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Cardiopulmonary fitness in children with asthma versus healthy children

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ABSTRACT
Objectives To evaluate, with a cardiopulmonary exercise test (CPET), the cardiopulmonary fitness of children with asthma, in comparison to healthy controls, and to identify the clinical and CPET parameters associated with the maximum oxygen uptake (VO$_{2\text{max}}$) in childhood asthma.

Design This cross-sectional controlled study was carried out in CPET laboratories from two tertiary care paediatric centres. The predictors of VO$_{2\text{max}}$ were determined using a multivariable analysis.

Results A total of 446 children (144 in the asthma group and 302 healthy subjects) underwent a complete CPET. Mean VO$_{2\text{max}}$ was significantly lower in children with asthma than in controls (38.6±8.6 vs 43.5±7.5 mL/kg/min; absolute difference (abs. diff.) of −4.9 mL/kg/min; 95% CI of (−6.5 to −3.3) mL/kg/min; p<0.01) and represented 94%±9% and 107%±17% of predicted values, respectively (abs. diff. −13%; 95% CI (−17 to −9%); p<0.01). The proportion of children with an impaired VO$_{2\text{max}}$ was four times higher in the asthma group (24% vs 6%, p<0.01). Impaired ventilatory efficiency with increased VE/VCO$_2$ slope and low breathing reserve (BR) were more marked in the asthma group. The proportion of children with a decreased ventilatory anaerobic threshold (VAT), indicative of physical deconditioning, was three times higher in the asthma group (31% vs 11%, p<0.01). Impaired VO$_{2\text{max}}$ was associated with female gender, high body mass index (BMI), FEV1, low VAT and high BR.

Conclusion Cardiopulmonary fitness in children with asthma was moderately but significantly altered compared with healthy children. A decreased VO$_{2\text{max}}$ was associated with female gender, high BMI and the pulmonary function.

Trial registration number NCT04650464.

INTRODUCTION
Asthma is the most common paediatric chronic disease worldwide, leading to frequent hospital admissions and school absenteeism. Paediatric asthma has become a serious public health issue and current management mainly relies on symptom
control in order to ensure to children with asthma a normal quality of life.2 Asthma is characterised by chronic inflammation of lower airways, marked by expiratory airflow limitation and repeated respiratory symptoms, including wheezing, shortness of breath, chest tightness and cough.3 Asthma symptoms, associated with patient’s fear of exertional dyspnoea, may limit the ability to be physically active, leading to a sedentary lifestyle, and ultimately affect child’s quality of life.4

In 1980, the WHO stated that functional capacity explorations best reflected the impact of chronic disease on health-related quality of life.5 Therefore, cardiopulmonary exercise test (CPET) with maximum oxygen uptake (VO2max) assessment has become the reference functional examination in cardiorespiratory diseases,6 first in adult population, and more recently in paediatric population. Indeed, in children, VO2max is associated with patient-reported outcomes, such as health-related quality of life.7 The existence of an impaired cardiopulmonary fitness in children may be related to various limiting factors, such as cardiac limitation, ventilatory limitation, physical deconditioning or even psychological barriers to physical activity.8

Most paediatric studies on cardiopulmonary fitness have enrolled healthy children, children with cardiac conditions9 or children with cystic fibrosis.10 By contrast, the level of VO2max in children with asthma from large paediatric CPET cohorts has been scarcely reported, especially in comparison with healthy children.11–14 Previous reports suggested that ventilatory exercise limitations could be related to the severity of bronchial obstruction,15 16 but the predictors of VO2max and the level of physical deconditioning in children with asthma remain unclear.17 18

In this study, we aimed to evaluate the cardiopulmonary fitness, assessed by a CPET, in a large cohort of children with asthma, and to compare the results to healthy controls. We also intended to identify the predictors of VO2max in children with asthma.

**METHODS**

**Study design and population**

This cross-sectional controlled study was carried out from January 2015 to December 2019 in two tertiary care paediatric centres (Montpellier University Hospital and Saint-Pierre Institute, France). Children aged 5–18 years old, and measuring at least 120 cm, were recruited in two paediatric CPET laboratories. Children with absolute contraindications for CPET were not eligible.9

Two groups were identified: children with asthma and healthy control children.

The asthma group consisted of children followed up for asthma and referred to one of the two centres by paediatricians, pulmonologist or general practitioners. The level of asthma severity was assessed by the therapeutic burden from the Global Initiative for Asthma (GINA) classification.3 From patients’ interviews, the absence of any physical activity, apart from physical education at school, was indicative of sedentary lifestyle. Also, exercise-related symptoms (chest pain or excessive dyspnoea) were reported.

As in our previous similar CPET controlled paediatric studies, the control group consisted of children referred for non-severe functional symptoms linked to exercise (murmur, palpitation or dyspnoea) or for medical sports certificate.9 19 20 These children were classified as controls after a completely normal check-up, including physical examination, ECG, echocardiography and spirometry. Children with any chronic disease, medical condition (cardiac, neurologic, respiratory, muscular or renal), or medical treatment, and those requiring any further specialized medical consultation were not eligible.

**Paediatric laboratory functional tests: spirometry and CPET**

Functional tests procedures in both centres were harmonized before the study started. We used the Quark CPET calibrated gas analyser (Cosmed Srl., Pavonna di Albano, Italy).
Spirometry tests were repeated at least three times to ensure reproducibility, and the results of FEV1, FVC and FEV1/FVC ratio (FEV1/FVC%) were expressed in Z-scores.

Both centres used the same CPET paediatric cycle ergometer protocol to obtain a homogeneous incremental overall duration between 8 and 12 min. Whenever the VO2max did not reach a plateau, which is common in children, the peak VO2 was collected. VO2max values were normalised as percentage of the predicted VO2max. A VO2max<80% of predicted values indicated impaired cardiopulmonary fitness.

The ventilatory anaerobic threshold (VAT) was measured using the V-slope method. A decreased VAT <55% of predicted VO2max values was in favour of physical deconditioning. The ventilatory efficiency (VE/VCO2 slope) was measured from the maximum exercise. A VE/VCO2 slope >30 indicated impaired ventilatory efficiency. The maximal voluntary ventilation, the breathing reserve (BR), the oxygen pulse, the oxygen uptake efficiency slope (OUES) and some respiratory variables at maximal exercise were collected (detailed CPET protocol and parameters available in online supplemental material).

**Statistical analysis**

The study population was described using means and SD or median and interquartiles (Q1–Q3) for quantitative variables, and with frequencies for categorical variables. The continuous variable distributions were tested using the Shapiro–Wilk test. Quantitative variables were compared using Student’s t-test when the distribution was Gaussian and using the Mann–Whitney test otherwise. For qualitative variables, groups were compared using the χ² test or Fisher’s exact test.

Depending on the distribution of variables, correlations were performed using Pearson’s or Spearman’s coefficients.

We compared CPET parameters between asthma and control groups with generalised linear models adjusted on gender, age and body mass index (BMI).

A linear model was used to compare the variation of VO2max per year between asthma and control groups. This analysis was stratified on gender because the interaction between age and gender was significant (p<0.01). The results were illustrated with a scatter plot and their regression line for each group. On these figures, the p value represented the slope comparison between asthma and control groups.

A multiple linear regression was used to identify the explanatory factors for VO2max in the asthma group. The clinically relevant variables (such as the BR to explore ventilatory limitation, the VAT to reflect muscular deconditioning and usual spirometric parameters), some clinically relevant interactions (such FEV1*BMI or VAT*BMI and BR*BMI) and the variables with a p value ≤0.2 in the univariate analysis were included in the model. The final model was obtained using an upward selection based on the corrected Akaike information criterion and with an exit threshold of 0.10. The normality of residuals in the final model was tested using the Shapiro–Wilk test.

The statistical significance was set at 0.05 and analyses were performed using Statistical Analysis Systems Enterprise Guide V.4.3 (SAS Institute).

**Ethics**

The study was conducted in compliance with the Good Clinical Practices protocol and Declaration of Helsinki principles. Informed consent was obtained from all parents or legal guardians.

**RESULTS**

**Population**
A total of 446 children were included in the study (centre 1, n=236; centre 2, n=210): 144 in the asthma group and 302 in the control group. No family refused to participate.

There was no difference between the two centres in terms of demographic data and asthma severity assessed by the therapeutic burden from the GINA classification (p=0.35). Moreover, asthmatic and control children were similar, except for anthropometric and spirometry data (table 1). No adverse events were reported during the exercise tests.

In the asthma group, 70% of patients had a specific asthma treatment and one-third was classified in the step 4 or 5 of GIN classification. FEV1, FVC and ratio FEV1/FVC were significantly lower in the asthma group. Most patients with asthma felt chest pain or excessive dyspnoea during daily exercise, and one-third had a sedentary lifestyle.

**CPET results**

All enrolled children performed a maximal exercise test and both groups were similar in terms of maximum load. In the control group, the mean VO2max per body weight was normal (43.5±7.5 mL/kg/min), representing 107%±17% of the predicted values. In the asthma group, the mean VO2max per body weight was good, overall (38.6±8.6 mL/kg/min), representing 94%±19% of the predicted values, but was significantly lower than in healthy controls, with an absolute difference of −4.9 mL/kg/min and a 95% CI of (−6.5 to −3.3) mL/kg/min (p<0.01).

Expressed in VO2max percent-predicts, this represented an absolute difference of −13% (95% CI (−17 to −9)); p<0.01). We found similar results after adjustment on age, gender and BMI. The proportion of children with an impaired VO2max was four times higher in the asthma group than in the control group (24% vs 6%, p<0.01, respectively). The VAT was significantly lower in the asthma group (26.7±6.9 vs 29.1±6.4 mL/kg/min), with an absolute difference of −2.4 mL/kg/min (95% CI (−3.7 to −1.1) mL/kg/min; p<0.01).

Expressed in VO2max percent-predicts, this represented 65%±16% of predicted VO2max and an absolute difference of −6% (95% CI (−9 to −3)); p<0.01). The proportion of children with a decreased VAT <55% was three times higher in the asthma group (31% vs 11%, p<0.01).

In the asthma group, the VE/VCO2 slope, the proportion of children with an impaired ventilatory efficiency and the PetCO2 were higher. The RR, Vt and oxygen pulse values were significantly lower in
the asthma group. No significant differences were observed for respiratory rate, ventilatory equivalents and OUES values.

After adjustment of CPET parameters on age, gender and BMI, similar differences between asthma and control groups were observed for VO2max, VAT, VE/VCO2 slope and BR (table 2). In female children, VO2max decreased significantly faster with age in the asthma group than in controls (−1.36 mL/kg/min per year, 95% CI (−1.87 to −0.84) vs −0.55 mL/kg/min per year, 95% CI (−0.96 to −0.15), p=0.02, respectively) (figure 1). We observed a decrease of 1.96% of predicted VO2max per year of age in girls with asthma. No difference was observed in male subjects (−0.36 mL/kg/min per year, 95% CI (−1.04 to 0.33) vs 0.10 mL/kg/min per year, 95% CI (−0.27 to 0.48), p=0.20, respectively, for asthma and control groups) (figure 2).

Predictors of VO2max in the asthma group

A lower VO2max was associated with female gender, high BMI, low FEV1, low VAT and high BR, in both univariate and multivariable analyses (table 3). However, no association was found between VO2max and the level of asthma severity from the GINA classification. There was no significant interaction between BMI with FEV1, VAT and BR. The final multivariate model explained 82% of the variability of VO2max in the asthma group.
Overall, the cardiopulmonary fitness of children with asthma was good ($\text{VO}_{2\text{max}} > 90\%$). However, their VO$_2$\text{max} was lower than that of healthy subjects, with a mean difference of 13% between their respective percent-predict values. Moreover, the VO$_{2\text{max}}$ was impaired in nearly one-fourth of children with asthma, which was four times higher than in healthy subjects. The VO$_{2\text{max}}$ decrease was associated with lower FEV$_1$.

**Figure 1** Relationship between age and VO$_2$\text{max} in female subjects. Equations of the VO$_2$\text{max} models according to age for asthma and control groups were reported. The p value illustrates the comparison between the two slopes.

Previous reports on cardiopulmonary fitness in children with asthma are controversial, as some studies found VO$_{2\text{max}}$ values similar to healthy controls, whereas others found lower VO$_{2\text{max}}$ values in children with asthma. However, those studies enrolled small numbers of subjects and used heterogeneous CPET protocols. Unsurprisingly, the VO$_{2\text{max}}$ was lower in children with high BMI, as adipose tissue does not consume oxygen, as well as in girls, reflecting the well-known gender differences in muscle mass and adipose tissue. Exercise-induced symptoms may be associated with misdiagnosis of asthma in overweight subjects.

Therefore, in this study, CPET parameters’ comparisons used generalised linear models adjusted not only on gender and age, but also on BMI, in order to determine the impact of paediatric asthma on aerobic fitness. Interestingly, the results of this study suggest the existence of an early onset of physical deconditioning in childhood asthma. Indeed, the VAT was a predictor of VO$_{2\text{max}}$ and nearly one-third of children with asthma had low VAT values, which was three times higher than in healthy controls. Moreover, asthma severity, as assessed by the GINA classification, was not associated with VO$_{2\text{max}}$. 
Nevertheless, few subjects with severe asthmatic forms were included in this study. In this cohort, most children with asthma felt chest pain or excessive dyspnoea during daily exercise, and one-third had a sedentary lifestyle. In the literature, barriers to physical activity in children with asthma have been mainly related to an altered self-perception of physical capacity and, to a lesser extent, to insufficient asthma control, dynamic hyperinflation and air trapping during effort, or exercise-induced bronchoconstriction.

Indeed, some children may limit their activities for fear of experiencing symptoms during exercise. They gradually adopt a sedentary lifestyle, responsible for increased symptoms during exercise, which will ultimately aggravate the vicious circle of physical deconditioning. This is supported in this study by the VO_2max decrease over time in the asthma group (1.36 mL/kg/min/year in girls and 0.36 mL/kg/min/year in boys).

Furthermore, this study provided original data on ventilatory parameters during exercise in childhood asthma. Previous studies failed to identify any significant differences in exercise ventilatory parameters between children with and without asthma. Globally, children with asthma were prone to some degree of ventilatory inefficiency, as reflected by the VE/VCO2 slope. Previous reports have described the hyperventilation syndrome as indicative of ventilatory limitation in children with asthma, but this has not been observed in our study, where higher PetCO2 values at the end of exercise have been observed. Interestingly, in children with asthma from our cohort, a higher BR was a predictor of a lower VO2max, suggesting that exercise limitation in childhood asthma does not only rely on the respiratory impairment but also includes a certain degree of physical deconditioning.
As a result, the use of CPET in childhood asthma follow-up provides a comprehensive assessment of cardiopulmonary fitness and evaluates the impact of the obstructive lung disease on physical capacity. Ultimately, the CPET identifies the patients most at risk of physical deconditioning in this population, and therefore could be the first step of exercise rehabilitation in childhood asthma. Unfortunately, cardiopulmonary rehabilitation programmes in asthma have been scarcely developed, despite preliminary positive results in small studies focused on physical training. Nevertheless, previous studies have highlighted the benefits of regular physical activity in asthma in terms of disease control, lung function and mental health. Moreover, regular physical activity is highly recommended by GINA in the global management of asthma. In a near future, evaluation and promotion of physical activity in children with asthma and impaired physical fitness could therefore be supported by structured rehabilitation programmes, including both exercise training and patient education, as recently reported in other paediatric conditions.

### Table 3: Clinical determinants of VO$_{2\text{max}}$ in the asthma group (linear regression)

<table>
<thead>
<tr>
<th>Variables</th>
<th>N</th>
<th>r</th>
<th>$\beta$ (95% CI)</th>
<th>P value</th>
<th>$\beta$ (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>144</td>
<td>-0.3</td>
<td>-0.05 (-1.34 to -0.36)</td>
<td>&lt;0.001</td>
<td>-0.07 (-0.02 to -0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)*</td>
<td>144</td>
<td>-0.52</td>
<td>-0.13 (-0.70 to -0.09)</td>
<td>&lt;0.0001</td>
<td>-0.07 (-0.02 to -0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1 (Z-score)*</td>
<td>144</td>
<td>0.15</td>
<td>0.51 (-0.06 to 1.90)</td>
<td>0.07</td>
<td>0.06 (0.39 to 1.32)</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC (Z-score)*</td>
<td>144</td>
<td>0.18</td>
<td>1.69 (0.08 to 2.10)</td>
<td>0.04</td>
<td>-0.09 (-0.12 to -0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV1/FVC (Z-score)</td>
<td>144</td>
<td>-0.03</td>
<td>-0.29 (-1.20 to 0.09)</td>
<td>0.09</td>
<td>-0.09 (-0.12 to -0.06)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VAT (ml/kg/min)*</td>
<td>144</td>
<td>0.06</td>
<td>1.60 (0.17 to 1.48)</td>
<td>&lt;0.0001</td>
<td>0.07 (0.76 to 0.98)</td>
<td>&lt;0.0001</td>
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<td>BR (%)*</td>
<td>144</td>
<td>-0.13</td>
<td>-0.09 (-0.17 to -0.01)</td>
<td>0.04</td>
<td>-0.09 (-0.12 to -0.06)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Gender*</th>
<th>N</th>
<th>Means±SD</th>
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<tbody>
<tr>
<td>Male</td>
<td>88</td>
<td>34.6±9</td>
</tr>
<tr>
<td>Female</td>
<td>56</td>
<td>34.6±9</td>
</tr>
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<td>Regular controller treatment</td>
<td>144</td>
<td>0.38 (3.50 to 2.74)</td>
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<tr>
<td>No</td>
<td>43</td>
<td>38.3±8.8</td>
</tr>
<tr>
<td>Yes</td>
<td>101</td>
<td>38.7±8.8</td>
</tr>
<tr>
<td>Sbos GINA severe</td>
<td>144</td>
<td>1.68 (1.93 to 3.48)</td>
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<tr>
<td>No</td>
<td>95</td>
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</tr>
<tr>
<td>Yes</td>
<td>49</td>
<td>37.8±8.1</td>
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<tr>
<td>Montelukast treatment</td>
<td>144</td>
<td>-0.40 (-0.81 to 0.30)</td>
</tr>
<tr>
<td>No</td>
<td>116</td>
<td>38.5±8.1</td>
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<tr>
<td>Yes</td>
<td>28</td>
<td>38.6±8.7</td>
</tr>
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<td>Sedentary lifestyle*</td>
<td>144</td>
<td>4.97 (1.84 to 8.10)</td>
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<tr>
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<td>88</td>
<td>40.1±8.7</td>
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<tr>
<td>Yes</td>
<td>44</td>
<td>35.2±8.3</td>
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<tr>
<td>Symptoms during daily exercise</td>
<td>144</td>
<td>1.09 (0.84 to 1.27)</td>
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<tr>
<td>No</td>
<td>34</td>
<td>37.7±8.8</td>
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<tr>
<td>Yes</td>
<td>110</td>
<td>38.8±8.6</td>
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<tr>
<td>Associated pathology</td>
<td>144</td>
<td>1.11 (-2.90 to 5.15)</td>
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<tr>
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<td>123</td>
<td>38.7±8.7</td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>37.6±8.1</td>
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Values are correlation coefficients ($r$) or means±SD.

*Variables associated with VO$_{2\text{max}}$ in both univariate and multivariate analyses are marked in bold.

CONCLUSION

Cardiopulmonary fitness in children with asthma was moderately but significantly altered, in comparison with healthy children, and VO$_{2\text{max}}$ was impaired in one-fourth of children with asthma. A decreased VO$_{2\text{max}}$ was associated with female gender, high BMI, low VAT and low FEV1. Nearly one-third of children with asthma had low VAT values, suggesting an early onset of physical deconditioning. Children with asthma were prone to ventilatory inefficiency during exercise. The use of CPET in the follow-up of paediatric asthma evaluates the impact of the obstructive lung disease on
cardiopulmonary fitness and identifies the children most at risk of physical deconditioning. Further work will have to determine the interest of CPET in promotion of physical activity and cardiopulmonary rehabilitation for childhood asthma.

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Contributors
Study concept and design: JM, PA. Drafting of the manuscript: FS, M, PA. Critical revision of the manuscript for important intellectual content: All. Statistical analysis: HH, M-CP. Blinded funding: PA. Guarantor: PA. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests
None declared.

Patient consent for publication
Consent obtained from parent(s)/guardian(s).

Ethics approval
This study involves human participants and was approved by IRB MTP 2020-02-202000335 Participants gave informed consent to participate in the study before taking part.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
All data relevant to the study are included in the article or uploaded as supplementary information.

REFERENCES


