of CV abnormalities in our population sample.

Potential limitations

Our study has some potential limitations which should be borne in mind when interpreting the findings. First of all, the relatively small size of the population sample may have contributed to the lack of statistical significance observed when the mono-dimensional parameters and, above all, the LV mass assessment in the different groups were compared. Moreover, the enrolment of a group of SDB patients with a lower degree of disease severity (i.e. patients with PS) may have, at least in part, limited the statistical power regarding the detection of differences in LV dimension and function. The lack of polysomnographic recording in control subjects is another limitation, which may have potential impact on our findings. Another limitation of our study is that we did not score arousal during sleep, and we did not calculate respiratory event arousal. Considering that respiratory arousal is an expression of autonomic activation due to respiratory events, these analysis may help to explain the lack of differences found between snoring and OSAS children in CV abnormalities in our study.

Conclusion

In conclusion, our study confirms previous reports, indicating that OSAS is a predisposing factor for CV disease mediated by a chronic inflammation process, such as oxidative stress, as a consequence of intermittent hypoxia [16]. We speculate that an association between the inflammatory pattern and an initial diastolic dysfunction and LV remodelling may exist in children with SDB. Further studies with longer follow-up and involving a larger population sample, to demonstrate this association and confirm our speculative hypothesis, are warranted, in order to confirm our findings and to influence the early therapeutic approach of paediatric SDB, to prevent CV system damage.

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