Assessment of small airways disease

DM Seminar

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Small airways

- Small airways constitutes the zone between the conducting and the respiratory lung zones
- Are < 2 mm in size
- Consist of respiratory & terminal bronchioles
- Are devoid of cartilage and mucous secreting glands

Fishman's textbook of pulmonary disease 4 th edi
Am J Respir Crit Care Med Vol 157. pp S181–S183, 1998

Respiratory resistance = Raw + Peripheral resistance

Am J Respir Crit Care Med Vol 157. pp S181–S183, 1998
Lung function :Cotes 6 th edition

“Zone of silence”?

- Normally contribute about 10% of the total resistance to flow
- Brown and colleagues confirmed this theory of small-airway resistance almost 20 years ago

Am J Respir Crit Care Med Vol 157. pp S181–S183, 1998
J. Appl. Physiol. 27(3):328–335.

- Both small & large airways were blocked sequentially
- Small-airway obstruction had no measurable effect on the pressure–volume curves of dog lungs
- Vital capacity unimpaired due to collateral ventilation
- In pig lungs, which lack collateral channels, the vital capacity was reduced by 50%
- Pulmonary resistance increased by approximately 10%.

J. Appl. Physiol. 27(3):328–335.

The experiment showed that small-airway obstruction has very little effect on the mechanical properties of the lung

J. Appl. Physiol. 27(3):328–335.

What about the ventilation?

- There was an increase in the slope of single breath Nitrogen washout
- Thus, in species with collateral ventilation (such as humans) small-airway obstruction has little effect on lung mechanics, but it does affect ventilation distribution.

The authors suggested that in symptomatic patients with normal PFT's, there is abnormality in the distribution of the ventilation

Large V/S Small airways

Large airways

- Less cross sectional area
- Turbulent flow
- Resistance affected by gas density
- No surfactant lining over the epithelium

Small airways

- Larger cross sectional area
- Laminar flow
- Gas density has no effect on resistance
- Surfactant lining and hence low surface tension

Fishman's textbook of pulmonary disease 4 th edi
Am J Respir Crit Care Med Vol 157. pp S181–S183, 1998

Why this difference b/w large & small airways ?

Larger total cross-sectional area

↓

Low velocity of air flow

↓

Laminar flow

↓

Low resistance

Criteria for small airways obstruction

- Abnormal ventilation distribution
- Normal elastic & flow resistive properties
- Independence of maximal expiratory flow or flow resistance to gas density
- Gas trapping

Am J Respir Crit Care Med Vol 157. pp S181–S183, 1998

Practical issues

- Inaccessibilty
- Complex methods of assessment
- Sometimes invasive techniques
- Unanimously accepted approach to assess small airways is lacking
- Under recognition
- Limited awareness

Methods to assess small airways

- Spirometry
  - FEF25–75
  - Lung volume measures, including forced vital capacity (FVC), residual volume (RV), total lung capacity and functional residual capacity
- Impulse oscillometry
- Nitrogen washout test
- Biomarkers
- Imaging
- Invasive like transbronchial lung biopsies

Spirometry

- Measures volumes of air as a function of time
- Primary signal measured in spirometry may be volume or flow
- Assess and monitor obstructive pulmonary diseases
- FEV1,FVC,FEV1/FVC,FEV3,FEV6,FEF25-75%
- FEV1 does not provide comprehensive evaluation of the whole bronchial tree

Eur Respir J 2005; 26: 948–968

Indications for spirometry

- Diagnose
- Monitor
- Evaluate disability & Impairment
- Epidemiological

Eur Respir J 2005; 26: 948–968

FEF 25-75%

- Lueallan and Fowler added maximal midexpiratory flow, later labeled as forced expiratory flow, midexpiratory phase (FEF25–75)
- In 1967, Macklem and Mead divided airway resistance between central and peripheral components

Eur Respir J 2005; 26: 948–968

- Mean of flow between 25-75% of FVC
- Calculated from a blow with largest sum of FEV1 & FVC
- Highly dependent upon FVC & patient effort

Eur Respir J 2005; 26: 948–968

- Small airways disease is diagnosed if FEF25–75 values are < 75 to 80 % of mean percentage of predicted values, and FEV1 or FEV1/FVC were > 75 to 80% of the mean percentage of predicted values

J Occup Med 1986; 28:817–820
CHEST 2006; 129:369–377

- In patients with early obstructive airway disease FEV1 & FVC are normal
- The change in flow rates at mid to low lung volume (FEF25 -75%) has been shown to be significantly lower during initial stages
- FEF 25-75% may be considered as a measure of small airway caliber

J Allergy Clin Immunol. 1988;82:19–22.
Thorax 1997;52:1036–1039

In more advanced disease FEF 25-75% less reliable

Resp Med Vol.95 (2001) 703-719

- FEF 25-75 % may be used to assess small airways function in mild to moderate severe disease
- It may be unreliable in severe disease due to variability of FVC

Impulse oscillometry

- Determines breathing mechanics by superimposing small external pressure signals on the spontaneous breathing of the subject
- Minimises demands on the patient
- Requires only passive cooperation of the subject

Eur Respir Mon, 2005, 31, 72–105.

Methodology of impulse oscillation technique

- External forcing signal either mono or multi frequency applied continously or in a time discrete manner
- Commonly 5 impulses per seconds are used

Eur Respir Mon, 2005, 31, 72–105.

Interpretation of oscillation mechanics

- Monofrequency oscillations provide a measure of total respiratory impedance
- Monofrequency enumerates airway resistance, and elastic and inertive behaviour of lungs and chest wall at one oscillation frequency
- Impedence = resistance + reactance

$$Zrs = Rrs + Xrs$$

Eur Respir Mon, 2005, 31, 72–105.

- Multifrequency oscillation methods provide measures of respiratory mechanical properties in terms of Zrs, as a function of frequency (f)
- Recognizes characteristic respiratory responses at different oscillation frequencies

Respiratory resistance

- Includes proximal and distal airways (central and peripheral), lung tissue and chest wall resistance
- Normally, central resistance dominates
- Rrs at 5 Hz (Rrs5) is within ± 1.64 sd : Normal
- Rrs5 values between 1.64 and 2 sd above predicted : Mild obstruction
- > 2 sd : moderate obstruction
- > 4 sd above predicted : severe obstruction

Healthy subjects

- Rrs is almost independent of oscillation frequency
- Rrs may increase slightly at higher frequencies due to the upper airways shunt effect

Eur Respir Mon, 2005, 31, 72–105.

Obstruction

- Rrs5 is increased above normal values
- Site of airway obstruction is inferred from the pattern of Rrs, as a function of oscillation frequency
- Proximal airways obstruction elevates Rrs evenly independent of oscillation frequency
- In distal airways obstruction, Rrs is highest at low oscillation frequencies and falls with increasing frequency

Diagnostic evaluations

- Impulse oscillometry measures quiet breathing
- Particularly useful in patients with neuromuscular disease , lung transplantation,children as it is effort independent

- R5 = Total resistance
- R20 = Central resistance
- Peripheral resistance= R20-R5

Lung (2011) 189:121–129

Respiratory reactance (Xrs)

- Xrs incorporates the mass-inertive forces of the moving air column in the conducting airways
- Interpretation of Xrs is primarily influenced by the oscillation frequency
- In contrast to Rrs, concepts of Xrs are not yet widely appreciated
- Distal capacitive reactance at 5 Hz (Xrs5) manifests increasingly negative values either in restriction or in hyperinflation

Resonant frequency

- Resonant frequency (fres) is defined as the point at which the magnitudes of capacitive and inertive reactance are equal
- Separate low-frequency from high-frequency Xrs
- In normal adults, fres is usually 7–12 Hz

Reactance area (AX)

- Is a quantitative index of total respiratory reactance Xrs at all frequencies between 5 Hz and resonant frequency

Oscillometry V/S Plethysmography

Plethysmography

- Measures airways resistance (Raw)
- Raw influenced mainly by large airways

Oscillometry

- Measures chest wall & lung tissue resistance in addition to airways resistance
- Rrs mainly influenced by small airways

Lung (2011) 189:121–129

Closing volume

- The fundamental features of ‘airway closure’ were described in a landmark paper by Dollfuss and colleagues in 1967

CHEST, 72: 6, DECEMBER, 1977
British Journal of Anaesthesia 99 (6): 772–4 (2007)

Principle of 'first in, last out'

J. Physiol. Sci. Vol. 57, No. 6; Dec. 2007; pp. 367–376

- The concept of airway closure was applied in a number of important and disparate ways
- At first, closing volume (CV) was considered useful to study lung disease caused by smoking or air pollution, as a marker of small airway damage which could not be detected by simple spirometry
- In healthy young adults, the normal closing volume averages about 10 percent of the vital capacity

J. Physiol. Sci. Vol. 57, No. 6; Dec. 2007; pp. 367–376

- Narrowing or obstruction of small peripheral airways causes closing volume to enlarge
- Also increases in old age,smokers, obesity & postoperative period
- Despite this in a given scenario closing volume estimation is an important parameter to assess small airways

J. Physiol. Sci. Vol. 57, No. 6; Dec. 2007; pp. 367–376
CHEST, 72: 6, DECEMBER, 1977

Density dependent flow

- Comparison of Flow-volume curves obtained while breathing air with curves obtained after equilibration using a mixture of 80 percent helium and 20 percent oxygen.
- The results are expressed as % of increase in maximal flow at same lung volumes or
- As the volume at which flow-volume curves coincide with each other (volume of isoflow)

The Journal of Clinical Investigation Vol51 December1972
Fishman’s textbook of pulmonary medicine 4 th edi

- In normal subjects, at lung volumes greater than 10 percent of the vital capacity (VC), the primary site of resistance to airflow is in the larger airways, where flow is turbulent and, therefore, density-dependent
- At lung volumes less than 10 percent of the VC, the primary site of resistance is in the smaller airways, where flow is laminar and, therefore, not density-dependent

The Journal of Clinical Investigation Vol51 December1972
Fishman's textbook of pulmonary medicine 4 th edi

- In disease of the small airways, the primary site of resistance shifts at large volumes from the larger to the smaller airways
- As a result, the flow-enhancing effect of the less-dense gas disappears at volumes well above 10 percent of the VC

The Journal of Clinical Investigation Vol51 December1972
Fishman's textbook of pulmonary disease 4 th edi

Dynamic Compliance

- Change in lung volume during airflow produced by a given change in transpulmonary pressure
- Under conditions of nonuniformity of ventilation, increases in breathing frequency are associated with a fall in dynamic compliance

The Journal of Clinical Investigation Volume48 1969
Fishman’s textbook of pulmonary diseases 4 th edi

Principle

- Time constant (RC) of small airways are in the order of 0.01 sec
- A fourfold difference b/w RC causes frequency dependent fall in dynamic complaince

J. Appl. Physiol.1967 22: 395

Biomarkers

- Exhaled nitric oxide (eNO) is the most widely used marker in exhaled breath
- Alveolar nitric oxide, derived by measurements of eNO at multiple expiratory flows (MEFe- NO), has largely been investigated as a potential hallmark of distal lung inflammation
- However, since alveolar nitric oxide measurement is derived from a computational extrapolation that follows eNO evaluation at different flow rates, rather than being directly quantified, the clinical significance of such a marker is not firmly established

Allergy 65 (2010) 141–151
Eur Respir Rev 2011; 20: 119, 23–33

- NO can be from large or small airways
- Distinction between the two more informative
- The two-compartment model allowed separation of airway versus alveolar NO

Allergy 65 (2010) 141–151
Eur Respir Rev 2011; 20: 119, 23–33

A two-compartment model of pulmonary nitric oxide exchange dynamics
Nikolaos M. Tsoukias and Steven C. George
J Appl Physiol 85:653-666, 1998.

By this model the relative contribution of exhaled NO from large or small airways can be assessed

Imaging

- Novel area for the direct assessment of small airway involvement in asthma and COPD
- Indirect measures of small airway patency can be obtained
- In particular, air trapping and ventilation heterogeneity, which can be related to small airway closure, have been quantified using HRCT and correlated to functional parameters of small airway abnormalities

Allergy 65 (2010) 141–151
Eur Respir Rev 2011; 20: 119, 23–33

- Air-trapping is a key finding for depicting small airways obstruction on HRCT scans
- Size of the large and intermediate airways reflect airway dimensions in the smaller airways
- Expiratory HRCT measurements correlate best with pulmonary func- tion tests (PFTs), particularly with measures of air trapping

International Journal of COPD 2007:2(3)

- However, use of HRCT to study small airways is highly technical and remains problematic
- Small airways are at the lower limit of HRCT resolution, measurements of airway dimensions are themselves unreliable
- Radiation exposure

MRI

- Absence of ionising radiation
- Good spatial and temporal resolution
- Gadolinium infusion or by inhalation of ^3He can be used for contrast
- In the lung, low-proton spin density in alveolar gas and abundant gas-tissue interfaces substantially impair conventional native ^1H-MRI

Allergy 65 (2010) 141–151
Eur Respir Rev 2011; 20: 119, 23–33

- Spin polarisation can be increased in two non-radioactive noble gas isotopes, ^{3}He and ^{129}Xe, by exposure to polarised laser light
- When inhaled, such “magnetized” gases provide high-intensity MR images of the pulmonary airspaces
  - morphologic imaging of airways and alveolar spaces
  - analysis of the intrapulmonary distribution of inhaled aliquots of these tracer gases
  - diffusion-sensitive MRI-techniques allow mapping of the “apparent diffusion coefficient” (ADC) of ^{3}He within lung airspaces

SWISS MED WKLY 2001;131:503–509

OPTICAL COHERENCE TOMOGRAPHY

- Optical imaging method that can visualize cellular and extracellular structures at and below tissue surface
- Uses a low coherence near infrared light such as that from a 1,300 nm super- luminescent diode source
- Through a fiberoptic catheter, OCT directs half of the light toward the tissue surface while the other half is directed at a moving mirror

Am J Respir Crit Care Med Vol 180. pp 588–597, 2009

- The reflected light from these sources is then captured by a detector
- The imaging procedure is performed using fiberoptic probes that can be miniaturized to enable imaging of airways down to the terminal bronchioles
- For imaging small airways in that it has superior resolution and produces sub- surfaces approaching near-microscopic resolution and requires no ionizing radiation
- The main disadvantage of OCT is that it requires bronchoscopy

Am J Respir Crit Care Med Vol 180. pp 588–597, 2009

- Imaging seems promising as a tool for assessing airways but more research is needed

Body plethysmograph

- Derived from the Greek plethusmos (enlargement), and is related closely to plethus (fullness) and plethora (fullness)
- Indeed, the fundamental function of a whole-body plethysmograph is the measurement of intrathoracic gas volume (TGV) and volume change

Eur Respir Mon, 2005, 31, 15–43
Respiratory Medicine (2011) 105, 959e971

Rationale of body plethysmography

- Spirometry cannot provide information on residual volume (RV) and total lung capacity (TLC)
- A complete measurement cycle of plethys-mography even includes spirometry

Eur Respir Mon, 2005, 31, 15–43
Respiratory Medicine (2011) 105, 959e971

Principle of plethysmography

Boyle-Mariotte law

For a fixed amount of gas in a closed compartment the relative changes in the compartment's volume are always equal in magnitude but opposite in sign to the relative changes in pressure

$$P1V1=P2V2$$

Eur Respir Mon, 2005, 31, 15–43
Respiratory Medicine (2011) 105, 959e971

Shift Volume

- As long as air is flowing, the increase in lung volume is slightly greater than the volume of air that has passed through the airways into the lung
- This small difference represents a lag in mass flow during the breathing cycle and is called "shift volume"

Eur Respir Mon, 2005, 31, 15–43
Respiratory Medicine (2011) 105, 959e971

Hyperinflation

- RV or RV/TLC (>95 <140% predicted) : mild
- RV or RV/TLC (>140< 170% predicted) : moderate
- RV or RV/TLC > 170 % predicted : severe

Eur Respir Mon, 2005, 31, 15–43
Respiratory Medicine (2011) 105, 959e971

Resistance

Resistance = Pressure/Flow

Conclusion

- Spirometry still is the easiest tool for small airway assessment
- However FEF25-75 % is highly variable
- Single breath N2 test is a simple & reproducible way of assessing small airways
- Impulse oscillometry needs to be developed as a tool for patient management
- Imaging holds promise but needs further probing

THOUGH SIZE MATTERS BUT SOMETIMES EVEN SMALL CAN OUTDO THE BIG