The Future of Pulmonary Function Testing?

Paul D. Scanlon, MD
Mayo Clinic
Rochester MN
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Dr. Scanlon has received research grants from Boehringer Ingelheim, Forest, GlaxoSmithKline, Novartis, AG Pearl and Pfizer and serves as a consultant for GlaxoSmithKline and Merck, but these do not create a conflict related to the following presentation.
Disclosure / Conflict of Interest
Paul D. Scanlon, M.D., FCCP

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Consultant to GlaxoSmithKline, Merck

No “Off label” use discussed

No investments or speakers contracts
Learning Objectives

- Speculate on likely future developments in Pulmonary Function Technology
- Identify current issues that need progress into the future
- Discuss the role of the Pulmonary Function Lab as a key component of the practice of Pulmonary Medicine
<table>
<thead>
<tr>
<th>Rank</th>
<th>Hospital</th>
<th>Points</th>
<th>Specialties</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Johns Hopkins Hospital, Baltimore</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Massachusetts General Hospital, Boston</td>
<td>29</td>
<td>16</td>
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<tr>
<td>3</td>
<td>Mayo Clinic, Rochester, Minn.</td>
<td>29</td>
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<td>4</td>
<td>Cleveland Clinic</td>
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<td>14</td>
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<td>5</td>
<td>UCLA Medical Center, Los Angeles</td>
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<td>13</td>
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<td>6</td>
<td>Northwestern Memorial Hospital, Chicago</td>
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<tr>
<td>7</td>
<td>New York-Presbyterian University Hospital of Columbia and Cornell, N.Y.</td>
<td>17</td>
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<tr>
<td>7</td>
<td>UCSF Medical Center, San Francisco</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>Brigham and Women’s Hospital, Boston</td>
<td>16</td>
<td>10</td>
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<tr>
<td>10</td>
<td>UPMC-University of Pittsburgh Medical Center</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>

Mayo Clinic:  
#3 Overall  
#1 in Pulmonology
The Future of Pulmonary Function Testing?

- What’s New, What’s cool
- Current - not well publicized
- Right under your nose
- In development
- Not yet (maybe never?)
1964
Star Trek Technology

- Tricorder
- Biobed Monitor
What is the Next High Tech Addition to the PF Lab?
The Future/The Present

NEW AND COOL:
- eNO → “Sniffers” (Exhaled Breath Condensate, other)
- Micro-analyzers, faster analyzers
- Effortless testing
- Noninvasive distance monitoring – triaxial accelerometers, vital signs, etc.
- Noninvasive sleep monitoring and beyond

MUNDANE, UNDER YOUR NOSE:
- Reference equations
- Organization, Productivity, Turn-around
- Revenue & “Profit”
- Burden of Technology
- Quality Assurance
- Underutilization by PCP’s
- Transplant monitoring
- Reference Equations
- “Race Correction”
- Complex Disorders – Mixed (1%), Nonspecific (10%), Complex Restrictive (5%)
Scientific Background - NO Science Molecule of the Year 1992

- NO in exhaled breath first described in 1991
- Increased in asthmatics, reduced by ICS
- Correlates with eosinophilic inflammation and reactivity
- Also increased by viral RTI, SLE, cirrhosis, lung tx rejection
- Role in COPD complex, likewise in CF
- Decreased by smoking acutely & chronically
- Reduced in HIV, PHTN
- Complementary to spirometry, BD and MeCh in asthma
FE_{NO} and Airway Inflammation

DN Payne, Relationship between exhaled nitric oxide and mucosal eosinophilic inflammation in children with difficult asthma, after treatment with oral prednisolone.

AJRCCM 2001;164:1376-81
Measurement of Nasal NO

- Nasal insufflation recommended
- 50-100 ml/sec flow
eNO Methodology

- $\text{FE}_{\text{NO}}$ expressed in ppb
- Inhale RV $\rightarrow$ TLC  Exhale slowly @ 10-20 mmHg, 50ml/sec
- Avoid nasal contamination
- 6-second exhalation to achieve a 3-second plateau
- Variation < 10% or 1ppb
- One minute wait between
- Report mean of 3 measures within 10%

![Graph showing NO concentration (ppb) and airway opening pressure versus time for three separate exhalations by the same subject, showing reproducible profiles and plateaus.](image-url)
Hardware

- Several manufacturers:
  - Sievers 280i® - original device
  - Aerocrine NIOX® Mino
- Chemiluminescence - photochemical reaction of NO with ozone under vacuum
eNO Normal Values?

- Normal oral eNO typically 3-7 ppb
- Current recommendation:
  - Oral  Children < 12 yo < 36.5 ppb
  - Adults < 39 ppb
  - Nasal > 187 ppb

Lab Volumes

- CPT 96092 Exhaled nitric oxide, oral
  Mayo Rochester Lab: #2242 in 2013
- CPT 96091 Exhaled nitric oxide, nasal
  Mayo Rochester Lab: #1327 in 2013


The Challenge of Exhaled Breath Condensate

- Many volatile compounds can be measured in exhaled breath condensate: hydrogen ions (pH), hydrogen peroxide, ammonia, nitrogen oxides, leukotrienes, prostaglandins, isoprostanes, adenosine, peptides and cytokines.
- The problem is variable volatility and dilution factors. What is the concentration of the substance in the lung represented by an amount measured in EBC? What is significant?
- Identification of novel compounds that are significant at low concentrations may circumvent that problem. Proteomics labs are hot in pursuit.

Many reports have been noted of use of dogs to identify patients with cancer – are there identifiable volatile substances that can be used to identify cancer or other conditions?

A recent abstract suggests so: presented by Dr. Michael Bousamra, University of Louisville, at Annual Meeting of The Society of Thoracic Surgeons in Orlando, FL, January 2014.

Exhaled breath condensate from patients with "suspicious" lung lesions, was analyzed with silicone microprocessor and mass spectrometer for presence of volatile carbonyl aldehydes and ketones.

Elevation of three or four cancer-specific carbonyl compounds seen in 95% of patients with a lung mass. Of those with negative EBC, 80% had negative biopsies. (Positive predictive value 95%, Negative predictive value 80%)

After surgery, elevated carbonyl concentrations returned to normal.
Improved PF Analyzers

- Methodologies for spirometry and lung volumes are fully evolved.
- DLCO still lingers in terms of speed, sensitivity and precision of analyzers. The promise of faster more sensitive analyzers is the ability to analyze smaller samples for sicker patients. Limits have moved only very slightly and slowly over 3 decades.
“Effortless Testing”

- Spirometry requires maximal repeatable effort. Impulse oscillometry (IOS) applies pressurized oscillations to airway and measures reflected energy to calculate airway resistance and reactance at various frequencies. Only passive cooperation is required of the patient, making it relatively “effortless”.

- Development of commercially usable system took >20 years after theoretical development (Jeff Fredberg). Utility has been mainly in very young children. Minimal utilization thus far in our lab (2/mo vs. 1365 spirometries/mo).
Noninvasive Remote Activity Monitors

- Ideal device is inobtrusive, has telecommunications capability, monitors orientation, motion, rotation, acceleration in 3 axes, monitors other functions (HR, RR, T, BP, SpO2, glucose, redox, other), has emergency communications capability.

- Sophisticated data analyses required to distinguish types of activity (e.g. running vs. riding in car)

Non-Invasive/Ambulatory Sleep Monitoring and Beyond

- Many of the same functions, plus EEG, eye movement, breath monitoring (chest & abdominal motion, airflow, airway pressure)
- Mayo Clinic research expedition to Mt. Everest to test extreme physiology and remote monitoring
Under our Noses
Organization, Productivity, Turn-Around
What is a reasonable turnaround time for a PFT (order to final report)?

A. 2 weeks
B. 1 week
C. 2 days
D. 1 day
E. ½ day
What is a reasonable turnaround time for a PFT (order to final report)?

A. 2 weeks
B. 1 week
C. 2 days
D. 1 day
E. ½ day
Reported Turn-Around Time

- Survey of North American PF Labs - Average TRT:
  - <1 day 15%
  - 1-2 d 30%
  - 3-4 d 27%
  - 5-6 d 15%
  - >7 d 3%

- Mayo Clinic PFL: ½ day to Electronic Medical Record

ATS PFL Registry Abstract AARC 2005, OF-05-037
Acceptable Turn-around & Staffing Needs

Routine PF Laboratory Appointment Availability
What is the most profitable section of your Pulmonary Division?

A. Outpatient Clinic
B. Inpatient Service
C. PF Lab
D. Sleep Lab
E. Outpatient procedures
What is the most profitable section of your Pulmonary Division?

A. Outpatient Clinic
B. Inpatient Service
C. PF Lab
D. Sleep Lab
E. Outpatient procedures
Mayo Clinic Stats

Largest integrated group practice in world:
   Main Campuses in MN, AZ, FL, 70 other communities in MN, IA, WI, GA
   4,100 physicians and scientists, 3,400 fellows, residents, students
   61,100 total employees (all sites)
   1,165,000 patients in 2012

5 schools: medical, graduate, graduate medical, CME/CPD, allied health sciences

$8.84B Revenue    $11.3B Total Assets
$395M Net Income, 4.5% operating margin
   – PF Lab ~ $3M

$361M Development, 191,619 gifts
$634M Research, $251M Education
>$2B Endowment

Funding for Research, Education, Centers for: Science of Health Care Delivery, Individualized Medicine, Innovation, Cancer, Professionalism, Humanities in Medicine
Acceptable Turn-around & Staffing Needs

- When providers do not get test results in timely fashion, they learn to work without them.
- Unmet demand goes away…
- We design scheduling and staffing to accommodate requests quickly and “checkers” immediately.
- Employees schedules maximize staffing at times of heaviest demand.
- New hires are justified by demand and NOI.
“Some of it is soft and some of it is hard, but the main thing is that all of it is money.”
Burden of Complex Technology

- Planned obsolescence of both hardware and supporting layers of software, databases, networks, EMR (e.g. 4/1/14 death of Windows XP)
- Increasingly complex and costly management of above
- All must be replaced periodically at great cost and effort
Quality Assurance

- Quality assurance in PF testing requires staff training, quality monitoring and feedback, regular calibrations, biological QC testing, and comprehensive equipment maintenance program.
- With comprehensive quality assurance, consistent very high quality is achievable.

Technician Training and Feedback
Improve Test Quality

GPA

Volume grade
Flow grade

Quality control feedback started
Site visits and training update

Lung Health Study
Underutilization by Primary Care Practitioners

- 32% of patients with a new dx of COPD had spirometry within 2.5 years of dx, <1/2 with BD
- “Nobody would ever think of treating hypertension without measuring BP” – Dr. Tom Petty
- Guidelines encourage spirometry in primary care setting
- Continued work within Mayo Health System to achieve compliance

Transplant Monitoring

- Home spirometry monitoring program
- 89 Post Transplant patients
- Spirometry identifies rejection, pneumonia, infection, BOS
- Survival worse if disenrolled after first year.

K Mukai et al. Role of Home Spirometry in the Detection of Lung Transplant Adverse Events. In Progress
Reference Equations

- NHANES/Hankinson recommended for 8-80yo
- Wang recommended for <8 yo
- Quanjer GLI 2012 spirometry refs are new
- Stocks & Quanjer for Lung Volumes
- Crapo & Morris for DLCO
Hankinson/NHANES and GLI 2012 “All Age” generate race/ethnicity specific equations, although Hankinson has recently suggested return to “Ethnic adjustment” factors applied against a more robust all-inclusive reference population equation:

ATS/ERS: 88% for African American, 88-94% for Asian apply to FVC, FEV1, TLC (little or no adjustment for Hispanic, Native American).

Most “race correction” schemes do not address mixed ethnicity (GLI does).

More detailed reference calculations may be possible in future with detailed genetic markers of ancestry.


The 2005 ATS Interpretation Standard has no discussion of complex disorders other than brief reference to “mixed” without further comment. Examples include obstructive disorders or interstitial disorders in combination with chest wall limitation (e.g. due to obesity, effusion, kyphosis or scoliosis), muscular weakness, poor performance, superimposed obstruction, etc. How should one interpret these?
66 y/o M  Previous mild obstruction, new mesothelioma
Ht: 176.0  Wt: 82.9  BMI 26.8

- Restriction is moderate or moderately severe
- Overall impairment is severe or very severe
- What is the severity of obstruction?
New Idea for Mixed Disorders (i.e. Obstruction Plus Restriction)

- Grade degree of restriction based on TLC
- Grade overall impairment based on FEV1
- Previously grading of obstruction was considered indeterminate
- **Severity of obstruction is calculated as:**
  \[ \text{FEV1 \% pred} \div \text{TLC \% pred} \]

66 y/o M  Previous mild obstruction, new mesothelioma
Ht: 176.0  Wt: 82.9  BMI 26.8

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>3.45</td>
<td>52%</td>
</tr>
<tr>
<td>RV</td>
<td>1.62</td>
<td>73%</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>46.8</td>
<td>141%</td>
</tr>
<tr>
<td>FVC</td>
<td>1.68</td>
<td>38%</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.05</td>
<td>29%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>62.6</td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>10.9</td>
<td>41%</td>
</tr>
</tbody>
</table>

- Very severe mixed abnormality, moderate restriction, super-imposed moderate obstruction, minimal (no) bronchodilator response (old ATS)

29% ÷ 52% = 55.8%
66 y/o M  Previous mild obstruction, new mesothelioma  
Ht: 176.0  Wt: 82.9  BMI 26.8

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Percentage</th>
<th>Reference Value</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>3.45</td>
<td>52%</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>1.68</td>
<td>38%</td>
<td>1.76</td>
<td>+5%</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.05</td>
<td>29%</td>
<td>1.18</td>
<td>+13%</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>62.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLCO</td>
<td>10.9</td>
<td>41%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Very severe mixed abnormality, moderately severe restriction, super-imposed moderately severe obstruction, no bronchodilator response (2005 ATS)
An 80 patient has a TLC or 88% predicted, FVC 58% pred, FEV1 56% pred, FEV1/FVC 0.69 (LLN 0.66), DLCO 75% pred

Would you call this:

- A. Normal
- B. Moderate restriction
- C. Moderate obstruction
- D. Poor performance
- E. Something else
An 80 patient has a TLC or 88% predicted, FVC 58% pred, FEV1 56% pred, FEV1/FVC 0.69 (LLN 0.66), DLCO 75% pred

Would you call this:

A. Normal
B. Moderate obstruction
C. Moderate restriction
D. Poor performance
E. Something else

Answer: E. Something else
PFT Scenario

An 80 patient has a TLC or 88% predicted, FVC 58% pred, FEV1 56% pred, FEV1/FVC 0.69 (LLN 0.66), DLCO 75% pred

Would you call this:

- A. Normal
- B. Moderate restriction
- C. Moderate obstruction
- D. Poor performance
- E. Moderate Nonspecific Abnormality
What causes a low FVC with normal TLC & FEV1/VC?

- Not necessarily obstruction
- “Nonspecific pattern” (Hyatt, Iyer)
- Commonly seen in asthma & obesity, also COPD, weakness, chest wall abn, heart failure
- 9-10% of all PFT’s at Mayo Clinic
- 50% have normal Raw (unpublished)
- Pattern stable 3-5 yrs in >60%

Hyatt et al. Chest 2009; 135: 419-424
Iyer et. al. Chest 2011; 139: 878-86
Conditions Associated With an Abnormal Nonspecific Pattern of Pulmonary Function Tests*

Robert E. Hyatt, MD, FCCP; Clayton T. Cowl, MD, FCCP; Julie A. Bjorling; and Paul D. Scanlon, MD, FCCP

Background: Little is known about a fairly frequent abnormal result: reduced FEV₁ and FVC with a normal FEV₁/FVC ratio, this a nonspecific pattern (NSP). We sought to identify mechanisms producing it.

Methodology:

**Table 1—Subject Characteristics (n = 100)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
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</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>61.7 (14.4)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>30.7 (5.8)</td>
</tr>
<tr>
<td>Subjects with BMI ≥ 30 kg/m², %</td>
<td>50</td>
</tr>
<tr>
<td>Male/female gender, No.</td>
<td>62/38</td>
</tr>
<tr>
<td>TLC, L</td>
<td>5.77 (1.1)</td>
</tr>
<tr>
<td>TLC, % predicted</td>
<td>94.4 (9.4)</td>
</tr>
<tr>
<td>RV, L</td>
<td>2.93 (0.8)</td>
</tr>
<tr>
<td>RV, % predicted</td>
<td>142.1 (29.5)</td>
</tr>
<tr>
<td>FVC, L</td>
<td>2.84 (0.75)</td>
</tr>
<tr>
<td>FVC, % predicted</td>
<td>69.9 (7.6)</td>
</tr>
<tr>
<td>SVC, L</td>
<td>3.13 (0.52)</td>
</tr>
<tr>
<td>Key wc</td>
<td>2.16 (0.39)</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>2.16 (0.39)</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>67.6 (8.6)</td>
</tr>
<tr>
<td>Abbreviations</td>
<td></td>
</tr>
<tr>
<td>FRC = maximum forced expiratory flow, L/s</td>
<td>7.34 (2.05)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>99.1 (17.2)</td>
</tr>
<tr>
<td>FEV₁/FVC, % predicted</td>
<td>99.1 (17.2)</td>
</tr>
<tr>
<td>DLCO, mL/min/mm Hg</td>
<td>23.8 (5.7)</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>94.6 (15.7)</td>
</tr>
</tbody>
</table>

*Data are presented as mean (SD) unless otherwise indicated.

**Table 2—Distribution of BMI by Gender**

<table>
<thead>
<tr>
<th>BMI, kg/m²</th>
<th>Men (n = 62)</th>
<th>Women (n = 38)</th>
<th>Combined (n = 100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25</td>
<td>10 (16.1)</td>
<td>13 (34.2)</td>
<td>23 (23)</td>
</tr>
<tr>
<td>25–29.9</td>
<td>20 (32.2)</td>
<td>7 (18.4)</td>
<td>27 (27)</td>
</tr>
<tr>
<td>30–34.9</td>
<td>16 (25.8)</td>
<td>9 (23.7)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>35–39.9</td>
<td>12 (19.4)</td>
<td>6 (15.8)</td>
<td>18 (18)</td>
</tr>
<tr>
<td>≥ 40</td>
<td>4 (6.5)</td>
<td>3 (7.9)</td>
<td>7 (7)</td>
</tr>
</tbody>
</table>

**Table 3—Summary of Patient Diagnosis**

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Men</th>
<th>Women</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. AHR without obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. AHR with obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Chronic lung disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Other</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 4—Conditions in “Other” Category**

<table>
<thead>
<tr>
<th>Conditions</th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>5</td>
</tr>
<tr>
<td>Muscle disease</td>
<td>4</td>
</tr>
<tr>
<td>Respiratory muscle weakness</td>
<td>2</td>
</tr>
<tr>
<td>Paralysis of left hemidiaphragm</td>
<td>1</td>
</tr>
<tr>
<td>Mitochondrial disease</td>
<td>1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4</td>
</tr>
<tr>
<td>Metastatic</td>
<td>4</td>
</tr>
<tr>
<td>Chest wall</td>
<td>5</td>
</tr>
<tr>
<td>Large hiatal hernia</td>
<td>3</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>1</td>
</tr>
<tr>
<td>Chest trauma</td>
<td>1</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>7</td>
</tr>
<tr>
<td>Pulmonary sarcoid</td>
<td>1</td>
</tr>
<tr>
<td>Vocal cord dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Arthritis</td>
<td>1</td>
</tr>
<tr>
<td>Mixed connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal aortic aneurysm</td>
<td>1</td>
</tr>
<tr>
<td>Coronary artery disease after coronary artery bypass graft surgery</td>
<td>2</td>
</tr>
</tbody>
</table>
The Nonspecific Pulmonary Function Test
Longitudinal Follow-up and Outcomes

Vivek N. Iyer, MD, MPH; Darrell R. Schroeder, MS; Kenneth O. Parker, MS;
Robert E. Hyatt, MD, FCCP; and Paul D. Scanlon, MD, FCCP

Background: The nonspecific (NS) pulmonary function (PF) pattern refers to a PF test with a normal total lung capacity (TLC), normal FEV/FVC ratio, and a low FEV1, a low FVC, or both. Currently, no information is available regarding the long-term stability of the NS pattern or variables that predict changes in subjects with an initial NS PF pattern.

Methods: From 1990 to 2005 we identified 1,284 subjects with an NS pattern on initial PF testing with one or more follow-up PF tests 6 months or more after the initial NS test result. Lung volumes, diffusing capacity, and spirometry data were analyzed. A multivariate, multinomial logistic regression model was used to study the association between different variables and the final PF pattern.

Results: Overall, 3,674 PF tests were performed in 1,284 subjects over a median follow-up period of 3 years. At last follow-up, 818/1,284 (64%) subjects continued to show the NS pattern, whereas 208/1,284 (16%) showed a restrictive pattern, 191/1,284 (15%) an obstructive pattern, 42/1,284 (3%) a normal pattern, and 25/1,284 (2%) a mixed pattern. The multinomial logistic regression analysis showed that increasing values for specific airway resistance and the difference between TLC and alveolar volume were predictors of a change to an obstructive pattern on follow-up.

Conclusions: The NS pattern is a distinct and stable PF test pattern with roughly two-thirds of patients continuing to show this pattern on follow-up testing. Current interpretation guidelines erroneously label the NS pattern as representing obstruction and need to be changed to reflect these data.

CHEST 2011; 139(4):878–886

Abbreviations: ATS = American Thoracic Society; BD = bronchodilator; DLco = diffusing capacity for carbon monoxide; DLcoUN = uncorrected diffusing capacity for carbon monoxide; IQR = interquartile range; NS = nonspecific; PF = pulmonary function; Sraw = specific airway resistance; SVC = slow vital capacity; TLC = total lung capacity; VA = alveolar volume

Figure 1. Pulmonary function pattern at last follow-up (N = 1,284).
77 y/o F: Sleep Apnea, Pulm HTN, DMII, Polymyalgia Rheumatica, Ex-Smoker - 5 Pack Years
Ht : 151.0 Wt: 89.4 BMI: 39.2

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
<th>Percentage</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLC</td>
<td>3.71</td>
<td>86%</td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td>2.07</td>
<td>101%</td>
<td></td>
</tr>
<tr>
<td>RV/TLC</td>
<td>55.9</td>
<td>118%</td>
<td></td>
</tr>
<tr>
<td>FVC</td>
<td>1.29</td>
<td>57%</td>
<td>1.54</td>
</tr>
<tr>
<td>FEV₁</td>
<td>1.02</td>
<td>56%</td>
<td>1.22</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>78.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PI max</td>
<td>-27</td>
<td>42%</td>
<td></td>
</tr>
<tr>
<td>PEmax</td>
<td>81</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>SRaw</td>
<td>5.3</td>
<td>115%</td>
<td></td>
</tr>
<tr>
<td>DLCO(adj)</td>
<td>8.8</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>SPO₂</td>
<td>93%</td>
<td></td>
<td>(no ex)</td>
</tr>
</tbody>
</table>

“Abnormal. FEV₁ and FVC are moderately reduced in a nonspecific pattern with a normal TLC and FEV₁/FVC ratio. The reduced maximal respiratory pressures indicate muscle weakness or poor performance and likely contribute to the abnormality. Obesity may contribute as well. The normal airway resistance argues against an obstructive process, although flows improve slightly after bronchodilator. The reduced DLCO indicates a parenchymal or vascular disorder. Resting oximetry is normal. The patient was unable to exercise.”
Another Embarrassingly Unnamed PFT Abnormality

A 68 yo patient has a TLC or 72% predicted, FVC 34% pred, FEV1 38% pred, FEV1/FVC 0.69, DLCO 49% pred

Would you call this:

- A. Mild restriction
- B. Severe restriction
- C. Mild-to-Severe restriction
- D. Severe obstruction
- E. Something else
A 68 yo patient has a TLC or 72% predicted, FVC 34% pred, FEV1 38% pred, FEV1/FVC 0.69, DLCO 49% pred

Would you call this:

A. Mild restriction
B. Severe restriction
C. Mild-to-Severe restriction
D. Severe obstruction
E. Something else
In 1986, ATS said to quantify severity of restriction based on TLC or FVC. People have argued ever since which to grade when they are not concordant. Rather than argue which, consider that when they are discordant, there is almost always something else going on.

What sort of something else?

1) Chest wall limitation (obesity, scoliosis, kyphosis, effusion, etc.)
2) Weakness
3) Heart failure
4) Poor test performance (effort?)
5) Occult obstruction

This accounts for 5% of all PFT’s!

Complex Restrictive Disorder?
Not defined by ATS
64 y/o F. Mild Pulmonary Hypertension, Bronchiectasis, Never-Smoker, Obese. Ht: 149.5 Wt: 74.0 BMI: 33.3

<table>
<thead>
<tr>
<th>LUNG VOLUMES</th>
<th>PREDICTED</th>
<th>RANGE</th>
<th>CONTROL</th>
<th>POST-DILATOR**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORMAL</td>
<td></td>
<td>FOUND</td>
<td>%PRED.</td>
</tr>
<tr>
<td>TLC (Pleth)</td>
<td>4.22</td>
<td>3.12</td>
<td>2.52*</td>
<td>60%</td>
</tr>
<tr>
<td>VC</td>
<td>2.51</td>
<td>1.77</td>
<td>0.73*</td>
<td>29%</td>
</tr>
<tr>
<td>RV</td>
<td>1.71</td>
<td>&lt;2.22</td>
<td>1.79</td>
<td>104%</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>40.6</td>
<td>&lt;53.1</td>
<td>71.0*</td>
<td>175%</td>
</tr>
<tr>
<td>FRC</td>
<td></td>
<td></td>
<td>1.8</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>SPIROMETRY</th>
<th>PREDICTED</th>
<th>RANGE</th>
<th>CONTROL</th>
<th>POST-DILATOR**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORMAL</td>
<td></td>
<td>FOUND</td>
<td>%PRED.</td>
</tr>
<tr>
<td>FVC</td>
<td>2.51</td>
<td>1.77</td>
<td>0.60*</td>
<td>24%</td>
</tr>
<tr>
<td>FEV1</td>
<td>2.07</td>
<td>1.52</td>
<td>0.45*</td>
<td>22%</td>
</tr>
<tr>
<td>FEV1/FVC</td>
<td>82.7</td>
<td>71.6</td>
<td>75.8</td>
<td></td>
</tr>
<tr>
<td>FEF25-75</td>
<td>2.2</td>
<td>&gt;1.0</td>
<td>0.2*</td>
<td>10%</td>
</tr>
<tr>
<td>FEFmax</td>
<td>5.0</td>
<td>&gt;2.3</td>
<td>2.0*</td>
<td>41%</td>
</tr>
<tr>
<td>MVV</td>
<td>86</td>
<td>&gt;53</td>
<td>20*</td>
<td>23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OXIMETRY</th>
<th>PREDICTED</th>
<th>RANGE</th>
<th>CONTROL</th>
<th>POST-DILATOR**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NORMAL</td>
<td></td>
<td>FOUND</td>
<td>%PRED.</td>
</tr>
<tr>
<td>O2 Sat</td>
<td>96</td>
<td>&gt;93</td>
<td>90*</td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td>101</td>
<td></td>
<td>119</td>
<td></td>
</tr>
</tbody>
</table>

*Outside normal range.  + weight exceeds 95th percentile.
**Bronchodilator was Albuterol

**COMMENTS:** Abnormal. Complex restrictive disorder. TLC is mildly to moderately reduced, indicating a restrictive disorder. The disproportionate very severe reduction in FVC suggests an additional process such as superimposed obstruction, chest wall limitation, neuromuscular weakness, or poor performance. There is no evidence of obstruction and no immediate response to bronchodilator. (The improvement in FEFmax is likely related to improved effort or performance.) Oxygen saturation is reduced at rest and falls further during exercise.
51 yo F Myeloma, former smoker
Cognitive Impairment
Ht: 176 Wt: 111kg BMI: 35.2

TLC  4.90  80%
FVC  1.90  48%
FEV₁ 1.40  45%
FEV₁/FVC 73.8  94%
DLCO (corr) 15.8  63%
PI max -30  39%
Pemax 100  70%
SRaw 12.4  267%

Is this mild to severe restriction?
Is it ILD?
Anything else going on?
Obesity/Chest wall limitation, weakness, poor performance, obstruction
What Causes a Disproportionate Reduction in FVC vs. TLC (↑RV)?

All of the following except:

A. Neuromuscular weakness
B. Upper airway obstruction
C. Chest wall limitation (e.g. obesity, scoliosis)
D. Superimposed obstruction
E. Poor performance
What Causes a Disproportionate Reduction in FVC vs. TLC (↑RV)?

All of the following except:

A. Neuromuscular weakness
B. Upper airway obstruction
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What Causes a Disproportionate Reduction in FVC vs. TLC (↑RV)? All of the following except:

A. Neuromuscular weakness
B. Upper airway obstruction
C. Chest wall limitation (e.g. obesity, scoliosis)
D. Superimposed obstruction
E. Poor performance
Complex Restrictive Disorders
TLC or FVC for Grading Severity?

- The combination of TWO restrictive processes, such as ILD plus weakness, can result in disproportionate reduction in FVC vs. TLC.
- The important issue is not whether to grade restriction based on TLC vs. FVC (or FEV1), but rather, to recognize complexity.
- Recommendation: I grade the primary restrictive process using TLC % Predicted. I grade overall impairment with FVC % Predicted.
REPEAT: What Causes a Disproportionate Reduction in FVC vs. TLC (↑RV)?

All of the following:

A. Neuromuscular weakness
B. Chest wall limitation (e.g. obesity, scoliosis)
C. Superimposed obstruction
D. Poor performance

Note that all can result in increased RV, not necessarily due to “air trapping”.
“PV Disorders” Includes:

- Pulmonary parenchymal disorders including early ILD & emphysema
- Anemia
- Pulmonary vascular disorders

Isolated Reduction in DLCO

- 38,095 PFT’s in MC database
- 179 (0.45%) with isolated low DLCO
- 27 with CT available
- 13 have emphysema, 11 with fibrosis also
- Other 14 have ILD, PH or other findings
- 22% never smokers

61 y/o M  Dyspnea with Exertion, Chronic Bronchitis, Current Smoker – 40 Pack years
Ht : 180.8  Wt: 97.8  BMI: 29.9

“Abnormal. There is an isolated mild reduction in DLCO, consistent with a pulmonary parenchymal or vascular process. Spirometry and oximetry are normal, and there is no response to bronchodilator.”
The patient has both emphysema and fibrosis. Both are more common causes of isolated reduction in DLCO than vascular diseases, often present together.

58 y/o F, Severe Combined Emphysema and Pulmonary Fibrosis (CEPF), Continued smoker, died of lung cancer

Ht : 162.3  Wt: 60.2

- Balanced obstruction and restriction
- Spirometry may be preserved
- Severe gas exchange abnormality

**FVC** 3.40  107%  3.33  -2%
**FEV₁** 2.56  100%  2.62  +2%
**FEV₁/FVC** 75.1  78.6
**FEFmax** 6.6  115%  7.2  +8%
**DLCO** 7  32%
**SPO₂** 91% → 73%

Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity

V. Cottin*, H. Nunes‡‡, P-Y. Brillet¹, P. Delaval†, G. Devouassoux§, I. Tillie-Leblond†, D. Israel-Biet***, I. Court-Fortune&&, D. Valeyre‡, J-F. Cordier* and the Groupe d’Etude et de Recherche sur les Maladies “Orphelines” Pulmonaires (GERM’O’P)

**ABSTRACT:** The syndrome resulting from combined pulmonary fibrosis and emphysema has not been comprehensively described.

The current authors conducted a retrospective study of 61 patients with both emphysema of the upper zones and diffuse parenchymal lung disease with fibrosis of the lower zones of the lungs on chest computed tomography.

Patients (all smokers) included 60 males and one female, with a mean age of 65 yrs. Dyspnoea on exertion was present in all patients. Basal crepitations were found in 87% and finger clubbing in 43%. Pulmonary function tests were as follows (mean±sd): total lung capacity 86%±17, forced vital capacity (FVC) 88%±18, forced expiratory volume in one second (FEV₁) 80%±21 (% predicted), FEV₁/FVC 69%±13, carbon monoxide diffusion capacity of the lung 37%±16 (% predicted), carbon monoxide transfer coefficient 46%±10. Pulmonary hypertension was present in 47% of patients at diagnosis, and 55% during follow-up. Patients were followed for a mean of 2.1±2.8 yrs from diagnosis. Survival was 97.5% at 2 yrs and 54.6% at 5 yrs, with a median of 6.1 yrs. The presence of pulmonary hypertension at diagnosis was a critical determinant of prognosis.

The authors hereby individualise the computer tomography-defined syndrome of combined pulmonary fibrosis and emphysema characterised by subnormal spirometry, severe impairment of gas exchange, high prevalence of pulmonary hypertension, and poor survival.

* Eur Resp J 2005; 26:586-93
Summary

- The timeline from scientific development to practical application is 10-30 years, so our future is already in basic science labs as well as in our own hands. The two-way wrist TV of the present is the iPhone of the future. It will not disappoint.
- There is ample opportunity for improvement with current technology as well.
- In American healthcare, procedures are overcompensated, compared with cognitive services. The pulmonary function lab is a neglected cash cow. Money is influence. We can exert ours more aggressively. Our patients will benefit.
“This is fine as far as it goes. From here on, it’s who you know.”
I remember when the 1914 building was complete, Dr. Will was rather disturbed, fearing it was too big and too elegant. Dr. Henry S. Plummer, however, had deliberately included a degree of distinction in the plans of the building. He thought it ought to be beautiful in its exterior and interior aspects, for he felt that perhaps in many instances the patients and their relatives would be surrounded by architectural beauty for the first time and would thus be helped to find some measure of peace and solace while waiting their appointments with the physician."

Leda Stacy *Twenty-Eight Years at the Mayo Clinic* (1957)
In connection with the construction of the building, it was pleasing to note his respect for the emotions of mankind and his recognition of the significance of emotional reactions. Never did the white, cold marble of the mausoleum type come into the calculations. Where marble was used, it was the warmly colored marble that would please the eye and quiet the apprehensions. In such understanding and execution of purpose Henry Plummer was perhaps at his best.

William J. Mayo, 1938
“I call architecture frozen music.”
- Johann Wolfgang von Goethe
“I envision Mayo’s architecture as an important tool in the healing process...I wanted to design a building where the healing process begins the moment a patient enters the front door.” Cesar Pelli
THREE PROBLEMS:

- FEV1/VC Ratio
- Low FVC with nl FEV1/FVC & TLC
- “PV disorders”
Comment on FEV1/VC Ratio

- ATS/ERS Committee was a joint committee but over-weighted with Europeans. A conflict emerged over FEV1/FVC ratio (American) vs. FEV1/VC ratio (European Tiffeneau Index). ATS was outgunned.

- \( \text{FEV1/VC} \leq \text{FEV1/FVC} \rightarrow \) Use of FEV1/VC in comparison with predicted FEV1/FVC ratio will cause overestimation of obstruction
2005 ATS/ERS Pulmonary Function Interpretation Algorithm

For identification of obstruction
Use LLN for FEV1/FVC
NOT a fixed ratio of 0.70

Roberts SD, Farber MO, Knox KS, Phillips GS, Bhatt NY, Mastronarde JG, Wood KL. FEV1/FVC Ratio of 70% Misclassifies Patients With Obstruction at the Extremes of Age. Chest 2006;130;200-206

Also see Falling Ratio Working Group at:
http://www.spirxpert.com/controversies/controversy.html
Impairment/Severity Stratifications
Adapted from 1986 ATS Disability Standard

**Obstruction (80/60/40)**

- **FEV1/FVC < LLN*** AND:
  - Borderline – FEV1 ≥ LLN*
  - Mild - FEV1 60% - LLN*
  - Moderate – FEV1 41-59%
  - Severe FEV1 31* - 40%
  - Very Severe ≤ 30%*  

**Restriction (80/60/50)**

- **FEV1/FVC ≥ LLN* AND**
  - TLC < LLN AND:
    - Mild – FVC 60% - LLN*
    - Moderate - 51 to 59%
    - Severe ≤ 50%
    - Very Severe (≤35%?)*

* modifications

### 2005 Severity Classification - Spirometry

<table>
<thead>
<tr>
<th>DEGREE OF SEVERITY</th>
<th>FEV₁, % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>&gt;70%</td>
</tr>
<tr>
<td>MODERATE</td>
<td>60-69</td>
</tr>
<tr>
<td>MODERATELY SEVERE</td>
<td>50-59</td>
</tr>
<tr>
<td>SEVERE</td>
<td>35-49</td>
</tr>
<tr>
<td>VERY SEVERE</td>
<td>&lt;35</td>
</tr>
</tbody>
</table>

“The number of categories and the exact cut-points are arbitrary.”

Enright: Caution re shifting of disease severity, false positives, excess therapy, potential conflict of interest in clinical practice guidelines

### Severity Classification - DLCO

Table 8. Degree of severity of decrease in DLCO.

<table>
<thead>
<tr>
<th>DEGREE OF SEVERITY</th>
<th>DLCO % predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD</td>
<td>&gt; 60% and &lt; LLN</td>
</tr>
<tr>
<td>MODERATE</td>
<td>40-60%</td>
</tr>
<tr>
<td>SEVERE</td>
<td>&lt;40</td>
</tr>
</tbody>
</table>

Legend: DLCO: diffusing capacity for carbon monoxide; LLN: lower limits of normal.
Table 7. Reported significant changes in FVC, FEV₁, FEF₂₅-₇₅, and DLCO over time.

<table>
<thead>
<tr>
<th></th>
<th>FVC</th>
<th>FEV₁</th>
<th>FEF₂₅-₇₅</th>
<th>DLCO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within a day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>≥5</td>
<td>≥5</td>
<td>≥13</td>
<td>&gt;7%</td>
</tr>
<tr>
<td>COPD patients</td>
<td>≥11</td>
<td>≥13</td>
<td>≥23</td>
<td></td>
</tr>
<tr>
<td><strong>Week to week</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects</td>
<td>≥11</td>
<td>≥12</td>
<td>≥21</td>
<td>&gt;6 units</td>
</tr>
<tr>
<td>COPD patients</td>
<td>≥20</td>
<td>≥20</td>
<td>≥30</td>
<td>&gt;4 units</td>
</tr>
<tr>
<td><strong>Year to year</strong></td>
<td>≥15</td>
<td>≥15</td>
<td>-</td>
<td>&gt;10%</td>
</tr>
</tbody>
</table>

Legend: variables as in tables 4 and 5.

Results for spirometry are rounded to the nearest integer (21, 116). The within day DLCO variability is from a study of diurnal variation in healthy nonsmokers (118). The week-to-week coefficient of repeatability (CR) is given for DLCO in units of ml/min/mmHg, as calculated from CRs originally stated in units of mmol/min/kPa (125). The year-to-year variability of healthy adults is given using a 95% confidence interval (144). CRs from repeatability testing done in your own laboratory should be substituted for the values in this table.
Day-to-Day Variability at Mayo Clinic

- FEV1  220 ml
- FVC  250 ml
- TLC  320 ml
- DLCO  3.2 units

±2 SD from Biological QC database using trained normal subjects
Johannes Kepler's Uphill Battle

"...so, you see the orbit of a planet is elliptical.

What's an orbit?

What's a planet?

What's 'elliptical'?
"You have no idea how political this place is."
References - Pulmonary Function


Enright’s minority opinion from ATS/ERS Committee.


Recommended NHANES reference equations for spirometry


Recommended change in reference equations is not without effect on interpretation


Thoughtful review of current PF interpretation.
References - Pulmonary Function
