ORIGINAL ARTICLE

Contributions of signal analysis to the interpretation of spirometry

Anogeianaki A[1,2], Negrev N[1], Ilonidis G[2]

1. Department of Physiology, Medical University of Varna, Bulgaria
2. 4th Department of Medicine, Hippokration Hospital, Faculty of Medicine, Thessaloniki, Greece

Abstract

Aim: Chronic Obstructive Pulmonary Disease (COPD) is taking on catastrophic proportions. However, there is still a need for more objective and quantitative methods for its diagnosis and stratification. The present study explores the effectiveness of signal analysis methodologies as the means to increase the effectiveness of spirometry in diagnosing and stratifying COPD.
Methods: Since expiratory flow at the mouth results from converging airflows, it is possible to use signal analysis to identify changes in the characteristics of airflow along the respiratory tree. This was achieved by non-invasively identifying alterations in the frequency spectrum of the Forced Expiratory Flow (FEF) curve of 108 patients (49 men and 59 women, 12–75 yrs of age) presenting with (a) clinically and spirometrically normal respiratory profile, (b) COPD, (c) restrictive lung disease and (d) interstitial fibrosis. Fundamental to the study design was the notion that the characteristics of the expiratory output of the respiratory system are determined by the bronchial tree and the upper respiratory tract
Results: A number of quantitative measures for the power spectrum of the FEF curve were identified, which permit the definition of specific rules and allow for the accurate classification of, at least, the basic types of respiratory disease.
Conclusions: (a) It is for the first time that airflow resonances are identified in the sub-audible (< 20 Hz) range of the power spectrum of the FEF curve. (b) COPD patients present with FEF curves which have different power spectral characteristics from those of healthy individuals ($p < 0.01$), at frequencies lower than 3.66 Hz. (c) In COPD, in restrictive lung disease and in interstitial fibrosis, the lower resonant frequencies of the spectrum of the FEF curve predominate. *Hippokratia 2007; 11 (4): 187-195*

Key words: *pulmonary disease, spirometry, chronic obstrunctive pulmonary disease, sugnal analysis, forced expitatory flow*

Corresponding author: Anogeianaki A, Department of Experimental Physiology, Faculty of Medicine, Aristotle University of Thessaloniki, 54124 Thessaloniki, Greece, e-mail: antonia@med.auth.gr

COPD is a leading cause of morbidity and mortality that will influence the economics of health long into the foreseeable future. By 2020 it will become the third leading cause of death all over the world, with immense direct and indirect costs[1]. Still, not only we do not know how many people have COPD but the number may be much larger than we think (2). In fact, prevalence estimates vary with the WHO estimate of 0.8% differing from what is reported in the 32 different data sources reviewed by Halbert, RJ et al[2] by as much as 20-fold. The main reason for this state of affairs is attributable to the different statistical qualifications of the populations studied, to the differences in the criteria used to define COPD and to the lack of a standard method for diagnosing COPD. Spirometry, for example, is performed by non-uniform methodologies while the threshold for deducing the presence of COPD is variously defined. In addition, clinical criteria such as the presence, intensity and persistence of coughing, cannot be easily monitored or quantified. Therefore, more objective, quantitative, ways are needed, for the diagnosis, evaluation and stratification of, both, COPD and therapeutic outcomes[3-11]. The present study attempts to utilize spirometry for estimating lung dysfunction by applying signal analysis techniques in its interpretation.

Relevant facts from the Ontogeny, Anatomy and Physiology of the Lungs: The interpretation of spirometry is based on good knowledge of lung architecture, ontogeny and respiratory physiology. Ochs M et al[12], have shown that mean alveolar number is 480 million (range: 274 to 790 million) and that the total alveolar number is closely related to total lung volume. It is estimated that the total alveolar surface area is 70 to 120 square meters, or about 70 times greater than body surface area and that the alveolar surface area correlates positively with metabolic rate regardless of body size, whereas lung volume correlates positively with the height of the individual.

There are three distinct types of conducting pathways: Cartilaginous (trachea and bronchi), membranous (bronchioles) and terminal respiratory units (respiratory bronchioles and alveolar structures or acinus). Trachea represents the 0eth generation of airway branching while gas exchange normally takes place after the 15th generation of branching. As one moves away from the trachea, the airway diameter decreases with each new generation while, correspondingly, the total cross-sectional area increases. This led to the assumption that the velocity of airflow decreases at each consecutive order of branching and therefore airflow remains linear.

The terminal respiratory unit represents the functional unit of the lung. The distinguishing feature of the terminal respiratory unit is the presence of alveoli. Like the membranous conducting airways, structural support for the terminal respiratory unit arises from the connective tissue framework of the lung. The alveoli line the walls of

both the respiratory bronchioles and alveolar ducts, both of which are perfused with pulmonary capillary blood. In general, both respiratory bronchioles and alveolar ducts give off 2 to 5 generations of daughter branches before they empty into an atrium consisting of one to three dome-shaped alveolar sacs.

Respiratory Oscillatory Phenomena: The respiratory system is a collection of physical components interacting with one another and with the environment. The simplest model of the complex respiratory system is that of a single balloon, attached to a pipe. This gross oversimplification, allows for physical concepts to be utilized in the analysis of the respiratory system: The relationship, for example, between the pressure applied at the opening of the model and its volume, during emptying of this balloon, can be described as a first order model. Using regression analysis one can calculate the elastance (i.e., the tendency of the lung to recoil toward its original dimensions upon removal of the distending or compressing force) and the resistance of the airways.

When air flows at high velocities, especially through an airway with irregular walls, flow is normally disorganized, even chaotic, and tends to form eddies. This is called turbulent flow, and is found mainly in the largest airways, like the trachea.

Given the characteristics of flows described above, it has been traditionally assumed that during quiet breathing, laminar flow exists from the medium-sized bronchi down to the level of the bronchioles, or that during exercise or during a forced exhalation manoeuvre, when the air flow is more rapid, laminar flow will be confined to the smallest airways.

Transitional flow, which has some of the characteristics of both laminar and turbulent flow, is also found along the bronchial tree. In fact, the idea that a transition zone exists between airways characterized by laminar flow and those characterized by turbulent flow, has been the basis for introducing the Peak Expiratory Flow (PEF) in the assessment of COPD[13-20].

Expiratory flows are limited throughout most of the forced expiratory manoeuvre[21-23]. Above a certain level of expiratory effort, expiratory flow is independent of the applied pleural pressure while the driving pressure for air flow is exclusively due to the elastic recoil pressure. This, in combination with turbulence, brings up the phenomenon of closure of the small airways which may be due to the operation of a "Starling resistor" (Figure 1) or, alternatively, to the phenomenon of wavespeed limitation on the expiratory flow[24]. In this respect, Dawson SV and Elliott EA[24] point out that maximum expiratory flow

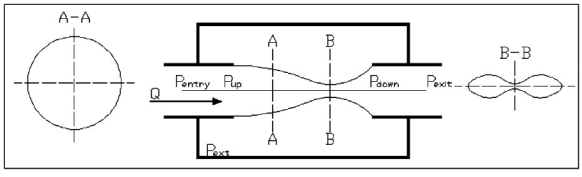

Figure 1. *The operation of the Starling resistor*

-volume (MEFV) curves are easily reproducible for any given subject because, beyond a critical level of effort, the flow is independent of pleural pressure, which is a measure of the effort expended by the chest wall.

The closure of the airways has been experimentally studied by many authors who typically use the experimental paradigm of the Starling resistor[25] as the basis of their analyses (Figure 1). The experiment exhibits many of the same characteristics as lung airways: Inside a pressure chamber (pressure p_{ext}) that represents the lung parenchyma surrounding a bronchial airway, a thin elastic tube of length L, undeformed internal radius R and wall thickness h is mounted between two rigid tubes. Air flows through the tube at a steady flow rate. The flow can be controlled either by the flow rate Q or by the pressure drop $p_{entry} - p_{exit}$ that is applied between the two ends of the rigid tube. If p_{ext} sufficiently exceeds the air pressure inside the tube, then the tube buckles. Two distinct cases can be observed: (a) When $p_{up} - p_{down}$ increases while $p_{up} - p_{ext}$ is kept constant then a maximal flow rate Q will be eventually reached, and (b) When the flow rate Q increases while $p_{up} - p_{ext}$ is kept constant, $p_{up} - p_{down}$ will eventually reach a limit. At sufficiently large Reynolds numbers, the system readily produces self-excited oscillations[26-27]

In a manner similar to the Starling resistor described above, during forced expiration flow-related frictional and convective accelerative intrabronchial pressure losses occur. At some point along the airways from the alveoli to the mouth, the flow-related pressure losses will equal the lung elastic recoil pressure and the difference between the intrabronchial and extrabronchial pressures will be zero. This point is called the equal pressure point (EPP). Downstream (towards the mouth) from the EPP, the airways are compressed by the pressure surrounding the airway wall which will be greater than the decreasing intrabronchial pressure, thus leading to dynamic compression of the airway lumen. Beyond the point where closure of the small airways limits expiration, the lungs can only become smaller by direct compression of gas (Boyle's law) by further action of the expiratory muscles. At this point, the amount of air left in the lung is designated Residual Volume (RV). RV increases in chronic bronchitis and in emphysema. Conversely, if the lungs are stiffer, the increased tension in the lung tissue holds the airways open with closure occurring later in expiration, thus reducing the RV. In summary, stiff lungs from fibrosis cause a low Total Lung Capacity (TLC) and low RV, emphysema causes a high TLC and a high RV and chronic bronchitis causes a high RV. Vital capacity (VC) depends on the relative changes in RV and TLC but usually the overall effect in lung disease is a reduction in VC.

There are many models that portray the different conditions under which oscillatory behavior may arise from the flow of fluids through tubes[28-34]. These models confirm that lung wheezes are caused by flow limitation in collapsed airways[35]. However, although spectral analysis is a very efficient way to analyze oscillatory phenomena, it has found very limited use in the analysis of pulmonary function. A

first attempt, for example, by Michaelson ED et al[36], detected small differences in magnitude of the spectral components between non-smokers and smokers. Siegelova J et al[37] also studied the periodic oscillations of breathing pattern parameters in 34 healthy subjects by computing autocorrelation functions and power spectral density from three minute resting spirometric records. Sullivan KJ et al[38] utilized a method similar to that of Michaelson ED et al[36] to partition the variations observed in pressure into separate lung and chest wall components. They evaluated the mechanical impedance of each component in the range of 4 to 40 Hz using cross and power spectral analysis and spectral averaging. Beydon L et al[39], like Sullivan KJ et al[38], used spectral analysis on pulmonary volume measurements during high-frequency jet ventilation in anesthetized man to assess the validity of indirect spirometry during conventional intermittent positive-pressure ventilation and high-frequency jet ventilation. Finally, Frey U et al[40] systematically relied upon spectral analysis to show that the frequency spectra of the flow amplitudes between 0.13 and 10 Hz followed a power law whose exponent did not significantly change with age in healthy infants or infants with a history of wheezing disorders but it was significantly lower in infants with chronic lung disease. Frey U[41] also used spectral analysis to deal with airway diameter and airway wall compliance as important determinants of flow limitation and wheezing in infants[24,42].

Classical Spirometry and Spectral Analysis of the Spirogram: Because the lung has a very large reserve capacity, measurement of either the PO_2 or PCO_2 in the blood is not an adequate measure of lung transport and regulatory efficiency. As a result, the lung can sustain considerable damage before blood gases, and therefore the body tissues themselves, are affected. For this reason, a number of other ways of estimating lung function have been developed in an attempt to identify deterioration in lung function before it affects tissue function. These tests are based on measurement of static lung volumes, on measurement of ventilation or dynamic lung volumes and on the determination of gas exchange across the alveolar–capillary membrane. Our study concentrated on the first two of these types, since its purpose was to improve the usefulness of an already available methodology (FVC manoeuvre) and to expand its capability to provide physiological explanations for phenomena of lung dysfunction.

Pulmonary function tests can, collectively, differentiate between obstructive, restrictive and mixed obstructive / restrictive pathology. However, they do not give a good explanation of the origin of oscillatory phenomena (wheezes, crackles etc) which are not only very common but, also, they are very useful in clinical medicine. Spectral analysis, on the other hand, is a very efficient way to analyze oscillatory phenomena, but has found very limited use in the analysis of pulmonary function and, then, only in very specific situations. Therefore, spectral analysis can be viewed as a necessary complement to the classical spirometric methodologies, especially when we have to differentiate between fixed from variable airway obstruction and to differentiate between central (intra- or extra-thoracic) and peripheral obstruction.

The two techniques that provide a link between pulmonary function tests and spectral analysis are Pneumotachography and Maximum Expiratory Flow Volume (MEFV) measurements.Pneumotachography is the recording of the gas flow with respect to time and it represents the first derivative of the expired gas volume with respect to time. The spirogram can be deduced from the pneumotachogram by integration and, vice versa, the pneumotachogram can be deduced from the spirogram by differentiation. The Maximum Forced Expiratory Flow (MEF_{max}) occurs in less than 0.1 second and in healthy adults it amounts to 10-15 liters per second.

MEFV measurements are considered the best way to explore the mechanical properties of the lung parenchyma and airways while its shape is determined by the variable site of the flow limiting segment. During forced expiration the flow limiting site is normally located in the central intra-thoracic airways[43-45], especially the lobar and segmental airways[46-48] and does not move beyond the subsegmental airways[49].

In general, pulmonary function tests can detect the presence of pulmonary functional abnormalities, quantify their degree and follow the time course of disease can differentiate between obstructive, restrictive and mixed obstructive/restrictive pathology, can differentiate between fixed and variable airway obstruction as well as between central and peripheral obstruction, can help in the evaluation of the presence and degree of increased airway responsiveness, can help in the assessment of the risk of therapeutic or diagnostic interventions and monitor the effects of therapy and can contribute to an accurate prognosis of disease and disability.

Conclusions from Reviewing the Literature - Objectives and Tasks: The objective of the present study is to apply signal analysis on spirometry to better estimate lung dysfunction, through an alternative interpretation of its results. This entails testing the validity of the claim that the Fourier Transform (FT) of the derivative of the FVC curve can be used to identify COPD and, at the same time, differentiate it from other common pulmonary pathologies, as well as establishing a link between the potential findings from using the FT of the first derivative of the FVC curve (which is equivalent to the FEF curve) and the findings of classical spirometry for the cases of restrictive and obstructive pulmonary disease. To do this, one has to non-invasively measure the frequency spectrum of expiratory flow, keeping in mind that the respiratory system, despite the complexity of its air conducting components (i.e., the bronchial tree), can be adequately described in terms of a "source - filter" model whereby the source and the filter are joined together by a Starling resistor. This task, therefore, translates into identifying the frequencies that are generated by the onset and the operation of the Starling resistor phenomenon in the lungs during forced expiration[50-53]. They also have to base their findings on well established methodologies (spirometry) and on classical indices used to interpret spirometry.

Subjects and Methods

Selection Procedure: We carefully generated and collected spirometric records of 108 serially presenting patients (49 men and 59 women, 12–75 yrs of age), from a series of 138 patients who regularly visited the 4th Department of Medicine's outpatient respiratory unit at the Hippokrateion Hospital in Thessaloniki, Greece. Patients were properly informed about the research protocol and their permission was obtained to enrol them in the test population. Data collection was done according to the guidelines issued by the Hippokrateion Hospital ethics committee. Spirometry was carried out on all patients and along with the data regarding the different spirometric indices, the electronic form of the spirometric curve produced by the FVC manoeuvre was obtained and digitally stored for off line processing. Four groups of patients were sought: (a) Patients with no diminution of their predicted pulmonary function who were classified, both clinically and on the basis of spirometry, as normal. (b) Patients with COPD. (c) Patients with restrictive lung disease and (d) patients with interstitial fibrosis disease. Details concerning the age, gender and physical characteristics of the subjects, including information on their smoking habits, are given in Table 1 and Table 2.

Reaffirming the suitability of the patients: Tests were performed at the outpatient clinic. Patients that were pregnant, obese or presented with an enlarged stomach were excluded. Excluded were, also, patients who recently had chest pains or a heart attack, who were on medication for a lung problem, who had used medication that expands the lungs' airways within 4 hours of the test, who had smoked or exercised strenuously for 6 hours before the test, who used sedatives or who were not able to breathe normally because of pain. Particular care was exercised to ensure that patients were not restrained by their clothing and those who wore dentures were asked to wear them during the test to help them form a tight seal around the mouthpiece of the spirometer.

Description of procedures and precautions taken during spirometry: During measurement of the vital capacity (VC) what corresponds to "Slow Vital Capacity" (SVC) in the Anglo-American literature was first measured. Following SVC determination our subjects were instructed to perform the same manoeuvre with maximal force in order to determine their FVC. The procedures used complied with the recommendations of the European Respiratory Society[54,55]. Subjects that could not produce reproducible curves were not included in our sample since they did not meet the requirements for reproducibility[56,57].

Separating Obstructive from Restrictive Disease: There

Table 1. *Details concerning the subjects of the study*

	Number	Age range (yrs)	Mean age (yrs)	SDV age	Median age (yrs)	Mean height (cm)	SDV height	Median height (cm)
Healthy males	21	17 – 69	41.95	15.72	43	174.86	8.46	175
Non-healthy males	28	24 - 83	58.22	16.53	60	168.96	8.46	170
All males	49	17 - 83	51.11	17.97	51.5	171.54	8.88	170
Healthy females	31	18 - 73	44.73	15.83	44	161.43	5.44	160
Non-healthy females	28	12 - 80	55.96	15.28	60.5	159.36	7.06	160
All females	59	12 - 80	50.16	16.44	53.5	160.43	6.31	160
All subjects	108	12 - 83	50.59	17.07	52.5	165.46	9.37	165

Table 2. *Details concerning the smoking habits of the subjects of the study*

	Number	Age range (yrs)	Mean age (yrs)	SDV age	Median age (yrs)	Cigarette - years	SDV Cigarette - years
Healthy males non smokers	14	17 - 69	36.43	15.48	40	-	-
Healthy males smokers	7	41 - 65	53	9.45	56	31.25	12.60
Non-healthy males non smokers	7	24 - 59	44.83	12.25	47	-	-
Non-healthy males smokers	21	24 - 75	62.05	15.80	69	40.55	25.87
All males non smokers	21	17 - 69	38.95	14.80	42	-	-
All males smokers	28	24 - 83	59.79	14.85	62.5	38.22	23.41
Healthy females non smokers	28	18 - 73	45.48	16.02	46	-	-
Healthy females smokers	3	28 - 55	38	14.80	31	10	5
Non-healthy females non smokers	22	12 – 74	54.36	16.74	57.5	-	-
Non-healthy females smokers	6	55 - 69	61.83	5.67	61	31.67	9.31
All females non smokers	50	12 - 74	49.47	16.78	52	-	-
All females smokers	9	28 - 69	53.89	14.73	59	24.44	13.33
All subjects non smokers	71	12 - 80	46.42	16.82	46	-	-
All subjects smokers	37	24 - 83	58.35	14.84	61	34.87	22.05

are two main types of lung disease that can be found with lung function tests: obstructive and restrictive. The identification and separation of patients into obstructive or restrictive cases were done on the basis of Table 3. Further grouping was done on the basis of clinical picture and non spirometric tests.

Table 3. *Lung function values*
(Result as predicted for age, height, sex, weight, or race)

Lung function test	Obstructive disease	Restrictive disease
FVC	Normal or ? than predicted value	Lower than predicted value
FEV_1	Lower with higher FEV_2 and FEV_3	Normal or lower with higher FEV_2 and FEV_3
FEV_1 / FVC	Lower	Normal or higher
FEF 25% - 75%	Lower	Normal or lower
PEF	Lower	Normal or higher
Maximum voluntary ventilation (MVV)	Lower	Normal or lower
SVC	Normal or lower	Lower
TLC	Normal or higher	Lower
FRC	Higher	Normal or higher
RV	Higher	Normal or higher
Expiratory Reserve Volume (ERV)	Normal or lower	Normal or lower
RV / TLC	Higher	Normal or higher

Test equipment: Respiratory volumes were measured using the Spirolite® 363 which features real time graphics, simultaneously displaying the flow/volume loop and the volume/time curve allowing for immediate review. The analog signal was converted to digital values at a sampling rate of 155 Hz. Volume and flow calibrations were made daily with a calibrated syringe selectable from 1 to 9 litres at ATPS. Daily calibration was performed on days testing was performed. Flow and volume resolution and frequency response were tested, and found to be well within the guidelines of the American Thoracic Society (ATS, 1987). Parametric data i.e. FEV1, FVC, Forced mid-Expiratory Flow (FEF25–75%), FEF when 25, 50 and 75% of FVC has been exhaled (FEF25, 50, & 75%) and FEV1/FVC were calculated from the best effort, and stored for further analysis, together with a graphic display of the flow volume curve. The parametric data were analysed as percentage of predicted[58].

Data analysis: Data analysis and recording of parameters were exclusively performed on a portable 3 GHz IBM PC equipped with Windows XP professional Service Pack 2 operating system and the Matlab® software package. In order to proceed with data analysis, the FVC curves had first to be converted into FEF curves. This was achieved through differentiation, i.e., by digitally subtracting the value of each time instant of the curve (volume at a given instant) from the next. In this way the curve that resulted was a "flow-velocity at a given instant" curve, expressed in units of "volume differences"/"time differences". Power spectra of the FEF curves were calculated using a Fast Fourier Transform (FFT) of the full FEF curve augmented to 10 sec by zero padding. Data processing included data filtering (Hanning Filter), data "zero – padding" to achieve uniform spectral resolution and smoothing of the power spectrum curve by a "running average filter" with length 5 points (low pass filter). The Mean Squared Error (MSE) measure was used to explore the deviation of the FT, for each condition studied, from the Mean Normal FT Vector (MNFTV) which was constructed on the basis of the FEF curves of the 52 healthy individuals. In order to test the hypothesis that different curves (obtained through the averaging of the FT transformations of the forced expiratory curves) statistically differed among themselves, a Student-t test was performed between the sets of measurements (points on the curves that are obtained from patients with one pathology which represent the same frequency) that gave rise to each average curve. Due to the interpolation procedure used, all the curves representing the different pathologies have 15401 points (each representing a different frequency) but these reduce to 155 unique and distinct frequency components where the Student-t test can be applied (the rest are repetitions). Therefore, the testing for statistical difference between two conditions involves 155 Student-t tests, i.e., one for each frequency component that each FT transform contains. This procedure is justified by the fact that the unique and distinct frequency components of the FT transform are "orthogonal" to each other, i.e., they are by definition statistically independent. Therefore, in comparing two different curves (obtained through the averaging of the FT transformations of the forced expiratory curves) that reflect different pathologies, one does not only decide if there are statistically significant differences between the two conditions but they also identify the frequency components where the differences exist! The null hypothesis was that the two curves being tested each time were the same. The results were plotted as fluctuations of the significance of the difference, while the significance level for p was set at 0.01 before a particular frequency component was identified as important for deciding a patient's classification. In all the following pairs of curves were tested: (a) normal vs. restrictive, (b) normal vs. interstitial fibrosis, (c) normal vs. obstructive, (d) restrictive vs. obstructive, (e) interstitial fibrosis vs. obstructive and (f) restrictive vs. interstitial Fibrosis

Results

The average (population) spectra for (a) healthy subjects, (b) COPD patients, (c) patients with restrictive lung disease and (d) patients with interstitial fibrosis are presented in Figure 2. The MSE of each of the FT components for every patient presenting with each of these conditions was calculated, with respect to the average value of their corresponding FT components of the 52 healthy individuals (Table 4). In addition, the Student t-test was used to show that every one of the FT components of every pathophysiologically distinct population were different from those corresponding to the other populations. From these calculations it became evident that the ability of the method to differentiate among the different conditions on the basis of FT alone, to a high degree of statisti-

Table 4. *Exploring the deviation of the FEF amplitude spectrum from MNFTV for each condition studied*

	Mean of MSE	STD of MSE
HEALTHY SUBJECTS	75.8214	91.9909 (121.3%)
COPD	321.2428	222.4441 (69.2%)
RESTRICTIVE LUNG DISEASE	312.3215	259.4052 (83.1%)
INTERSTITIAL FIBROSIS	174.5190	163.3868 (93.6%)

cal significance, is remarkable. Indeed, when comparing the statistical significance profile of the different spectral analysis results, one can identify characteristic differences among them. Thus:

(a) All frequency components of the power spectrum of the FEF curve of COPD patients below 3.66 Hz differ from those of healthy individuals ($p < 0.01$). However, the frequency components of the power spectrum of the FEF curve of patients with interstitial fibrosis or of patients with restrictive lung disease are not statistically different than the corresponding components for healthy individuals.

(b) The frequency components of the power spectrum of the FEF curve of patients with restrictive lung disease below 4.14 Hz differ from those of healthy individuals ($p < 0.01$).

(c) The frequency components of the power spectrum of the FEF curve of patients with restrictive lung disease between 7.13 and 8Hz differ from those of COPD patients ($p < 0.01$).

(d) When comparing patients with restrictive lung disease and patients with interstitial fibrosis we find that the frequency components between 3.34 Hz and 3.66 Hz and the frequency components at 3.98 Hz and 4.13 Hz, differ between the two groups ($0.001 < p < 0.01$).

(e) The analysis of the spectra themselves shows that in COPD, in restrictive lung disease and in interstitial fibrosis, the lower resonant frequencies predominate. In COPD spectral peaks are equispaced along the spectrum, while in restrictive lung disease and in interstitial fibrosis they present with a "double peak" pattern and they cover a narrower range of frequencies than in COPD (Figure 2).

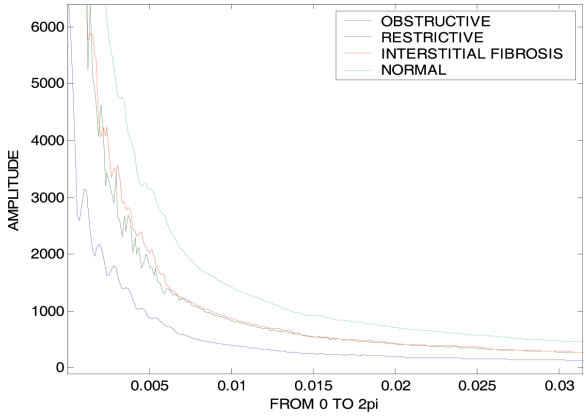

Figure 2. *Comparison of the average amplitude spectra of the FEF curve of normal subjects and of patients with respiratory disease*

Discussion

As mentioned, the MSE for each of the FT components and for every patient presenting with one of the three conditions reported above, were calculated, with respect to the average value of their corresponding FT components of the 52 healthy individuals. The results from this initial investigation indicated that while for healthy subjects mean MSE (measured in arbitrary units) was 75.8214 and its standard deviation (STD) was 91.9909, in the case of COPD the corresponding numbers were 321.2428 and 222.4441 respectively. Similarly, for Restrictive Lung Disease the corresponding numbers were 312.3215 and 259.4052 and for Interstitial Fibrosis 174.5190 and 163.3868 respectively (see Table 4 and Figure 2). Visual inspection of the results shows that, in the case of healthy individuals, the curve enveloping all successive FT components is rather smooth. However, it is highly rugged in the case of COPD. Furthermore, despite the fact that the amplitudes of the spectral components in the case of Restrictive Lung Disease are only slightly different than the spectral components of Interstitial Fibrosis, the "roughness" of the spectral envelope, in Restrictive Lung Disease is very similar to that for COPD while in the case of Interstitial Fibrosis the spectral envelope is much smoother.

The findings reported agree with the findings of Pedersen OF et al[59] who observed that alveolar pressure continues to increase after PEF is achieved, suggesting flow limitation somewhere in the airways of their subjects. This led them to the conclusion that closure occurs in central airways at PEF in most subjects, but they could not exclude that closure also occurs in more peripheral airways. The implications of these findings for the present study are very substantial, in that they indicate that there are positions in the peripheral airways, of not only the asthmatic but also of normal subjects where closure of the airways occurs. In addition, they point out that the shape of the (alveolar pressure driven) flow curves means that the intervening length of the airway (between the point of closure and the mouth) is acting as a pipe instrument, without interfering with the continuity of flow through it. The work of Pedersen OF et al[59] also supports the notion that a mechanism of closure induces the airways to vibrate resulting in the resonance phenomena that can be identified through spectral analysis of the FEF curve. It is therefore feasible, based on the statistical significance of the spectral components of the FEF curve, to utilize the FT of the FEF curve as an index for the classification of chronic lung disease as it is summarized in Figure 3.

From a structural point of view, the maximal flows that can be conveyed through airways are related not only to diameter, but airway wall compliance[24], something that has been demonstrated in vitro on immature animals[60,61]. Still, there is a lot of uncertainty as to whether high compliance of airway walls holds in vivo. Neither is it certain that the strength of the airway-parenchyma attachment of human infants and the relationship between lung and

Groups Compared	Frequency
	a b c d e
Normal - COPD	0000000000000000000000xx0xxxxxxxxxxxxxxxxxx000000x
Normal – Interstitial Fibrosis	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Normal – Restrictive Disease	x0000000000000000000000000xxxxxxxxxx000xxxxxxxxxx
COPD - Interstitial Fibrosis	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
COPD - Restrictive Disease	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
Interst. Fibr. – Restr. Disease	xxxxxxxxxxxxxxxxxxx000x00xxxxxxxxxxxxxxxxxxxxxxxx
a = 0.155 Hz; b = 1.550 Hz; c = 3.100 Hz; d = 4.650Hz; e = 6.200 Hz	
"x" indicates that the specific band is not statistically significant when comparing curves (spectra) from the pairs indicated on the left ($p > 0.01$); "0" indicates that the specific band is statistically significant when comparing curves (spectra) from the pairs indicated on the left ($p < 0.01$). Then: **0** & **0** = Frequencies where COPD is distinct from Normal ($p< 0.01$) **0** & **0** = Frequencies where Restrictive is distinct from Normal ($p< 0.01$); also **0** & **0** = Frequencies where Interstitial Fibrosis is distinct from Restrictive ($p< 0.01$)	

Figure 3. *Utilizing the FT of the FEF curve as an index for the classification of chronic lung disease*

chest wall compliance[62] is not different from what is observed during in vitro handling of animal tissue or during in vivo animal experiments.

Spectral analysis of the FEF curve in connection with the clinical assessment of the patients from whom they were recorded, suggests that it may be possible to differentiate between healthy individuals and patients with different pulmonary pathologies. This presents an advantage over interpretations that are based on models relying on assumptions about the high importance of compliance in determining air-flow[63] and it has important physiological, clinical and research implications since one can resort to drugs, such as bronchoconstrictors, to reduce the flow in the airways of the respiratory system. Furthermore, spectral analysis of the FEF curve affords a special, in vivo, insight into the complex interacting systems that determine air flow during maximal expiratory effort. However, any physiological interpretation of in vivo obtained results must be very cautious since it can only be undertaken by reference to simplified models. With this in mind we can take note that:

(a) As expected[59,64], in the very peripheral airways, air-flow velocity is significantly reduced, causing these distal airways to resonate at a lower frequency.

(b) Deviations from this pattern[65] can be explained by the strong influence of wall compliance on air-flow velocity and the resonant frequency of airways.

(c) Furthermore[59], it is the frequencies generated by vibrations set up by airflow velocity and airway compliance which induce resonance phenomena. These phenomena are represented in the spectrum of the FEF curve.

(d) Based on the arguments of Dawson SV and Elliott EA[24], we can hypothesize that anything that influences air-flow velocity affects the spectrum of the FEF curve and, therefore, we can resort to bronchoconstrictors in an attempt to evaluate the significance of airflow velocity and airway compliance on determining the resonant frequencies that are detected by spectral analysis of the FEF curve.

Conclusions

Our results demonstrate the feasibility of applying spectral analysis on the FEF curve in order to classify patients as well as clinical assessment does, at least as far as of the classification into healthy subjects, COPD patients, patients with restrictive lung disease and patients with interstitial fibrosis is concerned. However, investigation of the factors that determine airway patency and function is essential to the further improvement of our understanding of the impact of airway structure and function upon forced expiration.

The results presented show that:

(a) For the first time, airflow resonances were identified at the sub-audible (<20Hz) range of frequencies in the power spectrum of the FEF curve.

(b) All frequency components of the power spectrum of the FEF curve of COPD patients were examined and those lower than 3.66 Hz were shown to be statistically different than those of healthy individuals ($p < 0.01$).

(c) In COPD, in restrictive lung disease and in interstitial fibrosis, the lower resonant frequencies of the spectrum of the FEF curve predominate.

It is hoped that these results can be used to further advance spirometry and, potentially, to aid in the planning of lung reduction surgery in COPD, a hope that did not exist when this thesis was conceived but which became apparent as it progressed, springing from the results obtained.

References

1. Viegi G, Pedreschi M, Pistelli F, et al. Prevalence of airways obstruction in a general population: European Respiratory Soci-

ety vs American Thoracic Society definition. Chest 2000; 117 (5 Suppl 2): 339S-45S
2. Halbert R J, Isonaka S, George D, Iqbal A. Interpreting COPD prevalence estimates: what is the true burden of disease? Chest 2003; 123:1684-1692
3. Krejci C S, Trent E J, Dubinsky T. Thoracic sonography. Respir Care 2001; 46:932-939
4. Que C, Kolmaga C, Durand L G, Kelly S M, Macklem P T. Phonospirometry for non-invasive measurement of ventilation: methodology and preliminary results. J Appl Physiol 2002; 93:1515-1526
5. Oud M. Lung function interpolation by means of neural-network-supported analysis of respiration sounds. Med Eng Phys 2003; 25:309-316
6. Allen G M, Shortall B P, Gemci T, Corcoran T E, Chigier N A. Computational simulations of airflow in an in vitro model of the pediatric upper airways. J Biomech Eng 2004; 126:604-613
7. Charleston-Villalobos S, Cortes-Rubiano S, Gonzalez-Camarena R, Chi-Lem G, Aljama-Corrales T. Respiratory acoustic thoracic imaging (RATHI): assessing deterministic interpolation techniques. Med Biol Eng Comput 2004; 42:618-626
8. Kandaswamy A, Kumar C S, Ramanathan R P, Jayaraman S, Malmurugan N. Neural classification of lung sounds using wavelet coefficients. Comput Biol Med 2004; 34:523-537
9. Murphy R L, Vyshedskiy A, Power-Charnitsky V A, et al. Automated lung sound analysis in patients with pneumonia. Respir Care 2004; 49:1490-1497
10. Van Hirtum A and Berckmans D. Objective recognition of cough sound as biomarker for aerial pollutants. Indoor Air 2004; 14:10-15
11. Thamrin C, Sly P D, Hantos Z. Broadband frequency dependence of respiratory impedance in rats. J Appl Physiol 2005; 99:1364-1371
12. Ochs M, Nyengaard J R, Jung A, Knudsen L, et al. The number of alveoli in the human lung. Am J Respir Crit Care Med 2004; 169 :120-4
13. Alencar A M, Buldyrev S V, Majumdar A, Stanley H E, Suki B. Avalanche dynamics of crackle sound in the lung. Phys Rev Lett 2001; 87:088101
14. Elad D, Soffer G, Zaretsky U, Wolf M, Shiner R J Time-frequency analysis of breathing signals: in vitro airway model. Technol Health Care 2001; 9:269-280
15. Hall G L, Hantos Z, Sly P D. Altered respiratory tissue mechanics in asymptomatic wheezy infants. Am J Respir Crit Care Med 2001; 164:1387-1391
16. Harper P, Kraman S S, Pasterkamp H, Wodicka G R. An acoustic model of the respiratory tract. IEEE Trans Biomed Eng 2001; 48:543-550
17. Saarinen A H, Rihkanen H, Malmberg L P, Pekkanen L, Sovijarvi A R. Disturbances in airflow dynamics and tracheal sounds during forced and quiet breathing in subjects with unilateral vocal fold paralysis. Clin Physiol 2001; 21:712-717
18. Broersen P M T and de Waele S. Detection of methacholine with time series models of lung sounds. IEEE Trans Instr and Measur 2000; 49:517-523
19. Oud M, Dooijes E H, van der Zee J S. Asthmatic airways obstruction assessment based on detailed analysis of respiratory sound spectra. IEEE Trans Biomed Eng 2000; 47:1450-1455
20. Bauer T T, Merget R, Kollmeier J, Schultze-Werninghaus G. Forced expiratory wheezes in a patient with dynamic expiratory narrowing of central airways and an oscillating pattern of the flow- volume curve. Respiration 1999; 66:163-166
21. Fry D L, Ebert R V, Stead W W, Brown C C. The mechanics of pulmonary ventilation in normal subjects and patients with emphysema. Am J Med 1954; 16: 89-97
22. Fry D L and Hyatt R. Pulmonary mechanics. A unified analysis of the relationship between pressure, volume and gas flow in the lungs of normal and diseased human subjects. Am J Med 1960; 29: 672-689
23. Hyatt R, Schilder D, Fry D L. Relationship between maximal expiratory flow and degree of lung inflation. J Appl Physiol 1958; 13: 331-336
24. Dawson S V and Elliott E A. Wave-speed limitation on expiratory flow-a unifying concept. J Appl Physiol 1977; 43:498-515
25. Massiot O. Modelling flow-induced collapse in human airways. Thesis. University of Twente, Enschede, 2004; ISBN 90-365-2103-3
26. Luo X Y, Hinton J S, Liew T T, Tan K K. LES modelling of flow in a simple airway model. Med Eng Phys 2004; 26:403-413
27. Bertram C D, Raymond C J, Butcher K S. Oscillations in a collapsed-tube analog of the brachial artery under a sphygmomanometer cuff. J Biomech Eng 1989; 111:185-91
28. Campbell D M. Nonlinear dynamics of musical reed and brass wind instruments. Contemp Phys 1999; 40: 415
29. Pedley T J. The Fluid Mechanics of Large Blood Vessels, Chapter 6. Cambridge University Press, 1980
30. Cancelli C and Pedley T J. A separated-flow model for collapsible-tube oscillations. J Fluid Mech 1985; 157:375
31. Pedley T J. Longitudinal tension variation in collapsible channels: a new mechanism for the breakdown of steady flow. ASME J Biomech Eng 1992; 114:60
32. Story B H, Titze I R. Voice simulation with body cover model of the vocal folds. J Acoust Soc Am 1995; 97:1249-1260
33. Hayashi S, Hayase T, Kawamura H. Numerical analysis for stability and self-excited oscillation in collapsible tube flow. ASME J Biomech Eng 1998; 120:468
34. Kounanis K and Mathioulakis D S. Experimental flow study within a self oscillating collapsible tube. J Fluids Struct 1999; 13:61
35. Grotberg J B and Gavriely N. Flutter in collapsible tubes: a theoretical model of wheezes, J Appl Physiol 1989; 66:2262
36. Michaelson E D, Grassman E D, Peters W R. Pulmonary mechanics by spectral analysis of forced random noise. J Clin Invest 1975; 56:1210-30
37. Siegelova J and Kopecny J. Spectral analysis of breathing pattern in man. Physiol Bohemoslov 1985; 34:321-331
38. Sullivan K J, Durand M, Ye T H, Chang H K. Evaluation of lung mechanics in rabbits using short duration flow pulses. Am Rev Respir Dis 1989; 140:17-24
39. Beydon L, Bourgain J L, Benlabed M, Bourgain L. Pulmonary volume measurements during high-frequency jet ventilation in anesthetized man. Crit Care Med 1990; 18:1102-1106
40. Frey U, Silverman M, Suki B. Analysis of the harmonic content of the tidal flow waveforms in infants. J Appl Physiol 2001; 91:1687-1693
41. Frey U. Why are infants prone to wheezing? Swiss Med Wkly 2001; 131:400-406
42. Bertram CD. Flow phenomena in floppy tubes Contemporary Physics 2004; 45: 45-60
43. Smaldone G C and Bergofsky E H. Delineation of flow-limiting segment and predicted airway resistance by movable catheter. J Appl Physiol 1976; 40: 943-952
44. Hyatt R E, Wilson T A, Bar-Yishay E. Prediction of maximal expiratory flow in excised human lungs. J Appl Physiol: Respir Environ Exerc Physio 1980; l48: 991-998
45. Mink S N and Wood L D. How does HeO2 increase maximum expiratory flow in human lungs? J Clin Invest 1980; 66: 720-729
46. Macklem P T and Wilson N J. Measurement of intrabronchial pressure in man. J Appl Physiol 1965; 20:653-663
47. Macklem P T. Airway obstruction and collateral ventilation. Physiol Rev 1976; 51: 368-436
48. Macklem P T, Thurlbeck W M, Fraser R G. Chronic obstructive disease of small airways. Ann Int Med 1971; 74: 167-177
49. Smaldone G C and Smith P L. Location of flow-limiting segments via airway catheters near residual volume in humans. J Appl Physiol 1985; 59: 502-505
50. Morris M J, Madgwick R G, Collyer I, Denby F, Lane D J.

Analysis of expiratory tidal flow patterns as a diagnostic tool in airflow obstruction Eur Respir J 1998; 12: 1113–1117
51. Lausted C G, Johnson A T. Respiratory resistance measured by an airflow perturbation device. Physiol Meas 1999; 20: 21-35
52. Oostveen E, MacLeod D, Lorino H, et al. The forced oscillation technique in clinical practice: methodology, recommendations and future developments Eur Respir J 2003; 22: 1026–1041
53. Lambert R K, Beck K C. Airway area distribution from the forced expiration maneuver J App Physiol 2004; 97: 570–578
54. Quanjer P H, Lebowitz M D, Gregg I, Miller M R, Pedersen O F. Peak expiratory flow. Conclusions and recommendations of a working party of the European Respiratory Society. Eur Respir J 1997; 10 (Suppl 24): 2S-8S
55. Miller M R, Crapo R, Hankinson J, et al. General considerations for lung functiontesting Eur Respir J 2005; 26: 153–161
56. Ferris B G. Health effects of exposure to low levels of regulated air pollutants. A critical review.J Air Pollut Control Assn 1978; 28: 482-489
57. Kanner R E, Renzetti A D, Stanish WM, Barkman H W , Klauber M R.. Predictors of survival in subjects with chronic airflow limitation. Am J Med 1983; 74:249-255
58. Quanjer PH. Standardised lung function testing. Report of a Working Party of the European Community for Coal and Steel. Bull Eur Physiopathol Respir 1983; 19 (Suppl. 5): 45–51
59. Pedersen O F, Brackel H J L, Bogaard J M, Kerrebijn K F. Wave-speed-determined flow limitation at peak flow in normal and asthmatic subjects. J Appl Physiol 1997; 83: 1721-1732
60. Shaffer T H, Bhutani V K, Wolfson M R, Penn R B, Tran N N. In vivo mechanical properties of the developing airway. Pediatr Res 1989; 25:143-146
61. Panitch H B, Deoras K S, Wolfson M R, Shaffer T . Maturational changes in airway smooth muscle structure-function relationships. Pediatr Res 1992; 31:151-156
62. Papastamelos C, Panitch H B, England S E, Allen J L. Developmental changes in chest wall compliance in infancy and early childhood. J Appl Physiol 1995; 78:179-184
63. Habib R H, Suki B, Bates J H, Jackson A C. Serial distribution of airway mechanical properties in dogs: effects of histamine. J Appl Physiol 1994; 77: 554-66
64. Jackson A C, Giurdanella C A, Dorkin H L. Density dependence of respiratory system impedances between 5 and 320 Hz in humans. J Appl Physiol 1989; 67: 2323–2330
65. Henschen M, Stocks J, Brookes I, Frey U. New aspects of airway mechanics in pre-term infants. Eur Respir J 2006; 27:913-920