

AARC Clinical Practice Guideline

Methacholine Challenge Testing: 2001 Revision & Update

MCT 1.0 PROCEDURE:

Methacholine challenge test. This guideline does not address other bronchial challenges (eg, histamine, exercise, occupational exposures, specific antigens, isocapnic hyperventilation.)

MCT 2.0 DESCRIPTION/DEFINITION:

2.1 The methacholine challenge test is one method of assessing airway responsiveness. In this test, the patient inhales an aerosol of one or more concentrations of methacholine. Results of pulmonary function tests (eg, spirometry, specific conductance) performed before and after the inhalations are used to quantitate response. This guideline applies to adults and children capable of adequately performing spirometry or body plethysmography and of cooperating during the course of the challenge.

2.2 A positive test is defined as a decrease from the baseline forced expiratory volume in the first second (FEV₁) or of the postdiluent FEV₁ value of 20%, or of a decrease in specific conductance of 35-45% from the baseline or postdiluent value.¹⁻⁴

MCT 3.0 SETTINGS:

Possible settings include:

- 3.1** pulmonary function laboratory;
- 3.2** clinic or physician's office;
- 3.3** field site (eg, occupational setting or workplace).

MCT 4.0 INDICATIONS:

Indications for testing include:

- 4.1** the need to exclude a diagnosis of airway hyperreactivity (ie, asthma);^{1,2,5-9}
- 4.2** the need to evaluate occupational asthma;^{1,2}
- 4.3** the need to assess the severity of hyperresponsiveness;^{1,2}
- 4.4** the need to determine the relative risk of developing asthma;²

4.5 the need to assess response to therapeutic interventions;²

MCT 5.0 CONTRAINDICATIONS:

5.1 Absolute contraindications are:

5.1.1 ventilatory impairment: FEV₁ <50% of predicted or < 1.0 L;² [This may be a relative contraindication depending on the age or size of the patient or on the presence of a restrictive lung disorder (reduced forced vital capacity, or FVC, with a relatively normal FEV₁/FVC)];

5.1.2 heart attack or stroke within the previous 3 months;^{1,2}

5.1.3 known aortic or cerebral aneurysm;^{1,2}

5.1.4 uncontrolled hypertension [The American Thoracic Society (ATS) suggests systolic pressure > 200 and/or diastolic pressure >110 mm Hg.].²

5.2 Relative contraindications are:

5.2.1 ventilatory impairment: FEV₁ > 50% or > 1.5L but < 60% of predicted;²

5.2.2 inability to perform spirometry of acceptable quality;²

5.2.3 significant response to the diluent, if administered (ie, > 10% fall in FEV₁ from baseline);¹⁰

5.2.4 upper- or lower-respiratory-tract infection within previous 2 to 6 weeks;^{1,11,12}

5.2.5 current use of cholinesterase-inhibitor medication (for myasthenia gravis);²

5.2.6 pregnancy (The effect of methacholine on the fetus is unknown.);¹³

5.2.7 lactation;¹³

5.3 Failure to withhold medications may affect the methacholine challenge test. Recommended periods for withholding medications are generally based on their duration of action.^{1,2} Laboratories may choose to develop a simplified withholding schedule that makes allowances for any of the following used by the patient:

Agent	Withholding Time
short-acting inhaled bronchodilators	6-8 hours
long-acting inhaled bronchodilators (eg: salmeterol, formoterol)	48 hours
anticholinergic aerosols (eg: ipratropium)	24 hours
tiotropium	up to 1 week ¹⁴
disodium cromoglycate	8 hours
nedocromil	48 hours
oral beta ₂ -adrenergic agonists	24 hours
theophyllines, depending on specific preparation ²	12-48 hours
leukotriene modifiers	24 hours ²
corticosteroids, inhaled or oral (may decrease hyperresponsiveness)	Duration of effect is unknown but may be prolonged. ^{15,16}

5.4 Foods: Ingestion of coffee, tea, cola drinks, chocolate, or other foods containing caffeine may decrease bronchial responsiveness. These substances should be withheld on the day of test.

5.5 Other factors that may confound results include:

5.5.1 smoking,¹⁷

5.5.2 occupational sensitizers,¹⁸

5.5.3 respiratory infection,^{11,12}

5.5.4 specific antigens,¹⁹

5.5.5 vigorous exercise.²⁰⁻²² (Performing other bronchial challenge procedures or exercise testing immediately prior to methacholine challenge may affect interpretation.)

MCT 6.0 HAZARDS/COMPLICATIONS:

Possible hazards or untoward reactions include:

6.1 bronchoconstriction, hyperinflation, severe coughing;

6.2 hazards associated with spirometry, such as dizziness, light-headedness, chest pain;²³

6.3 possible exposure of testing personnel to provocative substance.

MCT 7.0 LIMITATIONS OF METHOD & VALIDATION OF RESULTS:

7.1 Limitations of pulmonary function testing used to quantitate response including intralaboratory variability for each pulmonary function test variable:

7.1.1 In some patients, spirometry may

not be sensitive enough or specific enough to detect response, and other measurements such as airways resistance (R_{aw}) and/or specific conductance (sG_{aw}) may be used. Differences of opinion exist regarding the spirometric values that best track response in particular airways.^{1,2,24}

7.1.2 Deep inspiration taken while performing spirometry variably alters bronchial tone and may result in either bronchoconstriction or bronchodilatation.²⁵⁻²⁷

7.1.3 Poor patient effort during pulmonary function testing can produce false-positive results and make interpretation more difficult or impossible. Results from spirometry should be acceptable according to the most recent ATS recommendations, and the quality of the flow-volume curves should be examined after each maneuver.^{2,28}

7.1.4 Spirometry should be performed according to the current acceptability guidelines of the ATS. Alternatively, the expiratory maneuver can be shortened to about 2 seconds after the methacholine doses are inhaled if FEV₁ is the only outcome measure. If this shortened expiratory maneuver is used, care should be taken to assure that the inspiration is maximal.² After the inhalation of diluent (if used) and of each dose of methacholine, FEV₁ measurements should be made at 30 and 90 seconds after the last inhalation. The time interval between doses should be standardized at 5 minutes to keep cumulative effect constant.

7.2 A limitation of the method is the variability due to the effects of various factors including medications, time of day, and differences in technique and equipment.

7.3 Inconsistencies in technique and equipment can affect the amount of agonist reaching the airways and, thus, the subject's response—making meaningful interpretation difficult or impossible. Factors influencing response that must be controlled and held constant across testing include nebulizer output and particle size, volume inhaled, length of breath-hold, and inspiratory flow.^{2,29,30}

7.4 If clinical suspicions are not confirmed by

one test, additional tests may be indicated.

7.5 The final test report should include:

- 7.5.1** PC₂₀FEV₁ (ie, the provocative concentration that causes a 20% fall in FEV₁).
- 7.5.2** comment on the adequacy of spirometric effort and quality of other measurements;
- 7.5.3** notation regarding medications known to confound interpretation of results (Section 5.3) taken by the patient prior to testing;
- 7.5.4** presence or absence of other factors known to confound interpretation of results (Section 5.4);
- 7.5.5** clinical signs and symptoms and clinical appearance during the course of the test and after final dose;
- 7.5.6** bronchodilator and dose administered at end of challenge;
- 7.5.7** tabular display of data for each test phase including response to bronchodilator at end of challenge.

MCT 8.0 ASSESSMENT OF NEED:

Need is established by documenting in a subject the presence of one or more of the listed indications or as established by progression through the institution's or the laboratory's protocol decision tree.

MCT 9.0 ASSESSMENT OF TEST QUALITY & VALIDITY OF RESULTS:

The consensus of the committee is that all diagnostic procedures should follow the quality model de-

scribed in the NCCLS GP26-A A Quality System Model for Health Care.³¹ (Fig. 1) The document describes a laboratory path of workflow model that incorporates all the steps of the procedure. This process begins with patient assessment and the generation of a clinical indication for testing through the application of the test results to patient care. The quality system essentials defined for all health care services provide the framework for managing the path of workflow. A continuation of this model for respiratory care services is further described in NCCLS HS4-A A Quality System Model for Respiratory Care.³² In both quality models the patient is the central focus.

9.1 General considerations include:

- 9.1.1** As part of any quality assurance program, indicators must be developed to monitor areas addressed in the path of workflow.
- 9.1.2** Each laboratory should standardize procedures and demonstrate intertechnologist reliability. Test results can be considered valid only if they are derived according to and conform to established laboratory quality control, quality assurance, and monitoring protocols.
- 9.1.3** Documentation of results, therapeutic intervention (or lack of) and/or clinical decisions should be placed in the patient's medical record.
- 9.1.4** The type of medications, dose, and time taken prior to testing and the results of the pretest assessment should be docu-

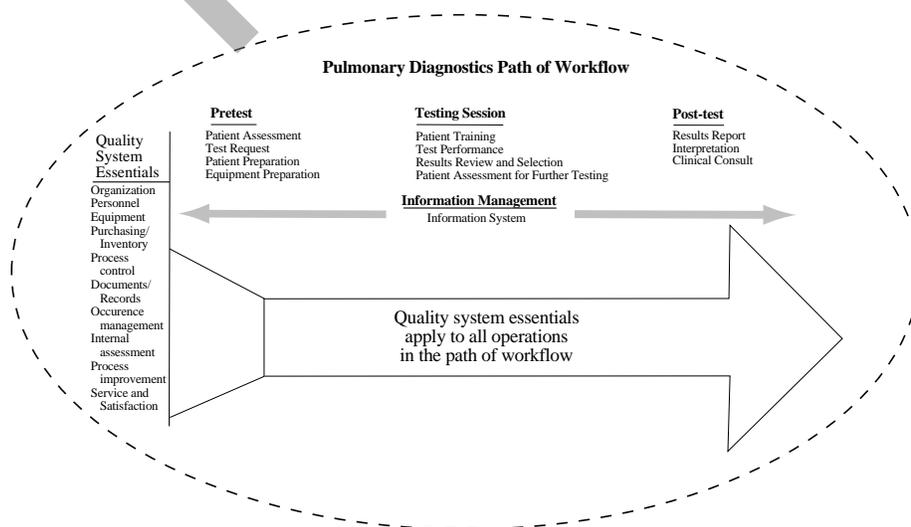


Fig. 1. Structure for a Quality System Model for a Pulmonary Diagnostics Service (From Reference 31, with permission)

mented.

9.1.5 Report of test results should contain a statement by the technician performing the test regarding test quality (including patient understanding of directions and effort expended) and, if appropriate, which recommendations were not met.

9.1.6 Test results should be interpreted by a physician, taking into consideration the clinical question to be answered.

9.1.7 Personnel who do not meet annual competency requirements or whose competency is deemed unacceptable as documented in an occurrence report should not be allowed to participate, until they have received remedial instruction and have been re-evaluated.

9.1.8 There must be evidence of active review of quality control, proficiency testing, and physician alert, or 'panic' values, on a level commensurate with the number of tests performed.

9.2 Calibration and quality control measures specific to equipment used in methacholine challenge include:

9.2.1 the size of the dose received and, thus, the response and its interpretation include nebulizer output, particle size, inspiratory flow, lung volume at beginning of inspiration, and breath-hold time (These factors must be held constant across the testing procedure and from one test to another.);

9.2.2 excessive variability in measured values including a nonreproducible baseline (FEV₁ variation of more than 0.2 L after repeated efforts) makes test results more difficult to interpret.²⁸

9.3 Recommendations related to equipment maintenance and calibration made in the Clinical Practice Guidelines for spirometry²³ and measurement of specific conductance³³ should be addressed.

MCT 10.0 RESOURCES:

10.1 Equipment:

10.1.1 Spirometers must meet or exceed ATS requirements²⁸ and be calibrated appropriately. All other equipment must be appropriately calibrated and maintained.

10.1.2 A high quality nebulizer with consistent output should be used to produce the aerosol. The particles produced by the nebulizer should have a mass median aerodynamic diameter (MMAD) of 1-4 microns.¹ If more than one nebulizer is used in the testing of a given subject, nebulizer output should be measured for each nebulizer to assure a consistent dose. If output measurement is not possible, we recommend the use of the same nebulizer to deliver all concentrations to a given patient.

10.1.3 The gas powering the nebulizer and/or dosimeter should be at the correct driving pressure or flow (as specified by the manufacturer) and should be maintained at that pressure or flowrate consistently throughout the test.

10.1.4 Reagents:

10.1.4.1 The Food & Drug Administration (FDA) approved form of methacholine powder (Provocholine) is available in prepackaged vials ready for dilution. Provocholine and diluent can be obtained from Methapharm Inc, 131 Clarence St, Brantford, Ontario, Canada, N3T 2V6; Telephone 800.287.7686.

10.1.4.2 The recommended diluent used to dissolve the methacholine is sterile normal saline (0.9% sodium chloride) with or without a preservative (eg, 0.4% phenol).²

10.1.4.3 Various strategies have been described for dosing schemes.^{10,13,34-38} The range of doses is 0.02-25.0 mg/mL, generally given in doubling doses^{1,10,13,24,29} (ie, 0.02 mg/mL, 0.04 mg/mL, 0.08 mg/mL.). The dosing scheme most recently recommended by the ATS is: diluent, 0.03, 0.06, 0.125, 0.25, 0.5, 1, 2, 4, 8, and 16 mg/mL.² If a shortened dosing protocol is desired, the ATS recommends: diluent, 0.06, 0.25, 1, 4, and 16 mg/mL.² Caution should be used with the shortened protocol when testing small children with asthma symptoms. The use of the diluent step is optional.²

10.1.4.4 In general, higher concentrations of methacholine solution (ie, > 1.25 mg/mL) are stable for at least 4 months when stored at 4° C.³⁹⁻⁴¹ The

package insert for Provocholine recommends that solutions > 0.25 mg/mL be stored for no longer than 2 weeks, with weaker solutions mixed on the day of testing.¹³

10.1.4.5 A pharmacist or other well-trained individual should prepare the methacholine reagents according to the manufacturer's recommendations, using sterile technique.

10.1.4.6 Reagents should be clearly labeled with dose, date prepared, and expiration date.

10.1.4.7 The test should be administered in a well-ventilated room (with at least 2 complete air exchanges per hour).²⁸ A filter to collect excess particles or an exhaust system to remove provocative material from the room may be desirable.

10.1.4.8 Oxygen, bronchodilators, and resuscitation equipment should be readily available.^{1,24}

10.1.4.9 The need for written consent should be determined within the specific institution.

10.1.4.10 A pretest questionnaire should be used. An example of a questionnaire can be found in the ATS Methacholine Challenge Guideline.²

10.2 Personnel:

10.2.1 Methacholine challenge tests should be performed under the direction of a physician trained in pulmonary function testing and experienced in bronchial provocation. Personnel performing the test should be experienced in patient assessment, knowledgeable of and have demonstrated competency in performing this challenge (including reversal of methacholine response), know the associated hazards, and be certified in basic life support. Attainment of the CPFT and/or RPFT credentials is recommended.

10.2.2 During the testing procedure, a physician knowledgeable in provocation testing procedures and trained to treat acute bronchospasm and use resuscitation equipment must be close enough to respond in an emergency.

MCT 11.0 PATIENT MONITORING:

11.1 The FEV₁ is the primary variable to be monitored, and the results of spirometry should meet acceptability and reproducibility recommendations proposed by the ATS.²⁸ A shortened expiratory maneuver can be used in some situations and may be acceptable, and reproducibility after inhalation of some methacholine concentrations may be difficult.²

11.2 The test should be administered according to the specific protocol, with the number of breaths and the breathing pattern documented.

11.3 Breath sounds, pulse rate, pulse oximetry, and/or blood pressure may be monitored to assist in patient evaluation and test interpretation.⁴²⁻⁴⁵ Patients should not be left unattended during the procedure.

11.4 In the case of a positive response to provocation (ie, $\geq 20\%$ fall in FEV₁), bronchodilator may be administered to speed recovery. Spirometry should be repeated after bronchodilator administration to ensure that ventilatory function has returned to near baseline (ie, at least 85% of baseline).⁴⁶

MCT 12.0 FREQUENCY:

12.1 To ensure that a previous methacholine challenge test does not affect a later test, 230 minutes should be allowed to elapse before the test is repeated.⁴⁷ Tolerance of methacholine may occur in patients who are not asthmatic when tests are repeated at less than 24-hour intervals.^{48,49}

12.2 When a test is to be repeated, medications, exposures, time of day, and nebulizer employed should be held constant, if possible.

MCT 13.0 INFECTION CONTROL:

13.1 The staff, supervisors, and physician-directors associated with the pulmonary laboratory should be conversant with "Guideline for Isolation Precautions in Hospitals"⁵⁰ and develop and implement policies and procedures for the laboratory that comply with its recommendations for Standard Precautions and Transmission-Based Precautions.

13.2 The laboratory's manager and its medical director should maintain communication and cooperation with the institution's infection control service and the personnel health service to help assure consistency and thoroughness in

complying with the institution's policies related to immunizations, post-exposure prophylaxis, and job- and community-related illnesses and exposures.⁵¹

13.3 Primary considerations include adequate handwashing,⁵² provision of prescribed ventilation with adequate air exchanges,⁵³ careful handling and thorough cleaning and processing of equipment,⁵⁰ and the exercise of particular care in scheduling and interfacing with the patient in whom a diagnosis has not been established.⁵⁰

13.4 Sterility of reagents should be maintained by proper storage and aseptic handling.

MCT 14.0 AGE-SPECIFIC ISSUES:

Test instructions and techniques should be given in a manner that takes into consideration the learning ability and communication skills of the patient being tested.

14.1 Neonatal: This CPG does not apply to neonatal populations.

14.2 Pediatric: This CPG is appropriate for children who can perform good quality spirometry or body plethysmography ≥ 5 years of age).

14.3 Geriatric: This CPG is appropriate for the geriatric population.

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The current Pulmonary Function Clinical Practice Guidelines Committee updated an earlier version (Bronchial provocation. *Respir Care* 1992;37(8):902-906) and gratefully acknowledge the contributions of Robert Brown, Michael Kochansky, and Kevin Shrake who provided input to that earlier version.

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