Chapter 6
Breathing Out: Forced Exhalation, Airflow Limitation

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6.1 Expiratory Mechanics

Spirometry requires that a subject exhales fully at maximal speed from the starting point of full inspiration total lung capacity (TLC). The speed at which the subject can expire is governed by the many mechanical properties of the pulmonary system, including the elastic recoil of the lungs and the compliance of the chest wall and airways, as well as the physical properties of air itself.

At the point of full inspiration (itself determined by respiratory muscle strength), the glottis is open, and there is no airflow. Therefore, the intraluminal pressure throughout the respiratory tract from the mouth (P_{MO}) to the bronchi (P_{BR}) to the alveoli (P_A) is universally equal to barometric pressure (P_{BAR}). Due to the stretching of the lungs, the elastic recoil of the lungs (P_{EL}) is opposing inflation, resulting in small, negative intrapleural pressure (P_{PL}) (Fig. 6.1a).

At the start of the maximal exhalation, an additional force is applied to the thoracic cavity by the contraction of the accessory expiratory muscles. This causes the pleural pressure (P_{PL}) and alveolar pressure (P_A) to increase far beyond atmospheric pressure (P_{BAR}), which results in expulsion of air from the lungs. The intraluminal pressure (P_{BR}) is now gradated throughout the respiratory tract, from the maximum in the alveoli (P_A) to the minimum at the mouth (P_{MO}). The point at which P_{PL} is equal to P_{BR} is referred to as the "equal pressure point", above which airway compression occurs (as P_{PL} is greater than P_{BR}). At the beginning of a forced expiration, airway compression first occurs in the trachea (Fig. 6.1b), where the dorsal membrane allows for the cartilaginous rings to bend, forming a slit-like aperture. As the

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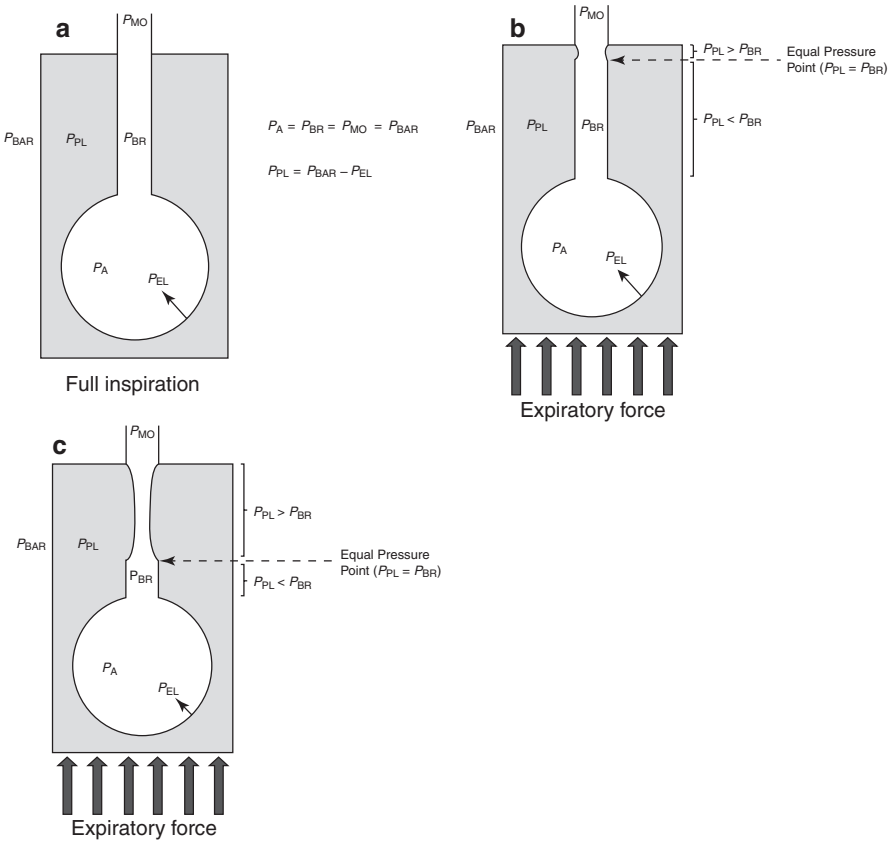

Fig. 6.1 A model of the respiratory tract, showing the relationship of intraluminal and intrapleural pressures (**a**) at full inspiration. Intraluminal pressures are equal, although the respiratory system is not at rest. (**b**) At the beginning of a forced expiration, where the equal pressure point is in the trachea; (**c**) towards the end of a forced expiration, where the equal pressure point has progressed to the peripheral airways

lungs continue to empty, the equal pressure point moves further away from the mouth, through the larger airways, and into the peripheral airways (Fig. 6.1c). The end of expiration is determined by the point at which small airway closure ("residual volume") finally occurs and airflow ceases.

While the equal pressure point mechanism explains expiratory flow limitation on the basis of the viscous properties of a gas flowing through a collapsible tube, another mechanism invokes flow limitation on the basis of the Bernoulli effect, which depends on the density of the gas. By this mechanism, the flow ($\dot{V}$) of air through a collapsible tube can never exceed the speed at which a wave can be propagated through it, regardless of the driving force ($P_A - P_{MO}$) behind it. This is referred

to as "wave speed theory" and is dependent on the cross-sectional area of the airways (A), the collapsibility of the airway under pressure (dA/dP), and the density of the gas (r):

$$\dot{V} = \sqrt{\left[A \times \left(dA / dP \right) / r \right]}$$

This formula indicates that maximal flow varies (1) directly with the area (A) of the tube, such that narrowing of the tube results in reduced flow (as occurs in asthma); (2) directly with the stiffness (dA/dP) of the tube, such that a more collapsible tube results in reduced flow (as occurs in emphysema); and (3) inversely with the density of the gas, such as occurs with a mixture of helium and oxygen, which results in higher flow due to the lower density of the gas mixture. During wave propagation, the sides of the tube would oscillate inward and outward to accommodate the wave of pressure, and at some point, the inward oscillation would result in a narrowing, or choke point, that would limit flow. This is analogous to the equal pressure point explained above.

6.2 The Measurement of Forced Expiration

A spirometry test involves a full inspiration followed by a complete expiration. The expiration is performed in either in a relaxed manner for a vital capacity (VC) or at maximum speed for a forced vital capacity (FVC). The first spirometers able to measure an FVC did so directly, producing a time/volume "spirogram" (Fig. 6.2a), integral to which is the forced expiratory volume in 1 s (FEV_1). Modern systems more commonly measure flow, which yield a flow-volume loop (Fig. 6.2b) and derive volume parameters indirectly via integration. Flow-volume loops also include various flow parameters at stages throughout the expiration, including the peak expiratory flow (PEF), MEF_{75} (maximal expiratory flow when 75% of FVC remains), MEF_{50} (when 50% of FVC remains), MEF_{25} (when 25% of FVC remains), and the maximal mid-expiratory flow (MMEF) (average flow between 25% and 75% of FVC). However, the clinical usefulness of these additional flow parameters for general clinical management is not well supported. Many modern spirometers also allow for the measurement of a forced inspiratory vital capacity (FIVC) after an FVC, which includes the MIF_{50} (maximal inspiratory flow when 50% of FVC remains). Both of these inspiratory measurements can be useful in certain respiratory disorders (e.g. upper airway obstruction – see later). The ratio of MEF_{50}:MIF_{50} is approximately 1.0 in healthy subjects, but it can vary with different types of airflow obstruction. Visual pattern (shape) recognition of the flow-volume loop is important when interpreting spirometry, and a flow/volume aspect ratio of 1:2 in equivalent units (i.e. L/s vs. L) is recommended.

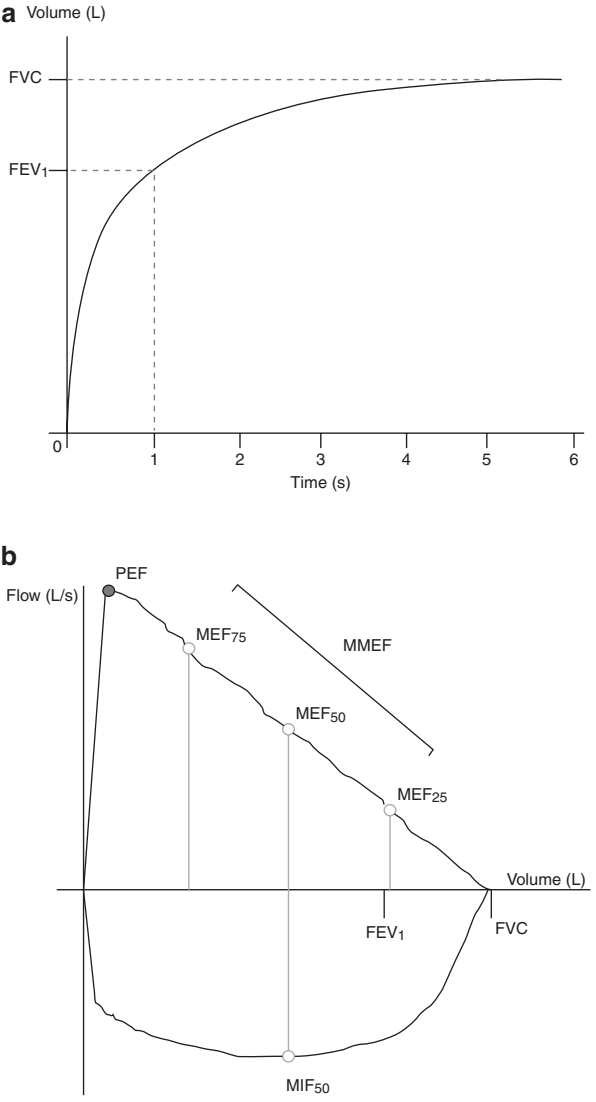

Fig. 6.2 (**a**) A classical expiratory "spirogram" from a healthy individual, showing the FEV_1 (volume expired at 1 s) and FVC (total volume expired). (**b**) A typical flow-volume loop from a healthy individual, showing the expiratory loop (above the *x*-axis) and inspiratory loop (below the *x*-axis). Highlighted are all flow parameters (measured directly) and volume parameters (derived by the integration of flow)

6.2.1 Indications and Contraindications

The most common symptom that patients present with in respiratory clinics is dyspnoea (shortness of breath), which may be present only on exertion or even at rest. There are many causes of dyspnoea (both respiratory and non-respiratory) and spirometry is a good starting point for physiological assessment to determine if there may be a respiratory cause. It is also a useful tool for determining the severity of

disease and monitoring progressive pathology or the response to treatment. There are also a number of other indications for spirometry, all of which are listed below:

- To determine the presence or absence of ventilatory dysfunction
- To determine the severity of lung disease
- To monitor lung function changes over time
- To assess short-term and long-term effects of interventions
- To determine the effects of occupational/environmental factors
- To assess the potential risk for surgical procedures ("pre-operative assessment")
- Pre-lung transplant assessment (as part of full lung function assessment)
- To assess disability
- For legal reasons or insurance evaluation
- As an outcome measure for clinical research

As spirometry involves a sustained forced expiratory manoeuvre, it increases intrathoracic, intra-abdominal, and intracranial pressure. Therefore, there are a number of reasons when it may be inappropriate for a patient to perform spirometry, which have been primarily designed to protect the patient from potential discomfort/pain/death but also abolish any risk of cross infection and to ensure results are representative of clinical stability. Most common contraindications are relative and include:

- Recent thoracic, abdominal, or ocular surgery
- Pneumothorax
- Thoracic, abdominal, or cerebral aneurysm (exceptions may be made for smaller aneurysms, e.g. <9 mm)
- Haemoptysis
- Active respiratory infection (exceptions may be made in cases of chronic infective diseases such as bronchiectasis)
- Unstable cardiovascular status
- Recent myocardial infarction or pulmonary embolism
- Nausea and vomiting
- Any other condition that may affect the ability to perform the test (e.g. inability to sit upright, cognitive dysfunction)

6.2.2 Pre-test Instructions

There are a number of pre-test recommendations for spirometry to optimise test performance and ensure that a true baseline measurement is recorded. The patient should be aware of these at least 24 h prior to testing. Ideally, patients should:

- Stop smoking for 24 h before the test (although, realistically, this may have to be shortened to ensure patient compliance)
- Not consume alcohol for at least 4 h before testing

- Avoid vigorous exercise for at least 30 min before testing
- Avoid eating a substantial meal for at least 2 h before testing
- Stop taking bronchodilators for the duration of their action (this may not be necessary for COPD monitoring, where post-bronchodilation spirometry may be preferable)

Therefore, any relevant clinical information that is likely to impair the performance of a spirometry test should be checked and noted when the patient arrives before testing commences.

6.2.3 Test Performance

Spirometry can be a physically and technically demanding test. Furthermore, patients who have never performed lung function tests before may understandably be anxious. Therefore, before attempting spirometry, the physiologist should take time to explain clearly to the patient what they will be required to do. It is also often useful to physically demonstrate a forced manoeuvre, so the patient appreciates how forceful the expiration will need to be. It is often necessary for the physiologist to adopt different styles of explanation and coaching for different patients.

The test procedure for performing spirometry is as follows:

- The patient should then be seated in an upright position in a chair with armrests with the chin level and both feet flat on the floor.
- Nose clips are recommended to minimise the chance of leak from the nose.
- Both relaxed VC and FVC manoeuvres start with a full inspiration. Some spirometers will require this before the mouthpiece is inserted (“open circuit”), whereas others will require tidal breathing through the spirometer first (“closed circuit”).
- Following a full inspiration, the patient must expire fully and continually in either a relaxed manner (for VC) or as forcibly as possible (for an FVC) while maintaining an upright position and an airtight seal around the mouthpiece with the lips.
- For an FVC manoeuvre, it is recommended that expiration commence within 1 s of reaching full inspiration.
- The person performing the test should continually encourage and coach the patient during expiration to ensure maximal effort and good technique.

6.2.4 Normal Ranges

Clinical interpretation of lung function data requires the comparison of obtained results to reference equations based on an individual’s height, age, sex, and race. These equations allow for the derivation of percent predicted values and standardised residuals (or “z-scores”).

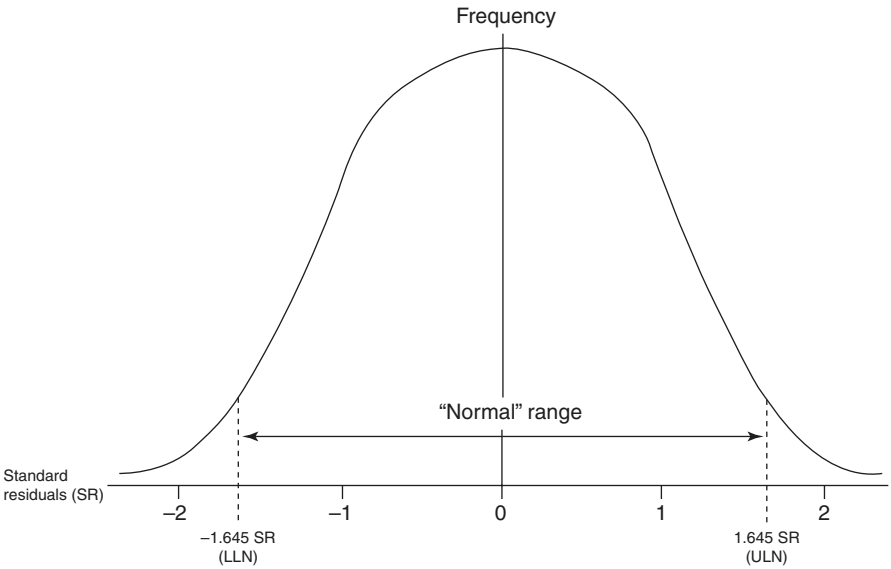

Fig. 6.3 A normal distribution curve with standardised residuals. The normal range only includes 90% of this population, which ranges from the lower limit of normal (LLN) at −1.645 SR to the upper limit of normal (ULN) at 1.645 SR. The probability of a value outside this range being "normal" is less than 5% ($p < 0.05$)

Traditionally, a threshold of 80% predicted was used to define normality. Although this may be comparatively easy to understand, it is now generally considered outdated as standardised residuals (SRs) can more accurately define the normal range. The normal range using SRs includes 90% of the population within the normal distribution curve, with the "lower limit of normal" (LLN) at −1.645 SR (Fig. 6.3). This method is not without limitations, although the probability of a measured value below the LLN being normal is less than 5% which, statistically, is considered non-significant (i.e. $p < 0.05$).

Recently, the European Respiratory Society Global Lung Function Initiative (GLI) has developed new reference equations, derived from lung function data from 74,187 healthy individuals. Importantly, this initiative included 3–95-year-old male and female never-smokers from multiple ethnic groups. Consequently, there is now a robust set of worldwide spirometry reference equations available for the first time.

Reference equations are discussed in greater detail in Chap. 14.

6.3 Patterns of Ventilation

Spirometry can identify both obstructive and restrictive ventilatory defects. Obstructive defects occur due to a narrowing of the airways. As mentioned, the cross-sectional area of the airways is a defining factor in airflow, and the result of

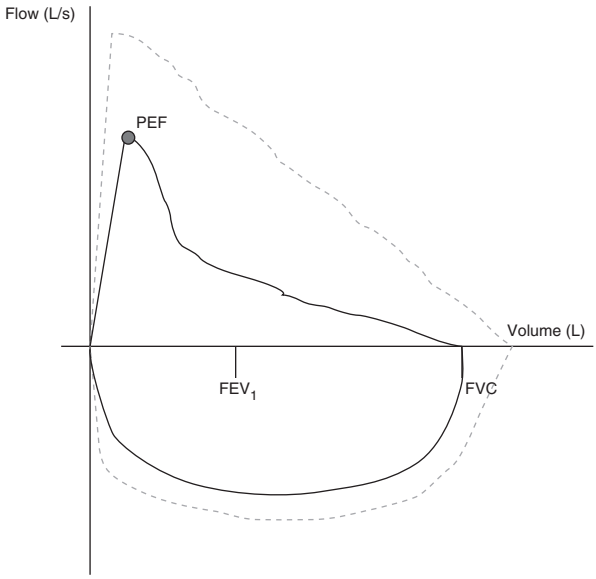

Fig. 6.4 A typical flow-volume loop from a patient with peripheral airflow obstruction. FEV_1 is considerably more reduced than FVC (which is often normal until more severe disease develops), leading to an FEV_1/FVC ratio below the normal range. For reference, a normal flow-volume loop is represented by the grey dotted line

airflow obstruction is decreased airflow due to increased airway resistance. Most obstructive defects affect the peripheral airways, leading to airflow obstruction predominantly on exhalation and a reduction in FEV_1 relative to the FVC (i.e. an FEV_1/FVC ratio below the normal range). Traditionally, the presence of airflow obstruction has been defined as an FEV_1/FVC ratio below 70%. However, the LLN is likely to be more appropriate at defining what is normal for an individual, as it accounts for natural age-related decline in lung function (e.g. emphysema can develop naturally in old age). Common diseases that cause peripheral airflow obstruction include chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, and cystic fibrosis. A typical flow-volume loop from a patient with airflow obstruction is shown in Fig. 6.4.

Following diagnosis of airflow obstruction from the FEV_1/FVC ratio, it may be further categorised into different severities based on the FEV_1% predicted. While the use of % predicted over SRs is contentious, it unfortunately remains the most widely accepted method of stratifying the severity of airflow obstruction. However, the use of SRs can easily replace % predicted once practitioners accept and remember their importance (Table 6.1). In addition to spirometry, it is also important to consider other factors such as breathlessness, cough, exercise capacity, and exacerbation frequency to give a more robust assessment of the impact of the disease as a whole.

The ratios between other volume parameters have also been suggested as a more accurate measure of airflow obstruction than FEV_1/FVC. These include FEV_1/VC (as patients can often expire more when doing so in a relaxed VC manoeuvre), FEV_3/FVC (which may be a better marker of early disease), and FEV_3/FEV_6 (FEV_6 is more repeatable than FVC and FEV_3/FEV_6 has also been shown as a marker of early small airway disease). However, these ratios are yet to be implemented in general clinical practice, and the FEV_1/FVC ratio remains the current standard.

Table 6.1 The most widely accepted methods of stratifying the severity of airflow obstruction in current use (GOLD and ERS/ATS), which are based in the FEV_1 expressed as a percentage of the predicted value

Severity of airflow obstruction	Global Initiative for Obstructive Lung Disease (GOLD)	European Respiratory Society (ERS)/American Thoracic Society (ATS)	Proposed SR range
	FEV_1	FEV_1	FEV_1
Mild	>80% predicted	>70% predicted	> −2
Moderate	50–80% predicted	60–70% predicted	−2.5 to −2
Moderately severe	n/a	50–60% predicted	−3 to −2.5
Severe	30–50% predicted	35–50% predicted	−4.0 to −3.0
Very severe	<30% predicted	<35% predicted	< −4

An example SR range (based on the ERS/ATS guidelines) to more accurately stratify airflow obstruction is included alongside

Larger obstructions (e.g. goitre, stenosis, tumour) can occur within the larger airways, which may impede expiratory airflow, inspiratory airflow, or both. This is dependent on whether the upper airway obstruction is intra- or extrathoracic and whether it is fixed (non-moveable) or variable (moveable). This is best determined physiologically by assessing the shape of the flow-volume loop, where truncation (flattening) of the expiratory/inspiratory curves indicates upper airway obstruction. A fixed extrathoracic obstruction will lead to flattening (often severe) of both the expiratory and inspiratory curves. A fixed intrathoracic airway obstruction will also cause a truncation of both the expiratory and inspiratory curves, but it may be less pronounced if the obstruction is in one of the bronchi rather than the trachea (as the degree of obstruction in relation to the total cross-sectional area of the airways is less). A variable extrathoracic obstruction will only impede inspiratory flow due to the negative intraluminal pressure on forced inspiration, whereas the positive intraluminal pressure in the upper airway on forced expiration effectively "pushes" the obstruction away from the airway lumen. The reverse is true in cases of variable intrathoracic upper airway obstruction, where obstruction only occurs on forced expiration due to an effective "amplification" of the dynamic airway compression at the site of obstruction. These are best understood from visual pattern recognition of the flow-volume loops (Fig. 6.5).

Therefore, the flow-volume loop has a number of advantages over the more basic spirogram in airflow obstruction. Visual assessment of the shape can itself be indicative of pathology (e.g. upper airway obstruction). Comparison of the maximal expiratory flow-volume curve (MEFVC) to a partial expiratory flow-volume curve (PEFVC) has been used to demonstrate the effect of a deep inhalation on airflow. In addition, volume-dependent changes in airflow that occur with differing degrees of gas compression on forced exhalation may be demonstrated by comparing flow measured at the same volume ("iso-volume") using a body plethysmograph vs. flow at the mouth, where mouth flow is typically less due to increased gas compression. This difference is generally more pronounced in airflow obstruction (Fig. 6.6) than in health, but this method has predominantly been a research tool rather than a clinical outcome.

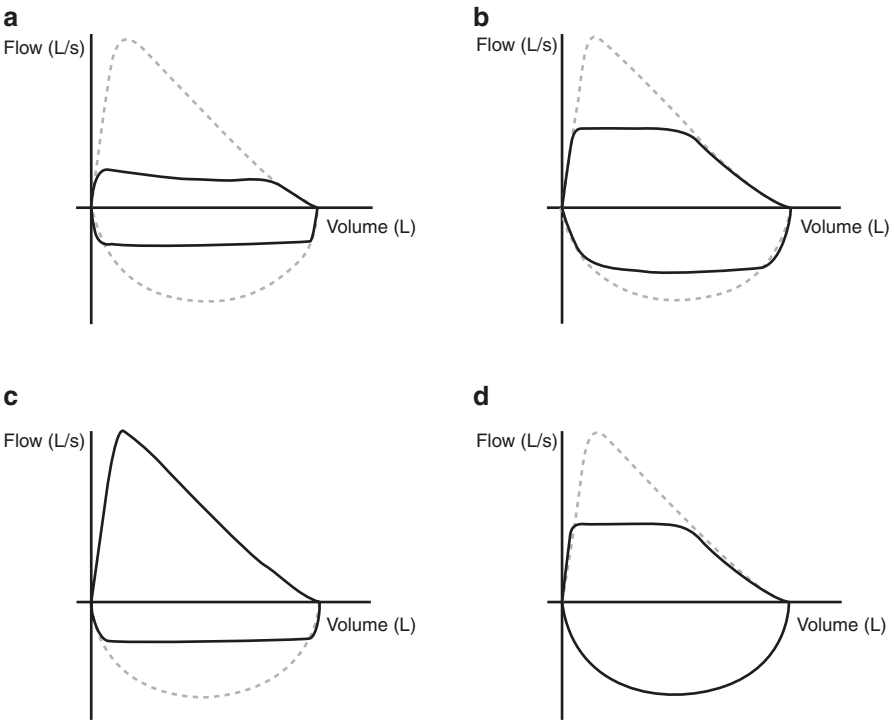

Fig. 6.5 Typical flow-volume loops from patients with various forms of upper airway obstruction. (**a**) Fixed thoracic obstruction (truncation of both expiratory and inspiratory curves); (**b**) fixed intrathoracic obstruction (truncation of both expiratory and inspiratory curves, which *may* be less pronounced as shown here), depending on the location of the obstruction); (**c**) variable extrathoracic obstruction (severe truncation of the inspiratory curve only); (**d**) variable intrathoracic obstruction (truncation of expiratory curve only, which may also be less pronounced, depending on the location of the obstruction)

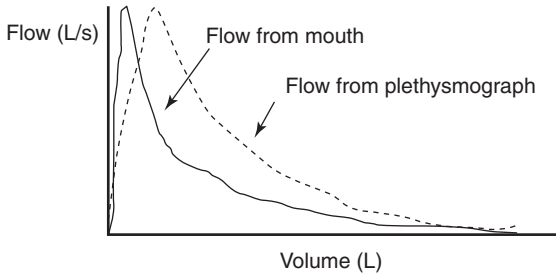

Fig. 6.6 Typical maximal expiratory flow-volume curves from a patient with emphysema. Isovolumetric analysis shows a marked difference in expiratory flow due to a greater degree of gas compression on forced exhalation when measured from volume changes in a body plethysmograph (dashed line) than volume changes expired at the mouth (solid line)

Restrictive ventilatory defects may be defined as a reduced ability of the lungs to expand, which can result from different pathophysiological processes. The pathology may be intrapulmonary, where fibrotic changes can lead to reduced compliance and the lungs themselves cannot expand as easily (e.g. pulmonary fibrosis, systemic lupus erythematosus, sarcoidosis). Alternatively, the pathology may be extrapulmonary, where the lungs are healthy but pathology outside the lungs restricts their expansion. This could be within the pleura (e.g. where plaques may form, making the pleura less compliant), the thoracic cage (e.g. skeletal abnormalities such as kyphoscoliosis, ankylosing spondylitis), or the muscles driving lung expansion (e.g. neuromuscular disease, inflammatory/metabolic myopathies). Obesity can also result in extrapulmonary restriction due to the excessive weight limiting thoracic expansion. In isolated ventilatory restriction, there is a concurrent and relative reduction on both FVC and FEV_1 with a preserved FEV_1/FVC ratio, which may actually increase in severe disease when patients can inspire so little, the vast majority (if not all) is expired within 1 s. On most cases, the shape of the flow-volume loop resembles that of a healthy individual but with an overall reduction in size and, in some instances (particularly advanced fibrotic lung disease), a partly convex expiratory loop due to reduced compliance (Fig. 6.7a). In cases of respiratory muscle weakness, there may be a rounding of the expiratory loop, a more abrupt end to expiration, and an abnormally slow inspiratory flow near full inflation (Fig. 6.7b).

There may also be cases where patients develop a mixed obstructive/restrictive defect, which occurs in approximately 1% of patients. This could either be due to two separate pathologies (e.g. COPD with fibrosis) or one pathology that causes both effects (e.g. sarcoidosis). In these cases, the FEV_1/FVC ratio will be below the normal limit together with an FVC below the normal range. However, it is worth noting that, in cases of severe airflow obstruction alone, FVC may also be below the normal limit. Therefore, a mixed defect would most likely demonstrate a reduced FVC that is disproportionately large compared to the degree of airflow obstruction. To confirm a true mixed defect, TLC should be measured. If TLC is normal, then the low FVC is solely due to severe obstruction, whereas if TLC is reduced, a true mixed defect is present. When this is the case, the severity of airflow obstruction can be more accurately assessed by adjusting the decrement in the FEV_1% predicted by the degree to which the TLC is reduced (i.e. adjusted FEV_1% predicted = measured FEV_1% predicted/measured TLC % predicted).

An interesting pattern that is described is a low FVC in the setting of a normal FEV_1/FVC, thus suggesting restriction, but a normal TLC, thus ruling against restriction. This has been called the "non-specific" pattern and appears to include patients with obstruction, restriction, chest wall disease, and neuromuscular weakness. Another recently described pattern has been called "complex restriction", which describes the situation where the FVC is disproportionally reduced compared to the reduction in TLC, with a relatively normal or elevated RV/TLC and normal FEV_1/FVC. This has been found to occur in about 4% of patients. Typically these patients had problems with impaired lung emptying such as neuromuscular disease, chest wall restriction, or subtle air trapping.

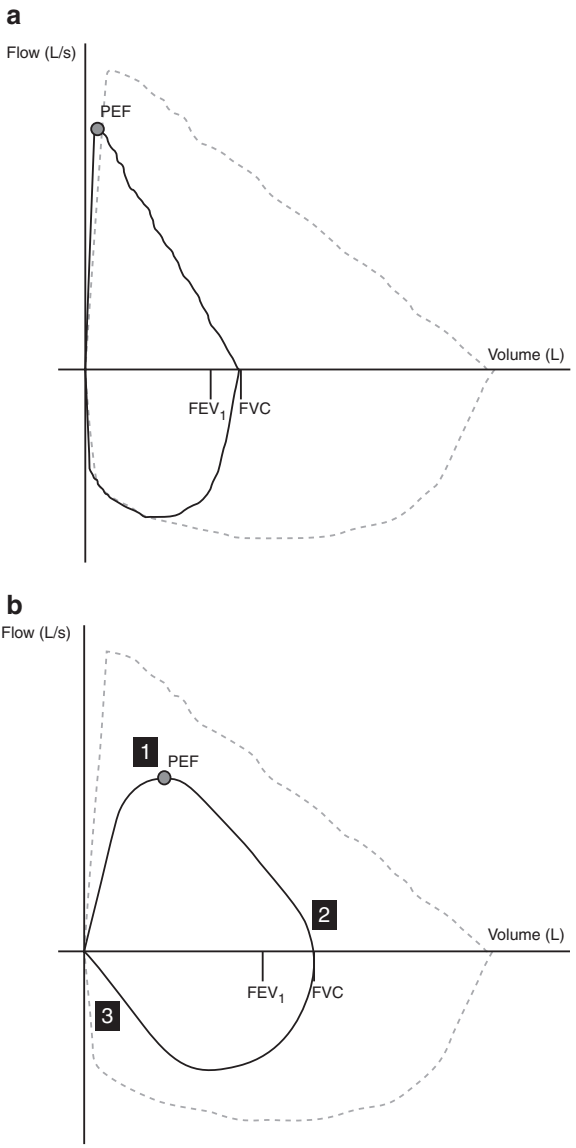

Fig. 6.7 Typical flow-volume loops from patients with ventilatory restriction. FVC and FEV_1 are reduced in proportion. (**a**) General restriction (including fibrotic lung disease, pleural disease, and skeletal abnormalities), (**b**) respiratory muscle weakness (common features are labelled and may include (1) a rounding of the expiratory curve, (2) an abrupt end to expiration, and (3) a slower inspiratory flow near full expansion)

6.4 Technical Performance

There are three components of an FVC manoeuvre; (i) a maximal inspiration followed immediately by (ii) the sharp "blast" at the start of a forced expiration, continuing on to (iii) complete exhalation. Therefore, the achievement of accurate spirometry is highly effort-dependent and requires good technical performance at all stages of the test. Consequently, poor technique/effort at any stage can affect the

measurements. For instance, submaximal effort at the start of expiration will not only underestimate PEF but, due to a smaller degree of dynamic airway compression, can actually overestimate FEV_1 (so-called "negative effort dependence"). Achievement of a full FVC can also be physically demanding, particularly for patients with advanced lung disease. The European Respiratory Society (ERS)/American Thoracic Society (ATS) 2005 guidelines outline recommendations for the achievement of technically acceptable spirometry. It is important that the time between maximal inspiration and the start of the forced expiration is minimal (2 s maximum), as a long delay may reduce expiratory power and affect PEF and FEV_1 (likely due to stress relaxation of elastic elements). Furthermore, the PEF at the start of the forced expiration must be achieved almost immediately following commencement of exhalation, and guidelines recommend an expiratory "extrapolation volume" less than 5% of FVC or 150 ml (whichever is greater) (Fig. 6.8).

Continued effort to achieve a true maximum exhalation without pause or intermittent inhalation is also difficult, particularly for patients with severe airflow obstruction. Guidelines recommend a minimum exhalation time of 6 s and an expiratory plateau (<0.025 L change in >1 s) denote a technically acceptable FVC endpoint. However, it is worth noting that patients with airflow obstruction, who can

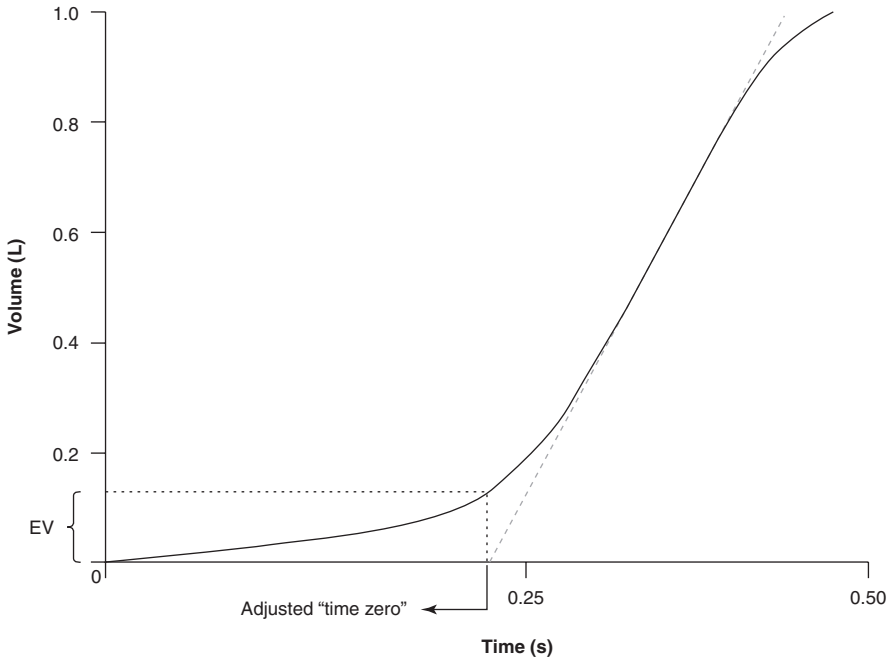

Fig. 6.8 An expanded view of the start of a spirogram. A line (grey dashed) through the steepest part of the expiratory curve (which equates to PEF) yields an adjusted "time zero" at the intersect of the time axis. The extrapolation volume (EV) is the volume at which a vertical line from the adjusted time zero intersects the expiratory curve. Guidelines recommend that EV should not exceed 5% of FVC

often expire for far longer than 6 s, may not achieve an expiratory plateau. In all cases, it is the responsibility of the physiologist to encourage patients to achieve their maximum, and it is generally at the very start and towards the end of forced expiration that most encouragement is needed.

It is also the operator's responsibility to recognise and attempt to correct any technical errors. As mentioned, a submaximal effort at the start will adversely influence PEF and FEV_1 measurements, although it should be noted that flow-volume loops from patients with respiratory muscle weakness may look "submaximal" despite maximum effort on their part (Fig. 6.7). A cough may also occur during forced expiration, which may either be a "cough-like" PEF due to brief glottis closure after full inspiration (this may overestimate PEF, but the manoeuvre may still be technically acceptable) or a true cough later in the forced expiratory manoeuvre. If a true cough occurs before 1 s, it will render the attempt unacceptable, as FEV_1 will be affected. If it occurs after 1 s, the attempt may still be acceptable (FEV_1 will certainly be valid), providing expiration is continuous and the end of test criteria are met. Patients also often strain too hard during a forced expiration, which not only makes it more difficult to expire and could lead to cough or even syncope but may also underestimate results due to increased upper airway resistance. Glottis closure (a Valsalva manoeuvre) is also relatively common (which may occur due to straining) and will underestimate FVC due to premature airway closure. Other causes of early termination include unsustained effort and complete obstruction of the spirometer tube by the tongue. A partial obstruction by the tongue may actually result in an accurate FVC, but FEV_1 will commonly be affected due to impeded airflow from the lungs into the spirometer. Finally, the patient must maintain an airtight seal around the mouthpiece to avoid leak (nose clips are also recommended for the same reason). How some of these common errors appear on expiratory flow-volume curves are shown in Fig. 6.9.

6.4.1 Repeatability Criteria

In order for spirometry to be accurately interpreted, a number of separate manoeuvres with repeatability at a single session must be obtained. A satisfactory spirometry session requires a minimum of three technically acceptable manoeuvres. The ATS/ERS guidelines recommend that the difference between the largest FEV_1 and FVC values within the test session should be within 150 ml (or 100 ml if FVC is <1 L). In contrast, the ARTP (Association of Respiratory Technology and Physiology (UK)) guidelines recommend 100 ml or 5% (whichever is larger), which may more robustly account for the variation in absolute values between individuals. In reality, many good respiratory physiology departments can achieve <70 ml repeatability in 80% of subjects tested. Both guidelines recommend that the maximum for each parameter be reported, even if they are not from the same attempt. Neither

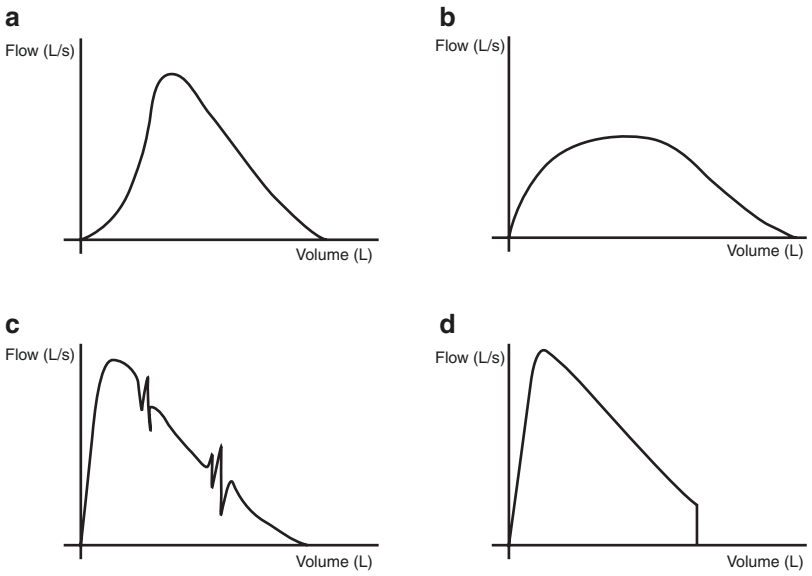

Fig. 6.9 Examples of how common technical errors appear on expiratory flow-volume curves, including (**a**) a slow start, (**b**) poor effort (at the start of forced expiration), (**c**) cough, and (**d**) glottis closure

guidelines propose a repeatability criterion for PEF as part of an FVC manoeuvre (even though it can influence FEV_1), although the ATS/ERS guidelines address this indirectly by suggesting that the "shape" of the expiratory flow-volume curve should be repeatable. These guidelines also recommend that, as a stand-alone measurement, PEF should be repeatable within 0.67 L/s. It should be noted that poor repeatability can sometimes be a clinical feature (e.g. bronchoconstriction on repeated attempts or fatigue due to muscle weakness).

A maximum of eight FVC manoeuvres should be attempted, and, in cases where repeatability acceptability criteria are not met, the best results may still be reported (providing they are technically acceptable) with an interpretative note. Over time, patients can often learn how to perform more technically acceptable spirometry through practice with repeat testing.

6.4.2 Quality Assurance

Spirometry is a biomedical diagnostic procedure and should, consequently, have appropriate quality assurance (QA) standards to ensure the measurements and their interpretation are both accurate. QA is a set of procedures implemented to guarantee

that spirometry testing adheres to international standards (e.g. ATS/ERS). It includes both assessment of the patient's performance of spirometry during testing by qualified physiologists and also separate quality control (QC) procedures to ensure the equipment itself is accurate. QC procedures include:

- Equipment calibration/verification
- A log of calibration/verification results
- Documentation of equipment faults and repairs
- Documentation of software upgrades

Calibration is different from verification, although they are both performed in the same manner using a precision syringe (usually a 3-L syringe with an accuracy of less than 15 ml). Calibration is the checking of a spirometer with a known standard (e.g. 3-L volume), followed by the adjustment of the spirometer to the exact value of that standard. In contrast, verification does not allow for the adjustment of the spirometer but is, rather, a check that the device is measuring within acceptable limits (e.g. +3% of the known value). Syringe calibration/verification (often termed "physical QC") should be performed daily before patient testing (and following equipment transfer). For flow-measuring spirometers, it is also recommended that calibration/verification be performed using variable flows (to represent the different flows at which patients may expire/inspire). Older volume-measuring devices (e.g. wedge-bellows spirometer) may instead require daily verification with a 3-L syringe together with leak checks and quarterly time checks (with a stopwatch) to ensure the carriage moves at an accurate speed. In addition, it is important that every syringe is checked for accuracy by the manufacturer (usually annually).

An additional simple QC procedure is to perform regular tests on healthy subjects (e.g. physiology staff). This biological (or "physiological") QC is usually performed weekly and matched to an individual's expected range (determined from previous repeat testing) but may also be used as a robust and full assessment of equipment performance that allows for the differentiation of patient and equipment error in instances where acute technical issues are suspected.

6.5 Bronchodilator Reversibility Assessment

As spirometry is a physiological test of airway ventilation, it is often used to assess the short-term effects of pharmacological agents that aim to improve airway calibre and, hence, ventilation. Bronchodilators may be categorised into two general types: (i) beta-2 agonists and (ii) antimuscarinic agents. These drugs are inhaled either as an aerosol or dry powder (via a handheld inhaler device) or nebulised.

Beta-2 agonist act on the beta-2 adrenergic receptors which, in turn, produce cyclic adenosine monophosphate (cAMP) through the coupled G-protein, adenylyl cyclase. In the lungs, cAMP has a number of downstream signalling effects, including decreased intracellular calcium, inactivation of myosin light chain kinase, and increased potassium conductance. These effects lead to the relaxation of the smooth

muscle surrounding the airways and concordant bronchodilation (increased airway calibre). The effect of beta-2 agonists is direct and rapid, with peak bronchodilation occurring within 20 min. Inhaled antimuscarinic agents achieve bronchodilation via a different signalling pathway. These are anticholinergic drugs that block acetylcholine activity by binding to muscarinic acetylcholine receptors. Acetylcholine is a neurotransmitter released by neurones into the neuromuscular junction to activate muscles. Therefore, inhibition of this pathway in the lungs inhibits contraction of the smooth muscle around the airways, leading to bronchodilation. The mode of action is indirect and, hence, less rapid than a beta-2 agonist, with peak bronchodilator effect occurring after approximately 45 min.

Bronchodilation reversibility assessments include the assessment of baseline spirometry followed by bronchodilator administration and, after the recommended time for peak effect (20 min for beta-2 agonists and 45 min for antimuscarinic agents), repeat "post-bronchodilator" spirometry. Therefore, it is essential that patients withhold their bronchodilators for up to 24 h (depending on the duration of the bronchodilator effect) prior to baseline spirometry.

Determining a positive bronchodilator response is not straightforward. There are a number of published guidelines (Table 6.2), where the definition of a positive response is based either on absolute change (ml), a percentage change, or both. A percentage change may be more appropriate than an absolute change, as it expresses the change more accurately in terms of the baseline value. Moreover, a percentage change is also independent of demographic factors (particularly height) that influence the natural variability of an individual's measurement. For instance, 160 ml could be within the natural variability of the FEV_1 from an individual who is very tall, whereas a very short individual may struggle to increase their FEV_1 by over 160 ml following bronchodilation, particularly if they have severe airflow obstruction and a very small baseline FEV_1 (e.g. <50 ml). It has recently been shown that a bronchodilator response expressed as change in % predicted is a good predictor of mortality in patients with suspected respiratory disorders. Another strategy for determining a bronchodilator response is to measure the change in FEV_1 and/or FVC after bronchodilator in relation to the individual's intratest variability in these parameters when measured at baseline. If the change after bronchodilator statistically exceeds this intratest variability, then one might conclude that there has been a statistically significant response. Whether or not such a change is clinically significant would still need to be determined.

Table 6.2 Published guidelines from four sources stating the criteria that define a positive bronchodilator response

Guidelines	Criteria
Association of Respiratory Technology and Physiology (ARTP)	160 ml in FEV_1 and/or 330 ml in FVC
British Thoracic Society (BTS)	200 ml and 15% in FEV_1
Global Initiative for Obstructive Lung Disease (GOLD) and ERS/ATS 2005	200 ml and 12% in FEV_1
National Institute for Health and Care Excellence (NICE) (2010)	400 ml in either FEV_1 or FVC

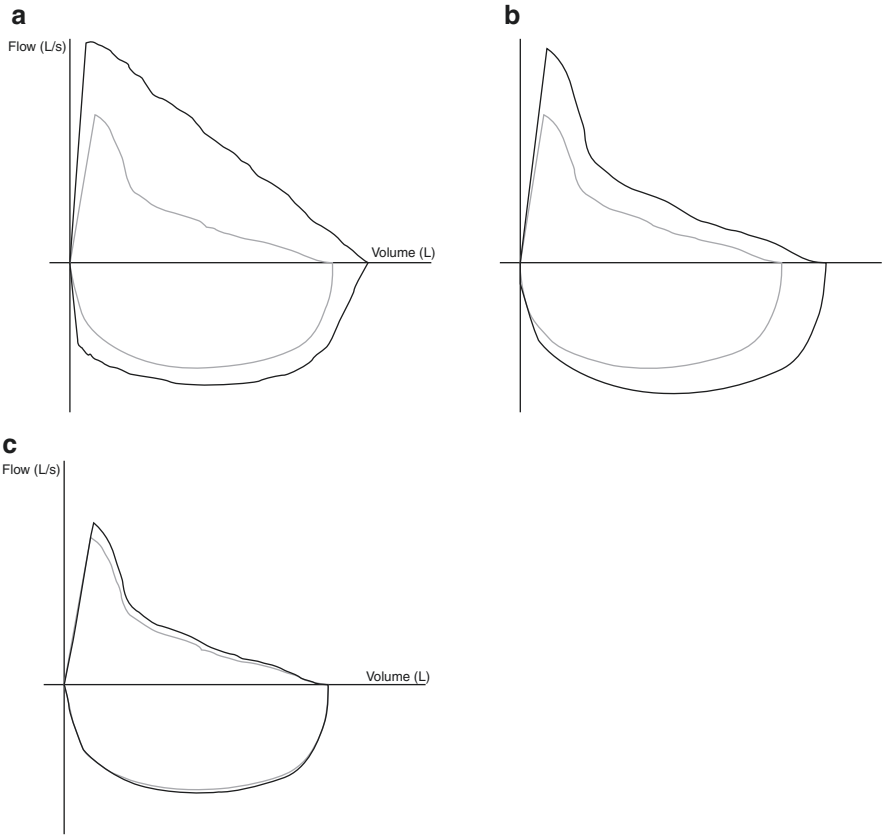

Fig. 6.10 Typical flow-volume loops representing pre-bronchodilator (grey) and post-bronchodilator (black) spirometry from patients with (**a**) full reversibility, (**b**) partial reversibility, and (**c**) no reversibility ("fixed" obstruction)

Following bronchodilation, patients will either demonstrate full reversibility (with post-bronchodilator spirometry within normal limits), partial reversibility (with a positive bronchodilator response but post-bronchodilator spirometry still showing airflow obstruction), or no significant reversibility ("fixed" airflow obstruction) (Fig. 6.10). Full reversibility is generally only seen in asthma in response to a beta-2 agonist, where the diagnosis is further supported if the patient is young and has never smoked (or has minimal smoking history). Partial or no reversibility is common in COPD, bronchiectasis, and chronic severe asthma, and it is well recognised that these conditions can occur concurrently. It is important to note that the lack of a significant bronchodilator response does not mean that bronchodilators are not clinically useful as, for many patients (particularly those with COPD), bronchodilators can improve airway calibre over the tidal breathing range, reduce hyperinflation and the work of breathing, and lead to an improvement in symptoms. Common clinical differences between asthma and COPD (which should be elucidated during clinical consultation to support diagnostic spirometry) are listed in Table 6.3.

Table 6.3 Common clinical features that may help differentiate asthma and COPD in developed countries

Clinical feature	Asthma	COPD
Smoker/ex-smoker	Possibly	Nearly all
Symptoms in younger age (<35 years)	Common	Rare
Dyspnoea	Variable	Chronic and progressive
Chronic, productive cough	Rare	Common
Diurnal and day-to-day symptom variation	Significant	Uncommon
Nighttime waking with dyspnoea + wheeze	Common	Rare

It is worth noting that each can occur in both conditions but are usually far more common in one. It is also possible to have asthma with COPD (sometimes referred to as "asthma-COPD overlap syndrome"). Combining clinical history with diagnostic spirometry (and sometimes other tests, such as imaging) is more likely to give an accurate diagnosis

6.5.1 Bronchial Challenge Testing

Normal spirometry does not exclude a diagnosis of asthma where, in many cases, bronchoconstriction and airflow obstruction may only develop in response to certain triggers (e.g. an allergen). Therefore, if a patient with normal spirometry presents with symptoms and clinical signs of asthma, it may be beneficial to perform a bronchial challenge test to support the diagnosis.

There are various means by which the airways can be provoked to induce bronchoconstriction, which may be classified as direct or indirect. Direct stimuli act directly on the effector cells (e.g. smooth muscle cells, bronchial capillary endothelial cells, and secretory cells in the airway epithelium), and the most common of these in clinical practice is methacholine, although histamine has also been used. Indirect stimuli induce bronchoconstriction by acting on intermediate cells (e.g. inflammatory cells, epithelial cells) that then stimulate effector cells. Common indirect stimuli include mannitol, hypertonic saline, exercise, and eucapnic voluntary hyperpnoea (hyperventilation of cold, dry air). The physiological effects of the stimulus are assessed by comparing pre- and post-stimulus spirometry (particularly FEV_1), with a decrease of 10–20% (depending on the test) indicating a positive response. In cases where a pharmacological agent is used, a "provocative dose" (PD) or "provocative concentration" (PC) is calculated, which may be cumulative if the protocol uses increasing doses (e.g. mannitol).

Mannitol is a good example of an indirect agent that is now widely used for bronchial challenge testing. It is inhaled as a dry powder (housed within small capsules) through a small handheld device. Once inhaled, it increases the osmolarity of the bronchial mucosa and induces the release of inflammatory mediators (including histamine, prostaglandins, and leukotrienes) from mast cells and eosinophils. Spirometry is performed 1 min after each dose, and a positive response is defined as a 15% fall in FEV_1 compared to baseline within a total cumulative mannitol dose of 645 mg.

The mannitol challenge test has a reasonable sensitivity but will only detect around 60% of asthma cases (i.e. 40% of asthmatics will not respond to mannitol).

However, it has very high specificity, meaning that, if a mannitol test shows a positive response, a diagnosis of asthma can be made with confidence.

As the aim of a challenge test is to induce bronchoconstriction, it is important that patients withhold all treatments that are known to influence bronchial responsiveness for sufficient time to render their effects negligible (e.g. bronchodilators, antihistamines, and leukotriene modifiers such as montelukast).

6.5.2 Assessment of Airway Sensitivity to Inhaled Antibiotics

Patients with obstructive lung disease often have acute exacerbations, which may be defined as a sustained worsening of symptoms beyond natural day-to-day variability and may require a change in treatment (e.g. short course of oral antibiotics +/- steroids). In many cases, exacerbations are caused by bacterial colonisation, and a proportion of patients may even be chronically colonised and exacerbate frequently (most commonly those with bronchiectasis, cystic fibrosis, or COPD). For such patients, prophylactic nebulised antibiotic therapy may be indicated. However, some patients may experience adverse and allergic reactions to certain inhaled antibiotics. Therefore, it is essential to perform an assessment of airways sensitivity to a proposed antibiotic to ensure that it does not induce bronchospasm.

The assessment should be performed in a clinically stable state and involves the measurement of baseline spirometry followed by nebulised antibiotic administration and repeat spirometry at 15 and 30 min post-antibiotic (this is a recommended minimum, and it may also be useful to assess at 45 and 60 min post-antibiotic). Due to the possibility of bronchospasm, a beta-2 agonist (e.g. salbutamol 2.5 mg) should be made available. It is also important to monitor the patient to ensure symptoms (e.g. wheeze, dyspnoea) do not manifest or worsen following antibiotic administration. If FEV_1 does not decrease by >15% and >200 ml from baseline and the patient does not experience symptomatic side effects, the antibiotic may be safely prescribed. If FEV_1 does decrease by >15% and >200 ml from baseline or the patient experiences symptoms of bronchospasm, the patient has had an adverse reaction. Testing should be terminated and the beta-2 agonist administered immediately. It may then be useful to reassess the patient 20 min after the beta-2 agonist to ensure spirometry and symptoms have returned to baseline.

6.5.3 Peak Flow Monitoring

PEF when measured as part of an expiratory flow-volume curve is far less informative then FEV_1 and FVC. However, as a stand-alone measurement, it can be a useful domiciliary monitoring tool for suspected asthma (where diurnal variability of symptoms is common). It may be particularly useful in patients who do not have an accurate perception of symptoms when their asthma is worsening (so-called “poor perceivers”). PEF monitoring may also be useful to diagnose occupationally-related

asthma. PEF meters are cheap and easy to use and do not require a power supply, making them ideal for home monitoring. As the patient will be monitoring their own PEF, it is important that they are correctly educated on the performance of a technically acceptable PEF manoeuvre prior to issue.

To monitor diurnal variation accurately, it is necessary for the patient to measure their PEF at three intervals throughout the day: in the morning, around noon, and in the evening. Generally, the patient will perform three or four PEF measurements in each of these sessions and select the best of a consistent group. It is also useful for monitoring purposes that the patient keep the session times consistent day-to-day and also ensure that any bronchodilators they are prescribed are used at the same time every day (e.g. to measure their morning PEF before taking bronchodilators every day). Measuring PEF three times daily in this manner (usually for a 2-week period) is necessary for detecting variations in lung function throughout the day that asthmatics often experience. For instance, asthmatics often have worse lung function early in the morning and later in the evening, with improvement in the middle of the day. In contrast, patients whose asthma only occurs when exposed to an occupational allergen are more likely to have lower PEF when at work.

In addition to a diagnostic aid, PEF monitoring can also be used to demonstrate therapeutic benefits. For example, an asthmatic patient may show a gradual but sustained improvement in PEF following the prescription of an inhaled corticosteroid. In this case, it may not be necessary to perform PEF three times per day. Monitoring PEF only twice per day is often sufficient (Fig. 6.11), with a minimum

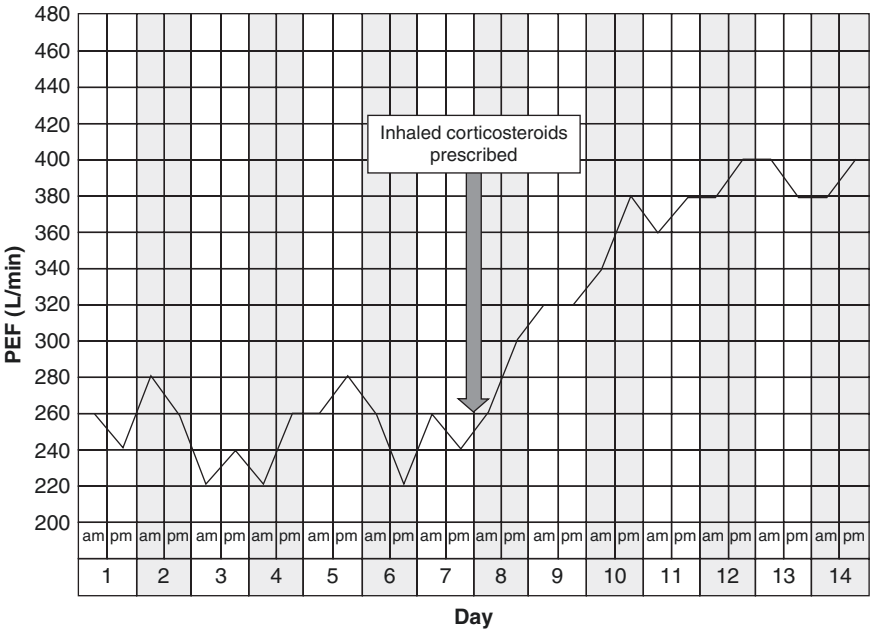

Fig. 6.11 A typical daily PEF diary showing improvement in PEF following the prescription of an inhaled corticosteroid at day 8. Patients may not demonstrate a therapeutic response to PEF within 7 days of treatment, so the post-treatment monitoring period may need to be extended to 2 or 3 weeks

of 1 week before and after the prescription of medication. However, noticeable therapeutic benefit may not occur until 3 weeks, so post-treatment monitoring may need to be extended.

6.6 Summary

The measurement of expiratory flows provides robust information about pulmonary ventilation, which may become compromised in a variety of respiratory disorders. Spirometry can be performed on small, portable devices, making it one of the most common and readily available lung function tests. It is ideal for use in both primary and secondary care as a diagnostic aid and monitoring tool. However, due to the maximal effort required from the patient and the associated technical issues, spirometry should only be performed and interpreted by fully trained and certified healthcare practitioners.

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