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TECHNICAL NOTE

Time constant histograms from the forced expired volume signal: a clinical evaluation

J.P. Revelly, F. Feihl, T. Liebling, C. Perret

Time constant histograms from the forced expired volume signal: a clinical evaluation. J.P. Revelly, F. Feihl, T. Liebling, C. Perret.

ABSTRACT: We evaluated a multicompartment analysis of forced expiration, based on modelling the lung as a set of twenty parallel compartments emptying exponentially with time constants ranging from 0.1–10 s; the forced expired volume signal was represented by a histogram showing the fraction of forced vital capacity as a function of compartmental time constants. We applied this technique to 80 healthy and 12 asthmatic subjects. The histograms computed from three consecutive forced expirations were poorly reproducible in 18 of the 80 healthy and 2 of the 12 asthmatic subjects. In the asthmatics, the time constant histograms conveyed no additional information on bronchial obstruction, beyond that already present in standard spirometric indices. A simulation study showed a high sensitivity of the histograms to the truncation of the terminal part of forced expiration. We conclude that the usefulness of the time constant histogram technique appears doubtful.

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The simplest method for obtaining information on the mechanical properties of the respiratory system is to record the expired volume during a maximal forced expiration (spirometry). Traditional spirometric indices make use of only one or two points of the forced expired volume *versus* time signal (spirogram); conceivably, some of the information present on the complete signal may be lost.

The global shape of forced expiration can be considered, either in the flow domain (*i.e.* the flow-volume curve), or in the time domain (*i.e.* the volume *versus* time curve). Global analysis in the flow domain (Mead's slope ratio [1], curvilinearity index [2]) as well as in the time domain (transit times analysis) [3] have been described. There are theoretical [4] and practical [5] reasons for expecting more sensitivity to mild airway obstruction from the latter. However, the reproducibility of transit time analysis has been questioned [6] because of the high sensitivity of the computed moments to the variable duration of the forced expiration (truncation). There is no agreement on how expiratory time should be normalized in transit time analysis [7, 8].

An alternative analysis of forced expiration in the time domain has been proposed by PIMMEL *et al.* [9]. Based on a multicompartment parallel model of the respiratory system, the spirogram is viewed as the weighted sum of a large number of exponential processes. From preliminary data, Pimmel suggests that this method is reproducible and sensitive to airway obstruction. We report a more extensive study of the reproducibility and information content of Pimmel's method.

Methods

Subjects

Spirometry was performed in 80 normal subjects (36 males and 44 females; 35 smokers and 45 nonsmokers, mean age 29.8±5.9 yrs). Subjects were considered normal if they had none of the following: history of cardiovascular or respiratory disease, chronic cough, asthma, allergic rhinitis, recent (<28 days) airway infection, abnormal spirometry (see below).

In addition, forced expirations were recorded from 12 patients with allergic asthma (7 males and 5 females; mean age 27.3±7.7 yrs). At study time, all patients were asymptomatic and had a forced expiratory volume in one second (FEV_1) above 70% of the predicted value; none required long-term treatment of any kind.

Instrumentation and spirometric technique

The forced expiratory flow *versus* time signal was recorded by means of a pneumotachograph (Fleisch No. 3, Metabo SA, Epalinges, Switzerland) connected to a differential pressure transducer (type 17212, Gould-Godard, Bilthoven, Holland). The response of the flow measuring system was linear within ±1% between 0–8 $l \cdot s^{-1}$. Volume was obtained by numerical integration of the digitized (12 bits, 50 Hz) flow signal. Results were stored on disk for later processing. The subjects performed forced expirations in the sitting

position [10], wearing a noseclip. The first three technically acceptable spirograms (see below) were retained for analysis.

Zero time was determined by backward extrapolation to zero volume change from the point of maximal flow [11]. Forced vital capacity (FVC), FEV_1, peak expiratory flow (PEF) and maximal mid-expiratory flow rate ($FEF_{25-75\%}$) were computed. For each spirometric index, the highest value obtained from three forced expirations was recorded and expressed as a percentage of the predicted value published by the European Coal and Steel Community (ECSC) [12]. Spirometry was deemed abnormal if at least one of the four indices was lower than the predicted value minus 1.64 times the ECSC standard deviation (RSD_a; standard error of the estimate of the normal value of a pulmonary function test as a function of age, sex and height) [12].

Criteria for technical acceptability included all of the following: 1) differences between largest and smallest FVC and FEV_1 obtained from three forced expirations <5% of the mean value [13]; 2) forced expiration completely terminated, *i.e.* 25 ml exhaled in the terminal 0.5 s [13]; 3) volume actually expired at back-extrapolated time zero <100 ml [14].

Multicompartment analysis

The method described by PIMMEL *et al.* [9] was used, with minor modifications. In this method, the respiratory system is modelled as a set of parallel compartments, each contributing to a fraction of the total FVC. In order to understand this model, it is best to first envisage a single compartment lung (fig. 1, upper). During forced expiration, the volume of such a lung is assumed to decrease exponentially, with a time constant T. The next step is to envisage a two compartment parallel model (fig. 1, middle). The forced expired volume *versus* time signal is then a weighted sum of two exponential processes with time constants T_1 and T_2. The fractions contributed by each compartment to total FVC are the weights f_1 and f_2 assigned to each exponential. Of course, f_1 and f_2 add up to one. The model can be graphically represented by a two-bar histogram with the compartment time constant along the horizontal axis, and the weight along the vertical axis. Going one step further, we get the model proposed by Pimmel: 20 parallel compartments (fig. 1, lower). The 20 compartmental time constants are chosen to encompass the range of physiologically plausible values; the fastest compartment empties with a time constant of one tenth of a second; the slowest compartment has a time constant of ten seconds. All time constants are spaced evenly on a logarithmic scale. Such a model can be represented in the form of a 20-bar time constant histogram. What Pimmel did was to fit the model to real forced expired data; this means that he estimated the set of weights f_i which gave the best fit of the model to real data.

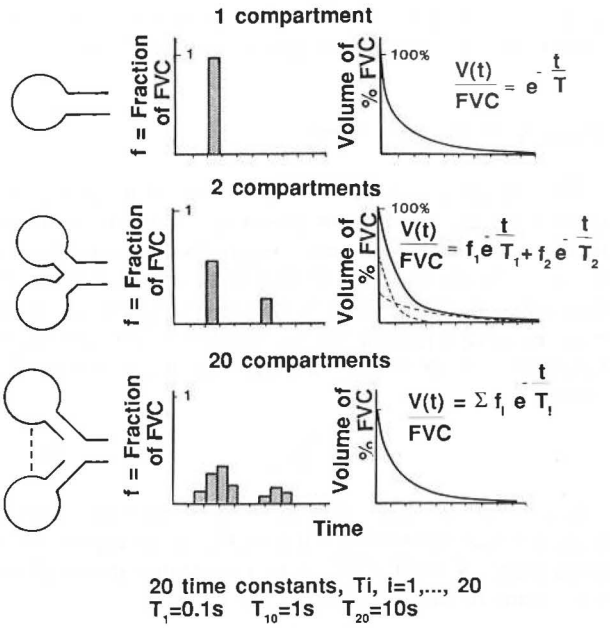

Fig. 1. – One compartment, two compartment and twenty compartment models of forced expiration. FVC: forced vital capacity; V(t): expired volume *vs* time. In the two compartment model, $f_1+f_2=1$. In the twenty compartment model $\Sigma f_i=1$.

Below is a more formal description of multicompartment analysis. The expired volume *versus* time signal V(t) generated by the model is:

$$V(t)/FVC = \sum_{i=1}^{20} f_i e^{-t/Ti};\ i = 1,...,20 \qquad (1)$$

In Pimmel's method, 20 compartments are defined (m=20). The compartments are ordered according to the value of T_i and numbered from 1 to 20. The T_i are defined according to equation 2:

$$T_i = 0.1 \times 100^{(i-1)/19};\ i = 1,...,20 \qquad (2)$$

The model is then fitted to 50 points of real spirographic data (back extrapolated points included) selected at times:

$$t_j = 0.1 \times 100^{(j-1)/49};\ j = 1,...,50 \qquad (3)$$

The f_i are computed using a linear least squares algorithm with smoothing and a non-negativity constraint [9]. The set of f_i given by this algorithm will be called the time constant histogram (TCH) recovered from the spirogram to which the the fit was applied. A TCH can be displayed graphically as a function of T_i as shown in figure 1. A smoothing parameter of 5×10^{-4} is used; this value was determined empirically and is somewhat larger than that reported by Pimmel (1×10^{-4}).

The algorithm was implemented in Pascal on a Vax 8600 computer. It was applied to simulated noise-free spirograms generated from variously shaped known

histograms using equation 1; the agreement between the known and recovered histograms was excellent.

Analysis of the histograms

The fraction of total FVC (f_i) assigned to each compartment may be zero or positive. Adjacent compartments with positive f_i may be grouped into modes. A mode is made of all compartments included between two adjacent local minima of the histogram. A mode may be characterized by its weight w and its mean position $\bar{c}$. w is simply the sum of the f_i within the mode:

$$w = \sum_{i=min}^{max} f_i \quad (4)$$

where min and max are the lowest and the highest compartment numbers in the mode. w is expressed in percentage of total FVC. $\bar{c}$ is a weighted mean of the compartment numbers within the mode:

$$\bar{c} = \sum_{i=min}^{max} if_i / \sum_{i=min}^{max} f_i \quad (5)$$

$\bar{c}$ is expressed in arbitrary units ("compartment number") and may take fractional values. It might seem more logical to characterize the position of the mode by a mean time constant $\bar{T}$ expressed in seconds:

$$\log \bar{T} = \sum_{i=min}^{max} \log T_i \times f_i / \sum_{i=min}^{max} f_i \quad (6)$$

However, in order to express the position of the mode, $\bar{T}$ and $\bar{c}$ are equivalent, because, according to equations 2 and 6:

$$\bar{c} = 9.5 \log \bar{T} + 10.5 \quad (7)$$

Reproducibility of the histograms

The histograms showed considerable intra-individual variability at the lower end of the time constant spectrum, as already noted by PIMMEL *et al.* [9]. This may be due to the strong influence of the initial effort dependant data points on the weights attributed by the algorithm to the fastest time constants. For this reason, modes with a mean position lower than 3 compartments were not considered in the analysis that follows.

The reproducibility of the histograms obtained from forced expirations repeated in the same subject was tested according to the criteria defined in the original publication [9] (Pimmel's criteria): the histograms should have the same number of modes; the mean position $\bar{c}$ and the weight w of each mode should not vary by more than one compartment number and 5% of FVC, respectively. The reproducibility was also tested using our less stringent criteria; the histograms should have the same number of modes, and the mean position of each mode should not vary by more than 1.6 compartment numbers.

Results

All analysed spirograms were approximated satisfactorily by the multicompartment model: the average±SD in all analysed spirograms of the root mean square (RMS) error of the fit was 0.5±0.4% of FVC with a maximum value of 2% of FVC. Sixty two of the 80 healthy subjects and 7 of the 12 asthmatic subjects yielded non-reproducible histograms according to Pimmel's criteria. Eighteen healthy and 2 asthmatic subjects had non-reproducible histograms according to our criteria (fig. 2).

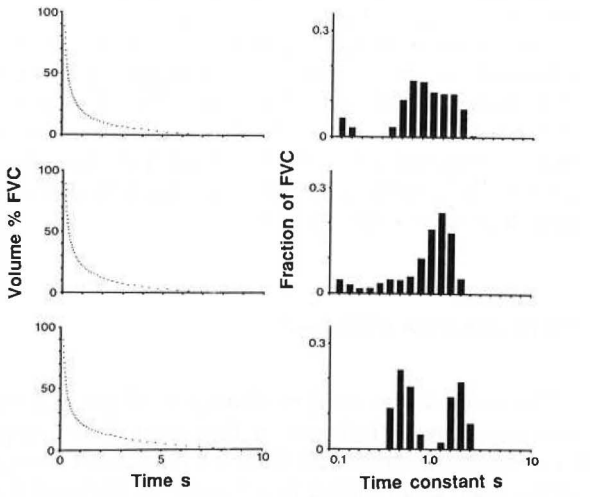

Fig. 2. – Poorly reproducible time constant histograms recovered from three consecutive forced expirations in the same subject. The successive values of FVC and FEV_1 showed less than 5% variation (see Methods). FVC: forced vital capacity; FEV_1: forced expiratory volume in one second.

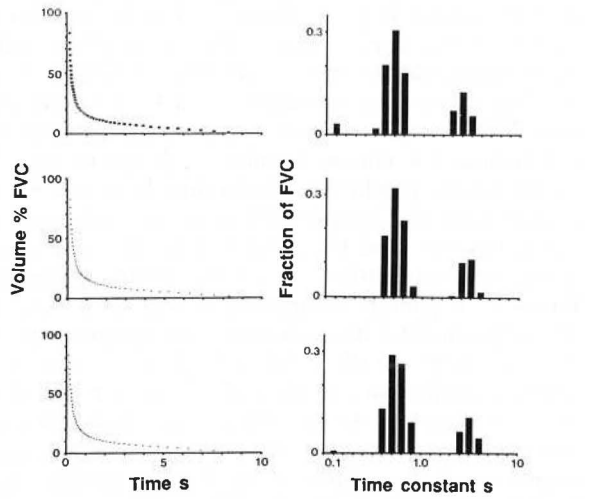

Fig. 3. – Bimodal, reproducible time constant histograms recovered from three consecutive forced expirations in the same subject. FVC: forced vital capacity. Histograms (right hand part of the figure) obtained by fitting equation 1 (see text) to 50 points of forced expired data (left) sampled from the continuous volume *versus* time signal (equation 3, see text).

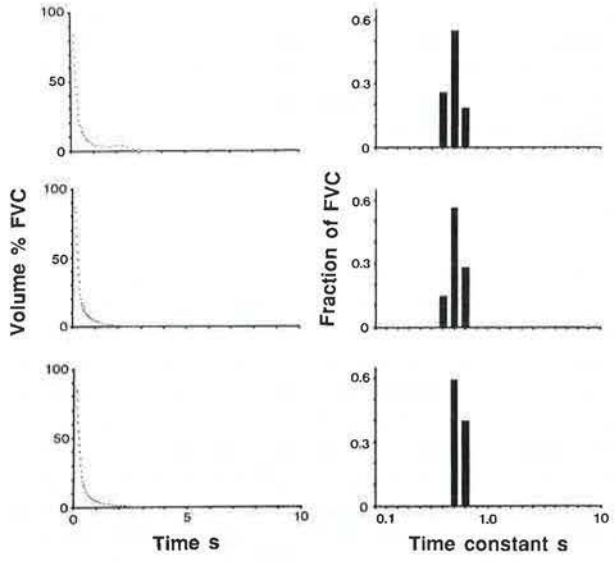

Fig. 4. – Unimodal, reproducible time constant histograms recovered from three consecutive forced expirations in the same subject. FVC: forced vital capacity.

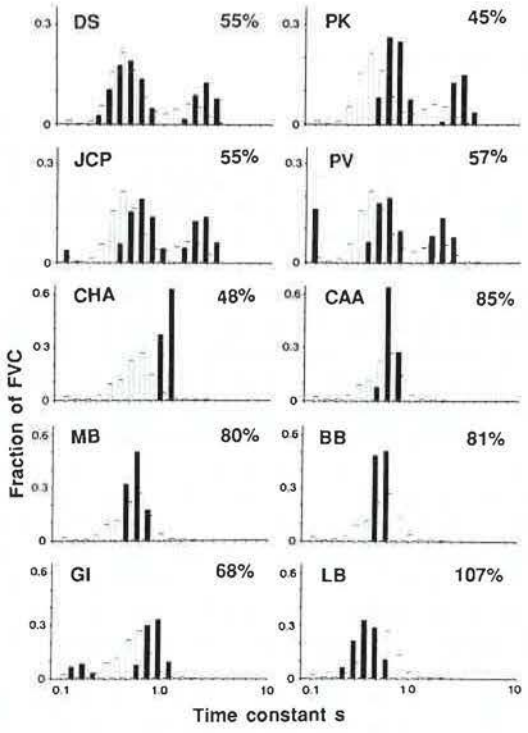

Fig. 5. – Time constant histograms (TCH) in the ten asthmatic patients who had reproducible TCH. The solid bars are the mean of three TCH recovered from consecutive forced expirations. The dotted outlines show the mean normal histogram for comparison. The bimodal (unimodal) outline is an average of all reproducible bimodal (unimodal) TCH found in the healthy subjects. The percentage figures are the mid-expiratory flow rate ($FEF_{25-75\%}$) of each patient as a percentage of the predicted value. The modes with the smallest time constant in subjects JCP, PV and GI were disregarded (see Methods). FVC: forced vital capacity.

The shape of the reproducible histograms was bimodal (fig. 3) in the majority (46 out of 62) and unimodal (fig. 4) in a minority (16 out of 62) of the healthy subjects.

In the 10 asthmatics with reproducible histograms, bimodal shapes were found in 4 and unimodal shapes in 6 subjects. The histograms (mean of three histograms obtained from three forced expirations) of each asthmatic subject were compared to the mean histogram in the healthy group (fig. 5). In the healthy group, unimodal and bimodal histograms were averaged separately. The patients with evidence of airway obstruction according to standard spirometric criteria (decreased $FEF_{25-75\%}$) showed a position shift of their histograms towards compartments with slow time constants. On the other hand, the patients with normal $FEF_{25-75\%}$ appeared to have normal histograms as well.

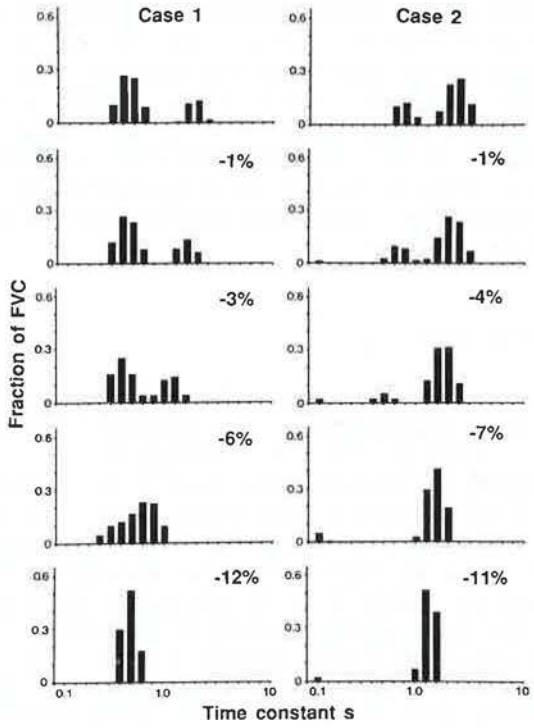

Fig. 6. – A numerical simulation to show the effects of spirogram truncation on the recovered time constant histograms (TCH). The bimodal TCH in the upper row were recovered from two real fully terminated forced expirations (case 1 and case 2). The TCH recovered from the same spirograms with the terminal part removed are displayed on the following rows; the amount of truncation is shown in percentage of FVC (forced vital capacity).

Discussion

Relationship to other methods

As stated in the introduction, there are two distinct approaches to global analysis of forced expiration, one in the flow domain, the other in the time domain. Indices derived in the flow domain, such as Mead's slope ratios [1], curvilinearity index [2] or a more recently described multivariate analysis of the flow-volume curve

[15], give more weight to the initial part of forced expiration. On the contrary, indices derived in the time domain, such as transit time moments (transit time analysis) [3] or time constant histograms, give more weight to the terminal part of forced expiration. In theory, the latter is selectively modified by mild airway obstruction [16], which should therefore be more easily detected by analyses performed in the time, rather than in the flow, domain. Indeed, it was found that transit time moments discriminated smokers from nonsmokers better than did slope ratios [5].

There are similarities between transit time analysis and the time constant histogram method. Indeed, PERMUTT and MENKES [4] introduced a model of forced expiration similar to ours, except that they used a continuous distribution of time constants. They showed that if this distribution obeys a log-normal law, its parameters are related to the first and second order transit time moments through simple mathematical formulae, so that identical information is obtained from the computation of either the low order transit time moments or the distribution parameters. However, our method is not equivalent to transit time analysis, because it makes no assumption on the particular shape of the distribution of time constants; therefore, no unique relationship exists between low order transit time moments and time constant histograms.

Reproducibility

In our hands, the reproducibility of the time constant histogram method appeared less satisfactory than initially reported [9]. This lack of reproducibility does not depend on any implementation error of the algorithm, which was numerically verified (see Methods). Neither is it due to any inherent inability of the multicompartment model to approximate some spirographic data, because the quality of the fit was always satisfactory. The root mean squares obtained in the present study were comparable to those reported by PIMMEL *et al.* [9]; indeed, the largest RMS were recovered from spirograms with short expiratory times which yielded reproducible unimodal histograms (fig. 4). We must examine whether the poor reproducibility was in any way related to the technical modifications we introduced into the original method. Firstly, while Pimmel recorded the volume *versus* time signal with a rolling seal spirometer, we used a pneumotachograph, which has a much shorter mechanical and thermal response time [17]. This should ensure minimal distortion of the recorded signal and, therefore, is unlikely to degrade the reproducibility of the histograms. Secondly, we used a higher value (5×10^{-4}) of the smoothing parameter, as compared to Pimmel (1×10^{-4}). This should stabilize the shape of the recovered histograms [18]. Thus, neither one of the above technical modifications can explain the relatively poor reproducibility of the time constant histograms in our study.

We must admit that in at least 25% of cases, repeated forced expiratory spirograms obtained from the same subject were reproducible by usual standards and nevertheless were different enough to result in wildly variable histograms. In such cases, the histograms appear to convey no usable information. This is a clear limitation of the method.

Asthmatic subjects

We compared the histograms of individual asthmatic subjects with either no or mild airway obstruction (FEV_1 >70% of predicted, see Methods) to the mean histogram of the healthy group (fig. 5). In this way, we tended to overestimate the differences between asthmatics and healthy subjects, because we disregarded the histogram variability in the latter group. Nevertheless, the patients whose histogram differed from the mean of the healthy group also had a reduced $FEF_{25-75\%}$ and no patient with a normal $FEF_{25-75\%}$ had an abnormal histogram. Morever, the way the abnormal histograms deviated from the norm was rather uniform, being essentially a shift towards slower time constants with little variation in shape as shown in figure 5. Thus, in this particular group of asymptomatic asthmatics, the time constant histogram method conveyed no additional information regarding bronchial obstruction, as compared to spirometric indices.

Physiological interpretation

It might be hoped that the time constant histogram method should give physiological information on inhomogeneities of lung mechanical properties during forced expiration. However, such a physiological interpretation is probably not possible for several reasons. Firstly, the time constant model will give information on the inhomogeneity of lung mechanical properties only if it can be assumed that the model's elements are linear. This assumption is questionable. Indeed, the forced expiration generated by a single compartment lung with certain alinear mechanical properties could well produce a very "inhomogenous-looking" histogram, if analysed by our method. Even if linearity of the lung elements could be accepted, other problems arise. In young healthy subjects, the usual flow limitation mechanisms do not operate during the terminal part of a forced expiration; in these subjects, the terminal part is therefore effort-dependent [19]. Furthermore, the onset of diaphragmatic contraction may be an important determinant of the termination of a forced expiration [20]. In practice, in an individual subject, it is generally impossible to know how far towards the end of a forced expiration flow is limited by purely intrapulmonary factors. For these reasons, the results of any analysis taking into account the tail of the spirogram, such as the time constant histogram method, are potentially influenced by extrapulmonary phenomena. For instance, the slow modes observed in many normals may be determined in part by the viscoelastic behaviour of the thorax towards end expiration.

When bronchial obstruction is present, flow is most probably limited during the entire course of a forced expiration. In this situation, the duration of the forced expiration increases and an inspiratory reflex may interrupt the manoeuvre before "true" FVC has been exhaled (truncation). In order to examine the effects of truncation on the recovered histograms, we performed a numerical simulation (fig. 6). We took actual spirograms which originally yielded bimodal histograms; we progressively suppressed a larger and larger portion of the terminal part, and recomputed histograms from the truncated signals. Truncation produced:1) a shift of the modes towards the fast compartments; 2) sometimes a redistribution of the mode weights in favour of the slow mode (see case 2, fig. 6); and 3) an eventual disappearance of the bimodal shape. It may appear parodoxical that truncation of the terminal part of the spirogram, during which the influence of the slow compartments dominates should sometimes cause an increased slow mode (see case 2, fig. 6). Truncation does indeed remove information on slow compartments, whose fractional volume will then be estimated inaccurately. Whether the result is an over- or underestimation of the slow mode probably depends on the particular data set.

In the cases studied, the shape of the recovered histograms was changed from bimodal to unimodal by removing the last 6–7% of FVC (*i.e.* hardly more than the accepted variability of FVC in standard spirometry). Therefore, even if the linearity assumptions hold and even if flow limitation exists up to the termination of the forced expiration, the shape of the recovered histograms may heavily depend on an extrapulmonary factor, namely on how long the subject is able to sustain a forced expiratory effort. The time constant histogram method does not appear more immune than transit time analysis to the truncation effect.

In summary, the time constant histogram method appears less reproducible than previously reported. In a small group of asymptomatic asthmatics, it conveyed no additional information on bronchial obstruction, beyond that already present in standard spirometric indices. The information content on mechanical inhomogeneities within the lung is limited: 1) by the underlying linearity assumptions which may not hold for the real lung; 2) by the truncation effect; or 3) in subjects able to perform a complete forced expiration, by the fact that flow may be determined by extrapulmonary factors during the terminal part of the manoeuvre. Therefore, the clinical usefulness of the time constant histogram method appears doubtful.

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Histogrammes avec constante de temps obtenus à partir du signal du volume expiratoire forcé: une évaluation clinique.
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RÉSUMÉ: La manoeuvre d'expiration forcée reste le test fonctionnel pulmonaire le plus simple et le plus utilisé. Traditionnellement, seuls un ou deux points du spirogramme

(volume expiré en fonction du temps) sont pris en considération pour calculer des indices fonctionnels. Toutefois, l'avénement des ordinateurs rend possible des analyses prenant en compte la globalité du spirogramme. Une approche qui a été décrite (*J Appl Physiol*, 1981, 51, 1581) mais pas évaluée, consiste à modéliser le poumon comme un ensemble de 20 compartiments en parallèle, se vidangeant exponentiellement en fonction du temps avec des constantes de temps variant de 0.1 à 10 secondes. Le spirogramme est représenté par un histogramme portant en ordonnée la fraction de la capacité vitale forcée se vidangeant avec une constante de temps donnée. Nous avons appliqué cette technique à 80 sujets sains et 12 patients asthmatiques. Les histogrammes calculés à partir de trois expirations forcées consécutives étaient mal reproductibles chez 18/80 sujets sains et 2/12 asthmatiques. Des 10 asthmatiques avec histogrammes reproductibles, 6 avaient des indices spirométriques témoignant d'une obstruction bronchique modérée (FEV_1 >70%, $FEF_{25-75\%}$ <70% des valeurs prédites); leurs histogrammes étaient probablement anormaux; les autres asthmatiques avaient des indices spirométriques et des histogrammes normaux. Une étude par simulation sur ordinateur a montré que les histogrammes sont très sensibles à la troncation de la partie terminale de l'expiration forcée. Nous concluons que l'utilité de cette technique est douteuse car les histogrammes: 1) sont mal reproductibles chez environ 25% des sujets; 2) ne paraissent pas fournir davantage d'information sur l'obstruction bronchique, comparés aux indices spirométriques traditionnels; 3) sont sujets à des artéfacts lorsque l'expiration forcée est tronquée.

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