Pressure-volume analysis of the lung with an exponential and linear-exponential model in asthma and COPD


ABSTRACT: The prevalence of abnormalities in lung elasticity in patients with asthma or chronic obstructive pulmonary disease (COPD) is still unclear. This might be due to uncertainties concerning the method of analysis of quasistatic deflation lung pressure-volume curves.

Pressure-volume curves were obtained in 99 patients with moderately severe asthma or COPD. These patients were a subgroup from a Dutch multicentre trial; the entire group was selected on the basis of a moderately lowered % predicted forced expiratory volume in one second (FEV1) and a provocative concentration of histamine producing a 20% decrease in FEV1 (PC20) <8 mg ·mL-1 obtained with the 2 min tidal breathing technique. The curves were fitted with an exponential (E) model and an exponential model which took the linear appearance in the mid vital capacity range into account (linear-exponential (LE)).

The linear-exponential model showed a markedly better fit ability, yielding additional parameters, such as the compliance at functional residual capacity (FRC) level as slope of the linear part (b), and the volume at which the linear part changed into the exponential part of the curve (transition volume (Vtr)), Ve/total lung capacity (TLC) = 0.79 (SD 0.07) showed a close positive linear correlation with obstruction and hyperinflation variables, which might be due to airway closure, already starting at elevated lung volumes. The exponential shape factor K was closely correlated with b and mean values (K=1.32 (SD 0.05) kPa-1; b=2.96 (SD 1.16) L·kPa-1) and the relationship with age was comparable with data reported in healthy individuals. The shape factor of the linear-exponential fit showed no correlation with any elasticity related variable. Neither the elastic recoil at 90% TLC, as obtained from the linear-exponential fit, nor its relationship with age were significantly different from healthy individuals.

We conclude that, for a more accurate description of the lung pressure-volume curve, a linear-exponential fit is preferable to an exponential model. However, the physiological relevance of the shape parameter (Kle) is still unclear. These results indicate that patients with moderately severe asthma or COPD had, on average, no appreciable loss of elastic lung recoil as compared with healthy individuals.

Eur Respir J., 1995, 8, 1525–1531.

Measurements of lung elastic recoil, derived from static or quasistatic deflation lung pressure-volume (P-V) curves, are aimed at assessing the influence of, e.g. disease processes and ageing on lung elasticity.

The nonlinear behaviour of the lung elastic recoil pressure (Pe) versus lung volume has led to the use of various indices from the curve (e.g. compliance between functional residual capacity (FRC) and FRC+0.5 L [1]; Pe at defined fractions of total lung capacity (TLC) [2–4] or the fit of an adequate model to the entire curve and subsequent use of model parameters. Although several mathematical descriptions have been proposed [5], exponential curve analysis has been most frequently applied [2, 3, 6–10]. The fit of an exponential (E) model yields, in addition to the maximal volume (Vmax) and the shift of the curve with respect to the pressure axis (Po), a shape parameter (K) describing elastic behaviour independently from lung volume. Such exponential analysis has proved useful to describe, e.g. the effect of ageing [2], and to characterize emphysema [7–10].

We also developed a model description taking a combined linear and exponential appearance into account (linear-exponential (LE) model). The rationale for this choice was the apparently linear behaviour of most curves, starting from the inflection point, usually covering a considerable part of the mid vital capacity range. In
earlier investigations [2, 3], it has been shown that, because of this linear part, using data points from a level above FRC often increased the goodness of fit of the exponential model.

This LE model has been applied in patients entered in a multicentre study [11, 12], who were selected on the basis of moderately lowered forced expiratory volume in one second/inspiratory vital capacity ratio (FEV1/VC) and bronchial hyperresponsiveness.

Clinically, the patients were classified as asthma, asthmatic bronchitis, or chronic obstructive pulmonary disease (COPD), as previously described by Kerstiens et al. [12]. The linear-exponential model has been compared with an exponential description, and the indices derived from the model have been interpreted in terms of lung mechanics behaviour.

Patients and methods

Patients

From 274 patients (176 males and 98 females; aged 18–60 yrs, median 40 yrs) entering a Dutch multicentre trial, a random sample of 99 patients (71 males and 28 females; aged 19–59 yrs, median 40 yrs) also underwent quasistatic P-V curves.

A detailed report of the trial and the results has been reported previously [11, 12]. Three groups of patients, selected on the basis of two functional criteria mentioned below, were treated for 2.5 yrs with either an inhaled corticosteroid plus a β2-agonist, a β2-agonist plus an anticholinergic agent, and a β2-agonist plus placebo. Data used in this study were obtained before entrance to the trial. Selection criteria were an FEV1 level ranging 4.5–1.65 standard deviations (SD) below the predicted value and greater than 1.2 L, or FEV1/VC ratio lower than 1.64 SD below the predicted value provided that TLC was higher than 1.64 SD below the predicted value. Reference values used were those from the European Coal and Steel Community (ECSC) [1]. Another selection criterion was hyperresponsiveness to inhaled histamine causing a 20% decrease in FEV1 (PC20) with respect to baseline, as obtained with the 2 min tidal breathing method adapted from Cockcroft et al. [13]. In all patients, PC20 was lower than 8 mg·mL⁻¹. All measurements were obtained after withdrawal of bronchodilators at least 8 h before the measurements.

By using data from a standardized history, a clinical diagnosis was made closely adhering to the American Thoracic Society (ATS) criteria [14, 15]. On the basis of these criteria, three groups were defined, as has been reported extensively elsewhere [12].

Group 1. Patients reporting attacks of breathlessness and wheeze (asthmatic attacks) without chronic (i.e., for more than 3 months a year) cough or sputum production (Asthma Group).

Group 2. Current or former smokers without a history of asthmatic attacks, reporting either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both, were included in the chronic obstructive pulmonary disease group (COPD Group).

Group 3. Patients with both asthmatic attacks or recurrent wheeze and chronic cough and sputum production (Asthmatic Bronchitis Group).

Within our group of 99 patients 37 were diagnosed as having asthma, 31 asthmatic bronchitis, and 15 COPD. Seventeen patients fulfilled the objective criteria and underwent the set of measurements at baseline but dropped out at an early stage before a final clinical diagnosis was established.

Exclusion criteria were pregnancy, a history of occupational asthma or other serious diseases (for example tuberculosis, myocardial infarction, and malignancy), the use of oral corticosteroids, β-blocking drugs, nitrates or anticoagulants or the continuous use of antibiotics.

Spirometry

VC and FEV1 were measured by spirometry (calibrated water-sealed spirometers). TLC, functional residual capacity (FRC) and residual volume (RV) were obtained using the closed circuit He-dilution technique. The standardized procedures and reference values used were those from the ECSC [1].

Quasistatic pressure-volume curves

Transpulmonary pressure (Ptp) was measured via a Validyne transducer (P45) coupled to an oesophageal balloon catheter with the balloon located in the lower third of the oesophagus. Ptp was estimated as oesophageal pressure (Poes) minus mouth pressure. Simultaneous recording of volume changes was obtained during a slow expiration from TLC level (deflation curve). From the 99 patients, 174 technically satisfactory P-V curves were obtained. Criteria for acceptance of curves were the absence of irregularities, as e.g. caused by an oesophageal spasm, which sometimes occurred directly after start of deflation, or a mean expiratory flow exceeding the previously described criterion of 0.3 L·s⁻¹ [1]. If more than one curve was obtained per patient the curves were matched at TLC level, according to Clement et al. [16], and mean curves were obtained through the mean Ptp at the various volume levels. The measuring procedure was identical to that described in the ECSC report [1]. Because we are not aware of a computer algorithm recognizing data at similar points within the cardiac cycle, the curves were smoothed by drawing a line by hand through katacrotic points of the cardiac pulsations on the curve that could be recognized as closure of the aortic valves. Volume data were obtained at equal Ptp intervals, yielding on average 10–30 data points up to TLC level. Data points were taken beyond the volume level at which the inflection point in the curve, indicating
a disproportionate rise in $P_T$ at decreasing volume, occurred [2, 3, 7]. This inflection point was generally at, or slightly above, the FRC level obtained from the closed circuit He wash in method [1]. The data points which were obtained, were subsequently used for curve analysis.

Analysis of P-V curves

Two models were fitted to the data points. The first model is an extension of the exponential model of Salazar and Knowles [6], with a parameter describing a linear horizontal shift along the pressure axis ($P_o$). The equation is:

$$V = V_{\text{max},E} \left[ 1 - \exp \left( -K_E \left( P - P_o, E \right) \right) \right]$$

(1)

with $V_{\text{max},E}$ = maximal volume level (L); $P_o, E$=intercept with the $P$ axis (kPa); $K_E$=index of curvature (kPa$^{-1}$). This equation was used because it represents a clear interpretation in terms of scaling of the volume axis ($V_{\text{max},E}$), the linear shift with respect to the $P$-axis ($P_o, E$), and the degree of curvature ($K_E$).

As a second model we fitted a linear-exponential (LE) model to the data. The curve was considered as a linear part from the first data points on, changing into an exponential part, described by equation (1), at an elevated volume level. The transition from the linear into the exponential part was determined such that the mean square (MS) deviation between experimental data points and model fit was minimal. The model equations are:

$$V = a + bP$$

(2) for $V \leq \text{transition volume (} V_{tr} \rangle$

$$V = V_{\text{max},LE} \left[ 1 - \exp \left( -K_{LE} \left( P - P_o,LE \right) \right) \right]$$

(3)

with indices defined as in equation (1) for the E fit. The fit procedure was such that in case of n experimental data points the first p data points were used for the linear part and (n-p) for the LE fit. In the fit procedure, p was used as a least squares criterion for the fit of the upper exponential part.

In figure 1 a representative example is given for an E and LE fit to an experimental pressure-volume curve. - - - : curve through katacrotic points, smoothed by hand. Data points are at equal pressure intervals. - - - - : E fit. The LE fit coincides with the experimental curve. $P_T$: transpulmonary pressure equal to oesophageal minus mouth pressure; $V_r$: transition volume equal to volume at which the linear part changed into an exponential part. Curve fit from 50% of total lung capacity (TLC). For further explanation see text.

For both models, a Marquardt [17] algorithm was applied for the linear least squares analysis, whilst the input of experimental data points was done by hand using a personal computer.

Statistical analysis

Linear regression analysis and linear correlation analysis were used to study the relationship between the model parameters and lung function variables. Group comparisons were made with the two sample Student's t-test. Because multiple correlations were studied, the Bonferroni correction was used for the adaptation of the probability level for significance, which was taken as a p-value equal to 0.001. All analyses were performed with a statistical package Statgraphics (STSC, Inc., USA).

Results

The mean FEV1/VC in the 99 patients subgroup was 0.55 (SD 0.11), which was the same for the entire group, participating in the multicentre study. Also, mean age and sex distribution in the subgroup did not deviate significantly from the whole group. Our subgroup had a mean RV/TLC of 0.34 (SD 0.08) and mean FRC/TLC of 0.53 (SD 0.08). The average of the mean square (MS) deviation between experimental and fitted volume data, obtained in the whole set of curves, was 0.0054 L$^2$ (SD 0.0052 L$^2$) for the exponential (E) fit and 0.00034 L$^2$ (SD 0.00066 L$^2$) for the linear-exponential (LE) fit, yielding on average a four times smaller mean deviation between fitted and experimental data points for the LE fit.
For analysis of the P-V curves, the mean volume level, from which the data were sampled for analysis, was 0.59 TLC (SD 0.08).

The variables, obtained by both fits, are listed in table 1. K from the exponential model (KE) was dependent on age (r=0.45; p<0.0001; K=0.55+0.020 age). The standard error of the slope estimate (0.0041) indicated a significant increase of KE with age. This relationship is shown in figure 2, together with that found by GIBSON et al. [7] in a group of healthy individuals; the regression lines show good agreement. The shape factor KE and the lung compliance estimate Cst, estimated from the slope (b) of the LE fit, were closely correlated (r=0.70; p<0.0001) (fig. 3). For Cst, the age dependency was not significant (p=0.002).

The asymptote values of both fits (Vmax,E and Vmax,LE, (table 1) showed on average a slight overestimation of TLC, which was, however, minor for the LE fit. Pel at 90% Vmax,LE (P90), calculated from the LE fit parameters as a measure of lung elastic properties, was closely related with both KE (r=0.60; p<0.0001) and Cst (r=0.38; p<0.0001). A close relationship also existed with age (r=-0.49; p<0.0001; P90=-2.22-0.0196 age) (fig. 4). The standard error of the slope of this relationship (0.0035) indicated a significant decrease with age. Figure 4 also presents data described in the report on standardization of lung function [1], based on a study by DE TROYER and YERNAULT [18]. These data are comparable with our age dependency. Although the K variable from the exponential fit showed a close relationship with other elasticity related variables, such as Cst and P0, this was not the case for the shape factor from the LE fit (KLE). KLE was not significantly related to Cst (p=0.0014). Although a significant relationship existed with P90 (r=-0.45) the correlation coefficient was lower than that for KE (r=-0.60).

The additional parameter from the LE fit, the volume at which the linear part changed into the exponential part (Vtr), was expressed as a fraction of TLC. Vtr/TLC appeared to be closely related to variables determined either by the degree of airway obstruction (FEV1/VC: r=0.43; p<0.0001) or the amount of hyperinflation (RV/TLC: r=0.39; p<0.0001; FRC/TLC: r=0.33; p=0.0008). The relationship with FEV1/VC is presented in figure 5. Mean Ptp, defined as Ptp at Vtr, was 1.00 kPa (SD 0.37 kPa). Although Ptp and Vtr/TLC were significantly correlated (r=0.34, p<0.001) no significant correlation existed between Ptp and the obstruction or hyperinflation indices. The measure of hyperreactivity, expressed as

### Table 1. Variables obtained by the E and LE fit

<table>
<thead>
<tr>
<th>Fit variable</th>
<th>Exponential model</th>
<th>LE model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vmax/TLC</td>
<td>1.07 (0.06)</td>
<td>1.02 (0.02)</td>
</tr>
<tr>
<td>K</td>
<td>kPa^{-1}</td>
<td>1.32 (0.05)</td>
</tr>
<tr>
<td>P0</td>
<td>kPa</td>
<td>-0.26 (1.0)</td>
</tr>
<tr>
<td>a</td>
<td>L</td>
<td>2.58 (0.96)</td>
</tr>
<tr>
<td>b</td>
<td>L·kPa^{-1}</td>
<td>2.96 (1.16)</td>
</tr>
<tr>
<td>Vtr/TLC</td>
<td></td>
<td>0.79 (0.07)</td>
</tr>
<tr>
<td>Ptp</td>
<td>kPa</td>
<td>1.00 (3.7)</td>
</tr>
</tbody>
</table>

Values are presented as mean and sd in parenthesis. Vmax: asymptote value; K: shape factor; P0: intercept with pressure axis; a: volume intercept of the linear part of the LE fit; b: slope of the linear part of the LE fit; Vtr/TLC: volume, expressed as fraction of TLC, at which the linear part changes into the exponential part; Ptp: Ptp at Vtr. For further abbreviations see legend to figure 1.

For analysis of the P-V curves, the mean volume level, from which the data were sampled for analysis, was 0.59 TLC (SD 0.08).

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of quasistatic hyperinflation was also present. Comparison of FEV1/VC, 20% uniformly accepted or exact definitions exist [13, 19, criteria over confusing diagnostic labels, for which no This underlines our preference for objective functional ences, thus our study group can be seen as a random and those in the entire group showed no significant differ- ence for P90 between the Asthmatic Bronchitis and the COPD Group (mean 1.25 kPa, SD 3.1 kPa).

Discussion

A linear-exponential model was developed for the fit of quasistatic P-V curves. The model also takes the linear part in the mid vital capacity range into account and proved to give a markedly better fit than the exponential model. Moreover, a parameter Vtr, being the volume at which the linear part changes into the exponential part, is hypothesized to be related to early airway closure. Both models were tested in a group of 99 patients with either asthma, asthmatic bronchitis or COPD.

The patients in our study, being a subgroup of those participating in a Dutch multicentre trial [11, 12], were selected on the basis of two functional criteria related to airway obstruction and hyperresponsiveness, these being prominent features in patients with obstructive airway disease. We found, except for a weak significant difference for P90 between the Asthmatic Bronchitis and COPD Groups, no other significant differences between the clinical diagnosis groups for P90, FEV1, Cst and Vtr. This underlines our preference for objective functional criteria over confusing diagnostic labels, for which no uniformly accepted or exact definitions exist [13, 19, 20].

On the basis of the RV/TLC and FRC/TLC values, besides the moderately obstructive pattern, moderate hyperinflation was also present. Comparison of FEV1/VC, age and sex distribution in our subgroup compared with those in the entire group showed no significant differences, thus our study group can be seen as a random and unbiased selection from the whole group.

Model fits of the pressure-volume curves

Until now, the preferred model for analysis of lung P-V curves, has been the exponential model. We used a mathematical description which was directly related to shift on pressure axis (P0), scaling factor of volume axis (Vmax), and shape factor (KE). In our investigation, the mean volume level from which the data were fitted was 59% of TLC. This volume level can be considered as sufficiently accurate for an exponential description [3], and is in accordance with that used by COLEBATCH et al. [3] (50–60% of TLC), and slightly larger than that used by GIBSON et al. [7] (52–56% of TLC).

GIBSON et al. [7] performing exponential fits to static pressure-volume curves of normal and diseased lungs, already indicated the apparently linear behaviour of a number of curves at or just above FRC level, influencing the accuracy of the fit. This accuracy was subsequently improved by taking a larger minimum volume as the start for the data analysis.

This led us to develop a model, intended as a mathematical description of the curve, in which this linear appearance was taken into account, and in which a minimum least squares approach was based on a linear part changing into an exponential upper part. In normal lungs [21], and in our patient group, the mean square error between fitted and experimental data improved about 15 times with respect to the exponential fit, indicating a markedly better "goodness of fit" and, thus, a more reliable mathematical description of curve pattern.

The mean value of the volume at which the linear part changed to an exponential upper part (Vtr) was 0.79 TLC. Thus, on average, from the lowest level of the analysed volume range (mean value=0.59 TLC) over about 0.2 TLC the linear appearance was more prominent than the contribution to the exponential fit. The slope of the linear part was interpreted as lung compliance, usually determined as the slope between FRC and FRC+0.5 L [1].

As shown in table 1, in addition to the improvement in goodness of fit by the LE model, the mean Vmax/TLC was only slightly larger than 1, whilst in the exponential model this ratio was about 1.07. Therefore, P90% TLC was calculated from equation (3) with the LE fit parameters.

Elasticity indices from the models

The mean lung compliance, denoted by the LE fit parameter b (2.96 L·kPa−1; table 1) was comparable with earlier results in healthy persons, in which also no significant correlation with age was found [22, 23].

The K factor from the exponential fit has been proposed to be superior to the compliance estimate as an overall measure of lung elastic properties, independent of lung size [9]. Our values, shown in figure 2, fit well in those of a group of 83 healthy individuals [7]. In our case a significant age dependency was found. We also found a strong relationship with compliance (fig. 3), as has been reported previously [2].

Fig. 5. – Volume at which the linear part of the curve changed into the exponential part (Vtr), as fit parameter from the linear-exponential (LE) fit related to FEV1/FVC in the 99 patients. FEV1: forced expiratory volume in one second; VC: vital capacity; TLC: total lung capacity.

log2 PC30, had no significant relationship with any of the model parameters.

The variables P90, FEV1, Cst and Vtr/TLC were also compared between the clinical diagnosis groups: Asthma (n=37), Asthmatic Bronchitis (n=31) and COPD (n=15). A significant difference (p<0.05, two sample analysis by t-test) was found only for P90 between the Asthmatic Bronchitis Group (mean 1.61 kPa, SD 4.7 kPa) and the COPD Group (mean 1.25 kPa, SD 3.1 kPa).
Because of the lower variation coefficient of $P_{90}$ at 90% of TLC this pressure index ($P_{90}$) was proposed by Yernault et al. [4] to be the most representative measure of elastic recoil normalized to a specific volume level. This index, which we derived from the LE fit, also coincided with data from a healthy population, including the age dependency (fig. 4) [18]. A highly significant relationship existed with the K factor from the exponential relationship, indicating the connection of both indices with lung elastic properties.

The K factor from the linear-exponential fit showed no statistical relationship with compliance and a less significant relationship with $P_{90}$, when compared with the exponential fit K factor. From this, it may be concluded that the KL/E parameter is less useful for expression of overall lung elastic behaviour, although further investigations may reveal a relationship with lung elastic behaviour from about 70–80% TLC upwards. The $P_{90}$ values of both fits showed no relationship with other elasticity indices. The reason may be that, because of the extrapolation of these values over a large volume range to $V=0$, their spread is large and, for instance, $P_{90}$ can be considered as a more reliable and physiologically interpretable measure of the position of the curve along the $P$ axis.

The lack of significance of the log$_2$ PC$_{20}$ with either elasticity related indices shows no relationship between bronchial hyperresponsiveness and lung elastic behaviour. For our patient group, having a moderate airway obstruction without medication, the elasticity indices were, on average, comparable with those of a healthy population. In earlier studies [24, 25], a slight decrease of elastic recoil, without an appreciable change in curve pattern, was reported for a small number of comparable patients. This was not detectable in our group.

The transition from lineal to exponential part, expressed as fraction of TLC ($V_t/TLC$)

$V_t$ can be considered as an additional variable, obtained from the LE fit. $V_t/TLC$ showed a significant relationship with the variables related to airway obstruction (FEV$_t$/VC) and hyperinflation (RV/TLC and FRC/TLC). The mean expiratory flow during the quasistatic manoeuvre was very low, according to the report on standardization of lung function [1]. Also, because a lower level was set on the inclusion criterion for FEV$_t$ (4.5 below the predicted value) we believe dynamic compression at these low flows and this degree of obstruction unlikely. Another mechanism may be the influence of airway closure on $P$-$V$ curve pattern, as stressed in other studies [2, 3, 7, 25, 26]. As airways close during expiration, the distal part of the lung will be excluded from further deflation and, during the continuing expiration, alveolar pressure in the isolated areas will progressively exceed that in the remaining lung with open airways. Below the volume at which airway closure begins, transpulmonary pressure will progressively exceed the elastic recoil pressure, thus explaining the point of inflection, the linear appearance at FRC level, and subsequently the positive pressure swing near RV level.

Airway closure, as measured by the helium bolus technique or the nitrogen dilution technique, usually occurs below FRC level in healthy individuals [26]. There is evidence, however, that the real start of airway closure is at markedly larger volume levels. Glaister et al. [27] studied isolated dog lungs in a low density fluidized bed, in order to simulate a pleural pressure gradient. $P$-$V$ curves were fitted with an exponential model and the results support the hypothesis that opening and closure of lung units takes place at even high transpulmonary pressure. Moreover, they state that much of the character of the vital capacity $P$-$V$ curve may be attributed to the sequential opening and closure of lung units. Obstruction of peripheral airways may cause dynamic hyperinflation of FRC. Moreover, early airway closure causes an increase of RV and also, because of its influence on elastic recoil of lung parenchyma, an increase of relaxed FRC. So the significant correlations of $V_t$/TLC with the hyperinflation and obstruction parameters can be explained by their relationship with comparable underlying mechanisms.

Although $P_{90}$ at $V_t$/TLC was closely correlated with $V_t$/TLC, no correlation existed with either obstruction or hyperinflation variables. The correlation between $P_{90}$ and $V_t$/TLC can be explained by their relationship via the model equations. Although all participating centres used the same protocol, slight differences in amount of air in the oesophageal balloons may have caused a lack of correlation between $P_{90}$ and obstruction or hyperinflation indices. Differences in amount of air may cause a shift of the $P$-$V$ curves along the abscissa ($P$ axis), causing an increased variance in $P_{90}$, without however changing the pattern of the $P$-$V$ curve.

We conclude that, besides the well-established exponential fit yielding a K factor related to overall lung elastic behaviour, an additional linear-exponential fit gives a more accurate mathematical description of lung pressure-volume curves. This enables an improvement of the accuracy of derived indices, such as $P_{90}$ and compliance, and so an improvement of the diagnostic value. The additional fit parameter $V_t$/TLC may be related to early airway closure, which determines its physiological significance.

Our results show that the patients from this multicentre study, of whom our subgroup represented a random selection with respect to hyperresponsiveness, airway obstruction, age and sex distribution, behaved on average as healthy individuals with regard to elasticity indices. This leads to the conclusion that abnormalities in lung elastic properties do not predominate in these moderately severe patients with asthma or COPD.

Study group

The Dutch Chronic Nonspecific Lung Disease (CNSLD) group consists of a steering committee (K.F. Kerrebijn, Ph.H. Quanjer and H.J. Sluiter††), of members from the Departments of Pulmonology of the University Hospital of Amsterdam (E.M. Pouw, D.F.M.E. Schoonbrood, C.M. J.M. BOGAARD ET AL.
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References

11. Postma DS, Brand PLP, Kerstjens HAM, Sluiter HJ and the Dutch CNSLD study group. Feasibility and baseline