The bronchodilator response in preschool children: a systematic review

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Abstract

Background The bronchodilator response (BDR) is frequently used to support diagnostic and therapeutic decision-making for children who wheeze. However, there is little evidence-based guidance describing the role of BDR testing in preschool children and it is unclear whether published cut-off values, which are derived from adult data, can be applied to this population.

Methods We searched MEDLINE, EMBASE, Web of Science and Cochrane databases (inception - September 2015) for studies reporting response to a bronchodilator in healthy preschool children, response following placebo inhalation, and the diagnostic efficacy of BDR compared with a clinical diagnosis of asthma/recurrent wheezing.

Findings We included 14 studies. Thirteen studies provided BDR data from healthy preschool children. Two studies reported response to placebo in preschool children with asthma/recurrent wheezing. Twelve studies compared BDR measurements from preschool children with asthma/recurrent wheeze to those from healthy children and seven of these studies reported diagnostic efficacy. Significant differences between the BDR measured in healthy preschool children compared with that in children with asthma/recurrent wheeze were demonstrated in some, but not all studies. Techniques such as interrupter resistance, oscillometry and plethysmography were more consistently successfully completed than spirometry. Between study heterogeneity precluded determination of an optimum technique.

Interpretation There is little evidence to suggest spirometry-based BDR can be used in the clinical assessment of preschool children who wheeze. Further evaluation of simple alternative techniques is required. Future studies should recruit children in whom airways disease is suspected and should evaluate the ability of BDR testing to predict treatment response.

Introduction

In school-aged children and adults asthma is diagnosed clinically using patient history and objective investigations which include respiratory function testing[1]. In adults and older children the bronchodilator response (BDR) can be used to quantify reversible airways obstruction and to support diagnostic and therapeutic decision-making. ERS guidelines for adult patients recommend that an increase in forced expiratory volume in the first second of expiration (FEV_1) of 200 ml and 12% of the baseline value represents a positive BDR test[1]. More recently, a guideline for asthma diagnosis and management has been proposed; this endorsed these cut-offs but found no evidence against which to assess their use in children[2]. No guidance at all was provided relating to objective testing of preschool-aged children, (normally 2 – 5 years of age inclusive).

It is unlikely that adult guidelines can be applied to preschool-aged children. A cut-off based upon absolute increase in FEV_1 does not account for changes in lung size with growth. Similarly, whilst expressing the increase as a percentage of baseline might adjust for lung size[1,2], it remains unclear whether percentage cut-offs derived from adult data can be applied to preschool children. Finally, difficulties associated with technique and cooperation are likely to limit the accuracy and repeatability of spirometry-based BDR testing in young children[3]. Alternative techniques have been developed and the American and European Respiratory Societies have published a position statement on preschool lung function testing[4]. This was based upon literature published before 2007, it offered little guidance on the best method to measure and express BDR in preschool children and did not present definitive cut-off values.

This review sought to systematically assess studies relating to BDR determination in preschool children, including those published since the ATS/ERS statement. First, to determine a clinically meaningful and significant response to bronchodilator we reviewed studies describing the magnitude of BDR in healthy preschool children or change in lung function following placebo inhalation in preschool children with wheezing disorders. Second, we reviewed studies assessing the ability of the BDR to discriminate healthy preschool children from those with asthma or recurrent wheezing. Finally, we considered the optimal means of measuring and expressing BDR in preschool children.

Methods

This review was conducted according to a prospectively designed protocol (online supplementary material).

Search strategy

Potentially eligible studies were identified from MEDLINE, EMBASE, Web of Science and the Cochrane Database. Searches were built to identify all English language studies referencing bronchodilator response or a variant or abbreviation of this in the title or abstract. Studies were limited to those conducted in humans and preschool-aged participants. Searches were run from the inception of each database until 25th September 2015. Additional studies were identified by manually checking the citations of each study selected for inclusion.

Study selection

Studies of preschool children were included if they presented numerical data describing either BDR in healthy children alone or comparing this with BDR in children with asthma or recurrent wheeze. Eligible studies included those measuring either response to bronchodilator in healthy control children, or change in lung function following placebo inhalation in children with asthma or recurrent wheeze. Where possible the clinically significant or meaningful bronchodilator response cut-off was calculated. The method of Sourk and Nugent was used to calculate a cut-off which included only the greatest 5% of responses found in healthy preschool children[5]. To assess diagnostic efficacy, studies comparing the response to bronchodilator in preschool children with asthma or recurrent wheeze to that in those without were identified. All methods of measuring and expressing the bronchodilator response were permitted. Piloting the inclusion criteria revealed that many studies were not strictly limited to children conventionally considered of preschool age. Studies were included if no participant was aged 7 years or older and at least two thirds of the participants were 2 years of age or older but younger than 6 years. Studies displaying data from preschool-aged children separately from data from older individuals were also eligible for inclusion. To reduce the influence of outliers upon BDR cut-off, studies were also excluded if the number of participants per group was low (less than 20). Modified QUADAS-

2 criteria were used to assess study quality[6]. (Table S1) Following current recommendations, formal scores were not assigned but a subjective assessment made and summarised[7].

Data synthesis

Considerable heterogeneity was expected with respect to participants' diagnoses and included studies' choice of physiological parameters, BDR protocol and method of BDR expression. For this reason no meta-analyses were planned. However, where possible the results of studies of comparable physiological parameters were compared. For simplicity, where multiple means of expression were employed, comparisons were made using BDR expressed as percentage change in lung function relative to baseline since this mode of expression is recommended in ERS guidelines and we wished to assess the applicability of this guideline to the preschool population[1].

Results

Study selection and quality

After excluding duplicates, 254 studies were screened, 22 full papers assessed and fourteen selected for inclusion (Figure 1 & Table 1). One study measured BDR in healthy preschool children only[8], 12 provided BDR data from healthy children alongside measurements from children with asthma or recurrent wheeze, 12 compared BDR in preschool children with asthma or recurrent wheeze to that in those without, and seven reported diagnostic sensitivity and specificity. Two studies measured change in lung function following placebo inhalation in children with asthma or recurrent wheeze[9,10].(Table 1) Using modified QUADAS-2 criteria study quality was moderate(Table S2). However, few studies stated whether the BDR test was applied independently of the reference standard,not all studies followed the ERS protocol completely, and many selected a threshold to maximise sensitivity and specificity in the study population[11-14]. BDR was not tested in every participant in every study, younger and healthy children were less likely to complete testing[8]. Most studies reporting diagnostic efficacy, rather than apply the BDR test to individuals under investigation for wheezing disorders, used a case-control design,

comparing the BDR measured in preschool children with asthma or recurrent wheeze to that in healthy children.

Spirometry BDR in healthy preschool children

The largest study of BDR in preschool children without asthma presented data from 42 children. These children although currently healthy were at high risk of asthma due to previous wheeze[15]. Three smaller studies included 30 children or fewer (Table 2)[9, 11, 14]. In one only seven of the 30 participants achieved an expiratory time greater than one second[11]. Shin *et al* selected children for testing based upon ability to complete the testing protocol[14]. In the remaining studies success ranged from 23% to 95%[9,11,15], and within studies success rates increased with age[9]. No study reported an upper 95% confidence limit for healthy preschool children. This could be calculated as 19% and 13%, respectively, from Borrego *et al*'s and Shin *et al*'s data (Table 2).Two studies reported change in $FEF_{0.75}$ following bronchodilator (calculated upper 95% confidence limits both 15%)[9,14] and two reported change in $FEV_{0.5}$ (calculated upper 95% confidence limits 22% and 20%)[11,14].

Spirometry response after placebo inhalation in preschool children with asthma

Borrego *et al* reported percentage change relative to baseline following placebo inhalation for 43 preschool children with mild-moderate doctor-diagnosed asthma[9]. The mean (SD) reported changes for FEV_1 and $FEV_{0.75}$ were 2.6% (7.5%) and 2.1% (5.2%), equating to upper 95% confidence limit cut-offs of 18% and 13% respectively(Table 2).

Ability of spirometry BDR to identify children with asthma or recurrent wheeze

Four studies reported spirometry BDR data from both healthy preschool children and those with asthma or recurrent wheeze[9,11,14,15], although one included only 7 healthy children with successful FEV_1 measurements[11](Table S4). BDR protocol, diagnostic criteria, asthma severity and treatment level varied between studies. No study measured diagnostic sensitivity and specificity for spirometry-based BDR in preschool children with respiratory symptoms potentially attributable to asthma. However Marotta *et al* measured BDR in children at high risk of asthma due to previous wheeze. No significant difference between those with and without asthma was found in this study[15]. By contrast, three case-control

studies comparing healthy preschool children to those with doctor-diagnosed asthma found significant between-group differences in BDR[9,11,14].(Table S4) Using cut-offs optimised to the population tested Shin *et al* reported 80% sensitivity and 72% specificity associated with a 5.3% FEV_1 increaserelative to baseline[14], whilst Linares Paserini et al reported 30% sensitivity and 90% specificity using an 11% $FEV_{0.5}$ increase relative to baseline[11]. Borrego *et al* reported that 15% of healthy preschool children had a greater than 12% increase relative to baseline[9], no study presented both sensitivity and specificity of a 12% cut-off.

Alternatives to spirometry

Interrupter resistance

Three case-control interrupter resistance (Rint) studies compared data from healthy preschool children with those with asthma or recurrent wheeze[12,13,16](Table S5). The only reported test failures were four of the 41 healthy children studied by Nielsen *et al* who did not tolerate wearing a facemask. These studies contained between 37 and 82 children in each group. Two studies reported mean percentage changes in Rint relative to baseline of -8%[16]to -9.7%[13], respectively; corresponding5th percentiles in healthy children were -32% and -25%. Mele et al used the 5th percentile from healthy children to identify children who not only had a history of recurrent wheeze but were also currently symptomatic; 35% sensitivity and 93% specificity were found[16]. Two studies proposed cut-offs based upon optimising sensitivity and specificity within their population. In one, a 20% cut-off relative to baseline was associated with 76% sensitivity and 80% specificity[12] whilst the other found 58% sensitivity and 70% specificity using a cut-off of 2.5 intra-subject standard deviations of baseline Rint[13].

Forced oscillometry

A study recruiting 154 healthy preschool children[8] reported a 5th percentile value for change in respiratory system resistance at 8 Hz (Rrs_8) relative to baseline of -34% and a 95th percentile for change in respiratory system reactance at 8 Hz (Xrs_8) of 61%.(Table S5) There were three case-control FOT studies. One reported an unexpected greater decrease in Rrs_8 relative to baseline following bronchodilator in healthy children than in those with asthma; (median (10th, 90th percentiles) -18.7% (-35.0, -4.4%) versus -16.0% (-33.1, 9.7%))[17].

Unsurprisingly, using the 5th percentile for healthy children (-37% of baseline) as a cut-off yielded low sensitivity (2%). Relative changes in respiratory admittance data from this cohort also failed to demonstrate significant differences between healthy children and those with asthma[18]. Oostveen *et al* found absolute change in Rrs_4 and percentage change in area under the reactance curve relative to baseline to be most discriminative for identifying persistent wheezing[19]; fifth percentile values for -5.5 $hPasL^{-1}$ and -31 $hPasL^{-1}$ were associated with 13% and 23% sensitivity respectively with 96% specificity in both cases. Overall success rates were 85%-95% increasing with age up to 100% in children aged 4 years or older.

Impulse Oscillometry

An early Impulse Oscillometry (IOS) study by Hellinckx *et al* measured BDR in 228 healthy children and in those with mild asthma; BDR did not differ significantly between the two groups[20] so results were combined, the 95th percentile for Rrs_5 was -41.4%. Four further studies reported measures of respiratory resistance in healthy children alongside measurements made in children largely recruited from outpatient clinics with potentially more severe asthma or wheeze[13-15,21]. Successful tests were completed in 80-90% of participants. Where reported, the mean change relative to baseline in Rrs_5 for healthy children ranged from -9.5% to -17%. The only study to report the 5th percentile in healthy children reported a value of -29%[13]. Only one study compared BDR measured in children with and without asthma within a high risk population[15]. Median (IQR) percentage change Rrs_5 relative to baseline values for 28 children with asthma were -17.0 % (-32.8% to -9.9%) and -26.9% (-39.2% to -17.1%) for 45 children without asthma but at high risk due to previous wheeze. The difference in median BDR between those with and without asthma was greater still for atopic children. Two studies used receiver operator characteristic (ROC) curves to optimise diagnostic efficacy. Nielsen *et al* reported 76% sensitivity and 65% specificity using a cut-off of one within subject SD in pre-bronchodilator Rrs_5[13]. Shin *et al* reported 87% sensitivity and 62% in using an Rrs_5 cut-off of -15.6% relative to baseline[14].

Plethysmography

One study measured change in specific airways resistance (sRaw) relative to baseline using plethysmography[13]. Mean BDR was -16.3% in 37 healthy preschool children and the 95th percentile was -32%, optimal sensitivity (66%) and specificity (81%) were associated with a cut-off of three within individual standard deviations (difference between two baseline measurements / √2). Measurement failed due to facemask intolerance in 10% of children.

Comparison of spirometry and alternative measures of lung function

Few studies compared multiple techniques and comparisons between studies were limited by methodological differences. Success rates varied most between studies for spirometry but overall spirometry generally had lower success than other techniques. Three studies compared the discriminative ability of impulse oscillometry with that of spirometry. Two studies found the IOS technique but not spirometry BDR significantly different between healthy preschool children and those with asthma or wheeze[15,21], whilst another study considered spirometry superior based upon area under a ROC curve[14]. Also using ROC analysis Nielsen and Bisgaard found plethysmographic sRaw more discriminative than Rint or FOT measures[13].

Comparison of methods of expressing the BDR

Mele *et al* reported that absolute changes in Rint in their study were not associated with baseline values and that absolute or z-score change in Rint were associated with greater sensitivity and specificity than either change in percentage of baseline or predicted values[16]. Similarly, Oostveen *et al* found BDR based upon absolute FOT values more frequently distinguished children with persistent wheeze from those without than did BDR based upon relative change[19]. In contrast, Calogero *et al* found absolute BDR values to be associated with height and recommended expression in terms of change as a percentage of predicted value or as change in z-score to avoid this issue[8]. Simpson *et al* found a significant difference in percentage change in Rrs_8 relative to baseline between children with asthma and those without, but no difference using absolute BDR values[18].

Discussion

This review found evidence that spirometry-based BDR can be performed in preschool children but success rates vary and are generally low likely reflecting the experience of the laboratory. Furthermore, the ability to distinguish healthy children from those with asthma or recurrent wheeze is limited by both variability associated with repeated measures and by the overlap between BDR measurements made in these groups. There is also evidence that BDR can be measured in preschool-aged children using a number of alternative techniques, including interrupter resistance, oscillometry, and plethysmography. Whilst many of these alternative techniques require specialist expertise to conduct, interpret or both, BDR measured using these techniques has been demonstrated to differ significantly between healthy children and those with asthma or recurrent wheeze. Unfortunately, few studies have directly compared these techniques and there is insufficient evidence that any technique is superior.

Recently, attention has focused upon the contribution of objective testing to asthma diagnosis. The NICE guideline for 'diagnosing and monitoring asthma in adults, children and young people' recommends spirometry BDR testing should be offered to adults and children greater than 5 years of age with a FEV_1/FVC ratio < 70%[2]. However, no preschool study supported the use of a 200 ml absolute increase in FEV_1 in association with a 12% increase relative to baseline in this population. An absolute cut-off based upon adult data is unlikely to be valid in children due to differences in lung size. Moreover, the between occasion variability demonstrated in placebo studies suggests that poor technique may limit the repeatability of spirometry measurements in preschool-aged children, potentially increasing the relative change necessary to exceed spontaneous variability[9,10].

Ultimately the low success rates associated with spirometry in preschool children unless assessed in a specialist laboratory limit its usefulness in this population. Unfortunately, whilst numerous alternative techniques have been used in both healthy children and those with wheezing disorders[11-19,21], there is insufficient evidence to identify the optimal means of measuring BDR in children who wheeze. We note, however, that some techniques have been demonstrated to be superior to spirometry for quantifying other lung diseases in this age group, for example multiple breath wash out in cystic fibrosis[22]. Similarly the optimal means of expressing BDR requires further investigation. Since changes in lung function occur

with both growth and disease, a measure of BDR should be independent of both height and baseline lung function. Whilst this has led to proposals that BDR should be expressed either as a z-score change[8, 23]or as a percentage of predicted[13], both approaches need testing in well powered studies.

In this review we used broad search terms within a comprehensive literature search to systematically review data relating to BDR determination in preschool children. We were able to identify studies describing a clinically significant BDR and diagnostic efficacy in preschool children using spirometry and alternative techniques. Our conclusions are constrained by the quality and variability of identified studies. Many studies recruited very small numbers of children and few, if any, recruited adequate numbers to be considered reliable reference data[24]. Potential sources of bias include the low number of studies assessing diagnostic efficacy in a clinically relevant population of individuals, and the high number of studies using a case-control design or selecting a threshold to maximise sensitivity and specificity. A further problem was incomplete and inconsistent reporting of results and methodology. Heterogeneity precluded meta-analysis and limited the comparisons that could be made between studies.

Given the predominance of case-control designs, it is difficult to assess the diagnostic efficacy of BDR within a clinical population of children with symptoms potentially attributable to asthma. A cut-off which theoretically best discriminates health from disease can be calculated from receiver operator characteristic curves. However, where significant overlap exists between healthy individuals and those potentially requiring treatment clinical factors should be considered before deciding a threshold. The relative weight placed upon sensitivity and specificity may differ according to age. For example, lower cut-offs increase sensitivity but may increase the risk of over-treatment with inhaled steroids leading to undesirable effects upon young children's growth[25]. An important criterion by which to judge a diagnostic test is the test's ability to predict response to treatment; this is particularly the case for conditions such as asthma where there is no gold-standard test beyond clinical diagnosis. Pertinent to this issue are observations in both children and adults that greater bronchodilator responses were measured in individuals responding to inhaled

steroids[26,27]; and some evidence that BDR can predict treatment response in preschool children with wheeze[28].

Current guidelines recommend measuring spirometry BDR as a component in the diagnostic pathway for asthma but are not based on evidence relevant to children and no recommendations are made for preschool-aged children. Clear evidence-based guidelines are needed to ensure the correct patients receive trials of asthma treatments. Our findings have implications for practice in terms of serving as a reminder that healthy children demonstrate considerable BDR which overlaps with that seen in children with asthma or other wheezing disorders. Based upon available evidence spirometry does not appear fit for this purpose in preschool-aged children, although other techniques may be better and merit further evaluation. The relative lack of high quality published data to inform clinical decision making suggests further studies are required. Recommendations for further research include studies of 1) BDR in children suspected of having a chronic wheezing disorder, 2) the ability of BDR to predict treatment response, and 3) new techniques which can be reliably conducted outside of a specialist lung function laboratory.

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Figure 1. PRISMA flow diagram