Pulmonary Function Testing and Asthma

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Overview

- Role in diagnosis
- Quality testing
- Spirometry in children
- Methacholine challenge testing
- Eucapnic voluntary hyperventilation testing
- Common flow volume loop abnormalities
Spirometry – the Maneuver

• Three phases:
  – Maximal inspiration
  – “Blast” of exhalation
  – Continued exhalation to the end of test
Spirometry – What it Tells

- Measures volume and speed of maximal expiratory effort
- Detects abnormal flow
- Detects rapid changes in airway caliber
- Assesses changes in function over times
Spirometry – The Numbers

- FVC = Forced Vital Capacity*
- FEV1 = Forced Expiratory Volume in (first) second*
- FEV1/FVC = Ratio of above
- FEF25-75 = Average rate of flow at mid-exhalation*

* Often expressed as “% predicted”
Progressive Obstruction

Normal  Mild-Mod  Severe
Spirometry Pre & Post

• Pre and post – what?
  – Bronchodilator (albuterol)
  – Broncho “provoker”

• How much change is significant?
  – FVC and FEV1 = 12% from baseline
  – FEF25-75 = 25% from baseline
(+) Bronchodilator Test

Baseline

Post-Albuterol

18% improvement FEV1
Asthma & Spirometry: Diagnosis

- Reversible airway obstruction – a key feature of asthma
- Spirometry – potential “proof” of disease
- Normal baseline spirometry does not rule out asthma
Asthma & Spirometry: Management

- Severity class at diagnosis (FEV1% pred)
- Monitoring control (FEV1% personal best)
- Detection of significant dysfunction in asymptomatic patients
- Recommended yearly
Spirometry – the Maneuver

• Three phases:
  – Maximal inspiration
  – “Blast” of exhalation
  – Continued exhalation to the end of test

The Results Aren’t Useful if the Test Isn’t Done Correctly
Spirometry Equipment
Hand Held Spirometers

• Pros
  – Portable
  – User friendly

• Cautions
  – Lack of flow volume & volume time loops
  – Calibration
  – Reference options
Great Patient Coaching

• Correct posture
• Avoid leaks
  – Nose clips
  – Lips sealed on mouthpiece
• Avoid occlusion by tongue
• Rapid inhalation
• Start exhalation within 1 sec
• Cheerleading to finish!
Quality Criteria

- Within maneuver criteria
- Between maneuver criteria
Quality Killers

- Valsalva maneuver (glottic closure) or hesitation causing stop in airflow
- Leak at mouth
- Tongue or teeth obstructing mouthpiece
- Cough during maneuver
- Early cut off
- Lack of maximal effort throughout
Tongue Obstructing Mouthpiece

Flow

Volume
Slow Start

Flow

Volume
Slow Rise

Flow

Volume
Broad Late Peak

Flow

Volume
Glottic Closure (Cough)

Flow

Volume
Incomplete Exhalation

Flow

Volume
Why Complete Exhalation Matters

Flow

FVC

Volume
End of Test Criteria

- The patient cannot or should not continue
- The volume time curve shows no change in volume for $\geq 1$ sec
- Patient has tried to exhale
  - $\geq 3$ secs (if $< 10$ years old)
  - $\geq 6$ sec (if $> 10$ years)
Between Maneuver Evaluation

- Minimum 3 satisfactory maneuvers
- Two largest FVC’s within 0.25 L
- Two largest FEV1’s within 0.15 L
- Flow volume loops overlap
- Up to 8 more attempts reasonable
Test Result Selection

- Largest FVC & FEV1 are chosen – even if not from same curve
- FEF 25-25% is taken from maneuver with largest sum of FVC and FEV1
Post bronchodilator testing

- Total doses:
  - Albuterol: 400 µg (4 doses of 100 µg)
  - Ipatroprium: 160 µg (4 doses of 40 µg)

- Wait times
  - Albuterol: 10 to 15 minutes
  - Ipatroprium: 30 minutes

Post bronchodilator testing: Pre-testing medication

- Goal: Detect reversible airflow limitation
  - No short acting beta agonist for 4 hrs prior
  - No LABA, oral beta agonist, or theophylline for 12 hrs prior

- Goal: Assess whether function can be improved over current therapy
  - All routine medications should be given
Spirometry in Kids

- Challenges
- Expected results
- Utility
Tips for Kid Spirometry

- Kid-friendly technicians
- Bright, pleasant atmosphere
- Encouragement & praise
- Avoid scolding/intimidation
- Visual feedback (kid software)
- May need “practice sessions”
Spirometry in Very Young

- Possible
- Computer animation
- Longer to peak
- Shorter total exhalation time
- Beware post bronchodilator “learning” improvement
Overview

• Role in diagnosis
• Quality testing
• Spirometry in children

• Methacholine challenge testing
• Eucapnic voluntary hyperventilation testing
• Common flow volume loop abnormalities
Bronchoprovocation Testing

- Pulmonary function tests are tools in the diagnosis of asthma
  - Measurement of peak expiratory flow rate and spirometry are the most often used pulmonary function tests in the diagnosis of asthma
  - May be normal between symptomatic episodes or symptoms may only occur with certain exposures, activity

- Characteristics of asthma
  - Variable airflow limitation
    » May have airflow limitation only after exposure to a trigger

- Bronchial Hyperresponsiveness to external triggers (BHR)
  » Excessive response to an aerosolized provocation that triggers little or no response in a normal person
  » Distinguish most patients with asthma
  » Rationale for bronchoprovocation testing
  » Inflammation of the airways is associated with and may underlie airway hyperresponsiveness.
Bronchoprovocation Testing

- Patients with bronchial asthma have an increased airway responsiveness to various bronchoconstrictor stimuli
- Chemical agents, such as histamine, methacholine and leukotrienes or physical stimuli, such as cold air; hyperventilation and exercise

Table 1. Comparison of Direct and Indirect Challenges

<table>
<thead>
<tr>
<th>Variable</th>
<th>Direct challenge</th>
<th>Indirect challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism</td>
<td>Direct effect on airway receptors</td>
<td>Intermediate pathways; many involve mediator release</td>
</tr>
<tr>
<td>Examples</td>
<td>Histamine</td>
<td>Osmotic mediator release: exercise, EVH, hypertonic saline, mannitol</td>
</tr>
<tr>
<td></td>
<td>Methacholine</td>
<td>Nonosmotic mediator release: AMP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other: propranolol, bradykinin, tachykinins</td>
</tr>
<tr>
<td>Dependent on</td>
<td></td>
<td>+ +</td>
</tr>
<tr>
<td>ASM function</td>
<td>+++</td>
<td>Nil to minimal</td>
</tr>
<tr>
<td>Airway caliber</td>
<td>+++</td>
<td>+ +</td>
</tr>
<tr>
<td>Inflammation</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Dose required</td>
<td>Methacholine/histamine, top dose of</td>
<td>AMP, top dose of approximately 100 mg</td>
</tr>
<tr>
<td></td>
<td>approximately 1.0 mg</td>
<td>Mannitol, top dose of 625 mg</td>
</tr>
<tr>
<td>Dose limited</td>
<td>No</td>
<td>Yes for exercise, EVH, AMP, hypertonic saline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No for mannitol (?)</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Specificity</td>
<td>Low to fair (pretest probability)</td>
<td>High</td>
</tr>
<tr>
<td>Caveats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms current</td>
<td>+++</td>
<td>+ + +</td>
</tr>
<tr>
<td>Normal FEV₁</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>No TLC breaths</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Diagnostic value</td>
<td>Rule out asthma</td>
<td>Confirm asthma</td>
</tr>
<tr>
<td></td>
<td>Help diagnose asthma, especially</td>
<td>Evaluate for EIB</td>
</tr>
<tr>
<td></td>
<td>if symptoms mimicked</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AMP, adenosine monophosphate; ASM, airway smooth muscle; EIB, exercise-induced bronchoconstriction; EVH, eucapnic voluntary hyperpnea; FEV₁, forced expiratory volume in 1 second; TLC, total lung capacity.
Bronchoprovocation Testing

• Direct challenge tests
  • Early spirometry measures used
    » 20% improvement with bronchodilators as a (+) response
    » 20% decline with bronchoconstrictors as a (+) test for bronchoconstriction

• Provocation challenge concentration that results in a 20% decline in FEV1
  » PC20
Methacholine challenge testing

- Cholinergic agonist, induces bronchoconstriction
- Patient inhales one or more increasing concentrations of methacholine
- Results of spirometry performed before and after the inhalations used to quantify response

- Test is stopped if the FEV1 decreases 20% or more from baseline
  - Corresponding methacholine concentration is recorded as the PC$_{20}$
- Test is considered negative if the FEV1 does not decrease by 20% at the maximum concentration
Methacholine challenge testing

- 2 methods
  - 5-breath technique
    » Individual takes 5 deep breaths of each methacholine concentration from a nebulizer
    » 5 sec inhalation and 5 sec breath hold then performs spirometry after each dose
  - Tidal breathing technique
    » Inhales the methacholine concentration over 2-min while breathing normally (tidal breathing) from a nebulizer
    » Then performs spirometry after each concentration
- Maximal inhalation and breath hold results in bronchodilation and bronchoprotection
Methacholine Challenge Testing

• Absolute Contraindications
  • Severe airflow limitation (FEV1<50% predicted or <1.0L)
    » Difficult to interpret methacholine challenge if baseline obstruction
    » If baseline obstruction present, perform bronchodilator study to evaluate for a significant response (>12% and >200mL increase in FEV1 or FVC)
  • Heart attack or stroke in last 3 months
  • Uncontrolled HTN (SBP>200, DBP>100)
  • Known aortic aneurysm
Methacholine Challenge Testing

- Relative Contraindications
  - Moderate airflow limitation (FEV1 < 60% pred or <1.5L)
  - Inability to perform acceptable quality spirometry
  - Pregnancy, nursing mothers
    - Methacholine category C
    - Unknown if excreted in breast milk
  - Use of cholinesterase inhibitor medication (MG)
## Methacholine Challenge Testing

**FACTORS THAT INCREASE BRONCHIAL RESPONSIVENESS**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Duration of Effect</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to environmental antigens</td>
<td>1-3 wk</td>
<td>25</td>
</tr>
<tr>
<td>Occupational sensitizers</td>
<td>Months</td>
<td>55, 56</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>3-6 wk</td>
<td>57, 58</td>
</tr>
<tr>
<td>Air pollutants</td>
<td>1 wk</td>
<td>59</td>
</tr>
<tr>
<td>Cigarette smoke</td>
<td>Uncertain*</td>
<td>60</td>
</tr>
<tr>
<td>Chemical irritants</td>
<td>Days to months</td>
<td>61</td>
</tr>
</tbody>
</table>

*Studies of the acute effects of smoking on airway hyperreactivity and methacholine challenge testing are not consistent (60). There is some evidence of a brief acute effect that can be avoided by asking subjects to refrain from smoking for a few hours before testing.*

Methacholine Challenge Testing

**FACTORS THAT DECREASE BRONCHIAL RESPONSIVENESS**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Minimum Time Interval from Last Dose to Study</th>
<th>Ref. No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting inhaled bronchodilators, such as isoproterenol, isoetharine, metaproterenol, albuterol, or terbutaline</td>
<td>8 h</td>
<td>45, 46</td>
</tr>
<tr>
<td>Medium-acting bronchodilators such as ipratropium</td>
<td>24 h</td>
<td>20, 47</td>
</tr>
<tr>
<td>Long-acting inhaled bronchodilators, such as salmeterol, formoterol, tiotropium</td>
<td>48 h</td>
<td>48, 49</td>
</tr>
<tr>
<td>(perhaps 1 wk for tiotropium)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral bronchodilators</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid theophylline</td>
<td>12 h</td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting theophyllines</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>Long-acting theophyllines</td>
<td>48 h</td>
<td></td>
</tr>
<tr>
<td>Standard β₂-agonist tablets</td>
<td>12 h</td>
<td></td>
</tr>
<tr>
<td>Long-acting β₂-agonist tablets</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td>Cromolyn sodium</td>
<td>8 h</td>
<td></td>
</tr>
<tr>
<td>Nedocromil</td>
<td>48 h</td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine, cetirizine</td>
<td>3 d</td>
<td></td>
</tr>
<tr>
<td>Leukotriene modifiers</td>
<td>24 h</td>
<td></td>
</tr>
<tr>
<td><strong>Foods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coffee, tea, cola drinks, chocolate</td>
<td>Day of study</td>
<td>52</td>
</tr>
</tbody>
</table>

*Note: The authors do not recommend routinely withholding oral or inhaled corticosteroids, but their antiinflammatory effect may decrease bronchial responsiveness (53, 54). Inhaled corticosteroids may need to be withheld depending on the question being asked.*
# Methacholine Challenge Testing

## Table 4
### Dilution Schemes for the Two Recommended Methacholine Dosing Schedules

<table>
<thead>
<tr>
<th>Label</th>
<th>Strength</th>
<th>Take</th>
<th>Add NaCl (0.9%)</th>
<th>Obtain Dilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Dilution schedule* using 100-mg vial of methacholine chloride and the 2-min tidal breathing protocol</td>
<td></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</td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution A</td>
<td>3 ml</td>
<td>B: 8 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution B</td>
<td>3 ml</td>
<td>C: 4 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution C</td>
<td>3 ml</td>
<td>D: 2 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution D</td>
<td>3 ml</td>
<td>E: 1 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution E</td>
<td>3 ml</td>
<td>F: 0.5 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution F</td>
<td>3 ml</td>
<td>G: 0.25 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution G</td>
<td>3 ml</td>
<td>H: 0.125 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution H</td>
<td>3 ml</td>
<td>I: 0.0625 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution I</td>
<td>3 ml</td>
<td>J: 0.031 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Optional dilution schedule using 100-mg vial of methacholine chloride and five-breath dosimeter protocol</td>
<td></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</td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution A</td>
<td>9 ml</td>
<td>B: 4 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution B</td>
<td>9 ml</td>
<td>C: 1 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution C</td>
<td>9 ml</td>
<td>D: 0.25 mg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 ml of dilution D</td>
<td>9 ml</td>
<td>E: 0.0625 mg/ml</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Schedule obtained from Methapharm (Brantford, ON, Canada).
Methacholine Challenge Testing

- **Endpoints**
  - **Primary:** change in FEV1
    - Curves should meet spirometry criteria for acceptability and reliability
  - **Others**
    - Forced inspiratory curves (flow-volume loops)
    - Airway resistance and conductance by plethysmography
    - Peak flows
Methacholine Challenge Testing

CATEGORIZATION OF BRONCHIAL RESPONSIVENESS

<table>
<thead>
<tr>
<th>PC&lt;sub&gt;20&lt;/sub&gt; (mg/ml)</th>
<th>Interpretation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 16</td>
<td>Normal bronchial responsiveness</td>
</tr>
<tr>
<td>4.0-1.6</td>
<td>Borderline BHR</td>
</tr>
<tr>
<td>1.0-4.0</td>
<td>Mild BHR (positive test)</td>
</tr>
<tr>
<td>&lt; 1.0</td>
<td>Moderate to severe BHR</td>
</tr>
</tbody>
</table>

The following factors should be taken into consideration when interpreting PC<sub>20</sub> results for an individual patient:

- Pretest probability of asthma, including current asthma symptoms
- Presence or degree of baseline airway obstruction
- Quality of the patient’s spirometry maneuvers
- Pretest questionnaire results (effects modifiers; see Tables 2 and 3)
- Symptoms reported by the patient at the end-of-test
- Degree of recovery after bronchodilator administration
Methacholine Challenge Testing

- Prevalence of asthma ~7%
- Positive methacholine challenge in general population

<table>
<thead>
<tr>
<th>BHR Rate</th>
<th>BHR criteria*</th>
<th>Study population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>8</td>
<td>100 adults age 20—60 with no history of smoking, cough, asthma, family history of asthma, rhinitis, atopy, or recent upper respiratory illness</td>
<td>Malo et al. [1983]</td>
</tr>
<tr>
<td>8%</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>2.5</td>
<td>50 non-smoking adults age 18—35 with no history of allergy, asthma, rhinitis, or recent respiratory infections</td>
<td>Casale et al. [1988]</td>
</tr>
<tr>
<td>6%</td>
<td>5.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td>10.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28%</td>
<td>25.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3%</td>
<td>2.5</td>
<td>63 ROTC students age 18—31 with no history of asthma</td>
<td>Roth et al. [2001]</td>
</tr>
<tr>
<td>10%</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13%</td>
<td>2.5</td>
<td>1,567 adults with no history of smoking, asthma, atopy, or recent respiratory infection; rate in males 4% versus 15% in females</td>
<td>Jayet et al. [2005]</td>
</tr>
<tr>
<td>11%</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>23%</td>
<td>2</td>
<td>318 patients age 18—75 from physician general practice survey; rate in males 13% versus 31% in females</td>
<td>Trigg et al. [1990]</td>
</tr>
</tbody>
</table>

Background rates—general population surveys

- 13% (median) 12.5 13,161 randomly selected individuals age 20—44, tested at 35 locations in 16 countries (range of 3—28% for different testing centers) | Chinn et al. [1997] |
- 12% 2.5 799 randomly selected French adults from Paris and Montpellier age 20—44; rate 12—30% in males; 34—43% in females | Leynaert et al. [1997] |
- 13% males 12.5 931 randomly selected German adults age 20—65 | Wassmer et al. [1997] |
- 28% females 12.5 516 randomly selected Indian adults age 20—44 | Chowgule et al. [1998] |
- 14% males 2.5 7,126 randomly selected Swiss adults age 18—60 | Schwartz et al. [2002] |
- 22% females 14% 2.5 888 randomly selected Finns and Russians age 25—54 | Petays et al. [2003] |
# Methacholine Challenge Testing

<table>
<thead>
<tr>
<th>Condition</th>
<th>Specific factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical</td>
<td>Smoking</td>
</tr>
<tr>
<td></td>
<td>Current smokers</td>
</tr>
<tr>
<td></td>
<td>Ex-smokers</td>
</tr>
<tr>
<td></td>
<td>Passive cigarette smoke exposure</td>
</tr>
<tr>
<td></td>
<td>Bronchitis</td>
</tr>
<tr>
<td></td>
<td>Bronchiectasis</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>Normal variation</td>
<td>Cardiovascular conditions</td>
</tr>
<tr>
<td></td>
<td>Mitral valve stenosis</td>
</tr>
<tr>
<td></td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td></td>
<td>Vasospastic angina</td>
</tr>
<tr>
<td></td>
<td>C-reactive protein (CRP)</td>
</tr>
<tr>
<td></td>
<td>Carotid intima thickness</td>
</tr>
<tr>
<td></td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>Crohn's disease</td>
</tr>
<tr>
<td></td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td></td>
<td>Gastroesophageal reflux</td>
</tr>
<tr>
<td>Allergy</td>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td>Sjogren's syndrome</td>
</tr>
<tr>
<td></td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>Athletes</td>
</tr>
<tr>
<td></td>
<td>Hockey players</td>
</tr>
<tr>
<td></td>
<td>Skiers</td>
</tr>
<tr>
<td></td>
<td>Swimmers</td>
</tr>
<tr>
<td></td>
<td>Football players</td>
</tr>
</tbody>
</table>

Methacholine Challenge Testing

- Excellent sensitivity for diagnosing asthma
  - Nearly all individuals who have significant asthma will react to a relatively low methacholine dose
  - A “negative” test makes the diagnosis of asthma unlikely
    » Must have recent symptoms
    » Athletes with exercise-induced symptoms may have false negative
Methacholine Challenge Testing

• Specificity or positive predictive value of the test is poor
  • Other factors are associated with increased methacholine sensitivity
  • A “positive” test does not necessarily mean an individual has asthma
  • Must be interpreted in the context of the patient’s symptoms

• The positive predictive value increases when the measured PC20 is lower
  • Positive predictive value of a PC20 < 8 mg/mL in a random population is below 50%
    (50% of the subjects in a random population with a PC20 < 8 mg/mL have clinically current asthma symptoms)
  • If the PC20 < 1 mg/ml, the specificity and positive predictive value approach 100%

• Positive predictive value is also higher in a group of individuals with:
  • A higher pretest probability (those who are more likely to have asthma based on their symptoms)
  • The methacholine induced symptoms resemble the naturally occurring symptoms for which the test was ordered
Methacholine Challenge Testing

Predicted Values from NIIANES III

<table>
<thead>
<tr>
<th></th>
<th>PRED</th>
<th>ACTUAL</th>
<th>%PRED</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPIROMETRY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forced Vital Capacity (FVC; L)</td>
<td>2.6</td>
<td>2.01</td>
<td>77</td>
</tr>
<tr>
<td>Forced Exp. Vol. 1 (FEV1; L)</td>
<td>1.99</td>
<td>1.54</td>
<td>77</td>
</tr>
<tr>
<td>% FEV1 / FVC</td>
<td>77.2%</td>
<td>76.6%</td>
<td>90</td>
</tr>
<tr>
<td>Mid Exp. Flow (FEF25-75; L/sec)</td>
<td>1.9</td>
<td>1.25</td>
<td>66</td>
</tr>
<tr>
<td>Peak Flow (PF; L/sec)</td>
<td>5.32</td>
<td>4.8</td>
<td>90</td>
</tr>
</tbody>
</table>

**INSPIRATORY LOOP**

FEF50% / FIF50%

\[
\leq 1.0\quad 1
\]

**METHACHOLINE BRONCHOPROVOCATION**

<table>
<thead>
<tr>
<th>Control</th>
<th>NaCl</th>
<th>Dosage</th>
<th>Methacholine mg/ml</th>
<th>0.025</th>
<th>0.25</th>
<th>2.5</th>
<th>10</th>
<th>25</th>
<th>Post BD</th>
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<tbody>
<tr>
<td>FVC</td>
<td>2.19</td>
<td>2.16</td>
<td>1.96</td>
<td>1.61</td>
<td></td>
<td></td>
<td></td>
<td>2.06</td>
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</tr>
<tr>
<td>% Chg</td>
<td>9%</td>
<td>-1.4%</td>
<td>-10.5%</td>
<td>-26.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>1.47</td>
<td>1.53</td>
<td>1.36</td>
<td>1.04</td>
<td></td>
<td></td>
<td></td>
<td>1.38</td>
<td></td>
</tr>
<tr>
<td>% Chg</td>
<td>-4.5%</td>
<td>4.1%</td>
<td>-7.5%</td>
<td>-29.3%</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>FEF25-75</td>
<td>1.02</td>
<td>1.01</td>
<td>1.04</td>
<td>0.75</td>
<td></td>
<td></td>
<td></td>
<td>0.88</td>
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<tr>
<td>% Chg</td>
<td>-18.4%</td>
<td>-1%</td>
<td>2%</td>
<td>-26.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pk Fl</td>
<td>4.26</td>
<td>3.16</td>
<td>3.92</td>
<td>3.52</td>
<td></td>
<td></td>
<td></td>
<td>4.32</td>
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</tr>
<tr>
<td>% Chg</td>
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<td>-25.8%</td>
<td>-8%</td>
<td>-17.4%</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>FEF50/PIF50</td>
<td>1.58</td>
<td>1.3</td>
<td>0.93</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
<td>0.98</td>
<td></td>
</tr>
</tbody>
</table>

**TECHNICIAN COMMENTS (methacholine bronchoprovocation):**

**PHYSICIAN INTERPRETATION (methacholine bronchoprovocation):**

The methacholine challenge test is positive for "moderate to severe" bronchial hyper-responsiveness. There is a high probability that a clinical diagnosis of asthma exists. However, responsiveness should be viewed in light of the clinical symptoms for shortness of breath, cough or wheezing.
Bronchoprovocation: Indirect Challenges

- Act on inflammatory cell mediators and neurally-mediated pathways
- Better reflection of active airway inflammation
- More specific for asthma
- Same contraindications as methacholine
- Same patient preparation
  - Avoid antihistamines for 48 hrs, exercise for at least 4 hrs

- Exercise Challenge
  - Common trigger, best studied
  - Loss of water in bringing large volumes of air to the lungs in a short period of time

**Exercise or eucapnic hyperpnea with dry air leads to**

- Dehydration of the airway surface liquid (ASL) → cooling
- Increase in $[\text{Na}^+]$, $[\text{Cl}]$, $[\text{Ca}^{++}]$, $[\text{K}^+]$
- Increase in osmolarity of ASL
- Water moves from cells to restore ASL
- Mediators released e.g. Prostaglandins, Leukotrienes, Histamine
  - In those with bronchial hyperresponsiveness
  - Bronchial Smooth Muscle contraction ± Edema
  - Airway narrowing & reduction in FEV$_1$
Exercise Testing

- Inhale dry, cool air during exercise
  - Ambient room temperature of 20-25C (68-77F)
  - 50% relative humidity or less
  - Water content of inspired air < 10mg/L (medical grade compressed air)
- Treadmill or bicycle
- Exercise at target for at least 4 minutes (6-8 min preferred)
  - Target HR of 80-90% max predicted
  - Target ventilation based on predicted MVV or work rate
    - MVV=35*FEV1
- Perform baseline spirometry and after exercise
  - 1, (3), 5, 10, 15, 20 minutes
  - Most nadir in 5-10 minutes after stopping exercise
- Abnormal response is fall in FEV1 by 10%
- Fall of 15% may be more diagnostic of EIB
Eucapnic Voluntary Hyperventilation

- Developed in mid-1990s for evaluation of army recruits
- EIB in elite athletes, International Olympic Committee-Medical Commission
- Hyperventilation of a dry gas
- Gas consists of 21% oxygen, 5% CO₂, rest nitrogen
- FEV1 measured at baseline
- Hyperventilate at 6 minutes at a target ventilation rate of 30*FEV1
  - Report achieved ventilation as % of MVV (35*FEV1)
- Measure FEV1 at 3, 5, 10, 15 and 20 minutes

Eucapnic Voluntary Hyperventilation

- If reach at least 60% MVV
  - Fall of 10% considered abnormal response
    » 10-19.9% considered mild
    » 20-29.9% moderate
    » >=30% severe
- Secondary criteria less well defined
  - Maximum mid-expiratory flow rate, Peak expiratory flow rate, FVC
- A threshold of >10% change in FEV1 had a specificity of 90%, with a sensitivity of 63.3% for diagnosis of asthma (Chest 1995; 108:1240-45)
Eucapnic Voluntary Hyperventilation

Predicted Values from NHANES III

<table>
<thead>
<tr>
<th></th>
<th>PRED</th>
<th>PRE ACTUAL</th>
<th>%PRED</th>
<th>POST ACTUAL</th>
<th>%CHG</th>
</tr>
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<tbody>
<tr>
<td>SPIROMETRY - Pre/post Bronchodilator</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Forced Vital Capacity (FVC; L)</td>
<td>5.93</td>
<td>6.34</td>
<td>107</td>
<td>6.38</td>
<td>1</td>
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<tr>
<td>Forced Exp. Vol. 1 (FEV1; L)</td>
<td>4.94</td>
<td>4.87</td>
<td>99</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>% FEV1 / FVC</td>
<td>84.1%</td>
<td>76.8%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mid Exp. Flow (FEF25-75; L/sec)</td>
<td>5.12</td>
<td>4.37</td>
<td>85</td>
<td>4.57</td>
<td>5</td>
</tr>
<tr>
<td>Peak Flow (PF; L/sec)</td>
<td>10.38</td>
<td>9.63</td>
<td>93</td>
<td>10.27</td>
<td>7</td>
</tr>
</tbody>
</table>

INSPIRATORY LOOP

FEF50% / FIF50% <=1.0 1.85 *

BRONCHOPROVOCATION: EUCAPNIC VOLUNTARY HYPERVENTILATION (EVH)

Baseline-------------------Minutes Post Hyperventilation-------------------

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>3</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>PostBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC</td>
<td>6.34</td>
<td>5.12</td>
<td>5.77</td>
<td>5.85</td>
<td>5.85</td>
<td>5.67</td>
<td>6.38</td>
</tr>
<tr>
<td>% Chg</td>
<td>-19.2%</td>
<td>-9%</td>
<td>-7.7%</td>
<td>-7.7%</td>
<td>-10.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV1</td>
<td>4.87</td>
<td>2.97</td>
<td>3.21</td>
<td>3.57</td>
<td>3.69</td>
<td>3.51</td>
<td>5</td>
</tr>
<tr>
<td>% Chg</td>
<td>-39%</td>
<td>-34.1%</td>
<td>-26.7%</td>
<td>-24.2%</td>
<td>-27.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF25-75</td>
<td>4.37</td>
<td>1.49</td>
<td>1.51</td>
<td>1.9</td>
<td>2.21</td>
<td>2.1</td>
<td>4.57</td>
</tr>
<tr>
<td>% Chg</td>
<td>-65.9%</td>
<td>-65.4%</td>
<td>-56.5%</td>
<td>-49.4%</td>
<td>-51.9%</td>
<td></td>
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</tr>
<tr>
<td>Pk Fl</td>
<td>9.63</td>
<td>4.97</td>
<td>5.29</td>
<td>5.9</td>
<td>5.96</td>
<td>6.05</td>
<td>10.27</td>
</tr>
<tr>
<td>% Chg</td>
<td>-48.4%</td>
<td>-45.1%</td>
<td>-38.7%</td>
<td>-38.1%</td>
<td>-37.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEF50/FIF90</td>
<td>1.85</td>
<td>1.1</td>
<td>0.9</td>
<td>0.9</td>
<td>0.91</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Target Ventilation (FEV1 * 30): 146.1 L/min
Calculated Exercise Maximum Voluntary Ventilation (35 * FEV1): 170.5 L/min
Achieved average minute ventilation during EVH: 104.5 L/min
Achieved average ventilation/MVV %: 61.3

Technician Comments (EVH):
Patient was wheezing after the 6 minutes of hyperventilation.

Physician Comments (EVH):
The patient exhibits severe hyperventilation-induced bronchospasm.
Flow-Volume Loop

- Air Flow vs. Volume

- Flow volume curve is graphic representation of the inspiratory and expiratory maneuvers

Effort

**Dependent** flow-limiting segment at upper airways

**Independent** flow limiting segment at lower airways

Expiration

Inspiration
Flow-Volume Loop

- Early glottic closure
- Variable effort
- Cough

- Get this with spirometry
- Always look at the flow volume curve when interpreting PFTs
Flow-Volume Loop

- Obstruction

- Restriction
Flow-Volume Loop

- Other information that can be obtained from the flow volume curve
  - Large airway obstruction
  - Upper airway or vocal cord dysfunction
Flow-Volume Loop

cords, var extra  trachea, var intra  fixed obstr
Flow-Volume Loop

*SPIROMETRY

<table>
<thead>
<tr>
<th></th>
<th>PRED</th>
<th>ACTUAL</th>
<th>%PRED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity (FVC;L)</td>
<td>4.91</td>
<td>4.44</td>
<td>90</td>
</tr>
<tr>
<td>Forced Exp. Vol. 1 (FEV1;L)</td>
<td>3.7</td>
<td>3.35</td>
<td>91</td>
</tr>
<tr>
<td>% FEV1/VC</td>
<td>75.5%</td>
<td>75.5%</td>
<td></td>
</tr>
<tr>
<td>Mid Exp. Flow (FEF25-75;L/sec)</td>
<td>3.02</td>
<td>2.53</td>
<td>84</td>
</tr>
<tr>
<td>Peak Flow (PF;L/sec)</td>
<td>9.38</td>
<td>9.89</td>
<td>105</td>
</tr>
</tbody>
</table>

*INSPIRATORY LOOP

FEF50%/FIF50% (normal<=1.0)

Tech comments: Pt. with difficulty throughout testing with cough and wheezing
Flow-Volume Loop

- Paradoxical vocal fold motion (PVFM)
  - Involuntary, episodic adduction of vocal folds during inspiration
  - Resulting in > 50% glottic closure
- Often misdiagnosed as asthma
- Most asymptomatic PVFM patients have normal PFT
- Truncatated inspiratory limb of flow volume loop
- Methacholine may trigger PVFM, but not a sensitive test for PVFM
- Direct visualization via laryngoscopy gold standard

Ibrahim et al. 2007 Postgrad Med J.
Flow-Volume Loop

- Normal baseline spirometry and negative EVH
Flow-Volume Loop

- 24yo WM with SOB/DOE, wheezing
- No PMHx, medications
- PSHx sig for exp lap 6 months prior after MVA
- Dx with asthma but no improvement with meds
- Normal spirometry
- Decreased peak flow
- Consistent with asthma
Flow-Volume Loop

- Fixed airway obstruction
- Post-intubation tracheal stenosis/stricture

**SPIROMETRY**

<table>
<thead>
<tr>
<th>Test</th>
<th>Pred</th>
<th>Actual</th>
<th>% Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forced Vital Capacity (FVC;L)</td>
<td>4.78</td>
<td>4.63</td>
<td>97</td>
</tr>
<tr>
<td>Forced Exp. Vol. 1 (FEV1;L)</td>
<td>4.11</td>
<td>3.64</td>
<td>89</td>
</tr>
<tr>
<td>% FEV1/FVC</td>
<td>86.1%</td>
<td>78.6%</td>
<td></td>
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<tr>
<td>Mid Exp. Flow (FEF25-75;L/sec)</td>
<td>4.63</td>
<td>3.50</td>
<td>76</td>
</tr>
<tr>
<td>Peak Flow (PF;L/sec)</td>
<td>9.59</td>
<td>5.07</td>
<td>53*</td>
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</table>

**INSPIRATORY LOOP**

<table>
<thead>
<tr>
<th>Test</th>
<th>Pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEF50%/FIF50% (normal&lt;=1.0)</td>
<td>1.38*</td>
</tr>
</tbody>
</table>