Ventilation heterogeneity in obesity

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Pellegrino R, Gobbi A, Antonelli A, Torchio R, Gulotta C, Pellegrino GM, Dellacà R, Hyatt RE, Brusasco V. Ventilation heterogeneity in obesity. *J Appl Physiol* 116: 1175–1181, 2014. First published March 20, 2014; doi:10.1152/japplphysiol.01339.2013.—Obesity is associated with important decrements in lung volumes. Despite this, ventilation remains normally or near normally distributed at least for moderate decrements in functional residual capacity (FRC). We tested the hypothesis that this is because maximum flow increases presumably as a result of an increased lung elastic recoil. Forced expiratory flows corrected for thoracic gas compression volume, lung volumes, and forced oscillation technique at 5–11–19 Hz were measured in 133 healthy subjects with a body mass index (BMI) ranging from 18 to 50 kg/m^2. Short-term temporal variability of ventilation heterogeneity was estimated from the interquartile range of the frequency distribution of the difference in inspiratory resistance between 5 and 19 Hz (R_{5-19_IQR}). FRC % predicted negatively correlated with BMI ($r = -0.72$, $P < 0.001$) and with an increase in slope of either maximal ($r = -0.34$, $P < 0.01$) or partial flow-volume curves ($r = -0.30$, $P < 0.01$). Together with a slight decrease in residual volume, this suggests an increased lung elastic recoil. Regression analysis of R_{5-19_IQR} against FRC % predicted and expiratory reserve volume (ERV) yielded significantly higher correlation coefficients by nonlinear than linear fitting models ($r^2 = 0.40$ vs. 0.30 for FRC % predicted and $r^2 = 0.28$ vs. 0.19 for ERV). In conclusion, temporal variability of ventilation heterogeneities increases in obesity only when FRC falls approximately below 65% of predicted or ERV below 0.6 liters. Above these thresholds distribution is quite well preserved presumably as a result of an increase in lung recoil.

body mass index; lung volumes; respiratory resistance; forced oscillation technique

OBESITY is consistently associated with decrements in lung volumes, with functional residual capacity (FRC) being reduced more than residual volume (RV) (4, 19, 20, 22–24, 32, 45, 51, 54, 60). Thus expiratory reserve volume (ERV) markedly decreases and tidal breathing takes place at a low lung volume. Under these conditions, some airways tend to narrow or even close during expiration, a fact expected to cause ventilation heterogeneities (51). Despite such functional changes, oxygen saturation has been found to be within the normal range (46, 54, 60) or only slightly reduced (4, 51) and interregional ventilation distribution preserved even for elevated body mass index (BMI) values (20). An early study using ^{133}Xe showed that ventilation was abnormally shifted to upper lung regions in a group of obese subjects with extremely reduced ERV (21 ± 9% of predicted) but not in a group with moderately reduced ERV (50 ± 8% of predicted), even if BMI was similar (38 ± 5 vs. 40 ± 4) (20). Analogous results were reported in two other studies (9, 22), supporting the idea that the decrease of FRC in obesity does not critically affect the interregional distribution of ventilation and gas exchange until ERV is almost obliterated.

Several investigations reported an increase in lung elastic recoil with a reduction of lung compliance both in awake (3, 19, 46) and anesthetized-paralyzed obese subjects (41). In only one study lung compliance was found to be normal in obesity (38) but this does not disprove that lung elastic recoil was increased. Indeed, if RV is decreased as reported in several studies (23, 24, 45, 51, 57), then a normal lung compliance would reflect a parallel shift of the pressure-volume curve, thus suggesting higher lung recoil pressure at all lung volumes.

Lung elastic recoil is a major determinant of airway caliber and thus flow (35). We reasoned that if obesity is associated with an increase in lung elastic recoil and thus flow, then this could help explain why ventilation remains quite homogeneously distributed across the lungs despite the decrease in FRC, unless the latter is severely reduced. To test this hypothesis we studied lung function in subjects with BMI ranging from 18 to 50 kg/m^2. Ventilation heterogeneity was inferred from the variability of the frequency dependence of respiratory resistance measured by forced oscillation technique. The underlying assumptions were that ventilation distribution can be assessed from the difference in respiratory resistance between 5 and 19 Hz (R_{5-19}) (10, 13, 28, 30, 39, 42, 47) and its variability over time as estimated from the short-term interquartile range of probability density (R_{5-19_IQR}) can provide a better estimate than mean value (12, 49, 50).

METHODS

Subjects

The study was conducted in 133 subjects with no history of smoking, free of any disease potentially affecting lung function other than obesity. They were divided into three groups according to the BMI (Table 1): 49 under-to-normal weight (BMI 18–25 kg/m^2), 32 overweight (BMI 26–30 kg/m^2), and 52 obese (BMI >30 kg/m^2). The study protocol was approved by the local Ethical Committee, and written informed consent was obtained from each subject prior to the study.

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Table 1. *Subjects' anthropometric characteristics and main lung functional data*

	Controls	Overweight	Obesity	ANOVA
Sex, M/F	21/28	19/13	17/35	0.06
Age, yr	43 ± 11*†	52 ± 10*	49 ± 11†	0.002
Height, cm	169 ± 8*	166 ± 11	163 ± 9*	0.014
BMI, kg/m^2	22 ± 2#‡	27 ± 2#§	39 ± 6‡§	<0.001
FEV$_1$, liters	3.46 ± 0.76‡	3.27 ± 0.69§	2.81 ± 0.78‡§	<0.001
FEV$_1$, % of predicted	107 ± 10†	110 ± 13¶	100 ± 14†¶	0.001
VC, liters	4.24 ± 0.91‡	4.04 ± 0.93§	3.45 ± 0.91‡§	<0.001
VC, % of predicted	109 ± 11	110 ± 17	103 ± 15	0.11
FEV$_1$/VC, %	82 ± 6	81 ± 5	81 ± 5	0.79
TLC, % of predicted	106 ± 9#†	101 ± 11#¶	94 ± 11†¶	<0.001
FRC, % of predicted	111 ± 15*†	88 ± 14*¶	71 ± 14†¶	<0.001
RV, % of predicted	104 ± 15*†	92 ± 13*§	84 ± 16†§	<0.001
ERV, liters	1.46 ± 0.43*†	0.92 ± 0.51*§	0.51 ± 0.27†§	<0.001
DL$_{CO}$, % predicted	92 ± 10	95 ± 15	96 ± 14	0.222
DL$_{CO}$/VA, % predicted	98 ± 12‡	104 ± 13	109 ± 19‡	0.008
SaO$_2$, %	97 ± 2‡	96 ± 1	96 ± 2‡	0.007

Data are means ± SD. BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; VC, slow inspiratory vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; ERV, expiratory volume reserve; DL$_{CO}$, diffusing lung capacity for carbon monoxide; VA, alveolar volume. SaO$_2$, oxygen saturation. Differences between groups, except for sex, were examined by analysis of variance (ANOVA) and Holm-Sidak post hoc test whenever applicable. Pairs of symbols indicate statistically significant differences between conditions. #, ‡, §: $P < 0.05$; *, †, ¶: $P < 0.01$. Sex categories were examined with χ^2.

Lung Function Measurements

Spirometry and lung volumes were measured in a body plethysmograph (Autobox, SensorMedics, CA) following the ATS/ERS recommendations (36, 56). Briefly, after at least four regular breaths, thoracic gas volume was measured with the subject panting against a closed shutter at a frequency slightly <1 Hz, cheeks being supported by hands. After the shutter was opened, the subjects took a full inspiratory capacity (IC) and then forcefully expired from total lung capacity (TLC) to RV for at least 6 s to measure forced vital capacity (FVC) and 1-s forced expiratory volume (FEV$_1$). The same procedure was used to measure the partial flow-volume curves with the only difference that the forced expiratory maneuver was initiated from about 70% of FVC (40). FRC was calculated from thoracic gas volume corrected for any difference between the volume at which the shutter was closed and the average end-expiratory tidal volume of the four preceding regular breaths. Single-breath lung diffusion capacity for carbon monoxide (DL$_{CO}$) was measured following the ATS/ERS recommendations (31). Predicted values were from Quanjer et al. (43) for spirometry and lung volumes and from Cotes et al. (7) for DL$_{CO}$.

Respiratory impedance was measured by a forced oscillation system previously described (8, 14, 15). Sinusoidal pressure oscillations (5, 11, and 19 Hz; ~2 cmH$_2$O amplitude) were generated by a 16-cm-diameter loudspeaker (model CW161N, Ciare, Italy) and applied at the mouth during tidal breathing. The loudspeaker was mounted in a rigid plastic box and connected in parallel to a mesh pneumotachograph and mouthpiece on one side and to a low-resistance high-inertance tube on the other side. Overall load under this breathing frequency was 0.98 cmH$_2$O·l·s^{-1}. Airway opening pressure and flow were recorded by piezoresistive transducers (DCXL10DS and DCXL01DS Sensortechnics, respectively) and sampled at 200 Hz. A 15 l/min bias flow of air generated by an air pump (CMP08, 3A

Health Care) was used to reduce dead space to ~35 ml. Respiratory resistance and reactance were computed by a least-squares algorithm (25, 26) at 5 Hz (R$_5$ and X$_5$, respectively) and 19 Hz (R$_{19}$ and X$_{19}$, respectively). Artifacts due to glottis closure or expiratory airflow limitation were avoided by discarding breaths showing any of the following features: *1*) tidal volume <0.1 liter or >2.0 liter; *2*) difference between measured flow oscillation and ideal sine wave with the same Fourier coefficients >0.2 (34); and *3*) ratio of minimum to average X$_5$ > 3.5 (14). The same breaths were used to measure tidal volume (V$_T$), breathing frequency (BF), and minute ventilation (V̇$_E$).

Study Protocol

Prestudy day. The subjects were recruited from the medical staff of the hospital and local advertisement. Those who accepted to participate attended the laboratory on a prescreening day for medical history and clinical examination including measurements of blood pressure, heart rate, and simple spirometry. If the inclusion/exclusion criteria were met, the subjects were informed of the aim and protocol of the study and requested to sign the consent.

Study day. The following measurements were obtained: lung volumes, three sets of partial and maximal forced expiratory maneuvers in the body plethysmograph, DL$_{CO}$, impedance during 5 min tidal breathing followed by a final deep inhalation (DI), and oxygen saturation (SPIROPRO, Viasys Healthcare, Yorba Linda, CA).

Data Reduction and Statistical Analysis

Mean R$_5$, X$_5$, R$_{5-19}$, and R$_{5-19\_IQR}$ were calculated over the tidal breaths recorded before the DI. Specific inspiratory conductance (sG$_5$) was calculated as 1/(R$_5$·FRC).

Maximal and partial forced expiratory flows recorded at the mouth were plotted against plethysmographic volume to correct for thoracic gas compression. The slopes of maximal and partial flow-volume curves (FV-slmax and FV-slpart, respectively) were then calculated by linear regression analysis over the linear part of the descending limb of flow-volume curves below the notch. Expiratory reserve volume (ERV) was computed from the difference between FRC and RV.

Differences between groups were tested for statistical significance by a one-way analysis of variance (ANOVA) with Holm-Sidak post hoc test for multiple comparisons or χ^2 with Yates correction wherever applicable.

Relationships between lung function parameters were estimated by linear and nonlinear regression analyses. The nonlinear model that provided the highest increase in the adjusted r^2 of the fitting had the following hyperbolic form: $y = a/(x + b)$. Comparison of the goodness-of-fit between a linear and nonlinear model was done by the Akaike information criterion (AIC). The probability that the nonlinear model was more appropriate than the linear model was estimated from the evidence ratio (ER) (18), with the greater the ER, the more appropriate the model.

Values of $P < 0.05$ were considered statistically significant. Data are presented as means ± SD.

A minimum sample size of at least 127 subjects was required for a power of 0.95 to obtain a correlation coefficient of at least 0.4 between R$_{5-19\_IQR}$ and FRC % predicted, or ERV.

RESULTS

Group Differences

Standard pulmonary function tests showed significant reductions of static lung volumes, i.e., TLC, FRC, RV, ERV, in both overweight and obese compared with under-to-normal weight subjects and also in obese compared with overweight subjects (Table 1). Forced oscillation data showed significant increments of both R$_5$ and R$_{19}$ in obese compared with either under-to-normal weight or overweight subjects (Table 2).

Table 2. *Main FOT and breathing pattern parameters*

	Controls	Overweight	Obesity	ANOVA
R_5, cmH$_2$O·s·l^{-1}	2.39 ± 0.53‡	2.84 ± 1.08§	3.90 ± 1.13‡§	<0.001
R_{19}, cmH$_2$O·s·l^{-1}	2.53 ± 0.54‡	2.77 ± 1.12§	3.60 ± 1.03‡§	<0.001
R_{5-19}, cmH$_2$O·s·l^{-1}	-0.15 ± 0.18‡	-0.06 ± 0.22§	0.30 ± 0.42‡§	<0.001
X_5, cmH$_2$O·s·l^{-1}	-0.71 ± 0.24‡	-0.96 ± 0.56§	-1.32 ± 0.46‡§	<0.001
sG_5, cmH$_2$O^{-1}·s^{-1}	0.13 ± 0.03	0.15 ± 0.04	0.14 ± 0.04	0.08
R_5, IQR	0.24 ± 0.13‡	0.28 ± 0.21§	0.52 ± 0.34‡§	<0.001
R_{5-19}, IQR	0.12 ± 0.05#‡	0.17 ± 0.07#§	0.28 ± 0.16‡§	<0.001
V_T, liters	0.87 ± 0.34	0.86 ± 0.32	0.96 ± 0.37	0.168
BF, min^{-1}	13 ± 4	14 ± 4	15 ± 4	0.158
$\dot{V}_E$, l/min	10.7 ± 3.1‡	11.1 ± 4.0§	13.5 ± 4.4‡§	0.002

Data are means ± SD. FOT, forced oscillation technique; R_5 and R_{19}, inspiratory resistance at 5 and 19 Hz, respectively; X_5, inspiratory reactance at 5 Hz; sG_5, specific inspiratory conductance at 5 Hz; IQR, interquartile range; R_{5-min}, inspiratory resistance at 5 at maximum lung inflation; V_T, tidal volume; BF, breathing frequency; $\dot{V}_E$, minute ventilation. Pairs of symbols indicate statistically significant differences between conditions. #, ‡, §: $P < 0.05$.

These differences were associated with a significantly more negative X_5, a negative frequency dependence of resistance (positive R_{5-19} difference), and increments of both R_{5_IQR} and R_{5-19_IQR}. Average FV-sl$_{max}$ and FV-sl$_{part}$ were slightly higher in the overweight and obese subjects compared with their counterpart (Table 3).

Relationships Between Variables

Significant linear correlations were observed between BMI and FEV$_1$% predicted ($r = -0.37$, $P < 0.01$), VC% predicted ($r = -0.29$, $P < 0.01$), FRC % predicted ($r = -0.72$, $P < 0.001$), TLC% predicted ($r = -0.52$, $P = 0.001$), and RV% predicted ($r = -0.46$, $P = 0.005$) and absolute values of ERV ($r = -0.70$, $P = 0.001$), R_5 ($r = 0.64$, $P = 0.001$), R_{5_IQR} ($r = 0.55$, $P = 0.001$), R_{5-19} ($r = 0.65$, $P = 0.001$), R_{5-19_IQR} ($r = 0.69$, $P = 0.001$), X_5 ($r = -0.57$, $P = 0.001$) (Fig. 1). No significant relationship was observed between BMI and FEV$_1$/VC ($r = 0.09$, $P = 0.31$). Altogether these findings are consistent with BMI causing a progressive restrictive disorder with decrease in airway caliber within the tidal breathing range and ventilation heterogeneities.

Nonlinear regression analysis of R_{5-19_IQR} against FRC (% predicted) and absolute ERV yielded better goodness of fit than linear analysis. With FRC, the adjusted r^2 was 0.40 and AIC -568 by nonlinear model vs. 0.30 and -586 by linear model (ER = 8999); with ERV, the adjusted r^2 was 0.29 and AIC -562 with nonlinear model vs. 0.19 and -579 (ER = 3705). Visual inspection of these relationships (Fig. 2) suggests that mechanical heterogeneity developed when FRC decreased approximately below 65% of predicted or ERV below 0.6 liter.

The decrease in FRC was correlated with a slight but significant increase in FV-sl$_{max}$ ($r = -0.34$, $P < 0.01$) and FV-sl$_{part}$ ($r = -0.30$, $P < 0.01$) (Fig. 3). Together with a decrease in RV and similar sG_5, this is suggestive of increased

Table 3. *Flow-volume data*

	Controls	Overweight	Obesity	ANOVA
FV-sl$_{max}$, s^{-1}	0.16 ± 0.06#	0.20 ± 0.06#	0.18 ± 0.05	0.019
FV-sl$_{part}$, s^{-1}	0.16 ± 0.06	0.20 ± 0.08	0.18 ± 0.07	0.055

Data are means ± SD. FV-sl$_{max}$ and FV-sl$_{part}$, slopes of the plethysmographic maximal and partial flow-volume loops, respectively. Pairs of symbols indicate statistically significant differences between conditions: #$P < 0.05$.
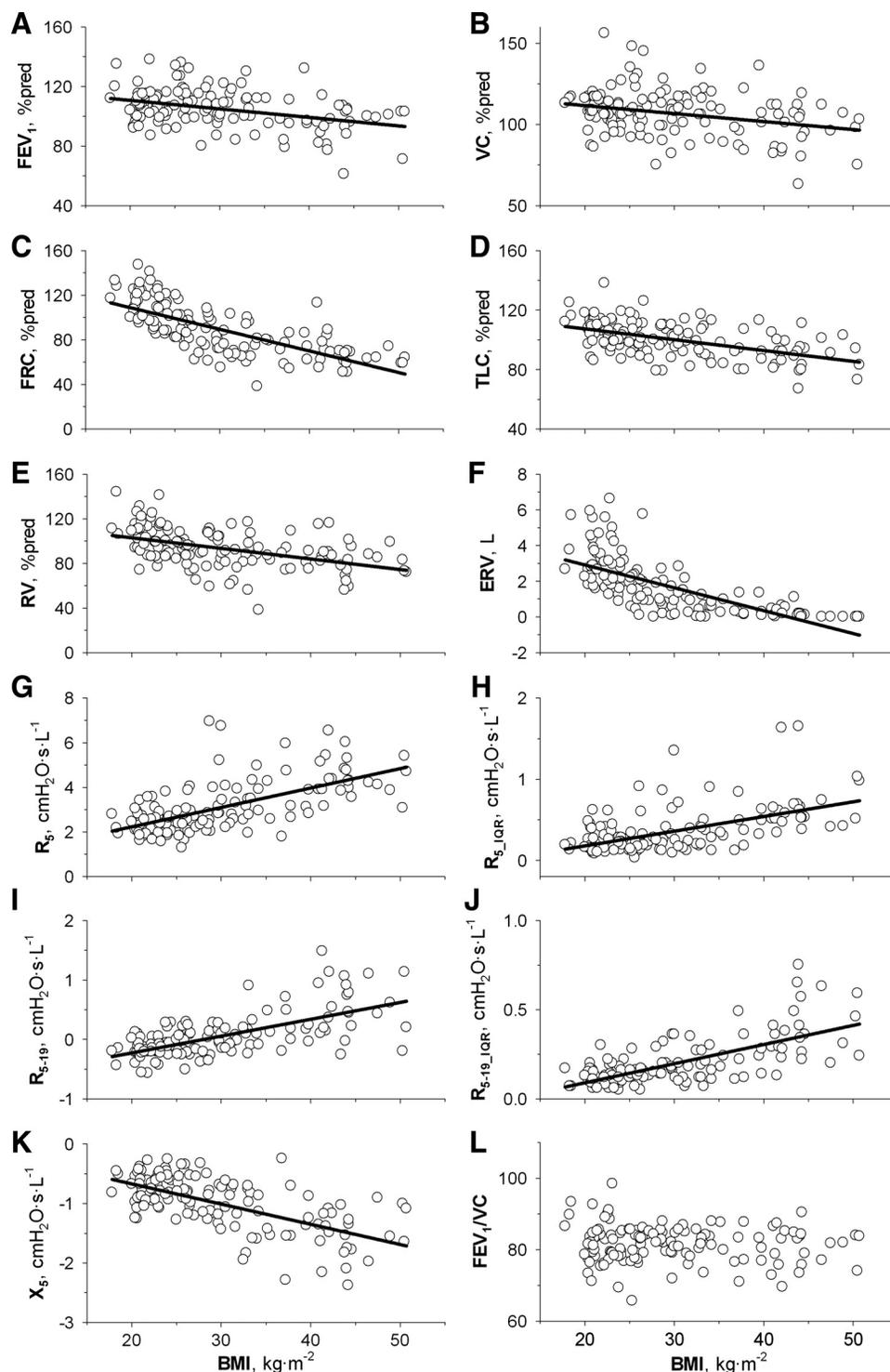
lung elastic recoil. No significant differences were observed between FV-sl$_{max}$ and FV-sl$_{part}$ ($P = 0.13$).

DL$_{CO}$/VA but not DL$_{CO}$ was significantly correlated with BMI ($r = 0.34$; $P = 0.001$), % predicted FRC ($r = -0.314$ $P < 0.001$), and absolute ERV ($r = -0.197$; $P < 0.03$).

SaO$_2$ was weakly but significantly correlated with BMI ($r = -0.35$; $P < 0.001$), % predicted FRC ($r = 0.23$; $P < 0.01$), and R_{5-19_IQR} ($r = -0.19$, $P < 0.03$). $\dot{V}_E$ slightly increased with BMI ($r = 0.37$, $P < 0.05$) as a result of an increase in breathing frequency ($r = 0.47$, $P < 0.05$).

DISCUSSION

The main results of this study are that *1*) R_{5-19_IQR} increased exponentially with the reduction of FRC and hyperbolically with the reduction of ERV, suggesting that ventilation heterogeneities develop in obesity when FRC decreases approximately below 65% of predicted, or ERV below 0.6 liter, whereas it remains near normal above these thresholds; and *2*) the slope of flow-volume loop was weakly but significantly correlated with the decrease in FRC, suggesting an increased lung stiffness associated with reduction of lung volume in obesity.

Comments on Methodology

In this study we used a forced oscillation technique to assess ventilation heterogeneity. Modeling and experimental studies have suggested that low-frequency dependence of resistance reflects ventilation heterogeneity in the periphery of lung (10, 13, 28, 30, 39, 42, 47). We could not measure resistance below 5 Hz but we think it reasonable to assume that increased R_{5-19} reflects an increased heterogeneity, although we cannot state at which level of airway tree. Regions with different time constants as a result of micro-atelectases, hypoventilation, or nonuniform distribution of pleural pressure (3, 4, 9, 19, 20, 22, 33, 38, 41, 54) are expected to produce parallel heterogeneities indeed, although also the interplay between increased chest wall and parenchymal stiffness and gas inertia in obesity can promote serial heterogeneities, as reported in animal models under different conditions (1, 27). Recent studies have shown that ventilation distribution is quite ephemeral over time under conditions of airflow obstruction (16, 37, 44) or unloading (15). Therefore, we used the temporal fluctuations of the ventilation distribution (R_{5-19_IQR}) rather than its mean value, as they are expected to be more informative about the nature of the underlying phenomena (12, 49, 50).

Fig. 1. *A–L*: scatterplots of forced expiratory volume in 1 s (FEV$_1$), slow vital capacity (VC), functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV), expiratory reserve volume (ERV), inspiratory resistance at 5 Hz (R$_5$), interquartile range of R$_5$ (R$_{5\_IQR}$), difference between inspiratory resistance at 5 and 19 Hx (R$_{5–19}$), interquartile range of R$_{5–19}$ (R$_{5–19\_IQR}$), inspiratory reactance and 5 Hz (X$_5$) and FEV$_1$/VC vs. body mass index (BMI). Included in the panels are the slopes of the linear regression analysis whenever significant (straight lines).

The effect of obesity on lung stiffness was inferred from the flow-volume loops and sG$_5$ rather than from direct but invasive measurement of esophageal pressure. A body plethysmograph was used to correct for thoracic gas compression and partial maneuvers to avoid volume history effects. According to lung mechanics theory, a downward parallel shift of the slopes of flow-volume loops results from an increase in lung elastic recoil at all lung volumes (48, 53), whereas an increased slope would reflect an increased elastance at higher than lower volumes. Both patterns were observed in the present study on either maximal or partial forced expiratory loops. Together with the lack of difference in sG$_5$ among groups, this strongly suggests that lung elastic recoil was increased in obese subjects.

Interpretation of Results

R$_{5–19\_IQR}$ increased linearly with BMI but remained almost constant until FRC was decreased to ~65% of predicted or
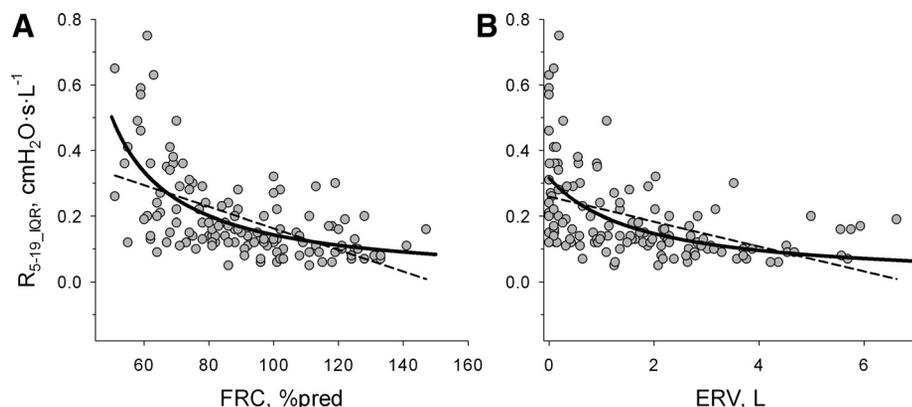
Fig. 2. R_{5-19_IQR} plotted against FRC % predicted (A) and expiratory reserve volume (ERV) (B). Linear (dashed line) and nonlinear (solid line, *Eq. 2*) regression lines are shown in each panel. The relationships between R_{5-19_IQR} vs. FRC % predicted and ERV were better fitted by a nonlinear than linear model. See text for details. This indicates that ventilation becomes more and more uneven for values of FRC % predicted < 65% and ERV < 0.6 liter.

ERV fell below 0.6 liter. This is reminiscent of the study by Holley et al. (20) in eight obese individuals, in four of whom ventilation was quite uniform despite a decrease in mean ERV to 0.68 liter whereas in the other four it was preferentially distributed to the upper lung regions. In the latter, ERV was reduced to values below 0.3 liter. Our threshold of 0.6 liter is in line with these results.

According to lung mechanics principles, a decrease in FRC is associated with a decrease in airway size proportional to the square root of lung volume (21). Therefore, obesity should be associated with airway narrowing within the tidal breathing range. Modeling studies predict that minimal differences in airway caliber between peripheral airways at bifurcation lead to differences in intraluminal pressure and thus transmural pressure (Ptm) (2). The airway with smaller Ptm will carry less flow, and tidal inspiratory volume will be therefore preferentially distributed to the other airway, thus favoring heteroge-
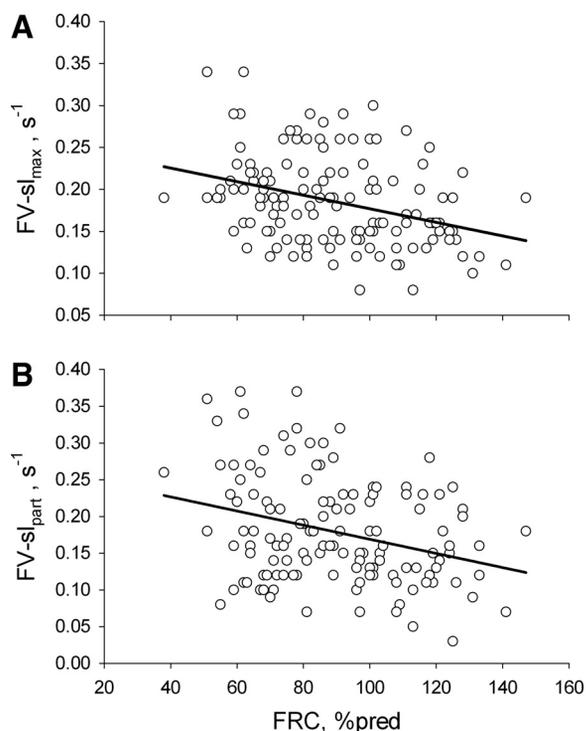

Fig. 3. Linear regression analysis of the slopes of the maximal (FV-sl$_{max}$, *A*) and partial (FV-sl$_{part}$, *B*) plethysmographic flow-volume loops plotted against FRC % predicted.

neous ventilation. At a first glance, this is what was not observed in our obese individuals despite the decrease in FRC, an intervention expected to unload the airways and cause ventilation heterogeneities. In theory, two mechanisms could have counteracted the effects of obesity on ventilation. An increase in V_T could have partly restored the equilibrium between airways of different caliber, thus allowing them to distend during inspiration (2). Our findings appear to play against this hypothesis as V_T was not significantly increased in obese individuals compared with other groups nor was associated with a decreased R_{5-19_IQR}. Presumably, such a mechanism is unsuitable to the case as it would require too much effort to distend a respiratory system made stiff by obesity. We favor the hypothesis that an increased lung stiffness would have counteracted the tendency of airways to close by its effect on transmural pressure (2). That this might be so is suggested by the following findings. First, sG_5 was similar between groups, a fact that would rule out any intrinsic airway disease in obesity (45, 48). Second, flow at mid-to-low lung volumes was increased in obesity, as shown by a parallel shift of the descending limb of flow-volume curve due to a decrease in RV, or a slight increase in slope, or both. With flow determined by lung recoil and airflow resistance, our findings are consistent with obesity being associated with an increase in lung stiffness. This reasoning finds support in previous studies reporting an increase in flow as a result of an increase in transpulmonary pressure in healthy subjects exposed to chest wall strapping (48, 53). In a study by Stubbs and Hyatt (48), strapping caused an increase in the flow-volume slope in addition to a parallel shift. This was associated with similar changes in the pressure-volume curve relationship. This analogy with our findings makes us confident that until the decrease in lung volumes does not exceed a given threshold in obesity, the increase in lung stiffness can protect ventilation from becoming more heterogeneous and worsen gas exchange. These findings open the question of what causes an increase in lung elastic recoil in obesity. The design of our study cannot address this issue. It is speculated that compression of the alveolar surface with no change in area (52), surface tension (58), and microatelectases (59) occurring with chest restriction could play a role. Derecruitment of the latter did not presumably play a major role in our model as this should have caused a decrease in maximal flow and an increase in RV, which is the opposite of what observed with the increase in BMI. Also the slight increase in breathing frequency observed in obesity is in

line with this reasoning, the latter being a potential result of neural stimuli arising from lung periphery (6).

Below thresholds that we estimate to be around 65% for FRC % predicted or 0.6 liter for ERV, our data show that ventilation heterogeneity increased out of proportion to the decrease in lung volumes. Two major mechanisms could have contributed to this pattern. First, with decreasing lung volume the load surrounding the airways became too low to contrast the inward airway recoil due to decreased airway radius or airway smooth muscle adaptation to short length (2, 11, 17, 32). Second, the occurrence of expiratory flow limitation could have contributed to aggravate flow discrepancies between parallel units with some of them exposed to large positive pressure especially within the gravity-dependent lung regions. Although the nonlinear analysis better described the relationship between R_{5-19_IQR} and FRC % predicted or ERV compared with linear analysis, we cannot give its terms a specific mechanical meaning.

The differences found in the present study between obese and nonobese groups are remarkably similar to those recently reported by Mahadev et al. (33). However, they could not find significant correlations between %predicted FRC and indexes of peripheral airway function derived from multibreath washout analysis (55), which may appear at variance with the correlations found in the present study between R_{5-19_IQR} and % predicted FRC. There are different reasons for this discrepancy. First, the number of subjects was much larger in our than their study. Second, R_{5-19_IQR} may be sensitive to heterogeneities of both central and peripheral airways, whereas their analysis was more specifically sensitive to heterogeneities within small acinar and conductive airways. Third, R_{5-19_IQR} reflects temporal fluctuations, thus carrying more information than time-unrelated signals.

In clinical practice, follow-up of obesity is generally conducted by assessing BMI due to the ease of measurement in any settings including home. Although our findings document significant relationships between BMI and main respiratory parameters, the correlation factors highlight quite large scatter between variables. This might be related to differences in fat distribution within subcutaneous and visceral abdominal compartments, and across the trunk, which variably interfere with lung function (28).

Clinical Implications and Conclusions

The present study allows to draw a picture of the effects of the decrease of lung volumes in obesity on ventilation distribution. For values of FRC > 65% of predicted and ERV > 0.6 liter, ventilation remains quite uniform. It is speculated that this is because on an increase in lung elastic recoil as documented by the changes in flow, a fact that would allow flow and ventilation to be accommodated within larger airways. Crossing these thresholds signals the end of flow compensation as FRC is now too close to RV and the latter cannot decrease any longer. Under these conditions, the airways are now exposed to reduced lung elastic recoil and some tend to narrow or close more than others, thus contributing to ventilation inhomogeneity across the lungs. Association with changes in lung perfusion distribution will cause altered gas exchange.

In this perspective, the observed thresholds of FRC % predicted and ERV might assume a crucial role in clinical practice more than BMI. If indeed, above the thresholds interventions suitable for body weight control are presumably sufficient to control the condition; below them the clinical approach needs further reinforcement of treatment as well as gas exchange evaluation.

DISCLOSURES

A. Gobbi, R. Dellacà and Politecnico di Milano University (institution of A. Gobbi and R. Dellacà) own stocks of a spin-off company involved in the development of forced oscillation devices.

AUTHOR CONTRIBUTIONS

Author contributions: R.G.P., R.L.D., R.E.H., and V.B. conception and design of research; R.G.P., A.A., R.T., C.G., and G.M.P. performed experiments; R.G.P., A.G., and V.B. analyzed data; R.G.P., A.G., A.A., and V.B. interpreted results of experiments; R.G.P. and A.G. prepared figures; R.G.P., A.G., R.E.H., and V.B. drafted manuscript; R.G.P., A.G., A.A., R.T., C.G., G.M.P., R.L.D., R.E.H., and V.B. edited and revised manuscript; R.G.P., A.G., A.A., R.T., C.G., G.M.P., R.L.D., R.E.H., and V.B. approved final version of manuscript.

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