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Mini-Review

The Role of Small Airways in Connective Tissue Disorders

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ABSTRACT

The role of small airways in the pathogenesis of interstitial lung diseases is not well understood because this lung area is overlooked in conventional lung function testing methods. Only in recent years new approaches has been developed allowing us to investigate in more detail this silent lung zone. Small airways are membranous bronchi with diameter less than 2 mm which are incorporated into elastic lung network and which patency changes depending of respiratory phase. Pathologic changes in lung parenchyma influence patency of small bronchi and vice versa-the closure of small bronchi induces ventilation/perfusion mismatch in lungs that results in hypoxemia. High Resolution Computed Tomography (HRCT) can visualize small airways, detect wall thickness and presence of pathologic processes in and around airways walls but cannot evaluate the impact of the lesion into overall lung function. At the present time two methods are recognized to be able to detect obstruction in small airways-Forced Oscillation Technique (FOT) and Nitrogen Washout Test (NWT). FOT is based on the introduction of air waves of different frequencies into the airways during quiet breathing. The penetration of airwaves depends on their frequencies and allows selecting for measurement selected level of bronchial tree for measurement of resistance and reactance. NWT is based on equilibration of nitrogen concentration among lung regions after inhalation of pure oxygen. Sloping of alveolar Plato indicates on uneven gas distribution among lung units that may be caused by closure of part of small airways.

Keywords: Small airways; Interstitial lung diseases; Forced oscillation technique; Nitrogen washout test; Connective tissue diseases

INTRODUCTION

Different Connective Tissue Diseases (CTD) use to affect lungs and manifest with non-specific respiratory symptoms, like dry cough, shortness of breath and are diagnosed as Interstitial Lung Diseases (ILD). Most commonly lung involvement occurs in Systemic Sclerosis (SSc), myosites (DM/PM) and Rheumatoid Arthritis (RA), but less commonly-in Sjoegren Syndrome (SjS) and Systemic Lupus Erythematosus (SLE) [1]. High Resolution Computerized Tomography (HRCT) is a golden standard for diagnosis of ILD, this method can visualize small airways, detect the localization of the lesion, measure bronchial wall thickness and presence of pathologic processes in and around the airways walls but cannot evaluate the impact of particular lesion into overall lung function [2,3]. Lung function examination typically reports on restrictive pattern of ventilatory failure and reduced transfer factor or diffusion capacity [4]. Lung biopsy of patients with idiopathic pulmonary fibrosis revealed reduction of small airways diameter, peribronchiolar inflammation, fibrosis, epithelial metaplasia and Bronchus-Associated Lymphoid Tissue (BALT) suggesting that small airways may be involved primarily in ILD [5].

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LITERATURE REVIEW

Methods of small airways diagnostics

Small airways are considered a "silent zone" because these airways are overlooked in conventional respiratory function tests [6]. Conventional methods like spirography or body plethysmography were based on airflow measurements generated by respiratory muscles in breathing requencies or during forced expiratory manoeuvres. Under these conditions small airways are in series with the rest of the airways and their impact in total airways resistance is hardly detectable [7]. Invention by DuBois et al. of Forced Oscillation Technique (FOT) in 1956 made a background for further improvements and implementation in clinical practice [8]. The method is based on introducing air waves of different frequencies into the patient's airways. Typically for human airways examination are used frequencies between 5 Hz and 35 Hz. Oscillations-induced air flow and pressure swings are recorded for calculation of resistance to airflow. Total resistance called Impedance consists of three components: Resistive, elastic and inertial ones. Resistive components arise from friction of air by airways walls and its magnitude depends on the radius of airways. Elastic one is created by lung and airways elastic recoil and depends on the stiffness of these tissue. The inertial component depends on the frequency of oscillations but does not depend on the measured object. Inertial components grow with increasing the frequency of oscillations and dies gradually along the airways. Only waves of lowest frequencies pass the small airways and reach alveoli [9]. It is empirically detected that healthy human airways allow to path to alveoli frequencies in the range from 5 Hz to 20 Hz. So, this is the basis for isolated resistance measurement of small airways. R5 resistance at 5 Hz, indicates resistance of all airways, R20 is the highest frequency that reaches small airways and correspondingly R5-20 is the measure of resistance of small airways.

The elastic component of impedance, named reactance (X) reflects the rebound response of airways and lung and is recorded as airflow of opposite direction; therefore reactance at lower frequencies has a negative value. Inertial forces kill the pressure created by lung elastance; therefore, reactance gradually drops with increase of oscillation frequencies [10]. Small airways have a diameter less than 2 mm and their walls do not contain cartilaginous elements. These membranous bronchi are tightly incorporated into elastic network of lungs and their patency is determined by the balance between constricting and dilating forces. During inspiration when lung elastance grows their diameter increases, but during expiration-decreases [11,12]. Additional forces that tend airways to collapse are smooth muscle tone and the pressure of blood in neighboring capillaries. This pressure in healthy lungs is influenced by gravity, so in vertical position capillary pressure is higher in the lower parts of the lungs that exert pressure towards small airways tending them to collapse at the end of expiration when opposing traction forces from lung elastic network are minimal [12]. In pathologic conditions when damming of blood occurs in lung interstitium, or in emphysema, when elastic recoil of lungs is reduced, small airways by the end of expiration collapse totally and air trapping occurs. Lung volume at which air trapping starts during the expiration is named a Closing Volume (CV) and it can be measured by Nitrogen washout technique [13]. The test is performed following way: After maximally deep expiration patient inhales 100% oxygen up to the Total Lung Capacity Level (TLC) and after short breath holding starts slow expiration until reaching Residual Volume Level (RV). Nitrogen sensor measures the changes in N_2 concentrations which run through 4 stages. First one containing pure oxygen reflect the air from anatomic dead space, second is transitional zone when N_2 concentration sharply grows reaching so called alveolar Plato. During Plato phase (or 3rd phase) nitrogen concentration is slowly sloping until 4th phase starts with next sharp raise of N_2 concentration. The volume of air remaining in lungs at the moment of IV phase onset is named Closing Volume (CV). CV indicates the moment during the course of expiration when the airways start to close and air trpping occur. The III phase slope is used to measure the air distribution heterogeneity in the lungs. In healthy lungs the 3rd phase slope is very small, but it becomes significant if different parts of lungs do not distribute oxygen equally. N_2 slope is expressed as N_2 concentration change per liter of expired air. The usefulness of nitrogen washout test for diagnosis of small airways was studied by Panagopoulos and colleagues. Author's measured lung function by classic spirometry, body plethysmography, Impulse Oscillometry (IOS) di using capacity for carbon monoxide, performed single breath nitrogen washout test detecting the phase III N_2 slope and CV/VC on two groups of SSc patients with and without signs of ILD approved by HRCT. Authors found that Phase III slopeN2SBW and R50-R20 showed the highest diagnostic performance for detecting small dysfunction among all the group of SSc patients airways (61% and 37.5%, respectively). At the same time radiographic features of SAD on HRCT were observed only in 22% of SSc-ILD patients and in none of SSc-non-ILD patients. Authors concluded that R5-R20, phase III slopeN2SBW are more sensitive for early detection of ILD than HRCT [4].

Takeishi and colleagues with their study gave a significant impact in understanding the differences between obviously similar causes of small airways obstruction. Authors compared two groups of patients: One with Obstructive Lung Disease (OLD) and another with ILD-typical restrictive disorder. Lung static and dynamic compliances significantly differed between the groups. Static compliance was three times higher in ILD group compared to OLD and healthy control group. At the same time in all groups taken together significant correlation between oscillometric parameters R5,R5-20, X5, Fres and Phase III N_2 slope was found. Reactance indices X5, Fres, as well, significantly correlated with spirograhic parameters VC and FEV-1. However, no correlation was found between lung compliance and any of oscillometric indices. These results confirm that oscillometric reactance parameters are not substantially influenced by lung elastance.

Pathogenesis of respiratory failure in interstitial lung diseases

Respiratory failure in ILD that manifests as resting or exertional hypoxemia has several pathogen etic sources. Restrictive changes in lungs due to pathologic processes in lung interstitium; affected gas diffusion gas-blood interface, ventilation/perfusion mismatch and pathologic changes in pulmonary vasculature. Restrictive changes in lung parenchima during exacerbation period may develop due to inflammatory edema and infiltration with leukocytes, but during chronic course due to fibrosis. These changes increase the work of breathing that overloads the respiratory muscles and lead to their fatigue. Typical indicators of this process are reduced Vital Capacity (VC) in spirogrphic examination, reduced Total Lung Capacity (TLG) and Residual Volume (RV) in body plethysmography and the decrease of Static (Cst) and Dynamic Compliance (Cdyn) in examination of lung mechanics [7] .

Affected gas diffusion through gas-blood barrier occur due to thickening of alveolo-capillary membrane due to inflammatory process in lung parenchima, deposition of hyaline membranes on alveolar walls during acute process and due to shrinkage of alveolar surface in chronic process. Such changes are reflected as reduced transfer factor (diffusion capacity) DLco and DLco/VA, but more precise indicator is alveolo-arterial gradient for oxygen $P(A\text{-}a)O_2$, or FiO_2/PaO_2 [14]. Ventilation/perfusion mismatch is an important factor that determines the oxygenation of arterial blood. In healthy lungs there acts so-called alveolar-vascular reflex which over distribute blood from alveoli which are not well ventilated to areas of good ventilation [15]. HRCT images show that in ILD alveolar involvement in gas exchange is mosaic-like [16]. Besides of atelectatic regions that are not aerated there are over distended areas. In inflammation arterioles under the influence of inflammatory mediators are kept open and this induces blood shunting.

DISCUSSION

This in turn gives venous admixture to arterial blood. From another side, over distended alveoli create parallel dead space that increases work of breathing. These way small bronchi passively evoke ventilation/perfusion mismatch [17]. Besides of arterial blood deoxygenation mismatch may be suspected from mosaic pattern of attenuation and bronchial wall thickening in HRCT scans, indicating on air trapping and from indicators of small airways obstruction in oscillometric measurements [9-20].

CONCLUSION

Pathologic changes in blood vessels most commonly are found in SSc. Leasons manifest as vasculites, endothelilitis and alveolar hemorrhage Specific palmary vasculitis are Granulomatosis with Polyangiitis (GPA), or Wegener granulomatosis, Eosinophilic Granulomatosis with Polyangiitis (EGPA) or Churg-Strauss syndrome. These diseases fall out of our topic and will not be discussed in more detail. For succesful patient-focused treatment of ILD important role plays understanding the pathogenesis of lung affections in each individual case.

REFERENCES

1. Jeganathan N, Sathananthan M. Connective tissue disease-related interstitial lung disease: Prevalence, patterns, predictors, prognosis, and treatment. Lung. 2020;198(5):735-759.
2. Nathan SD, Pastre J, Ksovreli I, Barnett S, King C, Aryal S, et al., HRCT evaluation of patients with interstitial lung disease: Comparison of the 2018 and 2011 diagnostic guidelines. Ther Adv Respir Dis. 2020;14:568-575.
3. Torres PP, Rabahi MF, Moreira MA, Escuissato DL, Meirelles GD, Marchiori E. Importance of chest HRCT in the diagnostic evaluation of fibrosing interstitial lung diseases. J bras pneumol. 2021:e20200096.
4. Panagopoulos PK, Georgakopoulou VE, KALLIANOS A, Chatzinikita E, Pezoulas VC, Malagari K, et al., Small airways dysfunction in patients with systemic sclerosis and interstitial lung disease. Front Med (Lausanne). 2022:3324.
5. de Mello GC, Carvalho CR, Kairalla RA, Saldiva PH, Fernezlian S, Silva LF, et al., Small airway remodeling in idiopathic interstitial pneumonias: A pathological study. Respiration. 2010;79(4):322-332.
6. Mead, J, The lung's "quiet zone". N Engl J Med. 1970;282(23): 1318-1319.
7. Takeichi N, H Yamazaki, K Fujimoto. Comparison of impedance measured by the forced oscillation technique and pulmonary functions, including static lung compliance, in obstructive and interstitial lung disease. Int J Chron Obstruct Pulmon Dis. 2019;14:1109-1118.
8. DuBois AB, Brody AW, Lewis DH, Burgess Jr BF. Oscillation mechanics of lungs and chest in man. J Appl Physiol. 1956;8(6): 587-594.
9. Dadzie I, Quansah E, Puopelle Dakorah M, Abiade V, Takyi-Amuah E, Adusei R. The effectiveness of dipstick for the detection of urinary tract infection. Can J Infect Dis Med Microbiol. 2019.
10. Bickel S, Popler J, Lesnick B, Eid N. Impulse oscillometry: Interpretation and practical applications. Chest. 2014;146(3): 841-847.
11. King GG, Bates J, Berger KI, Calverley P, de Melo PL, Dellacà RL, et al., Technical standards for respiratory oscillometry. Eur Respir J. 2020;55(2).
12. Frizzelli A, Nicolini G, Chetta A. Small Airways: Not Just Air Ducts–Pathophysiological Aspects and Clinical Implications. Respiration. 2022;101(10):953-958.
13. Chambers D, Huang C, Matthews G. Basic physiology for anaesthetists. Cambridge University Press; 2019.
14. Milic-Emili J, Torchio R, D'Angelo E. Closing volume: A reappraisal (1967–2007). Eur J Appl Physiol. 2007;99(6):567-583.
15. Criner RN, Hatt CR, Galbán CJ, Kazerooni EA, Lynch DA, McCormack MC, et al., Relationship between diffusion capacity and small airway abnormality in COPDGene. Respir Res. 2019;20(1):1-4.
16. Halmagyi DF, Colebatch HJ, Starzecki B, Horner GJ. Pulmonary alveolar-vascular reflex. J Appl Physiol. 1964;19(1):105-112.
17. Yoo H, Hino T, Han J, Franks TJ, Im Y, Hatabu H, et al., Connective tissue disease-related interstitial lung disease (CTD-ILD) and interstitial lung abnormality (ILA): Evolving concept of CT findings, pathology and management. Eur J Radiol Open. 2021;8:100311.
18. Solyanik O, Hollmann P, Dettmer S, Kaireit T, Schaefer-Prokop C, Wacker F, et al., Quantification of pathologic air trapping in lung transplant patients using CT density mapping: Comparison with other CT air trapping measures. PLoS One. 2015;10(10):e0139102.
19. Orlandi M, Landini N, Sambataro G, Nardi C, Tofani L, Bruni C, et al., The role of chest CT in deciphering interstitial lung

involvement: Systemic sclerosis versus COVID-19. Rheumatology. 2022;61(4):1600-1609.

20. Kwon KY. Pathological interpretation of connective tissue disease-associated lung diseases. Yeungnam Univ J Med. 2019;36(1):8-15.