NEW LUNG FUNCTION STANDARDS

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Introduction

• Definition of airway obstruction still controversial

• FEV₁/FCV ratio declines with age and height even in healthy lifelong non-smokers

• Prediction equations
  – based on simple additive linear regression techniques
  – cover a limited age range (childhood, adolescence, adulthood) leading to discontinuities
    • 175-cm tall young male: FVC of 4.2 L
      – 97% predicted at 17.9 yrs of age (Polgar and Promadhat)
      – 83% predicted on his 18th birthday (ECSC/ERS)

• High percentage of misclassification, notably in COPD

• Need to
  – determine new spirometry prediction equations that cover as many ethnic groups as possible and an age from preschool children to old age
  – implement a new interpretation of spirometry
Historical review of reference equations

• **1960**: first recommendations by the European Community for Coal and Steel (ECCS)

• **1971**: update of ECCS recommendations
  – predicted values for spirometric indices and volumes (RV, TLC, FRC)

• **1979**: standardisation of spirometry in USA

• **1983**: revision of the ECCS report

• **≥ 1987**: revised standardisation reports in USA (spirometry) and Europe (wider range of PFTs)
• **Reference values from the ECCS**
  – based on males working in coal mines and steel works
  – not a representative reference population
  – no women tested, but nevertheless reference values for females issued: 80% of the values for males

• **In 2005**: ATS/ERS recommendations for standardised lung function testing
  – predicted values for North America (adults, children, adolescents / Caucasians, African- and Mexican-Americans)
  – rest of the world uncovered
• **From 2006**: increasing number of centers agreed to share data with Philip Quanjer ⇒ group

• **2008**: group named Global Lung Function Initiative (GLI) in Berlin

• **2010**: the group acquired ERS Task Force status
  
  – 72 centres in 33 countries
  – 97759 records of healthy non smokers (55.3 % females) aged 2.5 – 95 yrs
  – representation
    • poor from South America
    • absent from Malaysia, Indonesia and sub-Saharan Africa
  – GLI recommendations endorsed by 6 large international respiratory societies (ERS, ATS, ANZSRS, APSR, TSANZ, ACCP)
Situation in 2006

Predicted FEV$_1$ in white males according to 30 different authors

these prediction equations are used in many part of the world for diagnostic purpose !
relationship not characterised by straight lines
scatter non constant
scatter not proportionnal to the predicted value
Conclusion

• The models fit the measured values poorly

• Very large differences in predicting values according the different authors

• Separation of children/adolescents and adults
  – artificial
  – disjointed predictive values at transition
Use of percent of predicted

- **Interpretation of spirometric data**: expression of measured values as percent.
- **General rule**:
  - Deviation of 20% from the predicted normal value = significant.
  - 80% of predicted = lower limit of normal.
  - 120% of predicted = upper limit of normal.

**Fig. 6** - The lower limit of normal (LLN) for FEV₁ and FVC expressed as a percentage of the GLI-2012 predicted values in the 3-95 year age range.

**Fig. 7** - Percentage of healthy males and females in whom the measured FEV₁ or FVC is <80% predicted.
GLI: what’s new?

- Capturing the non-linear relationship between spirometric indices and age and height using standard linear regression techniques = not possible

- Method for capturing non-linear curves = add a spline to a linear relationship

Fig. 9 - The predicted FEV₁ without use of a spline (yellow-green line) provides a bad fit, the one which includes a spline (black line) fits well.
FEV₁/FVC: a pattern never described before
LLN and z-score

• In clinical medicine, the normal range is defined as the range of values which encompasses 95% of healthy population
  – LLN < P_{2.5} and ULN > P_{97.5}
  – 5% of false positive test results

• In respiratory medicine: LLN < P_5

• Various methods for deriving the LLN
  – the most elegant: based on a normal distribution of test results
• Spirometric data vary with age, height, sex and ethnic group
  – modelling of each component $\rightarrow$ z-score

• Z-score = measured – predicted value / SD

• Normal distribution of residuals: average of all z-scores = 0 and SD = 1

• Z-score: independent of age, height, sex and ethnic group

LLN in pulmonology = the 5th percentile when z-score is – 1.64
80% predicted

FEV₁/FVC < 0.70
Ethnicity

• Ethnic correction factors

  – predicted values in black subjects : 15 % below those in white

Fig. 16 - FEV₁/FVC ratio in healthy females of different ethnic origin.
Conclusions about LLN

- **GOLD stage 1 (FEV$_1$/FVC $< 0.7$ & FEV$_1$ $> 80\%$ predicted)** in asymptomatic subjects is not associated with
  - premature death
  - accelerated decline in FEV$_1$, development of respiratory symptoms, increased use in health care, decrease in QoL

- **FEV$_1$/FVC $< LLN$ is associated with
  - premature death
  - development of respiratory symptoms

The GOLD criterion is unscientific and clinically unfounded

Use of FEV$_1$/FVC $< 0.7$ for diagnosing airway obstruction
  $\Rightarrow$ under diagnosis in young subjects (< 45-50 yrs)
  $\Rightarrow$ over diagnosis in older subjects (> 45-50 yrs)
Comparison of predicted values in children

Fig. 22 - Comparison of predicted FEV1 and FVC in healthy boys and girls according to GLI-2012 [23], Zapletal [43], Stanojevic [16], Polgar [12], Quanjer [13], Hankinson [24], Knudson [44], Rosenthal [45] and Wang [46].
Comparison of predicted values in adults
Comparison of predicted values in obstructive adults

Fig. 26 - Percentage of patients with airway obstruction (FEV1/FVC < LLN) based on GLI-2012 [23] and NHANES [24] prediction equations.

Fig. 27 - Percentage of patients with airway obstruction (FEV1/FVC < LLN) based on GLI-2012 [23] and ECCS/ERS [10] predicted values.
Fig. 28 - Percentage of patients with airway obstruction (FEV1/FVC < LLN) based on GLI-2012 [23] predicted values, or with GOLD stage 2-4.
Interpretation of test results
Conclusions

• **GLI:**
  – based on a very large and representative population sample
  – provides regression equations for the 3-95 year age range, and for a number of ethnic group
• The age dependence of the LLN has been accounted for
• **Z-scores** offer the opportunity to interpret test results independent of age, height, sex and ethnic group
• Adoption of the GLI equations will lead to minor changes in the prevalence rate of airway obstruction in clinical populations
• Use of percent of predicted values leads to an unacceptable age bias and needs to be replaced by the use of z-scores
• The GOLD doctrine does not respect the clinically valid LLN and leads to considerable under and over diagnosis of airway obstruction
LLN z-score -1.64

80% predicted
FEV1/FVC < 0.70