Data based Modelling of Expired Airflow Clarifies Chronic Obstructive Pulmonary Disease

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Abstract: One of the major health challenges of the future is Chronic Obstructive Pulmonary Disease (COPD). It is characterized by airflow limitations, although current diagnosis does not give attention to the flow measurements. We aimed to develop a data-based model of the decline of the forced expiratory flow. Moreover, we analysed the relationship of model parameters with COPD presence and its severity. The data-based model was developed in 474 smoking individuals, who are at risk of having COPD, and have performed complete pulmonary function tests in order to identify whether the disease is present and at which stage. The time series of the decline of the flow was parameterised using the poles and steady state gain (SSG) of a second order transfer function model. These parameters were then linked with the presence of COPD. Observing SSG, median (IQR) in subjects with COPD was lower 3.9(2.7-5.6) compared to 8.2(7.1-9.3) in subjects without, ($p<0.0001$). Significant difference was also found when observing median (IQR) of two poles in subjects without disease were 0.9868(0.9810-0.9892) and 0.9333(0.9010-0.9529), respectively, compared to 0.9929(0.9901-0.9952) and 0.9082(0.8669-0.9398) in subjects with COPD ($p<0.001$ for both poles). Forced exhaled air can be used to expand understanding of the COPD. Moreover, the suggested parameterisation of the flow decline could be used to access COPD using spirometry.

1 INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is one of the major health challenges of the next decades. Currently it is 4th leading cause of death, while the World Health Organization anticipates that it will become the 3rd leading cause of death in less than 20 years from now (Mathers and Loncar 2006; Murray and Lopez 1997; WHO 2012). COPD is characterised by airflow limitation that is not fully reversible. It is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases, most often from cigarette smoke (Decramer et al. 2012). Up to almost one quarter of the adults aged 40 years and older may have mild airflow obstruction, according to the latest prevalence surveys (Mannino and Buist 2007). One of the challenges in such a disease is to identify patients at risk for brisk deterioration and to develop diagnostic tools which are directly clinically important (Agusti et al. 2010; Miravitlles et al. 2013).

Indications of COPD are production of sputum, signs of dyspnea, chronic cough or/and a history of exposure to the tobacco smoke (Rabe et al. 2007). However, the diagnosis itself is based on measuring differences in lung volume using a spirometer, as most common signs of COPD and patient history cannot accurately reflect COPD presence. Current diagnosis is simple and inexpensive to perform, but also lately debatable due to ability to overdiagnose or underdiagnose (Garcia-Rio et al. 2011). Various approaches have been developed to diagnose and characterize COPD, either by measuring volatile organic compounds in the exhaled air (Fens et al. 2009; Phillips et al. 2012), or by looking into

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computed tomography images (Bodduluri et al. 2013; Sorensen et al. 2012), or even by applying forced oscillation technique to stimulate respiratory system (Amaral et al. 2012). However, none of the techniques entered clinical practice, due to their complexity, costly undertaking or unsatisfactory results.

Surprisingly, mathematical data-based modelling was never performed when it comes to revealing background of COPD. Starting from that point and knowing that COPD, by its definition, is flow limited (Decramer, Janssens, & Miravitlles 2012; Dellaca et al. 2004) we hypothesized that modelling of the flow dynamics during exhalation may offer a more precise indication of COPD presence. This should lead to better understanding of the COPD and additional tool for diagnosis.

In the present study our objective was firstly to develop a mathematical data-based model for the decline of the forced expiratory flow. Secondly, to investigate how the parameters from the model are linked with COPD presence and its severity.

2 METHODS

2.1 Study Population

This study included data of 474 individuals who had performed complete pulmonary function testing (PFT) at cohort entry, including post-bronchodilator spirometry, body plethysmography and diffusing capacity. All included subjects were tested between October 2007 and January 2009 at the University Hospital of Leuven (Belgium), as described earlier (Lambrechts et al. 2010; Wauters et al. 2011). Briefly, participants were all current or former heavy smokers with at least 15 pack-years and with minimal age of 50 years. As COPD is smoking disease *per se*, restricting our study to only smoking individuals increased chances to observe more abnormal pulmonary functions and patients with higher risk for COPD. Individuals with suspicion or diagnosis of asthma were excluded, as well as patients with exacerbations due to COPD within last 6 weeks and patients with other respiratory diseases. The study was approved by the local ethical committee of the University Hospital Leuven, (KU Leuven, Belgium). All patients included in the study provided informed consent. The study design of the LEUVEN COPD cohort can be found on www.clinicaltrials.gov (NCT00858520).

According to the international COPD GOLD guidelines (Rabe et al. 2007), patients with COPD were identified when the post-bronchodilator FEV1/FVC ratio was <0.7, furthermore they were lined over different severity stages. The population consisted of 336 patients with diagnosed COPD comparing to 138 healthy controls. Stratified for disease severity from mild (GOLD I) to moderate (GOLD II), severe (GOLD III) and very severe (GOLD IV), the COPD population was comprised of 77, 101, 97 and 61 patients respectively. Table 1 describes the population characteristics within two separate groups, revealing typical characteristics for smoking and demographics of COPD patients admitted in hospitals.

2.2 Pulmonary Function Tests

All pulmonary function tests were performed with standardized equipment (Masterlab, Erich Jeager, Würzburg, Germany) by experienced respiratory technicians, according to the ATS/ERS guidelines (Miller et al. 2005). Spirometry data are post-bronchodilator measures and expressed as percent predicted of normal reference values (Quanjer et al. 1994).

Table 1: Study population characteristics; Values are median and IQR; BMI = body mass index; M = male; F = female; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; M = male; %pred. = percent predicted of normal reference values.

	Healthy	COPD
Patients, N	138	336
Sex, M/F	110/28	260/76
Age, years	60.7(57.3– 64.6)	65.1(59.5– 72.1)
Smoking, pack yr.	38.0(29.3– 52.0)	45.0(32.6– 60.0)
BMI, kg/m^2	26.4(24.0– 28.7)	25.0(22– 28)
FEV_1, %pred.	104.0(94–112)	53.0(35– 78)
FVC, %pred.	108.0(100–118)	89.0(71– 106)
FEV_1/FVC	0.75(0.73– 0.78)	0.47(0.37– 0.62)

2.3 Data based Modelling

To develop our data-based model we used MATLAB (7.14, The MathWorks, Natick, Massachusetts) and compatible toolbox for non-stationary time series analysis, system identification, signal processing and forecasting – CAPTAIN toolbox (Taylor et al. 2007). In all individuals the best expiratory curve (rule of highest sum of FEV1 and FVC (Miller et al. 2005)) within one spirometry was exported from the Masterlab system at a sampling rate of 125Hz. By extracting data points it was possible to reconstruct the best expiratory

manoeuvre in MATLAB. To observe the dynamics of the expiration, only the declining phase of expiration was analysed. Declining is the area that starts at peak flow and ends at the end of the expiration, far right tail (Figure 1).

When starting with data-based modelling, the appropriate model structure is determined using objective methods of time series analysis from a generic model class. The goal is to describe the data in a parametrically efficient way, but still having simplicity in the sense of model parameters and model order. Considering our study and our data, most appropriate model was a discrete-time transfer function (TF) model for a single input single output (SISO) system. The general form of such system is:

$$y_t = \frac{B(L)}{A(L)} u_t + \xi_t, \quad (1)$$

where y_t is the output; u_t is the input; ξ_t is additive noise, assumed to be zero mean; L is the backward shift operator; A(L) and B(L) are polynomials defined by the order of the model in the following form:

$$A(L) = 1 + a_1 L + \cdots + a_n L^n \quad (2)$$

$$B(L) = b_0 + b_1 L + \cdots + b_m L^m \quad (3)$$

where n represents the order of the system: a_1, …, a_n and b_0, b_1, …, b_m are the TF denominator and numerator parameters, respectively.

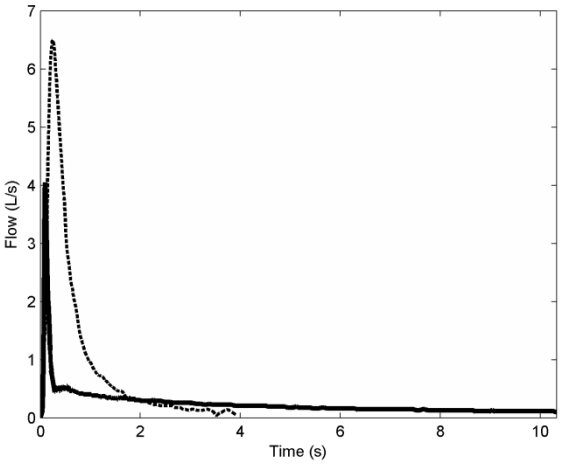

Figure 1: Two examples of expiratory manoeuvres; Solid line represents expiratory flow of an individual with diagnosed very severe COPD, while dashed line represents expiratory flow of a healthy individual. Decline is considered the section when the flow starts dropping from its maximum back to its minimum, over time.

Once the input-output data are available, TF parameters (Eq. (2) and (3)) can be identified using statistical procedures. For the input data, we used step-down for each model, while output signal was original measurements obtained from spirometry. The parameters of a TF model can be estimated using various methods of identification and estimation procedures (Ljung L. 1987; Young PC. 1984). In this study the Simplified Refined Instrumental Variable (SRIV) algorithm was used as a method for model identification. The advantage of SRIV lays not only in yielding consistent estimates of the parameters, but also in exhibiting close to optimum performance in the model order reduction context (Figure 2).

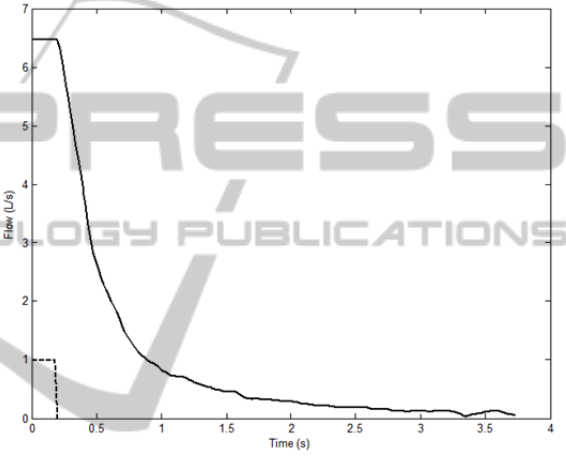

Figure 2: Step down (dashed line) used for each model as input signal; Solid line represents an example of declination, meaning output signal (different for each individual). We assumed that the time-series of the output had a constant value (first 10 data samples) then the drop started, it was also point for the step-down of the input. Based on these two signals SRIV estimates TF parameters.

An equally important problem to the parameter estimation is the identification of the objective model order which will result in low complexity. The process of model order identification can be performed by the use of well-chosen mathematical measures which indicate the presence of over parameterization. Often used successful identification procedure to select the most appropriate model structure is based on the minimisation of the Young identification criterion, (YIC) (Young 1981) (Eq. (4)).

$$YIC = \ln \frac{\hat{\sigma}^2}{\sigma_y^2} + \ln \left(\frac{1}{np} \sum_{i=1}^{np} \frac{\hat{\sigma}^2 \hat{p}_{ii}}{\hat{a}_i^2} \right) \quad (4)$$

where $\hat{\sigma}^2$ is the sample variance of the model residuals; σ_y^2 is the sample variance of the measured

system output about its mean value; np is the total number of model parameters; $\hat{a}_i^2$ is the square of the i-th element in the parameter vector $\hat{a}$; $\hat{p}_{ii}$ is the i-th diagonal element of the inverse cross product matrix P(N); $\hat{\sigma}^2\hat{p}_{ii}$ can be considered as an approximate estimate of the variance of the estimated uncertainty on the i-th parameter estimate.

YIC is a heuristic statistical criterion which consists of two terms, as shown in Eq. (4). The first term provides a normalised measure of how well the model fits the original data: the smaller the variance of the model residuals, in relation to the variance of the measured output, the smaller this term becomes. The second term is a normalised measure of how well the model parameter estimates are defined. This term tends to become bigger when the model is over-parameterised and the parameter estimates are poorly defined. Consequently, the best model should minimise the YIC and provide a good compromise between goodness of fit and parametric efficiency.

Finally, upon passing all listed steps, derivation of additional parameters which describe exhaled airflow was feasible. Firstly, using an individual TF for each subject, we were able to derive poles of the model. These poles were direct representatives of the dynamics of the observed model. Secondly, the steady-state gain (SSG) of the model is also derived. SSG is the ratio of the output and the input of the model in steady state, and it is obtained by:

$$SSG = \frac{\Delta y}{\Delta u} = \frac{\sum_{i=1}^{n_b} b_i}{1 + \sum_{i=1}^{n_a} a_i} \quad (5)$$

3 RESULTS

Using the already explained YIC, we discovered that the most appropriate model would be a second-order model. Looking into complete dataset, second-order model explains data with a YIC of -14.5 (-15.7 – -13.1) and R_T^2 of 0.997 (0.994 – 0.998) (values are median and IQR). Confirmation of the good model order identification is presented in Figure 3, where the original output signal with the simulated one is compared using the estimated parameters from second-order model.

In total, analysis was performed employing two poles (coming from second-order model) and SSG of the model from 423 individuals. From the included 474 individuals, 51 (=10.8%) had to be excluded, where 32 (=6.8%) due to missing data from the PFT and 19 (=4%) due to model instability.

More detailed investigation of poles of the model, meaning the dynamics of the airflow exhalation, resulted in clear difference when comparing subjects with and without COPD (see figure 4). Certainly, first pole was higher when COPD was present, indicating that the system starts faster when disease occurs. Median (IQR) poles in subjects without disease were 0.9868 (0.9810-0.9892) and 0.9333 (0.9010-0.9529), respectively, compared to 0.9929 (0.9901-0.9952) and 0.9082 (0.8669-0.9398) in subjects with COPD ($p<0.0001$ for first pole and $p<0.001$ for second pole). Stratifying for disease severity, same shift in poles with disease progression was noticed (Figure 5). This pointed that the dynamics of the system become faster with higher severity. Median poles were 0.9895 and 0.9346 for GOLD 1, 0.9916 and 0.9160 for GOLD 2, 0.9946 and 0.9009 for GOLD 3 and finally for GOLD 4 0.9959 and 0.8615.

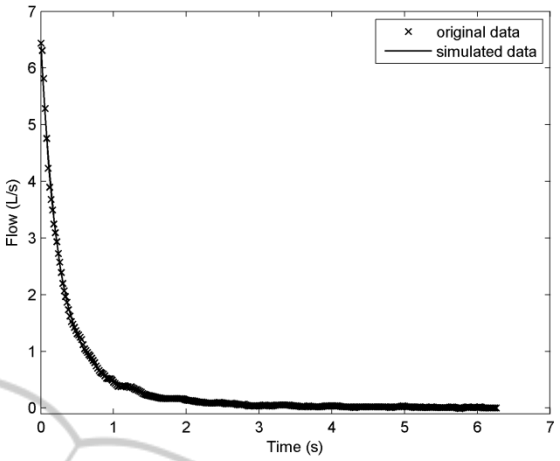

Figure 3: No difference between the original (marked with x) and the simulated (solid line) output signal is noticed (R_T^2 = 0.999, YIC = -17.6091) when using second-order model.

When focusing the analysis on the SSG of the model, similar conclusions as the ones with poles can be made. Median (IQR) SSG in subjects with COPD was significantly lower 3.9 (2.7-5.6) compared to 8.2 (7.1-9.3) in subjects without COPD, ($p<0.0001$). When disintegrating over severity of COPD, SSG decreased significantly ($p<0.0001$) with each GOLD stage: 6.8 (5.7-7.8), 5.0 (3.9-5.7), 3.1 (2.6-3.7) and 2.3 (1.7-2.8), respectively (Figure 6). This is manifested due to lower flow change that occurs when lungs are obstructive compared to healthy lungs.

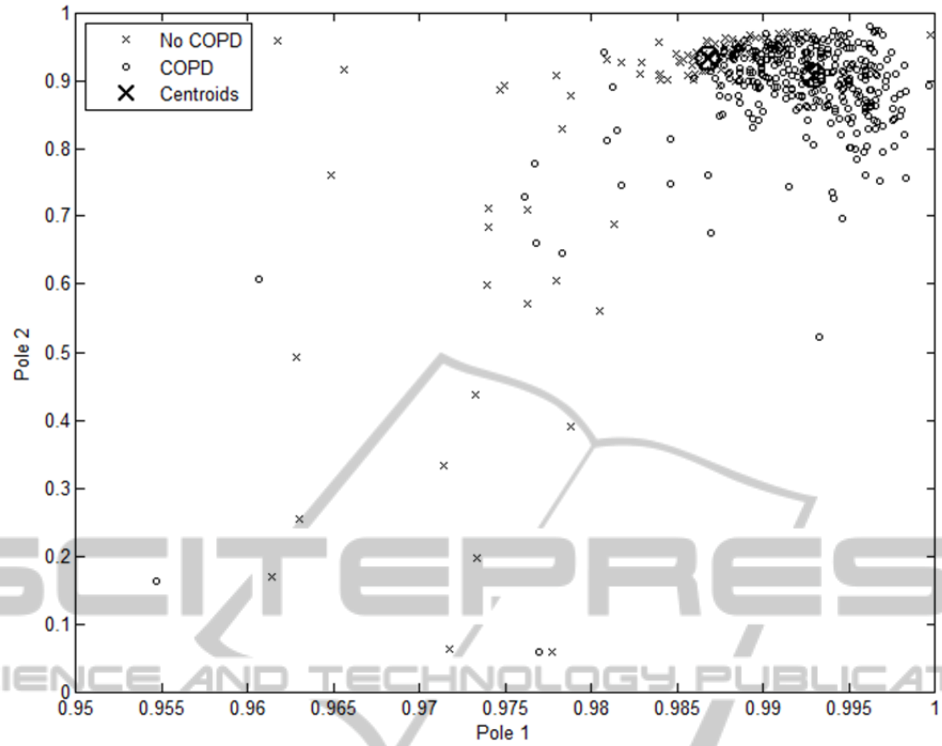

Figure 4: Pole distribution within two observed groups, with centroids pointing the median value of each group.

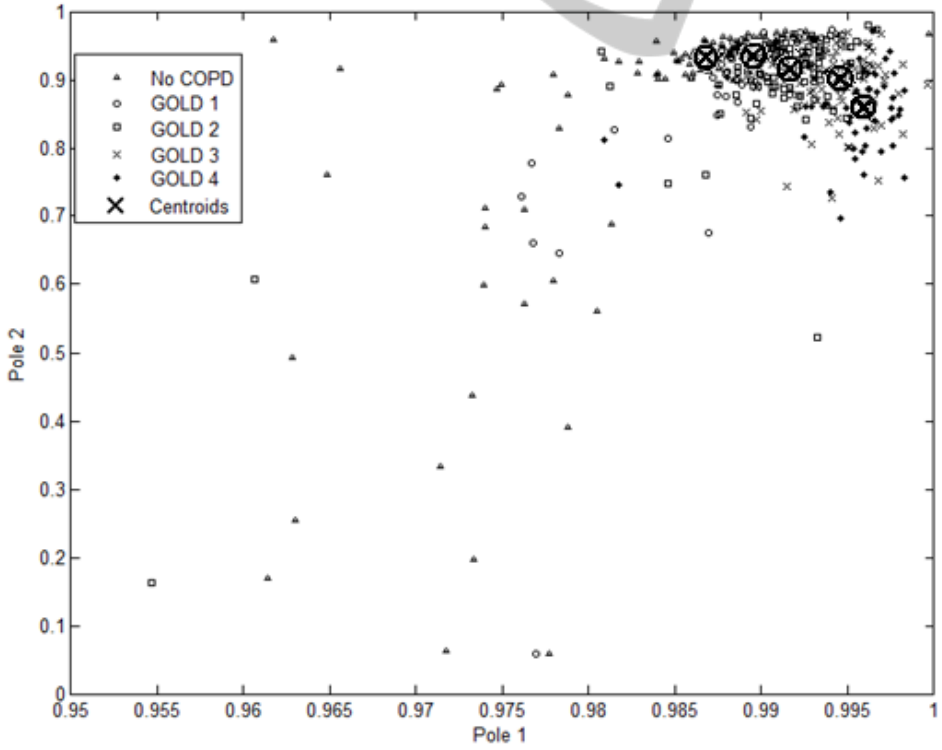

Figure 5: Distribution of poles when stratified for COPD severity (GOLD stages). Dynamics are faster with increase of severity. Centroids indicate median values of each GOLD stage. We see movement of centroids from left to right, in the order: from no COPD over each growing GOLD stage.

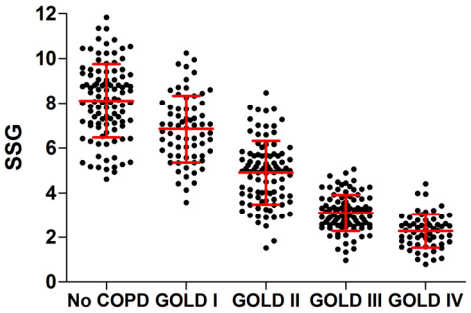

Figure 6: Decrease of SSG with each GOLD stage.

4 CONCLUSIONS

Our study demonstrates that chronic obstructive pulmonary disease observed at forced expiration can be described by a second order data based model, whereas model parameters relate very well with the presence and severity of COPD. Our method confirms that COPD is indeed a flow limited disease, and in certain way raise a question whether future diagnostic for COPD should go back to its basis, its definition, and take flow values at examination.

To the best of our knowledge, our study is the first to validate the concept of COPD-associated airflow dynamics in larger group of individuals comprising COPD patients of all severity stages, as well as smoking controls. In our population, we found that poles and steady state gain match well with severity of COPD. Interestingly, the estimated model resulted in significantly lower steady state gain within each severity stage. Moreover steady state gain was significantly different comparing to the healthy cases. This undoubtedly confirms that obstructive lungs are having much more difficulties to exhale flow and therefore, exhale it in much lower speed.

The concept we are introducing opens new opportunities for research in the field of respiratory mechanism and respiratory diseases. In general, by using airflow dynamics, with this study we provided additional explanation of COPD behaviour. We see that they anticipate that the faster dynamics of the system are probability to notice presence of COPD will increase. Moreover, with increase of dynamics, the severity stages of COPD are also increasing. This probably means that bigger obstruction of lungs cause decreased exhalation of air which results in faster emptying of the lungs (faster dynamics of the exhalation). Various reasons influence such occurrence, firstly it is common to observe airway narrowing or airway collapse to cause suddenly diminished airflow (Healy et al. 1984). Furthermore, in COPD, the greatest reduction in air flow occurs during expiration, as the pressure in the chest tends to compress rather than expand the airways (Koulouris and Hardavella 2011). One would assume that loss of lung tissue elasticity, typical for emphysematous type of COPD, plays additional role in accelerating exhalation dynamics, as it might be the case that lungs get faster its limits while exhaling (Papandrinopoulou et al. 2012).

When comparing with the other alternative approaches, advantage is that parameters obtained from model-based method can have physiological validity. Further, when used with routine spirometry during patient examination, this method is *de facto* simplest, fastest and cheapest to perform.

Additional strength of this study is the fact that observing dynamics of the flow decay represents same approach that many researchers had performed in the past, but based only on a visual basis of typical patterns (Bass 1973; Jayamanne et al. 1980). Today routinely, clinicians are capable to presume presence of Chronic Obstructive Pulmonary Disease, on the basis of visual assessment of flow decay, whereas with this study we offer more precise and automated way of inspection. Furthermore, we believe that the concept which we are introducing, is easy to understand and linked to physiological behaviour of the lungs. Moreover, we believe that extra value of this study comes from the study cohort itself. All patients are heavy smokers older than 50 years, meaning that they are all labelled as having risk of COPD, consequently inducing bigger challenge to distinguish between diseased and not diseased.

Finally, our method failed to provide valid measurements in 4% of the cases. This occurrence is inevitable, as we tried to automatize process where data selection and estimation algorithm are not always the optimal ones. Certainly, this could be avoided in most of the cases, if ensuring that exhalation ends with plateau (having stable ending).

Taken together, our data provide strong evidence that dynamics of the forced exhaled air can be used to get elevated understanding of the chronic obstructive pulmonary disease. Moreover, if characterized like in our model, flow decline can be used to access Chronic Obstructive Pulmonary Disease by spirometry.

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