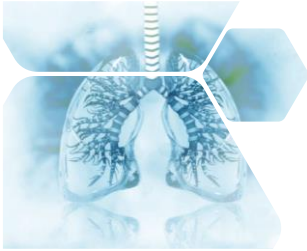



Heather Murgatroyd, BA RRT, CPFT, AE-C
Respiratory Clinical Specialist
Methapharm Respiratory




Direct Bronchial Challenge Testing




1

Disclaimer



I recognize that I must follow all guidelines and criteria regarding vested interest. I have the following real or perceived conflicts of interest that relate to this presentation:

**I am an employee of
Methapharm, Inc. -
manufacturer and distributor
of Provocholine®
distributor of Aridoj®
distributor of Vivatmo pro FeNO**





2

OBJECTIVES


At the conclusion of this presentation the attendee will be able to:

- Discuss the role of direct challenge testing in the diagnosis of asthma
- Identify direct bronchial challenge tests
- Identify the indications for direct bronchial challenge testing
- Recognize and discuss the ERS technical standard and guidelines for performing direct bronchial challenge tests
- Discuss the process of direct challenge testing


3

Direct Bronchial Challenge Testing
 Tell me about YOU!




I work, or have worked, in a pulmonary function lab

A. True
 B. False




4

Is it Asthma?
 Patient Presentation – Primary Care




- 25 y/o female
- Full-time Paralegal in a large, busy law office
- 65 inches/173 lbs.
- Vital signs are normal
- Lungs are clear
- Presents with complaints of shortness of breath, occasional chest tightness, occasional daytime cough, nocturnal cough, "thinks" she wheezes at times
- Symptoms appear to be random, she has not identified any triggers





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Question 1
 Patient Presentation – Primary Care



First step(s) at the initial visit:


A. Gather detailed medical history
 B. Physical exam
 C. Spirometry
 D. All of the above

Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007 U.S. Department of Health and Human Services National Institutes of Health: National Heart, Lung and Blood Institute.

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Diagnosing Asthma
Guidelines Expert Panel Report




- Gather detailed medical history
- Physical exam
- Spirometry to demonstrate obstruction and assess reversibility
- Additional studies, as indicated, to rule out alternate diagnosis
- Alternate diagnosis are ruled out

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Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007 U.S. Department of Health and Human Service National Institutes of Health, National Heart, Lung and Blood Institute.

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Question 2
Patient Presentation



Initial spirometry in office is inconclusive.


Next step:

- Send patient home with a SABA PRN trial
- Send patient to pulmonologist for further evaluation
- Refer patient to hospital pulmonary function lab for further testing
- Start patient on ICS and follow up in 4-6 weeks

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Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007 U.S. Department of Health and Human Service National Institutes of Health, National Heart, Lung and Blood Institute.

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Diagnosing Asthma
EPR on Spirometry



- Objective assessment of pulmonary function is necessary
- Medical history and physical exam might not be reliable for excluding alternate diagnosis
- Pulmonary Function measures do not often correlate directly with symptoms
- If performed in office and results are severe or questionable further assessment in a specialized pulmonary function lab is recommended
- Bronchoprovocation testing may be useful if asthma is suspected but spirometry is normal or near normal

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Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007 U.S. Department of Health and Human Service National Institutes of Health, National Heart, Lung and Blood Institute.

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Question 3

Patient Presentation



Pulmonary function test pre and post bronchodilator performed at hospital. Results are inconclusive. Patient reports continued periodic symptoms.

Next step(s):

- A. Refer to asthma allergy or pulmonology
- B. Trial SABA PRN
- C. Trial SABA/ICS
- D. Send for bronchoprovocation testing
- E. A or D

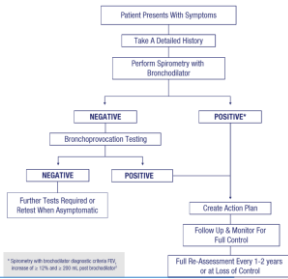


Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Full Report 2007 U.S. Department of Health and Human Service National Institutes of Health. National Heart, Lung and Blood Institute.

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Diagnosing Asthma

Algorithm



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Question 4

Bronchial Challenge Testing



There are 2 categories of bronchial challenge testing.

- A. True
- B. False



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Is It Asthma ?

Bronchial Challenge Testing

The diagram illustrates bronchial challenge testing. It features a central image of human lungs. To the left, under 'DIRECT TESTS', are 'METHACHOLINE' and 'HISTAMINE'. To the right, under 'INDIRECT TESTS', are 'EXERCISE TEST', 'MANNITOL', and 'EUCAPNIC VOLUNTARY HYPERVENTILATION'. A small image of lungs is in the top right corner.

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Cuerra AL, Wangler J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge test. Eur Respir J 2017; 49: 16015285

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Question 5

Direct Bronchial Challenge Testing

Direct Bronchial Challenge Tests

- A. Are delivered via nebulizer
- B. Are highly sensitive
- C. Work directly on bronchial smooth muscle receptors
- D. All of the above

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Anderson, S. Bronchial challenge tests: usefulness, availability and limitations. Breasline September 2011 Volume 8 No 1
ATS Pulmonary Function Laboratory management & Procedure Manual, 3rd Edition, Chapter 12, 2014.

15

History of Direct Challenge Testing

What is Available?

- Provocholine® received FDA approval in 1986
- Histamine introduced in 1958 as diagnostic test for asthma


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Bilton, J. et al. Histamine Challenge Testing: comparison of three methods. Thorax 1986;41:128-132

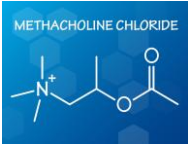
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Pharmacology

Methacholine Chloride is:



- A bronchoconstrictor to be administered in solution only, by inhalation, for diagnostic purposes
- Solution is made from powdered methacholine chloride and normal saline




METHACHOLINE CHLORIDE

methapharm Respiratory Provocholine® (methacholine chloride USP)
Package Insert, 8/2022


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Pharmacology

Histamine is:



- Histamine acid phosphate
- Solutions are generally made with histamine di-phosphate powder and phosphate-buffered saline




HISTAMINE

methapharm Respiratory P. J. Sterk, et al. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. European Respiratory Journal 1993 6: 53-63. DOI: 10.1183/09041950.053a1993

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Direct Challenge Tests


Comparing the Options




- Both agents can be delivered via nebulizer or dosimeter
- Dosing and delivery protocols are the same for each test
- Reproducibility is similar although bronchial hyperresponsiveness may be less reproduceable when testing with histamine
- PD₂₀ similar

methapharm Respiratory Higgin, BG et al. Comparison of histamine and methacholine for use in bronchial challenge tests in Community studies. Thorax 1986; 41:880-810.
P. J. Sterk, et al. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. European Respiratory Journal 1993 6: 53-63. DOI: 10.1183/09041950.053a1993
Coppo, RQ et al. Guidelines for Methacholine and Exercise Challenge Testing. Am J Respir Crit Care Med Vol 161 pp 308-320.


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Direct Challenge Tests
Comparing the Options 

- Both agents have excellent safety records
- Histamine is generally used in epidemiological studies
- Histamine reported to cause more voice change, flushing, headache and systemic side effects
- Methacholine produces more bronchial reactivity at a lower dose with less side effects


 Higgins, BG et al. Comparison of histamine and methacholine for use in bronchial challenge tests in Community studies. *Thorax* 1988; 43:605-610.
P.J. Sleek, et al. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *European Respiratory Journal* 1993 6: 53-63; DOI: 10.1183/09041950.053n1993

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Question 6
Referral to Pulmonologist 

Patient referred to Pulmonologist for further investigation. She reports continued symptoms and increased mental stress at work. Referred to local hospital for:


- A. EEG
- B. Chest CT
- C. Methacholine challenge test
- D. EGD

 Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of Methacholine challenge tests. *Eur Respir J* 2017;49:1601526


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Diagnosing Asthma
What is Methacholine Challenge Testing? 

- The administration of a bronchoconstrictor agent through a nebulizer
- A step dose response test
- Subjects with asthma are more sensitive to methacholine-induced bronchoconstriction than are healthy subjects


 Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of Methacholine challenge tests. *Eur Respir J* 2017;49:1601526

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Indications for the Methacholine Challenge 

US Product Insert

Provocholine® is indicated for the diagnosis of bronchial airway hyperreactivity in subjects who do not have clinically apparent asthma.



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Provocholine® (methacholine chloride USP) Package Insert, 8/2022
https://pubbay.com/illustrations/question-mark-question-response-1019820/

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Indications for the Methacholine Challenge 

Pediatric Use


Provocholine® is approved for patients 5 years of age and older and may be performed in children who can perform good quality spirometry



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Provocholine® (methacholine chloride USP) Package Insert, 08/2022

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Indications for Methacholine Testing 

2017 ERS/ATS Technical Standard

- Primary indication for a MCT is to help determine if current respiratory symptoms may be due to asthma or to make that diagnosis much less likely.
- Bronchial challenge tests are also used in screening applicants for situations where AHR would present a high safety risk, such as commercial diving, submarine service and some occupational exposures.


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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of Methacholine challenge tests. Eur Respir J 2017;48:1601526

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2017 ERS Technical Standard

Key Recommendations



- Medication withholding times were adjusted
- Recommending tidal breathing over dosimeter method
- Introducing new interpretation strategy of PD₂₀
 - Requires detailed nebulizer performance characteristics on output and respirable fraction in order to be calculated
- General updates, such as caffeine no longer needs to be withheld

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526


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2017 ERS Technical Standard

Key Procedure Recommendations



- Deep inspiration and breath hold not recommended
- Dosimeter is optional
- Tidal breathing is recommended
- Diluent step is recommended




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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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2017 ERS Technical Standard

PC₂₀ vs PD₂₀



PC₂₀ = Provocative Concentration to cause a 20% fall in FEV₁

PD₂₀ = Provocative Dose to cause a 20% fall in FEV₁

Variables to Dosing:

- Concentration of drug
- Output of the nebulizer*
- Inhalation time
- Particle size <5 µm
 - Particles too small do not contain methacholine
 - Particles too large deposit in posterior pharynx


*Please refer to the Appendix D of the ERS technical standards to obtain formulas for calculating PD₂₀ for your chosen nebulizer

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Safety Considerations
Side Effects



- 100,000s of MCTs have been performed without serious side-effects.
- Reported symptoms: Transient, generally mild, wheezing, cough, dyspnoea and chest tightness.
- Delayed or prolonged responses to methacholine are rare.




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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601528

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Safety Considerations
General Safety



- Ensure all staff performing the test are properly trained on equipment and emergency airway procedures
- Physician should be in the vicinity or available in case of emergency




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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601528

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Safety Considerations
Technologist Safety




- Minimize technologist exposure to methacholine aerosol
- Technologists with asthma should avoid testing or take extra precautions (e.g. masks, exhalation filters)
- Technologists should stand away from aerosol
- ERS technical standard suggests a minimum of two air exchanges per hour in the testing room

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601528

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Contraindications
For Direct Bronchial Challenge Testing




- Airflow limitation FEV₁ <60% predicted or 1.5 L (adults)
- Spirometry quality Inability to perform acceptable and reproducible spirometry maneuvers throughout the test
- Cardiovascular problems Heart attack or stroke in last 3 months, uncontrolled hypertension, known aortic aneurysm
- Other recent eye surgery or intracranial pressure elevation risk

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Contraindications
Specific to Methacholine Challenge Testing




- Pregnancy Pregnant mothers should avoid testing. Category C drug.
- Lactation Should not be given to nursing mothers
- Additional medication Should not be given to patients taking concerns cholinesterase inhibitor medication (e.g. for myasthenia gravis)

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Provocholine® (methacholine chloride USP) Package Insert. October 2017-PPR-07
Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Understanding the MCT
Factors Which May Impact MCT Results



- Coaching is essential - the MCT is effort and technique dependent
- Failure to withhold medications for the sufficient amount of time
- The time of day testing is performed in certain patients
- Some patient may only react to specific antigens (i.e. occupational asthma)


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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526


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Understanding the MCT

Factors Which May Impact MCT Results



- Improper calibration or function of testing equipment
- Incorrect preparation or storage of methacholine solutions
- Stability
- Temperature of solution
- Timing




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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017;49: 1601526

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Equipment and Supplies



- Nebulizer
- Dosimeter (optional)
- Methacholine chloride
- Gas source for nebulizer
- Spirometer
- Bronchodilators
- Ensure oxygen, and emergency equipment is available




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Preparing for an MCT

Dilution Protocol Options



ATS Short	ATS Long
16 mg/mL	16 mg/mL
4 mg/mL	8 mg/mL
1 mg/mL	4 mg/mL
0.25 mg/mL	2 mg/mL
0.0625 mg/mL	1 mg/mL
	0.05 mg/mL
	0.025 mg/mL
	0.125 mg/mL
	0.0625 mg/mL
	0.03125 mg/mL

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017;49: 1601526
Pneumofluor® (methacholine chloride USP) Package Insert, October 2017-PPR-07

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Preparing for an MCT

General Mixing Recommendations



- Can be performed by a pharmacist, respiratory therapist or other properly trained individual using sterile technique
- Precise mixing is very important for the accuracy of the test results and for the safety of patients



Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. *Eur Respir J* 2017; 49: 1601526

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Preparing for an MCT

Approved Diluents



- 0.9% sodium chloride solution for injection (saline)
- 0.9% sodium chloride solution with 0.4% phenol (saline with 0.4% phenol)



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Preparing for an MCT

Premixed Solution




- There is an FDA approved, sterile, premixed methacholine chloride solution available.




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Pre-Test Preparation
Patient Instructions



- A consent form may be completed.
- The procedure should be thoroughly explained to the patient prior to the start of the test.




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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Pre-Test Preparation
Patient Instructions



- Normal consumption of caffeine
 - coffee/tea
 - chocolate
- Avoid smoking for 1 hour
- Avoid alcohol for 4 hours




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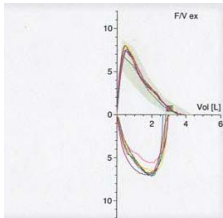
Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Performing an MCT
Pre-challenge Spirometry



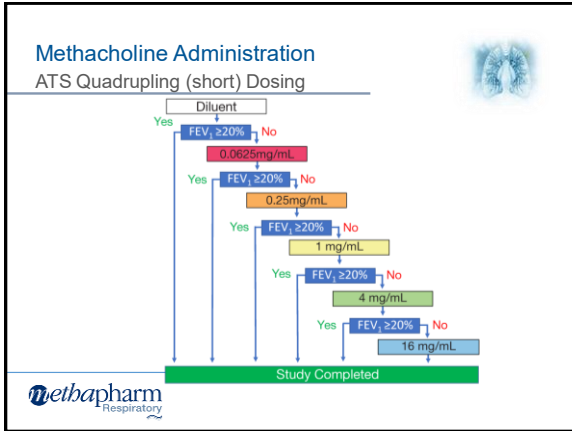
- Prior to delivering any methacholine, eligibility must be established.
- This should include full flow-volume loops and should meet current ATS repeatability criteria.



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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Performing an MCT

Procedure Based on ATS Short Protocol

Pre-challenge spirometry – full maneuver to ATS guidelines

Diluent Step - administer prior to administering methacholine, followed by full spirometry maneuver at 30/90 seconds. Highest FEV₁ becomes baseline for test.

Methacholine Delivery - Lowest concentration to highest concentration delivered via nebulizer of choice. Measure FEV₁ at 30 seconds and 90 seconds from the end of last inspiration of methacholine.

End of test - administer bronchodilator, FEV₁ should return to within 10% of baseline

If at any time the FEV₁ drops ≥ 20% from baseline, stop test and do not administer the next level of methacholine

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Interpretation of Results

Overview


- A **POSITIVE TEST** occurs when FEV₁ drops by 20% or more during the course of the test
- A **NEGATIVE TEST** occurs when the highest concentration is inhaled but FEV₁ drops by less than 20%
- MCT is more sensitive for ruling out asthma

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Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J 2017; 49: 1601526

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Diagnosing Asthma
Histamine Challenge Test




- Histamine was first used for bronchial challenges in the 1950's
- Progressively increasing doses are administered via nebulization
- Doses similar to methacholine challenge testing
- FEV₁ measured 30 sec and 90 sec after each dose
- End point is a 20% drop in FEV₁

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Lutz Beckert and Kate Jones (2012). Bronchial Challenge Testing. Bronchial Asthma: Emerging Therapeutic Strategies, Dr. Elizabeth Sapay (Ed.), ISBN: 978-953-51-0140-6

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Direct Challenge Study
Histamine Challenge Test




- Not widely used today
- Side Effects:
 - Headache
 - Flushing
 - Hoarseness

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Capo, R.D. et al. Guidelines for Methacholine and Exercise Challenge Testing. Am J Respir Crit Care Med Vol 161 pp 309-329, 2000
Hargreaves, F.E. et al. Bronchial responsiveness to histamine or methacholine in asthma: measurement and clinical significance. J Allergy Clin Immunol, November, 1981


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Question 7
Follow Up Visit Post MCT



Patient returns to Pulmonologist. Test reviewed and results of MCT are negative, patient's FEV₁ did not decrease \geq 20%. What else might the patient be diagnosed with?

- A. GERD
- B. Vocal Cord Dysfunction
- C. Anxiety
- D. All of the above



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Aaron, S.D., Vandemheen, K.L., FitzGerald, J.M., Ainslie, M., Gupta, S., Lemiere, C., Boulet, L. (2017). Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma. JAMA 317(5):269-279. DOI: 10.1001/jama.2016.19627

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All that Wheezes is Not Asthma!

Diseases that share symptoms with asthma

- Congestive Heart Failure
- Vocal Cord Dysplasia
- Vocal Cord Paralysis
- Allergies
- GERD / Aspiration
- Sinusitis
- Myocardial Ischemia
- Bronchiectasis
- Tumors
- Pulmonary Aspergillosis

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Aaron, S.D., Vandemheen, K.L., FitzGerald, J.M., Ainslie, M., Gupta, S., Lemiere, C., Boulet, L. (2017). Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma. *Jama*, 317(3).

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Diagnosing Asthma

The Need for Objective Testing

- Too often asthma is diagnosed based on symptoms alone
- Objective testing is under utilized
 - 42.7% of 465,866 newly diagnosed asthma patients – had spirometry to confirm diagnosis
 - 30% of patient with physician diagnosed asthma, were misdiagnosed
 - 56% had no evidence of objective testing




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Gershon et al. Pulmonary Function Testing in the Diagnosis of Asthma: A Population Study. *CHEST* 2012;141(1):109-1196
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Summary

- Diagnosis should not be made on numbers or symptoms alone
- Consider: history, symptoms (current and past), reasons for testing, spirometry quality, predicted values used, technologist notes
- Remember that lives are affected by these results!
 - Ability to work in the military and certain professions
 - Insurance, disability, legal claims
 - Quality of life
- Find the correct diagnosis




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Thank you!


Questions?



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Phone: 1-815-403-3396



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Aaron, S.D., Vandemheen, K.L., FitzGerald, J.M., Ainsle, M. Gupta, S. Lemiere, C., Boulet, L. (2017). Reevaluation of Diagnosis in Adults with Physician-Diagnosed Asthma. *Jama* 317(5):

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To et al. *BMC family Practice* (2015) 16:19 DOI 10.1186/s12875-015-0232-y



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