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

The increase in total cross-sectional area in the distal airways of the human lung enhances the mixing of each tidal breath with end-expiratory gas volume by slowing bulk flow and increasing gas diffusion. However, this transition also favors the deposition of airborne particulates in this region because they diffuse 600 times slower than gases. Furthermore, the persistent deposition of toxic airborne particulates stimulates a chronic inflammatory immune cell infiltration and tissue repair and remodeling process that increases the resistance in airways < 2 mm in diameter four to 40-fold in COPD. This increase was originally attributed to lumen narrowing because it increases resistance in proportion to the change in lumen radius raised to the fourth power. In contrast, removal of one-half the number of tubes arranged in parallel is required to double their resistance, and approximately 90% need to be removed to explain the increase in resistance measured in COPD. However, recent reexamination of this problem based on micro-CT imaging indicates that terminal bronchioles are both narrowed and reduced to 10% of the control values in the centrilobular and 25% in the panlobular emphysematous phenotype of very severe (GOLD [Global Initiative for Chronic Obstructive Lung Disease] grade IV) COPD. These new data indicate that both narrowing and reduction in numbers of terminal bronchioles contribute to the rapid decline in FEV₁ that leads to severe airway obstruction in COPD. Moreover, the observation that terminal bronchiolar loss precedes the onset of emphysematous destruction suggests this destruction begins in the very early stages of COPD. *CHEST 2013; 143(5):1436-1443*

Abbreviations: He³ = helium 3.

COPD is caused by the persistent inhalation of toxic particles and gases primarily but not exclusively derived from tobacco smoke.¹ These types of repetitive lung tissue injuries stimulate a chronic inflammatory immune response in everyone who smokes and, in a susceptible minority, this process increases in both extent and severity as FEV₁ declines and persists long after the person has stopped smoking tobacco.² This

response to repetitive injury differs substantially from that observed following a single injury where the inflammatory immune cell infiltration begins to disappear as fibroblasts migrate into the site of injury to lay down a mature scar in the absence of infiltrating inflammatory cells. In that repetitive injury is associated with persistent inflammatory immune cell infiltration and abnormal scar tissue formation (ie, fibrosis) that persists long after the inhalation exposure has stopped.³ It is also of interest that different regions respond in different ways. For example, the chronic bronchitis that develops in cartilaginous airways is associated with enlarged bronchial mucus glands and goblet metaplasia of the airway epithelial lining.⁴⁻⁶ The small conducting airways < 2 mm in diameter that become the major site of airway obstruction in COPD⁷ show progressive thickening of their walls, infiltration of the wall tissue by inflammatory immune cells, and occlusion of the airway lumen by inflammatory exudates containing mucus as FEV₁ declines.² In contrast, dilatation and destruction of the gas-exchanging tissue

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Affiliations: From the James Hogg Research Centre, The University of British Columbia, Vancouver, BC, Canada.

Dr McDonough is currently pursuing postdoctoral studies at Imperial College London, London, England. Dr Suzuki is currently affiliated with Hokkaido University, Sapporo, Japan.

Correspondence to: James C. Hogg, MD, University of British Columbia James Hogg Research Laboratory, Room 168 Burrard Wing, St. Pauls Hospital, 1081 Burrard St, Vancouver, BC, V6Z1Y6, Canada; email: jim.hogg@hli.ubc.ca.

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beyond the terminal bronchioles defines emphysematous destruction of the lung. The purpose of this brief review is to discuss the relationship between small airways obstruction and emphysematous destruction based on new information gained using micro-CT imaging to obtain a better understanding of the three-dimensional anatomy of the peripheral lung and MRI imaging of hyperpolarized helium 3 (He^3) to obtain a clearer insight into the effect of the changes in anatomy on gas distribution in the centrilobular emphysematous phenotype of emphysema commonly observed in smokers.

PERIPHERAL LUNG ANATOMY

The boundary between purely conducting airways and gas-exchanging tissue is formed by the division of approximately $44,510 \pm 15,574$ (mean $\pm$ SD) terminal bronchioles into transitional bronchioles or first-order respiratory bronchioles where alveolar openings first appear (Fig 1).^{8,9} The alveolar openings steadily increase with successive generations of branching until they occupy the entire luminal surface of alveolar ducts and ducts branch for several more generations before terminating in closed alveolar sacs.⁸ The term “acinus” refers to a unit of lung supplied by a single terminal bronchiole; the term secondary lobule refers to groups

of acini identified by either a surrounding connective tissue septa (Fig 1B) or a shift in bronchiolar branching pattern (Fig 1C) from one where the prelobular bronchioles branch roughly every centimeter to intralobular bronchioles that cluster only millimeters apart.^{8,10} The variation in pathway length from the trachea to the gas-exchanging surface distributes 2-mm airways from the fourth to the 14th generation of airway branching and the intralobular bronchioles between the eighth and 22nd generation of airway branching.^{11,12} The color-coded map (Fig 2B) illustrates that single generations of branching contain airways of different size by replotting Weibel’s data concerning the location of airways of different size.^{9,11} One effect of the rapid increase in the total cross-sectional area as branching generation increases (Figs 3A, 3B) is slowing the velocity of bulk flow and enhancing the diffusion of gas to the alveolar surface. Although this transition facilitates mixing between inspired air and end-expiratory gas volume, it also exposes the transitional region of the lung to excess deposition of particles suspended in the air because they diffuse much slower than gas. For example, the 0.5- μm diameter airborne particles that have the greatest probability of reaching the transitional zone of the lung are roughly 1,000 times larger and have a diffusion constant approximately 1 million times smaller than gas molecules.¹⁵ Moreover, because

FIGURE 1. A microCT scan of a terminal bronchiole branching into two first-order respiratory bronchioles (ie, transitional bronchioles) where alveolar openings first appear (reproduced with permission from McDonough et al⁹). B, Bronchogram of a postmortem human lung where a cluster of terminal bronchioles are surrounded by a fibrous connective tissue septa to form a secondary lung lobule.⁸ C, A lobule as defined by Reid¹⁰ where the branching pattern switches from one where the branches are cm apart to one where the branches within the square are only mm apart. TB = terminal bronchiole.

their root-mean-square displacement per second by diffusion is approximately 600 times smaller than oxygen (ie, 10 $\mu\text{m/s}$ vs 6,000 $\mu\text{m/s}$), the particles are able to settle on the surface of the transitional zone of the lung between breaths.¹⁵ Furthermore, because the surface area of the preterminal, terminal, and transitional bronchioles is relatively small compared with the surface area of more distal air spaces, these airways receive the greatest dose of inhaled particles per unit of surface area.¹¹

PERIPHERAL AIRWAYS RESISTANCE IN NORMAL LUNGS

The older paradigm that the small conducting airways offer the most resistance to airflow in normal human lungs put forward by Rohrer in the 1920s^{16,17} began to change in the 1960s when Green repeated Rohrer's calculations using Weibel's new data and found that the smaller airways offered much less resistance than Rohrer's calculations indicated because both the total number and cross-sectional area of the smaller conducting airways were underestimated.^{11,16-18} However, the major shift in this paradigm occurred when Macklem and Mead¹³ provided the first direct mea-

surements showing that airways < 2 mm in diameter accounted for < 20% of total lower airway resistance in both anesthetized animal and postmortem human lungs. In a subsequent editorial, Mead¹⁹ referred to this region of the lung as a "quiet zone" within the lung where disease might accumulate over many years without coming to the attention of either patient or physician. This new paradigm initiated a period of intense investigation into abnormalities in the peripheral lung during the transition between health and disease.²⁰ However, this effort was eventually abandoned because the tests designed to detect small airways disease were unable to consistently identify the minority of smokers who would go on to develop COPD.²¹ Even though cross-sectional studies showed that pathology was present in the small airways when the FEV₁ was normal and that the pathology progressed as FEV₁ declined.²²

A Belgian group subsequently challenged the theory that small airways resistance was low in normal lungs using a technique similar to the one developed by Macklem and Mead (Fig 3C) to obtain data that was more consistent with Rohrer's calculations than with Green's.^{13,23} However, three subsequent reports on living humans with normal lung function from two

FIGURE 2. A, Bronchogram from a normal human lung to demonstrate that the pathways from the main stem bronchus to the alveoli vary substantially in length. B, A color-coded map of data replotted from Weibel¹¹ to demonstrate the distribution of airways of different sizes within each generation of airway branching. C, Data from Horsfield and Cumming¹² demonstrating that the intralobular branches (see Fig 1 for a description of a lobule) can be reached in as few as eight generations of branching when the shortest pathways are followed, that the mean number of branches required to reach the interlobular airways is approximately 14 and that it may take as many as 24 generations of branching when the longest pathways are followed.

FIGURE 3. A, Data from Weibel¹¹ showing the average airway diameter at each generation of branching measured directly from an airway cast. The red square with error bars shows the mean diameter of the terminal bronchioles measured by McDonough et al⁹ using microCT scan. B, Comparison of the total cross-sectional area of all the airways in each generation of airway branching measured by Weibel¹¹ to the total cross-sectional area of the terminal bronchioles measured from microCT images by McDonough et al.⁹ C, A retrograde catheter (arrow) placed in a small airway approximately 2 mm in diameter in the manner described in References 7 and 13. D, Chest radiograph from a living human with normal lung function where the bronchial pressure-measuring device developed by Yanai and colleagues¹⁴ was put in place through a bronchoscope. The direct measurement of the resistance of the small airways <2 mm in diameter provided in both postmortem human lungs^{7,13} and in living humans¹⁴ are consistent with Weibel's measurements of a rapidly increasing total cross sectional area of the distal airways.

different laboratories using different methods supported Macklem and Mead's original findings.^{14,24,25} In one of these studies, Yanai et al¹⁴ introduced a small catheter with a pressure-sensing device at its tip (Fig 3D) into the small airways of living humans with normal lung function and subtracted the resistance from mouth to catheter tip from measurements of total airways resistance measured during quiet breathing. In two other studies, Wagner and colleagues^{24,25} created pressure-flow curves in the peripheral airways by wedging a double-lumen catheter and delivering a constant flow of air at different rates through one lumen while measuring driving pressure through the other. The slope of the pressure flow curves produced by this procedure was then measured to obtain peripheral airway resistance. Table 1 summarizes the data from all of these sources and shows that total resistance in centimeters of water per liter per second of 0.18 ± 0.04 (25% of total resistance) measured in control lungs confirmed Macklem and Mead's original

findings and compare favorably to the 0.15 ± 0.03 and 0.18 ± 0.05 measured by Wagner and associates.^{24,25} Although the values reported by Yanai et al¹⁴ (0.70 ± 0.30) are somewhat higher, they still accounted for only 25% of the total resistance when it included the upper airways and larynx. This leaves the 1.24 ± 0.27 (77% of total resistance) measured by the Belgian group as a single outlier that is not easy to explain.²³

PERIPHERAL AIRWAY RESISTANCE IN COPD

In contrast to the disagreement concerning the resistance to flow offered by small airways <2 mm in diameter in normal lungs, all three groups that have made direct measurements of small airways resistance in COPD (including the Belgian group) reported that the small conducting airways <2 mm in diameter become the major site of increased resistance in COPD.^{7,14,23}

On theoretical grounds, the substantial increase in peripheral airways resistance measured in COPD is

Table 1— Summary of Direct Measurements of Total and Peripheral Airways Resistance in Human Lungs

Source	Control		Emphysema		Chronic Bronchitis ^a	
	Total	Peripheral	Total	Peripheral	Total	Peripheral
Hogg et al ⁷	0.69 ± 0.04	0.18 ± 0.04	3.66 ± 0.99	2.97 ± 0.93	...	...
Van Brabandt et al ²³	1.52 ± 0.27	1.24 ± 0.27	10.47 ± 3.79	9.44 ± 3.42	...	...
Yanai et al ¹⁴						
Inspiration	3.1 ± 0.1	0.7 ± 0.3	5.9 ± 0.8	2.8 ± 0.4	8.7 ± 1.1	4.6 ± 0.5
Expiration	4.0 ± 0.3	1.1 ± 0.4	7.3 ± 1.1	3.7 ± 0.6	10.6 ± 1.8	5.9 ± 0.8
Wagner et al ²⁴ /1990	...	0.15 ± 0.03	...	...	...	...
Wagner et al ²⁵ /1998	...	0.18 ± 0.05	...	...	...	...

Mean ± SE. All units are cm H₂O/L/s. The original Macklem and Mead data can be found in Reference 13. References in the Source column refer to studies where direct measurements of peripheral airways resistance have been reported.

^aAlthough the authors referred to these cases as chronic bronchitis, the obstruction was most likely attributable to the bronchiolitis present in some but not all cases of chronic bronchitis.¹⁴

easier to explain by generalized narrowing of most of small airways lumens rather than by a reduction in their number because lumen narrowing increases resistance in proportion to the reduction in the radius raised to the fourth power. However, in a system of tubes arranged in parallel, total resistance at each generation is obtained by addition according to the equation $1/R_T = 1/R_1 + 1/R_2 + 1/R_3 + \dots + 1/R_n$ meaning that removal of one-half of the tubes arranged in parallel is required to double their resistance. Therefore, if we accept the theory on the behavior of tubes arranged in parallel summarized by the above equation and begin with the value 0.70 ± 0.26 cm H₂O/L/s measured by Yanai et al¹⁴ in living humans with normal lung function, removal of one-half of the small airways will only increase their resistance to 1.4 cm H₂O/L/s. A value well below the 2.78 and 4.59 cm H₂O/L/s measured in living people with COPD in the same study (Table 1).²⁴ Furthermore, removal of one-half of the remaining airways (ie, a reduction to 25% of their starting numbers) would only increase small airways resistance to 2.8 cm H₂O/L/s which is barely within the lower range of the resistance they measured in COPD (Table 1). A reduction to 12.5% of their starting number is required to increase small airways resistance to 5.6 cm H₂O/L/s which falls in the upper range of the values measured in COPD by Yanai et al.¹⁴ Bignon et al²⁶ provided the first histologic evidence in support of the theory that the airways narrowed in COPD by showing that the proportion of bronchioles < 400 μ m in diameter increased in lungs from patients that died of respiratory failure caused by severe emphysema. Although Matsuba and Thurlbeck²⁷ reported a similar trend in people with less severe emphysema that did not reach statistical significance, they added the caveat that complete destruction of the smaller bronchioles might have buffered the downward shift in small airways diameters measured in their study. Importantly, both of these studies were done long before the stereology-based methodology for counting numbers of structures in three-dimensional

space became available and subsequently became accepted in guidelines published in a joint American Thoracic Society/European Respiratory Society statement.²⁸

The introduction of micro-CT imaging greatly simplified the application of the American Thoracic Society/European Respiratory Society guidelines because it made it possible to identify terminal bronchioles anatomically, counting their number per milliliter in known volumes of a representative lung tissue sample that allowed the total number of terminal bronchioles per lung pair to be computed. As the product of the mean number of terminal bronchioles per milliliter of sampled lung tissue and total lung volume measured from the multidetector CT scan of the intact lung specimen.⁹ In addition, the product of the total number of terminal bronchioles per lung pair and direct measurements of the mean lumen cross-sectional area provided the total cross-sectional area of the terminal bronchioles in the lung.⁹ Comparison of these new data to the mean of four published datasets of the individual lung casts showed excellent agreement between total numbers of terminal bronchioles per lung pair ($44,510 \pm 15,574$ vs $44,500 \pm 18,574$ mean ± SD).^{11,12,17,29} Moreover, terminal bronchiolar diameter (424 ± 76 μ m mean ± SD) and total cross-sectional area ($3,050.3 \pm 576.6$ mm²) were almost exactly the same (see Figs 3C, 3D) as those in Weibel's classic report.¹¹ In sharp contrast, lungs donated by patients with very severe COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] grade IV) treated by lung transplantation (Table 2) showed the number of terminal bronchioles per lung pair was reduced to approximately 10% of control values in the centrilobular emphysematous phenotype and to 25% of the control values in the panlobular emphysematous phenotype of COPD observed in α -1 antitrypsin deficiency. In addition, the mean diameter of surviving terminal bronchioles was reduced from 424 ± 76 μ m in the control subjects to 52 ± 30 μ m in centrilobular emphysema and 210 ± 48 μ m in the panlobular

Table 2—Comparison of Control to Patient Data

Characteristics	Control	CLE	PLE
No. of patients (No. of lungs)	4 (4)	4 (4)	8 (10)
Sex, female (male)	0 (4)	2 (2)	3 (5)
Age, y	53.8 ± 4.3	60.0 ± 1.6	49.6 ± 3.8
Pack-y	31.5 ± 7.5, n = 2	43.0 ± 5.5	17.9 ± 3.2
FEV ₁ , % pred	N/A	18.0 ± 2.7	19.0 ± 1.6
FEV ₁ /FVC	N/A	26.8 ± 2.9	32.6 ± 2.3
Total lung volume, % predicted	N/A	137.0 ± 3.6	140.1 ± 4.1
Lung volume, mL	3,251 ± 261	3,456 ± 602	3,794 ± 595
Lung mass, g	332 ± 11	358 ± 27	394 ± 41
No. of terminal bronchioles/mL	6.9 ± 1.2	0.7 ± 0.1	1.6 ± 0.5
Total no. of terminal bronchioles	22,300 ± 3,900	2,400 ± 600	6,200 ± 2,100, n = 7
Average terminal bronchioles cross-sectional area, mm ²	0.145 ± 0.025	0.004 ± 0.002	0.047 ± 0.012
Minimum terminal bronchiole lumen diameter, μm	424.0 ± 48.0	51.8 ± 30.0	210.2 ± 48.0
Total terminal bronchiole cross-sectional area, mm ²	3,050.3 ± 576.6	7.7 ± 5.1	514.1 ± 181.9, n = 7

CLE = centrilobular emphysema; N/A = not available; PLE = panlobular emphysema associated with α_1 -antitrypsin deficiency. (Adapted with permission from McDonough et al.⁹)

emphysematous phenotypes of COPD.⁹ The combination of micro-CT imaging and histology also showed this massive reduction in total number of terminal bronchioles is associated with thickening of the walls of the surviving bronchioles.⁹ More importantly, they also showed that the number of terminal bronchioles per milliliter lung was reduced before the alveolar dimensions measured as the mean linear intercept increased into the emphysematous range.⁹ These observations established that the primary cause of small airways narrowing is related to the pathology in the small airways themselves and that any further narrowing caused by emphysematous destruction lung elastic recoil on the supporting structure of the small airways must occur as a secondary phenomenon associated with the later onset of emphysematous destruction. Based on these findings, we speculate that the gradual decline in FEV₁ with age is explained by a parallel subtraction of terminal and perhaps preterminal bronchioles over time that has little effect on total resistance until large numbers of airways are destroyed. Moreover, we speculate that a similar mechanism of tissue remodeling and destruction could be responsible for both the bronchiolar and alveolar tissue in COPD.

THE SEQUENCE OF TISSUE DESTRUCTION IN COPD

Figure 4 was constructed from existing data where Figure 4A shows normal terminal bronchioles and Figure 4B shows Leopold and Gough's³⁰ original diagram of a primary centrilobular lesion that develops beyond the terminal bronchiole that was also described by McLean³¹ at about the same time. Figure 4C shows a fully developed centrilobular lesion outlined by radio-opaque dust in a study that showed these lesions are on the flat part of their pressure volume curve at about 80%

of their total gas volume and have a reduced compliance in relation to normal alveoli.³² Figure 4D represents the electrical analogue of the normal lung lobule where terminal bronchioles R1 and R2 supply normal alveoli C1 and C2³³ to a diseased situation (Fig 4E) where the normal alveoli beyond a destroyed R1 are collaterally ventilated from the centrilobular emphysematous lesion forming the surviving bronchiole R2 and the resistance between the centrilobular lesion and surrounding normal lung falls to very low levels. Although collateral flow resistance is difficult to measure within individual lobules, it has been measured across incomplete lobar fissures in postmortem lungs and within lobes of lungs in living people where both groups of investigators showed that collateral flow resistance falls from very high levels in normal lungs to very low levels in lungs from patients with emphysema.^{34,35} MRI imaging studies of the distribution of hyperpolarized He³ gas provided new information by demonstrating both large and small filling defects following the inspiration of He³ gas.^{36,37} In addition, Marshall and colleagues³⁷ demonstrated collateral movement of gas into the larger defects from the surrounding lung tissue during a 20-s breath hold following the inhalation of hyperpolarized gas. Based on these reports, we postulate that, within a normal lobule (Fig 4A), destruction of a terminal bronchiole is followed by: (1) the spread of the destructive process along surviving bronchioles to initiate the primary lesions of centrilobular emphysema (Fig 4B), (2) coalescence of several primary lesions forming larger centrilobular emphysematous spaces (Fig 4C), and (3) enlarged collateral channels formed by this centrilobular destruction ventilating the normal alveoli isolated by the initial destruction of the terminal bronchiole.³⁴ In contrast, the larger bullous lesions formed by coalescence of completely destroyed lobules fill through collateral channels formed at their boundary with the surrounding

FIGURE 4. A, Normal lung lobule containing six terminal bronchioles. B, Leopold and Gough's³⁰ original diagram of a primary centrilobular emphysematous lesion described almost simultaneously by themselves in the UK and by McLean³¹ in Australia. C, Bronchogram of a centrilobular emphysematous space formed by the coalescence of several primary lesions.³² D, The electrical analog of the peripheral lung used by Otis et al,³³ where S is the power source, R is resistance, and C is capacitance. E, Modification of the normal electrical analogue to include collateral channels R4, that have very high resistance in the normal lung and fall to very low levels in emphysematous regions of lungs affected by COPD.^{34,35} We postulate that the primary centrilobular lesions develop beyond surviving terminal bronchioles and that the fall in collateral resistance associated with emphysematous destruction provides ventilation to the normal alveoli located beyond destroyed terminal bronchioles. CLE = centrilobular emphysematous space.

normal lung because nearly all of the supplying bronchioles are completely destroyed within these bullous lesions.

SUMMARY

In the normal lung, the increase in total cross-sectional area of the conducting airways with each generation of branching facilitates gas mixing by slowing the bulk flow of gas and increasing its diffusion into the distal airspaces.^{11,15} However, this transition also favors the accumulation of airborne particles within this region of the lung because these particles diffuse approximately 600 times slower than gas.¹⁵ The accumulation of toxic particles in this lung region stimulates a persistent inflammatory immune response and tissue repair and remodeling process that sequentially destroys terminal followed by respiratory bronchioles to form centrilobular lesions. This is followed by the destruction of the entire lung lobule, and the coalescence of many destroyed lobules forms the larger bullous lesions. The observation that terminal bronchiolar destruction precedes emphysematous in COPD is consistent with recent reports showing that the early appearance of emphysematous destruction predicts a more rapid decline in FEV₁³⁸⁻⁴¹ because it is consistent with widespread destruction of terminal and possibly preterminal bronchioles before emphysema-

tous destruction appears. Collectively, these observations suggest that the reason treatment trials have failed to reverse the decline in FEV₁ is that large numbers of terminal bronchioles have already been destroyed.

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