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Inside this issue: Updates in Pulmonary Function Testing 2012-2015

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Pulmonary function testing has been a well-known and relatively accessible test for all specialists in respirology for more than half a century. Since the beginning of the 21st century, recent breakthroughs in molecular biology and high throughput gene analysis technologies have progressively led us to a new and exciting era of modern personalized medicine. Yet, lung function testing still keeps its value as a practical, easily performed and most valuable tool helping respiratory physicians to better characterize patients' phenotypes based on individual respiratory function, that now includes quantitative and qualitative assessment of breath. In this short review, we will attempt to briefly summarize the most recent developments in this field.

SPIROMETRY

Reference values of spirometry

Although Quanjer *et al* published the article "Multi-ethnic reference values for spirometry for the 3-95 year age range: The global lung function 2012 equations" in ERJ in 2012 (1) many spirometers still do not have this reference value incorporated in the machines. These Global Lung Initiative equations have been required for many international studies, so their upload in all spirometers is an urgent issue.

Using peak expiratory flow (PEF) of spirometry for COPD case finding

As the vast majority of individuals with COPD-up to 70-90%, are as yet underdiagnosed, the screening and case finding strategies in COPD remain a considerable problem.

In 2013, Jithoo *et al* reported data from 14 BOLD sites comprising 9.390 participants aged ≥ 40 years (2).These population-based subjects completed a questionnaire and spirometry.

The results showed that:

For moderate/ severe COPD:

* The use of questionnaire alone had high sensitivity (97%), but required confirmatory spirometry on 80% of participants,

* While the use of spirometric PEF had sensitivity of 83-84% but required confirmatory spirometry only in 19-22% subjects.

For severe COPD, PEF from spirometric test achieved 91-93% sensitivity and only < 9% of participants requiring confirmatory spirometry

The authors have come to the conclusion that a staged screening algorithm using the indice Peak Expiratory Flow (PEF) of spirometric test initially, followed by confirmatory spirometry as needed, was the most cost- effective case finding strategy.

New handheld spirometer

Most COPD and asthmatic patients are underdiagnosed.

Those patients visit primary care physicians first but these doctors usually under-use spirometry. The causes are the cost, time and effort consuming of the spirometric test, primary care doctors undergo little training and lack of confidence in interpreting the test.

The machine cost is also a problem, so a low cost and easy to use handheld spirometer is in demand. There are many kind of this type of devices on the market. The newest one from Vitalograph manufacturer- Ireland.

It is a Fleish pneumotachograph, giving the Flow-volume and Volume- time curves. The predicted sets include NHANES III, ERS and GLI with Lower Limit of normal values (LLN). The flow head is removable and can be used with a disposable filter. The most important advance in this kind of handheld spirometer is that the screen has been designed in a way that operator can watch the 3 best flows, and pre, post bronchodilator test results.

But as the device is compact, it can not show the Flow-volume and Volume-time curves simultaneously as in the laboratory based spirometer.

An update on contraindications for lung function testing

In this review article, Cooper BG suggested that surgical techniques now have improved and are less invasive (3) Besides, the guidelines on contraindications for lung function testing were published more than 30 years ago, so a revision is needed.

Author suggested that the previous recommendation of waiting for 6 weeks after surgical procedures or cardiovascular event before lung function exploration now could be reduced to less than 3 weeks.

ADVANCES IN MEASUREMENT OF LUNG DIFFUSING CAPACITY

The classical equation of Roughton and Forster (1957) for the transfer of CO from air to blood is:

$$\frac{1}{D_L CO} = \frac{1}{DmCO} + \frac{1}{DbCO} = \frac{1}{DmCO} + \frac{1}{\theta COxVc}$$

DmCO is the membrane conductance, related to the diffusing capacity of alveolar – capillary membrane

DbCO is lung capillary blood conductance, which depends on the reactivity of CO with Hb (θCO) and mass Hb in the lung capillaries. The last one depends on lung capillary blood volume (Vc). So

$$DbCO = \theta \mathrm{CO} \,.\, \mathrm{Vc}$$

To increase the sensitivity of the Lung Diffusing capacity for the carbon monoxide (DLCO) test, Martino J.B. *et al* (4) suggested a new method: the simultaneous measurement of D_LNO and D_LCO (NO/CO method). It will permit the partitioning the CO diffusing capacity into its consti-

tutive components: membrane conductance (DmCO) and lung capillary blood conductance (DbCO). Up to now, few clinicians routinely measure those two values as it is complicated and time consuming.

Martino *et al* showed, using the NO/CO method, that DLCO is mainly dependent on Vc, except when Dm is severely reduced.

DLNO is dependent equally on both Dm and Vc.

So authors has come to conclusion that in patients DLNO would be more sensitive to membrane alteration than DLCO, while DLCO is more sensitive to microvascular alteration.

By using simultaneous measurement of DLCO and DLNO, Dm and Vc values could be derived (5)

Instead of using DLCO result as a whole, authors have suggested that this NO/CO analysis could provide more information on the diseases of the lung diffusion.

INERT GAS WASHOUT MEASUREMENT

Inert gas washout test, using the simple- or multiple-breath washout technique have been used for over 60 years.

They offer complementary information to standard lung function tests, such as spirometry, by measuring ventilation distribution inhomogeneity and other indices.

But detailed guidelines for these methods are lacking.

In 2013, the ERS/ATS has released a consensus:

“Statement for inert gas washout measurement using multiple and simple- breath tests” (6). These methods are used for measurements of functional residual capacity, ventilation distribution inhomogeneity, trapped gas volume, closing volume and closing capacity. The consensus described the multiple- breath washout and simple breath washout test methods, equipment, suitability of current washout systems across age groups and the impact of inert gas choice (Helium, Nitrogen, Sulfur hexafluoride (SF6)).

These recommendations are mainly evidence based but there also include expert opinion from a working group experienced in the techniques discussed.

The statement is very comprehensive but the authors have raised important questions which remain unanswered for the washout systems, test procedure and result analysis and the interpreting washout test in infants and children is challenging.

Besides the normative data is to be collected for different age, sex and ethnic group and robust, accurate commercial devices which can be used for all age groups are highly expected.

FRACTIONAL CONCENTRATION OF NITRIC OXIDE (NO) IN EXHALED BREATH (FENO)

The first publication on exhaled NO is of Gustafsson *et al*, was in 1991 (7). American Thoracic Society (ATS) and European Respiratory Society (ERS) have published the first recommendations in 1997 which were updated in 2005, 2011 and 2015 (8,9,10).

Measurement of FeNO is the only non-invasive and reproducible test to detect airway inflammation.

NO measurement in exhaled breath supports the diagnosis of asthma and its phenotyping.

The correlation between exhaled NO measurement and asthma control have been confirmed in many articles, both on adults and children. FeNO measurement also contribute to inhaled corticosteroid adjustment, which is an important issue in asthma management, especially for pregnant patients.

Many articles have been published on the usefulness of exhaled NO measurement to assess

asthma patient compliance, the common problem for all chronic diseases.

Measuring the FeNO showed that this method could reduce the cost related to the asthma diagnosis and patient monitoring (11).

Besides asthma, changes in NO pulmonary production also occur in cystic fibrosis, primary cilary dyskinesia and interstitial involvement in systemic sclerosis and could be detected by NO measurement in exhaled breath.

The portable devices for FeNO measurement are now available that facilitate wider use in clinical practice as well as in research.

BREATHOMICS IN LUNG DISEASE – A NEW METHOD IN PULMONARY FUNCTION TESTING.

Exhaled volatile organic compounds (VOCs) are derived from the respiratory tract or from the pulmonary circulation. As such, they have been investigated as noninvasive biomarkers for lung disease diagnosis and monitoring.

Up to now, there are potential use of VOCs to discriminate lung cancer patients and healthy control subjects. VOCs also have been used to noninvasively diagnose pulmonary infectious diseases. In obstructive lung diseases there are many studies which have been successfully carried out:

Dragonieri S *et al*, Montuschi P *et al* have found that VOCs can distinguish healthy control subjects and asthmatic patients with accuracy of 86% to 100% (12,13). Fens and colleagues by using eNose were able to discriminate patients with asthma and COPD. This finding has been confirmed by external validation (sensitivity, 85%; specificity, 90%) (14)

In asthmatic children, using GC- MS method, light candidate asthma volatiles have been described.

Steroid responsiveness in asthmatic patient, predicted by the composite signal of exhaled VOCs, measured by eNose, has given the results which are even more accurate than by sputum eosinophils or exhaled nitric oxide.(15)

The level of exhaled pentane is high during an exacerbation and return to level of control subjects when the exacerbation subsided.(16)

Large multicenter trials, such as U- BIOPRED, are currently validating and assembling these biomarkers for phenotyping and endotyping patients with obstructive lung diseases. U-BIOPRED also aims to assess whether and how these techniques could be useful for patient management individually.

The potential benefits of VOCs biomarkers are noninvasive, quick and cheap.

But current level of VOCs techniques can only be classified as phase 2 to 4 on the 10- step technology readiness assessment (17).

We also need independent biomarkers to increase the reliability of identified one.

Guidelines for standardized methodology for VOCs is currently prepared by European Respiratory Society taskforce.

Potential confounders such as age, sex, pregnancy, medication, diet, smoking and others must be taken into consideration in measuring and interpreting identified VOCs.

Multitude of clinical conditions are related to many predominate volatiles, so the use of volatile biomarker profiles may identify a clinical condition better than a single one.

In conclusion, based on the current data, clinical application of exhaled breath- based diagnosis and phenotyping in pulmonary disease could be a reality in condition that all of the above mentioned concerns are resolved.

REFERENCES

1.Quanjer PH, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012 Dec;40(6):1324-43.

2.Jithoo A et al. Care finding options for COPD: Results from the BOLD Study. Eur Repir, 2013; 41: 548-555

3.Jithoo (BOLD)

4.Cooper BG. An update on contraindications for lung function testing. Thorax. 2011 Aug;66(8):714-23.

5.Martinot JB, Guénard HJ. TLNO/TLCO ratio is not the end of the road. Eur Respir J. 2014 May;43 (5):1535-6.

6.Barisione G, Bacigalupo A, Brusasco C, et al. Mechanisms for reduced pulmonary diffusing capacity in haematopoietic stem-cell transplantation recipients. Respir Physiol Neurobiol. 2014 Apr 1;194:54-61.

7.Robinson PD, Latzin P, Verbanck S, et al. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J. 2013 Mar;41(3):507-22.

8.Gustafsson LE, Leone AM, Persson MG, et al. Endogenous nitric oxide is present in the exhaled air of rabbits, guinea pigs and humans. Biochem Biophys Res Commun. 1991 Dec 16;181(2):852-7.

9.American Thoracic Society; European Respiratory Society. ATS/
ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. Am J Respir Crit Care Med. 2005 Apr 15;171 (8):912-30.

10.Dweik RA, Boggs PB, Erzurum SC, et al.
An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinicalapplications. Am J Respir Crit Care Med. 2011 Sep 1;184(5):602-15.

11.Dinh-Xuan AT, Annesi-Maesano I, Berger P, et al. Contribution of exhaled nitric oxide measurement in airway inflammation assessment in asthma. A position paper from the French Speaking Respiratory Society. Rev Mal Respir. 2015 Feb;32(2):193-215.

12.Price D, Berg J, Lindgren P. An economic evaluation of NIOX MINO airway inflammation monitor in the United Kingdom. Allergy. 2009 Mar;64(3):431-8.

13.Dragonieri S, Schot R, Mertens BJ, et al. An electronic nose in the discrimination of patients with asthma and controls. J Allergy Clin Immunol. 2007 Oct;120(4):856-62.

14.Montuschi P, Santonico M, Mondino C, et al. Diagnostic performance of an electronic nose, fractional exhaled nitric oxide, and lung function testing in asthma. Chest. 2010 Apr;137(4):790-6.

15.Vander Schee M P et al. Predicting steroid responsiveness in patients with asthma using exhaled breathing profiling. Clin Exp Allergy. 2013; 43 (11): 1217-1225.

16.Olopade CO et al. exhaled pentane levels in acute asthma. Chest 1997; 111(4): 862-865

17.Fens N, de Nijs SB, Peters S, et al. Exhaled air molecular profiling in relation to inflammatory subtype and activity in COPD. Eur Respir J. 2011 Dec;38(6):1301-9.

18.US Department of Defense. Technology readiness assessment (TRA). Washington, DC: Department of Defense; 2009.

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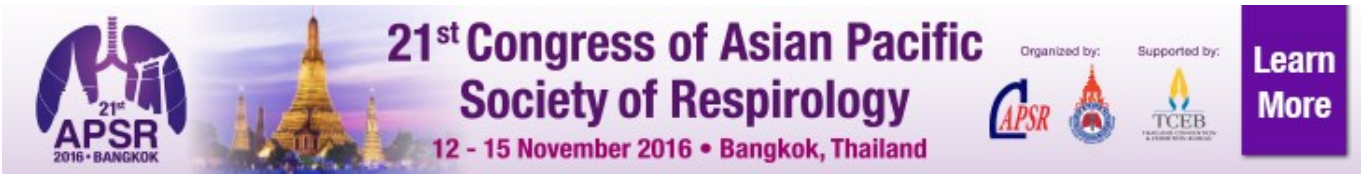

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