Bronchial Challenge Testing
The “Almost” Brand New ATS-ERS Guideline

Carl Mottram, RRT RPFT FAARC
Technical Director - Pulmonary Function Labs & Rehabilitation
Associate Professor of Medicine - Mayo Clinic College of Medicine
Brand New!!!
New ATS/ERS Bronchial Challenge Guideline

• Still in draft
  • Includes: methacholine, mannitol, exercise

• Methacholine challenge test writers:
  • Don Cockcroft MD
  • Allan Coates MD
  • Jack Wanger MS RRT
Bronchial Provocation - Guidelines

• American Thoracic Society (ATS)
  • Guidelines for Methacholine and Exercise Challenge Testing
    • www.thoracic.org
Inhalation Challenges - *Direct vs Indirect Stimuli*

**Direct stimulus**
- **Effector cells**
  - Airway smooth muscle cells
  - Bronchial endothelial cells
  - Mucus producing cells
- **Airflow limitation**

**Indirect stimulus**
- **Intermediary cells**
  - Inflammatory cells
  - Neuronal cells
Inhalation Challenges - Direct vs Indirect Stimuli

Direct Stimuli
- Methacholine
- Carbachol
- Histamine
- Prostaglandin
- Leukotrienes

Indirect Stimuli
- Adenosine (AMP)
- Bradykinin
- Metabisulfite / SO₂
- Exercise
- Hyper/hypotonic aerosol
- Isocap. hyperventilation
- Mannitol
- Propanolol (β-blockers)
Methacholine Challenge Test

• **Methacholine chloride** is a parasympathomimetic (cholinergic) bronchoconstrictor agent

• Methacholine is derived from acetylcholine, a naturally occurring substance in the body, and can cause the airways to tighten and swell, in sensitive people.
History of Methacholine Challenge

• First described by Tiffeneau in 1945

• Modification of the protocol by Reed et al. in 1965
  • 20 known asthmatic children and 20 asthmatic adults compared to normals’
  • FEV$_1$ decline 20%

A graphic comparison of the response of normals and asthmatics to the methacholine inhalation test. Dots indicate the values for individual subjects, and the lines the mean and 95% confidence limits.
Methacholine Challenge Test

**Clinical Indications**

- To establish or confirm a diagnosis of asthma when traditional methods such as spirometry pre- and post- bronchodilator have not established or eliminated the diagnosis

- Assess relative risk of developing asthma

- Assess the severity of asthma
Methacholine Challenge Test

*Predictive Power*

- Optimal when pretest probability of asthma is approximately 70%

- Negative predictive power higher than positive
  - excluding a diagnosis of asthma
Methacholine Test Methodology

Preparation of Methacholine

- FDA-approved methacholine produced by Methapharm (Provocholine)
- Mixed by pharmacist or well-trained individual with sterile technique
Methacholine Test Methodology

1999 Protocols

- Five-breath dosimeter protocol
- Two-minute tidal breathing dosing protocol
Patient Preparation

- When scheduled, patients should be given a list of medications to avoid prior to the test.

- At testing, explain the test, but don’t over do it
  - *Avoid the impact of suggestion.*

- Consent form (if required)

- Pre-test questionnaire
# Medication Withholding Schedule

<table>
<thead>
<tr>
<th>Medication</th>
<th>Minimum Time Interval from Last Dose to MCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting $\beta_2$ agonists (e.g. albuterol 200 mcg)</td>
<td>6 hours</td>
</tr>
<tr>
<td>Long-acting $\beta_2$ agonists (e.g. salmeterol)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Ultra-long $\beta_2$ agonists (Indacaterol: Arcapta Neohaler®)</td>
<td>48 hours</td>
</tr>
<tr>
<td>Anticholinergic (e.g. ipratropium)</td>
<td>12 hours</td>
</tr>
<tr>
<td>Long-acting anticholinergic (e.g. tiotropium)</td>
<td>72 hours</td>
</tr>
</tbody>
</table>

Latest version
Other Medication Issues with MCT

- Cromones, ICS, leukotriene modifiers:
  - Single doses have little or no effect
  - To offload anti-inflammatory effect, withhold time may be weeks
- Caffeine and caffeine-related products:
  - Little or no clinical significance
- Influenza vaccination, menstrual cycle, antihistamines, and oral contraceptives do not significantly affect airway responsiveness
Why Tidal Breathing Method?

- More recent data using only methacholine suggests differences, especially in those with mild responsiveness.
- Data suggests those with mild responsiveness using TB method will be considered normal using 5-breath method.
- Difference due to broncho-protective effect of maximal inspiratory maneuver.
Tidal Breathing Method

• Originally described as the two minute TBM using the English Wright nebulizer

• Different nebulizers have differing rates of delivery – characteristics should be defined

• Standardized time between start of nebulization and spirometry

• Use mouthpiece with nose clip to decrease environmental exposure
Tidal Breathing Method

- Tidal breathing from AeroEclipse II BAN driven by 50 psi gas source resulted in pulmonary deposition equivalent to Wright in approximately 12 seconds.

- A 20-sec time period was used in-vivo and data showed PC20 approximately 2 concentrations less for AeroEclipse system compared to 2 min on Wright.
**P_D** versus **P_C20**

**Methacholine Challenge**

*PD*<sub>20</sub> versus *PC*<sub>20</sub>

Donald W. Cockcroft

Department of Medicine, Division of Respirology, Critical Care and Sleep Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

**Provocative Dose of Methacholine Causing a 20% Drop in FEV<sub>1</sub> Should Be Used to Interpret Methacholine Challenge Tests with Modern Nebulizers**

Sharon D. Dell<sup>1,2,3,4</sup>, Sundeep S. Bola<sup>1,3</sup>, Richard G. Foty<sup>1,2</sup>, Laura C. Marshall<sup>1,2</sup>, Kathleen A. Nelligan<sup>1,2</sup>, and Allan L. Coates<sup>1,3</sup>

<sup>1</sup>Division of Respiratory Medicine, and <sup>2</sup>Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada; and <sup>3</sup>Department of Pediatrics, and <sup>4</sup>Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada


**P_D20** “Allow for better comparison between different methods”
Micro-nebulizer with Dosimeter

Dosimeter Actuation Times

- ATSTarget (0.009)
- 0.9 seconds
- 0.8 seconds
- 0.7 second

# Dosing Protocols/Schedules

<table>
<thead>
<tr>
<th>Canadian Protocol (mg/ml)</th>
<th>ATS 1999 (mg/ml)</th>
<th>Chai, et al. (mg/ml)</th>
<th>Provoch. Package (mg/ml)</th>
<th>Chatham, et al. (mg/ml)</th>
<th>Reed, et al. (mg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>16</td>
<td>25</td>
<td>25</td>
<td>4 br-25</td>
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<td>10</td>
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<td>2.5</td>
<td>4 br-5</td>
<td>1 br-5</td>
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<td>0.25</td>
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</tr>
<tr>
<td>1</td>
<td>1.25</td>
<td>0.625</td>
<td></td>
<td></td>
<td>Diluent</td>
</tr>
<tr>
<td>0.5</td>
<td>0.625</td>
<td>Diluent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.25</td>
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<tr>
<td>0.125</td>
<td>0.15</td>
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</tr>
<tr>
<td>0.06</td>
<td>0.07</td>
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<td></td>
</tr>
<tr>
<td>0.03</td>
<td>Diluent</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diluent</td>
<td>Diluent</td>
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</tr>
</tbody>
</table>
Methacholine Test Methodology

Safety

- Physician available during challenge
- Emergency medications and oxygen readily available
- Subject should not be discharged until $\text{FEV}_1 > 90\%$ of pre-challenge $\text{FEV}_1$
- Conduct test in well-ventilated room
Technologist Training and Competence Assessment

- Familiar with ATS document and knowledgeable about specific test procedures

- Competent to perform equipment set-up, verification of proper function, maintenance, and cleaning
Technologist Training and Competence Assessment

- Proficient at spirometry (ATS)
- Know contraindications to challenge testing
- Familiar with safety and emergency procedures
Technologist Training and Competence Assessment

• Know when to stop further testing

• Proficient in the administration of inhaled bronchodilators and evaluation of response to them

• Minimum of 20 supervised tests
Methacholine Test Methodology

• Prepare challenge material

• Assess subject’s pre-challenge lung function

• Administer control and re-measure lung function

• Administer challenge agent and re-measure lung function after each dose

• Stop challenge after a meaningful fall in lung function

• Administer bronchodilator and re-measure lung function
Methacholine Data Presentation

• Example:
  • Baseline FEV1 4.0L
  • Control (diluent) 3.75L
  • $3.75 \times 0.8 = 3.0L$
  • $3.75 \times 0.9 = 3.38L$
  • $PC_{20} = 3.00L$

Fig. 9.2  Ruppel 9th ed.
Methacholine Challenge Test

**Interpretation**

<table>
<thead>
<tr>
<th>Categorization of Airway Response to Methacholine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD(_{20})</td>
</tr>
<tr>
<td>((\mu\text{mole}))</td>
</tr>
<tr>
<td>&gt;2.0</td>
</tr>
<tr>
<td>0.5-2.0</td>
</tr>
<tr>
<td>0.125-0.5</td>
</tr>
<tr>
<td>0.03-0.125</td>
</tr>
<tr>
<td>0.008-0.03</td>
</tr>
</tbody>
</table>

**Proposed!!**

Latest version
Mannitol Challenge Testing
Mannitol Challenge Test

- **Indirect and osmotic stimulant**
  - Increases osmolarity of airway surface liquid
  - Release of inflammatory mediators from mast cells and basophils (e.g. leukotriene)

- Sugar alcohol, dry powder (stored below 25°C)

- Utilizes a special dry-powder inhaler (DPI)

- No diluent or nebulization required

- Aridol™ (Pharmaxis)
Mannitol Challenge Test

- Aridol Kit
  - Aridol capsules (mannitol)
  - 1 empty capsule
  - Osmohaler inhaler device (DPI)
Mannitol Challenge Procedure

**Dosing scheme**

- Total maximum dose = 635 mg
Mannitol Challenge Test

**Technique**

- During challenge subjects should exhale away from the Osmohaler to minimize humidity
- Do not wear rubber gloves when administering test and handling Aridol
- Special inhalation technique
- Inhalation of Aridol can cause coughing
- Challenge test time is critical and prolonged intervals between doses may affect results
Mannitol Challenge Test

Procedure

• Pre-challenge spirometry
  • $FEV_1$ at least 60% of predicted

• Administer 0 mg Aridol using Osmohaler

• At 60 seconds perform spirometry
Mannitol Challenge Test

Procedure

• Perform 2 acceptable FVC maneuvers (according to ATS/ERS Guidelines). Use the higher of these two values to calculate the change in FEV₁

• If Baseline FEV₁ is >10% lower than pre-challenge FEV₁ - stop challenge

• Calculate target FEV₁
  • highest Baseline value * 0.85
Report Results

• Percent decrease in FEV₁ from post 0 mg dose (Baseline) value

• PD₁₅ - 2 decimal places in mg/mL (eg, 33.85 mg)

• If no 15% fall in FEV₁ after highest dose, PD₁₅ reported as greater than 635 mg (negative test)
New ATS/ERS Bronchial Challenge Guideline
Pathophysiology of Exercise Induced Bronchospasm (EIB)

- Mucosal drying and increased osmolarity stimulate mast cell degranulation and smooth muscle contraction
- Rapid airway rewarming causing vascular congestion and edema
Factors Influencing EIB

- Heat and water loss from airway:

![Graph showing heat loss at different temperatures and relative humidities for evaporation and convection.]

- Heat Loss, KCal/liter

- Rel. Hum.
- Temp.
- 4 degrees
- 21 degrees
- 37 degrees

- Evap
- Conv.
New ATS-ERS Statement

• Exercise Challenge Testing

• Eucapnic Voluntary Hyperpnea
  • Eucapnic Voluntary Hyperventilation
  • Eucapnic Hyperventilation
  • EVH

• Cold Air Challenge

Latest version
Exercise Challenge Testing
Environment

• The inspired air should be relatively dry and less than 25°C. This can be accomplished by conducting the study in an air-conditioned room (with ambient temperature at 20-25°C) with low relative humidity (50% or less).

• Ideally, compressed air in a bag with two-way valve
Exercise Challenge Testing

Ergometer

- Treadmill preferred
  - Cycle is acceptable
- Ventilation preferred
  - Heart rate is acceptable
Exercise Challenge Procedure
Exercise Intensity

- Protocol should be designed to reach the target heart rate or minute ventilation over a short period of time, usually on the order of 2-3 minutes.
  - The rapid rise in work rate is needed because a warm-up period or prolonged lower level exercise may decrease the severity of EIB
Exercise Challenge Procedure

Exercise Intensity

- **Treadmill**
  - Quickly advance to a rapid, but comfortable, speed at treadmill slope of 5.5% then raise the slope until the desired heart rate or ventilation is obtained up to an inclination of 10%.
  - The speed and grade are held constant for at least 4 and preferably 6 minutes of exercise at this target level of exercise.
Exercise Challenge Procedure

Exercise Intensity

• **Cycle ergometer**
  • For cycle ergometer exercise, work rate is rapidly increased using the electromagnetic braking system to achieve the target ventilation/heart rate
  • The target heart rate or ventilation should be reached within 2-3 minutes. A valid test requires the target exercise intensity to be sustained for 6 minutes
Procedure: Exercise Protocol

- Minute ventilation
  - Ventilation should reach 40-60% of the predicted maximum voluntary ventilation (MVV)
  - Estimated MVV ($\text{FEV}_1 \times 40$)
Procedure: Exercise Protocol

• Heart rate response
  • 85% of target HR for adults
  • 90% of target HR for pediatric
  • Max HR = 210 - .65(age) or 220 - age
    • May be affected by medications or chronotropic insufficiency
Procedure: Post Exercise

- Brief cool-down period (1-2 minutes)
- ECG and B/P monitoring in recovery
- Post exercise PFT’s should be performed for approximately 30 minutes
- 5, 10, 15 and 30 minutes
Eucapnic Hyperventilation

• Technique first described in 1985 at Walter Reed Hospital

• Equipment
  • Tank with 5% CO2, 21% O2, Balance N2, (relative humidity 0%)
  • High flow regulator and flowmeter
  • Reservoir bag
  • Pneumotach
EVH - Methods

- CareFusion software
  - Feedback graphics on $V_E$ and PetCO$_2$
Eucapnic Hyperventilation

- FEV1 x 30 for 6 minutes (75%)
- Six minutes aiming at a target ventilation of 60-85% of MVV

Table 1—Protocol

<table>
<thead>
<tr>
<th>Challenge No.</th>
<th>Protocol</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Target (\dot{V}E) of 20x(FEV_1)_{base} for 6 min</td>
</tr>
<tr>
<td>2</td>
<td>Target (\dot{V}E) of 15x(FEV_1)_{base} for 12 min</td>
</tr>
<tr>
<td>3</td>
<td>Target (\dot{V}E) of 30x(FEV_1)<em>{base} for 2 min, immediately perform forced expiratory spirometry, target (\dot{V}E) of 30x(FEV_1)</em>{base} for 2 min, immediately perform spirometry, target (\dot{V}E) of 30x(FEV_1)_{base} for 2 min, followed immediately after and 5, 10, and 20 min after the final challenge with spirometry</td>
</tr>
<tr>
<td>4</td>
<td>Target (\dot{V}E) of 30x(FEV_1)_{base} for 6 min</td>
</tr>
</tbody>
</table>

Eucapnic Voluntary Hyperventilation as a Bronchoprovocation Technique: Development of a Standardized Dosing Schedule in Asthmatics


*Chest* 1996;109;1520-1524
Cold Air Challenge

- Adjunct to EVH or exercise challenge
- Reduces exposure time from 6-4 minutes
- Cold air generating device
Positive Test Threshold and Interpretation

- **Exercise Challenge Test**
  - A decrease of $\geq 10\%$ from the baseline \( FEV_1 \) is accepted by some as an abnormal response, but the specificity is higher with a criterion of 15\% from baseline

- **Eucapnic Hyperventilation**
  - $>10\%$
Summary

• **Methacholine**
  • Tidal breathing
    • 20 seconds or breath count?
  • $P_{D20}$ vs old $P_{c20}$
    • Requires nebulizer output

• **Mannitol** (those in USA would say “who cares?”)

• **Exercise section**
  • Exercise, EVH, Cold Air
Questions?