Methacholine versus Mannitol Challenge in the Evaluation of Asthma
Clinical applications of methacholine and mannitol challenges
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Methacholine vs Mannitol/ Eucapnic Voluntary Hyperpnea

- Direct vs indirect challenges: methods, specificity and sensitivity
- Influence of asthma medication
- Occupational asthma investigation
- Assessment of AHR in athletes
- Conclusions

Bronchoprovocation tests
Non-selective
- Direct: methacholine, histamine
- Indirect: Exercise, EVH, AMP, Mannitol

Selective
- Immunologic: allergen, LMW agents
- Nonimmunologic: NSAID/ASA, Sulfites...

DIRECT STIMULI

- Act directly on smooth muscle receptors
- Muscarinic agonists, histamine, LTs, PGs
- Response reflects smooth muscle function including airway calibre (remodeling)
- Inflammation affects smooth muscle
- Low dose needed for bronchoconstriction
- Highly sensitive (with a few exceptions)

A special thanks to:
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- Valérie Bougault
- Catherine Lemière
- Donald W. Cockcroft

for providing me slides/data for this presentation

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- Adviser for the Quebec Workmen Compensation Group (CSST)
- Chair of the Respiratory Guidelines Committee of the Canadian Thoracic Society
- President of the CEB Committee of the Global Initiative for Asthma (GINA)
- Laval University Chair in Knowledge Translation, Education and Prevention in Respiratory Diseases
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- Member of the HT (Knowledge Translation) Canada Network

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INDIRECT STIMULI

- Act indirectly to induce bronchoconstriction
- Many act through mediator release from inflammatory cells (hypertonic saline, mannitol)
- Reflect airway inflammation
- Smooth muscle function less important
- High dose usually needed to induce bronchoconstriction
- Highly specific

**Methacholine cut-points (ATS 2000)**

\[
\begin{align*}
PC_{20} &> 16 \quad \text{normal} \\
PC_{20} \quad &4-16 \quad \text{borderline} \\
PC_{20} \quad &1-4 \quad \text{mild AHR} \\
PC_{20} \quad &0.25-1 \quad \text{mod AHR} \\
PC_{20} \quad &< 0.25 \quad \text{severe AHR}
\end{align*}
\]

**Bronchoprovocation tests**

<table>
<thead>
<tr>
<th>DIRECT</th>
<th>INDIRECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle function</td>
<td>++++</td>
</tr>
<tr>
<td>Airway calibre</td>
<td>++++</td>
</tr>
<tr>
<td>Inflammation</td>
<td>++</td>
</tr>
<tr>
<td>Dose needed</td>
<td>low</td>
</tr>
<tr>
<td>Dose limitation</td>
<td>no</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>high</td>
</tr>
<tr>
<td>Specificity</td>
<td>somewhat low</td>
</tr>
<tr>
<td>Diagnostic use</td>
<td>rule out</td>
</tr>
</tbody>
</table>

**Histamine & methacholine cutpoint**

Initially selected at 8 mg/ml to identify all asthmatics now 8 ± one concentration. So, 4-16 is borderline.

**AHR // ASTHMA SEVERITY**

**SENSITIVITY AND SPECIFICITY OF METHACHOLINE CHALLENGE**

- PC_{20} = 8 or 16 mg/ml
- Sensitivity: Very high
- Specificity: Fair
- PPV: Very high
- NPV: Low in random pop
  - ↑ if ↑ pretest prob
  - ↑ if mch mimics Sx
  - ↑ if PC_{20} lower (eg PC_{20} = 1 mg/ml)

Cockcroft 1992
METHACHOLINE

- $mg/ml) is consistent with but not diagnostic of asthma
  - Diagnostic value (PPV) increased if:
    - $PC_{20} < 16\,mg/ml$
    - Higher pretest probability
    - Methacholine induced Sx mimic natural Sx (??)

- $16\,mg/ml) excludes current asthma with reasonable certainty
  - Several important caveats:
    - Symptoms must be clinically current
    - No deep inhalations during test
    - Attention to medication withhold
    - High intensity athletes with EIB may have a negative MCT

ATS 1999 GUIDELINES (2000)

Tidal Breathing
- 2 min tidal breathing
- Neb @ 0.13 mL/min
- 90 µL per dose

Dosimeter
- 5 Breaths B-hold
- 9 µL per breath
- 45 µL per dose

Both:
- Concentrations (0.03-32 mg/ml)
- Timing between doses (5 min)
- Timing of FEV$_1$ (30 & 90 sec)
- Calculation of $PC_{20}$

Determinants of AHR to methacholine

- Methacholine AHR has possibly two components, fixed and variable component
- The fixed component relates to and reflects chronicity
- The variable component relates to inflammation and therefore reflects disease activity
- The variable component may be the only AHR early in the course of the disease

METHACHOLINE AHR

- AHR ↑ with inflammatory stimuli (allergen)
- AHR ↓ with anti-inflammatory Rx (ICS)
- AHR modest correlation with airway eos
- AHR ↑ with (non asthmatic) airway obstruction, likely a geometric issue
- AHR shows a modest correlation with asthma severity
- AHR can be used to monitor Rx
INDIRECT AHR
• AHR ↑ more with inflammatory stimuli
• AHR ↓ more with anti-inflammatory Rx
• AHR better correlation with airway eos
• AHR no Δ with (non asthmatic) airway obstruction
• AHR shows a better correlation with asthma severity / asthma activity
• AHR better to use to monitor Rx

AHR & INFLAMMATION
Small correlation with methacholine
Better correlation with indirect (AMP)
Van den Berge 2001

Mannitol was more closely associated with asthma severity in terms of respiratory function and airway inflammation than methacholine challenge

Effects of medications on methacholine challenge

<table>
<thead>
<tr>
<th>Medication</th>
<th>Minimum time interval from last dose to study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting beta agonists</td>
<td>4h</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>24h</td>
</tr>
<tr>
<td>Long acting beta agonists</td>
<td>48h</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>1 week[7]</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Intermediate acting: 24h, long acting: 48h</td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>48h</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>48h</td>
</tr>
<tr>
<td>Hydroxyzine, cetirizine</td>
<td>3 days</td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>24h</td>
</tr>
</tbody>
</table>

The authors do not recommend routinely withholding oral or inhaled corticosteroids, but their antiinflammatory effect may decrease bronchial responsiveness. Inhaled corticosteroids may need to be withheld depending on the question being asked.  

ATS, 1999

Airway hyperresponsiveness, inflammation, and subepithelial collagen deposition in recently diagnosed versus long-standing mild asthma. Influence of inhaled corticosteroids

**Asthma and ICS – Phase III trial results**

Sensitivity to inhaled steroid in treated asthma - 56% of asthmatics (204/363) using ICS were positive to mannitol when the last dose was the day before.

<table>
<thead>
<tr>
<th>Clinical diagnosis of asthma N=487</th>
<th>Mannitol Positive</th>
<th>Mannitol Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=204 (42%)</td>
<td>N=283 (58%)</td>
<td></td>
</tr>
<tr>
<td>Asthma with active airway inflammation that will respond to ICS</td>
<td>Maintain or increase ICS dosage</td>
<td>Consider alternative diagnosis</td>
</tr>
<tr>
<td>Well controlled asthma</td>
<td>Consider reducing dosage of ICS</td>
<td></td>
</tr>
</tbody>
</table>

* PD15 = 15% fall in FEV1 to a dose ≤ 635 mg

**Predictive Markers of Asthma Exacerbation during Stepwise Dose Reduction of Inhaled Corticosteroids**

- Aim: To determine the predictive factors for failed reduction of ICS in 50 subjects with well controlled asthma
- 50 subjects well controlled asthma, median does of ICS: 1000 mcg BDP. ICS halved every 8 weeks. Histamine, mannitol challenge, spirometry, exhaled NO and induced sputum at baseline.
- Spirometry, sNO, sputum
- Study endpoints: asthma exacerbation; no ICS treatment for two months
- 39 subjects with asthma exacerbation

**ICS dose titration**

- AHR or a reference strategy based on symptoms and lung function.
- Initial ICS tapering to identify the minimal ICS dose then randomization into ICS titration according to mannitol or symptoms

**ICS increased every 2 months if:**

Control group
- Fall in PEF ≥20% from baseline
- Deterioration in FEV1 ≥20% from baseline
- Increase in use of reliever medication
- Increase in symptoms score >0.5 from baseline

Mannitol group
- ICS increased until PD10 ≥ 635 mg.
No difference in mannitol group over standard practice for the time to first exacerbation

27% less mild asthma exacerbation with the mannitol strategy compared to the control group. No difference in severe asthma exacerbations. Higher doses of ICS in the mannitol group

ICS dose titration with methacholine vs standard strategy, less mild asthma exacerbations, higher dose of ICS

AHR TO MONITOR Rx

Assessment of asthma-related impairment in subjects with occupational asthma

• 30 workers diagnosed with occupational asthma by specific inhalation challenges six years ago.
• Assessment of AHR by both methacholine and mannitol challenge

ICS titration (Sont et al. 1999)

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Methacholine (mg)</th>
<th>400</th>
<th>800</th>
<th>1200</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low dose</td>
<td>No requirement</td>
<td>ICS 400 mcg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medium dose</td>
<td>ICS 800 mcg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>ICS 1600 mcg</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Sont et al, Am J Respir Crit Care Med 1999

Lemiere et al JACI 2011
Mannitol was more closely associated with asthma severity in terms of respiratory function and airway inflammation than methacholine challenge.

In subjects in whom asthma-related disability needs to be assessed, mannitol may provide a better estimation than methacholine challenge.

### Prevalence of AHR and asthma in athletes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Controls</th>
<th>Dry</th>
<th>Cold</th>
<th>Humid</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 50)</td>
<td>(n = 25)</td>
<td>(n = 25)</td>
<td>(n = 25)</td>
<td>(n = 25)</td>
<td></td>
</tr>
<tr>
<td>Swimmers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 7.3 mg/ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skiers:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤ 15.8 mg/ml</td>
<td></td>
<td></td>
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</tbody>
</table>

**Prevalence of AHR and asthma in athletes**


### Airway hyperresponsiveness is more prevalent in asymptomatic skiers

**Correlations between log PC_{20} and EVH fall in FEV1 with the number of training hours per week in a swimming pool**

- r = 0.50
- (p = 0.02)

**Correlations between log PC_{20} and EVH fall in FEV1 with the number of training hours per week in elite skiers**

- r = 0.53
- (p = 0.02)

**Eucapnic voluntary hyperventilation vs MC Challenge**

**Eucapnic voluntary hyperventilation**

- Percentage of swimmers with a positive EVH test
- Methacholine challenge
- Percentage of swimmers with AHR according to the threshold chosen

**Swimmers: 7.3 mg/ml**

**Skiers: 15.8 mg/ml**

Bougault et al. 2010

**Airway Responses to Eucapnic Hyperpnea, Exercise, and Methacholine in Elite Swimmers.**


Possible mechanisms of development of asthma and airway hyperresponsiveness in athletes

- Hyperventilation with airways heat and water loss, increased penetration of pollutants and allergens
- Epithelial ‘damage’ with loss of protective microvascular leak/plasma exsudation and trigger of a repair process
- Changes of contractile properties of the airway smooth muscle, airway remodelling ± inflammation
- Asymptomatic airway hyperresponsiveness
- Symptomatic asthma

AHR in athletes: a transient phenomenon?

![Graph showing AHR in athletes](image)

Bourgault et al. 2010

Effect of continuing or finishing high-level sports on airway inflammation, bronchial hyperresponsiveness, and asthma: A 5-year follow-up study of 42 highly trained swimmers

- Histamine responsiveness

Conclusions

- Methacholine and mannitol challenges.
- The AHR to mannitol is predictive of the occurrence of asthma exacerbations when ICS dose is further reduced.
- AHR to both methacholine and mannitol may be helpful for titrating the dose of ICS.
- Mannitol seems more associated with activity of asthma than methacholine.