Bronchial Provocation
Methacholine Challenge Testing

Adapting to the
ERS Task Force Technical Standard

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University of Wisconsin Hospital and Clinics
Disclosures

• Presenter for MGC Diagnostics Cardiopulmonary seminar.
• Presenter for Methapharm.
• Education consultant for ERT.

• The University of Wisconsin Pulmonary Lab uses a mix of PFT systems and devices including: MGC Diagnostics, Jaeger, Vyaire, ndd, nSpire, Ecomedics, Ganzorn, Hans Rudolph, Circassia....


2016 ATS Pulmonary Function Laboratory Management and Procedure Manual


Abstract : Developing Alternative Delivery System for Methacholine Challenge Tests, Allan L Coates, Kitty Leung, Sharon Dell, Bruce Culver

El-Gammal, Killian, Scime, et al.; Relationship between Wright and AeroElipse Nebulizers 2015
Objectives

- Goal of the Methacholine Challenge test.
- Indications / Contraindications.
- Key points from the new ERS technical standard.
- Methods and equipment used to perform the test.
- Airway resistance during BCT.
- Case examples and basics of interpretation.
- Pitfalls to obtaining a quality test.
- Tools related to methacholine challenge testing.
Principle / goal of methacholine challenge testing

• Assess airway responsiveness-pulmonary function
  – During exposure to increasing dose or concentration of methacholine chloride, what changes are seen in airway function?
  – Provocative dose that results in a 20% fall in FEV1 (PD20)

  – Options
    • Airway resistance (Decrease in sGaw: PD40)
    • Oscillometry (Increase in R5 or resonant freq)
What is Airway Hyper Responsiveness?

- An increased sensitivity and exaggerated response to non-allergic stimuli.
- AHR is associated with asthma.
- AHR is also seen in other diseases associated with airway inflammation and obstruction.
• AHR is common in athletes (cold related sports)
• AHR may increase during exacerbations
• AHR may decrease during Rx with antiinflammatory medications.
• AHR may be absent during asymptomatic periods.
Direct verses indirect stimuli

**Direct Stimuli**

- Methacholine Chloride
  - Synthetic derivative of neurotransmitter acetylcholine
- Histamine
  - Effector cells / Muscarinic receptors
  - Airway smooth muscle
  - Bronchial endothelial cells
  - Mucus producing cells

**Indirect Stimuli**

- Exercise
- Isocapnic /eucapnic hyperventilation
- Hyper / Hypotonic aerosols
- Mannitol

Airflow changes

Intermediary cells
- Inflammatory cells
- Neuronal cells
Patient types

• Typically ordered for:
  – Complaints of cough, dyspnea on exertion, help rule out asthma.
  – Medical evaluations:
    • Military
    • Firefighters
    • Boot camp
    • Scuba diving clearance
  – Appropriateness of therapy
  – Validation of inhaler use for sports.
Value of “Metha” Testing

• Clinician perspective:
  – Provides possible cause of impairment for patients complaining of coughing, dyspnea or chest tightness.
  – Often used as last resort for patients with vague symptoms.
  – Tool to give clearance for entry to military
  – Tool to evaluate if drug therapy is indeed needed.
  – Tool to help exclude a diagnosis of asthma
Value of “Metha” Testing

• Patient perspective:
  – Get answers… ?
  – Get ok- for career or activity
  – Workman comp claims

• Lab perspective:
  – Expanded scope of services / skills your pulmonary lab can offer.
  – Revenue
  – FTE justification
  – Research study participation
Value of Methacholine Test

- “Methacholine challenge testing is more useful in excluding the diagnosis of asthma than in establishing one because its negative predictive power is greater than its positive predictive power.”
- Pretest probability: wheezing, dyspnea, chest tightness, cough…
  - With exposure to cold
  - After exercise
  - During respiratory infections
  - Following inhalant exposures in workplace
Clinical Indications

• Assess airway responsiveness
• Spirometry before and after bronchodilators has not helped establish a diagnosis.
• Contribute to a dx of asthma
• Evaluation of occupational asthma
• Evaluate risk of developing asthma
• Assess severity of asthma
• Assess response to therapy
ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests


Contraindications*

Things that may alter the quality of the test or may put the patient at greater risk / discomfort.

**TABLE 1 Contraindications for bronchial challenge testing**

**Airflow limitation**
- FEV$_1$ <60% predicted (adults or children) or 1.5 L (adults)
- FEV$_1$ <75% predicted (adults or children) for exercise or eucapnic voluntary hyperpnoea challenge

**Spirometry quality**
- Inability to perform acceptable and repeatable spirometry manoeuvres throughout the test procedure

**Cardiovascular problems**
- Myocardial infarction or stroke in last 3 months
- Uncontrolled hypertension
- Known aortic aneurysm
- Recent eye surgery or intracranial pressure elevation risk

**General**
- Inability to perform any of the testing manoeuvres, such as inhaling the challenge agent consistently or difficulty with exercise on treadmill or bike; most commonly in young children or elderly patients
• **Low FEV1** (relative contraindication, children and adults)
  - FEV1 < 1.5 L (adults)
  - FEV1 < 60% of predicted (adults or children)
  - FEV1 < 75% of pred (adults or children) exercise or EVH.

• **Obstructive defect at baseline testing**
  - Low FEV1 and FEV1/FVC ratio
  - Already documented response to BDs (12% and 200 mL)

• **Poor quality spirometry**
  - A quality BCT relies on acceptable spirometry. *Unreliable baseline values or poor effort…reschedule/eval alternative endpoint.*
Contraindications*

- Cardiovascular problems:
  - Uncontrolled hypertension (>200 systolic / >100 mmHg diastolic)
  - Recent MI, stroke, arterial hypoxemia, known aortic aneurysm

- Recent eye surgery or any condition where increased intracranial pressure would be harmful is a contraindication. (absolute)
  - Lasix surg, detached retina, cerebral aneurysm

- Severe airflow limitation (FEV1< 50% pred or <1.0 L)
Relative contraindications *specific* to Methacholine testing:

- Pregnancy and nursing mothers
  - Category C drug (not known if causes fetal problems or if excreted in breast milk)
- Current use of cholinesterase inhibitor meds for myasthenia gravis
Staff Safety

• Minimize staff exposure to methacholine aerosol (distance, mask)
• Consider using a breath-actuated neb or dosimeter
  – Expiratory filters are available for BAN and APS devices.
• Use a mouthpiece not facemask to deliver methacholine.
• Test in a room with at least 2 complete air exchanges, exhaust ventilation or HEPA filtration.
• Consider excluding staff with AHR

Technologist Safety
Patient Safety

• Staff should be **well trained**
  – Competencies up to date
  – Senior staff or MD available
  – Minimize interruptions

• Stay with patient during entire test

• Rescue medications **must be in testing room** (Albuterol, epinephrine)

• Stethoscope, pulse oximeter, oxygen.

• Post test within 10% of baseline
Staff Qualifications (minimum)*

TABLE 2 Qualifications to perform bronchial challenge tests

The technician/respiratory scientist should:

1) Have background knowledge of respiratory diseases, be familiar with this guideline and knowledgeable about specific test procedures
2) Be capable of managing the equipment including set-up, calibration checks, verification of proper function, maintenance, hygiene and cleaning
3) Be proficient at spirometry
4) Know the contraindications to bronchial challenge testing
5) Be familiar with safety and emergency procedures
6) Know when to stop further testing
7) Be proficient with the administration of inhaled bronchodilators and evaluation of the response to them
Staff Qualifications... *to become proficient*

- Pulmonary lab director is responsible for evaluation / verification of training.
  - 4 days of hands on training*
  - 20 supervised tests for new technician/ respiratory scientist*

ERS TECHNICAL STANDARD A.L. COATES ET AL*
### Recommendations for withholding medications

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<tr>
<th>Medication</th>
<th>Minimum time interval from last dose to MCT h</th>
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<td>≥168</td>
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<tr>
<td>Oral theophylline</td>
<td>12–24</td>
</tr>
</tbody>
</table>
Patient preparation...scheduling*

• List of meds to avoid.
• Withhold: Alcohol 4 hrs, smoking 1 hr.

• Asthma meds (except bronchodilators) may be continued if the intent is to monitor the response to therapy.

• Single dose (cromones, inhaled corticosteroids, leukotriene modifiers) have minimal effect....if goal is to be free of antiinflammatory effect...4-8 weeks
Don’t worry about…

• Flu shots
• Menstrual cycle or contraceptives
• **Normal** dietary intake of caffeinated products
• Antihistamines
Methacholine Chloride

- Established compound used to assess airway hyperresponsiveness.
- Made in Canada by Methapharm
  - FDA approved
- White, water soluble powder, hygroscopic
- 20 mL vial contains 100 mg dry powder of Methacholine chloride USP
- Parasympathomimetic (cholinergic) bronchoconstrictive agent, inhalation only, for diagnostic purposes.

Methapharm.com
20 mL vial (100mg)

How Provocholine is Supplied

- Supplied in 20 mL amber glass vials containing 100 mg methacholine chloride powder for reconstitution
- Supplied in boxes of 6 vials

C₈H₁₈CINO₂
Premixed concentrations

• On the horizon…
  – Single doses?

• Advantages
  – No time required for mixing
  – Standardized concentrations
  – Can reduce dosing errors
Solution preparation*

- Reconstitution should be by pharmacist or other well trained person using sterile technique.

- Precise mixing is critical for accurate results and patient safety.

- Diluent can be sterile normal saline with or without phenol.
- Solutions should be warmed to room temperature before use.
Solution preparation

• Powder form: storage at room temp up to 3 years 59-86°F (15-30°C)

• Refrigerate reconstituted solutions at 36 - 46°F (2 - 8°C) for no more than 2 weeks

• Lowest concentrations are generally prepared the day of the challenge.
### Dilution Schedules

**Quadrupling and Doubling**

<table>
<thead>
<tr>
<th>Label strength</th>
<th>Take</th>
<th>Add NaCl (0.9%)</th>
<th>Obtain dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example of a dilution schedule for quadrupling concentrations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td>100 mg</td>
<td>6.25 mL</td>
<td>A: 16 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution A</td>
<td>9 mL</td>
<td></td>
<td>B: 4 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution B</td>
<td>9 mL</td>
<td></td>
<td>C: 1 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution C</td>
<td>9 mL</td>
<td></td>
<td>D: 0.25 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution D</td>
<td>9 mL</td>
<td></td>
<td>E: 0.0625 mg·mL⁻¹</td>
</tr>
<tr>
<td><strong>3 mL of dilution E</strong></td>
<td><strong>9 mL</strong></td>
<td></td>
<td><strong>F: 0.015625 mg·mL⁻¹</strong></td>
</tr>
<tr>
<td><strong>Example of a dilution schedule for doubling doses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 mg</td>
<td>100 mg</td>
<td>6.25 mL</td>
<td>A: 16 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution A</td>
<td>3 mL</td>
<td></td>
<td>B: 8 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution B</td>
<td>3 mL</td>
<td></td>
<td>C: 4 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution C</td>
<td>3 mL</td>
<td></td>
<td>D: 2 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution D</td>
<td>3 mL</td>
<td></td>
<td>E: 1 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution E</td>
<td>3 mL</td>
<td></td>
<td>F: 0.5 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution F</td>
<td>3 mL</td>
<td></td>
<td>G: 0.25 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution G</td>
<td>3 mL</td>
<td></td>
<td>H: 0.125 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution H</td>
<td>3 mL</td>
<td></td>
<td>I: 0.0625 mg·mL⁻¹</td>
</tr>
<tr>
<td>3 mL of dilution I</td>
<td>3 mL</td>
<td></td>
<td>J: 0.03125 mg·mL⁻¹</td>
</tr>
</tbody>
</table>

Using a 100-mg vial of methacholine and NaCl (0.9%) for diluent, the table shows the range of concentrations available to produce appropriate dose steps using examples of dilutions with quadrupling and doubling increases. If necessary, alternative concentrations can be produced from a different initial dilution step. For example, adding 5 mL of diluent to 100 mg methacholine would produce dilution A of 20 mg·mL⁻¹ and adding 8.3 mL of diluent to 100 mg methacholine would produce dilution A of 12 mg·mL⁻¹.
Methacholine protocols

• The PC20 or PD 20, provocative dose/ concentration that causes a 20% fall in FEV1 and is an attempt to help standardize interpretation of results.

Saline, 0.012565 mg/mL, 0.625 mg/ml, 0.25mg/ml, 1.0 mg/ml, 4.0 mg/ml, 16 mg/ml
baseline, 6 concentrations, post albuterol = 9 steps total
Dosing: protocols/methods/devices

- Two minute tidal breathing
- Five breath dosimeter
- Tidal breathing
  
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Figure 1. Schematic diagram illustrating typical nebulizer configurations for both the 2-min tidal breathing protocol (A, an English Wright nebulizer) and the five-breath dosimeter protocol (B, a DeVilbiss model 646 nebulizer). Both include an exhalation filter. Other models of nebulizers may be substituted (see Section II, H).

Images: ATS Guidelines for Methacholine and Exercise Challenge Testing 1999, AE BAN Monaghan Medical Corp
Major Recommendations: **PD\textsubscript{20}**

- Provocative dose causing a 20% fall in FEV1 (PD\textsubscript{20})
  - Should allow comparable results from various devices or protocols
  - “Switching to routinely reporting methacholine data using PD\textsubscript{20} will allow comparison of methods using different nebulizers and inhalation times”
Delivery devices*

• “Any suitable nebulizer or dosimeter may be used”
• Vendor must provide characterization of nebulizer output, and particle size.
• Vendor info will allow table of concentration-dose steps for inhalation protocol.
Inhalation Protocol

• Tidal breathing
• Statement says: “If using a breath actuated or continuous nebulizer… 1 minute (or more)” If breath actuated..this is too long.
  – 20 seconds
  – 6 breaths
• If using a dosimeter: a breath count calculated to deliver appropriate dose steps.

ERS statement authors do not recommend the deep breath method!
Justification: Deep breaths may cause bronchoprotection (dilation) and reduce sensitivity. (Leading to false negatives)
Dose steps*

- Dose one: 1-3 µg
  - “with subsequent doubling or quadrupling steps”
- Dose two: ___µg
- Dose three: ___ µg
- Dose four: ___µg

- No dose should >800 µg
- No need to mirror Wright neb dosing but it can be used as a reference.
Audience survey

- How many people use dosimeters?
- Do you use the same metha sequence you used 10 years ago?
- Do you do the 25mg concentration step?
- How many people use the BAN for methacholine?
Old Dosimeters
Salter Dosimeter

Salter Dosimeter
Aerosol Generating Device for precise administration of broncho-provocation agents

Precise Control of Nebulizer “on” time

Salter is out of production

Other vendors coming to US market with an integrated dosimeter
• Ganshorn

A simple explanation to calculate dose delivered:
Example: assuming the output of a nebulizer is 0.45 ml/min when driven by a compressed gas source at 50 psi 7 LPM. For a given medication concentration refer to the desired dose of Broncho-provocation agent.

The dose output may then be calculated as follows:
Dose Output= (concentration of medication) x (nebulizer output) x (nebulization duration)
Dose Output= mg/ml x ml/min x min
Integrated dosimeter: APS
(Automatic provocation system)

Fig.: MedicAid, MedicAid pro Sidestream
Integrated dosimeter: GANSHORN

- New PFT vendor in the US.
- Spirometer is FDA approved.
- Bodybox system with integrated dosimeter pending FDA approval.
Integrated dosimeters / programs

• Potential advantages:
  – Breath counter
  – Flow sensing / visual
  – Timer
  – Calculation of PD/PC values
  – Filter to capture expired aerosol
### Dosimeters sequences-APS

#### Table 1: UW Tidal PD 20 - Sequence

<table>
<thead>
<tr>
<th>Step</th>
<th>Conc.</th>
<th>Dose</th>
<th>Substance</th>
<th>min</th>
</tr>
</thead>
<tbody>
<tr>
<td>R 1</td>
<td></td>
<td></td>
<td>Baseline</td>
<td>0</td>
</tr>
<tr>
<td>P 2</td>
<td>0.0625 mg/ml</td>
<td>1.5 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 3</td>
<td>0.25 mg/ml</td>
<td>6 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 4</td>
<td>1 mg/ml</td>
<td>24 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 5</td>
<td>4 mg/ml</td>
<td>96 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>P 6</td>
<td>16 mg/ml</td>
<td>384 ug</td>
<td>Methacholine</td>
<td>1.0</td>
</tr>
<tr>
<td>D 7</td>
<td>4 Puffs</td>
<td></td>
<td>Albuterol MDI</td>
<td>15</td>
</tr>
</tbody>
</table>

#### Table 2: UW Tidal PD 20 - Response table

<table>
<thead>
<tr>
<th>Seq.</th>
<th>FEV 1</th>
<th>%Ref.</th>
<th>Conc.</th>
<th>Dose</th>
<th>Cumul.</th>
<th>Breaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.927</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R 1</td>
<td>2.878</td>
<td>98</td>
<td>0.0625 mg/ml</td>
<td>1.5 ug</td>
<td>1.5 ug</td>
<td>0</td>
</tr>
<tr>
<td>P 2</td>
<td>3.004</td>
<td>103</td>
<td>0.25 mg/ml</td>
<td>6 ug</td>
<td>7.5 ug</td>
<td>1.5 ug</td>
</tr>
<tr>
<td>P 3</td>
<td>2.600</td>
<td>89</td>
<td>1 mg/ml</td>
<td>24 ug</td>
<td>31.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 4</td>
<td>2.713</td>
<td>93</td>
<td>4 mg/ml</td>
<td>96 ug</td>
<td>127.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 5</td>
<td>2.066</td>
<td>71</td>
<td>16 mg/ml</td>
<td>384 ug</td>
<td>511.5 ug</td>
<td>10</td>
</tr>
<tr>
<td>P 6</td>
<td>2.917</td>
<td>100</td>
<td>4 Puffs</td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

**PD(20): 266.2 ug**
AeroEclipse II BAN

- Things to consider
  - Many may adopt
  - Nebulization is during entire inspiration
  - Output is robust
  - Cost per neb?
  - 6 breath option
    - (Jeff Haynes RRT, RPFT, FAARC)
Withholding medications*

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MCT: methacholine challenge test.
Withholding medications*

“Single dose is likely ok to test….withhold time maybe weeks”

• Cromolyn
• Inhaled corticosteroids
  – Beclomethasone, budesonide, flunisolide, fluticasone propionate, triamcinolone.
• Leukotriene modifiers
  – Montelukast (Singulair)
  – Zafirlukast
  – Zileuton
Procedure steps

- Allow 30 min room temp for solutions before use.
- Ensure equipment readiness/calibration
- Verify order, obtain informed consent
- Briefly explain procedure
- Obtain baseline pre-challenge measures
  - Spirometry
    - Raw or oscillometry (option)
Tidal Breathing: Diluent Step*

• Highly recommended step
• If FEV$_1$ changed is <10%, go to conc #1
• If FEV$_1$ improved > 20%, repeat diluent step
• If FEV$_1$ decreased ≥20%, stop challenge

- Sterile normal saline
- Sterile normal saline with preservative
- Use of buffer is not recommended
• Aerosolize diluent and coach patient to breath “quietly” while wearing nose clip.
• After appropriate time or breaths turn off flow meter and remove neb.
• Perform post-diluent spiro at 30 and 90 seconds after the nebulization is completed.
• Obtain acceptable FEV1, report highest.
Procedure Steps*

• Target FEV1 is: highest FEV1 x 0.80
• Nebulize concentrations
• Obtain post methacholine spirometry at 30 and 90 seconds after the nebulization is completed.
• Report highest FEV1 from acceptable trials.
  – Perform no more than 3 or 4 trials after each dose.
  – Full FVC is not required.
  – No > than 3 min to perform trials
  – Time interval between 2 serial concentrations should be 5 min
• Proceed with steps until >20% decrease in FEV1 is observed, or the last concentration is achieved.

• If FEV1 decreases >20% stop challenge and give bronchodilator.

• Administer a rapid acting inhaled bronchodilator, wait 5-10 min.

• Consider flow volume loops prior to bronchodilator if VCD is suspected.

• Ensure FEV1 returns to pre-challenge range (within 90%)
APS Quadrupling Concentration Option:

- Phillips Respironics SideStream disposable neb. # 4445
  - Min fill volume is 2 mL.
  - Compatible to the Jaeger MedicAid reusable neb.
- 10 tidal breaths
- APS device has a timer and breath counter
AeroEclipse II BAN Option

- Output is robust
- Nebulization can be set to breath actuated or continuous.
- Flow rate 7 L/s yields 0.39 ml/min
- Output as long as inspiratory flow is >13 L/min
- Might have limitations if used with very small children because of flow req.

Methods?
- The standard mentions 1 minute
- Studies mention: 20 seconds
- 6 breath /actuated mode option
  - (Jeff Haynes RRT, RPFT, FAARC)
English Wright Neb option: 2 min tidal

- Reusable acrylic nebulizer
- Low output (0.26 mL aerosol over 2 min)
- Anticipated to come back into production
- Quadrupling increments
- Cross-infection risk
- Evaporative loss is greater because of small particle size.

<table>
<thead>
<tr>
<th>Concentration mg/mL</th>
<th>Dose ug</th>
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<tbody>
<tr>
<td>0.0625</td>
<td>1.425</td>
</tr>
<tr>
<td>0.25</td>
<td>5.938</td>
</tr>
<tr>
<td>1</td>
<td>23.75</td>
</tr>
<tr>
<td>4</td>
<td>95</td>
</tr>
<tr>
<td>16</td>
<td>380</td>
</tr>
</tbody>
</table>

Roxon Medi-Tech, Montreal PQ, Canada
APS Dosimeter Single Concentration Option

• Load nebulizer with 16 mg/mL concentration
• 1, 2, 5, 13 breath sequence
• Labs that use this method like it.

• Has obvious conveniences
  – Less dilutions to mix
  – Less transfers of challenge substance
## Method comparison

<table>
<thead>
<tr>
<th>Methods used with same subject</th>
<th>5 breath APS (Deep breath)</th>
<th>10 breath APS (tidal)</th>
<th>1,2,5,13 breath APS (tidal)</th>
<th>6 breath Aeroeclipse II (tidal, breath actuated)</th>
<th>2 minute (tidal) English-Wright Neb</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5 concentration</td>
<td>5 concentration</td>
<td>1 concentration</td>
<td>5 concentration</td>
<td>5 concentration</td>
<td></td>
</tr>
<tr>
<td>FEV1 decrease Max conc / Dose</td>
<td>0 16mg/mL/</td>
<td>-6 16mg/mL/ 384ug</td>
<td>-10 16mg/mL/</td>
<td>-12 16mg/mL/</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>Minimal</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Max conc / Dose**

- 0 16mg/mL/
- -6 16mg/mL/ 384ug
- -10 16mg/mL/
- -12 16mg/mL/
Perform baseline spirometry

FEV₁ > 60% predicted? 

Yes

Administer diluent or first dose of methacholine and perform spirometry after the appropriate delay

FEV₁ decline > 20% 

Yes

Record signs and symptoms. Give albuterol, wait 10 min and perform spirometry

No

Administer next dose of methacholine and perform spirometry after the appropriate delay

FEV₁ decline > 20% 

Yes

No

400 µg dose given? 

Yes

FEV₁ decline > 10% 

No

No

Study completed

ERS TECHNICAL STANDARD A.L. COATES, Wanger et al.

FIGURE 1 Testing sequence flow chart. FEV₁: forced expiratory volume in 1 s. #: FEV₁ < 1.5 L in adults is an additional contraindication. Reproduced and modified from [3] with permission.
### Physician Interpretation
#### Categorization of Airway Response to Methacholine

<table>
<thead>
<tr>
<th>PC20 (mg/mL)</th>
<th>PD20 (µg) microgram</th>
<th>PD20 (micromole)</th>
<th>AHR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;16</td>
<td>&gt;400</td>
<td>&gt;2.0</td>
<td>Normal AHR</td>
</tr>
<tr>
<td>4-16</td>
<td>100-400</td>
<td>0.5-2</td>
<td>Borderline AHR</td>
</tr>
<tr>
<td>1-4</td>
<td>25-100</td>
<td>0.125-0.5</td>
<td>Mild AHR</td>
</tr>
<tr>
<td>0.25-1</td>
<td>6-25</td>
<td>0.3-0.125</td>
<td>Moderate AHR</td>
</tr>
<tr>
<td>&lt;0.25</td>
<td>1.5-6</td>
<td>0.008-0.03</td>
<td>Marked AHR</td>
</tr>
</tbody>
</table>
Reporting of results

Details you want to consider including:

- Medications
  - Cardiac and respiratory meds
- Reason for the test / Indications
- Symptoms reported
- Tabular data
  - Steps
  - Substance
  - Concentrations
  - Breaths
  - FEV1
  - Flow volume and volume time curves
  - Options: Airway resistance / Oscillometric data
Interpretation: Direct Bronchial Challenge Test*

• Diagnostic tool to help assess probability of asthma.
• Best when:
  – Pretest probability is 30-70%
  – Recent symptoms evident (within past few days)
  – No deep inhalations that might provide bronchoprotective effect
• MCT is more valuable in helping to exclude a dx of asthma because: -pred > +pred value
Why add a resistance parameter?

• Changes in FEV1 are usually mirrored in changes seen in plethysmography resistance (Raw, Gaw, sGaw) as well as oscillometry data (R5, Resonant Freq, R5-20)

• Confirms changes seen in spirometric data.

• Poor effort is easier to identify.

Oscillometry (Increase in R5 or resonant freq)
Why add a resistance parameter?

Options:

Airway resistance
(Decrease in sGaw: PD40)
Pitfalls to a quality methacholine BCT

- Staff are unfamiliar with steps and need more training/experience.
- Distractions during testing
- Equipment issues
- Medication dosing errors.
- Poor instruction/effort
- Deep breaths during dosing

- Practice or limit staff performing testing
- Minimize any phone use
- Use a timer
- Maintain equipment
- Use a worksheet / checklist
- Retrain seasoned staff.
Interpretation*

- Negative MCT; \textbf{PD20} >400 \mu g or \textbf{PC20}>16 essentially excludes asthma if symptoms were very recent.
- False negative results are infrequent if symptoms are recent.
- False negative results are possible if medications are not withheld.
- Probability that MCT reflects asthma increases the lower the PD20 or PC20, with symptoms similar to those reported.
• CPT code 94070: Multiple spirometric determinations bronchospasm eval
• CPT code 95070 for administration of methacholine
• CPT code J-7674: One unit for each mg of methacholine
44 yr old Female: Cough, eval for asthma

- Reports dyspnea with exposure to co-workers perfume and when bleach wipes are used in the office.
**Case study**

- 56 yr old, female, dyspnea, eval for possible asthma, 66 inches, 205 lbs, BMI 33, never smoked. FENO: 46 ppb

<table>
<thead>
<tr>
<th>Test</th>
<th>LLN</th>
<th>Pred</th>
<th>Baseline</th>
<th>%Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC [L]</td>
<td>2.90</td>
<td>3.63</td>
<td>3.50</td>
<td>96 %</td>
</tr>
<tr>
<td>FEV 1 [L]</td>
<td>2.20</td>
<td>2.83</td>
<td>2.63</td>
<td>93 %</td>
</tr>
<tr>
<td>FEV1/FVC [%]</td>
<td>69</td>
<td>79</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>PEF [L/s]</td>
<td>4.94</td>
<td>6.76</td>
<td>6.08</td>
<td>90 %</td>
</tr>
<tr>
<td>FEF 25 [L/s]</td>
<td>5.61</td>
<td>5.61</td>
<td>5.75</td>
<td>102 %</td>
</tr>
<tr>
<td>FEF 50 [L/s]</td>
<td>4.23</td>
<td>4.23</td>
<td>2.73</td>
<td>65 %</td>
</tr>
<tr>
<td>FEF 75 [L/s]</td>
<td>1.77</td>
<td>1.77</td>
<td>0.75</td>
<td>42 %</td>
</tr>
<tr>
<td>FEF 25/75 [L/s]</td>
<td>1.28</td>
<td>2.59</td>
<td>2.05</td>
<td>79 %</td>
</tr>
<tr>
<td>FVC IN [L]</td>
<td>2.90</td>
<td>3.63</td>
<td>3.49</td>
<td>96 %</td>
</tr>
<tr>
<td>PIF [L/s]</td>
<td>4.80</td>
<td>4.80</td>
<td>3.73</td>
<td>78 %</td>
</tr>
<tr>
<td>FIF 50 [L/s]</td>
<td>2.37</td>
<td>3.80</td>
<td>3.57</td>
<td>94 %</td>
</tr>
<tr>
<td>FET [s]</td>
<td></td>
<td></td>
<td>9.10</td>
<td></td>
</tr>
</tbody>
</table>
Case study 56 yr old

Technologist note: Pt effort appeared maximal. She reported chest tightness after 4 mg/mL dose. Symptoms of chest tightness was relieved after albuterol given.

### Methacholine Challenge Report

<table>
<thead>
<tr>
<th>Step</th>
<th>Subst.</th>
<th>Conc</th>
<th>Brths</th>
<th>Pred FEV 1</th>
<th>FEV 1 RAW</th>
<th>sGAW</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2</td>
<td>Methacholine</td>
<td>0.062 mg/mL</td>
<td>5</td>
<td>2.63</td>
<td>3.29</td>
<td>0.09</td>
</tr>
<tr>
<td>P3</td>
<td>Methacholine</td>
<td>0.25 mg/mL</td>
<td>5</td>
<td>2.59</td>
<td>3.29</td>
<td>0.09</td>
</tr>
<tr>
<td>P4</td>
<td>Methacholine</td>
<td>1 mg/mL</td>
<td>5</td>
<td>2.52</td>
<td>3.29</td>
<td>0.09</td>
</tr>
<tr>
<td>P5</td>
<td>Methacholine</td>
<td>4 mg/mL</td>
<td>5</td>
<td>2.46</td>
<td>3.29</td>
<td>0.09</td>
</tr>
<tr>
<td>P6</td>
<td>Methacholine</td>
<td>16 mg/mL</td>
<td>5</td>
<td>2.35</td>
<td>3.29</td>
<td>0.09</td>
</tr>
<tr>
<td>D7</td>
<td>Albuterol MDI</td>
<td></td>
<td>4</td>
<td>2.05</td>
<td>3.29</td>
<td>0.09</td>
</tr>
</tbody>
</table>

PC[-20] FEV 1 12.44 mg/mL Conc.
Case study: Positive response?
Chest tightness noticed after pressure washing houses with 15% chlorine. No previous history of breathing problems.

Methacholine Challenge Report

<table>
<thead>
<tr>
<th>Step</th>
<th>Subst.</th>
<th>Conc</th>
<th>FEV 1</th>
<th>RAW</th>
<th>SGAW</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>Baseline</td>
<td></td>
<td>2.65</td>
<td>3.69</td>
<td>0.09</td>
</tr>
<tr>
<td>P2</td>
<td>Methacholine</td>
<td>0.063 mg/ml</td>
<td>2.60</td>
<td>4.32</td>
<td>0.08</td>
</tr>
<tr>
<td>P3</td>
<td>Methacholine</td>
<td>0.25 mg/ml</td>
<td>2.62</td>
<td>4.05</td>
<td>0.08</td>
</tr>
<tr>
<td>P4</td>
<td>Methacholine</td>
<td>1 mg/ml</td>
<td>5.32</td>
<td>10</td>
<td>-17</td>
</tr>
<tr>
<td>P5</td>
<td>Methacholine</td>
<td>4 mg/ml</td>
<td>2.20</td>
<td>4.95</td>
<td>-41</td>
</tr>
<tr>
<td>P6</td>
<td>Methacholine</td>
<td>16 mg/ml</td>
<td>1.98</td>
<td>13.34</td>
<td>0.02</td>
</tr>
<tr>
<td>D7</td>
<td>Albuterol MDI</td>
<td></td>
<td>2.61</td>
<td>3.35</td>
<td>0.10</td>
</tr>
</tbody>
</table>

PC[-20] FEV 1: 6.727 mg/ml Conc.

4-16 mg/mL borderline AHR...82% decrease in sGaw!
Methacholine Challenge Worksheet

Breaths:

Baseline FEV1: 2.60
Repeatable? Y N
X .80
Med / Allergies reviewed? Y N
20% change: 2.28

Pretest probability: wheezing, dyspnea, chest tightness, cough...

During respiratory infections
With exposure to cold
After exercise
Following inhalant exposures at work or with activities

Signs / Symptoms during testing:
YES CHEST THROAT TIGHTNESS

Patient effort: Poor Fair Good Excellent

M.O'Brien 2018 Methacholine Worksheet
Tools: Training and Competency Assessment

- Template you can use to create your labs competency check off list.
- Questions to keep staff engaged.

**Annual Competency Assessment / Training --- Bronchial Challenge Test - Methacholine**

**Core competencies**

2. Understands dilution scheme used in our lab.
3. Obtains methacholine dilutions from pharmacy and allows to equilibrate to room temp.
4. Calibrates pulmonary testing system.
5. Demonstrates understanding of workflow for BCT
   a. Verifies order.
   b. Assesses appropriateness of testing.
   c. Allergy and medication review in EMR.
   d. Reviews possible contraindications.
   e. Briefly explains testing procedure to the patient.
   f. Obtains signed consent form.
   g. Obtains acceptable and repeatable baseline spirometry (resistance optional).
   h. Calculates 20% fall in FEV1.
   i. Demonstrates clean technique when transferring concentrations for nebulization.
   j. Encourages tidal breathing during dosing and minimizes any TLC maneuvers.
   k. Monitors time appropriately between dosing, Spiro, dosing...
   l. Recognizes a 20% decrease in FEV1.
   m. Administers bronchodilators via nebulizer or MDI.
   n. Assess response to inhaled bronchodilator.
   o. Output of report with appropriate technologist notes.
   p. Post PDF in EMR.
   q. Charge for technical component.
6. New staff: Four days of supervised testing / practice and 20 supervised tests.
7. Experienced staff: 1 day of supervised testing.
8. Is familiar with safety and emergency procedures.

**Questions: True / False**

1. PD20 is now preferred over PC20 to characterize the response to methacholine. T F
2. Methacholine is a direct airway challenge that mimics the response of acetylcholine with muscarinic receptors on airway smooth muscle. T F.
3. It is ok to test a patient with a history of uncontrolled HTN when the systolic BP is >200 mmHg and systolic BP is 90 mmHg. T F.
4. A primary contraindication to performing bronchial challenge testing is:
5. Changes in airway resistance parameters can help confirm changes observed in FEV1. T F.
Tools: PD20 Calculators

- Manual calculators
- Online sources
- Vendors are working on this development

**APPENDIX 3.2.4**

**Calculation of the Provocative Dose (PD)**

1. Responsiveness is expressed as the dose of inhaled methacholine that causes a threshold response.
2. The term PD20FEV\(_1\) is defined as the dose that causes a 20% fall in FEV\(_1\). The term PD\(_{20}\)Gaw is defined as the dose that causes a 40% fall in sGaw.
3. The PD\(_{20}\) is obtained by linear interpolation between the final two doses. The formula is as follows:

\[
PD_{20} = \text{anilog} \left[ \frac{\log D1 + \frac{(20 - R1)(\log D2 - \log D1)}{(R2 - R1)}}{D2 - D1} \right]
\]

where:
- D1 = next-to-last dose of methacholine
- D2 = final dose of methacholine
- R1 = percent fall in FEV\(_1\) after D1
- R2 = percent fall in FEV\(_1\) after D2

**Example calculation of PD\(_{20}\)FEV\(_1\), using the highest FEV\(_1\) value from the two FVC tests at 150 and 210 seconds.**

<table>
<thead>
<tr>
<th></th>
<th>150 s</th>
<th>210 s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline FEV(_1)</td>
<td>3.24</td>
<td>3.30</td>
</tr>
<tr>
<td>Post-diffuent FEV(_1)</td>
<td>3.24</td>
<td>3.29</td>
</tr>
<tr>
<td>Post 0.03 mg/ml FEV(_1) (Cum Dose = 1.275 µg)</td>
<td>3.24</td>
<td>3.29</td>
</tr>
<tr>
<td>Post 0.06 mg/ml FEV(_1) (Cum Dose = 3.825 µg)</td>
<td>2.98</td>
<td>3.03**</td>
</tr>
<tr>
<td>Post 0.125 mg/ml FEV(_1) (Cum Dose = 9.138 µg)</td>
<td>2.53</td>
<td>2.55**</td>
</tr>
</tbody>
</table>

*percent fall in FEV\(_1\) from diffuent = 7.9%
**percent fall in FEV\(_1\) from diffuent = 22.5%
Tools: Online Self Study, Dilution Steps
Negative (PC20>16 or PD20> 400)

The baseline FEV1 of _____ is in a normal range and greater than predicted. The shape of the flow volume curve is linear at baseline and throughout the challenge.

After ____ breaths of 16mg/mL concentration of methacholine there was a _____% decrease/ increase in FEV1 and no significant change in airway resistance parameters. Following administration of the bronchodilator there was no change/ ____% increase in FEV1 and normalization of airway resistance.

This is a negative methacholine challenge.

Methacholine challenge testing is more useful in excluding a diagnosis of asthma than establishing one because its negative predictive value, when respiratory symptoms are present, is greater than its positive predictive.
Borderline, Mild, Moderate, Marked
The baseline FEV1 of _____ is _____% of predicted. The shape of the flow volume curve is linear / slightly curvilinear at baseline.

After inhalation of the 0.0625, 0.25, 1, 4, 16 mg/mL concentration the FEV1 decreased _____%.
The calculated PD20 is _________.

Changes observed in airway resistance confirm the decrease observed in FEV1.

Based on the PD20 of ________ micrograms, the response to methacholine is categorized as:

<table>
<thead>
<tr>
<th></th>
<th>PD20</th>
<th>PC20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline AHR</td>
<td>100-400</td>
<td>4-16</td>
</tr>
<tr>
<td>Mild AHR</td>
<td>25-100</td>
<td>1-4</td>
</tr>
<tr>
<td>Moderate AHR</td>
<td>6-25</td>
<td>0.25-1</td>
</tr>
<tr>
<td>Marked AHR</td>
<td>1.5-6</td>
<td>&lt;0.25</td>
</tr>
</tbody>
</table>

Following bronchodilator administration, the FEV1 returned to baseline / increased from baseline. Airway resistance parameters also normalized / improved following bronchodilatation.

Clinical correlation is required.
Summary / Predictions

- Methacholine testing using a **tidal breathing method and PD20 for characterization of AHR** is the preferred method.

- Methacholine challenge helps to exclude a dx of asthma.

- Use of pre-mixed methacholine concentrations will make it easier for labs wanting to perform occasional testing or those that don’t have pharmacy onsite to assist.

- Better characterization of nebulizers by manufactures will continue slowly.

- Labs need adapt to the current methacholine testing standard, update policies, retrain and monitor competency.