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Wheeze is an unreliable endpoint for bronchial methacholine challenges in preschool children

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Abstract

Background: Onset of wheeze is the endpoint often used in the determination of a positive bronchial challenge test (BCT) in young children who cannot perform spirometry. We sought to assess several clinical endpoints at the time of a positive BCT in young children with recurrent wheeze compared to findings in school-aged children with asthma.

Methods: Positive BCT was defined in: (1) preschool children ($n = 22$) as either persistent cough, wheeze, fall in oxygen saturation (SpO_2) of ≥5%, or ≥50% increase in respiratory rate (RR) from baseline; and (2) school-aged children ($n = 22$) as the concentration of methacholine (MCh) required to elicit a 20% decline in FEV_1 (PC_{20}).

Results: All preschool children (mean age 3.4 years) had a positive BCT (median provocative MCh concentration 1.25 mg/ml [IQR, 0.62, 1.25]). Twenty (91%) school-aged children (mean age 11.3 years) had a positive BCT (median PC_{20} 1.25 mg/ml [IQR, 0.55, 2.5]). At the time of the positive BCT, the mean fall in SpO_2 (6.9% vs. 3.8%; $p = .001$) and the mean % increase in RR (61% vs. 22%; $p < .001$) were greater among preschool-aged than among school-aged children. A minority of children developed wheeze at time of positive BCT (23% preschool- vs. 15% school-aged children; $p = .5$).

Conclusions: The use of wheeze as an endpoint for BCT in preschool children is unreliable, as it rarely occurs. The use of clinical endpoints, such as ≥25% increase in RR or fall in SpO_2 of ≥3%, captured all of our positive BCT in preschool children, while minimizing undue respiratory distress.

KEYWORDS
asthma, bronchial hyper-responsiveness, lung function, methacholine challenge, preschool children, spirometry, wheezing

Abbreviations: BHR, bronchial hyper-responsiveness; bpm, breath per minute; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; MCh, methacholine; PC_{20}, concentration of methacholine required to elicit a 20% decline in FEV_1; PC_{wheeze}, concentration of methacholine required to cause wheeze; SpO_2, oxygen saturation by pulse oximetry.

1 | INTRODUCTION

Although childhood asthma is among the most common chronic illnesses in children, the natural history of wheezing especially in the first 4 years of life remains to be more fully elucidated. Because over half of all preschool children with recurrent wheeze will no longer have active wheezing by grade school,[1–3] several studies have attempted to characterize differences between those with asthma and those in whom wheezing resolves. In addition to subjective features associated with persistent wheezing, such as a history of eczema, wheezing in the absence of a viral respiratory tract infection, and a parental history of asthma,[1] bronchial hyper-responsiveness (BHR) has been identified as an important predictor of the persistence and severity of wheezing in later childhood.[4,5] Bronchial provocation challenges are the gold standard for assessing BHR, but the assessment of BHR in young children who cannot perform spirometry is problematic as there is no universally accepted endpoint for the determination of a positive challenge as there are for older children and adults in whom the PC_{20} FEV_1 is used.[6]

Previous studies have proposed that a positive bronchial challenge in children unable to perform spirometry can be determined by the presence of wheezing by auscultation or the so-called PC_{wheeze}.[7] Additional parameters for a positive challenge in this group include a reduction in oxygen saturation (SpO_2), an increase in respiratory rate (RR), and/or the presence of cough. Although some studies reported the incidence of wheeze at the time of a positive methacholine (MCh) challenge by auscultation as high as 80%,[7] there is conflicting evidence. A retrospective chart review of 50 consecutive MCh challenges in preschool-aged children by auscultation performed at the National Jewish Health found only 37% of children to wheeze at the time of a postive challenge.[8] Although Noviski et al.[9] reported a positive correlation between PC_{wheeze} and PC_{20}, they found the PC_{wheeze} to occur at consistently higher concentrations of MCh than the PC_{20}. Bentur et al.[10] found that in older children, wheeze consistently appeared at concentrations of MCh higher than that required to cause a 20% fall in FEV_1.

We hypothesized that the current parameters used to assess BHR in young children with suspected asthma result in a greater degree of respiratory compromise compared to older children undergoing a MCh challenge where the PC_{20} FEV_1 is used. To address this concern, we performed a prospective study where the physical examination findings and SpO_2 at the time of a positive MCh challenge in preschool children were compared with those of older children undergoing MCh challenge and spirometry.

Key Message

There is no universally accepted endpoint for the determination of a positive bronchial challenge in children who cannot perform spirometry, although the onset of wheeze is often utilized. Our study shows that in preschool children undergoing a methacholine challenge, (1) the use of wheeze as an endpoint for positive test is unreliable as it rarely occurs; (2) continuous SpO_2 monitoring during the challenge is necessary; and (3) the use of clinical endpoints, such as ≥25% increase in respiratory rate or fall in SpO_2 of ≥3%, are sufficient to identify a positive methacholine challenge in preschool children. These endpoints can detect the presence of bronchial hyper-responsiveness, while minimizing undue respiratory distress in preschool children with suspected asthma.

2 | METHODS

This was a prospective study conducted at National Jewish Health, a national referral center for respiratory diseases, between 2005 and 2006. The study was reviewed and approved by the National Jewish Health Institutional Review Board. Informed consent was obtained by each participant's parent/guardian, and assent was obtained from each school-aged participant. Patients aged 1–17 years were eligible for entry into the study. The preschool-aged group included patients aged 1–5 years with a history of recurrent respiratory symptoms (daytime and nocturnal cough, cough and wheezing with viral respiratory tract infections, and/or activity) and at least one documented episode of wheeze. Exclusions included need for treatment with an oral glucocorticoid or respiratory tract illness within 4 weeks of entry. The school-aged group included patients aged 6–17 years with a history of physician-diagnosed asthma. Subjects were excluded if they had an upper or lower respiratory infection or had required oral glucocorticoids within the past 4 weeks. Additional exclusion criteria for both groups included preterm birth (≤36 weeks).

All subjects refrained from using short-acting bronchodilators for at least 8 h and long-acting bronchodilators for at least 24 h before the challenge. The MCh challenge utilized a 2-min tidal breathing technique, using a low-output nebulizer and a facemask or mouthpiece. Compressed air powered the nebulizer at a flow of 5 L/min. Starting with placebo, nebulized treatments were given by mask or mouthpiece over 2 min, followed by each doubling-concentration of MCh (from 0.31 mg/ml, 0.625 mg/ml, 1.25 mg/ml, etc.) every 5 min until the challenge was considered "positive" or until a concentration of 25 mg/ml was reached.[11] Continuous pulse oximetry and heart rate were monitored. The SpO_2 was considered valid when it was steady for at least 5 s with a good waveform and a heart rate that correlated with those detected manually. The lowest SpO_2 meeting these criteria was recorded for each dose. Following cessation of the nebulization, auscultation was performed in six posterior lung fields (right: upper, middle, and lower; left: upper, middle, and lower) and three anterior fields (right: upper and middle; left: upper) by the same investigator (LS) for 10–15 s in each field, and the RR was noted.

A challenge was considered positive in the preschool-aged group when one of the following parameters was met: ≥5% change from baseline SpO_2, a stethoscope detected wheezing or presence of persistent coughing (3 or more in a row), or increased RR by 50% or

more.[12] Immediately upon completion of a positive challenge, each subject received 2.5 mg of nebulized albuterol. Vital signs and pulse oximetry were repeated following the completion of the albuterol treatment.

School-aged subjects performed spirometry using the Jaeger$_{20}$ pulmonary function testing system. Spirometry was conducted according to the American Thoracic Society recommendations with at least 3 acceptable maneuvers and recording of the 3 highest FVC and FEV_1 values. A positive challenge in the school-aged group was determined by the concentration of MCh that induced a 20% fall from baseline FEV_1 obtained by linear interpolation of the logarithmic dose–response curve (PC_{20}). After the challenge was complete, the subject received 2.5 mg of nebulized albuterol. A final spirometry was obtained 10–15 min after bronchodilator therapy, and subjects were not discharged until the FEV_1 had returned to within 5% of baseline FEV_1.[11]

2.1 | Statistical analysis

Spirometry measurements of FVC and FEV_1 are presented as percentages of predicted values. Changes in several parameters before and after the MCh challenges were evaluated using paired *t* tests. Data that were non-normally distributed are expressed as median values with interquartile range (IQR). The normally distributed data are described by mean and standard error of the mean (SEM). *p* values <.05 are considered significant. Data were analyzed using JMP Pro (SAS Institute, Inc., 1989–2007).

3 | RESULTS

A total of 44 subjects (59% male) underwent MCh challenge test: 22 subjects in the preschool-aged group and 22 in the school-aged group (Table S1). Two school-aged subjects had FEV_1 PC_{20} values of ≥25 mg/ml and were excluded from the analysis. The remainder had positive challenges, all reacting at MCh concentrations of ≤10 mg/ml. Table 1 summarizes the baseline characteristics of the study population. At baseline, the preschool- and grade school-aged groups had comparable normal SpO_2, and had expected age-appropriate differences in heart and respiratory rates. There was no difference in the history of severe wheezing episodes requiring emergency room visits or hospitalization between the two age groups (Table 1).

3.1 | Preschool-aged group

All 22 subjects in the preschool-aged group had a positive challenge with a median MCh dose of 1.25 mg/ml (IQR: 0.625, 1.25), with all subjects reacting at a MCh concentration of ≤2.5 mg/ml. The challenge was considered positive due to a ≥5% fall in SpO_2 in 20 of 22 (91%) subjects and due to the presence of persistent dry cough in the remaining 2 subjects. No challenge was deemed to be positive primarily due to the development of wheezing. At the time of a positive MCh challenge, the mean decrease in SpO_2 was 6.9% (±0.6) from baseline, while the mean increase in RR was 13.8 (±1.6) breaths per minute (bpm), which represents a 61%

TABLE 1 Baseline characteristics

	Preschool-aged group (*n* = 22)	School-aged group (*n* = 20)
Mean age (years)	3.4 ± 0.3	11.3 ± 0.8**
Male, *n* (%)	15 (68)	11 (55)
Height (cm)	97 ± 2.6	115 ± 4.2**
BMI (kg/m^2)	16.1 ± 0.9	20.8 ± 0.3**
History of asthma controller therapy, *n* (%)	4 (18)	15 (75)**
Lifetime oral steroid courses	1 ± 0.3	7 ± 3*
Lifetime emergency care visits for asthma	1.7 ± 0.6	2.2 ± 0.7
Lifetime hospitalizations for asthma	1.0 ± 0.4	0.8 ± 0.4
Baseline SpO_2 (%)	96 ± 0.3	96 ± 0.3
Baseline heart rate (bpm)	113 ± 3.2	93.5 ± 3.2**
Baseline respiratory rate (bpm)	24 ± 1.3	17 ± 0.8**
Baseline FVC (% predicted)	N/A	100.6 ± 3.1
Baseline FEV_1 (% predicted)	N/A	95.6 ± 3.8
Baseline FEV_1/FVC ratio (%)	N/A	80.7 ± 1.4
Baseline FEF_{25-75} (% predicted)	N/A	82.8 ± 7

Note: Data are presented as mean ± standard error of the mean, unless otherwise indicated.

Abbreviations: FEV_1, forced expiratory volume in 1 s; FEF_{25-75}, forced expiratory flow at 25%–75% of forced vital capacity; FVC, forced vital capacity; N/A, not applicable; SpO_2, oxygen saturation by pulse oximetry.

*p value < .05; **p value < .001.

increase from baseline. Additionally, 21 of 22 (95%) patients had at least one clinical sign. Cough occurred most frequently in 16 of 22 (73%) patients, presence of intercostal retractions occurred in 13 of 22 (59%) patients, while wheeze was noted in 5 of 22 (23%) patients. One patient had a positive MCh challenge based purely on desaturation without any associated physical findings. The lowest SpO_2 recorded at the time of a positive MCh challenge was 84%.

3.2 | School-aged group

The median MCh concentration at the time of a positive bronchial challenge was 1.25 mg/ml (IQR: 0.55, 2.5). At least one clinical finding was noted in 14 of 20 (70%) subjects, with cough occurring in 13 of 20 (65%) patients. Wheezing and retractions were rarely noted, occurring in 3 of 20 (15%) and 2 of 20 (10%) subjects, respectively. Nine subjects (45%) experienced a fall in SpO_2 of ≥5%, and one subject's SpO_2 fell 5% with no accompanying wheeze, cough, or retractions. At the final MCh dose, the mean FEV_1 fell from 95.6 (±3.8) to 63.9 (±3.6) % of predicted, which represents a 33% change from baseline (Figure 1). The mean fall in SpO_2 was 3.8% (±0.5), while the mean increase in RR was 3.6 bpm (±0.6), which represents a 22% change from baseline. The lowest SpO_2 at the time of a positive MCh challenge was 88%. There was no relationship between the change in FEV_1 and SpO_2 at the time of a positive MCh challenge ($r = .17$, $p = .48$).

3.3 | Comparison between preschool-aged and school-aged challenges

Although both the preschool-aged and school-aged groups had similar levels of BHR with median MCh doses of 1.25 mg/ml, all of the preschool-aged group reacted at a concentration of methacholine of ≤2.5 mg/ml compared with the school-aged group in which some patients did not react until reaching 10 mg/ml (Figure 2). In addition, the mean fall in SpO_2 among the preschool-aged group was significantly greater than that among school-aged children (Table 2). As seen in Figure 3, not only was the fall in SpO_2 greater but it also occurred more rapidly among the preschool children compared with the school-aged children. Lastly, the preschool children displayed a significantly greater increase in RR than the school-aged group at the time of a positive challenge (Table 2). There was no difference in the proportion of children who wheezed between groups at the time of a positive challenge (23% vs. 15% for preschool- and grade school-aged groups, respectively; $p = .52$).

4 | DISCUSSION

In contrast to earlier reported studies,[5,13,14] we found wheezing at the time of a positive MCh challenge to be an infrequent finding, occurring in less than 25%. Despite the absence of wheezing, the preschool-aged group developed significant respiratory compromise

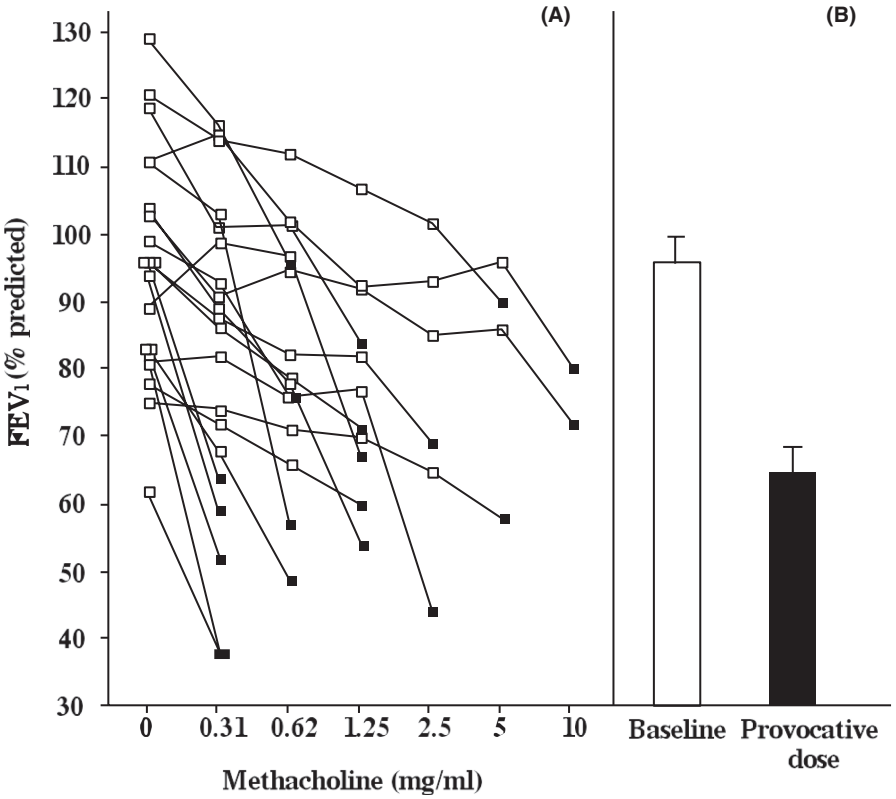

FIGURE 1 (A) Serial FEV_1 values for each school-aged subject during the methacholine challenge. Open squares represent FEV_1 values at each methacholine dose prior to a fall in FEV_1 of ≥20%, while closed squares represent the FEV_1 values at the time of a positive methacholine challenge. (B) Mean FEV_1 values at baseline and at the time of a positive methacholine challenge. Data are presented as mean ± SEM

characterized by a significant increase in RR, presence of retractions, and hypoxemia. Our findings are of a significant clinical interest, as only 8 of the 40 subjects studied (20%) would have been considered to have a positive MCh challenge if wheeze was the primary endpoint.

The most common finding among the preschool children studied was oxygen desaturation, with over 90% experiencing a fall in SpO_2 of ≥5%. Of surprise, 45% of the school-aged children were also noted to have a fall in SpO_2 of ≥5% from baseline at the time of a positive challenge, a value far higher than that reported in adults.[15] Additionally, some patients experienced desaturation in the absence of any other physical examination findings, which is similar to the findings of Wilson et al.[16] Although previous studies have challenged the importance of SpO_2 monitoring during bronchial challenges in adults,[15] our study reinforces the absolute necessity of SpO_2 monitoring in preschool children undergoing bronchial challenge testing. This is especially important as other physical signs may be absent despite a significant fall in SpO_2.

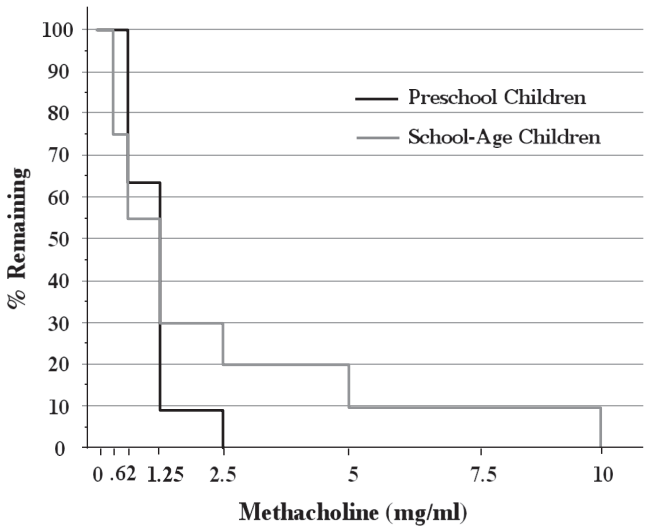

FIGURE 2 Percentage of children remaining in the challenge as the methacholine dose is escalated

The school-aged children in our study experienced a mean decrease in FEV_1 of 33% at the time of a positive MCh challenge. Associated with this decline in lung function were a mean fall in SpO_2 of 3.8% and a mean increase in RR of 22%, yet only 15% developed wheezing. Spence et al.[17] performed extended, symptom-limited MCh challenge testing in adult asthmatic patients with the aim to determine the relationship between wheeze and airflow limitation. Wheezing occurred late in the challenge long after airflow limitation had been established. The geometric mean concentration of MCh at the onset of airflow limitation was 0.5 mg/ml, while the concentration required to induce wheeze occurred at 6 times the concentration of MCh (3.2 mg/ml).

Compared with the older group, the preschool children had a greater drop in SpO_2 and a greater increase in RR, suggestive of a greater decline in lung function at the time of a positive MCh. The relationship between lung function and SpO_2 is complex and not fully understood. It has been postulated that the hypoxemia associated with MCh results from ventilation–perfusion mismatch due to bronchoconstriction, vasodilation, or a combination of both.[15] Among the school-aged children, no relationship was noted between the change in FEV_1 and SpO_2, suggesting that forced expiratory maneuvers such as the FVC and FEV_1 are insufficiently sensitive to measure the ventilation defect associated with MCh inhalation. Studies that have compared lung function and SpO_2 during acute asthma exacerbations have found the degree of hypoxemia to be greater, and to persist for a longer period of time, than the degree of airflow limitation.[18,19]

Ideally, we would have compared changes in lung function with other parameters such as oxygen saturation and auscultation for the presence of wheeze in the preschool-aged children. Unfortunately, there is no gold-standard lung function maneuver for preschool-aged

TABLE 2 Comparison of findings at the time of a positive methacholine challenge in preschool- vs. school-aged children

	Preschool-aged group (n= 22)	School-aged group (n= 20)	*p* value
Median MCh concentration (mg/ml)	1.25 (0.63, 1.25)	1.25 (0.55, 2.5)	.1
% with 1 or more PE finding, *n* (%)	21 (95)	14 (70)	.03
% with wheeze, *n* (%)	5 (23)	3 (15)	.5
% with intercostal retractions, *n* (%)	13 (59)	2 (10)	<.001
% with persistent cough, *n* (%)	16 (73)	13 (65)	.6
Mean SpO_2 (%)	89 ± 0.5	92.5 ± 0.5	<.001
Mean change in SpO_2 (%)	−6.9 ± 0.6	−3.8 ± 0.5	.001
% patients with SpO_2 ≤ 90%, *n* (%)	16 (73)	4 (20)	<.001
Mean RR (bpm)	38 ± 2.2	20 ± 1.1	<.001
Mean change in RR (bpm)	13.8 ± 1.6	3.6 ± 0.6	<.001
Mean change in RR (%)	61 ± 7	22 ± 4	<.001

Abbreviations: MCh, methacholine; RR, respiratory rate; SpO_2, oxygen saturation by pulse oximetry.

Data are presented as mean ± standard error of the mean, or median (interquartile range), unless otherwise indicated.

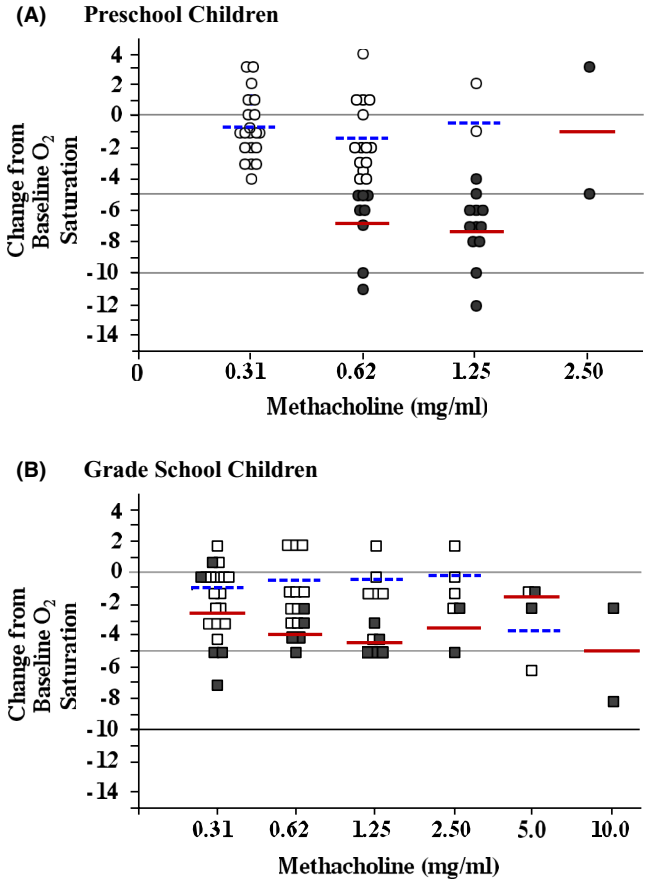

FIGURE 3 Change in SpO_2 from baseline with increasing doses of methacholine in preschool (A) and school-aged (B) children. Open circles and squares represent the SpO_2 values of each child at methacholine doses prior to the development of a positive response, while closed circles (preschool-aged children) and closed squares (school-aged children) represent SpO_2 values of each child at the time of a positive methacholine challenge. Dashed blue lines represent the mean SpO_2 values at each dose of methacholine in children who did not develop a positive reaction, while the solid red lines represent the mean SpO_2 values at each concentration of methacholine where children developed a positive response to methacholine challenge

children, especially children aged 2–4 years. Impulse oscillometry can be performed in young children,[6] but only 50% of 3-year-old children can reliably and consistently perform this procedure,[20] making it a suboptimal test when serial measures are required as occurs when performing a MCh challenge. In addition, there is less standardization for impulse oscillometry as an alternative method of quantifying the response to bronchial challenges.[6,21] Kivastik et al.[22] evaluated the utility of interrupter resistance (Rint) as an outcome measure and found it to detect BHR at lower MCh doses than wheeze or oxygen desaturation. Unfortunately, only 65% of the children studied were able to perform acceptable Rint measurements at all concentrations until reaching a positive MCh challenge.

Other investigators have also reported wheeze to be an infrequent physical examination finding at the time of a positive challenge.[16,23] In an attempt to increase the sensitivity of wheeze as an indicator of airway limitation during bronchial challenges, computer-assisted analysis of breath sounds has been shown to substantially increase the sensitivity of wheeze as an endpoint.[24] This technology may prove to be a useful advance, but at present, it is not widely performed and requires significant expertise, and the equipment is not readily available.

Our study clearly demonstrates that the currently employed endpoints, such as the development of wheezing, used to indicate airflow limitation during a MCh challenge in children who cannot reliably perform spirometry, result in undue respiratory compromise.

In conclusion, despite multiple other physical findings that support a positive MCh challenge in young children, wheezing is an infrequent finding. We suggest endpoints such as a fall in SpO_2 ≥3% or an increase in respiratory rate ≥25% would provide sufficient sensitivity to detect the presence of BHR in young children unable to complete spirometry, as these endpoints would have captured all of our positive MCh challenge results. Further studies involving larger numbers of preschool children are needed to confirm the validity of these new endpoints.

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CONFLICT OF INTEREST

Dr Spahn is currently employed by AstraZeneca. This study was designed, implemented, funded, and written before his employment with AstraZeneca. AstraZeneca had no involvement in any phase of this study. The remaining authors have no conflict of interest to report.

AUTHOR CONTRIBUTIONS

Lora Stewart: Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal). **Naomi Miyazawa:** Conceptualization (equal); Data curation (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal). **Ronina Covar:** Conceptualization (equal); Data curation (equal); Formal analysis (lead); Investigation (equal); Methodology (equal); Writing – original draft (equal). **Christopher Mjaanes:** Conceptualization (equal); Data curation (equal); Investigation (equal); Methodology (equal); Writing – original draft (equal). **Reed Shimamoto:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal). **Melanie Gleason:** Conceptualization (equal); Data curation (equal); Methodology (equal); Project administration (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (supporting). **Diego Peroni:** Formal analysis (equal); Methodology (equal); Software (equal); Supervision (equal); Writing – review & editing (equal). **Joseph D. Spahn:** Conceptualization (equal); Data curation (equal); Formal

analysis (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Supervision (equal); Writing – original draft (equal); Writing – review & editing (lead). **Pasquale Comberiati:** Conceptualization (equal); Data curation (equal); Formal analysis (equal); Methodology (equal); Writing – original draft (equal); Writing – review & editing (lead).

PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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