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Asthma Outcomes: Pulmonary Physiology

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Abstract

Background—Outcomes of pulmonary physiology have a central place in asthma clinical research.

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Objective—At the request of National Institutes of Health (NIH) institutes and other federal agencies, an expert group was convened to provide recommendations on the use of pulmonary function measures as asthma outcomes that should be assessed in a standardized fashion in future asthma clinical trials and studies to allow for cross-study comparisons.

Methods—Our subcommittee conducted a comprehensive search of PubMed to identify studies that focused on the validation of various airway response tests used in asthma clinical research. The subcommittee classified the instruments as core (to be required in future studies), supplemental (to be used according to study aims and in a standardized fashion), or emerging (requiring validation and standardization). This work was discussed at an NIH-organized workshop in March 2010 and finalized in September 2011.

Results—A list of pulmonary physiology outcomes that applies to both adults and children older than 6 years was created. These outcomes were then categorized into core, supplemental, and emerging. Spirometric outcomes (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], and FEV₁/FVC) are proposed as core outcomes for study population characterization, for observational studies, and for prospective clinical trials. Bronchodilator reversibility and pre- and post-bronchodilator FEV₁ also are core outcomes for study population characterization and observational studies.

Conclusions—The subcommittee considers pulmonary physiology outcomes of central importance in asthma and proposes spirometric outcomes as core outcomes for all future NIH-initiated asthma clinical research.

Keywords

Spirometry; airway responsiveness; peak expiratory flow monitoring; lung volumes; gas exchange

INTRODUCTION

Asthma clinical research lacks adequate outcomes standardization. As a result, our ability to examine and compare outcomes across clinical trials and clinical studies, interpret evaluations of new and available therapeutic modalities for this disease at a scale larger than single trial, and pool data for observational studies (eg, genetics, genomics, pharmacoeconomics) is impaired.³ Several National Institutes of Health (NIH) institutes that support asthma research (the National Heart, Lung, and Blood Institute; National Institute of Allergy and Infectious Diseases; National Institute of Environmental Health Sciences; and the Eunice Kennedy Shriver National Institute of Child Health and Human Development), as well as the Agency for Healthcare Research and Quality, have agreed to an effort for outcomes standardization. This effort aims at (1) establishing standard definitions and data collection methodologies for validated outcome measures in asthma clinical research with the goal of enabling comparisons across asthma research studies and clinical trials and (2) identifying promising outcome measures for asthma clinical research that require further development. In the context of this effort, 7 expert subcommittees were established to propose and define outcomes under 3 categories—core, supplemental, and emerging:

- *Core outcomes* are identified as a selective set of asthma outcomes to be considered by participating NIH institutes and other federal agencies as requirements for

institute/agency-initiated funding of clinical trials and large observational studies in asthma.

- *Supplemental outcomes* are asthma outcomes for which standard definitions can or have been developed, methods for measurement can be specified, and validity has been proven, but whose inclusion in funded clinical asthma research will be optional.
- *Emerging outcomes* are asthma outcomes that have the potential to (1) expand and/or improve current aspects of disease monitoring and (2) improve translation of basic and animal model-based asthma research into clinical research. Emerging outcomes may be new or may have been previously used in asthma clinical research, but they are not yet standardized and require further development and validation.

Each subcommittee used the recently published *American Thoracic Society (ATS)/European Respiratory Society (ERS) Statement: Asthma Control and Exacerbations—Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice*⁴ (hereafter referred to as the *ATS/ERS Statement*) as a starting point and updated, expanded, or modified its recommendations as the subcommittee deemed appropriate. Each subcommittee produced a report that was discussed, modified, and adopted by the Asthma Outcomes Workshop that took place in Bethesda, Md, on March 15 and 16, 2010. The reports were revised accordingly and finalized in September 2011. The Pulmonary Physiology Subcommittee prepared and presented to the workshop its recommendations in regard to pulmonary physiology outcomes as they pertain to asthma. These recommendations, as adopted by the workshop, are presented in this article.

Asthma is a disease characterized by repeated episodes of airway obstruction. Therefore, physiologic assessment of acute and chronic changes in lung function is critical for phenotyping patients with asthma and evaluating the efficacy of therapeutic interventions. Multiple lung function tests are available for the assessment of patients with asthma; however, relatively few methodologies have been adequately standardized, have been tested adequately for variability and sensitivity, and have sufficient normative data from healthy individuals. Therefore, few tests can be recommended as core measures for all clinical research studies. Future research should focus upon supplemental and emerging methodologies that may provide improved phenotyping of airway disease and assessment of therapeutic efficacy, particularly for young children.

SPIROMETRY

Summary

- Spirometry is a highly standardized test that can be performed reproducibly in both children and adults.
- Spirometry is a useful measure of severity of airflow limitation in asthma and is predictive of clinical outcomes.

- Normal values for spirometry are well established for healthy populations in the United States.

Definition and Methodology for Measurement

Spirometry measures maximal expiratory flow and exhaled volume during a forced expiratory vital capacity maneuver. The test is widely available and is highly standardized in terms of performance, methodology, and equipment specifications.⁵ Although many measures can be derived from the spirogram, the primary outcome measures are forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and their ratio, FEV_1/FVC . Peak expiratory flow (PEF) and forced mid-expiratory flow (FEF_{25-75}) also are derived from the spirogram, but are of secondary importance. The spirogram also may be displayed as a flow volume loop from which instantaneous and expiratory flows may be recorded at specified lung volumes. Although obstructive changes may occur in the small airways of patients with asthma as reflected by slowing in the terminal portion of the expiratory flow volume curve (eg, expiratory flow between 25% and 75% of the FVC), the FEF_{25-75} is not a specific measure of small airway obstruction. In addition, this measure is highly variable (effort dependent) and depends on FVC, which can increase with expiratory time or post-bronchodilator in patients with obstructive disease such as asthma.

For special purposes, partial forced expiratory flow-volume curves from end-tidal inspiration may be plotted for comparison against flow-volume curves from total lung capacity (TLC) to determine whether a full inspiration causes bronchodilation or bronchoconstriction. Flow-volume curves also may be generated with gases different than room air with respect to density or viscosity (eg, helium) to determine whether the flow regime at the site of flow limitation is turbulent or laminar.

Spirometry is usually performed in a clinic or laboratory setting with equipment that meets the ATS/ERS guidelines⁵ under the supervision of a qualified technician. In some circumstances, spirometry may be performed without supervision, in field or home settings, using portable handheld devices.

Medical and Scientific Value

Because airflow limitation caused by bronchoconstriction and airway inflammation is the hallmark of the pathology underlying asthma symptoms, spirometry is a fundamental test for characterizing asthma severity, asthma control, and response to treatment. Spirometry by itself is not useful in establishing the diagnosis of asthma, because airflow limitation may be mild or absent in some persons with asthma, particularly children. Variability of airflow limitation over time, the association with symptoms, and the response to treatment can be considered defining characteristics of asthma in the appropriate clinical setting.⁶ Variability of the inspiratory portion of the flow-volume loop may be helpful in suggesting a diagnosis of vocal cord dysfunction, which can mimic asthma, but this variability does not, by itself, either rule in or rule out a diagnosis of asthma. With the existing handheld devices for home spirometry, closer monitoring of lung function can be achieved. However, it is not known whether daily FEV_1 monitoring offers an advantage in allowing for better characterization or management of asthma, compared with PEF.

Range of Values

The recommended reference ranges for FEV₁ and FVC based on height, age, sex, and race/ethnicity (white, black, and Mexican-Hispanic) for the US population aged 8 to 80 years were derived from the third National Health and Nutrition Examination Survey (NHANES-3), conducted from 1988 to 1994.⁷ There are less well-established normal ranges for other racial and ethnic groups and individuals at the extremes of age and height.^{8–13}

Repeatability

Spirometry measures are highly repeatable within a single testing session, with 90% of adults able to reproduce FEV₁ within 120 mL (milliliters) and FVC within 150 mL.¹⁴ About 75% of children can attain similar levels of within-session repeatability.¹⁵ Between-session variability is less than 200 mL in 95% of sessions in normal individuals and is less than 225 mL in 90% of sessions in patients with chronic obstructive pulmonary disease (COPD).¹⁶ Intersession variability in patients with asthma has not been as well established but likely depends on control of the disease as well as other sources of measurement variability. Due to diurnal variability in lung function, it is recommended that serial measurements be done around the same time each day, to the extent possible. In addition, depending on the goals of the study, bronchodilators should be withheld prior to scheduled testing (eg, inhaled long-acting β -agonist [LABA] and anticholinergic medications for 12–24 hours, inhaled short-acting anticholinergic medications for 6 hours, and inhaled short-acting β -agonists [SABAs] for 4–6 hours). The decision of whether to withhold asthma drugs prior to spirometry depends on the research hypothesis being tested and on safety considerations.

Responsiveness

Response of spirometry outcomes to bronchodilators is very rapid for some agents and can occur within minutes. Response to environmental or anti-inflammatory strategies may take weeks to months. Both FEV₁ and FVC improve in response to asthma treatment because there is not only an increase in airway caliber but also a reduction in the residual volume (RV). For this reason, the FEV₁/FVC ratio may show little or no change despite effective treatment. The minimal clinically important difference (MCID) in FEV₁ has not been rigorously established for asthma, but it is likely that changes of 100–200 mL in FEV₁ are clinically important.^{17, 18}

Validity

Reduced spirometry outcomes are associated with severity of asthma symptoms, reduced quality of life, exacerbation frequency, likelihood of hospitalization, and likelihood of respiratory failure.^{19–21} However, individual patients, particularly children, may have normal spirometry, despite frequent or severe symptoms. Moreover, some asthma therapies such as anti-IgE may result in little improvement in spirometry but still reduce frequency and severity of exacerbations.

Associations

In adults, decreased baseline (pre-bronchodilator) percent predicted FEV₁ is associated with asthma severity and the symptom of shortness of breath. The association of markers of

inflammation with spirometric measures is variable and complex.²² In children, decreased baseline (pre-bronchodilator) percent predicted FEV₁ also is associated with asthma severity; however, the correlation between FEV₁ and markers of inflammation such as the fractional exhaled nitric oxide (FeNO) and symptoms is poor.²³

Practicality and Risk

Spirometry is a safe, widely available, low-risk procedure that can be performed repeatedly by adults and children above age 5. The test is effort dependent; therefore, optimum performance requires attention to details such as calibration, coaching, and assessment of maneuver quality. Where spirometry is the primary outcome of a clinical study, central review and feedback can maintain high-quality, reproducible testing.²⁴

Demographic Considerations

Reference values for adults are based on height, age, sex, and race/ethnicity. Reference values for children are based on sex and height, although models including children as young as 4 years of age have been proposed.¹⁰ Therefore, accurate measurements of height are important for establishing correct reference values.

Priority for NIH-Initiated Clinical Research

FEV₁, FVC, and FEV₁/FVC are considered core pulmonary physiology outcomes for describing a population with asthma, assessing response to treatment in clinical trials, and characterizing populations in epidemiologic and genetic studies. This is in agreement with the *ATS/ERS Statement*, which characterizes spirometry as 1 of the fundamental measures of asthma control.⁴ Handheld, self-administered spirometry is considered an emerging outcome; more information regarding its usefulness and its advantages over PEF is needed. Even if spirometry is proposed as a core outcome, retrospective population studies or database analyses such as those involving patients encountered in clinical practice, emergency departments, or hospitals or accessed by pharmacy, insurance, or medical records may still be of value in the absence of spirometry.

Future Directions or Research Questions

Further research is needed to determine the MCID in spirometry in patients with asthma.

PRE- AND POST-BRONCHODILATOR SPIROMETRY (BRONCHODILATOR REVERSIBILITY)

Summary

- Bronchodilator reversibility is a measure of the magnitude of airway smooth muscle relaxation.
- Bronchodilator reversibility is diminished in patients with well-controlled asthma as well as those with predominant inflammatory narrowing or remodeling of the airways, so it is not a good measure of asthma severity or response to therapy.

- The recommended method for measurement of bronchodilator reversibility is 4 inhalations of albuterol followed by spirometry in 15 minutes.

Definition and Methodology for Measurement

Bronchodilator reversibility testing is undertaken when a clinician or researcher wishes to determine whether a patient shows evidence of reversible airflow limitation. Baseline spirometry is performed after bronchodilator medications are withheld for an appropriate period and again after administration of bronchodilator test agents (10–15 minutes after SABAs, 30 minutes after short-acting anticholinergic agents⁵). Change in FEV₁ is the most common parameter followed, although change in FVC also can be useful. Other measurements obtained via spirometry could be chosen as endpoints, but their value is less established; eg, FEV₁/FVC or FEF_{25–75}.

Various bronchodilator administration protocols have been devised. One standard procedure involves the administration of 4 separate doses (90–100 µg [micrograms]) of albuterol/salbutamol (total dose 360–400 µg) delivered from a valved spacer device at 30-second intervals.⁵ For the anticholinergic agent ipratropium bromide, the total dose is 4–8 inhalations from a metered dose inhaler.⁵ Both the amount and type of agent used for bronchodilator reversibility testing can be altered, depending on specific circumstances. Lower doses of bronchodilator can be administered if medication side effects are a concern. In addition, maximum bronchodilator reversibility testing can be performed by increasing the total dose of albuterol to a maximum of 8 puffs (720–800 µg^{25, 26}) or until a plateau in FEV₁ is reached.²⁷ Another approach is to use a combination of albuterol and ipratropium bromide.²⁸ The test is usually performed in a clinic or laboratory setting with equipment that meets the ATS/ERS guidelines⁵ and with the supervision of a qualified technician who is certified to administer these agents.

The preferred method is the administration of 4 separate puffs (90 µg/puff) of albuterol using a spacer device at 30-second intervals, followed by spirometry after 15 minutes.

The most acceptable definition of “significant” bronchodilator response is that of the ATS/ERS guidelines for interpretation of spirometry and consists of an improvement in FEV₁ greater than 12% and 200 mL.⁸ Increments of less than 8% (or less than 150 mL) are likely to be within measurement variability.^{8, 29, 30} Other criteria that have been used to define “significant” bronchodilation include a 9% or 10% increase in percent predicted FEV₁^{28, 31} or a 15% change from baseline (without regard to the absolute change).^{8, 28}

Medical and Scientific Value

Bronchodilator reversibility testing is potentially useful for establishing the diagnosis of asthma, because airflow obstruction that is at least partially reversible is characteristic, although not highly specific, of asthma.⁶ In addition, such testing is helpful in assessing the clinical effect of subsequent bronchodilator treatment, although lack of an acute response does not always correlate with clinical efficacy.³⁰ Spirometry after the administration of a bronchodilator has been used to monitor changes in lung function over time.³² Maximum bronchodilator reversibility testing with a combination of a SABA and short-acting anticholinergic agent has been used to estimate the proportion of a patient population with at

least partially reversible airflow limitation,^{28, 33} whereas maximum bronchodilator reversibility testing with albuterol has been used to estimate the “best” lung function obtainable by patients with asthma of different severities.²²

Range of Values

The response to a bronchodilator is a continuous, not a dichotomous, variable; therefore, any cutoff level for a “positive” bronchodilator response is arbitrary.^{8, 29} The bronchodilator response can be expressed as percent change from baseline (percent change), change in percent predicted (delta percent predicted), or absolute change (in liters [L]).

The 95% CI for percent change from baseline of FEV₁ in healthy persons has been reported to range from 7.7% to 10.1% (0.22 to 0.36 L) and in patients with obstructive lung diseases from 10% to 15% (0.16 to 0.25 L⁸). The 95% CI for percent change from baseline of FVC in healthy individuals has been reported to range from 5.1% to 10.7% (0.23 to 0.40 L) and in patients with obstructive lung diseases from 14.9% to 15% (0.33 to 0.51 L⁸). The mean percent change in FEV₁ following 200 µg salbutamol (albuterol) was 7.9%, 5.1%, and 3.6% in patients with severe, moderate, and mild asthma, respectively (as defined by bronchial responsiveness), compared with 1.3% in controls.³⁴

Repeatability

Bronchodilator reversibility appears to vary considerably when a standard threshold criterion for a “positive” test (percent change from baseline, change in percent predicted, or absolute change in lung function) is employed as the endpoint.³³ Factors contributing to this variability include baseline lung function and the duration of bronchodilator medication withholding.^{8, 35–38} If the absolute value of the FEV₁ after bronchodilator administration is the endpoint, the repeatability may increase greatly and should be as good as that described for spirometry.^{26, 39}

Responsiveness

An individual should be considered to have clinically significant bronchodilator reversibility if he/she achieves a 12% (and 200 mL) improvement in FEV₁ from baseline following the administration of 4 puffs of albuterol, as described above (in the section “Definition and Methodology for Measurement”). As described in the section on spirometry, changes of 100 to 200 mL in FEV₁ are probably clinically important in individuals with asthma.^{17, 18} SABAs typically produce a response within 10 to 15 minutes, while short-acting anticholinergic agents require approximately 30 minutes.⁸

Validity

Bronchodilator reversibility is a useful tool for assisting in the diagnosis of asthma^{6, 31} and as an adjunctive, but unreliable, tool to help differentiate asthma from COPD.^{40, 41} Although bronchodilator reversibility is helpful in predicting responsiveness to subsequent bronchodilator treatment, the lack of an acute response to a bronchodilator does not always correlate with clinical efficacy.^{8, 30}

Bronchodilator reversibility is useful for the characterization of both individual subjects as well as subject populations both in the context of a clinical trial and in observational studies such as genetic association studies. It has not been widely used as an outcome measure in standard clinical trials; rather, it has been more commonly used as a potential predictor of the clinical response to bronchodilators, although this kind of predictive value is not consistently present.³⁰ On the other hand, post-bronchodilator spirometry can be used as a clinical trial outcome.³²

Associations

Because bronchodilator response is influenced by baseline lung function,^{35–38} increased reversibility correlates with increased asthma severity.²² More recent analyses of patients with asthma via unbiased cluster analysis suggest that among individuals with severe asthma, those with greater maximum bronchodilator reversibility have a more “atopic” asthma phenotype.⁴² A direct relationship also has been reported between the log of methacholine concentration that produced a 20% decrease in FEV₁ (log₁₀PC₂₀FEV₁) and the percent change in FEV₁ after maximum bronchodilation with albuterol.²⁷

Practicality and Risk

The practicality and risks of bronchodilator reversibility testing are similar to those described in the section on spirometry (above), with the added risks and time required for bronchodilator administration. Drug administration and additional spirometry may add as much as 45 to 60 minutes to the testing procedure.⁵ Inhaled SABAs and anticholinergic medications have an excellent safety profile. When maximum bronchodilator reversibility testing is performed, side effects can be minimized by administering the bronchodilator incrementally.^{25, 26}

Demographic Considerations

Less-than-expected bronchodilator responsiveness has been reported among individuals of Puerto Rican descent as well as blacks and Mexican Americans. Puerto Ricans of all ages and black children with moderate to severe asthma demonstrate the lowest responsiveness overall.⁴³

Priority for NIH-Initiated Clinical Research

Bronchodilator reversibility testing is considered to be a core measure for describing an asthma population prior to entering a clinical trial and characterizing populations in epidemiologic and genetic studies, but a supplemental measure for assessing treatment in clinical trials, unless evaluating a bronchodilator therapy.

Future Directions or Research Questions

Further research is needed to:

1. Determine the role of bronchodilator reversibility testing and maximum bronchodilator reversibility testing in assigning patients with obstructive lung diseases to specific disease categories

2. Maximize the usefulness of these tests in predicting subsequent response to bronchodilator and other therapeutic agents and to subcategorize patients into clinically meaningful clusters with implications for both natural history of disease and response to therapeutic agents (in particular, explore the role of postbronchodilator spirometry and maximum reversibility as outcomes in clinical trials of anti-inflammatory or immunomodulatory agents)

PEAK EXPIRATORY FLOW

Summary

- PEF is a measure of maximum instantaneous expiratory flow that is used as an indicator of airway caliber in asthma.
- PEF can be self-administered on a daily basis and results recorded manually or electronically to obtain day-to-day or within-day variability.
- PEF is not useful for distinguishing restrictive from obstructive ventilatory defects.

Definition and Methodology for Measurement

The PEF is defined as the highest instantaneous expiratory flow achieved during a maximal forced expiratory maneuver starting at TLC. Because the PEF is reached very early in a forced expiratory maneuver, the forced expiratory maneuver can be of brief duration and is therefore easier to perform than the sustained expiratory effort required of an FVC maneuver. PEF may be measured with either a mechanical or an electronic peak flow meter. Electronic peak flow meters often have the capability to store multiple PEF readings over time for download and review. When measured with a peak flow meter, the PEF is usually expressed in units of liters per minute (L/min); in contrast, when PEF is measured with spirometry systems, it is usually expressed in units of liters per second (L/sec).

PEF variability is defined as the degree to which the PEF varies among multiple measurements performed over time. PEF variability can be determined from a written diary of mechanical peak flow meter readings over time or from downloaded electronic data. Various indices have been proposed to express PEF variability. The best indices to distinguish individuals with disease from healthy persons in epidemiologic studies may be measures of percentage diurnal variability.⁴⁴

Medical and Scientific Value

PEF is a valid indicator of ventilatory impairment. As a diagnostic test, it has the disadvantages of being unable to distinguish obstructive from restrictive ventilatory impairment and of being relatively insensitive (compared with spirometry measures) to differences in small airway obstruction among different people.⁴⁴ However, PEF can be useful for following the degree of ventilatory impairment over time in individuals with known asthma. The PEF is a valuable indicator of the severity of an acute asthma exacerbation, and the management of acute exacerbations should be guided by PEF measurements.⁴⁵

Individuals with asthma exhibit diurnal variability of PEF⁴⁶ but overlap in PEF diurnal variability between patients with asthma and healthy people exists, which limits the value of PEF monitoring as a diagnostic test for asthma in the general population. Workers with occupational asthma may experience variability in PEF that is related to their work schedule, making serial PEF measurements a valuable diagnostic test for occupational asthma.⁴⁷ The degree of diurnal and day-to-day variability of PEF have been proposed as indicators of asthma severity and airway hyperresponsiveness.^{48–50}

Range of Values

Because PEF varies with height, age, sex, and race/ethnicity, reference equations predicting PEF on the basis of these variables have been developed in healthy population samples,^{7, 51, 52} and PEF is often expressed as a percentage of the predicted value.

In healthy persons, there is diurnal variation in PEF. Daily variation in PEF appears to be greater for younger children (6% to 8%) than for adolescents and adults (4% to 5%).⁵¹ A recent study of healthy schoolchildren, aged 6 to 16 years, assessed the normal range of diurnal PEF and FEV₁ variability (diurnal amplitude as a percentage of the day's mean) as measured with electronic meters. The mean PEF variation was 6.2% (95th percentile 12.3%), and the mean FEV₁ variation was 5.7% (95th percentile 11.8%).⁵² Various factors such as age, sex, smoking status, atopy, and respiratory symptoms have been shown to affect PEF variability.^{47, 49, 53}

Repeatability

The PEF has a relatively high degree of reproducibility, both within a given test session and between sessions. Among healthy adult subjects, the intra-individual (between-session) variability, expressed as the coefficient of variation (CV), has been reported to range from 2% to 14%.^{45, 54} Among a population-based sample of 7-year-old children, within-session and between-session CVs have been reported to be 7% and 12%, respectively.⁷

Responsiveness

PEF has been used as a primary outcome in clinical trials of asthma medications and other interventions, in both chronic and acute management of asthma. When used in this way, PEF is usually expressed as change from baseline average values. In asthma clinical trials, a change in morning PEF of 25 L/min from baseline values is considered clinically significant.^{25, 55} However, an MCID in PEF variability has not been established with certainty. Baseline PEF as well as PEF variability have been responsive to both anti-inflammatory agents as well as bronchodilators.

Validity

As a measure of lung function, PEF values (percent personal best or percent predicted) and various measures of PEF variability show moderate correlations with other measures of airflow limitation such as FEV₁, FEF_{25–75}, and FEF₅₀.^{45, 56, 57} The correlation between Mini-Wright PEF and PEF using FVC maneuvers in spirometry is between 0.6 and 0.7.⁵⁴ The mean ($\pm$ SD) internal validity of PEF obtained by peak flow meter compared with that measured by spirometry is $2.3 \pm 12.5\%$ (range -21% to 32%) with a mean bias of 6.0 ± 47.3

L/min higher in the peak flow meter values. In absolute terms, the mean $\pm$ SD difference between the 2 measurements is 4.1 ± 49 L/min (range -104 L/min to 102 L/min).⁵⁸

Diagnostic accuracy measurements (sensitivity, specificity, positive predictive value, and negative predictive value) are available for PEF.^{45, 56} In children, PEF will predict patients with abnormal FEV₁ with a sensitivity of 87% and will classify those with normal FEV₁ correctly with a specificity of 73%.⁵⁶

Associations

In addition to the relationship of PEF to other measures of lung function and airway hyperresponsiveness among persons with asthma, PEF indices have been modestly associated with symptom scores⁵⁷ and track well with medication response.^{32, 59, 60} However, the ability of PEF to reflect responses to interventions is inconsistent across studies, which may reflect the imprecision of a self-administered, effort-dependent test or a placebo effect. The correlation of PEF variability with impairment and risk or other indices of asthma control is uncertain, so the value of PEF variability as an indicator of these asthma outcomes is unclear.

PEF indices—including PEF variability—correlate with airway hyperresponsiveness, particularly in those with an established diagnosis of asthma,^{25, 47, 49, 50} but this association is moderate at best.^{49, 50, 56, 58} Low sensitivity and positive predictive values have been reported for PEF variability indices against current physician-diagnosed asthma.⁵⁸

Current conventional PEF indices have not consistently been associated with asthma exacerbation events. However, the use of more innovative analyses such as visual perception and pattern recognition skills,⁶¹ a hierarchical Bayesian model,⁶² or fluctuation analysis⁶³ may provide better objective evidence for the use of ambulatory monitoring to predict acute worsening of asthma using PEF.

Practicality and Risk

The PEF has the advantages of being relatively easy to perform and being measurable with a relatively small and inexpensive instrument. Thus, it is suitable for individual testing at home, in the workplace, and in an outpatient healthcare setting. Adherence is likely to be better with self-recording electronic meters than with manual flow meters that require data to be recorded in a daily diary. The risks are very small and limited to dizziness and, rarely, fainting associated with forced expiratory maneuvers. Therefore, these maneuvers should be done in the sitting position.

Demographic Considerations

Demographic considerations are included in the discussion under “Range of Values” (above).

Priority for NIH-Initiated Clinical Research

The subcommittee recommends use of the PEF as a supplemental outcome in clinical asthma research. The test is particularly useful for characterization of the study population

for prospective clinical trials if spirometry is not performed. Assessment of the variability of PEF is also considered supplemental for study population characterization, interventions, and observational studies.

Future Directions or Research Questions

Further research is recommended to:

1. Evaluate reliability of electronic real-time peak flow monitoring
2. Establish normative values in different ethnic and minority populations
3. Establish standards for devices and procedures for ambulatory monitoring of PEF

AIRWAY RESPONSIVENESS

This section describes 4 tests of airway responsiveness: (1) methacholine inhalation challenge, (2) exercise challenge, (3) isocapnic hyperventilation challenge, and (4) mannitol inhalation challenge.

Methacholine Inhalation Challenge

Summary

- Methacholine inhalation challenge provides a measure of airway responsiveness but is not sufficiently sensitive or specific to include or exclude a diagnosis of asthma.
- The challenge is performed by inhalation of increasing concentrations of methacholine until the FEV₁ falls by 20% or more.
- The magnitude of airway responsiveness is indicated by the concentration that causes a 20% fall in FEV₁.
- The methodology of the test is not adequately standardized to be used as a core measure across studies but may provide supplemental information on mechanisms of effectiveness of some asthma interventions.

Definition and methodology for measurement—Methacholine inhalation challenge (or methacholine bronchoprovocation) is performed by having individuals breathe increasing concentrations of aerosolized methacholine (a derivative of acetylcholine that binds to specific muscarinic receptors) and measuring bronchoconstriction using spirometry, airway conductance, or even auscultation in very young children. The most widely used measure of responsiveness is the concentration that causes a 20% decline in FEV₁ from the baseline reference value: the PC₂₀. Other methods of quantifying the test result use either the cumulative dose that causes a 20% decline in FEV₁ (PD₂₀) or the slope of the dose-response curve. Some researchers have used changes in airway conductance, FEF_{25–75}, or forced oscillation parameters to assess changes in airway caliber. There also has been interest in the changes in FVC because they represent changes in airway closure, a strong determinant of the changes in FEV₁.⁶⁴

The ATS/ERS guidelines are the most widely used of the published standards for the procedure.^{1, 65} The preparation of the solution and the conduct of the test differ between the ATS/ERS recommendations and the Food and Drug Administration (FDA)-approved prescribing information for methacholine.⁶⁶ Dosimeters and nebulizers used for methacholine inhalation challenge testing have different performance characteristics, and protocols using tidal breathing may differ from those using a dosimeter.^{67, 68} Thus, in practice, variability between studies may stem from many different methods used to conduct the test: duration of medication withholding prior to the challenge; tidal breathing versus dosimeter; the number of steps and concentrations used (4 to 12 levels); the lowest (0.01 to 1 mg/mL) and highest (16 to 32 mg/mL) methacholine concentrations; the type and output of nebulizer; the timing, repetition, and selection of spirometric maneuvers; and the reference value from which declines in FEV₁ are measured (pretest baseline versus post-diluent inhalation). Moreover, no threshold value of PC₂₀ is generally accepted as corresponding to a diagnosis of airway hyperresponsiveness or is considered diagnostic for asthma. The recommended standard method for testing methacholine responsiveness is the dosimeter method, using a calibrated nebulizer and dosing schedule as recommended by ATS/ERS.¹ Whether the 5-dose or the 10-dose schedule is used depends on the research question. The 10-dose schedule has greater resolution of differences among populations and changes of airway responsiveness over time than the 5-dose schedule.

Medical and scientific value—While the biologic mechanisms responsible for asthma are not completely understood, increased sensitivity to bronchoconstriction with provocative agents, including methacholine, is generally believed to be a fundamental pathophysiologic mechanism. Heightened responsiveness to methacholine is considered to be a central manifestation of symptomatic asthma and may be an indicator of unremitting asthma. Accordingly, improvement of airway responsiveness to methacholine is considered 1 of the dimensions of therapeutic response in asthma and can be considered a valid proof of concept for a treatment aimed at modifying the course of the disease.

Range of values—Airway responsiveness to methacholine has been measured in several samples representative of the general populations of Europe and the United States.^{69–71} There is no generally agreed-upon threshold for a normal response; however, up to 26% of such a sample will demonstrate a 20% or greater decline in FEV₁ with methacholine inhalation challenge testing.⁷² Usually, however, patients with active asthma have a lower PC₂₀ than those without the disease. Lower lung function, young age, female sex, atopy, and cigarette smoking have all been associated with greater degrees of airway responsiveness.

Repeatability—Methacholine inhalation challenge using the tidal breathing method is highly reproducible within the same week ($R_2 = 0.99$) and over several weeks ($R = 0.87$).^{73, 74} In persons with atopic asthma, airway responsiveness to methacholine varies with seasonal exposure. The season with the greatest prevalence and severity of airway responsiveness among persons with asthma varies among studies, likely depending on selection of the population, exposure to viral infections, and local allergens.^{75–77}

Responsiveness—Bronchodilators (β -agonists and anticholinergic agents) are protective against a bronchoconstrictor response to methacholine; thus, they should be withheld prior to testing. Patients show development of tolerance to LABAs over several weeks, resulting in diminished bronchoprotective effects of these drugs.⁷⁸ Several studies show that inhaled corticosteroids can decrease airway responsiveness to methacholine after several weeks of treatment. There is no evidence to support a dose-response relationship for this protective effect.⁷⁹ Montelukast, a leukotriene antagonist that also has some anti-inflammatory effects, has been shown to improve the PC₂₀ in children with wheezing but does not affect methacholine responsiveness in adults with asthma.^{80–83} Omalizumab (anti-IgE treatment) also has no or minimal effects on airway responsiveness to methacholine.⁸⁴

Validity—Methacholine hyperresponsiveness is more prevalent among people with asthma than those without asthma, but the sensitivity and specificity of the test for the diagnosis of asthma varies so widely that, by itself, it is insufficient to rule in or rule out a diagnosis of asthma without other supportive clinical findings. A similar variability in sensitivity and specificity exists in pediatric studies. The variability in diagnostic accuracy may be due to the many methodological differences between studies (see “Definition and methodology for measurement,” above) and the lack of a uniformly agreed-upon reference definition for the diagnosis of asthma. If used in epidemiologic studies, methacholine inhalation challenges may add marginal diagnostic value to information obtained from questionnaires.⁸⁵ The diagnostic value of methacholine inhalation challenge testing is highest in individuals with active symptoms of asthma in the setting of normal lung function.⁸⁶

Associations—The magnitude of airway responsiveness to methacholine is widely believed to correlate with the severity of asthma. However, no studies support or refute this conclusion in adults, most likely because patients who have the most severe impairment of lung function and the most active symptoms are not considered safe candidates for methacholine inhalation challenge testing.

Airway responsiveness to methacholine has a high correlation with measures of airway responsiveness to other stimuli such as histamine, exercise, and cold air inhalation and is associated with markers of airway inflammation such as expired nitric oxide (NO) and eosinophils in sputum.^{67, 86, 87} Modest associations between airway responsiveness to methacholine and eosinophils or mast cells in bronchoalveolar lavage and subepithelial reticular basement membrane thickness have been reported.⁸⁸

Practicality and risk—Commercially available spirometers and dosimeters with software to guide the test are widely available. Because the test may occasionally induce severe bronchospasm, personnel who prepare the solutions and who administer the test should be properly trained and certified. Emergency equipment, including oxygen and bronchodilators, should be readily available, and the testing should be performed in a medically secure environment with a physician available to assess and treat potential complications. These requirements limit the practicality of this test in an unsupervised field setting.

Patients who are having symptoms of an asthma exacerbation should not undergo methacholine inhalation challenge testing. Although clinical guidelines suggest limiting the

test to individuals with asthma who have an FEV₁ greater than 70% of the predicted value, published evidence shows that patients with levels of FEV₁ of less than 60% the predicted value can safely undergo the challenge in a supervised research setting.⁸⁹ However, the physiology of a 20% reduction in FEV₁ in an individual with low lung function may differ considerably from that in an individual with normal lung function, and the outcomes of the challenge may not be comparable between those 2 situations.

The commercially available methacholine package in the United States has a “black box” warning indicating that methacholine inhalation challenge testing “should not be performed on any patient with clinically apparent asthma.”⁶⁶ This warning has led to the perception that this test carries more than minimal risk for children, and its use in research must be balanced against the benefit to the subject. Despite the theoretical risk, the test has been safely performed in large numbers of children without serious complications⁹⁰ and has been shown to be feasible in children as young as 3 years old.⁹¹

Demographic considerations—The prevalence of airway responsiveness to methacholine is correlated with the baseline level of lung function as well as age and sex. In general, clinical and demographic characteristics that are associated with lower lung function are associated with greater prevalence of airway responsiveness to methacholine.⁷¹

Priority for NIH-initiated clinical research—Methacholine inhalation challenge testing is designated as a supplemental test in clinical trials or epidemiologic/genetic research. It is currently the most widely used test of airway responsiveness in clinical research and clinical practice. Despite this prevalence, its utility as an outcome in asthma clinical research is limited because it may not always be used in people with severe asthma and the methodology is not standardized adequately to permit comparison among studies. Nonetheless, the subcommittee recommends this test as an important supplemental outcome because of its relationship to the central pathophysiology of asthma and its precision. It should not be used as the sole diagnostic criterion for asthma, but may provide useful information when combined with other clinical information.

Future directions or research questions—There is a need to develop standardized methods for methacholine inhalation challenge testing that are more efficient than the current methods and make use of modern high-efficiency nebulizer or dry-powder inhaler technology.

Exercise Challenge

Summary

- Exercise challenge measures airflow limitation after a maximum exercise test.
- A decline in FEV₁ of 10% or more is indicative of a positive test.
- A positive test is highly specific for a diagnosis of asthma in children but less so in adults.

- Standardization of the test requires careful control of the temperature and humidification of the inspired air as well as documentation of adequate exercise ventilation.

Definition and methodology for measurement—Exercise challenge is a commonly used airway challenge technique to assess the presence of airway hyperresponsiveness and is most frequently used for epidemiologic,⁹² pediatric,^{93, 94} or athletic performance studies. Exercise studies can be conducted using a number of protocols: The ATS guidelines of 1999⁹⁵ suggest a protocol using a motor-driven treadmill or cycle ergometer. The exercise protocol is designed to take the subject to 80% to 90% predicted heart rate for at least 4 minutes to achieve a ventilation of 40% to 60% of the maximal voluntary ventilation (MVV) ($FEV_1 \times 35$); inhalation of cold or dry air during testing is often included to increase the probability of a positive test.⁹⁶ Ventilation, temperature, and humidity of the inspired air should be controlled, as these are the principal sources of response variability.^{96, 97} FEV_1 is measured 5, 10, 15, 20, and 30 minutes after cessation of the exercise. As with other bronchial challenge tests, an inhaled β -agonist should be administered to reverse bronchoconstriction after the test.

Medical and scientific value—A positive exercise challenge is useful for establishing the diagnosis of asthma, especially if lung function is normal, response to bronchodilator reversibility is minimal, and the probability of asthma is high.¹ Patients with mild disease often present with exercise-induced bronchospasm (EIB) as a symptom,⁹⁸ but EIB symptoms alone are not specific or sensitive enough for establishing the diagnosis of asthma.⁹⁹ Exercise appears to be superior to cold air hyperventilation challenge in the diagnosis of asthma with respect to sensitivity, as well as positive and negative predictive values, but inferior to methacholine inhalation challenge, which shows greater sensitivity and allows assessment of severity.^{97, 100–102} On the other hand, there is some evidence that exercise challenge also can be used to stratify asthma severity.^{103–105}

Range of values—The ATS guidelines¹ recommend that a greater than 10% fall in FEV_1 from a pre-exercise baseline is indicative of a positive response, with a similar cutoff for children and young adults.¹⁰⁶ Some studies have suggested that 15% is a more specific cutoff.^{92, 107} This cutoff is lower than for other challenge tests because the physiologic effect of exercise is to increase FEV_1 so that 2 opposing effects may be simultaneously present.^{1, 92} In children 3 to 6 years old, the upper 95% CI of the fall in FEV_1 fall ranged from 8.2% to 15.3%,^{92, 108} with a 13% fall in $FEV_{0.5}$.¹⁰⁹ Attention needs to be paid to vocal cord or other upper airway dysfunction as a cause of false-positive responses.^{1, 110}

Repeatability—The CV for the repeatability of this challenge 1 month apart is 21%.¹¹¹ Attention to a standard protocol is required to ensure adequate sensitivity and reproducibility.

Responsiveness—A number of asthma medications reduce the bronchospastic response to exercise; these include nedocromil sodium,¹¹² leukotriene antagonists,^{113, 114} inhaled corticosteroids,^{115–118} a variety of β -agonists,¹¹⁹ and β -agonists combined with corticosteroids.¹²⁰

Validity—The use of exercise challenge is an adjunct approach to the assessment of airway hyperresponsiveness. In certain populations^{1, 92} or special situations (eg, athletics), exercise may be the most appropriate and relevant testing methodology.^{93, 94} In children, the specificity of a positive exercise challenge for the diagnosis of asthma is high, but the sensitivity is low.¹²¹ Exercise challenge specificity is lower for adults than for children.^{98, 102}

Associations—Some studies show a correlation of EIB to asthma severity.^{103–105} The response to exercise also is related to the degree of atopy; inflammatory products in sputum, blood, and urine; and eosinophil counts.^{104, 117, 122, 123} The degree of correlation between the responses to exercise challenge and to other challenge modalities varies.^{101, 102, 107}

Practicality and risk—The practicality of exercise challenge is limited by the need for a treadmill or cycle ergometer, electrocardiogram equipment, and controlled inspired-air conditions. The test carries a small risk of injury, severe bronchospasm, and untoward cardiovascular events.¹ The procedure takes about an hour to perform. In addition, the individual must be properly prepared with appropriate clothes and shoes, and medications must be withheld as per other airway provocation tests. Like any exercise or any airway provocation test, exercise challenge should be performed with adequate medical supervision.

Demographic considerations—Exercise challenge testing has been widely used in children, where the risks are low and this mode of challenge is relevant. No evidence suggests racial differences. The use of exercise challenge testing in the elderly is problematic for several reasons, including lower maximal ventilation.

Priority for NIH-initiated clinical research—Exercise challenge constitutes an alternative means of assessing airway hyperresponsiveness in asthma populations. The test may be most useful in pediatric populations or athletes with asthma. The subcommittee considers exercise challenge a supplemental outcome in assessing acute and chronic responses to therapeutic interventions and in characterizing populations in epidemiologic and genetic studies.

Future directions or research questions—Further research is needed to:

1. Test whether different exercise challenge methodologies, such as free-range exercise, can be standardized to improve practicality while maintaining or improving validity
2. Determine whether EIB represents a unique asthma phenotype
3. Determine the diagnostic value of exercise challenge in various ethnic and minority populations

Isocapnic Hyperventilation Challenge

Summary

- Isocapnic hyperventilation challenge (via the inhalation of cold, dry air) induces bronchoconstriction in many people with asthma, but is not considered a diagnostic test for asthma.
- The wide application of the test is limited by the lack of standardization of the methodology and complexity of the necessary technology.

Definition and methodology for measurement—Isocapnic (or eucapnic) hyperventilation challenge (also known as “eucapnic voluntary hyperpnea”) is used as a diagnostic test in asthma, to assess the presence of airway hyperresponsiveness and to examine the pathophysiology of airway reactions to dry air.^{124, 125} This test has been used in adults and in children as young as 2 years old.¹²⁶ Two challenge protocols have been used: The first involves a single step, where subjects hyperventilate room air or cold air at MVV ($FEV_1 \times 25\text{--}35$) for 3–6 minutes, and the second involves multiple steps, with increasing ventilation rates from 20% to 100% MVV.^{127, 128} Exhaled air is continuously monitored by a carbon dioxide (CO₂) analyzer, which directs the addition of CO₂ to the inhaled air so that isocapnic (eucapnic) conditions are maintained throughout the challenge. Alternatively, the challenge can be conducted with air containing 5% CO₂. A publication by the ERS has offered a standardized methodology for isocapnic hyperventilation testing.¹²⁷

Medical and scientific value—Because of its high specificity for asthma, isocapnic hyperventilation challenge can be used to confirm the asthma diagnosis in patients with questionable symptoms (see “Validity” below), although a negative challenge does not rule out asthma. Responsiveness to isocapnic hyperventilation in patients with asthma increases with disease severity.¹²⁹ The same can be said for the use of isocapnic hyperventilation as a test to confirm asthma in clinical research or in epidemiologic and genetic studies. Notably, approximately 15% of patients with COPD have a positive isocapnic hyperventilation challenge.¹³⁰

Isocapnic hyperventilation challenge is a useful research tool for the study of the mechanisms of the effects of cold, dry air on the airways.^{131, 132} Also, because it is thought that EIB is caused by loss of water and perhaps heat, leading to a state of airway surface hypertonicity and/or cooling, isocapnic hyperventilation is considered a useful tool in studying the mechanisms of EIB.^{133, 134}

Range of values—In most published studies, a 9% to 10% reduction in FEV_1 from baseline is considered the cutoff for a positive response to isocapnic hyperventilation challenge.^{128, 129} The same cutoff is used in children and in adults. As with exercise challenge, attention needs to be paid to vocal cord or other upper airway dysfunction as a cause of false-positive responses.

Repeatability—The intraclass correlation coefficient of the single-step isocapnic hyperventilation challenge for repeated testing within 4 weeks has been reported to be as high as 0.98.¹³⁰

Responsiveness—SABAs and LABAs can prevent airway responses to isocapnic hyperventilation.^{132, 133} Evidence that cromolyn and nedocromil can prevent the response also has been generated, although the duration of action of these agents is short.^{132, 134} Similarly, the response to isocapnic hyperventilation can be decreased with chronic use of inhaled corticosteroids, but the results are not consistent.^{135, 136} Small studies have shown that montelukast in children¹³⁵ and 5-lipoxygenase inhibitor in adults¹³⁶ have protective effects in isocapnic hyperventilation challenge. Responses to anticholinergic drugs, antihistamines, and calcium antagonists vary.^{137–139} Isocapnic hyperventilation-induced bronchospasm is blocked by inhaled acetazolamide and furosemide.¹⁴⁰ Larger clinical trials using isocapnic hyperventilation as an outcome to determine the size of a clinically relevant drug effect on this test do not exist.

Validity—Isocapnic hyperventilation challenge has variable sensitivity in detecting physician-diagnosed asthma, ranging from 20% to 95%.^{141–143} This wide range is due to the variability in the stringency of the criteria for the clinical diagnosis of asthma. The sensitivity is higher with cold air, compared with room air temperature. Specificity is high, ranging from 80% to 100%.^{141, 142}

Associations—The single-step and the multistep isocapnic hyperventilation challenge protocols have high agreement.¹²⁸ Positive correlations between isocapnic hyperventilation challenges and exercise challenges have been reported.¹²⁵ More variable data have been published regarding the relationship between isocapnic hyperventilation outcomes and “direct” bronchoprovocations, such as with methacholine or histamine.^{124, 128, 144–146}

Practicality and risk—The widespread use of isocapnic hyperventilation challenge testing in asthma clinical research has significant limitations; namely, the need for a heat exchanger and either a CO₂ sensor for adding CO₂ into inhaled air or a special air mixture of 5% CO₂, as well as the need for a balloon or a special computer program to assist in the maintenance of high ventilatory rate during the challenge. The risk for severe bronchospasm is theoretically increased when the single-step challenge is used, but centers with experience in this technique do not report increased rates of severe airway obstruction compared with other forms of bronchoprovocation.

Demographic considerations—Isocapnic hyperventilation testing has been used in children as young as 2 years old.¹⁴⁷ There is no information to suggest a differential racial response. The use of isocapnic hyperventilation testing in older adults may be problematic because they may not be able to achieve the required ventilatory rates.

Priority for NIH-initiated clinical research—Despite its long history of use, the isocapnic hyperventilation challenge test is not fully standardized, and it is not clear that this procedure offers specific advantages over other types of bronchoprovocation as a general asthma characterization outcome or as a specific outcome capable of identifying a particular asthma phenotype. In addition, there is minimal experience in large clinical trials, and no specific therapeutic modality for which this test should be preferentially used has been identified. Thus, the subcommittee does not propose isocapnic hyperventilation challenge as

a supplemental outcome in asthma research, but rather as an emerging outcome requiring further standardization and validation.

Future directions or research questions—Further research is needed to:

1. Standardize isocapnic hyperventilation (single-step versus multistep, duration, CO₂ monitoring/adding versus fixed CO₂ concentration, air temperature)
2. Provide additional validation data on the standardized technique
3. Identify characteristics (phenotype) of patients with high responsiveness to this stimulus
4. Examine whether isocapnic hyperventilation challenge is of value as an adjunct outcome in clinical trials that test a particular type of anti-asthma medication

Mannitol Inhalation Challenge

Summary

- Mannitol inhalation challenge is a promising method of assessing airway hyperresponsiveness by imposing an osmotic stress on the airways; therefore it may induce bronchoconstriction by the same mechanisms as exercise or isocapnic hyperventilation.
- Mannitol inhalation challenge has the advantage of being a simple, commercially available, standardized challenge method.
- Currently, there is limited information on the clinical and scientific utility of this test as a subject characterization method or as an outcome measure for clinical research.

Definition and methodology for measurement—The mannitol inhalation challenge is a recently described technique to assess airway hyperresponsiveness. It is classified as an indirect challenge test,⁹⁷ as mannitol is not thought to directly stimulate airway smooth muscle contraction. The use of mannitol grew from the theory that exercise, hypertonic saline, and isocapnic hyperventilation represent osmotic stress to the airways.^{148, 149} The test was first reported in 1997¹⁵⁰ and involves inhaling increasing doses of a dry powder form of mannitol.

Medical and scientific value—Bronchial challenge testing is useful in the diagnosis and treatment of asthma when the baseline values are within normal limits and there is a high pretest suspicion of asthma.¹ Mannitol responsiveness may be an indication of mast cell release of prostaglandin D₂,¹⁵¹ but other mechanisms, including sensorineural stimulation by increased airway fluid osmolarity, also have been postulated. As an alternative to other challenge methods such as exercise, isocapnic hyperventilation, or even methacholine, mannitol may prove to be a more convenient challenge procedure.

Range of values—The current technique calls for the calculation of the mannitol cumulative provocative dose inducing a fall of FEV₁ of 15% or more (PD₁₅) derived from

the dose response curve. The cutoff for “normal” remains unclear, because either a PD₁₅ 635 mg or a PD₁₅ 350 mg have been reported as abnormal results.¹⁵² The PD₁₅ for mannitol decreases toward 30 mg with increasing disease severity,¹⁵⁰ but this finding needs confirmation; moreover, mannitol inhalation challenge has been reported to be negative in persons with no current or past history of asthma. In this regard, mannitol responsiveness is probably not equivalent to methacholine responsiveness.

Repeatability—Studies determining the repeatability of the mannitol PD₁₅ are limited, but ± 0.5 log variability has been reported.¹⁵⁰

Responsiveness—A single dose of nedocromil sodium significantly reduces the mannitol PD₁₅; also, a significant reduction in the PD₁₅ has been observed with the inhaled corticosteroid budesonide at a daily dose of 800 μ g to 2400 μ g, after 6–9 weeks.¹⁵² In 1 study, treatment of individuals with asthma with 800 μ g of budesonide for 6 months normalized airway responsiveness to mannitol.¹⁵³ It is unclear at this point what a clinically meaningful change in mannitol PD₁₅ would be.

Validity—The outcome of mannitol inhalation challenge correlates with the outcomes obtained by hypertonic saline,¹⁵⁰ exercise,¹⁵⁴ adenosine 5'-monophosphate,¹⁵⁵ and methacholine inhalation challenge.¹⁵⁰ One study¹⁵⁶ reported a sensitivity of 58.8% (56.7% to 62.6%), specificity of 98.4%, positive predictive value of 90.9%, and negative predictive value of 89.8% with a receiver-operator characteristic curve area of 0.89 (0.83–0.95) for physician-diagnosed asthma. Other reports suggest that sensitivity and specificity are lower than (60% to 78% and 62% to 98%, respectively), but similar to, that of methacholine.¹⁵⁷ The sensitivity of mannitol inhalation challenge was reported to be higher in children than adults (86% versus 60%), but specificity was lower (68% to 95%). However, this finding is not consistent.¹⁴⁹

Associations—The PD₁₅ to mannitol tracks improvements in symptoms in 1 study,¹⁵³ but few longitudinal studies are available. The decrease in mannitol responsiveness with inhaled corticosteroid treatment has been correlated to the changes in FEV₁ and symptoms.¹⁵³

Practicality and risk—Other than a spirometer, the mannitol inhalation challenge requires no special equipment; therefore, it has a practical advantage over other bronchoprovocations. The mannitol inhalation challenge does not evoke severe lung reactions, but cough is very common.¹⁴⁹ As with other forms of bronchial challenge, mannitol should not be administered in people whose pretesting lung function is low (FEV₁ <70% predicted) or who present with “clinically apparent asthma,” according to the FDA-approved package insert.

Demographics—The only published studies of mannitol inhalation challenge have been conducted in whites; few studies have been conducted in children.^{158, 159}

Priority for NIH-initiated clinical research—The mannitol inhalation challenge is considered an emerging measure of airway responsiveness, because the method has not been fully standardized.

Future directions or research questions—Further research is needed to:

1. Determine the within-day and between-days repeatability and variability of the mannitol inhalation challenge
2. Determine whether the “mannitol-positive” patient with asthma represents a distinct phenotype
3. Assess airway responsiveness to mannitol in children and in various ethnic/minority populations
4. Assess the effects of therapeutic agents on airway responsiveness to mannitol beyond those already investigated

LUNG VOLUME TESTING

Summary

- Lung volume testing by either body plethysmography or dilutional gas methods is used to measure elevated RV caused by peripheral airway closure, an indirect measure of airway smooth muscle tone and airway geometry.
- The test is safe and noninvasive, but the need for specialized equipment and skilled testing personnel limits its utility in large-scale clinical studies.

Definition and Methodology for Measurement

By assessing lung volumes or their combinations (capacities), one can measure the physical size and mechanical properties of the lung/chest wall.¹⁶⁰ Vital capacity (VC), TLC, functional residual capacity (FRC), and RV are the most informative. Measurement of TLC, RV, and FRC requires 2 separate measurements: First, FRC is measured with either dilutional gas methods (helium dilution or nitrogen washout) or body plethysmography (preferred method), and then a slow vital capacity (SVC) maneuver is performed to determine TLC and RV.

Medical and Scientific Value

Lung volume is a principal determinant of airway caliber, and its assessment provides a measure of structural changes and delineates pathogenic processes.¹⁶⁰ TLC and FRC measurements also can serve as surrogates for the pressure-volume characteristics of the lung. In addition, reductions in FEV₁ have been shown to result largely from a decrease in FVC, which is the consequence of air trapping.²⁷

In children with asthma, the development of the size of the lung can be monitored with TLC to determine the relationship of lung growth to airway caliber.¹⁶¹

Range of Values

Normative data for adults and children have been published. However, these data are old, and because lung volumes reflect height and the average height has increased, predictive lung volumes tend to be low. Use of the FRC/TLC or RV/TLC ratios diminishes this limitation as well as other problems with predictive reference equations.⁸

Repeatability

Intra-test variability in healthy individuals (CV) is $\pm 5\%$ for TLC, $\pm 5\%$ for FRC (approximately ± 200 mL, and $\pm 10\%$ for RV^{8, 162}; however, this variability is higher in persons with asthma. One study in children with asthma reported CVs of 2.1% and 5.5% in children with well-controlled and poorly controlled asthma, respectively.¹⁶³

Responsiveness

Chronic or acute asthma causes increases in RV, FRC, and TLC (RV more so than FRC, which in turn increases more than TLC).^{8, 27, 164} Chronic elevation in RV between asthmatic episodes is not unusual, especially in more severe disease.^{38, 165, 166}

Very few studies have used lung volumes as the outcome variable in treatment trials. Yamaguchi¹⁶⁷ compared the effects of hydrofluoroalkane-beclomethasone dipropionate (BDP) versus chlorofluorocarbon-BDP on lung volumes and found no effect on RV percent predicted or RV/TLC, although study participants did not have overt hyperinflation at baseline. Some cross-sectional studies show lung volumes approaching normal values in patients with nonsevere asthma receiving inhaled corticosteroids.³⁸ Improvement in RV has been reported with montelukast treatment.¹⁶⁸ No studies were identified that used lung volumes to follow the effects of long-term therapy.

Validity

FRC measured by dilution is less sensitive to disease activity (air trapping) than that measured by body plethysmography.⁸ Increased FRC or TLC is pathognomonic for obstructive disorders,^{8, 160} particularly asthma.^{27, 166, 168} RV correlates well with airway responsiveness.^{165, 168} One study (Tantucci 1999¹⁶⁹) found that changes in FRC in response to methacholine were more sensitive than changes in FEV₁ in patients presenting with normal spirometry.

Associations

In persons with severe asthma, acute and chronic increases in lung volumes (RV, FRC) accompany spirometric changes (FEV₁, FVC); hence, elevation in RV and FRC may indicate disease severity.^{27, 163, 169} One study (Ansarin 2001¹⁷⁰) showed an inverse correlation of RV/TLC to increased FeNO. It has been reported that TLC and FRC are associated with eosinophilia in mucosal biopsies but RV is not.¹⁷¹

Practicality and Risk

Measurements by body plethysmography or dilutional gas methods such as helium dilution or nitrogen washout require specialized training, patient skill, and equipment that is readily available but expensive. The tests carry no significant risks.

Demographic Considerations

Reference values for adults are based on height, age, and sex, whereas values for children are based on age and height.⁸ Reference values for lung volumes show considerable

variability based on differences in methodology of testing and acquisition of a normative population. Studies on various ethnic populations are limited.

Priority for NIH-Initiated Clinical Research

Lung volume measures are considered supplemental for characterizing study populations, prospective clinical trials, and observational studies.

Future Directions or Research Questions

Further research is needed to:

1. Assess the utility of lung volumes in large, long-term treatment trials
2. Acquire normal reference data for lung volumes in various populations using well-standardized methods

SPECIFIC AIRWAY RESISTANCE AND CONDUCTANCE

Summary

- Measurement of airway resistance is a direct indicator of airway caliber; increased resistance is dominated by narrowing of central airways.
- Airway resistance is a useful measure of airway constriction or relaxation in response to experimental interventions, but has limited value as a clinical outcome measure.
- Airway resistance is measured with several different techniques, which vary considerably in complexity and expense.

Definition and Methodology for Measurement

The measurement of airway resistance (R_{aw}) and its reciprocal, airway conductance (G_{aw}), is most commonly achieved with the body plethysmograph,¹⁷² but other techniques (eg, shutter occlusion) have been used. Because R_{aw} is so dependent on lung volume, specific resistance ($sR_{aw} = R_{aw}/FRC$) or specific conductance (sG_{aw}) are preferred endpoints.

Medical and Scientific Value

Airway resistance, if measured together with FRC, is much less effort dependent than spirometry and provides an assessment of the caliber of central airways.^{168, 173–175} sG_{aw} is more sensitive than spirometry to the effects of bronchodilation with β -agonists.^{175, 176} Using sR_{aw} or sG_{aw} one can demonstrate hyperresponsiveness to methacholine or hyperpnea in asthma.^{1, 174, 177}

Range of Values

sG_{aw} is much less age, race/ethnicity, and sex dependent than spirometry. Thus, a single lower limit is commonly used for the normal range. R_{aw} greater than 2.4 cm H₂O/L/sec and sG_{aw} less than 0.15 (L/sec/cm H₂O)/L are considered abnormal.^{178, 179}

Repeatability

Intra-test variability is $\pm 10\%$ in adults¹⁷⁸ and $\pm 30\%$ in children.¹⁸⁰ Bisgaard¹⁷⁷ reports a CV of 8% to 11% and a short-term intraclass correlation of 0.86.

Responsiveness

sR_{aw} or sG_{aw} have been used most frequently to assess acute effects of β -agonists,^{175, 176} but reports of the effects of inhaled corticosteroids^{147, 181} or leukotriene antagonists are limited.^{135, 168} There are limited reports of long-term effects of asthma therapy or more recently developed therapies (eg, anti-IgE).

Validity

Multiple studies have shown differences in airway resistance between individuals without asthma and those with asthma.

Associations

In general, respiratory resistance is inversely related to FEV₁, but in some individuals this relationship is not observed.¹⁷³

Practicality and Risk

The measurement of airway resistance requires access to a body plethysmograph, which is relatively expensive but has minimal risk.

Demographic Considerations

The measurement of airway resistance is affected by age and sex in children but not in adults.¹⁷⁸ Limited predictive data are available.

Priority for NIH-Initiated Clinical Research

Given that various, albeit well-standardized, methodologies exist but no single method can be recommended, and because limited predictive data are available, airway resistance is considered an emerging outcome of lung function for asthma clinical research.

Future Directions or Research Questions

Further research is needed to:

1. Standardize the methodology for measuring airway resistance
2. Determine the situations for best utilization of airway resistance
3. Investigate the phenotype and interpretation of subsets of patients with asthma who only respond to treatment with changes in airways resistance
4. Investigate the role of airway resistance as an outcome in long-term trials and other therapy modalities beyond β -agonists
5. Obtain better normative value sets for predicted value determinations

FORCED OSCILLATION TECHNIQUE

Summary

- Forced oscillation technique (FOT) measures the pressure-flow characteristics of the airways over a range of frequencies that define the impedance spectrum of the lung.
- The measurement has the advantage that it can be done during quiet breathing by untrained subjects at repeated intervals.
- At present, there are no widely recognized, standardized, clinically meaningful outcome measures derived from FOT, but it is an area of active investigation.

Definition and Methodology for Measurement

FOT is used to measure respiratory impedance by imposing external forced oscillations upon tidal breathing. The test has multiple methodologies, which vary with respect to equipment, imposed waveforms, and frequencies. In addition, the parameters used to quantify the impedance spectrum are not standardized.

Medical and Scientific Value

FOT has great potential to increase our understanding of the complex responses of the lung as well as to improve the assessment of very young and very old subjects who may have limited ability to perform spirometry. Moreover, evaluation of airway impedance at different frequencies may permit discrimination of processes that affect central compared with peripheral airway caliber.

Range of Values

Normative data for adults and children have been published; however, the data are still relatively limited and are specific to the equipment and impedance parameters.^{182, 183}

Repeatability

Intra-test variability of 5% to 15% and day-to-day variability of 10% have been reported for adults and children.¹⁸²

Responsiveness

At a single frequency, FOT can track changes in airway caliber during the breathing cycle. This methodology has been used to evaluate how deep breathing affects airway caliber.¹⁸⁴ Changes in FOT parameters have been demonstrated when assessing airway responsiveness to bronchodilators and bronchoconstrictors; however, clinically significant changes have not been defined.^{185, 186} Similarly, minimal clinically important changes following therapeutic interventions have not been defined.¹⁸²

Validity

Multiple studies have demonstrated differences in the respiratory impedance of groups of individuals with asthma compared with healthy controls; however, no FOT parameter is currently recognized as diagnostic.¹⁸²

Associations

Respiratory system resistance, which is obtained from FOT, is inversely related to FEV₁ and is thus duplicative if both are obtained. However, with improved understanding of FOT, the additional information obtained from the frequency spectrum with FOT may add value to spirometry by providing information as to the behavior of central versus peripheral airways.¹⁸²

Practicality and Risk

The current commercially available equipment is of moderate cost and is relatively easy to use. The test poses minimal risk. However, because of the complexity of the device, careful attention to detail is necessary to obtain reproducible results. There are no generally accepted measures for quality of the waveforms and reproducibility of results.

Demographic Considerations

The effects of age, sex, and race/ethnicity need to be considered. However, these factors are not adequately addressed in the available reference data. FOT has great potential for evaluation of young children. However, as with adults, adequate reference data are lacking, the methodology is not fully standardized, and the ability to define the presence of airway disease or of a clinically significant change in the state of the airways is not well established. In addition, the higher impedance of the lower airways in children potentially makes the confounding effects of the upper airways even more important than in adults.

Priority for NIH-Initiated Clinical Research

FOT is considered an emerging outcome based on the absence of a standardized methodology and outcome parameters, as well as the lack of adequate reference data.

Future Directions or Research Questions

Further research is needed to:

1. Standardize the FOT methodology
2. Establish reliable reference values
3. Determine the validity of FOT as an efficacy outcome in clinical trials with chronic asthma medications in children and older adults
4. Determine the validity of FOT as a means to assess the state of small versus large airways

PERIPHERAL AIRWAY RESISTANCE

Summary

- Peripheral airway resistance (Rp) is measured with a wedged bronchoscope and is considered to measure the resistance in small peripheral airways and collateral channels.
- The utility of peripheral airway resistance as a baseline measure or clinical outcome measure is not established.
- The applicability of the test is limited by the requirement for a semi-invasive procedure that has limited application in patients with severe or symptomatic asthma.

Definition and Methodology for Measurement

Rp is defined as the pressure measured by a pressure transducer at the tip of a bronchoscope wedged into a nondependent segment of the lung, divided by the flow rate of the insufflated gas (Pb/V) delivered through the bronchoscope.¹⁸⁷ Using a double-lumen catheter inserted into the instrument channel of the bronchoscope, pressures produced by 3 or more levels of gas flow (5% CO₂ in air) between 50 and 500 mL/min (milliliters per minute) are used. Rp is believed to represent the resistance attributable to the small airways and collateral pathways that lie between the bronchoscope and the distal segment.¹⁸⁸

Medical and Scientific Value

Rp is the only technique that can assess the resistance of the distal lung compartment. In patients with asthma, Rp is 2 to 7 times higher than in healthy individuals, despite comparable FEV₁ measurements.^{187, 189, 190} This technique also has been used to determine peripheral airway responsiveness and found to correlate with overall airway hyperresponsiveness, asthma severity, and RV.^{187–191}

Range of Values

Rp is expressed as cm H₂O/mL/min. In healthy individuals, baseline values are approximately 0.011 ± 0.003 . In individuals with asthma, baseline values range from 0.041 ± 0.015 in those with mild asthma to 0.113 ± 0.02 in those with moderate asthma.^{189, 191} In 1 study that assessed diurnal variation, no significant difference was found between the Rp at 4 PM and that measured at 4 AM, when compared within groups with asthma of similar severity and within healthy controls.¹⁹¹ Following administration of histamine aerosol (100 mg/mL) via the double-lumen catheter, values did increase in healthy controls from 0.011 ± 0.003 to 0.040 ± 0.007 . In comparison, Rp increased from 0.041 ± 0.015 to 0.193 ± 0.036 in individuals with mild asthma.¹⁸⁹

Repeatability

In several studies involving serial measures of Rp following “whole-lung” inhalation exposures to allergens or ozone, Rp was highly reproducible and unaffected by these

provocations.^{192, 193} Overall, however, there is limited information about the reproducibility of this test over long time periods in substantial numbers of patients.

Responsiveness

In individuals with asthma, Rp is sensitive to changes induced by local application of isoproterenol,^{187, 189} histamine,¹⁸⁹ bradykinin,¹⁹⁴ and dry air,^{188, 190} consistent with effects on smooth muscle. However, Rp is not altered 28 hours after whole-lung bronchoprovocation with allergen in individuals with mild allergic asthma¹⁹² or in healthy persons 24 hours after repetitive ozone exposures.¹⁹³ The effects of chronic anti-inflammatory treatment on Rp have not been examined, and an MCID in Rp has not been determined.

Validity

The validity of Rp measurement as a diagnostic tool in asthma or as an outcome for the assessment of therapeutic interventions has not been rigorously tested. Yet the large differences between persons with mild, intermittent asthma with normal FEV₁ and healthy individuals¹⁸⁹ suggest that this test has excellent discriminatory ability.

Associations

Limited studies have shown relationships of Rp to airway responsiveness,^{187, 189, 190} disease severity, and RV.¹⁹¹

Practicality and Risk

Rp measurement involves bronchoscopy and specialized equipment that can be performed only at specialized centers.

Demographic Considerations

No reference values have been established for Rp. Children have not been studied.

Priority for NIH-Initiated Clinical Research

Rp is considered an emerging outcome for use in population characterization and in observational studies as well as in prospective trials.

Future Directions or Research Questions

Further research is needed to:

1. Examine whether Rp measurements correlate with other measures of peripheral airway function; eg, FOT
2. Examine whether Rp has unique value in assessing responsiveness to chronic asthma treatment

PRESSURE-VOLUME CURVES

Summary

- Pressure-volume curves (PV curves) of the lung are used to study the static mechanical characteristics of the lung; specifically, compliance and maximum elastic recoil pressure.
- The applicability of PV curves is limited by the special equipment required for measurement as well as the requirement to insert an esophageal balloon; there is also limited information on the clinical utility of the measurements.

Methodology for Measurement and Other Considerations

Measurements of the PV characteristics of the lung are used in people with asthma to determine the cause of hyperinflation, the role of small airway disease, and the cause of decrease in expiratory flow. To obtain PV curves of the lung an esophageal balloon needs to be introduced into the lower third of the esophagus to measure transpulmonary pressure; volume is determined by body plethysmography or spirometry. The subject then performs static expiratory respiratory maneuvers. While some studies show that the PV curve in asthma is shifted upward without a loss in elastic recoil¹⁹⁵ and hence maintains expiratory driving pressure,¹⁹⁶ other studies show a decrease in recoil^{197–199} that may relate to severity. However, 1 study showed loss of recoil after allergen challenge.²⁰⁰ Following cold air isocapnic hyperventilation challenge, the inspiratory limb of the PV curve was shifted down and to the right, indicating increased pressure required to open previously closed airways.¹⁷⁴ Tests of small airway disease rely on the assumption that the expiratory PV curve is unchanged.¹⁹⁹ Little is known about the responsiveness of the PV curves to treatment except for 1 report.¹⁹⁸ There is no widely accepted standard methodology to determine PV curves. Also, normative values, information on test variability, and data on the relationship to clinical outcomes are very limited; therefore, PV curves are considered to be an emerging methodology and require additional research to determine their role as a clinical asthma outcome measure.

Future Directions or Research Questions

Further research is needed to:

1. Standardize and simplify methodology for pulmonary PV curves for application to clinical research
2. Establish normative values with standardized methods
3. Determine whether shifts in the PV curve constitute a predisposing risk factor for asthma or are the result of the altered lung biology in asthma

GAS EXCHANGE

Diffusing Capacity for Carbon Monoxide

Summary

- The diffusing capacity for carbon monoxide (DLCO) test measures the integrity and surface area of the alveolar-capillary membrane of the lung.
- The DLCO test may be elevated in asthma, but this is not a specific finding.
- The DLCO is most useful to rule out other lung diseases such as emphysema or interstitial lung disease.

Methodology for measurement and other considerations—The single-breath DLCO test is measured according to well-validated guidelines² and is designed as a measure of gas transfer or alveolar-capillary integrity. The maneuver is performed by inhaling a defined mixture of CO and helium (as a tracer gas) from residual volume followed by a 10-second breath-hold and exhalation into a new bag where gas is collected. The value is corrected for hemoglobin, as anemia can lower the DLCO.² With regard to asthma, the DLCO is generally in the normal range but can be elevated.^{201, 202} The elevation in DLCO noted in asthma is thought to be secondary to increased lung perfusion, particularly in the apices.²⁰¹ A study of 80 individuals with asthma found that 62 had values greater than 100% predicted, with a mean value for the group of $117 \pm 17\%$ predicted.²⁰¹ Of 45,000 patient encounters (from 16,778 patients) evaluated retrospectively, 254 individuals exhibited DLCO values greater than 85% predicted.²⁰² Of those, 80 (33%) carried the diagnosis of asthma.²⁰² No significant relationship has been observed between the DLCO and spirometric variables or atopic status.²⁰¹ Weak correlations were noted between DLCO corrected for alveolar volume and FEV₁ or RV.²⁰¹

DLCO can be used in the diagnosis of asthma if COPD or other lung diseases that can decrease the DLCO are under consideration.^{203, 204} Because the methodology is well established and reference values are available, DLCO is considered a supplemental outcome in asthma clinical research for population characterization, to be used when there is a need to rule out the diagnosis of COPD.

Arterial Blood Gases and Pulse Oximetry

Summary

- Arterial blood gases and pulse oximetry are useful as supplemental measures to assess oxygenation and ventilation in patients with acute symptomatic disease.

Methodology for measurement and other considerations—Although alveolar ventilation (as assessed by arterial P_{CO₂} [partial pressure of carbon dioxide]) and oxygenation (as assessed by arterial P_{O₂} [partial pressure of oxygen]) typically are normal in individuals with stable asthma, ventilation and gas exchange may be altered during severe acute airway obstruction. The *National Asthma Education and Prevention Program Expert Panel Report 3*⁶ recommends assessing ventilation and gas exchange in patients with asthma who have severe acute obstruction and in those unable to perform forced expiratory

maneuvers. Pulse oximetry also can be used to assess oxygenation as percentage arterial hemoglobin saturation, with the advantage of continuous noninvasive monitoring, but with the caution of inaccuracy in some individuals and a lack of assessment of P_{CO_2} (alveolar ventilation). Therefore, it is best used in conjunction with arterial blood gas measurements in patients with severe acute asthma.^{205, 206} Venous blood P_{CO_2} correlates with arterial P_{CO_2} and is sometimes used as a surrogate marker for ventilation status,²⁰⁷ although its predictive accuracy precludes routine use as a substitute for arterial blood samples. Measures of ventilation and gas exchange are supplemental outcome variables for studies involving individuals with asthma who have severe acute obstruction or comorbidities that affect ventilation or gas exchange.

MULTIPLE BREATH WASHOUT

Summary

- The multiple breath washout is an emerging measure of homogeneity of ventilation distribution in the lungs.
- The test is limited by lack of standardization and lack of information on clinical associations of the several parameters that can be derived from this test.

Methodology for Measurement and Other Considerations

Multiple breath washout (MBW), which was initially developed to measure functional residual capacity, evaluates the elimination from the lung of nitrogen or nonresident inert gases, such as helium or sulphur hexafluoride. As airway disease progresses, heterogeneity of ventilation distribution within the lung increases and a longer time and a greater expired volume are required to complete the washout.^{208, 209} MBW requires relatively little patient cooperation, which is particularly advantageous when studying young children, although tidal volume and respiratory rate can affect parameters used to quantify the washout.^{210, 211} Recent advancements in analyzing the breath-by-breath changes in the slope of phase III during the washout provide additional insights into the mechanisms of ventilation inhomogeneity.^{212, 213} Several studies suggest that MBW analyses may be more sensitive to alterations in airway function than conventional spirometry, particularly early in the disease process.²¹⁴ No standardized methodologies currently exist for the washout technique or the analysis and information on variability and normative data are inadequate. Therefore, MBW is listed as an emerging methodology and requires additional research.

WHEEZE AND COUGH RECORDERS

Summary

- Wheeze and cough recorders are promising technologies for assessment of asthma symptoms in ambulatory patients or in patients who are too young to perform other lung function tests.
- There is limited information on the utility of these devices for asthma research.

Methodology for Measurement and Other Considerations

Wheeze and cough recorders have been developed to objectively monitor the presence, frequency, and severity of these clinical manifestations of asthma.^{215, 216} They may be used for monitoring patients during sleep, at home or work, or during bronchial challenges in young children where lung function testing is not feasible. The paucity of published scientific literature on these devices makes it impossible at this time to make a strong recommendation about their role in asthma clinical research.

NASAL AIRWAY RESISTANCE AND ACOUSTIC RHINOMETRY

Summary

- Nasal airway resistance and acoustic rhinometry measure mechanical obstruction of the nose, which is a common finding in asthma.
- Lack of normal values and standardized methodology limit the usefulness of these measures at the present time.

Methodology for Measurement and Other Considerations

The vast majority of people with asthma also suffer from some form of nasal disease, ranging from intermittent rhinitis to chronic rhinosinusitis. This indicates that asthma affects not only the lower airways but also the entire respiratory system. From this perspective, it is anticipated that future clinical research may need to include simultaneous monitoring of physiologic outcomes of both the upper and lower airways. Nasal airway resistance and acoustic rhinometry are physiologic outcomes that measure the patency of the nasal airways. Nasal airway resistance can be measured through anterior or posterior rhinomanometry or through FOTs.²¹⁷ Acoustic rhinometry uses sonar principles to map the anatomy of the nasal airways.^{218–220} Another technique, rhinostereometry, uses optical principles.²²¹ These outcomes have been used in many studies for several decades. Some trials in individuals with rhinitis have used a modified peak flow meter to measure peak nasal inspiratory or even expiratory flow.^{222–224} The techniques are not invasive and are relatively simple to perform, and the required equipment is not prohibitively expensive. The methodologies for both outcomes have been described in detail, although no consensus guidelines for the use of either method have been published. In addition, because no normative values are available, it is difficult to compare absolute values between studies. These outcomes should be considered emerging in that standardization and various forms of validation are required prior to their use in asthma clinical research.

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Abbreviations

μg	Microgram(s)
ATS	American Thoracic Society
BDP	Beclomethasone dipropionate
CO₂	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CV	Coefficient of variation
DLCO	Diffusing capacity for carbon monoxide
EIB	Exercise-induced bronchospasm
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEF_{25–75}	Forced expiratory flow between 25% and 75% of vital capacity
FeNO	Fractional exhaled nitric oxide
FEV_{0.5}	Forced expiratory volume in 0.5 second
FEV₁	Forced expiratory volume in 1 second
FOT	Forced oscillation technique
FRC	Functional residual capacity
FVC	Forced vital capacity
G_{aw}	Airway conductance
L	Liter(s)
L/min	Liter(s) per minute
L/sec	Liter(s) per second
LABA	Long-acting β-agonist
MBW	Multiple breath washout
MCID	Minimal clinically important difference
min	Minute(s)
mL/min	Milliliter(s) per minute
mL	Milliliter(s)
mmHg	Millimeter(s) of mercury
MVV	Maximal voluntary ventilation
NHANES-3	Third National Health and Nutrition Examination Survey
NIH	National Institutes of Health

NO	Nitric oxide
PC₂₀	Provocative concentration that causes a 20% fall in FEV ₁ from baseline
P_{CO2}	Partial pressure of carbon dioxide
PD₁₅	Provocative dose that causes a 15% fall in FEV ₁ from baseline
PEF	Peak expiratory flow
P_{O2}	Partial pressure of oxygen
PV curve	Pressure-volume curve
R_{aw}	Airway resistance
R_p	Peripheral airway resistance
RV	Residual volume
SABA	Short-acting β -agonist
sG_{aw}	Specific airway conductance
sR_{aw}	Specific airway resistance
SVC	Slow vital capacity
TLC	Total lung capacity

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TABLE I

Recommendations for classifying pulmonary physiology asthma outcome measures for NIH-initiated clinical research for adults (≥ 18 years of age) and adolescents (aged 12 to 17 years)

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/ effectiveness outcomes	Observational study outcomes *
Core outcomes	Spirometry (pre- and post-bronchodilator)	Spirometry (without bronchodilator)	Spirometry (pre- and post-bronchodilator)
Supplemental outcomes	PEF monitoring Airway responsiveness [†] Lung volumes Gas exchange [‡]	PEF monitoring Airway responsiveness [†] Lung volumes Spirometry (pre- and post-bronchodilator) Gas exchange [‡]	PEF monitoring Airway responsiveness [†] Lung volumes Gas exchange [‡]
Emerging outcomes	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Peripheral airway resistance Pressure/volume curves Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Peripheral airway resistance Pressure/volume curves Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Peripheral airway resistance Pressure/volume curves Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry

NIH, National Institutes of Health; PEF, peak expiratory flow.

* Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies (GWAS), and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

[†] Methacholine inhalation and exercise challenge

[‡] Pulmonary diffusing capacity; arterial blood gases and pulse oximetry

[§] Isocapnic hyperventilation challenge; mannitol inhalation challenge

TABLE II

Recommendations for classifying pulmonary physiology asthma outcome measures for NIH-initiated clinical research for children (aged 5 to 11 years)

	Characterization of study population for prospective clinical trials (ie, baseline information)	Prospective clinical trial efficacy/ effectiveness outcomes	Observational study outcomes *
Core outcomes	Spirometry (pre- and post-bronchodilator)	Spirometry (without bronchodilator)	Spirometry (pre- and post-bronchodilator)
Supplemental outcomes	PEF monitoring Airway responsiveness [†] Lung volumes Gas exchange [‡]	PEF monitoring Airway responsiveness [†] Lung volumes Spirometry (pre- and post-bronchodilator) Gas exchange [‡]	PEF monitoring Airway responsiveness [†] Lung volumes Gas exchange [‡]
Emerging outcomes	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry	Self-administered spirometry Airway responsiveness [§] Specific airway resistance/conductance Forced oscillation technique Multiple breath washout Wheeze and cough recorders Nasal airway resistance Acoustic rhinometry

NIH, National Institutes of Health; PEF, peak expiratory flow.

* Observational study designs include cohort, case control, cross sectional, retrospective reviews, and genome-wide association studies (GWAS), and secondary analysis of existing data. Some measures may not be available in studies using previously collected data.

[†] Methacholine inhalation and exercise challenge (children aged 5 to 7 years are less likely to perform well on these tests)

[‡] Pulmonary diffusing capacity (breath holding is difficult in children aged 5 to 7 years); arterial blood gases and pulse oximetry

[§] Mannitol inhalation challenge: approved down to age 6 in the United States

TABLE III

Methods for measuring and reporting core and supplemental pulmonary physiology outcomes for all ages

Spirometry FEV₁ and FVC FEV₁/FVC	Measured by ATS/ERS guidelines and using NHANES-3 normative values. Serial measures should be performed at the same time each day, if possible. Report: - Percent predicted values (at baseline and at any other time point, if applicable) - Changes over the course of a study: - Percent change from baseline in the absolute value - Absolute change from baseline (mL) - Change from baseline in the percent predicted value Report: - Ratio of absolute values (at baseline and at any other time point, if applicable) - Changes over the course of a study: - Absolute change from baseline in the value of the ratio - Change from baseline in the percent predicted value (Indicate whether bronchodilator was withheld prior to test)
Bronchodilator reversibility (spirometry pre- and post-bronchodilator)	Preferred method: (1) Withhold bronchodilator before the measure (12–24 hours for long-acting β-agonist or anticholinergic; 4–6 hours for SABA); (2) administer 4 separate puffs of albuterol (90 μg of albuterol base/puff) with spacer at 30-second intervals between puffs, followed by spirometry after 15 minutes. Report: - Pre- and post-bronchodilator FEV₁ (expressed as percent predicted) - Percent change from pre- to post-bronchodilator in the absolute value of FEV₁ - Absolute change in FEV₁ from pre- to post-bronchodilator (in mL)
PEF	Report: - Percent predicted values (NHANES-3 normative values) - Percent change from baseline in the absolute values over the course of the study - Absolute change from baseline over the course of the study (in L/min) - Variability (diurnal amplitude as a percentage of the day's mean)
Airway responsiveness (Methacholine inhalation and exercise challenge tests are supplemental outcomes; isocapnic hyperventilation and mannitol inhalation challenge tests are emerging outcomes)	Methacholine inhalation challenge: Preferred method: Dosimeter method, using a calibrated nebulizer and dosing schedule per ATS guidelines¹ (choice of 5- or 10-dose schedule depends on research question; 10-dose schedule has greater resolution) Report: - PC₂₀ Exercise challenge: Preferred method: Motor-driven treadmill or cycle ergometer, using ATS guidelines¹; control ventilation and the temperature and humidity of inspired air to reduce response variability Report: - Percent reduction in FEV₁ from baseline
Lung volumes	Preferred method: - FRC, by body plethysmography - TLC and RV by an SVC maneuver following FRC Report:

	• FRC, RV, and TLC percent predicted (predictive equations are old and require revision) • FRC/TLC (ratio of absolute values) • RV/TLC (ratio of absolute values)
Gas exchange	Preferred method: Measuring DLCO using ATS/ERS guidelines² Report: • DLCO percent predicted (normal range between 81% and 140% predicted) • DLCO mL/min/mmHg Alternative methods: • Arterial blood gases (assessed by arterial P_{O₂}, P_{CO₂}) • Pulse oximetry (reported as percentage of arterial hemoglobin saturation)

ATS/ERS, American Thoracic Society and European Respiratory Society; DLCO, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FRC, functional residual capacity; FVC, forced vital capacity; L/min, liter(s) per minute; µg, microgram(s); min, minute(s); mL, milliliter(s); mmHg, millimeter(s) of mercury; NHANES-3, third National Health and Nutrition Examination Survey; NIH, National Institutes of Health; PC₂₀, provocative concentration causing a 20% fall in FEV₁ from baseline; PCO₂, partial pressure of carbon dioxide; PEF, peak expiratory flow; PO₂, partial pressure of oxygen; RV, residual volume; SABA, short-acting β-agonist; SVC, slow vital capacity; TLC, total lung capacity.

TABLE IV**Key points and recommendations**

1	Spirometry without a bronchodilator is a core measure for characterizing the lung function of study participants in clinical trials and observational studies, and is a core measure for clinical trials of efficacy.
2	Bronchodilator reversibility (pre- and post-bronchodilator spirometry) is a core physiologic measure to characterize participant populations for clinical trials and observational studies.
3	Increased airway responsiveness expressed as bronchoconstriction with provocative agents (bronchial challenge) is characteristic to patients with asthma; however, the absence of adequately standardized methodologies, the personnel requirements to perform the study, and the constraints inherent in evaluating patients with severe disease limit bronchial challenge testing to a supplemental physiologic measurement for all types of studies. Some forms of bronchial challenge are considered emerging outcomes.
4	Children over 5 years of age can generally cooperate to perform the core spirometric measurements, particularly when evaluated by personnel experienced at testing young children. The development of shortened standardized protocols for bronchial challenge testing, as well as further development and standardization of emerging methodologies such as forced oscillatory resistance, will increase the success rate in young children.