Funzionalità respiratoria ed Asma in età prescolare

Incontri FIMP- Caserta 2005

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A.O. "G. Rummo" - Benevento

ASMA

Sintomo — wheezing — ilante

Malattia — Asthma — e — aeree

Asthma syndromes in children

- ✓Infant Wheeze → Happy wheezer
  - → Post bronchiolitis
  - → Airway function ↓
  - → Prematurity
  - → Smoke exposed
- ✓Atopic Asthma
- ✓Wheezy bronchitis
- ✓Cough

TO DIAGNOSE ASTHMA IN INFANTS THINK OF THE "3R"

Reattività

- Dovrebbe esserci un fattore trigger facilmente identificabile, di solito un'infezione virale

Reversibilità

- L'ostruzione delle vie aeree è reversibile dopo somministrazione di broncodilatante

Ricorrenza

- Di solito più di tre episodi

Finder Curr. Probl. Pediatr. 1999; 29: 65

A CLINICAL INDEX TO DEFINE ASTHMA RISK

Major ← CRITERIA → **Minor**

Major

1) Parental asthma
2) Eczema
3) Atopy

Minor

1) Allergic rhinitis
2) Wheezing apart from cold
3) Eosinophilia (≥ 4%)

At least one → (+) ← Two

Or

- early wheezing → 59%

or

- frequent early wheezing → 76%

Risk of asthma development

Castro-Rodriguez and Martinez A.J.R.C.C.M. 2000; 162: 1403

Prognostic factor for asthma and wheezing illness from childhood to adulthood

Helms PJ, Amin SS - Breathe 2004 1:131

Persistence	Resolution	Uncertain
✓Female	✓Male	✓Prematurity
✓Onset < 2 years	✓Onset>2 years	✓Bronchiolitis
✓Personal atopy		✓Family atopy
✓Severe disease		✓Maternal smoking
✓Bronchial hyperresponsiveness		

Allergici si nasce?

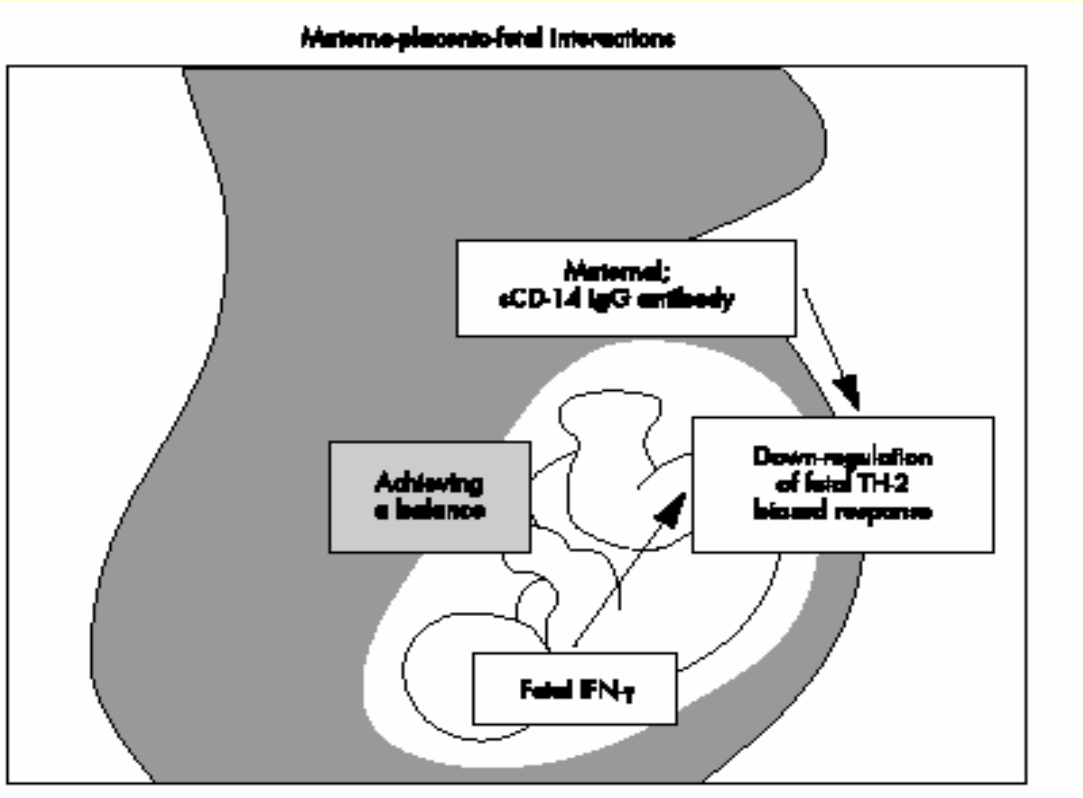
Il pattern Th2 è presente in tutti i neonati

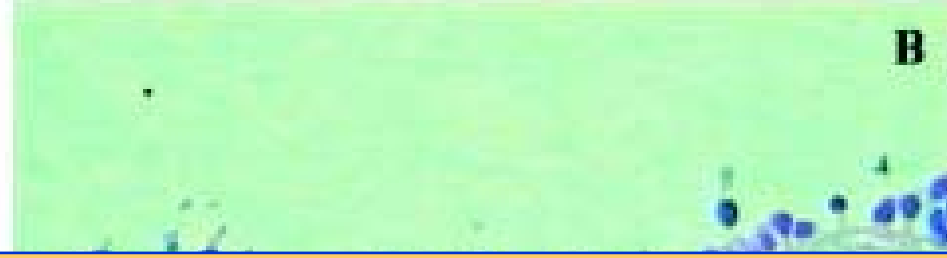
The early life origins of asthma and related allergic disorders

J O Warner

A focus on the way the disease evolves in early life

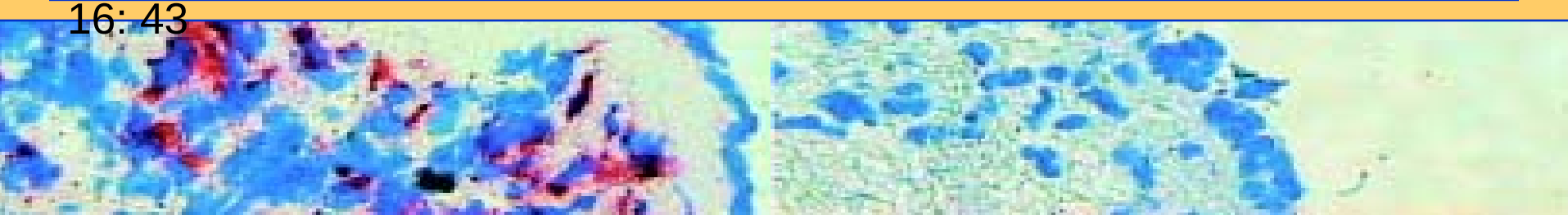
Arch Dis Child 2004;89:97–102.





Sebbene il remodelling è stato considerato essere secondario ad un'infiammazione di lunga durata, studi bioptici in bambini piccoli hanno mostrato una ristrutturazione morfologica già quattro anni prima dell'inizio dei sintomi (*ERJ* 1997; 10: Suppl.25, 160s), indicando un processo che inizia precocemente nello sviluppo dell' asma ed avviene contemporaneamente allo stabilirsi dell'infiammazione persistente.

Eur Respir J 2003; 22: Suppl. 44, 24s–29s- Pediatr Allergy Immunol 2005; 16: 43



Sito dell'infiammazione

- ✓Piccole vie aeree
- ✓Grandi vie aeree
- ✓Zona silente (<2 mm)

Tipo di cellula coinvolta

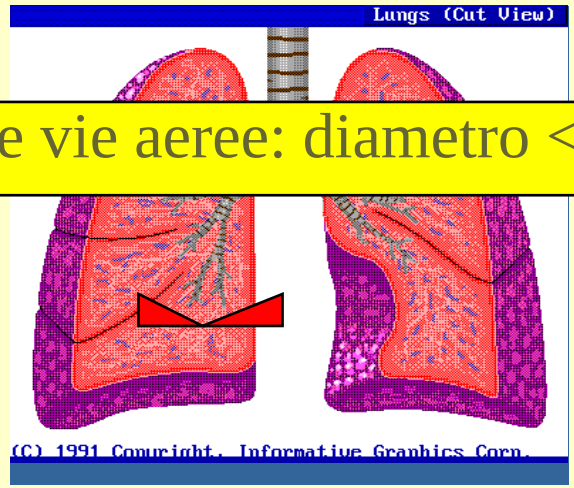
- ✓Eosinofili
- ✓Neutrofili

Danno funzionale

Riduzione dei meccanismi di compenso

Distal Lung
La zona silente

Mead J et al. – J Appl Physiol 1970 ; 28: 596



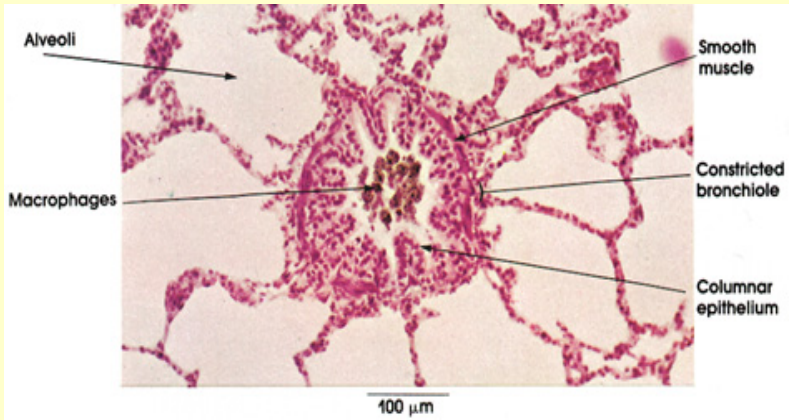
Piccole vie aeree: diametro < 2 mm

Studi fisiopatologici evidenziano che l'unità "Distal Lung", che include le piccole vie aeree (< 2 mm) ed il parenchima polmonare, partecipa alla patogenesi dell'Asma.

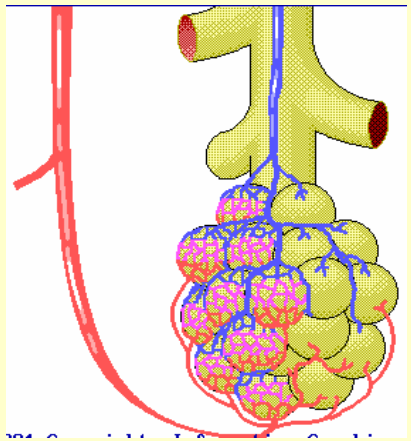
M. Kraft Eur Respir J 1999; 14: 1403-1417

Distal Lung

Parenchima Polmonare



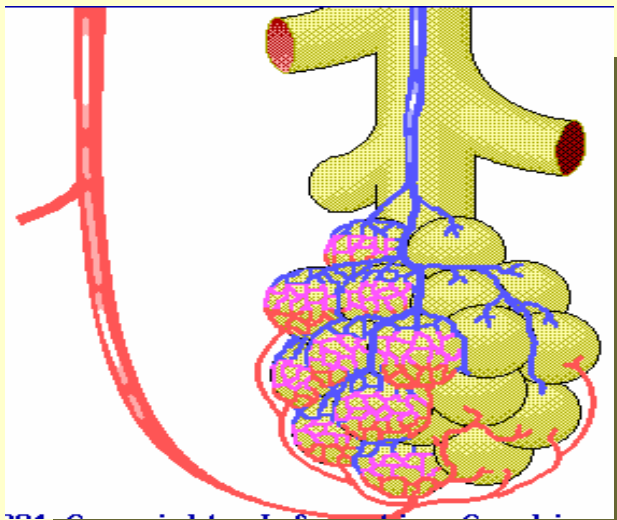
Vie Aeree < 2 mm

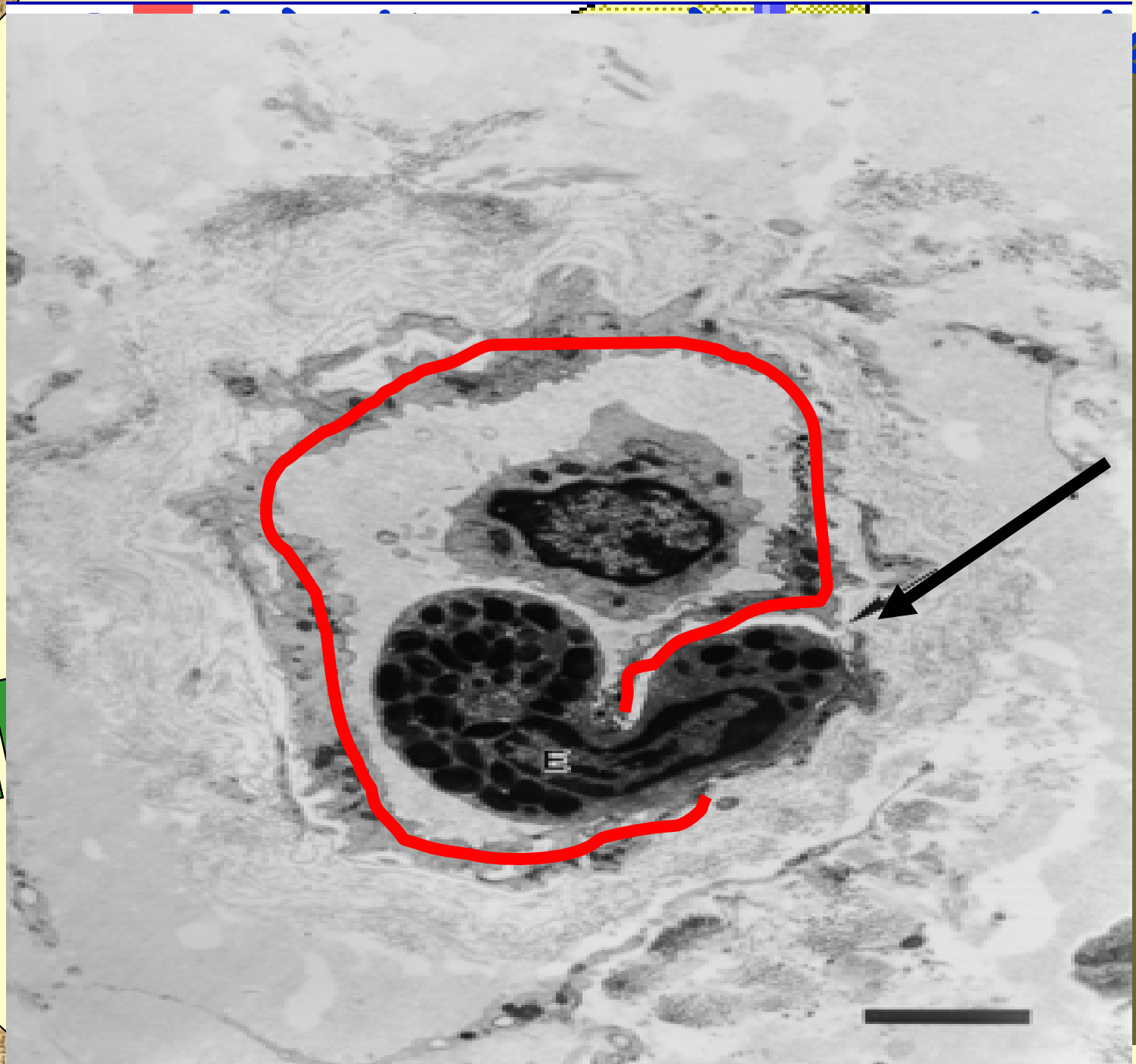


La Zona Silente del Polmone

La sezione trasversale complessiva delle piccole vie aeree è significativamente più grande di quella delle grandi vie aeree

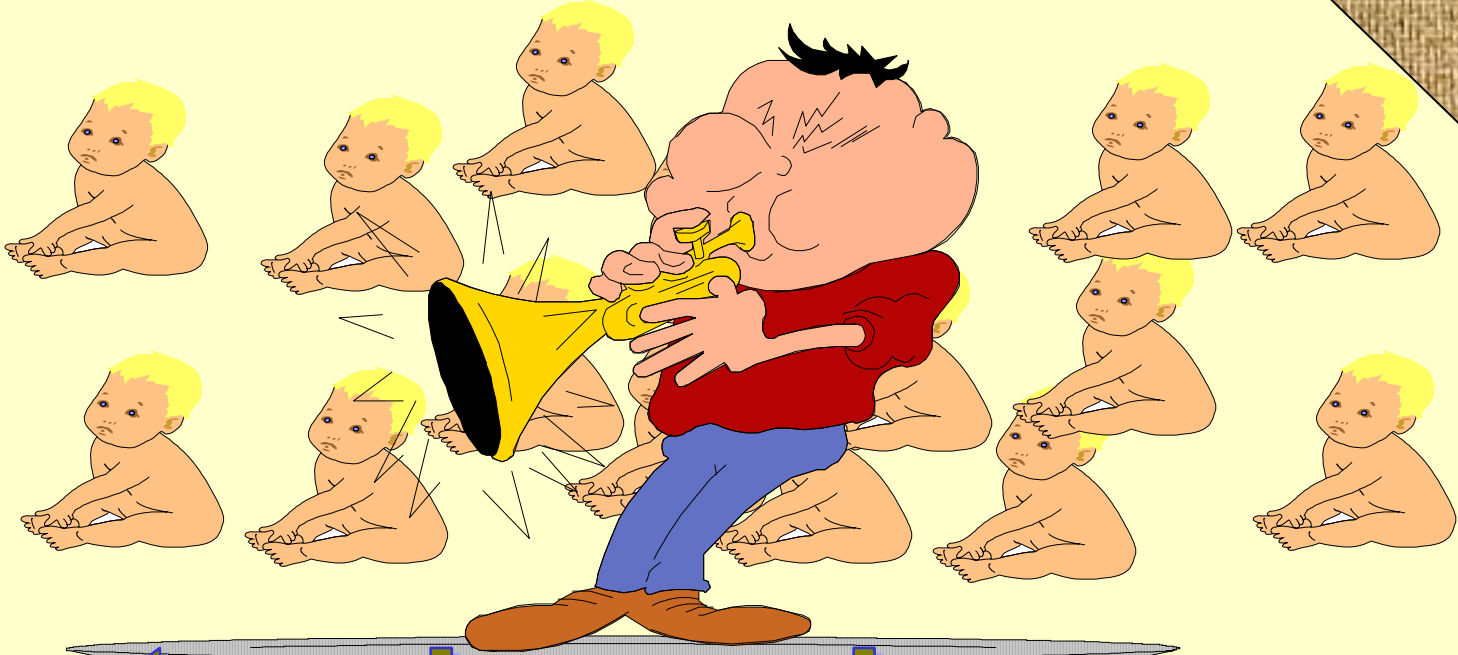
Weibel ER . – Morphometry of the Human Lung. NY Academic Press 1963





Sviluppo polmonare nel bambino

- **alla nascita: prevalgono le vie aeree sugli alveoli**
- **nei primi tre anni: sviluppo progressivo degli alveoli e delle ramificazioni periferiche**
- **Il bambino, nei primi 3 - 4 anni, presenta una maggiore tendenza alla chiusura ed al collasso delle piccole vie aeree**
- **dai 4 agli 8 anni la situazione tende ad avvicinarsi a quella dell'adulto**



maturazione polmonare

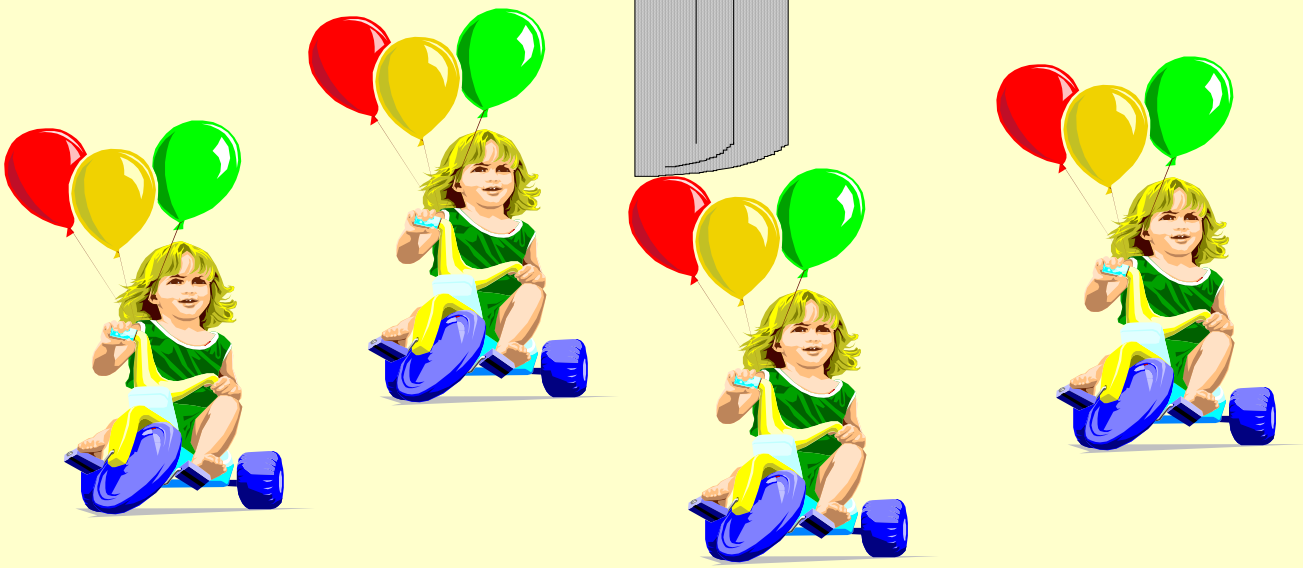


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Table 1 Proportion of asthmatics with lung eosinophilia

Study	Case definition*	Method	Definition of eosinophilic and non-eosinophilic asthma based on cut off values**	No	Eosinophilic asthma
Studies in adults:					
Fahy *et al* (1995)[22]	Acute severe asthma	Sputum	2% eosinophils¶	18	50%
Turner *et al* (1995)[24]	Mild asthma with exacerbation in past 2 weeks	Sputum†	4% eosinophils¶	34	47%
Pizzichini *et al* (1996)[27]	Stable asthma	Sputum	2% eosinophils¶	19	58%
Wenzel *et al* (1999)[18]	Severe asthma, corticosteroid (CS) dependent	Bronchial biopsy	Mean eosinophil count +2SD (exact value not given)	34	59%
Pavord *et al* (1999)[23]	Asthma patients treated with β_2 agonists	Sputum	3% eosinophils¶	23	61%
Pavord *et al* (1999)[23]	Asthma of variable severity	Sputum†	3% eosinophils	26	88%
Jatakanon *et al* (1999)[23]	Persistent asthma of variable severity:	Sputum	2% eosinophils	55	60%
	• Mild persistent			23	78%
	• Moderate persistent			16	38%
	• Severe persistent			16	56%
Lemière *et al* (1999)[24]	Asthma of variable severity	Sputum	2% eosinophils	6	33%
Berlyne *et al* (1999)[20]	Asthma of variable severity	Sputum†	2% eosinophils	84	52%
			Mean eosinophil count + 2SD (87×10^2/g)	84	82%
Tarodo de la Fuente *et al* (1999)[25]	Asthma of variable severity	Sputum	2% eosinophils	38	34%
	• Mild untreated			9	22%
	• Moderate treated with ICS			12	25%
Studies in children:					
Gibson *et al* (1998)[20]	Open population incl non-symptomatic subjects:	Sputum	2.5% eosinophils¶	(162)	(27%)
	• Symptoms in past 2 weeks‡			56	41%
	• BHR§			23	62%
Gibson *et al* (1999)[41]	Acute severe asthma	Sputum	2.5% eosinophils	37	88%
Marguet *et al* (1999)[19]	• Asthma with recurrent symptoms	BAL	2% eosinophils¶	14	57%
	• Infantile wheezers (age 5–46 months)			26	19%
Wilson *et al* (2000)[21]	Asthma of variable severity:	Sputum	2% eosinophils¶	36	19%
	• Not treated with ICS			21	29%
	• Treated with ICS			15	7%
Gibson *et al* (2001)[42]	Asthma defined as wheezing in last 12 months‡	Sputum	2.5% eosinophils	22	45%

*All asthma cases were recruited from symptomatic patients attending a clinic, unless indicated otherwise; these studies therefore only give a crude estimate of the proportion of asthma which is characterised by lung eosinophilia in selected populations.
†Induced and spontaneous sputum.
‡Children with asthma symptoms not recruited through a clinic.
§Children with bronchial hyperresponsiveness (BHR).
¶In case the authors did not define a cut off or when a cut off of less than 2% was chosen in the original study, we have set the cut off at 2%.
**Cut off was determined based on eosinophil counts in control subjects unless indicated otherwise.
††30 obstructed ICS treated patients were included in the study but in the figure only 26 could be observed. Individual sputum data for the other three asthma groups (ICS treated non-obstructed and ICS naive obstructed and non-obstructed patients) were not given in the article.
‡‡59 patients were included in the study but in the figure only 56 could be observed.

Una revisione della letteratura dimostra che, al massimo, solo il 50% dei casi di asma sono attribuibili a infiammazione eosinofila delle vie aeree (46% nei bambini). Douwes J et al. - Thorax 2002; 57: 643-648

Asthma and Neutrophils

Bronchial Neutrophilia in patients with noninfectious Status Asthmaticus – Lamblin C et al.-AJRCCM 1998; 157:394

Il nostro studio fornisce nuove conoscenze che confermano il coinvolgimento dei neutrofili nella **patogenesi dello stato asmatico**

The role of eosinophils and neutrophils in inflammation – Sampson AP – Clin Exp Allergy 2000; 30 suppl 1: 22

Non solo i neutrofili contribuiscono all'esacerbazione dell'asma acuto, ma sono anche abbondantemente presenti nelle vie aeree dei **pazienti con asma cronico severo.**

Bronchoalveolar lavage in asthmatic children: evidence of neutrophils activation in mild-t-moderate persistent asthma – Barbato A et al. Pediatr allergy Immunol 2001; 12:73

I nostri risultati dimostrano che l'infiammazione mediata dai neutrofili è maggiore **quanto più severo è l'asma**

The most notable difference of chronic severe asthma compared with mild to moderate disease is the increased number of neutophils

Review su infiammazione cronica in Asma e COPD- Current Opinion in Asthma and Clinical Immunology – February 2005; 5:77

Differential cytology of bronchoalveoalr lavage fluid in asthmatic children

Najafi N et al. Pediatr Pulmonol 2003 Apr; 35:302-8

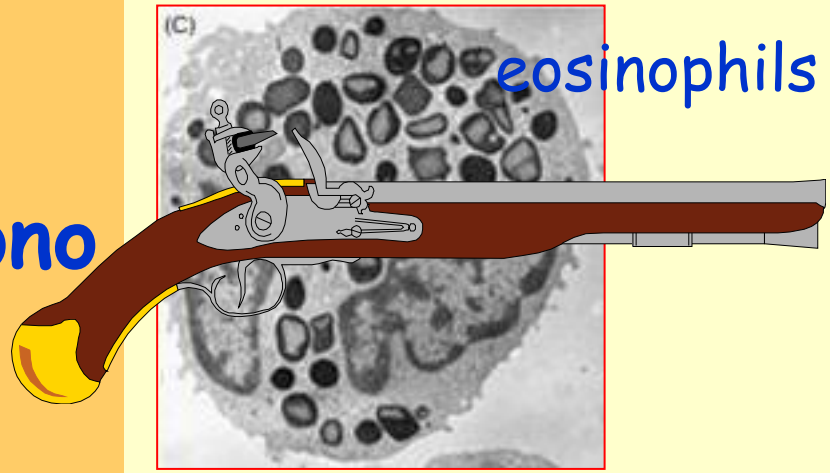
E' stato esaminato il liquido di lavaggio broncoalveolare in 39 bambini con nuova diagnosi di asma (19 allergici e 18 non allergici), in assenza di terapia antiinfiammatoria

Conclusioni:

L'infiammazione a cellule neutrofile potrebbe essere più importante nell'asma in età pediatrica

Eosinofili e Neutrofili

Eosinofili: **modulano la risposta infiammatoria allergica e contribuiscono alla distruzione dei parassiti**



eosinophils

Neutrofili: ***fagocitano e distruggono piccoli organismi, specialmente batteri***

neutrophils

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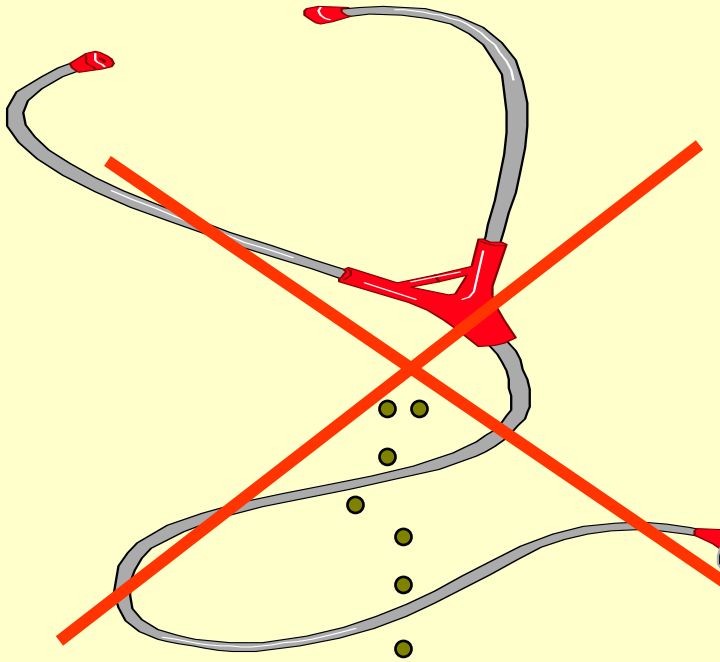
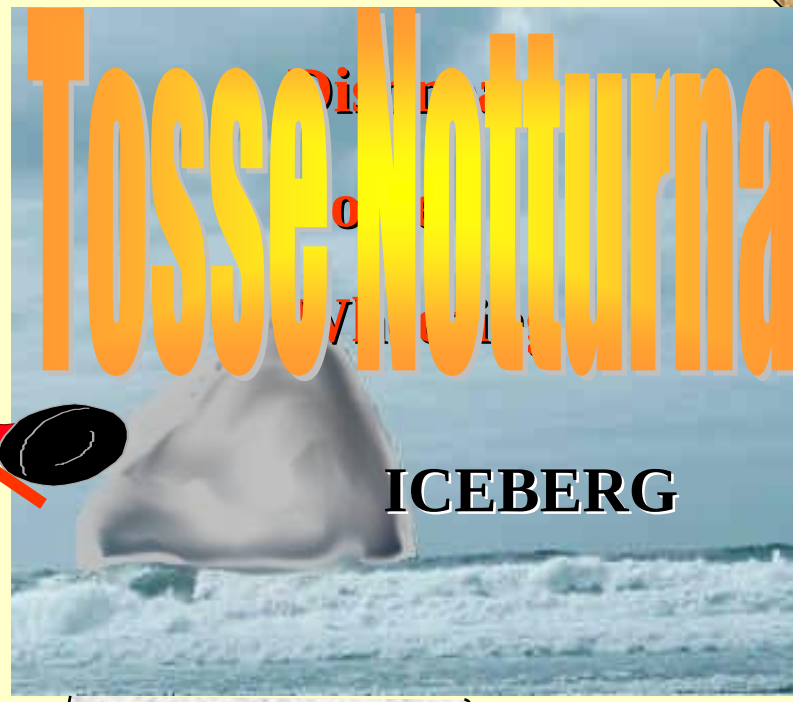
Alveoli
Smooth muscle
Constricted bronchiole
Macrophages
Columnar epithelium
100 μm

The Bronchial Lavage of Pediatric Patients with Asthma contain Infectious Chlamydia.

Webley WC et al. Department of Microbiology, University of Massachusetts, Amherst, MA, USA.

Am J Respir Crit Care Med. 2005 Feb 25





Infiammazione

Ostruzione piccole vie aeree

Test di Funzionalità Respiratoria

Childhood cough variant asthma and its relationship to classic asthma

Makoto Todokoro et al. *Ann Allergy Asthma Immunol.*

We also speculate that many cases of CVA in younger

children are classic asthma, but wheezing is not detectable

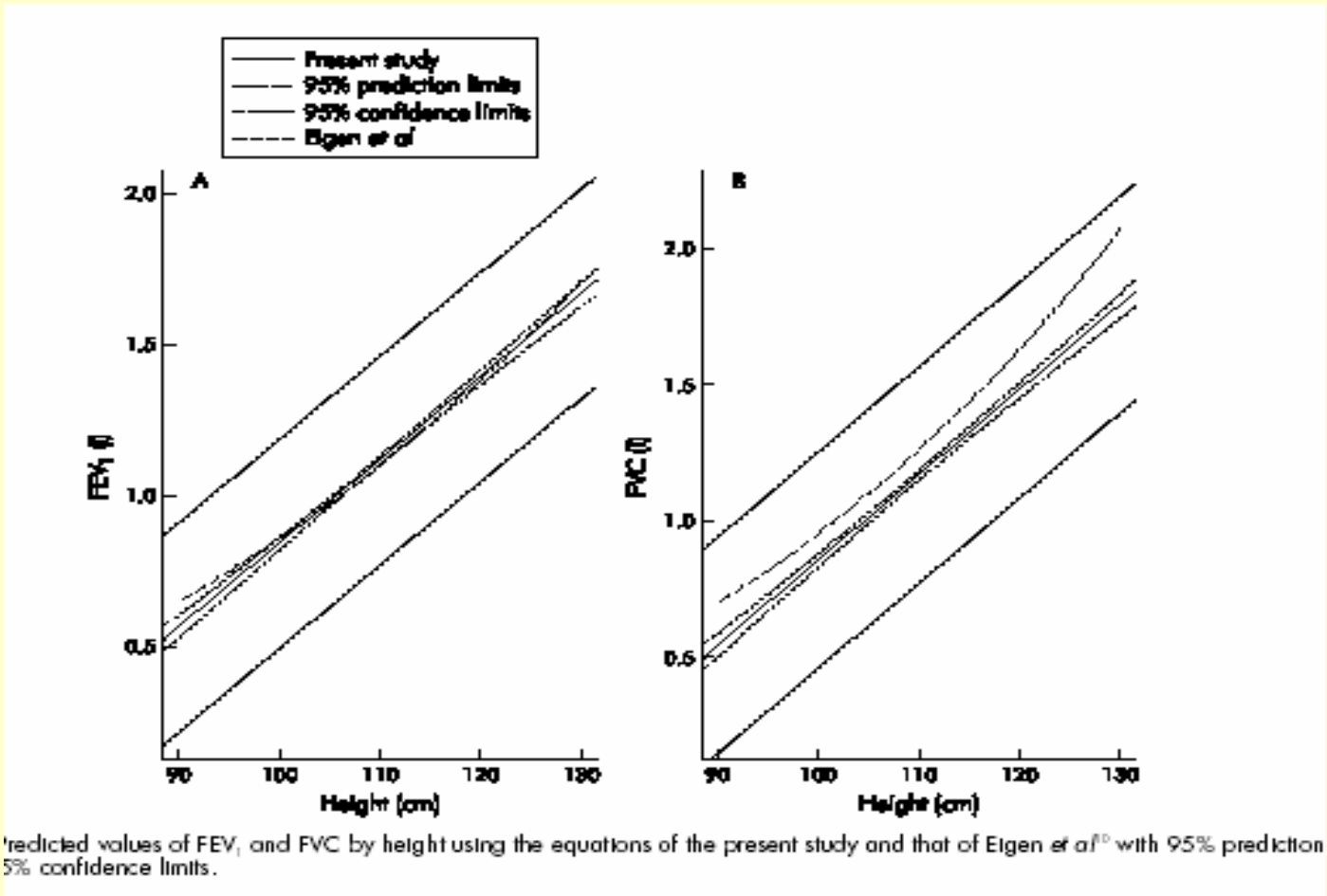
because of infantile specificity in respiratory physiology.

Diagnostica strumentale

- ✓Spirometria → Flussi e volumi vie aeree
- ✓Interruzione multipla (Rint) → Capacità di restituire energia
- ✓Oscillometria Forzata → Capacità di accumulare e restituire energia
- ✓Ossido nitrico → Infiammazione allergica

Feasibility of measuring lung function in preschool Children

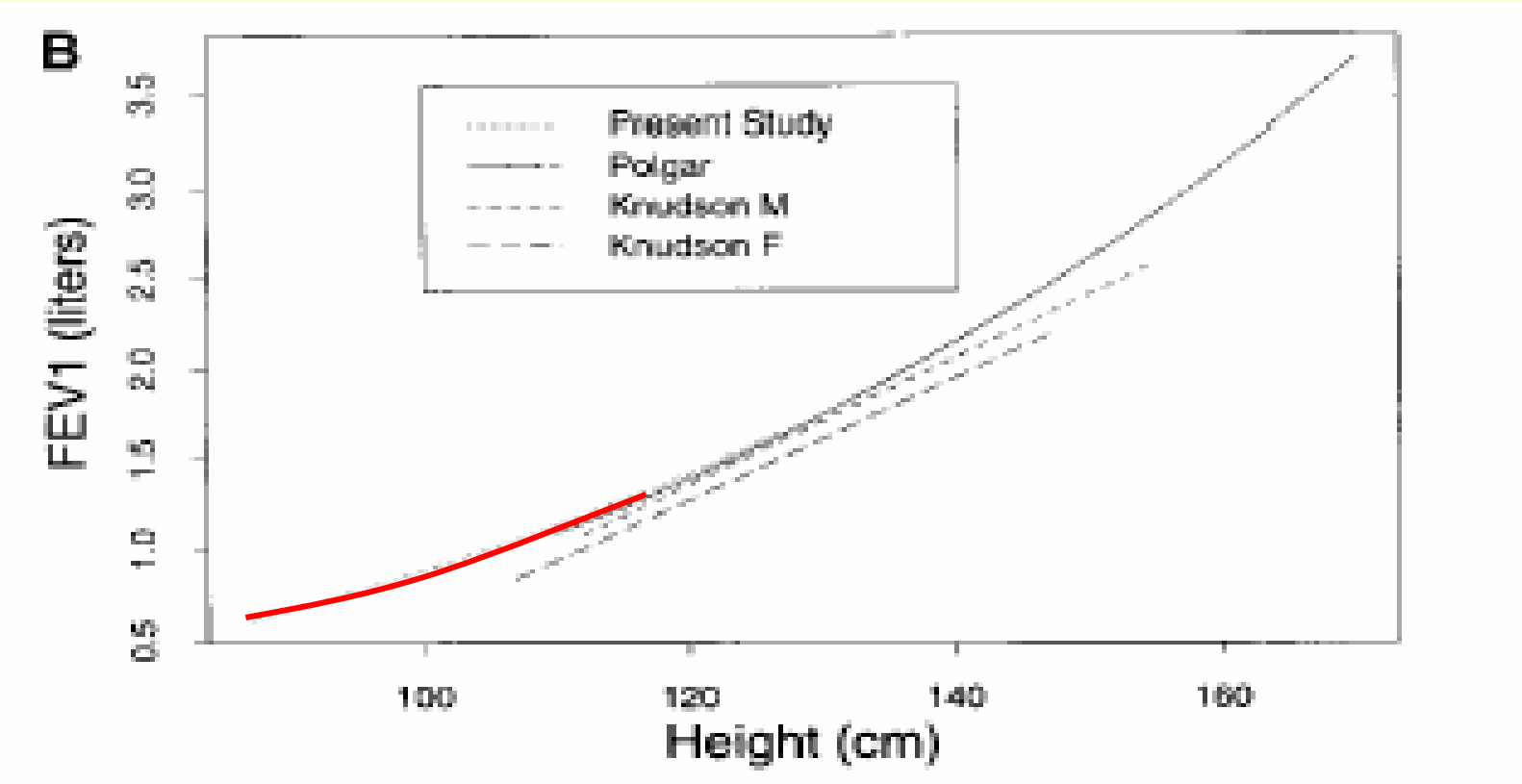
W Nystad et al. - Thorax 2002;57:1021–1027



Predicted values of FEV_1 and FVC by height using the equations of the present study and that of Eigen *et al*[9] with 95% prediction 5% confidence limits.

Spirometric Pulmonary Function in Healthy Preschool Children

HOWARD EIGEN et al. Am J Respir Crit Care Med Vol 163. pp 619–623, 2001



An Interactive Computer-Animated System (SpiroGame)

Facilitates Spirometry in Preschool Children

DAPHNA VILOZNI et al.

Am J Respir Crit Care Med Vol 164. pp 2200–2205, 2001

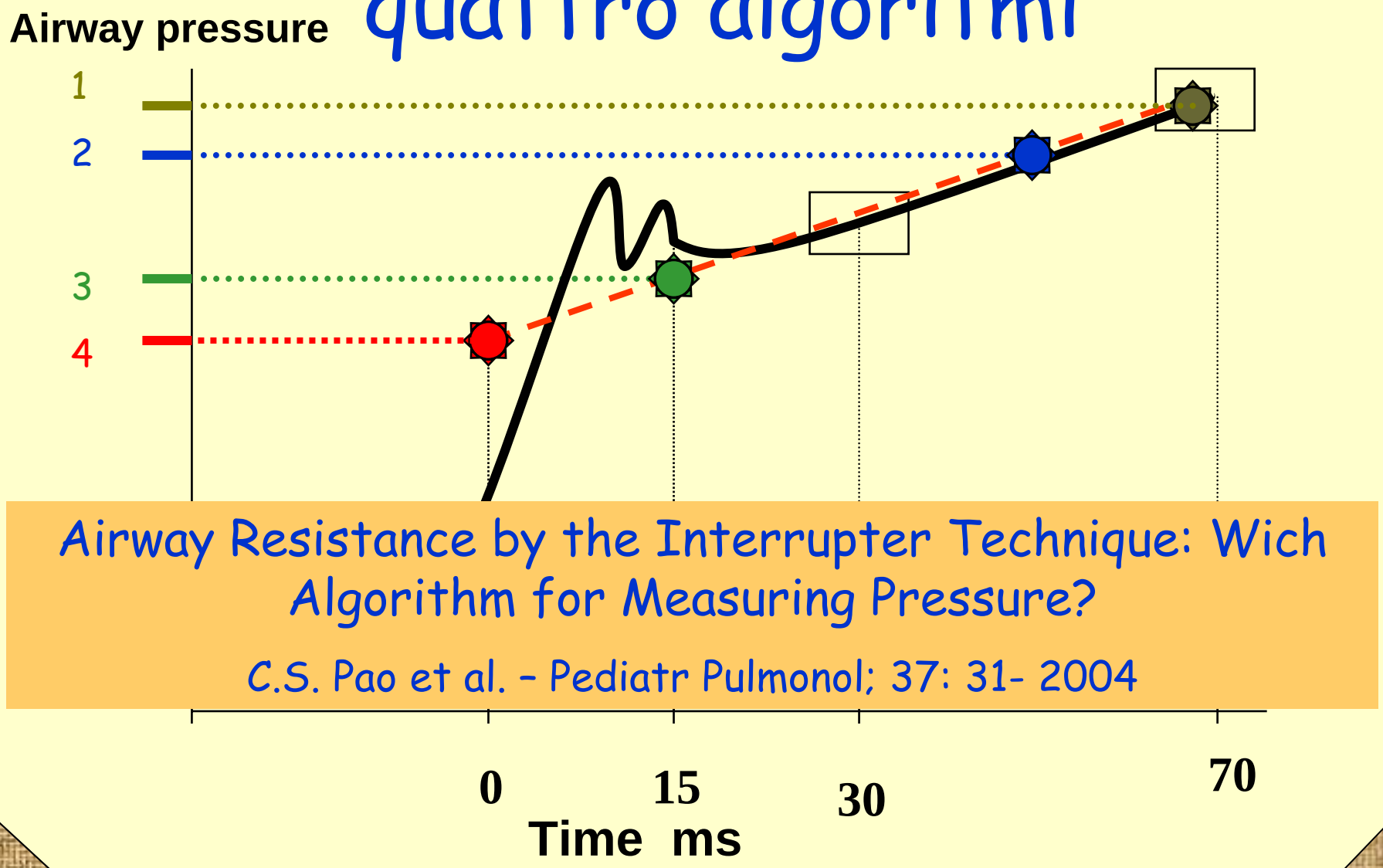
Tempi di chiusura e attendibilità

✓Il tempo totale di chiusura è di 100 ms ed impercettibile per il paziente

✓ Se il paziente non ha un'ostruzione importante il tempo per raggiungere l'equilibrio tra pressione alla bocca e pressione alveolare è di 70-80 ms

✓ Se il paziente ha un'ostruzione importante il tempo necessario all'equilibrio tra pressione alla bocca e pressione alveolare può superare i 100 ms, con una conseguente sottostima della pressione e quindi del valore del Rint

La Curva del Rint ed i quattro algoritmi



Airway Resistance by the Interrupter Technique: Wich Algorithm for Measuring Pressure?

C.S. Pao et al. – Pediatr Pulmonol; 37: 31- 2004

Dopo l’occlusione

(Pint)

$$\text{Rint} = \frac{\text{Pressione}}{\text{Flusso}}$$

Prima dell’occlusione

Interrupter Resistance and Wheezing Phenotypes at 4 Years of Age

JE. Brusseet al, Am J Respir Crit Care Med – 169: 209–213, 2004

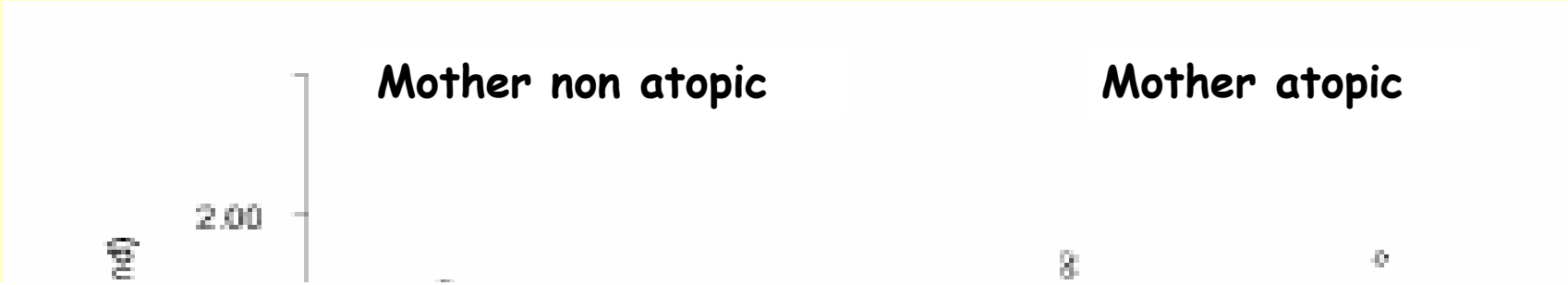


TABLE 2. MEAN INTERRUPTER RESISTANCE VALUES PER WHEEZING PHENOTYPE

Wheezing phenotype	Total Study Population			Nonatopic Mother			Atopic Mother		
	n	Mean (95% CI)*	z Score†	n	Mean (95% CI)*	z Score†	n	Mean (95% CI)*	z Score†
Never	482	0.95 (0.93, 0.97)	0.46	188	0.91 (0.88, 0.94)	0.31	294	0.98 (0.95, 1.01)‖	0.55
Early	236	0.95 (0.92, 0.98)	0.49	80	0.95 (0.90, 1.00)	0.49	156	0.96 (0.91, 1.00)	0.49
Late	22	0.96 (0.87, 1.05)	0.52	6	1.07 (0.85, 1.28)	0.89	16	0.92 (0.82, 1.02)	0.37
Persistent	98	1.08 (1.02, 1.14)¶,‡,§	0.96	29	1.10 (0.99, 1.21)¶,‡	1.04	69	1.07 (1.01, 1.14)¶,‡,#	0.92

Ripetibilità a breve termine della misurazione RINT in bambini in età prescolare

Lombardi E, Boccaccino A, Novembre E
Bernardini R, Sgarra L, Spinosa E, Vierucci A.

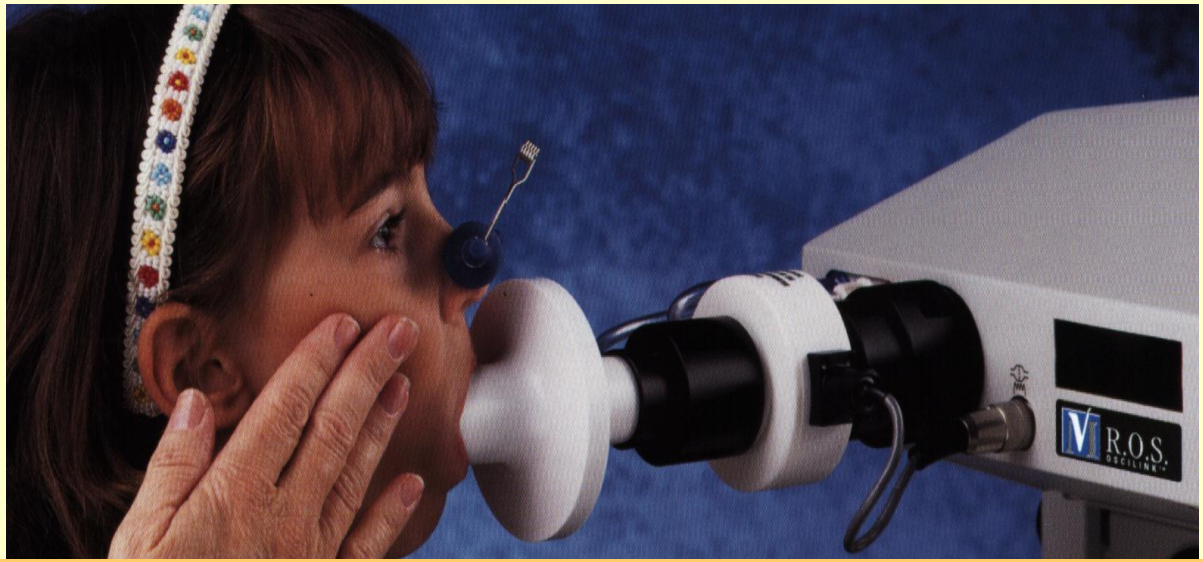
SIAIP – Firenze Marzo 2001

✓51 bambini di età media= 4,6 anni (range 2,6 – 6,5)

✓2 misurazioni (media di 6) consecutive ad 1 minuto di distanza

✓ ripetibilità : 2 DS dalla media delle differenze appaiate tra le due misurazioni

Bridge et al. ERJ 1999;13:792:	0,21	0,17	0,15
Lombardi et al.	0,20	0,25	0,28



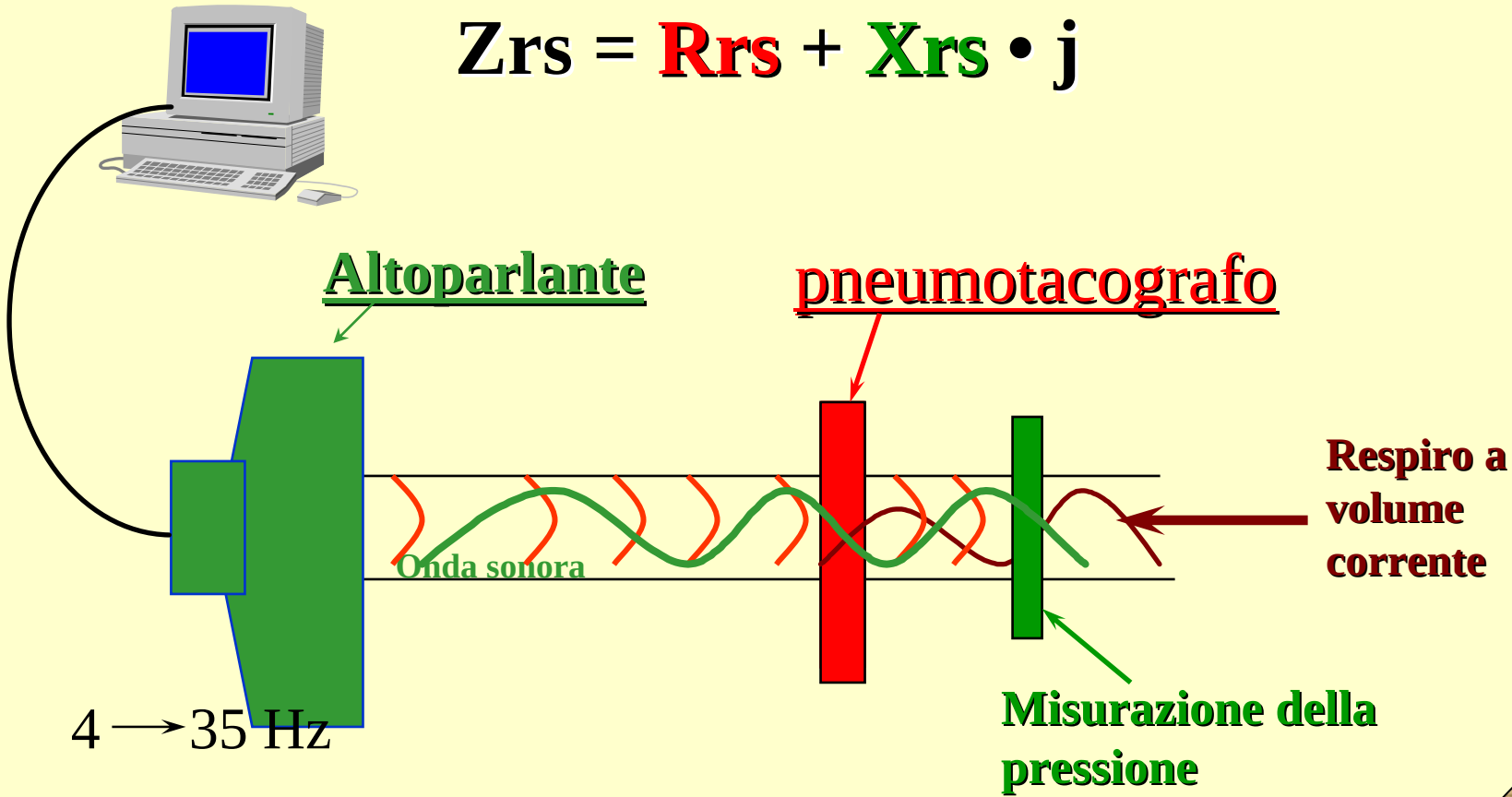
Oostveen E et al. for ERS TASK FORCE.

The forced oscillation technique in clinical practice: methodology, recommendations and future developments.

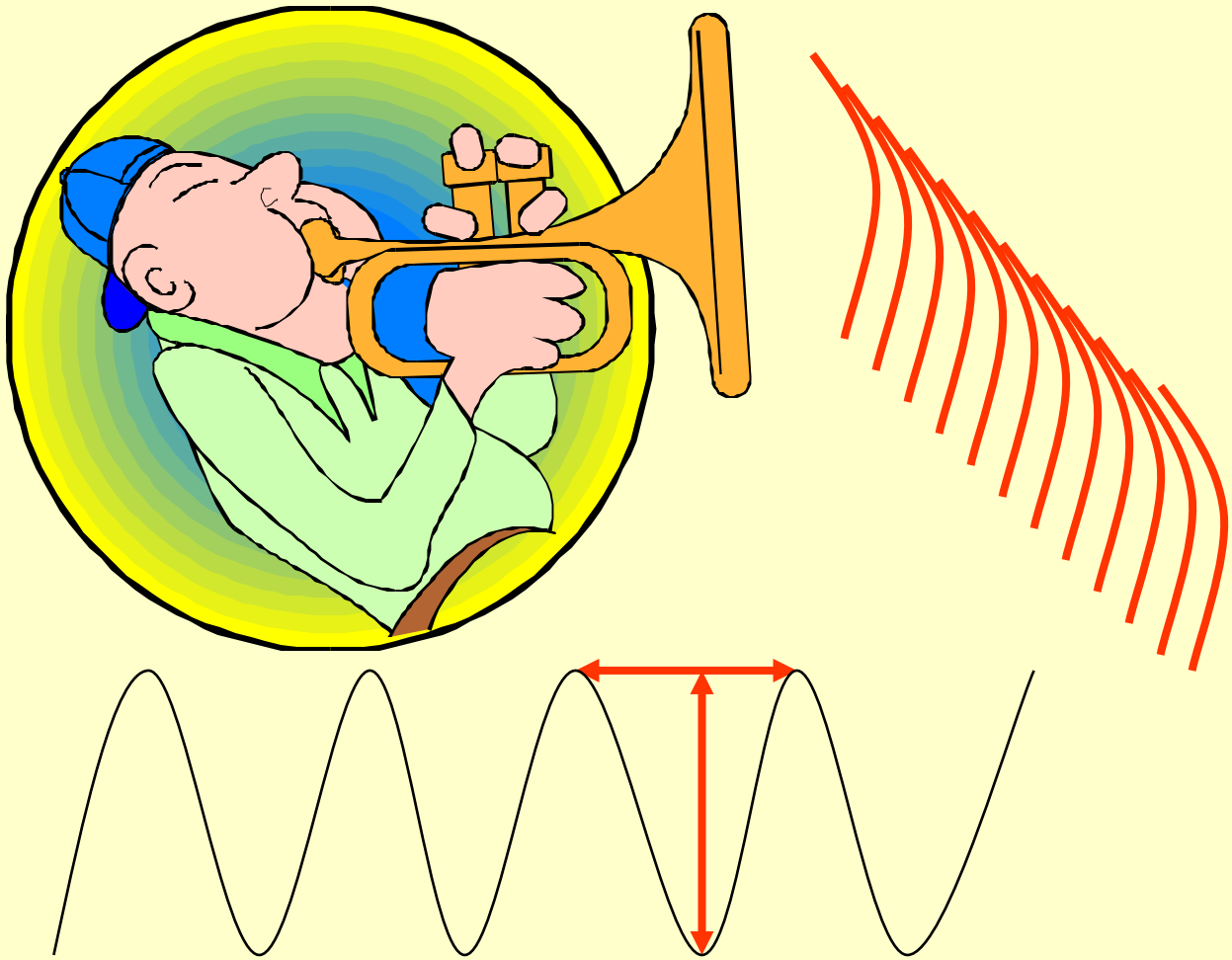
Eur Respir J 2003; 22: 1026–1041

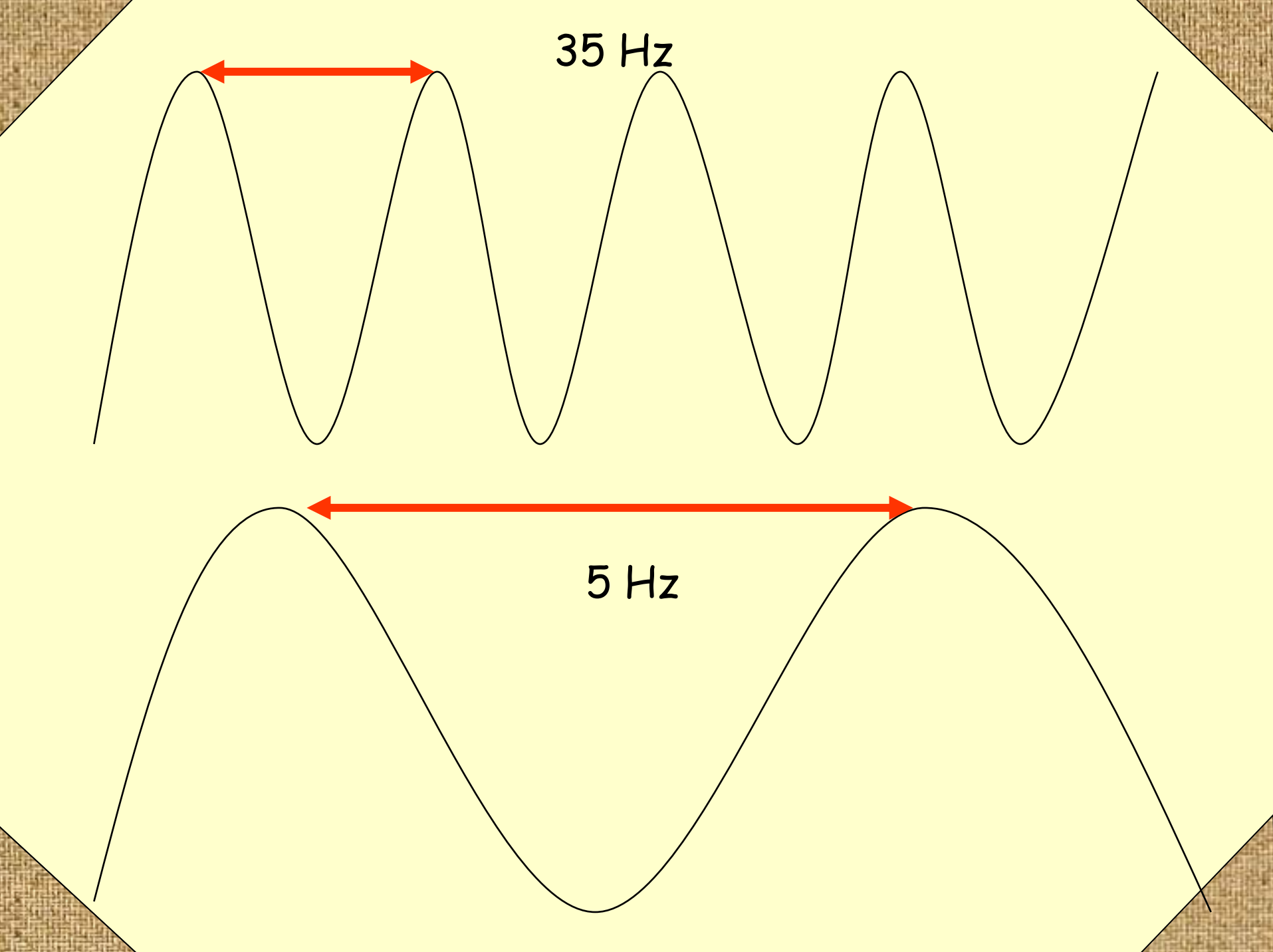
Principio dell'Oscillometria Forzata

$$Zrs = Rrs + Xrs \bullet j$$

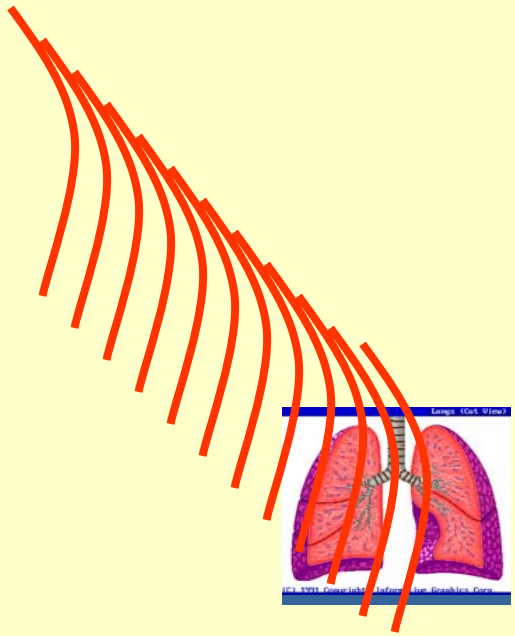


Onda sonora = onda elastica

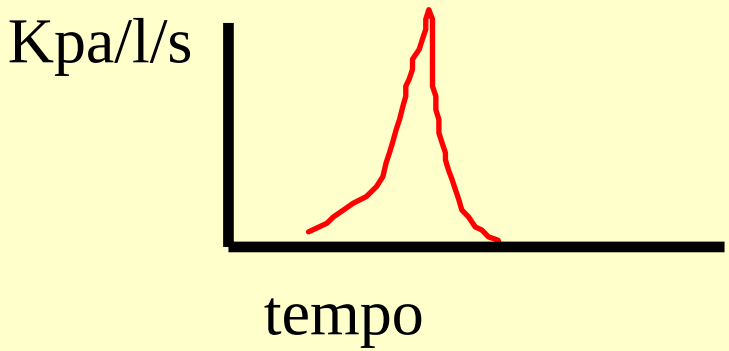


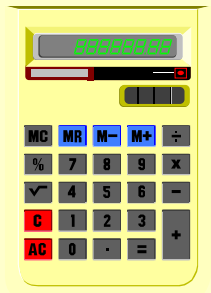

35 Hz
5 Hz

Onda sonora = onda elastica

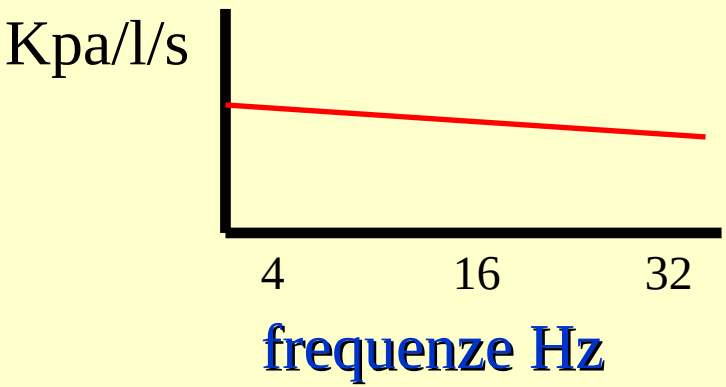


Fast Fourier Trasformation





FFT



Si può effettuare con
l’Oscillometria Forzata una
diagnosi differenziale della sede,
centrale o periferica,
dell’ostruzione respiratoria?

L’Oscillometria forzata può essere considerata una tecnica routinaria, anche se sofisticata, o è ancora riservata ad un uso sperimentale?

Oscillometry - a Fashion?

1956
Du Bois

Musers
Goldman

1970
Smidt
Korn
Landser

1985
Van de
Woestijne

Zwaart
2000

Monofrequent

Multifrequent

Parameter Interpretation

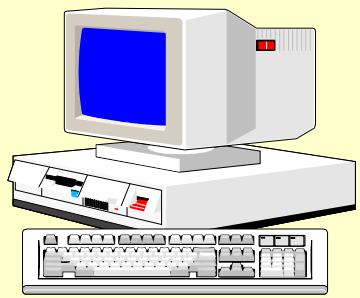
Analytics (FFT)

Z, φ

experimental laboratory

10 min

Zrs



2 min

R5, X5

routine !

15 sec

0.001 sec

World-wide use of Oscillometry

1995 - 50 multifrequent oscillometric units in use

2003 - 1,500 devices in clinical practise

- ⇨ Scandinavia (Finland) 100 - standard resistance measurement
- ⇨ Germany / Austria 550 - already in clinical routine (paediatric, occupational m.)
- ⇨ Netherlands 100 - clinical routine
- ⇨ China 200 - validated method
- ⇨ USA 220 - clinical trials
- ⇨ Asia, South America, Canada 150
- ⇨ France 150 - paediatric medicine
- ⇨ UK 30 - paediatric medicine