Bronchial **H**yper**R**esponsiveness (BHR)
and
Bronchial **P**rovocation **T**ests (BPT)
or Bronchial Challenge Tests (BCT)

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Overview of presentation

- Definition of BHR: what is it?
  - Direct vs indirect; specific vs nonspecific BHR
- How to measure nsBHR: direct BPTs
  - Histamine vs methacholine; PC vs PD methods
  - Patient preparation
  - Interpretation of results
- Clinical use of BPT: what does it tell us?
- Exercise-induced bronchoconstriction
  - Indirect BPTs used for diagnosis of EIBC

BHR: definition

- BHR is a subject's tendency or characteristic to develop an increased or exaggerated airway narrowing response when exposed to various stimuli

- BPTs (or BCTs) measure this quantified response to a quantified stimulus

BHR: definition

- BHR is a subject's tendency or characteristic to develop an increased or exaggerated airway narrowing response when exposed to various stimuli

- Airway narrowing response
  - Bronchoconstriction (BSM contraction): direct BHR
    - early, transient
  - Inflammatory airway wall thickening: indirect BHR
    - late, persistent

BHR: definition

Stimulus acts on effector cells

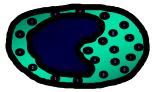
Bronchial smooth muscle cells

Endothelial cells

Mucus producing cells

Direct BHR

Stimulus acts on intermediary cells



Inflammatory cells

(mast cells)

Neuronal cells

Epithelial cells

Indirect BHR

BHR: definition

- BHR is a subject's tendency or characteristic to develop an increased or exaggerated airway narrowing response when exposed to various stimuli

- Various stimuli
  - Sensitising agents : cause specific (and indirect) BHR
    - allergens, occupational agents or drugs
  - Non-sensitising (non-allergic) stimuli: cause non-specific (direct or indirect) BHR
    - Direct: pharmacologic agents such as histamine, methacholine
    - Indirect: physical or physicochemical stimuli such as exercise, hyperventilation or inhalation of non-isotonic solutions

BHR: stimuli

- Specific
- Nonspecific

- Direct
- Indirect

- Specific
  - Indirect
- Nonspecific
  - Direct
  - Indirect

BHR: stimuli

	Direct	Indirect
Specific		Inhaled substance Allergen (occupational) Drug (a.o. aspirine, NSAID)
Nonspecific	Inhaled substance Histamine Cholinergic agent (methacholine, acetylcholine, carbachol) Prostaglandins Leukotrienes	Inhaled substance Adenosine, neuropeptides, β-blocker, metabisulphite, SO_2, ozone Endotoxin, PAF Physicochemical stimulus - Airway cooling & drying (exercise, EVH) - Non-isotonic aerosols (mannitol, hypertonic saline, distilled water)

SIC: methodology (1)

Sham procedure and specific challenge on 2 consecutive days

- Sham challenge: exposure to a similarly looking but non-sensitising substance (e.g., lactose powder, non-latex gloves, pinewood dust)
- Specific challenge: with the suspected workplace agent
- SIC is only possible when a specific workplace agent has been identified

'Realistic' testing, exactly mimicking the conditions at work

Sufficiently long total (cumulative) exposure (2-4 hrs)

- Progressive increase in duration of serial exposures (1', 5', 10', 15', 30', 60')
- Especially in workers removed from the workplace for long times

SIC: methodology (2)

Measurement of FEV_1 after each step and hourly for 6-8 hrs after end of exposure (detection of early, isolated late or dual reactions)

- Reproducible fall in FEV1 by at least 20% of baseline on 2 consecutive measurements

Measurement of NSBHR before (i.e. after sham-) and after specific challenge

- Significant decrease in PC_{20} or PD_{20} by at least 2 dilutions
- Return to baseline 1 month after the specific challenge

PEF self-monitoring until bed time (overnight stay in hospital)

Occupational agents*: 265 specific BPTs in UZ Brussel

Agents/Allergens	#	% total
LATEX	87	33
FARINOSE (bloem, α-amylase)	70	26
PERSULFATEN	18	7
DIEREN	18	7
HOUT	14	5
LIJM	6	2
ZETMEEL (smetpoeder, maïs, rijstkoeken)	6	2
KOELOLIE (SARTCUT e9)	5	2
PLANTEN (tomaat, suikerbiet, taxus)	4	2
VOEDINGSWAREN (vis, vruchten, eierpoeder, melkproteïne)	4	2
VEEVOEDERS	3	1
SOLDEERDAMPEN/LASSEN	3	1
ENZYMEN (Econase, Flaviatiase, transglutaminase)	3	1

*Excluding isocyanates

Top5 accounts for 78% of all specific BPTs performed

nsBPT: direct *vs.* indirect BHR

- Poor correlation between
  - direct BHR (to histamine or methacholine) and
  - indirect BHR (to exercise, non-isotonic solutions, propranolol, adenosine, bradykinin or neurokinin A)
- Indirect BHR (especially induced by physical stimuli)
  - probably correlates better with day to day symptoms in asthma than direct BHR (reason for false-negative results)
  - are less sensitive but more specific for asthma
- BPTs measuring direct BHR to pharmacologic agents (histamine or methacholine) are easier to standardise, quantify and perform

nsBPT: methodology

- Inhalation methods
  - 2’ tidal breathing method: PC method
    - Cockroft DW et al. Clin Allergy 1977; 7: 235-43
    - Hargreave FE et al. JACI 1981; 68: 347-55
  - 5xIC-breath dosimeter method: PD methods
    - Chai H et al. JACI 1975; 56: 323-7
    - Sterk PJ et al. Eur Respir J 1993; 6(Suppl 16): 53-83
    - Yan K et al. Thorax 1983; 38: 55-61. (for epidemiologic research)

nsBPT: PC vs PD method

- Both methods yield similar results*
  - Same levels of BHR
  - Same reproducibility of responses
  - Same variation in deposited dose

Ryan G et al. Am Rev Respir Dis 1981; 123: 195-9 (review).
Asher MI et al. Ann Allergy 1983; 50: 389-92 (histamine, children).
Beaupre A et al. Clin Allergy 1979; 9: 575-83 (histamine).
Britton J et al. Thorax 1986; 41: 128-32 (histamine).
Knox AJ et al. Eur Respir J 1991; 4: 497-502 (methacholine).

nsBPT: histamine vs methacholine

- Good correlation between BHR to histamine and BHR to methacholine (for PC_{20} method)*
  - Bennett JB et al. Br J Dis Chest 1987; 81: 252-9.
  - Peat JK et al. Am Rev Respir Dis 1991; 144: 338-43.
  - Bhagat RG et al. Am Rev Respir Dis 1984; 129: 221-4.
  - Toelle BG et al. Eur Respir J 1994; 7: 1798-1804.
- Histamine BHR results less reproducible
  - Juniper EF et al. Thorax 1978; 33: 705-10.
  - Chatham M et al. Am Rev Respir Dis 1982; 126: 235-40.
  - Higgins BG et al. Thorax 1988; 43: 605-10.
- More systemic side-effects with histamine

* PD_{20} slightly lower for histamine than for methacholine (in children):
LeSouëf PN. Lancet 1992; 339: 1282-4 and
Peat JK et al. Am Rev Respir Dis 1991; 144: 338-43.

nsBPT: precautions for PFT-tech's

- Tech should not have active asthma or BHR
- Fume hood and/or well ventilated testing room
  - > 2 complete room air exchanges/hr
- Low-resistance exhalation filters
- Exposure is lower with dosimeter method
- Stand well away from patient during nebulisation

Shapiro et al. JACI 1992; 89: 775-8:
20% of PFT-technicians reported symptoms

nsBPT: precautions for patients

- Baseline FEV_1 > 60% P
- Gradual increase in dose or concentration
  - Limitation of airway narrowing, V/Q mismatching and arterial hypoxemia
- Medical staff member in vicinity
- Emergency/rescue medication available
  - O_2
  - Inhaled SABA +/- SAAC (nebulizer or pMDI + spacer)
  - Parenteral bronchodilators (SC epinephrine, IV salbutamol)

nsBPT: preparation of patient

- Informed consent?
- Evaluate patient for contraindications

nsBPT: contraindications

- Absolute
  - Severe airflow limitation (FEV_1 < 50% P or < 1-1.2 L)
  - AMI or CVA < 3 mo
  - Uncontrolled AHT (> 200/100 mmHg)
  - Known aortic or cerebral aneurysm
  - Inability to understand the procedure
  - Pregnancy and nursing mothers

nsBPT: contraindications

- Relative
  - Moderate airflow limitation (FEV_1 < 60 %P or < 1.5-2 L or < P-3 SD or P-1.5 L in M and P-1.2 L in F)
  - Spirometry-induced airway obstruction
  - Recent (< 4 weeks) URT infection/cold
  - Recent asthma exacerbation
  - Epilepsy requiring drug treatment
  - Inability to perform acceptable-quality spirometry
  - Use of cholinesterase inhibitor treatment (for MG)

nsBPT: preparation of patient

- Informed consent?
- Evaluate patient for contraindications
- Review and note medication used

BPT: duration of drug withdrawal (to avoid false negative results)

Inhaled SABA	8 h
Inhaled LABA	48 h
Oral BA	12-24 h
SAAC	12-24 h
LAAC (tiotropium)	48 h – 1 wk
Oral LA theophylline	12-48 h
Inhaled DSCG	8 h – 1 wk
Inhaled steroid	12 h – 2 wk
Oral LTR-a	1-4 d
Oral antihistaminic	4 d – 6 wk
Caffeine (coffee, tea, cola, chocolate, 'energy' drinks)	Day of test

nsBPT: preparation of patient

- Informed consent?
- Evaluate patient for contraindications
- Review and note medication used
- Explain test to the patient
  - (Nonspecific) BPTs are safe
  - Warn for (usually minor) symptoms, but
  - Avoid stating that the test induces an 'asthma attack'

nsBPT: side-effects

- Early bronchoconstriction:
  - cough (in 25%)
  - dyspnea (in 21%)
  - wheezing (in 10%)
- Delayed or prolonged responses: extremely rare
- Extrapulmonary side-effects: more frequent with histamine than with methacholine
  - Dizziness (in 6%)
  - Headache (in 2%)
  - Flushing

Tashkin DP et al. Am Rev Respir Dis 1992; 145: 301-10

In case nsBPT reveals BHR

- Never leave patient unattended
- Note symptoms (Borg or VAS scale) & clinical signs
- Administer inhaled F/SABA (salbutamol)
- Redo spirometry after 10 min
- Patient should not leave PFT lab before post-BD FEV_1 > 90% B
- Provide instructions in case of relapse of symptoms during the next 24 hrs

nsBPT: measured response: measures of airway narrowing

- Tests needing a maximal inspiration
  - FEV_1 , PEF and FVC
  - Easier to perform and more reproducible
  - Maximal inspiration may cause either BD (in normals or mild asthma) or BC (in more severe asthma)
  - PEF effort-dependent, less reproducible and less sensitive
- Tests not needing a maximal inspiration
  - sR_{aw} , sG_{aw} and Vp30 (maximal flow at 30% VC using a partial FV curve)
  - More sensitive but less reproducible

nsBPT: measured response: measures of airway narrowing

- $PC_{20}FEV_1$ or $PD_{20}FEV_1$
  - Concentration or cumulative dose causing a 20% reduction in FEV_1*
- $PC_{35}sG_{aw}$ or $PD_{35}sG_{aw}$
  - Concentration or cumulative dose causing a 35% reduction in sG_{aw}*

* as compared to baseline or post-diluent value

Categorization of BR
according to ATS 1999

$PC_{20}FEV_1$ (mg/ml)	Interpretation
> 8 or 16	Normal BR: excludes asthma if prior probability of asthma is 30-70%
4-16	Borderline BHR or 'grey zone'
< 4	BHR
1-4	Mild BHR
< 1	Moderate-severe BHR: confirms asthma if prior probability of asthma is 30-70%

Positive nsBPT

	$PC_{20}FEV_1$ Normal > 8 mg/mL	$PD_{20}FEV_1$ Normal > 7.8 µmol (1.6 mg)
Not on iCS (or < 3 months)	< 4 mg/mL	< 0.8 mg < 4 µmol
On iCS (for ≥ 3 months)	< 16 mg/mL	< 3.2 mg < 16 µmol

Positive nsBPT
according to IOC-MC

	$PC_{20}FEV_1$ Normal > 8 mg/mL	$PD_{20}FEV_1$ Normal > 7.8 µmol (1.6 mg)
Not on iCS (or < 1-3 months)	≤ 4 mg/mL	≤ 0.4 mg (≤ 2 µmol) CD ≤ 0.2 mg nonCD
On iCS (for ≥ 1-3 months)	≤ 13.2 mg/mL ≤ 16 mg/mL	≤ 1.32 mg (≤ 6.6 µmol) CD ≤ 1.6 mg CD ≤ 0.8 mg nonCD

CD = cumulative dose

nsBPT: indications

- Clinical reasons
  - Diagnosis of asthma, including occupational asthma
    - In patients with suspected asthma but normal PFTs
    - Evidence-based surrogate for airway inflammation
  - Evaluation of persistent cough (cough-variant asthma)
  - Assessment of the severity and prognosis of asthma
    - Degree of BHR may predict the effect of treatment (with iCS)
  - Follow-up or monitoring of asthma: assessment of effectiveness of therapy
    - Negative test in asthmatic = good control of asthma
    - Positive test = currently active airway inflammation
- Research purposes
  - Evaluation of (new) treatments for asthma

nsBHR: differential diagnosis

- Asthma
- Smoking and COPD
  - Identification of COPD patients with significant inflammatory component to their disease
  - Confident prescription of appropriate medication.
- Cystic fibrosis
- Bronchitis and bronchiolitis
- Allergic rhinitis
- Recent (viral) URT infection: transient BHR
- Recent exposure to air pollutants, irritants
- Sarcoidosis
- Left heart failure

nsBPT

- Sensitivity & NPV > specificity & PPV
  - More useful in excluding asthma than in diagnosing it
- BHR may vary over time
  - Increases during exacerbations
  - Decreases during anti-inflammatory treatment

Factors increasing nsBHR (false positive results)

Factor	Duration of effect
Exposure to environmental allergens	1-3 wk
Occupational sensitisers	Months
Respiratory infection	3-6 wk
Air pollutants	1 wk
Cigarette smoke	6 hrs
Chemical irritants	Days-months
Exercise	6 hrs

Effect of medication on nsBHR (false negative results)

Drug	Acute administration	Long-term treatment	Withdrawal after long-term treatment
iSABA	reduction	no change	transient increase
iSAAC	?reduction		transient increase
Theophylline	reduction	no change	
DSCG	no change	?reduction	
iGCS	?small reduction	reduction	

Exercise-induced bronchoconstriction (EIBC)

- Transient asthma symptoms occurring (during or) after (vigorous) exercise
- Occurs in 90% of asthma patients
- Occurs in 10 – 50% of athletes without asthma, especially those engaging in
  - Endurance sports
  - Winter sports
  - Swimming pool sports

Pathophysiology of EIBC

- Due to exercise-related hyperventilation
  - Thermal effect
    - Airway cooling leads to vagal stimulation and vascular engorgement
  - Osmotic effect
    - Airway drying with increased osmolarity of surface lining fluid leads to inflammatory cell activation (mast cells ao.) and mediator release (histamine, LT, ao.)

Diagnosis of EIBC

- Symptoms
- Pulmonary function tests
  - Spirometry and bronchodilator test during symptoms
- Bronchial provocation tests

Diagnosis of EIBC
Recommended rank order (IOC-MC)

- Symptoms (during and) after X
- PFT
  - Spirometry with BDT during symptoms
  - Showing reversible obstruction
- If no obstruction: do BPT to demonstrate nsBHR
  - 'Direct' (histamine *or* methacholine) BPT:
    - However, poor sensitivity for EIBC (negative test does not exclude EIBC)
  - 'Indirect' BPTs: are preferred
    - Positive EVH test
    - Positive hyperosmolar aerosol BPT (hypertonic saline or mannitol)
    - Positive (field or lab) exercise BPT

Diagnostic methods and positivity criteria set by the IOC to document EIBC in athletes (1)

Method	Protocol	Positivity criteria
Bronchodilatation test	FEV_1 before and 15' after inhalation of a standard β_2-agonist	$\Delta FEV_1 \geq +$ 200 mL and $\geq +$ 12 % P
Methacholine BPT	Provocative dose (PD_{20}) or concentration (PC_{20}) of inhaled methacholine inducing an FEV_1 decrease from baseline $\geq$ 20 %	$PC_{20} \leq$ 4 mg/mL or $PD_{20} \leq$ 0.4 mg (cumulative dose), or $\leq$ 0.2 mg (noncumulative dose) in those not taking iCS $PC_{20} \leq$ 16 mg/mL or $PD_{20} \leq$ 1.6 mg (cumulative dose) or $\leq$ 0.8 mg (noncumulative dose) in those taking iCS for at least 1 month

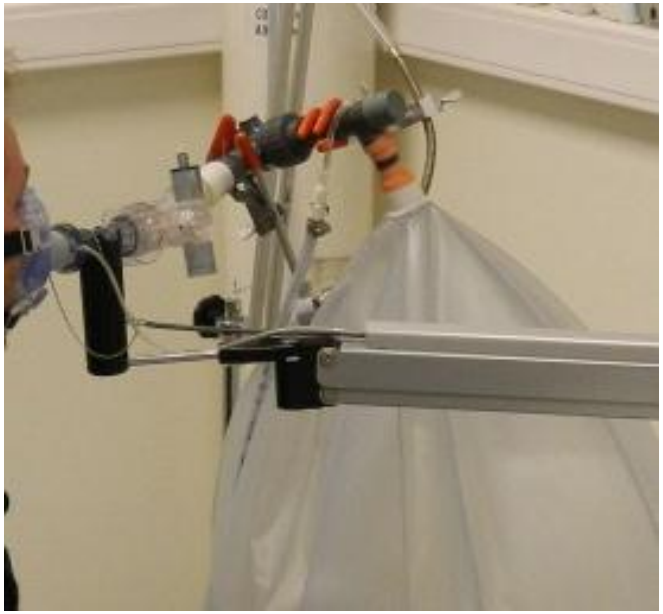
Diagnostic methods and positivity criteria set by the IOC to document EIBC in athletes (2)

Method	Protocol	Positivity criteria
Eucapnic voluntary hyperpnea	FEV_1 before and within 30' of 6' dry (or dry and cool) air inhalation at 85 % of predicted MVV	$\Delta FEV_1 \geq$ - 10 % baseline
Hypertonic saline inhalation	FEV_1 before and after inhaling 22,5 mL of 4,5 % NaCl	$\Delta FEV_1 \geq$ - 15 % baseline
Mannitol inhalation	Provocative dose of inhaled mannitol inducing a $\Delta FEV_1 \geq$ - 15 % baseline (PD_{15M})	$PD_{15M} \leq$ 635 mg of mannitol
Exercise challenge (field or laboratory)	FEV_1 before and within 30' after X-challenge achieving a F_c > 85 % for at least 4'	$\Delta FEV_1 \geq$ - 10 % baseline

Indirect nsBPTs: EVH test

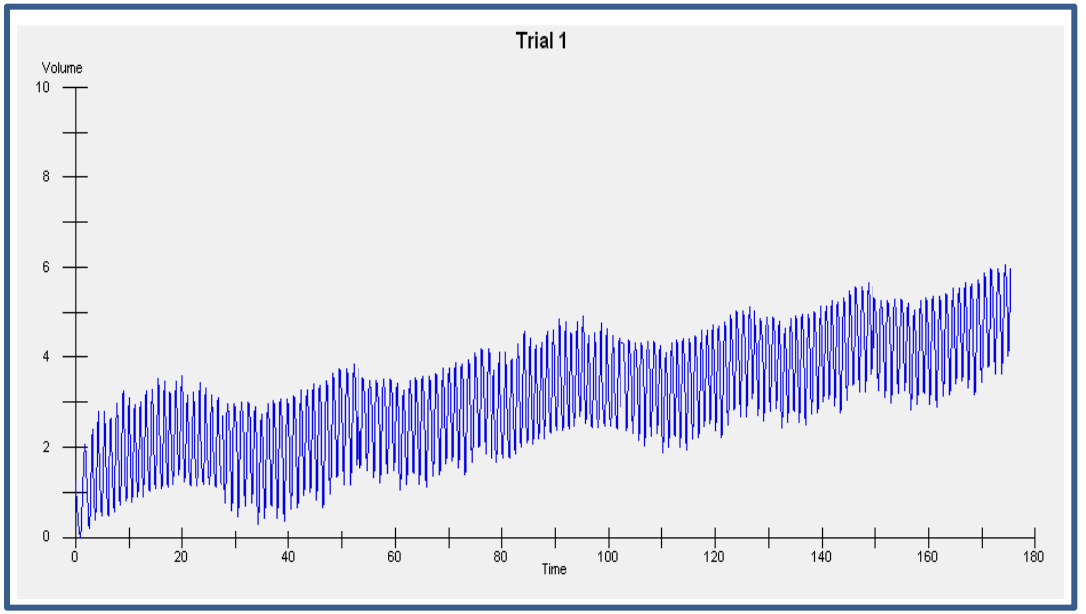
- Eucapnic Voluntary Hyperpnea test
  - Minute Ventilation: 30 x FEV_1 (75% MVV)
  - Duration: 6’
  - Dry gas mixture containing
    - 5% CO_2 in 21% O_2 and 74% N_2
    - at room T° (can be cooled)
  - Measurement of FEV_1 at 0’, 5’, 10’, 15’ and 20’ after the 6’ of EVH
  - Positive test: ΔFEV_1 > -10%B within 20’

Eucapnic Voluntary Hyperpnea (EVH) test



FEV_1 = 4.07 L (102 %P)
Target V_E = 4.07 x 30 = 122 L
V_t = 2.03 L
RR = 61/min
Test = 2.03 x 61 = 123.8 L/min
6 min = 5% CO_2 + 95% air at room T°

Positive test = FEV_1 drop > 10% from baseline within next 20 min.



Indirect nsBPTs: EVH test

- Feasable: athletes can maintain the required high minute ventilation
- Very reproducible
- Highly sensitive
- Safe
- Recommended test by IOC-MC

Thank you for listening

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