UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Fatebenefratelli Sacco

Funzione polmonare nell'asma grave

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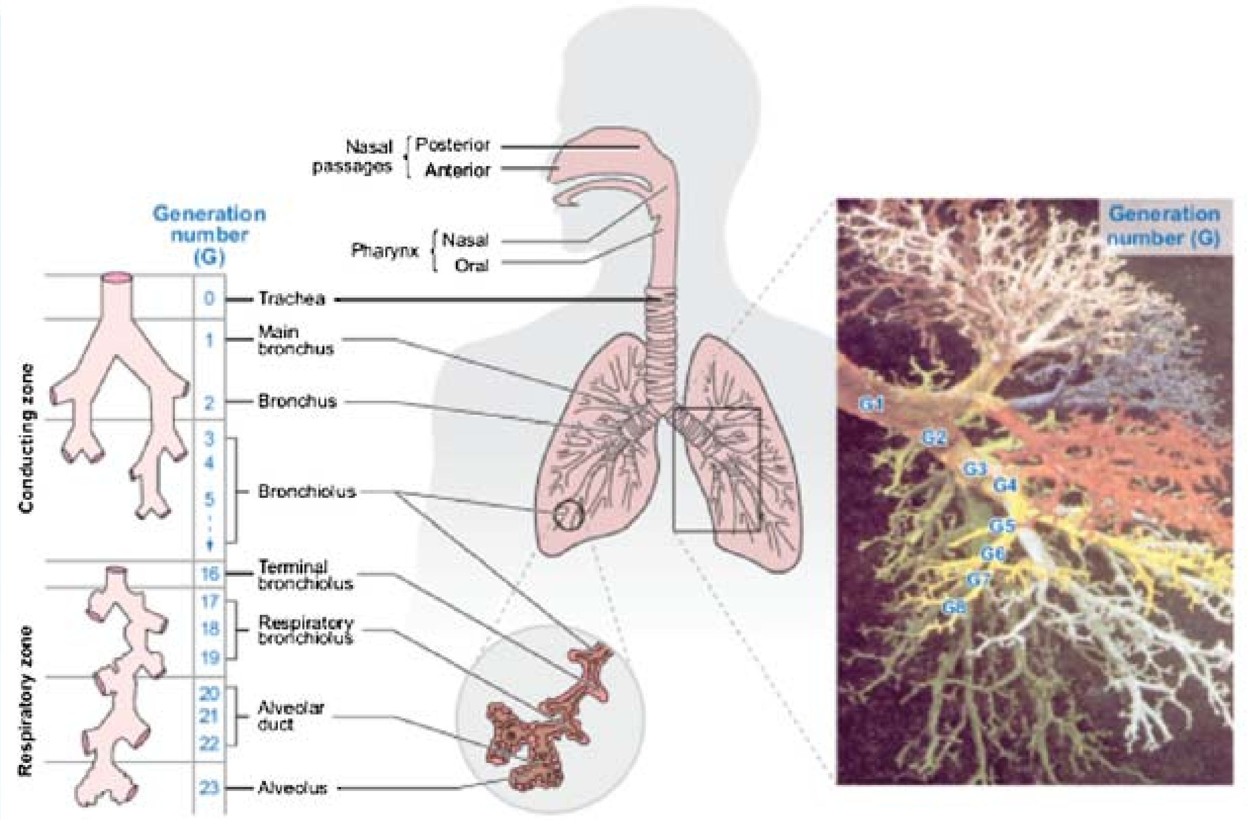

The small airways were subsequently defined as those airways with an internal diameter less than 2 mm

Scichilone N, Pulm Pharmacol Ther. 2013; Bonini Ther Adv Respir Dis 2015

Piccole vie aeree: caratteristiche anatomo-fisiologiche

<table>
<tr><th>Generazione bronchiale</th><th>Diametro (cm)</th><th>Area di sezione totale (cm^2)</th><th colspan="3">Classificazione delle vie aeree</th><th>Afflusso di sangue</th></tr>
<tr><td>0</td><td>1,8</td><td>2,54</td><td rowspan="17">Zona di conduzione</td><td rowspan="9">Grandi vie aeree (>2mm)</td><td rowspan="2">Trachea</td><td rowspan="17">Circolazione bronchiale</td></tr>
<tr><td>1</td><td>1,2</td><td>2,33</td></tr>
<tr><td>2</td><td>0,83</td><td>2,13</td><td rowspan="3">Bronchi</td></tr>
<tr><td>3</td><td>0,56</td><td>2,00</td></tr>
<tr><td>4</td><td>0,45</td><td>2,48</td></tr>
<tr><td>5</td><td>0,35</td><td>3,11</td><td rowspan="6">Piccoli bronchi</td></tr>
<tr><td>6</td><td>0,28</td><td>3,96</td></tr>
<tr><td>7</td><td>0,23</td><td>5,10</td></tr>
<tr><td>8</td><td>0,186</td><td>6,95</td></tr>
<tr><td>9</td><td>0,154</td><td>9,56</td><td rowspan="8">Piccole vie aeree (<2mm)</td></tr>
<tr><td>10</td><td>0,130</td><td>13,40</td></tr>
<tr><td>11</td><td>0,109</td><td>19,60</td><td rowspan="6">Bronchioli</td></tr>
<tr><td>12</td><td>0,095</td><td>28,80</td></tr>
<tr><td>13</td><td>0,082</td><td>44,50</td></tr>
<tr><td>14</td><td>0,074</td><td>69,40</td></tr>
<tr><td>15</td><td>0,066</td><td>113,00</td></tr>
<tr><td>16</td><td>0,060</td><td>180,00</td></tr>
<tr><td>17</td><td>0,054</td><td>300,00</td><td rowspan="7">Zona di scambio</td><td colspan="2" rowspan="3">Bronchioli respiratori</td><td rowspan="7">Arteriole</td></tr>
<tr><td>18</td><td>0,050</td><td>534,00</td></tr>
<tr><td>19</td><td>0,047</td><td>944,00</td></tr>
<tr><td>20</td><td>0,045</td><td>1600,00</td><td colspan="2" rowspan="4">Dotti e sacchi alveolari</td></tr>
<tr><td>21</td><td>0,043</td><td>3220,00</td></tr>
<tr><td>22</td><td>0,041</td><td>5880,00</td></tr>
<tr><td>23</td><td>0,041</td><td>11800,00</td></tr>
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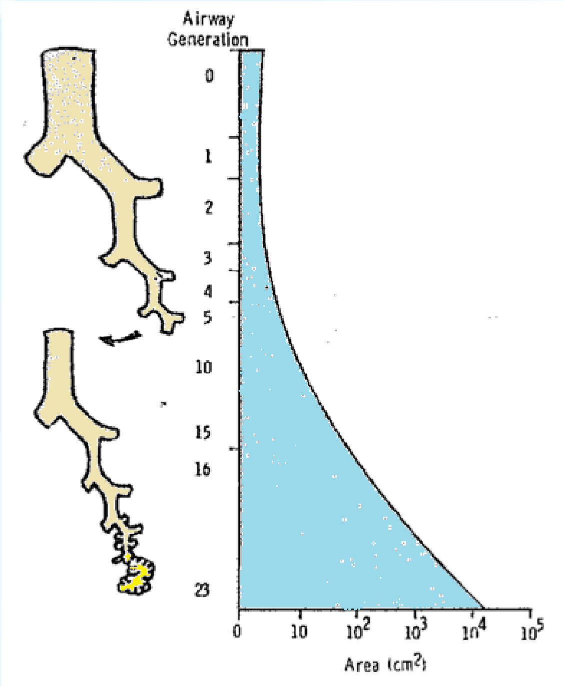
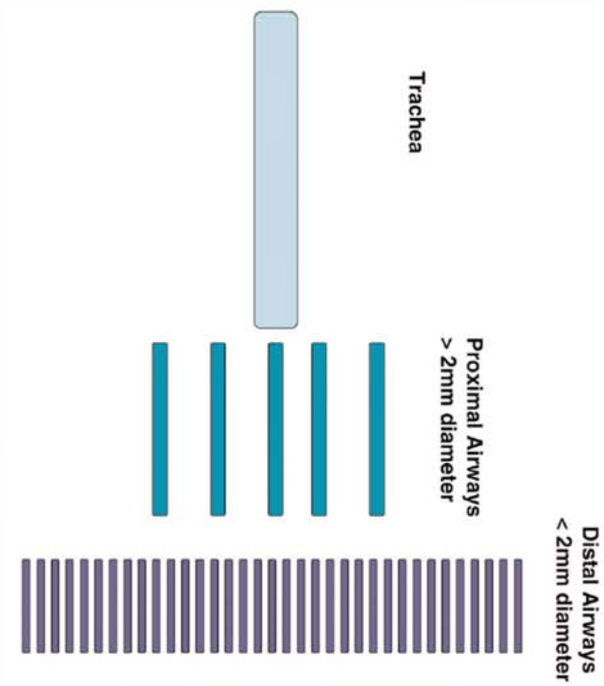
Clarke SW, Pavia D. Aerosols and the lung. Ed. Butterwoths. 1984

Small Airways: anatomical and physiological meaning





They are generally located from the eighth generation of airways to the respiratory bronchioles and account for 98.8% of the total lung volume

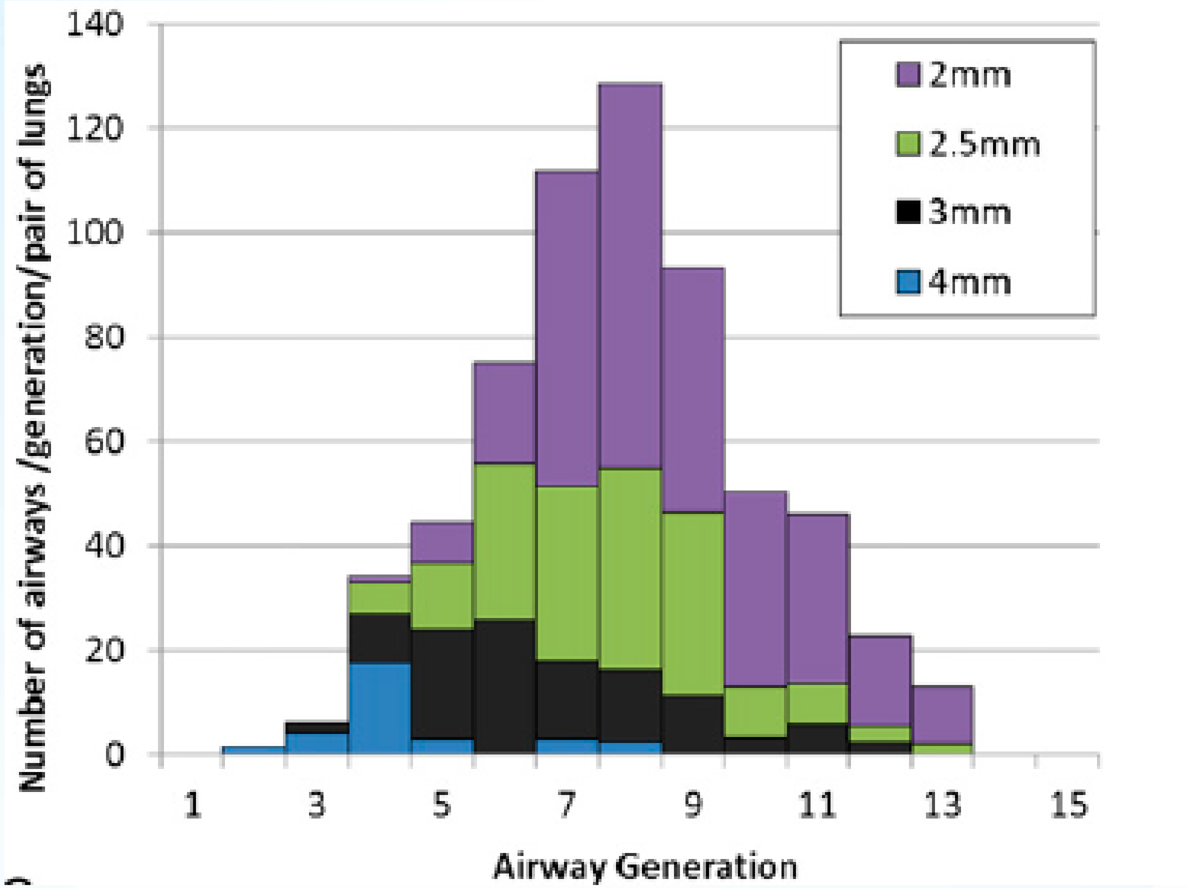
Jain N. Crit Care 2007; Bonini Ther Adv Respir Dis 2015;
Clarke SW, Pavia D. Aerosols and the lung. Ed. Butterwoths. 1984

CHEST Translating Basic Research Into Clinical Practice

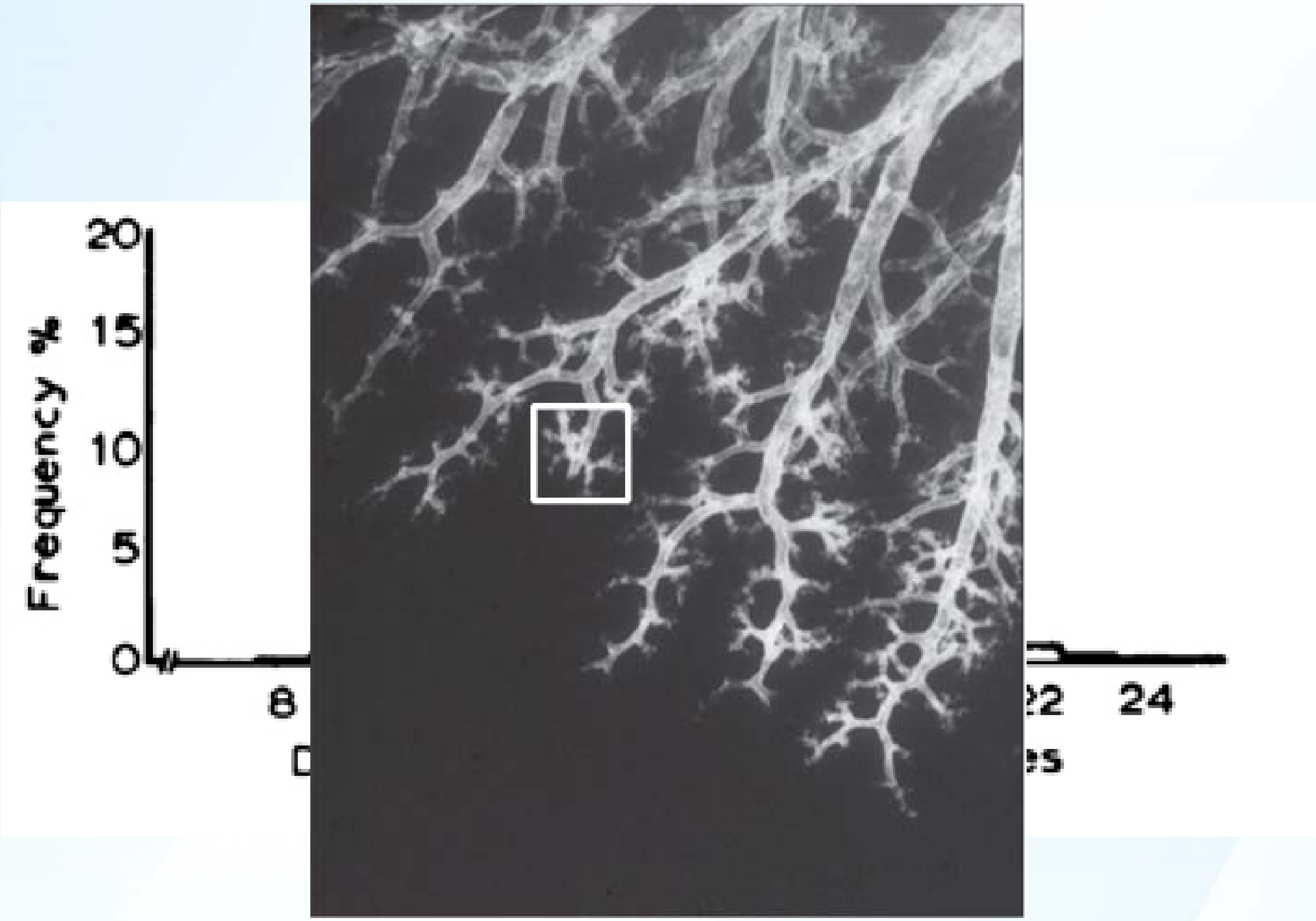
Small Airway Obstruction in COPD

New Insights Based on Micro-CT Imaging and MRI Imaging

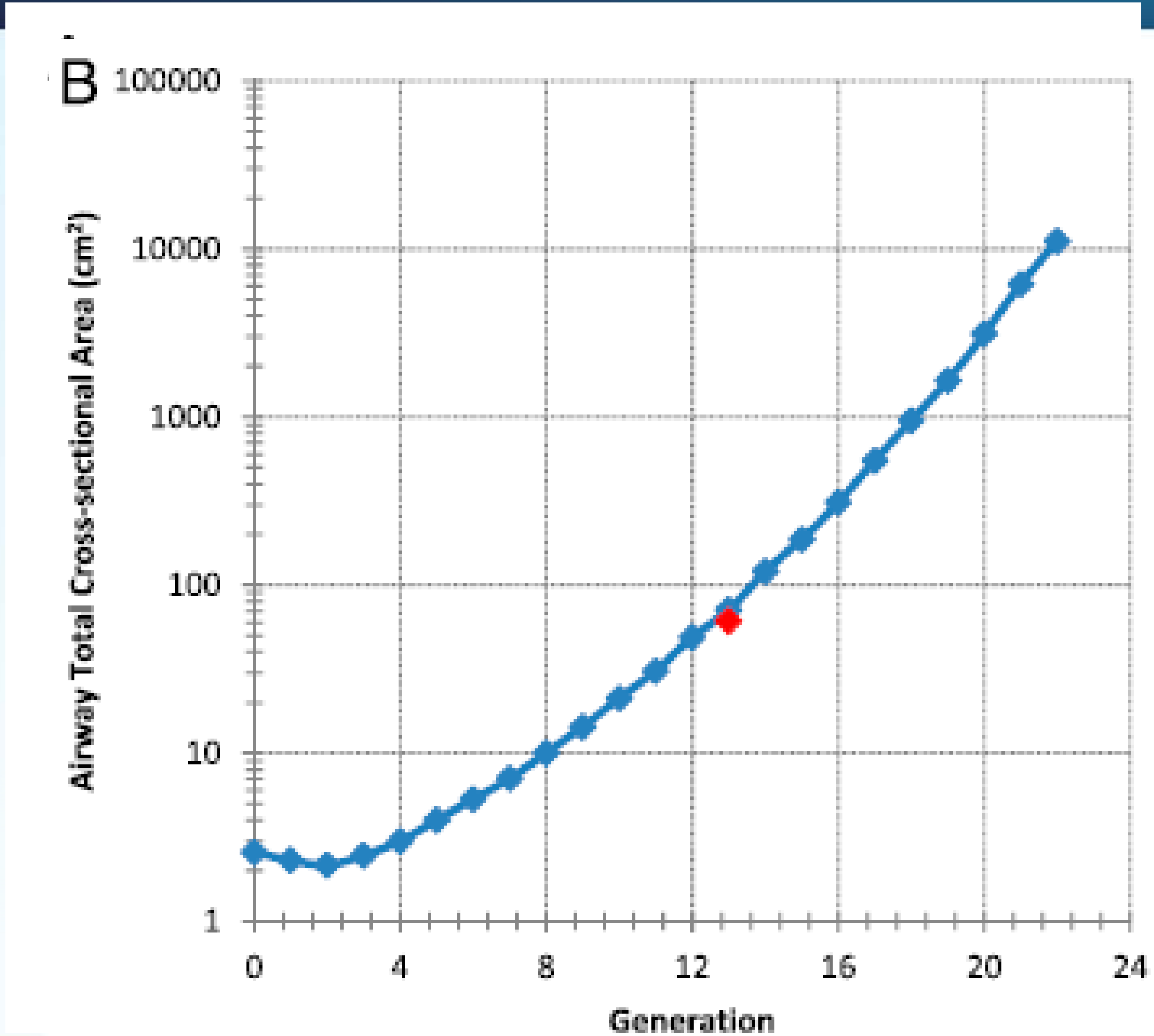
James C. Hogg, MD, PhD; John E. McDonough, PhD; and Masaru Suzuki, MD, PhD



CHEST 2013; 143(5):1436–1443



CHEST 2013; 143(5):1436–1443



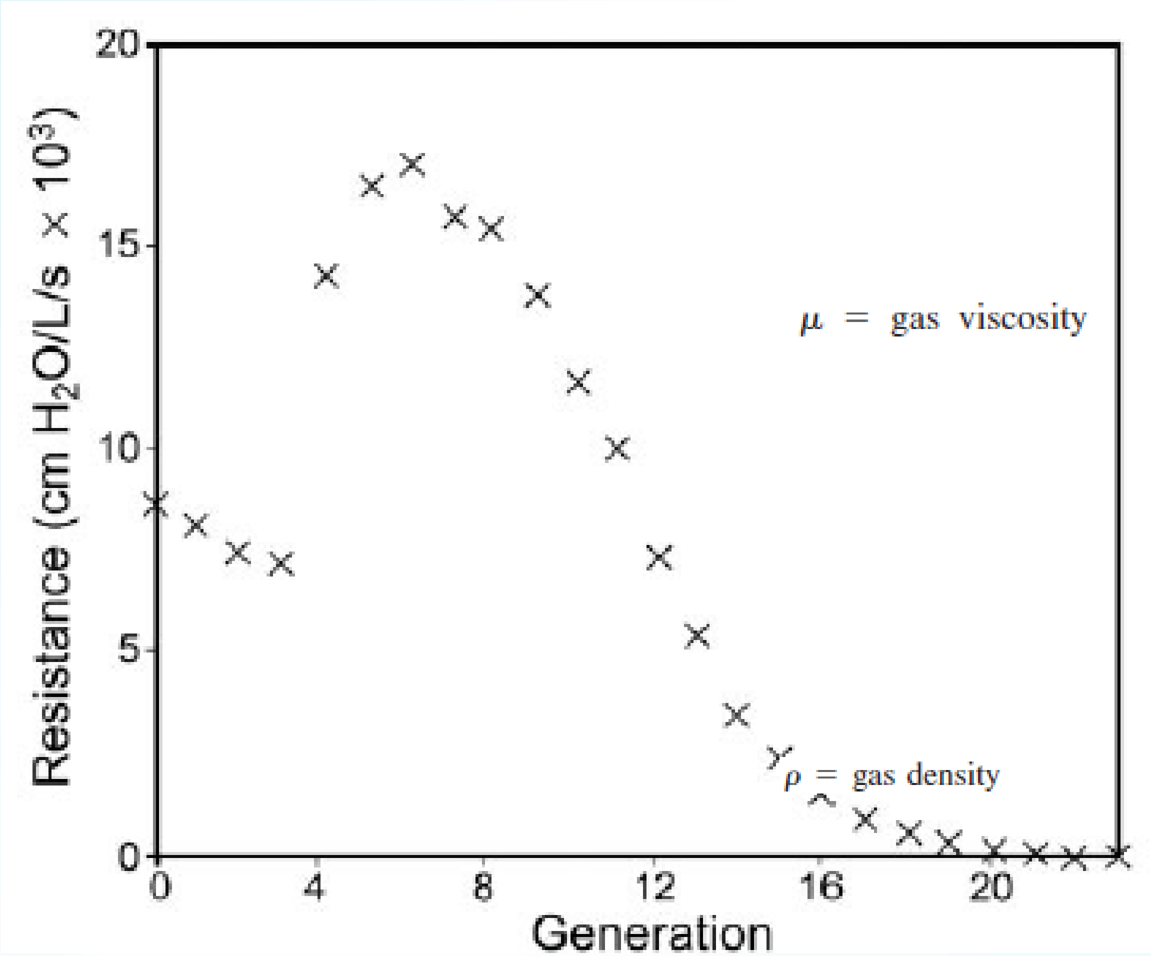
CHEST 2013; 143(5):1436–1443

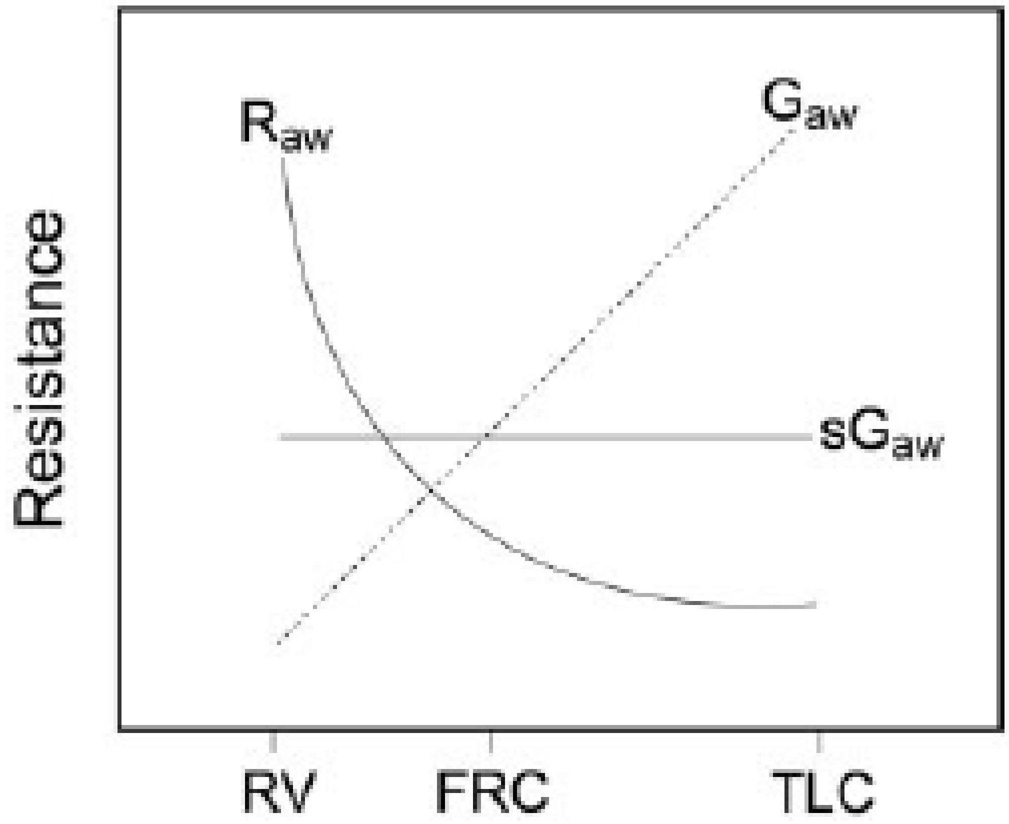
3. *Calculation of airway resistance:* To determine the airway resistance, it is necessary to know the ratio of alveolar pressure to airflow at the mouth, $P_A/\dot{V}$. The experiments yielded two slopes. First, with the shutter open, the slope $\dot{V}/P_P$ was measured on the S shaped line from the point of 1 liter per second of inspiratory flow to the point of 1 liter per second of expiratory flow.[8] Second, the slope P_A/P_P is generated with the shutter closed. The total airway resistance is calculated by taking the ratio of slopes:

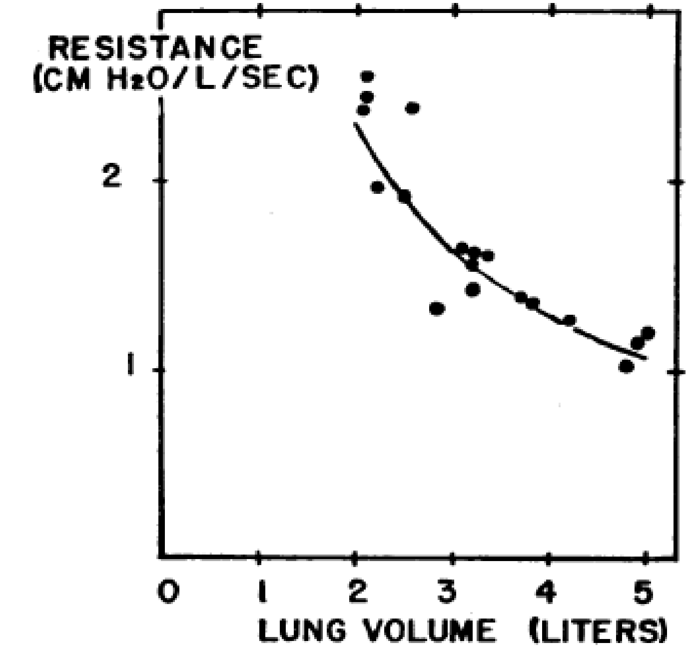
$$R = \frac{P_A/P_P}{\dot{V}/P_P}$$

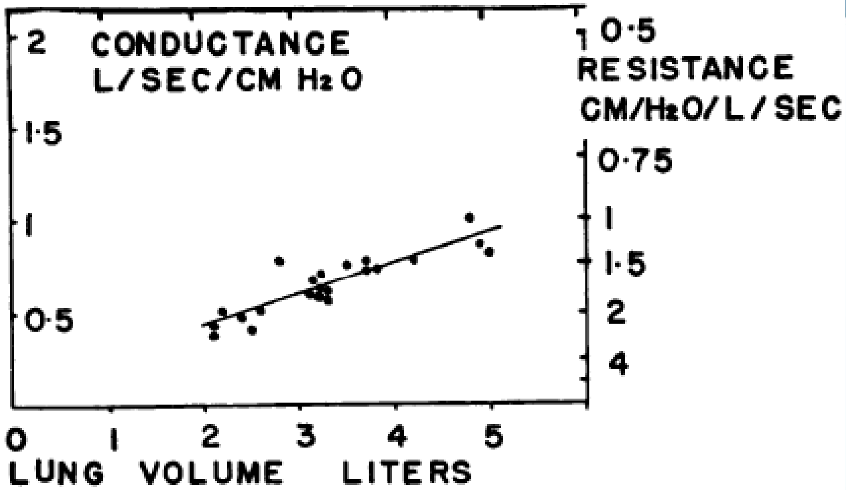
where P_A is alveolar pressure, $\dot{V}$ is airflow, P_P is plethysmograph pressure (the same with shutter open and closed), and R is resistance.

J Clin Invest. 1956 Mar;35(3):327-35.


Resistance (cm H2O/L/s × 10³)
Generation
μ = gas viscosity
ρ = gas density
0
5
10
15
20
0
4
8
12
16
20


Resistance
R_{aw}
G_{aw}
sG_{aw}
RV
FRC
TLC

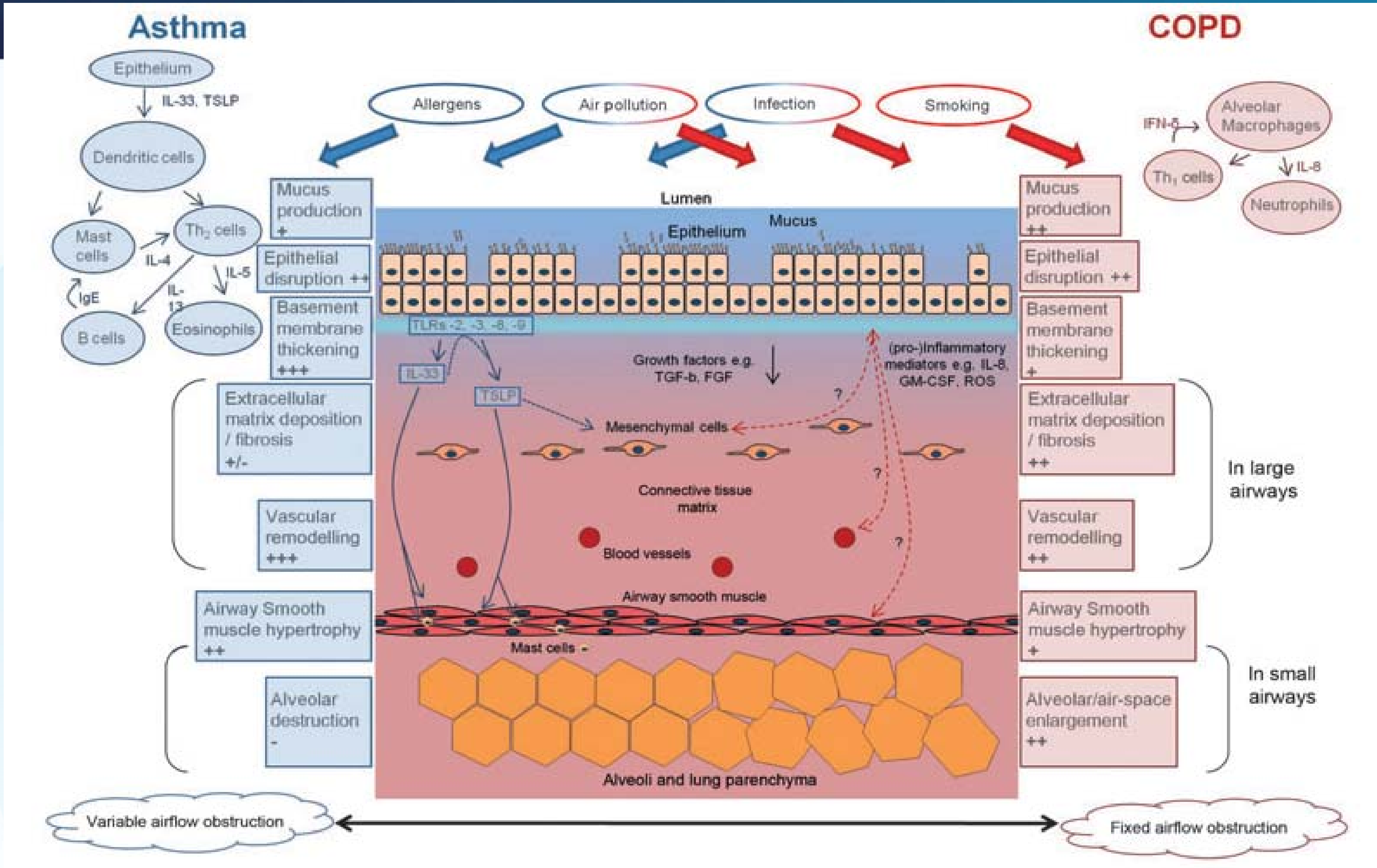




The major determinant of airway resistance is lung volume and age has little effect. The line expresses the

differences in age. A method is suggested for correcting changes in airway resistance for concomitant changes in lung volume during studies on airway resistance. Theoretical considerations

J Clin Invest. 1958 Sep;37(9):1279-85



S. Gonem *et al* *Clinical & Experimental Allergy*, 42, 1664–1683

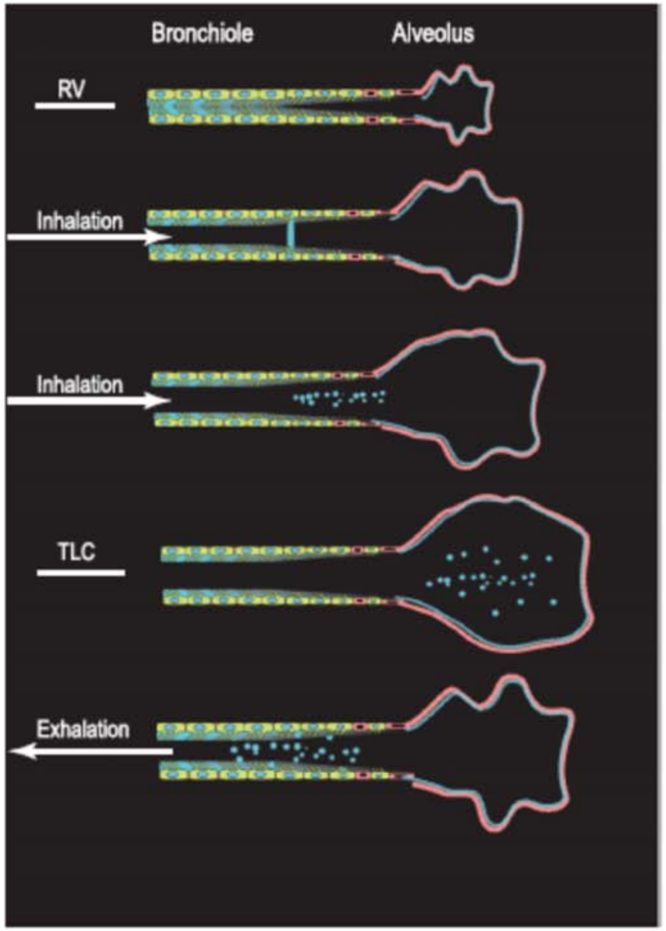


Fig. 4 Schematic illustration of the airway reopening concept. When airways close, opposing airway walls get in contact creating a plug of respiratory tract lining fluid. As the airway walls distend during inspiration, forming a meniscus that finally breaks and generate particles. By permission of the author

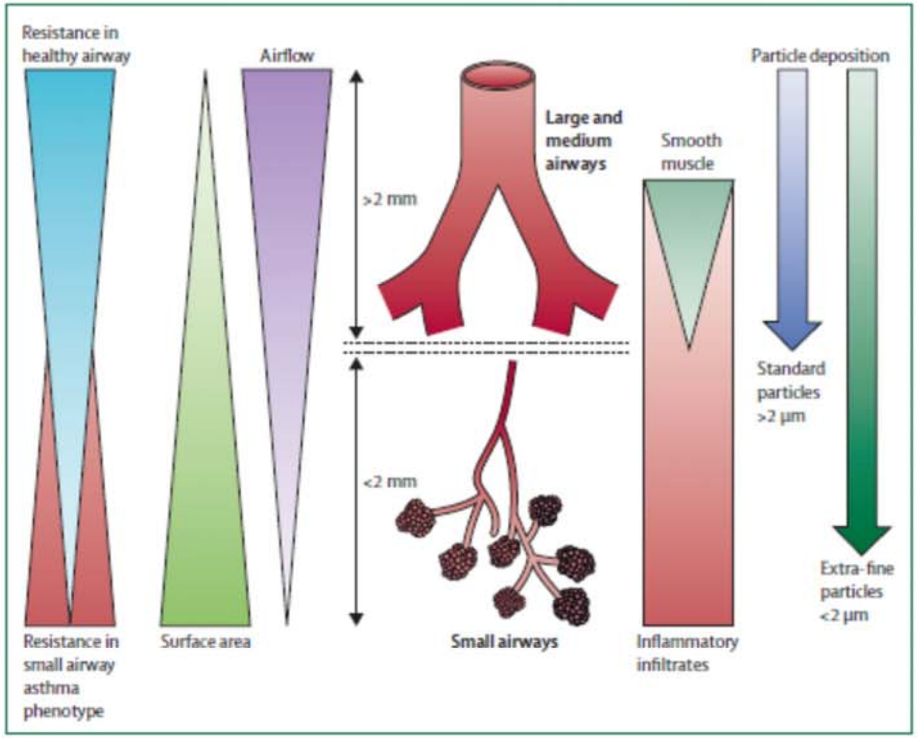


Figure: Small airway asthma phenotype

***Panel:* Clinical pattern recognition of the small airway asthma phenotype**

Suboptimum asthma control

- Asthma control questionnaire score higher than 1·5
- Daytime and night-time symptoms
- Regular use of relievers in response to bronchoconstrictor stimuli
- Oral corticosteroid use with viral exacerbations
- Failure to respond to conventional coarse-particle inhaled corticosteroids and long-acting β-agonists

Small airways dysfunction

Normal FEV_1 in conjunction with any of:

- Reduced FEF_{25-75}
- Abnormal airway resistance (R5–R20, R_{aw}) or reactance area (AX)
- Evidence of air trapping (closing volume, residual volume)
- Abnormal ventilation heterogeneity (S_{acin} and S_{cond})

FEV_1=forced expiratory volume in 1 s. FEF_{25-75}=forced mid-expiratory flow between 25% and 75% of forced vital capacity. R5–R20=peripheral airways resistance as difference between measurements at 5 Hz and 20 Hz. R_{aw}=plethysmographic airway resistance. S_{acin}=acinar (diffusion) dependent ventilation heterogeneity. S_{cond}=conductive (convection) ventilation heterogeneity.

Brian Lipworth, Arvind Manoharan, William Anderson *Lancet Respir Med* 2014; 2: 497–506

Frequency Dependence of Compliance as a Test for Obstruction in the Small Airways

Ann J. Woolcock, N. J. Vincent, and Peter T. Macklem

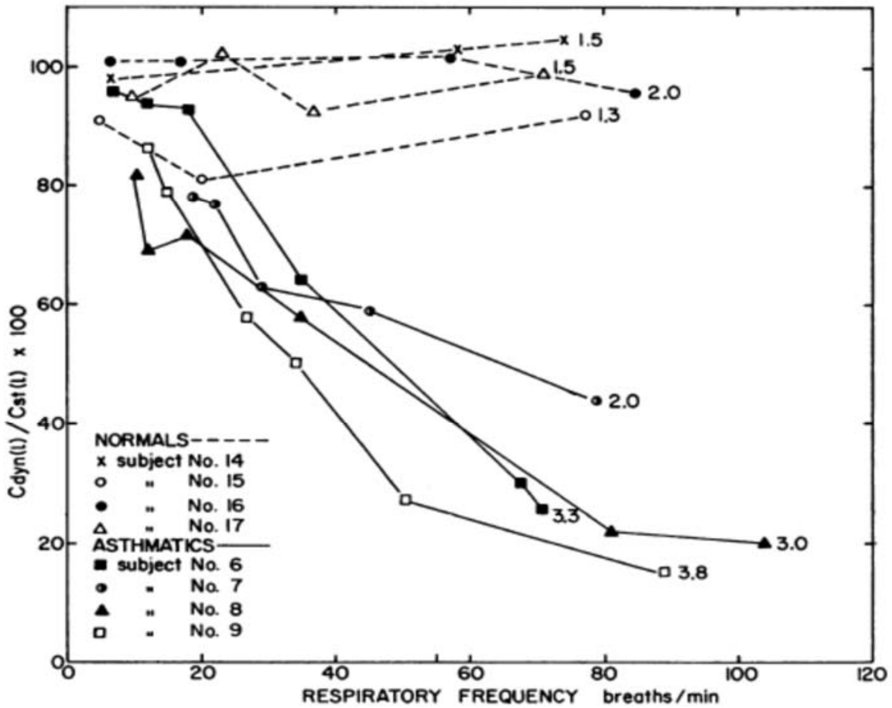


Figure 3 $C_{dyn}(l)$ as a percentage of $C_{st}(l)$ at different frequencies in four asthmatic subjects (——) and four normal subjects (- - - -) of similar age. The number at the right of each graph is the value obtained for R_L at the time of the study.

The Journal of Clinical Investigation Volume 48 1969

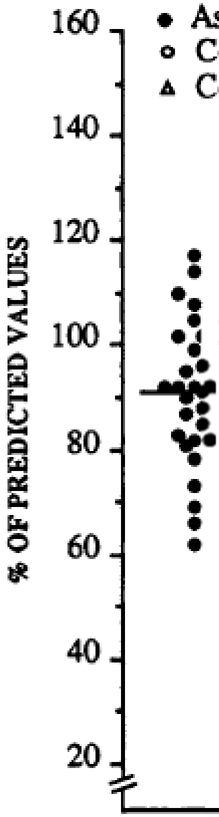
Persistence of Airway Obstruction and Hyperresponsiveness in Subjects With Asthma Remission*

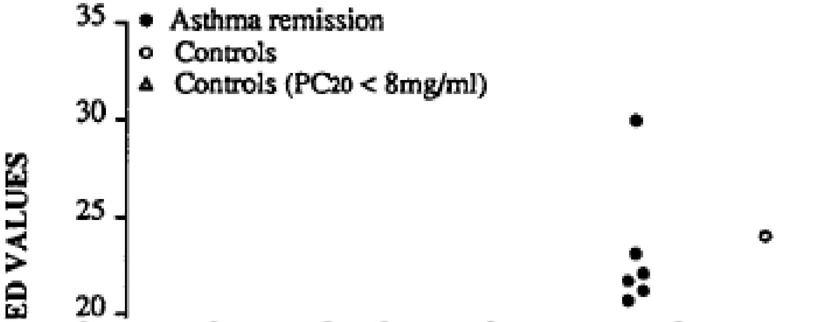
Louis-Philippe Boulet, M.D., F.C.C.P.; Hélène Turcotte, M.Sc.; and Annie Brochu, M.D.

Table 1—*Subjects' Characteristics*

	Asthma "in Remission"	Controls
No. of subjects	30 (20M, 10F)	30 (20M, 10F)
Age, yr, mean (range)	32.1 (18 to 61)	31.6 (20 to 67)
Atopy, No. of subjects	28	28
No. of positive responses	8.8 (0 to 20)	7.9 (0 to 20)
Past immunotherapy	10	2
Age at the onset of asthma, yr, mean ± SEM (range)	10.5 ± 1.8 (0 to 33)	—
Duration of symptomatic asthma, yr, mean ± SEM (range)	12.4 ± 1.7 (2 to 33)	—
Duration of remission, yr, mean ± SEM (range)	9.6 ± 1.3 (2 to 25)	—
Family history of asthma	11	10
Family history of atopy	16	21

(Chest 1994; 105:1024-31)





In conclusion, this study shows that airway hyperresponsiveness with or without airflow obstruction persists in many subjects who consider themselves to be in remission of asthma. This suggests that in those subjects, there may be ongoing airway inflammation or that they developed irreversible airway changes even if symptoms have disappeared or markedly decreased. The definition of "remission" of asthma has to be reconsidered and studies on remission should include measurements of airflow obstruction and airway responsiveness.

F /FVC

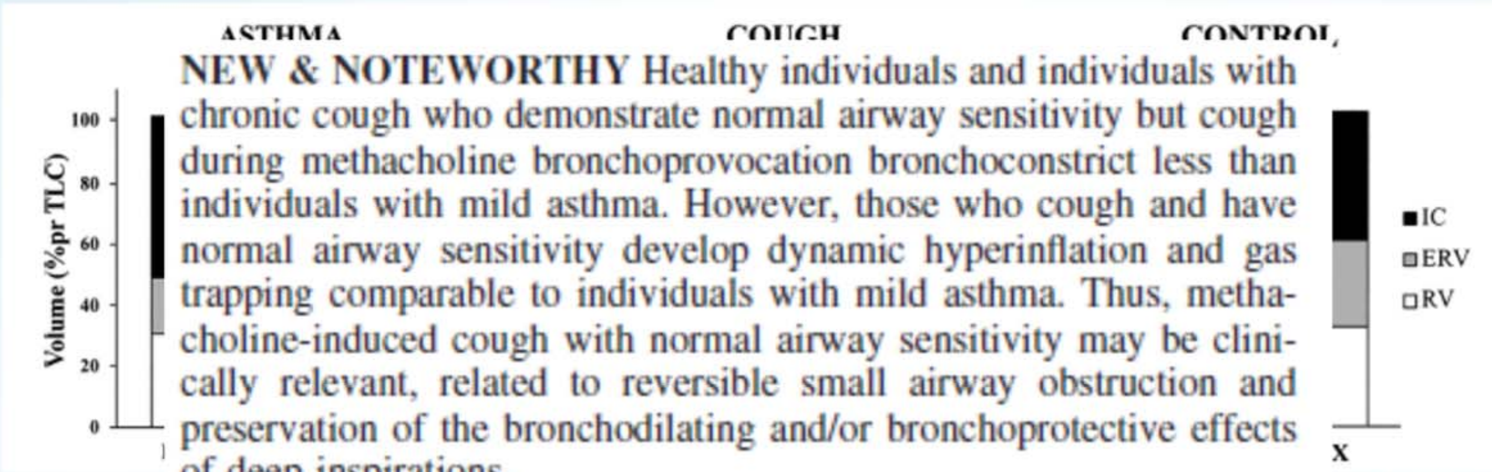
FIGURE 1. (C), for FE AR: 70.6± C: 100.2± AR: 97.8± ... 25 ith nd ere er- trols ean, cent; ean,

FIGURE 3. There was no significant difference between ex-asthmatics and controls for mean daily variations in PEFR over a 2-week period (AR: 4.6±0.4 percent; C: 2.9±0.3 percent). However, the difference was significant between ex-asthmatics and controls for the maximal daily variation in PEFR observed during that period (AR: 12.3±1.3 percent; C: 7.0±0.8 percent, p=0.021), although these fluctuations of airway caliber are very small.

(Chest 1994; 105:1024-31)

Small-airway obstruction, dynamic hyperinflation, and gas trapping despite normal airway sensitivity to methacholine in adults with chronic cough

Nilita Sood,[1,2] Scott E. Turcotte,[1,2] Nastasia V. Wasilewski,[1,2] Thomas Fisher,[1] Taylar Wall,[1] John T. Fisher,[2] and M. Diane Lougheed[1,2]



NEW & NOTEWORTHY Healthy individuals and individuals with chronic cough who demonstrate normal airway sensitivity but cough during methacholine bronchoprovocation bronchoconstrict less than individuals with mild asthma. However, those who cough and have normal airway sensitivity develop dynamic hyperinflation and gas trapping comparable to individuals with mild asthma. Thus, methacholine-induced cough with normal airway sensitivity may be clinically relevant, related to reversible small airway obstruction and preservation of the bronchodilating and/or bronchoprotective effects of deep inspirations.

J Appl Physiol 126: 294–304, 2019.

Review article

The role of small airways in monitoring the response to asthma treatment: what is beyond FEV_1?

Table 1. Lists of procedures that can be employed to assess small airway dysfunction

Procedure	Advantages	Limitations
NO measurement	High sensitivity for inflammation	Need for validity
Sputum induction	High reproducibility, high sensitivity for inflammation	Need for trained staff, time consuming
Transbronchial biopsies	'Gold standard'	Invasive
HRCT	High reproducibility	Side-effects, costs
Spirometry	Simplicity, high reproducibility	Poor correlation to severity
Oscillometry	Simplicity	Poor correlation to severity
Mch bronchoprovocation	High reproducibility, high sensitivity for diagnosis	Poor correlation to severity, time consuming
N2 wash-out	High reproducibility, high sensitivity for diagnosis	Need for trained staff
Asthma questionnaires, diary cards	High reliability, simplicity	Patient dependent

NO, nitric oxide; HRCT, high resolution computed tomography; Mch, methacholine; N2, nitrogen.

Scichilone et al. *Allergy 2009: 64: 1563–1569*

REVIEW ARTICLE

Treatment of the bronchial tree from beginning to end: targeting small airway inflammation in asthma

M. van den Berge[1,2], N. H. T. ten Hacken[1,2], E. van der Wiel[1,2] & D. S. Postma[1,2]

Table 1 Examples of studies showing an association between small airway disease and the presence and activity of asthma

Reference	Main findings
Wagner et al. (4)	Sevenfold increased peripheral airway resistance measured with the wedged bronchoscope technique in asthma *vs* healthy controls
	Baseline peripheral airway resistance correlates with bronchial hyper-responsiveness to methacholine
Kraft et al. (5)	Higher peripheral airway resistance at night than during daytime in nocturnal asthma
Kaminsky et al. (6)	Higher peripheral airway resistance correlates with exercise-induced bronchoconstriction
Zeidler et al. (7)	Natural cat allergen exposure increases both methacholine-induced air trapping on HRCT and closing volume measured with the single-breath nitrogen test 6 and 23 h later
In 't Veen et al. (8)	Asthma patients who have frequent exacerbations ($\geq$2 per year) have a higher degree of small airway disease measured with the single-breath nitrogen washout test than patients with infrequent exacerbations (<2 per year), whereas their FEV_1 and FEV_1/FVC are similar
Lee et al. (9)	A higher drop in FVC during PD_{20} methacholine is associated with more severe asthma

FVC, forced vital capacity; HRCT, high-resolution computed tomography.

Allergy **68** (2013) 16–26

Table 2 Overview of tests for small airway obstruction

	Ability to detect small airway abnormalities	Reproducibility	Advantages	Disadvantages

Table 2 (continued)

	Ability to detect small airway abnormalities	Reproducibility	Advantages	Disadvantages
Alveolar and bronchial NO	Alveolar NO related to: • RV/TLC and closing volume in severe asthma (27) • Ventilation heterogeneity in stable asthma (77) Bronchial NO related to: • Air trapping (CT)	Fair	• Noninvasive	• Relatively time-consuming (20 min) • Influenced by smoking, caffeine, diet
Small-particle AMP provocation	Closely related to: • Treatment response to small-particle aerosol (ciclesonide) (56)	Unknown	• Noninvasive • Promising new tool to investigate small airway inflammation	• Bronchial challenge test, relatively time-consuming • Little evidence
Late-phase sputum induction	• The concentration of surfactant protein A was significantly higher in a late-*vs* early-phase sputum, suggesting sampling of the more distal airways (78) • Small-particle HFA-beclomethasone, but not large-particle DPI-budesonide, significantly reduced the percentage of eosinophils and expression of IL-4 and IL-5 mRNA in late-phase sputum	Unknown	• Noninvasive	• High costs • Little evidence
Transbronchial biopsies	• The number of transbronchial biopsy eosinophils was found to be associated with TLC and FRC, but not with FEF_{25-75} or FVC Unfortunately, no data on RV/TLC were presented (79)	Unknown	• Direct measurement of small airway inflammation and remodeling	• Invasive • Few studies available on the association between markers of inflammation and/or remodeling in transbronchial biopsies and other parameters of small airway inflammation and/or dysfunction

Adapted with permission from reference (1). FVC, forced vital capacity; CT, computed tomography; MCh, methacholine; FEV_1, forced expiratory volume in 1-s; PC_{20}, provocative concentration causing the FEV_1 to drop with 20%; FEF_{25-75}, forced expiratory flow between 25% and 75% of the FVC; NO, nitric oxide; RV, residual volume; TLC, total lung capacity; SBNW, single-breath nitrogen washout test; MBNW, multiple-breath nitrogen washout test; AMP, adenosine 5′-monophosphate; IL, interleukin; FRC, functional residual capacity; DPI, dry powder inhaler; FOT, forced oscillometry.

(continued)

Table 2 Overview of tests for small airway obstruction

	Ability to detect small airway abnormalities	Reproducibility	Advantages	Disadvantages
ΔFVC at PC_{20}	Closely related to: • Disease severity (10) • MCh-induced air trapping (CT) • Maximal airway response to MCh (11)	Good	• Noninvasive • Easy to perform • Widely available	• Bronchial challenge test, time-consuming • High costs • Performing complete FVC maneuver twice at each dose is strenuous
FVC/SVC	• Detects and monitors small airway disease in BOS after lung transplantation (72)	Poor	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease
FEF_{25-75}	Closely related to: • Air trapping (CT) (73) • FEF_{25-75} is often normal when $FEV_1/FVC \geq 75\%$ (74)	Poor	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease • Wide range of normal • Dependence on FVC
IOS or FOT	Closely related to: • FEF_{25-75} (75) • Methacholine (MCh)-induced changes in ventilation Heterogeneity (76)	Fair	• Noninvasive • Easy to perform • Low costs • Not time-consuming	• Not a very specific test for the measurement of small airway disease
SBNW: closing volume	Closely related to:Alveolar NO in severe asthma (27)	Fair	• Noninvasive • Relatively low costs • Not time-consuming	• Difficult measurement to perform without flow restrictor • High variability • Lack of certainty about interpretation
MBNW	Closely related to: • Alveolar NO (77)	Good	• Noninvasive • Easy to perform	• Not widely available • High costs • Lack of certainty about interpretation
(MCh-induced) air trapping with CT	Closely related to: • ΔFVC at PC_{20} • High costs • RV/TLC (33)	Good	• Noninvasive • Direct visualization of air trapping, which may reflect small airway disease	• Radiation load is unfavorable • High costs • Time-consuming (approximately 70 min including MCh challenge)
RV/TLC	Closely related to: • N Alveolar NO in severe asthma (27) • Air trapping (CT) (33, 73)	Fair	• Noninvasive	Relatively time-consuming (30 min)

(continued)

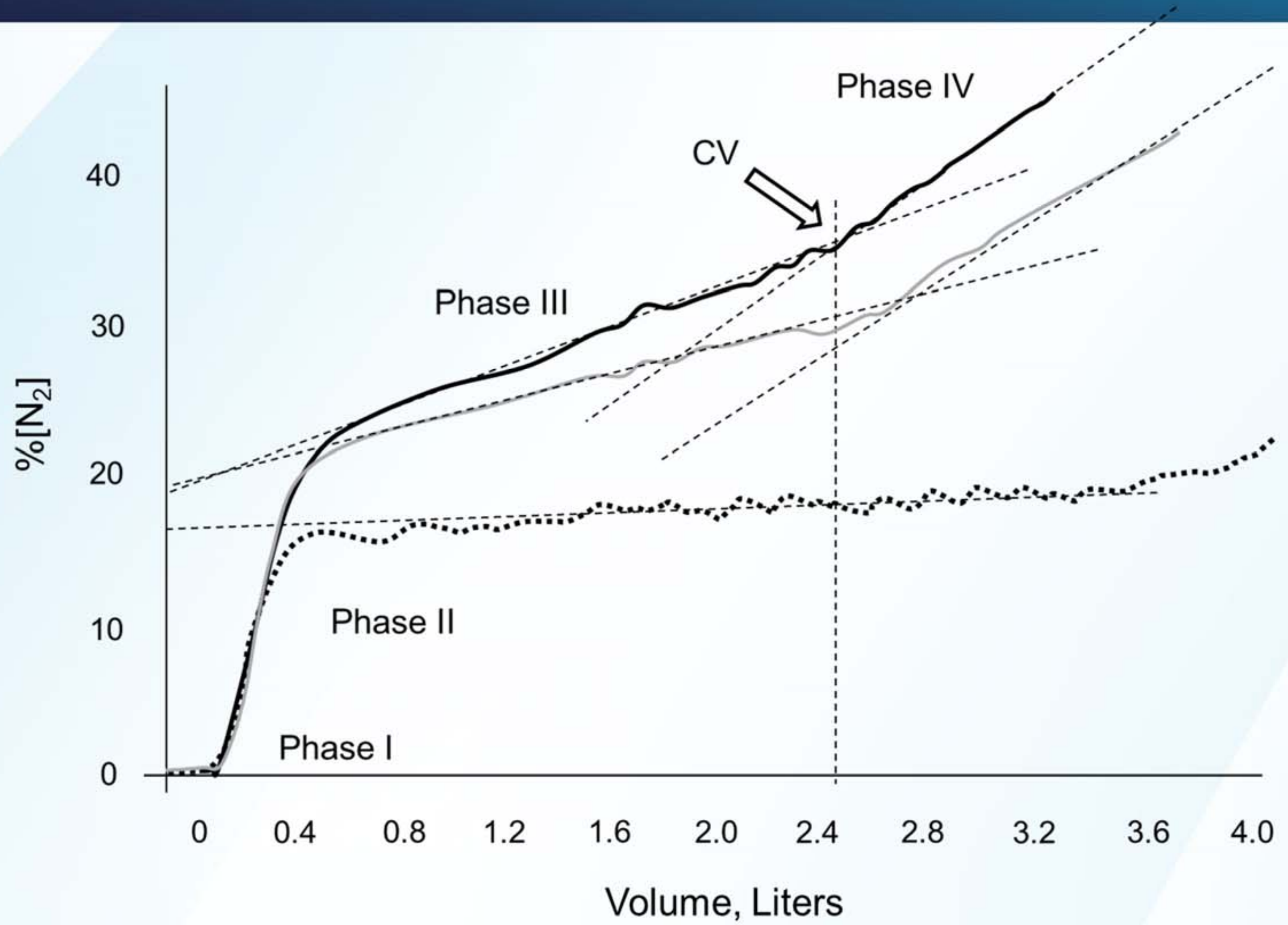
The Relations between Structural Changes in Small Airways and Pulmonary-Function Tests

M. Cosio, M.D., H. Ghezzo, M.S.C., J. C. Hogg, M.D., R. Corbin, M.D., M. Loveland, M.D., J. Dosman, M.D., and P. T. Macklem, M.D.et al.

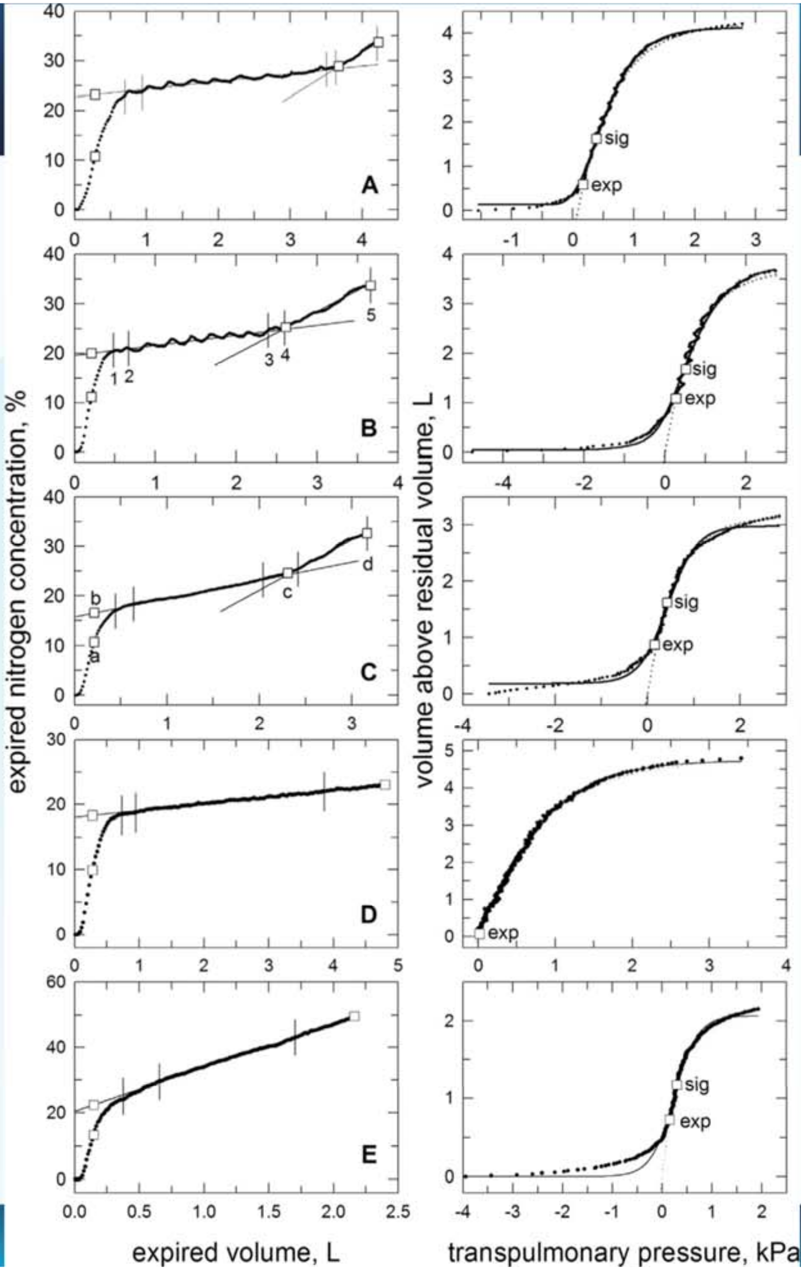
June 8, 1978
N Engl J Med 1978; 298:1277-1281
DOI: 10.1056/NEJM197806082982303

Abstract

To examine the relation between small-airways abnormalities and specific lung functions, we performed pulmonary-function tests in 36 patients, of whom two were nonsmokers, one to three days before open-lung biopsy for localized pulmonary lesions. The primary lesion in the small airways was a progressive inflammatory reaction leading to fibrosis with connective-tissue deposition in the airway walls. Increase in disease in small airways correlated with deterioration in lung function. Lesions could be reliably detected ($P<0.05$) by tests for closing capacity, the volume at which air and helium flow were equal (a test of airway caliber and elastic recoil), and the slope of phase III of the single-breath washout curve (which tests evenness of ventilation). These tests showed abnormalities at a time when the pathologic changes were still potentially reversible and when other tests were not appreciably changed. (N Engl J Med 298:1277-1281, 1977)



(Santus et al. Submitted)



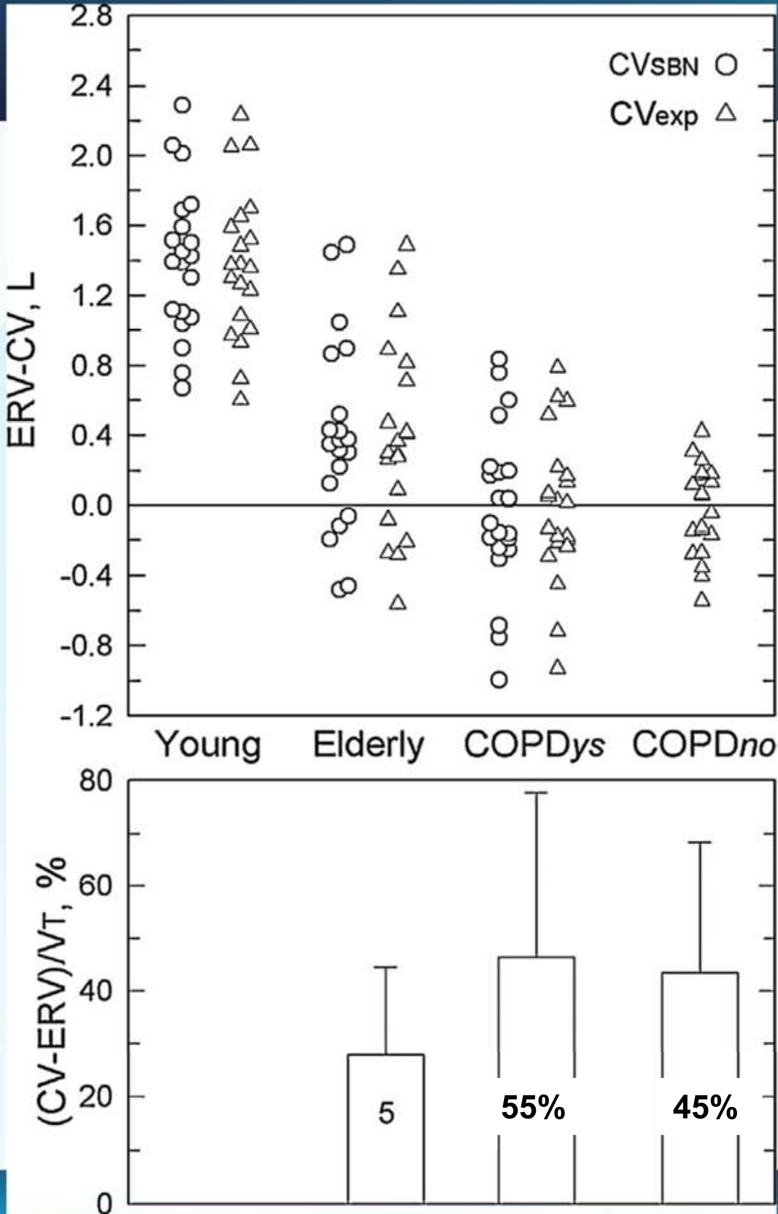
Airway occlusion assessed by single breath N_2 test and lung P-V curve in healthy subjects and COPD patients

Matteo Pecchiari[a], Dejan Radovanovic[b], Pierachille Santus[b], Edgardo D'Angelo[a,*]

Respiratory Physiology & Neurobiology 234 (2016) 60–68

FEV_1, L	1.32 ± 0.35
% predicted	50 ± 12

FEV_1, L	0.81 ± 0.26
% predicted	33 ± 9



Airway occlusion assessed by single breath N_2 test and lung P-V curve in healthy subjects and COPD patients

Matteo Pecchiari[a], Dejan Radovanovic[b], Pierachille Santus[b], Edgardo D'Angelo[a,*]

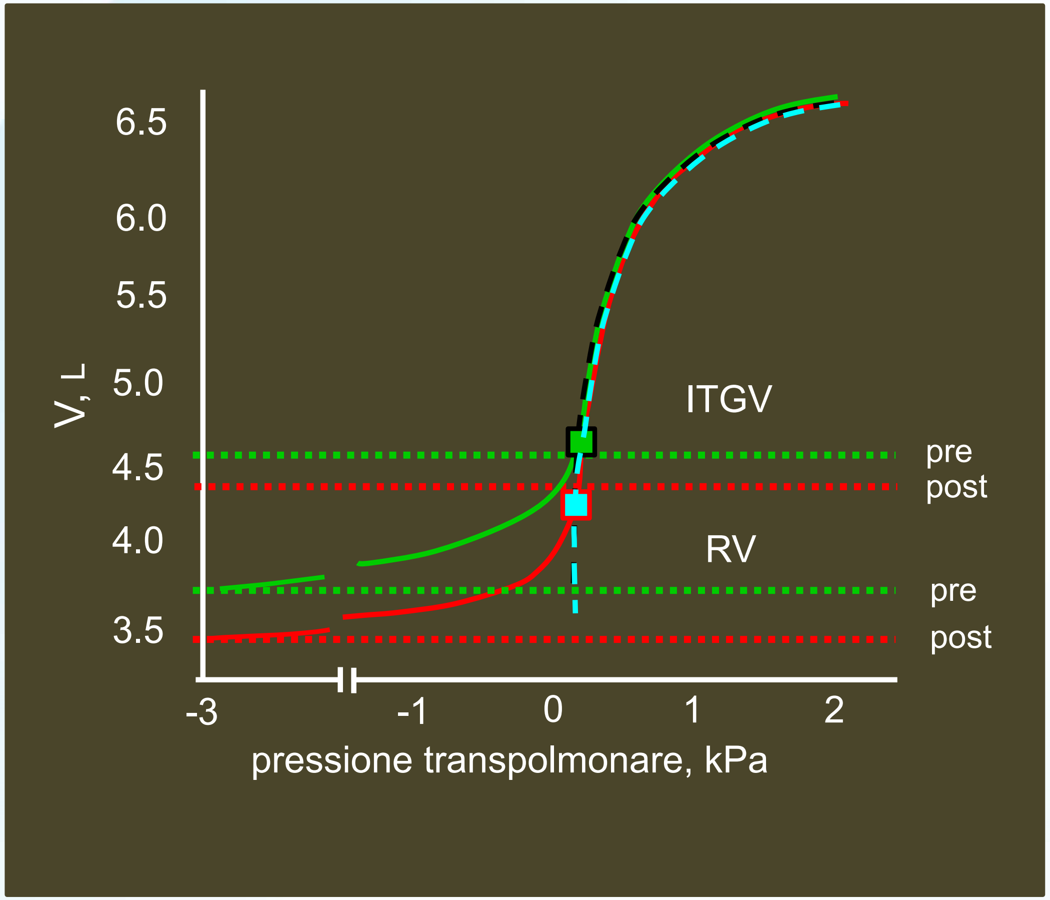
Respiratory Physiology & Neurobiology 234 (2016) 60–68

Furthermore, in these patients airway closure involves a substantially greater fraction of the resting tidal volume; consequently, cyclic opening and closing should cause greater damage as it affects already altered airways.

RESEARCH ARTICLE

Acute effects of long-acting bronchodilators on small airways detected in COPD patients by single-breath N_2 test and lung P-V curve

Matteo Pecchiari,[1] Pierachille Santus,[2] Dejan Radovanovic,[2] and Edgardo D'Angelo[1]



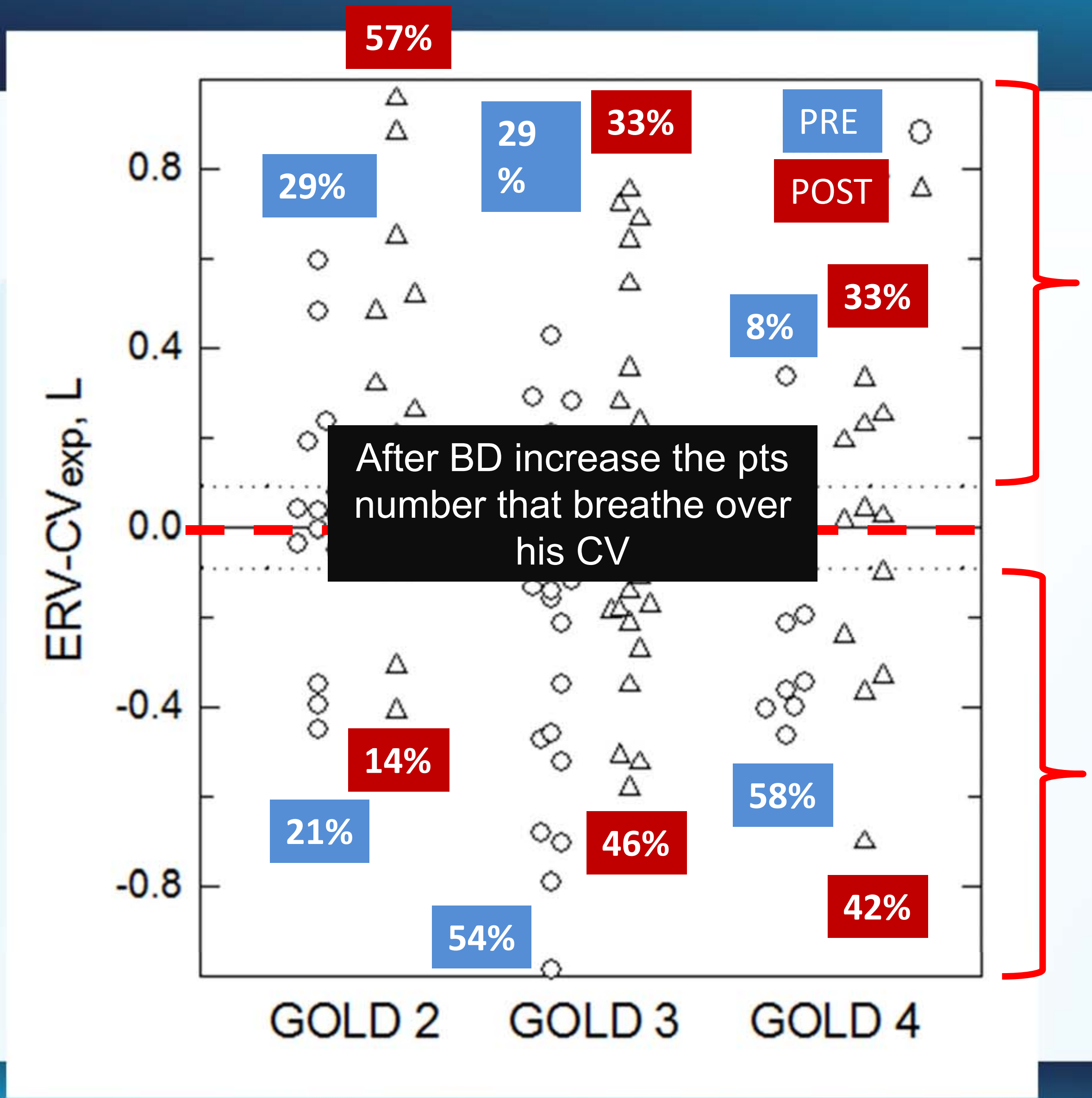
Bronchodilation improves the closing volume at every point of PL<PL,CV

Significantly improvment of **CVexp/VC** and **CVexp/TLC**

None critical closing pressure modification

The central point related all these changes is the reduction of **ITGV** and **RV** and the improvement of **ERV**

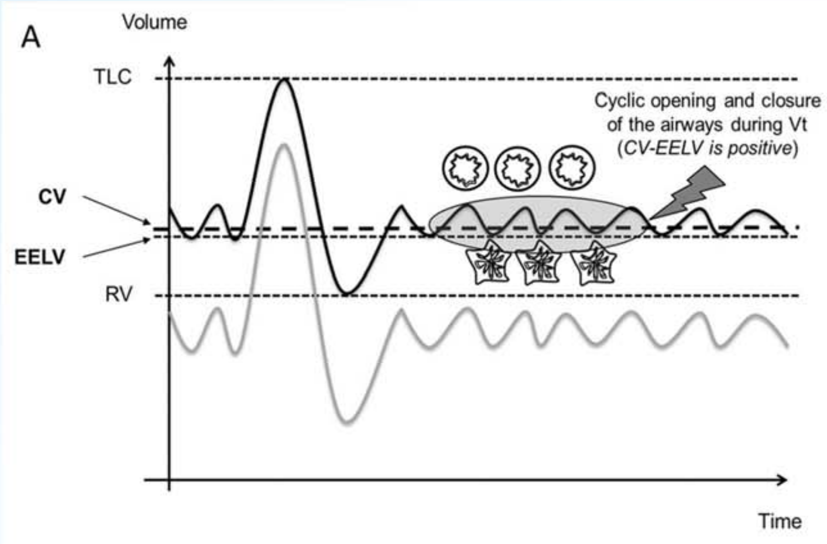
J Appl Physiol 123: 1266–1275, 2017.



LOW risk of small airways damage

HIGH risk of small airways damage

J Appl Physiol 123: 1266–1275, 2017.



(Santus et al. Submitted)

doi: 10.1111/cea.12257
Clinical & Experimental Allergy, 44, 499–507

ORIGINAL ARTICLE Asthma and Rhinitis

	Healthy controls (n = 18)	Mild–moderate asthma[†] (n = 43)	Severe asthma[†] (n = 31)
Age (years)	48.3 (3.9)	57.2 (2.0)	53.8 (2.5)
Sex (% male)	50	51	39
BMI (kg/m^2)	26.8 (1.2)	27.0 (0.8)	30.0 (1.4)
Atopy (% atopic)	–	79	71
Duration of asthma (years)	–	18.7 (2.9)	25.3 (3.2)
Age of onset of asthma (years)*	–	38.4 (3.3)	28.3 (3.8)
ICS dose (BDP equivalent [mcg])****	–	547 (66)	1726 (118)
Oral prednisolone use (%)****	–	0	45
Leukotriene receptor antagonist use (%)**	–	5	35
Oral theophylline use (%)**	–	0	19
Exacerbations in past year****	–	1.0 (0.28)	3.5 (0.56)
ACQ-6 score***	–	0.99 (0.12)	1.82 (0.22)
AQLQ(S) score*	–	5.65 (0.16)	5.00 (0.23)
FEV_1 (% pred.)***	113.3 (4.8)	90.8 (3.4)	86.9 (4.6)
FVC (% pred.)*	117.2 (5.6)	101.1 (3.0)	105.0 (4.2)
FEV_1/FVC (%)***	80.7 (1.0)	73.1 (1.5)	68.4 (2.2)
TLC (L)	6.39 (0.37)	6.14 (0.21)	6.00 (0.30)
TLC (% pred.)	104.3 (3.9)	104.9 (2.5)	107.8 (3.2)
RV/TLC (% pred.)***	89.2 (3.2)	110.4 (3.1)	108.7 (2.7)
VA (L)	5.58 (0.34)	5.07 (0.22)	4.88 (0.27)
VA/TLC (%)**	90.3 (1.7)	82.0 (1.6)	80.8 (1.4)
DLco (% pred.)	89.3 (2.9)	91.2 (2.5)	89.5 (2.9)
Kco (% pred.)	97.4 (2.9)	107.4 (2.7)	104.6 (3.0)
FRC_{mbw} (L)	2.52 (0.19)	2.45 (0.11)	2.39 (0.17)
LCI	7.28 (0.27)	7.79 (0.20)	7.94 (0.22)
S_{cond} (L^{-1})	0.033 (0.007)	0.051 (0.006)	0.038 (0.005)
S_{acin} (L^{-1})	0.118 (0.014)	0.175 (0.019)	0.184 (0.020)
R5 (kPa L^{-1} s)***	0.32 (0.03)	0.37 (0.02)	0.47 (0.03)[#]
R20 (kPa L^{-1} s)***	0.29 (0.02)	0.31 (0.01)	0.39 (0.02)[##]
R5-R20 (kPa L^{-1} s)[‡]*	0.03 (0.01–0.06)	0.05 (0.03–0.11)	0.05 (0.01–0.15)
X5 (kPa L^{-1} s)	−0.10 (0.01)	−0.13 (0.01)	−0.15 (0.02)
AX (kPa L^{-1})[‡]*	0.23 (0.16–0.54)	0.41 (0.24–0.66)	0.47 (0.23–1.27)

Table 3. Correlations between clinical outcome measures and physiological variables

	ACQ-6 score	AQLQ(S) score	FEV_1 (% pred.)
FEV_1 (% pred.)	−0.285*	0.289*	–
FVC (% pred.)	−0.230	0.299*	0.835**
FEV_1/FVC	−0.166	0.100	0.657**
TLC	−0.252*	0.254*	0.100
R5	0.341**	−0.405**	−0.340**
R20	0.369**	−0.430**	−0.169
log R5-R20	0.221	−0.250*	−0.379**
X5	−0.070	0.091	0.402**
log AX	0.173	−0.202	−0.492**

ACQ-6, Six-point Asthma Control Questionnaire; AQLQ(S), standardized Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; TLC, total lung capacity; RV, residual volume; V_A, alveolar volume (single-breath helium dilution); DL_{CO}, diffusing capacity of the lung for carbon monoxide; K_{CO}, carbon monoxide transfer coefficient; FRC_{mbw} functional residual capacity from multiple breath washout; LCI, lung clearance index; R5/R20, resistance at 5 Hz/20 Hz; R5-R20, resistance at 5 Hz minus resistance at 20 Hz; X5, reactance at 5 Hz; AX, reactance area. Pearson's correlation coefficients are shown. Significant correlations are indicated *($P < 0.05$) or **($P < 0.01$).

Table 4. Linear regression models assessing the contributions of physiological variables to ACQ-6 and AQLQ(S) scores

Dependent variable	Constant term	Independent variables	Unstandardized coefficient (B)	Standardized coefficient (β)	*P*-value	Model R^2
ACQ-6 score	1.129	R20 ($kPa\ L^{-1}\ s$)	3.276	0.330	0.005	0.187
		FEV_1 (% pred.)	−0.010	−0.229	0.046	
AQLQ(S) score	5.459	R20 ($kPa\ L^{-1}\ s$)	−4.355	−0.398	< 0.0005	0.229
		FVC (% pred.)	0.014	0.248	0.026	

Monitoring the Temporal Changes of Respiratory Resistance: A Novel Test for the Management of Asthma

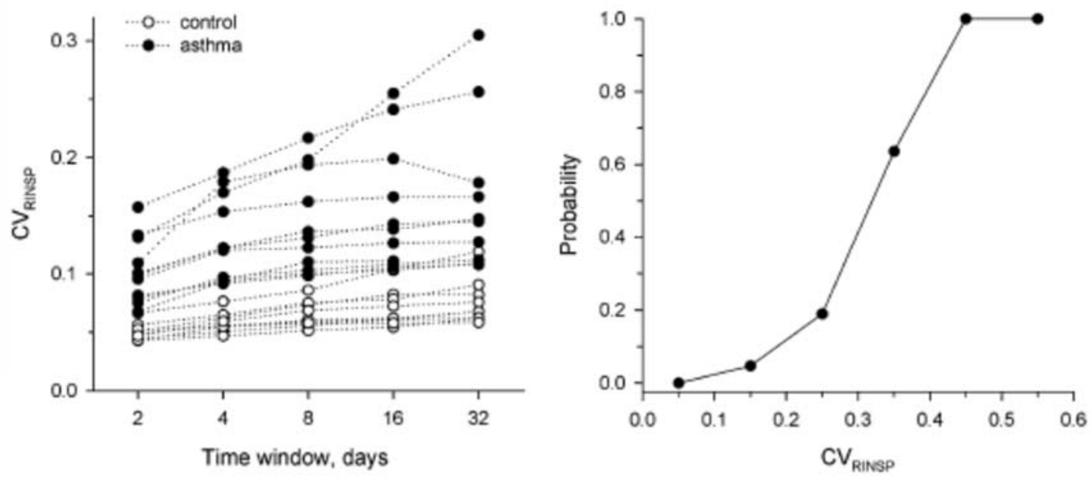


Figure 1. (*Left panel*) Long-term variability of the Rinsp characterized by the coefficient of variation (CV_{RINSP}) of individual subjects measured in the morning in individual subjects with asthma (*solid symbols*) and healthy subjects (*open symbols*) plotted against time windows. (*Right panel*) conditional probability computed on an individual basis that a given CV_{RINSP} calculated over the past 8 days is associated with an increase in Rinsp greater than or equal to twice the predicted respiratory resistance within the next week. Each point of the prediction curve is the average probability of an interval centered on that point.

Gullotta C et al. AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 185 2012

Overall and peripheral lung function assessment by spirometry and forced oscillation technique in relation to asthma diagnosis and control

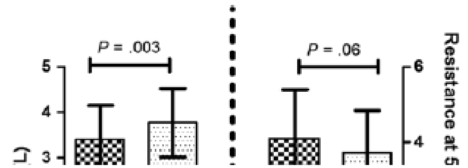


TABLE 3 Odds ratio (OR) for uncontrolled asthma, and AUC from ROC analysis for standardized lung function variables

Asthma control, n = 234	OR univariate analysis	AUC univar. analysis	OR multivariate[a] analysis	AUC multivar. analysis
Age, height, weight, sex				0.66
FEV_1	**0.50 (0.31, 0.79)**	0.66	0.62 (0.35,1.09)	0.69
FVC	0.75 (0.53, 1.06)	0.60	1.17 (0.64, 2.14)	0.65
FEV_1/FVC	**0.67 (0.48, 0.93)**	0.62	**0.58 (0.40, 0.84)**	**0.71**
FEF_{50}	**0.58 (0.39, 0.85)**	0.51	0.66 (0.42, 1.03)	0.68
R5	1.32 (0.98, 1.78)	0.58	1.35 (0.93, 1.95)	0.68
R19[b]	1.36 (0.96, 1.93)	0.60	1.22 (0.81, 1.84)	**0.71**
X5	**0.68 (0.51, 0.91)**	0.61	**0.69 (0.49, 0.97)**	0.69
f_{res}[b]	**1.38 (1.04, 1.82)**	0.59	**1.41 (1.02, 1.95)**	**0.72**
R5-R19[b]	**1.53 (1.12, 2.09)**	0.61	**1.57 (1.05, 2.35)**	**0.72**

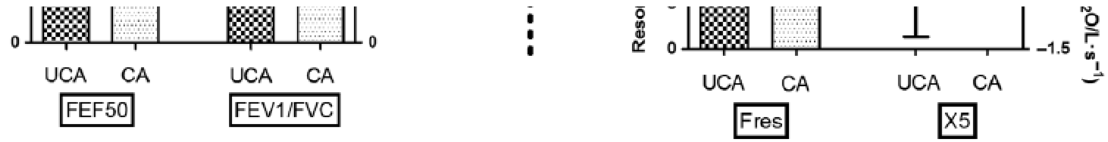


FIGURE 3 Overall lung function (top) and lung function variables reflecting peripheral airways (bottom) in uncontrolled (UCA) and controlled (CA) asthmatic subjects. The left part shows results from spirometry and the right part from FOT. Data presented as mean values ±SD

HEIJKENSKJÖLD-RENTZHOG ET AL.
Clin Exp Allergy. 2017;47:1546–1554.

Exploring the relevance and extent of small airways dysfunction in asthma (ATLANTIS): baseline data from a prospective cohort study

Dirkje S Postma, Chris Brightling, Simonetta Baldi, Maarten Van den Berge, Leonardo M Fabbri, Alessandra Gagnatelli, Alberto Papi, Thys Van der Molen, Klaus F Rabe, Salman Siddiqui, Dave Singh, Gabriele Nicolini, Monica Kraft, on behalf of the ATLANTIS study group*

Figure 4: Correlations between the clinical SAD score of participants with asthma and all variables measured

ACQ-6=Asthma Control Questionnaire-6. AQLQ=asthma quality of life questionnaire. AX=area of reactance. Decrease in FVC=percentage decrease in FVC from baseline at PC_{20} or PD_{20}. FEF_{25-75}=forced expiratory flow at 25–75% of FVC. FEF_{50}=forced expiratory flow at 50% of FVC. FRC=functional residual capacity. FVC=forced vital capacity. IVC=inspiratory reserve volume. PC_{20}=provocative concentration that causes a 20% decrease in FEV_1 from baseline during methacholine challenge. PD_{20}=provocative dose that causes a 20% decrease in FEV_1 from baseline during methacholine challenge. Predicted=values presented as a percentage of predicted values. R5=airway resistance at 5 Hz. R20=airway resistance at 20 Hz. Raw=airway resistance. RV=residual volume. S_{acin}*VT=ventilation heterogeneity of the acinar zone of the lungs. S_{cond}*VT=ventilation heterogeneity in the conductive zone of the lungs. sGaw=specific airway conductance. TLC=total lung capacity. X5=reactance at 5 Hz.

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The Physiology of Small Airways

PETER T. MACKLEM

In asthma, the involvement of airways from the glottis to the alveolar ducts is likely, and the site of this involvement determines the resulting pathophysiology. The small airways of less than 2 mm in diameter are pathways of low resistance and normally contribute about 10% of the total resistance to flow (1, 2). They are reportedly more resistant in the first few years of life (3), but experiments showing this have not been repeated, so that idea has neither been confirmed nor denied. Confirmation of these results would be an important advance, because if the small airways are high-resistance pathways in infancy, then bronchiolitis would be a much more serious condition in infants than in adults. Hogg and colleagues claimed that this was the reason that acute bronchiolitis was a serious disease in infants but apparently not in adults (3). If one-half of all small airways became completely obstructed, their combined resistance would double. However, the large airways would remain unobstructed and their resistance would not change. If small-airway resistance is only 10% of the total, doubling it would only increase total resistance by 10%. Thus it is difficult to detect small airway obstruction by the usual lung function tests.

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SMALL AIRWAY DISEASE ASSESSMENT