The practical application and interpretation of simple lung function tests in cystic fibrosis

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INTRODUCTION

Lung disease is the primary cause of morbidity and mortality in patients with cystic fibrosis (CF), accounting for up to 90% of fatalities in this disorder[1]. From early infancy onwards, the combination of infection and inflammation causes ongoing damage to airways and lung parenchyma, leading to progressive loss of lung function[2]. Slowing down the loss of lung function through reduction of pulmonary infection and inflammation is the cornerstone of treatment in CF, and is largely responsible for the significant improvement in survival rates observed in this disorder over the last few decades[1].

In every patient with CF, therefore, it is imperative to monitor the level of lung function carefully and repeatedly. Every paediatrician caring for children with CF should at least have basic knowledge on how lung function can be routinely measured, as well as on how to interpret the results in clinical practice.

In this and the following paper, the principles of measuring and interpreting lung function in CF will be discussed from a clinician's point of view. This article will focus on measurements of air flow and lung volumes[3]. A more detailed discussion on interpretation of lung function tests in asthma is available elsewhere[4].

LUNG VOLUMES AND CAPACITIES

Normal inspiration and expiration during resting conditions is called *tidal breathing*; the in- and expired volume is called *tidal volume* (Vt) (Figure 1, Table 1). Inspiration with maximal effort adds *inspiratory reserve volume* (IRV) to tidal volume. After complete expiration the patient will have exhaled tidal volume plus the *expiratory reserve volume* (ERV). After complete exhalation, there will be air left in the lungs, the amount of which is called *residual volume* (RV).

Combinations of two or more lung volumes are called lung capacities. Tidal volume plus inspiratory reserve volume and expiratory reserve volume is called *vital capacity* (VC). This is the maximal volume that can be exhaled after

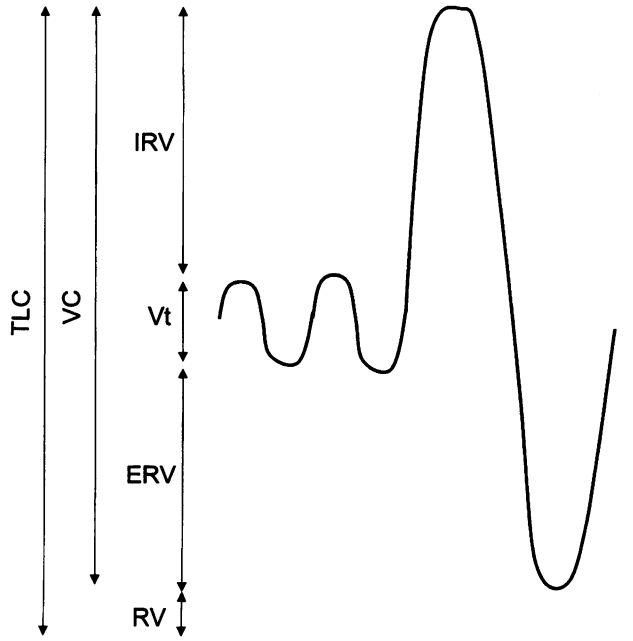

Figure 1 **Schematic representation of lung volumes and capacities (see Table 1)**

Table 1 **Abbreviations of lung volumes and capacities**

Vt	tidal volume: volume of air inspired and expired during normal quiet breathing
IRV	inspiratory reserve volume: volume of air that can be inspired during maximal inhalation over and above tidal volume
ERV	expiratory reserve volume: volume of air that can be expired during maximal exhalation over and above tidal volume
RV	residual volume: amount of air left in the lung after maximal expiration
VC	vital capacity: amount of air that can be maximally inhaled after full expiration
TLC	total lung capacity: total amount of air in the lungs after maximal inhalation
FEV_1	forced expiratory volume in 1s: amount of air that can be maximally expired in 1s, after compete inhalation
PEF	peak expiratory flow

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full inspiration. VC plus RV comprises the *total lung capacity*, or TLC.

These static lung volumes primarily yield information on the amount of air that can be contained in the lungs under certain conditions. Thus, they reflect lung function in the true sense of the word. However, they provide no insight on function of the airways through which air is transported into and out of the lungs. The speed with which air can be moved out of the lung is relevant in a variety of airway disorders, including CF. This *air flow* can be quantified by measuring the volume of air that can be maximally expired in a given amount of time, usually the *forced expiratory volume in one second* (FEV_1). The FEV_1 can be expressed as a percentage of the VC (FEV_1/VC ratio), in order to correct the FEV_1 to a certain degree for the patient's lung volume. The maximal air flow generated during forced exhalation is called *peak expiratory flow* (PEF) (Table 1).

SPIROMETERS AND PNEUMOTACHOGRAPHS

Spirometry is the technique used to measure VC and FEV_1. Traditionally, this was done with a water-sealed spirometer. The instrument consists of an air-filled bell hanging upside down in a container of water. Tubing connects the air inside the bell with the patient's mouth, a nose-clip occluding nasal air flow. With exhalation, the bell moves upward; with inhalation, it moves downward. Movements of the bell are quantified with a ruler and recorded. Carbon dioxide is removed from the expiratory gas by an absorber, and oxygen is supplied to the inspiratory gas to compensate for oxygen consumption during the procedure. Great care should be taken in calibration of the instrument and standardization of the measurement conditions, including to ATPS-BTPS corrections (ATPS: ambient-; and BTPS: body-temperature-pressure-saturation with water vapour)[3].

Water-sealed spirometers are quite bulky, and measurements can be made by hand only. No 'trend registration' of lung function changes over time, which are important in patient follow-up, is available. These drawbacks have been circumvented in newer instruments, called pneumotachographs, which primarily measure flow (in various ways), which is then integrated to volume. Modern pneumotachographs are invariably fully computerized, facilitating calibration, ATPS-BTPS corrections, comparison to reference values, and creating print-outs of results, including trend registration over time.

Both the water-sealed spirometer and the pneumotachograph will yield information on VC and FEV_1 in a single manoeuvre of forced expiration from full inspiration (TLC level) to complete expiration (RV level, Figure 1).

Reduced VC suggests reduction of lung volume (restrictive lung disease), which is present in many patients with CF with advanced lung disease in whom lung parenchyma has been destroyed due to chronic infection[2]. Strictly speaking, restrictive lung disease may only be diagnosed if TLC is reduced[3]. RV and TLC, however, cannot be measured with a single forced expiration, but require more complicated techniques such as gas dilution or body plethysmography (see following paper). From a practical point of view, therefore, reduction of VC in CF is commonly interpreted as reflecting restrictive lung disease. In this paper, the term 'restrictive lung disease' is used to describe a situation in which VC is diminished.

Reduced FEV_1 suggests narrowing of airways (obstructive lung or airways disease) which is almost invariably present in patients with CF[2], but also in symptomatic asthma, chronic obstructive pulmonary disease, and other disorders. Both for diagnostic and therapeutic purposes, it may be useful to assess the change in FEV_1 after inhalation of a bronchodilator. Interpretation of such bronchodilator response, or reversibility test, should always take prebronchodilator FEV_1 and the clinical situation into account[5,6].

COMPARISON TO REFERENCE VALUES

Lung function is considered to be abnormal in a patient when it is below the reference value. Such reference (or predicted) values of lung function are collected in populations of healthy non-smoking subjects. Lung function in such populations is highly variable. Even after correction for obvious confounders such as age, height, and gender, considerable variation remains between healthy subjects with respect to, for example, PEF, VC and FEV_1 (Figure 2)[7]. The reference values recorded in tables, formulas, and contemporary lung function software are the mean values of, say, FEV_1, for a healthy population of a certain age, height, and gender (comparable to the 50th percentile of a growth chart). An FEV_1 equalling this population mean can certainly be normal, but might also be low for a certain

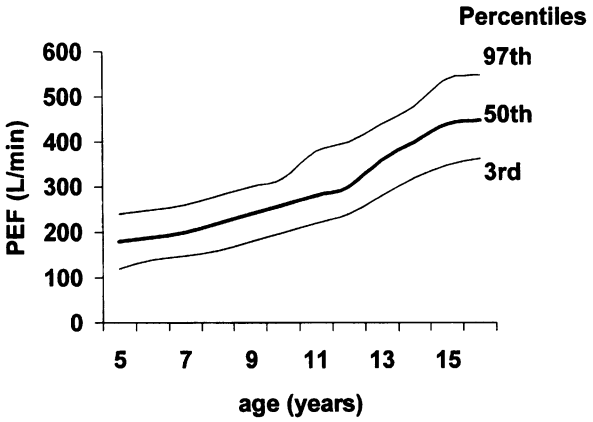

Figure 2 **Peak expiratory flow (PEF) in a population of healthy boys, aged 5–16 years.** Lines represent 3rd, 50th, and 97th percentiles of the distribution of PEF in this population. Note the considerable variation in PEF levels between these healthy children (Source: Brand, Ref 4)

patient whose FEV_1 is usually way above the reference value. This is why the term 'normal values' should be avoided. It also emphasizes that the true power of measurement of lung function lies in its repetition, looking at patterns of change over time in individual patients. This is particularly true in CF.

By agreement, lung function levels are considered to be reduced when being below the 90% confidence limit of the mean population value (i.e. 1.64 standard deviation scores (SDS) below the reference value; 1.96 SDS below the reference value corresponds to the 95% confidence limit)[3]. In clinical practice, the expression '% of the reference (or predicted) value (%pred)' is commonly favoured, because clinicians feel comfortable with its use and because it is felt to be more easily calculated[8]. 80%pred is then commonly used as a guideline to adjudge level of lung function to be normal (>80%pred) or abnormal (<80%pred). This would be a valid approach if 80%pred would equal the lower 90% confidence limit. Unfortunately, this is not true because the lower confidence limit equals a different percentage of the predicted value in patients of different ages, heights, and genders. Therefore, expressing lung function levels in SDS (as is done in growth curves) is preferable[8]. Because most lung function software will print out %pred but not SDS, the %pred will be used throughout this text. It should be emphasized, however, that a single measurement <80%pred only tells you that that particular patient probably has reduced lung function at that particular time-point.

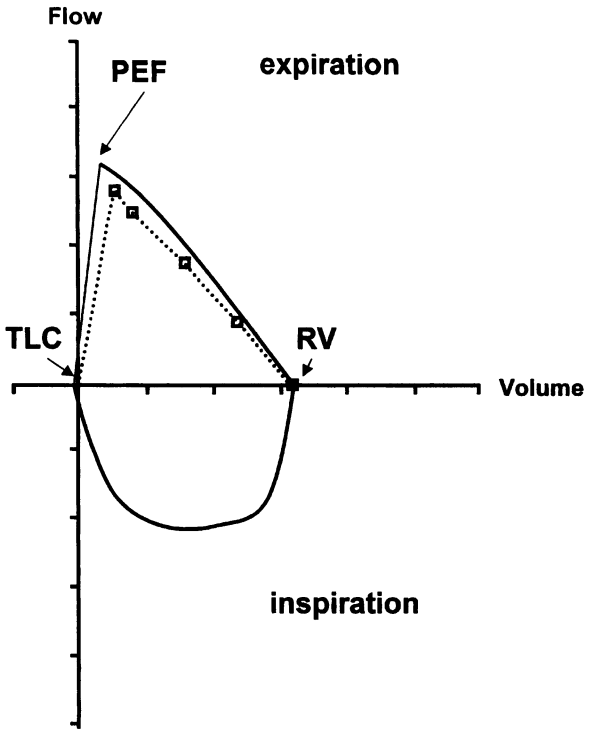

Figure 3 **Example of a normal flow-volume loop in a healthy individual.** See Table 1 for key to abbreviations. The X-axis represents volume (L) (the difference between TLC and RV being VC); the Y-axis represents flow (L/s). The expiratory part of the curve is above the X-axis, the inspiratory part is below it. The dashed line represents a connection between reference values for PEF (first open square), mid-expiratory flows at 25%, 50% and 75% of VC, and VC (open square on X-axis). The solid line is the patient's flow-volume loop. The FEV_1 cannot be read from the curve. Actual patient values of PEF, FEV_1, MEF_{25-75}, and VC would be given as percentages of the predicted (reference) values on the left-hand side of the curve

FLOW-VOLUME LOOPS—PRINCIPLES OF USE IN CF PATIENTS

Forced expiration from complete inhalation (TLC) to complete exhalation (RV) will yield information on VC and FEV_1 in a single manoeuvre. Reduced VC suggests restrictive lung disease, and reduced FEV_1 indicates obstructive lung disease.

In addition to values of VC and FEV_1, a print-out of the complete forced expiration manoeuvre as flow against volume (Figure 3) also provides information on mid-expiratory flow patterns. These mid- and end-expiratory flows are predominantly determined by the patency of medium-sized and small airways. Once the patient exceeds a threshold value of driving pressure, a further increase of the driving pressure (effort) does not improve mid- and end-expiratory flows any further[2]. As a result, mid- and end-expiratory flows are considered to be effort-independent. It should be stressed, however, that insufficient effort (driving pressure below the threshold value) will lead to reduced expiratory flows over the entire expiratory phase, irrespective of airway patency. In clinical practice, there are two days to find out whether the patient has reached sufficient driving pressure to judge expiratory flows in any clinically meaningful way. Firstly, the lung function technician can give you his or her impression of the amount of effort the patient has put into the manoeuvre. Secondly, poor effort leads to poorly reproducible curves and flows (differences between repeated measures exceeding 5–10%), whereas flow-volume loops blown with good effort show highly reproducible mid-expiratory flow patterns[9].

It is assumed that reduced flows at high lung volumes (close to TLC, shortly after the beginning of expiration) reflect large airways obstruction, whereas reduced flows at lower lung volumes (closer to RV, later in expiration) indicate obstruction of smaller airways.

The shape of the maximal expiratory flow-volume curve is highly indicative of the nature and severity of lung disease, for example in CF. This is illustrated in Figure 4.

Firstly, the VC can easily be read from the curve as the distance on the volume (or X) axis between the two ends of the expiratory (upper) part of the flow-volume loop (Figure 4, top). It is quite easy, even without looking at the

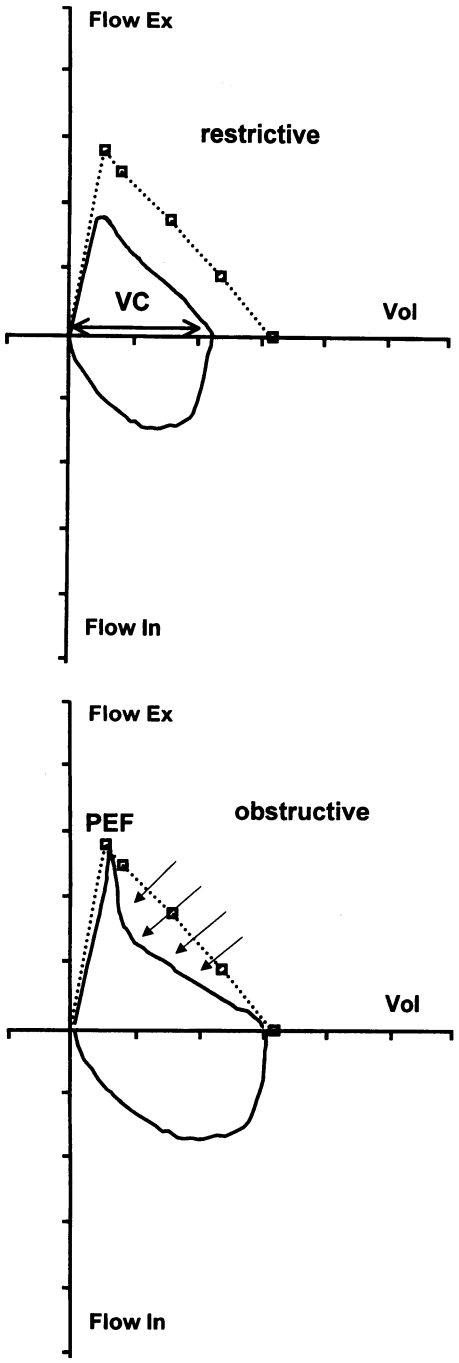

Figure 4 **Examples of flow-volume curves of patients with restrictive (top) and obstructive (bottom) lung disease.** See Table 1 for abbreviations. In restrictive lung disease (top), VC is reduced considerably. The shape of the flow-volume curve in restrictive lung disease is almost identical to that of a normal subject, the only difference being its smaller size in restrictive lung disease. Patients with obstructive lung disease (bottom) usually have normal VCs. Hence, the final part of the expiratory loop of the curve will cut through the X-axis at or around the predicted value. Air flow is reduced, as is apparent from the concave shape of the flow-volume curve (arrows). Reduced flows at high lung volumes (close to TLC, shortly after the beginning of expiration) reflect large airways obstruction, whereas flows at lower lung volumes (closer to RV, later in expiration) indicate obstruction of smaller airways. Note that PEF is (almost) normal in this patient. PEF is mainly determined by the calibre of large airways. It is, therefore, entirely possible that a patient has severe airways obstruction with normal PEF

numerical value of VC in relation to its reference value, that the VC is reduced considerably in the flow-volume loop depicted in the top panel of Figure 4. This curve represents restrictive lung disease. A patient with such restricted lung volume will have difficulty in generating enough expiratory force to blow normal peak expiratory flow,which explains why PEF is usually below the reference value in restrictive lung disease. From PEF, there is a steady, almost straight-lined decline of expiratory flow towards zero during the entire expiration. As a result, the shape of the flow-volume curve in restrictive lung disease (Figure 4, top) is almost identical to that of a normal subject (Figure 3), the only difference being its smaller size in restrictive lung disease.

By contrast, the shape of the flow-volume curve in obstructive lung disease (Figure 4, bottom) is completely different from that observed in healthy subjects (Figure 3). Patients with airways obstruction usually have normal VCs. Hence, the final part of the expiratory loop of the curve will cut through the X axis at or around the predicted value.

The main problem in obstructive airways disease is getting the air out of the lungs. During normal expiration, air flows out of the lung because pressure at the mouth is lower than pressure in the alveoli. Because the airways are closer to the mouth than the surrounding lung parenchyma (mainly consisting of the alveoli), during normal expiration pressure in the airways is a bit lower than that in the lung parenchyma surrounding it. As a result, intrathoracic airways tend to collapse slightly during normal expiration. Any intrathoracic airways obstruction will, therefore, manifest itself firstly in the expiratory phase of the breathing cycle. Due to the obstruction of the airways, it takes longer to move the same amount of air (for example, the VC) out of the lungs, and expiratory time is prolonged. The flow-volume loop does not contain a time axis, and the prolongation of expiration cannot be appreciated from it. However, air *flow* (which is volume divided by time) is highly dependent on expiratory time; if expiration is prolonged, flow will be reduced, and this can be read from the flow-volume loop.

In addition, the flow rate at different levels of expiration can be read directly from the curve. As stated above, these are clinically highly relevant because reduced flows at high lung volumes (close to TLC, shortly after the beginning of expiration) reflect large airways obstruction, whereas reduced flows at lower lung volumes (closer to RV, later in expiration) indicate obstruction of smaller airways. Therefore, the added value of the flow-volume loop over and above a numerical value for, say, FEV_1, is that the flow-volume curve not only provides information on the severity of airways obstruction, but also on its site.

Take for example the flow-volume curve in Figure 4, bottom panel. This patient has severely reduced mid-expiratory flows, indicated by the arrows. This means that

his or her small and medium sized airways are obstructed considerably. Because the flow-volume curve passes through the X axis at normal VC level (there is no evidence of restrictive lung disease), expiratory flow approaches predicted levels again as it gets closer to the end of expiration. It is noteworthy that PEF is (almost) normal in this patient. PEF is mainly determined by the calibre of large airways. It is, therefore, entirely possible that a patient has severe airways obstruction with normal PEF (as is the case with the patient in Figure 4, bottom). The (relatively) well maintained PEF, together with severely reduced mid-expiratory flows and more or less normal end-expiratory flows, results in a concave shape of the expiratory part of the flow-volume curve that is so characteristic of obstructive airways disease.

The beauty of flow-volume curves from a clinician's point of view, therefore, is that eyeballing such a curve will yield lots of information on current severity of obstruction and restriction in a patient with, for example, CF. The computer software gives the clinician the numerical values of important variables from the curve, such as PEF, VC, FEV_1, and mid-expiratory flow (summarized as MEF_{25-75}, which is the mean expiratory flow between 25% and 75% of expired VC), both in absolute terms and in %pred. The latter expression allows for tracking lung function over time. There are now many commercial systems available which will store a patient's previous levels of lung function in memory, and provide a print-out of changes of these levels over time in individual patients.

After the age of 6 years, almost every child can reliably blow a maximal expiratory flow-volume curve after a little bit of training, which should take no longer than 15–30 min. The principal drawback of flow-volume loops is that most children younger than 5 years will not be able to do the manoeuvre in any clinically meaningful way. At present, there is no routinely available method of measuring lung function in CF patients below that age, although new developments are evolving rapidly (see next paper).

PEAK EXPIRATORY FLOW

Being extremely popular in day-to-day follow-up of airway function in asthma, some discussion on the use of PEF in CF is warranted. There are three drawbacks to the use of PEF monitoring in CF. Firstly, PEF reflects large airway calibre[10]. Significant obstruction of small and medium-sized intrathoracic airways can occur before PEF decreases (Figure 4, bottom). Because airway disease in CF progresses from small airways upward (see below), reduction of PEF is a late sign of airways obstruction in CF[2]. Secondly, PEF is highly effort-dependent[10]. In a disease such as CF where chronic malnutrition and infection are not uncommon, this will increase the variation of PEF levels in patients with CF, irrespective of lung disease. This is why PEF monitoring has never become commonplace in CF management. By consensus, none of the CF patients are provided with PEF meters for home monitoring of lung function in any of the CF centres in the Netherlands. It is felt that it would give patients a false sense of security when their PEF levels remained normal, even when there was an increase of symptoms indicating an impending exacerbation. The first lung function variable to go down in a pulmonary exacerbation in CF would be either mid-expiratory flow (MEF_{25-75}), FEV_1, or VC, with PEF values only falling at the height of an exacerbation when its development is usually well recognized by patient and physician by clinical signs and symptoms.

Finally, diary records of PEF values can be misleading. It has been shown that asthmatic children frequently 'invent' PEF values that they never actually blew and record those in a diary[11]. In addition, it is quite easy to increase PEF as recorded on a portable PEF meter intentionally by increasing the expiratory flow explosively (for example by spitting into the apparatus).

PROGRESSION OF LUNG DISEASE IN CF

An in-depth discussion of the progression of lung disease in CF is beyond the scope of this paper and can be found elsewhere[1,2].

For the purpose of understanding and interpreting lung function results in CF, however, it is important to make a few summary points here. At birth, the lungs and airways of a patient with CF are normal, although, of course, the chloride channel is already malfunctioning. The earliest inflammatory changes are found in small airways, with increasingly larger airways becoming affected with increasing infection load. Chronic infection causes airway wall inflammation and repair, leading to scarring and bronchiectasis. Lung parenchyma is also affected in advanced disease, the end result being lung fibrosis and restrictive lung disease[1,2].

Pulmonary exacerbations of CF are usually accompanied by a relatively sudden decrease of pulmonary function, which may be obstructive, restrictive, or both. After treatment of such pulmonary exacerbations pulmonary function should return to pre-exacerbation levels, although some permanent damage and ongoing loss of lung function may occur after each exacerbation[1].

INTERPRETATION OF CHANGES IN LUNG FUNCTION IN CF

From the above discussion it should be apparent that monitoring lung function is invaluable in each and every patient with CF. The goal of such monitoring is to detect deterioration at an early stage.

Any decrease in pulmonary function should be compared to the expected variability of the lung function variable under scrutiny. Even in healthy subjects, lung function is quite variable, more so for PEF and mid-expiratory flows than for VC and FEV_1. Changes in FEV_1 are considered to be within the ranges of normal variability if they do not exceed 5% or 200 ml, whichever is greatest[3,12]. In patients with CF, this spontaneous variation appears to be considerably higher (up to 15–20%)[13]. In addition, the nature of the inspiratory manoeuvre preceding forced expiration (speed of inspiration, breath hold) significantly influences VC and FEV_1[14]. As a result, changes in lung function in CF must be interpreted cautiously.

If lung function truly decreases in CF this may have numerous causes (Box 1), the diagnostic work-up of which is beyond the scope of this paper. After making a presumptive diagnosis, appropriate therapy should be instituted, hopefully preventing irreversible damage to the lungs.

CLINICAL EXAMPLES

In this section, a number of practical clinical examples will be presented, each with a brief introduction to the clinical problem and numerical results from spirometry, followed by a short interpretation of the latter. The reader is encouraged to try and interpret the clinical and spirometry data for his- or herself before moving on to the authors' interpretation. A flow-volume loop is shown, always in the same format (Figure 3). Again, please try to interpret this for yourself and think of therapeutic measures you would take before reading the comment provided.

Case A

A girl, 16 years-of-age, has been diagnosed with CF in the neonatal phase when she presented with meconium ileus. She has been relatively stable ever since, with normal growth and development on standard therapy. So far, she has had approximately 3–5 courses of oral antibiotics annually. She now comes in for a regular outpatient clinic check-up and has blown her first lung function test ever. The results are given in Table 2.

At first glance, these results suggest restrictive lung disease: VC is low at 75%pred, with more or less normal

Box 1 **Causes of deterioration of lung function in cystic fibrosis**

- Progression of disease
- Pulmonary exacerbation
- Allergic bronchopulmonary aspergillosis
- Other pulmonary complication (e.g., pneumothorax, atelectasis, pulmonary haemorrhage)

Table 2 **Lung function test (spirometry) results in cases A–E**

Case A			
FEV_1	1.11 L	1.21 L	92
VC	1.12 L	1.49 L	75
PEF	189 L/min	180 L/min	105
Case B			
FEV_1	1.46 L	2.60 L	56
VC	2.31 L	3.16 L	73
PEF	290 L/min	340 L/min	85
Case C			
FEV_1	0.78 L	1.53 L	51
VC	1.10 L	1.81 L	61
PEF	135 L/min	217 L/min	62
Case D			
FEV_1	2.24 L	2.83 L	79
VC	4.04 L	3.92 L	103
PEF	400 L/min	380 L/min	105
Case E			
FEV_1	0.53 L	2.80 L	19
VC	1.84 L	3.40 L	54
PEF	90 L/min	340 L/min	26

FEV_1 and PEF. Now examine the flow-volume loop (Figure 5).

Examination of the curve confirms that VC is low; in addition, however, the concave shape of the curve indicates some obstruction as well (mid-expiratory flow is reduced,

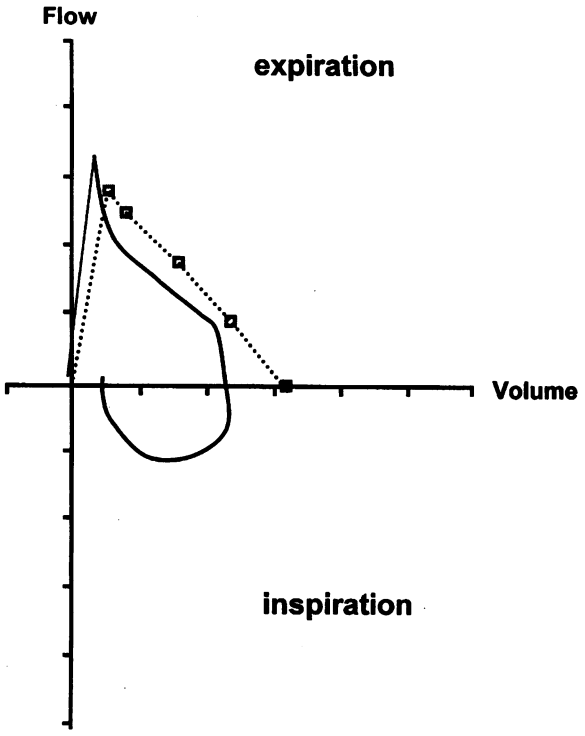

Figure 5 **Flow-volume loop of 6 year old girl with cystic fibrosis (case A)**

FEV_1 is somewhat reduced). The obstruction probably is true and reflects some degree of small airways disease, which is quite mild. It is unusual that expiratory flow drops steeply, from a relatively normal flow at 75% of VC to zero almost immediately thereafter. This suggests that the child finished expiration before reaching RV level (i.e. before exhalation was complete), which is quite common in children who perform spirometry for the first time. Current lung function software contains computer graphics incentives to stimulate the child to exhale forcefully (e.g. blow out candles) and completely (e.g. blow a balloon over a bed of nails).

Thus, this child blew a technically incorrect manoeuvre, failing to exhale completely. This could have been gleaned from the values of FEV_1 and VC as well. Their ratio is exactly one, indicating that the child exhaled her entire VC in one second, which is physiologically impossible. A normal FEV_1/FVC ratio in a child without airways obstruction amounts to 0.85–0.9.

Note that the mild small airways obstruction is better appreciated from the shape of the flow-volume curve than from the numerical values of the lung function test results.

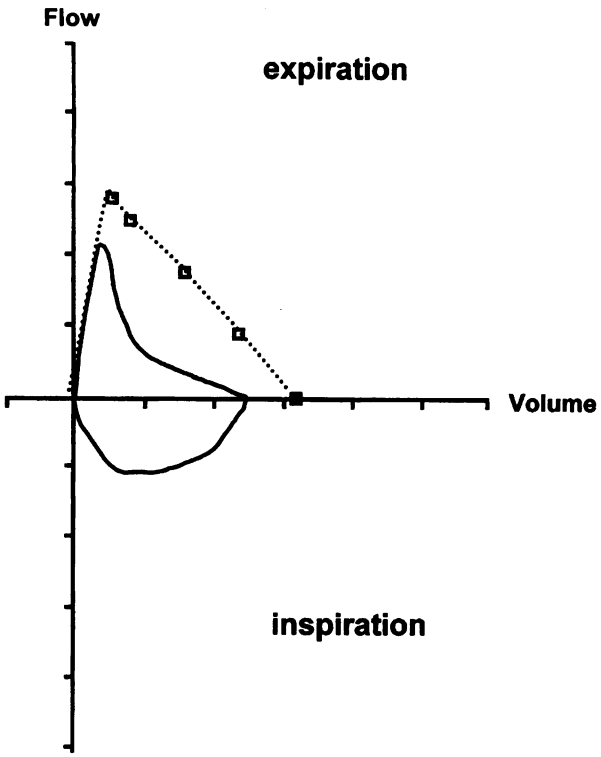

Figure 6 **Flow-volume loop of 14 year old boy with cystic fibrosis (case B)**

Case B

A boy, 14 years-of-age, with CF, has had serious nutritional and growth problems, largely overcome by nocturnal tube feeding. He has had numerous pulmonary exacerbations, but has been relatively stable over the last 2 years. Now he comes in for a quarterly check-up.

His latest lung function results, obtained 3 and 6 months ago, respectively, were: $FEV_1 = 57$ and 58%pred; $VC = 75$ and 75%pred; $PEF = 80$ and 90%pred. His current lung function results are shown in Table 2.

Both FEV_1 and VC are reduced, the former more than the latter. This suggests airways obstruction and some restriction, although faulty technique comparable to patient A cannot be excluded. The lung function test results are not very different from those obtained at previous visits. His flow-volume loop is depicted in Figure 6. Basically, it confirms the combination of restrictive and obstructive lung disease (concave curve, VC reduced). What is remarkable about this curve is that there is rapid attenuation of flow early in expiration, with low expiratory flows thereafter. This is reflected by an MEF_{25-75} of only 27%pred. Thus, the severity of airflow obstruction is, again, better appreciated from the flow-volume curve than from the numerical lung function test results. The flow-volume loop of this patient suggests advanced CF lung disease, which is relatively stable over time. Thus, there is no reason now to change therapy—the observed abnormalities are probably irreversible and reflect permanent damage to the lungs and airways.

Case C

This boy, 8 years-of-age, has had CF from the age of 2 months, but he has had very few problems since, apart from poor weight gain initially. Six months ago, he blew his first flow-volume loop ever, and his FEV_1 and VC were 90%pred and 84%pred, respectively. Now he comes in between scheduled visits because he's not feeling well: there is malaise, increased cough, and poor appetite. Chest auscultation reveals the same findings as always (mild crepitations). His spirometry results are given in Table 2.

Results show a dramatic decrease of VC, and especially of FEV_1, since the previous visit. Together with the increased complaints, this indicates a pulmonary exacerbation. This is confirmed by the flow-volume loop (Figure 7). PEF, FEV_1 and mid-expiratory flows are all considerably reduced. VCF is low, but, as in case A, end-expiratory flow drops to zero rapidly. The inspiratory curve has a saw-tooth appearance due to coughing during inspiration. The added value of the flow-volume loop in this patient is two-fold. First it shows poor technique, probably due to malaise. Secondly, it serves as a dramatic illustration of the fall in lung function due to this exacerbation when compared to the relatively normal curve obtained at the previous visit. This patient was admitted for treatment with i.v. antibiotics.

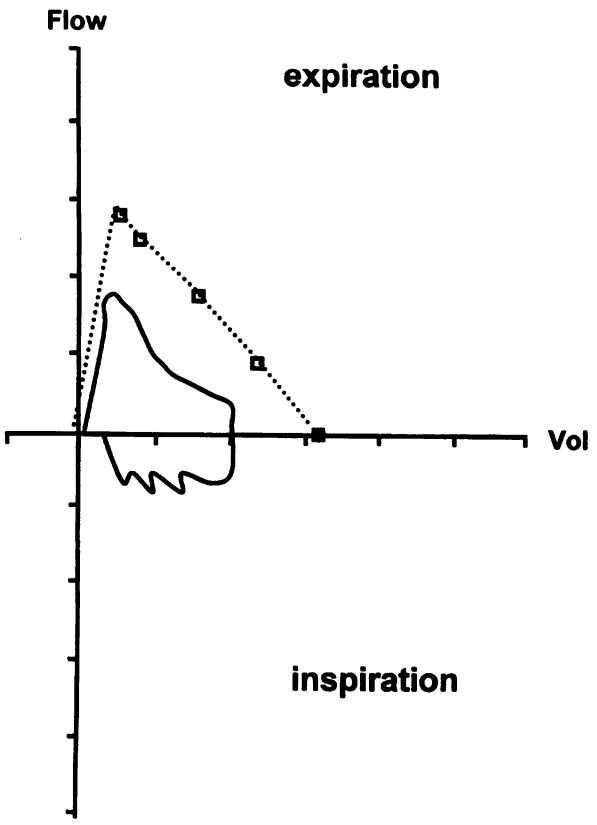

Figure 7 **Flow-volume loop of 7 year old boy with cystic fibrosis (case C)**

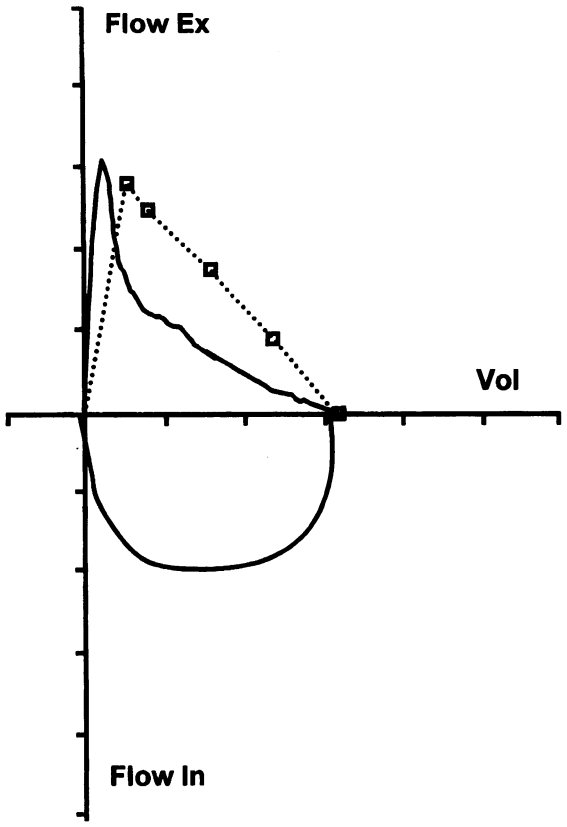

Figure 8 **Flow-volume loop of 12 year old girl with cystic fibrosis (case D)**

Case D

This girl, 12 years-of-age, was diagnosed with CF at the age of 4. She has had a mild clinical course so far, although she required three courses of antibiotics over the last year. Her growth is excellent. Lung function test results so far have been excellent, with normal VC values and FEV_1 values between 82 and 88%pred.

On regular follow-up, she reports wheeze, dyspnoea on exertion, and general malaise, which started about a month ago, and appears to deteriorate slightly but steadily. On physical examination she does not appear acutely ill, nor very fit. Chest auscultation reveals diffuse expiratory wheezing, no crackles. Her spirometry results are given in Table 2.

FEV_1 is slightly low, and somewhat lower than at previous visits. VC and PEF are normal, suggesting slight obstructive lung disease. Now examine her flow-volume loop (Figure 8). Here, the airways obstruction is expressed much more dramatically in a clearly concave flow-volume loop (MEF_{25-75} is only 39%pred), suggesting considerable small and medium-sized airways obstruction.

Such a sudden increase in airways obstruction in CF can mean two things: either the patient has developed asthma as well (the prevalence of asthma is as high in CF patients as it is in the general population), or she has contracted allergic bronchopulmonary aspergillosis (ABPA). The history is more consistent with the latter diagnosis than with the former, but differentiating between the two may be difficult. The diagnostic work-up includes a trial of bronchodilators and/or corticosteroids to assess reversibility of airways obstruction, a chest X-ray, and tests for ABPA (including total and specific IgE, specific IgG precipitins, aspergillus skin test, and eosinophil count)[1].

Case E

In this boy, 14 years-of-age, CF has always been a most troublesome disease, with very frequent pulmonary exacerbations, gastrointestinal problems, and poor weight gain and growth. Over the past 2 years he has been admitted to a district hospital seven times for pulmonary exacerbations. He now comes in for a check-up in your CF-centre for the first time in 2 years, with the question whether he can be included in your programme for home intravenous antibiotic therapy should he develop an exacerbation again. You decide to have him perform spirometry before you see him. The results are given in Table 2.

Clearly these results mean trouble. Either this patient has a severe exacerbation, or he has terminal lung disease (or both). The flow-volume loop dramatically illustrates the extremely poor lung function (Figure 9): there is hardly any

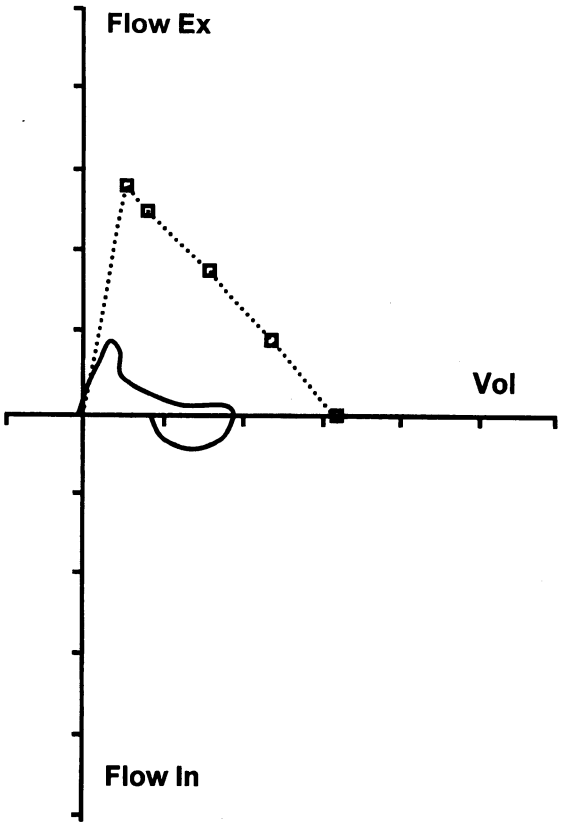

Figure 9 **Flow-volume loop of 16 year old boy with cystic fibrosis (case E)**

flow or volume left. This boy was scheduled for lung transplantation but died while on the waiting list.

DISCUSSION

Monitoring lung function is important in CF. A deterioration of FEV_1 and/or VC over the course of weeks to months suggests increased lung inflammation and infection[1,15,16], pulmonary exacerbations or other complications, early detection of which may facilitate successful therapy[17]. Such pulmonary exacerbations and complications are usually accompanied by an increase in symptoms, but this is not always the case. Symptoms may develop or increase so gradually that they may go unnoticed to patients and parents. It is assumed that monitoring lung function may help in the early discovery of such exacerbations, although this assumption is based more on clinical experience than on hard scientific evidence. In addition, the evidence that early and aggressive treatment of deteriorations in lung function results in a better long-term outcome is also limited[1]. It has been reported that aggressive antibiotic treatment of early colonization with *Pseudomonas aeruginosa* is associated with better maintenance of lung function[18]. In addition, recent evidence suggests that patients treated in a cystic fibrosis centre have a better clinical outcome than do patients who had not received cystic fibrosis centre care[19]. The main differences between treatment of CF patients in cystic fibrosis centres on the one hand, and 'regular' care in a district hospital on the other hand, are more aggressive nutritional management and earlier and more aggressive treatment of impending pulmonary exacerbations[19,20].

Rapid deterioration of lung function over the years is a strong predictor of risk of death in CF[21], and should prompt screening for lung transplantation. It appears that lung function is better maintained in patients in whom the upper lung lobes are affected than in those in whom the lower lobes are the predominant site of infection[22].

Currently, a critical issue in measuring lung function in CF is the risk of cross-infection, in particular with *Burkholderia cepacia* and other multiresistant bacteria[23–26]. These highly resistant microorganisms can be transferred to other patients through lung function equipment.

When there was only one multiresistant strain to worry about (*B. cepacia*), in many centres these patients were sequestrated from other patients not carrying the strain. They all came to the CF clinic on a specific day, and a specific pneumotachograph was earmarked for use in patients carrying such bacteria. This policy is now no longer valid because transmission of different strains of *B. cepacia* from one patient to another, possibly through the use of a shared pneumotachograph, has recently been described[27]. In principle, the same danger applies to other multiresistant strains.

It should be stressed that literature on this vital subject is currently largely lacking, so that the recommendations presented here are solely based on clinical experience in a limited number of patients, and on common sense. Currently, there appear to be two approaches to preventing cross-infection.

First, bacterial filters can be used[28]. These should be placed directly behind the mouthpiece of the spirometer or pneumotachograph, in order to prevent contamination of tubing and hardware. These mouthpieces and filters should either be disposable, or they should be sterilized after each use. It appears that the use of these filters increases resistance to air flow and reduces the measured lung function values by about 5% (H G M Heijerman, personal communication, August 1998). The efficacy of these filters must be examined further because conflicting data on the removal of exhaled bacteria have been published[29,30].

Secondly, an adaptation to the lung function apparatus, called the 'bag in bottle' system, can be applied[31]. In this system, the patient blows into a sealed balloon or bag which is mounted in a flexible chamber. This chamber, or bottle, is connected to the pneumotachograph (Figure 10). Flow changes are transmitted from the bag to the bottle and to the pneumotachograph, without the risk of contaminating

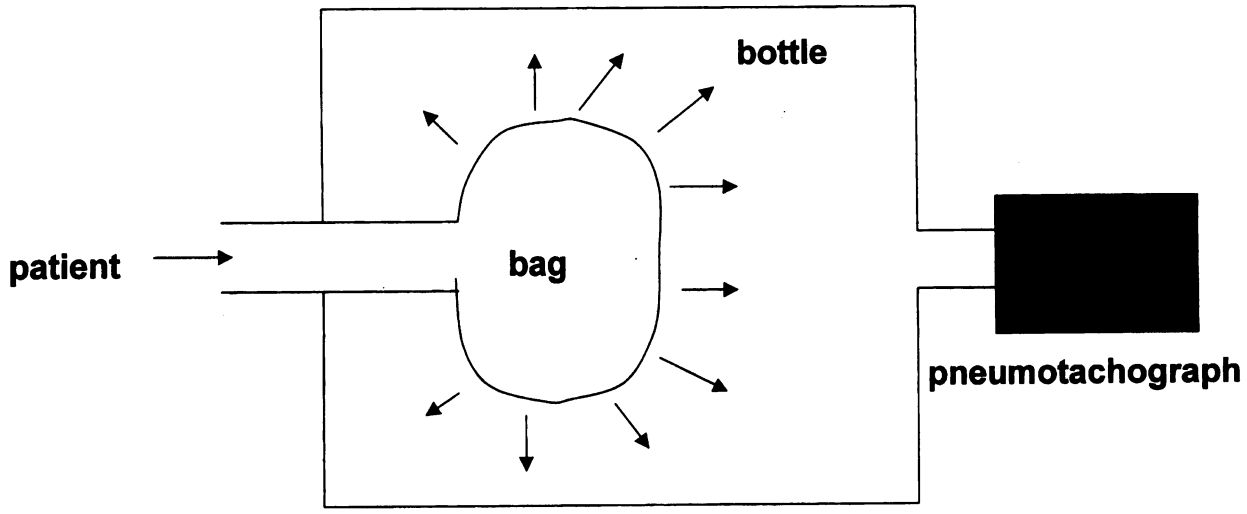

Figure 10 **Principle of 'bag in bottle' system, to prevent cross-infection of multiresistant bacteria between cystic fibrosis patients during routine lung function measurements.** The patient blows into a disposable bag, the movements of which are transferred to a bottle (which remains sterile), connected to the pneumotachograph

the bottle or the pneumotachograph itself. This method has been shown to be effective in eliminating cross-infection. The disadvantage of this method is that mouthpiece, tubing and bag have to be disinfected or disposed of after each patient.

For measurements of lung function to be reliable, rigorous quality control is of utmost importance. An in-depth discussion of this critical issue is available elsewhere[9]. All lung function equipment must be calibrated daily with a high-precision calibration syringe with a known volume. Failure to do so may make results impossible to interpret. Pressure and flow transducers must be kept clean and dry after each use, and gently assembled before a new test is begun.

Each lung function laboratory should have its own written protocols on how to perform certain lung function measurements. These protocols should be very detailed indeed, including recommendations on the time-frame of withdrawing medication prior to testing (Table 3), the use of caffeinated drinks before testing, resting the patient before testing, the positioning of the patient (seated or standing), the position of the head (flexed, neutral position, or extended), the use of nose-clips, the instruction given to the patient, the definition of a technically satisfactory manoeuvre, etc., as all of these factors may influence test results to a considerable degree. Within the context of a multicentre clinical trial, in which level of lung function was one of the principal end points, we found that variations in lung function protocols between centres (which thought they all measured lung function in exactly the same way) caused lung function test results to vary by as much as 5–10%[32,33].

Table 3 **Example of a protocol on withdrawal of asthma medication prior to a histamine challenge test or exercise test.** This list is given to children when an appointment is made for a histamine challenge or exercise test. Patients and their parents are asked to withhold medication for the time mentioned, prior to the test. If this is not possible due to increased symptoms, patients are asked to contact the laboratory to reschedule the appointment, or to do the test 'under required medication'. All patients are tested after at least 15 min of quiet, seated resting

Bronchodilators	
ipratropium bromide	8 hr
fenoterol, salbutamol, terbutaline	8 hr
formoterol, salmeterol	24 hr
theophyllines	48 hr
Inhaled corticosteroids	
beclomethasone, budesonide, fluticasone	8 hr
Antihistaminic agents	48 hr
except: astemizole	2 months
ketotifen	1 wk

Well trained and highly motivated lung function technicians are essential to get children (including those with CF) to perform reliable and optimal lung function tests. It is truly an eye-opener to observe the differences in flow-volume loops obtained by well meaning but poorly trained clinicians or nurses on the one hand, and those obtained by highly qualified lung function technicians on the other. Computer animation incentives can be very useful to improve performance in children.

Lung function results, including flow-volume loops, can only be interpreted when the clinician has sound knowledge on the basics of techniques and their drawbacks. This paper should help to serve this goal, but clinicians will inevitably

get a far better feeling for lung function when they perform the manoeuvre themselves sometimes, and when they visit the lung function lab repeatedly to review procedures and get acquainted with both the staff and the machines. Interpreting lung function test results isn't difficult, but, as with all other procedures in medicine, it takes a bit of practice and patience.

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