Junior Members Practical Courses

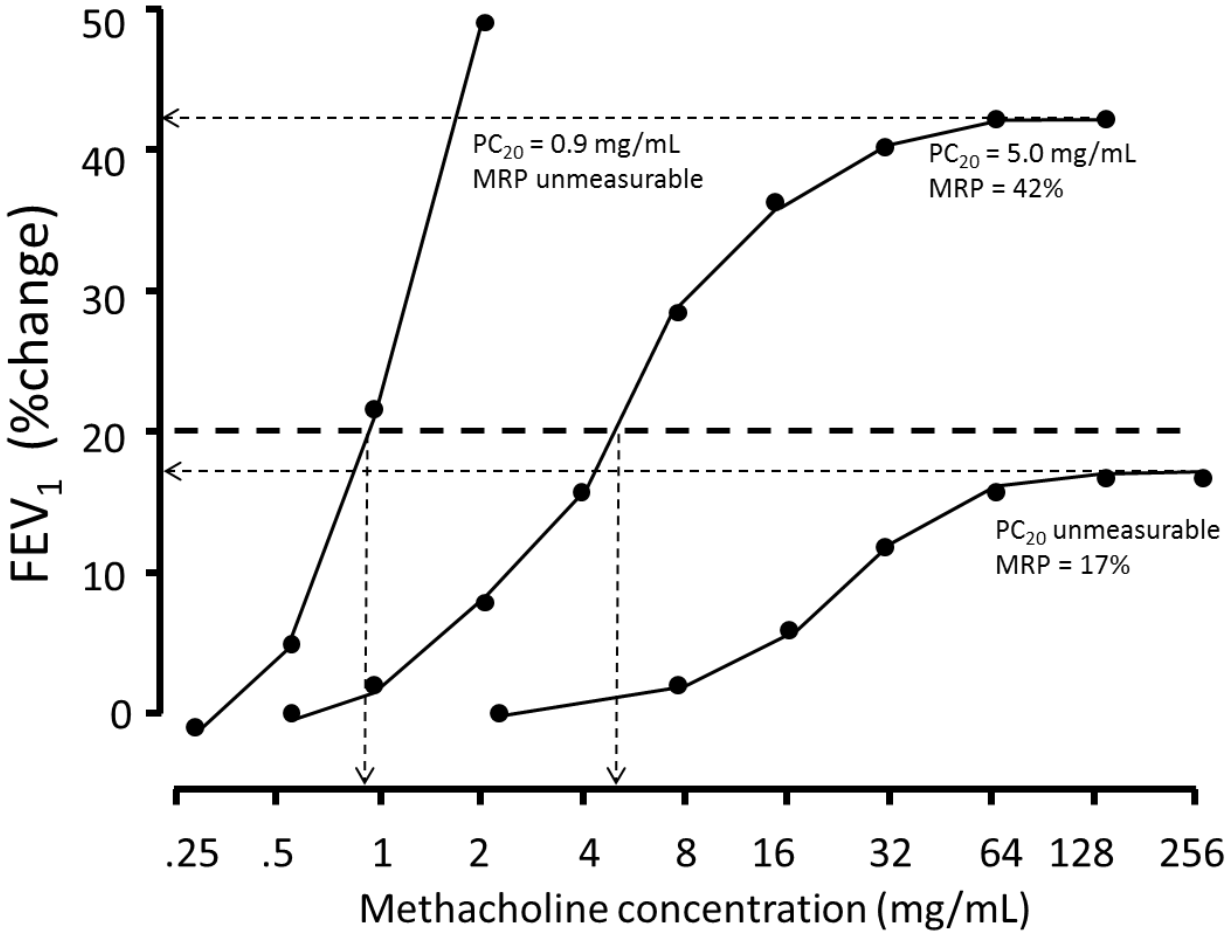
BRONCHIAL PROVOCATION TESTS

DONG IN SUH

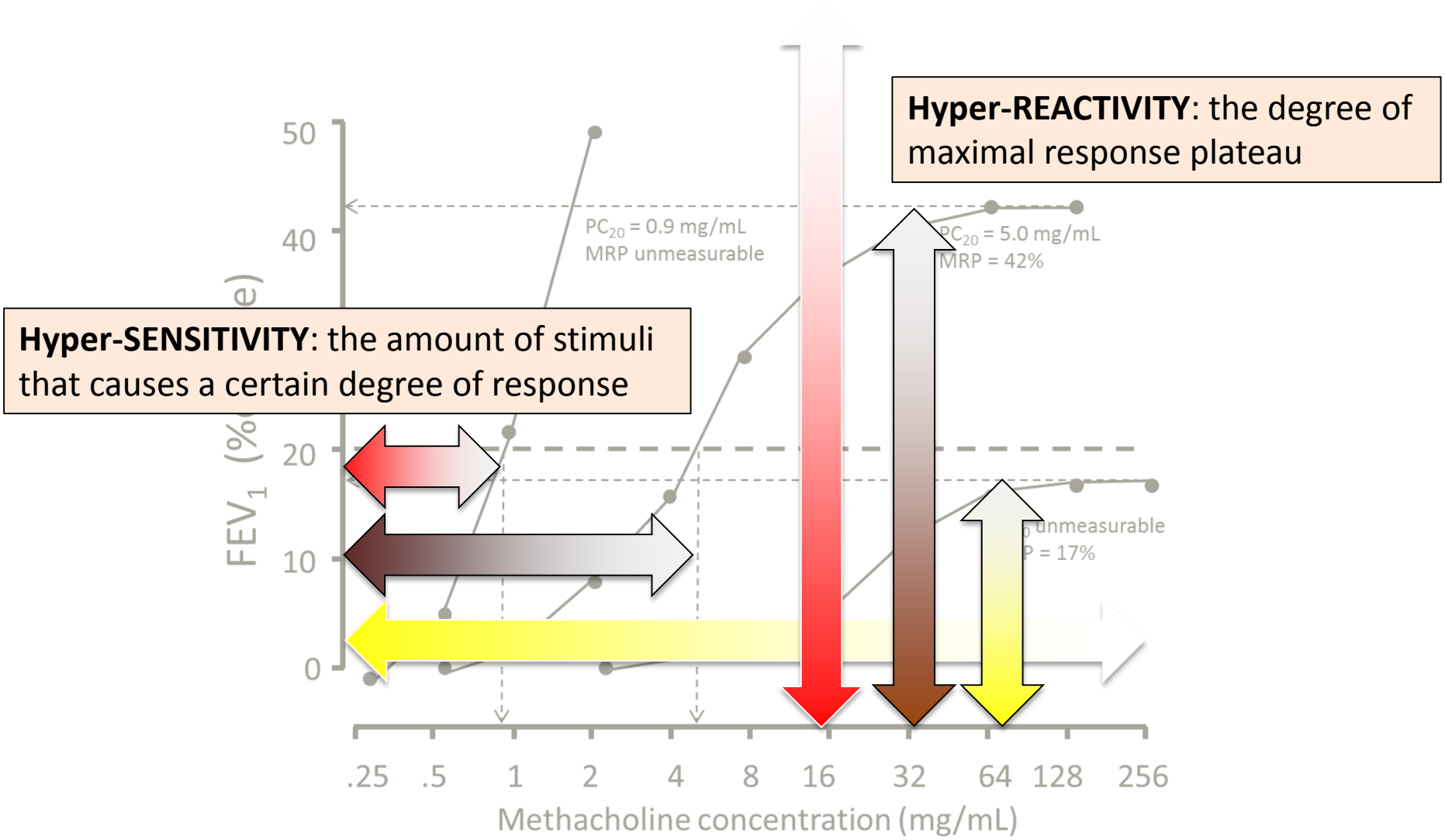
SOUTH KOREA

Rationale

- To demonstrate the Airway Hyper-Responsiveness



- To demonstrate the Airway Hyper-Responsiveness



Types of Bronchial Challenge Tests

- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. “SHOT-gun”
- Tidal breathing vs. Dosimeter method
- Outcome measures

Types of Stimuli

- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. "SUCT-ers"
- Tidal breath
- Outcome measures

Non-specific stimuli, i.e. Histamine, Methacholine, Cold air, Hyperventilation, Exercise, Hypertonic saline, Mannitol

Allergens, i.e. Dust mites, Dog epithelia, Pollens, Perfumes, or any suspected provoking factors

Types of Non-specific Stimuli

Direct stimulus

Histamine, Methacholine

Indirect stimulus

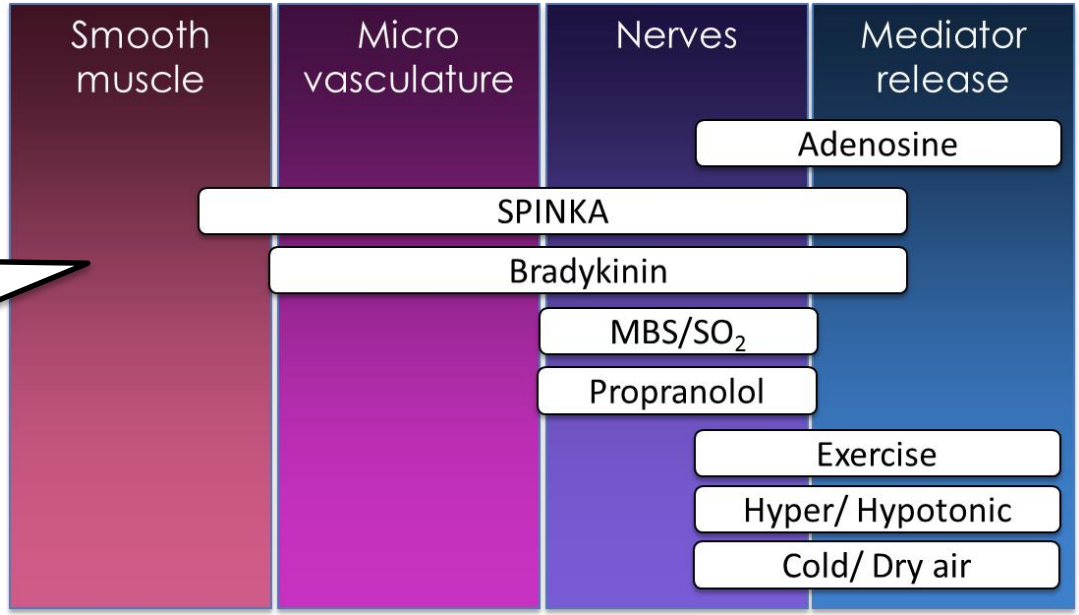
Effector cells

Intermediary cells

- Airway smooth muscle cells
- Bronchial endothelial cells
- Mucus producing cells

- Inflammatory cells
- Neuronal cells

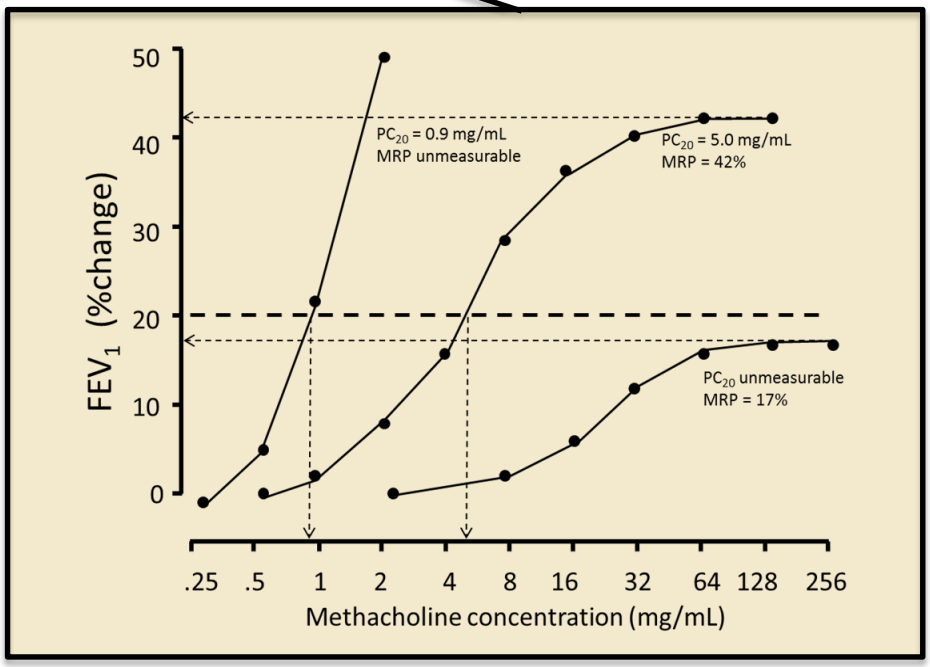
Airflow limitation

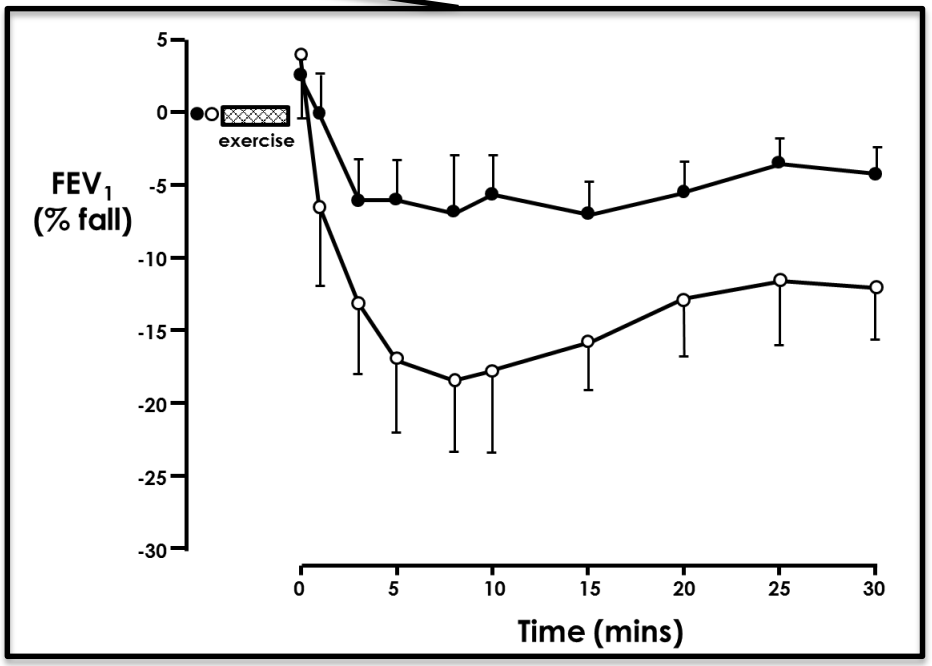


adapted from Van Schoor J et al., *Eur Respir J* 2000;16:514-33.

Types of Exposure

- Graded vs. "SHOT-gun"





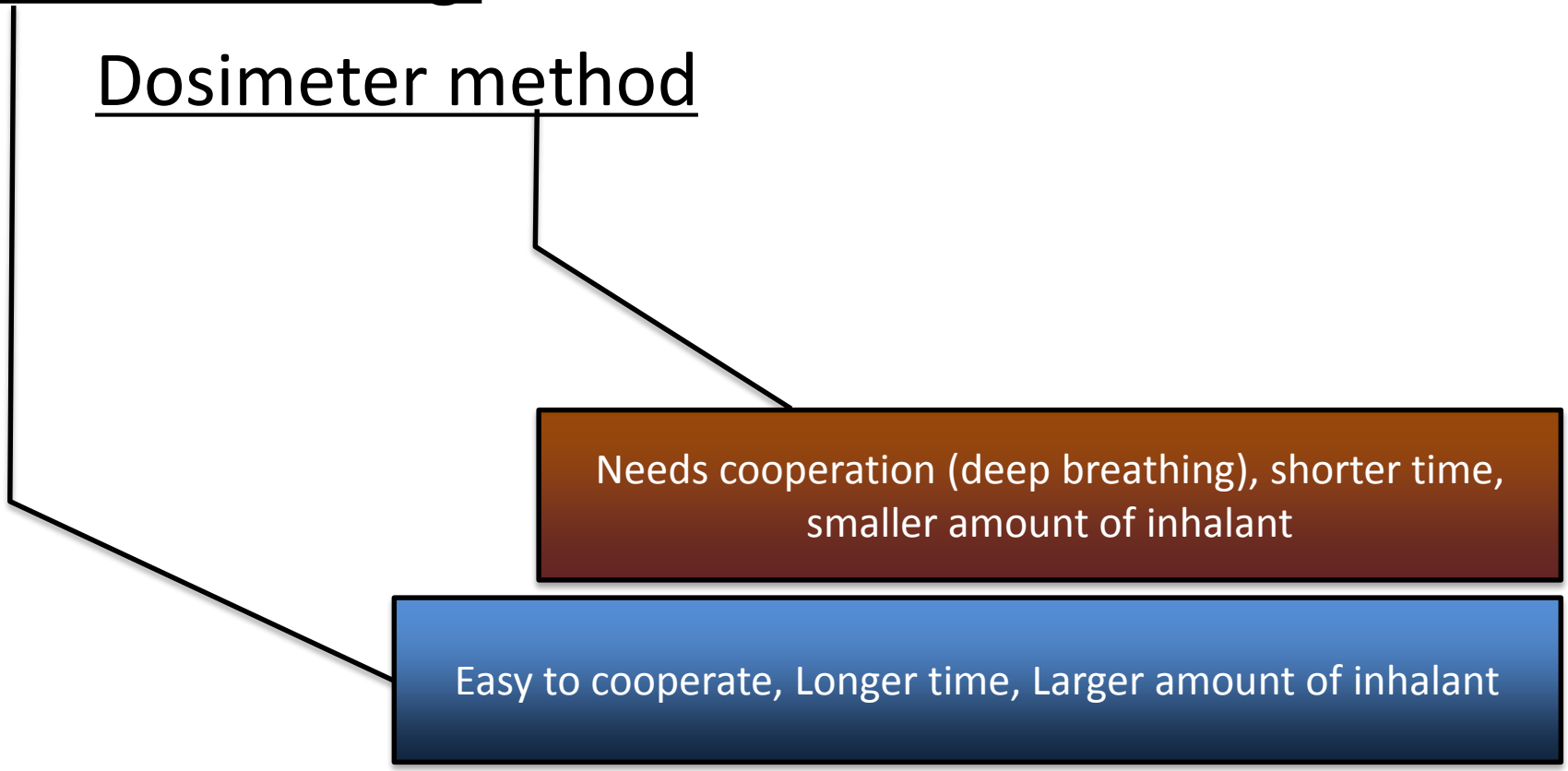
Different amount of (graded) stimuli
Same degree of responses

Same amount of stimuli
Different degree of responses

Types of Delivery

- Tidal breathing vs.

  Dosimeter method



Outcome Measures

- **<u>Any relevant responses</u>** to the asthma provocation
  - %fall in FEV_1
  - Provocative Concentration/ Dose (i.e. PC_{20}, PD_{20}, PD_{15}, etc.) to provoke a certain amount of response (measured by spirometry, IOS, etc.)
  - Endpoint Concentration (EPC) that causes wheezing or desaturation
  - Tachypnea, Cough count: not validated

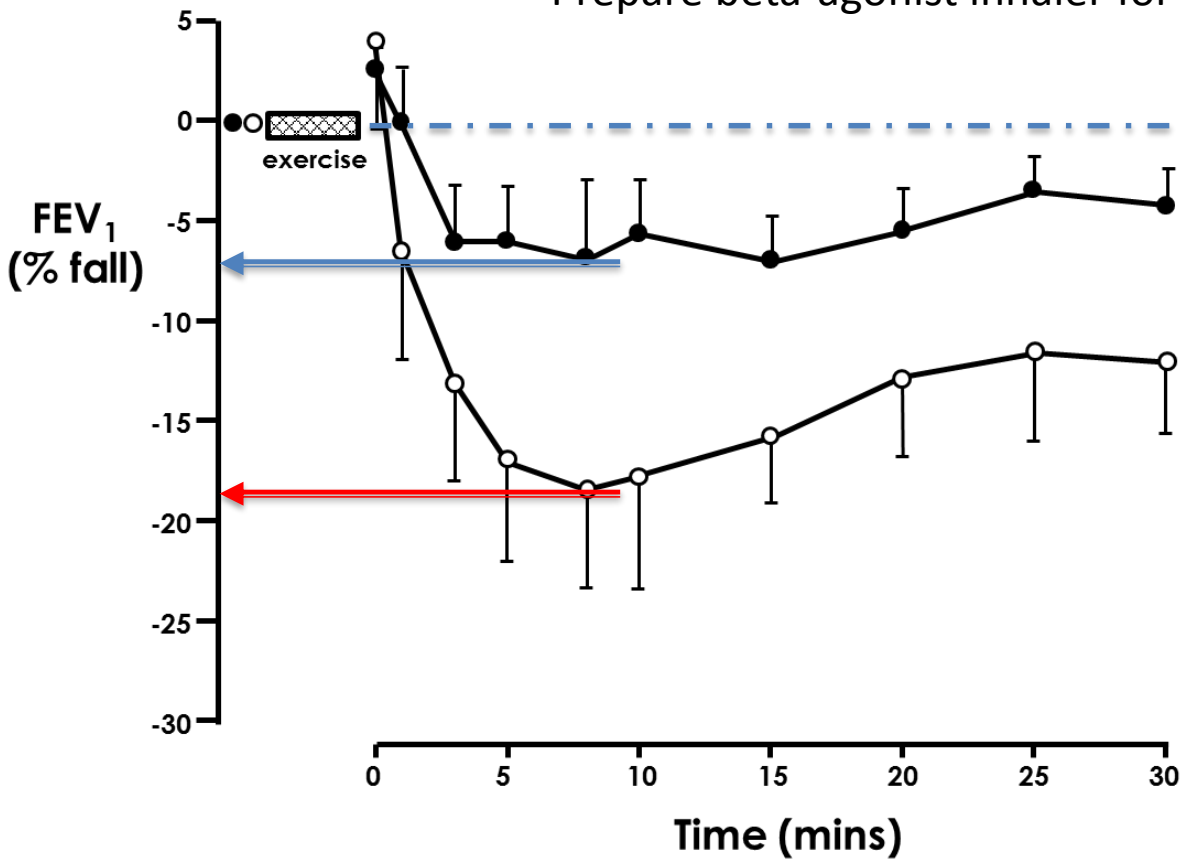
Exercise challenge test

- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. "SHOT-gun"
- Treadmill running, cycling, free-runnin , etc
- Outcome measures:
  - %fall in FEV_1 assessed by the spirometry (PFT)

Exercise challenge test

- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. "SHOT-gun"
- Treadmill running, cycling, free-running, etc.
- Outcome measures:
  - %fall in FEV_1 assessed by the spirometry (PFT)

- In Dry or conditioned air
- Maximal exercise for 4-6 min (a total of 6-8 min)
- EKG monitored, HR 80%-90% of predicted maximum
- If possible, monitor the ventilation:
  40%-60% of predicted MVV (35x FEV_1)
- Follow the serial FEV_1 right after the exercise
- Prepare beta-agonist inhaler for the severe response



Conventional MCT

Methacholine challenge test

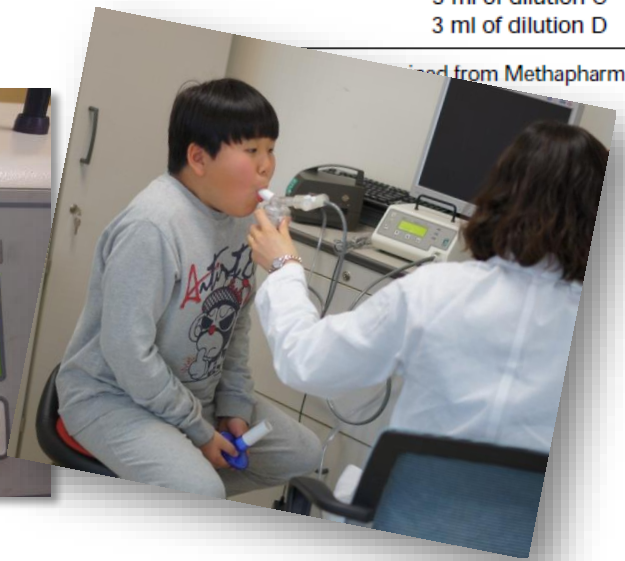
- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. “SHOT-gun”
- Tidal breathing vs. Dosimeter method
- Outcome measures: spirometry (PFT)

TABLE 4

DILUTION SCHEMES FOR THE TWO RECOMMENDED METHACHOLINE DOSING SCHEDULES

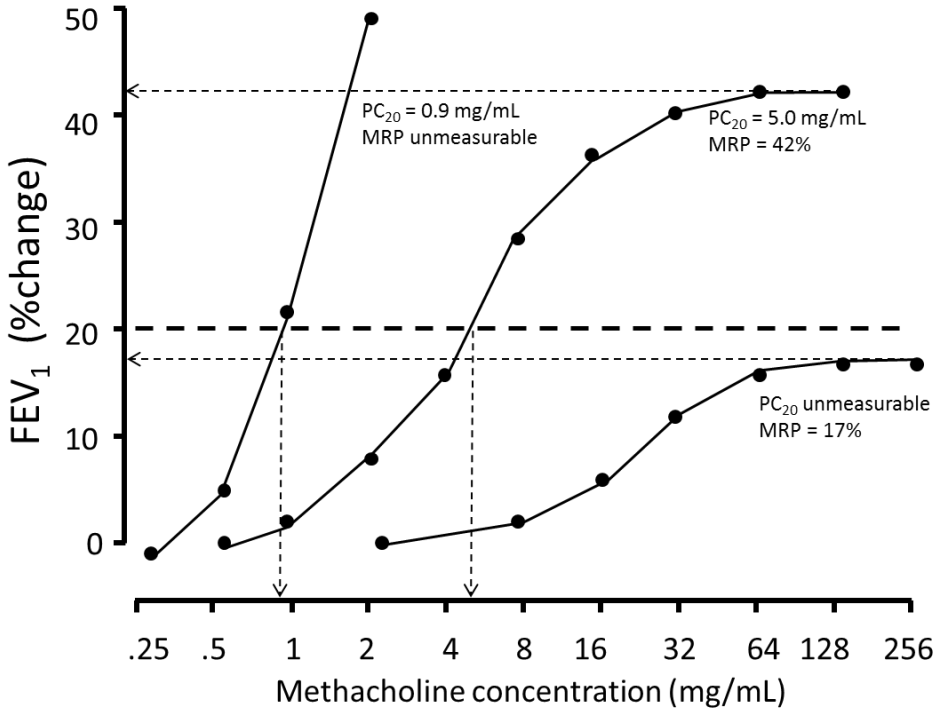
Label Strength	Take	Add NaCl (0.9%)	Obtain Dilution
A. Dilution schedule* using 100-mg vial of methacholine chloride and the 2-min tidal breathing protocol			
100 mg	100 mg	6.25 ml	A: 16 mg/ml
	3 ml of dilution A	3 ml	B: 8 mg/ml
	3 ml of dilution B	3 ml	C: 4 mg/ml
	3 ml of dilution C	3 ml	D: 2 mg/ml
	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

...ed from Methapharm (Brantford, ON, Canada).

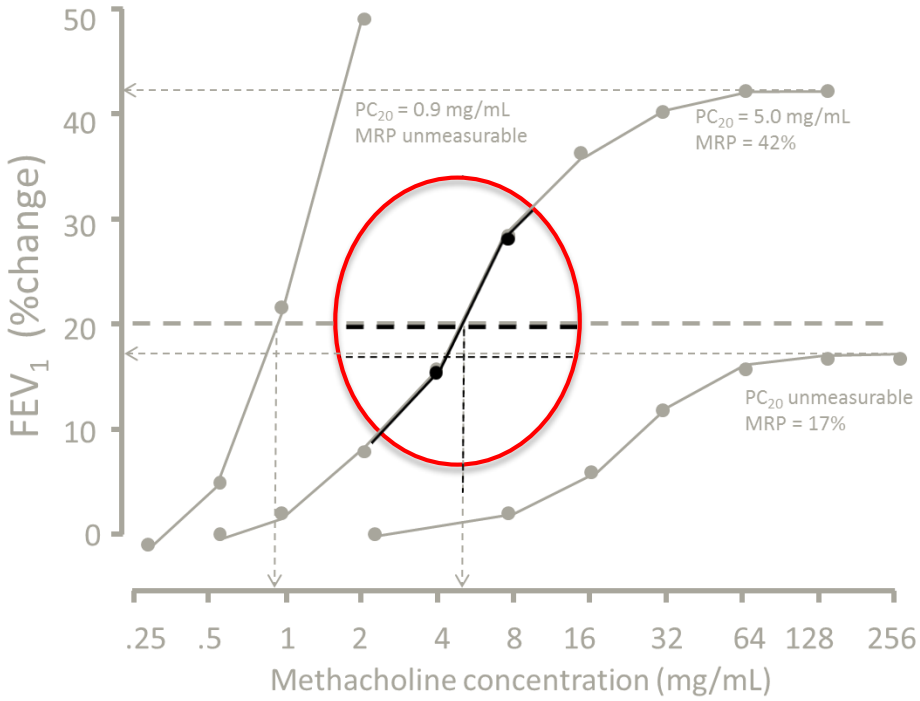


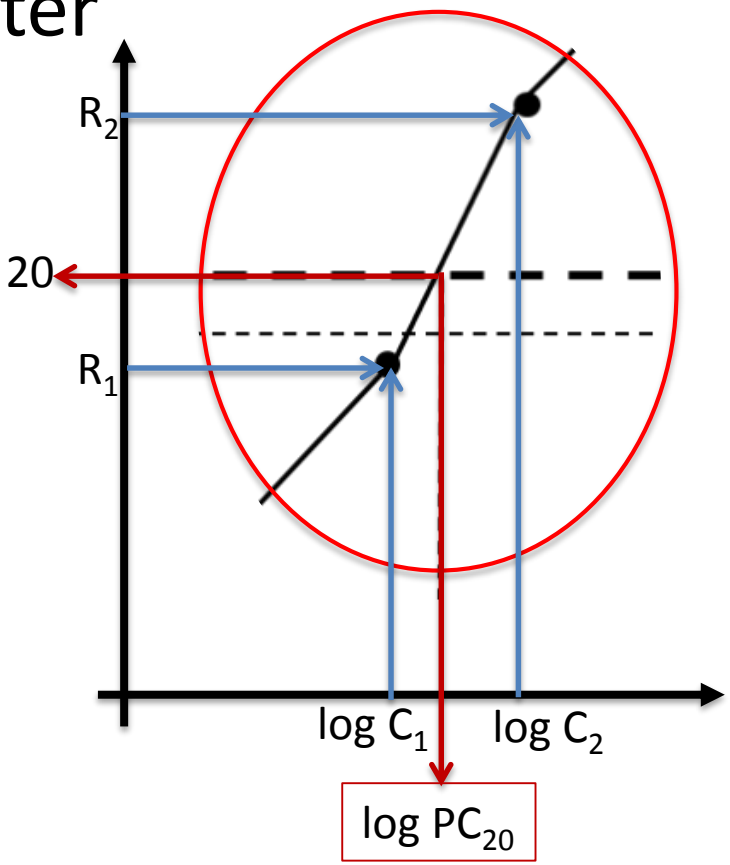
- Perform:
  - Determine the baseline
  - Determine the end-point
  - Repeat the “challenge– measure” process

    until either the FEV_1 falls into the <80% of baseline or subjects reached the last dose-steps



- Calculate the “BHR” parameter



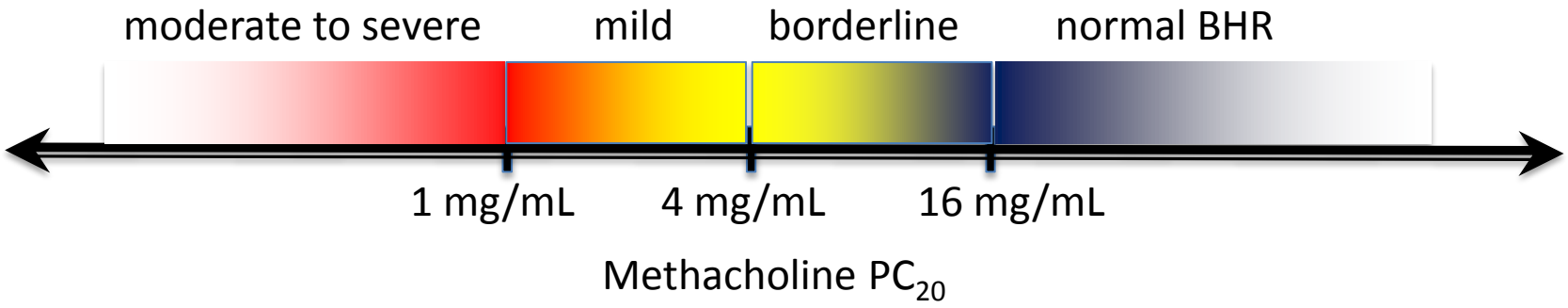


$$\frac{R_2 - R_1}{\log C_2 - \log C_1} = \frac{20 - R_1}{\log PC_{20} - \log C_1}$$

$$PC_{20} = \text{antilog}\left[\log C_1 + \frac{(\log C_2 - \log C_1)(20 - R_1)}{R_2 - R_1}\right]$$

Conventional MCT

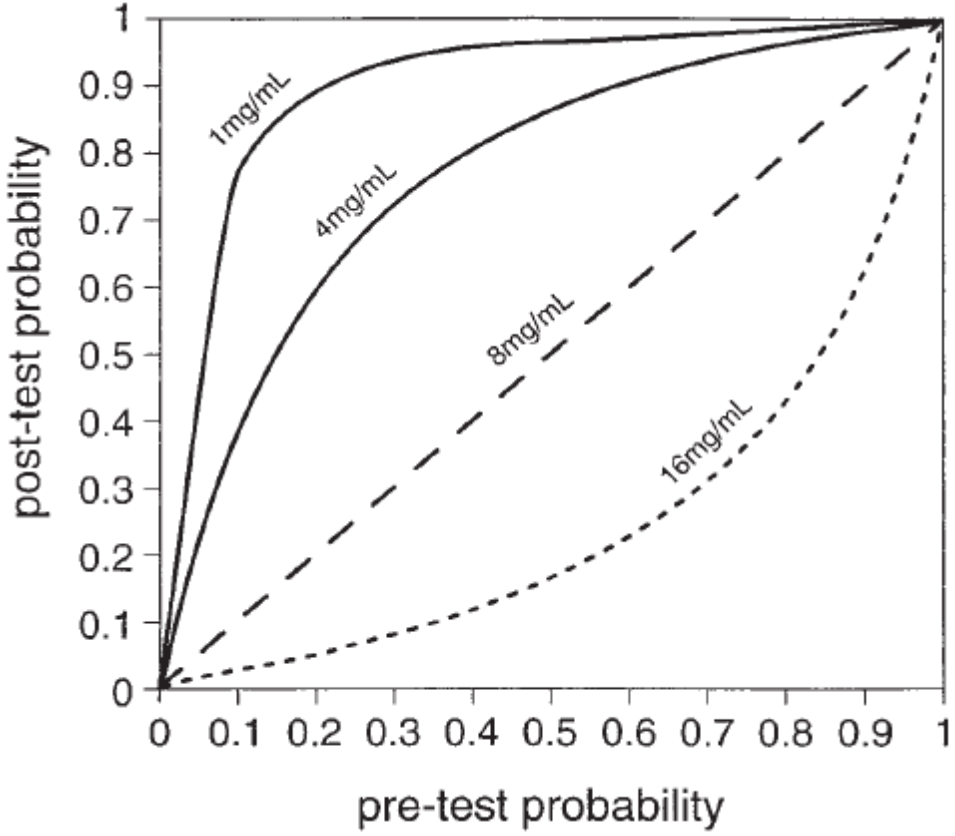
- Interpret results (1)



BHR severity does not always correspond well with clinical severity

Conventional MCT

- Interpret results (2)



approximations presented to illustrate the relationships and principles of decision analysis

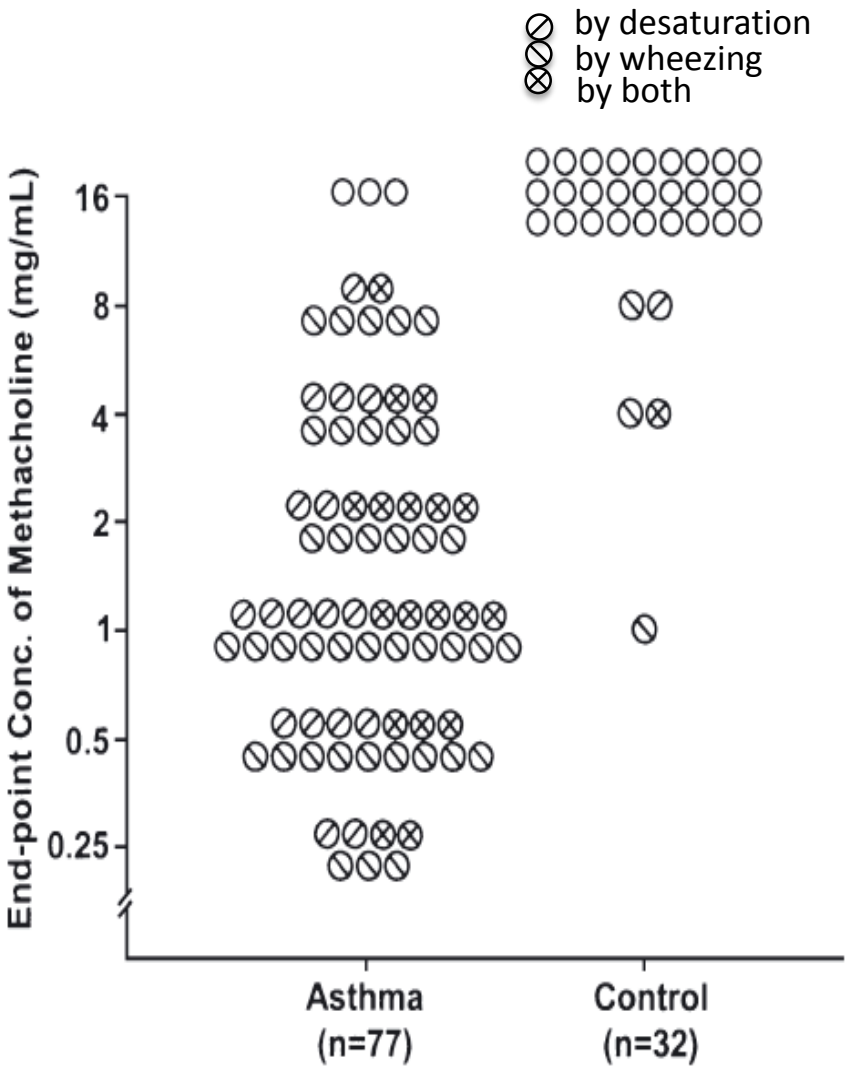
MCT for younger children

Methacholine challenge test

- Specific vs. non-specific
- Direct vs. Indirect
- Graded vs. “SHOT-gun”
- Tidal breathing vs. Dosimeter method
- Outcome measures: wheezing, desaturation

  describing as the “End-point concentration”

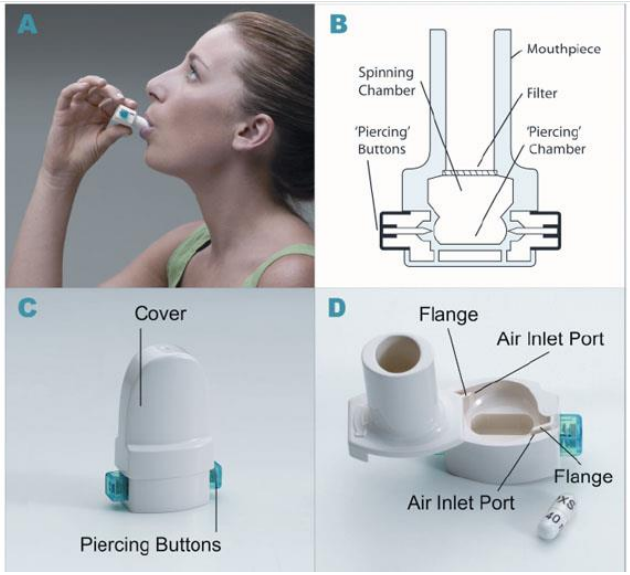
	Wheezing		Saturation (%)	RR (회/min)	
Baseline	ant. – / back –	ant. – / back –	lowest 99 / maint. 99	20	
0.25 mg/ml(4m)	ant. – / back –	ant. – / back –	lowest 98 / maint. 99	22	
0.5 mg/ml(2m)	ant. – / back –	ant. – / back –	lowest 96 / maint. 97	26	cough(±)
1 mg/ml(2m)	ant. – / back –	ant. – / back –	lowest 95 / maint. 97	28	cough(+)
2 mg/ml(2m)	ant. + / back +	ant. + / back +	lowest 93 / maint. 95	32	cough(+) retraction(+)
4 mg/ml(2m)	ant. / back	ant. / back	lowest / maint.		
8 mg/ml(2m)	ant. / back	ant. / back	lowest / maint.		
16 mg/ml(2m)	ant. / back	ant. / back	lowest / maint.		



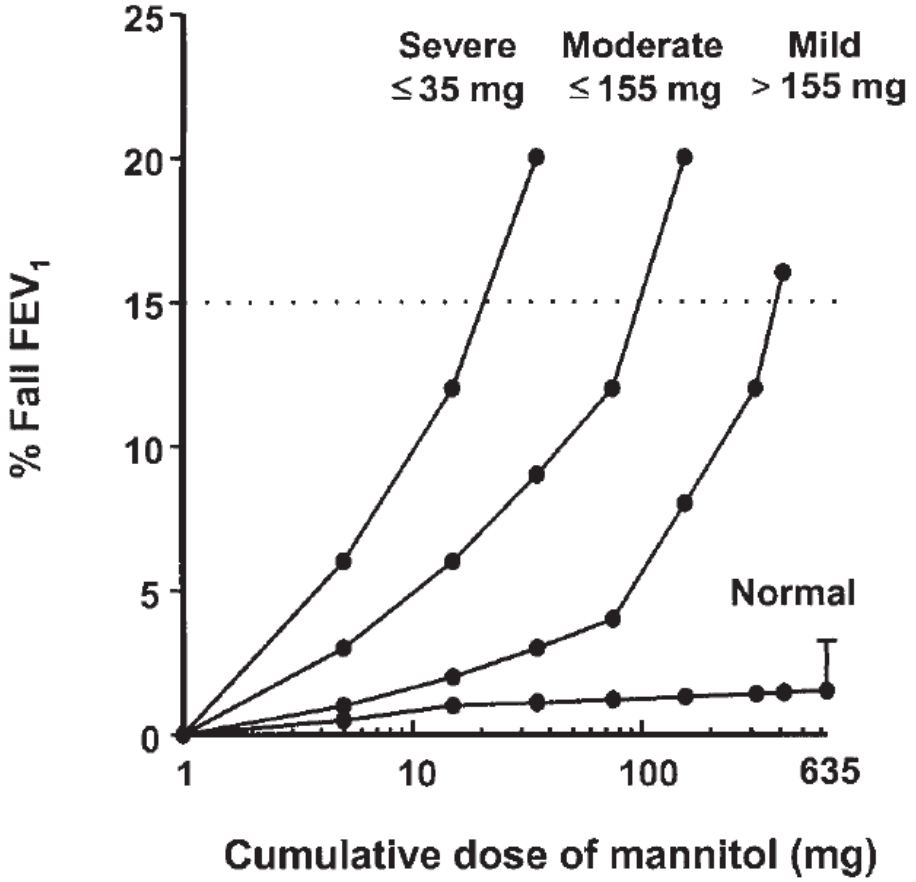
Choi SH et al., *Allergy* 2007;62:1119-24.

Mannitol challenge test

- Specific vs. Non-specific
- Direct vs. Indirect
- **Graded** vs. "SHOT-gun"
- Inhale capsules via a special device
- Outcome measures:
  - Amount of inhaled mannitol causing 15%fall in FEV_1 assessed by the spirometry (PFT)



Step	Dose for Step (mg)	Cumulative Dose (mg)
1	0	0
2	5	5
3	10	15
4	20	35
5	40	75
6	80	155
7	160	315
8	160	475
9	160	635



Anderson and Brannan. *Clin Rev Allergy Immunol* 2003;24:27-54.

Interpret results: for methacholine

FACTORS THAT INCREASE BRONCHIAL RESPONSIVENESS

Factor	Duration of Effect	Ref. No.
Exposure to environmental antigens	1–3 wk	25
Occupational sensitizers	Months	55, 56
Respiratory infection	3–6 wk	57, 58
Air pollutants	1 wk	59
Cigarette smoke	Uncertain*	60
Chemical irritants	Days to months	61

FACTORS THAT DECREASE BRONCHIAL RESPONSIVENESS

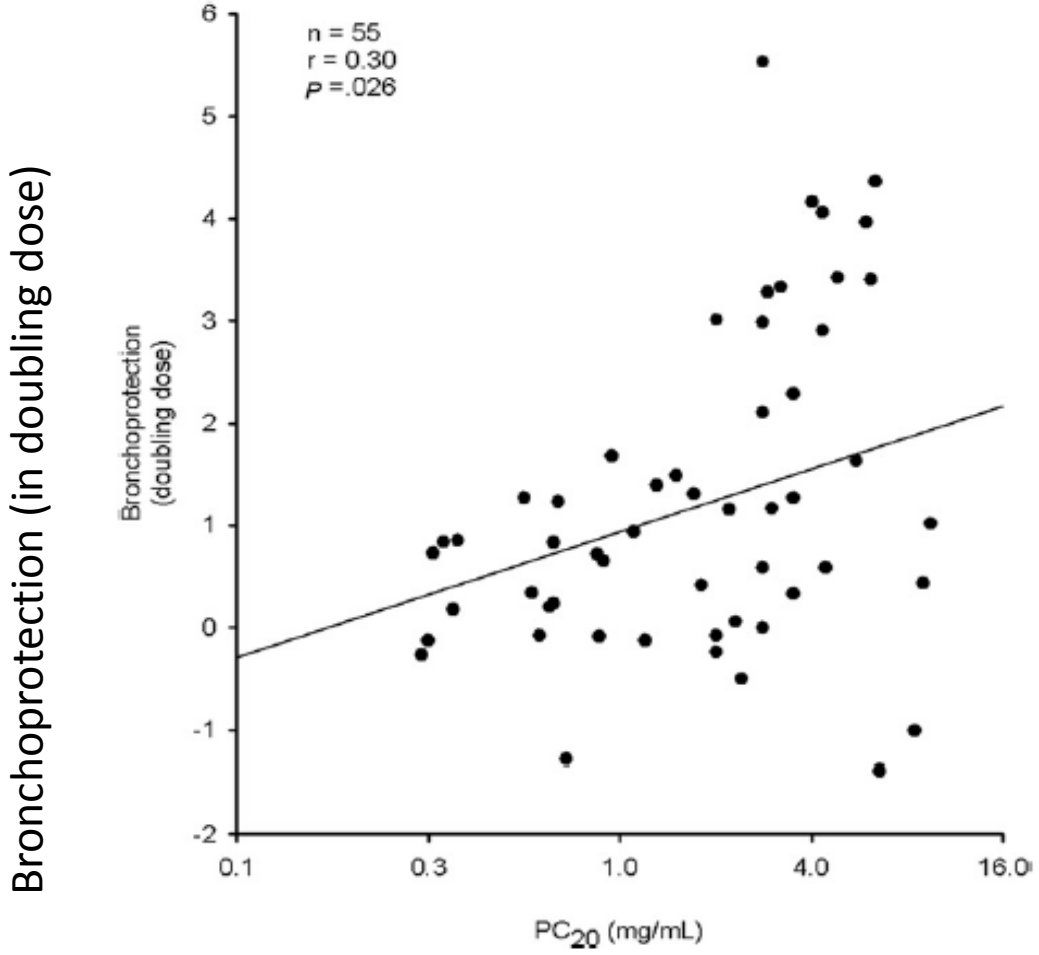
Factor	Minimum Time Interval from Last Dose to Study
Medications	
Short-acting inhaled bronchodilators, such as isoproterenol, isoetharine, metaproterenol, albuterol, or terbutaline	8 h
Medium-acting bronchodilators such as ipratropium	24 h
Long-acting inhaled bronchodilators, such as salmeterol, formoterol, 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

Interpret results: for exercise/ mannitol

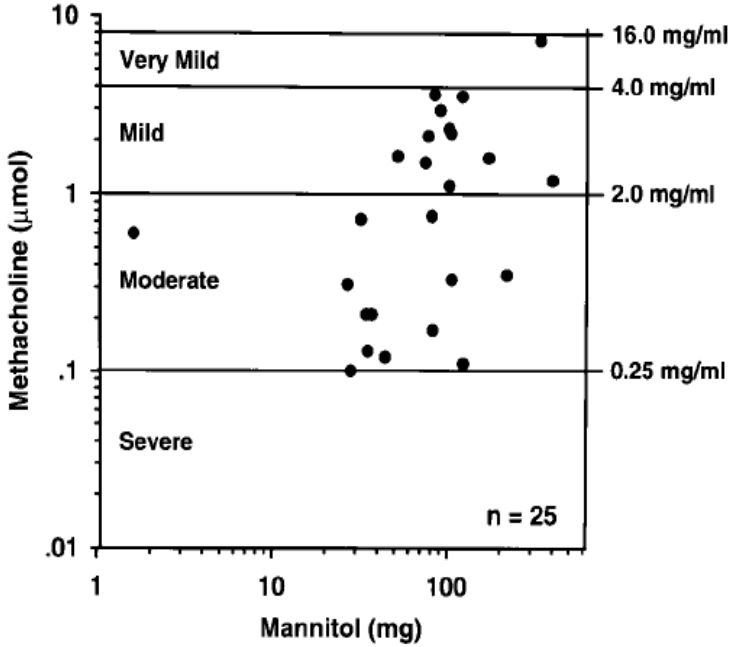
Table 1 Required medication withholding periods for medications before exercise tests

	Factor	Withholding Period
Inhaled agents	Short acting bronchodilators (isoproterenol, isoetharine, metaproterenol, albuterol, levalbuterol, terbutaline) (e.g. Proventil® or Ventolin®)	8 hr
	Inhaled anticholinergics or combination products (e.g. Atrovent® or Combivent®)	1 week
	Long acting inhaled bronchodilators (salmeterol, formoterol) (e.g. Serevent® or Foradil®)	2 weeks
	Inhaled corticosteroid/long acting inhaled bronchodilator combination (e.g. Advair®)	4 weeks
Oral bronchodilators	Theophylline	24 hr
	Intermediate theophylline	48 hr
	Long acting theophylline	48 hr
	Standard β-agonist tablets	24 hr
	Long acting β-agonist tablets	48 hr
Corticosteroids	There is no washout for topical corticosteroids applied to skin unless they are high potency steroids	4 weeks
Other medications	Hydroxyzine, cetirizine (and other antihistamines)	72 hr
	Tiotropium bromide	72 hr
	Nasals corticosteroids	1 week
	β-blockers	1 week
	Cromolyn sodium	2 weeks
	Nedocromil	2 weeks
	Leukotriene modifiers	6 weeks
Foods	Coffee, tea, cola drinks, chocolate (caffeinated foods)	12 hr
Strenuous exercise or exposure to cold air to a level that would be expected to interfere with challenges		12 hr
Tobacco		6 hr

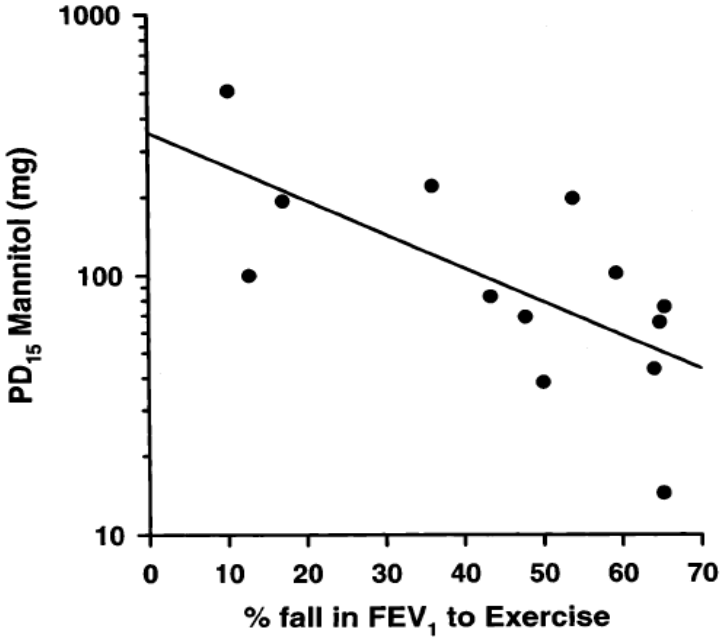
- Tidal breathing vs. dosimeter method



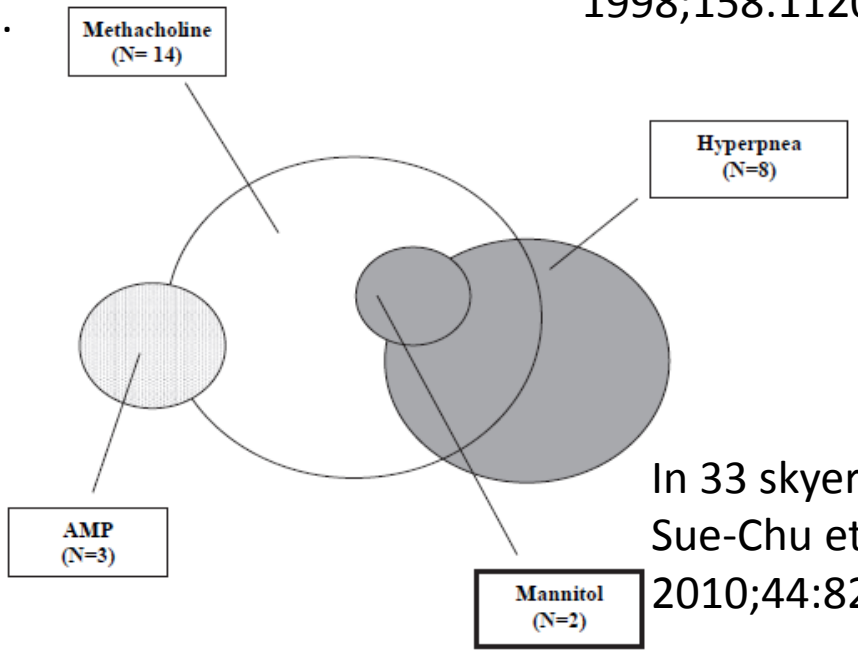
PC_{20} derived from the tidal breathing method



Anderson et al., *Am J Respir Crit Care Med* *1*997;156:758-65.



Brannan et al., *Am J Respir Crit Care Med* 1998;158:1120-6.



In 33 skyers.
Sue-Chu et al., *Br J Sports Med* 2010;44:827-32.

- Questions or Comments…?