ESTIMATION OF EXPIRATORY TIME CONSTANTS VIA FUZZY CLUSTERING

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ABSTRACT. Objective. In mechanically ventilated patients the expiratory time constant provides information about respiratory mechanics. In the present study a new method, fuzzy clustering, is proposed to determine expiratory time constants. Fuzzy clustering differs from other methods since it neither interferes with expiration nor presumes any functional relationship between the variables analysed. Furthermore, time constant behaviour during expiration can be assessed, instead of an average time constant. The time constants obtained with fuzzy clustering are compared to time constants conventionally calculated from the same expirations. **Methods.** 20 mechanically ventilated patients, including 10 patients with COPD, were studied. The data of flow, volume and pressure were sampled. From these data, four local linear models were detected by fuzzy clustering. The time constants (τ) of the local linear models (clusters) were calculated by a least-squares technique. Time constant behaviour was analysed. Time constants obtained with fuzzy clustering were compared to time constants calculated from flow-volume curves using a conventional method. **Results.** Fuzzy clustering revealed two patterns of expiratory time constant behaviour. In the patients with COPD an initial low time constant was found (mean $\tau1$: 0.33 s, SD 0.21) followed by higher time constants; mean $\tau2$: 2.00 s (SD 0.91s), mean $\tau3$: 3.45 s (SD 1.44) and mean $\tau4$: 5.47 s (SD 2.93). In the other patients only minor changes in time constants were found; mean $\tau1$: 0.74 s (SD 0.30), mean $\tau2$: 0.90 s (SD 0.23), mean $\tau3$: 1.04 s (SD 0.42) and mean $\tau4$: 1.74 s (SD 0.78). Both the pattern of expiratory time constants, as well as the time constants calculated from the separate clusters, were significantly different between the patients with and without COPD. Time constants obtained with fuzzy clustering for cluster 2, 3 and 4 correlated well with time constants obtained from the flow-volume curves. **Conclusions.** In mechanically ventilated patients, expiratory time constant behaviour can be accurately assessed by fuzzy clustering. A good correlation was found between time constants obtained with fuzzy clustering and time constants obtained by conventional analysis. On the basis of the time constants obtained with fuzzy clustering, a clear distinction was made between patients with and without COPD.

KEY WORDS. Expiratory time constants, mechanical ventilation, respiratory mechanics, COPD, fuzzy clustering, monitoring, expiration.

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INTRODUCTION

The importance of monitoring respiratory mechanics in patients on ventilatory support is generally accepted. Respiratory variables can be used to assess patients' pulmonary condition, to detect poor patient–ventilator interaction and consequently to optimise ventilator set-

tings. This applies in particular to patients with COPD in whom the determination of the degree of bronchial obstruction is essential to adjust medical treatment and ventilator settings and to prognosticate weaning outcome.

For the analysis of lung emptying the expiratory time constant is an important parameter. The expiratory time constant provides information on the mechanical properties of the respiratory system and can be used to predict the minimal time needed for complete expiration [1, 2]. Several methods have been proposed to determine the expiratory time constant [2–6]. However, these methods all have disadvantages, with respect to either measurement technique or analysis. One method interferes with the expiration; thereby altering the respiratory mechanics [4, 5]. Other methods are based on qualitative and subjective pattern recognition. Again other methods assume a linear relationship between flow and volume for the whole expiration; in patients with COPD, this has to be questioned in view of the presence of ventilatory inhomogeinity and expiratory flow-limitation [3, 6]. The latter problem has been avoided by analysing only the last 75% of expiration [2]. Although that method is applicable in the majority of patients, in many patients the time constant determined over 75% of expiration is not representative of expiratory lung mechanics.

In this study, a new method based on fuzzy clustering is proposed to determine expiratory time constants. Fuzzy clustering differs from other methods since it does not interfere with expiration, nor does the method presume any functional relationship between the variables analysed or rely upon subjective pattern recognition [7]. Furthermore, by fuzzy clustering the time constant behaviour over the whole expiratory phase can be estimated. Therefore, fuzzy clustering could be a valuable addition to the conventional methods describing lung emptying in mechanically ventilated patients. In this study, time constants are assessed with fuzzy clustering and compared to time constants obtained with a conventional method.

PATIENTS AND METHODS

Parameter estimation based on fuzzy clustering

The method is based on a straightforward extension of the classical linear single compartment model [8, 9]. This model describes the dynamic relation between the pressure P (cm H_2O), the air flow-rate V' (l/s) and the volume V (l) of the lungs:

$$P = Ers\,V + Rrs\,V' + P_0 \qquad (1)$$

P is the airway opening pressure, Ers is respiratory system elastance, Rrs is the respiratory system resistance and P_0 is the offset pressure, which represents the end-expiratory pressure. During expiration V' is considered a negative value. Ers, Rrs and P_0 are parameters to be estimated from data. It is well known that this linear model may yield too coarse an approximation of the given data, especially for patients with pulmonary disorders. Therefore, various modifications of Equation (1) have been proposed. Amongst these are the use of different variables for inspiration and expiration and the introduction of nonlinearities by considering E and R as functions of volume or flow [8, 9].

The method used in this paper is based on an automatic detection (localisation) of multiple local linear models [7]. Hence, no assumptions are made about the mathematical form or parameterisation of the nonlinearity. By observing the dependence of the local respiratory parameters on the location of the model in the flow–volume–pressure space, information on the condition of the respiratory system can be obtained.

The two main techniques used to obtain parameters of multiple models are *fuzzy clustering* and *linear least-squares* estimation [7, 10–13]. When using fuzzy clustering, the available data set is partitioned into fuzzy subsets that can be approximated by local linear regression models. Parameters of these models are then estimated by least-squares techniques.

Clustering techniques have the advantage of revealing structures in data without relying on assumptions common to conventional statistical methods, such as the underlying statistical distribution [14].

Clustering has been successfully used in a variety of fields, including classification, image processing, pattern recognition, modelling and identification. In the medical field an increasing number of applications can be found, such as; image processing for computer-aided diagnosis [15–17], signal processing in evoked potentials estimation [18] and analysis of time series for imaging [19].

Patients

Twenty patients admitted to a medical intensive care unit were studied. Patients were included if they fulfilled the following criteria: mechanical ventilation via an endotracheal or tracheostomy tube and absence of air leaks. Ten patients had a history of severe chronic obstructive pulmonary disease (COPD) according to the European Respiratory Society consensus; a clinical

Table 1. Patient characteristics

Patient	Age (years)	Sex	Diagnosis	FEV1 (% pred)
COPD1	60	F	COPD	21
COPD2	80	F	COPD, pneumonia	
COPD3	37	M	COPD	37
COPD4	71	M	COPD, pneumonia	25
COPD5	41	M	COPD	10
COPD6	70	M	COPD, cerebral bleeding	
COPD7	76	F	COPD	
COPD8	74	M	COPD	33
COPD9	80	M	COPD, pneumonia	
COPD10	55	F	COPD	32
Other11	77	M	Weaning problem	
Other12	46	F	Non-Hodgkin, stomatitis	
Other13	69	F	Guillain-Barré syndrome	
Other14	61	M	Dystrophia Myotonica	73
Other15	66	M	Drug induced lung injury	
Other16	42	M	Porphyria acuta	56
Other17	44	M	Pleural empyema, mild COPD	60
Other18	65	M	Mild COPD	55
Other19	71	F	Muscle weakness, mild COPD	56
Other20	47	M	Complications bone marrow transplantation	

FEV1 = forced expired volume in 1 s (% of predicted).

diagnosis of COPD and previous lung function data showing an forced expiratory volume in one second (FEV1) ‹50% of predicted (mean 29% of predicted, range 21%–37%) [20]. These 10 patients were ventilated because of respiratory failure due to an exacerbation of their COPD. In the other 10 patients, underlying diseases included a variety of medical conditions all complicated by respiratory failure and ventilator dependency. Patient characteristics are shown in Table 1.

All patients were mechanically ventilated with a Siemens Servo 300 ventilator (Siemens-Elema, Solna, Sweden). Ventilator settings were set by the primary physician and remained unchanged during the study, except that if ventilator positive end expiratory pressure (PEEP) was present, it was set to 0 cm H_2O. All patients were ventilated in the volume controlled mode with an average minute volume of 8.5 l/min (range 6.5–15.0 l/min). The average respiratory rate was 12 breaths per minute (range 8–20). The ratio between inspiratory and expiratory time was 35 : 65 in all patients. During the study the patients were sedated with midazolam (Roche Nederland B.V., Mijdrecht, The Netherlands). Informed consent was obtained from the patients or their next of kin. The measurements for this study were approved of by the local ethics committee.

Respiratory measurements

A heated pneumotachometer (Lilly, Jaeger, Wurzburg, Germany) was connected to the endotracheal tube to measure flow (V′). Volume (V) was obtained by integrating the flow signal. Airway opening pressure (P) was measured proximal to the pneumotachometer using a pressure transducer (Validyne, Validyne Co., Northridge, U.S.A.). A 12-bit AD converter was used to convert signals to digital data at a sample frequency of 100 Hz. Data were stored and analysed using a personal computer. On average, 3000 samples were collected from each patient.

A minimal drift in the volume signal was observed, which was mainly caused by leakage and by the difference in temperature and relative humidity between inspiration and expiration. This drift was corrected by adding an offset signal obtained by fitting a line or a low order polynomial through the volume minima in the individual cycles.

Conventional determination of the time constant

The time constant (τfv) was obtained by calculating the quotient of exhaled volume and the corresponding change in flow for the last 75% of exhaled volume [2].

In terms of an equation:

τfv   = (0.75*Vt)/(V$'$75,ex -V$'$end,ex)
0.75*Vt   = 75% of expiratory tidal volume (l)
V$'$75,ex   = flow at 75% of exhaled volume (l/s)
V$'$end,ex = flow at end–expiration (l/s)

Time constant estimation through fuzzy clustering

A detailed description of the underlying mathematics has been presented in a previous paper [7]. In our application the data set consists of the samples of pressure, flow and volume. Taking a sample frequency of 100 Hz and an average expiratory time of 3 s, for each patient 10 sets of 300 samples (i.e. 10 expirations) are obtained. From these samples a data set (Z) is constructed for each patient.

The objective of clustering is to partition a data set Z into a number of clusters. The number of clusters depends on the number of phenomena to look for. In this study, we are searching for several local linear relations within the data set. The fuzzy clustering technique searches for an optimal partitioning of the data-set into the local linear sub-models. The clustering algorithm assigns to each individual sample a set of membership values for each cluster. The membership value represents the degree to which the given sample belongs to each of the clusters. The sum of the membership values of each sample must be one. Subsequently, if the clusters are known, the algorithm calculates the parameters of the individual lines for each cluster. To this end, a threshold is defined for the membership degrees. A given point is assigned to a cluster if its membership degree exceeds the threshold. Standard least–squares estimation is used to compute the model parameters (the time constant).

As an example, consider a data set Z = {Z1,…Z7} consisting of 7 data-points given in Figure 1. This data set can be approximated by two local linear models (clusters). The membership degree, ranging from 0–1 denotes the membership of a data point to either of the two models. The corresponding membership values for each cluster of the individual points are e.g.:

	Z1	Z2	Z3	Z4	Z5	Z6	Z7
Membership value of cluster 1	1.0	1.0	1.0	0.5	0.0	0.0	0.0
Membership value of cluster 2	0.0	0.0	0.0	0.5	1.0	1.0	1.0

The first row shows the membership values of each individual sample for the first cluster, the second row

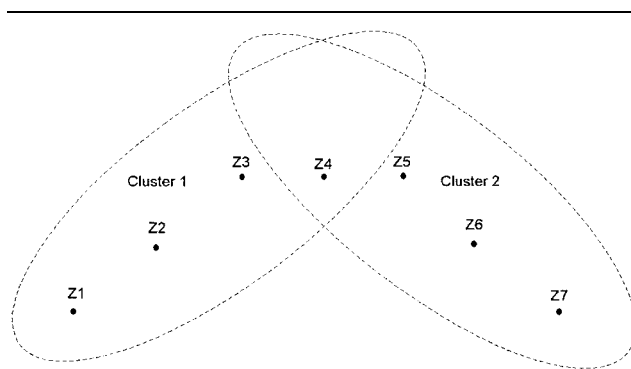*Fig. 1. An example of a data set Z = {Z1, …, Z7}. This data set can be approximated by two local linear models (clusters). A threshold of 0.8 is applied.*

the membership values for the second cluster. Membership value of Z4 reflects the fuzziness of the partition. The sum of all membership values for each point must be one. If e.g., the threshold is 0.8 then the lines are calculated through the points {Z1 – Z3} and {Z5 – Z7}. If the threshold below 0.5 then the lines are calculated through the points {Z1 – Z4} and {Z4 – Z7}.

Fuzzy clustering can be applied either to the entire respiratory cycle (or several cycles) or to the inspiration and expiration separately. In this study we have restricted the analysis to the expiration phase, to focus on the expiratory time constant behaviour.

Assuming a local linear model (1), any least–squares estimation method can then be applied to estimate the local E, R and Po for each cluster. During expiration in the absence of PEEP, pressure is zero, and Equation (1) becomes a first order differential equation [3], in which τ is defined as RC.

$$0 = 1/C * V + R * V'; \text{ thus } V + \tau V' = 0 \qquad (2)$$

In the present study, we have chosen to partition the data set Z for the expiration phase into 4 clusters. The data samples, belonging to the chosen clusters (threshold = 0.8) are used for the analysis of τ, assuming a local linear model given by Equation (3). In the results section, examples are given of clustering in the expiration phase. It has to be underlined that in this analysis the non-linear behaviour in parts of expiration is captured in the trend of τ. Furthermore, this analysis enables the description of the volume dependent behaviour of τ.
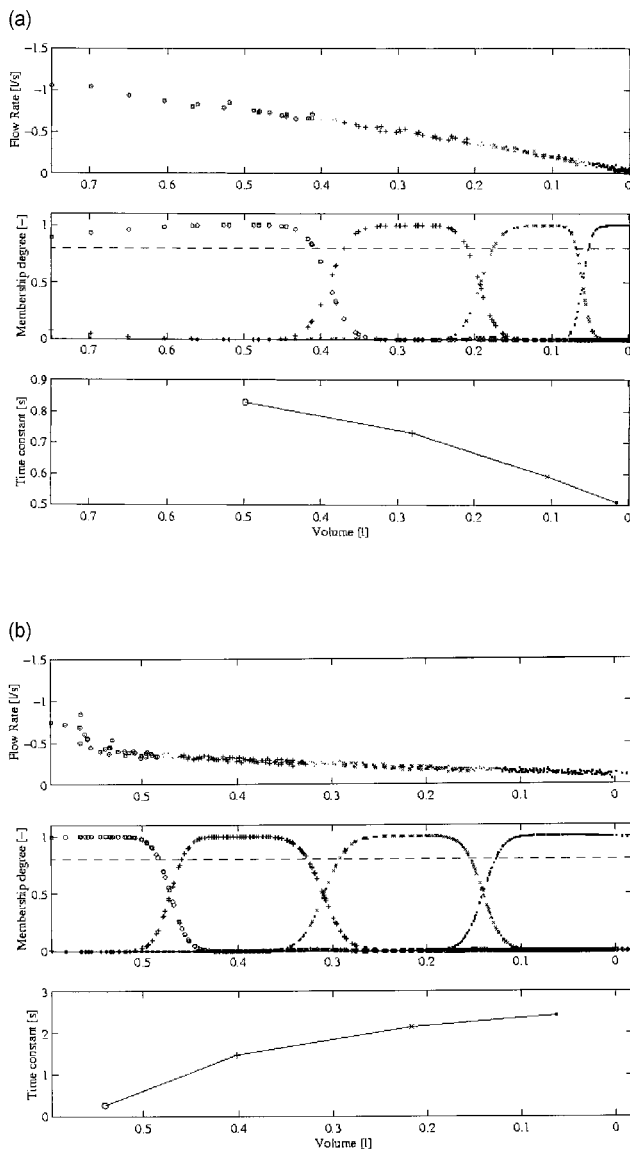
(a)

(b)

Fig. 2. a) Patient with other pathology. b) Patient with COPD. Top: flow-volume data partitioned into four clusters. Middle: membership degrees of the four clusters plotted against volume. − − − indicates the membership threshold value. Bottom: the time constants of the four local models plotted against the volume coordinate of cluster centres.

Statistical analysis

To assess the difference in time constants between patients with and without COPD, a Mann Whitney test was performed. A *p*-value < 0.05 was considered significant.

The time constants ($\tau 1$, $\tau 2$, $\tau 3$, and $\tau 4$) obtained with fuzzy clustering were compared to time constants ob-

Table 2. Time constants calculated with fuzzy clustering for the individual clusters

Patient	$\tau 1$ Cluster 1	$\tau 1$ Cluster 2	$\tau 3$ Cluster 3	$\tau 3$ Cluster 4	τfv Flow-volume
COPD1	0.22	3.59	6.75	8.04	5.14
COPD2	0.32	1.39	3.03	6.29	2.25
COPD3	0.32	1.40	2.05	2.47	2.25
COPD4	0.14	1.55	2.21	3.01	2.48
COPD5	0.15	0.84	3.36	12.34	0.97
COPD6	0.51	2.42	3.77	4.93	2.61
COPD7	0.18	1.53	2.49	3.15	2.36
COPD8	0.14	2.11	2.95	5.15	1.66
COPD9	0.51	1.69	2.86	4.15	2.61
COPD10	0.77	3.49	4.98	5.17	4.01
Other11	0.60	0.51	0.42	1.60	0.50
Other12	0.83	0.73	0.59	0.51	0.56
Other13	1.16	0.97	0.76	1.12	0.78
Other14	1.11	0.81	0.62	3.22	0.90
Other15	1.09	0.88	1.03	1.13	0.82
Other16	0.44	1.29	1.50	2.08	1.19
Other17	0.56	0.88	1.47	2.49	0.95
Other18	0.74	1.22	1.18	1.43	1.05
Other19	0.27	0.79	1.25	1.55	1.03
Other20	0.63	0.96	1.55	2.23	1.06

tained from flow volume curves (τfv) using Pearson correlation. A *p*-value < 0.05 was considered significant. Mean differences between the time constants found from flow-volume curves and fuzzy clustering were calculated.

RESULTS

Figure 2 compares the clustering results for a patient with COPD and a patient with other pathology. For all patients, the time constants of each cluster and of the flow volume curve are shown in Table 2. In the patients with COPD, in cluster 1 low time constants are observed with subsequently an increase in time constants in the following clusters; mean $\tau 1$ 0.33 s (SD 0.21 s), mean $\tau 2$ 2.00 s (SD 0.91s), mean $\tau 3$ 3.45 s (SD 1.44) and mean $\tau 4$ 5.47 s (SD 2.93). In the other patients only a minor change in time constants is found for cluster 2 and 3, with subsequently a slight increase in time constants in cluster 4 found; mean $\tau 1$ 0.74 s (SD 0.30), mean $\tau 2$ 0.90 s (SD 0.23), mean $\tau 3$ 1.04 s (SD 0.42) and mean $\tau 4$ 1.74 s (SD 0.78). In Figure 3, time constants for each cluster are shown for the patients with COPD and the patients with other pathology.

For all clusters the time constants were significantly different between the patients with and without
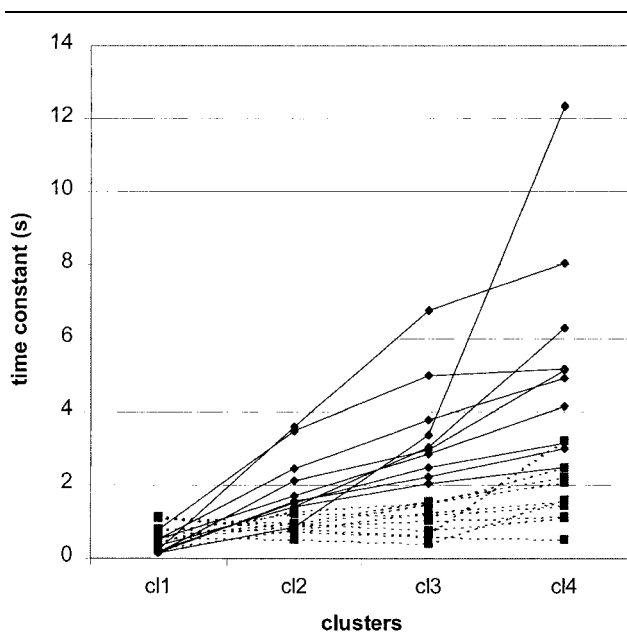
Fig. 3. Time constants for each cluster are shown for the patients with COPD (——) and the patients with other pathology (- - - -).

COPD; $\tau 1$ was significantly lower in the patients with COPD ($p < 0.01$), whereas $\tau 2$, $\tau 3$, $\tau 4$ were significantly higher in the patients with COPD ($p \leq 0.001$).

The correlations between the τfv and the time constants of the individual clusters were $r = 0.93$ ($p < 0.001$) for cluster 2, $r = 0.92$ ($p < 0.001$) for cluster 3 and $r = 0.75$ ($p = 0.040$) for cluster 4. Cluster 1 did not correlate significantly with the τfv. The mean differences between the τfv and the time constants of the clusters were: 0.31 (SD 0.52) for $\tau 2$, -0.48 (SD 0.70) for $\tau 3$ and -1.84 (SD 2.51) for $\tau 4$.

DISCUSSION

This study shows that in mechanically ventilated patients with and without COPD, fuzzy clustering can be applied to assess expiratory time constants. On the basis of the expiratory time constant behaviour detected by fuzzy clustering a clear distinction can be made between patients with and without COPD. Time constants obtained with fuzzy clustering correlated well with time constants obtained from flow volume curves.

The passive expiration is determined by the mechanical properties of the respiratory system. The driving pressure is provided by the elastic recoil pressure of the total respiratory system, which is the force to overcome the expiratory resistance. Brody has proposed to describe expiration as a single-compartment model, i.e. a single compartment of constant compliance emptying itself through a constant resistance [21]. However, in case of lung inhomogeneity, a multi compartment model will be more accurate. As a consequence, in patients with flow limitation the one-compartment model cannot be applied [9]. Chelucci et al. proposed a two-compartment model to describe the passive expiration, however, this was not applicable in mechanically ventilated COPD patients [22, 23].

In previous studies we have shown that the expiratory flow-volume curve provides information about mechanical properties of the respiratory system [1, 2, 22]. The inverse of the slope of these curves can be interpreted as a time constant, describing lung emptying. The time constant calculated from the last 75% of expiratory tidal volume was found to be most representative of respiratory mechanics during relaxed expiration [2]. This time constant represents effective single compartment behaviour, comprising peripheral airways obstruction, visco-elastic properties and unequal ventilation.

However, this time constant might not fully reflect physiological events. The 75% of exhaled volume is an artificially chosen percentage and does not always represent the pattern of lung emptying. In Figure 5, an example is given of an expiratory flow-volume curve of a patient (not from the present study), in whom a single time constant does not adequately reflect lung emptying.

In this study we applied a method based on automatic detection of multiple local linear models which enables the description of time constant behaviour during expiration [7].

The advantage of this method is that it is able to describe any shape of the flow-volume relationship without presuming a functional relationship (e.g., single or two compartment model), it does not interfere with the expiration and it does not rely on subjective visual inspection.

The shape of the expiratory flow-volume curve is different between patients with and without COPD [1, 2, 22, 24, 25]. In patients with COPD a initial peak-flow is observed, followed by a sudden decline in flow, resulting in a concave shape (Figure 4). This discontinuity between the initial and later part of the flow volume curve, is caused by airway compression. In patients without COPD the expiratory flow-volume curve is mostly characterised by a smooth transition between the initial and later part of the curve. This is also reflected in Figure 3, which clearly shows the distinction between the groups with and without COPD. The large changes of the time constant from cluster 1 to the consecutive clusters in the patients with COPD is also apparent in Table 2. In the patients with other pathol-
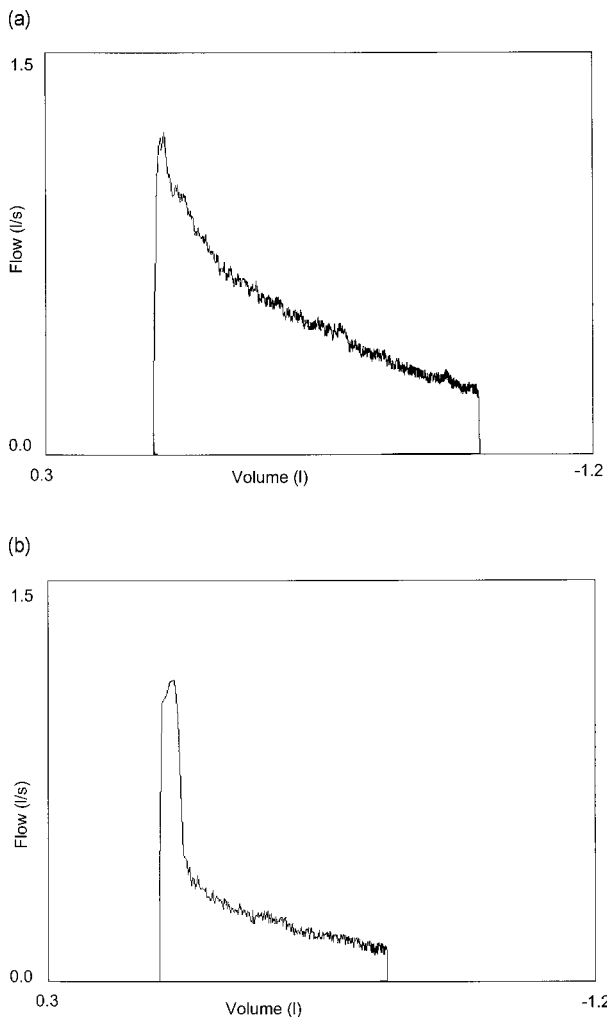
(a)

(b)

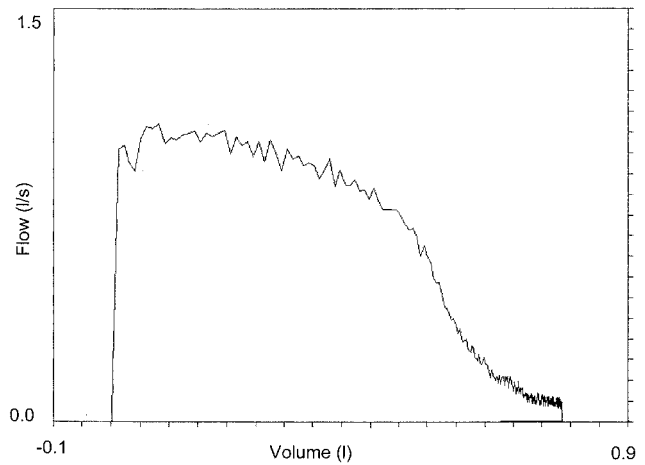*Fig. 4. An expiratory flow-volume curve of a patient without (a) and with COPD (b).*

Fig. 5. An example of an expiratory flow-volume curve of a patient, in whom a time constant determined from the last 75% of expired volume would not reflect lung emptying.

ogy two patterns are observed: in patients 11–15 a decrease in time constant is found after cluster 1, while in patients 16–20 an slight increase is found. This might be explained by the underlying diseases. Patient 10–15 have a normal or even low lung compliance. These patients were ventilated because of muscular weakness or hypoxemic respiratory failure. Patients 16–20 were ventilated for various medical conditions, but 4 patients had mild COPD (FEV1 between 50%–70% of predicted), in one patient no lung function data were available.

In Figure 3, some overlap is found between the curves of patients with COPD and the patients with other pathology. This overlap is mostly found in cluster 1, which represents the early rapid phase, which is largely determined by extra-thoracic resistive elements. The overlap found is therefore not clinically relevant. In three patients a minor overlap is found at end-expiration, which is mainly caused by the relatively high time constant in cluster four of patient 14. We think that this is due to noise in the signal at end-expiration.

Not only the time constant behaviour was found to be discriminative for COPD, but also the individual cluster time constants were able to discriminate between patients with and without COPD. For cluster 1 the time constant was significantly lower in the patients with COPD, while for the clusters 2–4 it was significantly higher in the patients with COPD. These findings also represent the shape of the flow-volume curves. As shown in previous studies, the early rapid component of the passive expiration predominantly reflects the resistive behaviour of the extrathoracic resistive elements [22]. By using fuzzy clustering this part can easily be distinguished from the consecutive slower component, which is more informative on the patients respiratory mechanics [22]. Furthermore, a large difference in time constants of cluster 1 and 2 was found to be very indicative for the presence of COPD.

The time constants of the clusters 2 and 3 correlated best with the time constant derived from the flow volume curve for the last 75% of tidal volume. However, the average $\tau 2$ is slightly higher than the τfv, whereas the average $\tau 3$ is slightly lower than the τfv. This confirms the idea that the τfv gives an effective time constant representing a time constant behaviour. By using the fuzzy clustering a better approximation of this time constant behaviour is obtained.

In this study it was chosen to use 4 clusters to describe the expiration. This is a compromise between the accu-

racy of the separate time constants and the number needed for a discriminatory time constant behaviour. A larger number of clusters would mean less data points in the analysis of local linear models, with consequently less accurate time constants for those regions. Four clusters proved to be sufficient to discriminate the pattern of expiration of patients with COPD from patients without COPD. Whether analyses with a larger number of clusters might have additional benefits, needs to be investigated.

In conclusion, in this study, fuzzy clustering was used to assess expiratory time constants in mechanically ventilated patients. Time constants obtained with fuzzy clustering correlated well with time constants obtained from the same part of the flow-volume curves by a conventional method. Besides making a distinction in patients with and without COPD, fuzzy clustering might also be useful to identify other pulmonary conditions.

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