The Latest Trends in Asthma Research

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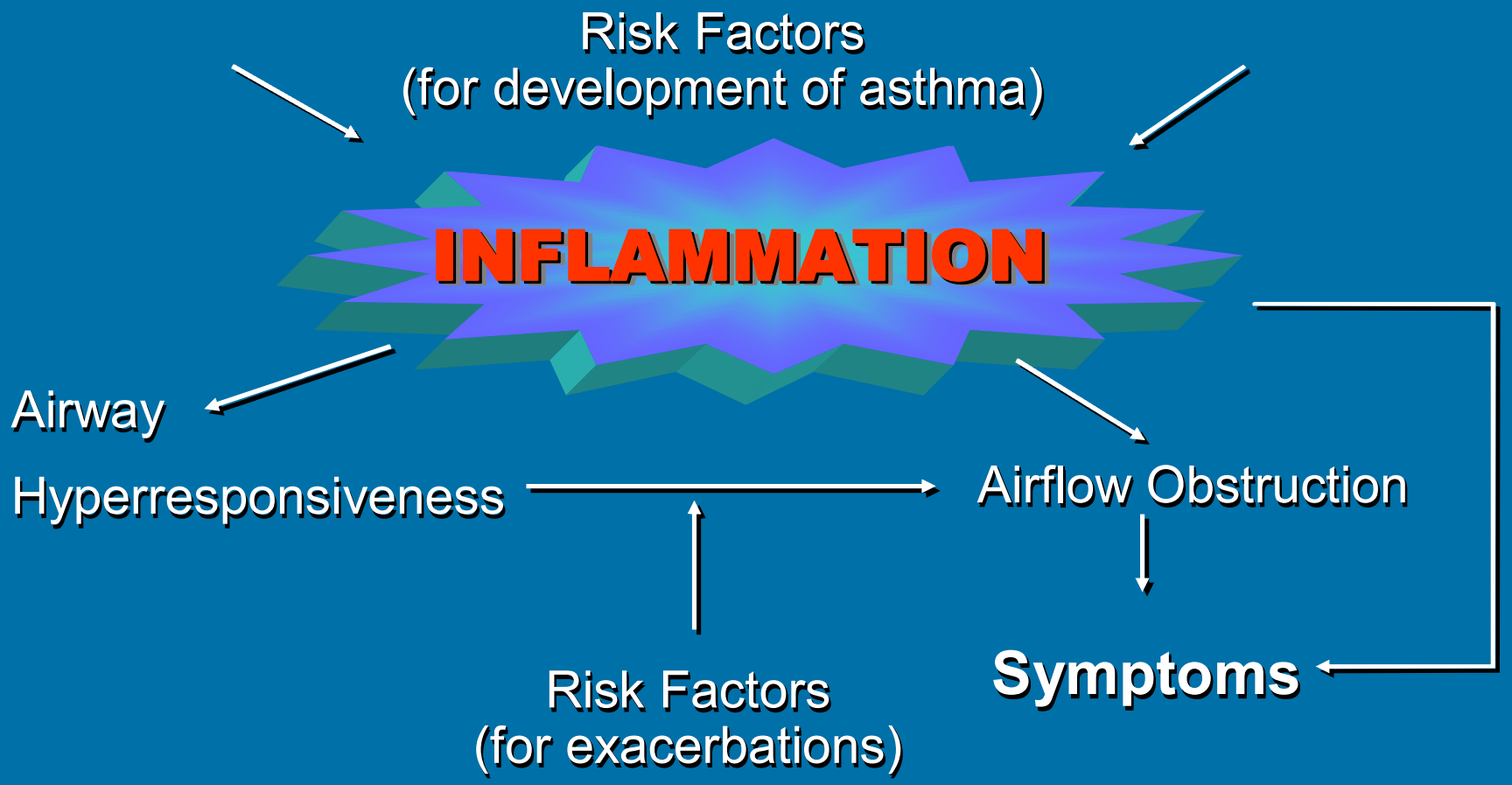
Asthma monitoring – routine approach:

- Asthma symptoms
  - Daytime
  - Nighttime
- Rescue medication need
- Objective measurements
  - Spirometry
  - PEFR monitoring

Mechanisms Underlying the Definition of Asthma



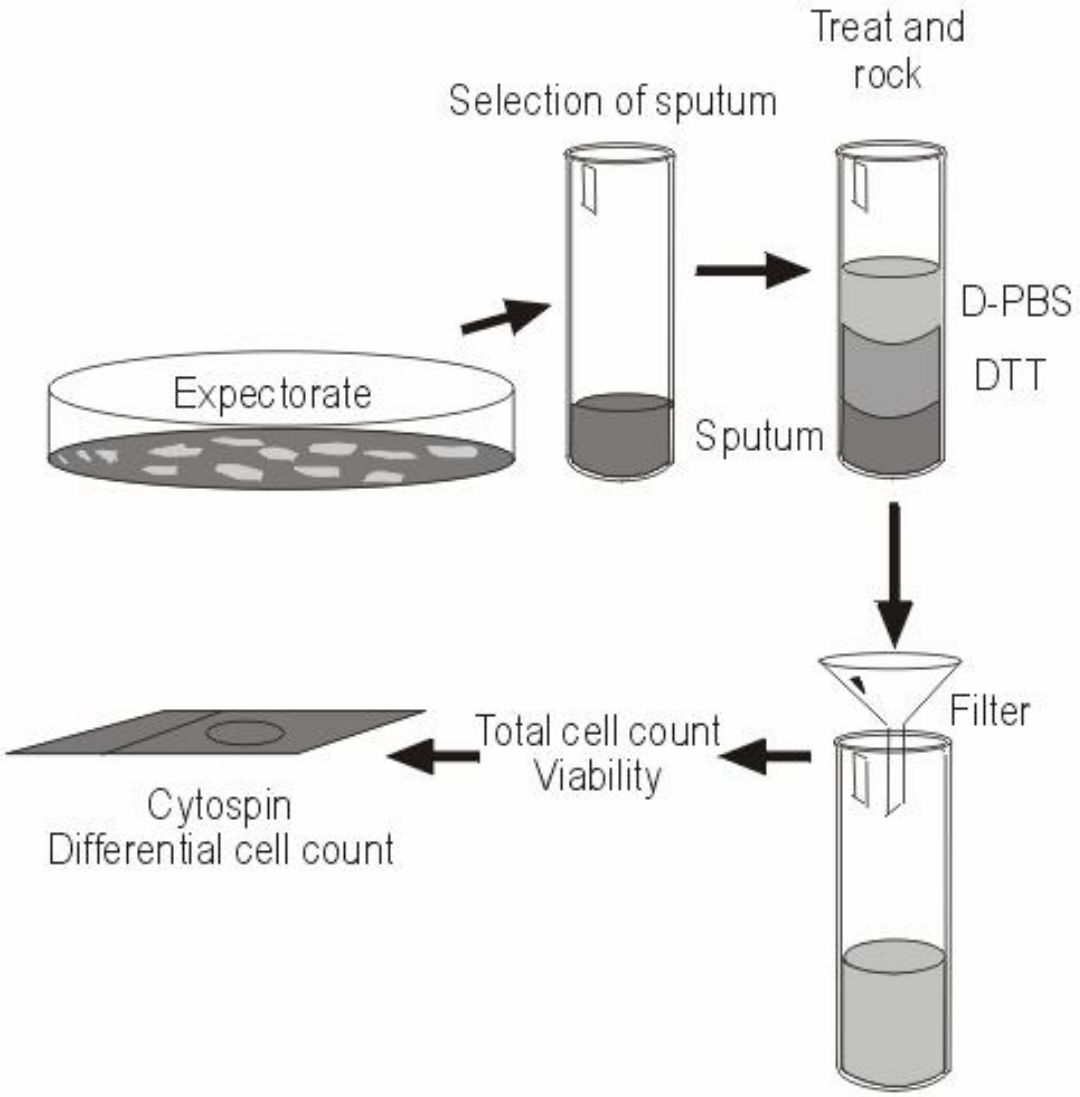
Classification of methods for assessment of inflammation in asthma

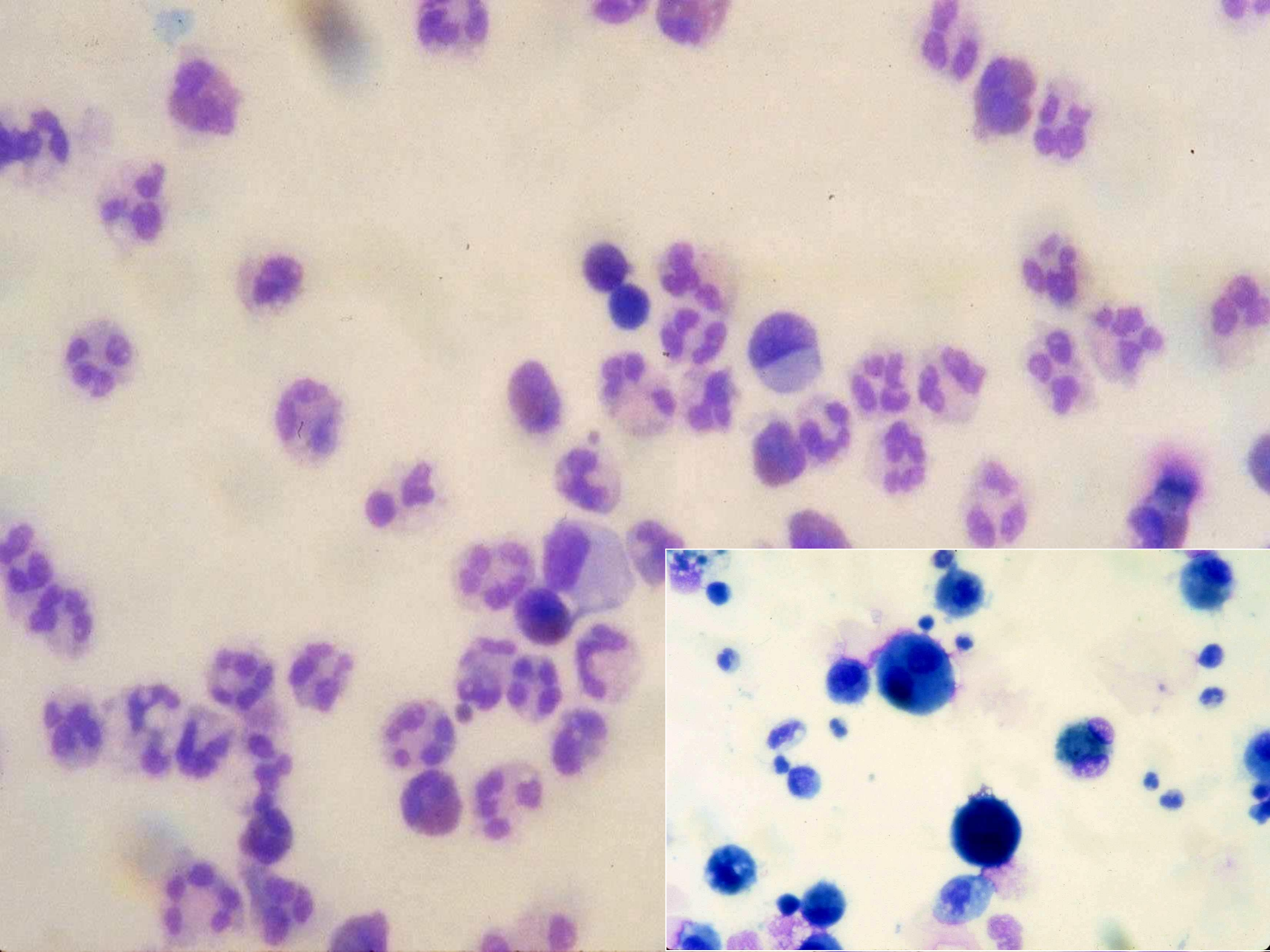
1	**Direct**	Invasive	**Bronchial biopsy** **Bronchoalveolar lavage**
2	**Moderately direct**	Less invasive	**Induced sputum** **Exhaled nitric oxide** **Breath condensate**
3	**Indirect**	Least invasive	**Blood** **Urine**

Pizzichini et al., 2005

Induced Sputum

Cytospin preparation scheme





Reproducibility:

- Total cell counts
- Differential cell counts
- Immunochemical markers
- Fluid phase components

- *Between portions of the same specimen*
- *Between specimens on consecutive days*
- *Between observers*

Gibson et al., 1989, Pin et al., 1992, Popov et al., 1993

Responsiveness to Interventions:

- Allergen challenge
- Exacerbations
  - Natural
  - Experimental
- Antiinflammatory treatment

Non-responsiveness:

- Hypertonic saline
- Methacholine challenge

Validity:

- Sputum measurements correlate partially with other “gold standards”
- Sputum indices are characteristic of specific disease states
- Sputum examination adds a new dimension to classical features of well known diseases
- Sputum examination helped coin a new concepts like “chronic eosinophylic bronchitis”

Spontaneous vs. Induced Sputum

	Spontaneous sputum	Induced sputum
Cell viability	<	
Squamous cells contamination	>	
Fibrinogen	>	
Quality of slides	<	

Pizzichini et al., 1996

Sputum examination

Advantages:

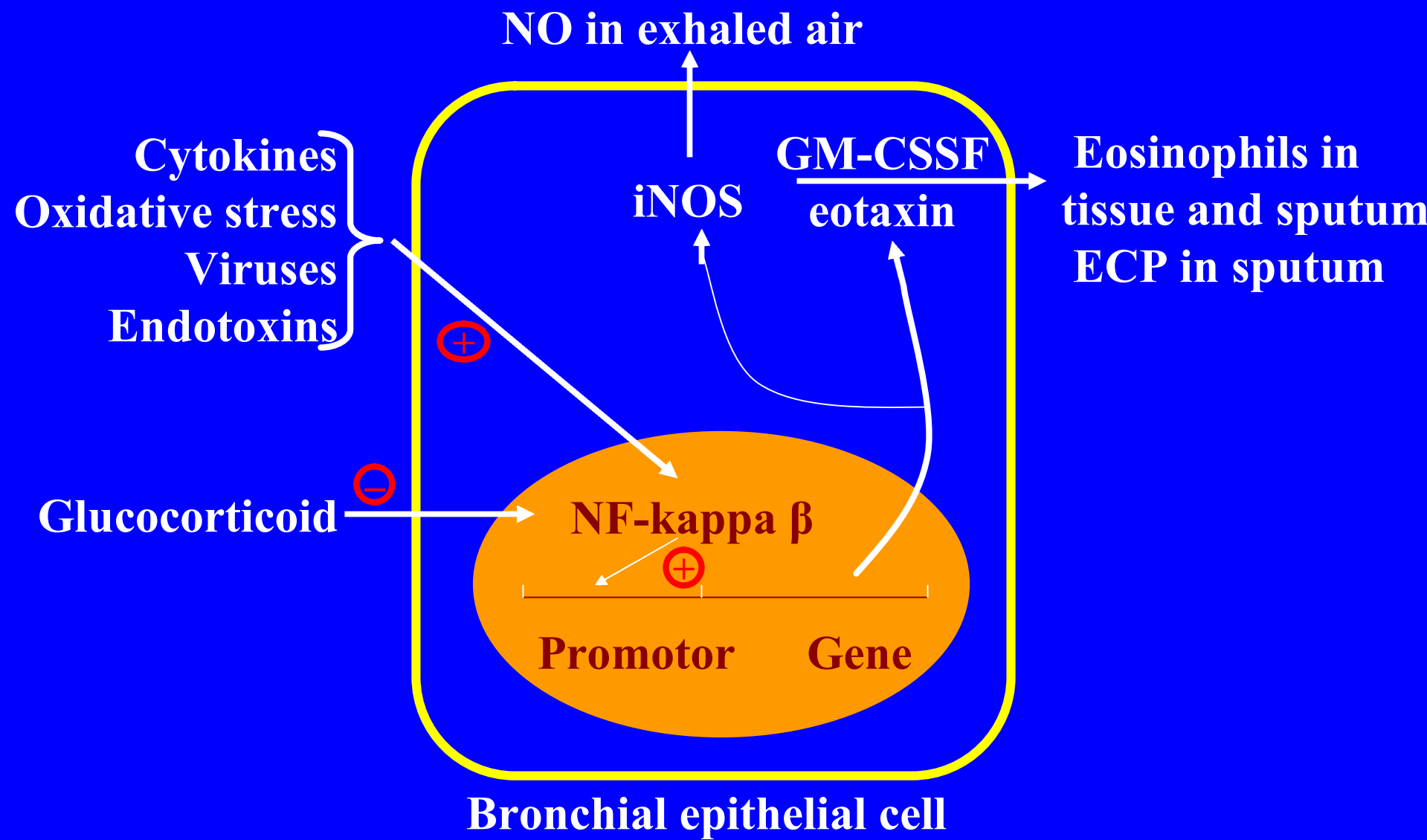
- Safe
- Acceptable to the patients
- Repeated measurements possible
- Possible in severe asthma

Sputum to assess airway inflammation - hurdles along the road:

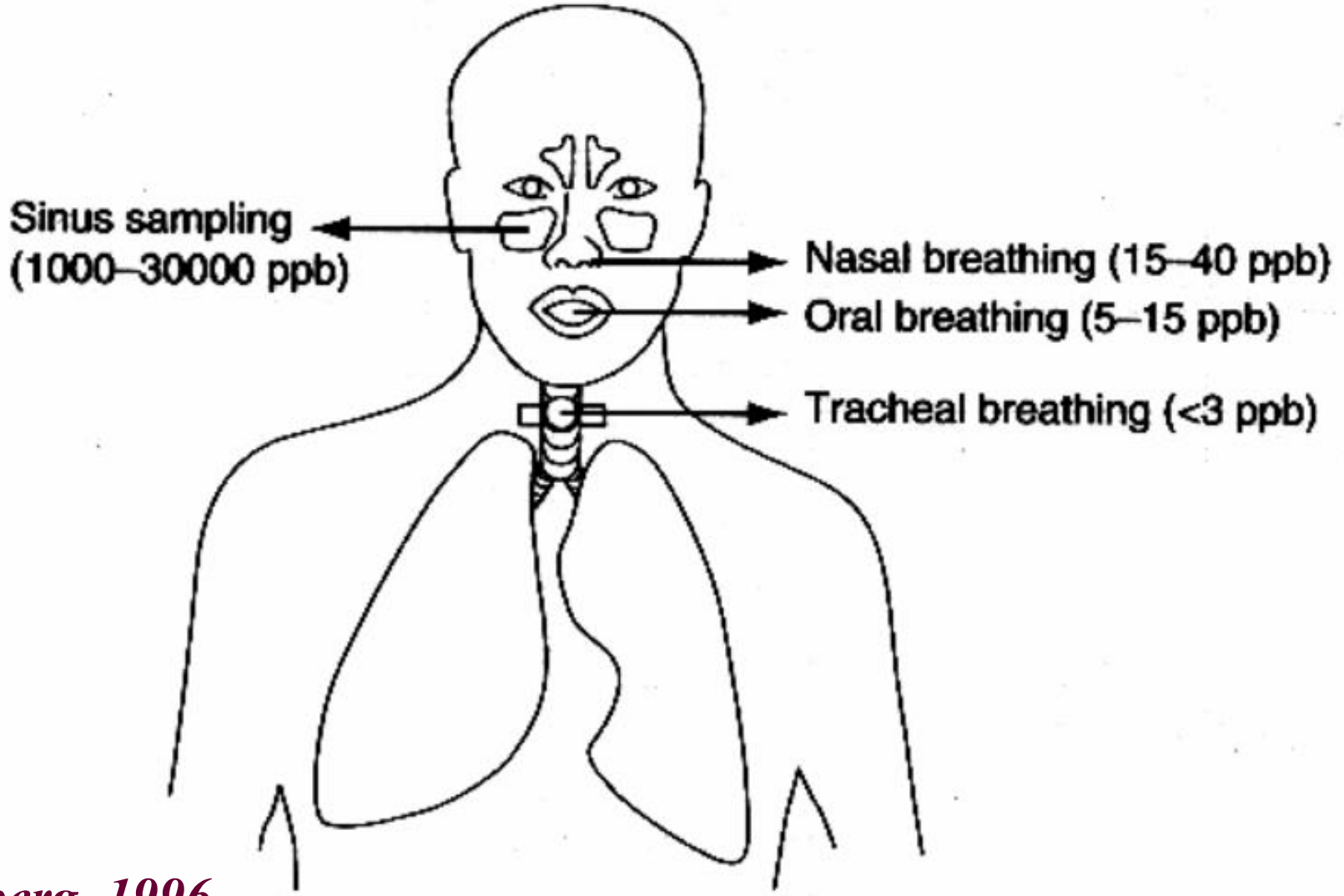
- Time consuming protocol
- Fixed coupling of sputum processing to the time-point of sputum collection
- Inability of all subjects to cough out sputum

Exhaled nitric oxide

Mechanism of NO induction by airway inflammation:



NO production by different parts of the airways



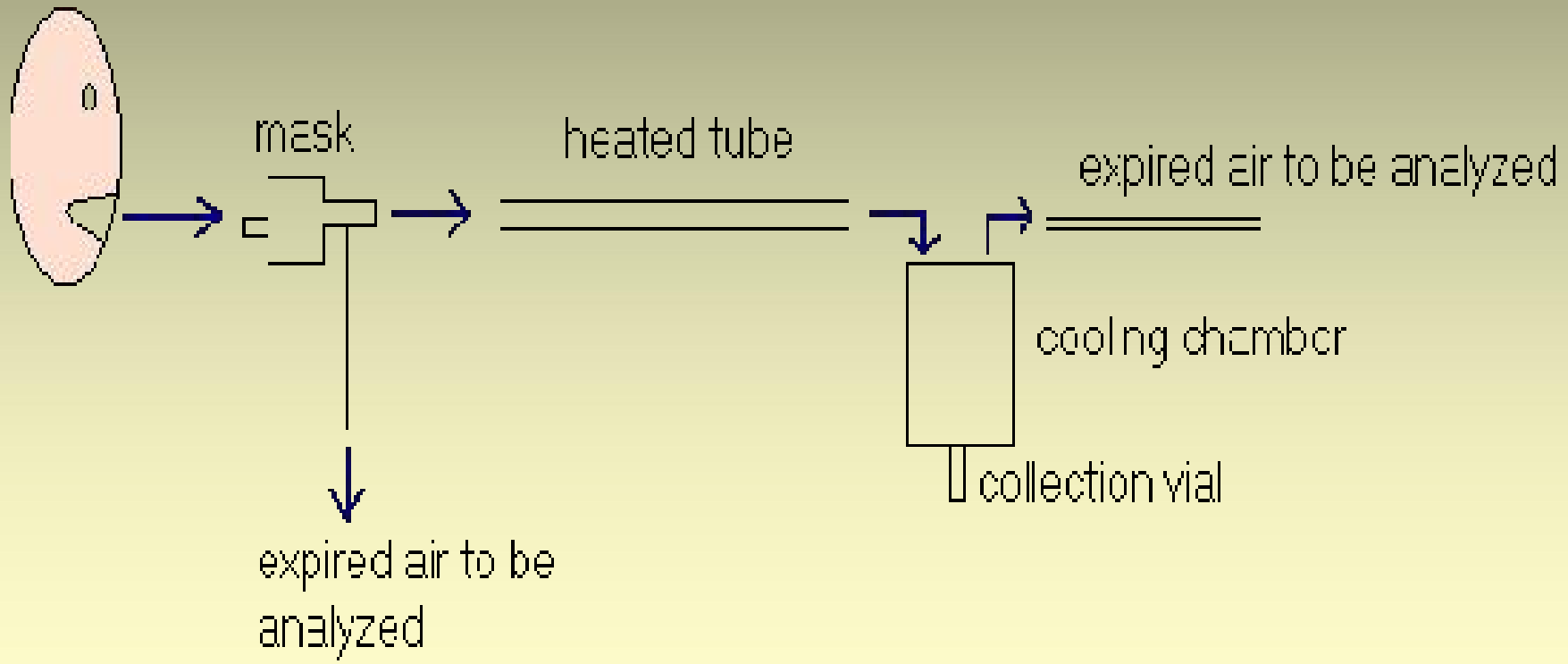
J Lundberg, 1996

Technical problems related to NO measurements

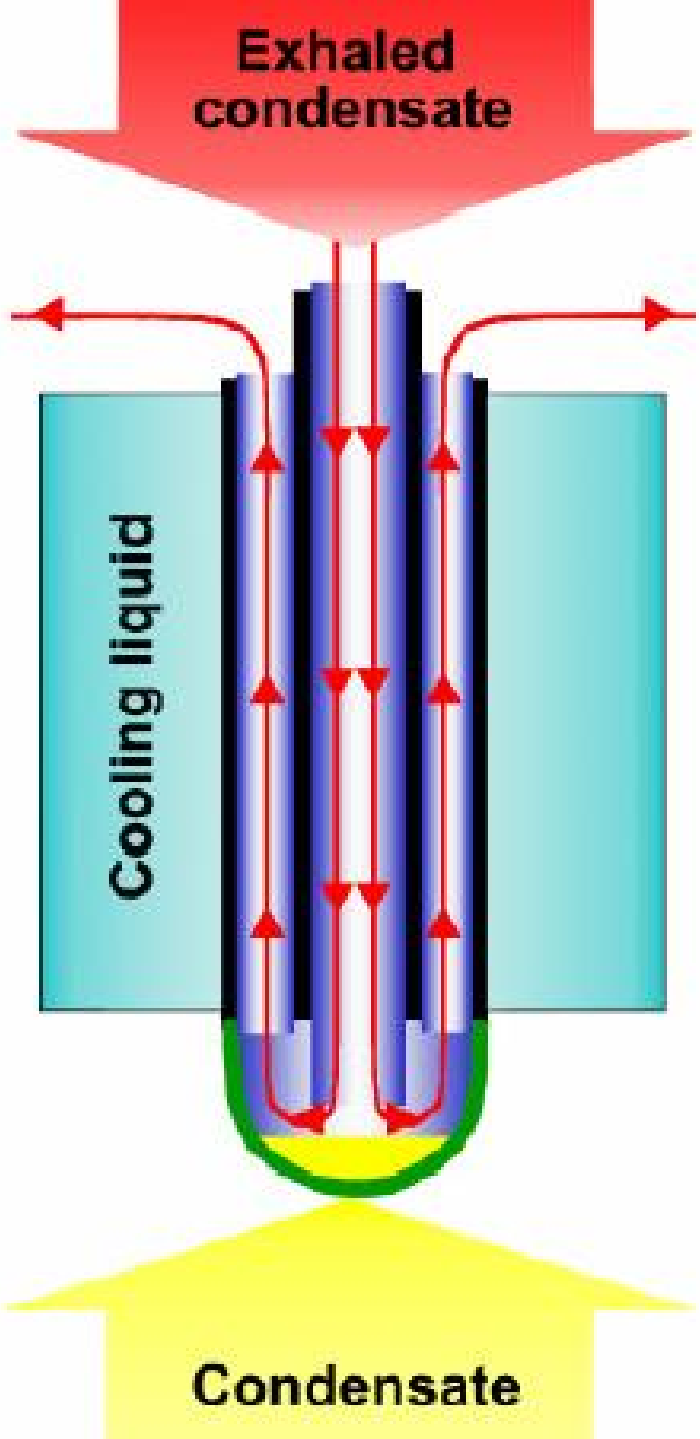
- Results are influenced by:
  - Spirometry (↓)
  - Bronchodilator use (↑)
  - CO2
  - Smoking
  - Exhalation rate
- Nasal gas bias
- Standartization (related to anthropometric measures)

Exhaled Breath Condensate

Scheme of a breath condensate collecting system



Principle of formation of condansate



Breath condensate parameters

Substance	Results
Nitrotyrosine	2 - 25 ng/ml
Isoprostane	5 - 60 pg/ml
Leukotriene B4	<15 - 7520 pg/ml
Leukotrienes CDE4	< 1 - 284 pg/ml
Prostaglandin E2	< 5 - > 1000 pg/ml
H_2O_2	< 0,05 - 1,25 µmol/l
EPX	< 1 - 80,5 ng/ml
Thromboxan B2	< 0,7 - 12,2 pg/ml
Interleukin 8	< 16 - 931 pg/ml
ECP	< 1 . 70,8 pg/ml
Nitrite	< 0,1 - 26,5 µmol/l
Chloride	0,2 - 14 µg/ml
Total protein	0,8 - 51,4 µg/ml
Urea	0,6 - 43,5 µg/ml
Amylase	< 0,1 % sputum

CLINICAL APPLICABILITY OF NON-INVASIVE METHODS

- Prediction of asthma control
- Assessment of drug effectiveness

Global INitiative for Asthma

2006

Levels of asthma control

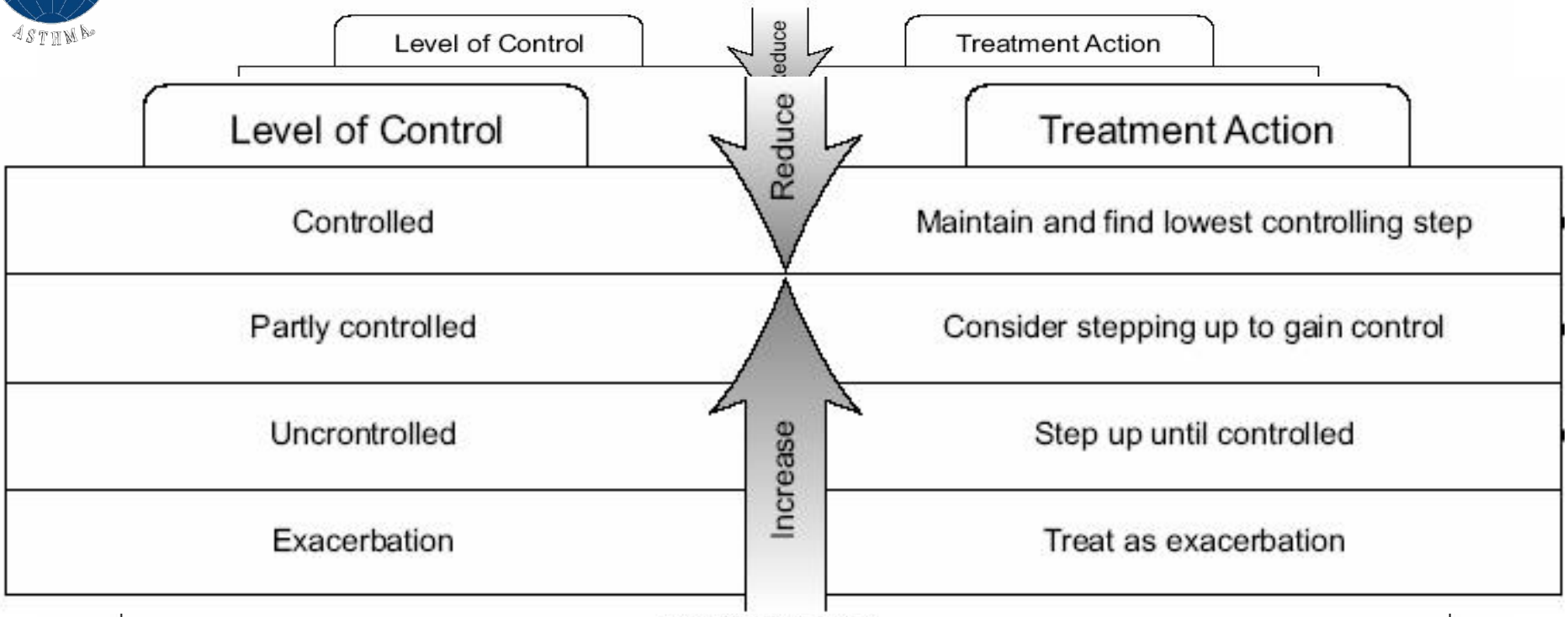
'06

Levels of Asthma Control			
Characteristic	**Controlled (All of the following)**	**Partly Controlled (Any measure present in any week)**	**Uncontrolled**
Daytime symptoms	None (twice or less/week)	More than twice/week	**Three or more features of partly controlled asthma present in any week**
Limitations of activities	None	Any	
Nocturnal symptoms/awakening	None	Any	
Need for reliever/ rescue treatment	None (twice or less/week)	More than twice/week	
Lung function (PEF or FEV_1)‡	Normal	< 80% predicted or personal best (if known)	
Exacerbations	None	One or more/year*	One in any week†

* *Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate.*
† *By definition, an exacerbation in any week makes that an uncontrolled asthma week.*
‡ *Lung function is not a reliable test for children 5 years and younger.*

Management Approach Based On Control

For Children Older Than 5 Years, Adolescents and Adults



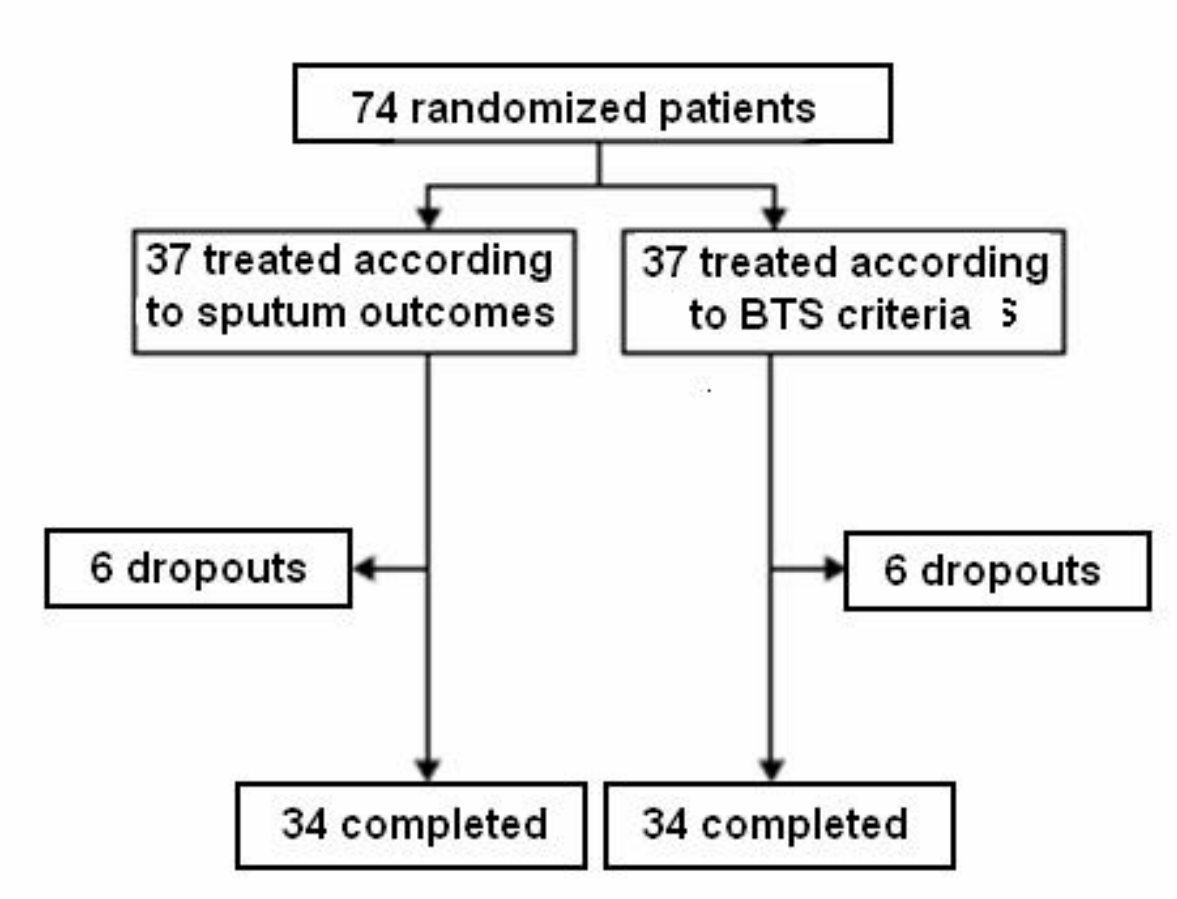
As needed rapid-acting β_2-agonist	As needed rapid-acting β_2-agonist			
Controller options	Select one	Select one	Add one or more	Add one or both
	Low-dose inhaled ICS*	Low-dose ICS plus long-acting β_2-agonist	Medium-or high-dose ICS plus long-acting β_2-agonist	Oral glucocorticosteroid (lowest dose)
	Leukotriene modifier Ü	Medium-or high-dose ICS	Leukotriene modifier	Anti-IgE treatment
		Low-dose ICS plus leukotriene modifier	Sustained release theophylline	
		Low-dose ICS plus sustained release theophylline		

Lancet, 2002;360:1715-1721

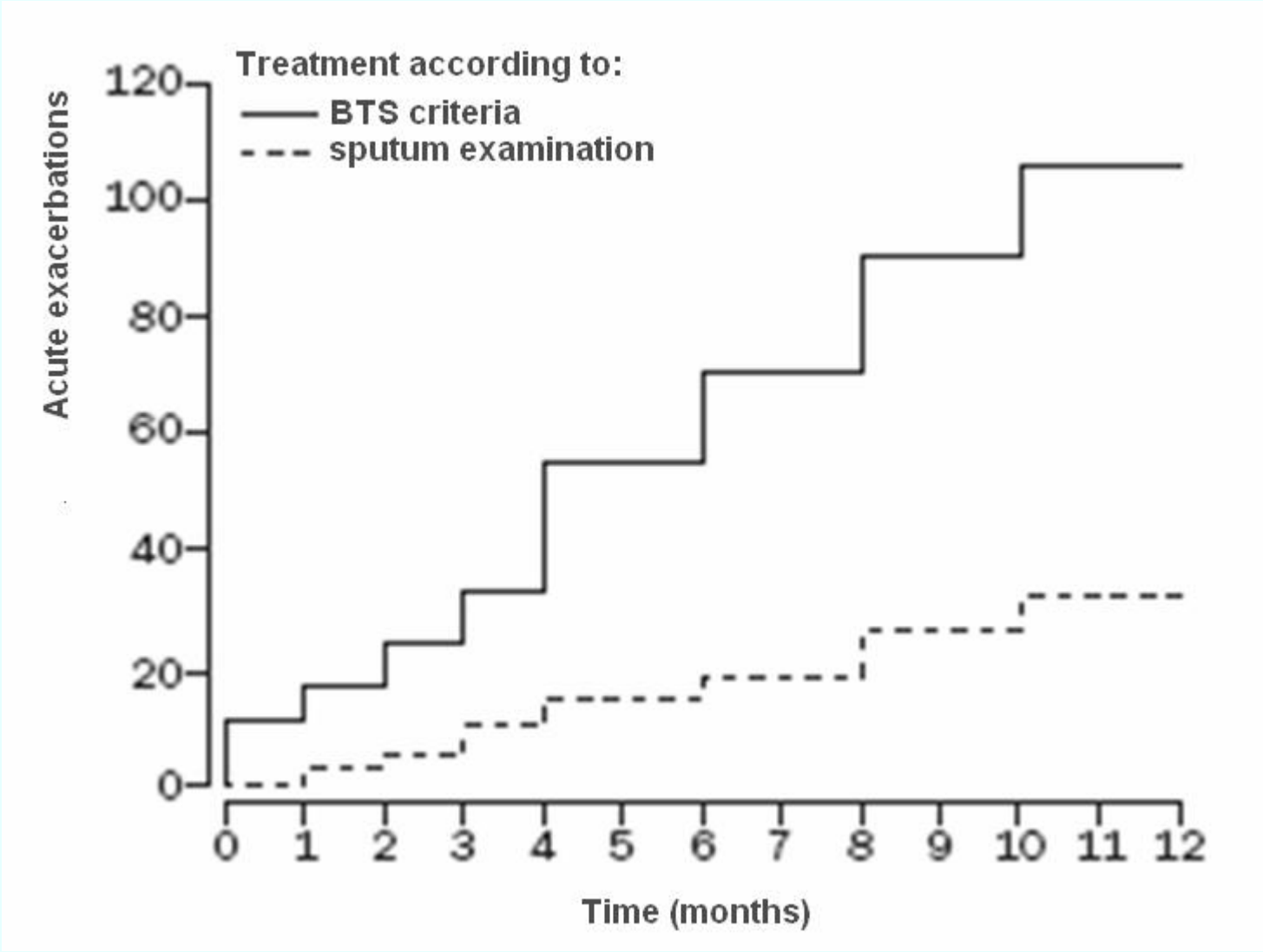
Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial

Ruth H Green, Christopher E Brightling, Susan McKenna, Beverley Hargadon, Debbie Parker, Peter Bradding, Andrew J Wardlaw, Ian D Pavord

Asthma Exacerbations and Sputum Eosinophils: Randomized Controlled Trial



Green R et al. 2002



Green R et al. 2002

Food for thought:

- When will the new non-invasive methods find their place in international guidelines in routine practice?
- Among the new methods: will any of them outweigh the others?
- Will the new methods replace any of the classical approaches for the diagnosis and monitoring of asthma?
- What will be the cost-benefit ratio for the health-care systems?
- Is there still space for “brand new” approaches for monitoring of asthma inflammation?

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745 Measurement of Exhaled Breath Temperature to Assess Changes in Airway Inflammation

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RATIONALE: Inflammation is characterized by increased heat production. Inflamed airways contribute to overall exhaled breath temperature (EBT) which can be detected and is perhaps clinically useful to assess.

METHODS: A simple device to measure EBT tested for reproducibility in 11 healthy controls. The ability to discriminate between healthy controls (n=17) and asthmatics (n=19), and to detect changes in asthma control in 14 asthmatics before and after anti-inflammatory treatment was assessed.

RESULTS: The reproducibility in healthy subjects calculated as intra-class correlation coefficient was 0.99. The reproducibility of atrial and axillary temperatures measured in parallel was much lower, suggesting EBT is a more consistent physiological variable. There was a difference between the exhaled air temperature of asthmatics (34.41 ± 0.27°C) and controls (35.02 ± 0.2°C), but there was considerable overlap (p=0.081). There was also a difference between the exhaled air temperature of asthmatics before (35.33 ± 0.17°C) and after treatment (34.64 ± 0.21°C).

CONCLUSIONS: The EBT device can measure the temperature of exhaled air in human subjects in a simple way. EBT may assist in determining the degree of control of asthmatic airway inflammation.

Funding: Association Asthma

Exhaled breath temperature device (EBTD)

Exhaled Breath Temperature device Study

Aim:

We have developed a device and method to measure exhaled breath temperature and evaluated its repeatability, discriminative capacity to differentiate between asthmatics and non-asthmatics, and ability to assess changes in the asthmatic airways after anti-inflammatory treatment.

Popov TA et al., JACI 2006

Exhaled Breath Temperature device Study

Design:

- Reproducibility in 11 healthy subjects (4 men and 7 women, age range 20 ÷ 65 years) and compared it to their axillary and atrial (ear) temperature.
- Comparison between 17 healthy subjects (5 men and 12 women, age range 20 ÷ 65 years) and 19 outpatients with asthma (8 men and 11 women, age range 17 ÷ 45 years) with different levels of disease severity and control.
- Assessments before and after systemic steroid treatment in 14 asthmatics (6 men and 8 women, age range 17 ÷ 65 years) hospitalized for exacerbations of their asthma

Popov TA et al., JACI 2006

Exhaled Breath Temperature Study

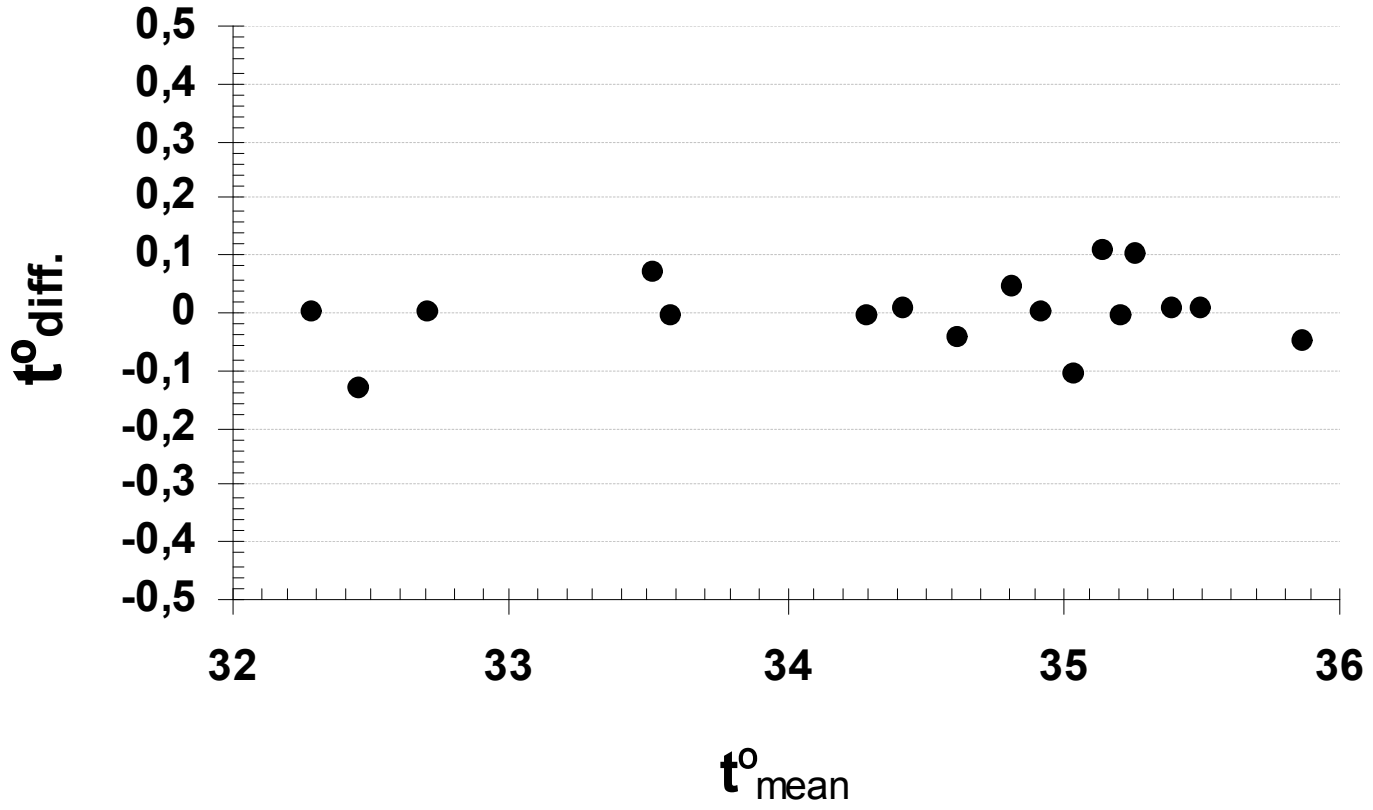
Results 1:

Day-to-day variability of measurements:

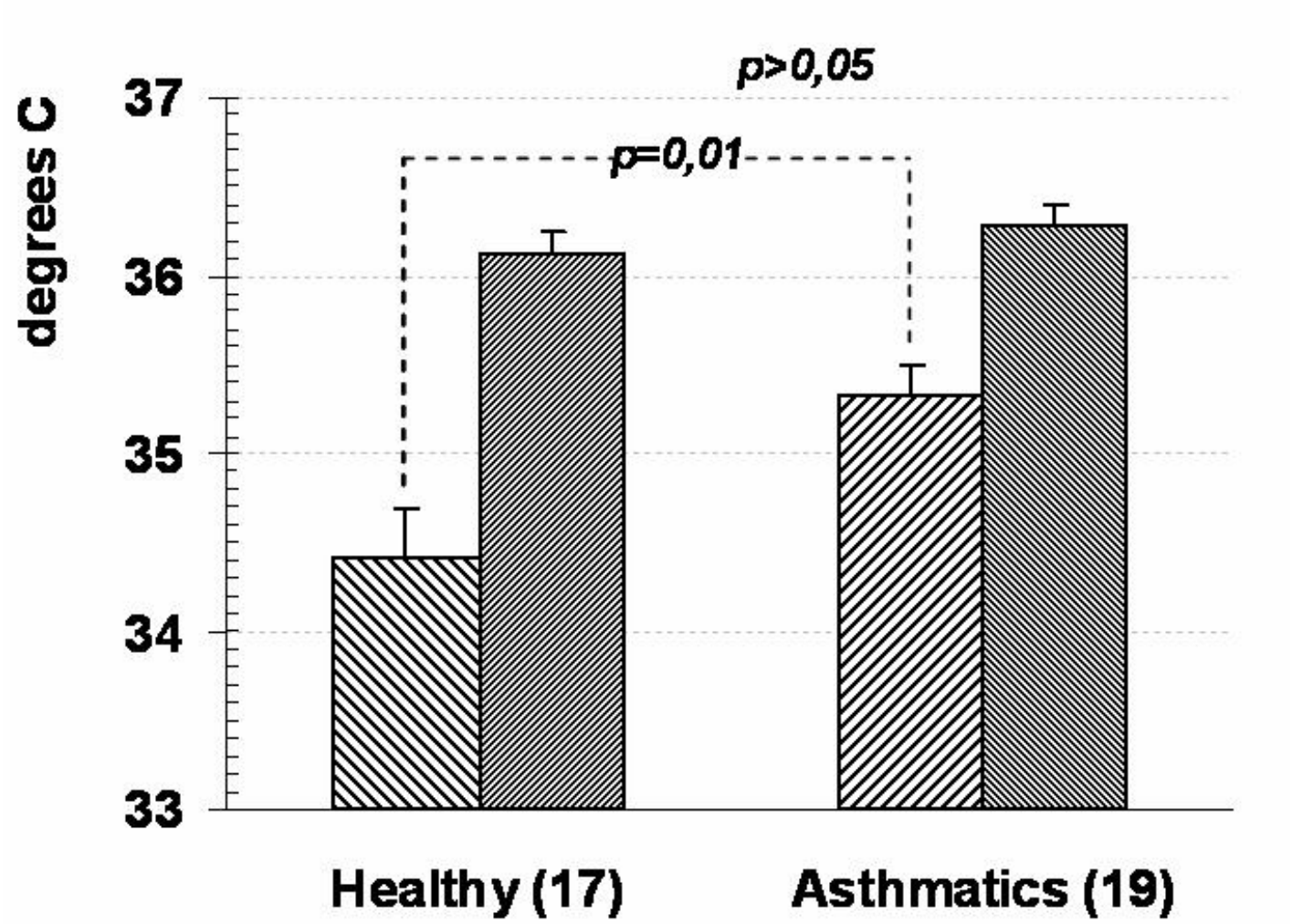
- **Common Mean** **34.10**
- **Common Inter-Item Correlation** **0.99**
- **Reliability of Scale (Unbiased)** **0.99**

Popov TA et al., JACI 2006

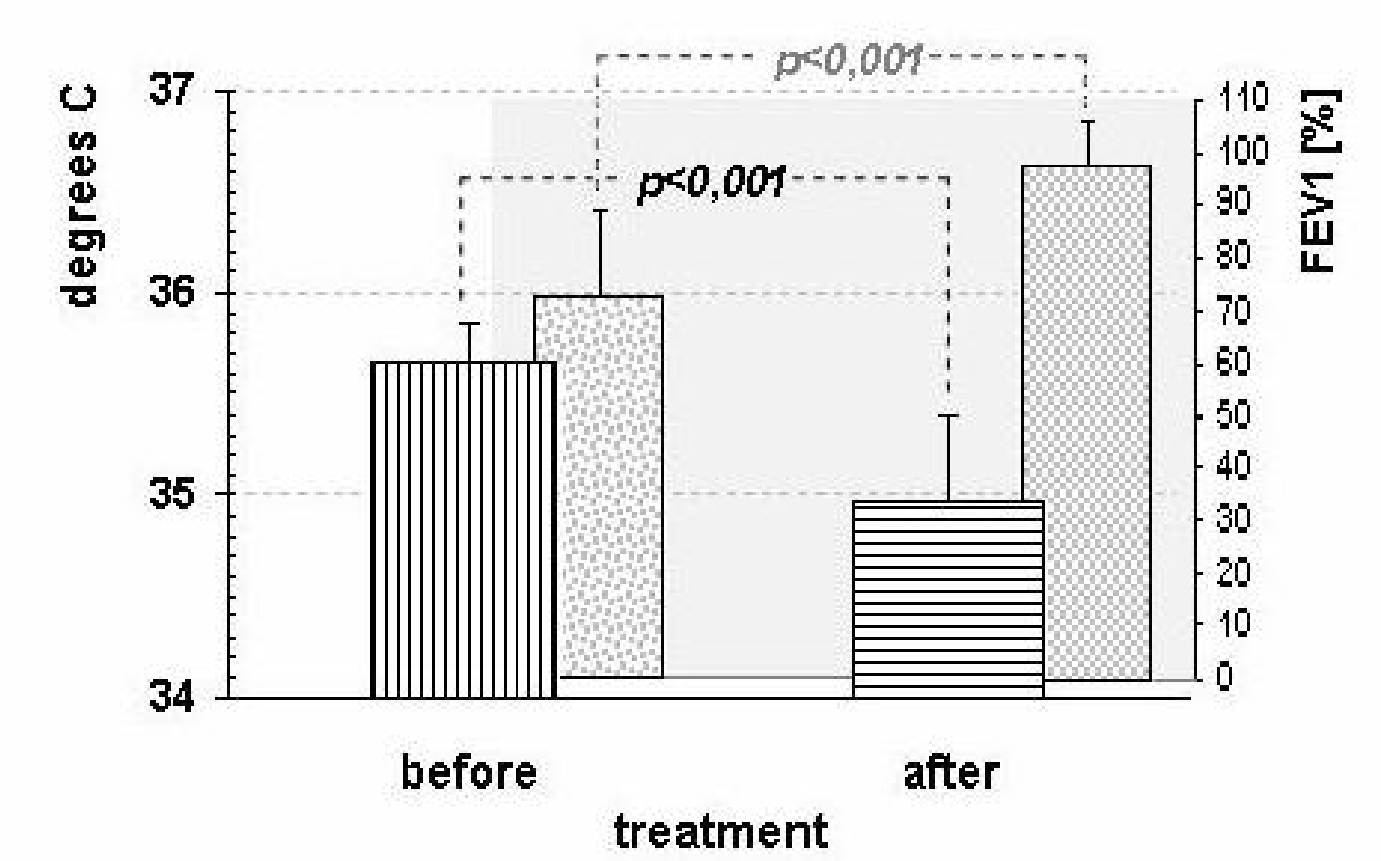
Bland Altman plot of day-to-day EBT measurements



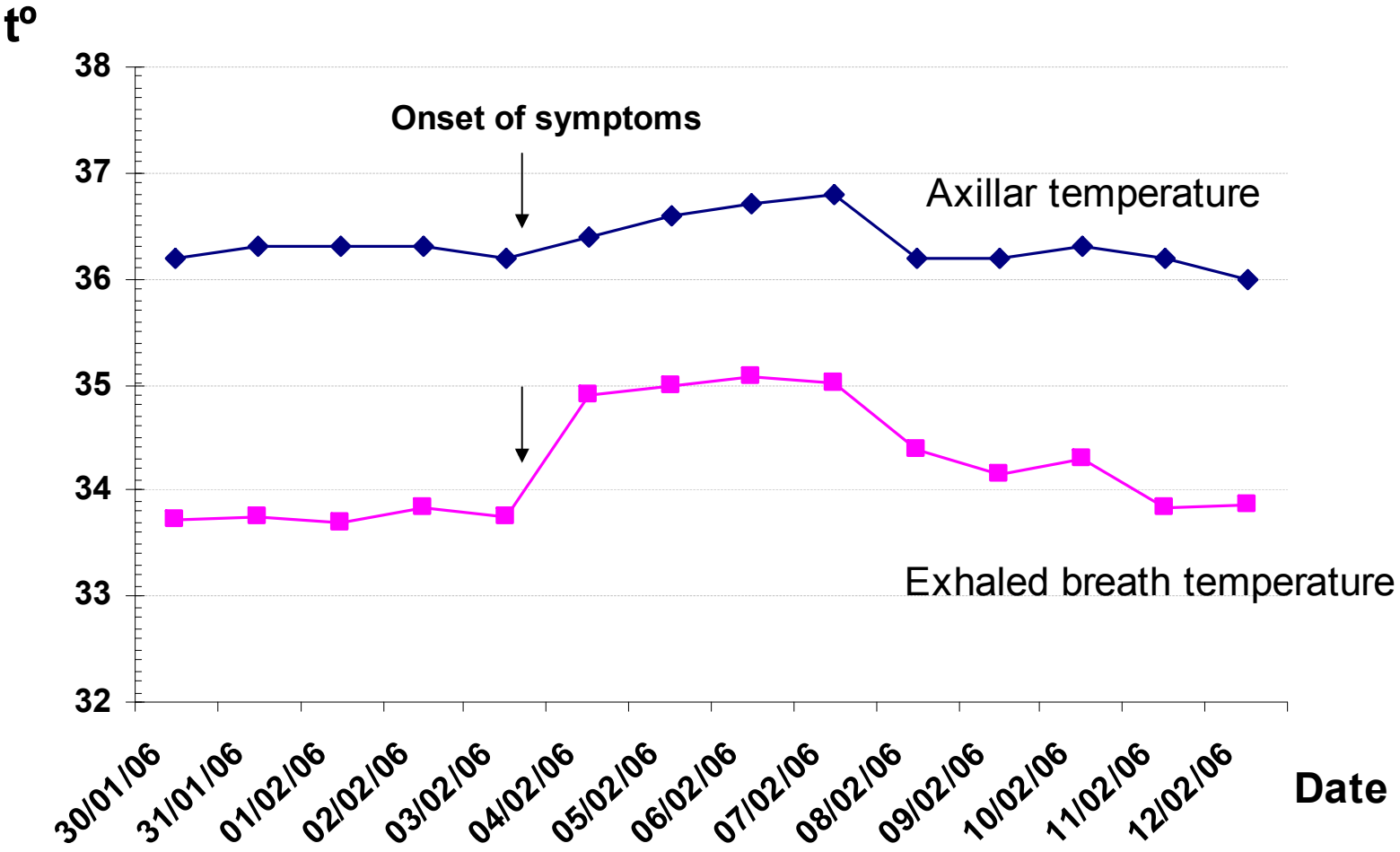
EBTD



EBTD


p<0,001
p<0,001
degrees C
37
36
35
34
FEV1 [%]
110
100
90
80
70
60
50
40
30
20
10
0
before
after
treatment

Episode of mild upper airway viral infection



Exhaled Breath Temperature device Study

Conclusions:

- **The device we constructed can measure the temperature of exhaled breath in human subjects in a simple and user-friendly way.**
- **Further experiments are warranted to find out if it can be applied as individual device for asthmatics to assess the degree of control of their airway inflammation.**

Popov TA et al., JACI 2006

ELSEVIER

Journal of Psychosomatic Research 60 (2006) 545–547

Journal of Psychosomatic Research

Short report

Kissing selectively decreases allergen-specific IgE production in atopic patients

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Received 13 April 2005

Abstract

Objective: Stress enhanced allergic skin wheal responses and allergen-specific IgE production. In contrast, mothers' kissing caused relaxation in infants, and kissing by lovers or spouses to atopic patients reduced allergic skin wheal responses. I studied the effect of kissing on production of allergen-specific IgE and cytokines in atopic patients. **Methods:** Twenty-four patients with mild atopic eczema and 24 patients with mild allergic rhinitis kissed with lovers or spouses freely for 30 min while listening to soft music. Just before and immediately after kissing, blood mononuclear cells were separated cultured for allergen, and production of allergen-specific immunoglobulin and cytokine was measured. **Results:** Kissing selectively decreased allergen-specific IgE production with skewing cytokine pattern toward Th1 type. **Conclusion:** Kissing may alleviate allergic symptoms by decrease in allergen-specific IgE production.

Keywords: Kissing; Atopic eczema; Allergic rhinitis; Japanese cedar pollen; Allergen-specific IgE production

Study design

In the kissing study, subjects from one group kissed with their lover or spouse freely for 30 min alone in a room with closed door while listening to soft music (Beauty and the Beast, When You Wish Upon a Star, My Heart Will Go On, Love is a Many Splendored Thing, Moon River, Sunrise Sunset, Can You Feel the Love Tonight) [7]. In the control study, which was conducted after 2 weeks, each subject from two groups embraced a lover or spouse, but without kissing, for 30 min in the same room while listening to the same music. Alternatively, the other 12 subjects from the AD or AR patients first conducted the control study, and after 2 weeks, they conducted the kissing study. Just before and immediately after each study, blood was sampled and mononuclear cells were separated, and they were cultured

Methods

Subjects

Twenty-four patients with mild atopic dermatitis (AD) (12 females and 12 males; mean age, 28 years; range, 22–34 years), who were allergic to Japanese cedar pollen (JCP), house dust mite (HDM), and latex, and 24 patients with mild allergic rhinitis (AR) (12 females and 12 males; mean age, 26 years; range, 21–32 years), who were allergic to JCP, were recruited after obtaining informed consent. All of the patients were outpatients at the Department of Allergy, Satou Hospital. Allergy to each allergen was confirmed by positive serum allergen-specific IgE levels (mean±S.E.M.) as follows: JCP-specific IgE, 57.1±3.2 IU/ml in AD patients and 70.3±4.1 IU/ml in AR patients; HDM-specific IgE, 72.5±4.5 IU/ml in AD patients; latex-specific IgE 36.9±1.4 IU/ml in AD patients. All of the AD patients were treated with application of mixtures of pinetar (Yoshida Pharmaceuticals, Tokyo, Japan) and zinc ointments, but without oral medication [5].

Effect of kissing on JCP-specific immunoglobulin and cytokine

	Ig and cytokine production							
	AD				AR			
	Control study		Kissing study		Control study		Kissing study	
	Before	After	Before	After	Before	After	Before	After
(A) JCP-specific immunoglobulin (ng/ml)								
IgE	2.3 (0.2)	2.5 (0.2)	2.6 (0.2)	1.1 (0.1)*	4.9 (0.4)	4.7 (0.5)	4.5 (0.5)	2.9 (0.3)*
IgG_4	1.9 (0.2)	2.2 (0.2)	2.0 (0.2)	1.7 (0.2)	6.2 (0.6)	6.4 (0.6)	6.9 (0.8)	6.6 (0.7)
IgA_1	1.6 (0.1)	1.9 (0.1)	1.4 (0.2)	1.6 (0.1)	3.5 (0.3)	3.8 (0.4)	3.2 (0.3)	3.5 (0.4)
(B) Cytokine (pg/ml)								
IFN-γ	152 (9)	135 (8)	143 (9)	286 (11)**	346 (25)	309 (21)	358 (26)	457 (35)**
IL-12	157 (10)	148 (9)	144 (9)	207 (9)**	268 (16)	282 (19)	234 (18)	377 (28)**
IL-4	203 (11)	235 (12)	209 (11)	134 (8)*	573 (38)	548 (37)	594 (45)	416 (32)*
IL-10	168 (11)	186 (11)	180 (13)	106 (4)*	259 (10)	282 (12)	290 (13)	153 (8)*
IL-13	239 (12)	256 (13)	278 (12)	145 (9)*	465 (31)	433 (34)	491 (37)	352 (24)*

AD or AR patients embraced lovers or spouses without kissing (control study) or with kissing (kissing study) for 30 min while listening to music. Before and after each study, blood mononuclear cells were separated and cultured with JCP. Production of JCP-specific IgE, IgG_4 and IgA (A) and cytokines (B) was measured. Values are means (S.E.M.).

* $P<.01$, significant decrease compared to before.

** $P<.01$, significant increase compared to before.

Thank you!