Ventilation heterogeneity in smokers :
role of unequal lung expansion and peripheral lung structure

Sylvia Verbanck, Mathias Polfliet, Daniel Schuermans,
Bart Ilsen, Johan de Mey, Eef Vanderhelst, Jef Vandemeulebroucke.

ONLINE SUPPLEMENT

Experimental and predicted MBW concentration curves

Figure E1 shows in both of its panels, the expected MBW concentration curve (open circles) obtained by recombining the CT derived specific ventilation on all lung voxels. This is the semilog N_2 washout concentration curve that would be predicted for each subject, if measured at the mouth and if only heterogeneity of local expansion were at play. The deviation from linearity due to local ventilation (expansion) heterogeneity can be appreciated versus the corresponding linear washout curves expected from a perfectly homogeneous lung of the same volume (dashed line). Also shown are the actual MBW concentration curves (solid circles +SD bars) obtained experimentally at the mouth in these two smokers, one with a relatively low and another with a high degree of acinar ventilation heterogeneity compared to the group as a whole (Table 1).

From any one simulated or experimental N_2 washout curve, both alveolar mixing efficiency (AME) and lung clearance index (LCI) are derived; in Figure E1 both indices are indicated on the experimental curve in panel B. AME is computed from the first breath and is simply defined as the ratio of N_2 concentration of the first exhalation to that which would be ideally obtained by perfect dilution of a subject's tidal volume into the subject's lung volume with a given subject's dead space. The exact formulation for AME can be found in the original studies (E1) or in Verbanck et al (E2) where the instrumental dead space is explicitly incorporated. LCI is defined as the intercept of the mean expired N_2 concentration curve with the 1/40th pre-test concentration line, which is a standard definition as per recent guidelines (E3).

In both panels of Figure E1, N_2 concentration for the first breath is seen to decrease with respect to pre-test N_2 concentration as a result of dilution (dashed line) and various sources of ventilation heterogeneity (open and closed circles). In either patient, unequal expansion alone (open circles) cannot account for the degree of experimental N_2 concentration decrease at onset of MBW (closed circles). The smoker with the greatest acinar abnormality (panel B) displays the greatest decrease in N_2 concentration at the MBW onset. Since the amount of N_2 that is not expired by the subject at the onset of the MBW, eventually needs to get washed out towards the end of the MBW, a lower N_2 concentration at onset (and thus lower AME) automatically results in a corresponding increase in N_2 concentration at end of washout (and thus increased LCI). The resulting intrinsic relationship between AME en LCI has been scrutinized by prior lung model simulations of acinar ventilation heterogeneity (E2).

Effect of Body posture on MBW

Differences between upright and supine MBW indices were significant for FRC ($P<0.001$), LCI ($P=0.001$), AME ($P<0.001$), Sacin ($P=0.004$), but not for Scond ($P>0.1$). On average, the greatest changes were observed for FRC (-18%) and Sacin (+11%). Correlations between the postural change in any of the above indices to postural change in FRC only reached significance for Sacin (Figure E2) : $Sacin_{(SUPINE)}$-$Sacin_{(UPRIGHT)}$ was inversely related to the difference $FRC_{(SUPINE)}$-$FRC_{(UPRIGHT)}$ ($r=-0.42$; $P=0.0025$).

REFERENCES

E1) Crawford AB, Cotton DJ, Paiva M, Engel LA. Effect of lung volume on ventilation distribution. J Appl Physiol 1989;66:2502-2510.

E2) Verbanck S, Paiva M. A simulation study of diffusion-convection interaction and its effect on multiple breath washout indices. Respir Physiol Neurobiol 2018;258:5-11.

E3) Robinson PD, Latzin P, Verbanck S, Hall GL, Horsley A, Gappa M, Thamrin C, Arets HG, Aurora P, Fuchs SI, King GG, Lum S, Macleod K, Paiva M, Pillow JJ, Ranganathan S, Ratjen F, Singer F, Sonnappa S, Stocks J, Subbarao P, Thompson BR, Gustafsson PM. Consensus statement for inert gas washout measurement using multiple- and single- breath tests. Eur Respir J 2013;41:507-522.

E4) Galbán CJ, Han MK, Boes JL, Chughtai KA, Meyer CR, Johnson TD, Galbán S,Rehemtulla A, Kazerooni EA, Martinez FJ, Ross BD. Computed tomography-based biomarker provides unique signature for diagnosis of COPD phenotypes and disease progression. Nat Med 2012;18:1711-1715.

FIGURE LEGENDS

Figure E1 :

Semilog N_2 washout concentration curves : dots: predicted by ideal mixing; open circles: predicted based on CT-derived unequal local expansion; closed circles: average of 3 experimental MBW measurements at the mouth (mean+SD bar). Note that all curves cross over to obtain similar total exhaled N_2 concentration by the end of the MBW test, but the similar area under the N_2 curves cannot be appreciated here due to the semilog representation; grey area indicates N_2 concentration below 1/40 pre-test value.

Panel A :

A smoker with relatively low degree of acinar ventilation abnormality, where N_2 concentration from the 1^{st} breath of the experimental MBW falls slightly below that predicted by local expansion heterogeneity alone, and the cross-over of N_2 washout curves leads to a slightly longer N_2 washout tail. Ideal mixing for this subject would obtain AME=100% (by definition) and LCI=4.2. Local expansion heterogeneity leads to AME=97% and LCI=6.2; additional acinar abnormality effect further decreases AME to 85% and increases LCI to 6.9 in this subject.

Panel B :

A smoker with relatively high degree of acinar ventilation abnormality, where N_2 concentration from the 1^{st} breath of the experimental MBW falls markedly below that predicted by local expansion heterogeneity alone, and the cross-over of N_2 washout curves leads to a considerably longer N_2 washout tail. Ideal mixing for this subject would obtain AME=100% (by definition) and

LCI=4.5. Local expansion heterogeneity leads to AME=98% and LCI=5.6; additional acinar abnormality effect further decreases AME to 68% and increases LCI to 9.8 in this subject.

Figure E2 :

Changes in acinar ventilation heterogeneity (Sacin) from upright to supine, versus corresponding FRC changes. While FRC decreases from upright to supine, corresponding Sacin is seen to increase (r=-0.42; P=0.0025).

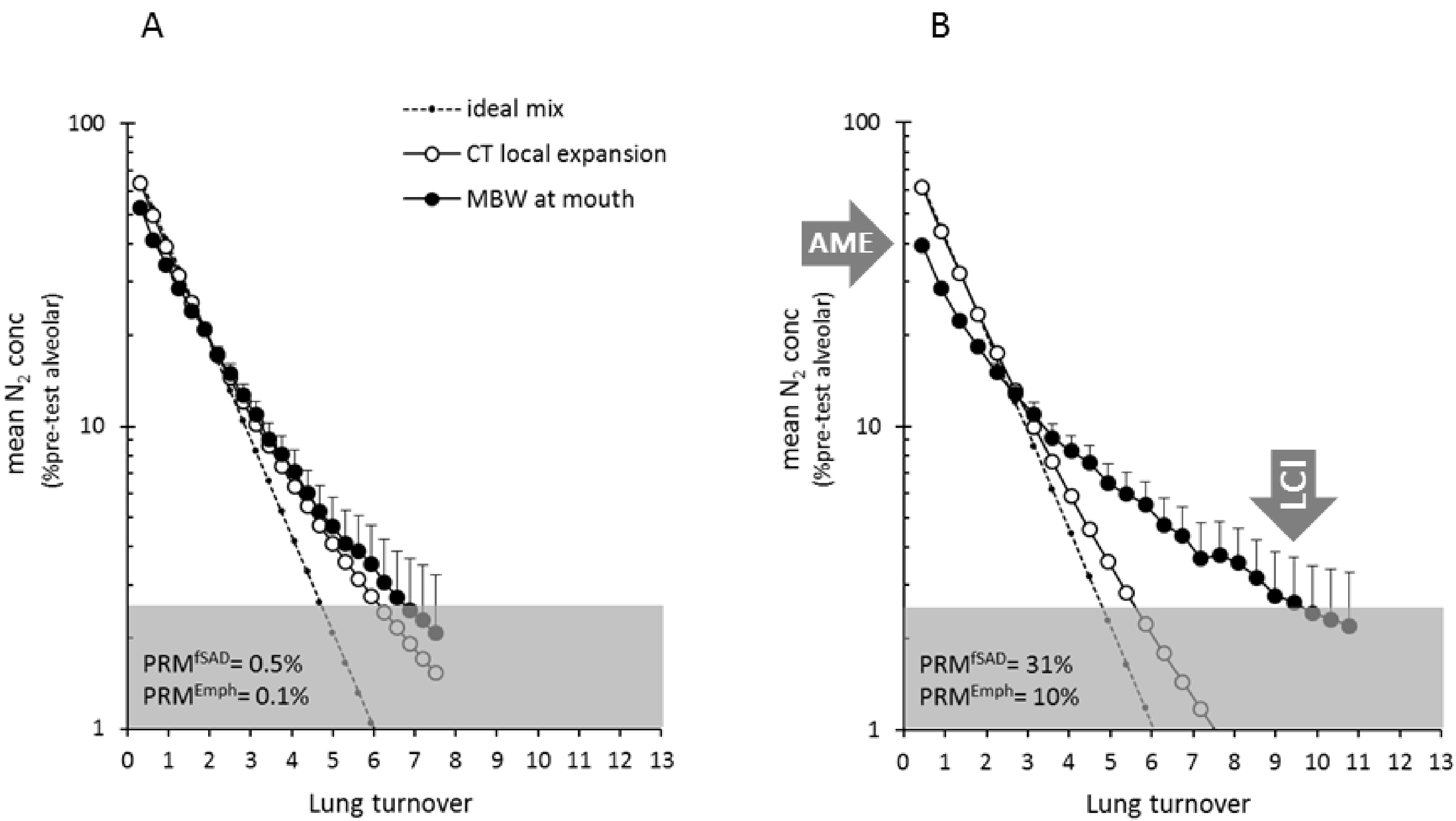
Figure E3 :

Representation of our smoker cohort in terms of its CT metrics PRM^{Emph}, PRM^{fSAD} (respectively, percentage lung affected by emphysema and functional small airway disease) in a plot of exactly same format and color coding as in Galban et al (E4), where they represented 194 subjects of the COPDGene cohort (their supplementary figure 3). Our smokers (falling in the GOLD0-III range) show a very similar behavior, at least in terms of respective ranges of PRM indices.

Figure E4 :

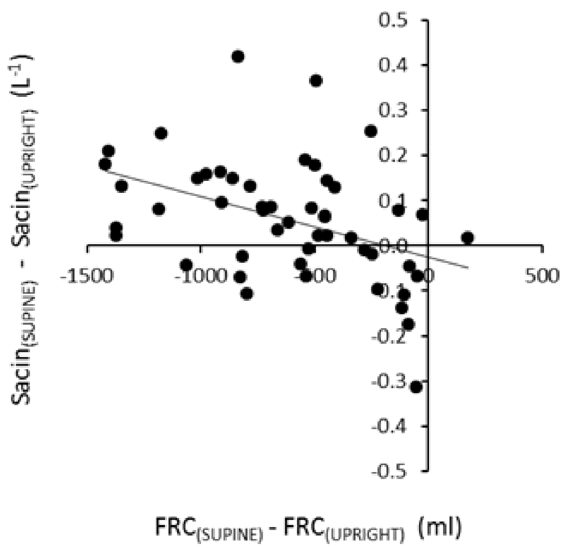
Gravitational gradient in specific ventilation ($\Delta V/V$ gradient) versus distance in the line of gravity with the subject supine, versus their PRM^{fSAD} (CT based functional small airway disease PRM index) in all smokers. There is a direct correlation between the negative gravitational gradient and PRM^{fSAD} (r=+0.65; P<0.001). At PRM^{fSAD}=0, the intercept value for $\Delta V/V$ gradient of -0.066 cm^{-1} is a normal value for supine man.

Figure E1



A
B
ideal mix
CT local expansion
MBW at mouth
100
10
1
mean N_2 conc
(%pre-test alveolar)
PRM^{fSAD}= 0.5%
PRM^{Emph}= 0.1%
PRM^{fSAD}= 31%
PRM^{Emph}= 10%
AME
LCI
0 1 2 3 4 5 6 7 8 9 10 11 12 13
Lung turnover

Figure E2



0.5
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
-0.5
-1500
-1000
-500
0
500
Sacin(SUPINE) - Sacin(UPRIGHT) (L-1)
FRC(SUPINE) - FRC(UPRIGHT) (ml)

Figure E3

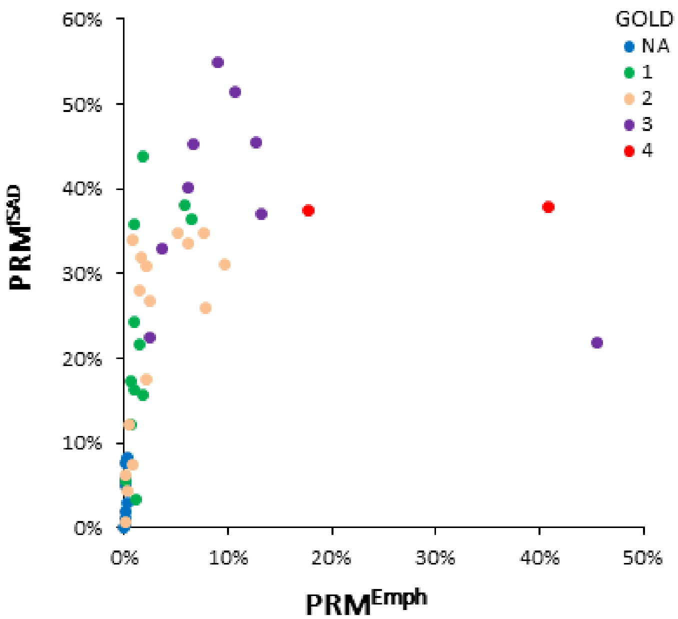
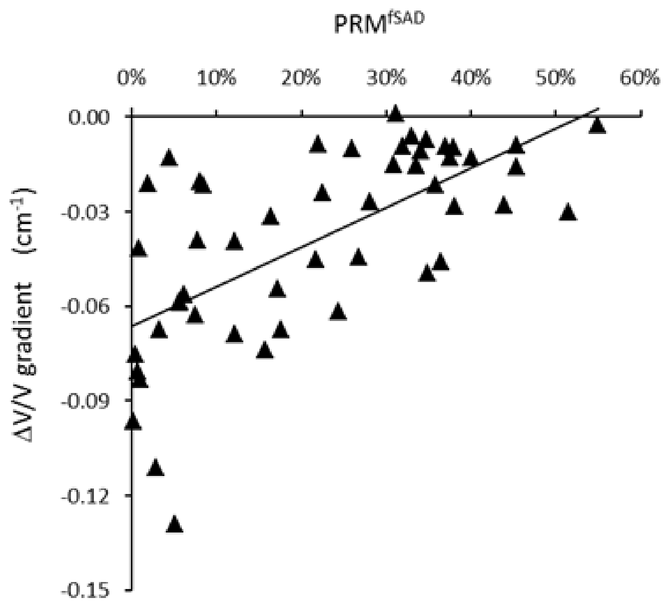


Figure E4


PRM^{fSAD}
0%
10%
20%
30%
40%
50%
60%
0.00
-0.03
-0.06
-0.09
-0.12
-0.15
ΔV/V gradient (cm^{-1})