

Is Static Hyperinflation a Limiting Factor During Exercise in Adolescents With Cystic Fibrosis?

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Summary. Increased work of breathing is considered to be a limiting factor in patients with cystic fibrosis (CF) performing aerobic exercise. We hypothesized that adolescents with CF and with static hyperinflation are more prone to a ventilatorily limited exercise capacity than non-static hyperinflated adolescents with CF.

Exercise data of 119 adolescents with CF [range 12–18 years], stratified for static hyperinflation, defined as ratio of residual volume to total lung capacity (RV/TLC) > 30%, were obtained during a progressive bicycle ergometer test with gas analysis and analyzed for ventilatory limitation.

Static hyperinflation showed a significant, though weak association (Φ 0.38; $P < 0.001$) with a ventilatorily limited exercise capacity (breathing reserve index at maximal effort > 0.70; FEV₁ < 80% predicted and reduced exercise capacity, defined as VO_{2peak} < 85% predicted). Analysis of association for increasing degrees of hyperinflation showed an increase to Φ 0.49 ($P < 0.001$) for RV/TLC > 50%. In adolescents with static hyperinflation, peak work rate (W_{peak}; 3.1 ± 0.7 W/kg (75.1 ± 17.3% of predicted), peak oxygen uptake (VO_{2peak}/kg (ml/min/kg); 39.2 ± 9.2 ml/min/kg (91.0 ± 20.3% of predicted), peak heart rate (HR_{peak}; 176 ± 19 beats/min) were significantly ($P < 0.05$) decreased when compared with non-static hyperinflated adolescents (W_{peak} 3.5 ± 0.5 W/kg (81.4 ± 10.0% of predicted); VO_{2peak}/kg (ml/min/kg); 43.1 ± 7.5 ml/min/kg (98.0 ± 15.1% of predicted); and HR_{peak} 185 ± 14 beats/min). Additionally, no difference was found in the degree of association of FEV₁ (%) and RV/TLC (%) with VO_{2peak}/kg_{pred} and W_{peak}/kg_{pred}, but we found the RV/TLC (%) to be a slightly stronger predictor of VO_{2peak}/kg_{pred} and W_{peak}/kg_{pred} than FEV₁ (%).

These results indicate that the presence of static hyperinflation in adolescents with CF by itself does not strongly influence ventilatory constraints during exercise and that static hyperinflation is only a slightly stronger predictor of W_{peak}/kg_{pred} and VO_{2peak}/kg_{pred} than airflow obstruction (FEV₁ (%)). **Pediatr Pulmonol.** © 2010 Wiley-Liss, Inc.

Key words: work of breathing; ventilatory limitation; cardiopulmonary exercise testing.

Funding source: Committee on Physiotherapy Research of the Royal Dutch Society for Physiotherapy (Wetenschappelijk College Fysiotherapie, Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF)).

INTRODUCTION

Limitation of exercise capacity in adolescents with cystic fibrosis (CF) has a multi-factorial cause. Reduced lung function and muscle mass are known to be most important factors leading to a limited exercise capacity.^{1,2} A decreased muscle mass reduces skeletal muscle function, including respiratory muscle strength, in adults with CF.³ Moreover, in children with CF a decreased skeletal muscle strength^{4,5} and endurance⁶ have been reported, even when corrected for a decreased lean body mass or lung function.^{4–6} This points to a possible intrinsic abnormality in muscle oxygen uptake in patients with CF, however, currently there is no firm evidence available.^{7–11}

Due to continuous airflow obstruction, as reflected by a decreased forced expiratory volume in 1 sec (FEV₁), and dynamic hyperinflation, as reflected by a decreasing

inspiratory capacity (IC) during exercise,¹² children with CF develop a rapid breathing pattern during exercise with a concomitant increase in the work of breathing (WOB)^{13–15} and oxygen cost.¹³ A decreased inspiratory

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Received 18 December 2009; Revised 9 June 2010; Accepted 26 June 2010.

DOI 10.1002/ppul.21329

Published online in Wiley Online Library (wileyonlinelibrary.com).

muscle function (strength and endurance) that has been observed in patients with CF will lead to a faster inspiratory muscle fatigue during exercise, which contributes to the reduced exercise capacity.^{16,17}

It seems that there is an interrelationship between lung function, muscle mass, energy expenditure (respiratory), muscle function, and exercise capacity in patients with CF.¹⁸

The objective of the current study was to investigate whether static hyperinflation makes adolescents with CF more prone to a ventilatory limitation during exercise. We hypothesized that adolescents with static hyperinflation are more prone to a ventilatorily limited exercise capacity than non-static hyperinflated adolescents with CF. Furthermore, we questioned if the amount of static hyperinflation (RV/TLC (%)) is a stronger predictor of exercise capacity than the degree of airflow obstruction FEV₁ (%pred).

MATERIALS AND METHODS

Subjects

Adolescents with CF (n = 119) of the Cystic Fibrosis Center of the University Children's Hospital and Medical Center Utrecht, the Netherlands, were measured for body weight, height, lung function, and exercise capacity as part of routine assessment measures at the annual medical check-up. All measurements were part of usual care, according to the policy of the medical ethical committee of the University Medical Center Utrecht, ethical approval and informed consent were not obliged. Data of the initial test of each participant (between 1998 and 2006) were selected for this study. Participants were stratified into static hyperinflated and non-static hyperinflated. Conform previous literature about children with asthma, we defined a ratio of residual volume to total lung capacity (RV/TLC), after using a bronchodilator, higher than 30% as moderate to severe hyperinflation.¹⁹ Analysis for increasing degrees of static hyperinflation was performed by including only patients with a certain level of static hyperinflation in the analysis (RV/TLC >30%, >35%, >40%, >45%, and >50%).

The definition used for determination of a ventilatory limitation during cardiopulmonary exercise test (CPET) was previously used by Sexauer et al.²⁰ including: [1] breathing reserve index at maximal effort >0.70 (calculated as peak minute ventilation (VE_{peak}) divided by maximal voluntary ventilation (MVV) were MVV is calculated as 35 × FEV₁), [2] a FEV₁ < 80% predicted, and [3] a reduced exercise capacity, defined as VO_{2peak} < 85% predicted.

Spirometry

Spirometry and body plethysmography were performed before and after bronchodilation with salbutamol

(800 µg), using a pneumotach system and a volume-constant plethysmograph (Master Lab system, E. Jaeger, Würzburg, Germany).

Lung function measurements included total lung capacity (TLC), residual volume (RV), and forced expiratory volume in 1 sec (FEV₁). The results were compared with predicted values for healthy subjects matched for age, body height, and gender.²¹

Cardiopulmonary Exercise Test (CPET)

Exercise capacity was assessed using a progressive CPET. CPET, after bronchodilation with salbutamol, performed on an electronically braked cycle ergometer (Jaeger physis; Carefusion, Houten, the Netherlands). The seat height was adjusted to the participant's comfort and leg length. Participants rested until all measured variables were stable. Cycling started at a workload of 0 W; the workload was incremented with 15 W/min until the patient stopped due to volitional exhaustion. The workload which could be overcome for the last 30 sec prior to exhaustion was considered to be the W_{peak}. Determination if a participants' effort was maximal was based on subjective and objective criteria. Subjective criteria are described as "unsteady biking," "sweating," "facial flushing," and "clear unwillingness to continue despite encouragement." Objective criteria were: [1] peak heart rate (HR) > 95% HR_{predicted} (210-age) and [2] respiratory exchange ratio (RER) > 1.00. Based on previous literature, we defined that a participant had to meet the subjective criteria and at least one out of two objective criteria for the test to be considered of maximal effort and character.²² Participants breathed through a mask that was connected to a calibrated metabolic cart (Oxycon pro, Carefusion). Expired gas was passed through a flow meter, oxygen analyzer, and a carbon dioxide analyzer. The flow meter and gas analyzer were connected to a computer, which calculated breath-by-breath minute ventilation (VE), oxygen uptake (VO₂), carbon dioxide production (VCO₂), and RER from conventional equations. Relative peak oxygen uptake (VO_{2peak}/kg) was calculated by dividing VO_{2peak} by total body mass. HR was monitored continuously by a three-lead electrocardiogram (Hewlett-Packard, Amstelveen, the Netherlands).

Reference Values

Reference values for VO_{2peak} and W_{peak} from healthy children and adolescents were obtained from previously studied Dutch children and adolescents.^{23,24}

Statistical Analysis

Data were expressed as mean ± SD. Data were analyzed using SPSS 15.0 for Windows and tested for normality with the Kolmogorov-Smirnov test. An alpha value of 0.05 was considered as statistically significant.

TABLE 1—Demographic Characteristics

	Female (n = 50)	Male (n = 69)	Total (n = 119)
Age (years)	13.7 ± 1.5	13.8 ± 1.8	13.8 ± 1.7
Height (cm)	156.6 ± 7.7	159.1 ± 11.4	158.1 ± 10.1
BM (kg)	43.8 ± 8.1	44.3 ± 10.7	44.1 ± 9.6
BMI (kg/m ²)	17.8 ± 2.1	17.2 ± 2.0	17.4 ± 2.1
RV/TLC (%) (before Ventolin)	36.3 ± 9.8	34.4 ± 12.8	35.2 ± 11.6
RV/TLC (%) (after Ventolin)	33.2 ± 9.6	32.1 ± 11.7	32.5 ± 10.9
FEV ₁ (%pred) (before Ventolin)	80.2 ± 19.2	76.8 ± 22.1	78.2 ± 20.9
FEV ₁ (%pred) (after Ventolin)	84.8 ± 20.1	81.5 ± 21.5	82.9 ± 20.9
HR _{rest} (beats/min)	102.1 ± 20.6	100.2 ± 14.5	101.0 ± 17.3
RER _{rest} (VCO ₂ /VO ₂)	0.92 ± 0.09	0.91 ± 0.08	0.91 ± 0.08
VO _{2peak} (L/min)	1.6 ± 0.4 ¹	1.9 ± 0.5	1.8 ± 0.5
VO _{2peak} (ml/min/kg) (%pred)	36.5 ± 6.3 ² (94.5 ± 16.7%)	44.2 ± 8.8 (94.0 ± 19.6%)	41.0 ± 8.7 (94.2 ± 18.4%)
W _{peak} (W)	133.3 ± 27.4 ¹	152.7 ± 48.0	144.6 ± 41.6
W _{peak} (W/kg) (%pred)	3.1 ± 0.5 ² (79.4 ± 12.3%)	3.5 ± 0.7 (76.9 ± 16.3%)	3.3 ± 0.7 (77.9 ± 14.8%)
HR _{peak} (beats/min)	180.1 ± 15.1	179.7 ± 19.0	179.9 ± 17.4
RER _{peak} (VCO ₂ /VO ₂)	1.18 ± 0.09 ³	1.13 ± 0.08	1.15 ± 0.09
VE _{peak} (L/min)	62.2 ± 15.6 ⁴	70.4 ± 22.7	67.0 ± 20.3

BM, body mass; BMI, body mass index; RV/TLC, ratio residual volume/total lung capacity; FEV₁, forced expiration volume in 1 sec; HR, heart rate; RER, respiratory exchange ratio (VCO₂/VO₂); VO_{2peak}, peak oxygen uptake; W_{peak}, peak work rate; VE_{peak}, minute ventilation at maximal effort. Values are presented as means ± SD.

¹Significant difference between gender groups (*P* < 0.05); non-parametric tested with Mann–Whitney *U*-test.

²Significant difference between gender groups (*P* < 0.001).

³Significant difference between gender groups (*P* < 0.01).

⁴Significant difference between gender groups (*P* < 0.05).

Possible differences between groups in the CF population were analyzed using one-way ANOVA when normally distributed and with the Mann–Whitney *U*-test when not normally distributed. Dichotomy variables were tested for association using the phi coefficient (Φ), and tested for significance using chi-square test. Prognostic value of FEV₁ and RV/TLC for exercise capacity was analyzed using standard multiple regression analysis.

RESULTS

Study Group Demographics

After determination of maximal effort and screening for completeness of data set, in total 119 adolescents, 50 females and 69 males were included.

Mean age was 13.8 years ± 1.7 (range 12–18 years), with a mean FEV₁ of 82.9% ± 20.9 (% predicted). FEV₁ and anthropometric values did not differ according to gender (Table 1). All measurements were obtained after bronchodilator.

Static Hyperinflation Versus Non-Static Hyperinflation

Overall, 54 (40.3%) patients were non-static hyperinflated (20♀; 34♂; RV/TLC (%) 23.4 ± 3.4; FEV₁ (%pred) 97.0 ± 13.6), whereas 65 (48.5%) patients were identified as static hyperinflated (30♀; 35♂; RV/TLC (%) 40.1 ± 9.0; FEV₁ (%pred) 71.4 ± 18.7). Peak exercise parameters and ventilatory parameters in static hyper-

inflated and non-static hyperinflated adolescents with CF are shown in Table 2. VO_{2peak}/kg, W_{peak}/kg, VE_{peak}, and HR_{peak} were all significantly lower in static hyperinflated patients compared to the non-hyperinflated patients (*P* < 0.05). Corrected for age and gender, the differences in VO_{2peak}/kg_{pred} (98.0 ± 15.1% in non-static hyperinflated and 91.0 ± 20.3% in static hyperinflated patients; *P* < 0.05), and in W_{peak}/kg_{pred} (75.1 ± 17.3 (%) in static hyperinflated and 81.4 ± 10.0 (%) in non-static hyperinflated patients; *P* < 0.05) remained (Table 2).

TABLE 2—Exercise Capacity in Static Hyperinflated and Non-Static Hyperinflated Patients With CF

	Static hyperinflation (N = 65)	Non-static hyperinflation (N = 54)
HR _{peak} (beats/min)	176 ± 19	185 ± 14 ¹
RER _{peak} (VCO ₂ /VO ₂)	1.14 ± 0.09	1.17 ± 0.08
VE _{peak} (L/min)	59.5 ± 17.2	76.0 ± 20.2 ²
VO _{2peak} /kg (ml/min/kg)	39.2 ± 9.2	43.1 ± 7.5 ²
VO _{2peak} /kg _{pred} (%)	91.0 ± 20.3	98.0 ± 15.1 ²
W _{peak} /kg (W/kg)	3.1 ± 0.7	3.5 ± 0.5 ²
W _{peak} /kg _{pred} (%)	75.1 ± 17.3	81.4 ± 10.0 ²

HR_{peak}, peak heart rate; RER_{peak}, respiratory exchange ratio at peak exercise; VE_{peak}, peak minute ventilation; VO_{2peak}/kg, peak oxygen uptake per kilogram body mass; W_{peak}/kg, peak work rate per kilogram body mass.

Values are presented as means ± SD.

¹*P* < 0.05 non-parametric tested with Mann–Whitney *U*-test.

²*P* < 0.05.

TABLE 3—Correlation Between Static Hyperinflation and Ventilatory Limitation for Different Degrees of Hyperinflation

	Phi coefficient	P-value
RV/TLC > 30%	0.38	<0.001
RV/TLC > 35%	0.52	<0.001
RV/TLC > 40%	0.50	<0.001
RV/TLC > 45%	0.50	<0.001
RV/TLC > 50%	0.49	<0.001

RV/TLC, residual volume/total lung capacity.
Values are Phi correlation coefficients with P-value.

Ventilatory Versus Non-Ventilatory Limitation

Twenty (29.4%; 7♀; 13♂) out of the 65 patients with static hyperinflation were ventilatorily limited during exercise while only 1 (1♂) of the 54 patients without static hyperinflation was ventilatorily limited during exercise. Phi coefficient (Φ) between ventilatory limitation and static hyperinflation was 0.38 ($P < 0.001$; see Table 3). Furthermore, for increasing degrees of hyperinflation, Phi coefficient increased to 0.52 ($P < 0.001$) in the RV/TLC range 30–50% (Table 3).

Lung Function and Exercise Capacity

As presented in Figure 1, baseline FEV₁ (%pred) after bronchodilator, showed a fair degree of association with VO_{2peak}/kg_{Pred} and W_{peak}/kg_{Pred} ($r = 0.44$ and $r = 0.46$, respectively (both $P < 0.001$), where RV/TLC, after bronchodilator, showed more variable degrees of association ($r = -0.43$ and $r = -0.47$, respectively (both $P < 0.001$) after bronchodilator). There was a strong association between FEV₁ (%pred) and RV/TLC after bronchodilator ($r = -0.84$; $P < 0.001$).

Multiple linear regression showed that, compared to FEV₁ (%pred), RV/TLC (%) was a somewhat stronger predictor for W_{peak}/kg_{Pred} (FEV₁ (%pred) B 0.161 and β 0.227 ($P = 0.135$); RV/TLC (%) B -0.371 and β -0.273 ($P = 0.073$)) and VO_{2peak}/kg_{Pred} (RV/TLC (%) B -0.343 and β -0.203 ($P = 0.188$); FEV₁ (%pred) B 0.239 and β 0.272 ($P = 0.078$)).

DISCUSSION

We hypothesized that adolescents with CF with static hyperinflation are more prone for a ventilatorily limited aerobic exercise capacity compared with non-static hyperinflated adolescents. We found a significant, but

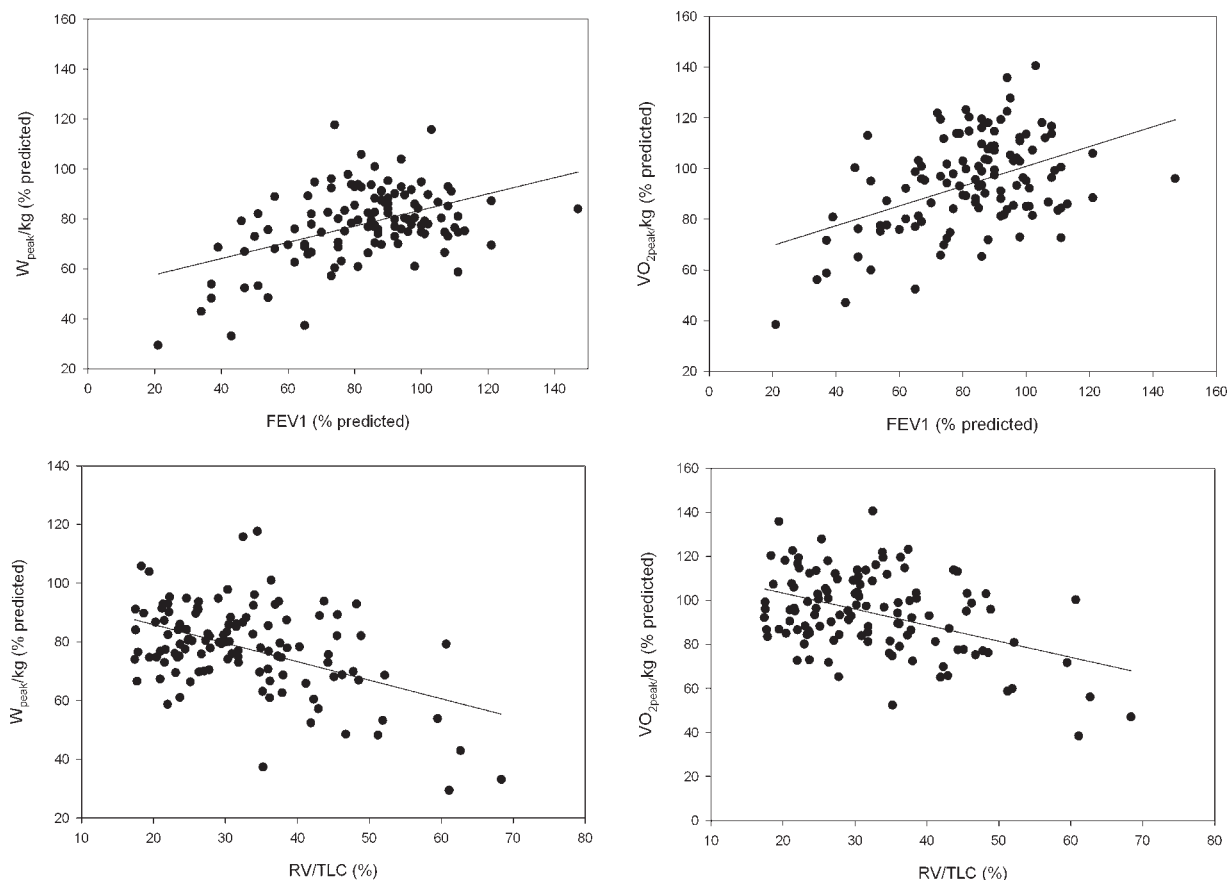


Fig. 1. Associations between lung function parameters and exercise capacity.

weak association (Φ 0.38; $P < 0.001$) between static hyperinflation (RV/TLC $> 30\%$) and ventilatory limitation at peak exercise. This indicates that the presence of static hyperinflation in adolescents with CF by itself does not strongly influence ventilatory constraints during exercise, which is in line with previous research.²⁰ Sexauer et al.²⁰ found an odds ratio of 0.96 ($P = 0.76$) for the RV/TLC ratio at rest as a weak non-significant predictor for ventilatory limitation in adults with CF. Confirmative results were found in a study among adult COPD patients, where the change in IC during exercise, reflecting dynamic hyperinflation, has been shown to be superior to static hyperinflation (resting IC) in estimating exercise tolerance.²⁵

Moreover, after analysis of the association between the degrees of static hyperinflation and a ventilatorily limited exercise capacity, the correlation coefficient slightly increased from 0.38 to 0.49 for RV/TLC $> 30\%$ and $> 50\%$, respectively.

Additionally, we found no difference in the degree of association of baseline FEV₁ (%pred) and RV/TLC (%), after bronchodilator, with VO_{2peak}/kgPred and W_{peak}/kgPred, however, RV/TLC (%) was a slightly stronger predictor of VO_{2peak}/kgPred and W_{peak}/kgPred than FEV₁ (%pred).

A point of discussion in the present study is the cut-off point in breathing reserve used to determine ventilatory limitation. Prioux et al. suggested a ventilatory reserve at peak exercise of 20% (MVV-VE/MVV $\times 100\%$), with a corresponding breathing reserve 0.8, in 11-year-old children, which increased to 30% (corresponding breathing reserve 0.7) at the age of 16 years. The mean age of our patients is 14 years, which could have influenced the prevalence of ventilatory limitation as we have used breathing reserve > 0.7 as cut-off point.²⁶ Furthermore, due to the narrow age range of our population, the present results could not be extrapolated to patients that are younger or older.

Based on the results we conclude that the presence of static hyperinflation after bronchodilator (RV/TLC $> 30\%$) in adolescents with CF by itself does not strongly influence ventilatory constraints during exercise and that static hyperinflation, as reflected by RV/TLC (%), is only a slightly stronger predictor of W_{peak}/kgPred and VO_{2peak}/kgPred than the FEV₁ (%pred), which is only reflecting the degree of airflow obstruction. The decreased exercise capacity in static hyperinflated adolescents could be explained by faster termination of peak exercise due to preliminary inspiratory muscle fatigue. The preliminary inspiratory muscle fatigue could be induced by the development of dynamic hyperinflation,^{14,15,24} which increases work¹²⁻¹⁵ and oxygen cost of breathing¹³ and causing intrapulmonary gas trapping and ventilation/perfusion mismatching,²⁷ which make a patient with CF more susceptible to ventilatory limitation during exer-

cise.¹⁵ Moreover, the greater fatigability of the inspiratory muscles could hypothetically induce a reflex vasoconstriction in the peripheral locomotor muscles and thereby compromises blood flow to the exercising limbs.¹⁷ Furthermore, the increase in WOB in patients with CF as a possible factor in ventilatorily limited exercise capacity could theoretically be elicited by the development of dynamic hyperinflation during exercise, instead of the presence of static hyperinflation at rest.

Beside the FEV₁ and possible dynamic hyperinflation, other factors, such as nutritional status, muscle mass, respiratory and peripheral muscle strength, and habitual daily physical activity are also important predictors of exercise capacity.^{1,2,4,28}

After all we suggest that, in future research, beside standard anthropometric and lung function measures, dynamic hyperinflation and flow-volume curves during exercise should be measured to facilitate a better understanding of the role of increased WOB as possible limiting factor in the exercise capacity of patients with CF.

ACKNOWLEDGMENTS

This study was funded by an unconditional research grant (DO-IT) from the Committee on Physiotherapy Research of the Royal Dutch Society for Physiotherapy (Wetenschappelijk College Fysiotherapie, Koninklijk Nederlands Genootschap voor Fysiotherapie (KNGF)). All measurements used in data analysis are part of standard routine care at the Cystic Fibrosis Center of the University Children's Hospital and Medical Center Utrecht, Utrecht, the Netherlands.

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