Comparison of ECSC/ERS-93 to the newly published GLI-17 reference values for carbon monoxide transfer factor

Ellie Oostveen[1], Eric Derom[2], Anne-Marie Vints[1], Giuseppe Liistro[3].

1. Dept. of Respiratory Medicine, Antwerp University Hospital and University of Antwerp,

2. Dept. of Respiratory Medicine, Ghent University Hospital

3. Université Catholique de Louvain (UCL), Institute of Experimental & Clinical Research - Pole of Pneumology, ENT and Dermatology, Brussels, Belgium. Department of Pneumology, Cliniques universitaires St-Luc, Brussels

Belgium

Corresponding author: G Liistro

Cliniques Universitaires Saint-Luc

10, avenue Hippocrate

1200 Brussels, Belgium

giuseppe.liistro@uclouvain.be

T +3227642832

F +3227642831

Keywords

Carbon monoxide transfer factor
Pulmonary function tests
Reference values

Abbreviations

ECSC/ERS-93 : predicted values from the European Community for Steel and Coal / European Respiratory Society, published in 1993.

GLI-17: predicted values from the Global Lung Function Initiative, published in 2017

TL,CO: Carbon monoxide transfer factor

Abstract

Background

The new predicted values for the carbon monoxide transfer factor (TL,CO) for Caucasians by the Global Lung Function Initiative are available since September 2017. These predicted values (GLI-17) were expected, because several authors have previously shown that the predicted values of Cotes et al. (ECSC/ERS-93), overestimated TL,CO. However, the authors omitted to compare their predicted values with the ECSC/ERS-93 equations, still in use throughout Europe.

We present the differences between the two sets of predicted values and in an attempt to improve the readability, we used the contour plots instead of the classical 2-dimensional representations.

Methods

Predicted values were computed for ages between 18 and 70 years and heights between 155 and 180 cm using Matlab software with increments of one unit (1 yr., 1 cm).

Results

We have showed that GLI-17 values of TL,CO are systematically lower the those of ECSC/ERS-93, but also that the magnitude of those differences varies according to age, size and sex. More specifically, differences increase in both males and females by decreasing age and height, reaching up to 16% in males and 24 in females.

Conclusion

The predicted values of TL,CO by Cotes at al. are systematically higher than the new GLI-17 values. Plotting all the possible differences between predicted variables using contour graphs allows to identify the groups of subjects susceptible to exhibit significant changes in their predicted values. Our findings should prompt physicians to investigate how switching to GLI-17 equations affects the clinical interpretation of TL,CO measurements in a real-live setting.

Introduction

The new predicted values of TL,CO by the working group of the Global Lung Function Initiative (GLI) [1] are available since September 2017. The GLI was undertaken since the 2005 ATS-ERS Task Force had concluded that the use of the ERS '93-reference values [2] are not appropriate. However, an alternative set of reference equations for spirometry for the use in European lung function laboratories was not suggested [3]. This activated Prof. Em. Quanjer in 2006 to start collecting normal data provided by authors of publications in international journals. After the publication of Stanejovic et al. on extended, complex models to describe spirometry data [4], the GLI working group was formed which became an ERS Task Force in 2010. Their final GLI collection of more than 74.000 spirometric data, resulted in an ERJ-publication on global, multi-ethnic reference values for forced expiratory maneuvers in 2012 [5]. It confirmed previous data by Roca et al. [6] that the former ERS '93 predicted values on FEV_1 and VC were too low by about 10 to 15%. Clinically, this means that when ERS '93 predicted values are used for spirometry, the disease severity is always underestimated and that restrictive lung disorders might be "overlooked" based on apparently normal spirometric results [7].

Recently, the work of the GLI working group has advanced to the publication of new global reference values on the transfer factor (TL,CO) for Caucasians [1]. Compared with earlier published reference TL,CO-values for children, the GLI values are not that different, however, for adults, the GLI reference values are noticeably lower [1]. To our disappointment, the authors omitted to compare them with the ERS-'93 prediction equations [8], which are still in use throughout Europe today. For the clinician confronted with the switch from old to new reference equations, it is crucial to understand the potential clinical impact of that switch.

Conventionally, differences between two sets of reference equations are graphically expressed by plotting the function variable (i.e. TL,CO) as a function of age for a given value of height. Such a bi-dimensional representation has good readability, however, at the expense of the information contained in a three-dimensional plot, where both height and age are variables. To improve the legibility of graphs presenting differences between equations using height and age as variables, we propose to use a completely different method: the contour plot.

Methods

For the present study, the GLI ‘17 predicted values of TL,CO and the GLI’17 values of lower limit of normal (LLN) were expressed as percentage of the predicted TL,CO based on the ERS-‘93 equations. The computations were separately performed for males and females for ages between 18 and 80 years and heights between 155 and 190 cm with increments of one unit (1 yr, 1 cm) using Matlab software (Matlab R2014b). Each possible combination of age (n= 63) and height (n= 36) yielded variables, giving matrices of [63x36] points per sex.

Results

The matrices of the differences in predicted TL,CO of GLI ’17 and ERS ’93 (expressed as percentage of the ERS’93 predicted value) were plotted in females (Figure, A) and males (B). The shape of the lines and the non-uniform distances between these lines can be attributed to the non-linearity of the GLI-‘17 equations, which contrasts with the linearity of the ERS-‘93 equations. Figure A & B depict that the GLI-‘17 predicted values of TL,CO are systematically lower than those of ERS-’93, except for short males at advanced age. The contour lines also show that the magnitude of those differences varies according to age, size and sex. More specifically, differences increase in both males and females by decreasing age and height, reaching up to 24% in females (A) and 16% in males (B). The bottom figures depict the contour lines of the LLN-values of GLI ’17 expressed as percentage of the predicted ERS’93 value of TL,CO as a function of both age and height in females (C) and males (D). This aids the clinician who still expresses the measured TL,CO as %predicted of the ERS ’93 values to decide whether TL,CO is abnormally low according to GLI ’17 (e.g. a measured TL,CO in a 40-years-old female, 170 cm tall, of 70%predicted (according to ERS ’93) is clearly above the LLN according to GLI ’17 and thus considered as normal).

Conclusion

To summarize, our analysis indicates that omitting to switch to the GLI equations for TL,CO may lead to extra, unnecessary clinical research, e.g. CT scan, in young females who apparently exhibit a suspiciously low TL,CO according to ERS ’93 reference values. We thus strongly recommend that lung function laboratories in Europe change to GLI reference equations for forced expiration and transfer factor as soon as possible. With the implementation of new reference equations, all

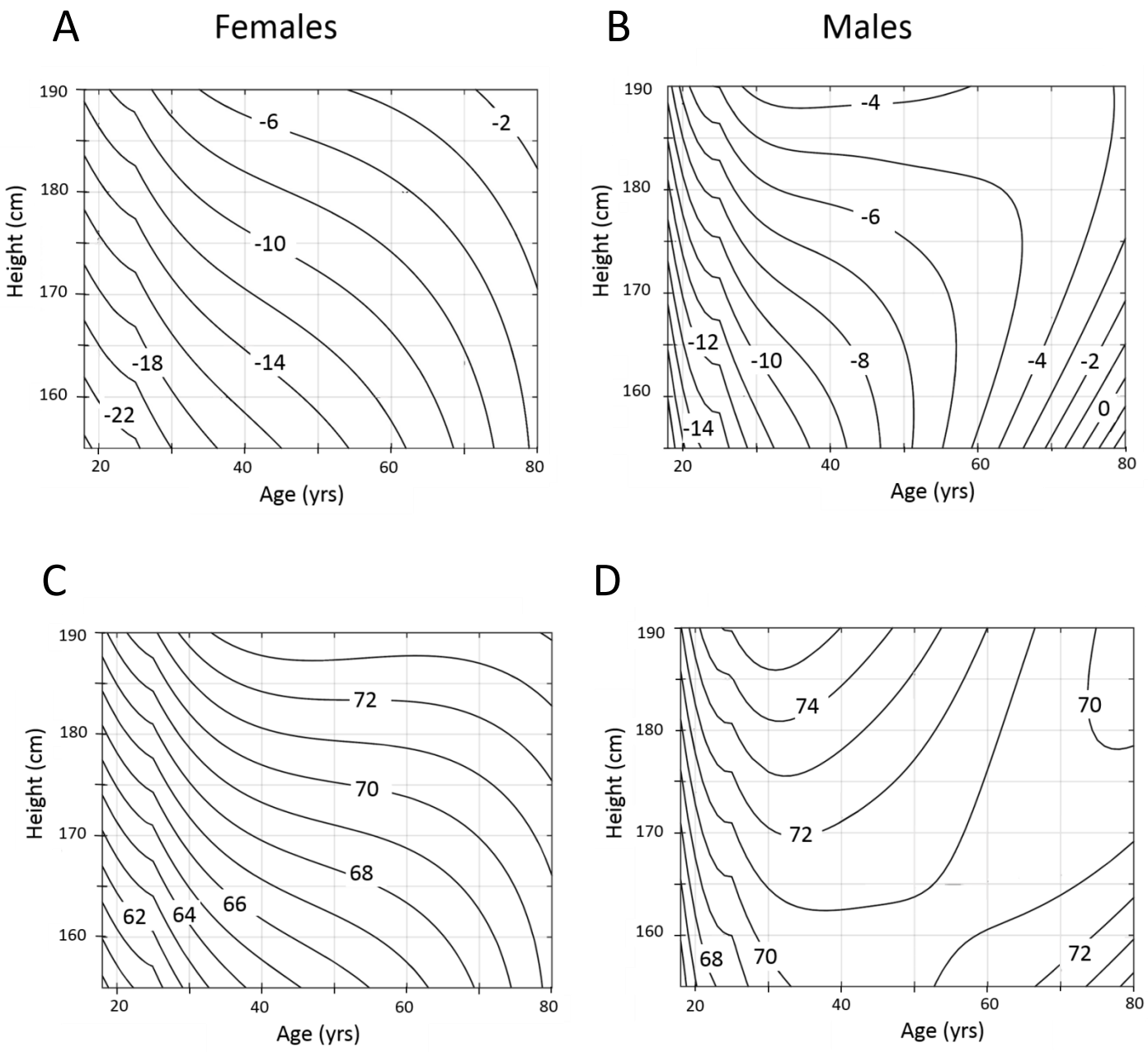
previous patient's measurements can be recalculated to reassess the patient's clinical status in the light of the revised normal values. In the meantime, our contour plots of the lower limit of GLI '17 expressed relative to the ERS '93 predicted value aids the clinicians who still use the ERS '93 equations to decide if a measured TL,CO-value is truly abnormally low.

Figure legend

Figure top: Relative difference in predicted TL,CO value between GLI '17 [1] and ERS '93 [8], expressed as percentage of the predicted TL,CO of ERS '93, as a function of age and height, for females (A) and males (B). Bottom: lower limit of the normal value according to GLI '17 expressed as relative value of the predicted TL,CO according to ERS '93, as a function of age and height, for females (C) and males (D)

Reference list

1. Stanojevic, S., et al., *Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians.* Eur Respi J, 2017. **50**(3): p. pii: 1700010. doi: 10.1183/13993003.00010-2017.
2. Quanjer, P., et al., *Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society.* Eur Respi J Suppl, 1993. **16**: p. 5-40.
3. Pellegrino, R., et al., *"ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING" Interpretative strategies for lung function tests. .* Eur Respir J, 2005. **26**: p. 948-968.
4. Stanojevic, S., et al., *Reference Ranges for Spirometry Across All Ages. A New Approach. .* Am J Crit Care Med, 2008. **177**: p. 253-260.
5. Quanjer, P., et al., *Multi-ethnic reference values for spirometry for the 3–95-yr age range: the global lung function 2012 equations.* Eur Respi J, 2012. **40**: p. 1324–1343.
6. Roca, J., et al., *References values for forced spirometry. Group of the European Community Respiratory Health Survey.* Eur Respir J, 1998. **11**(6): p. 1354-62.
7. Quanjer, P., et al., *Implications of adopting the Global Lung Initiative 2012 all-age reference equations for spirometry. .* Eur Respi J, 2013. **21**: p. 1046-1054.
8. Cotes, J., et al., *Standardization of the measurements of transfer Factor (diffusion capacity).* Eur Respi J Suppl, 1993. **16**: p. 41-52.


A
Females
B
Males
C
D
Height (cm)
Age (yrs)
190
180
170
160
20
40
60
80
-6
-2
-10
-18
-14
-22
-4
-6
-12
-10
-8
-4
-2
0
-14
72
70
68
62
64
66
74
70
72
68
70
72