Small Airway Disease in Asthma: Pathophysiology and Assessment

National Jewish Health

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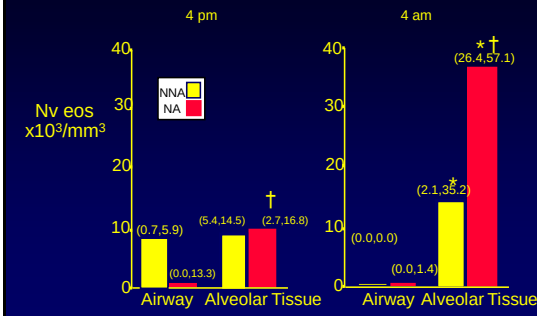
Small Airways How are they defined?

- Anatomically by lack of cartilage in airway wall
- Physiologically by size of catheter used to measure "peripheral airway" resistance
- Distal, peripheral or small airways probably reflect generations 7-19 with diameters of 0.5-2mm (terminal bronchioles, respiratory bronchioles and alveolar ducts)

Small Airways in Asthma

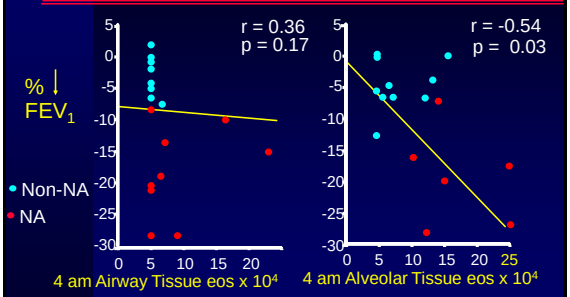
- Distal, peripheral or small airways probably reflect generations 7-19 with diameters of 0.5-2mm (terminal bronchioles, respiratory bronchioles and alveolar ducts)
- Physiologically this probably reflects the transition point from turbulent to laminar flow
  - For a given small airway generation the cross sectional area is larger than for a large airway generation. If flow is the same through both generations, linear velocity should be less for small airways. Reynolds number predicts laminar flow with low laminar velocity.

Airway & Alveolar Tissue Eosinophils



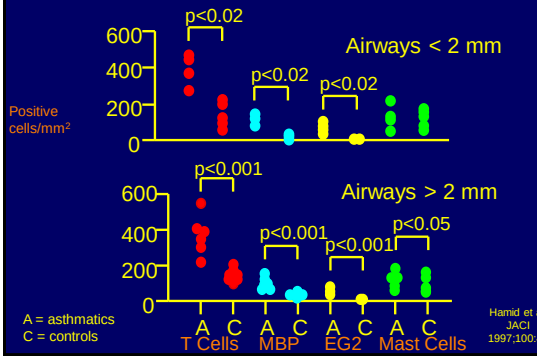
Kraft et al. AJRCCM; 1996;154:1505

% Overnight Fall in FEV1 vs. Tissue Eosinophils



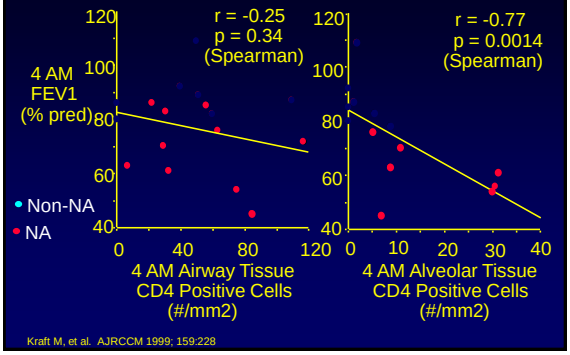
Kraft et al. AJRCCM; 1996;154:1505

Immunohistochemical Markers in the Large & Small Airways



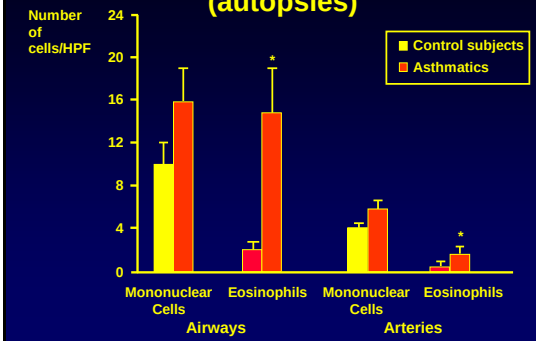
Hamid et al. JACI 1997;100:44

Alveolar Tissue CD4 Correlates with the FEV1



Kraft M, et al. AJRCCM 1999; 159:228

Eosinophils in small airways (autopsies)

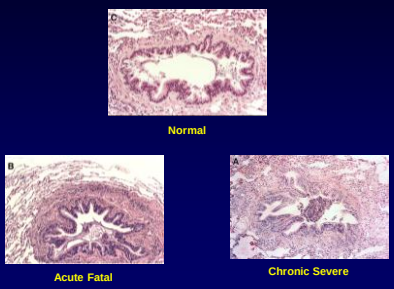


*$p<0.05$ vs. control subjects

Saetta, M ARRD, 1991; 143(1):138-43

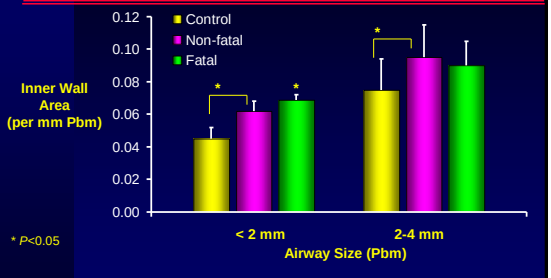
Is There Distal Lung Remodeling?

Small airway walls thickened in severe asthma



Courtesy Sally Wenzel

Small Airway Wall Thickness Increased in Cases of Both Fatal and Non-fatal Asthma



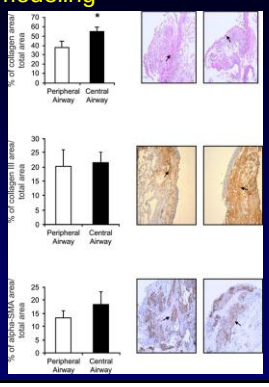
* $P<0.05$

Pbm = mm^2 per mm of basement membrane perimeter

Carroll N, et al. *Am Rev Respir Dis.* 1993;147:405-410.

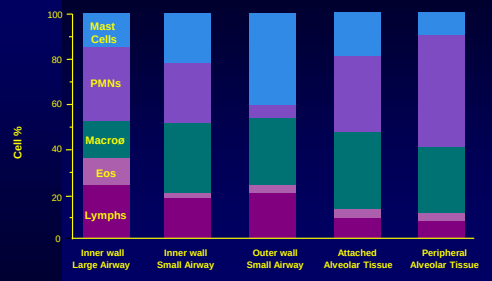
Small Airway Remodeling

Remodeling features of the central and peripheral airways



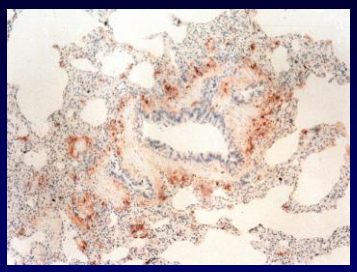
Bergeron et al. J Allergy Clin Immunol 2005;116:983-9

Pattern of inflammatory cells also differs by lung region



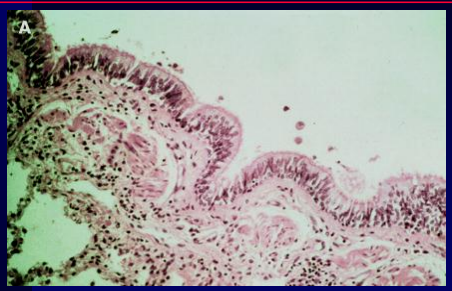
Balzar, Am J Respir Crit Care Med. 2005 Mar 1;171(5):431-9

Different distribution of inflammatory cells: Mast cells



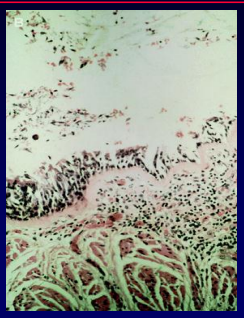
Courtesy Sally Wenzel

Histologic Section* of Intrapulmonary Bronchi Normal Subject Without Asthma



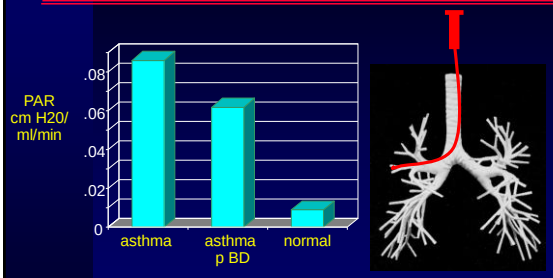
*original magnification x 180 Bousquet et al. AJRCCM 2000:16(5)1720

Histologic Section* of Intrapulmonary Bronchi Fatal Asthma



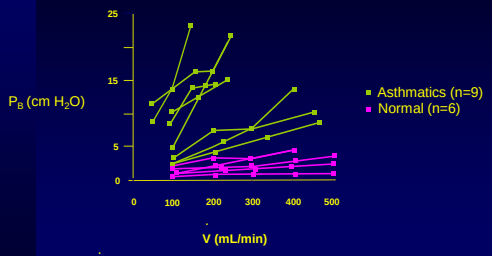
*original magnification x 180 Bousquet et al. AJRCCM 2000:16(5)1720

Measurement of Peripheral Airways Resistance: Wedged Bronchoscopic Technique



Wagner, et al ARRD 1990; 141:584

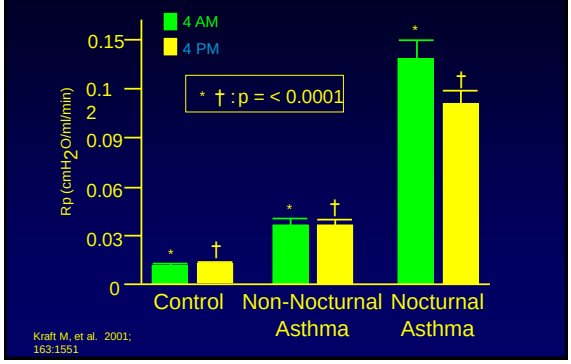
Peripheral Airway Resistance Is Significantly Increased in Patients with Asthma



Pressure (P_B)-flow (V) relationship

Wagner EM, et al. *Am Rev Respir Dis.* 1990;141:584-586.

Peripheral Resistance (Rp)

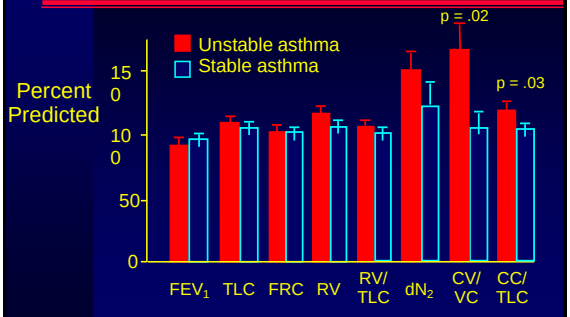


Kraft M, et al. 2001; 163:1551

Small Airways in Asthma

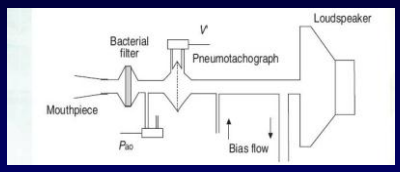
- How are they assessed?
  - Impulse oscillometry
  - Multiple breath nitrogen washout
  - Imaging
  - Inflammatory markers (systemic, expectorated, alveolar FeNO)
  - $FEF_{25-75\%}$
  - Airtrapping (RV, IC, SBN2 for CV/CC)
  - Aerosol bolus dispersion

The Small Airways: Role in Recurrent Exacerbations in Severe Asthma



in't Veen, et al. Am J Respir Crit Care Med. 2000;161:1902-1906.

IOS

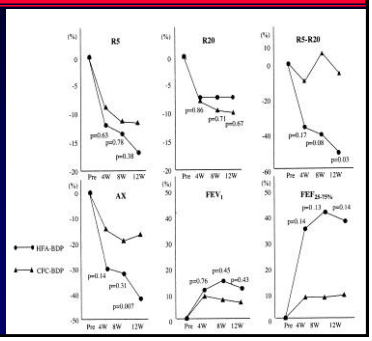


Yamaguchi M, et al. Pul pharm Ther 2009:22; 326

Clinical: Impulse Oscillometry

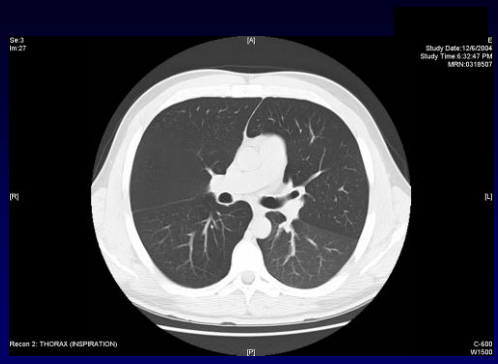
- 38 ICS naïve asthma patients with mild-to-moderate disease treated with either Qvar (400 mcg/day, n=26) or CFC BDP (800 mcg/day, n=12) for 12 weeks in open label fashion
  - Yamaguchi et al Pul Pharm Ther 2009 (e-pub)

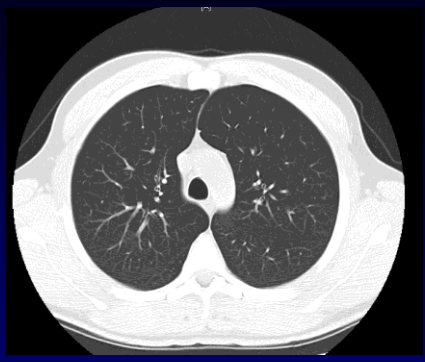
Clinical: Impulse Oscillometry



Yamaguchi M, et al. Pul pharm Ther 2009:22; 326

Imaging as a Possible Modality to Measure Small Airway function





CT & Alveolar Nitric Oxide and Small Airways

- 16 mild-to-moderate asthma (FEV1 62–120%)
- 5 weeks' treatment placebo or 320 mg ciclesonide daily
- Assessed: mean FeF 25-75%, % fall in FVC at provocative dose of AMP and MCh, expiratory lung volume on CT after MCh challenge, single-breath nitrogen closing volume and alveolar exhaled nitric oxide (eNO).

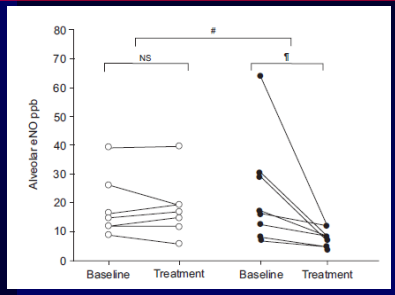
Cohen et al. Eur R J 2008;31:1213

CT & Alveolar Nitric Oxide and Small Airways

	Placebo		Ciclesonide	
	Baseline	Post-treatment	Baseline	Post-treatment
Subjects n	7		9	
Alveolar eNO ppb	14.7 (8.5-39.2)	16.5 (5.6-39.6)	17.3 (6.9-67.3)	8.5 (3.7-12.5)*,¶
FEF25-75% % pred	63 (34-87)	61 (54-86)	52 (29-66)	63 (30-97)*
Closing volume SBN_2 mL	140 (95-495)	105 (60-430)	230 (60-820)	115 (35-975)
ΔFVC % at PC20 of MCh	13.6 (4.9-15.3)	13.2 (2.5-19.4)	12.4 (6.1-16.8)	12.7 (5.6-19.7)
ΔFVC % at PC20 of AMP	12.2 (5.4-14.3)	14.1 (9.0-18.9)	12.0 (3.5-17.2)	12.3 (4.1-15.9)
Total expiratory lung volume on CT after MCh mL	2990 (2158-4636)	2973 (2368-4916)	4165 (2262-5576)	3831 (2338-5166)*

Cohen et al. Eur R J 2008;31:1213

CT & Alveolar Nitric Oxide and Small Airways



Cohen et al. Eur R J 2008;31:1213

ICS Therapy: Small vs Large Particles?

- Practical significance
  - Increased total lung deposition with more peripheral lung deposition and less oropharyngeal deposition
- Biologic significance
  - More effective topical anti-inflammatory effect both centrally and peripherally
- Clinical significance
  - To be discussed at follow up pro/con

Conclusions

- The distal lung appears to contribute to asthma pathogenesis and has physiologic consequences
- There are data to suggest that remodeling also occurs in the distal lung
- Should the distal lung be considered a therapeutic target