

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
18 December 2003 (18.12.2003)

PCT

(10) International Publication Number
WO 03/103493 A1

(51) International Patent Classification⁷: **A61B 5/085**

(21) International Application Number: PCT/EP03/06119

(22) International Filing Date: 10 June 2003 (10.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2002 A 001273 11 June 2002 (11.06.2002) IT

(71) Applicant (*for all designated States except US*): **PO-LITECNICO DI MILANO** [IT/IT]; Piazza Leonardo da Vinci, 32, I-20133 Milano (IT).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **DELLACA', Raffaele** [IT/IT]; Via Giovio, 21, I-22100 Como (IT). **ALIVERTI, Andrea** [IT/IT]; Via El Alamein, 1, I-22100 Como (IT). **PEDOTTI, Antonio** [IT/IT]; Via Amedeo d'Aostam 15, I-20129 Milano (IT).

(74) Agent: **MITTLER, Enrico M**; Mittler & C. s.r.l., Viale Lombardia, 20, I-20131 Milano (IT).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

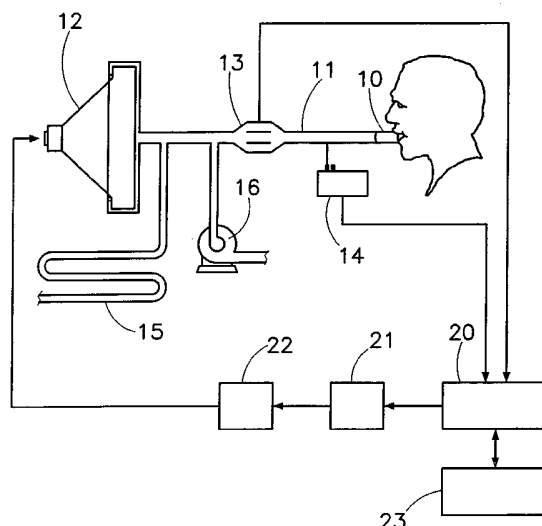
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for the following designation US*
- *of inventorship (Rule 4.17(iv)) for US only*

Published:

- *with international search report*
- *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

[Continued on next page]

(54) Title: SYSTEM AND METHOD FOR THE AUTOMATIC DETECTION OF THE EXPIRATORY FLOW LIMITATION



(57) Abstract: The present invention refers to a system and a method for the automatic detection of the expiratory flow limitation of a subject. In an embodiment thereof the system for the automatic detection of expiratory flow limitation of a subject comprises: means for determining the respiratory impedance of said subject composed of an imaginary component and, eventually, of a real part or, at least, means to apply a forcing signal with one or more spectral components to the airway opening of a subject combined with means to measure time courses of pressure and flow at the airway opening; means for determining at least one index linked to said respiratory impedance or pressure and flow time courses; means for indicating the positioning of said at least one index in relation to a preset threshold value.



WO 03/103493 A1



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

“System and method for the automatic detection of the expiratory flow limitation.”

DESCRIPTION

* * * * *

5 The present invention refers to a system and a method for the automatic detection of the expiratory flow limitation in patients.

 The human respiratory system is characterised by the phenomenon called expiratory flow limitation, that is by the fact that during expiration the flow of gases expelled depends on the expiratory pressures only up to a
10 certain threshold value, beyond which the flow cannot be increased even if expiratory pressures are increased. The threshold value is function of the lung volume (being higher at high volumes then decreasing with the reduction of the lung volume) and is, in healthy subjects, considerably higher than the maximum flows obtained during spontaneous breathing. The
15 difference between maximum expiratory flow and expiratory flow during spontaneous breathing measured at the same lung volume constitutes the reserve of expiratory flow. Such reserve is used in situations such as physical exercise, in which the metabolic requirements and, consequently, the lung ventilation increase. The resulting increase of the tidal volume and
20 of the respiratory frequency therefore requires the increase of both inspiratory and expiratory flows. Several obstructive pathologies of the respiratory system (chronic obstructive pulmonary disease or COPD, asthma, ..) modify the mechanical properties of airways and lung parenchyma, notably reducing the reserve values of expiratory flow until it
25 is annulled. In addition, the reduction can be so marked that it forces the patient to breathe at higher lung volumes than usual to make use of the dependence of the maximal flow on lung volume and to obtain the expiratory flows needed for a correct gas exchange. This phenomenon is known as "dynamic hyperinflation". Breathing at higher lung volumes,
30 however, means both using the inspiratory muscles in a geometric condition

which is unfavourable to them (reduced muscular length and consequent reduction of the capacity to produce force) and having the thoracic wall expanding to volumes at which it is more stiff. All these effects combine to determine a significant increase in the respiratory work, excessively tiring the respiratory muscles and thus limiting the capacity of the patient to carry out even simple physical activity. To know whether a patient is flow-limited during spontaneous breathing is therefore of fundamental importance for the diagnosis and definition of the rehabilitation and pharmacological therapy, as well as the assessment of their effectiveness.

As of today the methods used for identifying whether a subject is limited in the expiratory flow can be divided into two main categories: those based on the measurement of the oesophageal pressure and those that do not use this measurement. The former are currently considered the only reliable ones, but they require a latex balloon connected to a catheter-pressure transducer system for measuring the oesophageal pressure to be inserted into the lower third of the oesophagus. Esophageal pressure is considered an excellent estimate of the pleural pressure and therefore it allows the estimation of alveolar pressure. From the relationship between alveolar pressure and flow at the airway opening it is possible to assess the presence of expiratory flow limitation during quiet breathing in different ways (for example studying the so called "isovolume pressure flow curves" or analysing Mead and Whittenberger graphs). Unfortunately this procedure is invasive and it is not tolerated by a large percentage of subjects, in addition it requires a lot of time (both for the insertion of the balloon and for the patient to adapt to it) and it may significantly alter the breathing pattern of the subject.

The methods belonging to the second category are based on the determination of the flow-volume curves carried out in body plethysmograph and on the application of negative pressure to the airways during the expiratory phase or on abdominal compression. However these

methods are characterised by both theoretical and practical limitations and therefore they are usually considered not very reliable and, in the first case, require the collaboration of the subject.

5 A study by M. Vassiliou, R. Peslin, C. Saunier, C. Duvivier, entitled "Expiratory flow limitation during mechanical ventilation detected by the forced oscillation method", European respiratory Journal, 1996, suggests a method for determining expiratory flow limitations based on the forced oscillations technique able of indicating the possible presence of expiratory flow limitation induced by broncho constrictor drugs (methacholine) in rabbits submitted to mechanical ventilation. In this study it can be observed that expiratory flow limitation is responsible for systematic variations of the imaginary part (X_{rs}) of the total respiratory input impedance (Z_{rs}) in mechanical models of a single collapsible airway and in mechanically ventilated rabbits. The Applicant believes that the analyses described in the article mentioned above were carried out under extremely critical and particular conditions, that is on mechanically ventilated animals in which the limitation of the expiratory flow was induced pharmacologically and on mechanical models that simulate the behaviour of only one single airway and that therefore they do not reproduce real conditions occurring in humans with obstructive diseases (hundreds of thousands of airways placed in series and in parallel in the tracheal-bronchial tree constricted in a very heterogeneous pattern).

15 In view of the state of the technique, the object of the present invention is to provide a method and a system for assessing automatically in a non-invasive manner whether the expiratory flow limitation is present or not in a subject, without requiring subject collaboration and continuously in time.

25 In accordance with the present invention, said object is achieved by means of a system for the automatic detection of expiratory flow limitation of a subject comprising: means for determining the respiratory impedance of said subject composed of a real component and an imaginary component;

30

means for determining at least one index linked to said respiratory impedance; means for indicating the positioning of said at least one index in relation to a preset threshold value.

5 In accordance with the present invention, said object is also achieved by means of a Method for the automatic detection of the expiratory flow limitation of a subject comprising the phases of: determining the respiratory impedance of said subject composed of a real component and an imaginary component; determining at least one index linked to said respiratory impedance; indicating the positioning of said at least one index in relation to
10 a preset threshold value.

Thanks to the present invention it is possible to study patients in an absolutely non-invasive manner, without requiring their collaboration, under very different conditions, (during spontaneous breathing at rest, exercise, mechanical ventilation and various respiratory manoeuvres such as vital
15 forced and slow capacities, maximum voluntary ventilation, etc.). In addition, it allows to study subjects in various postures (erect, sitting, supine, prone).

In addition, it permits automatically, without any intervention, to detect the presence of expiratory flow limitations.

20 The characteristics and advantages of the present invention will appear evident from the following detailed description of an embodiment thereof, illustrated as non-limiting example in the enclosed drawings, in which:

Figure 1 shows schematically a system for the automatic detection of the expiratory flow limitation of a patient in accordance with the present
25 invention;

Figures 2a, 2b and 2c show the graphics of the volume, the flow, the impedance and the oesophageal pressure of a healthy patient, respectively of a patient with chronic obstructive pulmonary disease (COPD) but not flow-limited and a patient with COPD and flow-limited during spontaneous
30 breathing;

Figure 3 shows the sensitivity graphics with a continuous line, and specificity with a dotted line, in function of the value adopted as threshold for the various indices in accordance with the present invention;

Figure 4a shows a graph where a maximum flow-volume curve overlays a flow-volume curve obtained from spontaneous breathing;

Figure 4b shows the progress of Xrs and of the flow F over the time.

In Figure 1 the airways of a patient are connected by means of a mouthpiece 10 to a duct 11 that is connected to a loudspeaker 12. A sensor device 13 for measuring the flow of air inside and a sensor device 14 for measuring the air pressure is applied to the duct 11. A tube 15 at high inertia and an aspirator 16 are also applied to the duct.

The electrical signals related to the measurements of flow and pressure, supplied respectively by the devices 13 and 14, are connected to the circuits 20 of analogical-digital (A/D) and digital-analogical (D/A) conversion. The circuits 20, controlled by a microprocessor 23, provide an output signal that is applied in succession to a low pass filter 21, to a power amplifier 22 and then to a loudspeaker 12.

The determination of the time course of the respiratory impedance during the spontaneous breathing is carried out by applying a pressure signal to the airway opening of the patient consisting of the summation of one or more sinusoids among which at least one has a frequency no higher than 15 Hz. For example 4 sinusoids at frequencies of 2.5 Hz, 5.5 Hz, 9.5 Hz and 17.5 Hz.

Said pressure signal must preferably have an amplitude between 1-4 cmH₂O peak-peak (with the pressure generator connected to a resistive load of 2 cmH₂O/L*s); in any case the amplitude of the stimulus signal should not exceed 5 cmH₂O to avoid distortions due to the non-linearity of the respiratory system. The pressure signal, generated in the example in Figure 1 by a loudspeaker, can be generated by cylinder-piston systems or by suitable servo-controlled valves. For simplicity in the rest of the description we shall

refer to the pressure generator consisting of a loudspeaker, even though this choice is not bound to the functioning of the method herein presented as other devices can be used for this purpose (piston pumps, servo-controlled valves, etc.). The pressure waves generated are applied to the airway opening of the subject by means of a duct 11 in which the flow measuring devices 13 and pressure measuring devices 14 are housed. By airways opening we intend mouth, nose, tracheostomy, etc. Thus pressure and flow are measured, preferably near the entrance of the airways (if a long connection tube is used between the flow and pressure sensors and the subject the measurements must be corrected for mechanical properties of the tube). To enable the subject to breathe spontaneously during the measurement, a tube 15 connects the output of the generator of pressure waves with the outside environment. This tube is sized and shaped so as to offer a high impedance to high frequencies generated by the loud-speaker, while at the low frequencies of the spontaneous breathing the impedance must result very low (better if less than 1-2 cmH₂O/L*s for signals of frequency lower than 5Hz). The large dimensions of this tube (length about 1m and diameter about 3-4 cm) introduce considerable dead space, such as not to allow the subject to breathe ambient air. To reduce this dead space, an aspirator 16 (or a compressor) can be used which is able of producing a flow of about 0.2-0.4 l/s (independent from the oscillating pressure) that permits the expulsion of the gases expired by the subject and, thus, the exchange of the air contained in the tube. In alternative to the long tube 15 other systems with a similar function can be used, including a simple resistance of 2-3 cmH₂O/L*s connected between the generator and the flow measuring device to the atmosphere.

The flow and pressure signals are digitised at a proper sampling frequency, paying attention to avoid aliasing phenomenon by means of apposite filters.

The Applicant, from the analysis of the variations of Xrs during a single

respiration has observed that during spontaneous breathing the flow-limited patients presented considerable reductions in the reactance values measured in the expiratory phase. In addition, similar reductions were also discovered in healthy subjects during maximum forced expirations and, thus, in flow-limitation condition. The explanation of such phenomenon should be as follows. During the expiratory flow-limitation there are points of the airways distributed in the tracheo-bronchial tree (called choke points) in which the speed of propagation of the pressure wave becomes equal to that of the expired air. In these conditions eventual variations of pressure applied to the two ends of the tree (alveoli and airways opening) cannot exceed the choke points, and thus the flow no longer results to be dependent on the difference of pressure applied. The pressure oscillations applied at the opening of the airways with the above-described techniques cannot thus reach the alveoli during the expiratory flow limitation condition.

The inertance of the respiratory system at the frequencies considered is basically due to the upper airways and, at low frequencies, it assumes a marginal role in the definition of X_{rs} .

The compliance of the respiratory system is mainly due to the alveoli, as the compliance of the walls of the airways, additive to the former, results in being far lower, as is also that due to the quantity of air contained in the bronchial tree. The apparent 'closing' of the airways at the choke points thus causes the exclusion of the alveolar compliance from the measurement, producing a substantial reduction of the compliance observed, which in this condition is prevalently due to the airways walls. A reduction of the apparent compliance causes an increase of the negative component of X_{rs} and, thus, a substantial reduction of it during the expiratory phase if in the presence of flow-limitation.

Various methods can be used to calculate the input impedances of the respiratory system. That used in accordance with the present invention must be capable of calculating the time courses of the impedance during

spontaneous breathing at a frequency of at least 5-10Hz. The various methods for separating the components of the signal due to spontaneous breathing from those due to the forcing can in particular be based on the cross-correlation, the FFT or the estimation by least squares. These operations are carried out by the computer 23. In accordance with the present invention a method based on least square is used.

To be able to apply this method the stimulus signal S_{stim} must be a sinusoid or a sum of N sinusoids of known periods $T_1, T_2, \dots T_N$

$$S_{stim}(t) = K \sum_{i=1}^N \sin\left(\frac{2\pi}{T_i} t + \varphi_i\right)$$

10

with the following conditions:

$$\forall i \quad T_i \ll T_{resp} \quad \text{e} \quad T_i \gg T_c$$

where T_{resp} is the respiratory period and T_c is the sampling period.

15

The calculation proceeds in an iterative manner: each iteration processes a number of pressure samples equal to W and a number of flow samples equal to W. At the k-th iteration the samples from the k-th to the (k+W-1)-th are processed, the result is assigned to the time k+W/2 if W is even, and to the time k+(W-1)/2 should W be odd; the following is carried out under the hypothesis that W is even. The choice of parameter W is not critical, as W samples do not have to contain exactly a period of the stimulus signal. As we shall see further ahead in fact, the theory imposes $W \geq 1+2N$, by increasing said parameter minor influence of the noise is obtained but at the same time the faster variations of impedance are lost and the calculation times are lengthened. A good compromise between sensitivity to the noise and to the variations of impedance can be obtained using for W the minimum number of samples that a whole period of the slowest stimulus component contains.

25

Each iteration is composed of 2 steps.

First of all there is the extraction of the pressure and flow signals of the components due to the respiration and calculation of the coefficients to describe the components due to the stimulus in phasor notation.

5 For each signal a linear combination of N frequency sinusoids of frequencies equal to the stimulus frequencies is associated:

$$S(t) = r(t) + a_0 + \sum_{i=1}^N a_i \cos(2\pi f_i t) - b_i \sin(2\pi f_i t) = r(t) + a_0 + \sum_{i=1}^N \operatorname{Re}[(a_i + j b_i) e^{j 2\pi f_i t}]$$

10 where $r(t)$ represents the noise and Re the real part of a complex number.

As the signals are at discrete time, we have for the pressure:

$$S_p = A \cdot X_p + R_p$$

with:

$$A = \begin{bmatrix} 1 & \cos(\omega_1 t_1) & -\sin(\omega_1 t_1) & \dots & \cos(\omega_N t_1) & -\sin(\omega_N t_1) \\ 1 & \cos(\omega_1 t_2) & -\sin(\omega_1 t_2) & \dots & \cos(\omega_N t_2) & -\sin(\omega_N t_2) \\ \dots & \dots & \dots & \dots & \dots & \dots \\ 1 & \cos(\omega_1 t_W) & -\sin(\omega_1 t_W) & \dots & \cos(\omega_N t_W) & -\sin(\omega_N t_W) \end{bmatrix}$$

15

$$S_p = \begin{bmatrix} P(k) \\ P(k+1) \\ \dots \\ P(k+W-1) \end{bmatrix} \quad X_p = \begin{bmatrix} a_{p,0}(k+W/2) \\ a_{p,1}(k+W/2) \\ b_{p,1}(k+W/2) \\ \dots \\ a_{p,N}(k+W/2) \\ b_{p,N}(k+W/2) \end{bmatrix} \quad R_p = \begin{bmatrix} r_p(k) \\ r_p(k+1) \\ \dots \\ r_p(k+W-1) \end{bmatrix}$$

where $\omega_i = 2\pi/T_i$ pulsation of the i-nth component of the stimulus, $t_j = (j-1)T$ TC time associated to the j-th sample of the W selected.

Note that the matrix A remains identical for all the iterations.

Such a system allows a solution to the least square as long as $W \geq 1+2N$, and the solution to the least square is given by:

$$X_p = (A^T A)^{-1} A^T S_p$$

5 As a remains identical for all the iterations, it is possible to calculate $B=(A^T A)^{-1} A^T$ once and reduce the problem to a vector-matrix product: $X_p=B S_p$.

10 The coefficient a_0 represents the component of the signal due to the respiration while the coefficients a_i and b_i enable the component of the pressure signal due to the stimulus to the i -th frequency to be written in phasor notation.

The same procedure is applied to the flow signal.

Thus the impedance is calculated at the various stimulus frequencies and at the time $k+W/2$ as ratio between the signal phasors:

15

$$Z_i(l) = \frac{a_{p,i}(l) + j b_{p,i}(l)}{a_{\dot{v},i}(l) + j b_{\dot{v},i}(l)}$$

where $l = k + W/2$ and $1 < i < N$ and Z_i is the impedance to the i -nth stimulus frequency.

20 Each iteration requires $2(W-1)(1+2N)$ sums and $2W(1+2N)$ products between real numbers, and N ratios between complex numbers; therefore this method can be competitive in comparison to other methods in terms of execution speed. This calculation method thus enables us to obtain the time progresses of the impedance at numerous frequencies, with the possibility of freely choosing these frequencies, as long as the second requisite is

25 respected. It is important to point out that this method provides time progresses of the impedance filtered with a moving average filter of amplitude W .

The possibility of varying the parameter W permits the choice of the

most suitable compromise between sensitivity to the noise and passing band of that filter.

To be able to reduce the impact of the noise on the assessment of the impedance in the case of multifrequency signals with a high number of components ($N > 3-4$) the method proposed above can be modified as follows.

The pressure and flow signals are decomposed in a component due to the respiration and N components due to the various frequencies of the stimulus by means of a series of numeric Butterworth filters of suitable order (typically of the 4th order). A low-pass filter with cut-off frequency of suitable frequency (1-3Hz for spontaneous breathing) separates the component due to the respiration, a series of N band-pass filters instead separates the components due to the various stimulus sinusoids. The i -nth band-pass filter has a passing band centred on the i -th frequency of the stimulus signal and an adjustable bandwidth BW_i . Using this procedure N couples of pressure and flow signals are obtained from the couple of pressure and flow signals in input, each relating to a certain component of the stimulus. Then we proceed to the calculation of the N impedances relating to the N stimulus frequencies using the method proposed above.

The method proposed first is thus used in monofrequency modality in this variant, given that the couple of signals that is passed contain only one dominating frequency.

The effect of the decomposition of the signals with the band-pass filters is to obtain couples of signals with a better signal/noise ratio than that of the starting couple of signals. In fact, as the respiratory system is not linear, the spectrum of the original pressure and flow signals will also contain, in addition to the stimulus frequencies and to the background noise, all the harmonics of such frequencies and the spurious frequencies generated by the crosstalk effect. If N stimulus frequencies are chosen according to a pattern that excludes the possibility that a frequency is a whole multiple of any other

component of the signal, it is possible to prevent the harmonics from falling on the N frequencies chosen; opting instead for a pattern of the type non-sum non-difference of order 2 or greater, the spurious frequencies generated by the crosstalk are prevented from falling on the N frequencies of the stimulus. In this manner, the effect of a narrow band-pass centred on the i -
5 n th frequency of stimulus will be to remove the background noise, the other $N-1$ components caused by the stimulus, all the harmonics and also the spurious frequencies, thus improving the signal/noise ratio.

The parameter BW_i must be sized taking into account several
10 considerations. The variation in the time of the impedance at the frequency i -th $Z_i(t)$ is reflected in an amplitude modulation of the pressure and flow signals, this means that the spectrum of said signals will contain, besides the frequencies of the stimulus with their harmonics and the background noise, also the components around the stimulus frequencies due to the amplitude
15 modulation of the signals. For the theory of the signals, this surrounding has semi-amplitude equal to the maximum modulation frequency, a frequency that here corresponds to the fastest of the spectrum components of the impedance. The parameter BW_i sets the width of the surrounding considered for the i -th frequency, then limits the speed of variation that can be observed
20 of $Z_i(t)$ at $BW_i/2$ Hz. Therefore, also the choice of the parameter BW_i constitutes a compromise: keeping the value of BW_i low the background noise and the harmonics of the stimulus are eliminated more effectively, but at the same time the fastest variations of $Z_i(t)$ are lost; vice versa, a high value of BW_i permits even the fastest variations of $Z_i(t)$ to be gathered but
25 does not effectively remove the background noise and the harmonics of the stimulus signal.

Finally it can be noted that the parameters BW_i and W_i both have the collateral effect of limiting the maximum speed of variation that can be observed in $Z_i(t)$, with the band-pass filter that is applied before the filtering
30 by mobile media actuated by the method. Consequently, it is advisable that

the limitation in frequency on $Z_i(t)$ comes about by means of the band-pass. This is achieved by choosing BW_i and W_i so that the following relation is met:

$$BW_i < \frac{2fc}{W_i}$$

5

where fc is the chosen sampling frequency.

In Figures 2a-2c the graphs are shown, upon varying of the time T , the volume V (l), the flow F (l *sec⁻¹), the impedance X_{rs} at 5 Hz (cm H₂O/ l*sec⁻¹) and the oesophageal pressure P_e (cm H₂O) of a healthy patient (fig. 2a), of a patient with chronic obstructive pulmonary disease (COPD) but not flow-limited (fig. 2b), and a patient with chronic obstructive pulmonary disease (COPD), with expiratory flow limitation (Fig. 2c).

10

The graphics of the impedance X_{rs} show two curves, one in a continuous line for the real part and one with a dotted line for the imaginary part.

15

In particular take note of the variations of the imaginary part for the patient with chronic obstructive pulmonary disease (COPD), limited flow (Fig. 2c).

20

The use of the difference between the inspiratory and expiratory values of X_{rs} can thus be used to identify conditions of expiratory flow limitation calculating the values of suitable indices. In particular some different indices are suggested that can be used both singularly and in combination with each other, said indices are: the minimum value of X_{rs} reached during the expiration (X_{rsm}), the average value of X_{rs} during all or part (for example considering the central third part) of the expiratory phase (X_{rsem}), the difference between the maximum value of X_{rs} reached during the inspiratory phase and the minimum value of X_{rs} reached during the expiration (X_{rspp}), the difference between the average value of X_{rs} in all or

25

part of the inspiratory phase and the average value of X_{rs} during all or part of the expiratory phase (X_{rsdm}), and the regression coefficient (r^2) combined with compliance data obtained fitting the impedance data on a resistance-inertance-compliance series model, the latter only if multifrequency forcing signal is used.

In particular, the latter index is based on the fact that, as already mentioned, during the expiratory flow-limitation (EFL) the measurements of input impedance Z_{in} would reflect only the mechanical properties of the airways between the airway opening and choke points. As already known, it is possible to model expiratory Z_{in} with a simple lumped parameter model consisting of a resistance (R), compliance (C) and inertance (I) in series.

The equation of motion of the respiratory system obtained considering this model is:

$$P = \frac{1}{C}V + R \dot{V} + I \ddot{V}$$

Where P is the pressure at the airway opening and V is the volume measured at the airway opening (eventually obtained integrating the flow), R is the resistance, C the compliance and I the inertance of the whole respiratory system.

This model would be valid for healthy subjects, providing a series of a resistant R, an inductor I and a capacitor C, for the whole respiratory system. The model is invalid for COPD patients without flow limitation due to heterogeneity. However, based on our hypothesis, the model would become valid again for COPD with flow limitation but only during expiration and reflecting only the airways between the mouth and choke points. Now, the R and I represent the resistance and inertance of these airways and the C becomes the airway wall compliance which is the only shunt pathway downstream from the choked airways.

If a multifrequency forcing signal is applied to the subject and the resulting data are used to fit the model, the regression coefficient (r^2) or other indices of the performance of how the model fits the data can be used to discriminate the status of subject's airways. In the Table 1 mean $\pm$ SD of the inspiratory and expiratory values of the parameters estimated on 15 subjects are presented as example. The subjects were aged matched healthy (5 subjects), COPD with no expiratory flow limitation (5 patients) as measured by Mead and Whittenberger method and COPD presenting EFL during quiet breathing (5 patients) accordingly to Mead and Wittenberger method. The C estimated during EFL in COPD were an order of magnitude below the C for healthy subjects, suggesting that in COPD, the C does reflect airway wall compliance rather than parenchymal and chest wall tissues. Moreover, consistently with our hypothesis, the simple series model fits COPD patients data well (see r^2 values in Table 1) only during expiration and only if flow limitation is present. This approach then constitutes a potential diagnostic test for identifying the onset of EFL during spontaneous breathing and for estimating the airway wall compliance. The use of the performance index of the model fitting is, in fact, a sensible index of expiratory flow limitation: if it changes to low values to good values passing from expiration to inspiration it means that the subject is flow-limited. Therefore, the time course of the performance index of the model fitting can be used as described for Xrs signal to determine indices and thresholds for the detection of EFL. Moreover, this approach has potentially the capability of being implemented without passing through the computation of Zin, but fitting directly pressure and flow data to the model (for example as reported in the article of Lauzon, A. M. and J. H. Bates. Estimation of time-varying respiratory mechanical parameters by recursive least squares. J Appl. Physiol 71, 1159-1165, 1991) and computing the performance index time course. This time course can be used similarly to Xrs computing the values of the suggested four indices. For example, to

discriminate flow-limited COPD from healthy subjects it is possible to analyse changes of the performance index between inspiration and expiration or to consider also the estimated value for the compliance or both. However, this method based on del fitting, differently from the other indices computed on Xrs only, requires that the forcing signal applied to the subject presents more than two frequency components to have reliable estimations.

TABLE 1

		EXPIRATION				INSPIRATION			
		R	C	I	r ²	R	C	I	r ²
Control	mean	2.89	0.0441	0.0075	0.85	2.58	0.0274	0.0079	0.90
	SD	0.10	0.0038	0.0004	0.08	0.18	0.0042	0.0005	0.05
COPD NON EFL	mean	3.56	0.0156	0.0017	0.47	3.01	0.0144	0.0028	0.56
	SD	0.10	0.0019	0.0006	0.09	0.02	0.0011	0.0005	0.05
COPD EFL	mean	3.97	0.0032	0.0060	0.90	5.04	0.0076	-0.0025	0.36
	SD	0.08	0.0001	0.0008	0.03	0.12	0.0006	0.0016	0.06

Once the values of the selected index have been obtained, they are compared with a threshold value, for the mean value during the expiration, that could be equal to 0.77. The exceeding or not of the threshold by the index is used to identify condition of flow-limitation. As an example, the sensitivity values are shown in Figure 3, with a continuous line, defined as the number of respirations in which the flow-limitation is identified and the number of respirations indicated as flow-limited using the Mead and Whittenberger method (which is a graphic method for detecting the presence of expiratory flow limitation, and it is based on the alveolar pressure vs flow at the mouth graph and it is considered a reliable gold-standard for detecting expiratory flow limitation) and specificity, with a dotted line, defined as the number of respirations in which the absence of flow-limitation is identified and the number of respirations indicated as not flow-limited using the Mead

and Whittenberger method as a function of the value adopted as threshold for the various indices analysing a population of COPD patients during spontaneous breathing using a stimulus frequency of 5Hz. In these graphics it can be seen that the indices based on the reactance guarantee zones in which both sensitivity and specificity are equal to 100%. The use of a threshold value within said zone (for example at its centre) allowed us to define a method for detecting the expiratory flow limitation able to provide equal or better performances than those of the Mead and Whittenberger method but with the important advantage of not requiring the use of the oesophagus balloon. Table 2 shows as an example the optimal values obtained to be used as threshold. Optimal reference values can be obtained also considering equations that take into account other parameters such as, the characteristics of the subjects. As it is possible that subjects who are very different from each other (for example a child and an elderly person) give absolute reactance values that are different from each other, and to some measure depend on several specific characteristics of the subject, it could be useful to make the threshold values depend on the type of subject under examination. The same problem is typical of numerous measurements in pneumology, for example each spirometry is accompanied by the aforementioned values for the various indices measured (vital capacity, volume expired in a second, etc.). The threshold values can thus be obtained considering equations that take into account other parameters, such as, the anthropometrical characteristics of the subjects. For this purpose it is possible, starting from the analysis of the values that the various indices assume in the various subjects belonging to a wide and heterogeneous population, to identify the correlations between the parameters that characterise the subject (for example sex, age, weight, race, height, vital capacity, functional residual capacity, etc) and its optimal threshold values for the various indices. From such correlations simple equations can be obtained that predict the optimal threshold values as function of the most

significant parameters, so as to improve the specificity and sensitivity of the method.

TABLE 2

Index	Total interval (cmH ₂ O/l*s ⁻¹)	Excellent interval (cmH ₂ O/l*s ⁻¹)	Excellent region (%)	Excellent threshold (cmH ₂ O/l*s ⁻¹)
Xrsem	-10,5 ÷ -0,3	-4,7 ÷ -4,2	5,9	- 4,5
Xrsm	-20,4 ÷ -0,6	-7,6 ÷ -6,3	6,5	- 6,9
Xrsdm	-0,6 ÷ 9,0	1,9 ÷ 3,4	15,4	2,7
Xrspp	0,2 ÷ 19,7	5,7 ÷ 6,3	3,1	6,0

It is important to point out that while the indices calculated using the averages can discriminate if a breath is flow-limited or not, the use of the threshold values calculated for Xrsm or Xrspp can also enable the determination of the exact time in which the flow-limitation starts to occur, by carrying out the comparison with the instantaneous value of Xrs. In this case the flow-limitation conditions present can be identified only in part of the expiration (partial flow-limitation) as shown in Figure 4a, where a maximum flow-volume curve overlays a flow-volume curve obtained from spontaneous breathing (left). The arrow points out the moment in which the two curves overlay each other, and thus when the flow-limitation phase starts. Analysing the course in time of Xrs and of the flow F (Fig. 4b) it can be seen that, when the respiration becomes flow-limited, Xrs descends below the threshold value calculated for the index Xrsm. This approach can also be applied to the study of the flow-volume curves obtained during the execution of forced partial or maximal vital capacity manoeuvres.

In addition, even though it is necessary to use only one frequency for determining whether a subject is flow-limited or not, the study of the dependence of the values of the various indices with the frequency might give useful information on localization and heterogeneity of the choke points.

CLAIMS

1. System for the automatic detection of expiratory flow limitation of a subject comprising:

means for determining the respiratory impedance of said subject

5 composed of a real component and an imaginary component;

means for determining at least one index linked to said respiratory impedance;

means for indicating the positioning of said at least one index in relation to a preset threshold value.

10 2. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 1 characterised in that said means for determining at least one index is linked to the imaginary component of said respiratory impedance.

15 3. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 1 characterised in that said device for determining the respiratory impedance of said subject comprises: a device for generating at least one oscillating pressure signal at a preset frequency;

a duct for applying said at least one oscillating pressure signal to the respiratory system of said subject;

20 a device for measuring the flow and the pressure inside said duct.

4. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 2 characterised in that said at least one index corresponds to the minimum value of said imaginary component reached during the expiration.

25 5. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 2 characterised in that said at least one index corresponds to the average value of said imaginary component during all or part of the expiratory phase.

30 6. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 1 characterised in that said at least one

index corresponds to indices computed on the time courses of a performance index of the fitting of the impedance to a prefixed model or of the direct fitting to the flow and pressure measured at the airway opening with the prefixed model.

5 7. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 2 characterised in that said at least one index corresponds to the difference between the maximum value of said imaginary component reached during the inspiratory phase and the minimum value of said imaginary component reached during the expiration.

10 8. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 2 characterised in that said at least one index corresponds to the difference between the average value of said imaginary component during all or part of the inspiratory phase and the average value of said imaginary component during all or part of the
15 expiratory phase.

 9. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 3 characterised in that said means for determining the respiratory impedance of said subject comprise

 means for associating to each oscillating pressure signal a linear
20 combination of sinusoids of frequencies equal to the stimulus frequencies;
 means for determining the impedance by means of a system at the least square ;

 means for calculating the impedance at the various stimulus frequencies as ratio of the phasors.

25 10. System for the automatic detection of the expiratory flow limitation of a subject in accordance with claim 1 characterised in that said analysis comes about during the spontaneous breathing of said patients.

 11. Method for the automatic detection of the expiratory flow limitation of a subject comprising the phases of:

30 determining the respiratory impedance of said subject composed of a

real component and an imaginary component;

determining at least one index linked to said respiratory impedance;

indicating the positioning of said at least one index in relation to a
preset threshold value.

5 12. Method for the automatic detection of the expiratory flow
limitation of a subject in accordance with claim 11 characterised in that said
phase of determining at least one index is linked to the imaginary component
of said respiratory impedance.

10 13. Method for the automatic detection of the expiratory flow
limitation of a subject in accordance with claim 11 characterised in that said
phase determining the respiratory impedance of said subject comprises the
phases of generating at least one oscillating pressure signal at a preset
frequency; applying said at least one oscillating pressure signal to the
respiratory system of said subject; measuring the flow and the pressure
15 inside said duct.

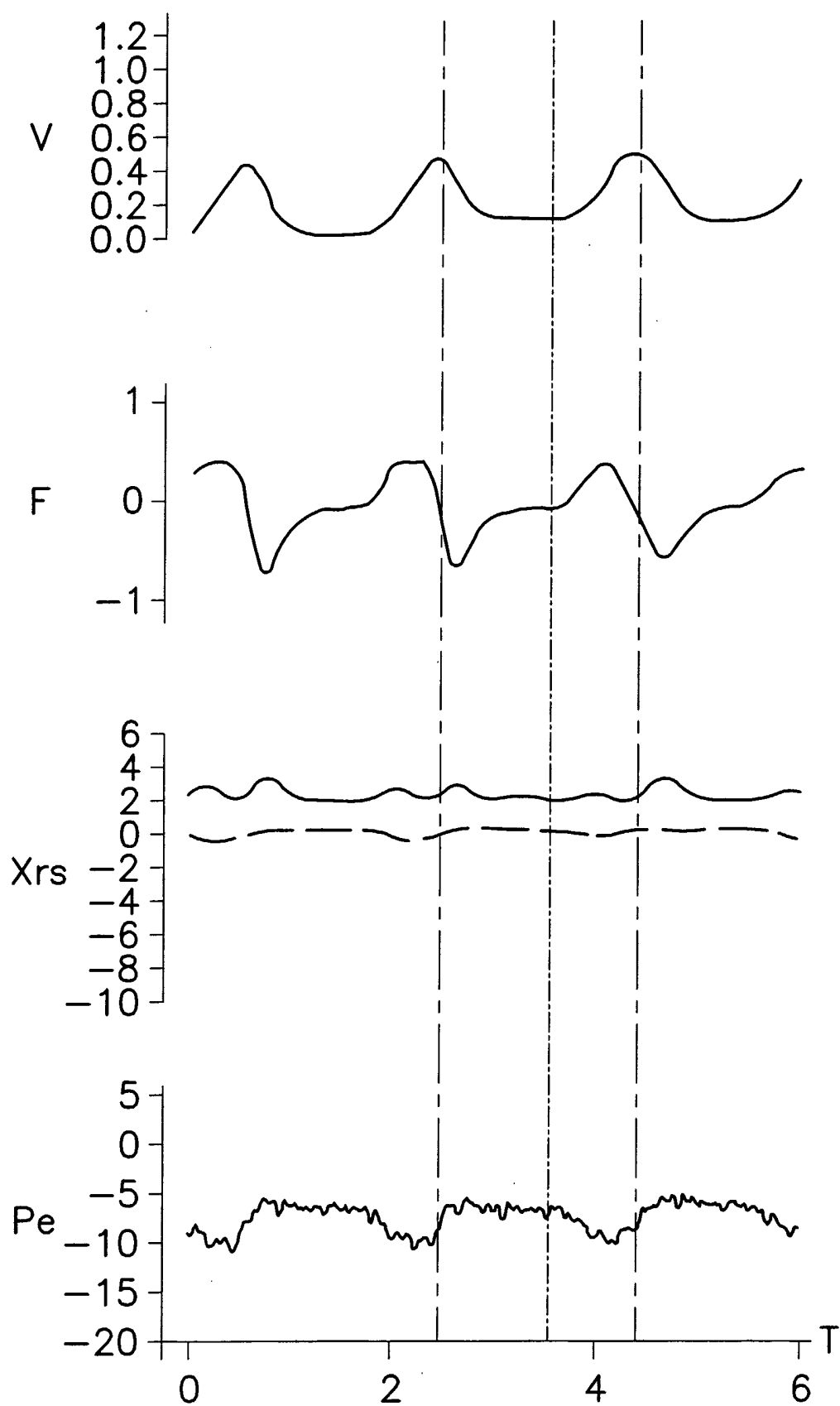
 14. Method for the automatic detection of the expiratory flow
limitation of a subject in accordance with claim 11 characterised in that said
at least one index is obtained assessing the difference between the
inspiratory and expiratory values of said respiratory impedance of said
20 subject.

 15. Method for the automatic detection of the expiratory flow
limitation of a subject in accordance with claim 11 characterised in that said
preset threshold value is calculated on the basis of an analysis of a
population of said subjects.

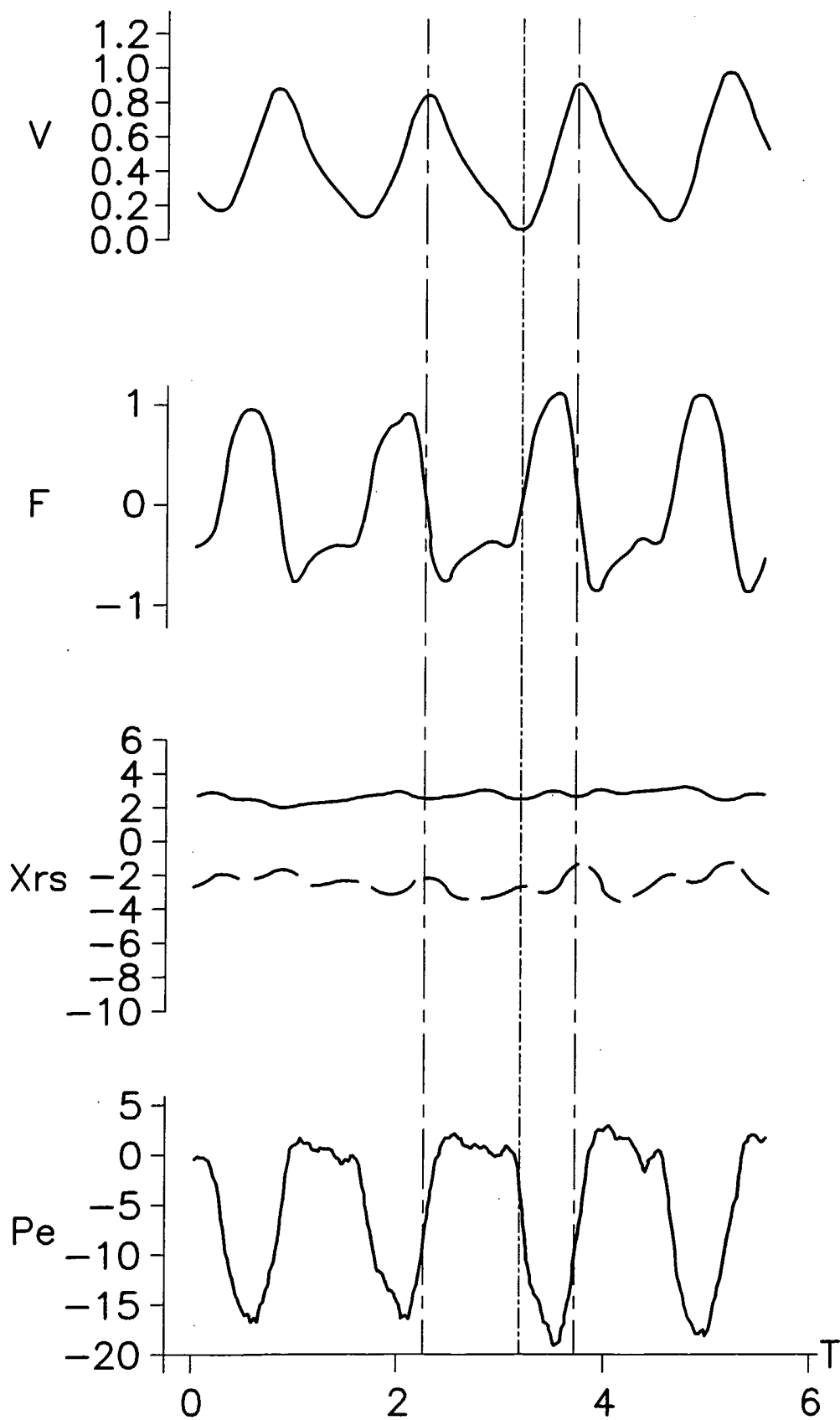
25 16. Method for the automatic detection of the expiratory flow
limitation of a subject in accordance with claim 11 characterised in that said
preset threshold value is calculated on the basis of an equation that takes into
account the parameters that characterise a plurality of populations of said
subjects.

30

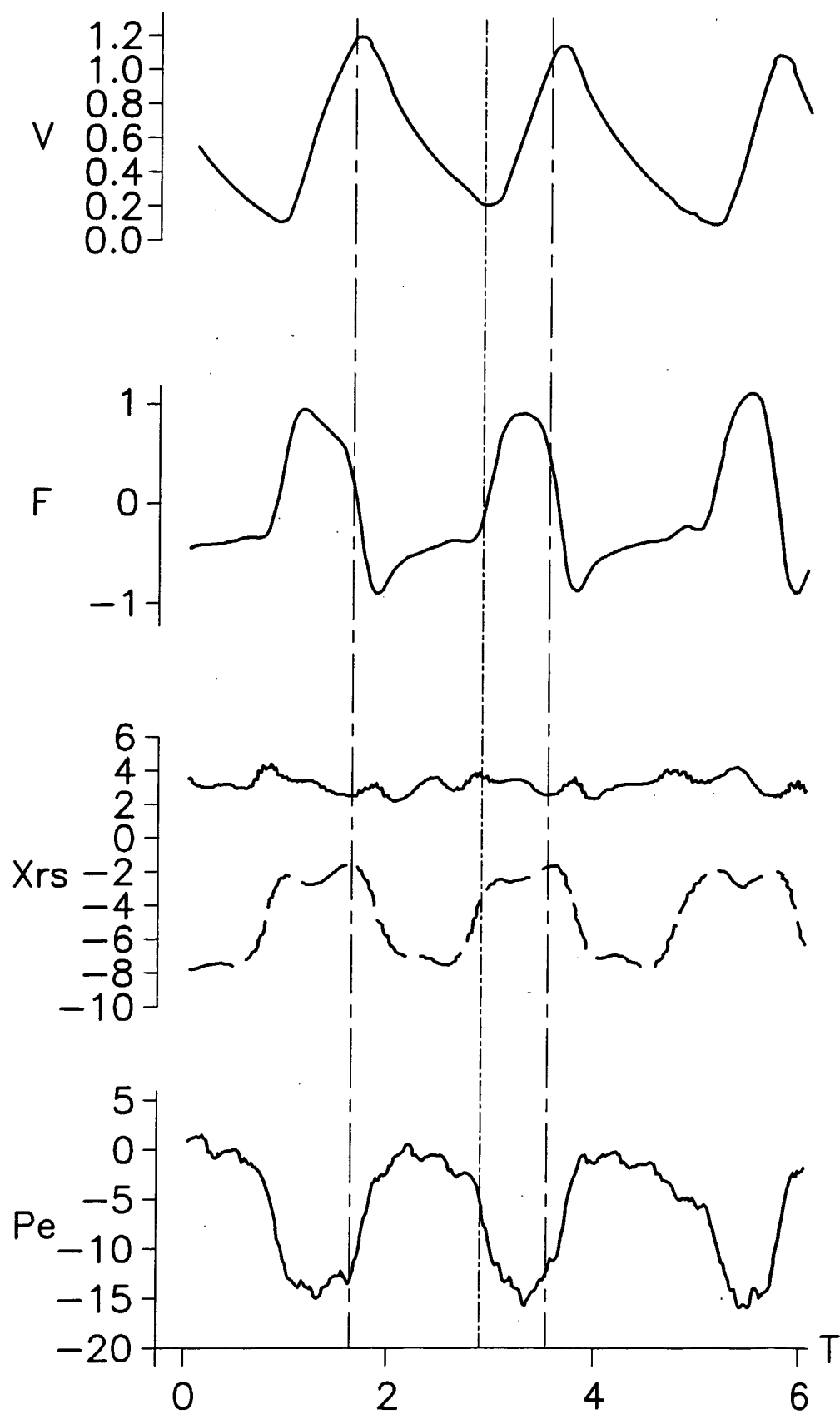
2/6

FIG.2a

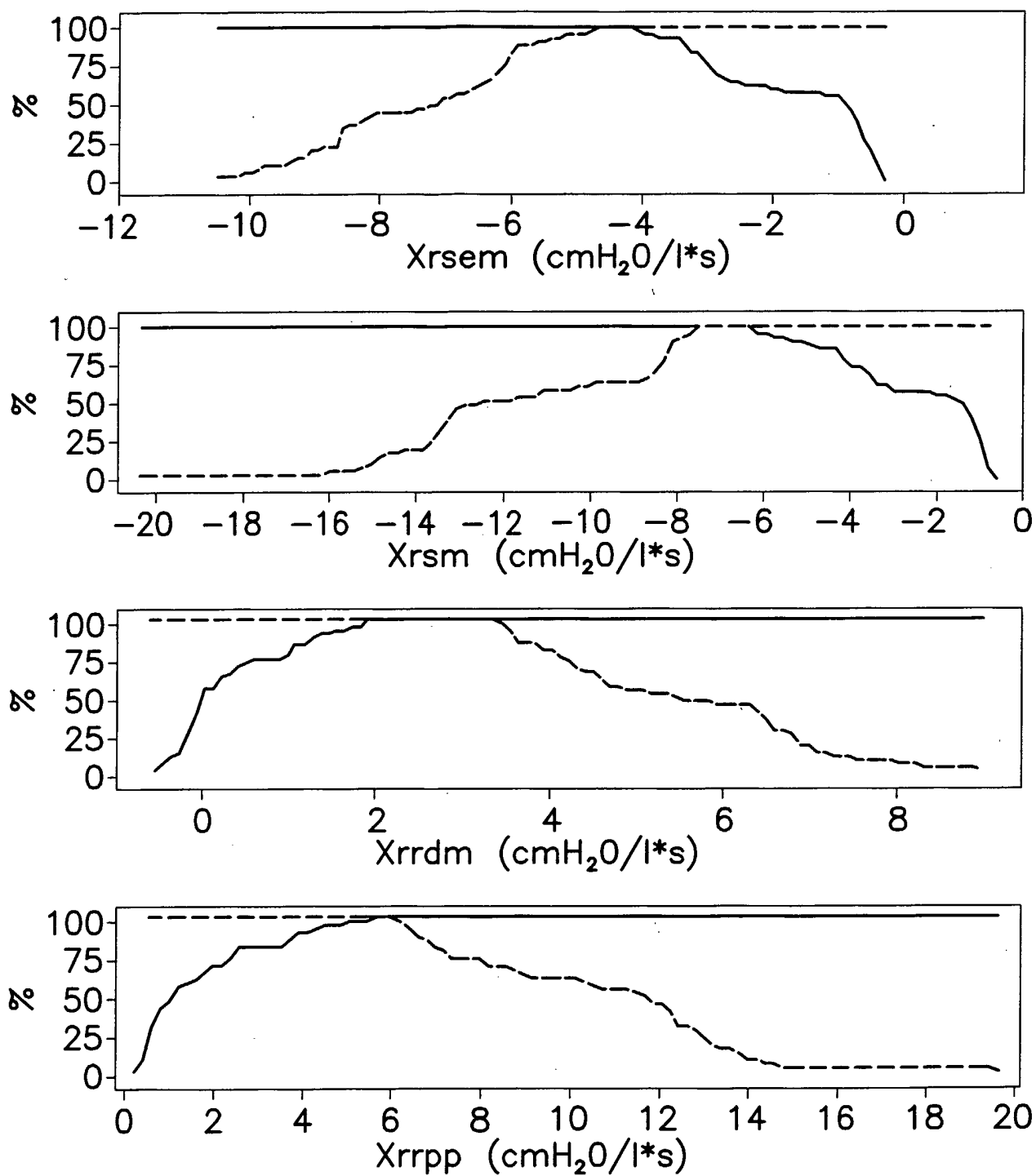
3/6

FIG.2b

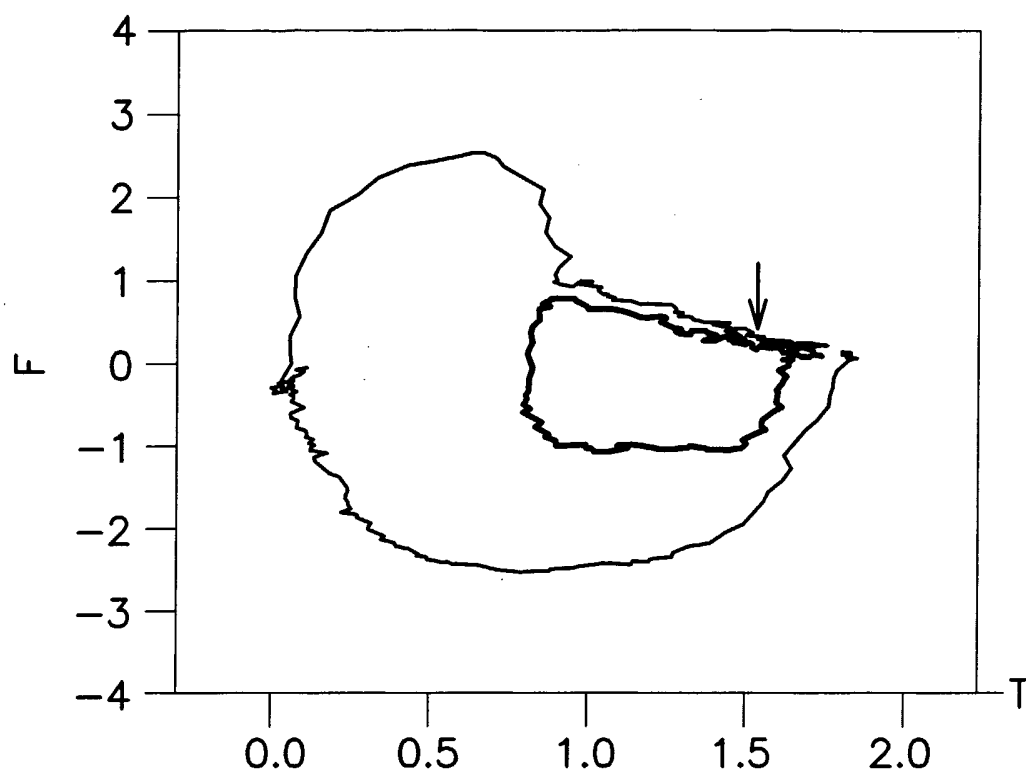
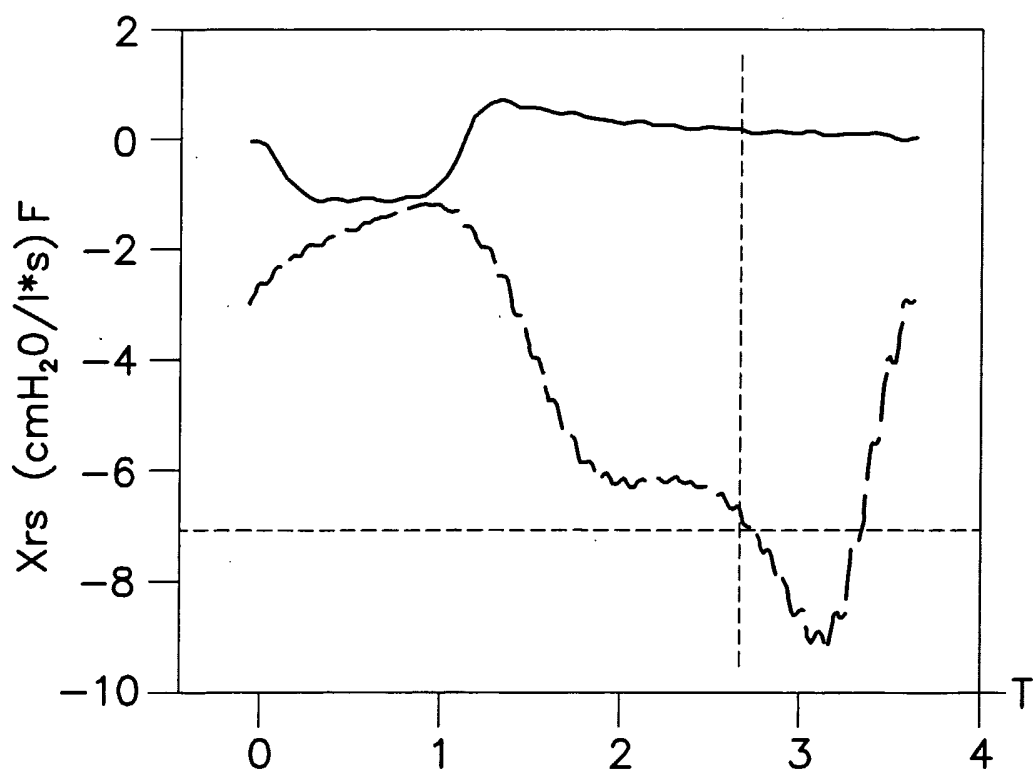
4/6

FIG.2c

5/6

FIG.3

6/6

FIG. 4aFIG. 4b

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/06119

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61B5/085

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 373 585 A (SCHUMANN KLAUS ;WALLISER DIETER DR (DE)) 20 June 1990 (1990-06-20) abstract; figure 1 ---	1,11
A	US 6 066 101 A (LAUSTED CHRISTOPHER G ET AL) 23 May 2000 (2000-05-23) column 5, line 20-57 column 15, line 17-34 ---	1,11
A	US 4 197 859 A (PRESTELE KARL) 15 April 1980 (1980-04-15) summary of invention -----	1,11



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

29 October 2003

Date of mailing of the international search report

05/11/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Papone, F

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/06119

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0373585	A	20-06-1990	DE 3903857 A1 EP 0373585 A1 JP 2271835 A	21-06-1990 20-06-1990 06-11-1990
US 6066101	A	23-05-2000	NONE	
US 4197859	A	15-04-1980	DE 2714216 B1 CH 627068 A5 FR 2385373 A1 GB 1579116 A NL 7801418 A	20-04-1978 31-12-1981 27-10-1978 12-11-1980 03-10-1978