MGC DIAGNOSTICS®

medisoft®
CARDIO-RESPIRATORY INSTRUMENTATION

NEWSLETTER
Volume # 1
SPECIAL EDITION

WELCOME

We are proud to introduce the first volume of the MGC Diagnostic Newletter! We hope that this bulletin will be a helpful and informative resource regarding some hot topics in the cardiorespiratory field.

Also In This Special Asthma Management Issue:

LUNG FUNCTION TESTING TOOL BOX

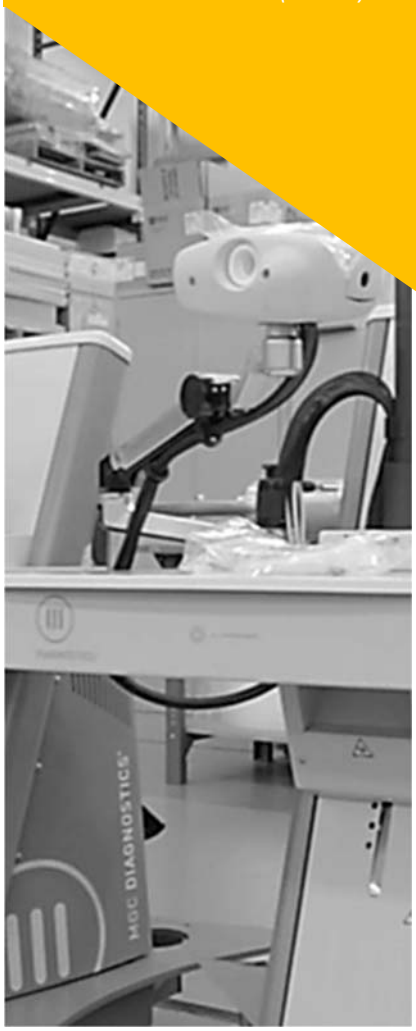
Spring has returned, and while most of us look forward to pleasant weather, beautiful flower blossoms and increased time outdoors, it can also be problematic for those who suffer from asthma.

> CONTINUE READING ON PG. 4

CHANGES TO BRONCHIAL CHALLENGE TESTING

In 2017, new ERS Standards regarding bronchial challenge testing, focusing on methacholine challenge tests were released. There are three notable changes from prior recommendations.

> CONTINUE READING ON PG. 6



BEYOND THE METHACHOLINE TEST

Airway hyperresponsiveness (AHR) has been found associated with clinical symptoms of asthma, such as chronic cough, wheezing and bronchospasm, however AHR is not specific for asthma.

CONTINUE READING ON PG. 10

THE FUTURE OF DIAGNOSTICS

EDITORIAL

I am delighted to introduce the first volume of the MGC Diagnostics newsletter. We intend to make this a regular publication to keep you in touch with news and developments related to Cardio Respiratory Science.

Beginning in 2012, MGC Diagnostics was created by combining Medical Graphics Corporation and Medisoft SA. Both companies, founded in 1977, have longstanding histories as innovative developers of Pulmonary Function, Gas Exchange and Metabolic diagnostic devices. Our Medical Graphics group, based in St. Paul, Minnesota, manufactures product predominantly for North America with strong distribution partners in the United Kingdom, Australia, France, Spain, Hong Kong, China and throughout Latin America. The Medisoft Group is located in Sorinnes, Belgium, manufactures and distributes product worldwide including the United States, Canada, Australia, the Middle East and Asia, with a predominant footprint in its home markets of France and Belgium.

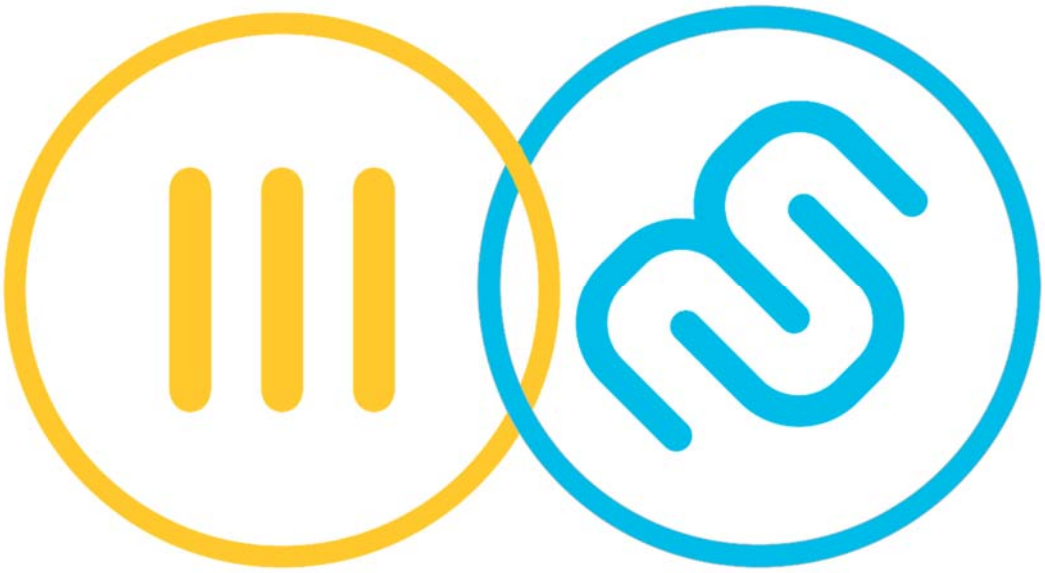
I am proud to lead what I believe is the best Cardio Respiratory Care Company in the industry. Our employees are passionate about providing customers the best instrumentation, support and education available. With more than 20% of our employees holding degrees in Pulmonary and Exercise Specialties, we take pride and value our strong relationships with clinicians utilizing our products and services. The remainder of our employees and global Business Partners are equally dedicated to Cardio Respiratory Diagnostics – focusing each day to 'Provide Unmatched Service and Support, Relentlessly Make Improvements and Anticipate and Solve Unmet Needs' – Because everyone who interacts with, uses or benefits from our Products is our Customer.

In this and future editions, we shall be reporting the newest academic and clinical highlights published by researchers focused on Cardio Respiratory Health. In addition, we will also highlight our diverse product solutions, highly specialized to identify, diagnose and monitor the management of our customer's ever-growing populations of patients with cardiorespiratory related disease.

I look forward to speaking with you each issue and ask that you provide your thoughts and feedback to assure we deliver a newsletter held to the quality that you expect. In the meantime, be sure to check out our websites (*www.mgcdiagnostics.com* and *www.medisoft.be*) and follow us on Twitter, YouTube and LinkedIn.

Sincerely,

Todd Austin BSc RRT-NPS RPFT
CEO MGC Diagnostics
taustin@mgcdiagnostics



SPRING IS HERE AND IT'S TIME TO PREPARE YOUR LUNG FUNCTION TESTING TOOL BOX

NN Le Dong

Medisoft Physiologist and Scientific Research

In the northern hemisphere, spring has returned. While most of us look forward to pleasant weather, beautiful flower blossoms and increased time outdoors, it can also be problematic for those who suffer from asthma.

Seasonal pollens and other outdoor risks may result in airway inflammation and worsen underlying asthma. The allergic asthma is a frequent form of hypersensitive reaction. It is estimated that about 1/4 of subjects who are sensitive to pollens also present allergic asthma. The Asthma and Allergy Foundation of America (AAFA) estimated that most asthmatic patients (60% of adults and 80% of children) have their disease triggered by allergies. In Europe, seasonal impact on asthma exacerbation varied from 47% in Sweden to 86% in Spain. In the US, about 2 million adults and 6 million children experience seasonal allergies.

Although typically the spring season is not associated with extreme weather conditions as is the case in winter and summer, the unpredictable fluctuation in temperature and humidity in the springtime period is still a risk for asthmatic patients. In most patients, exposure to pollens provoke mild symptoms of rhinitis, however the pathological effect could be more severe in those who present nonspecific bronchial hyperresponsiveness. Simulmtaneous exposure to pollens and air pollution (ozone and diesel exhaust) may trigger symptoms and increase the risk of exacerbation in patients with asthma and allergies. In his study in Detroit (Michigan, US), Mireku and collaborators (2009) found that a 10°F (+/- 5°C) increase in temperature would be associated with 2 additional emergency room visits due to asthma

exacerbation in children. Previous studies showed that the asthma related hospitalization, exacerbations and medication uses were closely correlated with pollen counts. Pollen counts peak in the spring, while warming weather and humidity may contribute to the worsening of asthma condition. Exercise-induced asthma is also a risk for those who are eager to get outdoors for physical activities as the weather becomes more pleasant.

Regular spirometry check-ups could help to improve asthma control and prevent exacerbations.

Beside the preventive strategies, a healthcare visit with pulmonology and allergy specialists before the pollen season is a good idea. A confirmation of persistent inflammations and allergies with bronchial hyperresponsiveness or skin test, regular spirometry check-up monitoring the ventilatory function and airway inflammation with spirometry, FOT or exhaled NO assessments, adjusting the asthma treatment plan with additional immunotherapy, could help to improve the asthma control and prevent the exacerbations in those patients. It has been shown that the allergen immunotherapies (AIT) may have a protective effect against the exacerbation risk during springtime period (**Figure 1**).

Though the efficacy of AIT measured on lung function was not conclusive, the bronchial challenge test, particularly by indirect stimuli or specific allergens, could be useful to detect the patients susceptive for AIT and evaluate their response to treatment. It has been found that nonspecific Bronchial Hyper-Responsiveness (BHR) activity increases with pollens allergy during pollination periods. The bronchial provocation test has also been included among the diagnostic tools in allergy departments, by a rational that this method allows for identifying new allergens for which skin or blood testing are not validated, or when skin tests are unreliable.

This special issue of the MGCD-Medisoft newsletter has been compiled to provide the reader the essential technical and clinical aspects of three pulmonary function testing techniques: bronchial provocation test, forced oscillometry and exhaled nitric oxide analysis with applications in asthma.

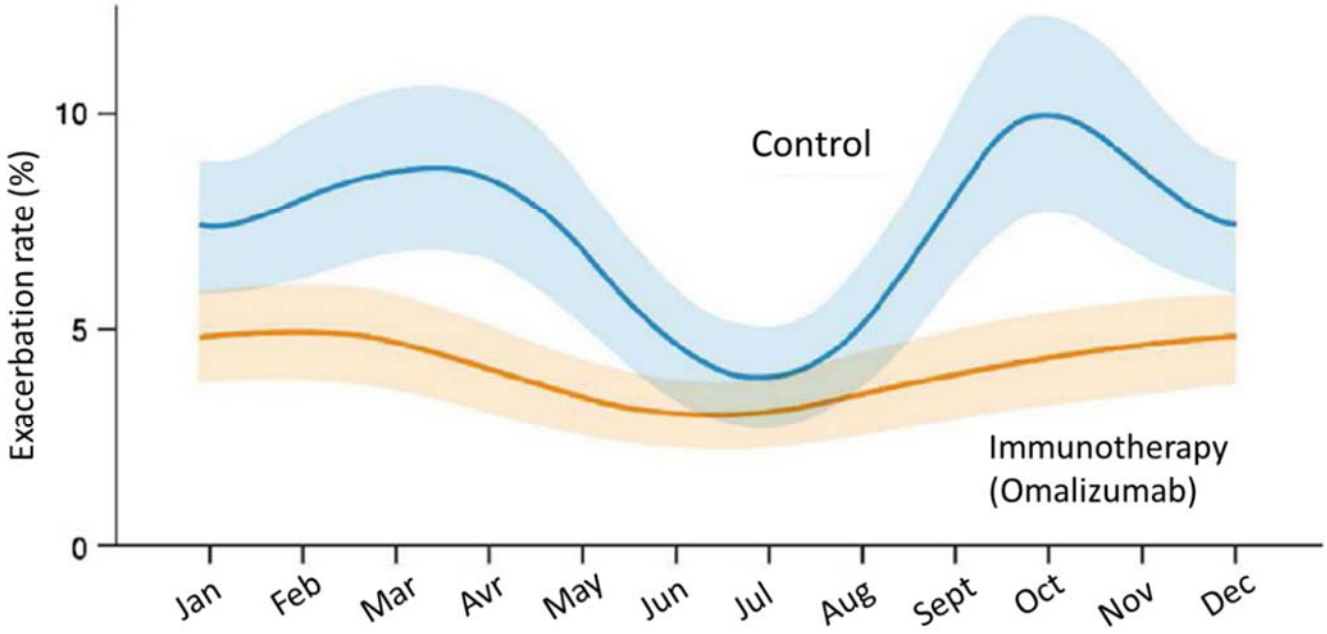
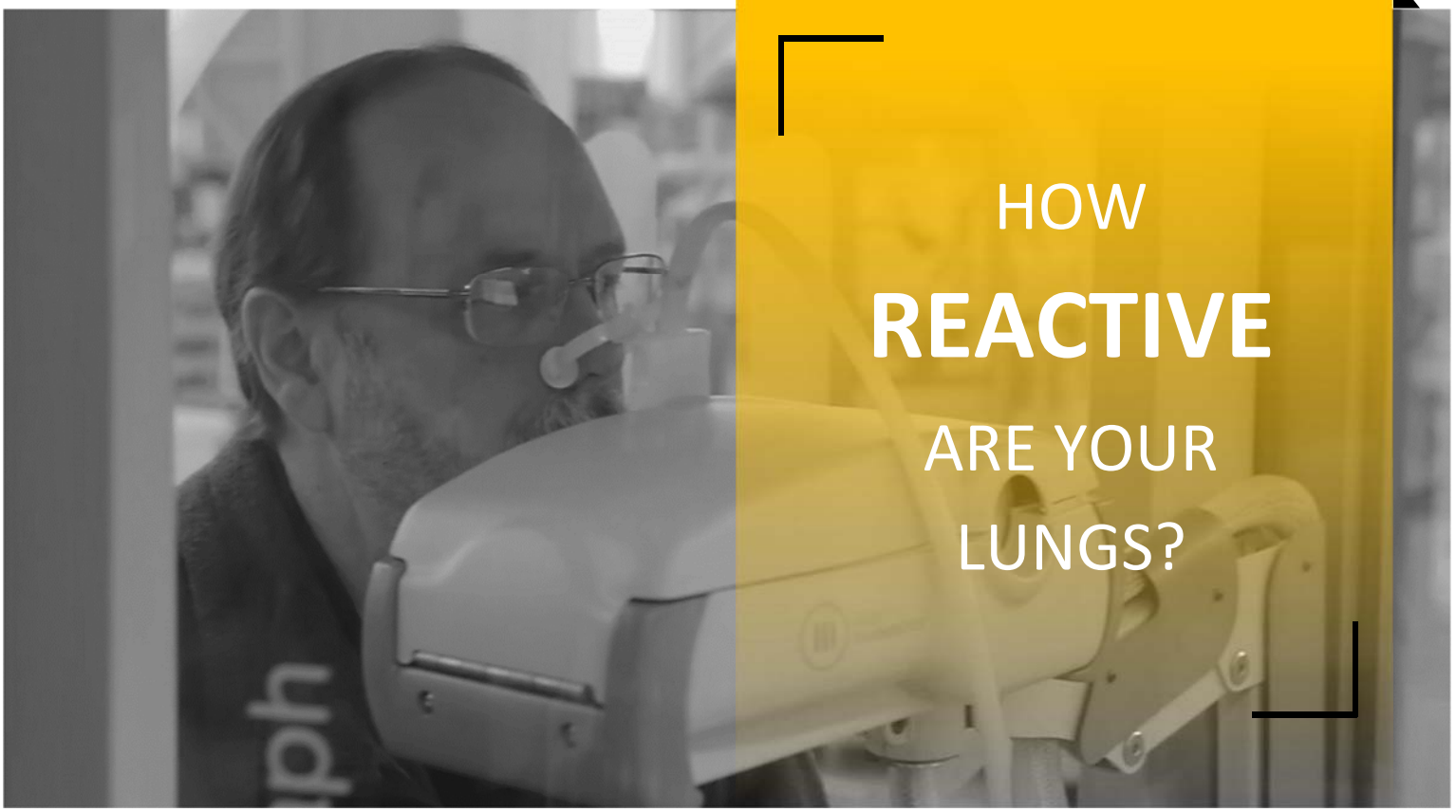


Figure 1: *Asthma exacerbation rate and beneficial effect of immunotherapy during a one year follow-up (Busse WW et al., N Eng J Med 2011;364:1005-15).*



BRONCHIAL CHALLENGE TESTING

CHANGES TO THE TECHNICAL STANDARD ON METHACHOLINE

R. Cook
Global Group Product Director

Introduction

In 2017, the European Respiratory Society (ERS) released the latest technical standard on bronchial challenge testing, focusing on methacholine challenge tests. The ERS and the American Thoracic Society (ATS) created a joint task force to update the previous publications concerning bronchial challenge testing. Because the timeline to complete this project exceeded the timeline for ATS support, the guidelines were "completed under ERS sponsorship, but with the participation of the full international panel." Even though the document was released as an ERS technical standard, it has been endorsed by the ATS.

While all aspects of testing are discussed, the changes to previous guidelines (1999) will be highlighted here.

The ERS cited the "notable" changes from prior recommendations as:

1. Base test results on provocative dose (PD20) rather than provocative concentration (PC20)
2. Inhalation of methacholine by tidal breathing
3. Using a breath-actuated or continuous nebulizer for 1 minute, or by a dosimeter with a suitable breath count

Provocative Dose (PD20)

The methacholine challenge test is designed to give increasing concentrations of methacholine until the subject has a response to the drug, or until you reach the end of the protocol if the subject has no response. The end point of the challenge test is to document

where a fall of at least 20% or more of the FEV1 from baseline occurs.

1999 ATS guidelines outlined the use of Methacholine concentration to define the fall of 20% of FEV1 (PC20). A PC20 of > 16 mg/ml was considered a normal bronchial response, less than 16 were graded as borderline, mild or moderate responses. The new 2017 ERS standards recommend to use the dose from each stage to calculate PD20, and interpret the results based on this value. The reason is that using the concentration method required a tight specification of delivery device, implying that this was difficult to do.

However, the calculation of the dose for each stage became more difficult and obscure. With the dose at each stage related to the concentration of the solution administered, the ERS published a way of calculating the dose based on four variables: concentration, nebulizer output, % droplets < 5µm, and the time of nebulization.

The concentration used at each stage is based upon a dilution method. The ERS standard has a dilution schedule (**Table 1**) for preparing the methacholine solutions.

Based on the nebulizer output, a final stage using 16 mg/ml may not be required as this can produce a dose far in excess of 400 µg. Essentially, any challenge test that goes above 400 µg, and the FEV1 does not fall by at least 20%, is considered normal based on **Table 2**. If the subject has a 20% fall in FEV1 at a dose less than 400 µg, then the interpretation of that test is outlined in the table.

Label strength	Take	Add NaCl (0.9%)	Obtain dilution
Example of a dilution schedule for quadrupling concentrations			
100 mg	100 mg	6.25 mL	A: 16 $mg \cdot mL^{-1}$
	3 mL of dilution A	9 mL	B: 4 $mg \cdot mL^{-1}$
	3 mL of dilution B	9 mL	C: 1 $mg \cdot mL^{-1}$
	3 mL of dilution C	9 mL	D: 0.25 $mg \cdot mL^{-1}$
	3 mL of dilution D	9 mL	E: 0.0625 $mg \cdot mL^{-1}$
	3 mL of dilution E	9 mL	F: 0.015625 $mg \cdot mL^{-1}$
Example of a dilution schedule for doubling doses			
100 mg	100 mg	6.25 mL	A: 16 $mg \cdot mL^{-1}$
	3 mL of dilution A	3 mL	B: 8 $mg \cdot mL^{-1}$
	3 mL of dilution B	3 mL	C: 4 $mg \cdot mL^{-1}$
	3 mL of dilution C	3 mL	D: 2 $mg \cdot mL^{-1}$
	3 mL of dilution D	3 mL	E: 1 $mg \cdot mL^{-1}$
	3 mL of dilution E	3 mL	F: 0.5 $mg \cdot mL^{-1}$
	3 mL of dilution F	3 mL	G: 0.25 $mg \cdot mL^{-1}$
	3 mL of dilution G	3 mL	H: 0.125 $mg \cdot mL^{-1}$
	3 mL of dilution H	3 mL	I: 0.0625 $mg \cdot mL^{-1}$
	3 mL of dilution I	3 mL	J: 0.03125 $mg \cdot mL^{-1}$

Using a 100-mg vial of methacholine and NaCl (0.9%) for diluent, the table shows the range of concentrations available to produce appropriate dose steps using examples of dilutions with quadrupling and doubling increases. If necessary, alternative concentrations can be produced from a different initial dilution step. For example, adding 5 mL of diluent to 100 mg methacholine would produce dilution A of 20 $mg \cdot mL^{-1}$ and adding 8.3 mL of diluent to 100 mg methacholine would produce dilution A of 12 $mg \cdot mL^{-1}$.

Table 1: *Dilution schedules for preparing methacholine solutions – 2017 ERS technical standard*

PD_{20} µmol (µg)	PC_{20} mg·mL^{-1}	Interpretation
>2 (>400)	>16	Normal
0.5–2.0 (100–400)	4–16	Borderline AHR
0.13–0.5 (25–100)	1–4	Mild AHR
0.03–0.13 (6–25)	0.25–1	Moderate AHR
<0.03 (<6)	<0.25	Marked AHR

PD_{20}: provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV_1); PC_{20}: provocative concentration causing a 20% fall in FEV_1; AHR: airway hyperresponsiveness. Information from [3].

Table 2: *Categorization of airway response to methacholine – 2017 ERS technical standard*

The PD20 value is then calculated:

$$PD20 = antilog[log\ D1 + ((log\ D2 - log\ D1)(20 - R1))/R2 - R1)]$$

D1 = second-to-last methacholine dose (dose preceding D2)
D2 = final dose of methacholine (dose resulting in a 20% or greater fall in FEV1)
R1 = percent fall in FEV1 after D1
R2 = percent fall in FEV1 after D2

Note: Because the equation above uses the log of dose, if D1 is the diluent stage, the dose is zero and the PD value cannot be calculated as the log of zero is an undefined number.

Dosing

The ERS recommends a starting dose of 1-3 µg with subsequent doubling or quadrupling of this initial concentration in the next stages. Doubling concentration protocols are recommended for research while quadrupling concentration protocols are recommended for clinical testing. The goal of designing the protocol used is to be able to deliver a dose ≥ 400 µg, but no greater than 800 µg. If the last stage in the protocol has a dose ≥ 400 µg, additional stages are unnecessary since a dose of 400 µg and a fall of less than 20% of FEV1 is considered a normal response.

After obtaining Pre-FVC efforts, the ERS recommends a diluent stage before delivering the methacholine concentrations in order to ensure there is no excessive Airway Hyper-Responsiveness. The diluent stage also gives the opportunity for the subject to learn the technique of inhaling from the nebulizer and practice performing spirometry. While only 1% of subjects responded to the diluent with a ≥ 20% fall in FEV1, a ≥ 10% change occurred in 5.8% of the subjects. Performing the diluent stage allows the technician to evaluate the subject prior to giving methacholine. If a large decrease in FEV1 after diluent occurs, the subject may be considered to be too unstable to continue and the test should be either rescheduled or cancelled. The diluent stage is then the stage to which all subsequent stages are compared to. After the delivery of the diluent or methacholine at each stage, FVC efforts are measured where a fall of a at 30 and 90 seconds after the nebulization is complete. For efforts after the diluent stage, a full FVC procedure is not required. Since a change in FEV1 from post-diluent value is the primary outcome measure, obtaining only an

acceptable quality FEV1 with each effort is required.

Tidal Breathing

The previous guidelines recommended that the subject inhale deeply to TLC and hold their breath for 5 seconds when using the 5 breaths dosimeter technique. This deep breath method is discouraged because the bronchoprotective (bronchodilator) effect reduces the sensitivity of the test. However, the ERS states that the effect is seen in normal subjects and mild asthmatics, but is lost with more severe disease. Regardless of the method for inhaling methacholine, dosimeter or time-based nebulizer, it's recommended that normal tidal breathing should be used by the subject.

The time duration or number of breaths for the tidal breathing is dependent on the nebulizer used. The previous recommendation for tidal breathing was 2 minutes while the ERS currently recommends tidal breathing for at least 1 minute. However, the length of tidal breathing or number of breaths at each stage will be greatly influenced by the performance characteristics of the nebulizer itself. In case of high output nebulizer, the tidal breathing time or counts could be reduced, and conversely for low output nebulizers.

Summary

The 2017 ERS technical standard has clarified and expanded on several points from the 1999 methacholine guidelines. The biggest challenge for the technician however, is to obtain a suitable nebulizer for delivering the methacholine and developing a protocol that follows the dosing schedules outlined by the ERS. Each type of nebulizer will dictate how to set up the dosing schedule and the amount of time the subject tidal breathes at each stage of the protocol. By not making this more specific, each facility must take steps to reduce potential errors and reduce the differences from one lab to another.

Each facility must develop a protocol to reduce potential errors and reduce the differences from one lab to another.

AIRWAY HYPER-RESPONSIVENESS

BEYOND THE METHACHOLINE TEST

NN Le Dong

Medisoft Physiologist and Scientific Research

Airway hyperresponsiveness (AHR) is defined as an excessive bronchoconstriction in response to a low stimulation with direct or indirect agents. AHR consists of one of the key physio-pathological features of asthma. AHR has been found associated with clinical symptoms of asthma, such as chronic cough, wheezing and bronchospasm, especially after physical efforts, allergen exposures or infections. However, AHR is not specific for asthma, as it could also present in allergic rhinitis, COPD, cystic fibrosis, respiratory infection or beta-blocker users.

The components of AHR have been hypothetically sub-categorized into persistent and variable factors. The persistent factors contribute to the airway structural changes, including the hypertrophy of bronchial smooth muscles and membrane thickening, observed in more severe patients. The variable aspect of AHR is associated with a persistent airway inflammation, which are variable and dependent on many conditional factors such as respiratory infections, exposure to allergens or air pollution, and responding to anti-inflammatory treatments. However, the AHR manifestation reflects either cumulative and synergistic processes within the airway, as the result of a multifactorial mechanism.

In clinical practice, AHR is evaluated in PFT laboratories by bronchial provocation tests (also known as bronchial challenge). The technique aims to establish a dose-response curve of the PFT outcomes (FEV1, FVC, airway resistance, conductance or reactance…) under a progressive stimulation.

As the AHR is multifactorial, different testing methods have been developed to better understand the underlying mechanisms and to suggest the appropriate treatments. The bronchoconstrictor stimuli could be classified into two types: direct or indirect, according to the dominant mechanism that provokes the airflow limitation (there may be an overlap, such as the histamine presents both direct and indirect effects).

Bronchial challenge test using direct stimuli such as methacholine, carbachol or histamine provoke bronchoconstriction by acting directly and primarily on the airway smooth muscle cells, mucous glands and microvasculature. Methacholine (acetyl-b-methylcholine chloride) is the most frequently used for direct challenge. It's a synthetic derivative of acetylcholine that specifically effects the muscarinic receptors while histamine binds to H1 receptors.

By contrast, the response to indirect stimulators is associated with the activation of inflammatory or neuronal pathways, and consecutive impacts of their intermediary messengers on the airway smooth muscle. Unlike the direct method, most of indirect provocation tests implied physical stimuli (exercise, cool air, hyperventilation, hypertonic saline or mannitol) instead of pharmaceutical agents. These physical effects include a dehydration within the airway, thus provoking physiological effects such as transient edema of the bronchial wall, hyper-osmilarity of periciliary fluid or abnormal response of microvascular structures. These effects will stimulate both neural and inflammatory pathways, such as mast cells degranulation, release of inflammatory

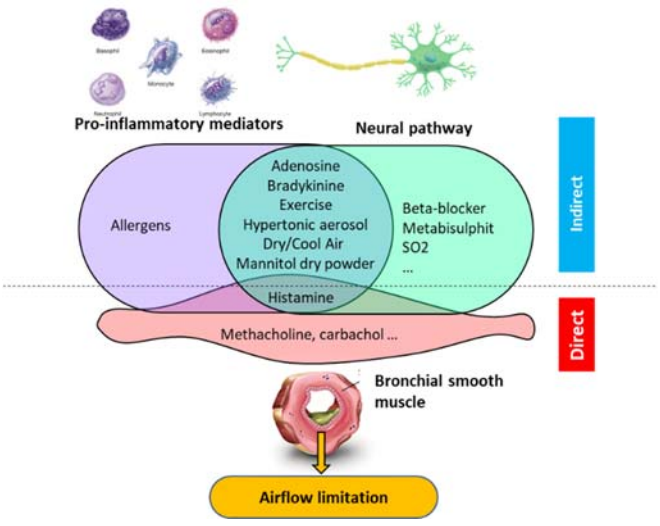


Figure 2: *Some direct and indirect bronchoconstrictor stimuli.*

mediators such as histamine, prostaglandin D2 and leukotrienes to develop a bronchospasm.

The direct provocation tests require a relatively low dose of stimuli with a possibility of extending the administered dose limit. AHRs to methacholine and histamine are considered equivalent as they are strongly correlated. Direct provocation tests are highly sensitive in excluding asthma (rule-out) but relatively not asthma-specific due to the fact that AHR is not specific to asthma. Therefore their results must be interpreted in combination with other clinical features.

The indirect challenges require a relatively higher dose of stimuli compared with methacholine. The physical challenges like exercise, eucapnic hyperpnea or dry air ventilation are dose limited, because it's impossible to extend the strength of stimulation beyond an individual limit. The indirect provocation tests are also dependent on the presence of inflammatory cells while the smooth muscles contribute less to a response.

In general, indirect challenges have higher sensitivity compared with methacholine provocation, therefore they function best to rule-in asthma. The indirect tests also show a greater usefulness than the direct tests in evaluation of the responses to treatment. Those tests are ideal for detecting exercise-induced and occupational asthma, or studying the response to inhaled corticosteroid therapy. Since 2010, dry powder mannitol has been approved by FDA (U.S. Food and Drug Administration) for testing AHR in subjects above 6 years old. This method presents more advantages over the direct challenges, including the ability to reflect both airway inflammation and AHR features in astham. It's presumed that the direct provocation tests likely reflect the presistent changes

in the airway structure, while the indirect techniques more likely explore the complex physio-pathological pathway in allergic and occupational asthma. Such distinct mechanisms between methacholine and indirect testing suggest a combined use of these two for asthma phenotyping. An amelioration of airway inflammation under inhaled corticosteroids, immunotherapy or following avoidance of indoor allergens would also be associated with a significant improvement in the results of indirect challenge, in contrast to the lack of change in methacholine test.

As the bronchial reactivity to indirect stimuli correlates better with the airway inflammation, indirect tests could be used to guide adjustment of corticosteroid treatment and asthma control monitoring. In addition, indirect AHR may have more advantages than other biomarkers such as FeNO, as they also cover non-eosinophilic inflammations. However, it was found that higher ICS doses are required to affect AHR outcome compared to the necessary dose to achieve clinical effectiveness, suggesting that further studies are needed to verify the usefulness of indirect AHR as a tool for asthma therapeutic guidance. Characteristics and applications of direct and indirect provocation testing are summarized in **Table 3**:

	Indirect test	Direct test
Smooth muscle function	Weak association	Strong association
Airway caliber	Weak association	Strong association
Airway inflammation	Strong association	Weak association
Required dose	High	Low
Dose limitation	Yes	No
Sensitivity	High	Fair
Specificity	Low	High
Application	Phenotyping, detecting occupational or exercise induced asthma, treatment following up	Rule out

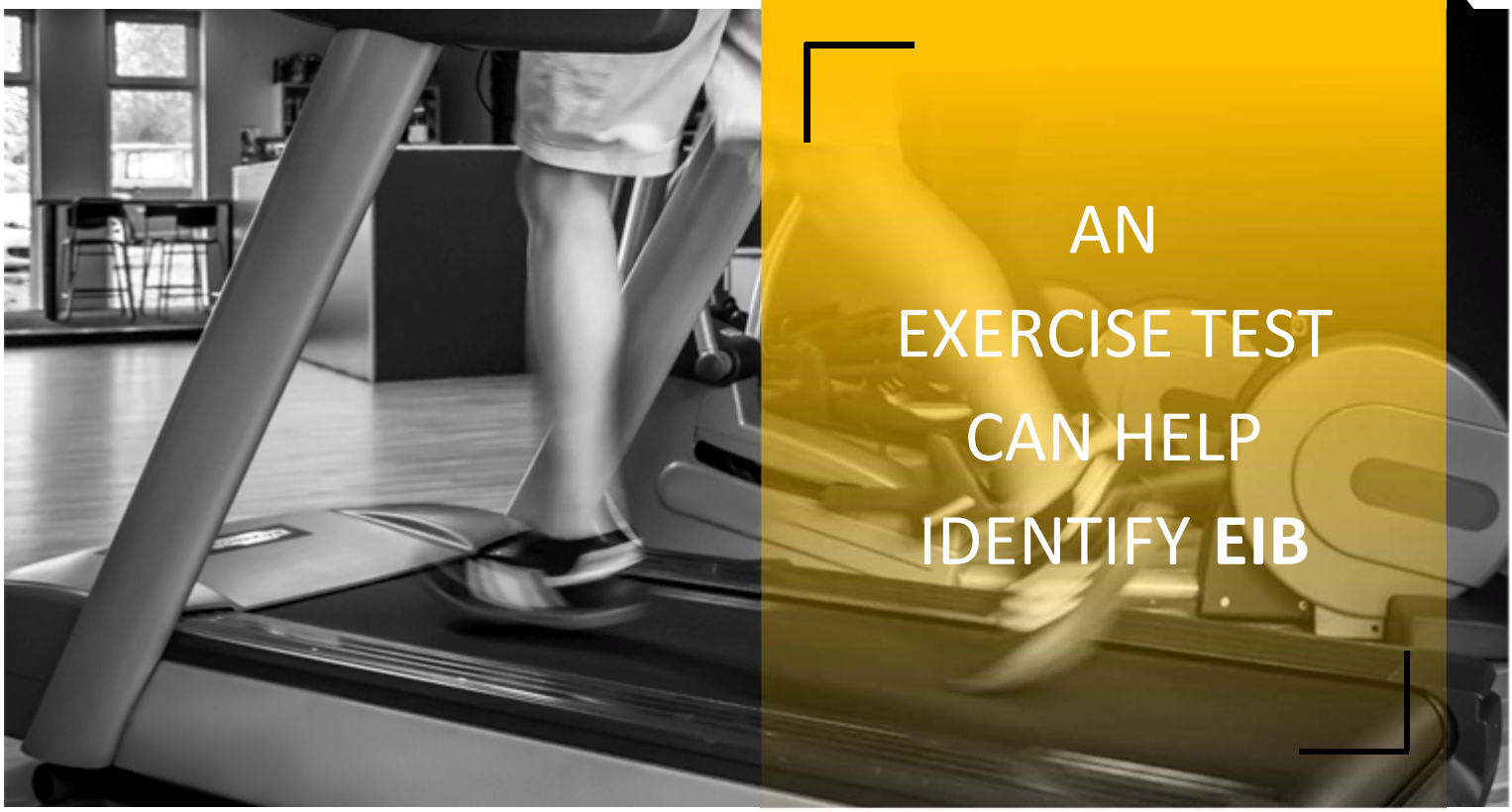
Table 3: *Characteristics and applications of direct and indirect provocation testing.*

The airway caliber plays an important role in determining positive diagnosis of direct AHR, however the provocation test is not limited to spirometry alone. A wide spectrum of PFT techniques could be used as the target outcome (see **Table 4**). Recent studies suggest that not only flow rate limitation, but ventilation heterogeneity may also contribute to the AHR, via both inflammatory and dynamic mechanisms. Physical modeling demonstrated that inhomogeneous ventilation and airway narrowing throughout the bronchial system might lead to an increase in airway resistance during a provocation. These findings support the use of small airway specific PFT markers, such as LCI, Scond in N2 washout or FOT. Despite a modest significance (up to 16% of common variability), the association between exhaled NO and AHR as reported in some studies may suggest a combination of FeNO and provocation test.

	Techniques and parameters							
	Spirometry		Plethysmography		FOT		Rint	SpO2
	FEV1	*FVC*	*sRaw*	*sGaw*	*Rsr*	*Xsr*		
Airway resistance	X		X	X				
Respiratory system resistance	X				X		X	
Airway closing and dynamic distension	X	X		X		X		
Ventilation/Perfusion mismatch								X

Table 4: *PFT techniques that could be used as endpoints in the evaluation of BHR.*
(Plantier L et al., Rev Mal Respir 2018;35:759-775).

In conclusion, AHR is a complex feature in asthma. The assessment of AHR is not simply limited to methacholine or forced spirometry, but implies multiple techniques and interesting questions for both clinicians and the lung function testing industry. Appropriate use of the provocation tests may provide useful information which contribute to clinical decision making in asthma.



EXERCISE CHALLENGE TESTING

FOR IDENTIFICATION OF EXERCISE-INDUCED BRONCHOCONSTRICTION (EIB)

D. Drumsta

Global Senior Product Manager – Gas Exchange

Exercise challenge testing for the objective assessment of exercise-induced bronchoconstriction (EIB) is a commonly used methodology for diagnosis. When this method is used in substitution of other surrogate testing, the ideal protocol will involve the use of a treadmill or cycle ergometer to achieve a rapid increase of ventilation. When possible, sports-specific exercise is used so the subject can be tested in the activity that elicits symptoms.

Per the technical standard on bronchial challenge testing produced by the European Respiratory Society in 2018, the exercise intensity is increased over a short time period of 2-3 minutes, and then maintained for an additional 6 minutes. The target ventilation achieved should be 60% of maximum (MVV or FEV1 x 40).

If heart rate measurement is possible during the test, the subject should also raise and maintain their heart rate above 85% of their age predicted max (220-age). The subject should avoid the use of asthma and anti-inflammatory medications, exposure to inhaled allergens, and exercise prior to the assessment as these may alter the response to the challenge test.

Post challenge FEV1 measurements are performed immediately after exercise, and then at 3, 6, 10, 15, and 30 minutes post exercise. Two acceptable FEV1 measurements within 0.15 L are recommended at each time point, with the most technically valid being used for reporting purposes. The severity of response may require more frequent measurements. The response is expressed as the percent fall in the lowest measured FEV1 (nadir), within 30 minutes post exercise, from the pre-exercise FEV1. The percent fall value of ≥ 10% is used to diagnose EIB. Severity can

Vigorous exercise, usually on a treadmill
Rapid increase in ventilation over the first 2–3 min to reach the target
Maintain target ventilation for ⩾4 min, preferably 6 min
Target ventilation is 60% of maximum (MVV or $FEV_1 \times 40$)
Heart rate of >85% of maximum can serve as a surrogate for ventilation target
Inspired air should be dry, and ambient temperature <25°C
Nose clips should be used during the exercise challenge
Serial assessments of spirometry for 30 min after exercise
Two spirometry manoeuvres are acceptable at each time point
Use the best technically valid FEV_1 at each time point
Frequent deep inspiration following exercise challenge may affect result

MVV: maximum voluntary ventilation; FEV_1: forced expiratory volume in 1 s.

Table 5: *Characteristics of hyperpnoea challenge tests – 2018 ERS technical standard*

be classified appropriately based on percent fall.

As mentioned, minimal ventilation and heart rate values must be achieved and maintained during the test. If a Cardio Pulmonary Exercise Test (CPET) system is available in the testing laboratory, the instrument and software application allow for the direct measurement of test subject ventilation, heart rate, and ergometer control. Most importantly, directly measuring the ventilation and heart rate during the exercise challenge can help to successfully diagnose the presence of EIB. Spirometry is also commonly available with CPET systems to measure pre/post FEV1 values. The software application controlling the CPET system provides the clinician reporting options, and ultimately efficient interpretation of the EIB test.

Opportunities for future research on EIB mechanisms and treatment options

A recent 2018 editorial, published in the European Respiratory Journal (Bonini et al., ERJ Open Res, 2018), discusses the need for further research regarding treatment options for the 5-20% of the general worldwide population effected by EIB.

The editorial cites a 5-year prospective study that noted a reduction, or in some cases a complete disappearance of symptoms related to EIB, in subjects that stopped exercising. Conversely, there is overwhelming evidence related to the overall health benefits associated with regular physical activity and exercise. Moderate exercise training has also been found to help to reduce airway inflammation and bronchial responsiveness in subjects with asthma. Considering this, the underlying question of how a specific individual be assessed for risk of EIB and treated based on the mechanism(s) that contribute to it, must be addressed.

The authors refer to recent discussions and literature surrounding different EIB endotypes, which are different subtypes of the condition. One emergent publication discussed in this editorial surrounds the mechanisms of EIB and biomarkers associated with these endotypes. In these cases, not only are widely accepted osmotic and thermal mechanisms discussed, but also epithelial sensitivity, neurogenic, and overall genetic susceptibility.

In summary, a better understanding of these different endotypes could greatly impact how individuals with EIB are managed and treated after diagnosis. This future research could allow for those affected by EIB to benefit from the positive effects that physical activity and exercise have on overall quality of life. Or, in the case of professional athletes, appropriately manage a condition that can have negative consequences in regards to their performance and success in their occupation.

EXHALED NITRIC OXIDE IN ASTHMA

AN UPDATE

NN Le Dong

Medisoft Physiologist and Scientific Research

It's been 28 years since the first detection of NO in exhaled breath by Gustafson et al., FeNO is becoming a popular method for the non-invasive evaluation of airway inflammation. The scientific impact of FeNO keeps growing, with an averaged publication rate of 23 articles per month in the last 10 years, most of them dedicated on clinical application of FeNO in asthma (**Figure 3**).

From a scientific point of view, the FeNO analysis should be classified as a breath analysis, along with other volatile organic compounds (VOCs) and exhaled biomarkers rather than a lung function test. However, as the FeNO measurement presents additional advantages compared to the traditional spirometry, this marker has been widely used beside lung function tests by healthcare practitioners in both clinical trial and daily practice. Recently, a partnership has been developed between Bedfont and MGC Diagnostics, like the previous cooperation between COSMED and Bosch Healthcare, showing a new trend of adding FeNO to the conventional lung function tests.

The discovery of increased FeNO in asthma in 1993 raised a new hope about a simple, non-invasive marker for both diagnosis and control of this disease. Fractioned NO in exhaled air is the only non-invasive and reliable marker allowing a daily monitoring of airway inflammation, which is a contributor in asthma and COPD exacerbations. In addition, as NO is conditioned by corticosteroid and eosinophilic inflammation, the FeNO test also supports the phenotyping of asthmatic patients (eosinophilic and T2 cells asthma endotypes) and provides the answers for other clinical problems (asthma control, optimized treatment by inhaled corticosteroids, …). In this view, FeNO would be the most successful volatile biomarker in the history. However, it has been realized later that FeNO alone cannot cover all the heterogenous aspects of asthma and should be used in combination with

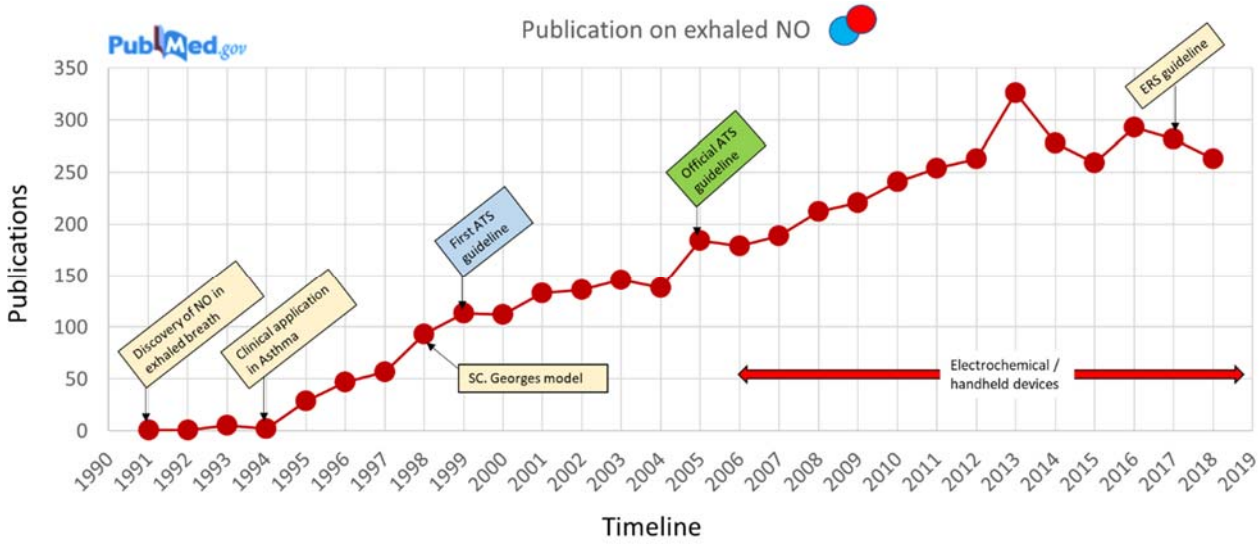


Figure 3: *Average publication of FeNO articles over the last 30 years – Data source: Pubmed.org*

other information (clinical symptoms, airflow limitation, bronchial hyperresponsiveness by spirometry or FOT) to confirm asthma diagnosis.

The latest meta-analytic studies also indicate the utility of FeNO to detect the asthmatic patients susceptive to treatment with ICs and/or having higher risks of asthma exacerbation. Evidences on the usefulness of FeNO in treatment tailoring are not conclusive. Even though the correlation between FeNO and asthma control is weak, incorporating FeNO to an asthma management plan would reduce the risk of exacerbation. However, this would not affect other outcomes such as hospitalization, quality of life or declined FEV1.

The most commonly performed FeNO test consists of the measurement at a single expiratory flow of 50mL.s-1 (FeNO50). This test would satisfy most clinical questions in asthma. The sampling maneuver and interpretation rules for FeNO50 have been well standardized by ATS (2005, 2011). Key factors to ensure the accuracy and reproducibility of FeNO50 test include an effective isolation of the lungs from upper airway by exhalation against buccal resistance at 5-15 cmH2O, control of expiratory flow rate at 50 ± 5 mL.s-1 for at least 6 seconds (4 seconds in children < 12 years old), and corresponding to an at least 3 seconds plateau of FeNO signal with a variability less than 10%.

Another testing mode is multi-compartment FeNO analysis. It consists of measuring FeNO at multiple expiratory flowrates. Several theoretical models were built in the period of 1998 to 2013, allowing to differentiate the anatomical sources of FeNO (bronchial or alveolar components). Despite being less popular than the standard mode, the multi-flow analysis may extend our knowledge about the NO exchange dynamic within the respiratory system and the physio-pathological role of NO in the distal airway inflammation. Only two analyzers still support the multi-flow measuring mode: Medisoft's FeNO+ and Ecomedic's CLD-88.

In clinical practice, the value of alveolar NO (CANO) can be estimated by analyzing the plateau of the curve of the signal measured FeNO to significant expiratory flow rates (> 250 mL.s-1). The CANO reflects the presence of NO not only in the alveolar air space (bronchial generations 19 to 23), but also from the distal airways (bronchial generations 16 to 23), thus including the bronchioles (generations 16 to 18) and the alveolar ducts (generations 19 to 22). The alveoli occupy a very special zone in the lungs, which contributes to gas exchange between inspired air and capillary blood. Therefore, the study of NO in the alveolar region could tell us not only the activities of NO biosynthesis, but also the physical properties of the alveolar tissues given the fact that the concentration of NO results from a balance between the production and alveolar-capillary diffusion of the gas.

Due to a high interest of this technique by both clinicians and medical equipment industry, FeNO analysis is a fast-expanding market with the participation of at least 6 available models (FeNO+, Niox-Vero, NObreath, FENOM-Pro, Vivatmo and CLD-88).

The early NO analysers were built on chemiluminescence technology (CLD-88, EndoNO), in which the NO molecules in gas sample are quantified from the electromagnetic radiation signal (photons) generated by the reaction between NO and ozone (O3). This technology is generally considered as "gold standard" with many advantages, including a high sensitivity (1 ppb) and very fast response time (0.5

sec.), allowing for real-time analysis. However, the chemiluminescence based instruments also represent some disadvantages: they have large size, heavy weight, high manufacturing and functioning costs, and require an external gas source for a frequent calibration. Those limitations have restricted the use of the FeNO test in routine practice or home-based monitoring.

The second generation of FeNO devices (FeNO+, Niox, NObreath, …) are based on an electrochemical NO sensor. These analyzers convert NO concentration into electrical signal via the catalyst within an electrochemical cell. They were first introduced around 2005 to 2007 and quickly became a favorite choice of many medical practitioners and pharmaceutical researchers. The electrochemical based NO analyzers came with a tradeoff between the utility and sensitivity. This technology allows for developing simpler; compact devices at lower cost but in exchange, we must accept some technical

FeNO analysis is a market that is expanding quickly.

drawbacks, such as slower response time and less sensitivity (typical detection threshold of 5 ppb), making the real-time analysis impossible.

Even though the FeNO test has been well standardized and is regularly updated by ATS and ERS taskforces, a lot of technical questions remain unclear and there is still a gap between ATS recommendations and daily practice. In brief, though the chemiluminescence is still the gold standard, the NO analyzer market has been over taken by the electrochemical technology since 2010. The only available chemiluminescence based device is the CLD-88 by Ecomedics. Most of the inter-device comparative studies revealed disagreement at different levels among the electrochemical devices, however none of these studies could verify the most important question about the validity of the ATS's criteria of FeNO steady state on electrochemical devices and how we could ensure the ATS's sampling protocol without real time FeNO signal monitoring?

For the economic aspect, the FeNO measurement has been demonstrated to have beneficial impact on the healthcare cost, by reducing the costs related to the diagnosis of asthma and treatment of exacerbation. However, the FeNO exam is currently reimbursed in the US and many European countries, but unfortunately not all.

In conclusion, the last 10 years have witnessed a remarkable growth of the FeNO analyzers market. The clinical value of exhaled NO measurement in asthma is becoming clearer. The usefulness of FeNO as a non-invasive marker of airway inflammation is widely recognized. The introduction of electrochemical technology has significantly improved both scientific impact and clinical utility of the FeNO test. More effective collaborations between the medical communities and medical device industry are needed to achieve the best solution for the questions related to technology and clinical benefits of this technique.

FORCED OSCILLATION TECHNIQUE

CLINICAL AND TECHNICAL ADVANCES

R. Perissin

Vice President, Worldwide FOT and Asthma Management Business Development

The Forced Oscillation Technique (FOT) is a increasingly popular technique worldwide for asthma management. This is successful due to the growing number of publications and the relevance of clinical evidences. The basic principle superimposes an oscillating pressure waveform, typically generated by a loudspeaker during normal tidal breathing. This gentle "force" is transmitted on to the patient airway at different frequencies, with the lowest frequency reaching the small, peripheral airways, and the higher frequencies to larger, central airways and provides additional information about mechanical properties of the lungs.

The lung's structural and mechanical properties react to this external, oscillating, multi-frequency pressure allowing the device to measure the real-time Impedance (Zrs) of the lung and its components: Resistance (Rrs) and Reactance (Xrs), which represents how air flows in and out of the lungs.

This specific FOT technique allows airways assessment Rrs and Xrs via a 'within-breath' analysis at rest and over different frequencies. Therefore, FOT determines on both inspiratory and expiratory cycles: location of airways obstruction, expiratory flow limitation at rest, quantitative assessment when compared to normative data, reversibility of the airflow obstruction and hypersensitivity of the airway.

Central and Peripheral Components of Airway Obstruction

Resistance (Rrs) provides information reflecting the degree of airways obstruction, comparable to FEV1, but measured at rest during normal tidal breathing. Rrs reflects central airways obstruction and can be measured at different oscillating frequencies. If Rrs decreases at higher frequency ("frequency dependent"), it is indicative of heterogeneous (mixed) obstruction.

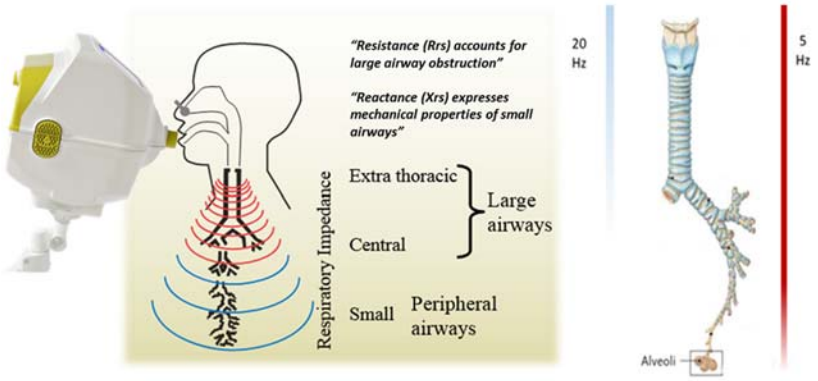


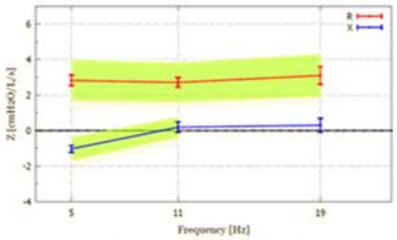
Figure 4: *The Resmon™ PRO FULL FOT System from MGC Diagnostics and Medisoft*

Reactance (Xrs) enables the clinician to determine how effectively the deep (peripheral) lung is ventilated. Changes in peripheral obstruction and/or airway compliance may affect Xrs, similar to FEF50-75. Xrs falls below predicted values at low oscillating frequencies in conditions such as peripheral obstruction, tidal expiratory flow limitation, alveolar gas trapping and chest wall restrictions (i.e. obesity, kyphoscoliosis, pregnancy, etc).

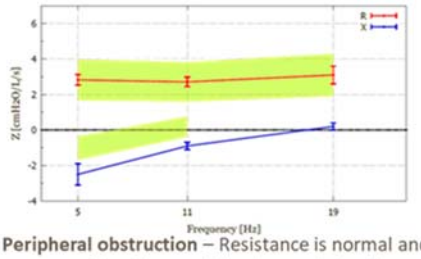
Resistance (Rrs) and Reactance (Xrs) measured "within breath" over different frequencies (5-11-19Hz) should be looked at together to localize the obstruction as peripheral or central. Furthermore, Resistance and Reactance are both reported as inspiratory, expiratory and total components.

The literature demonstrates that improvement in traditional FOT indices after bronchodilator may be variable. This is particularly true if the patient has expiratory flow limitations. EFL is consecutive to the choke point generated by intrinsic increase of the alveolar pressure at rest in very obstructive lung disease. Conversely, inspiratory resistances are not concerned by the check point, because of the inflating effect of the lungs. Thenforth, inspiratory Rrs are the most sensitive to bronchodilators and provide a sensitive index of bronchial reversibility.

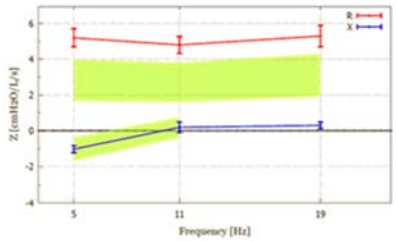
In conclusion, in front of a patient with expiratory flow limitations, the dilator effect must be observed with the inspiratory Rrs, but not with the expiratory Rrs or the whole Rrs of the lung.



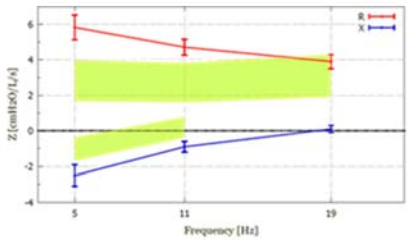
Normal – Both resistance (Rrs) and reactance (Xrs) are within the normal range



Peripheral obstruction – Resistance is normal and reactance more negative (i.e. possible airway obstruction, excluded alveoli, inhomogeneity of ventilation, or possible restriction)



Central obstruction – Resistance is increased and reactance is within the normal range (i.e, diseases affecting central airways)



Severe obstructive – Both resistance and reactance are outside the normal ranges and resistance is frequency dependent (i.e, severe asthma, severe COPD)

Figure 5: *Typical Clinical Cases of Resmon PRO FULL FOT System Tests*

Bronchial Challenge Testing With the Resmon PRO FULL

Due to its simplicity, the Resmon PRO FULL test is a much faster procedure requiring simply a set of accepted tidal breathing breaths to perform a bronchial challenge test observing the increase of resistance (Rrs) from the baseline. With the traditional method, as per ATS/ERS guidelines, 3 reproducible forced spirometry efforts at baseline and at every bronchial constriction level are required, until a drop of the FEV1 of at least 20% from the reference is observed or the maximal dose of the bronchoconstrictor agent is administered to the subject.

Therefore, based on the threshold above, the physician could use a softer, for a more conservative, approach and stop the test at 35% of increase of Rrs from baseline to a more aggressive at 50%, according to his/her experience as well as from the patient condition, only and exclusively at the physician discretion and responsibility.

Figure 6 is an example using a "balanced" threshold of 45% of increase, INSP Rrs at 5Hz.

	Population ages	Parameter	Threshold
ERS recommendations on FOT equipment	All intended	Rrs, lowest available frequencies	**35-50%**
Official ATS/ERS Statement: PFT in preschool children	< 6 years old	Rrs, low frequencies	**35-40%**

Table 6: *Thresholds for Positive Response for Bronchial Challenge Testing in FOT*

Set the response Threshold		45%
Cumulative DOSE (mg/mL)	**Rinsp 5 hz (cmH20/L*s)**	**%Baseline Change**
Baseline	1,8	-
2	1,9	6%
6	2,2	22%
14	2,4	33%
30	2,5	39%
62	3,0	67%
Post- BD	1,9	6%
PD45	*37,04*	

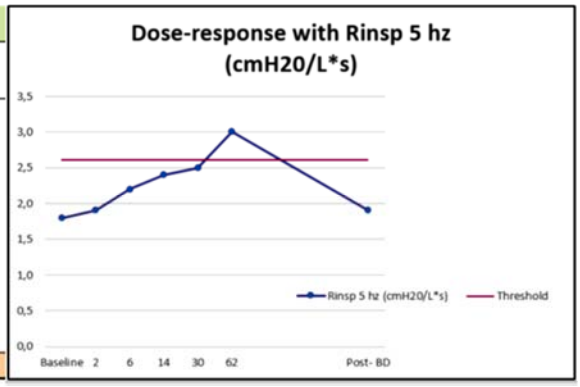


Figure 6: *Example of Bronchial Challenge FOT Test on Resmon PRO FULL FOT System*

Comparing Forced Spirometry vs. Forced Oscillation Technique

FORCED SPIROMETRY

- Forced spirometry can classify severity (mild, moderate, severe) of disease with FEV1/FVC (GOLD, GINA guidelines and ATS/ERS statement).
- Flow volume loop cannot accurately estimate the site of airflow obstruction (large or small airways) and hence the presence and extent of small airways disease.
- To confirm a diagnosis of restriction both requires a static lung volumes test.
- Flow volume loop requires repeated, forced and prolonged expiratory maneuvers, which may be difficult, particularly when ill.
- Forced Spirometry is rather insensitive to mild disease and doesn't have an optimal correlation with symptoms.
- Quality of the test is under the operator and patient dependency.
- Requires 3 repeatable maneuvers to meet ATS/ERS criteria.
- The forced expiration needs a preceding deep inhalation.

FOT

- FOT has not been approved but clinical studies are underway.
- FOT localizes the site of airflow limitation to large or small airways, assesses the extent of small airways disease, which may help the choice of inhaled medication, prescribed.
- To confirm a diagnosis of restriction both requires a static lung volumes test.
- The FOT needs only a several accepted breaths tidal breathing test and no deep inhalation.
- FOT has been shown to be more sensitive than spirometry in detecting mild disease even when not present in flow volume loop.p.
- Very little or no dependence from operator or patient.
- Less time consuming because of only some accepted breaths required.
- Only tidal breathing is required.

GET IN TOUCH

MGC DIAGNOSTICS CORPORATION

through it's subsidiaries Medical Graphics Corporation and Medisoft SA

US HEADQUARTERS
350 Oak Grove Parkway
Saint Paul, MN 55127-8599
www.mgcdiagnostics.com

EUROPE OFFICE – MEDISOFT
P.A.E de Sorinnes,
1 Route de la Voie Cuivrée
5503 Sorinnes
BELGIUM
www.medisoft.be

Newsletter Contact:

Sébastien Giot
Clinical and Product Specialist
sgiot@mgcdiagnostics.com