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(54) Title: A METHOD FOR THE EARLY IDENTIFICATION OF RECURRENCES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

(57) Abstract: A method for the early identification of recurrences of chronic obstructive pulmonary disease comprising the following steps of; measuring, with a predefined time frequency, a plurality of parameters that define the pulmonary function of a patient by means of the forced oscillation technique (FOT); calculating the trend of said plurality of parameters in a predefined time period; identifying an impending recurrence by comparing the parameters describing said trend of said plurality of parameters with predefined thresholds; where the step of calculating the trend of said plurality of parameters is achieved by calculation of an N order polynomial regression model; and the step of identifying an impending recurrence by comparing said parameters describing said trend with predefined thresholds comprises the step of comparing at least one coefficient of the N order polynomial regression with predefined thresholds.

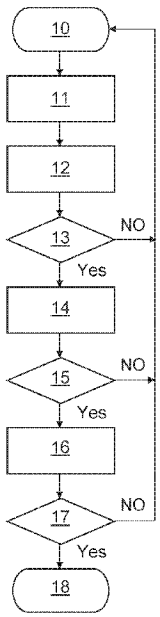

Fig. 1

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"A METHOD FOR THE EARLY IDENTIFICATION OF RECURRENCES OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE" SP2589

DISCLOSURE

The present invention refers to a method for the early identification of recurrences in patients suffering from chronic obstructive pulmonary disease.

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory disease characterized by persistent symptoms such as dyspnea, chronic coughing and expectoration and by persistent airflow limitation (GOLD 2017). Common risk factors include prolonged exposure to noxious particles and/or gases, such as cigarette smoke. The progression of COPD is characterized by stable periods interrupted by recurrences, namely acute deteriorations of the symptoms and the underlying inflammatory process which, in the most serious cases, can require hospitalization of the patient (Vogelmeier et al., 2017).

The frequency of the recurrence episodes has important consequences for the clinical history of the patient, accelerating functional decline of the lungs, increasing the risk of death, reducing the quality of life and increasing the social and economic costs associated with the pathology.

The evidence that early therapeutic intervention on the recurrence episodes can help to reduce their impact on the patients' health (Wilkinson, Donaldson, Hurst, Seemungal, & Wedzicha,

2004), together with the necessity to optimize the management of patients suffering from COPD, has stimulated the development of care models based on home monitoring programs. The majority of the programs proposed are based on the use of daily questionnaires for recording worsening of the symptoms perceived by the patients in combination with medical teleconsulting systems and patient education. Although these programs have demonstrated effectiveness in reducing hospitalizations and the number of patients accessing A&E due to recurrences of COPD (McLean et al., 2012), they have not been applied on a large scale due to the high implementation costs required.

An alternative approach consists in the combination of measurements of physiological parameters that can be performed by the COPD patient at home, without direct medical supervision, with automatic algorithms that are able to identify the recurrences early starting from analysis of the measurements performed. The medical personnel are therefore alerted only if the algorithm has identified a suspected deterioration in the state of health of one of the COPD patients being treated who, consequently, can be immediately contacted to verify his/her state of health and/or to optimize the course of treatment.

Since said approach does not require continuous review of the measurements taken by the medical personnel, it would allow the management of a large number of patients by a restricted medical team, thus guaranteeing implementation on a large scale.

The experimental studies in which said approach has been studied used measurements of cardiac frequency and blood oxygen saturation (measured by means of portable pulsometers), alone or in combination with mechanical respiratory measurements (with portable spirometers). Said studies have not demonstrated adequate effectiveness in improving the management of patients suffering from COPD during a recurrence (Ringbaek et al., 2015; Vianello et al., 2016).

The object of the present invention is to provide a method for early identification of recurrences of COPD, using respiratory function parameters measured by means of the forced oscillation technique (FOT).

In accordance with the present invention, said object and others are achieved by a method for the early identification of recurrences of chronic obstructive pulmonary disease comprising the following steps: measuring, with a predetermined time frequency, a plurality of parameters that define the pulmonary function of a patient by means of the forced oscillation technique (FOT); calculating the trend of said plurality of parameters in a predefined time period; identifying an impending recurrence by comparing the parameters describing said trend of said plurality of parameters with predefined thresholds; where the step of calculating the trend of said plurality of parameters is achieved by calculating an N order polynomial regression model; and the step of identifying an impending recurrence by comparing said parameters describing said trend with

predefined thresholds comprises the step of comparing at least one coefficient of the N order polynomial regression with predefined thresholds.

Further characteristics of the invention are described in the dependent claims.

The forced oscillation technique (FOT) is a non-invasive method for measuring the mechanical properties of the airways and lungs based on the recording of pressure and flow to the patient's mouth during the application of a low-pressure external stimulus oscillating at a frequency higher than that of spontaneous breathing. (Dubois, Brody, Lewis and Burgess, 1956). This characteristic allows the measurement to be performed during spontaneous breathing, therefore making it ideal for remote monitoring applications, without supervision, of the respiratory parameters as demonstrated for example in the pilot studies of Dellacà et al. (Raffaele L. Dellacà, Gobbi, Pastena, Pedotti and Celli, 2010) and Gulotta et al. (Gulotta et al., AJRCCM, 2012).

During the FOT measurement, small oscillations in pressure (approximately 1-3 cmH2O peak-peak) at a single or composite frequency (usually between 4 and 40Hz) are sent to the patient's lungs through the opening of the airways (nose and/or mouth) by using a mouthpiece or alternative interfaces such as nasal or facial masks. The response of the respiratory system is evaluated in terms of impedance (Zrs), which is the overall ratio between the pressure at the mouth and the airflow at the oscillation frequencies. The

impedance Zrs is usually divided into its real component, the resistance (Rrs), and the imaginary component, the reactance (Xrs).

Rrs and Xrs can be analysed both in the time domain, i.e. during the respiration cycle (intra-breath analysis) and in the frequency domain (frequency analysis).

In the first case (intra-breath analysis) Rrs and Xrs are calculated at each breath, as described for example in Dellacà et al. (Dellacà et al., ERJ, 2004). Rrs and Xrs can therefore be presented both for each breath or as a mean of all the breaths of a given measurement. The intra-breath analysis allows Rrs and Xrs to be used to automatically exclude some breaths from the measurement mean if they are affected by artefacts, such as swallowing, coughing, etc. An example of said algorithm is described in Gobbi et al. (Gobbi et al., IEEE Telemed, 2009). Furthermore, with respect to the frequency analysis, in the intra-breath analysis the number of frequencies contained in the pressure stimulus is usually lower; this allows improvement of the signal-noise ratio and further separation of the contribution of inspiration and expiration of both the Rrs (obtaining the inspiratory resistance, Rinsp, and expiratory resistance, Rexp, respectively) and the Xrs (obtaining the inspiratory reactance, Xinsp, and expiratory reactance, Xexp, respectively) at each stimulus frequency. The results of the inspiratory and expiratory parameters can be reported for both each breath and as a mean of the breaths without artefacts contained in the measurement itself. For example, the mean difference between Xinsp and Xexp at 5Hz within

an FOT test is indicated by the symbol ΔXrs and has been shown to be associated with expiratory flow reduction (R. L. Dellacà et al., 2004), a condition that occurs in patients affected by severe or very serious COPD. Since an FOT measurement is performed during quiet breathing, from said measurement it is also possible to derive various respiratory pattern parameters, for example the current volume (V_T), the mean inspiratory and expiratory flows and times, the respiratory frequency and minute ventilation.

The characteristics and advantages of the present invention will be evident from the following detailed disclosure of a practical embodiment thereof, illustrated by way of non-limiting example in the accompanying drawings, in which:

figure 1 shows a flow diagram of a method for early identification of recurrences of COPD, in accordance with the present invention;

figure 2 shows a graph exemplifying Rinsp measurements taken on the various days indicated on the X axis and in the window W2.

Referring to the attached figure, a method for the early identification of recurrences of COPD, in accordance with the present invention, comprises the steps of initiating 10 the procedure; measuring 11, with a predefined time frequency, a certain number of parameters that define pulmonary function and the respiratory pattern of a patient by means of the FOT technique; for each new measurement available, collecting 12 the parameters measured, thus

constituting the corresponding time series thereof; verifying 13 whether the adaptation period, calculated from the beginning of the time series, has finished, i.e. evaluating whether the number of measurements collected is higher than a first predefined number - if not, start again from the beginning 10, and if so, eliminate 14 the abnormal values; verifying 15 whether the number of measurements in a given time period (having eliminated the abnormal values) is higher than a predefined number - if not, start again from the beginning 10, and if so, calculate 16 the time trend of said parameters in a predetermined time period; verifying 17 whether the trend of the latter, evaluated by using appropriate statistical methods or mathematical models, is significantly higher or lower than predefined numbers - if not, start again from the beginning 10, and if so, an impending recurrence 18 has been predicted. Then start again from the beginning 10.

For the measurements 11 the patients are required to use an FOT device able to measure Rrs and Xrs separately during the inspiratory and expiratory phase, the derived parameters and the respiratory model parameters. Said device is composed of a generator of stimuli at low pressure (<5 cmH2O), a set of pressure and flow sensors, a patient interface, a respiration circuit and a calculation unit that operates the pressure generator, collects the data from the sensors and uses them to calculate the pulmonary impedance, the derived parameters and the respiratory pattern parameters according to specific algorithms. An embodiment

example of said device is described by Gobbi et al (Gobbi, Milesi, Govoni, Pedotti & Dellacà 2009).

During each measurement, the patients are required to wear a nose plug and adopt systems to reduce vibration of the cheeks (for example, by supporting them using their hands) while they breathe spontaneously through the device, for example for two minutes or until a predefined number of breaths has been recorded.

The parameters that define the pulmonary function of a patient measured by means of the FOT technique are one or more of the following: inspiratory resistance (Rinsp) measured at a frequency ranging between 2 and 10Hz; inspiratory reactance (Xinsp) measured at a frequency ranging between 2 and 10Hz; difference between inspiratory and expiratory reactance (ΔXrs) measured at a frequency between 2 and 10Hz.

The respiratory pattern of a patient is described by the set of the following parameters: current volume (V_T), mean inspiratory (Ti) and expiratory times (Te), respiratory frequency (RR), respiratory duty cycle (Ti*RR), mean inspiratory (Vt/Ti) and expiratory flow (Vt/Te) and minute ventilation (Ve).

In one embodiment example of the method, the patient is required to perform one FOT measurement per day. The mean FOT and respiratory pattern parameters of each new daily measurement, calculated according to the intra-respiratory analysis method previously described, are collected 12 in the corresponding time series of the patient in question.

Since the measurement 11 requires the patient to breathe through the FOT device by means of a measurement interface, for example a mouthpiece, it is possible that the first measurements may not be usable due to adaptation of the patient to said interface. Said measurements should preferably be excluded. In one embodiment example of the method an adaptation period 13 of 8 days has been considered, so that the measurements contained in said time period are excluded from the following calculations. This passage is optional as it may not be necessary.

If an FOT measurement produces abnormal values, for example when carried out with an incorrect posture, without correct support of the cheeks, with a wrong positioning of the mouthpiece and/or of the nose plug, leaks around the measurement interface, due to obstruction of the filter by teeth or tongue, coughing, partial or total closure of the glottis, they must be eliminated 14 from the time series.

In one embodiment of the present invention, a method for detecting the abnormal values uses the normalized distance of one or more parameters calculated from the FOT measurement and the current daily respiratory pattern with corresponding mean value, calculated from the measurements available within a time window of predefined length which includes the current and past FOT measurements.

In particular it was considered that if the value V of a given parameter, calculated as shown in the following equation, is higher

than a threshold value TR, the current FOT measurement OP must be considered abnormal and therefore discarded.

$$V = \frac{OP - m(OP(W1))}{m(OP(W1))} \geq TR \qquad (1)$$

where:

m(OP(W1)) is considered the mean of the values of a given parameter measured within the window W1, and

W1 is a time window of predefined length containing the FOT measurements to be considered in the calculation, the new measurement and the past measurements.

Other approaches can be used to detect abnormal values in a time series of measurements and adapted for this application.

In a preferred embodiment of the present invention, the window W1 lasts 8 days and the threshold TR is equal to 0.5. The measurement is considered an abnormal value and will be ignored if the previous equation is verified for at least one of the following parameters: current volume V_T, inspiratory resistance Rinsp measured at 5 Hz, respiratory reactance Xinsp measured at 5Hz.

It is preferably checked 15 that, after removal of the abnormal values, at least a predefined number of measurements are present in a given time period W2, in order to have a significant number of measurements. In a preferred embodiment of the present invention, the time window W2 was chosen equal to 10 days and the minimum number of FOT measurements that must be present in W2 equal to 5.

It is checked that in W2 there are at least X% measurements. For example, if X% = 50% and W2 = 10 days, it must be checked that there are at least 5 measurements in W2.

The trends of all or a part of the FOT parameters and respiratory model are then calculated 16, by means of appropriate statistical methods or mathematical models and starting from the measurements available in the same time period W2. For example, a trend could be quantified, for each parameter in question, by means of an N order polynomial regression model relative to the measurements performed and previously processed considering: 1) the coefficients of the polynomial equation calculated ($ß_0$ for the known term, $ß_1$ for the coefficient of the first degree term, and so on), 2) the statistical significances (p-value) of each coefficient against the null hypothesis of being equal to zero, and 3) the correlation coefficient of the polynomial regression (r^2).

For example, a linear regression model and the parameters Rinsp, Xinsp and DeltaXrs can be used, thus calculating $ß1_{Rinsp}$, $ß1_{Xinsp}$ and $ß1_{deltaXrs}$.

For each FOT parameter considered, it is evaluated whether the statistical regression model identifies a progression, calculating the probability of one or more parameters of the model ß1 being different from zero, comparing said probability (also known as p-value), with a threshold, for example $p<0.05$. If this criterion is verified, it can be affirmed that the statistical model describes the progression of the parameter FOT sustained over time.

The overall goodness of the regression is then evaluated and its physiological significance. For measurement of the goodness of the regression, the correlation coefficient r2 can, for example, be used, which must be greater than a given threshold. The physiological significance of the regression is evaluated through a criterion applied to ß1, which depends in turn on the FOT parameter considered. In this example, the criteria associated with the respective coefficients ß1 are: $ß1_{Rinsp} > 0$, $ß1_{Xinsp} < 0$, $ß1_{deltaXrs} > 0$.

If the statistical regression model identifies a progression for a given FOT parameter and, simultaneously, the regression has a valid physiological significance and a high goodness level, the method assigns a value 1 to a corresponding trend parameter MI, which otherwise remains = 0.

Therefore, for every parameter analysed, the trend is considered in the direction of worsening of the pathology if it is above or below a predefined threshold. If so, a value 1 is assigned to a corresponding trend parameter, MI_P. If not, the corresponding trend parameter MI_P is maintained at 0.

For example, we will therefore have three trend parameters MI_{Rinsp}, MI_{Xinsp} and $MI_{deltaXrs}$ and each of them can assume the value 1 or remain at 0.

Lastly, a recurrence is scheduled by applying the following equation (2) which calculates a weighted sum of the trend parameters just processed:

$$\sum_{p} MI_p * w_p \geq TH \qquad (2)$$

where W_P ($0 \leq W_P \leq 1$) is a weight associated with the trend parameter MI_P of the parameter *p* in question and TH is a threshold.

In a preferred embodiment of the invention a linear regression model was applied (with N = 1) to each of the following parameters: inspiratory resistance (Rinsp) measured at 5 Hz, absolute value of the inspiratory reactance (Xinsp) measured at 5 Hz, difference between inspiratory and expiratory reactance (ΔXrs) measured at 5 Hz.

Furthermore, for every parameter a value equal to 1 is assigned to the corresponding trend parameter MI_P if all the following conditions have been verified for the following values: the absolute value of the coefficient $ß_1$ (slope of the regression line) must be greater than 0, the corresponding p-value must be less than 0.05 and the correlation coefficient of the polynomial regression (r^2) must be greater than 0.4.

In one embodiment example of the present invention, the measurements performed on the patient are transferred to a microprocessor which carries out all the processing operations, according to the predefined program, and provides the final results to a viewer, identifying, in automatic mode, the presence of recurrences of chronic obstructive pulmonary disease.

An impending recurrence was identified using the weights W_P

equal to 1 and the predefined threshold TH equal to 1, i.e. if the value calculated was greater than or equal to 1 as in the following equation:

$$1 * MI_{Rinsp} + 1 * MI_{Xinsp} + 1 * MI_{\Delta xrs} \geq 1$$

The Applicant performed a test on 24 patients for 8 months taking daily measurements by means of FOT using a commercial instrument.

The characteristics of the 24 COPD patients monitored are shown in Table 1.

Throughout the study the patients were telephonically interviewed once a week to collect the following information: prescriptions and use of drugs and/or antibiotics, non-scheduled medical examinations and admissions to hospital.

The recurrences were classified as:

Slight: where there were changes in the current treatment or prescription of a short-acting bronchodilator,

Intermediate: where a corticosteroid was prescribed,

Severe: where systemic antibiotics were prescribed,

Very serious: when the patient was admitted to hospital.

In order to evaluate the performances of this method, all recurrences were grouped together, regardless of their severity. Furthermore, a sub-analysis was carried out only on severe and very serious recurrences, since the latter are considered the most critical events in terms of both the patient and the health service.

During the monitoring period, the patients reported a total of 26 recurrences, 13 of which were of slight or intermediate type, and

13 of severe or serious type. Of these, 18 (69%) were correctly identified by the method described above. Eight recurrences of slight or intermediate type (61.5%) and 10 recurrences of severe or very serious type (77%) were correctly identified by the method described above.

TABLE 1	
Sex (M/F)	20/4
Age (years)	72.3 ± 6.9
Height (cm)	156.8 ± 7.0
Weight (kg)	74.9 ± 14.5
Body mass index BMI (kg/m2)	26.5 ± 4.3
Maximum expiratory volume in 1 according to FEV1 (l)	1.1± 0.3
FEV1 (%pred)	41.3 ± 12.4
FEV1/FVC (%pred)	42.1 ± 11.9

CLAIMS

1. A method for the early identification of recurrences of chronic obstructive pulmonary disease comprising the following steps of: measuring, with a predefined time frequency, a plurality of parameters that define the pulmonary function of a patient by means of the forced oscillation technique (FOT); calculating the trend of said plurality of parameters in a predefined time period; identifying an impending recurrence by comparing the parameters describing said trend of said plurality of parameters with predefined thresholds; where the step of calculating the trend of said plurality of parameters is achieved by calculation of an N order polynomial regression model; and the step of identifying an impending recurrence by comparing said parameters describing said trend with predefined thresholds comprises the step of comparing at least one coefficient of the N order polynomial regression with predefined thresholds.

2. The method according to claim 1 characterized in that the measurement of the pulmonary function of a patient by means of the forced oscillation technique (FOT) is performed at least once every two days.

3. The method according to claim 1, characterized in that the parameters that define the pulmonary function are represented by one or more of the following: inspiratory resistance (Rinsp) measured at a frequency ranging between 2 and 10Hz; inspiratory reactance (Xinsp) measured at a frequency ranging between 2 and 10Hz; difference between inspiratory and expiratory reactance (ΔXrs)

measured at a frequency ranging between 2 and 10Hz.

4. The method according to claim 1, characterized in that it includes the step of simultaneously measuring the respiratory pattern parameters.

5. The method according to claim 1 or 4 characterized in that after the step of measuring a certain number of parameters that define the pulmonary function of a patient by means of FOT, the abnormal values of the above-mentioned parameters are eliminated.

6. The method according to claim 1 or 4 characterized in that the step of eliminating the abnormal values comprises the step of eliminating all the measurements taken in a given time period from the beginning of the measurements.

7. The method according to claim 5 characterized in that after the step of eliminating the abnormal values, there is the step of verifying whether the number of remaining measurements is higher than a predefined number.

8. The method according to claim 5 characterized in that the step of eliminating the abnormal values comprises the step of verifying for every measurement whether the normalized distance of each of said plurality of parameters that define the pulmonary function of a patient and the respiratory model thereof, from the mean value of said measurements taken in a given time period, is higher than a threshold value.

9. The method according to claim 1 characterized in that it comprises the step in which for each parameter of said plurality of

parameters the deterioration trend of the pathology is assessed according to whether it is above or below a predefined threshold; if so, a value 1 is assigned to a corresponding trend parameter (MI_P); if not, the corresponding trend parameter (MI_P) is maintained at 0.

10. The method according to claim 9 characterized in that it comprises the step of predicting a recurrence by performing a weighted sum of said trend parameters.

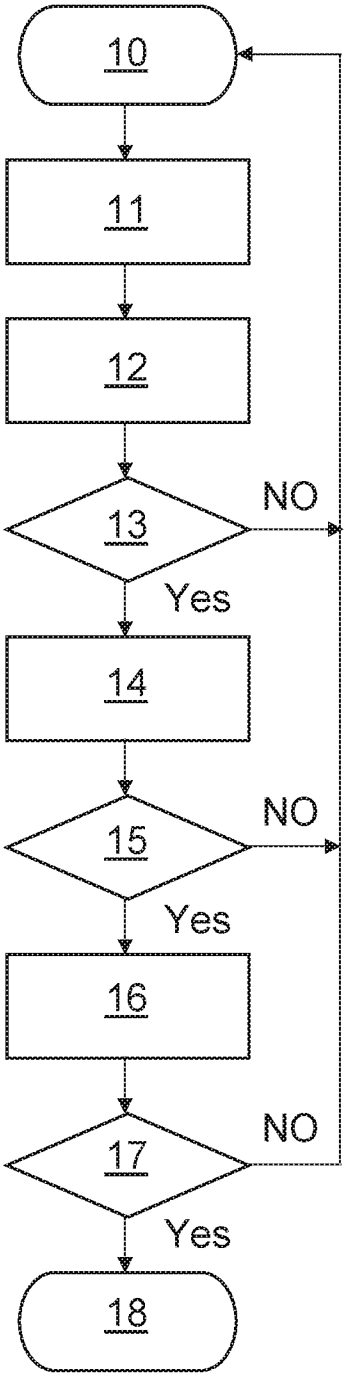

Fig. 1

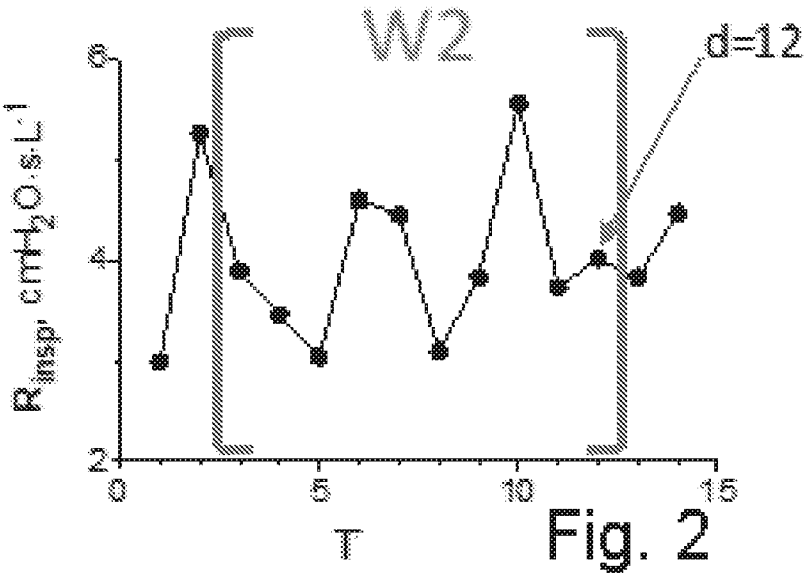

Fig. 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/055857

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61B5/085 A61B5/00 A61M16/00
ADD.

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)
A61B A61M

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 practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	paragraphs [0002] - [0009] paragraphs [0013] - [0032]	3
X	WO 2005/104944 A1 (UNIV DALHOUSIE [CA]; MAKSYM GEOFFREY N [CA]; LALL CAROLYN A [CA]) 10 November 2005 (2005-11-10) page 2, line 30 - page 4, line 3 page 7, lines 15-17 page 11, lines 1-22	1,2,4

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 September 2018	05/10/2018

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2018/055857

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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专利名称(译)	早期识别慢性阻塞性支气管肺病的复发率的方法		
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摘要(译)

一种早期识别慢性阻塞性肺疾病复发的方法，包括以下步骤： 以预定的时间频率，通过强制振荡技术（FOT）测量定义患者的肺功能的多个参数； 在预定时间段内计算所述多个参数的趋势； 通过将描述所述多个参数的所述趋势的参数与预定阈值进行比较来识别即将发生的复发； 其中，通过计算N阶多项式回归模型来实现计算所述多个参数的趋势的步骤； 通过将描述所述趋势的所述参数与预定阈值进行比较来识别即将发生的重复的步骤包括将N阶多项式回归的至少一个系数与预定阈值进行比较的步骤。