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The role of impulse oscillometry in the management of asthma when forced expiratory maneuvers are contraindicated: case series and literature review

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ABSTRACT

Objectives: The impulse oscillometry system (IOS) provides an alternative method of lung function testing for patients in whom forced expiratory manoeuvres are contraindicated, such as those with inherited vascular connective tissue disorders. Here we examine the role of IOS in the diagnosis and monitoring of asthma in such patients through a clinical case series and literature review.

Methods: The clinical case series comprised of data from 12 patients with inherited connective tissue disorders representing 32 clinical encounters. Of these, 11 encounters were for asthma diagnosis and 21 were for asthma monitoring. Symptoms, exhaled nitric oxide (FeNO) and IOS were assessed at each encounter.

Results: In the clinical case series, 5 of 6 patients with likely asthma (as determined by physician review and exhaled nitric oxide testing) had abnormal IOS parameters compared with 0 of 5 of those with unlikely asthma. In the monitoring group, 11 encounters resulted in treatment escalation (demonstrating suboptimal control), and 8 resulted in no change to treatment (good control). Six of 11 of those with suboptimal control had abnormalities in ≥ 3 IOS parameters, with R5 and R5-20 most frequently affected. Only 1 of 8 of those with good control had abnormalities in ≥ 3 IOS parameters.

Conclusions: IOS can be used as an alternative to conventional lung function testing to support the diagnosis and monitoring of asthma when forced expiratory manoeuvres are contraindicated. Larger studies are required to establish severity and treatment escalation thresholds and provide clearer comparisons with spirometry values.

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Introduction

Objective measures of pulmonary function hold prominent positions in guidelines for the diagnosis and treatment of respiratory disease (1). Such tests are valuable in the diagnosis and ongoing monitoring of many respiratory conditions, but problems arise when lung function testing is contra-indicated. Recommendations of when pulmonary function tests (PFTs) should be avoided have suffered from a lack of high quality data and consequently are based in large part on expert opinion (2). Moreover, until recently, alternative testing strategies for such patients have been lacking.

Reasons suggested to avoid forced manoeuvre PFTs have included conditions when maximal chest wall expansion or raised intrathoracic pressures might

exacerbate an existing condition, such as untreated pneumothoraces and recent surgical wounds (2). Co-existent cardiovascular conditions, particularly aortic aneurysms, have been highlighted as potentially more important contra-indications for forced expiratory manoeuvres (2), and it remains unclear whether forced expiratory manoeuvres are safe in patients at risk of vascular dissection owing to high risk inherited connective tissue disorders, such as Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome. Aortic aneurysm currently remains listed as a potential contra-indication to lung function testing in the American Association for Respiratory Care 1996 guidelines (3).

With at least 12% of the British population being diagnosed with asthma (4), the condition is a frequent

comorbidity in patients with inherited connective disorders. Indeed, evidence suggests that allergic conditions such as atopic asthma are over-represented in patients with the connective tissue disorder Loeys-Dietz syndrome because of the strong relationship between TGF β signaling and regulatory T cell function (5). Bronchial hyper-reactivity has also been reported to be over-represented in children with Marfan syndrome (6). Because patients with inherited connective tissue disorders are often treated prophylactically with beta-adrenergic blockade to reduce risk and slow progression of aortic dilatation (7), monitoring for asthma is of particular importance since such drugs can cause bronchospasm and risk reducing bronchodilator efficacy during severe asthma exacerbations.

The impulse oscillometry system (IOS) differs from spirometry by not relying on forced expiratory manoeuvres (8). It can be performed at tidal breathing and so offers an alternative approach when forced maneuver PFTs are contraindicated or when a patient cannot readily co-operate with complex procedures. Impulse oscillometry works by directing sound waves of multiple frequencies into the airways along a breathing tube. Higher frequency sounds (>20Hz) travel only short distances and so remain confined to the larger airways, while lower frequency sounds (<15Hz) reach down to the small airways and lung parenchyma. A pressure-flow transducer measures flow and pressure during tidal breathing, and allows respiratory impedance (Z_{rs} : the ratio of pressure to flow at each sound frequency) to be calculated. Z_{rs} represents a composite of respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}) (8).

The differential effect of airway size on the transmission of sound waves of differing frequencies enables the resistances of small airways to be distinguished from that of large airways. The resistance at 5 Hz (R_5) is taken to represent the total airway resistance, while the resistance at 20 Hz (R_{20}) gives the resistance of only the large airways. Consequently, the difference (R_5-R_{20}) gives the resistance due to small distal airways.

Reactance (X_{rs}) reflects the dampening effect on sound waves due to mass force of air moving into the lung (I, inertance) and the elastic recoil of lung tissue (C, capacitance). Together, these give a picture of how distensible the airways are. At lower frequencies, the capacitance component dominates and X_{rs} at 5 Hz (X_5) largely represents the ability of the lung to store elastic recoil in the small airways. By convention, increasing capacitance is designated negative values and increasing inertance has positive values. Hence conditions that reduce lung elasticity such as

pulmonary fibrosis and emphysema have increasingly negative capacitance values and therefore higher X_5 values. The resonant frequency (F_{res}) is the point at which inertance and capacitance are equal. This is increased in both obstructive and restrictive conditions. Reactance area (A_x) is the difference between X_5 and F_{res} and is related to respiratory compliance, reflecting small airways patency.

Owing to a lack of high-quality evidence, current asthma guidelines have neglected IOS. Similarly, few guidelines discuss alternatives to spirometry in the diagnosis and monitoring of patients who have both asthma and contraindications to forced expiratory manoeuvres. Here, we report the use of IOS in the diagnosis and monitoring of asthma in a small cohort of patients in whom spirometry is relatively contraindicated.

Materials and methods

Clinical setting

Our clinic works closely with the inherited cardiovascular conditions clinic and frequently receives requests to review patients likely to benefit from beta-adrenergic blockade. Beta-blockers are generally avoided in asthma due to the risk of acute bronchospasm, and hence their initiation and titration in patients with asthma requires close respiratory input.

Patient selection

All patients referred to one clinician at one large teaching hospital between January 2014 and December 2019 for asthma diagnosis or monitoring in whom forced expiratory maneuvers were contraindicated were retrospectively included in the study. Data were obtained from clinic letters and test results stored on the electronic patient record.

Clinical case series

Each time a patient was seen in clinic and IOS was undertaken was considered an 'encounter'. For each encounter, data regarding symptoms compatible with asthma, fraction of exhaled nitric oxide (FeNO) and IOS parameters (R_5 , R_{20} , R_5-R_{20} , X_5 , A_x , Z_5) were collected. A clinic visit and corresponding FeNO and IOS were considered part of the same encounter if they were requested by the clinician on the clinic letter for that visit, and were performed within 2 months of the clinic visit. Given that IOS was the focus of this study, clinic visits without corresponding

IOS data were excluded. Clinic visits without FeNO data were included. IOS was performed using the Vyntus® IOS system by Vyair Medical (9) and analyzed using the SentrySuite® software package (10).

Encounters were classified as to whether they were for asthma diagnosis, asthma monitoring or for consideration of the introduction of beta-adrenergic blockade in those with inherited aortopathies. All asthma monitoring encounters required patients to have a prior diagnosis of asthma or to have had a prior diagnostic encounter. To focus the data set on patients with asthma, all monitoring and beta-blocker decision encounters required participants to have a diagnosis of asthma.

The presence of symptoms, FeNO and IOS parameters were converted to binary data. For symptoms this was 'presence' or 'absence' of any symptom or group of symptoms that was felt by the treating physician to be indicative of poorly controlled asthma. For FeNO this was 'normal' or 'abnormal', with a normal value set at <25ppb (11). For each IOS parameter (R5, R20, X5, Z5, R5-20) this was 'normal' or 'abnormal' based upon the following cutoffs used by our respiratory physiology team (12). For R5, R20 and Z5 a score of $\geq 150\%$ predicted (Z score ≥ 1.645) was classified as abnormal (12). For reactance X5, the following equation was used: Predicted-X5 (Hz) $> 0.15 \text{ kPa.s.L}^{-1} = \text{abnormal}$ (12). For R5-20, small airways disease was considered present if $R5-20 > 0.07 \text{ kPa.s.L}^{-1}$ or 15% (13).

Outcomes were recorded for each encounter. For asthma diagnosis encounters, the outcomes were 'likely asthma' and 'unlikely asthma', based upon the clinician's impression in the clinic letter. For the asthma monitoring encounters, the outcomes were 'treatment escalation' or 'no change/reduction' based upon treatment changes recommended in the clinic letter, indicating suboptimal control or stability respectively. For the beta-blocker decision encounters, the outcomes were 'beta-blocker therapy permitted' and 'beta-blocker therapy not currently recommended', as documented in the clinic letter. A decision on beta-blockage was individualized, based on current asthma symptom control, airway physiological abnormalities, the history of exacerbations, and the cardiovascular risk.

Results

Twelve patients (4 males) were included in the study (mean age 46; range 30–69), representing 32 encounters in total. Of these, 11 encounters were for asthma diagnosis purposes and 21 were for asthma

monitoring. Amongst the monitoring encounters, 15 were for consideration of beta-blocker therapy, of which 12 were for patients with a known diagnosis of asthma.

Table 1 summarizes the reasons forced expiratory maneuvers were not recommended in these patients.

Asthma diagnosis: Of the 11 patients reviewed for diagnostic purposes, 6 were diagnosed with likely asthma and 5 with unlikely asthma (Table 2). Five out of 6 patients with 'likely asthma' had abnormalities in at least 1 IOS parameter, with 4 patients having abnormalities in 3 or more parameters, with Z5, R5 and R5-20 most frequently affected. None of the 5 patients with 'unlikely asthma' had abnormalities in any IOS parameter. Two of the six 'likely asthma' patients had abnormal FeNO readings compared with none of the 'unlikely asthma' patients. Half of the 'likely asthma' patients had symptoms compared with 2 of 6 of the 'unlikely asthma' patients.

Asthma control: Nineteen encounters were for asthma monitoring purposes. Eleven encounters resulted in treatment escalation, indicating suboptimal control, and 8 encounters resulted in no change or a reduction in treatment, indicating stable asthma. Of those with suboptimal control, 6 out of 11 had abnormalities in at least 3 IOS parameters, with Z5 and R5-20 most frequently affected (Table 3). 6 patients had elevated FeNO and 8 patients reported symptoms of asthma. Of those with stable asthma, 1 of 8 had at least 3 abnormal IOS parameters. R20 was the most frequently abnormal IOS parameter in this group. No patients had abnormal FeNO and only 1 reported symptoms of asthma.

Table 1. Reasons why forced expiratory manoeuvres were not recommended in the patient group.

Reason for relative contraindication to forced expiratory manoeuvres -	
Connective tissue diagnosis	Count
Loeys Dietz Syndrome	4
Vascular Ehlers Danlos Syndrome	3
Marfan Syndrome	1
Cutis Laxa	1
No specific syndromic connective tissue disease identified	
• Multiple aneurysms (abdominal, head and neck)	1
• Thoracic aortic aneurysm	1
• Aortic root dilatation	1
Reason for relative contraindication to forced expiratory manoeuvres -	
Anatomical diagnosis	Count
Aortic root abnormalities	4
Carotid dissection	1
Aneurysms at multiple sites	2
Strong family history of aneurysm	3
None of the above (identified connective tissue disorder by family tracing)	2

Table 2. Abnormalities seen in symptoms, FeNO and IOS parameters in those diagnosed with 'Likely Asthma' and 'Unlikely Asthma'.

		Likely asthma (n = 6)	Unlikely asthma (n = 5)
Number of abnormal IOS parameters	0	1	5
	1	1	0
	2	0	0
	3	1	0
	4	3	0
Specific abnormal IOS parameters	5	0	0
	R5	4	0
	Z5	4	0
	R5-20*	4	0
	R20	2	0
Elevated FeNO	X5	2	0
	Y	2	0
	N	4	5
Symptoms of asthma	N/A	0	0
	Y	3	2
	N	3	5

*R5-20 > 15%, indicating increased distal airways resistance.

Table 3. Abnormalities seen in symptoms, FeNO and IOS parameters in those with suboptimal and stable asthma control.

		Suboptimal control (n = 11)	Stable asthma (n = 8)
Number of abnormal IOS parameters	0	1	1
	1	2	3
	2	2	3
	3	5	1
	4	1	0
Specific abnormal IOS parameters	5	0	0
	R5	4	1
	Z5	7	3
	R5-20*	7	2
	R20	3	3
Elevated FeNO	X5	4	0
	Y	6	0
	N	3	4
Symptoms of asthma	N/A	2	4
	Y	8	1
	N	3	7

*R5-20 > 15%, indicating increased distal airways resistance.

Beta-blocker therapy: Twelve encounters were to determine if asthma was sufficient to permit initiation of beta-blockade for their co-existent inherited cardiovascular disease. Of these, 4 were not recommended to start beta-blockers presently and 8 were permitted based on of judgment of risk vs benefit (Table 4). All 4 encounters where beta-blockers were not recommended had abnormalities in at least 1 IOS parameter and 1 patient had abnormalities in 3 or more parameters. Interestingly, R5-20 was abnormal for all 4 encounters. Patients were symptomatic at 2 of the 4 encounters and had abnormal FeNO at 2 encounters. From the 8 encounters where control was deemed sufficiently stable to commence beta-blockers cautiously. 6 of 8 had abnormalities in at least 1 IOS

Table 4. Abnormalities seen in symptoms, FeNO and IOS parameters in those where beta-blocker decisions were made.

		Beta-blocker advised against (n = 4)	Beta-blocker permitted (n = 8)
Number of abnormal IOS parameters	0	0	1
	1	2	3
	2	1	3
	3	1	1
	4	0	0
Specific abnormal IOS parameters	5	0	0
	R5	2	3
	Z5	2	4
	R5-20*	4	3
	R20	1	3
Elevated FeNO	X5	0	1
	Y	2	1
	N	1	6
Symptoms of asthma	N/A	1	2
	Y	2	2
	N	2	6

*R5-20 > 15%, indicating increased distal airways resistance.

parameter and 1 had abnormalities in 3 or more parameters; with Z5 most frequently affected (4/6). Patients were symptomatic at 2 of 8 encounters and had abnormal FeNO at 1 encounter.

Discussion

In our case series of 32 diagnostic and monitoring encounters, we observed differences in individual IOS parameters and overall IOS results between patients with unlikely asthma, well-controlled asthma and sub-optimally controlled asthma in whom classical PFTs were relatively contraindicated.

From 11 diagnostic encounters, 5 of 6 of the likely asthma cases had abnormal IOS results, with almost all of these having three or more abnormal parameters. No patients with unlikely asthma had abnormalities in their IOS results, even when they had symptoms suggestive of asthma.

Two previous studies using IOS to help diagnose asthma and quantify the severity of airways obstruction have found differences in total (R5), large (R20) and small (R5-20) airways resistance between healthy individuals and those with severe asthma (14,15). In both studies, there were no significant differences in IOS parameters between those with mild asthma and healthy controls. This is comparable with spirometry, the current gold standard and most widely used method for assessing airways obstruction, which is often normal in patients with well-controlled asthma who are not symptomatic at the time of testing (16). Indeed, spirometry has a sensitivity value in the region of 23–29%, a specificity value of 90%, a Positive

Predictive Value (PPV) of 22–77% and a Negative Predictive Value (NPV) of 53–91% for the diagnosis of asthma, showing that spirometry forms only a part of the diagnostic work up for asthma and that other clinical factors must be taken into account when diagnosing the syndrome of asthma (17).

The most consistently abnormal IOS parameter in asthma in our case series and previous work is R5-20. This represents resistance in the small airways, the main site of airways obstruction in asthma, (18) giving validity to the findings. R5-20 has been shown to correlate well with FEF 25–75. FEF25–75 has been shown to predict severe asthma in adults independent from FEV1 (19) and is also a predictor of severe asthma in children in the setting of a normal FEV1 (20).

From our small sample of patients and in line with published work, IOS appears to perform comparably and play a similar role to spirometry as part of the asthma diagnostic work up.

In our case series, abnormalities in more than three IOS parameters occurred more frequently in those with suboptimal asthma control compared to those with stable asthma. Where asthma control was assessed for stability to introduce beta-blockade, IOS abnormalities were equally well represented in both groups, reflecting the complexity of the risk benefit calculation in this high cardiovascular risk group.

In a large study of 442 patients with asthma, R5 and R5-20 were found to be equally predictive of worse asthma control in the past year as spirometry measures FEV1 and FEF 25–75 (21). In another study, 30 patients with newly diagnosed mild-moderate asthma, IOS readings were taken at diagnosis, and then at 1 and 3 months after the initiation of inhaled corticosteroids therapy (22). A statistically significant improvement was seen in all IOS parameters tested (R5, R20 and X5) at 1 and 3 months of treatment. The IOS changes were considered equally sensitive as spirometry (FEV1, FVC and MMEF 25-75) in detecting short and longer-term treatment response in patients with asthma (21).

Our case series data fits with published work, where R5 and R5-20 were seen to be markers of poor control, and to show improvement with treatment initiation and escalation. However, both our data and previous studies have found that IOS abnormalities are not restricted to individual parameters and tend to be more widespread in poorly controlled disease, with improvements across multiple parameters occurring with treatment optimization (21). Changes in R5 and R5-20 were shown to correlate with FEV1

and FEF25-75, which are currently used to guide treatment escalation thresholds in current guidelines (1).

From this small set of data and previous studies, it appears that IOS parameters are more widely deranged in suboptimally controlled asthma compared with stable disease, and that R5-20 may be the most sensitive marker of loss of control. IOS parameters show intra-individual variation over time and hence can be used to monitor treatment response. Our study suggests that in combination with clinical history and FeNO, IOS plays a useful role in the asthma assessment process.

Limitations

Given that contraindications to forced expiratory maneuvers are relatively rare, our case series is limited by the small number of patients included, the retrospective nature of the study and the fact that all patients were assessed by one clinician. We do not have data on exacerbation frequency, bronchodilator reversibility or standardized asthma severity scores for each patient, which would have strengthened our findings.

We do not routinely use IOS to determine bronchial reactivity (BHR) or bronchodilator reversibility (BDR). Short et al (23) proposed a diagnostic criterion for clinically significant BHR in response to provocation testing of 40% increase in R5. However, the European Respiratory Society guideline on bronchial provocation testing states that there is substantially less supporting research and standardization than for spirometry in the use of bronchial provocation testing and that additional studies are required (24). The use of the bronchodilator response as determined by a decrease in R5 has also been proposed as a diagnostic tool for asthma. Galant et al (25) points out that there is great variability in defining a clinically relevant BDR as expressed by IOS ranging from 8.6% (26) to more than 40% (27). The authors propose a definition of BDR as determined by IOS to be greater than the 95% confidence interval response for R5 in healthy children and adults. They pool data from six pediatric and one adult study and propose a value of –40% in Δ R5. However, it is pointed out that this value may not be appropriate for distinguishing between asthmatic and non-asthmatic subjects. Interestingly, these studies find R5 to be the parameter of most value, whereas we find R5-R20 to be the most consistently abnormal in those with a diagnosis of likely asthma.

Further studies are needed to ascertain whether the use of BDR or BHR by IOS is more useful in our patient cohort than spontaneously-acquired IOS parameters, and if so, which IOS parameters are key.

In addition, IOS and clinic visits did not occur on the same date, so it is possible that symptoms may have changed from when IOS was performed and when the patient was seen in clinic, prompting a different conclusion by the clinician. Finally, in our data analysis we examined the number of different abnormal IOS parameters, but not the extent of the abnormality in individual parameters which could have led to over or underestimation of the IOS abnormalities.

Studies involving a greater number of patients are required to determine and validate asthma severity and treatment escalation thresholds in IOS parameters, as we currently have with spirometry. Furthermore, prospectively performing IOS and spirometry in individuals with asthma who can perform both techniques would be useful to compare parameters for their equivalence and test characteristics.

Conclusions

In summary, we found IOS to be a useful technique in asthma diagnosis and treatment monitoring in individuals where forced expiratory manoeuvres are contraindicated. A normal IOS profile makes the diagnosis of asthma unlikely, and an increasing number of abnormal IOS parameters indicates suboptimal airways control. IOS forms a part of the diagnostic and monitoring work-up of asthma when considered in the context of the patient's symptoms, FeNO and other clinical features. Our findings relate to real-world practice in a specialist clinic and support the findings from prospective studies.

Prospective studies are now needed to hone the use of impulse oscillometry in this clinical setting, and in particular to help improve the prediction of asthma exacerbation in this group of patients at high cardiovascular risk and thereby improve the risk-benefit assessment when considering commencing beta-blockade.

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Declarations of interest

None.

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References

1. British Thoracic Society. BTS/SIGN guideline on the management of asthma 2019. [Available from: <https://www.brit-thoracic.org.uk/quality-improvement/guidelines/asthma/>.]
2. Cooper BG. An update on contraindications for lung function testing. *Thorax*. 2011;66(8):714–723. doi:10.1136/thx.2010.139881.
3. AARC. Contraindications to use of spirometry. AARC clinical practice guidelines. *Respiratory Care*. 1996;41:629–636.
4. WHO. Asthma 2008. Available from: <https://www.who.int/respiratory/asthma/en/>.
5. Frischmeyer-Guerrero PA, Guerrero AL, Oswald G, Chichester K, Myers L, Halushka MK, Oliva-Hemker M, Wood RA, Dietz HC. TGF β receptor mutations impose a strong predisposition for human allergic disease. *Sci Transl Med*. 2013;5(195):195ra94. doi:10.1126/scitranslmed.3006448.
6. König P, Boxer R, Morrison J, Pletcher B. Bronchial hyperreactivity in children with Marfan syndrome. *Pediatr Pulmonol*. 1991;11(1):29–36. doi:10.1002/ppul.1950110106.
7. Cochrane Review. Beta blocker treatment in Marfan syndrome 2017. Available from: https://www.cochrane.org/CD011103/VASC_beta-blocker-treatment-marfan-syndrome.
8. Brashier B, Salvi S. Measuring lung function using sound waves: role of the forced oscillation technique and impulse oscillometry system. *Breathe (Sheff)*. 2015;11(1):57–65. doi:10.1183/20734735.020514.
9. Medical V. IOS Impulse Oscillometry 2020. Available from: <https://intl.vyaire.com/products/ios-impulse-oscillometry>.
10. Medical V. SentrySuite Software Solution 2020. Available from: <https://intl.vyaire.com/products/sentrysuite-software-solution>.
11. NIOX. Interpreting FeNO 2020. Available from: <https://www.niox.com/en-gb/feno-asthma/interpreting-feno/>.
12. Vogel J, Smidt U. Impulse oscillometry. Analysis of lung mechanics in general practice and clinic, epidemiological and experimental research. Frankfurt: PMI-Verlagsgruppe; 1994.
13. Crim C, Celli B, Edwards LD, Wouters E, Coxson HO, Tal-Singer R, Calverley PMA, ECLIPSE investigators. Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results. *Respir Med*. 2011;105(7):1069–1078. doi:10.1016/j.rmed.2011.01.010.
14. Gonem S, Natarajan S, Desai D, Corkill S, Singapuri A, Bradding P, Gustafsson P, Costanza R, Kajekar R, Parmar H, et al. Clinical significance of small airway obstruction markers in patients with asthma. *Clin Exp Allergy*. 2014;44(4):499–507. doi:10.1111/cea.12257.

15. Williamson PA, Clearie K, Menzies D, Vaidyanathan S, Lipworth BJ. Assessment of small-airways disease using alveolar nitric oxide and impulse oscillometry in asthma and COPD. *Lung*. 2011;189(2):121–129. doi:[10.1007/s00408-010-9275-y](https://doi.org/10.1007/s00408-010-9275-y).
16. McCormack MC, Enright PL. Making the diagnosis of asthma. *Respir Care*. 2008;53(5):583–590. discussion 90–2.
17. Schneider A, Gindner L, Tilemann L, Schermer T, Dinant G-J, Meyer FJ, Szecsenyi J. Diagnostic accuracy of spirometry in primary care. *BMC Pulm Med*. 2009;9(1):31. doi:[10.1186/1471-2466-9-31](https://doi.org/10.1186/1471-2466-9-31).
18. Yanai M, Sekizawa K, Ohru T, Sasaki H, Takishima T. Site of airway obstruction in pulmonary disease: direct measurement of intrabronchial pressure. *J Appl Physiol* (1985). 1992;72(3):1016–1023. doi:[10.1152/jap-pl.1992.72.3.1016](https://doi.org/10.1152/jap-pl.1992.72.3.1016).
19. Riley CM, Wenzel SE, Castro M, Erzurum SC, Chung KF, Fitzpatrick AM, Gaston B, Israel E, Moore WC, Bleecker ER, et al. Clinical implications of having reduced mid forced expiratory flow rates (FEF25–75), independently of FEV1, in adult patients with asthma. *PLoS One*. 2015;10(12):e0145476. doi:[10.1371/journal.pone.0145476](https://doi.org/10.1371/journal.pone.0145476).
20. Rao DR, Gaffin JM, Baxi SN, Sheehan WJ, Hoffman EB, Phipatanakul W. The utility of forced expiratory flow between 25% and 75% of vital capacity in predicting childhood asthma morbidity and severity. *J Asthma*. 2012;49(6):586–592. doi:[10.3109/02770903.2012.690481](https://doi.org/10.3109/02770903.2012.690481).
21. Manoharan A, Anderson WJ, Lipworth J, Lipworth BJ. Assessment of spirometry and impulse oscillometry in relation to asthma control. *Lung*. 2015;193(1):47–51. doi:[10.1007/s00408-014-9674-6](https://doi.org/10.1007/s00408-014-9674-6).
22. Yamaguchi M, Niimi A, Ueda T, Takemura M, Matsuoka H, Jinnai M, Otsuka K, Oguma T, Takeda T, Ito I, et al. Effect of inhaled corticosteroids on small airways in asthma: investigation using impulse oscillometry. *Pulm Pharmacol Ther*. 2009;22(4):326–332. doi:[10.1016/j.pupt.2009.01.005](https://doi.org/10.1016/j.pupt.2009.01.005).
23. Short PM, Anderson WJ, Manoharan A, Lipworth BJ. Usefulness of impulse oscillometry for the assessment of airway hyperresponsiveness in mild-to-moderate adult asthma. *Ann Allergy Asthma Immunol*. 2015;115(1):17–20. doi:[10.1016/j.anai.2015.04.022](https://doi.org/10.1016/j.anai.2015.04.022).
24. Coates AL, Wanger J, Cockcroft D, Culver BH, Bronchoprovocation Testing Task Force: Kai-Håkon Carlsen, Diamant Z, Gauvreau G, Hall GL, Hallstrand TS, Horvath I, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J*. 2017;49:1601526.
25. Galant SP, Komarow HD, Shin H-W, Siddiqui S, Lipworth BJ. The case for impulse oscillometry in the management of asthma in children and adults. *Ann Allergy Asthma Immunol*. 2017; 118(6):664–671. doi:[10.1016/j.anai.2017.04.009](https://doi.org/10.1016/j.anai.2017.04.009).
26. Komarow HD, Skinner J, Young M, Gaskins D, Nelson C, Gergen PJ, Metcalfe DD. A study of the use of impulse oscillometry in the evaluation of children with asthma: analysis of lung parameters, order effect, and utility compared with spirometry. *Pediatr Pulmonol*. 2012; 47(1):18–26. doi:[10.1002/ppul.21507](https://doi.org/10.1002/ppul.21507).
27. Oostveen E, Boda K, van der Grinten CPM, James AL, Young S, Nieland H, Hantos Z. Respiratory impedance in healthy subjects: baseline values and bronchodilator response. *Eur Respir J*. 2013; 42(6):1513–1523. doi:[10.1183/09031936.00126212](https://doi.org/10.1183/09031936.00126212).