Beyond the Lungs: Utility of Exhaled Breath in the Diagnosis and Monitoring of Systemic Diseases

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Interpretation of Exhaled Nitric Oxide Levels ($F_{ENO}$) for Clinical Applications: an official ATS Clinical Practice Guideline

Raed A. Dweik (Chair) (1, 2), Peter B. Boggs (3), Serpil C. Erzurum (1, 2), Charles G. Irvin (4), Margaret W. Leigh (5), Jon O. Lundberg (6), Anna-Carol Olin (7), Alan L. Plummer (8), D. Robin Taylor (9)


Revised: Fall 2009, ..., Fall 2010

ATS Board of Directors: Spring 2011

12 May 2011
An Official ATS Clinical Practice Guideline: Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications

Raed A. Dweik, Peter B. Boggs, Serpil C. Erzurum, Charles G. Irvin, Margaret W. Leigh, Jon O. Lundberg, Anna-Carin Olin, Alan L. Plummer, D. Robin Taylor, on behalf of the American Thoracic Society Committee on Interpretation of Exhaled Nitric Oxide Levels (FeNO) for Clinical Applications

This Official Clinical Practice Guideline of the American Thoracic Society (ATS) was approved by the ATS Board Of Directors, May 2011

- We recommend the use of FeNO in the diagnosis of eosinophilic airway inflammation (strong recommendation, moderate quality of evidence).
- We recommend the use of FeNO in determining the likelihood of steroid responsiveness in individuals with chronic respiratory symptoms possibly due to airway inflammation (strong recommendation, low quality of evidence).
- We suggest that FeNO may be used to support the diagnosis of asthma in situations in which objective evidence is needed (weak recommendation, moderate quality of evidence).
- We suggest the use of cut points rather than reference values when interpreting FeNO levels (weak recommendation, low quality of evidence).
- We recommend accounting for age as a factor affecting FeNO in children younger than 12 years of age (strong recommendation, high quality of evidence).
- We recommend accounting for persistent and/or high allergen exposure as a factor associated with higher levels of FeNO (strong recommendation, moderate quality of evidence).
- We recommend the use of FeNO in monitoring airway inflammation in patients with asthma (strong recommendation, low quality of evidence).
- We suggest using the following values to determine a significant increase in FeNO: greater than 20% for values over 50 ppb or more than 10 ppb for values lower than 50 ppb from one visit to the next (weak recommendation, low quality of evidence).
- We suggest using a reduction of at least 20% in FeNO for values over 50 ppb or more than 10 ppb for values lower than 50 ppb as the cut point to indicate a significant response to anti-inflammatory therapy (weak recommendation, low quality of evidence).
- We recommend that low FeNO less than 25 ppb (< 20 ppb in children) be used to indicate that eosinophilic inflammation and responsiveness to corticosteroids are less likely (strong recommendation, moderate quality of evidence).
- We recommend that FeNO greater than 50 ppb (> 35 ppb in children) be used to indicate that eosinophilic inflammation and, in symptomatic patients, responsiveness to corticosteroids are likely (strong recommendation, moderate quality of evidence).
- We recommend that FeNO values between 25 ppb and 50 ppb (20–35 ppb in children) should be interpreted cautiously and with reference to the clinical context (strong recommendation, low quality of evidence).
NO Measuring Systems

Circa 1990
Courtesy of LarsGustafsson

Circa 1995

Circa 2000

Circa 2005
13% O₂
5% CO₂
6% H₂O
75% N₂

1% Volatile Org. Compounds (VOC)

- Alkanes
- Aldehydes
- Ketones
- Alcohols
- Aromatics
- Amines
- Sulfides
- Furanes
Breath Chemical Analysis

- **acetone**
- **CO₂**
- **isoprene**
- **phenol**

**RT:** 0.00 - 56.99

**Relative Abundance**

**NL:** 4.19E5

**TIC MS test216**

*Courtesy of Steven Sunshine*
Breath Alcohol Test
EDITORIAL

Exhaled breath analysis: the new frontier in medical testing

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(Guest editor)
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E-mail: dweikr@ccf.org

Anton Amann
Department of Operative Medicine, Innsbruck Medical University, A-6020 Innsbruck, Austria and Breath Research Unit of the Austrian Academy of Sciences, Dammstrasse 22, A-6850 Dornbirn, Austria
Diseases / applications

Checking Your Blood Sugar Level - There are many different tools available for monitoring your blood sugar level; check with your doctor to see which one is best for you.

This instrument pricks your finger...

...and then a second instrument reads your blood sugar level.

Stages of liver damage

Fatty Liver

Liver Fibrosis

Cirrhosis

Deposits of fat cause liver enlargement.

Scar tissue forms.

Growth of connective tissue destroys liver cells.
Detection of Lung Cancer by Sensor Array Analyses of Exhaled Breath


Departments of Pathobiology and Pulmonary, Allergy, and Critical Care Medicine, Lerner Research Institute, and Department of Hematology and Medical Oncology, Cleveland Clinic Foundation, Cleveland, Ohio; and Smiths Detection, Inc., Pasadena, California
Chemiresistor Technology

Figure 2. Responses of 32 sensors in an electronic nose array. Collectively the responses can be used to distinguish good from unacceptable nanodino material.

Figure 5. Essential oils can be distinguished using the Cyranose 320.
EDITORIAL

The great challenge for exhaled breath analysis: embracing complexity, delivering simplicity

Raed A Dweik, MD
(Guest editor)
Conference Chair
Professor of Medicine
Director Breath Analysis Program, Pulmonary, Allergy and Critical Care Medicine/Respiratory Institute, Pathobiology/Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA
Bridging the Collaborative Gap: Realizing the Clinical Potential of Breath Analysis for Disease Diagnosis and Monitoring—Tutorial

Phillip X. Braun, Claire F. Gmachl, Senior Member, IEEE, and Raed A. Dweik

<table>
<thead>
<tr>
<th>Technologies</th>
<th>Adequately selective</th>
<th>Adequately sensitive</th>
<th>Robust/flow maintenance</th>
<th>Real-time operation</th>
<th>Self-administration</th>
<th>Adequately portable</th>
<th>Inexpensive</th>
<th>Adequate compound identification abilities*</th>
<th>Multi-species detection†</th>
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<tbody>
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<td>GC-MS</td>
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<td>Mini GC-MS</td>
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<td>Real-time MS (SIFT, PTR/PTR-ToF, IMS)</td>
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<td>Chemiluminescence</td>
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<td>Sensor Array/ E-nose</td>
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<td>Solid-state/MEMS†</td>
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<td>Diode laser spectroscopy</td>
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<td>Mid-IR laser spectroscopy</td>
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Key: 
- ● = meets requirement
- ○ = is likely to meet requirement
- ▲ = may meet requirement in some cases or in the future
- ▲ = fails to meet requirement

† Useful for discovery phase
* May be a requirement for some applications
‡ Micro-electromechanical systems (MEMS)
** Not useful for discovery phase
Electronic Nose

Mass Spectrometry
Select Ion Flow Tube (SIFT)-Mass Spectrometry (MS)

Reagent Ion Selection

Microwave plasma → Quadrupole mass filter → Sample inlet

0.3 torr
H₃O⁺
NO⁺
O₂⁺

10⁻⁵ torr
H₃O⁺
NO⁺
O₂⁺

R⁺

Analyte Ionisation

Flow tube
Carrier gas inlet

0.5 torr
R⁺
Reagent Ion
A
Analyte
P⁺
Product Ions
N
Neutral Products

Analyte Quantitation

Quadrupole mass filter → Particle multiplier

10⁻⁵ torr

[A] = \gamma \frac{[P^+]}{[R^+] \ k}

Instrument calibration factor
88 Individuals
25 Control
32 Asthma
17 Liver Disorder
14 PAH
Breath Analysis in Pulmonary Arterial Hypertension

Frank S. Cikach Jr, BS; Adriano R. Tonelli, MD; Jarrod Barnes, PhD; Kelly Paschke; Jennie Newman, LPN; David Groce, PhD; Luma Dababneh, MD; Sihe Wang, MD; and Raed A. Dweik, MD, FCCP
Liver Disease vs. Controls: Heat Map of Syft-MS Breath Data (Fetor Hepaticus)
Liver Disease vs. Controls: Visual Inspection of Syft-MS Breath Spectra

Control

Liver Disease

O$_2^+$

NO$^+$

H$_3$O$^+$
The Breathprints in Patients with Liver Disease Identify Novel Breath Biomarkers in Alcoholic Hepatitis
Ibrahim A. Hanouneh1, Nizar N. Zein1, Frank Cikach2, Luma Dababneh2, David Grove2, Naim Alkhouri1, Rocío Lopez3, Raed A. Dweik2

Clinical Gastroenterology and Hepatology 2014
Analysis of breath volatile organic compounds as a noninvasive tool to diagnose nonalcoholic fatty liver disease in children
Naim Alkhouria,c, Frank Cikachd, Katharine Enga, Jonathan Mosesa, Nishaben Patelb, Chen Yanga, Ibrahim Hanounhec, David Grove, Rocio Lopezbd and Raed Dweiked,e

European Journal of Gastroenterology & Hepatology 2013
Single Exhaled Breath Metabolomic Analysis Identifies Unique Breathprint in Patients With Acute Decompensated Heart Failure

Michael A. Samara, MD†
*W. H. Wilson Tang, MD‡§
Frank Cikach, Jr., BS||
Zeynep Gul, BA¶
Lily Tranchito, BS‡
Kelly M. Paschke, BA||
Jamie Viterna, BS‡
Yuping Wu, PhD#
Daniel Laskowski, BS||**
Raed A. Dweik, MD||**

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Heart Failure
-2 Log Likelihood 0.035
Wilks’ Lambda 0.109 (p<0.0001)
Renal Failure

- Training: Control
- Training: Renal Disease
- Validation: Control
- Validation: Renal Disease

- Renal Disease
- Control
Why Biomarkers in Exhaled Breath?

• **Advantages:**
  – non-invasive and non-intrusive
  – can be done repeatedly without limits to:
    • amount (unlike blood), never runs out
    • timing (unlike urine)
    • frequency (unlike CXR)
    • age (neonates to the elderly)
  – can be inexpensive
  – can be portable: hospital, clinic, home, remote areas, developing countries
  – promise of real time (point-of-care) results
  – promise of personalized medicine

• **Disadvantages / Challenges:**
  – confounders: host, diet, environment
  – lack of standardization: frequency, flow, pressure, respiratory cycle
  – poor reliability of prototypes
  – physician acceptance vs. resistance (but if you build it, **and it is useful**, …)
EDITORIAL

The great challenge for exhaled breath analysis: embracing complexity, delivering simplicity

Raed A Dweik, MD  
(Guest editor)  
Conference Chair  
Professor of Medicine  
Director Breath Analysis Program, Pulmonary, Allergy and Critical Care Medicine/Respiratory Institute, Pathobiology/Lerner Research Institute, Cleveland Clinic, Cleveland, OH, USA

‘Life is not measured by the number of breaths we take, but by the ones we analyze’

As the headspace of the blood, our exhaled breath contains a vast array of substances and molecules that hold great promise for monitoring our health and for the diagnosis and management of various lung and systemic diseases [1]. With recent advances in technology, essentially anything in the blood that is potentially volatile or has a volatile metabolite can be measured in exhaled breath [2]. This includes substances we produce endogenously as part of our normal (or disease-related) metabolism whether this is local in the lung or systemic in origin [3–6]. Since we are constantly inhaling air from our environment as we breathe in the ambient air, exhaled breath can also reflect our environmental exposure(s) [7]. Furthermore, our breath contains
Breath Analysis Dilemma / Challenge:
Embrace Ambiguity, Handle Complexity, Deliver Simplicity
Dweik Laboratory Research Team

Fellows
Metin Aytekin
Jarrod Barnes
David Grove

Students
Elif Kucera
Jamie Newman
Kelly Paschke

Physician Scientists
Gustavo Heresi
Adriano Tonelli

Technicians / Coordinators
Liping Tian
Frank Cikach
Jennie Newman