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Airway closing index in school-age children during exercise bronchoprovocation

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ABSTRACT

Objective: Airway Closing Index (ACI), the ratio of % change in FVC to % change in FEV₁ with bronchoprovocation, may represent changes in airflow due to airway closure, as opposed to airway narrowing. The objective of this study was to evaluate ACI during exercise bronchoprovocation (EB) in children.

Methods: Children, 6 to 18 years of age, who underwent EB using a stationary bicycle ergometer over a 6-year period were reviewed. Pulmonary function, including ACI, in patients with a positive exercise challenge, defined as $\geq 10\%$ decrease in FEV₁ following exercise, were compared to patients with a negative challenge.

Results: A total of 1030 children with a median age of 13 (IQR 11–15) underwent EB, of which 376 (37%) had a positive exercise challenge. There was wide variability in ACI, with a median of 0.75 (0.28–1.21). Median ACI in those with a positive test was 0.68 (IQR 0.41–0.93) compared to 0.84 (IQR 0.09–1.06) for those with a negative test, $p = 0.017$. Median ACI was higher in older children ($p < 0.001$) and females ($p < 0.0001$). Median percent change in FEV₁ following bronchodilator for children in the highest quintile for ACI was 4.5 (IQR 1.3–8.1) compared to 5.5 (IQR 2–9.2) for children in the lowest quintile, $p = 0.04$.

Conclusions: There is wide variability in the ACI in children undergoing EB. ACI was lower in children with a positive challenge, the significance is unknown. Children with higher ACI may have increased airway closure with bronchoprovocation, and less response to bronchodilators.

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Introduction

Asthma is a predominantly clinical diagnosis, with standard guidelines recommending confirmation of the diagnosis with spirometry (pulmonary function tests) in all patients than can adequately perform this test (1,2). Exercise-induced symptoms occur in many patients with asthma, but is also described in up to 20% of the population with little or no evidence for asthma (2,3). Higher prevalence has been described in athletes, including 30% of ice rink athletes (4) and 11%–29% of competitive swimmers (5). Exercise bronchoprovocation is commonly performed as part of the evaluation of children with either exercise limitation or symptoms with exercise in which EIB is in the differential diagnosis. The diagnosis of EIB can be established following an exercise bronchoprovocation test with the diagnostic criteria usually being $a \geq 10\%$ decrease in the forced expired volume in one second (FEV₁) from baseline following a standardized exercise protocol (3).

The physiology of these changes in FEV₁ are not well understood. Changes in FEV₁ reflects both airway narrowing and airway closure (6). Airway narrowing is due to a combination of baseline narrowing prior to a challenge, and bronchoconstriction resulting from the exercise challenge. Airway closure refers to the loss of open airways contributing to the FEV₁, as airways progressively become obstructed. Veen et al. (7) studied the closing volume, which is the proportion of lung volume closed off from the mouth at the end of complete exhalation, compared to the TLC/VC (total lung capacity/vital capacity) in 13 stable severe asthmatics and 15 unstable asthmatics. They found similar changes in FEV₁, TLC and VC, but higher closing volumes in the unstable asthmatics compared to stable severe asthmatics, suggesting there may be a significant component of airway closure in asthma.

Airway Closing Index (ACI), defined as the ratio of % change in FVC to % change in FEV₁, has been studied during methacholine challenge testing in adult patients. ACI may reflect, at least in part, the degree

of airway closure as a response to bronchoprovocation. Chapman et al. (8) reported airway closure to be associated with airway hyper-responsiveness, independent of airway narrowing, using the FVC and ACI. They reported that obese patients had a higher ACI compared to non-obese asthmatics (8), and significant changes in ACI in obese adults, pre- and post-bariatric surgery (9). Recently Kaminski et al. (10,11) reported in a large cohort of adult patients undergoing methacholine bronchoprovocation that older age and obesity were associated with higher ACIs.

There are no reported studies evaluating ACI in children undergoing bronchoprovocation, either with methacholine or with exercise. The primary objective of the study was to calculate ACI in children who have undergone exercise challenge testing, and to correlate it with other measures on spirometry, including response to bronchodilator. The secondary objective was to assess differences in ACI based on sex and body mass index. The hypothesis was that a significant proportion of school-age children will have airway closure following exercise bronchoprovocation.

Materials and methods

This is a single center, retrospective review of data obtained from children ages 6 to 18 years who underwent exercise bronchoprovocation over a 6 year period 2011–2017. The Institutional Review Board approved the conduct of the study. A standardized exercise protocol using stationary bicycle ergometry was employed in all subjects as described in the ATS clinical practice guidelines on exercise-induced bronchoconstriction (3). Bronchodilators were withheld prior to testing as per ATS guidelines.³ All patients were rapidly exercised by cycling at a load sufficient to achieve up to 80% of their targeted maximal heart rate. The same level of exercise was then sustained (constant load) until the patient complained of fatigue or respiratory symptoms. All patients underwent the same protocol, irrespective of age. Pre- and post-exercise pulmonary function testing were obtained as per ATS guidelines (3). Post-exercise spirometry were recorded at 5-, 10-, 15- and 30-min post-exercise. The lowest FEV₁ value recorded within 30 min after exercise was expressed as a percent of the pre-exercise value. A decrease in FEV₁ of $\geq 10\%$ with exercise was considered evidence of exercise-induced bronchospasm (positive test). 2.5 mg of albuterol was administered via handheld small volume nebulizer and all tests repeated. ACI was calculated as the ratio of %

change in FVC to % change in FEV₁. ACI in patients with $\geq 10\%$ decrease in FEV₁ were compared to ACI in patients with $< 10\%$ decrease in FEV₁, using Mann-Whitney test. BMI percentiles were calculated for age as per CDC guidelines (12). Patients with BMI $\geq$ than the 95th percentile (%) were considered obese, and those between 15th and 85th percentile were considered normal weight (12). Obese children were compared to children with BMI in the normal range for ACI, percent change in FEV₁, and percent change in other pulmonary function tests. ACI values were stratified by quintiles. Patients at the highest quintile were compared to those in the bottom quintile for response to bronchodilator. Patients were stratified by age groups as 6–9 years, 10–12 years, 13–15 years and 16–18 years and lung function compared using Kruskal-Wallis tests. Proportions were compared using chi-square tests or non-parametric equivalent. Two-sided *p* values of < 0.05 was considered statistically significant. Data analyses were performed using Stata v15.1 (Statacorp, TX).

Results

A total of 1030 children, 6 to 18 years of age, underwent exercise bronchoprovocation over the 6-year period. Median age was 13 (IQR 11–15), 42% were male. Median % decrease in FEV₁ with exercise was 6.3% (IQR 1.4–13.4). 376 (37%) had a positive exercise challenge. Table 1 compares pulmonary function in children with and without a positive bronchoprovocation test. There was no difference in age between those with a positive or negative test. 66% of children with a positive challenge were female, compared to 54% of children with a negative challenge, $p < 0.0001$. Children with a positive test had lower baseline FVC % predicted, FEV₁% predicted, and FEV₁/FVC. There was wide variability in ACI, with median of 0.75 (IQR 0.28–1.21). Median ACI in those with a positive test was 0.68 (IQR 0.41–0.93) compared to 0.84 (IQR 0.09–1.06) for those with a negative test, $p = 0.017$. Median BMI % for age was 67 (IQR 44–86) for those with a positive test compared to 72 (IQR 47–89) for those with a negative test, $p = 0.50$. 136 (13%) were obese. There were no differences in median ACI in obese children (0.73; IQR 0.36–1.07) compared to children with normal weight (0.79; IQR 0.26–1.26), $p = 0.509$. Table 2 summarizes differences in pulmonary function based on sex. Females were slightly older, had a lower median BMI, lower FVC and higher FEV₁/FVC at baseline. 41% of females had $\geq 10\%$ FEV₁ with exercise, compared to 30% of males,

Table 1. Comparison of children with and without positive exercise bronchoprovocation challenge.

Parameter	Negative exercise challenge	Positive exercise challenge	<i>p</i> value ^b
N (%)	654 (63%)	376 (37%)	
Age (y) ^a	13 (11 to 15)	13 (11 to 15)	0.992
Sex (female)	350 (54%)	247 (66%)	<0.0001
BMI (%ile) ^a	72 (47 to 89)	67 (44 to 86)	0.050
FVC (% pred) ^a	103 (94 to 114)	100 (90 to 109)	<0.0001
FEV ₁ (% pred) ^a	93 (85 to 103)	90 (81 to 99)	0.0003
FEV ₁ /FVC ^a (absolute ratio)	.85 (.80 to .89)	.86 (.81 to .91)	0.0022
% decrease in FVC ^a	3.11 (0.35 to 6.4)	11 (6.4 to 16.6)	<0.0001
% decrease in FEV ₁ ^a	2.3 (−0.74 to 5.6)	15.8 (12.8 to 21.4)	<0.0001
ACI ^a	.84 (0.09 to 1.06)	.68 (0.41 to 0.93)	0.0173
% increase in FEV ₁ with albuterol after exercise ^a	6.98 (3.1 to 11.4)	21.54 (14.1 to 30.2)	<0.0001

^aMedian (IQR).^bUnpaired *t*-test, Mann-Whitney or chi-square test.**Table 2.** Comparison of male and female children.

Parameter	Female	Male	<i>p</i> value ^b
N (%)	597 (58%)	433 (42%)	
Age (y) ^a	14 (12 to 15)	12 (10 to 14)	<0.0001
BMI (%ile) ^a	67 (44 to 87)	73 (50 to 91)	0.007
FVC (%pred) ^a	102 (92 to 111)	103 (94 to 115)	0.009
FEV ₁ (%pred) ^a	91 (84 to 100)	92 (83 to 105)	0.103
FEV ₁ /FVC (absolute) ^a	0.87 (0.83 to 0.91)	0.83 (0.79 to 0.87)	<0.0001
≥10% decrease in FEV ₁ , n (%)	247 (41%)	130 (30%)	0.0002
% decrease in FVC with exercise ^a	6.4 (2.5 to 11.8)	3.9 (0.6 to 8.3)	<0.0001
% decrease in FEV ₁ with exercise ^a	7.5 (2.0 to 14.5)	4.4 (0.5 to 11.4)	<0.0001
ACI ^a	0.81 (0.37 to 1.3)	0.63 (0.15 to 1.1)	<0.0001
%FEV ₁ increase, post-bronchodilator ^a	11.1 (5.5 to 19.1)	10.0 (4.5 to 17.8)	0.121

^aMedian (IQR).^bUnpaired *t*-test, Mann-Whitney or chi-square test.**Table 3.** Comparison of children in the highest ACI quintile and lowest ACI quintile.

Parameter	Lowest quintile	Highest quintile	<i>p</i> value ^c
N	206	206	
Age (y) ^a	13 (11 to 15)	14 (12 to 15)	0.870
BMI (%ile) ^a	46 (40 to 54)	46 (42 to 53)	0.910
FVC (% pred) ^a	102 (94 to 112)	106 (95 to 117)	0.046
FEV ₁ (% pred) ^a	93 (83 to 102)	94 (86 to 104)	0.136
FEV ₁ /FVC (absolute) ^a	0.85 (0.80 to 0.89)	0.85 (0.80 to 0.89)	0.730
% decrease in FVC with exercise ^a	0.95 (−0.52 to 2.82)	3.9 (0.6 to 8.3)	<0.0001
% decrease in FEV ₁ with exercise ^a	−0.37 (−1.75 to 4.1)	2.7 (1.1 to 5.7)	<0.0001
ACI ^a	−0.5 (−1.8 to −0.03)	2.12 (1.7 to 3.2)	<0.0001
%FEV ₁ increase, post-bronchodilator ^b	5.5 (2 to 9.2)	4.5 (1.3 to 8.1)	0.049

^aMedian (IQR).^bMean ± SD.^cUnpaired *t*-test, Mann-Whitney or chi-square test.

$p < 0.0001$. Females had greater % decreases in both FVC and FEV₁ with exercise. Median ACI in females was 0.81 (IQR 0.37–1.3), compared to 0.63 (IQR 0.15–1.1) for males, $p < 0.0001$. There was less % increase in FEV₁ after an inhaled bronchodilator following exercise in patients in the highest quintile for ACI (4.5; 1.3–8.1) as compared to those in the lowest quintile (5.5; 2–9.2), $p = 0.04$ (see Table 3). 14.1% of patients with an ACI in the highest quintile failed to return to their baseline FEV₁ compared to 7.3% of patients with an ACI in the lowest quintile, $p = 0.025$. Table 4 describes lung function stratified by age groups. Older patients had better lung function at baseline. However, the median change in FEV₁

following exercise was not different between age groups. The ACI was higher in older children.

Discussion

In this study, ACI in children during exercise bronchoprovocation had a wider range and higher median value (median ACI of 0.75) than adults following methacholine challenge in adults with asthma (0.6–0.67) and healthy adults (0.54) (8–10). Kaminski et al. (10,11), in a subset of children 6–18 years of age, reported median ACI values of 0.62 with methacholine testing. Subjects in that study with a higher PC20, i.e., less airway responsiveness, had a lower closing

Table 4. Changes in lung function with exercise, stratified by age.^a

	Age 6–12	Age 10–12	Age 13–15	Age 16–18	<i>p</i> value ^a
N	140	292	409	189	
Male (%)	95 (68)	146 (50)	123 (30)	69 (37)	<0.001
BMI %ile	43 (37 to 56)	47 (39 to 64)	50 (43 to 65)	51 (45 to 59)	0.23 ^b
FVC (%pred)	98 (91 to 108)	97 (89 to 104)	105 (95 to 116)	108 (98 to 118)	<0.001
FVC post-exercise (%pred)	94 (85 to 105)	92 (82 to 100)	98 (67 to 108)	99 (90 to 111)	<0.001
FVC % change with Exercise	−4.1 (−8.7 to 0.6)	−4.7 (−10.4 to −0.8)	−6.1 (−12.3 to −2.3)	−7 (−13.3 to −3.1)	<0.001
FEV1 pre (%pred)	88 (91 to 95)	87 (79 to 95)	94 (86 to 104)	98 (90 to 108)	<0.001
FEV1 post-exercise (%pred)	80 (73 to 90)	80 (70 to 90)	87 (77 to 98)	91 (80 to 101)	<0.001
FEV1 % change with Exercise	6.9 (15 to 0.9)	6.2 (15.2 to 1.0)	−6.9 (−15.6 to −1.5)	−6.7 (−16 to −1.8)	0.91
FEV1/FVC pre	0.83 (0.80 to 0.88)	0.84 (0.80 to 0.89)	0.86 (0.82 to 0.90)	0.86 (0.82 to 0.91)	<0.001
FEV1/FVC post-exercise	0.80 (0.75 to 0.86)	0.83 (0.77 to 0.88)	0.86 (0.80 to 0.92)	0.86 (0.81 to 0.91)	<0.001
ACI	0.43 (0.09 to 0.85)	0.69 (0.27 to 1.06)	0.83 (0.32 to 1.41)	0.89 (0.33 to 1.53)	<0.001
>10% change in FEV1, n (%)	51 (36)	120 (41)	160 (39)	70 (37)	0.67 ^b
% change in FEV1 post-BD	4.5 (0.5 to 8.4)	3.8 (−0.4 to 7.6)	3 (−0.7 to 7)	3.7 (−2.1 to 7.1)	0.19

^aAll values reported as medians (IQR), unless specified otherwise; median values compared using Kruskal-Wallis test.

^bChi-square test.

index, which is consistent with our study. It is possible that some children who present with symptoms of EIB may develop significant airway closure with exercise, which may not be reflected in a change in FEV₁. The physiology behind an elevated ACI in children compared to previous measurements in adults is not understood. This finding suggests that children develop relatively more airway closure during bronchoprovocation, though it is certainly possible that the responses to exercise are quite different than methacholine. Perhaps differences in respiratory system compliance between children and adults may contribute to this difference. Adult chest wall compliance has been demonstrated to decrease with age, though lung compliance does not (13). This is hypothesized to be multifactorial including osteoporosis, kyphosis of aging, along with decreasing FEV₁ (14). There has been reported increased airway hyper-reactivity with methacholine challenge in both young and old age as compared to middle-aged individuals, with less beta-adrenergic responsiveness following a challenge (14–16). Mansell et al. (17) suggested that differences in bronchodilator responses or airway closure in children as compared to adults may be partly due to differences in airway elastic recoil. Perhaps this may partially explain the increased ACI noted in this study.

ACI was not higher in obese children in this cohort, which differs from the higher ACI values reported in obese adults undergoing methacholine challenge testing (9,10). Though not completely understood, there are a number of mechanisms postulated for elevated ACI in obese adults including low lung volumes, increased peripheral bronchomotor tone, decreased distal airway compliance, inflammation in serum and adipose tissue, airway and pulmonary vascular remodeling (10). Perhaps, some of these changes require several years and therefore may not be as impactful in children.

Females had overall lower baseline function, a more dramatic response to exercise, and an elevated ACI. Similarly increased ACI values have been reported in adult females following methacholine challenge (10). It has long been known that sex plays a differential role in lung development, particularly through puberty. In early development, female lungs have earlier surfactant production, and have more rapid large airway growth (though fewer respiratory bronchioles) compared to their male counterparts (18). Airways in females, throughout their maturation in youth have lower airway resistance, as reported in measurements of specific airway resistances (sRaw) in 263 healthy patients, ages newborn to 54 years old (19). Young males may have larger airways with a lag in their growth pattern, or dysanaptic growth, as compared to females (20), and are thought to have larger conducting airways post-puberty (21). These patterns are thought to be due in part to hormonal differences, with both androgen and estrogen being key modulators of growth in both inhibitory and stimulatory effects (22). EIB has been demonstrated to be higher in females than males (23). In a study of 15,000 children, 7.4% of children had a positive 6-min free running test (24). Girls were more likely to have a positive test than boys (8.5% versus 6.4%, *p* < 0.001). Additionally, attempting to use symptoms as predictors for EIB as demonstrated by decreased peak flow measures yielded poor positive predictive value and sensitivity. Other studies have demonstrated higher rates of airway hyperactivity in females with exercise (23,25).

Children with the highest ACI values seemed to have poorer response to an inhaled bronchodilator after exercise, both in % change in FEV₁ as well as return to baseline FEV₁. This may have implications for treatment in patients with exercise-induced bronchospasm. Kaminski et al. (10,11) suggested that

airway closure may have important implications for asthma treatment as it may impact aerosol drug delivery to poorly ventilated areas of the lung as a result of such closure.

When stratified by age groups, older children had better lung function at baseline in our cohort. Following exercise, though the median change in FEV₁ was not different based on age, the ACI values were higher in older children. This was likely driven by the higher FVC values at baseline and following exercise. The implications of this phenomenon are unclear, but underscores the high variability in ACI in children, as also emphasizes the need to look beyond $\Delta > 10\%$ change in FEV₁ to explain symptoms of EIB in children.

There are limitations to the study due to the retrospective nature. Detailed clinical data including diagnoses, symptoms at presentation and prior treatments were not available for correlation. Though all patients were referred to the pulmonary function laboratory for evaluation of EIB, other concomitant diagnoses are not known. Detailed cardiopulmonary parameters including duration of exercise, ventilation, workload (in watts), oxygen consumption and related measures were not available. Late EIB (occurring 30 min or later after exercise), was not assessed.

Conclusions

There was wide variability in Closing Index (ACI) in children undergoing exercise bronchoprovocation, suggesting some children may develop airway closure and not just airway narrowing in response to exercise. Those with symptoms with exercise may have more airway closure which may not be reflected in their FEV₁ responses. Children may have higher ACI compared to adults. Older children and females have higher ACIs as compared to male. Obesity does not seem to impact ACI in children. Children with higher ACI values may have decreased response to bronchodilators after exercise induced bronchospasm.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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