Oscillometry and spirometry are not interchangeable when assessing the bronchodilator response in children and young adults born preterm

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Abstract

Introduction: The European Respiratory Society Oscillometry Taskforce identified that clinical correlates of bronchodilator responses are needed to advance oscillometry in clinical practice. The understanding of bronchodilator-induced oscillometry changes in preterm lung disease is poor. Here we describe a comparison of bronchodilator assessments performed using oscillometry and spirometry in a population born very preterm and explore the relationship between bronchodilator-induced changes in respiratory function and clinical outcomes. **Methods:** Participants aged 6-23 born [?]32 (N=288; 132 with bronchopulmonary dysplasia) and [?]37 weeks' gestation (N=76, term-born controls) performed spirometry and oscillometry. A significant bronchodilator response (BDR) to 400mcg salbutamol was classified according to published criteria. **Results:** A BDR was identified in 30.9% (n=85) of preterm-born individuals via spirometry and/or oscillometry, with poor agreement between spirometry and oscillometry definitions (k=0.26; 95%CI 0.18 to 0.40, p<0.001). Those born preterm with a BDR by oscillometry but not spirometry had increased wheeze (33% vs 11%, p=0.010) and baseline resistance (Rrs $_5$ z-score mean difference (MD)= 0.86, 95%CI 0.07 to 1.65, p=0.025), but similar spirometry to the group without a BDR (FEV $_1$ z-score MD= -0.01, 95%CI -0.66 to 0.68, p>0.999). Oscillometry was more feasible than spirometry (95% vs 85% (FEV $_1$), 69% (FVC), p<0.001), however being born preterm did not affect test feasibility. **Conclusion:** In the preterm population, oscillometry is a feasible and clinically useful supportive test to assess the airway response to inhaled salbutamol. Changes measured by oscillometry reflect related but distinct physiological changes to that measured by spirometry and thus these tests should not be used interchangeably.

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In the assessment of the airway response to salbutamol, oscillometry reflects related but distinct physiological changes to spirometry in preterm populations. Whilst oscillometry is a feasible and clinically useful supportive test, it should not be used interchangeably with spirometry.

Abstract:

Introduction: The European Respiratory Society Oscillometry Taskforce identified that clinical correlates of bronchodilator responses are needed to advance oscillometry in clinical practice. The understanding of bronchodilator-induced oscillometry changes in preterm lung disease is poor. Here we describe a comparison of bronchodilator assessments performed using oscillometry and spirometry in a population born very preterm and explore the relationship between bronchodilator-induced changes in respiratory function and clinical outcomes.

Methods: Participants aged 6-23 born [?]32 (N=288; 132 with bronchopulmonary dysplasia) and [?]37 weeks' gestation (N=76, term-born controls) performed spirometry and oscillometry. A significant bronchodilator response (BDR) to 400mcg salbutamol was classified according to published criteria.

Results: A BDR was identified in 30.9% (n=85) of preterm-born individuals via spirometry and/or oscillometry, with poor agreement between spirometry and oscillometry definitions (k=0.26; 95%CI 0.18 to 0.40, p<0.001). Those born preterm with a BDR by oscillometry but not spirometry had increased wheeze (33% vs 11%, p=0.010) and baseline resistance (Rrs_5 z-score mean difference (MD)= 0.86, 95%CI 0.07 to 1.65, p=0.025), but similar spirometry to the group without a BDR (FEV_1 z-score MD= -0.01, 95%CI -0.66 to 0.68, p>0.999). Oscillometry was more feasible than spirometry (95% vs 85% (FEV_1), 69% (FVC), p<0.001), however being born preterm did not affect test feasibility.

Conclusion: In the preterm population, oscillometry is a feasible and clinically useful supportive test to assess the airway response to inhaled salbutamol. Changes measured by oscillometry reflect related but distinct physiological changes to that measured by spirometry and thus these tests should not be used interchangeably.

Introduction:

The clinical review by members of the European Respiratory Society Oscillometry Taskforce[1] identified that oscillometry may have a key role in the management of survivors of very preterm birth (delivered <32

weeks completed gestation).[2]Over the lifespan, survivors of very preterm birth report increased respiratory symptoms, including wheeze, inhaled asthma medication use and re-hospitalization during early childhood compared to their term-born counterparts.[3] Lung function deficits, including reduced FEV_1, and abnormal respiratory mechanics are reported throughout childhood and into adulthood.[4-7] By school-age, ˜50% of very preterm-born children are diagnosed with asthma[5]; up to five times increased odds than those born at term.[8] Despite the high prevalence of asthma diagnoses in this patient group, preterm lung disease is typically non-atopic[9] with low exhaled nitric oxide (FeNO)[10], contrary to childhood asthma. Additionally, recent trials of inhaled corticosteroids (ICS) report only modest improvements in lung function.[11]

Even with ICS therapy a degree of airway reversibility exists for those born <32 weeks gestation.[11] A significant bronchodilator response has been reported in about one third of those born preterm[12], with the highest rates in those with a neonatal diagnosis of chronic lung disease of prematurity, bronchopulmonary dysplasia (BPD). Studies report 25-60% of school aged children with BPD respond to bronchodilators. [7,12-14]Despite this, there are reports of preterm-born children being undertreated with bronchodilators, possibly due to the belief that respiratory symptoms in this group are an inevitable consequence of airway injury and remodelling.[15] Further, recent findings from our group indicate that those most likely to respond to inhaled corticosteroids, display a degree of airway reversibility.[16] A thorough assessment of the efficacy of short acting bronchodilators is likely to become key to optimal patient management in this group.

The response to inhaled bronchodilators is typically assessed using spirometry, however the assessment of the bronchodilator response by oscillometry may offer additional advantages in the evaluation of preterm lung disease. As highlighted by the recent ERS review[5], there is evidence that oscillometry may be a useful tool in this patient group. At baseline, oscillometry outcomes are abnormal in those born very premature, with the worst abnormalities observed in those with bronchopulmonary dysplasia (BPD).[6,17,18] Additionally, in those born <32 weeks gestation oscillometry outcomes correlate with respiratory symptoms[5,18] and are sensitive to changes in lung function due to exposure to tobacco smoke.[19]High test feasibility may be of particular value in this population where patients are young and developmental delay is associated with severe respiratory disease.[20] Despite these advantages, the utility of oscillometry for the assessment of bronchodilator responses in preterm lung disease has yet to be explored.

Whilst few studies currently exist examining the bronchodilator response by oscillometry in those born preterm,[7,18] asthma studies have reported that an oscillometry assessment of the bronchodilator response may be better than spirometry at differentiating asthmatic from healthy children[21,22] and identifying individuals with poor asthma control.[23] Emerging evidence suggests that intra-breath oscillometry may identify a bronchodilator response in smokers and patients with COPD with greater sensitivity than spirometry.[24] Due to its ability to detect changes in the small airways, it may be that oscillometry is a more sensitive test in assessment of the bronchodilator response in those born preterm, however this has yet to be determined.

This study aimed to assess the feasibility and sensitivity of detecting a bronchodilator response by spirometry and oscillometry using published cut-offs in a preterm population. To further our understanding of the interpretation of these tests, we aimed to investigate the correlations and agreement between reported outcomes, and their association with clinical symptoms. We hypothesised that a greater response to bronchodilators would be observed in those born preterm (by all methods). We further hypothesised that there would be a correlation between oscillometry and spirometry bronchodilator induced changes, but that oscillometry outcomes would correlate with symptoms and identify individuals with a bronchodilator response that would not have been identified by spirometry alone.

Methods:

Participants

Preterm-born children and young adults, with and without a diagnosis of BPD, and healthy term-born controls, were assessed between the ages of 6 and 23 years (data are collated from two distinct cohorts ages 6-12[16] and 16-23 [25]). Elements of this lung function data have been presented in these publications. Preterm-born participants were delivered at 32 weeks gestation or less, hospitalised at King Edward Memorial Hospital

(KEMH) in Perth, Western Australia. Participants born preterm were classified as having bronchopulmonary dysplasia if they received 28 days of oxygen supplementation or more, as assessed at 36 weeks postmenstrual age.[26] Healthy term participants were born at 37 weeks gestation or more and had no history of recurrent respiratory symptoms or lung disease at the time of recruitment. Written informed consent was obtained from participants over 18 years of age and from parents or guardians for participants under 18 years. Ethical approval was obtained from the Child and Adolescent Health Service Human Research Ethics Committee (RGS367, RGS815).

History and Symptoms

Neonatal and maternal health data was obtained from medical records and the KEMH neonatal database. Respiratory symptoms history was obtained using validated general and respiratory questionnaires adapted from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaires.[27] Respiratory symptoms such as wheeze, shortness of breath, cough and rattly chest in the 3 months prior to the participant's study visit were parentally or self-reported, as appropriate.

Lung function assessment

Participants attended Perth Children's Hospital for lung function assessment. Respiratory mechanics were assessed using the TremoFlo C-100 (Thorasys Inc. Montreal, Canada). Spectral oscillometry was performed across 5-37Hz and intrabreath oscillometry was performed using a single 10Hz frequency. Spirometry was performed using the using the Medisoft Hypair or BodyBox 5500 (Medisoft Corporation, Sorinnes, Belgium). All tests were carried out according to American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[1,28,29]

Spirometry outcomes were expressed as z-scores according to the Global Lung Function Initiative equations.[30] Spectral oscillometry outcomes including respiratory resistance at 5Hz ($Rrs_{5)}$, resonant frequency (Fres), area under the reactance curve (AX) and respiratory system reactance at 5Hz (Xrs_5) were expressed as z-scores according to the reference equations published by Calogero *et al* (6-12 year data,[31]) and Oostveen *et al* , (16-23 year data,[32]). $Rrs_{5\text{-}20}$, and intra-breath oscillometry measures were expressed as raw values and absolute difference.[33]

Oscillometry and spirometry were performed before and after administration of 400µg salbutamol via a spacer. A bronchodilator response by spirometry was defined according to ATS/ERS guidelines as an increase of [?]200mls and 12% in FEV_1 or FVC[29] (the 200ml rule was omitted for children [?]12 years). A bronchodilator response by spectral oscillometry was defined according to ERS guidelines as a change of [?]-40% in Rrs_5, [?]50% in Xrs_5 or [?]-80% in AX across all age groups.[1]

Statistics

Data was analysed using IBM SPSS Statistics for Windows, Version 27.0 and GraphPad Prism 9.4.0. Normally distributed data are presented as means and standard deviations. Non-normally distributed data are presented as medians and interquartile ranges. Differences between two groups were analysed by independent samples t-test or Mann-Whitney U test depending on normality of the data. To compare three or more groups, the one-way ANOVA with Bonferroni Post-Hoc or the Kruskal Wallis test with pairwise comparisons was performed, as appropriate. For categorical data, the chi-squared test was used. Agreement between spirometric and oscillometric BDRs was assessed using kappa statistics, where Cohen's kappa coefficient (k) of >0.75 represented excellent agreement, 0.40–0.75 represented a fair to good agreement, and <0.40 was indicative of poor agreement.[34]

Results:

Study participants

Included in the study were 364 participants (76 term; 288 preterm) at a median (IQR) age of 12.9 years (9.8, 19.0), assessed at a single time point. There were no anthropometric differences between the preterm

and term cohorts (Table 1). Those born [?]32 weeks gestation had a high burden of respiratory symptoms, with 39% having received an asthma diagnosis during their lifetime.

Baseline lung function

Preterm participants had a lower FEV_1 (MD= -0.87; 95% CI -0.56, -1.17; p<0.001) and FEV_1/FVC z-score (MD= -0.85; 95% CI -0.57, -1.14; p<0.001), but not FVC z-score (Table 2) compared to term-born participants. Obstructive spirometry (defined as FEV_1 or FEV_1/FVC [?]-1·64 z-scores) was seen in 31.4% of preterm participants, compared to 8.6% of term born controls (X^2= 14.8, p<0.001).

Preterm-born participants also had abnormal respiratory mechanics as assessed by oscillometry. Spectral oscillometry z-scores revealed significant differences in reactance at 5Hz (Xrs_5) (MD= -0.52; 95% CI -0.26 to -0.79; p<0.001), area under the reactance curve (AX) (MD= 0.67; 95% CI 0.40 to 0.94; p<0.001) and resonant frequency (Fres) (MD= 0.62; 95% CI 0.33 to 0.91; p<0.001) for those born preterm, compared to term. Z-scores for respiratory resistance at 5Hz (Rrs_5) were not different between term and preterm groups (Table 2, p>0.05), however the difference between respiratory resistance at 5 and 20 Hz ($Rrs_{5\text{-}20}$) was greater in the preterm group (Table 2, p<0.001).

At 10Hz, inspiratory and expiratory resistance was higher and reactance was lower in the preterm group (Table 2), however the magnitude of the difference between inspiratory and expiratory reactance values ($X10_{insp\text{-}exp}$) was not different in those born preterm compared to term born controls (Table 2, p>0.05).

Assessment of the bronchodilator response

Oscillometry was more feasible than spirometry, with 95% of overall participants obtaining acceptable measures pre- and post-bronchodilator with oscillometry, compared to 85% for FEV_1(p<0.001) and 69% for FVC (p<0.001). However, the feasibility of achieving a successful bronchodilator assessment with either test was similar in term and preterm groups (p>0.05, Table 3).

A greater bronchodilator response was observed in the preterm group compared to the term group via both spirometry and oscillometry (Table 3). A small but significant improvement in FEV_1, but not FVC, was observed, relative to term born controls with a mean difference of 3.5% (95% CI 2.0 to 4.9; p<0.001). Similarly, improvements were observed in the oscillometry measures ΔRrs_5 (MD= -4.9%, 95% CI -8.7 to -1.0, p=0.013), $\Delta Rrs_{5\text{-}20}$ (MD= -0.39, 95% CI -0.56 to -0.23, p<0.001), ΔXrs_5 (MD= 11.4%, 95% CI 5.8 to 17.0, p<0.001) and ΔAX (MD= -14.1%, 95% CI -22.6 to -5.7, p=0.001).

Using published cut-offs, we observed a bronchodilator response in 24.1% of those born [?]32 weeks gestation by spirometry compared to 7.6% of term-born controls (p=0.003). Oscillometry detected a bronchodilator response in 16.4% of those born preterm, compared to 4.3% of term-born controls (p=0.009).

Intrabreath oscillometry revealed that the magnitude of the change in inspiratory reactance ($X10_{insp}$) and expiratory reactance ($X10_{exp}$) following bronchodilator was greater in those born preterm (Table 3). The magnitude of this change was however proportional across the breath cycle, with negligible within breath differences in reactance ($X10_{insp\text{-}exp}$) (MD= -0.01, 95% CI -0.1208 to 0.101, p=0.861) (Table 3). No significant bronchodilator induced decrease in inspiratory or expiratory resistance were observed in the preterm group, relative to the term-control group (Table 3).

Agreement between oscillometry and spirometry outcomes

Bronchodilator induced FEV_1% change and change in oscillometry outcomes were correlated (Figure 1), however these correlations were weak (R^2 <0.16, data not shown).

Of the 85 preterm individuals identified with a BDR (using published cut-offs), 76 had acceptable spirometry and oscillometry. Of these individuals, only 19 (25%) showed an agreement between tests; 38 (50%) were identified by spirometry only and 19 (25%) by oscillometry only (Figure 2). In the preterm group, agreement between tests was poor (k= 0.26; 95% CI 0.18 to 0.40, p<0.001). Similarly, in the term group, the agreement was extremely poor, with no overlap between tests (k= -0.06; 95% CI -0.10 to -0.01, p=0.641).

Oscillometry identified an additional 7 preterm-born individuals with a BDR that could not otherwise complete acceptable spirometry. Conversely, spirometry identified 2 preterm individuals with a BDR and no acceptable oscillometry measures.

Clinical characteristics by bronchodilator response status

In the preterm group, those with a BDR by either test were more likely to have abnormal baseline lung function (Table 4). Those with a spirometry BDR had the lowest pre-bronchodilator spirometry; this relationship was non-linear (R^2=0.44, p<0.001. Supplementary Figure E1). Similarly, those with an oscillometry BDR had the worst pre-bronchodilator oscillometry (Table 4), Whilst a BDR was more likely in those with lower baseline lung function, spirometry was not reduced in the group with a BDR by oscillometry alone, relative to the group without a BDR (FEV_1 z-score MD= -0.01, 95%CI -0.66 to 0.68, p>0.999). However, in the group that had a BDR by oscillometry but not spirometry, airway resistance was increased (Rrs_5 z-score MD= 0.86, 95%CI 0.07 to 1.65, p=0.025) as was wheeze (33% vs 11%, p=0.010), compared to those without a BDR.

Baseline lung function (oscillometry and spirometry) was lowest in those with a BDR detected by both tests (e.g., FEV_1 z-score MD= -2.14, 95%CI -2.89 to -1.39, p<0.001), compared to those without a BDR.

Discussion:

Here we describe the first comparison of bronchodilator assessments performed using oscillometry and spirometry in a preterm-born population. Both oscillometry and spirometry demonstrate that those in the preterm group have a greater response to salbutamol, however the magnitude of the change measured by spirometry and oscillometry was only weakly correlated. Similarly, when a response was defined as 'significant' using published thresholds, there was a poor agreement between tests.

Spirometry is the "gold-standard" with which to assess the bronchodilator response, however, we show that oscillometry provides additional information especially in preterm individuals with normal spirometry and respiratory symptoms (wheeze). Spirometry may not detect mild disease that presents as 'normal' between exacerbations, for example, an increase in FEV_1 [?]12% and 200mL was present in only 17.3% of asthmatics in a meta-analysis of 3 large population studies (n=2,833).[35] Spirometry can remain preserved in symptomatic individuals until an advanced stage of lung disease, whilst oscillometry is sensitive to changes in small airway function[36] and offers some advantages over spirometry in the identification of individuals with poor asthma control.[37,38] Our finding that preterm individuals with an oscillometry BDR only had increased respiratory symptoms, but normal spirometry, suggests that oscillometry has clinical value as a supplement to-, rather than surrogate for- assessing the bronchodilator response in this population.

Oscillometry is not a suitable surrogate for spirometry due to poor agreement between oscillometry and spirometry detected BDRs, and a weak correlation between ΔFEV_1 and oscillometry outcome measures. This has been reported previously in a retrospective review of 592 children with asthma or suspected asthma; 18% had a BDR by spirometry only, 9% by oscillometry only, and only 8% had a BDR by both tests.[39] Oscillometry and spirometry have different measurement techniques (tidal breathing vs forced manoeuvres) which likely partially explains this discrepancy. Performed during tidal breathing, oscillometry is perceived as a sensitive measure of small airway disease.[2] In contrast, spirometry measures flow and volume during a forced manoeuvre, and may be better able to determine the function of larger airways.[40] The lack of sensitivity of oscillometry to detect a significant FEV_1 change raises concerns surrounding the ability of oscillometry to detect more global changes in airway resistive forces. Notwithstanding, it may be that oscillometry has value in discriminating disease isolated to the small airways in those born preterm.

This poor agreement between oscillometry and spirometry BDR detection is likely exacerbated by the current published definitions of a BDR using both tests. Fixed cut-offs are typically recommended (e.g., [?]12% improvement and 200ml in FEV_1) and hence used here, however the response to a bronchodilator is inversely proportional to baseline lung function and therefore also dependant on age, height, and sex.[41] Whilst the recently published ATS/ERS guidelines have gone someway to addressing this in spirometry, recommending

that the magnitude of the change should be normalised to an individual's predicted value, rather than their baseline value[41], this had little influence on our results (supplementary tables E1 and E2). In oscillometry, there has been debate as to whether a BDR should be expressed as absolute, relative or z-score change, with the latest ERS technical standards advocating for relative change, until there are sufficiently robust healthy data for oscillometry to permit a z-score approach. The published cut-offs (ΔRrs_5 [?]-40%, ΔXrs_5 [?]50% or ΔAX [?]-80%) were developed from data from healthy children[1] and reports are emerging that these values may be too stringent for the adult population.[24,42]Using a z-score change that incorporates the variability of the reference data set may be a suitable way to address this limitation, however reference values for oscillometry are currently limited and, in part, device specific. There is currently no recommendation for cut-offs for the intrabreath oscillometry measures. Nevertheless, whilst the published cut-offs may be problematic, the weak correlation observed between ΔFEV_1% and oscillometry outcomes supports that the poor agreement is more likely reflective of the differences in airway physiology that these tests represent, rather the purely an issue of classification.

Ours is the first study to report within-breath changes with single-frequency oscillometry with $R10_{insp\text{-}exp}$ and $X10_{insp\text{-}exp}$ measures pre- and post-bronchodilator in preterm-born children. Our findings suggest these within-breath measures may be less useful than spirometry and conventional spectral oscillometry when assessing the bronchodilator response in this population. We observed no difference in the magnitude of the $R10_{insp\text{-}exp}$ and $X10_{insp\text{-}exp}$ response to a bronchodilator, rather changes were proportional across the breath cycle, and reflected global changes in resistance and reactance at 10 Hz. Recent studies have suggested that intra-breath oscillometry measures may be more useful in detecting wheeze[43] and predicting lower respiratory tract infections[44] in infants and young children than spectral oscillometry, and in adults with COPD.[45] We observed no differences in $X10_{insp\text{-}exp}$ measures between preterm and healthy participants at baseline, or in response to a bronchodilator, meaning that airway inhomogeneity is likely not the primary driver of airway obstruction in preterm-born individuals. Indeed, small studies measuring ventilation inhomogeneity using multiple breath washout report no differences between preterm and term-born infants.[46-48] Airway obstruction in preterm-born individuals may instead be more attributable to reduced compliance as suggested by our spectral oscillometry outcomes. As the literature around within-breath oscillometry is limited, there are no references for 'normal' measures and the physiology behind within-breath outcomes remains somewhat speculative. Further work is needed to explore the physiology of within-breath changes and its implications in individuals born preterm.

Consistent with previous findings we show that, whilst oscillometry is a more feasible test, being born 32 weeks gestation or less did not influence feasibility.[40] It should be noted that those with severe impairment were excluded at the time of recruitment, however our results show that for most survivors of preterm birth, similar test success rates should be expected for those born at term in the age range studied. It should be noted that these measurements were made during a research appointment, which is not subject to the same time constraints as a clinical service, however reviews of routine clinical testing reveal similar findings.[40] That oscillometry (intrabreath and spectral) is feasible in a preterm born population reinforces its value in both a research and clinical context.

Conclusions:

In the preterm population, oscillometry is a feasible and clinically useful supportive test for those unable to perform spirometry or where bronchial hyperresponsiveness is suspected in the presence of normal spirometry results. A bronchodilator response by spirometry and oscillometry reflects related but distinct physiological changes in the airways of those born preterm, and these tests should not be used interchangeably. Our observations that the response to a bronchodilator as measured by oscillometry and spirometry may reflect different aspects of airway physiology warrants further investigation to advance our understanding of preterm lung disease.

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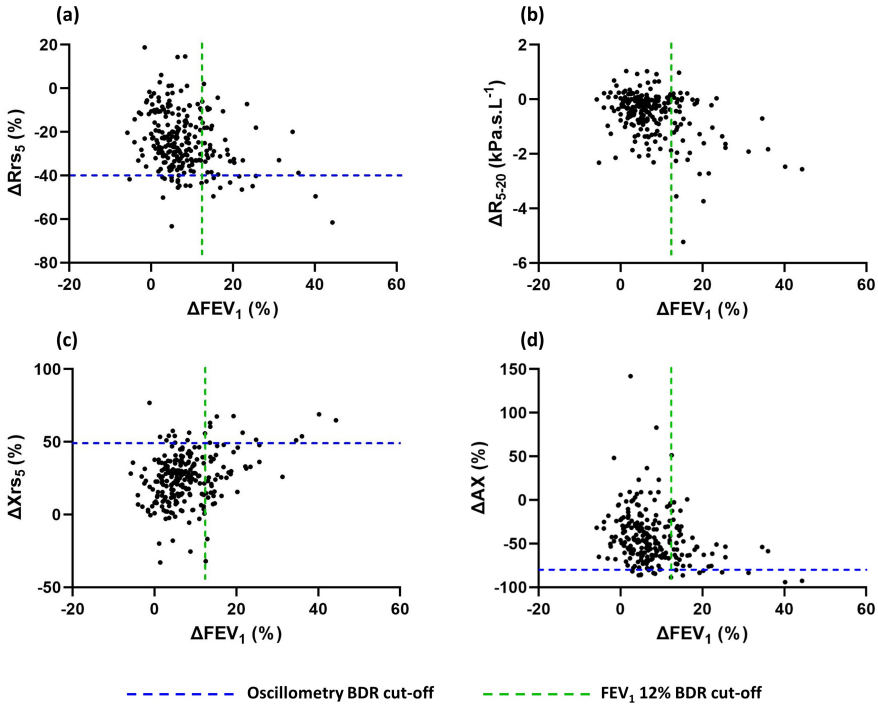

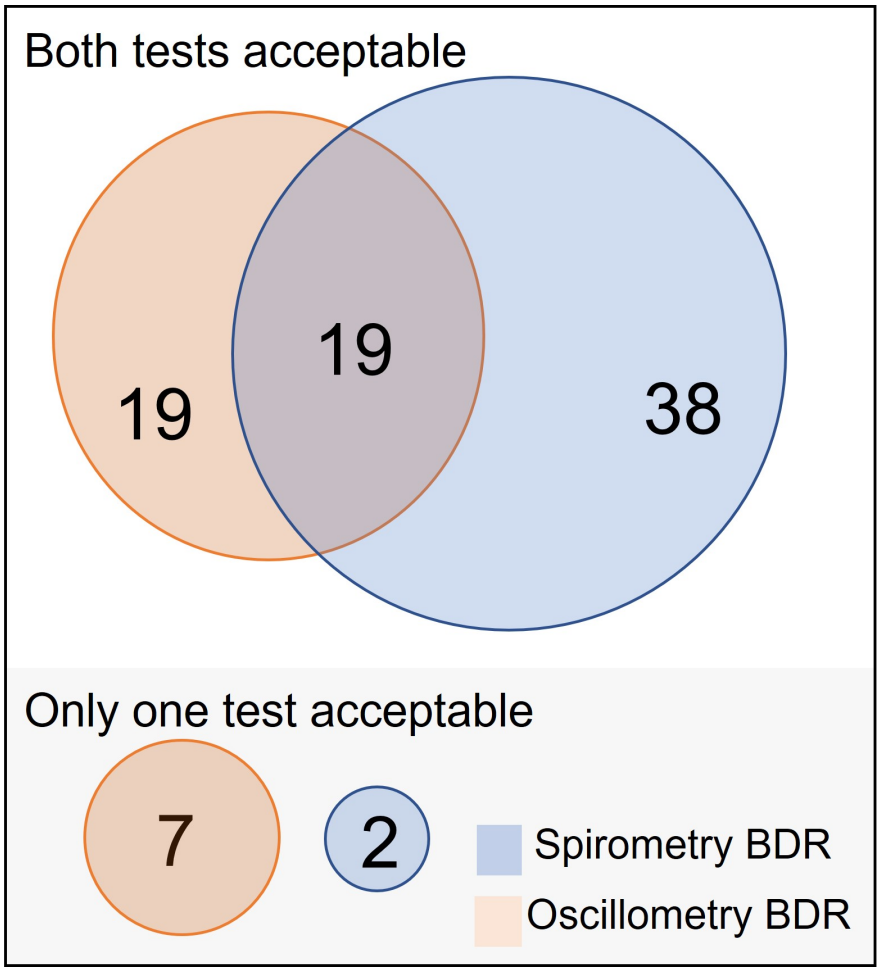

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