Challenge Tests
and
Cardiopulmonary Exercise Testing

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CHALLENGE TESTS

Bronchoprovocation Testing

- Bronchial hyperresponsiveness (BHR)
  - Complex interaction between airway inflammation, smooth muscle function and mechanics
  - Considered a key feature of asthma

- Measure of BHR used for diagnosis and monitoring of asthma in clinical practice and research

- Bronchoprovocation tests (BPT)
  - Response in every subject, even healthy ones
  - Abnormality defined by degree and ease of response

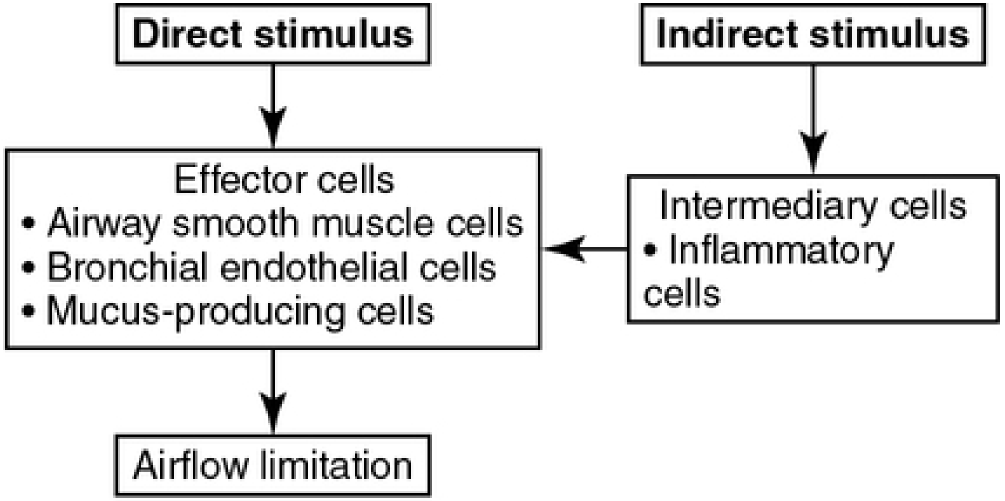
Indications for BPT

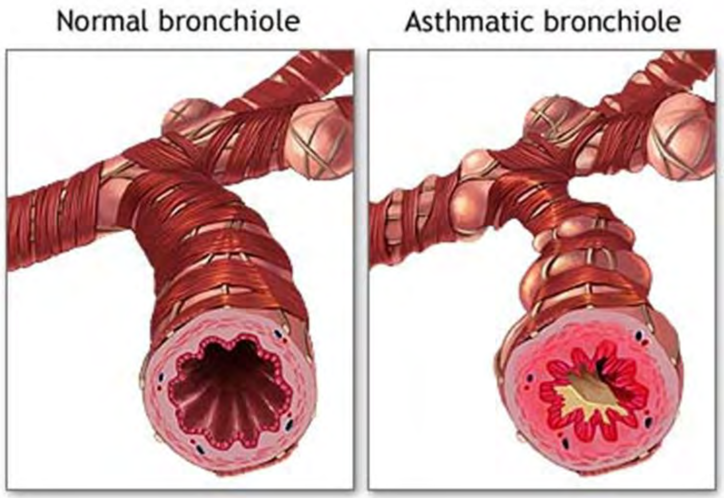
- Accurate diagnosis of asthma
  - Reversibility of airflow limitation through bronchodilator response
    - Diagnostic marker for active asthma
    - Not always demonstrable, especially in mild disease

- Assessment of the response to treatment

- *Identification of triggers for in cases involving specific environmental or occupational exposures*

Stimulus Mechanism in Asthma





Types of Challenges

- Direct challenge tests (eg. methacholine, histamine)
  - Cause airway narrowing by acting ‘directly’ on the receptor on effector cells, predominantly bronchial smooth muscles

- Indirect challenge tests (eg. exercise, hypertonic saline, cold air, mannitol, adenosine monophosphate)
  - Induce airflow limitation by action on cells other than smooth muscle cells, with other cells, mediators and receptors being involved
  - Closer association with inflammation, more specific for current clinically relevant asthma

Bronchoprovocation Tests

- Pharmacologic challenge
  - Methacholine
  - Mannitol
- Exercise challenge
- Eucapnic voluntary hyperventilation

Methacholine Challenge Test

- Synthetic acetylcholine derivative

- Dose-response of the airways to methacholine
  - Provocative concentration (PC_{20}) – the methacholine concentration which precipitates a 20% decrease in FEV_1

- Methacholine solutions and nebuliser apparatus are prepared in a standardized fashion

Methacholine Challenge Test

CONTRAINDICATIONS FOR METHACHOLINE CHALLENGE TESTING

Absolute:
- Severe airflow limitation (FEV_1 < 50% predicted or < 1.0 L)
- Heart attack or stroke in last 3 mo
- Uncontrolled hypertension, systolic BP > 200, or diastolic BP > 100
- Known aortic aneurysm

Relative:
- Moderate airflow limitation (FEV_1 < 60% predicted or < 1.5 L)
- Inability to perform acceptable-quality spirometry
- Pregnancy
- Nursing mothers
- Current use of cholinesterase inhibitor medication (for myasthenia gravis)

American Thoracic Society

Guidelines for Methacholine and Exercise Challenge Testing—1999

This Official Statement of the American Thoracic Society Was Adopted by the ATS Board of Directors, July 1999

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Methacholine Challenge Test

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

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

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Methacholine Challenge Test

Nebuliser should generate aerosol with particle size of 1.0 – 3.6 µm (mass median aerodynamic diameter, at output of 0.13 ml/min

English Wright Nebuliser
2 minute tidal breathing protocol

DeVilbiss model 646 nebuliser
5 breath dosimeter protocol

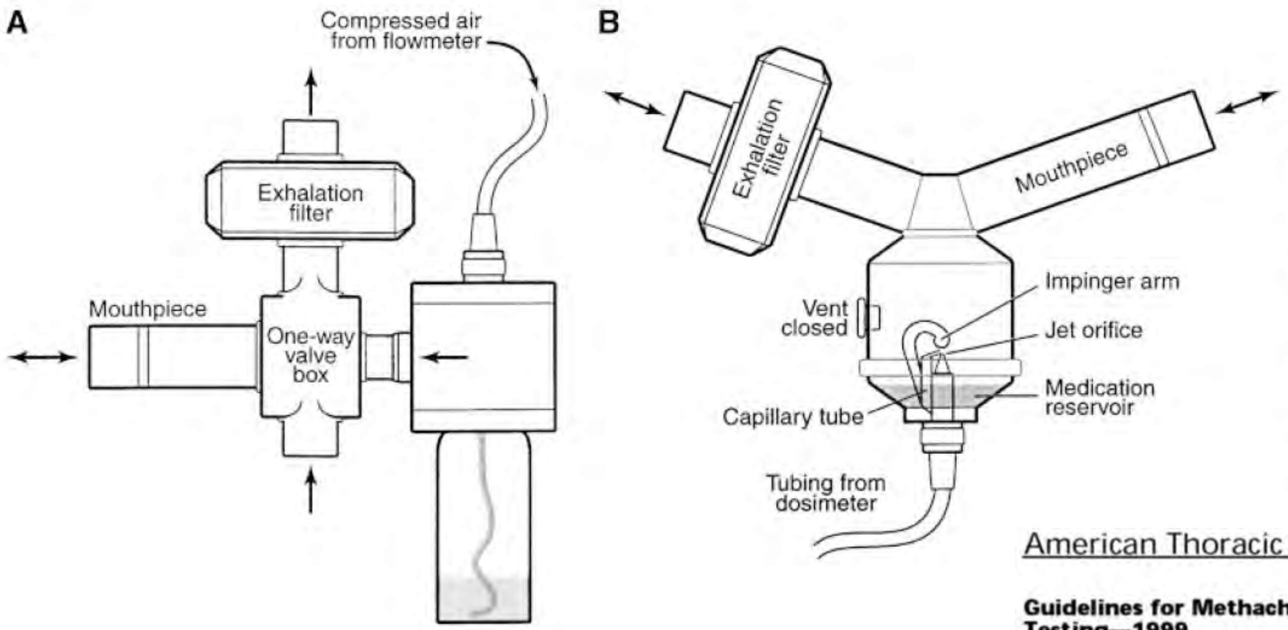

Figure 1. Schematic diagram illustrating typical nebulizer configurations for both the 2-min tidal breathing protocol (*A*, an English Wright nebulizer) and the five-breath dosimeter protocol (*B*, a DeVilbiss model 646 nebulizer). Both include an exhalation filter. Other models of nebulizers may be substituted (*see* Section II, H).

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Methacholine Challenge Test

Dosimeter activated for 0.6 seconds at the start of slow inhalation (over 5 seconds) from end exhalation during tidal breathing (Functional Residual Capacity) to Total Lung Capacity, and to hold for 5 seconds

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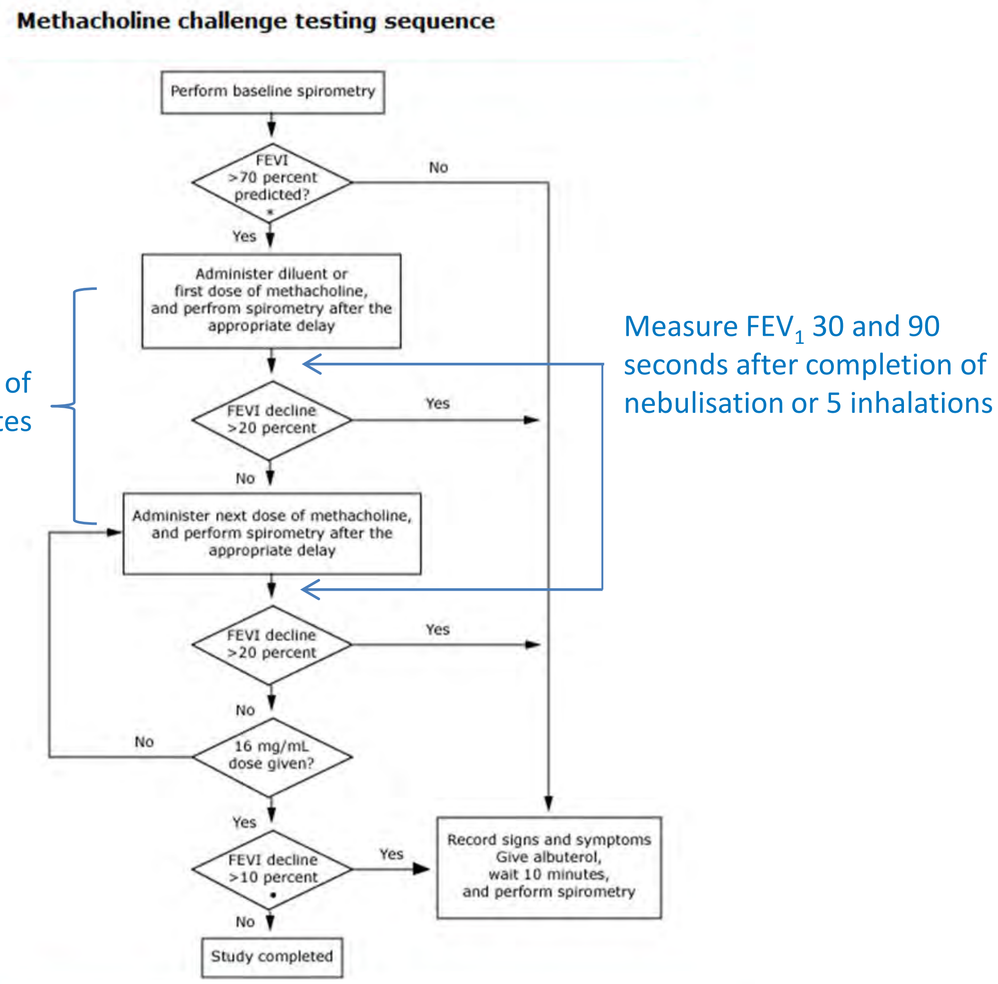
Methacholine Challenge Test



* The choice of the FEV1 value considered a contraindication may vary from 60 to 70 percent of predicted.
• The final dose may vary depending on the dosing schedule used. Final doses discussed in this statement are 16, 25 and 32 mg/mL.

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Methacholine Challenge Test

CATEGORIZATION OF BRONCHIAL RESPONSIVENESS

PC_{20} (*mg/ml*)	Interpretation*
> 16	Normal bronchial responsiveness
4.0–16	Borderline BHR
1.0–4.0	Mild BHR (positive test)
< 1.0	Moderate to severe BHR

* Before applying this interpretation scheme, the following must be true: (*1*) baseline airway obstruction is absent; (*2*) spirometry quality is good; (*3*) there is substantial postchallenge FEV_1 recovery.

- **PC20 for methacholine in patients with asthma is usually 8 mg/mL or less**
- **In asthmatic children, smaller concentrations of agonists (3 mg/mL) are needed to reach PC20**

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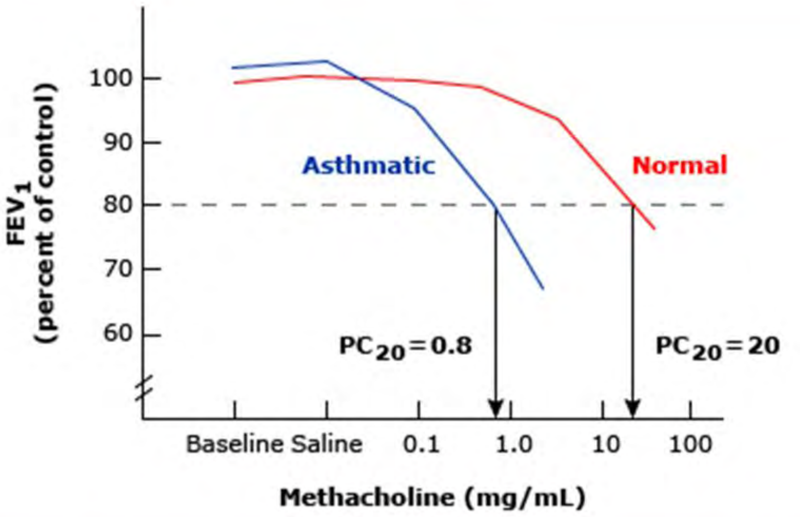
Methacholine Challenge Test

Bronchoprovocation testing



The effect of increasing the inhaled dose of methacholine in a healthy subject (red) and an asthmatic patient (blue). The provocative concentration is the amount of inhaled agonist required to drop the FEV_1 by 20 percent from the baseline (PC_{20} FEV_1) and is much less in the asthmatic than in the normal subject: 0.8 mg/mL versus 20 mg/mL. In general, a PC_{20} ≤8 mg/mL is consistent with asthma; and a PC_{20} >16 mg/mL is considered a negative test. Thus, an increase in airway responsiveness is characterized by a decrease in the PC_{20}.

UpToDate

Mannitol Challenge Test

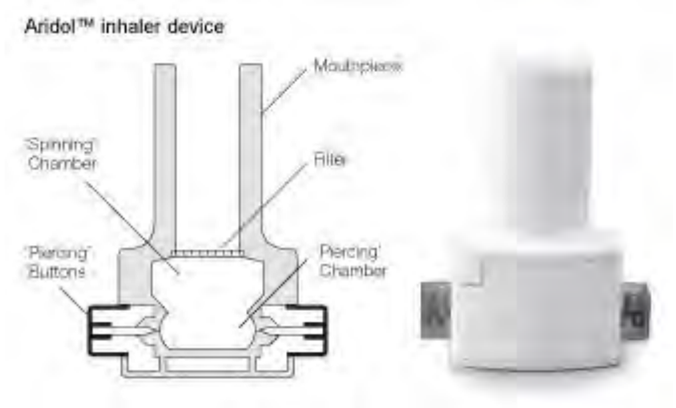
- Mannitol
  - Naturally occurring sugar, isomer of sorbitol
  - Generally regarded as safe, commonly used as an excipient
  - Stable at high levels of humidity
  - Not absorbed to any significant extent by the gastrointestinal tract

- Increases osmolarity of airway surface, resulting in release of mast cell mediators (eg. histamine, prostaglandin D2, leukotriene E4) which cause bronchoconstriction

- Prepared as a dry powder in capsules containing graduated doses that are administered via a dry powder inhaler (Aridol)
  - More convenient than challenges with metacholine, exercise, or isocapnic hyperventilation.

Mannitol Challenge Test

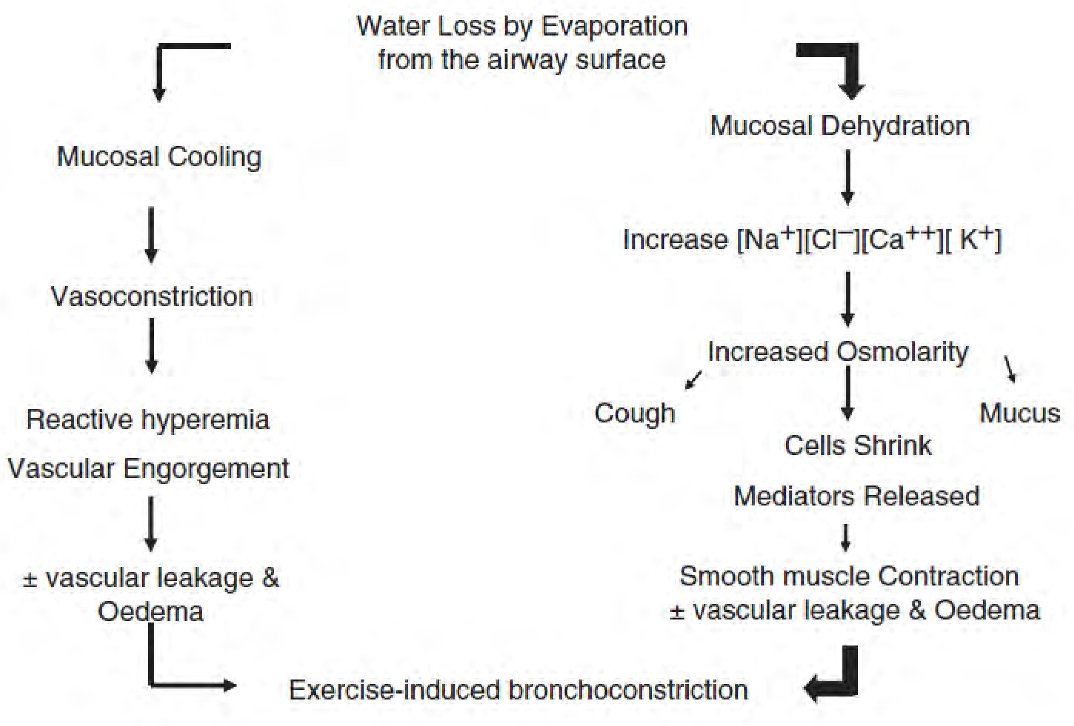
- Mannitol dry powder rapidly inhaled in progressively increasing doses (0, 5, 10, 20, 40, 80, 160, 160, 160 mg)
- FEV_1 measured at baseline and repeated at one minute after each dose
- If the FEV_1 decreases by 10 percent after a dose from the previous FEV1 then the challenge is considered positive
- A 15 percent fall from baseline FEV_1 at a total cumulative dose of ≤635 mg (known as the provocative dose or PD 15) is considered a positive response



www.aridol.info

Exercise Challenge Test

- Exercise induced bronchoconstriction (EIB)
  - Minute ventilation rises with exercise
  - Changes in airway physiology triggered by the large volume of relatively cool, dry air inhaled during vigorous activity
- Treadmill
  - Motor driven with adjustable speed and gradient
- Cycle ergometer
  - Electromagnetically braked
- Pulse oximeter
- Heart rate (HR) from 3 lead ECG



Sandra Anderson. European Clinical Respiratory Journal 2016

Exercise Challenge Test – Treadmill

- Treadmill speed and gradient chosen to produce 4–6 min of exercise at near-maximum targets with a total duration of exercise of 6–8 min
  - Children < 12 years, time is usually 6 min
  - Older children and adults, time is usually 8 min
- From a low speed and gradient, both are progressively advanced during the first 2–3 min of exercise until the HR is 80–90% of the predicted maximum (calculated as 220 – age in years)
  - *Ventilation rather than HR can be used to monitor exercise intensity*
  - *Ventilation should reach 40–60% of the predicted maximum voluntary ventilation (MVV, estimated as FEV1 x 35)*
- Treadmill speed and slope are chosen to achieve a target HR (or ventilation) that is maintained for at least 4 min
- A treadmill speed greater than 3 mph (about 4.5 km/h) and a gradient greater than 15%, or an oxygen consumption of 35 ml/min/kg or greater will usually achieve the target HR or ventilation in young healthy subjects

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Exercise Challenge Test – Cycle Ergometer

- Target work rate to achieve the target ventilation determined from equations relating work rate to oxygen consumption and oxygen consumption to ventilation, e.g.
  - Target work rate (in watts) = (53.76 x measured FEV1) – 11.07
- The work rate is set to 60% of the target in the first minute, 75% in the second minute, 90% in the third minute, and 100% in the fourth minute
  - Check HR and/or ventilation to determine if the exercise targets are achieved
  - Target exercise intensity to be sustained for 4–6 min
  - To ensure that the target minute ventilation is sustained, work rate may need to be reduced in the final minutes of exercise
- Important to reach the target HR or ventilation within 4 min
  - Rate of water loss determining factor for eliciting EIB
  - Refractoriness can develop if exercise is prolonged at submaximal work

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Exercise Challenge Test

- Spirometry (FEV1) measurements
  - Pre exercise, post exercise at 5, 10, 15, 20 and 30 min after cessation of exercise, EIB usually occurs 10 to 15 min after the end of exercise
  - 1 and 3 min post exercise may be included as severe EIB can be present at the cessation of exercise
  - If FEV1 returns from nadir to the baseline level or greater, testing may be terminated at 20 min post exercise
- b-agonist bronchodilator may be administered at any time to reverse bronchoconstriction
  - If patient experiences appreciable dyspnea
  - If the FEV1 has not recovered to within 10% of baseline when the patient is ready to leave the laboratory
  - Spontaneous recovery usually occurs within 20–40 min
- FEV1 at each post exercise interval plotted as a percentage of the pre exercise baseline FEV1
  - Decrease below 90% of the baseline FEV1 (10% decrease) generally accepted as abnormal response
  - Some consider value of 15% more diagnostic of EIB, especially if exercise has been performed in the field
  - Healthy subjects generally demonstrate increase in FEV1 after exercise

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Exercise Challenge Test

- Dry air less than 25ºC
  - Noseclip – nasal breathing decreases water loss from airways
  - Conduct study in air-conditioned room (ambient temperature 20–25ºC) with low relative humidity (50% or less)
  - Alternatively, inspire dry air through a mouthpiece and a two-way breathing valve
- Limitations
  - Level of exercise chosen may not mimic real-world triggers
  - Subjects with asthma triggered by cold dry air may not show maximal response in standard laboratory conditions
  - Sedentary subjects may not attain level of ventilation high enough to trigger EIB when exercising at 85% of their maximal HR
  - Very fit subjects may require high workload to reach 85% of their predicted HR or increase their ventilation significantly

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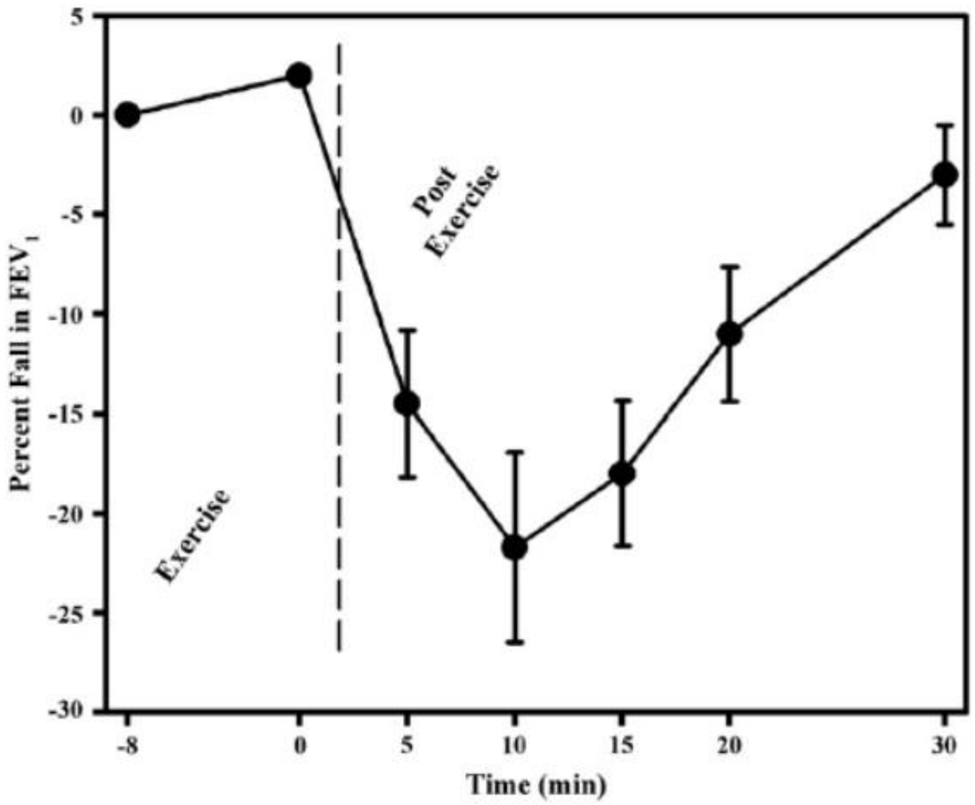

FIG 1. Typical change in FEV_1 in response to an 8-minute exercise challenge in EIB-positive individuals. Note the small improvement in FEV_1 immediately after exercise followed by significant falls in FEV_1 at 5 minutes after the cessation of exercise. Spontaneous recovery is most often nearly complete by 30 minutes postchallenge. Recovery can be accelerated by administration of an inhaled β_2-agonist.

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Exercise Challenge Test

	Exercise Induced Bronchoconstriction	Exercise Induced Vocal Cord Dysfunction
Dyspnoea	Expiratory	Inspiratory, usually audible
Occurrence	After exercise, with decrease in FEV1	During maximum exercise intensity
Diagnosis	10 or 15 percent decrease in FEV1	Continuous laryngoscopy during exercise testing

Eucapnic Voluntary Hyperventilation

- Dry air hyperventilation
  - Drying and hyperosmolarity of the airway surface (similar to effect of exercise)
  - Release of inflammatory mediators from inflammatory cells eg. mast cells (similar to mannitol inhalation)

- To prevent respiratory alkalosis and hypocapnia induced bronchoconstriction, CO_2 is mixed with inspired air, or gas mixture containing 5% CO_2, 21% O_2 and the balance N_2 is used

- EVH is one of the recommended challenge tests for identifying EIB in Olympic athletes, and also endurance athletes

Eucapnic Voluntary Hyperventilation

- Cold air/gas
  - Heat exchanger/cooling coil cools air/gas to –10 to –20ºC with near 0% relative humidity
  - Subject orally breathes between 30% to 70% of MVV, or at increasing levels of ventilation (eg. 7.5, 15, 30, 60 L/min and MVV) for 4 to 6 min
  - Maintain stable $P_{ET}CO_2$ by titrating CO_2 into air, or using gas composed of 5% CO_2, 21% O_2 and the balance N_2
- Ambient temperature
  - Dry gas mixture of 5% CO_2, 21% O_2 and the balance N_2
  - Subject orally breathes the gas mixture from 5L bag filled by a high output flowmeter, at ventilation of 30 x FEV1 for 6 min
- Spirometry performed immediately after hyperventilation and at 5 minute intervals
- A test is generally considered positive if the FEV_1 decreases by 10 to 15% or more

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Withholding Medications Before BPT

FACTORS THAT DECREASE BRONCHIAL RESPONSIVENESS

Factor	Minimum Time Interval from Last Dose to Study	Ref. No.
Medications		
Short-acting inhaled bronchodilators, such as isoproterenol, isoetharine, metaproterenol, albuterol, or terbutaline	8 h	45, 46
Medium-acting bronchodilators such as ipratropium	24 h	20, 47
Long-acting inhaled bronchodilators, such as salmeterol, formoterol, tiotropium	48 h (perhaps 1 wk for tiotropium)	48, 49
Oral bronchodilators		50, 51
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	52

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.

Bronchodilators

Caffeine

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Considerations in Scheduling BPT

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

*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.

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Considerations in Choosing BPT

- Methacholine
  - Most widely used direct challenge
  - Highly sensitive, provided symptoms are clinically current and deep inhalations are avoided during inhalation
  - Many causes of false-positive test result eg. allergic rhinitis, cystic fibrosis, heart failure, chronic obstructive pulmonary disease and bronchitis
  - Specificity is increased if the pretest probability of asthma is greater, if the methacholine responsiveness is moderate or greater, and if the methacholine-induced symptoms mimic the natural symptoms
  - Function best to exclude clinically current asthma, positive test result is consistent but not diagnostic of asthma

Ann Allergy Asthma Immunol. 2009 Nov;103(5):363-9
Direct and indirect challenges in the clinical assessment of asthma.
Cockcroft D, Davis B

Considerations in Choosing BPT

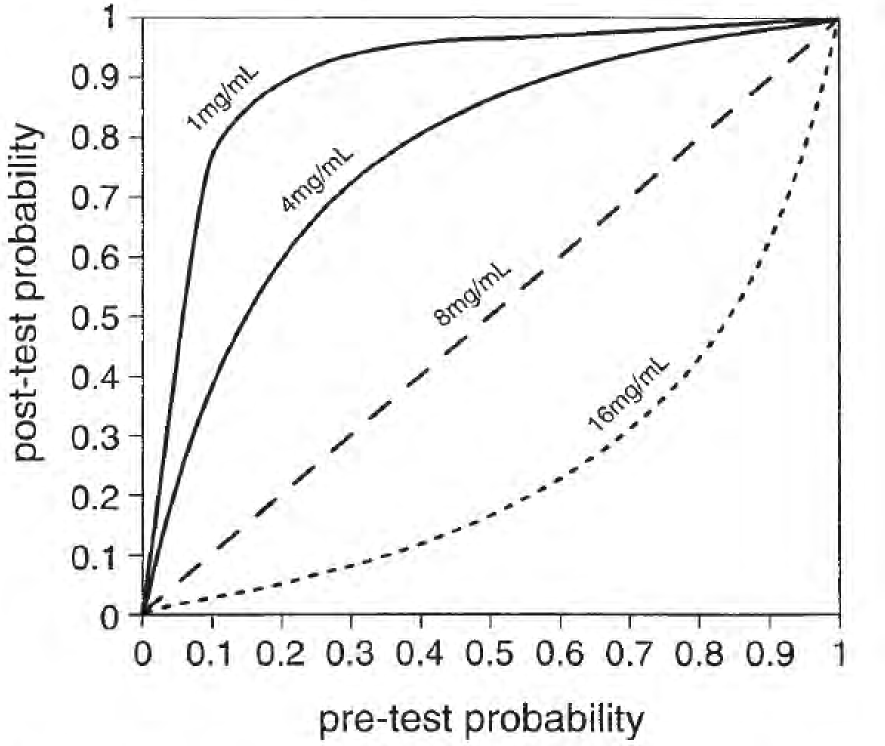

Figure 3. Curves illustrating pretest and posttest probability of asthma after a methacholine challenge test with four PC_{20} values. The curves represents a compilation of information from several sources (10, 152, 153). They are approximations presented to illustrate the relationships and principles of decision analysis. They are not intended to calculate precise posttest probabilities in patients.

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Considerations in Choosing BPT

- Indirect challenges
  - More specific for asthma but are insensitive, particularly for mild and/or well-controlled asthma
  - The lower sensitivity may relate to the fact that many indirect challenges (eg, exercise, eucapnic voluntary hyperpnea, adenosine monophosphate) are dose limited (ie, the dose of stimulus cannot be increased above a level based on physiology or solubility)
  - Indirect challenges also correlate better with airway inflammation and are more responsive to anti-inflammatory treatments
  - Superior for confirming asthma and are the challenges of choice when EIB is the question (eg, certification for international athletic competition, armed forces, scuba diving)
  - Indirect challenges would be preferred for monitoring of asthma control and used serially to help diagnose occupational asthma

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Considerations in Choosing BPT

	Direct BPT	Indirect BPT
Diagnosis of asthma	Sensitive Not so specific	Specific Not so sensitive
Response to inhaled steroids	Over 3 months	Over 1 to 3 weeks
Treatment effect monitored	Airway remodeling	Airway inflammation (EIB)

CARDIOPULMONARY EXERCISE TESTING

Exercise Testing in Children

- Exercise
  - Complex activity
  - Involvement of multiple systems - pulmonary, cardiovascular, haematopoietic, musculoskeletal and neuropsychological systems

- Exercise testing
  - Important diagnostic tool in the assessment of the cardiorespiratory status of the child
  - Dynamic assessment of pulmonary function
    - Under the stress of exercise, subtle functional deficits in the lung may be identified that were not apparent during conventional static pulmonary function testing
    - May detect early functional deficits due to early lung disease
  - Can help ascertain if exercise capacity is reduced
  - May also define aetiology of the reduced exercise capacity

Teoh et al. Exercise Testing in Children with Lung Diseases. Paediatric Respiratory Reviews 2009

Exercise Testing in Children

"Field tests" versus "laboratory tests" of exercise capacity in children

Field test	Laboratory test
Cheap to administer	Expensive equipment necessary
Easy access	Specific expertise required to conduct
Potentially less threatening to children	Potentially more threatening to young children
Useful in large population studies	Difficult to perform in large research studies
Limited long term validity data	Valid assessment short & long term
Less useful diagnostically	Useful diagnostic test
Cannot measure ventilation parameters	Good physiological ventilation measures

6 minute walk test (6MWT)
3 minute step test (3MST)
Modified shuttle test (MST)

Teoh et al. Exercise Testing in Children with Lung Diseases. Paediatric Respiratory Reviews 2009

Cardiopulmonary Exercise Testing

Important parameters of assessment during exercise tests in children

Heart rate (HR)
Oximetry
Blood pressure
Tidal volume (VT)
Peak oxygen uptake (VO2)
Oxygen pulse (VO2/HR)
Minute ventilation/carbon dioxide production (VE/VCO2)
Minute ventilation/maximum voluntary ventilation (VE/MVV)
Exercise flow volume loops
Pre/post exercise forced expiratory volume in 1 second (FEV1)
Physiological dead space (VD/VT) – usually derived value

VO2max/peak
Maximum oxygen consumption during exercise challenge
Considered best overall measure of cardiovascular fitness of healthy child

Teoh et al. Exercise Testing in Children with Lung Diseases. Paediatric Respiratory Reviews 2009

Cardiopulmonary Exercise Testing

Set-up for CPET	Apparatus	Primary outcome	Derivative
	Pulse oximeter	Sp_{O_2}	
			Ventilatory reserve
	Spirometry	FEV_1	Eq_{O_2}, Eq_{CO_2}
	Volume measurements	$\dot{V}_E$, TV, BF	$\dot{V}_E/\dot{V}_{O_2}$, $\dot{V}_E/\dot{V}_{CO_2}$
	Respiratory gas analysis	$P_{ET}O_2$, $P_{ET}CO_2$, $\dot{V}_{O_2}$, $\dot{V}_{CO_2}$	OUE, OUEP, OUES
	ECG	Heart rhythm, HR	RER Ventilatory threshold
	Cuff with a detector for Korotkoff sounds	Blood pressure	O_2-pulse
			$\Delta\dot{V}_{O_2}/\Delta WR$
	Ergometer **Treadmill**	WR	
	Borg-scale or VAS	Dyspnea, leg fatigue	

Figure 3. Selection of important parameters measured during cardiopulmonary exercise testing in pediatric populations. BF = breathing frequency (breaths · min^{-1}); CPET = cardiopulmonary exercise testing; $\Delta\dot{V}_{O_2}/\Delta WR$ = oxygen cost of work (ml · min^{-1} · W^{-1}); $EqCO_2$ = ventilatory equivalent for carbon dioxide; EqO_2 = ventilatory equivalent for oxygen; HR = heart rate (beats · min^{-1}); OUE = $\dot{V}_{O_2}$ efficiency; OUEP = $\dot{V}_{O_2}$ efficiency plateau; OUES = $\dot{V}_{O_2}$ efficiency slope; $P_{ET_{CO_2}}$ = partial end-tidal carbon dioxide tension (mm Hg); $P_{ET_{O_2}}$ = partial end-tidal oxygen tension (mm Hg); RER = respiratory exchange ratio; Sp_{O_2} = oxygen saturation as measured by pulse oximetry (%); TV = tidal volume; VAS = visual analog scale; $\dot{V}_E/\dot{V}_{CO_2}$ = slope of the relationship between the $\dot{V}_E$ and $\dot{V}_{CO_2}$; $\dot{V}_E/\dot{V}_{O_2}$ = slope of the relationship between the $\dot{V}_E$ and $\dot{V}_{O_2}$; WR = work rate (W). Note: adapted and modified from Reference 36.

Takken et al. Cardiopulmonary Exercise Testing in Paediatrics.
AnnalsATS 2017

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Cardiopulmonary Exercise Testing

- Protocols
  - Continuous
    - Ramped
    - Progressive incremental – increase by stages
  - Constant work rate
  - Discontinuous
    - Rest between stages
    - Preferred when invasive measures required e.g. finger stick or venous blood sampling

Cardiopulmonary Exercise Testing

TABLE 17. SUGGESTED NORMAL GUIDELINES FOR INTERPRETATION OF CARDIOPULMONARY EXERCISE TESTING RESULTS*

Variables	Criteria of Normality
$\dot{V}O_2$max or $\dot{V}O_2$peak	> 84% predicted
Anaerobic threshold	> 40% $\dot{V}O_2$max predicted; wide range of normal (40–80%)
Heart rate (HR)	HRmax > 90% age predicted
Heart rate reserve (HRR)	HRR < 15 beats/min
Blood pressure	< 220/90
O_2 pulse ($\dot{V}O_2$/HR)	> 80%
Ventilatory reserve (VR)	MVV − $\dot{V}_E$max: > 11 L or $\dot{V}_E$max/MVV × 100: < 85%. Wide normal range: 72 ± 15%
Respiratory frequency (f_R)	< 60 breaths/min
$\dot{V}_E/\dot{V}CO_2$ (at AT)	< 34
V_D/V_T	< 0.28; < 0.30 for age > 40 years
Pa_{O_2}	> 80 mm Hg
$P(A–a)O_2$	< 35 mm Hg

Adapted by permission from References 1, 3, 43, 235, 292, and 545.
* Maximum or peak cardiopulmonary responses except for anaerobic threshold and $\dot{V}_E/\dot{V}CO_2$ at AT.

ATS/ACCP Statement on Cardiopulmonary Exercise Testing
AJRCCM 2003

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Paediatric Exercise Physiology

Table 1. Commonly observed differences in exercise physiological parameters between adults and children

Variable	Difference with Adults
Cardiovascular	
$\dot{V}O_{2peak}$, L·min^{-1}	Lower
$\dot{V}O_{2peak}$, ml·kg^{-1}·min^{-1}	Higher
Submaximal HR, beats·min^{-1}	Higher
HR_{peak}, beats·min^{-1}	Higher
Stroke volume (sub)max, ml·beat^{-1}	Lower
Cardiac output (at %$\dot{V}O_{2peak}$)	Lower
Arteriovenous oxygen difference (at %$\dot{V}O_{2peak}$)	Higher
Blood flow to muscle	Higher
Systolic and diastolic blood pressure, mm Hg	Lower
Myocardial ischemia	Rare
Pulmonary	
Tidal volume, L	Lower
Breathing frequency, breaths·min^{-1}	Higher
$\dot{V}E_{peak}$, L·min^{-1}	Lower
Ventilatory drive, $\dot{V}E/\dot{V}CO_2$ slope	Higher
Ventilatory efficiency, $\dot{V}E/\dot{V}O_2$	Lower
Metabolic	
Fat oxidation	Higher
Carbohydrate oxidation	Lower
Peak blood lactate	Lower
Glycolytic capacity	Lower
A-lactic capacity	Lower
Lactate clearance	Same
Recovery after high-intensity exercise	Faster

Definition of abbreviations: HR = heart rate; HR_{peak} = peak heart rate; $\dot{V}E_{peak}$ = peak $\dot{V}E$; $\dot{V}O_{2peak}$ = peak $\dot{V}O_2$.

Takken et al. Cardiopulmonary Exercise Testing in Paediatrics.
AnnalsATS 2017

Cardiopulmonary Exercise Testing

Indications for exercise testing

In clinical practice, exercise testing in children may be performed for one or more of the following indications:

CPET

→ 1) Evaluation of overall fitness level.
→ 2) Evaluation of undiagnosed exercise limitation.
→ 3) Evaluation of exercise tolerance in a child with underlying respiratory or cardiovascular disease e.g. asthma, congenital heart disease.
4) Detection of exercise induced bronchoconstriction.
5) Detection of exercise induced arrhythmia.
→ 6) Assessment for response to specific treatment, exercise prescription or rehabilitation programme.

CPET

→ 7) Evaluation before specific treatment for baseline status or suitability for treatment e.g. chemotherapy, lung transplantation.
→ 8) Assessment post specific treatment for potential complications e.g. drug induced lung injury from chemotherapy.

Teoh et al. Exercise Testing in Children with Lung Diseases.
Paediatric Respiratory Reviews 2009

Cardiopulmonary Exercise Testing

Utility of exercise testing in children
Diagnostic tool as to why a child cannot exercise like their peers
○ Physical fitness issues/ deconditioning
○ Respiratory limitation
○ Cardiac compromise
Assessing response to therapy or intervention
Prognostic aid (in cystic fibrosis)

Survival rates greater in CF patients with higher levels of aerobic fitness

Teoh et al. Exercise Testing in Children with Lung Diseases.
Paediatric Respiratory Reviews 2009

Cardiopulmonary Exercise Testing

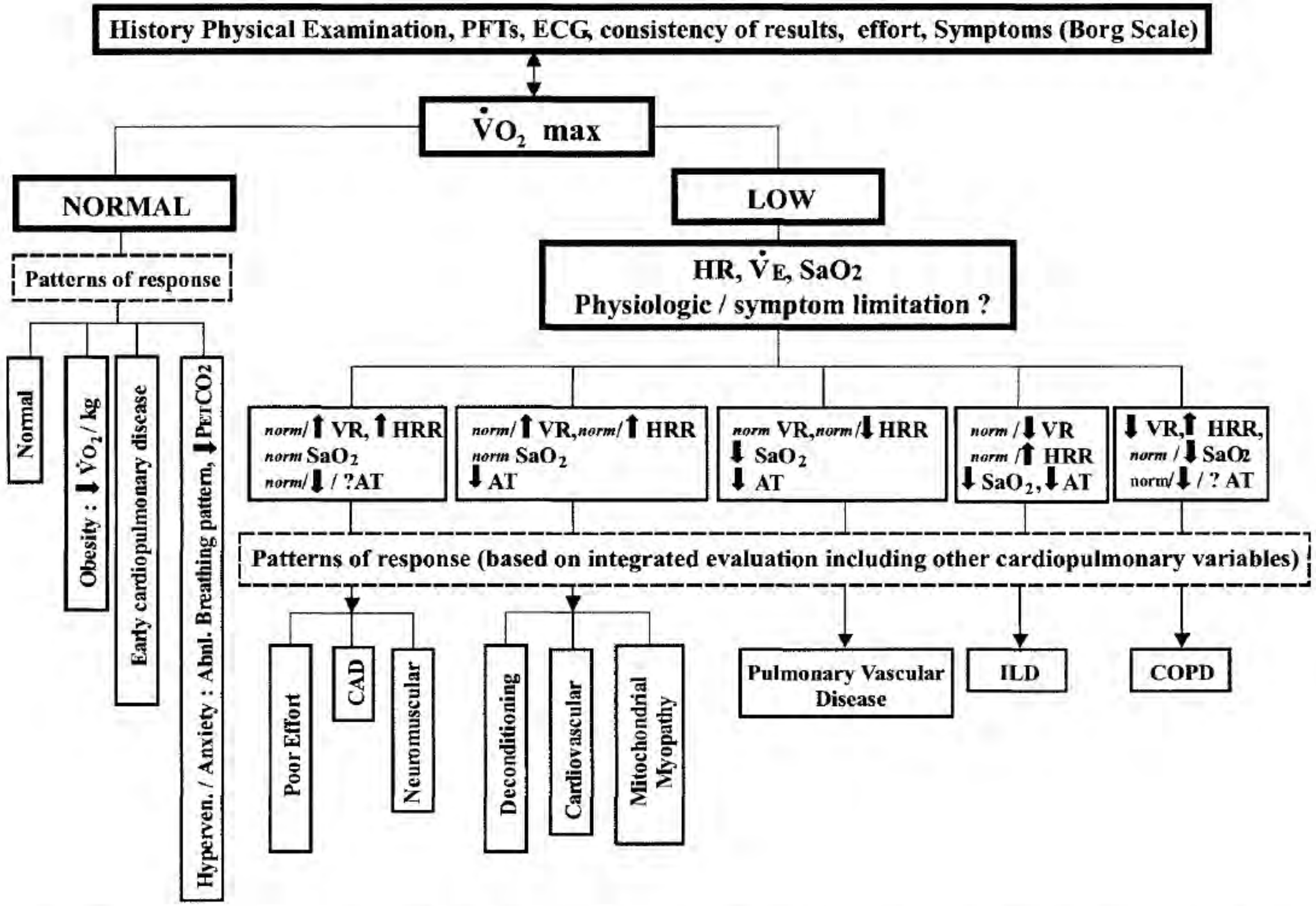

Figure 10. Basic strategy for the interpretation of peak CPET results begins with consideration of patient information and reasons for testing and with analysis of $\dot{V}O_2$max and subsequently simultaneous assessment of HR, $\dot{V}_E$, and Sa_{O_2}. The AT may be helpful at this point. Determination of physiologic limitation is accomplished by analysis of ventilatory reserve ($\dot{V}_E$/MVV) and heart rate reserve (HRR). Additional CPET measurements and patterns of response are established and (likely) associated clinical entities are considered, resulting in more specific diagnostic pathways (28). *CAD* = coronary artery disease.

Contraindications to CPET

Absolute contraindications for exercise testing

- Acute myocarditis, pericarditis or endocarditis
- Acute rheumatic fever
- Acute myocardial infarction
- Active pneumonia
- Active hepatitis
- Severe systemic hypertension
- Acute phase of Kawasaki disease
- Acute orthopaedic injury

Relative contraindications for exercise testing

- Severe left-ventricular outflow tract obstruction
- Severe right-ventricular outflow tract obstruction
- Congestive heart failure
- Ischaemic coronary artery disease
- Advanced ventricular arrhythmias
- Pulmonary vascular obstructive disease
- Pacemakers with defibrillation capabilities
- End-stage cystic fibrosis

Yu et al. Cardiopulmonary Exercise Testing in Children.
HK J Paediatr 2010

THANK YOU

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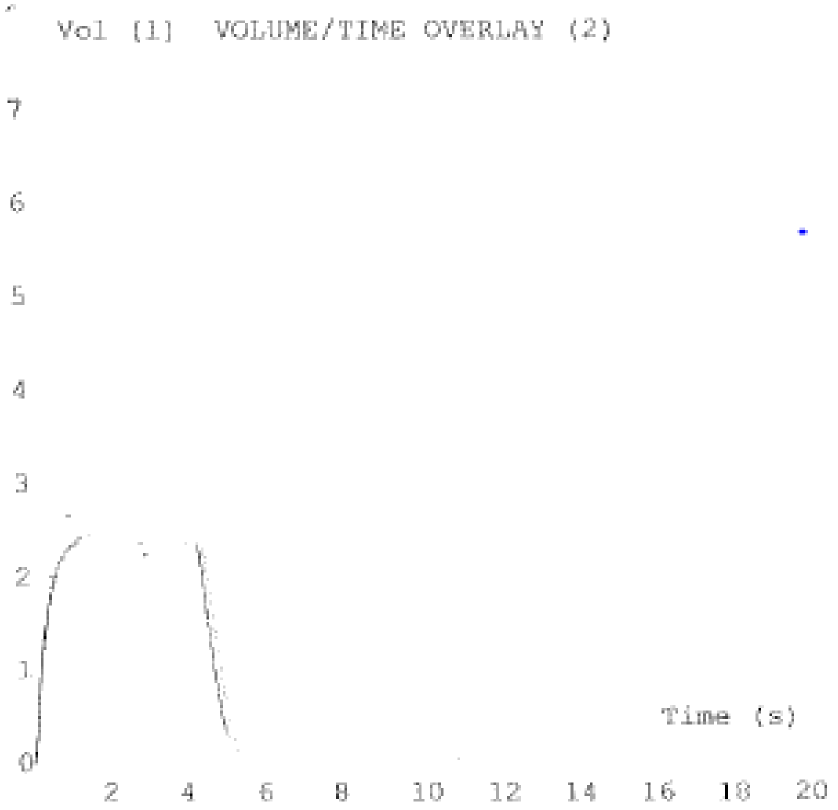
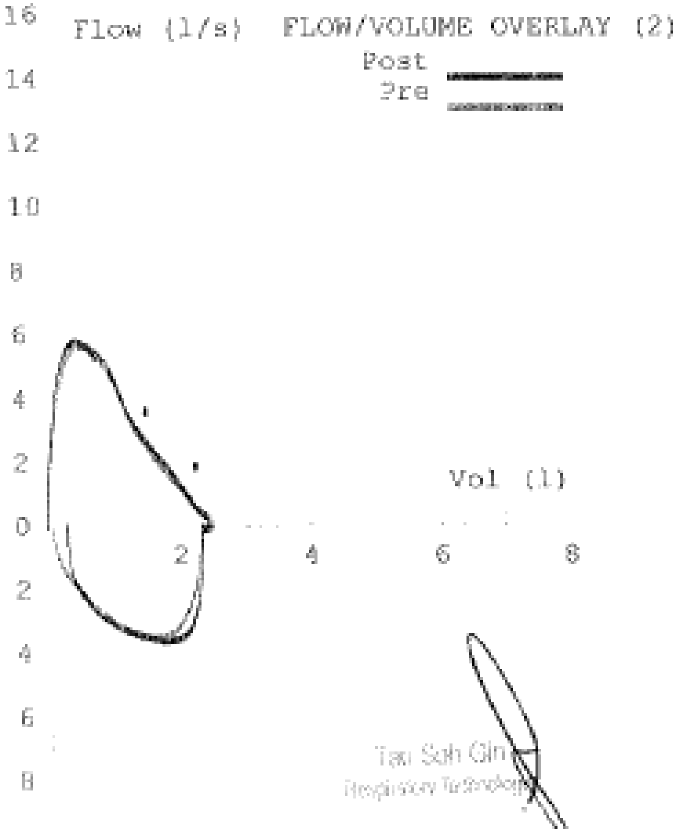
Case Study

- 13 year old girl
- Breathlessness past 2 years, monthly attacks with chest tightness and cough – usually after physical activity in school, uses MDI salbutamol, no hospitalizations
- No exacerbations from URTI episodes
- Occasional cough few times/week
- Has allergic rhinitis symptoms – responded to intranasal steroids, no eczema
- Family history of atopy – sister has allergic rhinitis
- Triggers at home – soft toys, but no smoking/carpets/pets

Case Study

- What are your thoughts?
  - Does she have asthma?
  - What would you do?





Parameter		Pred	Pre	%Pred	Post	%Pred	Change	%Change
FVC	L	3.01	2.49	83.0	2.44	81.1	-0.05	-2.2
FEV 1	L	2.65	2.30	86.7	2.32	87.5	0.02	1.0
FEV 1/FVC	%	87.61	92.18	105.2	95.18	108.6	2.99	3.0
PEF	L/S	5.76	5.73	99.5	5.88	102.1	0.15	2.6
FEF 25-75	L/S	3.17	3.06	96.8	3.32	105.0	0.26	8.5
FEF 75	L/S	1.89	1.55	82.1	1.86	98.5	0.31	19.9
FIVC	L	3.08	2.44	79.0	2.16	70.1	-0.28	-11.3
FIVC/FVC	%	102.58	97.71	95.3	88.60	86.4	-9.11	-9.1
FIF50/FEF50	%	75.00	98.57	131.4	94.56	126.1	-4.00	-4.0

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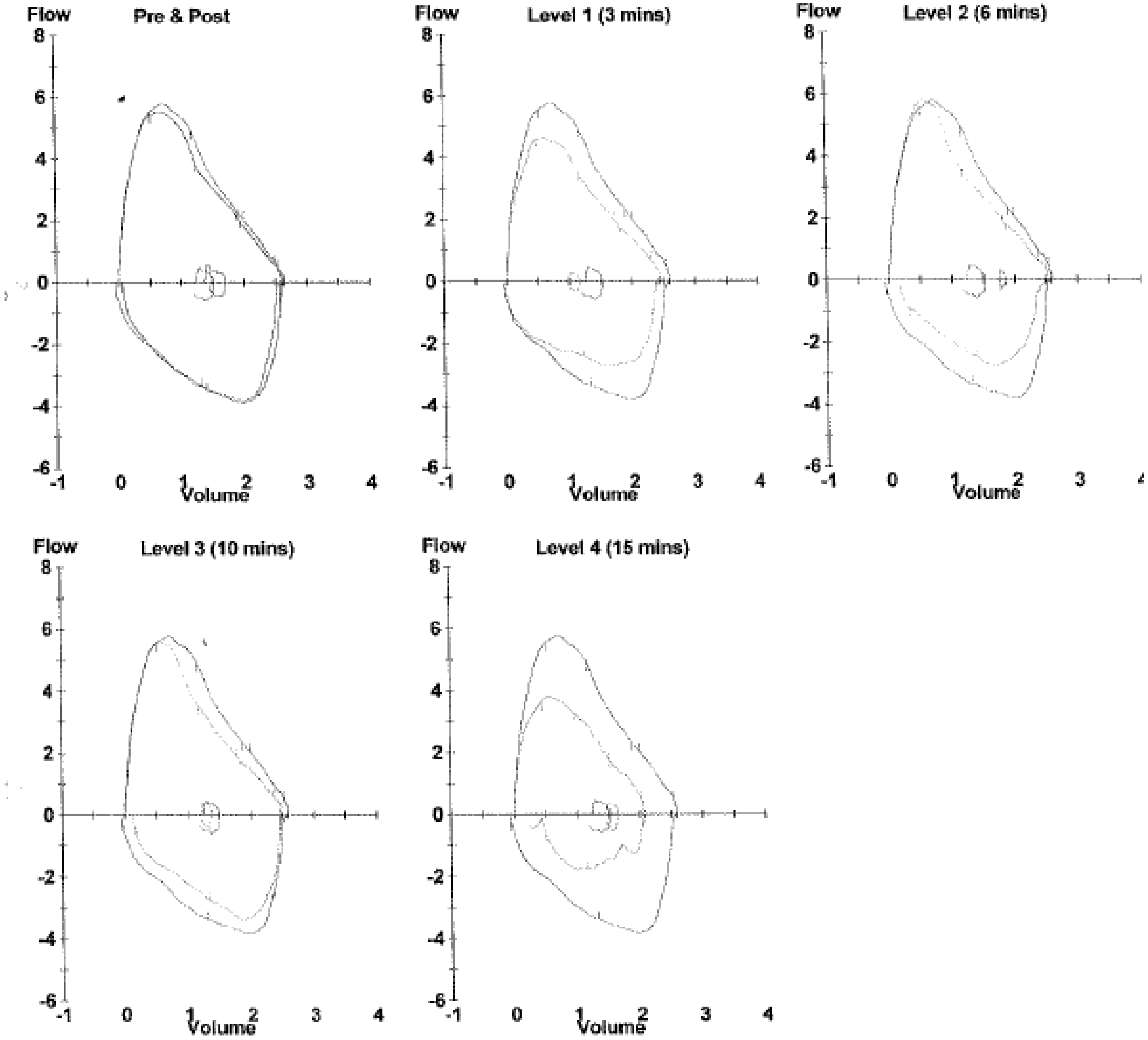
Case Study

- What are your thoughts
  - Do you think she has asthma?
  - What would you do with her symptoms of breathlessness triggered by exercise?


Flow
Pre & Post
Volume
Flow
Level 1 (3 mins)
Volume
Flow
Level 2 (6 mins)
Volume
Flow
Level 3 (10 mins)
Volume
Flow
Level 4 (15 mins)
Volume

		Baseline Spirometry			Post Exercise Spirometry						
		Ref	Pre Meas	Pre % Ref	Level 1 Meas	Level 2 Meas	Level 3 Meas	Level 4 Meas	Post Meas	Post % Ref	Post % Chg
FVC	Liters	3.05	2.66	87	2.47	2.54	2.53	2.10	2.61	86	-2
FEV1	Liters	2.69	2.49	93	2.33	2.39	2.37	2.05	2.56	95	3
PEF	L/sec	5.81	5.50	95	4.64	5.78	5.55	3.80	6.19	107	13
%Fall: FEV1%					-7	-4	-5	-18			3

Comments:

Patient was unable to complete all levels of post exercise spirometry as she complained of chest tightness and breathlessness during the test.

Target HR (0.8 X HR Max): 161 b/min
Predicted Maximum HR: 202 b/min
(210.0 - 0.65 X Age in years)

Resting HR: 87 b/min
Maximum Exercise HR: 166 b/min
% Pred. Max HR: 80%

Resting SpO2: 100 %
Max Exercise SpO2: 100 % Target HR (0.8 X HR Max)

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	Control	Length(mm)	Width(mm)	Mean(mm)	Erythema
1.	Histamine	7.0	6.0	6.5	(•) Yes ( ) No
2.	Diluent	2.0	2.0	2.0	( ) Yes (•) No

(I)	Aerosensitization	Length(mm)	Width(mm)	Mean(mm)	Erythema
1.	House Dust Mite Mix	5.0	5.0	5.0	(•) Yes ( ) No
2.	Cockroach Mix	2.0	2.0	2.0	( ) Yes (•) No
3.	Cat Hair (10,000 BAU/ml)	0	0	0	( ) Yes (•) No
4.	Dog epithelia	0	0	0	( ) Yes (•) No
5.	Blomia Tropicalis	5.0	4.0	4.5	(•) Yes ( ) No
6.	Kapok Seeds	0	0	0	( ) Yes (•) No
7.	Oil Palm	0	0	0	( ) Yes (•) No
8.	Alternaria	2.0	2.0	2.0	( ) Yes (•) No
9.	Curvaluria	0	0	0	( ) Yes (•) No
10.	Cladosporium	0	0	0	( ) Yes (•) No
11.	Aspergillosis	0	0	0	( ) Yes (•) No
12.	Candida	2.0	2.0	2.0	( ) Yes (•) No
13.	Penicillium	0	0	0	( ) Yes (•) No

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Case Study

- Started on low dose ICS (budesonide 200mcg/day)
- Improved after 3 weeks of use
- Patient tried stopping on her own
  - Symptoms recurred (though not as bad as previously)
- Reinforced adherence

THANK YOU