Analysis of forced expired volume signals using multi-exponential functions

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Abstract—*Patients with pulmonary disease are often unable to complete forced expiration manœuvres. The aim of the study is to evaluate whether forced vital capacity (*FVC*), the volume exhaled at the end of completed forced expiration, can be estimated by extrapolating volume–time curves obtained from uncompleted manœuvres. The suitability of mono-, bi-, and tri-exponential functions to characterise complete volume–time curves from 50 subjects is investigated. Mono-exponential modelling is insufficient, whereas bi-exponential fitting yields an adequate description for 47 data sets. Tri-exponential models lead to overfitting in all but three cases (normalised sum of least squares: 50.2 ± 34.5 for mono-, 2.76 ± 4.11 for bi-, 2.74 ± 4.19 for tri-exponential modelling; condition number of the correlation matrix: 1.0025 ± 0.0004 for mono-, 1.08 ± 0.08 for bi-, 34.7 ± 100.1 for tri-exponential fitting (mean ± SD)). Thus, FVC is estimated by the extrapolation of 27 uncompleted spirograms using bi- or tri-exponential models, depending on their accordance with measured data and on the identifiability of their parameters. This algorithm yields unbiased estimates (difference from measured inspiratory vital capacity: 0.01 ± 0.21 L). This method can be used for investigation of the lung function of subjects who cannot complete the forced expiration manœuvre.*

Keywords—*Lung function measurement, Spirometry, Forced expiration manœuvre, Model selection, Prediction of forced vital capacity*

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1 Introduction

OBSTRUCTIVE AND restrictive ventilatory diseases present a major public health problem. Recent epidemiological studies have revealed, for example, prevalence rates for asthma and chronic obstructive pulmonary disease (COPD) of about 4% each (HEDMAN *et al.*, 1999).

Spirometry and, in particular, forced expiration form one of the most widely applied clinical tests to assess obstructive or restrictive ventilation disorders in lung diseases such as asthma, COPD or lung fibrosis. The procedure consists of a slow maximum inhalation and a subsequent forced expiration, the latter being performed as quickly and completely as possible. The change in lung volume V is measured throughout the whole manœuvre as a function of time t, resulting in a time series $V(t)$, the spirogram.

Spirometric parameters of particular clinical interest are the volume exhaled within 1 s from the start of the forced expiration manœuvre FEV_1, the forced vital capacity FVC, i.e. the volume exhaled at the end of forced expiration (see Fig. 1), and the ratio FEV_1/FVC. Restrictive pulmonary diseases such as lung fibrosis are characterised by small values of FVC and normal ratios FEV_1/FVC, whereas a small value of FEV_1/FVC, in the presence of normal FVC indicates obstructive pulmonary diseases.

To guarantee the validity and reproducibility of spirometric measurements, the American Thoracic Society (ATS) recommends, above all, a minimum duration of the forced expiration manœuvre of 6 s and the existence of a plateau phase, i.e. constant volume during at least 2 s, at the end of forced expiration (AMERICAN THORACIC SOCIETY, 1995). However, patients with respiratory complaints, especially asthmatics and COPD patients, are often unable to fulfil these criteria. As a consequence, FVC is underestimated, and FEV_1/FVC is overestimated, which in turn can lead to false diagnosis and therapy.

Inspiratory vital capacity IVC reflects the same physiological quantity as FVC in normal subjects, but, in patients with considerably obstructed airways, it can be somewhat higher (CHHABRA, 1998). IVC can be measured in many subjects who are unable to complete forced expiration. However, measurement of IVC requires an additional manœuvre that is often not performed in daily routine. Therefore we investigated whether FVC could be reliably predicted by extrapolating forced expired volume signals from uncompleted forced expiration manœuvres. As measured FVC is not available when forced expiration cannot be completed, we used IVC to judge the estimated FVC in these cases.

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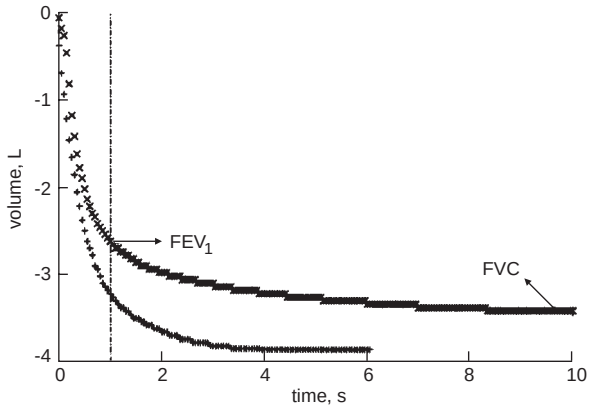

Fig. 1 *Forced expired volume–time curves from two completed forced expiration manœuvres; FEV_1 and FVC of the upper curve are highlighted*

Negative volumes representing expiration by convention, multi-exponential functions of the form

$$\hat{V}_M(t) = -A_0 + \sum_{j=1}^{M} A_j e^{-\mu_j t} \tag{1}$$

with positive constants $A_0, \ldots, A_M$ and $\mu_1, \ldots, \mu_M$, have been proposed to model expired volume $V(t)$ under different conditions, including forced expiration (CHELUCCI *et al.*, 1991; 1993; GUTTMANN *et al.*, 1995; PIMMEL *et al.*, 1981; REVELLY *et al.*, 1989). The number M of exponentials used varies from 1 to 20. PERMUTT and MENKES (1979), as well as ROTGER *et al.*, (1989), even developed a method based on a virtually infinite number of exponentials, i.e. a model of the form

$$\hat{V}(t) = -A_0 + \int_0^{\infty} a(\mu) e^{-\mu t} d\mu \tag{2}$$

with a constant A_0 and a continuous, non-negative function $a(\mu)$. From a physiological point of view, the fact that the human airways form a highly complex system calls for a complex model involving a high number of exponentials. However, from a statistical point of view, a model is inappropriate if the number of its parameters is so high that some of them are unidentifiable. Such overfitting increases the uncertainties, not only of the estimated parameters, but also of predicted future values $\hat{V}(t)$ for large times t. To our knowledge, the suitability of the above models with respect to the minimum M sufficient adequately to describe the forced expired volume signal $V(t)$ has not been investigated yet.

We used multi-exponential models according to eqn 1, with $M = 1$, 2 and 3, to analyse forced expired volume–time curves.

2 Materials

2.1 *Subjects*

Forced expired volume signals of 77 subjects, with and without pulmonary disease, were analysed. Fifty of these volume–time curves fulfilled all the requirements of the ATS (AMERICAN THORACIC SOCIETY, 1995), whereas 27 originated from uncompleted forced expiration manœuvres. All subjects had been presented to the Department of Pneumology of the University Hospital Freiburg for routine medical inspection. Diagnoses are briefly summarised in Table 1.

2.2 *Data*

Recording of forced expired volume signals was performed using a Masterlab device† that digitises and stores volume data with a resolution of 0.04 L and a sampling frequency of 20 Hz. The most important uncertainty in the volume measurement is due to discretisation, and so the standard deviation σ of the measurement error for each volume value was assumed to be $\sigma = 0.04/\sqrt{12}$ L, the variance of the uniform distribution in an interval of width 1 being $1/12$. To eliminate delays at the beginning of the forced expiration manœuvres, the first data points of the volume–time curves were discarded, as long as the difference between successive volume values was less than 0.08 L.

3 Model selection

3.1 *Methods*

We applied the Levenberg–Marquardt algorithm (PRESS *et al.*, 1992) to analyse the 50 volume–time curves $V(t)$ from completed manœuvres, using multi-exponential models as given in eqn 1. The parameters $A_0, \ldots, A_M$ and $\mu_1, \ldots, \mu_M$ were restricted to positive real values.

The Levenberg–Marquardt method aims to find the set of $(2M+1)$ parameters $\{A_0, \ldots, A_M, \mu_1, \ldots, \mu_M\}$ that minimises the quantity

$$\chi^2 = \sum_{i=1}^{N} \left[\frac{V(t_i) - \hat{V}_M(t_i)}{\sigma} \right]^2$$

for a given time series of volume measurements $\{V(t_i),\ i = 1, \ldots, N\}$. After completion, it also provides the estimated covariance matrix Cov for the selected parameters.

When a given data set is successively modelled by functions of the same type but with an increasing number of free parameters, χ^2 decreases. Accordingly, in our case, when fitting a forced expired volume–time curve with multi-exponential functions, as given by eqn 1, χ^2 is expected to decrease with increasing number of exponentials M. Plotting χ^2 against M, the optimum number of exponentials M^* is identified by a pronounced knee in the plot: For $M < M^*$, χ^2 sharply decreases with increasing M whereas, for $M \geqslant M^*$, no further substantial changes in χ^2 are observed.

The covariance matrix Cov can be transformed into the correlation matrix $Corr$ by normalisation:

$$Corr_{ij} = \frac{Cov_{ij}}{\sqrt{Cov_{ii} Cov_{jj}}}$$

The ratio of the highest and the lowest eigenvalues of $Corr$, the condition number c, contains information about the suitability of the model used in the fitting procedure: If all parameters are identifiable, c should be close to 1, whereas high values of c indicate overfitting.

We fitted functions as given by eqn 1, with $M = 1$, 2 and 3, to the 50 volume–time curves from completed forced expiration manœuvres. According to the criteria of the ATS, the end of the curves was considered to be reached when the expired volume had reached its plateau, i.e. when it had been constant for 2 s.

To find the number M of exponentials that is optimum to characterise forced expired volume signals, we considered the respective values of $\chi^2/(N - 2M - 1)$ and the condition numbers c. The denominator $(N - 2M - 1)$ normalises χ^2 with respect to the number of data points N and the number of free parameters $2M + 1$.

3.2 *Results*

For all the time series investigated, deviations of the obtained mono-exponential fitting functions from measured data are observed, whereas the fitting functions obtained with two and three exponentials are visually almost indistinguishable from

† Jaeger, Würzburg, Germany.

Table 1 Characteristics of participating subjects

		Completed forced expiration manœuvre		Uncompleted forced expiration manœuvre	
Diagnosis	sex	number	age, years	number	age, years
Obstructive pulmonary disease	F	7	34–64	2	48–73
	M	10	16–71	2	76–78
Restrictive pulmonary disease	F	3	22–56	3	56–73
	M	4	37–71	3	22–58
Obstructive and restrictive pulmonary disease	F	2	13–29	1	44
	M	3	20–46	4	36–71
No pulmonary disease	F	7	29–46	3	29–57
	M	14	29–65	9	20–53

measured data and from each other. This is also reflected by the respective values for $\chi^2/(N-2M-1)$ (Fig. 2): for mono-exponential models, $\chi^2/(N-2M-1)$ is at least one order of magnitude higher than for bi- and tri-exponential functions. For $M \geqslant 2$, $\chi^2/(N-2M-1)$ is constant for all but three data sets (mean $\pm$ standard deviation (SD) of $\chi^2/(N-2M-1)$: 50.2 ± 34.5 for $M = 1$; 2.76 ± 4.11 for $M = 2$; 2.74 ± 4.19 for $M = 3$).

The condition number c, depicted in Fig. 3, is always close to 1 for $M = 1$ (mean = 1.0025, SD = 0.0004) and $M = 2$ (mean=1.08, SD = 0.08), but reveals frequent overfitting for $M = 3$ (mean = 34.7, SD = 100.1).

An example of a volume–time curve from a completed forced expiration manœuvre together with the respective mono-, bi-, and tri-exponential functions is depicted in Fig. 4*a*. This data set favours a bi-exponential model ($\chi^2/(N-2M-1)$: 1.69 for $M = 2$; 1.72 for $M = 3$; c: 1.03 for $M = 2$; 15.4 for $M = 3$).

For three time series, minor differences in χ^2 between bi- and tri-exponential fitting functions, together with relatively low condition numbers for fits with $M = 3$, are observed ($\chi^2/(N-2M-1)$: 1.32, 1.47 and 2.80 for $M = 2$; 1.02, 1.08 and 1.75 for $M = 3$; c: 1.05, 1.04 and 1.02 for $M = 2$; 1.29, 1.37 and 1.08 for $M = 3$). However, the respective fitting functions with $M = 2$ and $M = 3$ are still visually almost indistinguishable (Fig. 4*b*).

Summarising, in 47 of 50 cases, fitting functions consisting of two exponentials yield a satisfactory description of the measured data, whereas the use of tri-exponential fitting functions leads to overfitting.

4 Estimation of *FVC*

4.1 *Methods*

Based on the above results, we developed the following strategy to estimate *FVC* from an incomplete volume–time curve: Having applied the fitting algorithm described above for bi- and tri-exponential models to the available volume data, $M = 2$ or $M = 3$ is chosen, depending on which one yields the lower value of

$$c \cdot \frac{\chi^2}{N-2M-1}$$

FVC is estimated by using $FVC_{est} = A_0$ according to eqn 1. Confidence intervals for FVC_{est} are obtained from the corresponding component of the covariance matrix

$$\sigma_{FVC_{est}} = \sqrt{Cov_{00}}$$

A high value of $\sigma_{FVC_{est}}$ for a particular data set, representing a high uncertainty, can occur in particular when the number of data points N is insufficient. Revealing that the method cannot be applied without reservation to estimate *FVC* in this case, this serves as an indicator for the reliability of the relevant measurement.

To evaluate the reliability of this algorithm when used to estimate *FVC* from extrapolated volume–time curves, we re-investigated the 50 complete spirograms. First, we determined, for each of the volume–time curves, the times t_{FVC} when *FVC* was reached:

$$t_{FVC} = \min_i(t_i \mid |V(t_i)| = FVC)$$

Starting from $t_{fit} = 6$ s and successively decreasing t_{fit} in steps of 1 s, we then calculated FVC_{est} from the 50 volume–time curves

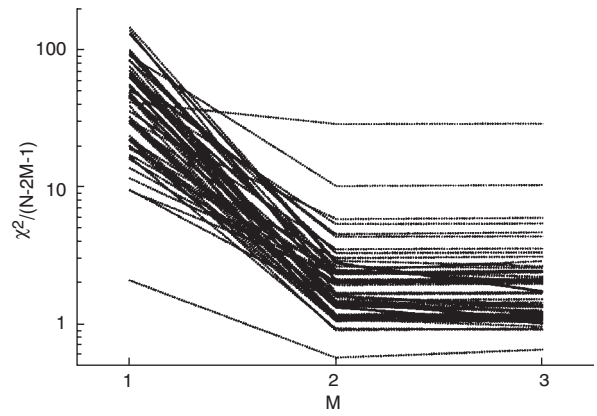

Fig. 2 *Normalised χ^2 for mono- ($M = 1$), bi- ($M = 2$), and triexponential fitting ($M = 3$) of 50 forced expired volume–time curves*

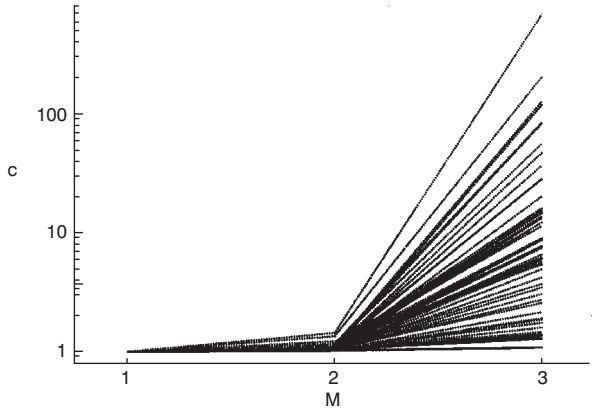

Fig. 3 *Condition number c for mono- ($M = 1$), bi- ($M = 2$), and triexponential fitting ($M = 3$) of 50 forced expired volume–time curves*

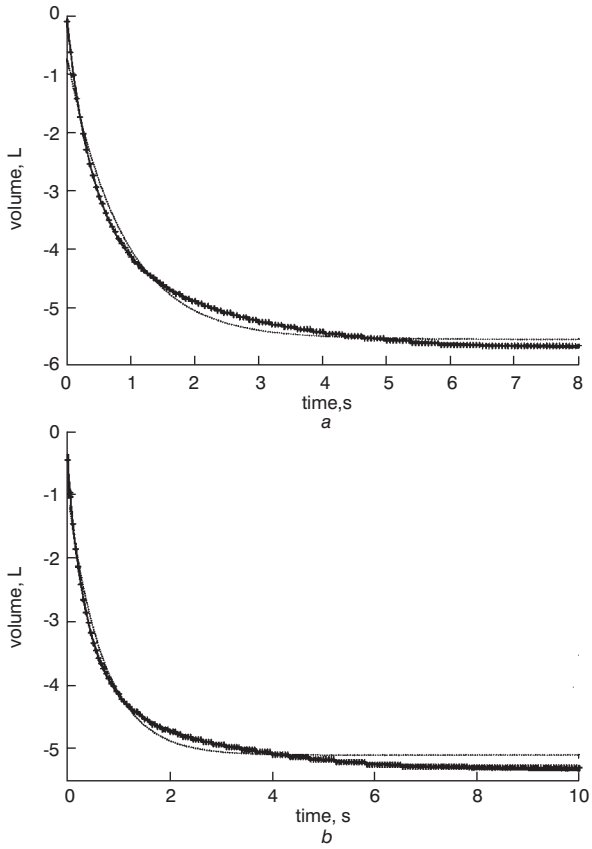

Fig. 4 *Forced expired volume–time curves of two subjects and fitted multi-exponential functions. a) represents a data set favouring a bi-exponential model. Bi- and tri-exponential fits are visually indistinguishable. The data set in b) led to the highest difference in $\chi^2/(N-2M-1)$ of all fitted data between bi- and tri-exponential fits and the smallest condition number for $M=3$. Slight differences between bi- and tri-exponential fits can be observed in the first second of the plot. (——) $M=3$; (– – –) $M=2$; (·····) $M=1$; + measured*

truncated at $\min(t_{fit}, t_{FVC})$ and compared them with the corresponding measured forced vital capacities.

Furthermore, the algorithm was applied to the 27 volume–time curves from uncompleted forced expiration manœuvres. As measured forced vital capacities were not available for these data sets, estimated forced vital capacities FVC_{est} and the corresponding maximum volumes V_{end}, reached at the end of the uncompleted forced expiration manœuvres, were compared with measured inspiratory vital capacities IVC instead, to assess the quality of FVC_{est}.

4.2 *Results*

Estimating forced vital capacities from originally complete volume–time curves truncated at t_{FVC} or $t_{fit} \geqslant 6$ s, we obtained values of $\Delta FVC = |FVC_{est} - FVC|$ of less than 0.2 L, i.e. within the limits of reproducibility suggested by the ATS (AMERICAN THORACIC SOCIETY, 1995), in 41 cases. Eleven data sets led to uncertainties $\sigma_{FVC_{est}} \geqslant 0.1$ L; among them were eight volume–time curves with $\Delta FVC \geqslant 0.2$ L. The remaining 39 data sets provided nearly unbiased estimates of FVC ($\Delta FVC = 0.055\,\text{L} \pm 0.063\,\text{L}$, mean ± SD) for $t_{fit} = 6$ s, as depicted in Fig. 5.

The number of spirograms leading to unreliable values of FVC_{est} increases with decreasing t_{fit}. However, when $\sigma_{FVC_{est}} < 0.1$ L, FVC_{est} is still nearly unbiased (e.g. for $t_{fit} = 4$ s: $\Delta FVC = 0.05\,\text{L} \pm 0.11\,\text{L}$, mean ± SD). The results are summarised in Table 2.

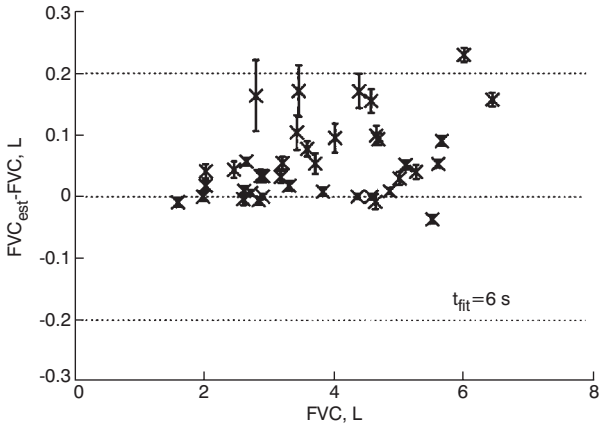

Fig. 5 *Estimated forced vital capacities FVC_{est} compared with measured forced vital capacities FVC of 39 completed volume-time curves truncated after 6 s; error bars correspond to estimated uncertainities $\sigma_{FVC_{est}}$; dotted horizontal lines represent the limits of reproducibility for vital capacity measurements suggested by the ATS (American Thoracic Society (1995)); the results of 11 data sets leading to $\sigma_{FVC_{est}} \geqslant 0.1$ L are not displayed*

We applied our method to the 27 volume–time curves from uncompleted forced expiration manœuvres (duration: 4.32 s ± 1.66 s, mean ± SD); bi-exponential models were selected in 25 cases, and tri-exponential functions were selected in two cases. Fig. 6 depicts the differences between the estimated forced vital capacities FVC_{est} and the corresponding inspiratory vital capacities IVC. Moreover, it shows the differences between IVC and the corresponding maximum volumes V_{end} reached at the end of the uncompleted forced expiration manœuvres.

Whereas V_{end} systematically underestimates vital capacity ($V_{end} - IVC = -0.23\,\text{L} \pm 0.13\,\text{L}$, mean ± SD), FVC_{est} yields unbiased estimates ($FVC_{est} - IVC = 0.01\,\text{L} \pm 0.21\,\text{L}$, mean ± SD). Four data sets led to high uncertainties for FVC_{est} ($\sigma_{FVC_{est}} \geqslant 0.1$ L), revealing that FVC_{est} does not represent a reliable estimate of vital capacity in these four cases. Nineteen of the 23 remaining estimated forced vital capacities lie within 0.2 L from IVC, which represents the limit of reproducibility suggested by the ATS for successive vital capacity measurements (AMERICAN THORACIC SOCIETY, 1995). On the other hand, only 13 of the values for V_{end} lie inside this interval.

5 Discussion

The first purpose of our study was to find the optimum number M^* of exponentials to characterise volume signals obtained during forced expiration manœuvres. Using a number of exponentials lower than M^* would lead to wrong estimates of the relevant parameters. On the other hand, a higher number of exponentials causes overfitting, which implies high uncertainties, in particular when the model is used to predict future values by extrapolation. Analysis of 50 data sets reveals that a

Table 2 Partition of results of FVC estimation applied to 50 spirograms from completed manœuvres truncated at t_{fit}; $\Delta FVC \geqslant 0.2$ L represents unfulfilled reproducibility criteria according to AMERICAN THORACIC SOCIETY (1995); $\sigma_{FVC_{est}} \geqslant 0.1$ L indicates unreliable estimation according to fitting algorithm

t_{fit}, s	$\Delta FVC \geqslant 0.2$ L, $\sigma_{FVC_{est}} \geqslant 0.1$ L	$\Delta FVC \geqslant 0.2$ L, $\sigma_{FVC_{est}} < 0.1$ L	$\Delta FVC < $ L, $\sigma_{FVC_{est}} \geqslant 0.1$ L	$\Delta FVC < $ L, $\sigma_{FVC_{est}} <$ L
$\geqslant 6$	8	1	3	38
5	10	2	2	36
4	15	2	1	32
3	22	2	2	24
2	39	0	6	5

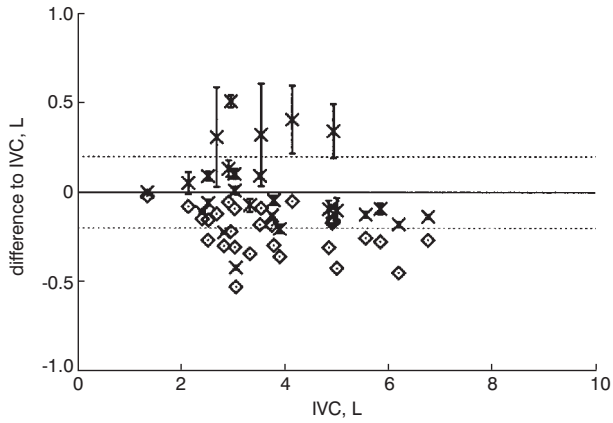

Fig. 6 *Estimated forced vital capacities FVC_{est} compared with final volumes V_{end} of the according 27 uncompleted volume–time curves and inspiratory vital capcities IVC; (×) FVC_{est}-IVC; (◇) V_{end}-IVC; dotted horizontal lines represent the limits of reproducibility for vital capacity measurements suggested by the ATS (American Thoracic Society (1995)). Note that four values of FVC_{est} have elevated uncertainties which serve as markers for unreliable estimates*

single exponential function cannot adequately describe forced expired volume–time curves. On the other hand, overfitting usually occurs when more than two exponentials are used.

Occasionally, small condition numbers c favour tri-exponential models. From a statistical point of view, it could even be argued that this only represents an artefact: Some time series contain irregularities that are due to slightly varying respiratory effort during the beginning of the forced expiration manœuvre. A tri-exponential model tends to reproduce these systematic errors more closely than a bi-exponential model, thereby improving the accordance with the measurements without supplying additional information.

Nonetheless, all aspects considered, bi-exponential functions are appropriate in 47 cases, whereas tri-exponential functions are appropriate in only three cases. We conclude that models with two exponentials can be used to describe the majority of forced expired volume–time curves, irrespective of the individual subject.

We would like to point out that the appropriateness of these models is only considered from a statistical point of view. It does not seem physiologically reasonable to represent the human respiratory system by a simple mechanical combination of two exponential relaxators. However, descriptive analysis of forced expired volume data with models consisting of a number of exponentials greater than two usually does not yield supplementary information but destabilises the fit.

The second aim of this study was to evaluate whether forced vital capacities can be reliably predicted from volume–time curves obtained from uncompleted forced expiration manœuvres. We found that our suggested extrapolation algorithm leads to unbiased estimates.

When truncating originally complete spirograms and extrapolating these artificially shortened volume–time curves, we occasionally obtained unacceptable estimates for forced vital capacity. However, violation of the reproducibility criteria suggested by the ATS was almost always associated with high uncertainties $\sigma_{FVC_{est}}$. They can be partly explained by the low number of data points of volume–time curves in relation to the typical time scale given by the smaller time constant μ_j of the respective bi-exponential model. We always found $\min(\mu_j) \cdot \min(t_{fit}, t_{FVC}) \leqslant 1$, in contrast to the data sets that led to low uncertainties $\sigma_{FVC_{est}}$. In such cases, our method signals its limits of applicability, and longer expiratory times are needed reliably to estimate FVC. By considering the confidence intervals of FVC_{est}, such unreliable estimates can be detected, and further misleading diagnostic interpretation can be avoided. Based on the results presented in Table 2, we suggest a value of $\sigma_{FVC_{est}} = 0.1$ L as a cutoff criterion for reliable estimates.

Comparing FVC_{est} obtained from incomplete spirograms with the corresponding measured inspiratory vital capacities, four out of the 27 data sets led to unacceptably elevated uncertainties ($\sigma_{FVC_{est}} \geqslant 0.1$ L). The corresponding bi-exponential models were also characterised by small time constants in proportion to the available number of data. In the majority of the other cases, FVC_{est} was within the limits of reproducibility recommended by the ATS when compared with measured IVC.

We conclude that the procedure presented here may help to simplify spirometry for subjects with respiratory problems by shortening the required duration of forced expiration maneouvres, without considerable loss of information.

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