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/m². Short-term temporal variability of ventilation heterogeneity was estimated from the interquartile range of probability density (R5–19_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/m²), 32 overweight (BMI 26–30 kg/m²), and 52 obese (BMI >30 kg/m²). The study protocol was approved by the local Ethical Committee, and written informed consent was obtained from each subject prior to the study.
Lung Function Measurements

Spirometry and lung volumes were measured in a body plethysmograph (Autobox, SensorMedics, CA) following the ATS/ERS recommendations (36, 36). 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 inspiration followed by a final deep inhalation (DI), and oxygen saturation (SPIROPRO, Viyassys Healthcare, Yorba Linda, CA).

Data Reduction and Statistical Analysis

Mean R5, X5, R5–19, and R5–19_IQR were calculated over the tidal volumes recorded before the DI. Specific inspiratory conductance (sGs) was calculated as 1/(R5·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 ascending 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 χ² 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 r² 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 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 R5–19_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 R5 and R19 in obese compared with either under-to-normal weight or overweight subjects (Table 2).

Table 1. Subjects’ anthropometric characteristics and main lung functional data

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Overweight</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F</td>
<td>21/28</td>
<td>19/13</td>
<td>17/35</td>
</tr>
<tr>
<td>Age, yr</td>
<td>43 ± 11†</td>
<td>42 ± 10†</td>
<td>49 ± 11†</td>
</tr>
<tr>
<td>Height, cm</td>
<td>160 ± 8</td>
<td>166 ± 11</td>
<td>163 ± 8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22 ± 2‡</td>
<td>27 ± 2‡</td>
<td>39 ± 6‡</td>
</tr>
<tr>
<td>FEV1, liters</td>
<td>3.47 ± 0.76‡</td>
<td>3.27 ± 0.69‡</td>
<td>2.81 ± 0.78§ &lt;0.001</td>
</tr>
<tr>
<td>FEV1, % of predicted</td>
<td>107 ± 10‡</td>
<td>110 ± 13‡</td>
<td>100 ± 14‡ &lt;0.001</td>
</tr>
<tr>
<td>VC, liters</td>
<td>4.24 ± 0.91‡</td>
<td>4.04 ± 0.93§</td>
<td>3.45 ± 0.91§ &lt;0.001</td>
</tr>
<tr>
<td>TLC, % of predicted</td>
<td>109 ± 11</td>
<td>110 ± 17</td>
<td>103 ± 15</td>
</tr>
<tr>
<td>FVC/VC, %</td>
<td>82 ± 6</td>
<td>81 ± 5</td>
<td>81 ± 5</td>
</tr>
<tr>
<td>R5, % of predicted</td>
<td>106 ± 9‡</td>
<td>101 ± 11‡</td>
<td>94 ± 11‡ &lt;0.001</td>
</tr>
<tr>
<td>FRC, % of predicted</td>
<td>111 ± 15†</td>
<td>88 ± 14†</td>
<td>71 ± 14§ &lt;0.001</td>
</tr>
<tr>
<td>RV, % of predicted</td>
<td>104 ± 15†</td>
<td>92 ± 13§</td>
<td>84 ± 16§ &lt;0.001</td>
</tr>
<tr>
<td>ERV, liters</td>
<td>1.46 ± 0.43‡</td>
<td>0.92 ± 0.51§</td>
<td>0.51 ± 0.27§ &lt;0.001</td>
</tr>
<tr>
<td>DLCO, % predicted</td>
<td>92 ± 10</td>
<td>95 ± 15</td>
<td>96 ± 14</td>
</tr>
<tr>
<td>DLCO/VA, % predicted</td>
<td>98 ± 12‡</td>
<td>104 ± 13</td>
<td>109 ± 19‡</td>
</tr>
<tr>
<td>SaO2, %</td>
<td>97 ± 2‡</td>
<td>96 ± 1</td>
<td>96 ± 2‡</td>
</tr>
</tbody>
</table>

Data are means ± SD. BMI, body mass index; FEV1, forced expiratory volume in 1 s; VC, slow inspiratory vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; ERV, expiratory reserve volume; DLCO, diffusing lung capacity for carbon monoxide; VA, alveolar volume. SaO2, 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 χ².

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Table 2. Main FOT and breathing pattern parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Controls</th>
<th>Overweight</th>
<th>Obesity</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R_s$, cmH2O·s·l$^{-1}$</td>
<td>2.39 ± 0.53§‡</td>
<td>2.84 ± 1.08§</td>
<td>3.90 ± 1.13.§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_{19}$, cmH2O·s·l$^{-1}$</td>
<td>2.53 ± 0.54‡</td>
<td>2.77 ± 1.12</td>
<td>3.60 ± 1.03.§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$R_{5–19}$, cmH2O·s·l$^{-1}$</td>
<td>0.15 ± 0.18‡</td>
<td>0.06 ± 0.222</td>
<td>0.30 ± 0.42§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$X_s$, cmH2O·s·l$^{-1}$</td>
<td>0.71 ± 0.24‡</td>
<td>0.96 ± 0.56‡</td>
<td>1.32 ± 0.46§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>sGs, cmH2O·s$^{-1}$·l$^{-1}$</td>
<td>0.13 ± 0.03</td>
<td>0.15 ± 0.04</td>
<td>0.14 ± 0.04</td>
<td>0.08</td>
</tr>
<tr>
<td>Rs, IQR</td>
<td>0.24 ± 0.13‡</td>
<td>0.28 ± 0.21§</td>
<td>0.52 ± 0.34§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rs–19, IQR</td>
<td>0.12 ± 0.05§‡</td>
<td>0.17 ± 0.07§‡</td>
<td>0.28 ± 0.16§‡</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>$V_t$, liters</td>
<td>0.87 ± 0.34</td>
<td>0.86 ± 0.32</td>
<td>0.96 ± 0.37</td>
<td>0.168</td>
</tr>
<tr>
<td>BF, min$^{-1}$</td>
<td>13 ± 4</td>
<td>14 ± 4</td>
<td>13 ± 4</td>
<td>0.158</td>
</tr>
<tr>
<td>$V_e$, l/min</td>
<td>10.7 ± 3.1†</td>
<td>11.1 ± 4.0§‡</td>
<td>13.5 ± 4.4§‡</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are means ± SD. FOT, forced oscillation technique; $R_s$ and $R_{19}$, inspiratory resistance at 5 and 19 Hz, respectively; $X_s$, inspiratory reactance at 5 Hz; sGs, specific inspiratory conductance at 5 Hz; IQR, interquartile range; $R_{5–19}$, inspiratory resistance at 5 at maximum lung inflation; $V_t$, tidal volume; BF, breathing frequency; $V_e$, minute ventilation. Pairs of symbols indicate statistically significant differences between conditions. #, ‡, §: $P < 0.05$.

These differences were associated with a significantly more negative $X_s$, a negative frequency dependence of resistance (positive $R_{5–19}$ difference), and increments of both $R_{5–19}$IQR and $R_{5–19}$IQR. Average FV-slmax and FV-slpart 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 FEVi% 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 ($r = -0.70, P = 0.001$), $R_{5–19}$ ($r = 0.64, P = 0.001$), $R_{5}$ ($r = 0.55, P = 0.001$), $R_{5–19}$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/NVC ($r = 0.09, P = 0.31$). 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) (Fig. 2) suggests that mechanical heterogeneity developed when FRC decreased 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.

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).
The effect of obesity on lung stiffness was inferred from the flow-volume loops and sG5 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 sG5 among groups, this strongly suggests that lung elastic recoil was increased in obese subjects.

**Interpretation of Results**

R5–19_IQR increased linearly with BMI but remained almost constant until FRC was decreased to ~65% of predicted or

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**Fig. 1.** A–L: scatterplots of forced expiratory volume in 1 s (FEV1), slow vital capacity (VC), functional residual capacity (FRC), total lung capacity (TLC), residual volume (RV), expiratory reserve volume (ERV), inspiratory resistance at 5 Hz (R5), interquartile range of R5 (R5_IQR), difference between inspiratory resistance at 5 and 19 Hz (R5–19), interquartile range of R5–19 (R5–19_IQR), inspiratory reactance and 5 Hz (X5) and FEV1/VC vs. body mass index (BMI). Included in the panels are the slopes of the linear regression analysis whenever significant (straight lines).
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 heterogeneous 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 VT 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 VT was not significantly increased in obese individuals compared with other groups nor was associated with a decreased R5–19_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, sG5 was similar between groups, a fact that would rule out any intrinsic airway disease (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 airflow 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 across the lungs. Association with changes in lung perfusion distribution will cause altered gas exchange.

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. Cross- ing 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.

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GRANTS

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DISCLOSURES

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

AUTHOR CONTRIBUTIONS


REFERENCES


