Residual Volume in a General Population* 
Effects of Body Size, Age, Cigarette Smoking, and Respiratory Symptoms

Rollo Ruoletti, M. D., F.C.C.P.; Giovanni Vieggi, M. D.; 
Laura Carrozzi, M. D.; Francesco Di Pode, B. S.; Paola Modena, M. D.; 
Licia Ballerin, M. D.; Sandra Baldacci, Ph. D.; Marzia Pedreschi, M. D.; 
Giuseppe Pistelli, M. D.; and Carlo Giuntini, M. D., F.C.C.P.

Residual volume (RV) was obtained by subtracting vital capacity from total lung capacity determined by the single breath helium dilution (TLCsb) to measure CO diffusing capacity in 2,680 subjects (8 to 64 years old) of a general population sample. There were 712 normal subjects (343 male and 469 female subjects) selected to evaluate the pattern of RV by age and to derive reference values for internal comparisons. From 8 to 20 years old, RV showed an increase because of the cross-sectional body size effect; after 20 to 30 years, RV was still increasing, however, at a lower level. Age and height coefficients were significantly related to RV in younger and older ages, both in male and female subjects. The RV percent predicted and RV/TLC percent were higher in smokers when compared to nonsmokers and exsmokers (the difference was significant in male subjects). A dose-response effect was observed between RV percent predicted, RV/TLC percent, and pack-years. The RV percent predicted and RV/TLC percent were significantly higher in smokers and nonsmokers with FEV, percent predicted below the normal limit (the difference was significant in male subjects). Moreover, higher values of RV percent predicted and RV/TLC percent were observed in subjects with wheezy symptoms in male smokers and nonsmokers. A negative significant correlation was observed between RV/TLC percent and the diffusing capacity adjusted for lung volume (Dl/VA) in smokers, exsmokers and nonsmokers of both sexes, confirming the hypothesis that the decrease in Dl/VA may be ascribed to the enlargement of terminal air spaces. In conclusion, determination of RV by the single breath helium dilution method is suitable in epidemiology, and it allows additional important information for understanding the physiopathologic mechanisms related to the pathogenesis of chronic obstructive lung disease.

The residual volume (RV) is usually derived after the determination of the functional residual capacity by body plethysmography3 or by rebreathing techniques (helium dilution or nitrogen wash-out).2,3 Few studies have been conducted to derive “reference” values of RV, using these complex and time-consuming methods.4,12 Neither technique is suitable in epidemiology; thus, subjects were not selected from representative samples of general populations.4,10

The following other methods based on single breath dilution have been used: (1) the single breath nitrogen test (SBN2) to measure the closing volume and the slope of the alveolar plateau;11 and (2) the single breath helium dilution used during the standard maneuver to measure the single breath carbon monoxide diffusing capacity (DLSb).12,13 The DLSb in recent years has been successfully used in epidemiologic surveys, and it allows the determination of total lung capacity (TLCsb).14-18 We have previously published the reference values for DLSb and TLCsb in a general population sample,14 and then, we have derived RV by the subtraction of the slow vital capacity from TLCsb, in the same subjects.

In this paper, we report reference equations derived from normal subjects, 8 to 64 years of age, selected within the sample; the age distribution of the sample allowed cross-sectional evaluations of the effect of body size and age. The effects of cigarette smoking and respiratory symptoms on RV were evaluated as well.

METHODS

A general population sample (n = 3,289), aged 8 to 64 years, living in the rural unpolluted area of the Po River Delta (North Italy, near Venice), was investigated from 1980 to 1992. Population characteristics, sampling methodology, questionnaire, prevalence rates of respiratory symptoms and disease, methods and reference equations for some lung function parameters have been previously reported.14,15,42 Briefly, the population sample was a multistage strati-

*From the CNR Institute of Clinical Physiology and Second Division of Internal Medicine, University of Pisa, Italy. This work was supported in part by the Italian National Research Council (CNR), Targeted Project “Prevention and Control Disease Factors—SP2—Contract 91.00171.PF41,” the Health Departments of the Veneto and Emilia Romagna Regions, by a grant of the Italian Electric Power Authority (ENEL) and CNR-ENEL Project “Interactions of Energy System with Human Health and Environment,” Rome, Italy.

Reprint requests: Prof. Giuntini, Istituto di Clinica Medica II, Università degli Studi di Pisa, Via Roma 67, 56126 Pisa, Italy

ATS = American Thoracic Society; CNR = Italian National Research Council; Dl/VA = diffusing capacity adjusted for lung volume; Dsbsingle = single breath carbon monoxide diffusing capacity; RV = residual volume; TLCsb = total lung capacity by single breath helium dilution method
fied family cluster design. The Italian National Research Council (CNR) standardized questionnaire was a modified NHLBI interviewer-administered questionnaire. Strict criteria were used to select normal subjects: absence of past and present respiratory symptoms; absence of cardiac-respiratory disease or hypertension; absence of childhood respiratory disease; absence of occupational exposure to bronchoirritants; absence of acute respiratory disease; absence of smoking habit (including occasional)14,15 A total of 712 normal subjects (243 male and 469 female patients) were able to perform the single breath CO diffusing capacity, and TLCsb reference values were obtained from single breath helium dilution.14

In order to analyze the relationships with symptoms, subjects ≥20 years old were divided in three groups as follows:

1. Chronic bronchitis group (COLD): presence of usual cough or usual phlegm most days for at least three months in a year for two consecutive years, or reported diagnosis of chronic bronchitis or emphysema or both (male subjects = 168; female subjects = 65);

2. Wheezy symptoms group (WHEEZ): presence of any wheeze or attacks of shortness of breath with wheeze or reported diagnosis of asthma or both (male subjects = 84; female subjects = 54).

3. Asymptomatic group (NOSYM): subjects without respiratory symptoms or reported diagnosis of pulmonary disease. In this group, the “normal” subjects selected for the reference equations are included (male subjects = 652; female subjects = 836).

Subjects were also classified as smokers if they smoked currently at least one cigarette daily; exsmokers if they smoked regularly at least one cigarette daily up to six months or more before the testing; and nonsmokers if they had never smoked any kind of tobacco regularly.

Lung function measurements were obtained using standard protocols developed by the CNR special project on chronic obstructive lung disease. Protocols are based on the American Thoracic Society (ATS) guidelines18 with some exceptions.14,15 Subjects performed in sequence the following measurements: slow vital capacity; single breath nitrogen test; single breath diffusing capacity for CO; and forced vital capacity.

Automated equipment (Hewlett-Packard 47804/S) was used for determining single breath diffusing capacity of CO (Dlsb). A pneumotachograph (Fleisch n 2) was used for volume measurement after integration of flow. A thermocconductivity analyzer was used for helium concentration measurements. The signals were fed into a computer (HP 9825A; Hewlett-Packard) by an A/D interface for the automated measurements. A demand valve connected to a tank allowed the delivery of the gas mixture (0.3 percent CO; 10 percent helium; 20 percent oxygen and the balance, nitrogen).

The equipment was checked periodically following ATS recommendations.18 The pneumotachograph was calibrated daily by a 3-L standard syringe. Resistance of the apparatus was in the range suggested by ATS.18 The gas analyzers were calibrated before testing each subject. After a few minutes of adaptation to the mouthpiece, the test was started. End-expiratory baseline was determined after the sampling of at least four tidal volumes. The subject exhaled to residual volume, and then rapidly inspired the gas mixture from the tank to total lung capacity (TLC); the valve system allowed the subject to hold the TLC breath for 10 s (breath-holding time). Then the subject exhaled rapidly to residual volume while the valve system allowed the collection of 1-L volume sample volume in a bag for gas concentration analyses, after the elimination of the dead space volume. Breath-holding time was computed from the moment when one half of the volume was inspired to the moment when washout was completed and collection of alveolar gas was started, following ATS recommendations.18 The protocol of the first cross sectional study of this longitudinal study did not include the collection of a blood sample; thus, hemoglobin and CO back pressure corrections were not performed.

The dead space clearance volume was 0.5 L for subjects of the pediatric age and for those with a VC <2.0 L, for the other subjects, the volume was 1.0 L.

The TLCsb was computed as follows and it was expressed in liters at BTPS:

\[ \text{TLCsb} = \text{IVC} \times \frac{\text{FHe}}{\text{FAHet}} \times (\text{ATPD} > \text{BTPS}) \times 1.05 \]

where

- IVC = inspiratory vital capacity – dead space
- FHe = inspired helium concentration
- FAHet = expired alveolar helium concentration at time t
- 1.05 = factor correcting for elimination of CO2

RV was computed by the subtraction of the slow vital capacity (VC) previously measured: \( \text{RV} = \text{TLCsb} - \text{VC} \).

The ratio RV/TLC expressed in percentage (RV/TLC percent) was also computed.

Analyses were performed at the University of Pisa Computer Center (CNUCE), using the Statistical Package for Social Sciences (SPSS) routines. Simple and multiple regressions and comparisons of means by analysis of variance and covariance (for adjustments) were performed.

The analysis of the relationships among RV, smoking, and respiratory symptoms was performed only in subjects ≥20 years old (men = 904; women = 955), because few subjects under 20 years old

MALES

FEMALES

FIGURE 1. Distribution of RV by age in normal male and female subjects. Values increase until 20 years and then continue to increase slightly in both sexes.
Table 1—Regression Parameters and Normal Limits for RV by Sex and Age Groups*

<table>
<thead>
<tr>
<th>Age Range, yr</th>
<th>C</th>
<th>Age</th>
<th>Height</th>
<th>Weight</th>
<th>R</th>
<th>S_y.x</th>
<th>% Predicted</th>
<th>95th Percentile</th>
<th>No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-18</td>
<td>-2.2665</td>
<td>. . .</td>
<td>0.0222</td>
<td>. . .</td>
<td>0.70</td>
<td>.34</td>
<td>153</td>
<td>161</td>
<td></td>
</tr>
<tr>
<td>19-64</td>
<td>-2.5864</td>
<td>0.0179</td>
<td>0.0243</td>
<td>. . .</td>
<td>0.46</td>
<td>.44</td>
<td>130</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Female subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8-17</td>
<td>-2.0939</td>
<td>0.0396</td>
<td>0.0207</td>
<td>-0.0096</td>
<td>0.61</td>
<td>.30</td>
<td>157</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>19-64</td>
<td>-1.3906</td>
<td>0.0159</td>
<td>0.0181</td>
<td>-0.0054</td>
<td>0.42</td>
<td>.39</td>
<td>137</td>
<td>279</td>
<td></td>
</tr>
</tbody>
</table>

*Abbreviations: C = constant; R = multiple correlation coefficient; S_y.x = standard deviation around the regression; and No. = number of subjects.

were smokers or complained of symptoms.

RESULTS

The distribution of RV by age in normal male and female subjects is shown in Figure 1. From 8 to 20 years, RV increased sharply because of the cross-sectional body size (growth effect): the increase was higher in male subjects. After 20 years, RV was still slightly increasing in both sexes.

In order to derive reference equations, regressions for height, body weight, and age were computed. Regressions were derived in male subjects 8 to 19 years and ≥20 years, while in female subjects, 8 to 18 years and ≥19 years, to take into account the cross-sectional “growth” effect.

In Table 1, the regression factors are reported for each age group in male and female subjects. In addition, the percent predicted values below which 95 percent of normal subjects fall (the normal 95th percentile percent predicted) are reported in Table 1. We used this criterion of normality because the distribution of RV in the age groups of both sexes is not Gaussian.

In male subjects 8 to 18 years old, the height coefficient was significant, while age and body weight coefficients were not. In men ≥19 years, also age and height coefficients were significant. In female subjects of both age groups, all the coefficients were significant, and body weight was negatively related to RV.

In male subjects, age adjusted mean values of RV percent predicted were significantly higher in smokers (106.4 percent) than in exsmokers (100.4 percent) and nonsmokers (103.9 percent) by analysis of variance. Also age adjusted mean values of RV/TLC percent were significantly higher in smokers (30.7 percent) than in exsmokers (29.9 percent) and nonsmokers (29.8 percent). In female subjects, no significant difference was found among the three smoking groups for RV percent nor for RV/TLC percent.

The rate of increase of RV percent with aging in those ≥20 years was higher in smokers than in nonsmokers of both sexes. The linear regression analysis gave significant coefficients only in smokers (r = .44 in male subjects, r = .29 in female subjects).

In addition, RV percent and RV/TLC percent were increasing with the increment of pack-years (ie, number of cigarettes/day multiplied by years of smoking divided by 20). Both the linear regressions were significant in male subjects (r = .30 for RV percent; r = .49 for RV/TLC percent) and in female subjects (r = .43 for RV percent; r = .24 for RV/TLC percent).

The relationships between the presence of airflow obstruction (ie, FEV₁ percent <95th percentile of percent predicted) and RV percent, RV/TLC percent were then investigated separately in smokers and in nonsmokers of both sexes by analysis of variance. In Table 2, mean values of RV percent and RV/TLC percent adjusted for age and pack-years in smokers and for age in nonsmokers are shown: higher values were present in smokers with airflow obstruction of both sexes, and the difference was significant by analysis of variance with the exception of RV percent in female subjects. For nonsmokers of both sexes, only age adjusted mean values of RV/TLC percent were significantly higher in those with FEV₁ <95th percentile.

Table 2—Mean Values of RV% Predicted and RV/TLC% in Relation to Airway Obstruction in Smokers and Nonsmokers of Both Sexes

<table>
<thead>
<tr>
<th>Sex</th>
<th>smokers</th>
<th></th>
<th>nonsmokers</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FEV₁&lt;95%</td>
<td>FEV₁&gt;95%</td>
<td>FEV₁&lt;95%</td>
<td>FEV₁&gt;95%</td>
</tr>
<tr>
<td>Male subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV%</td>
<td>110</td>
<td>104†</td>
<td>105</td>
<td>101</td>
</tr>
<tr>
<td>RV/TLC%</td>
<td>35</td>
<td>29†</td>
<td>31</td>
<td>24†</td>
</tr>
<tr>
<td>N</td>
<td>118</td>
<td>99</td>
<td>15</td>
<td>179</td>
</tr>
<tr>
<td>Female subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV%</td>
<td>97</td>
<td>99</td>
<td>103</td>
<td>99</td>
</tr>
<tr>
<td>RV/TLC%</td>
<td>37</td>
<td>31†</td>
<td>38</td>
<td>33†</td>
</tr>
<tr>
<td>N</td>
<td>23</td>
<td>28†</td>
<td>54</td>
<td>591</td>
</tr>
</tbody>
</table>

*FEV₁ <95%: subjects with % predicted FEV₁ below the value above which 95% of normal subjects fall.
†Mean values adjusted for age in nonsmokers and for age and pack-years in smokers.
‡p<0.001 by analysis of variance.
In Table 3, age-adjusted mean values of RV percent predicted and RV/TLC percent are reported in subjects with wheezy symptoms (WHEEZE), chronic bronchitis symptoms (COLD), and without symptoms (NO-SYM), separately in both sexes. In male subjects, those with wheezy symptoms had the higher values of RV percent and RV/TLC percent followed by those of the COLD group; the difference was significant. In female subjects, no significant difference was observed among the groups.

**Discussion**

In normal subjects, the distribution of RV by age shows the well-known increase in young ages because of the cross-sectional body size effect; this trend is present after 20 years, though it is less important. The increase in RV by age during adulthood and older ages reflects the redistribution of static lung volume which occurs with aging. In our previous paper, we have shown in the same subjects, the decrease in VC, FVC, and FEV₁ after 30 years. Both of these changes, increase in RV and decrease in VC, FVC, and FEV₁, occur in the absence of important changes in total lung capacity; in fact, the age coefficient for TLCsb in older ages is not significant. In Figure 2, percent predicted TLCsb, VC, and RV are reported from 8 to 64 years of age every two years, considering an increase in height, based on the US growth chart, up to 20 years, and then a fixed height (163 cm for women and 180 cm for men). Thus, the pattern shown in Figure 2 may be considered the epidemiologic evidence for the loss of elastic recoil with aging, causing the increase in RV and the reduction in VC, FVC, and FEV₁.

Age and height coefficients were always positively related to RV in both age groups of both sexes, while body weight was negatively related to RV only in female subjects, and its effect was relatively important. Female subjects in our population showed a higher percent predicted body weight when compared to male subjects and probably also in normal female subjects, body weight produces a small reduction of residual volume.

Cigarette smoke, as expected, does affect the residual volume. Age-adjusted mean values of percent predicted RV and RV/TLC percent were significantly higher in male smokers, and the increase was related to the duration and quantity of smoking, ie, pack-years both in male and female subjects. The increase in RV in smokers may be explained by the inflammatory changes present in the peripheral airway, which cause airway obstruction and, probably also by the anatomic changes in terminal air spaces (alveoli, alveolar ducts). Both of these mechanisms may be responsible for the increase in RV in smokers.

The first one is related to the presence of small airway inflammation with consequent peripheral airway obstruction which causes the reduction in forced expiratory flows. Both smokers and nonsmokers with FEV₁ below the normal limit have significantly higher values of RV percent predicted and RV/TLC percent, pointing out a strict relationship between the presence...
of airways obstruction and the increase in RV in this general population sample. Interestingly, the presence of wheeze, the symptom which reflects the reduction in the caliber of airway, was significantly associated with increased RV in male subjects.

In regard to the effect of the amount of cigarettes smoked, it is important to note that pack-years are highly related to age; thus, the relationship between RV and pack-years is partially explained by the aging effect. Nevertheless, the rate of the increase in RV percent with aging in smokers ≥20 years of both sexes is higher when compared to nonsmokers, pointing out the additional effect of smoking on the physiologic aging effect.

The second mechanism advocated to be responsible for the increase in RV in smokers is the enlargement of terminal air spaces.36,37 In our previous paper, we reported that in normal subjects, the morphometric parameter mean linear intercept (Lm) which measures the mean distance between alveolar walls was related to the decrease of diffusing capacity adjusted for the volume (DL/VA).14 In Figure 3, the relationships between RV/TLC percent and DL/VA in smokers, exsmokers, and nonsmokers of both sexes are reported.

**Figure 3.** RV/TLC percent by DL/VA in smokers, exsmokers, and nonsmokers of both sexes; regression lines are depicted, and significant negative correlations coefficients are always present. Males: smokers (n = 529) r = -.41, p<0.0001; nonsmokers (n = 195) r = -.23, p<0.001; exsmokers (n = 181) r = -.26, p<0.0004. Females: smokers (n = 263) r = -.29, p<0.0001; nonsmokers (n = 645) r = -.19, p<0.0001; exsmokers (n = 48) r = -.30, p<.03.
The linear correlations were significant in all cases, and the highest correlation coefficients were observed in smokers of both sexes, pointing out a reduction in DL/VA with an increase in RV/TLC percent. These results may be considered as an additional confirmation of our previous hypothesis. In fact, the increase in RV/TLC percent may reflect the enlargement of terminal airspaces, and consequently, is related to the decrease in DL/VA, which, in part, may be caused by the reduction in the gas phase conductance. Our results confirm the physiologic consequence of aging due to the loss of elastic recoil. In fact, the parameter, proposed by Colebatch et al.,\(^\text{32}\) to describe the pressure-volume curve (k), was found to be linearly related to the morphometric measurement Lm, \(Lm\), to increased size of terminal airspace.\(^\text{33}\) In smokers, Knudson et al.\(^\text{34}\) found that k was significantly associated with the decrease in DL/VA. The presence of the highest association between RV/TLC percent and DL/VA, in smokers of both sexes, pointed out the additional effect of smoking. Hence, our findings support indirectly the observation that the loss of elastic recoil due to the physiologic aging effect is associated with the enlargement of terminal air spaces and that these mechanisms are enhanced by cigarette smoking.

In regard to the use of the single-breath helium dilution to measure TLC and consequently RV, our data suggest its usefulness in epidemiologic studies. This method has been criticized for the lack of accuracy, namely for an underestimation of the lung volume, in the presence of important inhomogeneity of the distribution of ventilation, such as in patients with obstructive lung disease.\(^\text{35,36}\) However, Georges et al.\(^\text{37}\) compared TLC from multiple-breath helium dilution with that derived from single-breath and did not observe a significant difference in subjects without symptoms and disease. On the other hand, Burns and Scheinhorn\(^\text{38}\) were able to demonstrate a linear relationship between severity of airway obstruction and degree of underestimation of single-breath helium dilution TLC with respect to TLC determined by a roentgenographic method. The underestimation was 10.4 percent in patients with mild, 21.8 percent in those with moderate, and 38.0 percent in those with severe obstruction. They also found a very slight underestimation (2.3 percent) in normal subjects. Indeed, we have studied a general population sample characterized by very low prevalence rates of respiratory symptoms/diseases.\(^\text{39}\) In addition, few subjects had a consistent reduction of FEV\(_1\) percent predicted: eg, 31 had a FEV\(_1\) between 60 and 46 percent predicted (moderately obstructed), 11 had a FEV\(_1\) below 45 percent predicted (severely obstructed). Thus, we think that the determination of TLC by single-breath helium dilution appears to give a useful estimation of TLC in epidemiologic surveys, where it is less common to use such an accurate method as the roentgenographic determination of TLC. Further, we have compared our RV predicted values with those of the summary equations (derived by multiple-breath helium dilution) reported by Quanjer.\(^\text{10}\) For a man (180 cm and 50 years old), RV predicted by our equation was 2.14 vs 2.09 L of the RV predicted by summary equations; for a woman (160 cm and 50 years old), our predicted RV is 1.96 vs 1.69 L. Similar results hold true for all ages and in both sexes, and confirm that, at least in the general population, RV does not appear underestimated by the single-breath helium dilution method with respect to multiple-breath helium dilution procedure.

Finally, it is important to point out that the reference equations reported in this paper are mainly proposed for internal use within this epidemiologic study, as should be the case for every epidemiologic study or clinical laboratory.

In conclusion, our study showed the possibility of measuring the RV in general population surveys by the single-breath helium dilution technique and obtaining important additional information on lung function, related to the early effects of cigarette smoking and to the presence of respiratory symptoms.

ACKNOWLEDGMENTS: The authors thank Dr. Ciro Rampulla (Montescano-Pavia, Italy) who strongly advised the publication of these data, the participants of the study, Dr. G. Carmignani (University of Pisa, Italy), Professor T. Supigni (University of Ferrara, Italy), and Miss Patrizia Silvi for typing the manuscript.

REFERENCES
Montreal, 1953. Abstract of Communications, p 610
25 National Center for Health Statistics. NCHS growth charts. Rockville, MD: Health Resources Administration, 1976; (HRA) 76-1120, vol 25, no 3, supplement
32 Colebatch HJH, Greaves IA, Ng CKY. Exponential analysis of elastic recoil and aging in healthy males and females. J Appl Physiol 1979; 47:683-91