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Interpretation of Spirometry through Signal Analysis

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Abstract

Chronic obstructive pulmonary disease is attaining alarming proportions that requires more objective and quantitative ways for the diagnosis and the evaluation / stratification of, both, the disease and the therapeutic outcomes. Within this context, the present study explores the possibility to increase the effectiveness of spirometry through signal analysis.

Expiratory flow results from converging airflows at different levels of airway branching. Furthermore, along a branching network of air conduits, the characteristics of converging air currents determine those of the resulting air flow. Thus, for the human bronchial tree, the characteristics of air currents within the smaller branches are, ideally, conserved at the expiratory flow recorded at the mouth. This makes it theoretically possible to use signal analysis methodologies in order to identify the characteristics of airflow along the different levels of the respiratory tree. The present study reports on an attempt to identify alterations non-invasively in the frequency spectrum of the first derivative of the Forced Vital Capacity curve of patients presenting with different respiratory conditions. Such alterations can be attributed to the onset and operation of the airway closure phenomenon that limits airflow, during forced expiration. Fundamental to the design of the study was the notion that the forced expiratory output of the respiratory system is determined by the bronchial tree and the upper respiratory tract. These two entities shape the air flow that is expelled from the collective airspace of the bronchial tree subdivisions distal to the terminal bronchi.

At the end we were able to identify simple measures that are derived from the power spectrum of the derivative of the spirometric curve that permit the definition of specific filters and allow for the accurate classification of, at least, the basic types of respiratory disease.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality with great implications for the economics of health of both industrialized and developing countries, long into the foreseeable future. In 2006, COPD became the number four cause of death (after cardiovascular disease, cancer and stroke) in the USA. Within the next fifteen years, it will become the third leading cause of death all over the world with an immense global economic impact on both individuals and society. In 1993, for example, in the USA alone, direct and indirect costs of COPD exceeded USD 24 billion (1).

According to Bandolier (http://www.jr2.ox.ac.uk/bandolier/band113/b113-3.html; last accessed on 1/4/2007), the question of ìhow many people have COPD?î is ìdeceptively simpleî. Not only we do not know the answer, but in all probabil-

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ity, the number is much larger than we think (2). In fact, prevalence estimates for COPD vary. The largest discrepancy is the one between the WHO expert opinion estimate (world prevalence of 0.8%), and those reported in the 32 different data sources reviewed by Halbert et al. (2). These sources put COPD prevalence at between 1% and 18%, with most of them estimating it between 3% and 10%. The main reason for this state of affairs is attributable to the fact that the populations studied were not identical in their statistical qualifications to differences in the criteria used to define COPD and to the fact that there is no standard method for diagnosing COPD.

Spirometry, on one hand, depends on non-uniform methodologies. These usually involve some relationship of the Forced Expiratory Volume in 1 sec (FEV_1) to Forced Vital Capacity (FVC). However, the threshold for deducing the presence of COPD is variously defined. On the other hand, 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.

Review of the Relevant Literature

Development, Dimensions and Anatomy of the Human Lungs

The interpretation of spirometry requires a good knowledge of the lung architecture and of the physiology of respiration, including the mechanical properties of lung tissue and the ontogeny of the lung. The latter because the development of the lung is a dynamic process that maximizes gas transfer over the airway ìpipes,î while minimizing the total lung volume.

During growth from child to adult, Total Lung Capacity (TLC) increases 10 - fold. The developmental increase in lung volume is attributable to the increase of the number of new alveoli, with new alveoli being formed either by ìalveolarizationî of respiratory bronchioles (up until 3 years of age) or by multiplication of existing ones (during the first 8 years after birth). Ochs et al. (12), through detailed, systematic and unbiased studies, have shown that mean alveolar number is 480 million (range: 274 to 790 million) while the total alveolar number is closely related to total lung volume. Furthermore, they have shown that the mean size of a single alveolus is rather constant and that the alveolar volume is 4.2×10^6 μm^3. This figure implies that, irrespective of lung size, a cubic millimetre of lung parenchyma contains about 170 alveoli and a total alveolar volume (lumen plus tissue) has a volume of approximately 2820 cubic centimetres. 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 it correlates positively with the metabolic rate (regardless of body size), whereas the lung volume correlates positively with the height of the individual.

The conducting airways branch rapidly and, after about 23 to 25 orders of branching, they terminate in the alveoli. The airways can be anatomically classified into three distinct types: The cartilaginous airways (trachea and bronchi), the membranous airways (bronchioles) and the terminal respiratory unit (respiratory bronchioles and alveolar structures or acinus). Although, in most cases, the airways branch symmetrically, significant branching asymmetries are also observed. Trachea represents the 0^{eth} generation of airway branching. The gas exchange level is reached in as few as 10 generations of branching, although gas exchange airways typically begin at about the 19th order of branching with the appearance of the respiratory bronchioles. 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 bronchioles typically begin after the eighth and before the thirteenth generation of airway branching. They are quite numerous but also short, with ever narrowing diameters. They constitute about 25% of the volume in the conducting airways. They are embedded in the connective tissue framework of the lung so that they are passively dilated during inspiration and passively narrowed during expiration.

The terminal respiratory unit represents the functional unit of the lung and it is the site of gas exchange with the pulmonary capillary blood. Its distinguishing feature is the presence of alveoli. Structurally, it is supported by the connective tissue framework of the lung. The alveoli line the walls of the respiratory bronchioles and alveolar ducts, both of which are perfused with pulmonary capillary blood and both of which generally split into 2 to 5 generations of daughter branches before they empty into an atrium consisting of one to three dome-shaped alveolar sacs.

The Basis of Respiratory Oscillatory Phenomena and their Analysis

The respiratory system is a collection of physical components interacting with one another and with the environment. The simplest model of the respiratory system, for example, 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 between the pressure applied at the opening of the model and the increase from the Functional Residual Capacity (FRC) volume (i.e. from the volume when the pressure at the non-attached end of the pipe is equal to atmospheric pressure), during emptying of the balloon, can be described by a first order equation which connects the elastance of the balloon, the resistance of the pipe and the flow through the opening. Elastance, which is the reciprocal of compliance, is a measure of the tendency of a hollow organ (the lung in this case) to recoil toward its original dimensions upon removal of a distending or compressing force.

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. The driving pressure required to sustain turbulent flow is proportional to the square of the flow rate.

In contrast, when flow is of low velocity and through narrow tubes, it tends to be more orderly and streamlined. This is called laminar flow and it is directly proportional to the pressure difference between two points (driving pressure), the length of the tube, the viscosity of the gas and the inverse of the fourth power of the radius of the tube. It has been traditionally assumed that during quiet breathing, laminar flow exists from the medium-sized bronchi down to the level of the bronchioles and 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 characteristics of both laminar and turbulent flow, occurs between the two. The idea of a transition zone between airways characterized by laminar flow and airways characterized by turbulent flow forms 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. During forced expiration, the driving pressure is determined by the sum of elastic lung recoil pressure and actively applied pleural pressure. Since the second is also applied to the airway walls it is only the elastic recoil pressure that allows pressure inside the airways to be higher than that outside the airways. This, in combination with turbulence, brings about the phenomenon of closure of the small airways which may be due to the operation of a ìStarling resistorî or, alternatively, to the phenomenon of wavespeed limitation on the expiratory flow (24). Thus, Dawson and Elliott (24) point out that maximum expiratory flow -volume (MEFV) curves are easily reproducible for any given subject because, beyond a critical level of effort, because flow is independent of pleural pressure.

The Starling resistor experimental paradigm for the closure of the airways (25) forms the basis for most relevant analyses (Figure 1). The experiment exhibits many of the same characteristics as lung airways: Inside a pressure chamber (pressure p_{ext}), which represents the lung parenchyma surrounding a bronchial airway, a thin elastic tube with given length, undeformed internal radius and wall thickness is mounted between two rigid tubes. Air flows through the tube at a steady flow

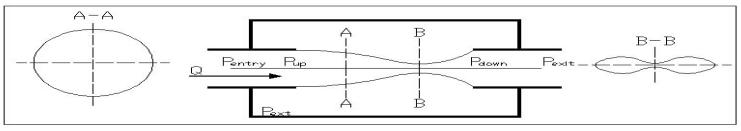

Figure1. The operation of the Starling resistor: Inside a pressure chamber (pressure p_{ext}), a thin elastic tube and undeformed internal diameter A-A is mounted between two rigid tubes. At the point where, flow-related pressure losses, result in an intratubular pressure smaller than p_{ext}, the elastic tube buckles. B – B is smallest diameter of the buckled tube. The flow along the elastic tube is determined by P_{entry} (the airway pressure at the point of entry which is equal to atmospheric in the case of the lung), P_{up} which is the pressure upstream from the buckling point, P_{down} which is the pressure downstream from the buckling point and P_{exit} which is the pressure at the point of exit.

rate. The flow can be controlled either by the flow rate Q or by the pressure drop p_{entry} ñ 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) If p_{up} ñ p_{down} increases while p_{up} ñ p_{ext} is kept constant then a maximal flow rate Q will be eventually reached.
(b) If the flow rate Q increases while p_{up} ñ p_{ext} is kept constant, p_{up} ñ p_{down} will eventually reach a limit. Finally, at sufficiently large Reynolds numbers, the system readily produces self-excited oscillations (26–27).

In a manner similar to the model 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 (Boyleís 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 (where the small airways are narrowed and inflamed) and in emphysema (where the elastic tissue supporting the small airways is lost and they collapse during expiration). Conversely, if the lungs are stiffer (fibrosis), 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 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.

In general, flow limitation in elastic tubes occurs at the speed at which the fluid in the tube propagates pressure waves which arise from the interaction of radial recoil force of the elastic wall of the tube and the axial inertial force of the fluid. Dawson and Elliott (24) however, note that the applicability of wavespeed limitation on the expiratory flow is limited because of the general lack of knowledge of the conditions that prevail at the choke point. Bertram et al (27), on the other hand, draw attention to three factors which play a role during forced expiration: The reduction of local pressure, the flow separation at the throat and the oscillatory phenomena which rely upon fluid inertia - both in the tube (to provide phase lag) and downstream (to set the oscillation frequency). These phenomena are similar to the ones produced by wind musical instruments (28).

Many models that attempt to describe how oscillatory behavior arises from the flow of fluids through tubes are of particular interest in pulmonary physiology

(29–34). These models affirm that lung wheezes indicate flow limitation in collapsed airways (35). Spectral analysis is a very efficient way to analyze oscillatory phenomena, but was scarcely used to describe pulmonary function and, then, only in very specific, limited situations. Michaelson et al (36), first detected small differences in magnitude of the spectral components between non-smokers and smokers as well as changes in the phase angle for the different spectral components when compliance is greater than the inertial reactance. Ten years later Siegelova et al (37) studied the periodic oscillations of breathing pattern parameters and report that the spectrogram of an individualís breathing pattern changes over a 2-year period. Sullivan et al (38) utilized a method similar to that of Michaelson et al (36), in the rabbit to conclude that the response of the respiratory system to short duration flow pulses may be used to evaluate pulmonary mechanical function, especially in uncooperative subjects like newborns and premature infants. Beydon et al (39) also used spectral analysis on pulmonary volume measurements during high-frequency jet ventilation in anesthetized man to conclude that indirect spirometry may measure tidal volume during intermittent positive-pressure ventilation and FRC changes during high-frequency jet ventilation, but it fails to measure tidal volume accurately during high-frequency jet ventilation. Finally, Frey et al (40) used 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 which was significantly lower in infants with chronic lung disease. Frey (41) also used spectral analysis to deal with airway diameter and airway compliance as important determinants of flow limitation and wheezing when measuring input impedance and anti-resonance phenomena in infants. Anti-resonance phenomena are related to the wave propagation velocity, i.e., the speed at which a small disturbance travels in a compliant tube filled with gas, (24, 42). They found that the frequency at which the first anti-resonance occurs is significantly lower in infants with wheezing disorders than in the control group, which implies that differences in airway wall compliance and developmental differences or alterations due to post-inflammatory remodelling, in airway wall mechanics, may be important in the pathogenesis of wheezing disorders.

Classical Spirometry and Spectral Analysis of the Spirogram

Because of the very large reserve capacity of the lung, blood PO_2 or PCO_2 are not adequate measures of pulmonary gas transport or regulatory efficiency. For this reason, other ways of estimating lung function have been developed 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 alveolarñcapillary membrane.

Static lung volume testing is based on the observation that when one attempts as deep an inspiration as possible a limit is eventually reached. This limit is due to the

resistance of the chest wall to further deformation and to our inability to stretch the lung tissues any further. The ìfoamyî nature of the lung ultrastructure means that, when the lung expands, the individual compartments of the lung will also expand, resulting in the enlargement of the lung ìair-spaceî. TLC is an accurate measure of the lung ìair-spaceî. It is, therefore, largely influenced by the stretch ability of the ìfoamyî ultrastructure of the lung or by the elasticity of the lung. The stiffer the lung is (i.e., the more difficult it is for the ìfoamyî ultrastructure of the lung to expand as it happens in fibrosis or lung parenchyma scarring), the less distensible it will be. On the other hand, damage to the elastic tissue of the lung (as in emphysema) will make it more distensible, leading to an increase in TLC. TLC also increases in some patients with asthma and chronic obstructive bronchitis. This is apparently due to compensatory mechanisms that force the lungs to overexpand in order to widen the airways.

Since breathing out from TLC is largely driven by the passive release of the energy that was previously stored in its distensible elements, it is reasonable to assume that the expiratory process will end at FRC or at the point where the tendency of the lung to contract is balanced by the thorax resisting further deformation. This point marks the end of a normal expiration. Further reduction of the lung ìair-spaceî and therefore further expiration, is only possible by the activation of the expiratory muscles. By maximally using the expiratory muscles, more air can be forced out of the lungs until, at least in older individuals, the phenomenon of closure of the small airways takes over and becomes the limiting factor in expiration. Most of the volume related measures can be determined by the different VC subdivisions while FEV_1 provides information about the intra-thoracic resistance to breathing, especially about the resistance in the small non-compressed airways, and is dependent on the elastic properties of the lung tissue and of the magnitude of the vital capacity.

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. Thus, the derivative of the volume-time curve is a measure of flow velocity. 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.

Maximum Expiratory Flow Volume (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 intrathoracic 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.

Finally, regarding their ability to differentiate between obstructive, restrictive and mixed obstructive/restrictive pathology, one must observe that an ìobstructive patternî is seen in asthma, chronic obstructive bronchitis and emphysema. In these cases FVC, FEV1 and FEV1% are all reduced while RV is increased. Furthermore, TLC is often reduced but is high in emphysema. On the other hand, a ìrestrictive patternî is seen in lung fibrosis in which case TLC, VC, FEV1 and RV are all reduced but FEV1% is normal or high. When other results do not give a clear pattern, RV can be very helpful, being high in airway obstruction and low in fibrosis. 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. Therefore, it can be viewed as a necessary complement to the classical spirometric methodologies, especially when we have to differentiate fixed from variable airway obstruction and between central (intra- or extra-thoracic) and peripheral obstruction. However, all efforts reported so far, have used spectral analysis as a tool to either correlate respiratory mechanics with other concomitant physiological activities (e.g., CNS activation) or to study collateral phenomena (e.g., wheezing) of respiratory pathophysiology.

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 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 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 ìsource – filterî 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

Subjects

Selection procedure

We carefully generated and collected spirometric records of 108 serially presenting patients (49 men and 59 women, 12ñ75 yrs of age), from a series of 138 patients who regularly visited the 4th Department of Medicineís outpatient respiratory unit at the Hippokrateion Hospital in Thessaloniki, Greece. Following routine examination and updating of their medical record, patients were 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. The whole procedure required approximately 30 min per subject.

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.

Informing the patient

Before starting, patients were informed about the test that was to follow and their informed consent was obtained. In the process they were informed that: (a) Lung function tests are usually painless but some of the tests may be tiring for people who have a lung disease. (b) They may cough or feel light-headed after breathing in or out rapidly but, in such a case, that they would be given a chance to rest between tests. (c) They may find it uncomfortable to wear the nose clip. (d) Breathing through the mouthpiece for a long period of time may be uncomfortable. (e) When

Table 1. Age and height characteristics of subjects. “n” = number of patients; “SD” = standard deviation; age is given in years; height is measured in cm.

	n	mean age ± SD (range)	mean height ± SD (range)
Healthy males	21	42.0±15.7 (17–69)	174.9±8.5 (162-198)
Non-healthy males	28	58.2±16.5 (24-83)	169.0±8.5 (150-186)
All males	49	51.1±18.0 (17-83)	171.5±8.9 (150-198)
Healthy females	31	44.7±15.8 (18-73)	161.4±5.4 (150-175)
Non-healthy females	28	56.0±15.3 (12-80)	159.4±7.1 (140-170)
All females	59	50.1±16.4 (12-80)	160.4±6.3 (140-175)
All subjects	108	50.6±17.1 (12-83)	165.5±9.4 (140-198)

Table 2. Details concerning the smoking habits of the subjects of the study. "n" = number of patients; "SD" = standard deviation; CY = cigarette-years; mean age is given in years.

	n	mean age±SD (range)	CY± SD
Healthy males non smokers	14	36.4±15.5 (17-69)	-
Healthy males smokers	7	53.0± 9.5 (41-65)	31.3±12.6
Non-healthy males non smokers	7	44.8±12.3 (24-59)	-
Non-healthy males smokers	21	62.1±15.8 (24-75)	40.6±25.8
All males non smokers	21	39.0±14.8 (17-69)	-
All males smokers	28	59.8±14.9 (24-83)	38.2±23.4
Healthy females non smokers	28	45.5±16.0 (18-73)	-
Healthy females smokers	3	38.0±14.8 (28-55)	10.0±5.0
Non-healthy females non smokers	22	54.4±16.7 (12-74)	-
Non-healthy females smokers	6	61.8± 5.7 (55-69)	31.7±9.3
All females non smokers	50	49.5±16.8 (12-74)	-
All females smokers	9	53.9±14.7 (28-69)	24.4±13.3
All subjects non smokers	71	46.4±16.8 (12-80)	-
All subjects smokers	37	58.4±14.8 (24-83)	34.9±22.1

given medication (those patients that consented to undergo a single shot methacholine challenge), it may cause them to shake or it may increase their heart rate. (f) If they feel any chest pain or discomfort, they must tell the doctor immediately.

For those patients that consented to undergo a methacholine challenge in addition to the above instructions, it was made clear that a single, minimal amount of methacholine was to be inhaled through the nebuliser. Before and after inhaling the substance, spirometry readings were taken to evaluate lung function. They were also informed that in rare cases, bronchospasm can occur with inhalation challenge testing. However, the patients were advised that they would be closely monitored during and after the test.

Methods

Reaffirming the suitability of the patients

Tests were performed at the outpatient clinic, where the test equipment was kept. Patients that were pregnant, obese or presented with an enlarged stomach were excluded. Before testing, the patients were asked if: (a) They recently had chest pains or a heart attack. (b) They take medication for a lung problem, such as asthma. Patients that had used medication that expands the lungs' airways within 4 hours of the test were not included in the sample. (c) They are allergic to any medications. (d) They had eaten a heavy meal just before this test because a full stomach may prevent the lungs from fully expanding. However, given that the outpatient clinic operates from 9:00 am to 12:00 noon, this was never the case. (e) They smoked or exercised strenuously for 6 hours before the test, but again, given the time frame of

the tests (morning) this was never found to be the case. (f) They used sedatives. Use of sedatives prior to the test was a reason for exclusion. (g) They were not able to breath normally because of pain. Along these lines, particular care was exercised in order to ensure that the patients were not restrained by their clothing since clothing may at times restrict breathing. (h) They wore dentures. If they did, they 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

Measurement of the vital capacity (VC) corresponds to measuring the volume change of the lung between a full inspiration and a maximal expiration. In our subjects the VC manoeuvre was initially performed rather slowly and the vital capacity was assessed during the expiratory manoeuvre. Starting from end-tidal volume our subjects were instructed to make a full inspiration and subsequently to exhale maximally. This represents the expiratory vital capacity or ìSlow Vital Capacityî (SVC) in the Anglo-American literature.

Following SVC determination our subjects were instructed to perform the same manoeuvre with maximal force in order to determine their FVC. In particular, our subjects were instructed to first fill their lungs to the fullest (i.e. to TLC), and then exhale forcefully and completely (to residual volume). In order to comply with the procedures recommended by the European Respiratory Society (54, 55), the following procedures were implemented during the determination of FVC: (a) the largest value of three technically satisfactory manoeuvres was reported. (b) Care was exercised so that the FVC reported did not differ by more than 150 mL from the next largest FVC. In the case where the FVC was 1.0 L or less, the FVC reported should not have differed by more than or 100 mL (55). (c) In case the above conditions could not be met and the difference continued to be larger than indicated after 6 manoeuvres were attempted, then the largest FVC was reported with a note that reproducible measurements could not be obtained. However, these subjects were not included in our sample since they did not meet the requirements for reproducibility (56, 57)

Separating Obstructive from Restrictive Disease

There are two main types of lung disease that can be found with lung function tests: obstructive and restrictive. In obstructive lung conditions, the airways are narrowed, usually causing an increase in the time it takes to empty the lungs. Obstructive lung disease can be caused by conditions such as emphysema, bronchitis, infection (which produces inflammation), and asthma. In restrictive lung conditions, there is a loss of lung tissue, a decrease in the lung's ability to expand, or a decrease in the lung's ability to transfer O_2 into the blood or CO_2 out of the blood. Restrictive lung disease can be caused by conditions such as pneumonia, lung cancer, scleroderma, pulmonary fibrosis, sarcoidosis, or multiple sclerosis. Other restrictive conditions include some chest injuries, being very overweight (obesity), pregnancy, and loss of lung tissue due to surgery. The identification and separation of patients into ob-

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 lower 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

structive 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.

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 internal thermal printer was used to review the curves, while data were also printed using an external printer through a standard Centronic connection. 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. Spirolite® 363 calibration reports print out automatically if printer is connected and is on-line. 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 (FEF25ñ75%), 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). In every test the following spirometric indices could be calculated:
(a) FVC
(b) FEV1
(c) FEV1/FVC

(d) FEF25-75%
(e) FEF75-85% or Late Expiratory Flow Rate
(f) FEF200-1200 or FEF between 200ml and 1200ml
(g) FEF50 or FEF at 50% of FVC
(h) PEF
(i) FIVC or Forced Inspiratory Vital Capacity
(j) FIF50 or Forced Inspiratory Flow at 50% of FVC
(k) FIF50/FEF50 or Ratio of FEF50 to FIF50
(l) PIF or Peak Inspiratory Flow

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 ìflow-velocity at a given instantî curve, expressed in units of ìvolume differencesî/ìtime differencesî.

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 ìzero ñ paddingî to achieve uniform spectral resolution and smoothing of the power spectrum curve by a ìrunning averageî filterî 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 ìorthogonalî 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 whether 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 patientís 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. In particular, the investigation of the MSE for each of the FT components and for every patient indicated that, in healthy

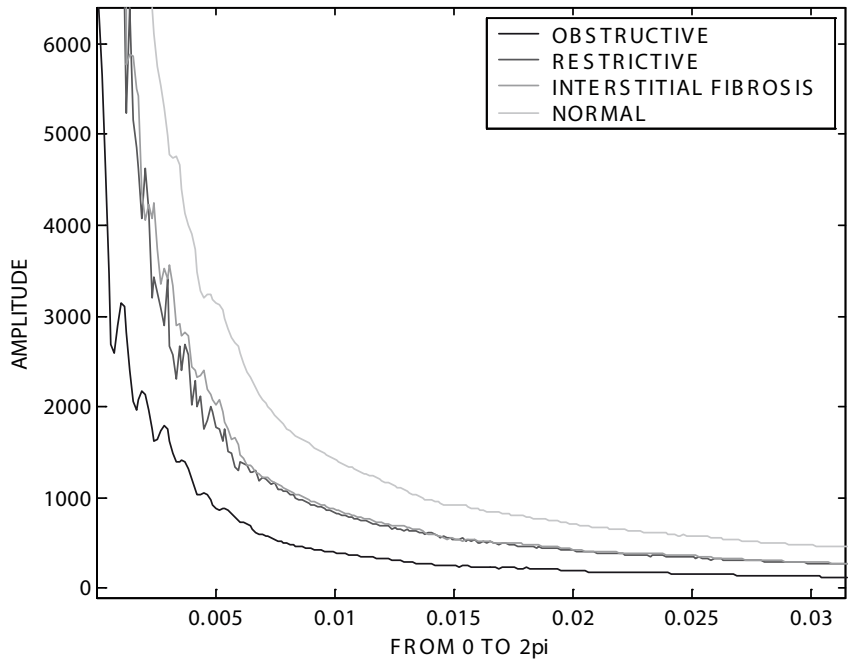

Figure 2. Comparison of the average amplitude spectra of the first derivative of the FVC curve of normal subjects and of patients with respiratory disease.

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%)

subjects, mean MSE (measured in arbitrary units) was 75.8214 and its standard deviation (STD) was 91.9909, while in 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. Figure 2 shows that, in healthy individuals, the curve enveloping all successive FT components is rather smooth, while it is highly rugged in COPD. Furthermore, despite the fact that the amplitudes of the spectral components in the case of Restrictive Lung Disease are only slightly different from the spectral components of Interstitial Fibrosis, the ìroughnessî 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.

These results, make it evident that the ability of the method to differentiate among the different conditions on the basis of FT alone, to a high degree of statistical 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 first derivative of the FVC 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 first derivative of the FVC curve of patients with interstitial fibrosis or of patients with restrictive lung disease are not statistically different from the corresponding components for healthy individuals.
(b) The frequency components of the power spectrum of the first derivative of the FVC 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 first derivative of the FVC 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 ìdouble peakî pattern and they cover a narrower range of frequencies than in COPD.

With regard to this last point, what becomes evident is that the early range of the average spectrum for the 52 healthy individuals shows three distinct but very small ìbumpsî (resonances) at 0.824 Hz, 1.168 Hz and 3.823 Hz (Figure 2). If, on the other hand, we examine the same range of the average spectrum for the 21 COPD patients, we will notice that a much more clear and distinctive pattern of characteristic resonances emerges at 0.253 Hz, 0.465 Hz, 0,691 Hz, 0.877 Hz, 1.097 Hz, and 1.319 Hz. What is more important, is that the COPD pattern shows a distinctive shift to the left, i.e., lower resonant frequencies predominate while the COPD pattern shows a rather equispaced placement of the resonance frequencies along the spectrum, i.e., the difference between the smallest and the largest observed distances (in Hz) between two successive resonances, is only 18.8% of the mean interval (distance) between two successive resonances. In contrast, when one examines the same range of the average spectrum for the 17 patients with restrictive lung disease and the 18 patients with interstitial fibrosis, we find that the distinctive shift to the left (i.e., to lower resonant frequencies) that characterized the COPD pattern when compared to that for healthy subjects is still present. This means that the lower resonant frequencies also predominate. However, in this case the appearance of ìdouble peaksî and the placement pattern that does not cover as wide a range of frequencies as in COPD (0.339 to 1.167 Hz for restrictive lung disease and 0.345 to 1.088 Hz for interstitial fibrosis versus 0.253 to 1.319 Hz for COPD).

Discussion

The results from the investigation of the MSE for each of the FT components and for every patient agree with the findings of Pedersen et al (59) who observed that alveolar pressure continued to increase after PEF is achieved, and concluded that, in most subjects, closure of the airways at PEF occurs in central airways, without excluding the possibility that closure may also occur in more peripheral airways. In terms of the present study this indicates that there are positions in the peripheral airways, not only of 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 indicates that the 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. This assertion means that points of closure that are established at PEF are detectable. Thus, the work of Pedersen et al (59) supports the notion that a mechanism of closure of the airways would also induce the airways to vibrate resulting in the resonance phenomena that can be identified through spectral analysis of the first derivative of the FVC curve. According to the basic theory of sound production in pipes, the frequencies which are generated by such vibrations,

so long as they fit exactly into the path from the vibration generator to the mouth, will be inducing resonance phenomena and they will be represented in the spectrum of the first derivative of the FVC curve. In addition, they will have a longer wavelength and therefore a lower frequency.

It is therefore feasible to utilize the FT of the FEF curve as an index for the classification of chronic lung disease if the following simple rules are followed:

(a) The power spectrum of the first derivative of the FVC curve at less than 0.3 Hz and between 1.2 Hz and 3.2 Hz should help distinguish normal subjects from COPD or restrictive lung disease patients.
(b) The power spectrum of the FEF curve between 3.8 Hz and 4.3 Hz should help distinguish normal subjects from patients with restrictive lung disease while excluding patients with COPD or interstitial fibrosis.
(c) The power spectrum of the FEF curve between 3.2 Hz and 3.8 Hz should help distinguish patients with restrictive lung disease from those with interstitial fibrosis.
(d) Finally, the appearance of peaks at the power spectrum of the first derivative of the FVC curve at less than 0.3 Hz and between 1.2 Hz and 1.5 Hz should help distinguish COPD patients from those with either restrictive lung disease or interstitial fibrosis.

The results demonstrate the feasibility of using spectral analysis to classify patients, at least as far as the classification into healthy subjects, COPD patients, patients with restrictive lung disease and patients with interstitial fibrosis is concerned. 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), as demonstrated in vitro for immature animals (60, 61). However, it is not certain if 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 chest wall compliance (62) is similar to what is observed during in vitro handling of animal tissue or during in vivo animal experiments. Therefore, the role of the structural and functional interactions that determine air flow during maximal expiratory effort can only be estimated in vivo.

On the other hand, the physiological interpretation of in vivo obtained results has to be very cautious since it can only be accomplished by reference to simplified models. For example, at higher frequencies, we have to assume that pressure waves, transmitted through the respiratory airways, follow the physical laws of acoustics. Thus, for a rigid straight tube of large diameter, the wave propagation velocity (v) corresponds to the first harmonic resonant frequency, a measure comparable to what we perceive as the sound pitch in a flute. The frequency of the wave is dependent on wave speed, which, in turn, depends on the gas density and the length of the rigid tube. In a branching network of compliant small tubes (such as the airways) the frequency at which this resonance will occur, will still be dependent on v, which will no longer depend on just the length of the airway and the gas

density, but also on the airway wall compliance and to airway diameter (for very small tubes). In the terminal airways of human adults the diameter is < 1 mm, and v is 62% of the free-field speed of sound (63). This means that in very peripheral airways, v is significantly reduced causing them to resonate at lower frequencies. Finally, the contribution of airway wall compliance may also be large since it influences v, and therefore influences the resonant frequency of compliant airways. In this respect, Henschen et al (64) present a clear clinical indication that maximal air flows through compliant tubes are related to v. Since the maximal flow in a compliant tube is the product of velocity and tube area (24), we can hypothesize that the ability of airways to carry large flows is influenced by airway path length, airway wall compliance and the frequency of the travelling pressure waves. Anything that influences these parameters will have an effect on the spectrum of the forced expiratory flow. However, one should also take into account that since the relationship between these parameters is highly non-linear (65 ñ 70), further analysis will be necessary to, hopefully separate the individual influence of each of these parameters.

Spectral analysis allows for physiological speculation as to what is the nature of the processes that characterizes each pattern. This is an advantage over interpretations based on assumptions about the high importance of compliance in determining air-flow (70) and models which derive from morphological data or published animal models. It also 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. In fact it points out to the necessity of resorting to the second step of the research reported here: To analyse, through spectral analysis methodologies the spirometric curves of patients with pulmonary disease, under methacholine challenge. With this in mind we can take note that:

(a) In very peripheral airways, air-flow velocity should be significantly reduced, causing these distal airways to resonate at a lower frequency (59, 63), as indicated by the data presented here.
(b) Deviations from this pattern, such as those reported by Henschen et al (64), can be explained by the strong influence that airway wall compliance has on air-flow velocity and on the resonant frequency of compliant airways.
(c) The frequencies generated by vibrations set up by airflow velocity and airway compliance (59) are increasingly represented in the spectrum of the first derivative of the FVC curve and they are characterized by their longer wavelength (i.e., their lower frequency).
(d) Following Dawson and Elliott (24), we can hypothesize that anything that influences air-flow velocity also affects the spectrum of the first derivative of the FVC curve and, therefore, we can use bronchoconstrictors to estimate how airflow velocity and airway compliance influence the resonant frequencies that are detected by spectral analysis.

Conclusions

The objective of the present study was to utilize common methods and measures (spirometry) for estimating lung dysfunction in order to investigate whether applying modern-day techniques (signal analysis) to their measures will aid in the interpretation of spirometry. The localization of airway resistance in specific parts (generations of bifurcation) of the airways is very important for the localization of pathological processes and it served as the starting point for the investigations described. A dual objective was set forth:

(a) To test whether the Fourier Transform of the first derivative of the FVC curve can be used to classify pulmonary disease. The Fourier Transform was chosen because it is a common modern-day technique in signal analysis that is very mature (i.e., widely available with modern statistical and data analysis computer software) so that it can be used by non-engineers (medical doctors) to aid in the interpretation of their findings. The first derivative of the FVC curve was chosen because it is a mathematical transformation that allows one to derive the FEF curve directly from the FVC curve.
(b) The second objective, which was conditional on the first, was to establish a link between the potential findings from the Fourier Transformation of the first derivative of the FVC curve and distinct lung pathophysiological conditions. In particular, the distinction between restrictive and obstructive disease was examined, both because of the relative abundance of patients available and because of the availability unequivocal diagnoses of the condition of the patients that participated in the present study.

The results presented unequivocally 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 first derivative of the FVC curve.
(b) All frequency components of the power spectrum of the first derivative of the FVC 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 first derivative of the FVC curve predominate.
(d) It is possible to utilize the FT of the FEF curve as an index for the classification of chronic lung disease provided that simple rules (filters) are specified for this purpose.

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.

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