

Extrafine: nuova frontiera nel trattamento delle patologie ostruttive respiratorie

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SCDU Pneumologia Presidio Molinette



Conflict of interest statement

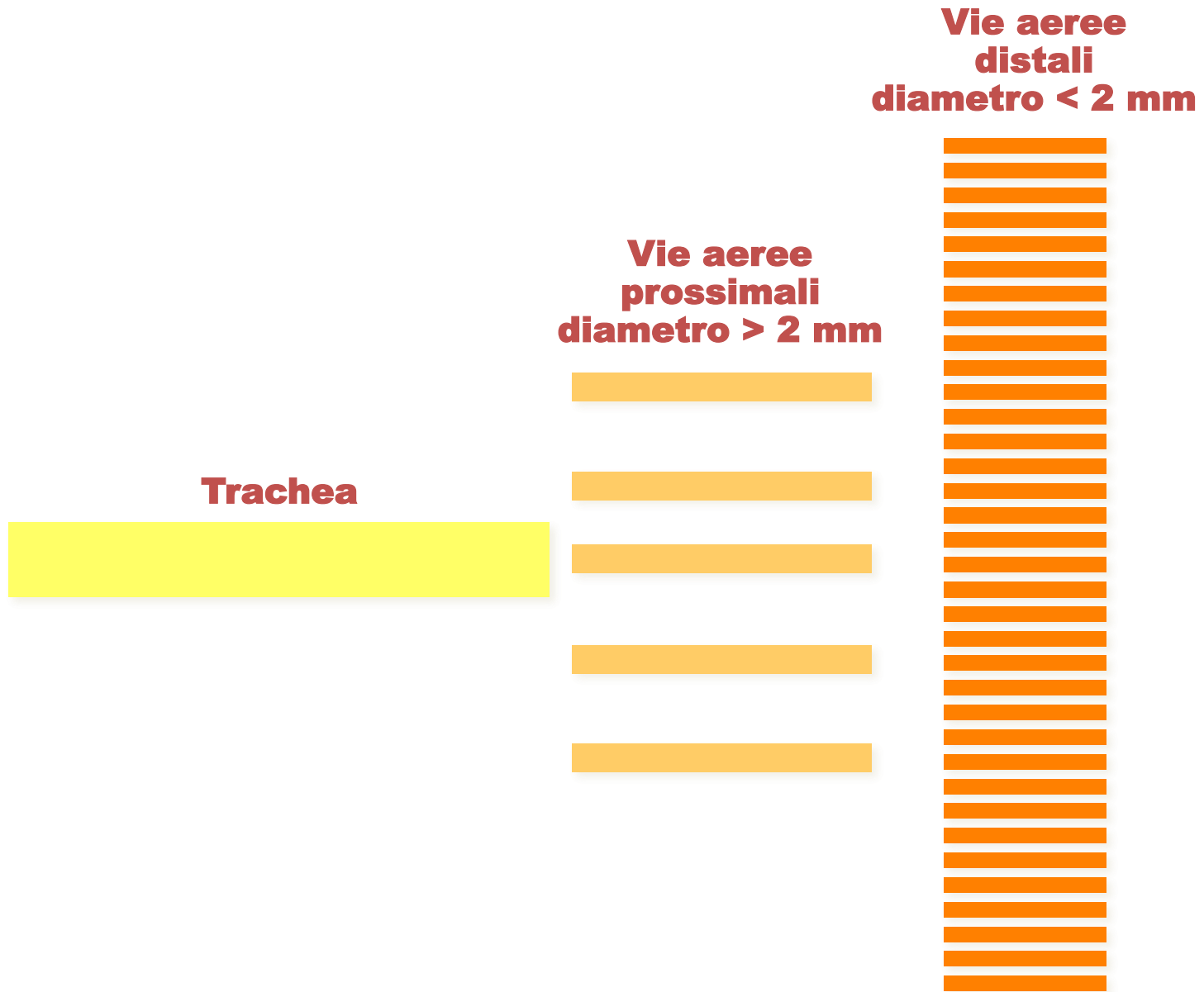
- **Speaker's hononaria from:**

- Astra Zeneca, Boehringer Ingelheim, Pfizer, GSK, Menarini, Novartis, Chiesi, Almiral, Mundipharma, ABC Farmaceutici, Dompè, Guidotti and Malesci, Biotest

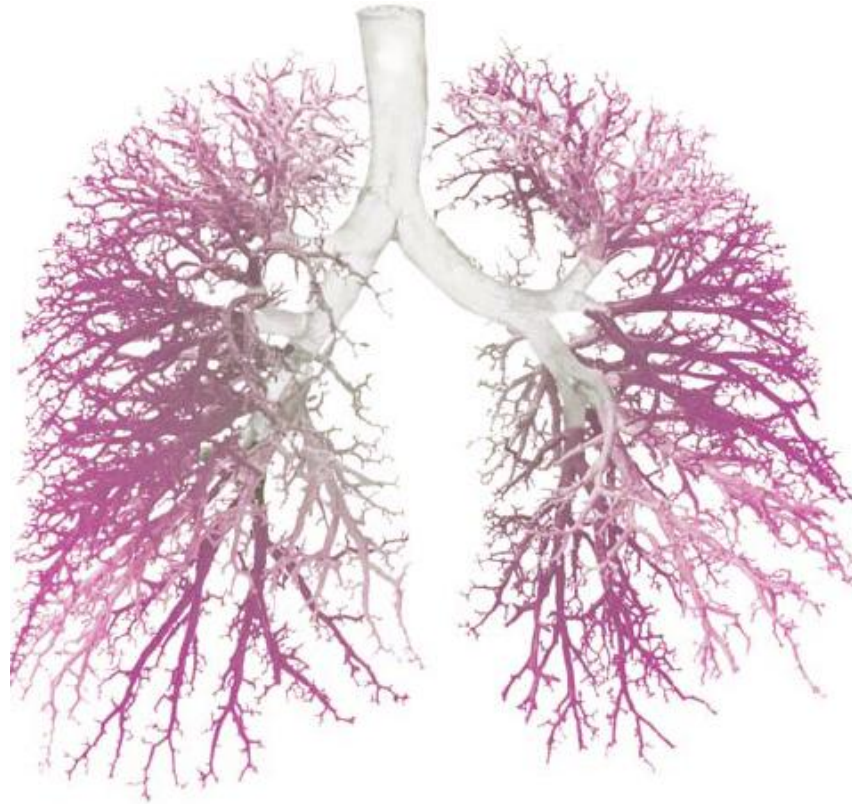
- **Consultant for training:**

- Almiral, Novartis, Biotest.





Principali differenze tra vie aeree prossimali e distali



Vie aeree centrali¹⁻⁵

Diametro Interno	>2 mm
Superficie totale	Ridotta
Densità dei recettori dei corticosteroidi	Alta
Densità dei recettori β_2 -adrenergici	Bassa

Vie aeree periferiche¹⁻⁵

Diametro Interno	≤ 2 mm
Superficie totale	Ampia
Densità dei recettori dei corticosteroidi	Alta
Densità dei recettori β_2 -adrenergici	Alta

L'immagine mostra le vie aeree polmonari⁶

References:

1. Tashkin DP. Allergy and Asthma Proc 2002; 23:233-42, 2 Barnes Nature 1982, 3 Adcock IM et al. Am J Respir Crit Care Med 1996; 154:771-82, 4 Lipworth BJ Respiratory Medicine 2000; 94:S13-S16. 5. Tulic et al. Respir Res 2001; 2:333-339. 6. McMinn RMH et al. Atlante a colori di anatomia umana, Volume 2. Casa editrice Ambrosiana 1995

Principali differenze tra vie aeree prossimali e distali

VIE AEREE PROSSIMALI

Diametro > 2 mm

Piccola area di sezione trasversa

80-90% delle resistenze totali

Flusso turbolento

***Assenza di scambi gassosi
(spazio morto anatomico)***

VIE AEREE DISTALI

Diametro < 2 mm

Grande area di sezione trasversa

10-20% delle resistenze totali

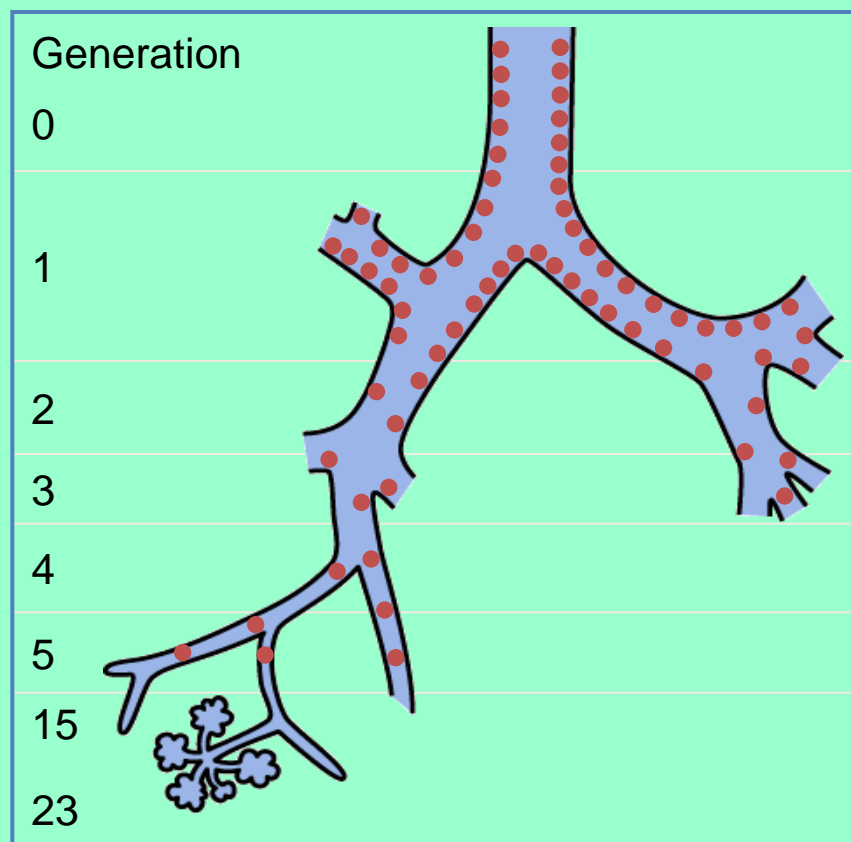
Flusso laminare

Contributo agli scambi gassosi

Piccole vie aeree: sono così piccole?

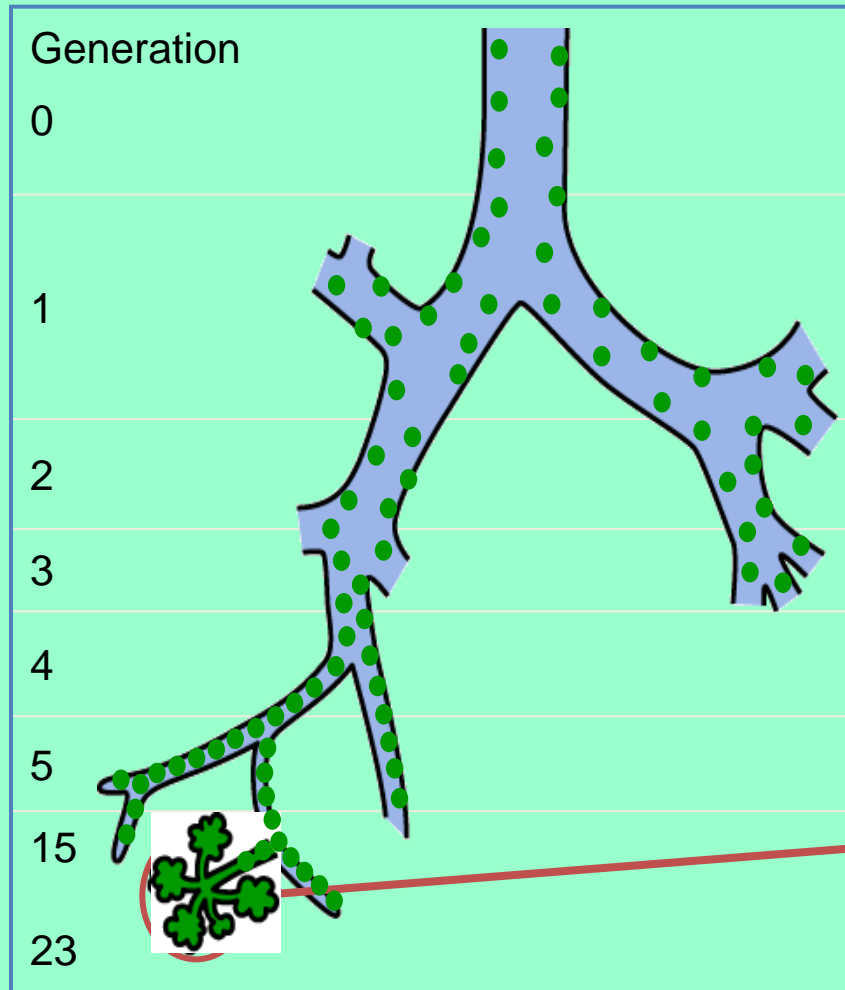


Localizzazione dei recettori muscarinici (M1-M2-M3):

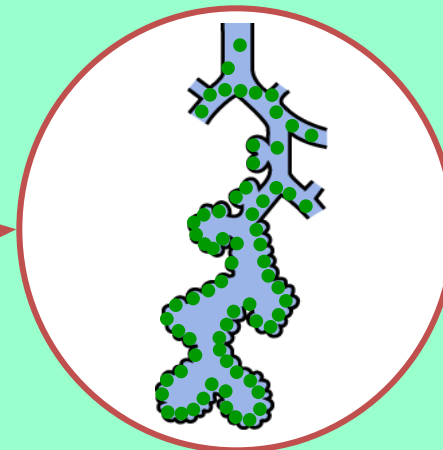


- Muscolatura bronchiale
- Cellule epiteliali
- Terminazioni nervose
- Ghiandole submucosali

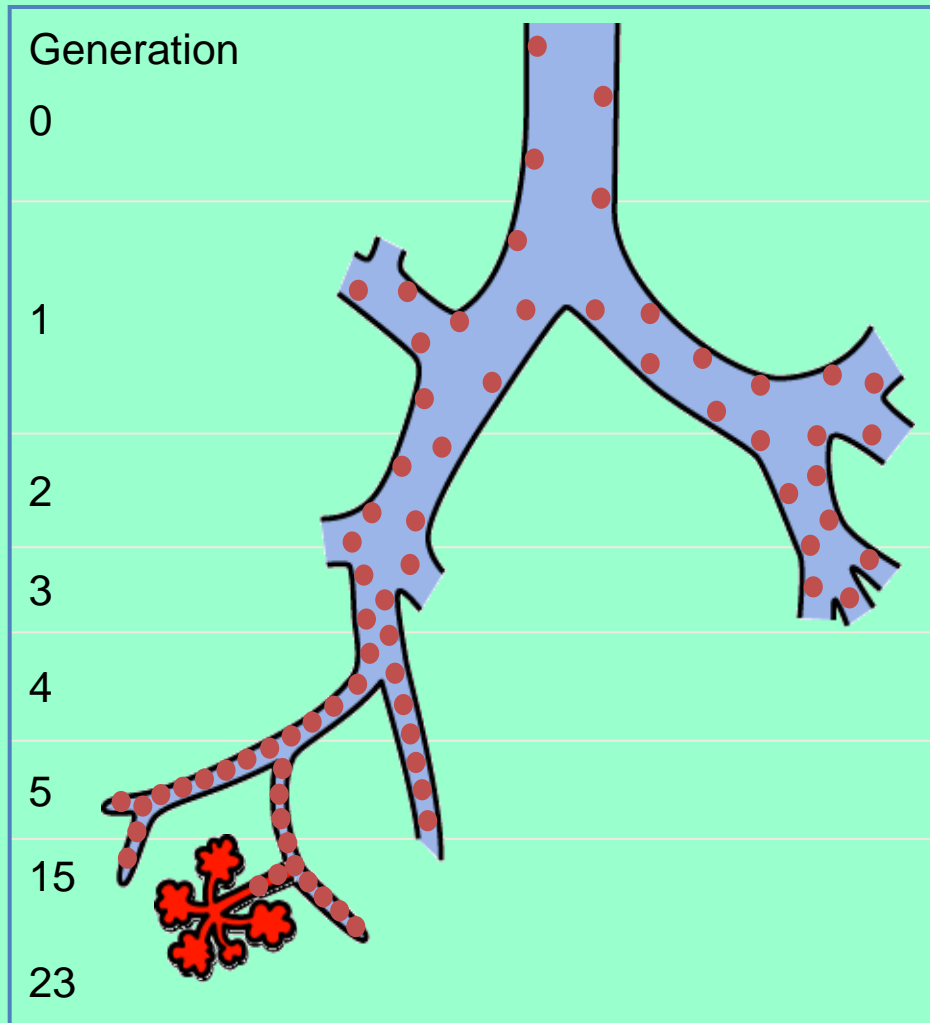
Localizzazione dei recettori dei corticosteroidi



- Alveoli
- Cellule dell'endotelio vascolare
- Cellule del muscolo liscio vascolare
- Cellule dell'epitelio bronchiale



Localizzazione dei recettori beta-2:



Barnes, Nature, 1982

- Muscolatura bronchiale
- Cellule epiteliali
- Endotelio vascolare e tessuto muscolare liscio
- Terminazioni nervose presinaptiche
- Cellule infiammatorie (eosinofili, linfociti, macrofagi)

DEFINIZIONE: 2006

Other clinical signs are only likely to be present if patients are examined during symptomatic periods. Features of hyperinflation result from patients breathing at a higher lung volume in order to increase outward retraction of the airways and maintain the patency of smaller airways (which are narrowed by a combination of airway smooth muscle contraction, edema, and mucus hypersecretion). The combination of hyperinflation and airflow limitation in an asthma exacerbation markedly increases the work of breathing.

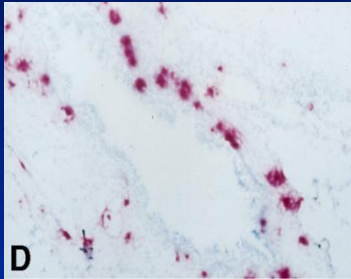


GLOBAL STRATEGY FOR
ASTHMA MANAGEMENT AND PREVENTION

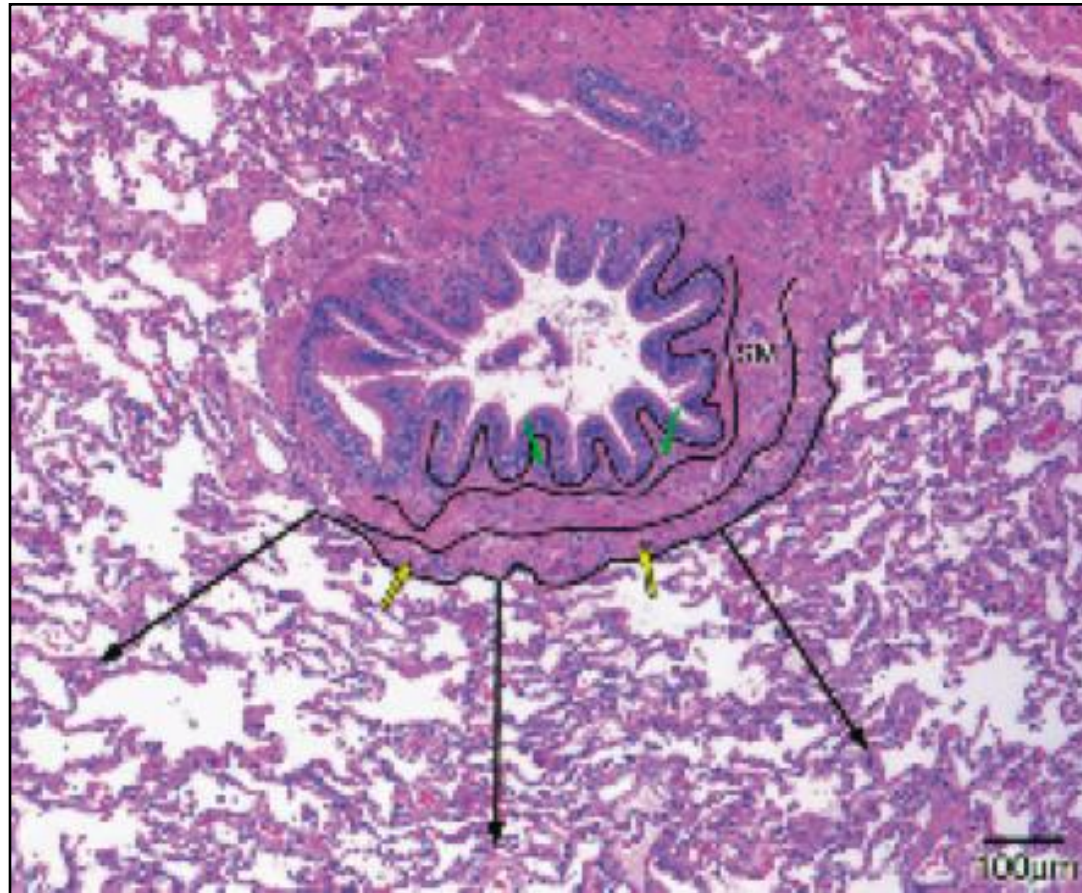
Revised 2006

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***Vi è evidenza di infiammazione
nelle piccole vie aeree?***



Preparato istologico di via aerea periferica



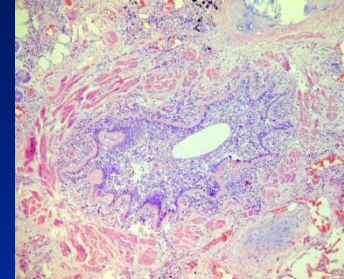
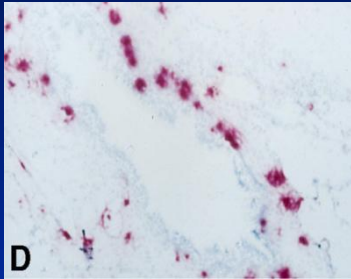
REVIEW

Update on the roles of distal airways in asthma

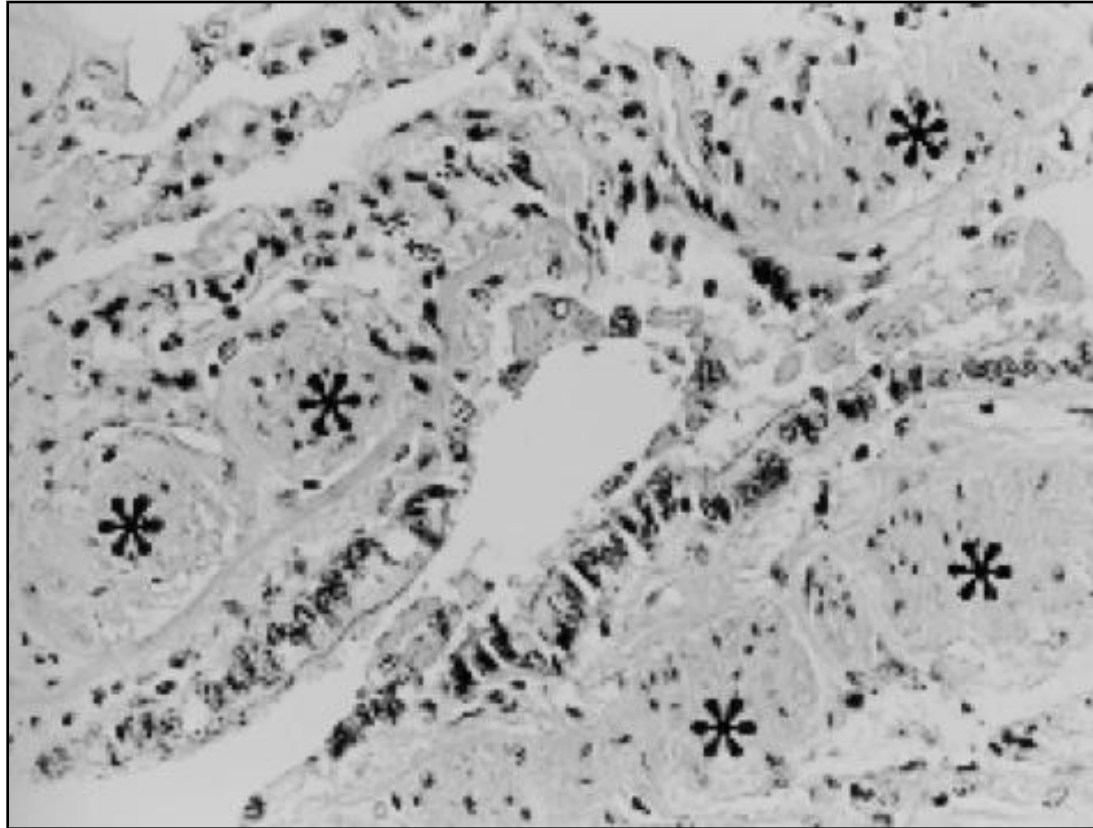
CONCLUSION

Both proximal and distal airways are implicated in asthma pathophysiology. Although inflammatory cell infiltrate and activation appear similar in proximal and distal airways in most cases of asthma, both the magnitude of inflammation and activation of inflammatory cells appear to be more important in distal airways in severe and uncontrolled asthma. Involvement of distal airways appears to occur early in life.

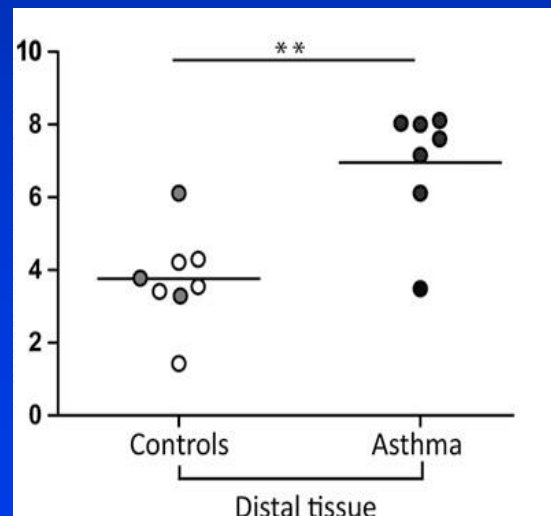
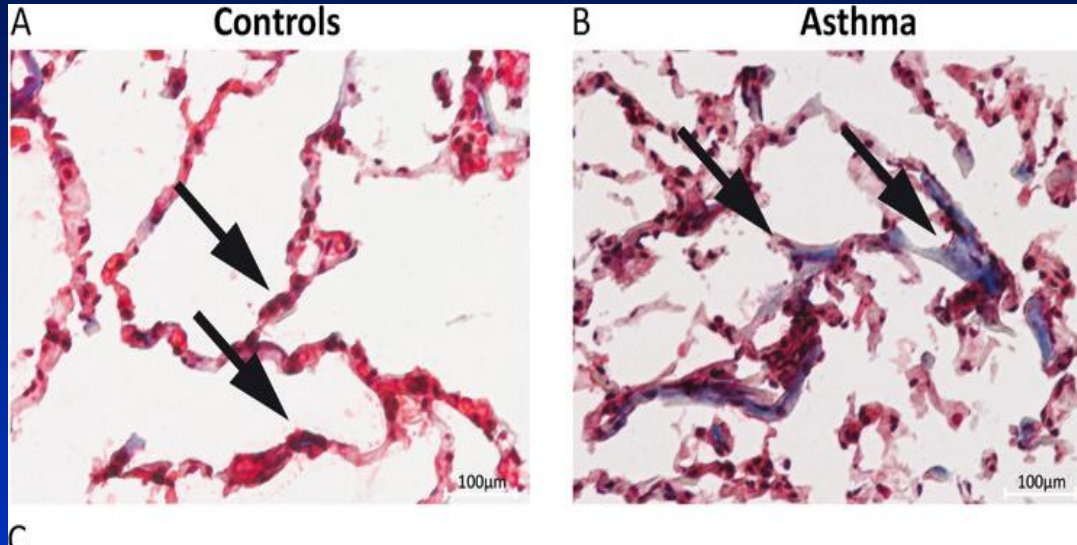
***Vi è evidenza di rimodellamento
nelle piccole vie aeree?***



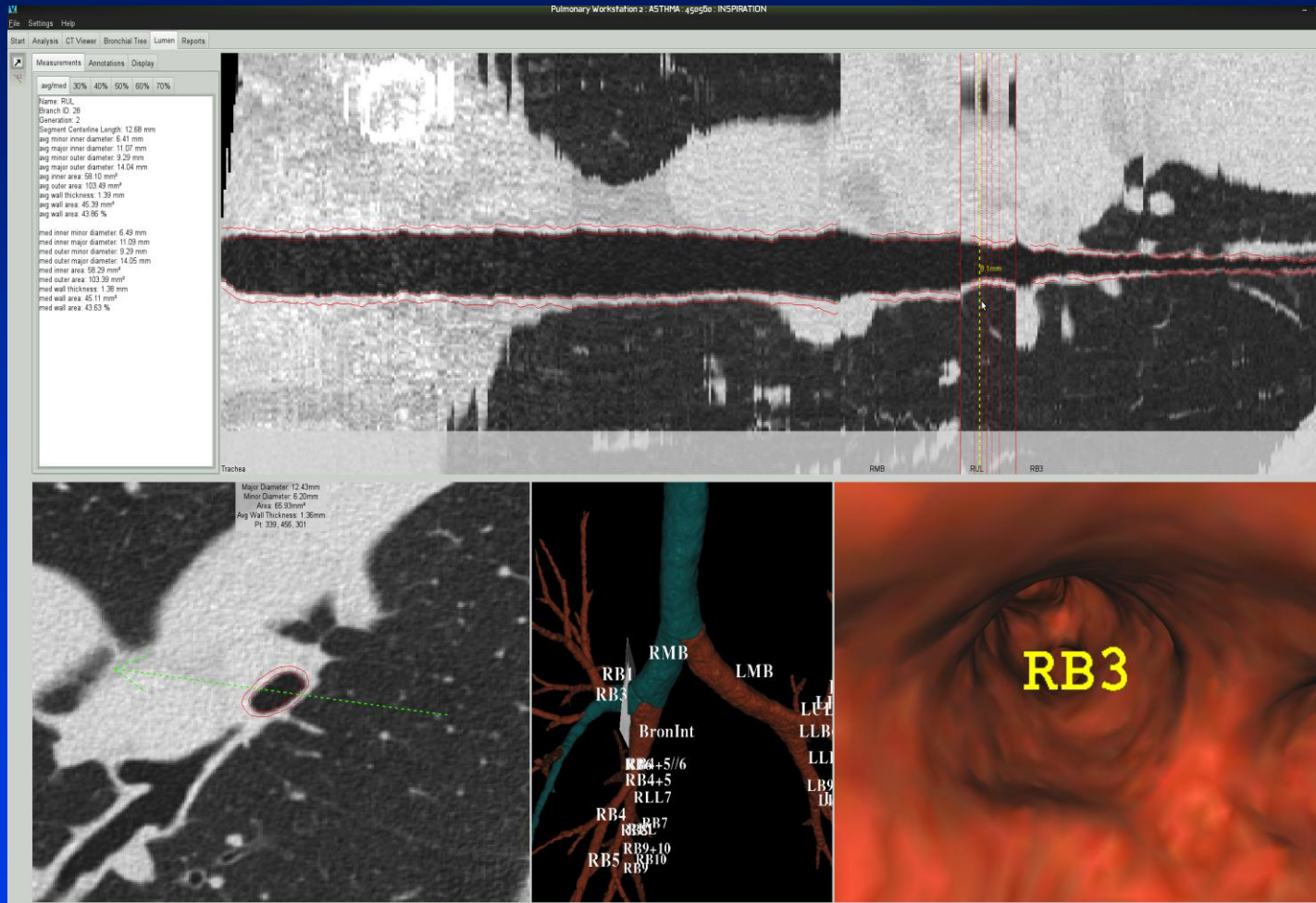
Rimodellamento delle piccole vie aeree per ipertrofia del muscolo liscio nell'asma fatale



Altered matrix production in the distal airways of mild asthmatics

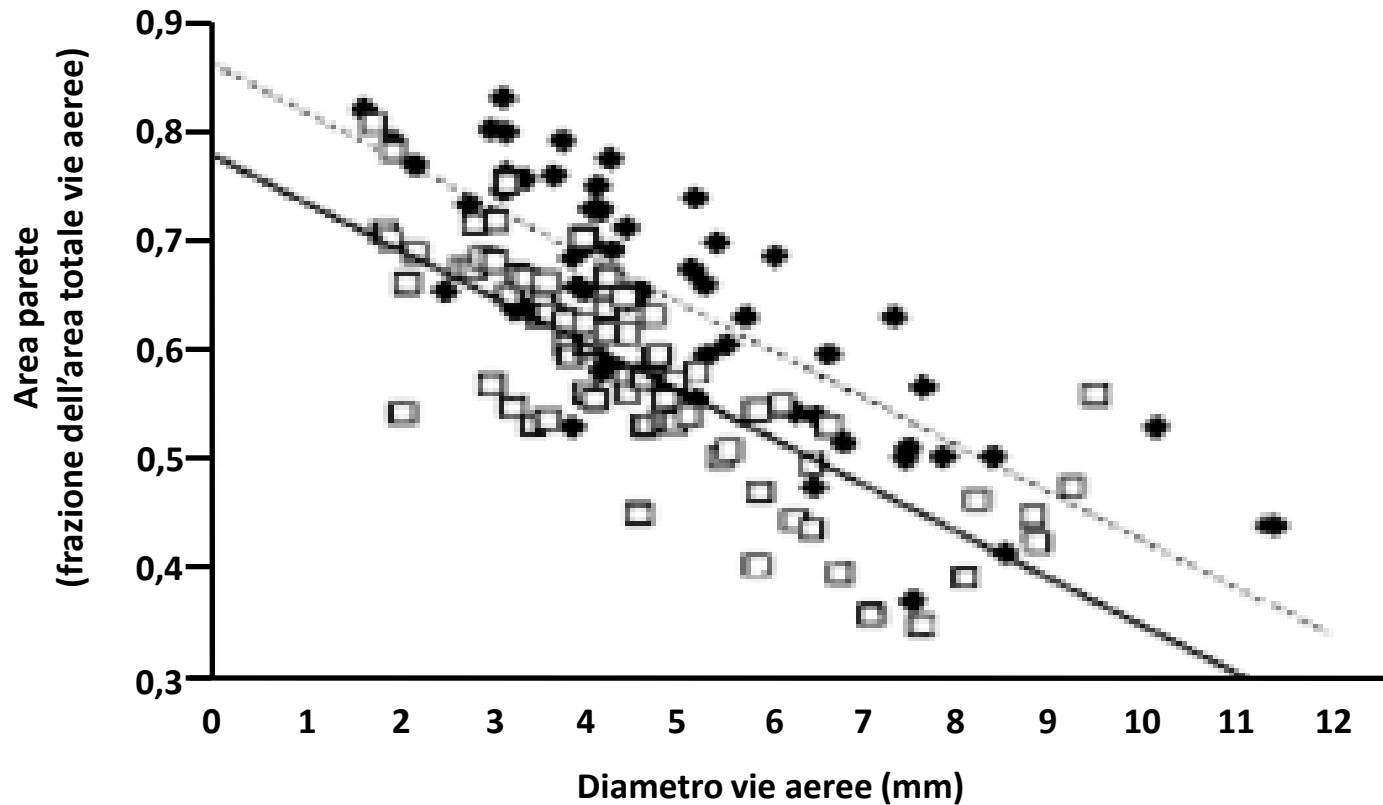


Imaging e valutazione dello spessore della parete bronchiale

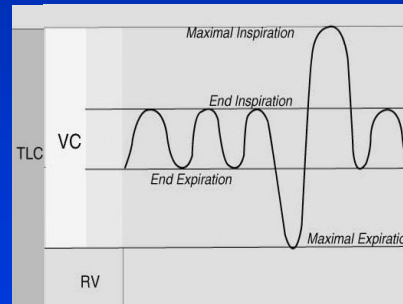
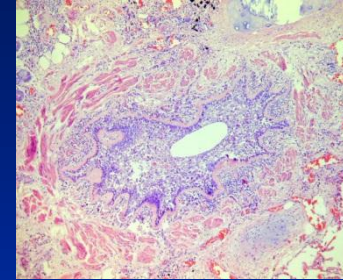
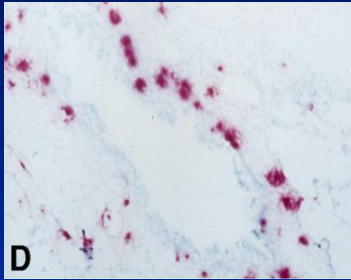


VIDA software package (Dept. of Radiology, Univ. of Iowa)

Lo spessore della parete bronchiale mediante HRCT è aumentato negli asmatici rispetto ai soggetti sani

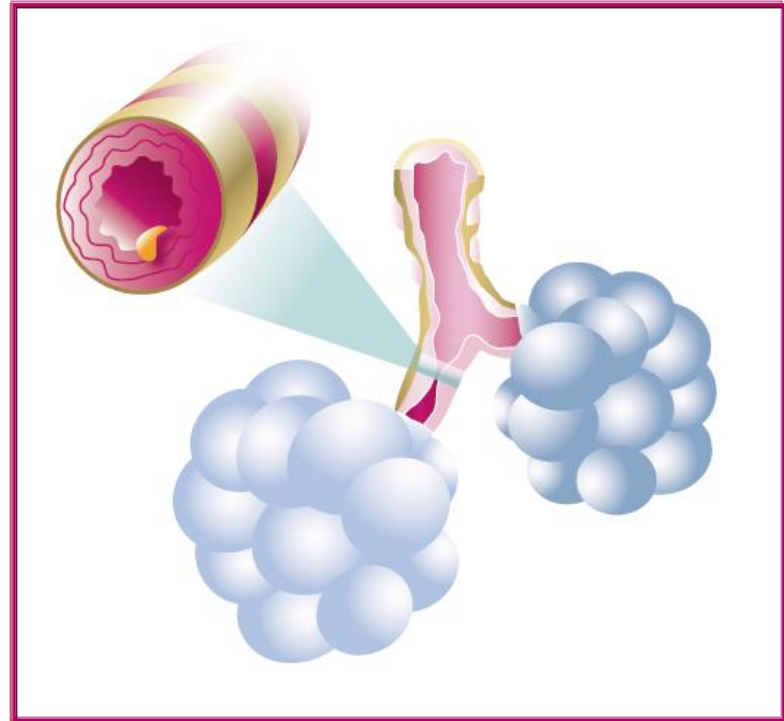


L'infiammazione e il rimodellamento delle piccole vie aeree si traducono in alterazioni funzionali?



Air Trapping

- Air trapping: ritenzione anormale di aria nei polmoni dopo l'espiazione, il paziente non è in grado di espellere completamente l'aria a causa dell'ostruzione delle piccole vie aeree.¹⁻³

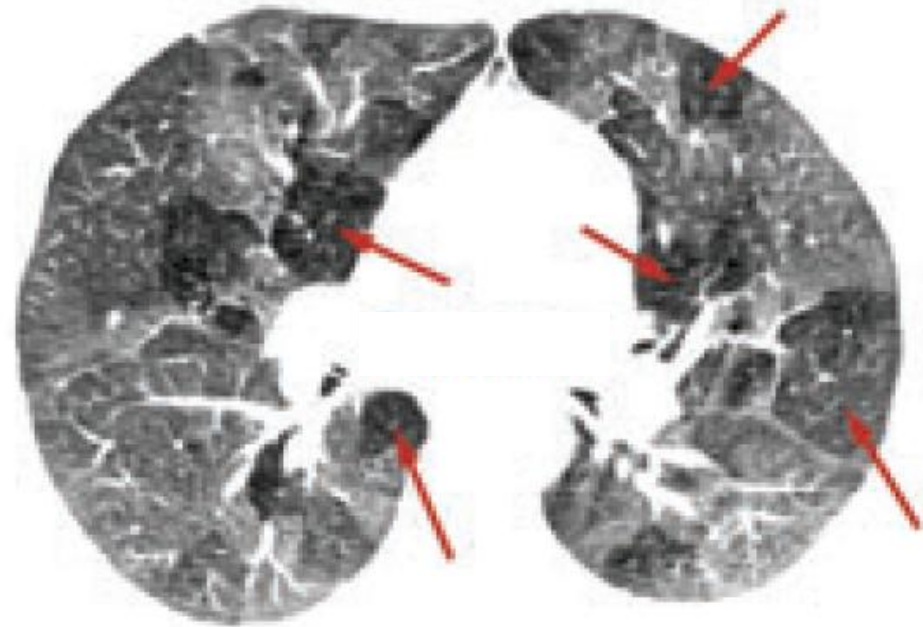


Rappresentazione schematica dell'ostruzione dovuta ad airtrapping nelle piccole vie aeree ⁴

Valutazione dell'air trapping tramite HRTC



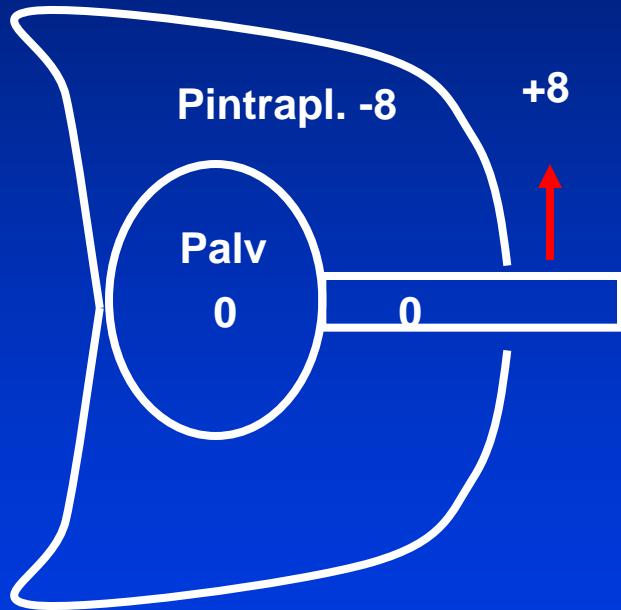
Fase inspiratoria



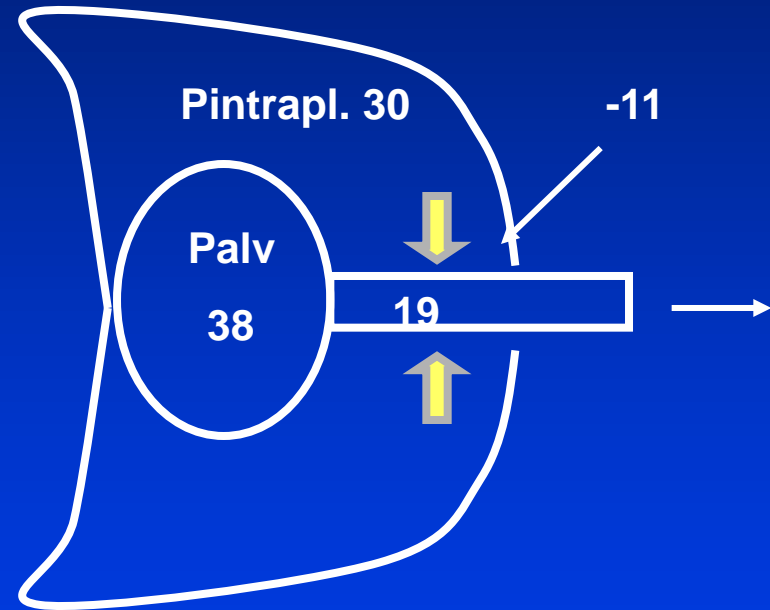
Fase espiratoria

Compressione dinamica delle vie aeree

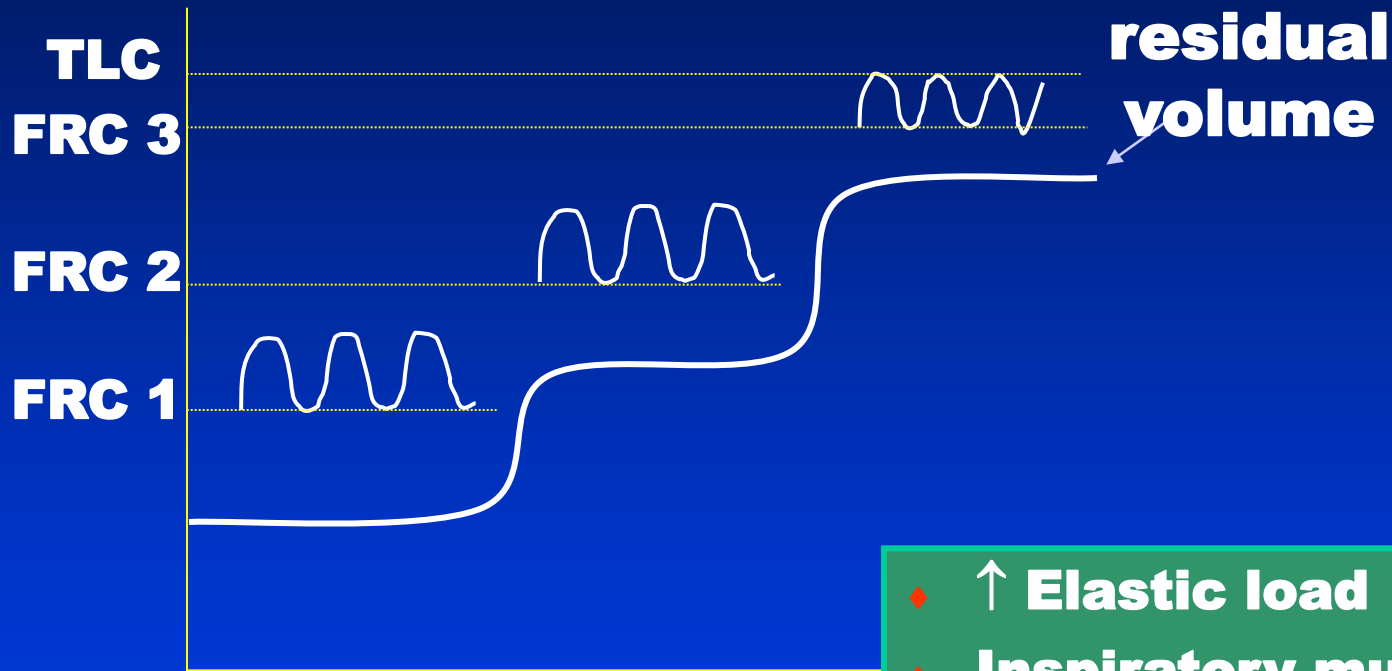
Fine-inspirazione



Espirazione forzata

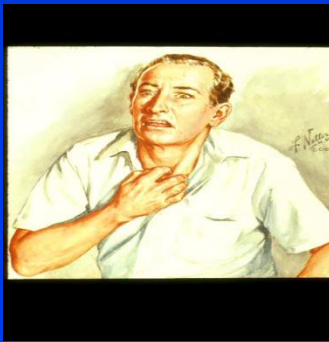
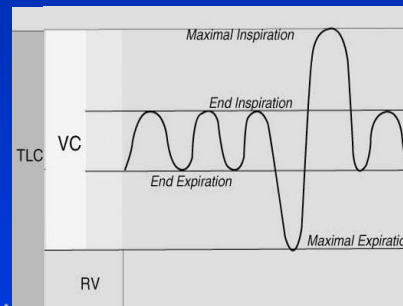
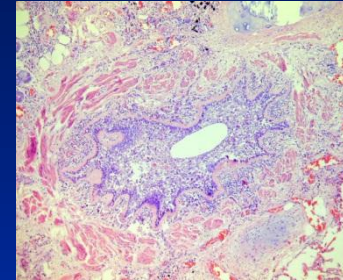
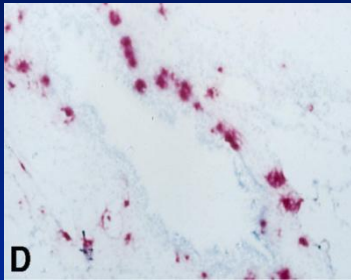


Air trapping e iperinflazione polmonare



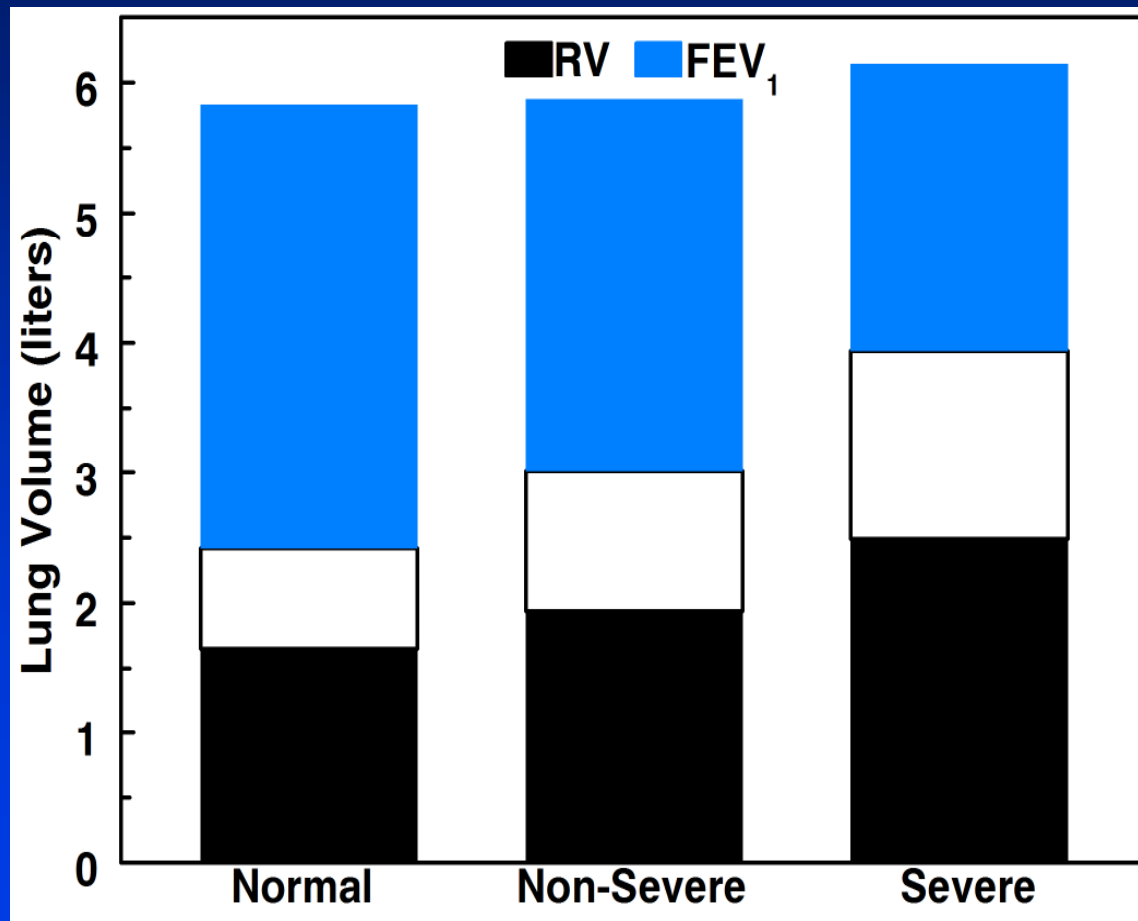
- ◆ **↑ Elastic load**
- ◆ **Inspiratory muscle weakness**
- ◆ **Reduced V_T expansion**
- ◆ **Early ventilatory limitation to exercise**
- ◆ **Dyspnea**

Le alterazioni funzionali delle piccole vie aeree si traducono in sintomi respiratori?

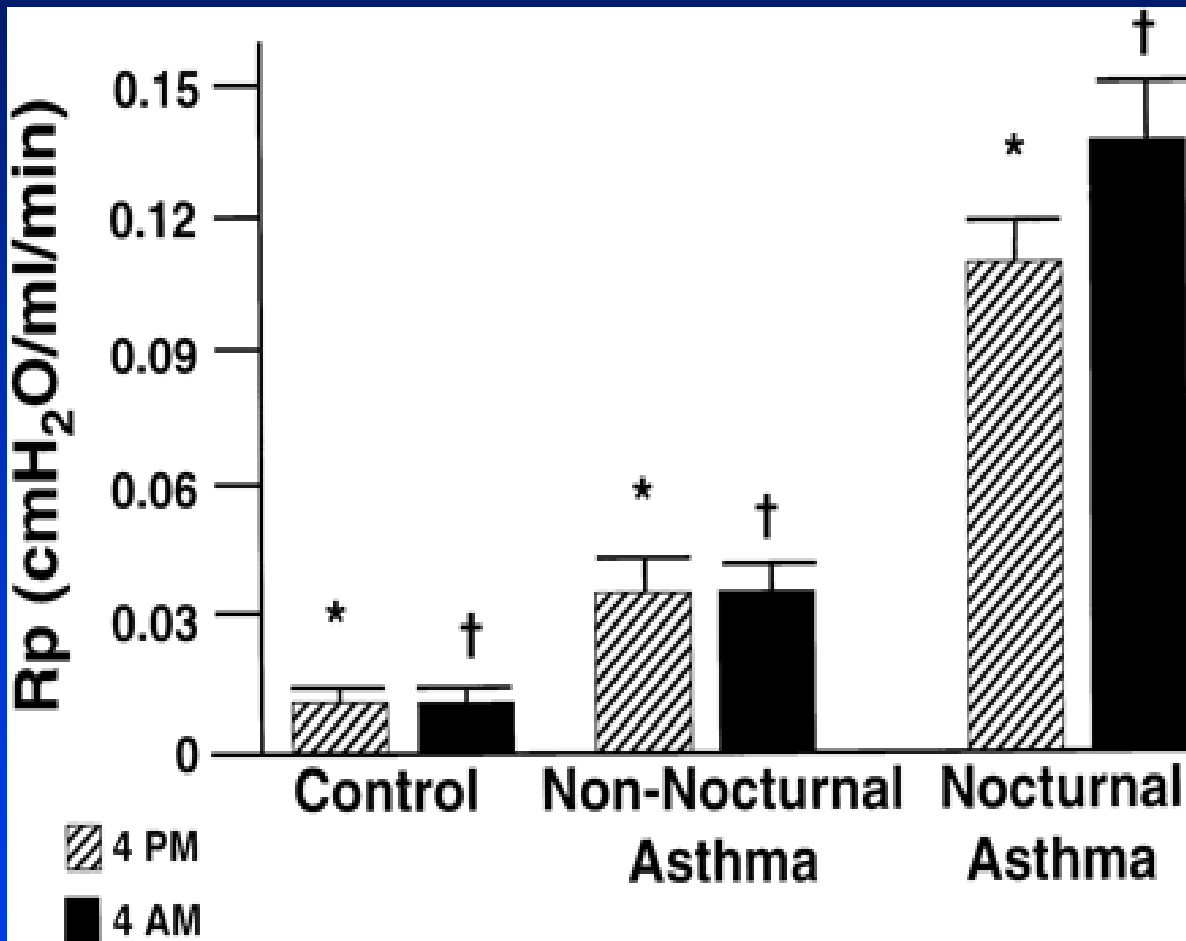


Parametri funzionali nell'asma grave

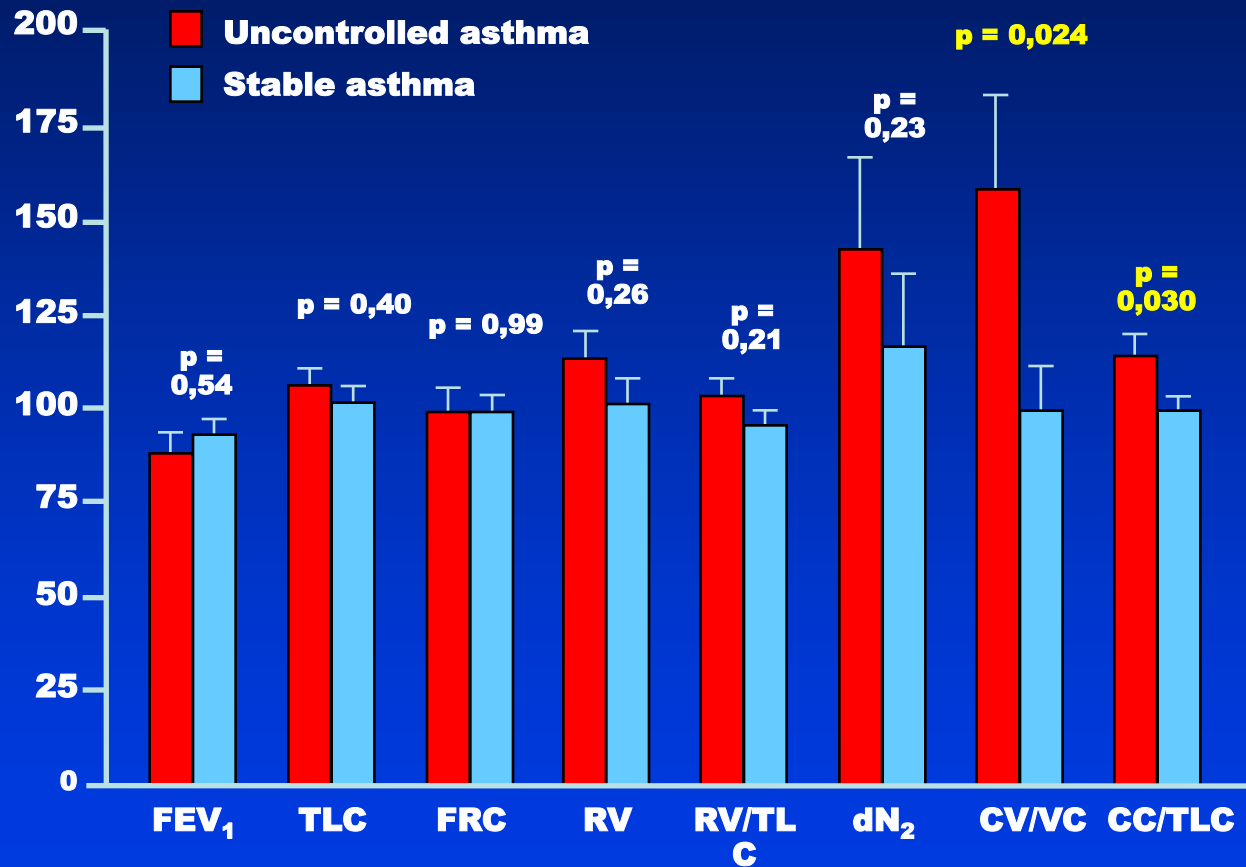
Air trapping



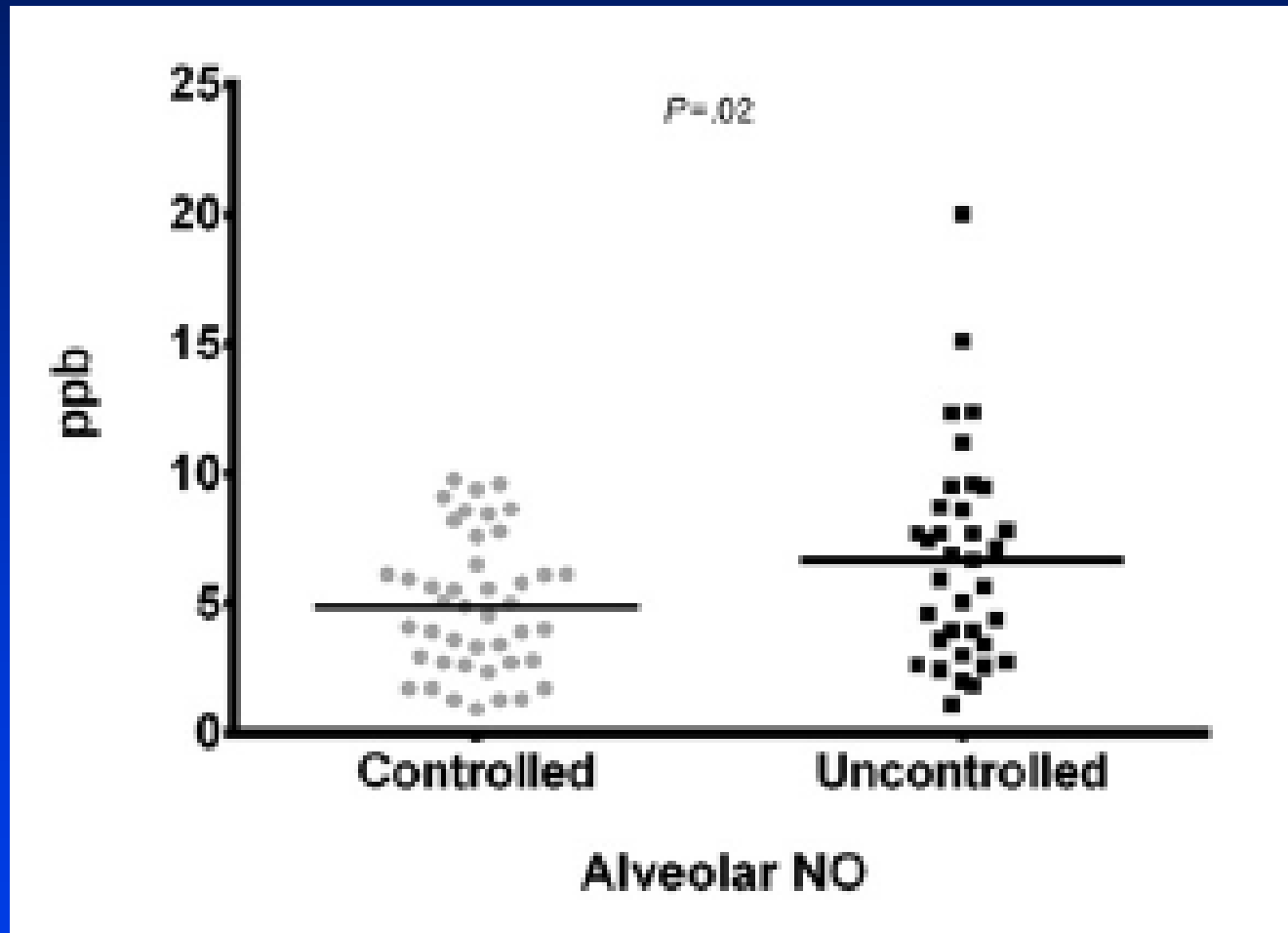
Le resistenze periferiche sono aumentate nell'asma notturno



L'asma con frequenti riacutizzazioni si associa ad alterazioni funzionali delle piccole vie aeree

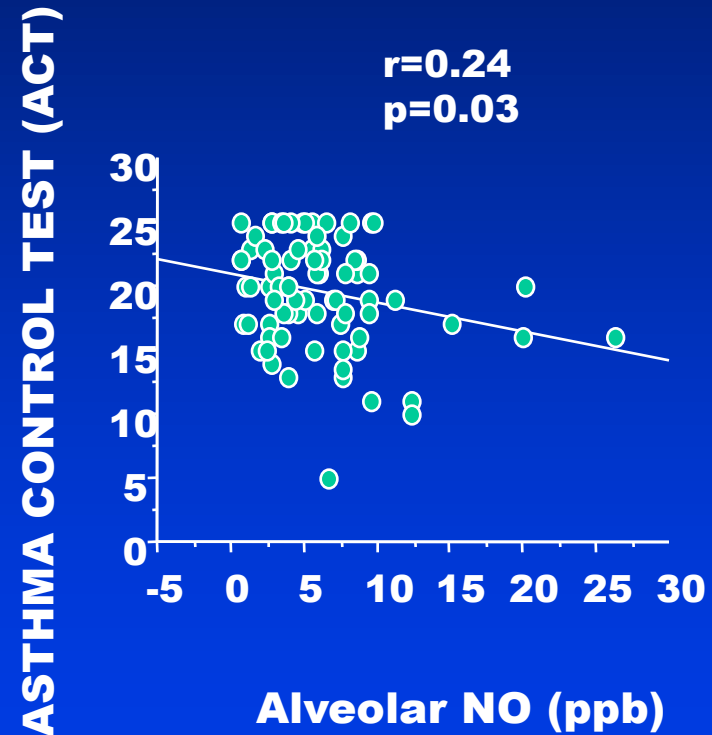
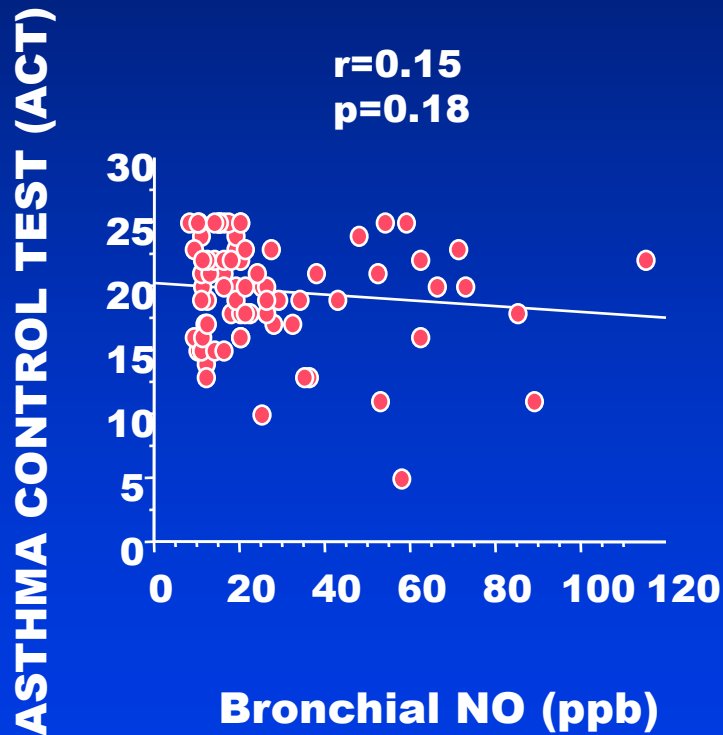


L'asma non controllato si associa ad alterazioni infiammatorie delle piccole vie aeree



L'asma non controllato si associa ad alterazioni infiammatorie delle piccole vie aeree

Alveolar NO

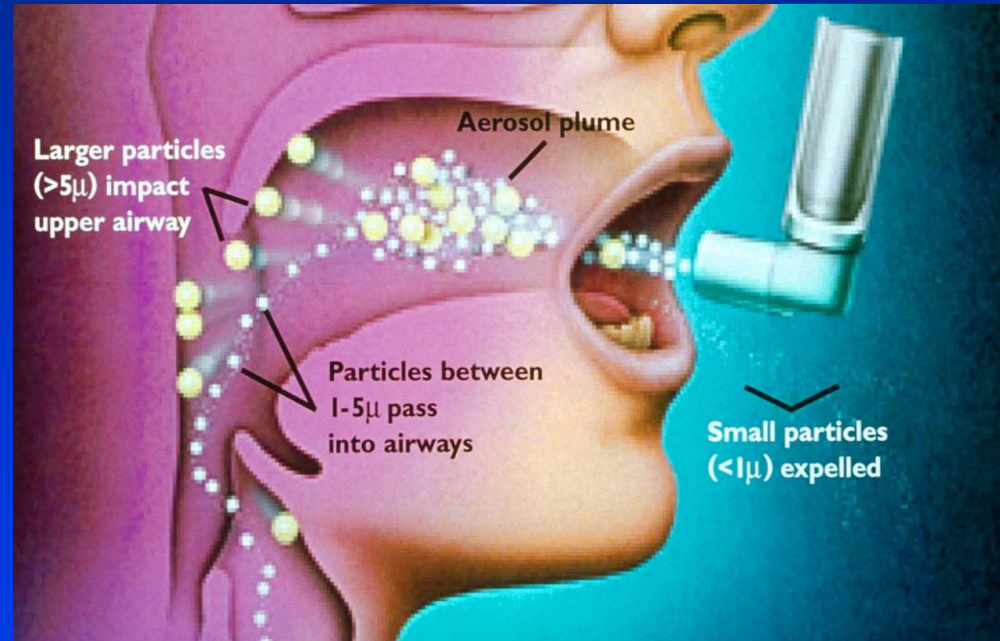


I fattori che condizionano la deposizione polmonare

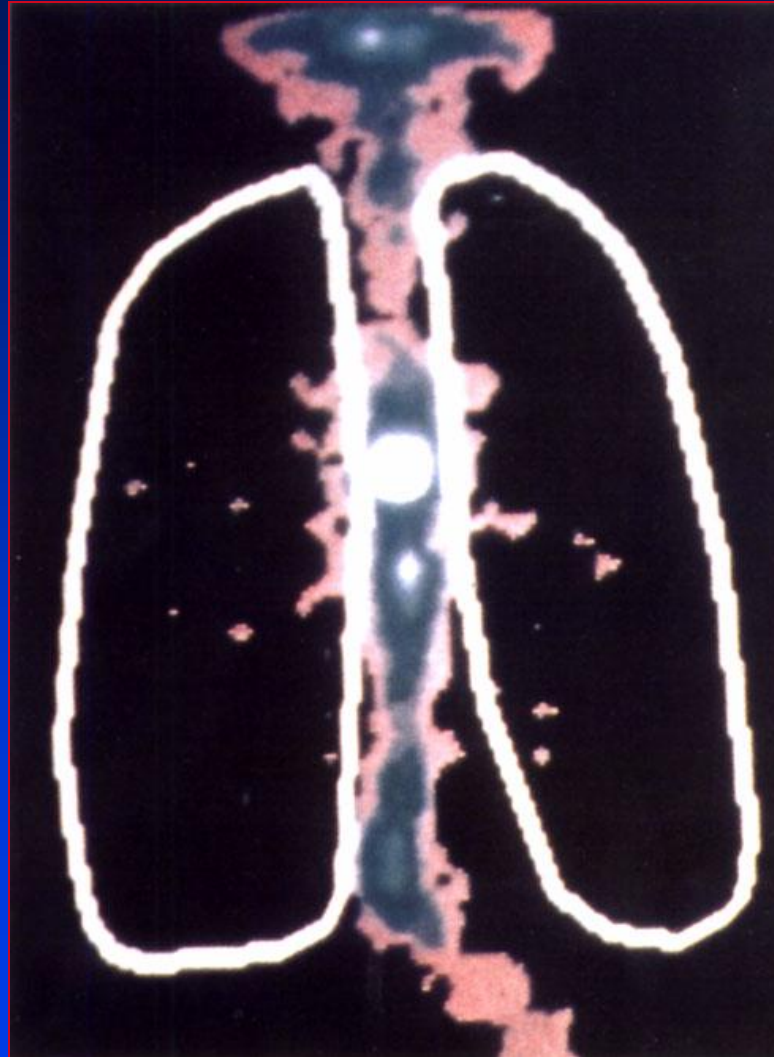
Erogatore



Dimensioni delle particelle

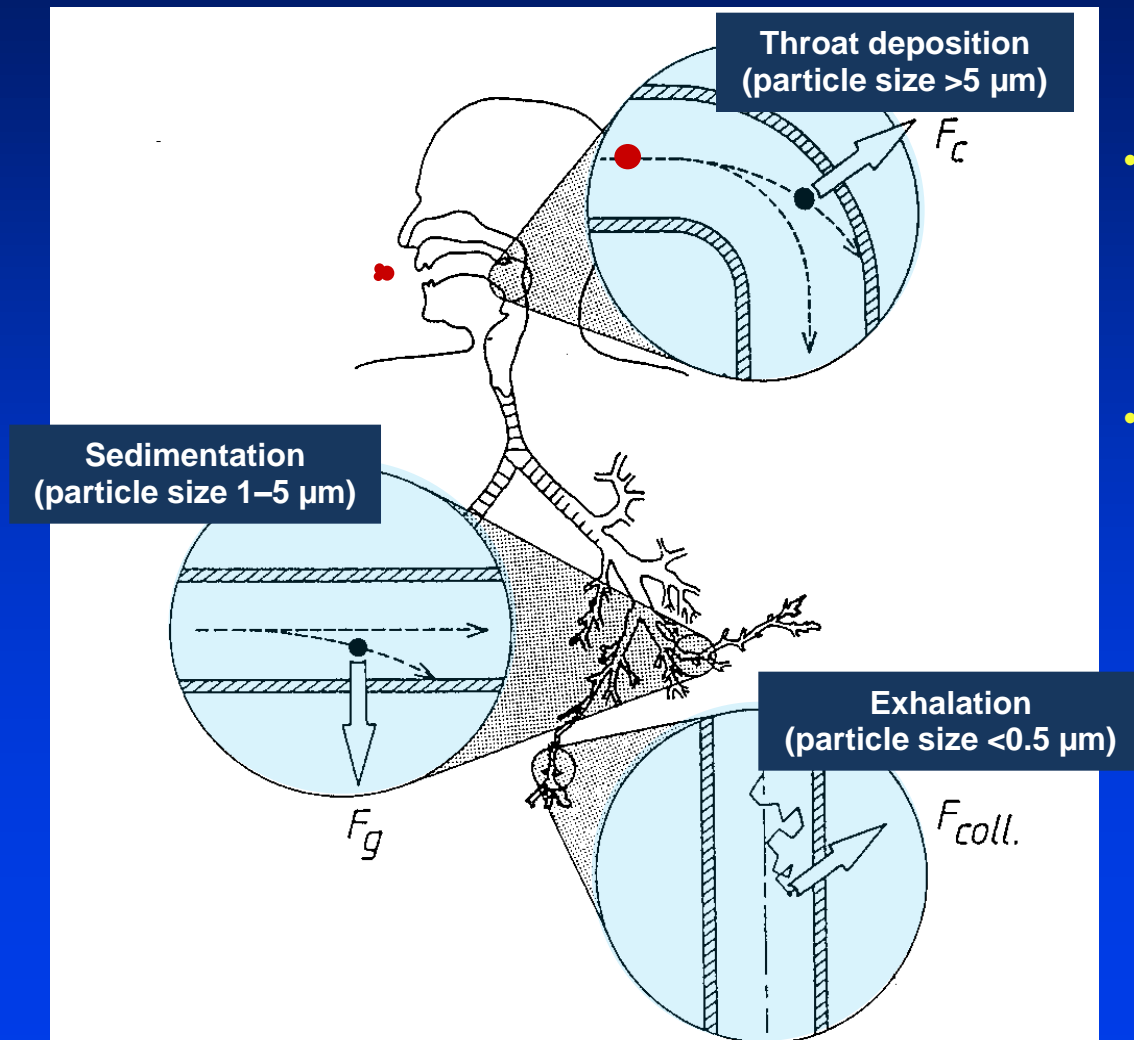


Deposizione di radiomarcato in soggetto con tecnica inalatoria scorretta



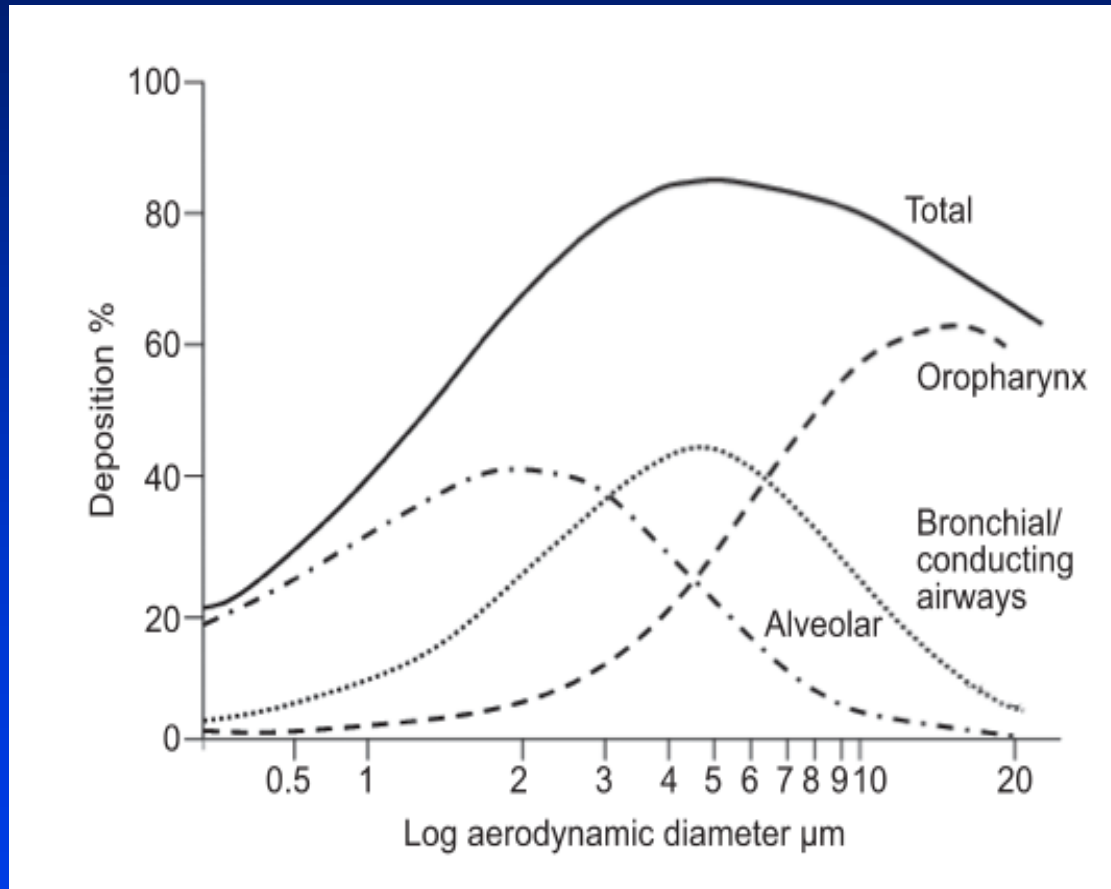
How particle size affects penetration and deposition

- The efficacy with which inhaled drug particles reach the target site in the lung is determined by:



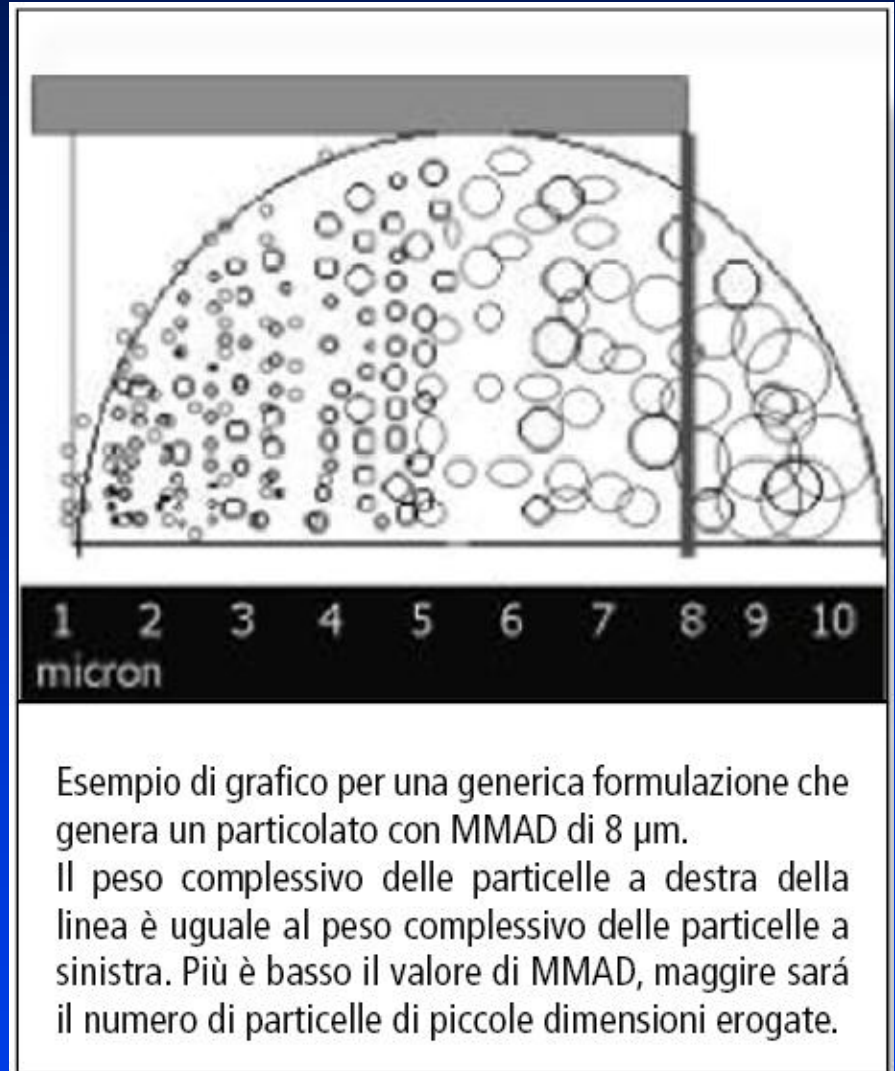
- Penetration of the particles into the airways
- Deposition of the particles on the wall of the airways

Deposizione del farmaco in funzione delle dimensioni delle particelle

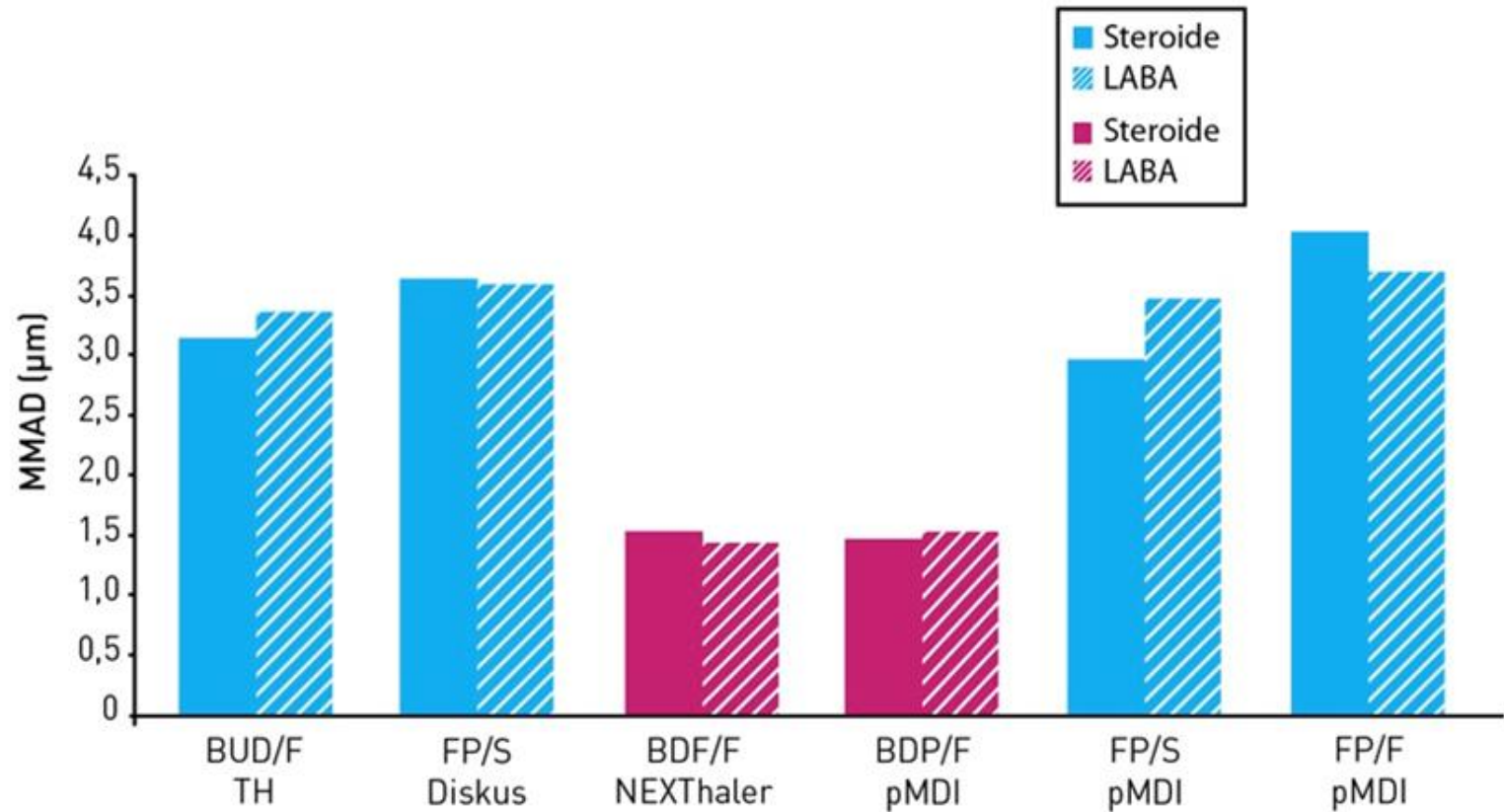


Diametro aerodinamico mediano di massa (MMAD)

Per descrivere la dimensione delle particelle che costituiscono un aerosol si indica il diametro (in μm) che divide in due (mediano) la distribuzione della massa delle particelle della nube aerosolica.

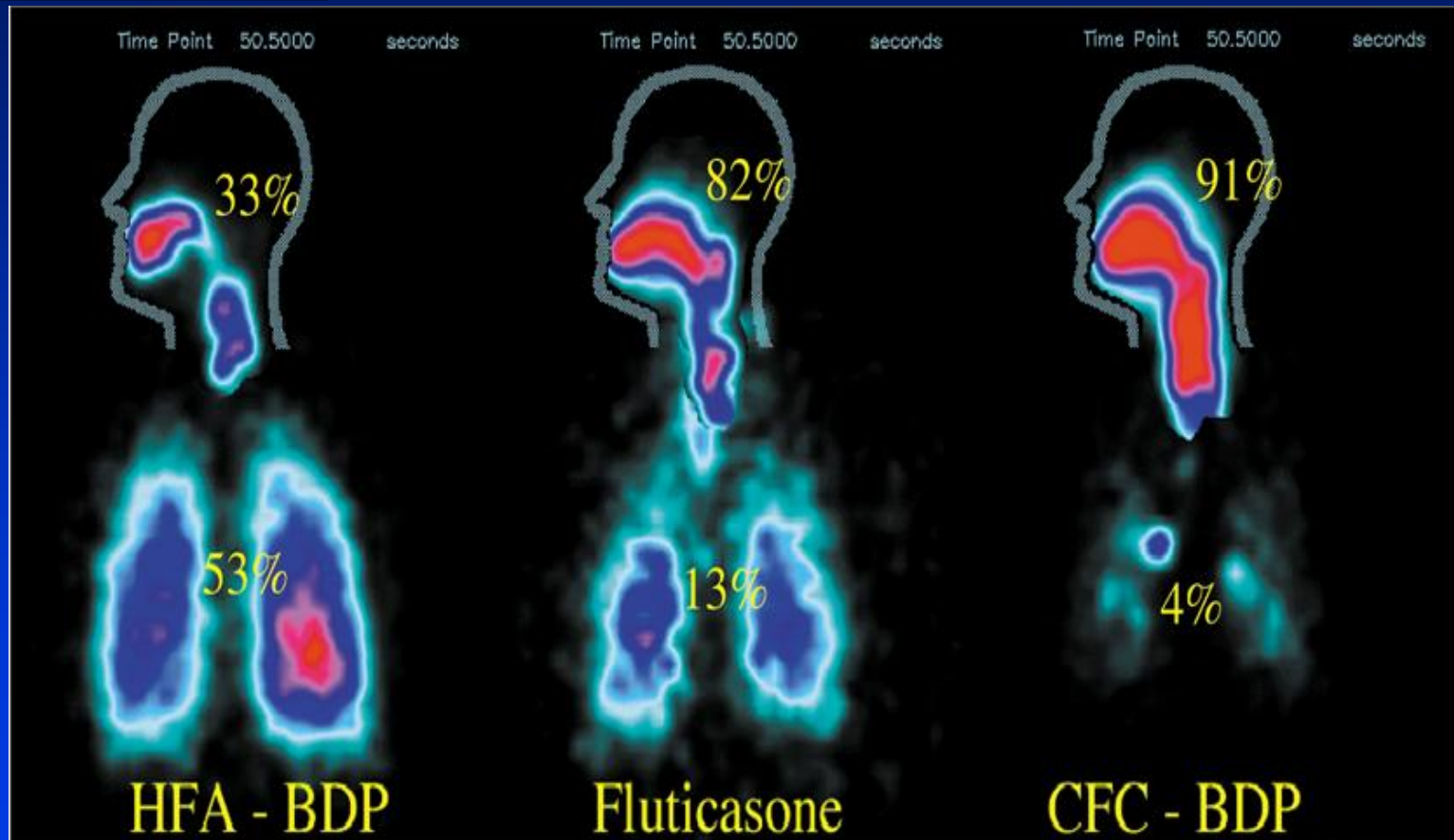


BDP/F SPRAY e NEXThaler erogano particelle di dimensioni (MMAD) dimezzate rispetto alle altre associazioni ics/labA



Soluzione, sospensione e formulazione

EXTRAFINE

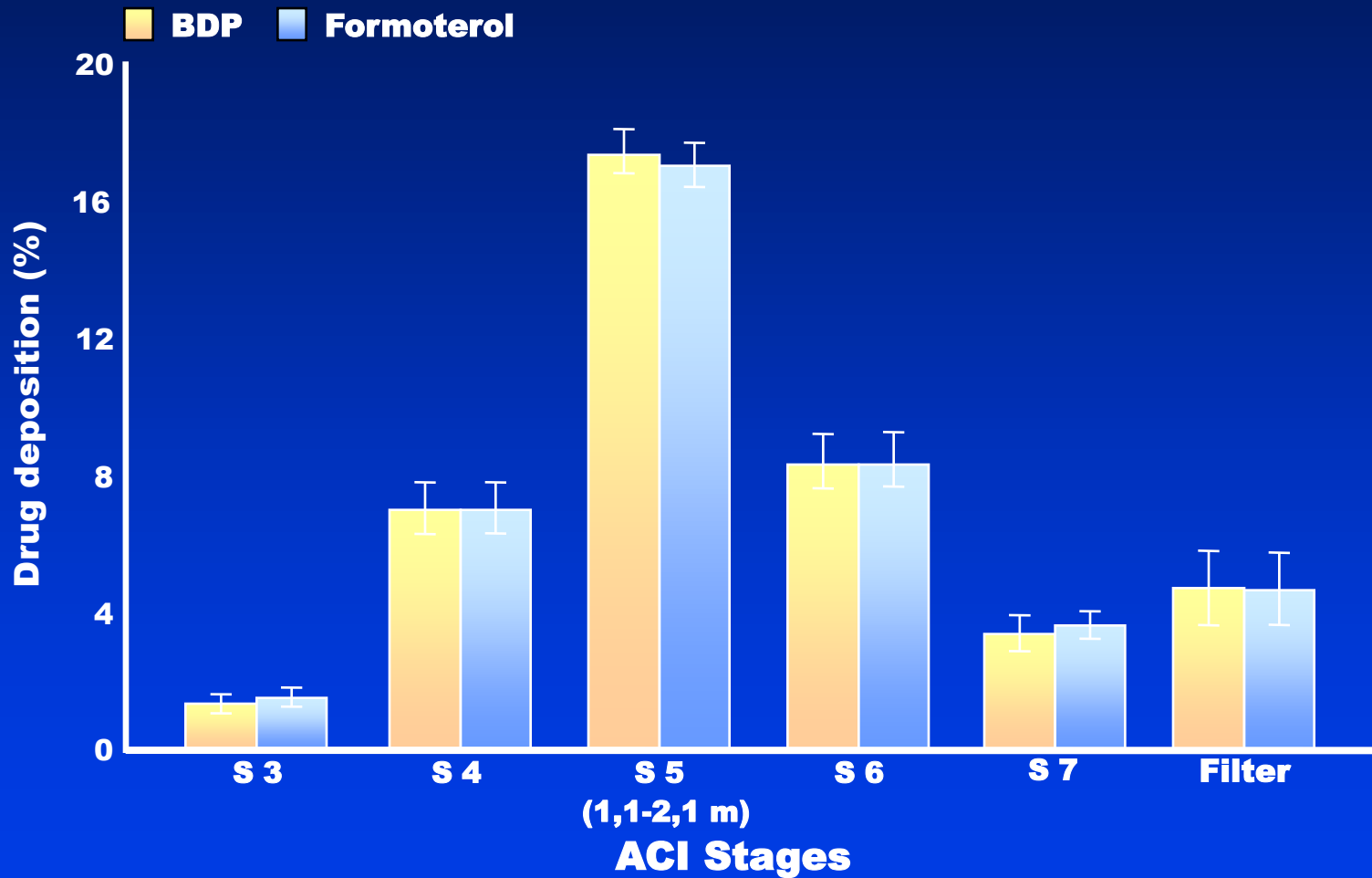


solution

suspension

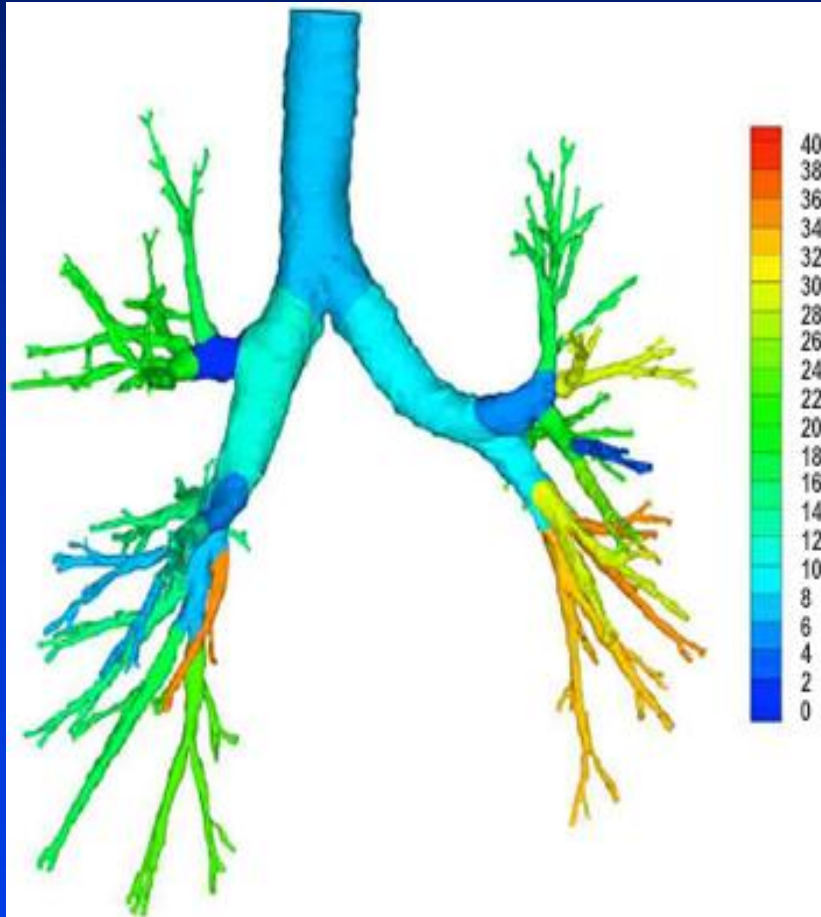
suspension

Co-deposition of BDP and formoterol HFA ultrafine



Andersen Cascade Impactor (mean \pm SD). Delivered dose

Extrafine BDP/F guarantees uniform treatment of inflammation and bronchoconstriction both in large and small airways



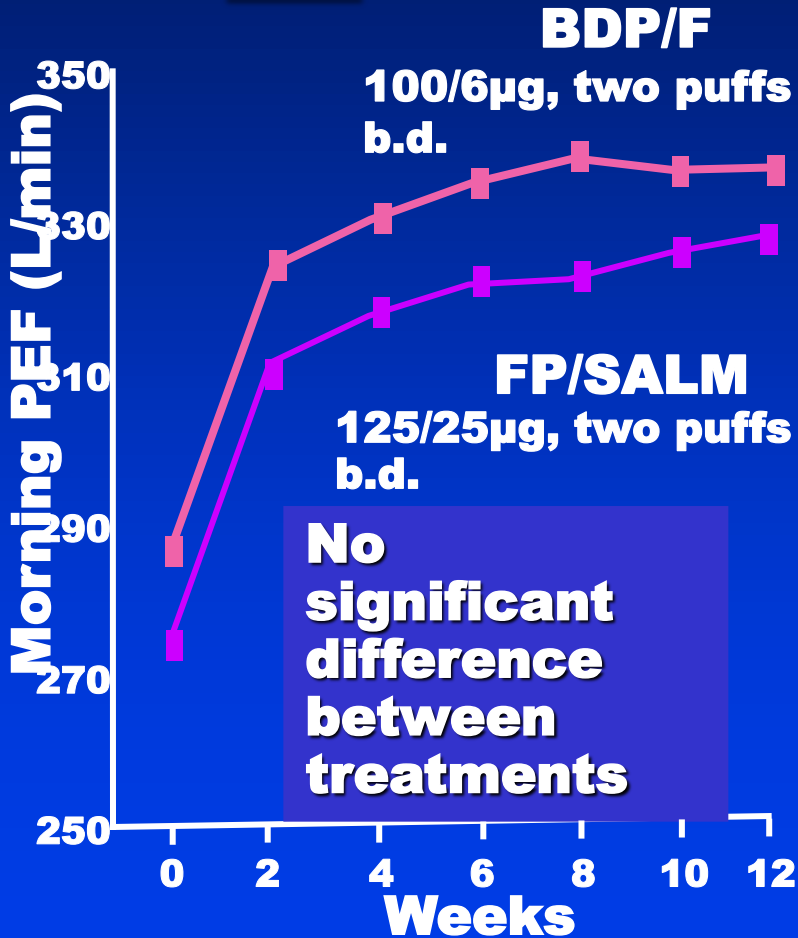
Airway volume changes from baseline (%) after 6 months of treatment and appropriate wash-out period for SABA.

Open-label clinical trial, 24 stable asthma patients, extrafine BDP/F fixed-dose combination vs baseline

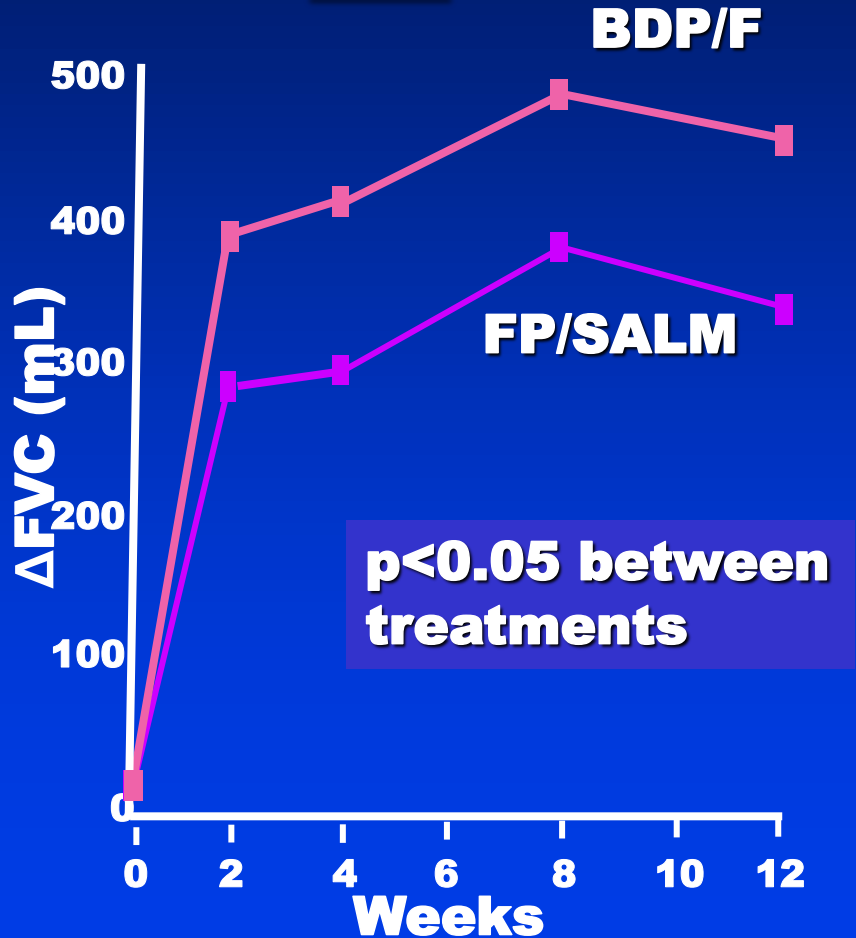
BDP/F provides greater improvement of FVC in asthma

228 moderate-to-severe asthma

PEF



FVC



Papi A et al; Allergy 2007

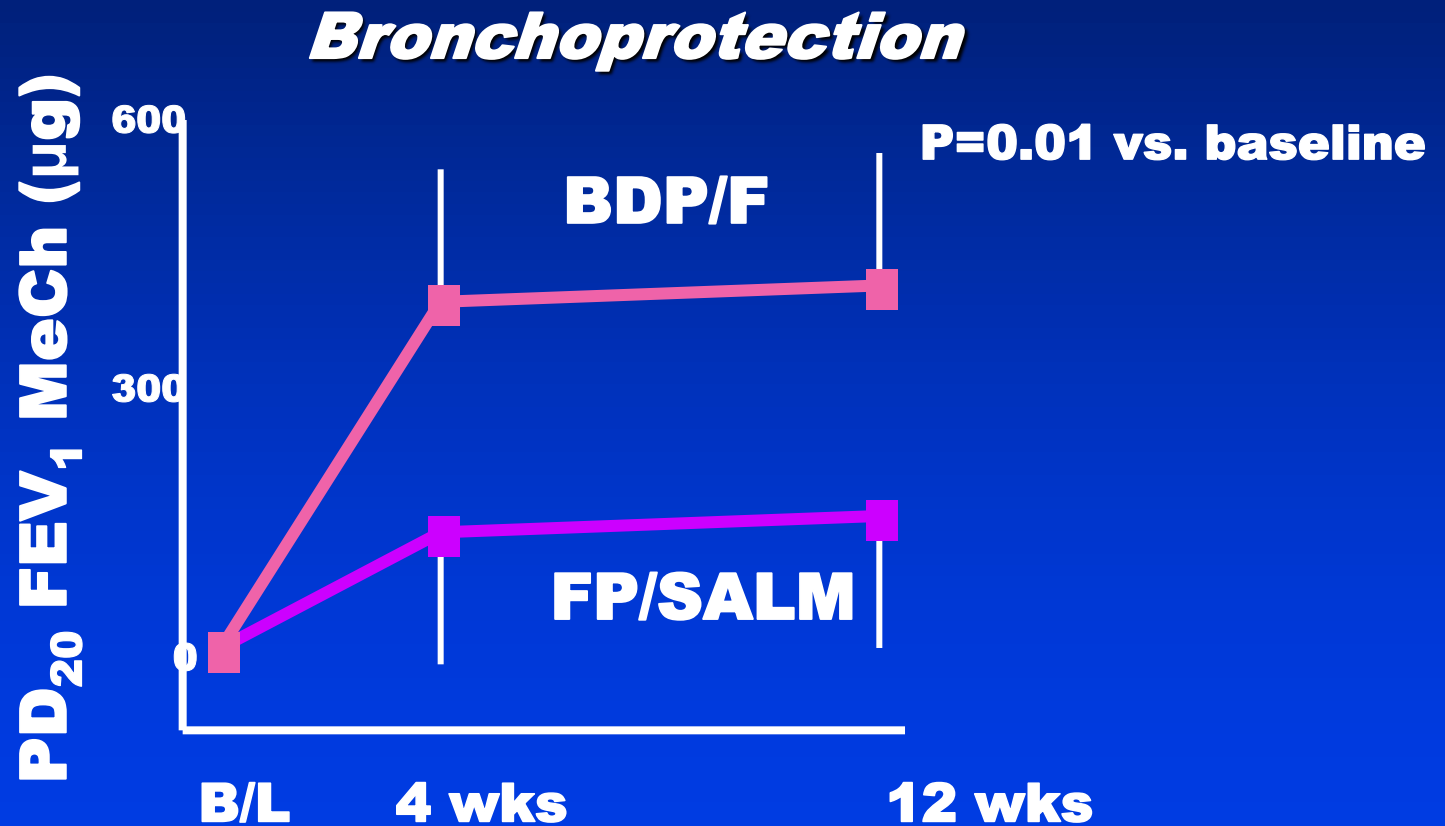
Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma

N. Scichilone¹, S. Battaglia¹, C. Sorino¹, G. Paglino¹, L. Martino¹, A. Paternò¹, R. Santagata¹, M. Spatafora¹, G. Nicolini² & V. Bellia¹

¹Department of Medicine, Pneumology, Physiology and Human Nutrition (DIMPEFINU), University of Palermo, Palermo, Italy; ²Medical Department, Chiesi Farmaceutici, Parma, Italy

Additional effects of extra-fine BDP/F on small and large airways

30 moderate-to-severe asthmatic patients





Available online at www.sciencedirect.com

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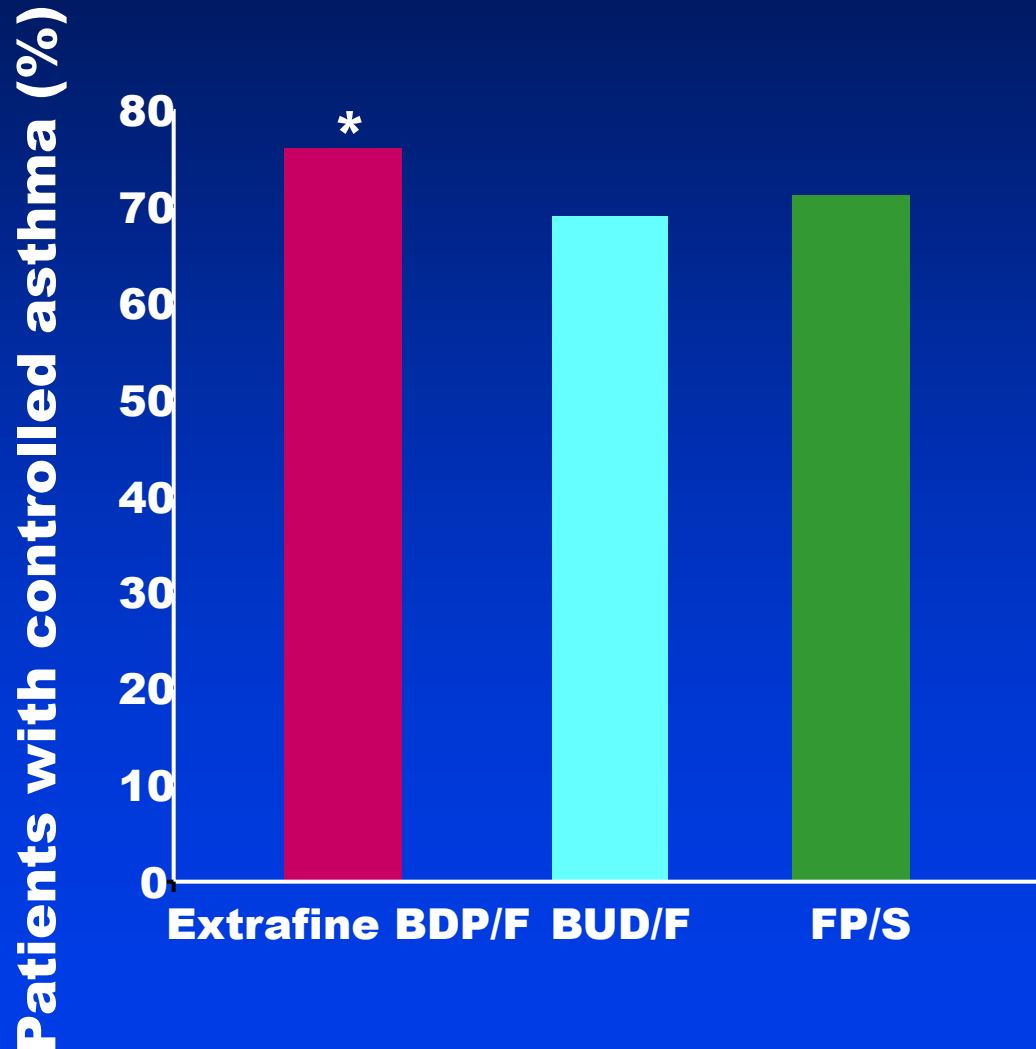
journal homepage: www.elsevier.com/locate/rmed



Real-life prospective study on asthma control in Italy: Cross-sectional phase results

Luigi Allegra ^a, Giovanni Cremonesi ^b, Giuseppe Girbino ^c,
Eleonora Ingrassia ^b, Serafino Marsico ^d, Gabriele Nicolini ^{b,*},
Claudio Terzano ^e, On behalf of the PRISMA
(PRospective Study on asthMA control) Study Group

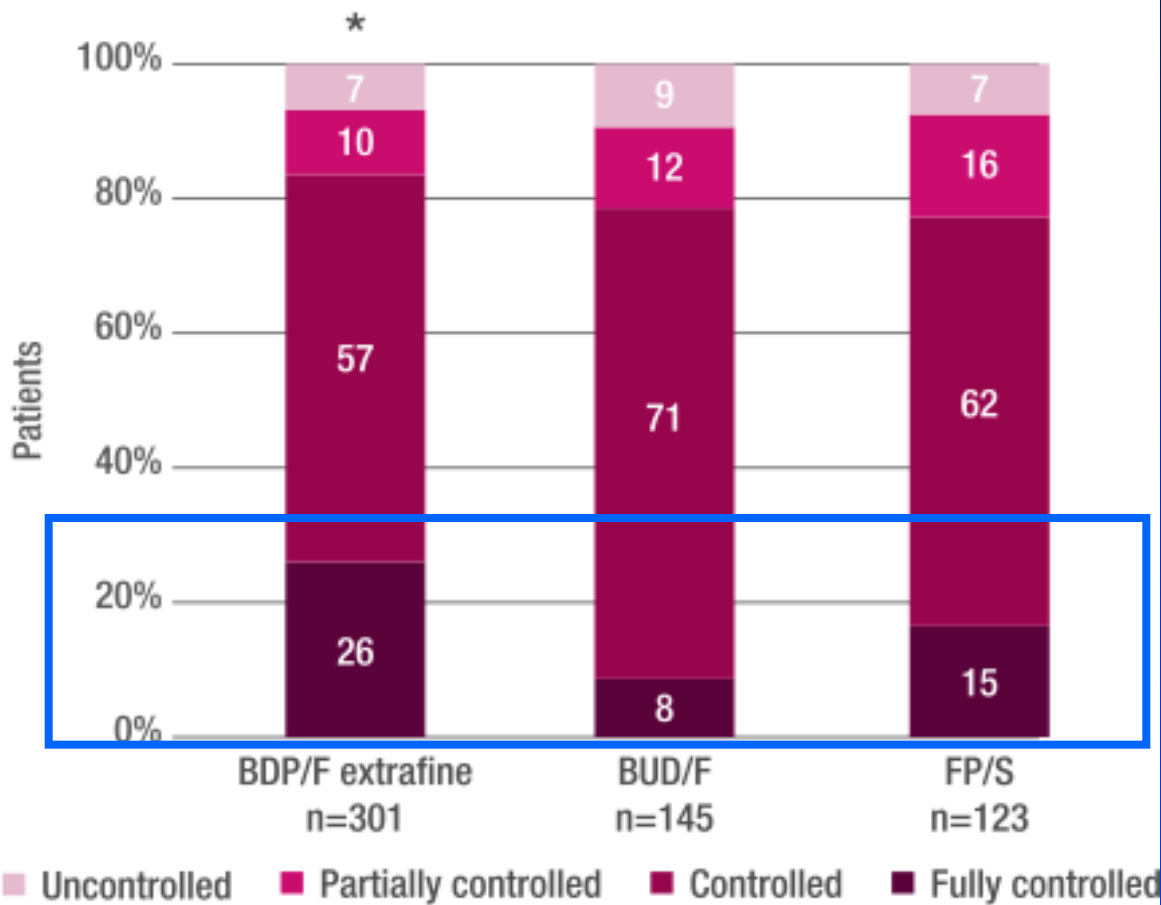
In a real-life study, extrafine BDP/F provides a greater percentage of controlled patients than larger particle formulations



**p<0.05 vs BUD/F*

Cross-sectional phase of a prospective study involving 2848 patients (1358 patients using ICS/LABA fixed combinations). No difference in asthma severity between groups at the time of diagnosis.

In a real-life study, extrafine BDP/F provides a greater percentage of controlled patients than larger particle formulations

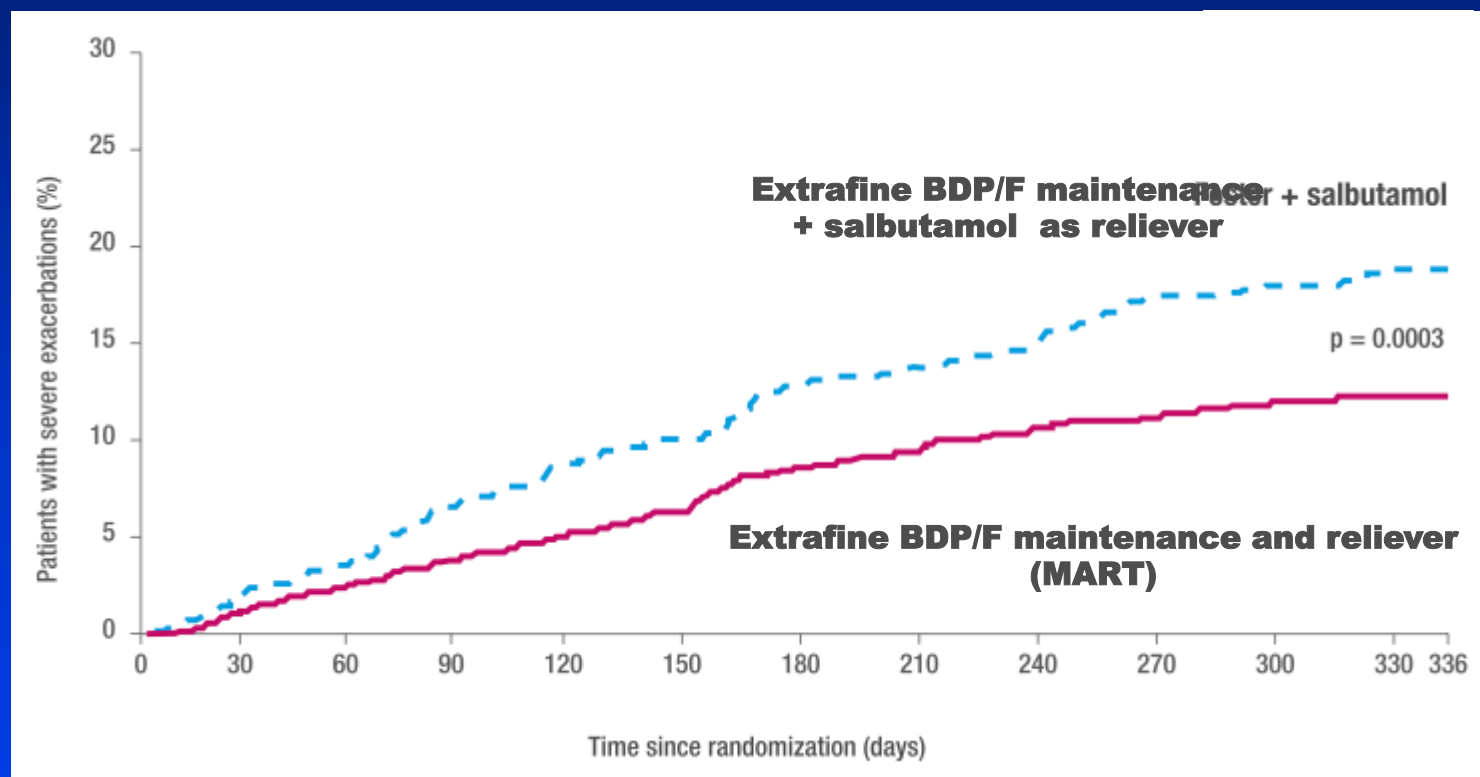


*Bonferroni's corrected $p < 0.001$ BDP/F vs BUD/F

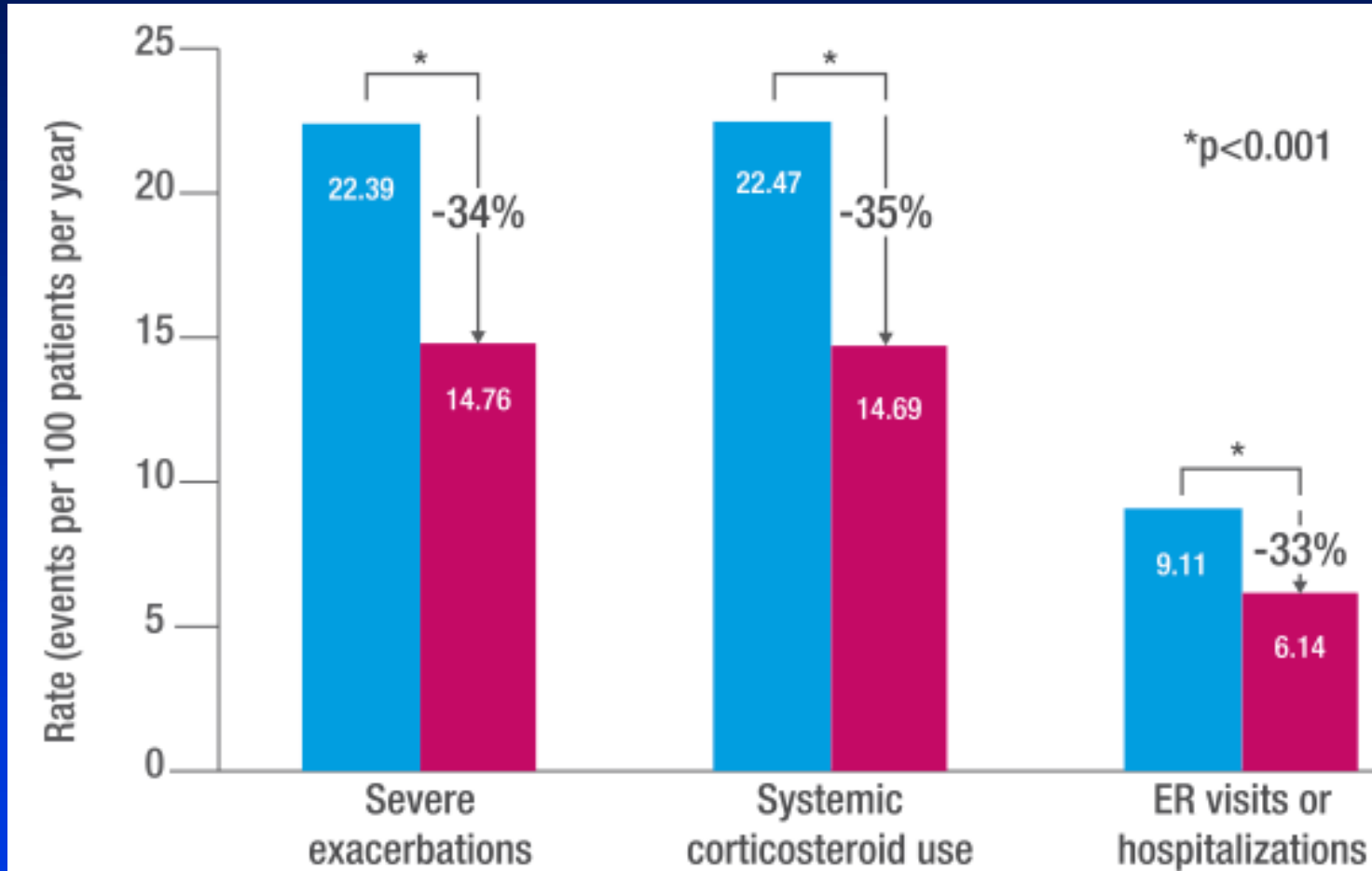
Prospective phase of a real-life study involving 1017 adult patients with uncontrolled or partially controlled asthma, including 569 patients treated with an ICS/LABA fixed-dose combination

Extrafine BDP/F MART® provides significantly prolonged time to first severe exacerbation

1714 patients with asthma and history of exacerbation



Extrafine BDP/F MART® provides significantly prolonged time to first severe exacerbation



■ Extrafine BDP/F maintenance + salbutamol as reliever

■ Extrafine BDP/F maintenance and reliever (MART)

Papi et al, The Lancet Respir Med 2013

Controllo dell'Asma

- **L'obiettivo principale del trattamento è ottenere il “buon controllo” dell'asma**
- **La terapia di associazione ICS/LABA costituisce la strategia migliore per il buon controllo della malattia**
- **Tra le terapie di associazione, le combinazioni con maggiore frazione di particelle fini sembrano offrire i migliori vantaggi**

Le prime sigarette...



“...anormalità patologiche possono essere già presenti nelle vie aeree periferiche di giovani fumatori.

I bronchioli membranosi presentano epitelio danneggiato e un maggior numero di cellule infiammatorie murali...”

La bronchiolite è sempre presente nei fumatori

TABLE 1. *Summary of findings in 156 patients*

	Current smokers	Ex-smokers	Never smokers	Total
RB present	83	24	2	109
RB absent	0	25	22	47
Total	83	49	24	156

RB, respiratory bronchiolitis.

Istologia delle piccole vie in fumatori e non-fumatori

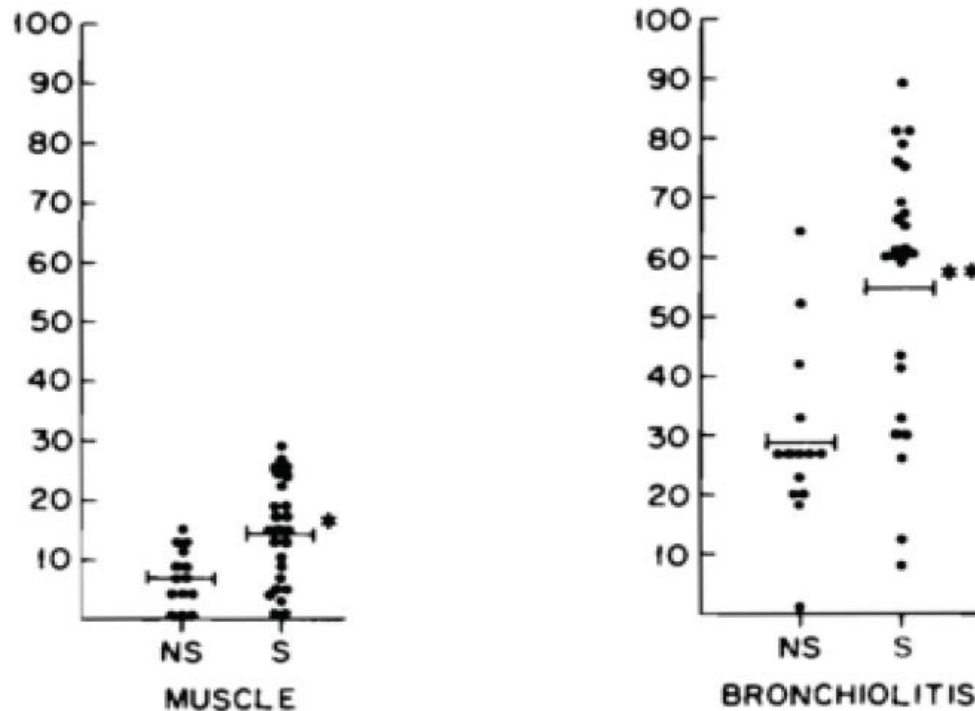


Fig. 2. Scores for individual pathologic features in the small airways of nonsmokers (NS) and smokers (S) (* $p < 0.05$, ** $p < 0.01$).

Istologia delle piccole vie in fumatori e non-fumatori

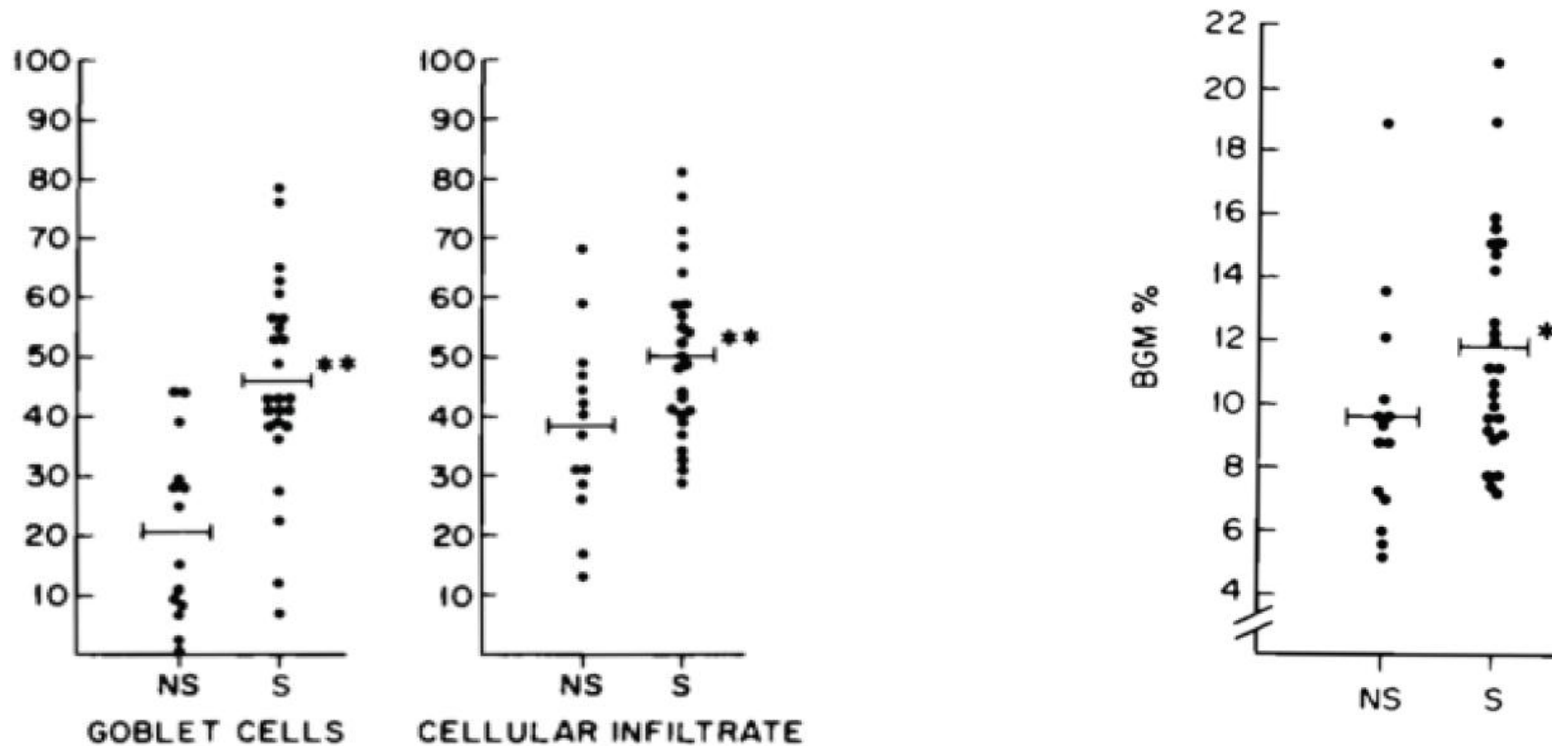
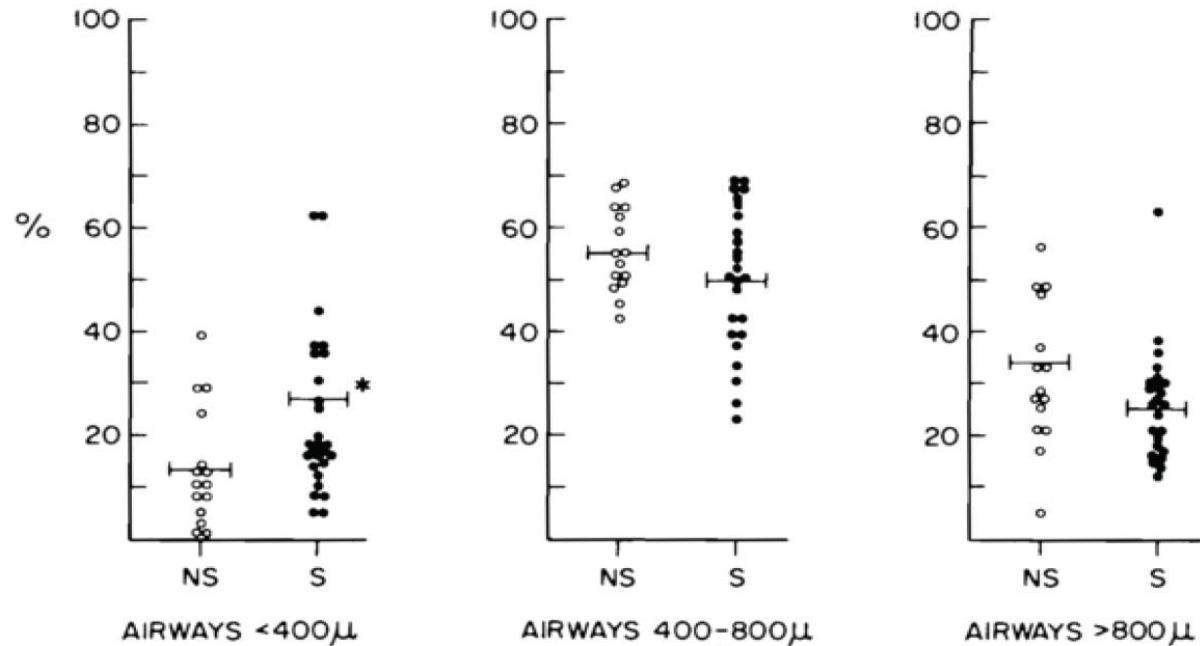


Fig. 2. Scores for individual pathologic features in the small airways of nonsmokers (NS) and smokers (S) (* $p < 0.05$, ** $p < 0.01$).

BGM% = Bronchial gland mass %

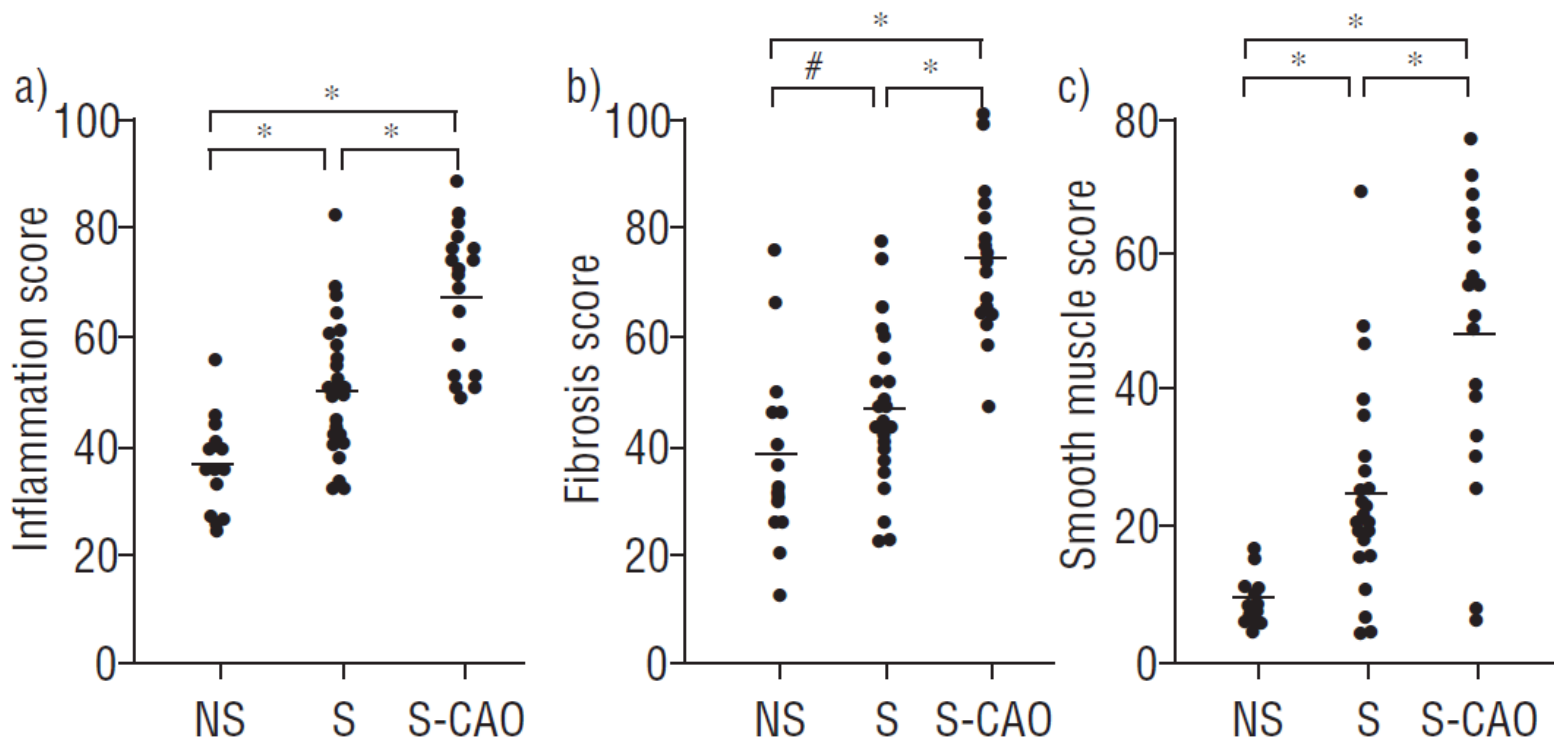
La bronchiolite e calibro delle vie aeree



Percentage of airways of different size intervals in nonsmokers (NS) and smokers (S) (* $p < 0.05$).

Il fumo porta ad una riduzione del calibro delle vie aeree periferiche

Infiemmazione nelle piccole vie



* $p < 0,05$
non significativo

NS: non fumatori
S: fumatori
S-CAO: fumatori con BPCO

Piccole vie aeree e BPCO

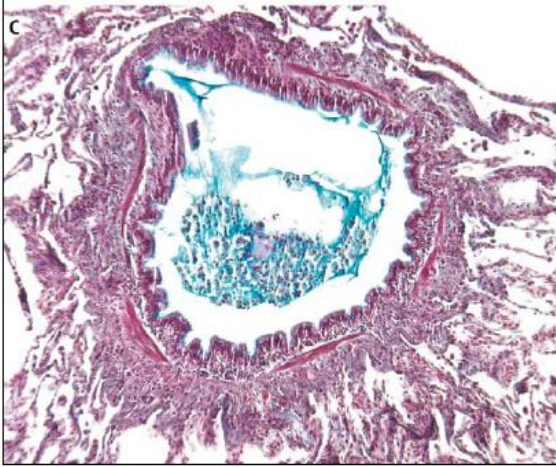
Meccanismi alla base della limitazione del flusso aereo nella BPCO

- «Small airways disease»
- Infiammazione delle vie aeree
- Fibrosi
- Occlusione del lume
- Aumento della resistenza al flusso
- Distruzione del parenchima
- Perdita di attacchi alveolari
- Riduzione del ritorno elastico

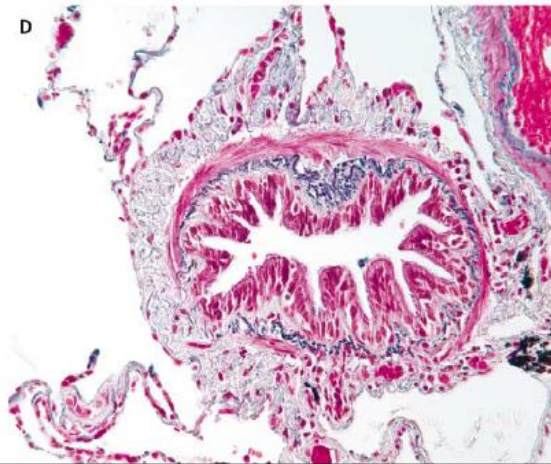


LIMITAZIONE DEL FLUSSO AEREO

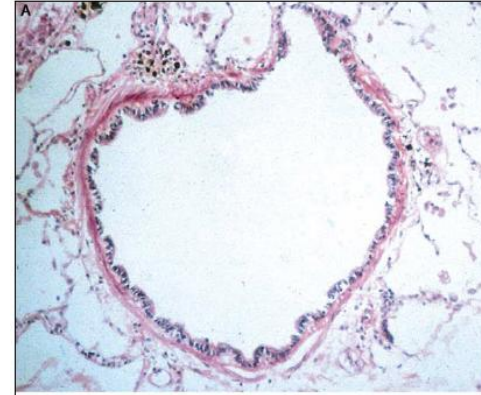
Piccole vie aeree in BPCO



Piccole vie aeree in BPCO



Hogg TT. Lancet 2004



Piccola via aerea normale

- Formazione di tappi di muco
- Ipertrofia del muscolo liscio
- Ispessimento della membrana basale
- Perdita di attacchi alveolari
- Riduzione del lume

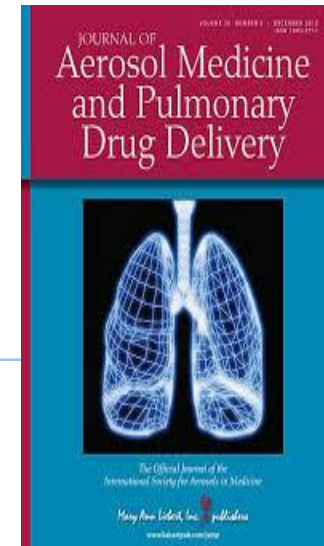
Un'elevata quota di pazienti BPCO presenta anomalie periferiche

Table I. HRCT features noted in individual COPD patients.

HRCT features	No. of patients	Percentage of study subjects
Saber-sheath trachea with tracheal index < 0.67	14	35
Thoracic cage ratio > 0.75 at carina	5	12.5
Thoracic cage ratio > 0.75 at 5 cm below carina	11	27.5
Sterno-aortic distance > 4 cm	5	12.5
Thoracic cross-sectional area/height ² > 80.00 cm ² /m ²	28	70
Vascular attenuation	25	62.5
Vascular distortion	8	20
Mosaic attenuation pattern	16	40
<u>Directly visible small airways</u>	<u>36</u>	<u>90</u>

Caratteristiche riscontrabili all'HRCT in pazienti BPCO

Studio De Backer 2010

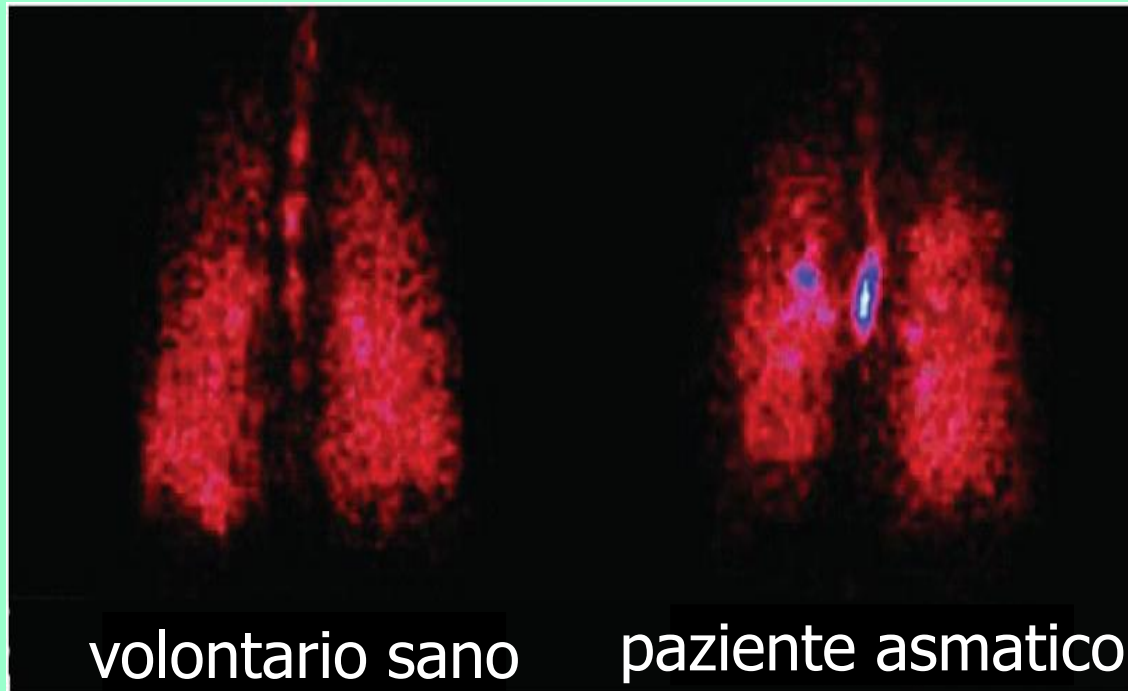


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Pp. 137–148
DOI: 10.1089/jamp.2009.0772

Lung Deposition of BDP/Formoterol HFA pMDI in Healthy Volunteers, Asthmatic, and COPD Patients

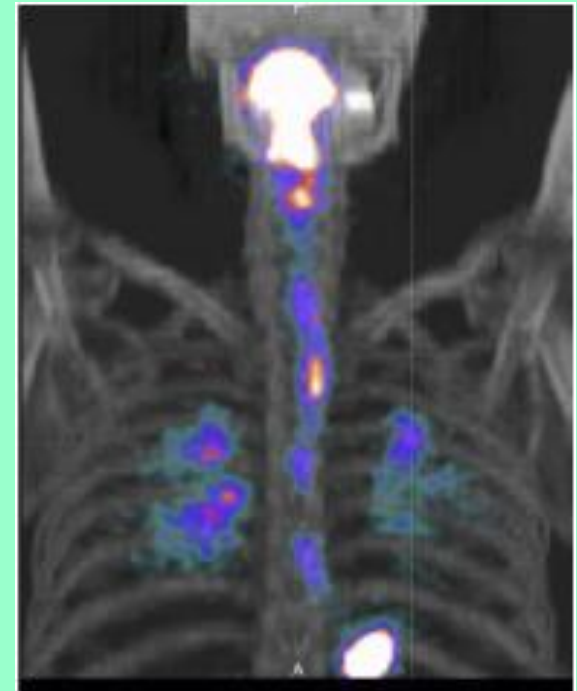
Distribuzione nelle vie aeree di formulazioni Extrafine e non Extrafine

BDP/F extrafine 100/6 μg Spray



Nicolini et al. Therapeutics and
clinical risk management 2008

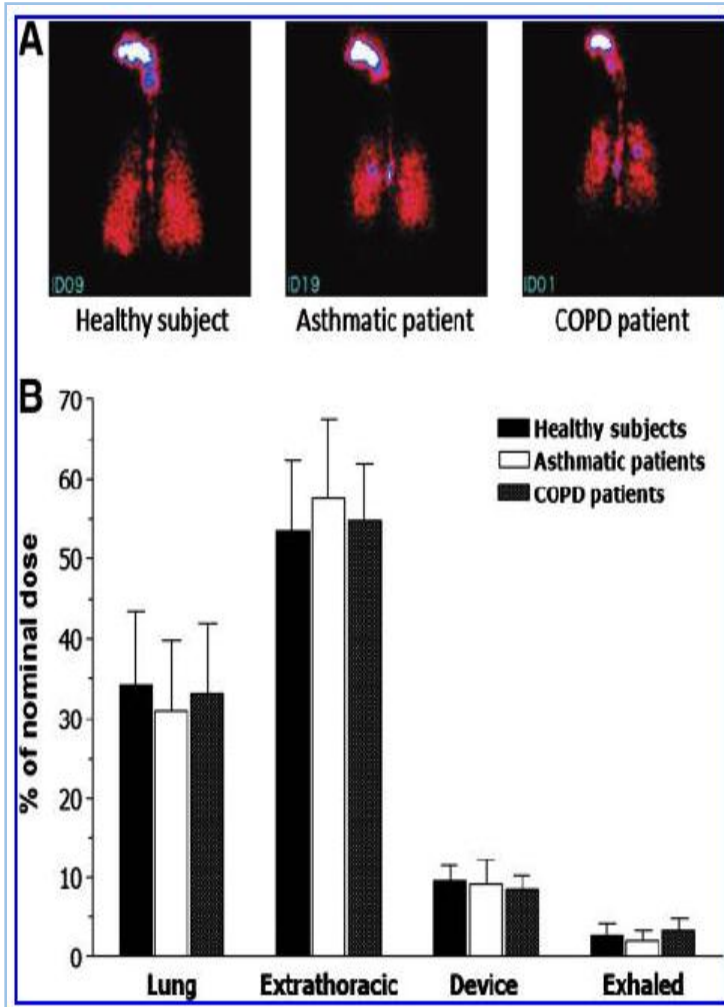
FP/S 125/25 μg Spray



Leach CL, Ann Allergy Asthma Immunol
108 (2012) 195–200

Risultati

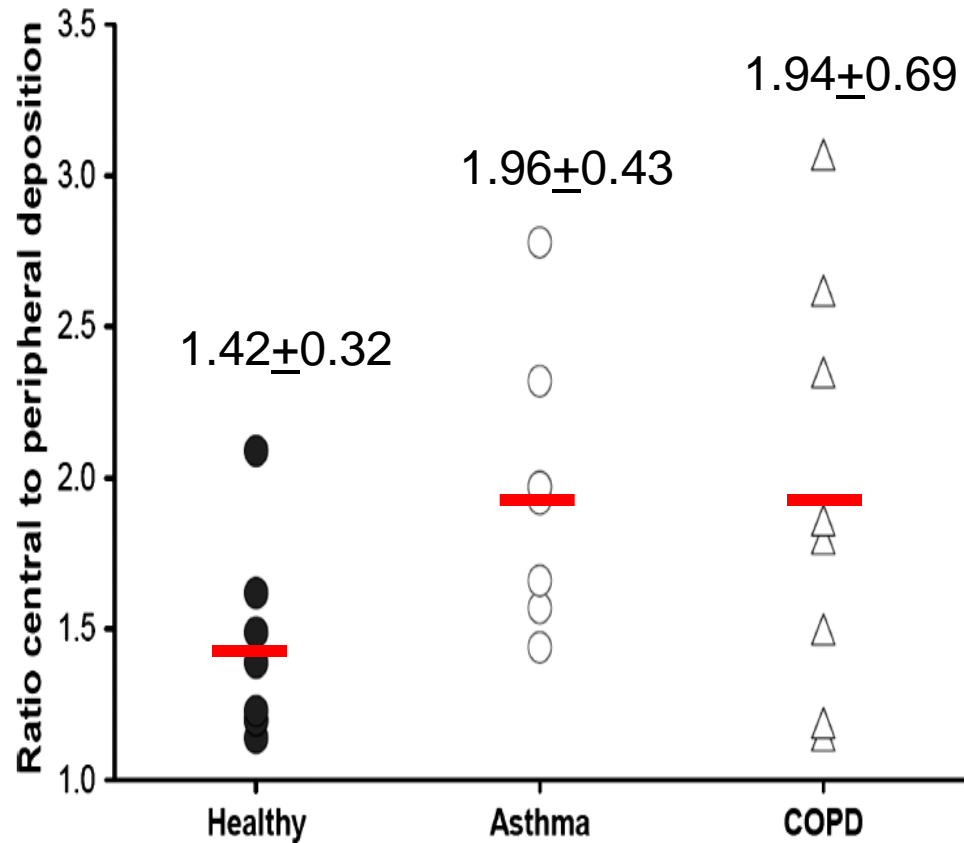
Deposizione bronchiale



FEV1 (% pred) al basale

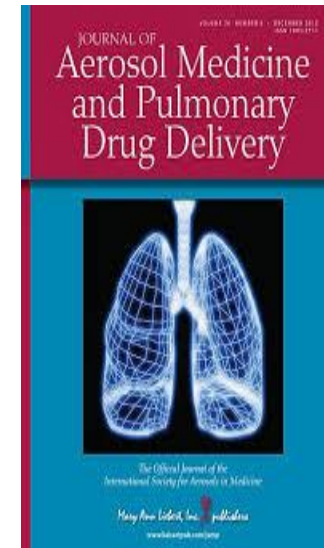
- Volontari sani: 112,13 ± 11,89
- Asmatici: 70,75 ± 8,33
- BPCO: 43,67 ± 7,26

Rapporto deposizione centrale/periferica



Studio De Backer 2015

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Pp. 88–99
DOI: 10.1089/jamp.2013.1064



The Effects of Extrafine Beclometasone/Formoterol (BDP/F) on Lung Function, Dyspnea, Hyperinflation, and Airway Geometry in COPD Patients: Novel Insight Using Functional Respiratory Imaging

Jan De Backer, MSc, PhD¹, Wim Vos, MSc, PhD¹, Samir Vinchurkar, MSc, PhD¹,
Cedric Van Holsbeke, MSc, PhD¹, Gianluigi Poli, MSc, PhD,² Rita Claes, BSc,³
Rodrigo Salgado, MD, PhD,⁴ and Wilfried De Backer, MD, PhD³

Schema dello studio

Studio De Baker	
Disegno dello studio	Studio di Imaging in aperto, non controllato, non randomizzato
Obiettivo	Valutare l'efficacia dello switch da formulazioni non-extrafine a BDP/F su volumi polmonari e qualità di vita in varie condizioni patologiche
Pazienti	N. 27 pazienti BPCO (GOLD II-IV) in trattamento con farmaci in formulazione non-extrafine.
Trattamenti	BDP/F 100/6, 2x2 (daily dose 400/24 mcg)
Durata dello studio	6 mesi
Parametri esaminati	Variazioni di volumi, resistenze, funzione polmonare, qualità di vita a 4-6h post-inalazione e a 6 mesi (pre-dose), tramite Functional Respiratory Imaging (FRI)

Variazione in SGRQ (a 6mth)

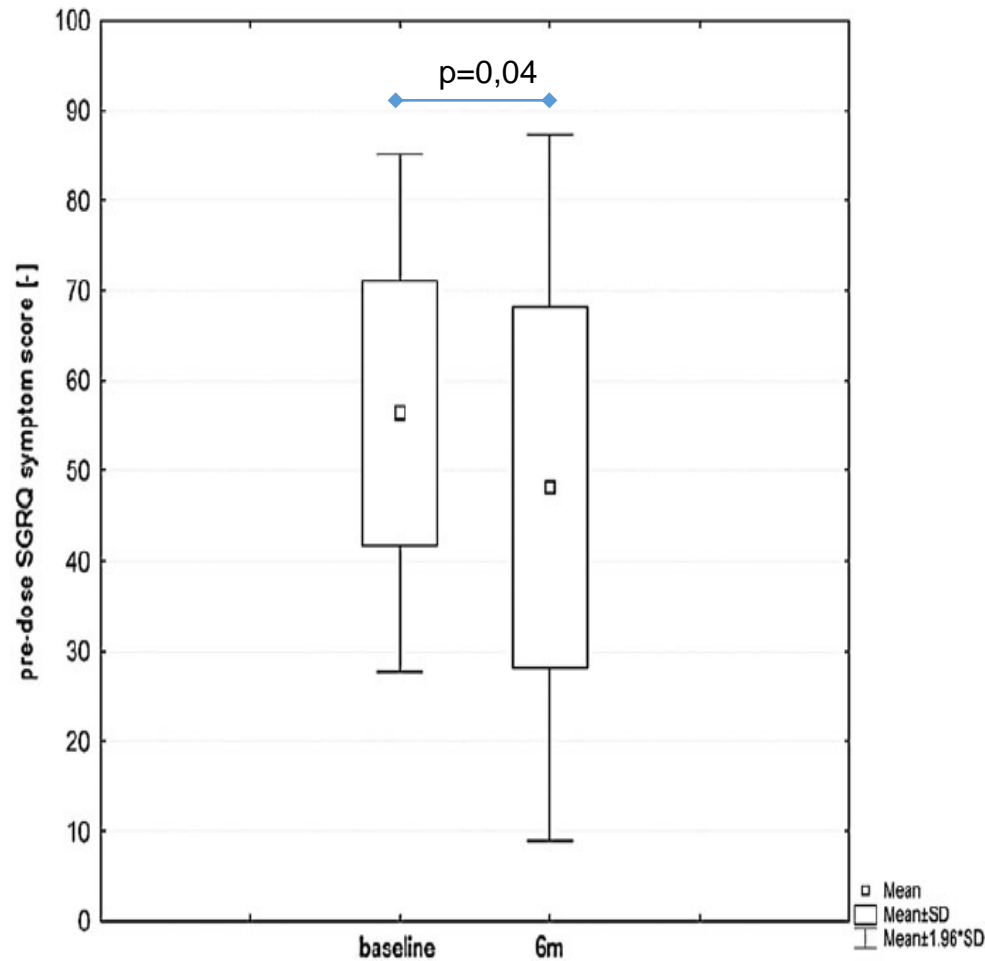


FIG. 6. Changes in SGRQ symptom score at baseline and after 6 months of treatment recorded prior to bronchodilation.

Conclusioni

- Lo switch a BDP/F porta ad miglioramento a breve (4-6 h) termine in Volumi e resistenze polmonari misurati all'imaging (siRaw, siVaw, iTLC)

Conclusioni

- Lo switch a BDP/F porta ad miglioramento a breve (4-6 h) termine in parametri di funzionalità polmonare (FEV1, FRC, TLC)

Conclusioni

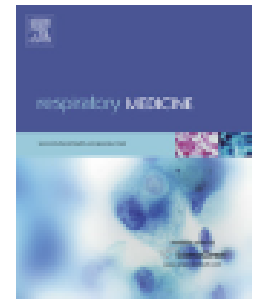
- Lo switch a BDP/F porta ad miglioramento a lungo termine (6mth) dell'iperinflazione (iTLC) con conseguente miglioramento della qualità di vita (SGRQ).



available at www.sciencedirect.com



journal homepage: www.elsevier.com/locate/rmed

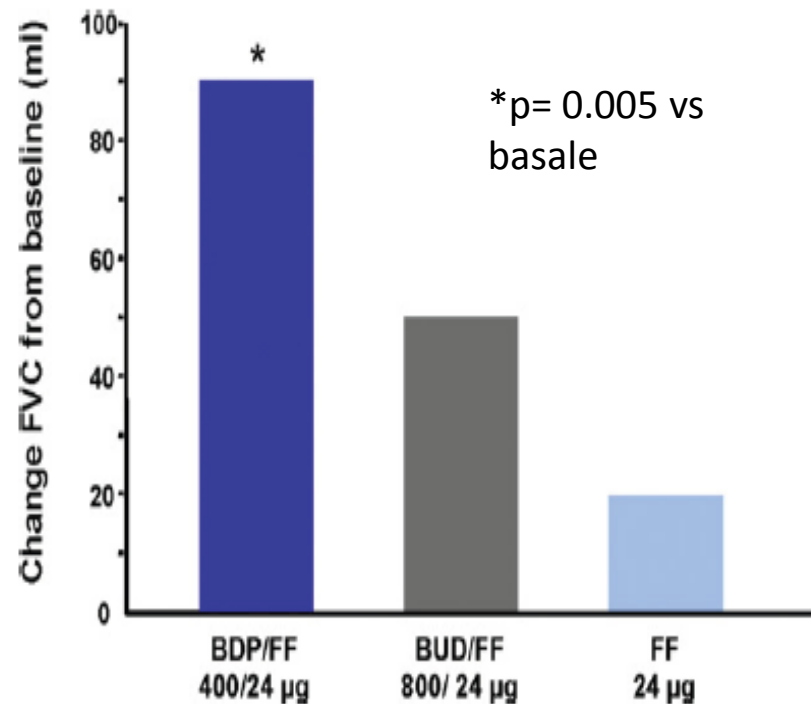


Beclomethasone/formoterol in the management of COPD: A randomised controlled trial


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F. Sergio^d, G. Varoli^d, A. Papi^e, V. Brusasco^f

Studio Calverley: risultati

Differenza significativa nel valore dell'FVC pre-dose del mattino, (settimana 48), rispetto al basale, per BDP/F ($p=0.005$).



Conclusioni

- **Piccole vie**
 - **Ruolo nell'asma**
 - **Extrafine in asma**
 - **Studi clinici in asma**
 - **Ruolo nella BPCO**
 - **Extrafine in BPCO**
 - **Studi clinici in BPCO**
 - **Obiettivi terapeutici**
- 

Extrafine: nuova frontiera nel trattamento delle patologie ostruttive respiratorie

Paolo Solidoro,
SCDU Pneumologia Presidio Molinette

