Bronchoprovocation tests in children and adults

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Working Definition of Asthma

Asthma is a disorder of the airways with the following pathophysiological characteristics

- Chronic inflammation
- Variable airflow obstruction
- Hyperresponsiveness to a variety of “triggers”

“Twitchy” Airways

Bronchial hyperresponsiveness is:

- **An abnormal increase in airflow limitation following exposure to a stimulus;**
- **Alternatively, a threshold response (e.g., ≥20% fall in FEV1) which occurs at a lower point (dose) than in a healthy individual.**

Use of provocation tests

- Epidemological studies
- Clinical studies
- Asthma: diagnosis and differential diagnosis
- Follow-up of asthma treatment

BRONCHIAL PROVOCATION TESTS for ASTHMA

- **For diagnosis of asthma in cases where spirometry and reversibility test are not enough.**
  - **Low specifity %36-54**
  - **High sensitivity % 84-94**
- **To rule out asthma diagnosis**
  - **High negative predictive value**
- **To determine the severity of asthma**
- **To determine the response to treatment**

ATS 1999

Contraindications

Absolute

- Severe airflow limitation
  (FEV_1 <50% pred., or < 1.0 L)
- Heart attack or stroke in last 3 months
- Uncontrolled hypertension
- Known aortic aneurysm

Relative

- Moderate airflow limitation
  (FEV_1 <60% pred., or < 1.5 L)
- Inability to perform acceptable spirometry
- Pregnancy
- Nursing mothers

Safety of a Low Starting FEV_1

- 88 patients with FEV_1 <60% predicted (22% - 59%)
- Mean baseline FEV_1 1.39 $\pm$ 0.28 L (0.64 – 2.4 L)
- Testing was safe and successful
- 84 patient's FEV_1 returned to 90% of baseline, and 4 required a 2^{nd} treatment

Martin, Wanger, Irvin, et al. Chest 1997;112:53-56

Types of stimuli

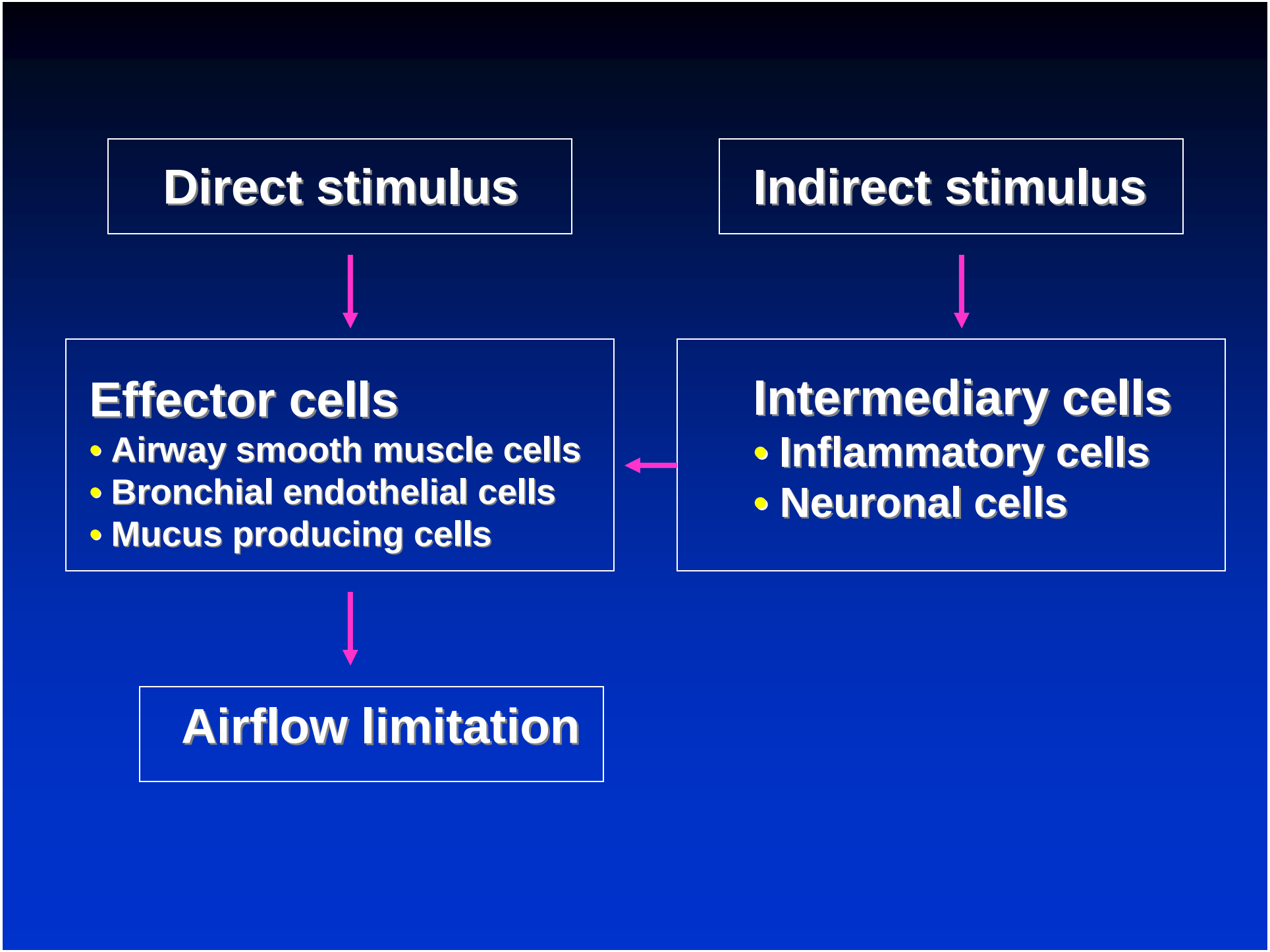
- Spesific
  - Allergen
  - Aspirin, food
- Exercise tests

- Nonspesific
  - Metacholine
  - Histamine
  - AMP
  - Cold air
  - Nonisotonic solutions
  - Leukotrienes
  - Serotonin
  - Prostoglandin
  - Tachycinin

Types of Stimuli

- **Direct Stimulus**
  Cause airflow limitation by a direct action on effector cells (e.g., airway smooth muscle cells, mucus producing cells).

- **Indirect Stimulus**
  Cause airflow limitation by an action of cells other than effector cells, which then interact with the effector cells.


Direct stimulus
Indirect stimulus
Effector cells
• Airway smooth muscle cells
• Bronchial endothelial cells
• Mucus producing cells
Intermediary cells
• Inflammatory cells
• Neuronal cells
Airflow limitation

Direct Stimuli

- Acetycholine
- Methacholine
- Carbachol
- Histamine
- Prostaglandin D_2
- Leukotrienes

Indirect Stimuli

- Adenosine
- Bradykinin
- Metabisulfite / SO_2
- Exercise
- Hyper/hypotonic aerosol
- Isocap. hyperventilation
- Mannitol
- Propanolol (β-blockers)

FACTORS THAT DECREASE BRONCHIAL RESPONSIVENESS

Factor	Minimum Time Interval from Last Dose to Study
Medications	
Short-acting inhaled bronchodilators, such as isoproterenol, isoetharine, metaproterenol, albuterol, or terbutaline	8 h
Medium-acting bronchodilators such as ipratropium	24 h
Long-acting inhaled bronchodilators, such as salmeterol, formoterol, tiotropium	48 h (perhaps 1 wk for tiotropium)
Oral bronchodilators	
Liquid theophylline	12 h
Intermediate-acting theophyllines	24 h
Long-acting theophyllines	48 h
Standard β_2-agonist tablets	12 h
Long-acting β_2-agonist tablets	24 h
Cromolyn sodium	8 h
Nedocromil	48 h
Hydroxazine, cetirizine	3 d
Leukotriene modifiers	24 h
Foods	
Coffee, tea, cola drinks, chocolate	Day of study

Factors that increase Bronchial Hyperresponsiveness

Factor	Duration of effect
Exposure to environmental antigens	1-3 weeks
Occupational sensitizers	Months
Respiratory infections	3-6 weeks
Air pollutants	1 week
Cigarette smoke	Uncertain, ind. variation
Chemical irritants	Days to months

What do most people use to evaluate airway hyperreactivity?

- Questionnaire to prominent and active investigators using bronchial provocation techniques.

- 44 of 94 responses

- Methacholine (63%)
  Histamine (17%)
  Exercise (8%)
  Specific antigens (5%)

Scott GC, Braun SR.
Chest 1991;100:322-328.

Direct Stimuli

Methacholine

- Most widely used
- Well standardized
- Easy to obtain today
- Better differentiates reactive/nonreactive airways

Histamine

- Good correlation with methacholine
- More side effects
- Development of tachyphylaxis

Metacholine

Synthetic acetylcholine derivative
Metabolized by choline esterase
Effects blocked by atropin and other anticholinergi

pH < 6 Cons > 0.3 mg/ ml	→	Stable at least 3 months at 4ºC

Mch should be diluted with saline and NOT with buffered solutions

Patient Preparation

- Withhold medications that will interfere
- Explain the test, but don't over do it
  - *They aren't going to have an asthma attack!!*
  - *Avoid the impact of suggestion.*
- Consent form
- Pre-test questionnaire
- Withhold coffee, tea, cola drinks, chocolate for day of study

Medication Withholding Schedule

• Short-acting inhaled bronchodilators	8 hrs
• Med.-acting bronchodilators (e.g., ipratropium)	24 hrs
• Long-acting bronchodilators	48 hrs
• Oral bronchodilators	12-48 hrs
• Cromolyn sodium	8 hrs
• Nedocromil	48 hrs
• Leukotriene modifiers	24 hrs

2 min tidal breathing

- Dilutions of Mch are prepared and kept at RT for 30 min before use

DILUTION SCHEMES FOR THE TWO RECOMMENDED METHACHOLINE DOSING SCHEDULES

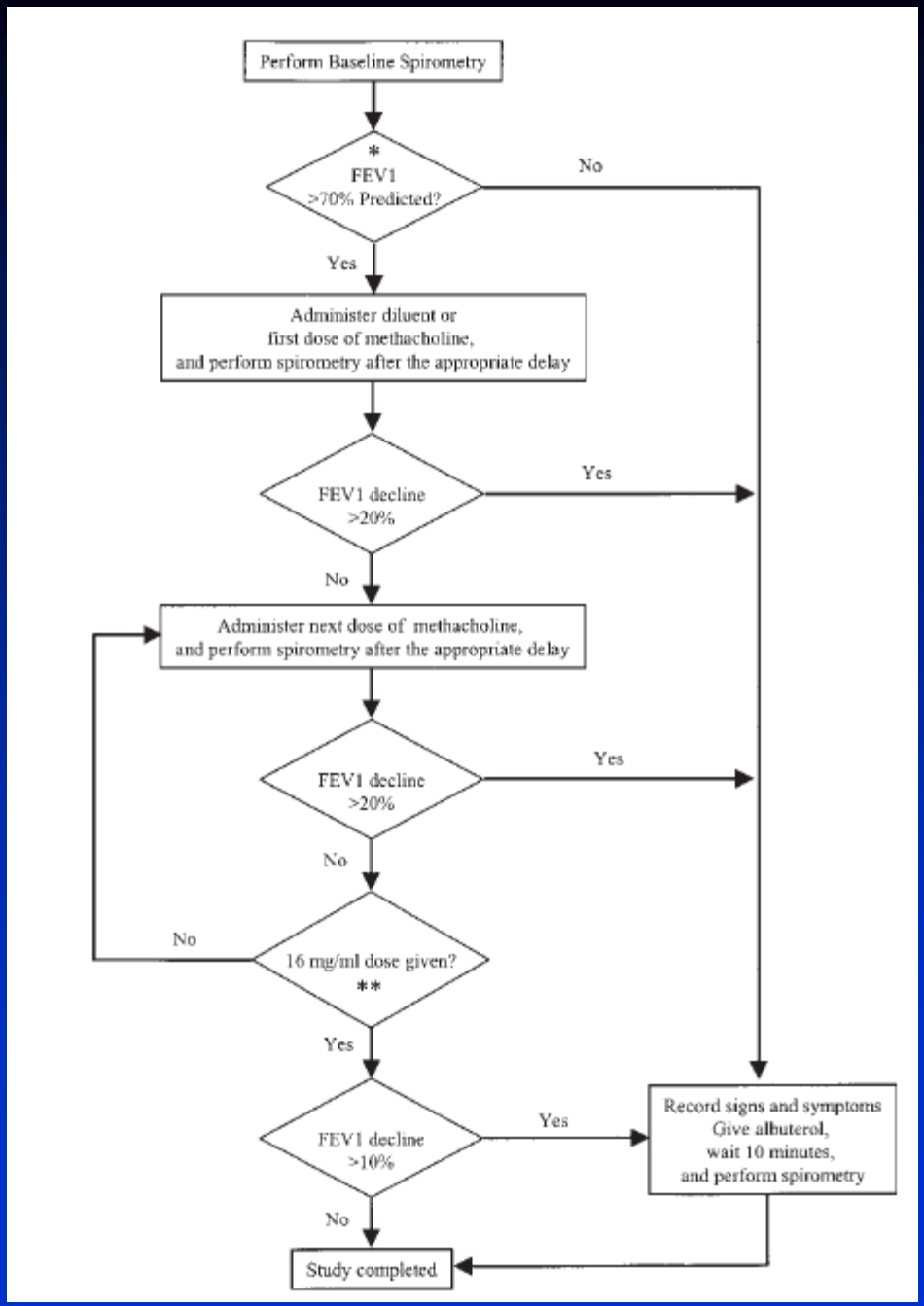
Label Strength	Take	Add NaCl (0.9%)	Obtain Dilution
A. Dilution schedule* using 100-mg vial of methacholine chloride and the 2-min tidal breathing protocol			
100 mg	100 mg	6.25 ml	A: 16 mg/ml
	3 ml of dilution A	3 ml	B: 8 mg/ml
	3 ml of dilution B	3 ml	C: 4 mg/ml
	3 ml of dilution C	3 ml	D: 2 mg/ml
	3 ml of dilution D	3 ml	E: 1 mg/ml
	3 ml of dilution E	3 ml	F: 0.5 mg/ml
	3 ml of dilution F	3 ml	G: 0.25 mg/ml
	3 ml of dilution G	3 ml	H: 0.125 mg/ml
	3 ml of dilution H	3 ml	I: 0.0625 mg/ml
	3 ml of dilution I	3 ml	J: 0.031 mg/ml
B. Optional dilution schedule using 100-mg vial of methacholine chloride and five-breath dosimeter protocol			
100 mg	100 mg	6.25 ml	A: 16 mg/ml
	3 ml of dilution A	9 ml	B: 4 mg/ml
	3 ml of dilution B	9 ml	C: 1 mg/ml
	3 ml of dilution C	9 ml	D: 0.25 mg/ml
	3 ml of dilution D	9 ml	E: 0.0625 mg/ml

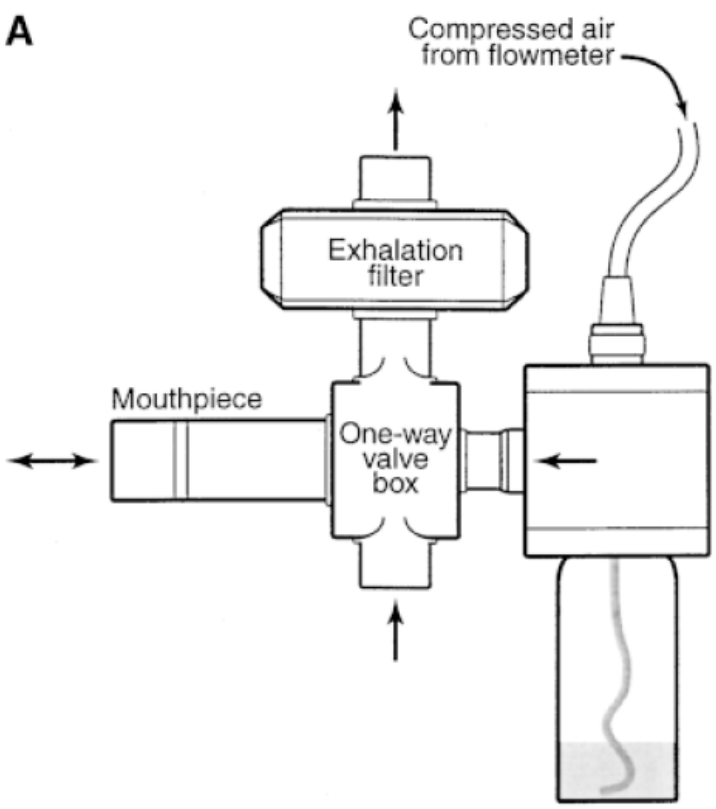
2 min tidal breathing

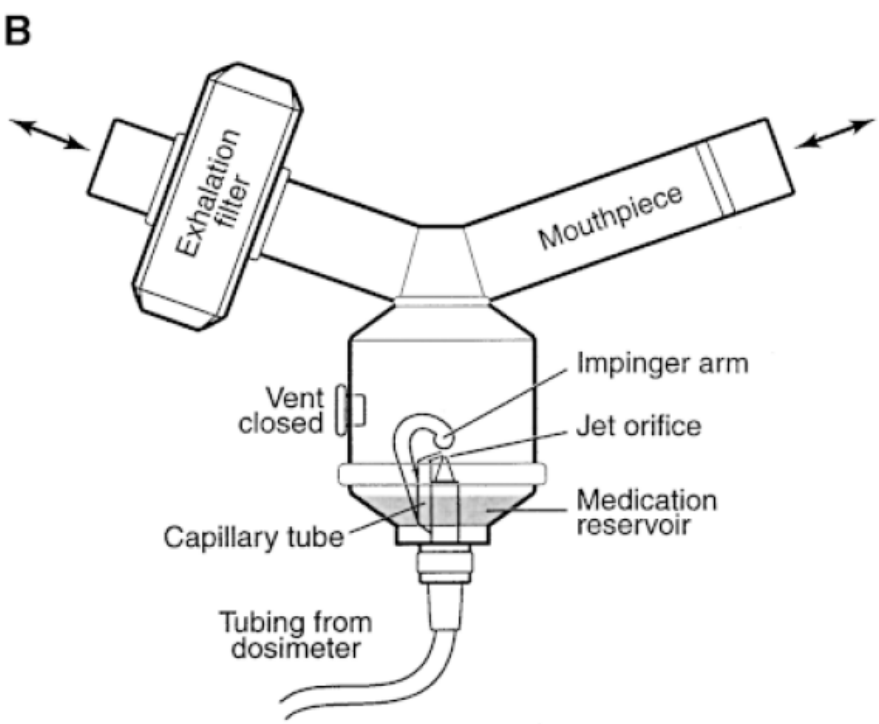
1. Basal (diluent) spirometry
2. Nose clip
3. 2 min tidal breathing
4. FEV1 within30-90 sn
5. Max 3 min and 3-4 manouvers for FEV1; best FEV1
6. 5 min between two nebulizations
7. Salbutamol at the ned of the test followed by spirometry in 10 min

5 breath dosimeter

- 0.0625, 0.25, 1, 4, 16 mg/ml
- During tidal breathing
- At the end of exhalation (at functional residual capacity), slow and deep inhalation
- Start the dosimeter right after the start of inhalation
- Inhalation time : 5 sec
- Breath holding at TLC: 5 sec
- Five repeats of the same procedure
- Total duration: 2 min


Perform Baseline Spirometry
*
FEV1
>70% Predicted?
No
Yes
Administer diluent or
first dose of methacholine,
and perform spirometry after the appropriate delay
FEV1 decline
>20%
Yes
No
Administer next dose of methacholine,
and perform spirometry after the appropriate delay
FEV1 decline
>20%
Yes
No
16 mg/ml dose given?
**
No
Yes
FEV1 decline
>10%
Yes
Record signs and symptoms
Give albuterol,
wait 10 minutes,
and perform spirometry
No
Study completed


A
Compressed air
from flowmeter
Exhalation
filter
Mouthpiece
One-way
valve
box


B
Exhalation
filter
Mouthpiece
Impinger arm
Vent
closed
Jet orifice
Medication
reservoir
Capillary tube
Tubing from
dosimeter

Technical Factors and Aerosols

- Nebulizer output
- Aerosol particle size
- Tubing
- Lung volume
- Inspiratory flow rate
- Breathhold time

Spirometry

- Change in FEV_1 is the primary outcome measure
- Spirometry should meet ATS guidelines for acceptability
- The quality of the spirogram should be examined after each maneuver
- Full FVC efforts lasting $\geq$ 6 sec should be performed at baseline and after diluent
- If the FEV_1 is the only outcome measure, the expiratory maneuver can be shortened to about 2 sec at other stages
- If shortened maneuver is used, assure inspiration is complete

Provocative Concentration (PC)

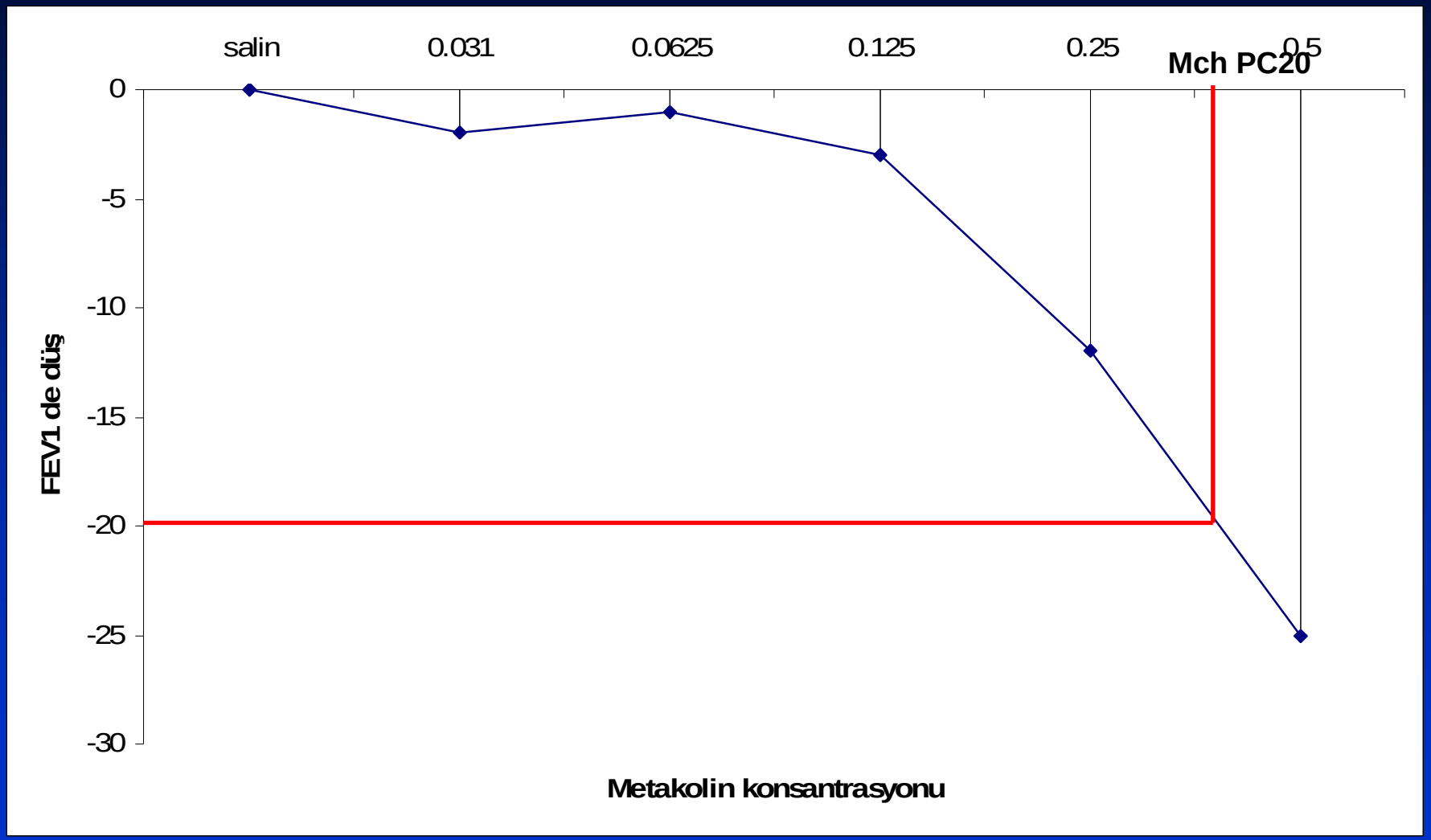
The exact concentration that causes a specific fall in a PFT parameter:

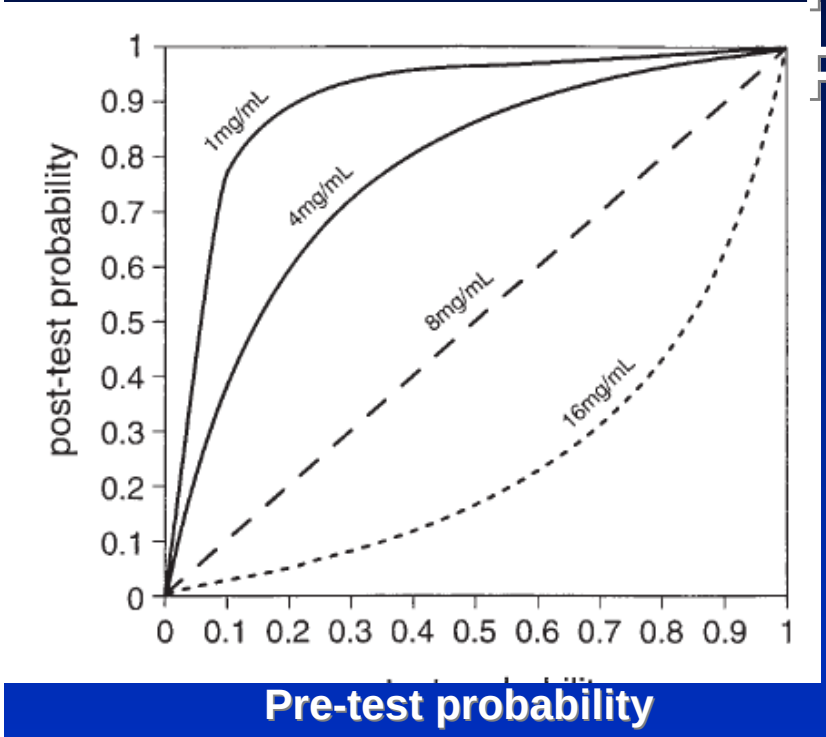
$PC_{20}FEV_1$

Concentration that causes a 20% fall in FEV_1

$PC_{40}SG_{aw}$

Concentration that causes a 40% fall in specific conductance


salin
0.031
0.0625
0.125
0.25
0.5
Mch PC20
0
-5
-10
-15
-20
-25
-30
FEV1 de düş
Metakolin konsantrasyonu



- Asthma probability= % 30–70
PC20=16 mg/ml
Patient does not have asthma

- Asthma prob % 30–70
PC20 = 1.0 mg/ml,
Asthma

- Astım olasılığı % 30–70
1.0 mg/ml <PC20 <16 mg/ml
Asthma (??)

1 < PC20 1 < 16 mg/ml
No asthma symptom

1. Mild intermittent asthma but the patient is not well aware of symptoms

2. Patient does not exercise or confront stimuli that can cause bronchoconstriciton

3. Mild BHR is due to another reason such as a recent UTI or smoke exposure

4. Asymptomatic asthma which will clinically be overt in a few years (% 15-45)

Quality Control

- Nebulizer output
  - Verify output initially & after every 20 uses, until an appropriate testing schedule is established for lab.
  - Output for 2-min. TB neb. = 0.13 to 0.15 mL/min $\pm$ 10%
  - Output for DeVilbiss neb. = 0.009 mL/actuation $\pm$ 10%
- Verify concentrations of solutions
- Verify challenge procedure
- Keep records of QC procedures

Safety

Precautions for Patient Safety

- Trained staff close enough to respond quickly to an emergency
- Medications to treat bronchospasm must be present in testing area
- A stethoscope, sphygmomanometer, and pulse oximeter should be available

Safety

Precautions for Technician Safety

- Try to minimize technician exposure
- Testing room should have adequate ventilation (> 2 AC/hr)
- Use of exhalation filters useful in TB method
- Those with asthma are at increased risk and should take extra precautions to minimize their exposure

Categorization of Response

PC_{20} (mg/mL)	Interpretation
> 16	Normal BHR
4.0 - 16	Borderline BHR
1.0 - 4.0	Mild BHR (positive test)
< 1.0	Moderate to severe BHR

Exercise-induced Bronchoconstriction (EIB)

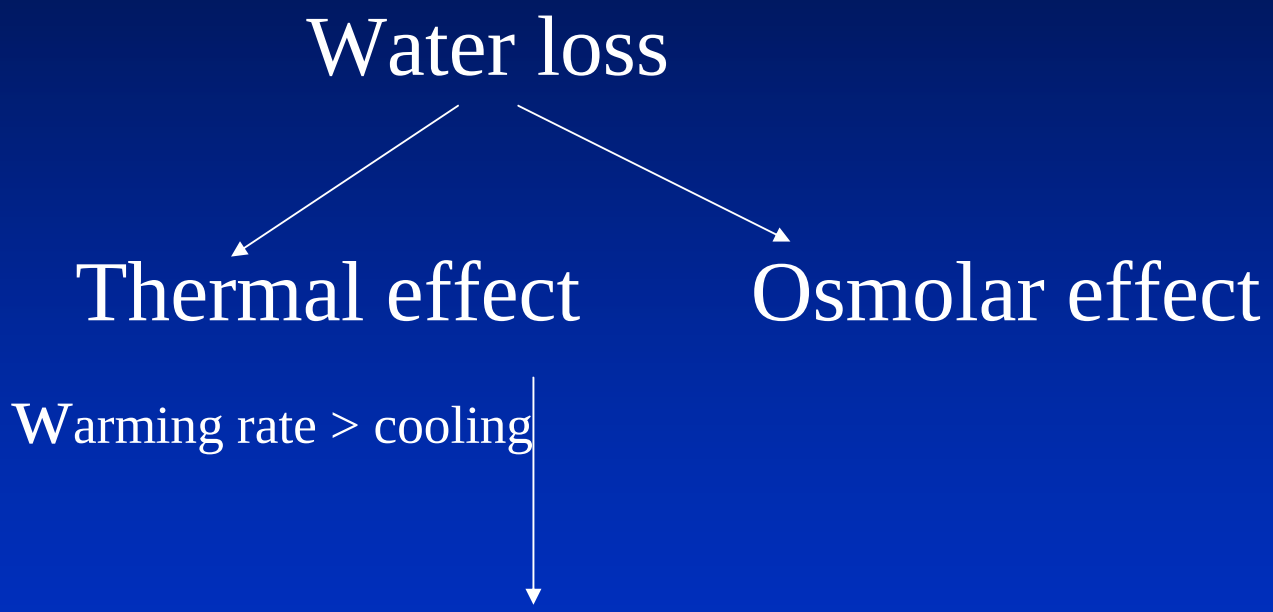
Exercise-induced Asthma (EIA)

EIB Factors

- Exercise needs to be continuous
- Type of exercise matters
- Intensity: 60-80% max causes greatest severity
- Duration
- Air temperature and humidity

Exercise induced bronchoconstriction

Exercise provocation



Vascular hypothesis

- Cooling of the airways
- Vasoconstricton in bronchial vessels
- End of exercise
- Sudden and significant increase in the blood volume in peribronchial vascular plexus
- Reactive hyperemia and edema in airway walls.

Osmolar hypthesis

- Water loss due to evoporation
- Increase in ion concentration in the periciliary fluid
- Hyperosmolarity
- Mediator release
- Bronchoconstriction

Diagnosis of EIA

- History and Physical exam
- Free running test
- Exercise provocation

Inhalation

- Nose clips
  - Decreases water loss form the nasal airway.
- 25ºC dry air
  - AC 20-25 ºC and < 50 % relative humidity
  - , Filled baloons with two way valves

Exercise provocation

- Treadmill
- Bicycle ergometry

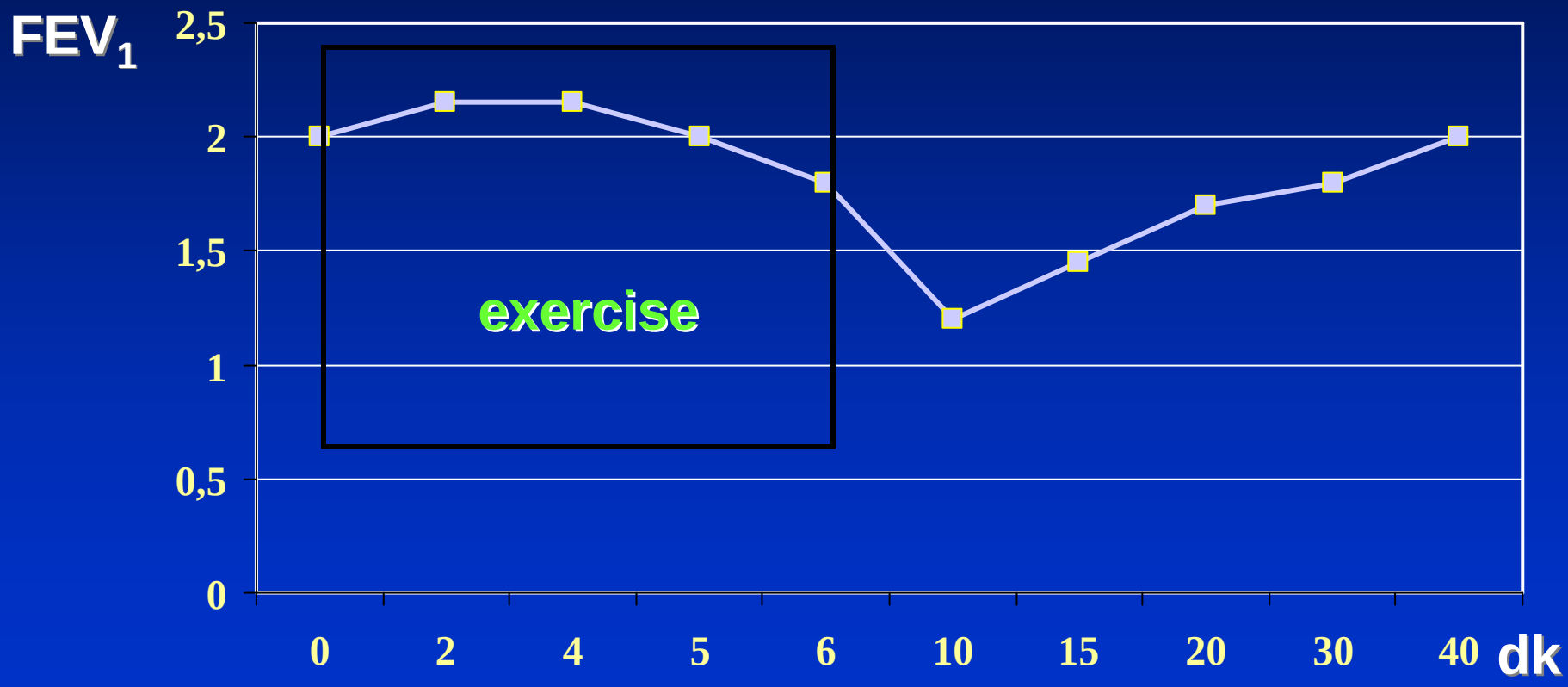
Exercise provocation

- Total duration
  - » < 12 years = 6 min
  - » > 12 years = 8 min
- By adjusting the speed and inclination, reach 80-90% of max heart rate within the first 2-3 min
  - » Max heart rate= 220- yaş
- By adjusting the speed and inclination, reach 40-60% of max voluntary ventilatio within the first 2-3 min
  - » MVV= FEV1 x 35

Exercise provocation

- 4 min running at max heart rate
  - 4.5 km/s ve % 15 eğim
- 1, 5,10,15,20,25,30 min FEV1
- > %10 düşme

Exercise Test Graphics



ADENOSIN MONOPHOSPHATE
AMP

Adenosine

- Adenosine 5’ – monophosphate (AMP)
- Indirect stimulant
- Releases histamine & other mediators from mast cells
- Action is blocked by antihistamines
- May reflect extent of airway inflammation better than methacholine

AMP

- AMP sodium salt(Sigma-Aldrich, A1752)
- Saline solubility > adenozin
- > 3.125 mg/ml 4ºC stability > 25 weeks
- 5 breath dozimeter or 2 min tidal method
  3.125, 6.25, 12.5, 25, 50, 100, 200, 400 mg/ml
- PC20

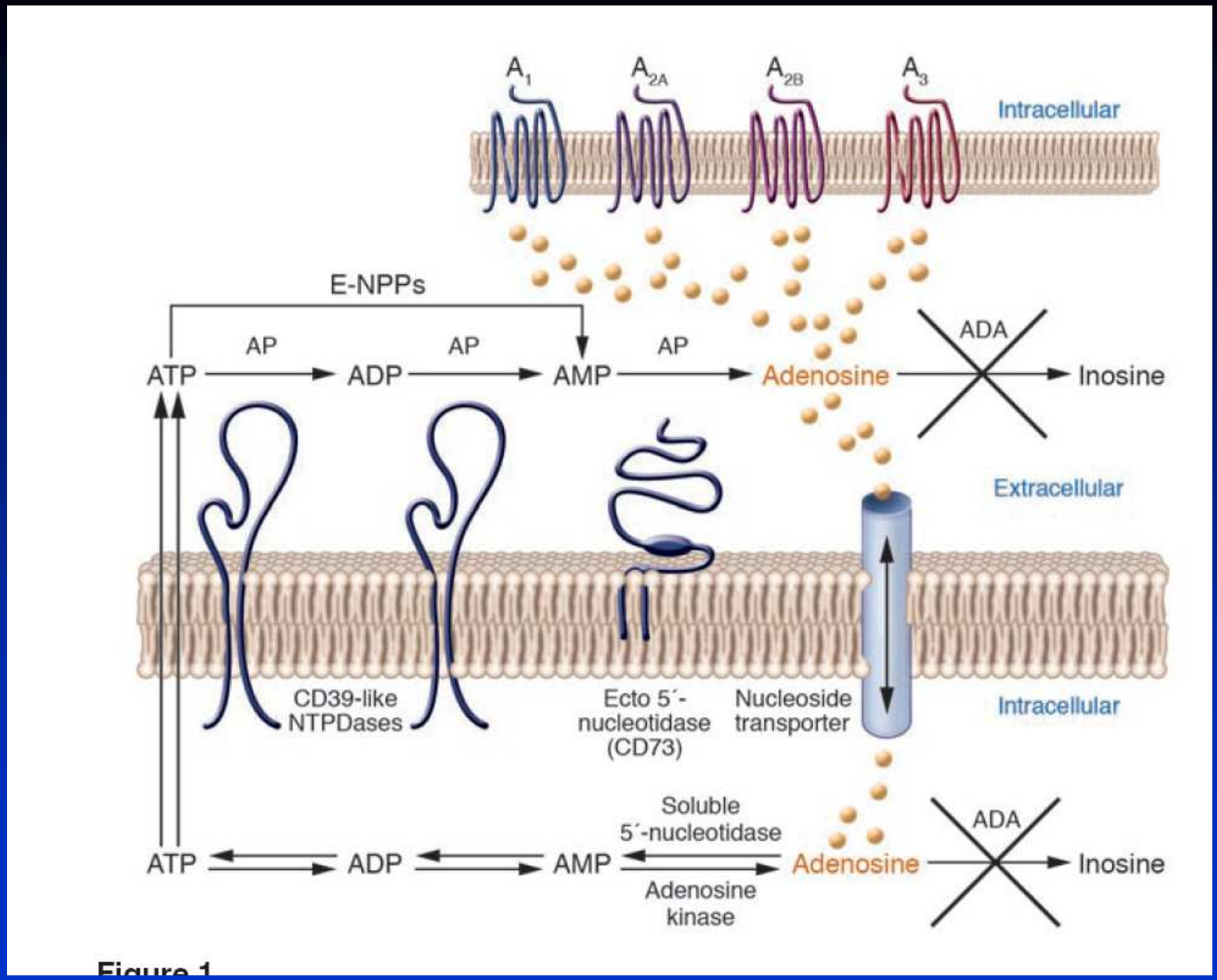
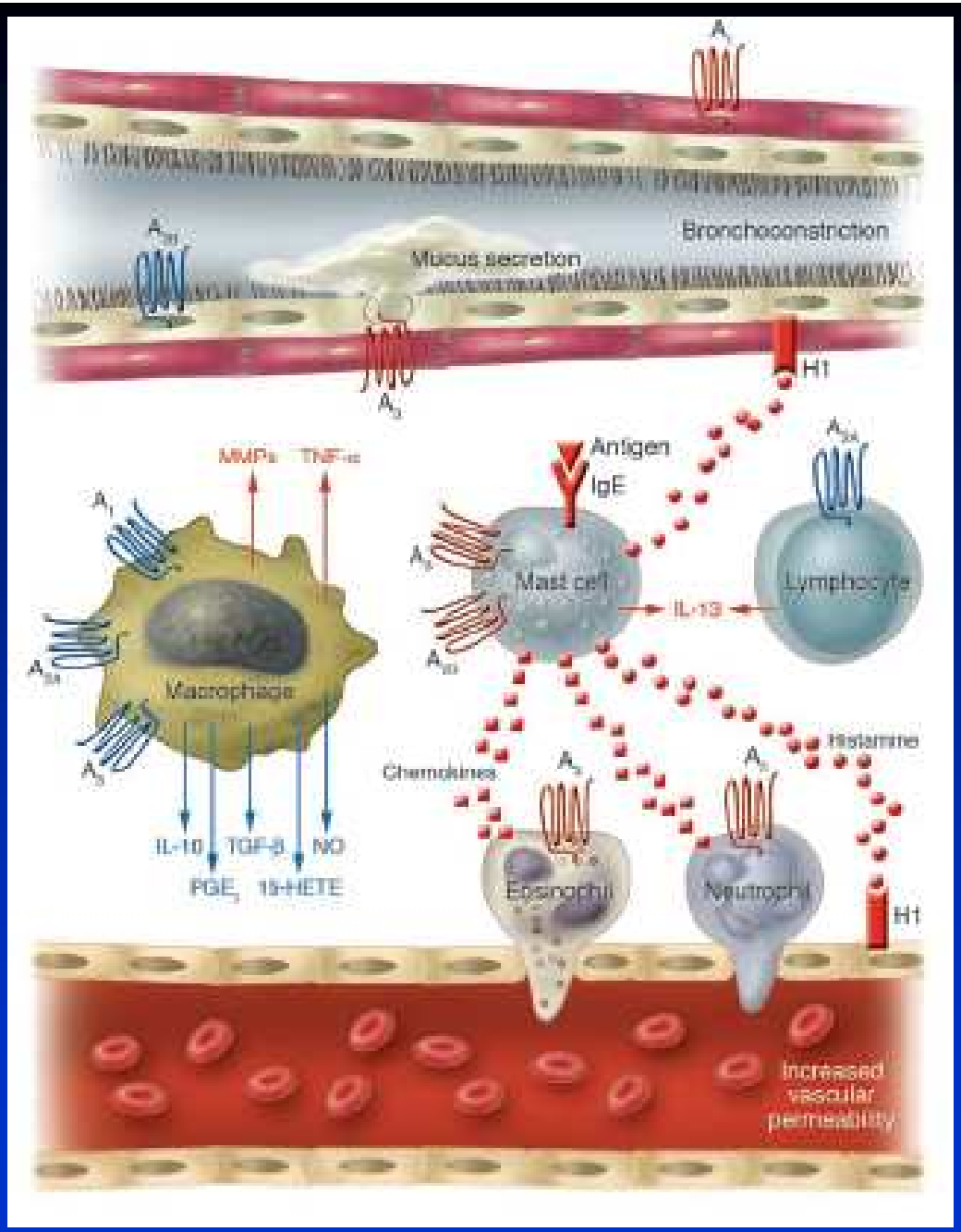


Figure 1

Stephen L. Tilley and Richard C. Boucher,
The Journal of Clinical Investigation Volume 115 Number 1 January 2005



Stephen L. Tilley and Richard C. Boucher,
The Journal of Clinical Investigation Volume 115 Number 1 January 2005

Specific Antigen

- Performed when proof of sensitivity, avoidance, or immunotherapy required
- Most commonly used in research
- Immediate and late responses
- Strong and lasting responses

Adenosine

- Inhalation of aerosol
- Diluent usually 0.9% saline
- Dosing scheme range 0.04 to 320 mg/mL
- Quadrupling doses reported to be safe and efficient - DeMeer et al., Thorax 2001;56:362-365

Hypertonic saline provocation

- Devilbiss Ultraneb 2000
  - 2 way valve (Laerdal valve No 560 200/850 500, Devilbiss
  - 60 cm tube (Devilbiss no. 8885)
- Hypertonic sterile saline (4.5 %)
  - 30 sec, 1 min, 2 min, 4 min, 8 min
  - Total 14.5 min
- FEV1 measurement 1 min after the end of inhalation
- > %15 fall: test positive

Saline provocation evaluation

- Positive / negative
  - > %15 poSitive
  - < % 15 negative
- Response / dose ratio (RDR)
  - Fall in FEV1 % / quantitiy of inhaled saline

Mannitol

- Naturally occurring sugar, isomer of sorbitol
-
- Indirect stimulant

- Dry powder

- Osmotic stimulant for the airway mucosa

- Proposed doses:
  - 0, 5, 10, 20, 40, 80, 160, 160, 160
  - Cumulative dose 0-63

- Endpoint: 15% fall in FEV1

Mannitol

- Proposed doses:
  - 0, 5, 10, 20, 40, 80, 160, 160, 160
  - Cumulative dose 0-63
- Endpoint: 15% fall in FEV1
  ↑ measured 1 min after each dose
- Interval between doses: 2min
- PD!5> 636 Normal

	Sensitivity (95% CI)	Specificity (95% CI)
Mannitol vs Hypertonic Saline	80.7 (76.4, 85.1)	86.7 (82.6, 90.7)
Mannitol vs Clinical Dx	59.8 (55.4, 64.2)	94.5 (89.9, 99.2)
Hypertonic Saline vs Clinical Dx	65.1 (60.9, 69.3)	95.2 (91.1, 99.3)
Excluding all taking ICS		
Mannitol vs Clinical Dx	70 (62.1, 78.2)	95 (90.7, 99.3)
Excluding M-ve taking ICS		
Mannitol vs Clinical Dx	89 (85.3, 92.1)	95 (90.7, 99.3)

Respir Res. 2005; 6(1): 144.

Oral Challenges

- Performed when proof of sensitivity needed
- Common agents and prevalence
  - Metabisulfite: 5 – 10% in adults
  - Tartrazine: <5%
  - ASA: 4 to 20%
- Time for reaction varies

Occupational Challenges

- Specific challenges considered the gold standard for dx of occupational asthma
- Agents
  - Natural organic (flour, wood dust)
  - Pharmaceuticals (cimetidine)
  - Organic chemicals (isocyanates)
  - Inorganic chemicals (nickel salts)
- Immediate and late responses
- Need for controls (placebo)

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