"Controlled *versus* free breathing for multiple breath nitrogen washout in healthy adults". Blake M. Handley, Edward Jeagal, Robin E. Schoeffel, Tanya Badal, David G. Chapman, Catherine E. Farrow, Gregory G. King, Paul D. Robinson, Stephen Milne and Cindy Thamrin. *ERJ Open Res* 2021; 7: 00435-2020

It has recently been brought to the attention of the authors of this article that a critical sensor error exists in the Exhalyser D device (Eco Medics AG, Duernten, Switzerland), pertaining to lack of compensation for crosstalk between the oxygen and carbon dioxide sensors. Updated software (Spiroware version 3.3.1) containing a correction for that error has since been distributed by the manufacturer.

Since the data in this study were collected using that device and reported using a previous software version (3.1.6), with potential implications on study results and interpretation, the authors have reanalysed the original data in the updated software. The updated tables and figures are shown below, and have been corrected in the published article. The supplementary material for this article has also been updated.

The authors confirm that the main messages of their article remain unaltered: that the indices of ventilation heterogeneity S_{cond} and S_{acin} derived from free-breathing and controlled-breathing multiple-breath nitrogen washout protocols are not comparable, and that the differences in S_{acin}, in particular, are related to differences in the breathing pattern.

TABLE 1 Participant characteristics, lung function and multiple-breath nitrogen washout (MBNW) parameters

	Whole group	Repeatability subgroup
Females/males n	11/16	6/9
Age years median (range)	34 (19–65)	30 (23–41)
BMI kg·m^{-2}	24.6±3.4	25.1±4.2
Lung function		
FEV_1 % predicted[#]	105±14	101±30
FEV_1/FVC %	83±6	84±5
TLC_{pleth} % predicted[¶]	101±23	107±11
FRC_{pleth} % predicted[¶]	97±27	104±20
MBNW parameters		
Controlled breathing		
FRC_{CB} L	2.94±0.89	2.96±0.88
LCI_{CB}	6.49±0.47	6.39±0.36
$S_{cond_{CB}}$ L^{-1}	0.019±0.011	0.025±0.012
$S_{acin_{CB}}$ L^{-1}	0.056±0.020	0.061±0.022
V_T mL	1124±37	1127±37
V_T/FRC_{MBNW}	0.40±0.16	0.42±0.15
RR breaths·min^{-1}	10.2±0.89	9.86±1.0
Free breathing		
FRC_{FB} L	2.92±0.86	3.00±0.87
LCI_{FB}	6.70±0.59	6.57±0.57
$S_{cond_{FB}}$ L^{-1}	0.019±0.012	0.018±0.014
$S_{acin_{FB}}$ L^{-1}	0.085±0.039	0.091±0.041
V_T mL	880±324	912±304
V_T/FRC_{MBNW}	0.31±0.12	0.32±0.14
RR breaths·min^{-1}	12.3±3.53	13.6±3.10

Data are presented as mean±SD unless otherwise stated. For the repeatability subgroup, results are from the first visit. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; TLC: total lung capacity; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conductive zone ventilation heterogeneity; S_{acin}: acinar zone ventilation heterogeneity; V_T: mean tidal volume across measurements; RR: respiratory rate; pleth: body plethysmography; CB: controlled breathing protocol; FB: free breathing protocol. [#]: reference equations for predicted values from Quanjer *et al.* [13]; [¶]: reference equations for predicted values from Quanjer *et al.* [14].

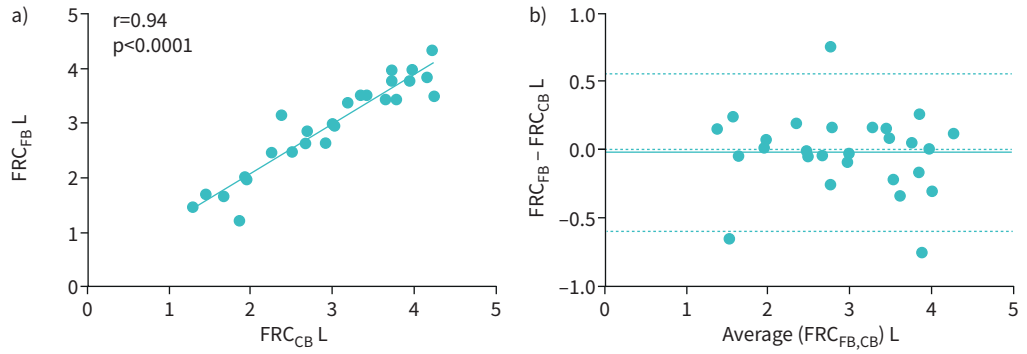

FIGURE 1 Functional residual capacity measured by controlled breathing (FRC_{CB}) and free breathing (FRC_{FB}) protocols. a) There was strong correlation between the protocols (r=0.96, p<0.0001). b) Bland–Altman plot showing good agreement between the protocols (mean difference (95% limits of agreement) −0.009 (−0.592, 0.555) L, p=0.75).

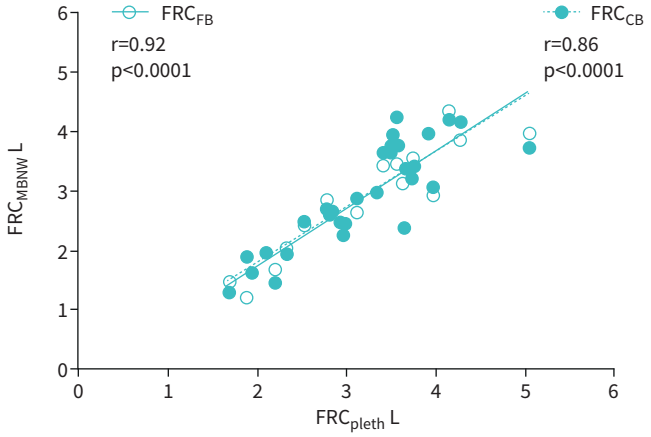

FIGURE 2 Functional residual capacity measured by controlled breathing (FRC_{CB}) and free breathing (FRC_{FB}) protocols *versus* the gold-standard body plethysmography (FRC_{pleth}). There was good correlation between FRC measured by both protocols and FRC_{pleth} (r=0.86 and r=0.92, respectively, p<0.0001 for both). MBNW: multiple breath nitrogen washout.

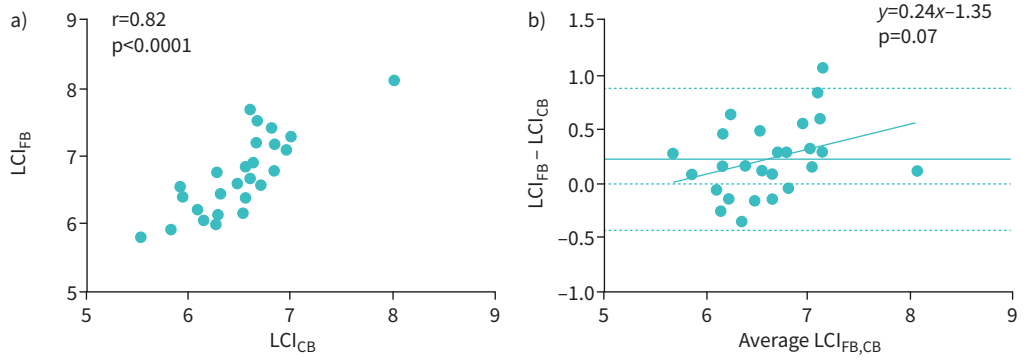

FIGURE 3 Lung clearance index measured by controlled breathing (LCI_{CB}) and free breathing (LCI_{FB}) protocols. a) There was strong correlation between the protocols (r=0.82, p<0.0001). b) Bland–Altman plot showing that free breathing produced a higher LCI compared to controlled breathing (mean difference (95% limits of agreement) 0.21 (−0.44, 0.87), p=0.003)). There was a trend towards proportional bias confirmed by linear regression (p=0.07).

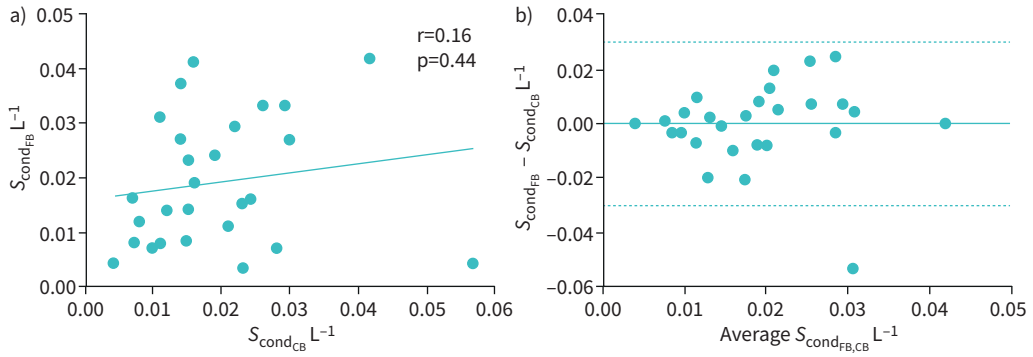

FIGURE 4 Ventilation heterogeneity in conducting airways measured by controlled breathing ($S_{cond_{CB}}$) and free breathing ($S_{cond_{FB}}$) protocols. a) There was no significant correlation between the protocols (r=0.16, p=0.44). b) Bland–Altman plot showing high between-protocol variability (mean difference (95% limits of agreement) 0.0002 (−0.03, 0.03 L^{-1}, p=0.94)). There was no evidence of proportional bias, regardless of outliers (p=0.83).

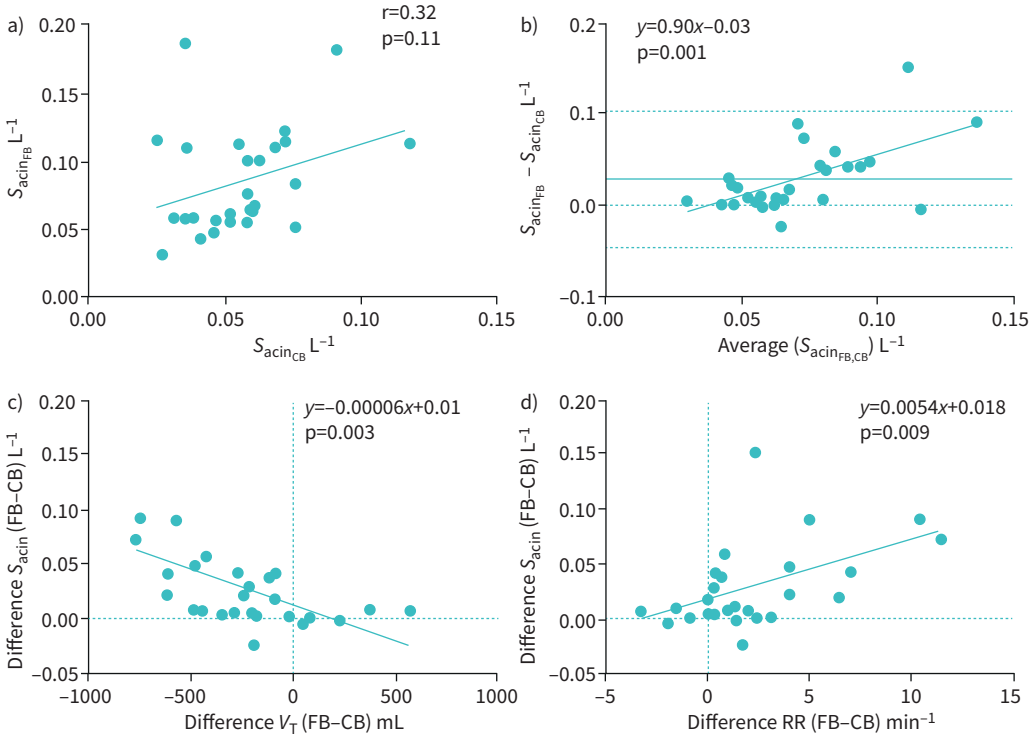

FIGURE 5 Ventilation heterogeneity in distal/intra-acinar airways measured by controlled breathing ($S_{acin_{CB}}$) and free breathing ($S_{acin_{FB}}$) protocols. a) There was relatively poor correlation between the protocols (r=0.33, p=0.11). b) Bland–Altman plot showing that free breathing produced higher S_{acin} compared to controlled breathing (mean difference (95% limits of agreement) 0.03 (−0.045, 0.103) L^{-1}, p<0.0005)). There was also significant proportional bias confirmed by linear regression (p=0.002). The between-protocol difference in S_{acin} ($S_{acin_{FB}}$–$S_{acin_{CB}}$) was predicted by the between-protocol differences in c) tidal volume ($V_{T_{FB}}$–$V_{T_{CB}}$, regression p=0.004) and d) respiratory rate (RR_{FB}–RR_{CB}, regression p=0.009). One participant was excluded from S_{acin} analyses due to negative value in one trial.

TABLE 2 Within- and between-session variability for the controlled and free breathing protocols

	Within-session CoV	Between-session difference	95% LOA	Between-session ICC
Controlled breathing				
FRC_{CB} L	3.0±1.9%	−0.02±0.47	−0.94–0.91	0.927
LCI_{CB}	2.4±1.7%	0.13±0.34	−0.53±0.79	0.849
$S_{cond_{CB}}$ L^{-1}		−0.003±0.009	−0.021–0.015	0.867
$S_{acin_{CB}}$ L^{-1}		−0.002±0.02	−0.039–0.034	0.828
Free breathing				
FRC_{FB} L	3.9±2.4%	−0.04±0.026	−0.54–0.47	0.979
LCI_{FB}	3.1±2.2%	0.15±0.51	−0.84–1.14	0.704
$S_{cond_{FB}}$ L^{-1}		0.006±0.016	−0.026–0.038	0.411
$S_{acin_{FB}}$ L^{-1}		0.003±0.054	−0.103–0.109	0.278

Data are presented as mean±SD unless otherwise stated. Mean differences are Visit 2 minus Visit 1. CoV: coefficient of variation; 95% LOA: 95% limits of agreement; ICC: intra-class correlation coefficient; FRC: functional residual capacity; LCI: lung clearance index; S_{cond}: conducting airways ventilation heterogeneity; S_{acin}: distal/intra-acinar airways ventilation heterogeneity.

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