Small Airways Disease

"Respiratory Function In Small Airways And Asthma"

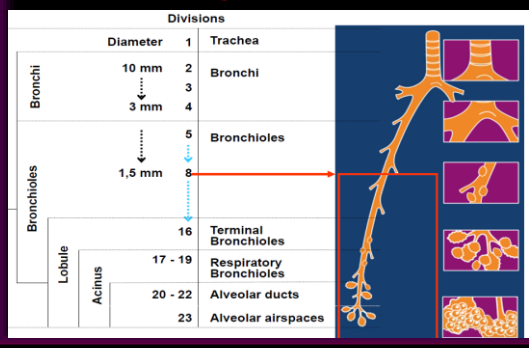
Thomas B Casale, MD
Professor Of Medicine
Chief, Allergy/Immunology
Creighton University
Omaha, NE USA

Relevant Questions On Small Airway Involvement In Asthma

- How can 'small airway disease' be defined?
- What is the link between small airway abnormalities and clinical presentation in asthma ?
- When does small airway involvement become relevant in the natural history of the disease?
- Is it possible to reverse small airway abnormalities with pharmacological treatment?

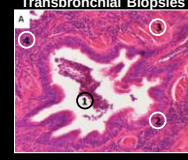
Contoli et al Allergy 2010; 65: 141–151

Disease Process in Asthma is Located in All Parts of Bronchial Tree Including Small Airways and Alveoli

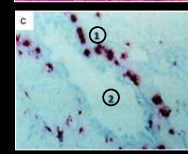


Pathophysiologic Changes in the Small Airways of Asthma Patients

Transbronchial Biopsies



① Lumen occlusion
② Subepithelial fibrosis
③ Increase in smooth muscle mass
④ Inflammatory infiltrate



① Immunostaining of eosinophils in small airway with major basic protein (in red)
② Shows large number of eosinophils around the small airway

Contoli M, et al. *Allergy*. 2010;65:141-151.

Small Airway (<2 mm) Principals

- Account for less that 10% of total airflow resistance
- Nerves generally do not penetrate that deep into the small airways
- Do not have cartilaginous support
- Surfactant is important to their patency
- Without parenchymal airway independence, activation of small airway smooth muscle leads to uninhibited small airway narrowing

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

5

Small Airway (<2 mm) Principals

- Estimated to be 24,000 small airways and bronchioles
- Thousands could be narrowed or totally obstructed without significant loss of lung function
- Most important mechanism to preserve airway function in small airways appears to be their sheer number

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

6

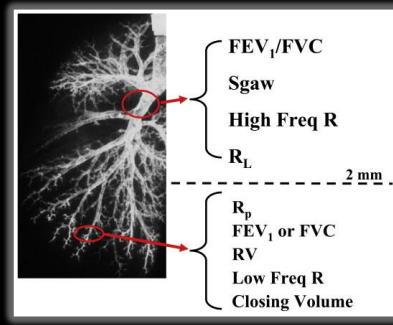
Definition of Small Airway Obstruction

- Dysfunction that involves only small airways can be defined as a situation when:
  - static lung compliance is unaltered
  - resistance is not significantly increased or marginally so
  - frequency dependence of compliance or resistance is present

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

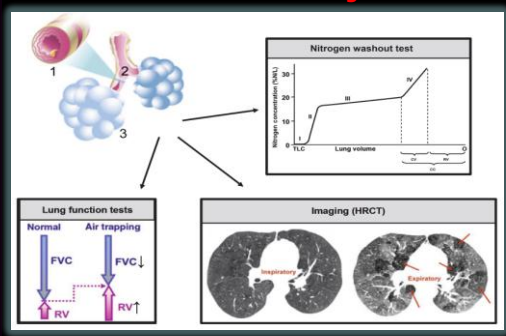
7

Function Of Tracheobronchial Tree As Reflected By Physiologic Measures



Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

Assessment Of Air Trapping As A Result Of Small Airways Closure



Contoli et al Allergy 2010; 65: 141–151

FEV1

- Does not provide comprehensive evaluation of the whole bronchial tree
- Does reflect cross-sectional area of the lung
- Highly related to FVC in asthma because of an increase in RV caused by airway closure
  - FEV1/FVC ratio appears to measure central airway remodeling
- Does not properly reflect small airway abnormalities

Contoli et al Allergy 2010; 65: 141–151

FEF25–75

- **Pros:**
  - **Noninvasive**
  - **Easy to perform**
  - **Related to air trapping by CT scan**
- **Cons:**
  - **Serial measures are highly variable**
  - **Influenced by large airway obstruction and volume changes**
    - **Often normal when FEV1/FVC> 75%**
  - **Did not correlate with small airway inflammation as determined by bronchoscopic lung biopsies**

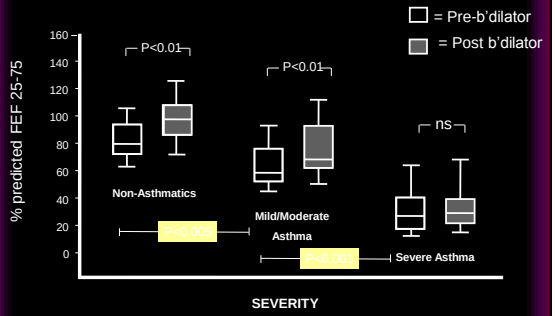
Contoli et al Allergy 2010; 65: 141–151

Small Airways Dysfunction Defined by a Reduction in $FEF_{25\%-75\%}$

- May be better measure of small airways function than FEV_1, particularly in children, but controversial
- Decreases following exercise without changes to FEV_1
- Useful measure with methacholine challenge tests

Wagner EM, et al. *Am Rev Respir Dis*. 1990;141:584-588; Fonseca-Guedes CH, et al. *Pediatr Pulmonol*. 2003;36:49-54; Sutherland ER, et al. *J Allergy Clin Immunol*. 2004;113:1046-1050; Cirillo I, et al. *Ann Allergy Asthma Immunol*. 2006;96:692-700; Marseglia GL, et al. *Allergy Asthma Proc*. 2007;28:747-8.

Impaired Lung Function with Loss of Reversibility in Severe Asthma

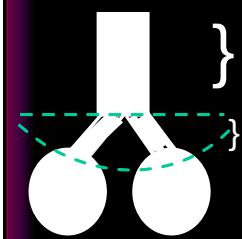


Residual Volume and FVC

- Both are:
  - Noninvasive
  - Easy to perform
  - Reproducible
- RV has shown a closer relationship with changes in peripheral resistance, indicating it could correlate with small airway functions
- FVC improvements have been observed after treatment with extrafine formulations when compared with non-extrafine treatments:
  - Suggesting greater reduction in air trapping, which reflects small airway obstruction

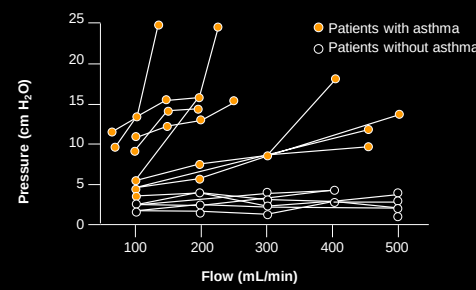
Contoli et al Allergy 2010; 65: 141–151

Impact of Small Airways on Resistance Measures



Resistance Measure Obstruction	Normal	Peripheral Airway
Central Airways	0.9	0.9 $cmH_2O\ L^{-1}\ s^{-1}$
Peripheral Airways	0.1	0.2 $cmH_2O\ L^{-1}\ s^{-1}$
Total Airways	1.0	1.1 $cmH_2O\ L^{-1}\ s^{-1}$

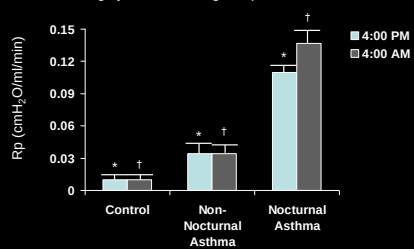
Increased Peripheral Airway Resistance in Patients With Asthma



Wagner EM, et al. *Am Rev Respir Dis.* 1990;141:584-588.
Adapted from Wagner et al in Martin RJ. *J Allergy Clin Immunol.* 2002;109(2, suppl):S447-S460.

Increased Peripheral Resistance in Patients With Asthma

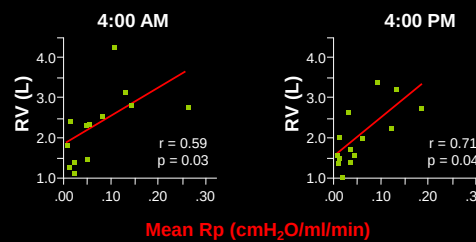
Distal lung dysfunction at night in patients with asthma



*P<.05 between the groups at 4:00 PM.
†P<.05 between the groups at 4:00 AM.

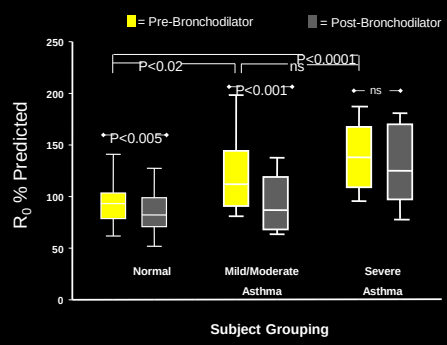
Kraft M, et al. *Am J Respir Crit Care Med.* 2001;163:1551-1556.

Positive Correlation Between Peripheral Resistance and Residual Volume: Evidence for Air Trapping

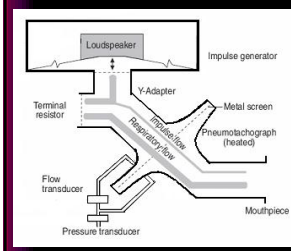


Kraft M, et al. *Am J Respir Crit Care Med.* 2001;163:1551-1556.

Increased Small Airways Resistance in Asthma with Loss of Reversibility in Severe Asthma



IOS Methodology



• Measures the relationship between pressure waves applied externally to the respiratory system, and resulting respiratory airflow.

• Brief pulses of pressure generated by a loudspeaker instantaneously moving back and forth, superimposed on the subject's spontaneous breathing

Smith HJ et al. Eur Respir Rev 2009; 18: 56–64

Principles of Forced Oscillation

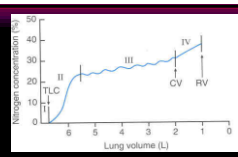
- **Airway resistance can be measured with IOS.**
  - **Small airway obstruction is associated with an increase in resistance predominantly at lower frequencies (frequency-dependence resistance)**
- **Simple and fairly reproducible measure**
- **Time consuming: 30 min**
- **Correlates with FEF 25-75%**
- **More sensitive than FEV1 for measuring physiological effects of bronchodilators**

IOS Clinical Relevance

- Peripheral airway function as evaluated by IOS [R5–R20 (the fall in resistance from 5 to 20 Hz) and X5 (reactance at 5 Hz)], in addition to the proximal airway index (R20), significantly correlated with:
  - health status
  - dyspnea
  - disease control.
- Multiple regression analyses revealed that peripheral airway function significantly contributes to these, independently of the proximal airway index.
- In contrast, FEV1 did not significantly contribute to health status or dyspnea.

Takeda et al, Respiration 2010;80:120

Nitrogen Washout Tests



- Can distinguish between ventilation inhomogeneity originating in peripheral vs. more proximal conducting airways
  - analysis of washout curve generated in single-breath or multiple-breath tests can provide information regarding distal lung abnormalities
- Can determine closing volume
- Good reproducibility and sensitivity

Contoli et al Allergy 2010; 65: 141–151

Closing Volume (CV) and Closing Capacity (CC)

- CV=volume of gas in the lungs in excess of RV at the time when small airways close during maximal exhalation
  - Normally increases with age and in obstructive airway disease
  - Can be used to detect obstructive disease in high-risk patients before clinical signs appear
- CC=CV + RV
- Alterations in single-breath nitrogen washout CV correlated with:
  - Poor asthma control and recurrent exacerbations
  - Elevated alveolar NO in severe asthma

van den Berge et al, *Chest 2011;139;412-423*

Difficult-to-Control Vs. Stable Asthma

- There were no significant differences in lung function except increased closing volume and closing capacity in difficult to treat asthmatics.
  - "This is indicative of small airway pathology in these patients"
- "Delivery of anti-inflammatory medication to the small airways in this subgroup is of specific clinical relevance".

AJRCCM 2000;161:1902-6

Proof Of Treatment: ICS

Parameter	HFA-BDP (1.1 µm)			CFC-FP (3.8 µm)		
	Pre	Post	p	Pre	Post	p (BvsF)
CV (L)	.51	.44		.57	.76	<.005
CV/VC	18	14.2	(.02)	15.8	18.8	<.02
RV%	196	184	(.05)	205	205	
FEV_1 Post Br Dil	67.6	71.9	(.02)	66.4	67	
FEF_{25-75} (post)	42.5	51	(.002)	36.6	36	<.04

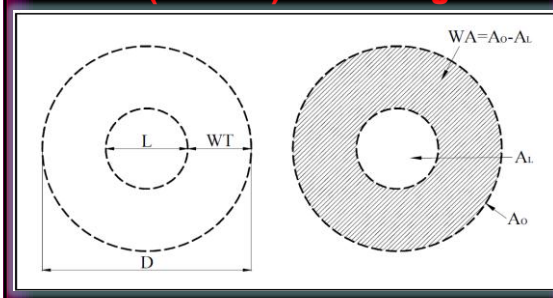
Thongngarm, et al. J Asthma 2005;42:257-63

High Resolution CT (HRCT)

- Can only estimate wall thickness of bronchi > 2 mm in diameter
- Air trapping and ventilation heterogeneity, which have been related to small airway closure, have been quantified using HRCT and correlated to functional parameters of small airway abnormalities
- More severe asthma is associated with more severe air trapping indicating small airway disease.
- Problems:
  - Costly
  - Technically demanding
  - Hampered by exposure of patients to radiation

Contoli et al Allergy 2010; 65: 141–151

HRCT Assessments In Small Bronchi (1-5 Mm) Of 5 Lung Levels



D – airway external diameter L – airway luminal diameter WT – wall thickness
AO – airway outer area AL – airway luminal area WA –airway wall area.

J. Kosciuch et al, J Physiol Phamacol, 2009

Relations Between Airway Wall Thickness Or Lumen Dimension And Lung Function In Asthma

	WA	WA/BSA	WA%	WT	BWT	A_L
Post-bronchodilator RV (%pred)	NS	NS	r=0.72 P<0.05	NS	r=0.72 P<0.05	r=-0.48 P=0.1
Post-bronchodilator FEV_1 (L)	NS	NS	r=-0.5 P=0.1		r=-0.53 P=0.1	NS
Post-bronchodilator FEV_1 (%pred)	NS	NS	NS	NS	NS	NS
PC_{20} (mg/ml)	NS	NS	NS	NS	NS	NS
Post-bronchodilator Raw (cmH_2O/l/s)	NS	NS	NS	NS	NS	r=-0.75 P<0.05

J. Kosciuch et al, J Physiol Phamacol, 2009

Distal Lung Hyperreactivity

- Important site of airway hyperreactivity (AHR).
- Reactivity of small airways in asthmatics is increased vs. normals to both nonspecific (Ach) and specific (Ag-mediated) stimuli.
  - Less responsive to bronchodilators
- Limitation: AHR has poor correlation to asthma severity and test is time consuming.
- Peripheral resistance was correlated to RV and RV is correlated to AHR….Thus airway closure could be the sole cause of AHR

Contoli et al Allergy 2010; 65: 141–151

Is There A Simple Paradigm to Define Small Air Disease In Asthma?

- Dysfunction that involves only the small airways can be defined as a situation when:
  - Static lung compliance is unaltered
  - Resistance is not significantly increased or marginally so
  - Frequency dependence of compliance or resistance is present
- Findings associated with distal lung disease:
  - Increased RV
  - Decreased FVC
  - Normal FEV1/FVC ratio

Source: Journal of Allergy and Clinical Immunology 2009; 124:S72-S77 (DOI:10.1016/j.jaci.2009.08.048)

Do Small Airway Changes Correlate With Lung Function?

- One study in nocturnal asthma demonstrated that higher numbers of eosinophils in the alveoli correlate with increased airway obstruction at night.
- Flunisolide-induced reduction in smooth muscle area in the small airway walls correlates with improved midexpiratory flow rates.
- Small airway disease appears also to be present in milder asthma, because several studies showed a higher degree of air trapping on HRCT scan .
- Definitive conclusions are hard to draw because asthma is a heterogeneous disease and different asthma populations have been investigated, the number of studies is small, and different techniques have been applied to characterize aspects of inflammation and remodeling.

van den Berge et al, *Chest 2011;139;412-423*

Summary

- Asthma is an inflammatory disease of large and small airways
- Well-controlled asthma is important to reduce the risk of exacerbation and improve quality of life
- Assessing and treating small airway disease may be important in achieving asthma control and better long-term outcomes
- Long-term studies with treatments aimed at small airways are needed to provide evidence that enduring patient outcomes improve