The methods other than spirometry in the early diagnosis of COPD

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SUMMARY

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Chronic obstructive pulmonary disease (COPD) is a major cause of mortality and morbidity around the world. The diagnosis od COPD is based on the presence of clinical symptoms and the fact that the ratio of post-bronhodilator forced expiratory volume in 1 second to forced expiratory vital capacity(FEV$_1$/FVC) is less than 0.70. Persistent limitation of airflow which is a characteristics of COPD is reproducible and most common lung function test that is why it is usually measured by spirometry. The small airway diseases and the parenchymal destruction play a role in the pathogenesis of COPD at different rates over time resulting in chronic airflow limitation. These pathologies are not always together at the same time and the contribution of those to the development of COPD differ from one individual to another. The pathophysiological involvement of small airways in COPD has been confirmed. When the obstruction of the small airways occur either by mucus, smooth muscle hypertrophy, inflammatory infiltration or air wall thickening; then the consequence is the increased resistance and ventilation impairment. The parenchymal destruction can be estimated via scanning and at the initial assessment of a COPD patient, it gives information about the concomitant pulmonary diseases and/or differential diagnosis. There is an increasing interest on symptomatic individuals whose whose COPD diagnosis has not been confirmed yet with spirometry but diagnosis is based on alternative methods and approaches. Although these methods nowadays are commonly used for the clinical research, they will offer an opportunity to the clinician to find out the COPD patients at an early stage. Herein we will discuss the available methods other than spirometry in the early diagnosis of COPD before the overt disease is confirmed.

Key words: *Chronic obstructive lung diseases; diagnosis; small airways; spirometry*

ÖZET

KOAH erken tanısında spirometri dışındaki yöntemler

Kronik obstrüktif akciğer hastalığı (KOAH) tüm dünyada mortalite ve morbidite nedenidir. KOAH tanısı, klinik semptomların varlığında 1. saniye içinde bronkodilatör sonrası zorlu ekspirasyon hacminin 1. saniye içinde zorlu ekspiratuvar vital kapasiteye (FEV$_1$/FVC) oranının 0.7'den küçük olması ile konulur. KOAH'ın karakteristik bir özelliği olan hava akımının kalıcı olarak kısıtlanması tekrarlanabilir ve en sık kullanılan akciğer fonksiyon testidir, spirometri ile ölçülür. Küçük hava yolu hastalığı ve parankimal yıkım, KOAH patogenezinde farklı oranlarda rol oynar ve zamanla kronik hava akımı kısıtlanmasıyla sonuçlanır. Bu patolojiler her zaman aynı anda birlikte olmayabilir ve KOAH patogenezine katkısı kişiden kişiye farklılık gösterir. Küçük hava yolu hastalığının KOAH patogenezindeki yeri kanıtlanmıştır. Küçük hava yolu hastalığı; mukus, düz kas hipertrofisi, inflamatuvar infiltrasyon veya hava duvarı kalınlaşmasına bağlı olarak geliştiğinde, sonuç artan direnç ve havalanma bozukluğu olmaktadır. Parankimal yıkım görüntüleme metodları ile tahmin edilebilir. KOAH hastasının ilk değerlendirmesinde, eşlik eden akciğer hastalıkları ve/veya ayırıcı tanıda görüntüleme metodlarından faydalanılır. KOAH tanısı henüz spirometri ile kanıtlanmayan ancak tanısı alternatif yöntem ve yaklaşımlara dayanan semptomatik bireylere ilgi artmaktadır. Günümüzde spirometriye alternatif yöntem ve yaklaşımlar genellikle klinik araştırmalar için kullanılmasına rağmen, KOAH hastalarını erken aşamada saptayabilmek için klinisyene fırsat sunmaktadır. Bu amaçla, KOAH henüz kanıtlanmamışken erken tanıda spirometri dışındaki mevcut yöntemleri tartışacağız.

Anahtar kelimeler: *Kronik obstrüktif akciğer hastalığı; tanı; küçük hava yolu; spirometri*

INTRODUCTION

In the pathogenesis of chronic obstructive pulmonary disease (COPD) both the small airway diseases and destruction of the lung parenchyma are contributed to the chronic airflow limitation which is the characteristic feature of the COPD. The small airways are the ones whose luminal diameter is < 2 mm mostly branching from 8th generation and account for 98.8% of the total lung volume (1). They have little or no cartilage support and narrow lumen which makes them easily collapsible. On the other hand, since the cross-sectional areas increase from the proximal airways to the small airways, small airways' contribution to the resistance of the entire lung is < 10% in healthy individuals (1). The data on the contribution of small airways disease in the onset or progression of COPD is scarce and hard because COPD represent a heterogeneous phenotypes. The recent studies focus on the assessment of small airway diseases in terms of detecting the early COPD candidates as named preCOPD recently. Parenchyma leads to airflow limitation by losing the alveolar attachment of bronchi that results in premature closing of the surrounding airways. This parenchymal pathology resulting in emphysema can be estimated by computed tomography (CT) which also identifies bronchial wall thickening and gas trapping. One of the research questions about COPD is about the outcomes between the symptomatic COPD patients who were confirmed by spirometry and symptomatic individuals whose COPD diagnosis has not been confirmed with spirometry but rather is based on approaches and methods as scanning, physiological abnormalities measured by complementary tests (2). Also several procedures have been suggested to study at the small airways of the lung on ventilation heterogeneity and air trapping (3). We will discuss the methods in the early diagnosis of COPD in which the diagnosis is not based on spirometry.

Lung Function Spirometry

Spirometry is a worldwide used tool to assess the pulmonary ventilation. The FVC manoeuvre is the fundamental manoeuvre of the test for assessing pulmonary function. The presence of COPD symptoms in addition to reduced FEV$_1$/FVC ratio is the diagnositc criteria for COPD according to the Global Initiative for Chronic Obstructive Lung Diseases (GOLD)(4). This fixed ratio measurement is simple and independent from the reference values. The most commonly used prognostic parameter for monitoring the disease is FEV$_1$ and the change of liters in FEV$_1$ is the primary outcome in almost all the clinical studies. Although spirometry provides information about the pulmonary ventilation, the use of post -bronchodilator fixed ratio can lead to overdiagnosis of COPD in the elderly population and underdiagnosis in the young population under 45 years (5). That means there is a probability of misdiagnosis of about 15% of the cases. Since post-bronchodilator FEV$_1$/FVC ratio is preserved in the emphysema dominant COPD patients, spiromety is insufficient in the diagnosis of the diseases (3). The European Respiratory Society (ERS) offers the use of lower limit of normal (LLN) as an alternative (5). There are data showing that FEV$_1$/FVC ratio obtained by spirometry in COPD is higher than obtained with LLN (6).

Since the studies of understanding the pathogenesis of COPD is increasing in number aiming to identify early diagnosis of the disease at the risky population, we return to the point where the COPD begins. The pathology studies revealed the importance of small airways in early dignosis of COPD candidates in the preventive medicine, by showing the damaged small airways leading to the development of airflow limitation and emphysema. Here, the methods other than spirometry in the diagnosis of small airway disease suggesting pre-COPD, in symptomatic, at risk individuals with normal spirometry will be discussed.

Static Lung Volumes

The lung volumes are influenced by the parenchyma, airways and structural support of the surrounding tissues. Residual volume (RV) is the lowest lung volume available at the end of deep expiration in the lungs. The RV correlates with the degree of inflammatory changes in small airways in COPD (7). As a result of a mildly increased RV (> 120% of predicted), an increased RV/TLC (> 35%) can be a marker for the diagnosis of air trapping and hyperinflation in small airways since TLC is increased more in obstructive lung disease (8). FRC/TLC is another parameter that reflects air trapping and hyperinflation such as RV/TLC. In a study, an increase in FRC/TLC was found in 7% of the patients without airflow obstruction (9). Static lung volumes can be measured by gas washing, gas dilution and plethysmography methods.

Plethysmography

Plethysmography is an assessment method of the lung volumes which provides a measurement of air trapping and hyperinflation. It is not affected by the distribution of the ventilation and gives information about the airway resistance (Raw) which is the pressure applied by the gas flowing out of the lungs for each unit of flow rate.

Measurement of lung volumes by body plethysmography may provide reliable information but is performed in limited number of centres.

Single and Multiple-Breaths Washout

Gas washout techniques have been using for fifty years. Its principle is based on the ventilation distribution inhomogeneity on different lung volumes. The gas chosen for washout tests has to be safe, not to join in gas mixing and not to dissolve in any structural part of the lung. The most widely used Single -Breath washout (SBW) test is with an endogenous

gas N2. Another endogeneous gas is argon and the exogenous gases are sulfur hexafluoride, helium, and methane. During the process the patient exhale to residual volume (RV), then inhale 100% oxygen to the total lung capacity and then washout during exhalation from TLC to RV (10). The measurement of the N2 concentrations by analyzer at the beginning of the test and washout are based on the calculation of volumes by comparison. N2 concentrations is shown into four phase, which are Phase 1; containing ignored nitrogen due to anatomical dead space, Phase 2; a rapid increase due to bronchial phase, Phase 3; a gradual increase in concentration of nitrogen due to alveolar phase, and finally Phase 4; a short rapid rise due to airway closing (10). This point is known as the closing volume (CV) at which the small airways start to close. In a normal lung small airways close at RV. The sum of closing volume and RV is called as closing capacity. In the case of small airway diseases, early collapse of the small airways may result in an increased CV. Even in 1970s, increased CV with age in smokers has been shown, suggesting it is a sensitive marker of small airway impairment (11). More recent studies reported that CV correlates well with RV/TLC (12).

The Phase 3 slope of nitrogen provides information on the ventilation heterogeneity. Ventilation occurs by convection and diffusion in the lung (10). If the airway disease exists, it doesn't affect the whole lung equally resulting in differently ventilated subunits. In the affected units of the lung, inspiratory oxygen mixes less so those units have a higher N2 concentration which causes a rise of the Phase 3 slope. The double tracer gas (DTG)-SBW test is performed by using a gas mixture, such as helium (He) and sulfur hexafluoride (SF6) due to their different diffusion properties (13). Some studies reported that both N2-SBW and DTG-SBW detects early inflammatory changes of small airway pathology (14,15). And a few studies comparing ventilation differences in healthy subjects and COPD patients confirmed phase 3 slope is clearly increased in COPD patients, also studies have shown washout tests catch the changes of small airways in smokers and COPD patients (16,17).

In a study examining phase 3 slope, airway closure and expiratory flow limitation in 10 smokers with normal spirometry and 40 confirmed COPD patients, it is shown that in smokers the phase III slope was increased, and further increased with GOLD severity

(17). Boeck et al. assessed small airways in COPD patients by SBW and DTG tests and showed phase III slope of nitrogen and double tracer gas was increased in patients with COPD compared with healthy subjects. Further they found phase 3 slope was associated with FEV_1 predicted, RV/TLC and diffusing capacity of the lung for carbon monoxide (DLCO) (18).

Multiple Breath Washout

The patient inhales 100% oxygen from FRC and wash out breath by breath until the exhaled nitrogen concentration is nearly less than 2% (1/40 of the original starting concentration) for at least three breaths following each other in the multiple breaths washout (MBW) tests (10). The gas mixing efficiency is measured by a formula and called as lung clearing index (LCI). It reveals the ventilation hetereogenity in conducting airways (Scond) and the small airways in acinar regions (Sacin) (10). It is highly reproducible (19). It was shown that LCI differentiate COPD and healthy subjects, in a previous emphysema study. LCI raises in the case of airflow obstruction that is supported by the findings of previous emphysema research in providing evidence of the discriminative ability of LCI between healthy and COPD subjects (20). Besides scond and sacin are increased in COPD but also can recognise small airway impairment at the acinar entrance in ≤ 10 pack years smokers than spirometry (21). In another study MBW test has claimed to predict small airways changes in smokers before conventional spirometry becomes abnormal (22).

However MBW needs poor cooperation, still needs standardization technique although MBW does not need good cooperation, still needs standardization. It is not available in every center and is time consuming.

The Diffusing Capacity of the Lungs for Carbon Monoxide (DLCO)

In addition to static lung volumes, a measurement of the diffusion capacity can also be helpful to detect small airway disease. DLCO is low (< 80% of predicted) in emphysema because of the loss of lung parenchyma and the mismatch of ventilation and perfusion (23). Single breath carbon monoxide diffusing capacity of the lung (DLCO) impairments in COPD have been previously associated with emphysema and are often seen in individuals with more advanced disease. A recent study showed CT defined small airway abnormality was associated with lower DLCO in GOLD 0 smoker individuls (24). In another study, from a cohort of 1570 smokers normal spirometry/normal DLCO group assessed over 45 ± 20 months, 3% developed GOLD-defined COPD. In contrast, in the normal spirometry/low DLCO group, followed over 41 ± 31 months, 22% developed GOLD-defined COPD (25). These studies suggest that DLCO measurement is a useful method in the diagnosis of pre-COPD.

The diffusing capacity of the lungs for carbon monoxide (DLCO) is designed to reflect properties of the alveolar-capillary membrane, specifically the ease with which oxygen moves from inhaled air to the red blood cells in the pulmonary capillaries. The single breath DLCO maneuver begins with a full exhalation to residual volume (RV), the mouthpiece is connected to the test gas (0.3 percent carbon monoxide [CO], tracer gas [eg, 10 percent helium or 0.3 percent methane], oxygen, and nitrogen), and the subject inhales rapidly to total lung capacity in < 4 seconds. Following a 10 ± 2 second breath hold, the subject exhales quickly and completely to RV. An alveolar sample of the exhaled gas is collected immediately following dead space washout and analyzed for calculation of the dilution of the tracer gas and the uptake of CO (26).

Airway Resistance

Airway resistance is the ratio of driving pressure to the rate of the airflow in the airways. The most frequent methods used to measure airway resistance are whole-body plethysmography, and measuring resistance using sound waves (the forced oscillation technique and impulse oscillometry) (27). All these methods allow to measure resistance during respiration at the level close to tidal volume, they do not require forced breathing manoeuvres or deep breathing during measurement. The most wide used method for measuring airway resistance is whole-body plethysmography. The results of plethysmography include among others the following parameters: airway resistance (Raw), airway conductance (Gaw), specific airway resistance (sRaw) and specific airway conductance (sGaw). In the Forced oscillation technique (FOT) and impulse oscillometry system (IOS) airway resistance is calculated basing on the changes in pressure and flow caused by air vibration. Choosing between FOT and IOS to measure respiratory resistance and reactance is like choosing between a vol-

ume-displacement spirometer and a flow sensor-based spirometer respectively (28). These two methods are measuring respiratory resistance using single frequency sound waves (FOT) or impulses of multiple frequency sound waves (IOS) are pushed into the lungs as pressure waves.

It should be keep in mind that FOT and IOS do not produce equal measurements of resistance and reactance, therefore predicted values derived by an FOT machine may not necessarily be applicable for IOS machines. Tanimura et al. showed that the resistance values varied by up to 10% from estimated values in both devices (29). Furthermore, there was a difference in frequency dependence for the resistance between devices. Clearly, more studies are required to establish reliable device-specific predicted values.

Forced Oscillation Technique

The FOT as a tool to measure lung function using sinusoidal sound waves of single frequencies generated by a loud speaker and passed into the lungs during tidal breathing. The output was a measure of respiratory impedance (Z_{rs}), which included the respiratory resistance (R_{rs}) and respiratory reactance (X_{rs}) measured over a range of frequencies (usually from 3 to 35 Hz). These parameters provided valuable information about the mechanical properties of the airways and lung parenchyma. The main advantage of this device was that the procedure was easy to perform and provided information about the lung which was different from that given by the spirometer.

Impulse Oscillometry

IOS is a device delivering pressure oscillations at different frequencies to the tracheobronchial tree. The impulses are applied at 0.2-second intervals during tidal breathing at a normal flow of air for at least 30 seconds (30). It assesses the respiratory resistance (R_{rs}) and reactance (X_{rs}), and the impedance of the total respiratory system (Z_{rs}). The resistance at 5 Hz (R_5) represents the total airway resistance, and the resistance at 20 Hz (R_{20}) represents the resistance of the large airways. Subtracting R_{20} from R_5 (R_5-R_{20}) reflects resistance in the small airways. The resonant frequency (Fres) is the frequency at which reactance is zero (30). Oscillometry has been proposed to be able to reflect more distal airway function compared to spirometry (31,32). A study, examining the resistance and the reactance measured by IOS, formed three group of patientsin which is the first group

included never smokers without respiratory symptoms, second group current smokers without respiratory symtoms and the third group with a diagnosis of chronic bronchitis, COPD or emphysema; and showed that self reported COPD group has a higher pulmonary resistance and lower pulmonary reactance than the individuals without self reported chronic bronchitis, COPD or emphysema (33). A study reported by Crim et al, compared the ECLIPSE cohort of COPD subjects and smoking and non-smoking controls and stated that COPD was associated with increased R_5, R_5-R_{20}, and reactance (34). They also claimed that respiratory system resistance and reactance, impaired in the COPD cohort as a whole, but not altered in all patients with COPD nor related specifically to the severity of the underlying airflow limitation. They also claimed COPD patients with normal respiratory system impedance represent a different clinical subtype of COPD, whose spirometry seemed to be better (35).

Sue and collegues compared the diagnostic value of spirometry and IOS for identifying small airway disease in heavy-smokers and COPD based on the objective assessment with endobronchial optical coherence tomography, and found Fres and peripheral airway resistance (R_5-R_{20}) conferred greater diagnostic values than FEV_1% and maximal mid-expiratory flow (MMEF%) predicted in distinguishing small airway diseases in never-smokers from heavy-smokers and heavy-smokers from patients with stage I COPD (36). Xia Wei et al. compared IOS parameters and spirometry for the assessment of the severity of COPD. They grouped COPD patients according to their GOLD stage and found FEV_1/FVC, which reflects airflow limitation, was consistent with IOS parameters, but the correlation was weaker than that with FEV_1% predicted (37).

It seems that IOS would be a diagnostic tool for the subjects who already has the pathological changes of airways but is not yet diagnosed with COPD.

Imaging Modalities

Chest X-Ray and computed tomography (CT) are the imaging modalities used to explore the concomitant lung diseases. CT is preferred to define the type and distribution of the emphysema. The presence of emphysema is related to decline of FEV_1 and mortality (38,39). More the emphysema progresses, lung density on CT scan reduces. The percentage of low density area and visual score were correlated with

FEV_1/FVC, and visual score was correlated with $FEV_1\%$ in a study on low-dose chest CT which aimed to clarify if the patterns of emphysema in smokers with normal spirometry findings were different from the clinical data of non-smokers (40). It showed that smokers with normal spirometry and abnormal CT findings may have potentials to develop an airflow obstruction in the future in comparison to non-smokers (40). In a study analyzing the patients' spirometry who has documented emphysema on CT scan showed that according to GOLD diagnosing criteria, 83% and according to LLN, 75% of the patients had airflow obstruction however GOLD; did not catch 6.9% and LLN 13.9% of the patients who had no obstruction but emphysema and clinical diagnosis of COPD (41). The airwall thickness measurement obtained from CT is also inversely correlated with lung function and related to small airway diseases (42). Another study performed inspiratory and expiratory CTs in 1140 male smokers with or without mild COPD to quantify emphysema, airwall thickness and air trapping, found that there was a significant difference in clinical characteristics between the patients according to the dominant radiological pathology they had on their CT (43). In a study to identify clinical and radiologic evidence of smoking-related disease in a cohort whose individuals from the Genetic Epidemiology of COPD (COPDGene) of current and former smokers who did not meet spirometric criteria for COPD which they called GOLD 0 in the study showed that FEV_1 percent predicted distribution and mean for the GOLD 0 group were lower but still within the normal range for the population. Current smoking was associated with more respiratory symptoms, but former smokers had greater emphysema and gas trapping. Advanced age is related to having more CT findings of the disease (44).

A study investigating whether the airwall thickening derived from CT is associated to diseases in smokers with or without COPD, showed that the Pi10, which was calculated from extracted airways and expressed as the square root of wall area of a hypothetical airway with internal perimeter of 10 mm, was increased in all GOLD stages and associated with worse FEV_1 predicted. Besides Pi10 was significantly higher in current smokers compared to former smokers and the average Pi10 of never smokers was significantly lower than both former and current smokers (45). In this study 2000 smokers and 46 never smokers group

were from the COPD Gene study and were followed up for 5 years so they had repetitive CT scans.

Visual assessment of CT scan is seemed to be successful in the early detection of COPD but the issue is exposure to radiation repeatedly if serial CT scan is needed. Also quantitative analysis of CT needs a detailed and standardized protocol and expert radiologist. And as mentioned in a study, physiological amount of emphysema should be considered in the population who has an evidence of emphysema on CT scan but does not have recognizable COPD clinic (46). High dose versus low dose CT performance is also needed to be validated.

Exhale NO

Lung inflammation and oxidative stress biomarkers such as nitric oxide (NO), endothelin-1, eotaxin-1, and hydrogen peroxide have been studied (11). NO is the most widely used biomarker in exhaled breath. Patients inhale to total lung capacity and then exhale for 10 seconds into the device of laser light scattering particle spectrometry in order to measure the amount of NO (47).

The exhaled NO (FeNO) is flow rate dependent and inversely correlated with the flow rate. ATS guideline offers the use of FeNO in clinical practise for the diagnosis of eosinophilic airway inflammation with moderate quality of evidence and in the determination of the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation with low quality of evidence (47). Then the role of exhaled FeNO measurements in patients with COPD remains not clear. A pilot study showed increases in FeNO were identified in a subset of patients with COPD, particularly in those previously diagnosed with both COPD and asthma suggesting that FeNO levels may be helpful in identifying patients with asthma-COPD overlap syndrome (48). Feng-Jia-Chen and collegues enrolled asthma, COPD and Asthma-COPD overlap syndrome (ACOS) patients in their study. They showed that FeNO value in patients with ACOS was significantly higher than that of the COPD group. The FeNO value in patients with asthma was significantly higher than that of the other groups so they concluded that FeNO is a good predictor for differentiating ACOS from COPD (49). It is claimed that exhaled NO may rise in COPD but less in comparison with asthma (50). It seems exhaled NO increase

is identified in a subset of patients with COPD, particularly in those previously diagnosed with both COPD and asthma.

CONCLUSION

The huge amount of COPD patients are diagnosed when the airflow limitation is clinically established. The small airways where COPD begins is still a silent zone to be discovered. None of those tests told above has been validated in the diagnosis of early diseases yet. Early diagnosis for COPD via available and validated tests in clinical practice is needed regarding the clinical and economic burden of the disease. We need further studies on prevention and early diagnosis of COPD before development of the overt diseases and monitoring the disease as well.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this articles.

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