In Clinical Practice

Ali Altalag · Jeremy Road · Pearce Wilcox
Kewan Aboulhosn *Editors*

Pulmonary Function Tests in Clinical Practice

Second Edition

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Preface

The volume of expelled air is believed to have been first measured by Galen in about 150 AD. However, it was not until the mid-1800s that Hutchinson designed a spirometer, very similar to the ones used today, which allowed routine measurement of exhaled lung volume. Finally, in 1969 Dubois designed the plethysmograph, which allowed a measure of the complete lung volume, which included the residual volume. Nowadays measuring spirometry has become routine with the advent of the pneumotachograph and computers. Although the technology is widely available and not excessive in cost, spirometry or the measurement of exhaled gas volume is still underutilized. To detect disease and assess its severity lung volume measures are extremely useful, indeed one might say mandatory, so the reason for this underutilization remains obscure. We hope that this book, which is aimed at the clinician, helps to explain the basics of lung volume measurement and hence increases its utility. The text also includes an overview of exercise and respiratory sleep diagnostic tests for the clinician.

Contents

Chapter 1
Spirometry

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract Spirometry represents the foundation of pulmonary function testing and in most instances spirometry derived measurements are the most clinically relevant. In spirometry, a device called a spirometer is used to measure certain lung volumes, called dynamic lung volumes. The two most important dynamic lung volumes measured are the forced vital capacity (FVC) and the forced expiratory volume in the first second (FEV_1). This section deals with the definitions, physiology and clinical applicability of these and other spirometric measurements.

Keywords Spirometry · Vital capacity · Forced vital capacity (FVC) · Forced expiratory volume in the first second (FEV_1) · Flow-volume curve · Flow-volume loop · Volume-time curve · Obstructive disorder · Restrictive disorder

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DEFINITIONS [1, 2]

Forced Vital Capacity (FVC)

- Is the volume of air (in liters) that can be forcefully and maximally exhaled after a maximal inspiration. FVC is unique and reproducible for a given subject.
- The *Slow Vital Capacity (SVC)*—also called the *Vital Capacity (VC)*—is similar to the FVC, but the exhalation is intentionally slow. In a normal subject, the SVC is equivalent to the FVC; [3] while in patients with an obstructive lung disorder *(see* Table 1.1 *for definition)*, the SVC is usually larger than the FVC. The reason for this is that, in obstructive lung disorders, the airways tend to collapse and close prematurely because of the increased positive intra-thoracic pressure during a forceful expiration (dynamic compression). This leads to air trapping. Accordingly, a significantly higher SVC compared to FVC suggests air-trapping; Figure 1.1.
- The *Inspiratory Vital Capacity (IVC)* is the VC measured during inspiration rather than expiration. The IVC should equal the expiratory VC. If it doesn't, poor effort or an air leak should be suspected. IVC may be larger than the expiratory VC in patients with significant airway obstruction, as in this case the inspiratory negative intra-thoracic pressure opens the airways facilitating inspiration, as opposed to the dynamic narrowing of airways during exhalation as the intra-thoracic pressure becomes positive [4, 5]. Narrowed airways reduce airflow and hence the amount of exhaled air.
- FEV_6 is defined as the volume of air exhaled in the first 6 seconds of the FVC and its only significance is that it can some-

Table 1.1 Definitions of obstructive and restrictive disorders

Obstructive disorders:
Are characterized by diffuse airway narrowing secondary to different mechanisms (e.g. atopy in asthma, or environmental e.g. smoking in chronic obstructive pulmonary disease (COPD))
Restrictive disorders:
Are a group of disorders characterized by abnormal reduction of the lung volumes, either because of alteration in the lung parenchyma or because of a disorder of the pleura, chest wall or ventilatory muscles

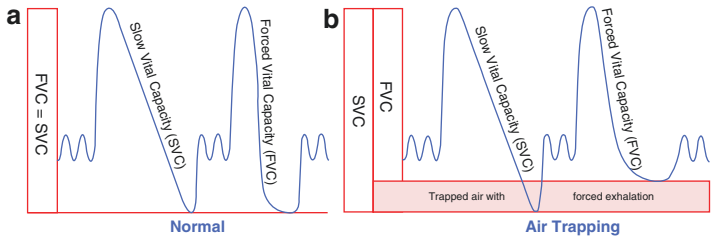


FIGURE 1.1 FVC and SVC are compared with each other in a normal subject (**a**) and in a patient with an obstructive disorder (**b**). In the case of airway obstruction, SVC is larger than FVC, indicating air trapping

times substitute for the FVC in patients who fail to exhale completely or to be substituted for FVC for "office" spirometry [6]. The inability to meet FVC criteria is one of the main quality assurance issues with non PFT lab spirometry and is mitigated when using FEV_6.

Forced Expiratory Volume in the First Second (FEV_1)

- FEV_1 is the volume of air in liters that can be forcefully and maximally exhaled in the first second after a maximal inspiration. In other words, it is the volume of air that is exhaled in the first second of the FVC, and it normally represents ~70–80% of the FVC (age dependent).

FEV_1/FVC Ratio

- This ratio is used to differentiate an obstructive from a restrictive pattern, *see* Table 1.1 *for definitions*. In obstructive disorders, FEV_1 decreases more significantly than FVC, consequently the ratio will be decreased; while in restrictive disorders, the ratio is either normal or increased as the drop in FVC is either proportional to or more marked than the drop in FEV_1.
- Normally, the FEV_1/FVC ratio is greater than 0.7, but it decreases (to values <0.7) with normal aging [7]. In children, however, it is higher and can reach as high as 0.9 [8]. The decline in this ratio as we age reflects the decrease in elastic recoil of the lungs that occurs with aging.

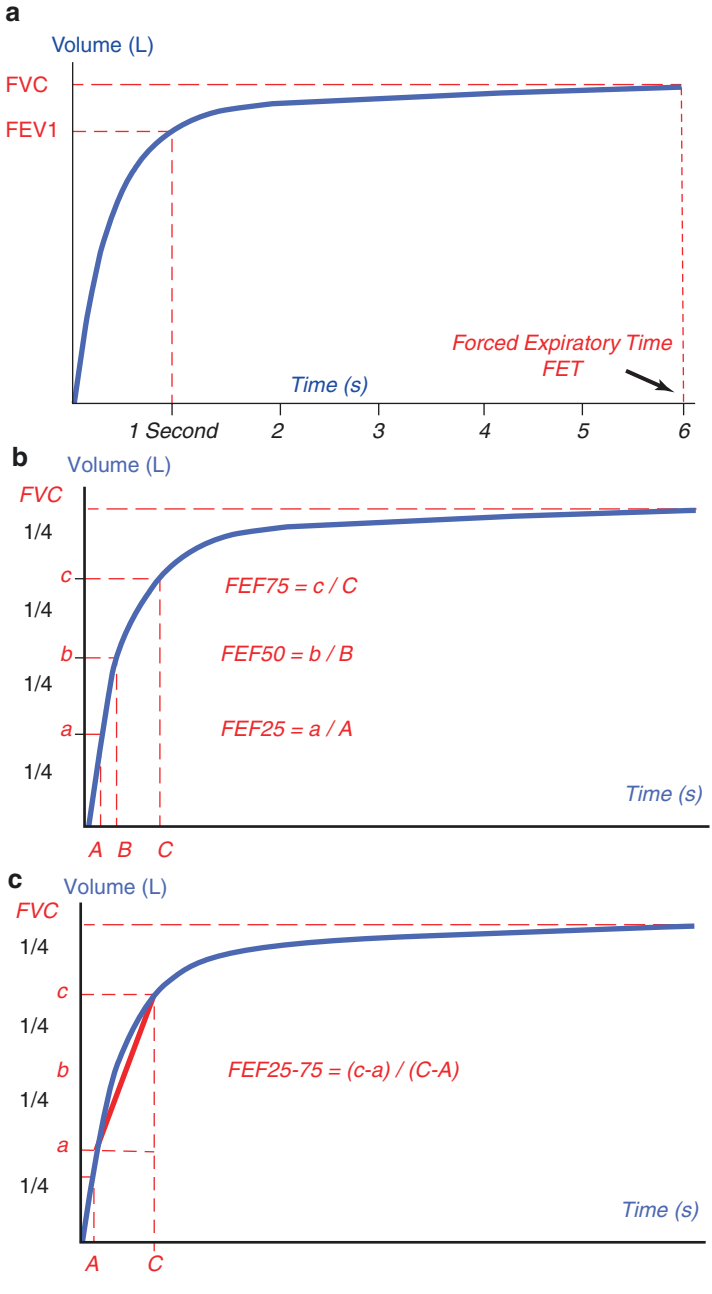
The Instantaneous Forced Expiratory Flow (FEF_{25}, FEF_{50}, FEF_{75}) and the Maximum Mid-Expiratory Flow (MMEF or $FEF_{25–75}$)

- The Instantaneous Forced Expiratory Flow (FEF) represents the flow of the exhaled air measured (in liters/second) at different points of the FVC, namely at 25%, 50% and 75% of the FVC. They are abbreviated as FEF_{25}, FEF_{50} and FEF_{75}, respectively; Figure 1.2b. The Maximum Mid-Expiratory Flow (MMEF) or $FEF_{25–75}$, however, is the average flow during the middle half of the FVC (25–75% of FVC); see Figure 1.2c. These variables still represent the effort-independent part of the FVC [9]. Collectively, they are considered more sensitive (but non-specific) in detecting early airway obstruction which tends to take place at lower lung volumes [10, 11]. Their usefulness is limited, however, because of the wide range of normal values and inherently greater variability [10].

Peak Expiratory Flow (PEF)

- Is the maximum flow (in liters/second) of air during a forceful exhalation. Normally, it takes place immediately after the start of the exhalation and it is effort-dependent. PEF drops with a submaximal effort in obstructive and, to a lesser extent, restrictive disorders. PEF measured in the laboratory is similar to the peak expiratory flow rate (in liters/minute) that is measured routinely at the bedside with a peak flow meter.

FIGURE 1.2 From the volume–time curve (spirogram) the following data can be acquired: (**a**) FVC is the highest point in the curve; FEV_1 is plotted in the volume axis opposite to the point in the curve corresponding to 1 second; duration of the study (the forced expiratory time or FET) can be determined from the time axis, 6 seconds in this curve. (**b**) $FEF_{25,50,75}$ can be roughly determined by dividing the volume axis into four quarters and determining the corresponding time for each quarter from the time axis. Dividing the volumes (a, b, and c) by the corresponding time (A, B, and C) gives the value of each FEF (FEF_{25}, FEF_{50}, FEF_{75}, respectively). Note that this method represents a rough determination of FEFs, as FEFs are actually measured instantaneously by the spirometer and not calculated. (**c**) $FEF_{25–75}$ can be roughly determined by dividing the volume during the middle half of the FVC (c–a) by the corresponding time (C–A). $FEF_{25–75}$ represents the slope of the curve at those two points


a
Volume (L)
FVC
FEV1
Forced Expiratory Time
FET
Time (s)
1 Second
2
3
4
5
6
b
Volume (L)
FVC
1/4
c
1/4
b
1/4
a
1/4
FEF75 = c / C
FEF50 = b / B
FEF25 = a / A
Time (s)
A
B
C
c
Volume (L)
FVC
1/4
c
1/4
b
1/4
a
1/4
FEF25-75 = (c-a) / (C-A)
Time (s)
A
C

SPIROMETRIC CURVES

The Volume-Time Curve (The Spirogram)

- Is the FVC plotted as volume in liters against time in seconds; Figure 1.2a.
- You can extract from this curve both the FVC and FEV_1. FEV_1/FVC ratio can be estimated by looking at where the FEV_1 stands in relation to the FVC; Figure 1.2a. In addition, the curve shape helps in determining that ratio: a decreased ratio will necessarily make the curve look flatter and less steep than normal, see Figure 1.16. The FEFs (FEF_{25}, FEF_{50}, FEF_{75}) and MMEF (FEF_{25-75}) can also be determined from the curve as shown in Figure 1.2b, c.
- This curve also provides an evaluation of the quality of the spirometry, as it shows the duration of the exhalation (The Forced Expiratory Time or FET), which needs to be at least 6 seconds for the study to be reliable. Quality control will be explained in more detail later in this chapter.
- If a post bronchodilator study is done, as in the case of suspected bronchial asthma, there will be 2 discrete curves. One curve will represent the initial (pre-bronchodilator) study whereas the second will represent the post-bronchodilator study. Looking at how the 2 curves compare to each other, gives an idea about the degree of the response to bronchodilator therapy, if any; Figure 1.16.

The Expiratory Flow-Volume Curve (FV Curve)

- Is determined by plotting FVC as flow (in liters/second) against volume (in liters); Figure 1.3.[1] This curve is often informative, as different disorders produce distinct curve shapes.

[1] The flow can be measured directly by a pneumotachograph. The volume is obtained by integration of the flow signal. Alternatively, a volume sensing device (spirometer) measures volume and the flow is derived by differentiating the volume signal. Either method allows expression of the flow-volume curve.

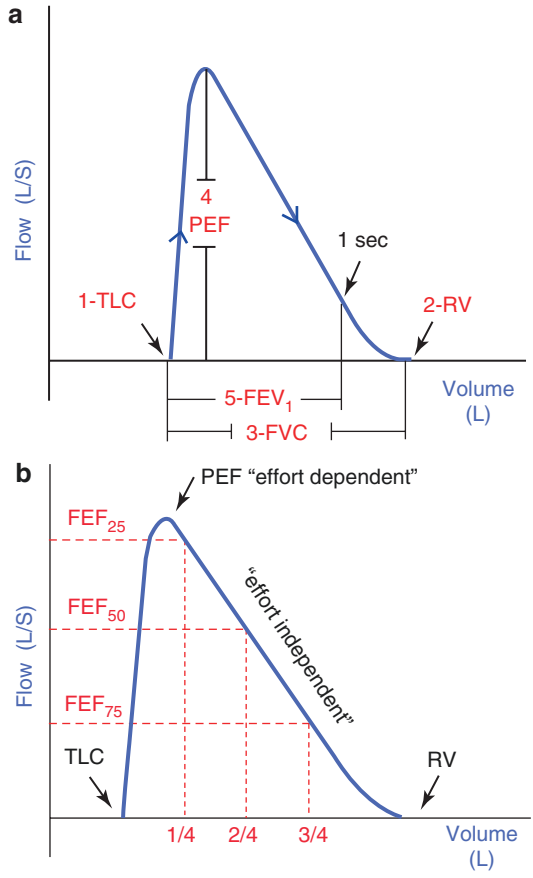


FIGURE 1.3 (**a**) The flow–volume curve: the following data can be extracted: (1) TLC is represented by the left-most end of the curve (cannot be measured by spirometry); (2) RV is represented by the right-most end of the curve (cannot be measured by spirometry); (3) FVC is represented by the width of the curve; (4) PEF is represented by the height of the curve; (5) FEV_1 is the distance from TLC to the 1 second mark. (**b**) The flow–volume curve demonstrating the effort-dependent and the effort-independent parts. Instantaneous FEFs are directly determined from the curve by dividing the FVC into four quarters and getting the corresponding flow for the first, second, and third quarters representing $FEF_{25,50,75}$, respectively as shown. The FEFs represent the slope of the FV curve

- The curve starts at full inspiration (at the *Total Lung Capacity or TLC: the total amount of air in the lungs at maximal inhalation;* Figure 1.3a) with 0 flow (just before the patient starts exhaling). The flow or speed of the exhaled air increases exponentially and rapidly reaches its maximum which is the PEF. The curve then starts sloping down in a near linear manner until just before reaching the volume axis when it curves less steeply giving a small upward concavity. The curve then ends at the *Residual Volume or RV (the amount of air that remains in the lungs after a maximal exhalation)* by touching the volume axis, i.e. a flow of 0 (or within 0.1 liters/second) [8] when no more air can be exhaled; Figure 1.3a.
- As you notice, there is no time axis in this curve, and the only way to determine the FEV_1 is by the reading device making a 1 second mark on the curve, which is normally located at ~ 70–80% of the FVC. See Figure 1.3a.
- Other data can be extracted from this curve including: $FEF_{25, 50, 75}$; as shown in Figure 1.3b. $FEF_{25–75}$ can't be determined from this curve.
- In summary, every part of the curve is informative; Figure 1.3:
  - The left-most end of the curve represents TLC (although a numerical amount cannot be discerned as the residual volume cannot be measured).
  - The curve's right-most end represents RV.
  - Its width (start to end on the X axis) represents FVC.
  - Its peak height represents PEF.
  - The distance from initiation to the 1 second mark represents FEV_1
  - The descending slope reflects the FEFs.
- Remember that we can't measure RV and hence TLC with spirometry alone, because we cannot measure the air remaining in the lung after a full exhalation with this method. Methods that can measure RV are discussed in the next chapter.
- The appearance of the curve is also important. It provides information about the quality of the study as well as being able to recognize certain disease states from its shape. These will be explained in detail later in this chapter.
- Two curves are often shown in different colors (blue and red) to depict pre- and post-bronchodilator studies, respectively, if a post-bronchodilator study was done; Figure 1.15.

The Maximal Flow-Volume Loop

- Combining the expiratory flow-volume curve, discussed earlier, with the inspiratory curve (that measures the IVC), produces the maximal flow-volume loop, with the expiratory curve forming the upper and the inspiratory curve forming the lower parts of that loop, see Figure 1.4.
- This loop is more informative than the expiratory flow-volume curve alone, as it also provides information about the inspiratory portion of the breathing cycle. For example, extra-thoracic upper airway obstruction, which occurs during inspiration, can now be detected.
- This loop commonly includes a tidal flow volume loop too, shown in the center of the maximal flow-volume loop; Figure 1.4. This loop represents quiet tidal breathing. Additional useful data can be acquired from this tidal loop when compared with the maximal flow volume loop. These data include the *Expiratory Reserve Volume (ERV)* and the *Inspiratory Capacity (IC);* Figure 1.4b—see next chapter for definitions. The values of ERV and IC estimated from this curve might be slightly different from the lung volume study measurements, where the SVC is measured instead of the FVC as these (FVC and SVC) can be different, as was discussed earlier. More details about these measurements will be discussed in the following chapter.

TECHNIQUE OF SPIROMETRY [1]

- The spirometer—the device used to record spirometry—should be calibrated every morning to ensure that it records accurate values. The temperature and barometric pressure are measured every morning, as variation in these measures affect the spirometry results[2] [1, 12–14].

[2] As air in the lungs is at BTPS (body temperature pressure standard) but collected at ATPS (ambient temperature pressure standard), a correction factor has to be applied to obtain the BTPS volumes as these are the reported volumes.

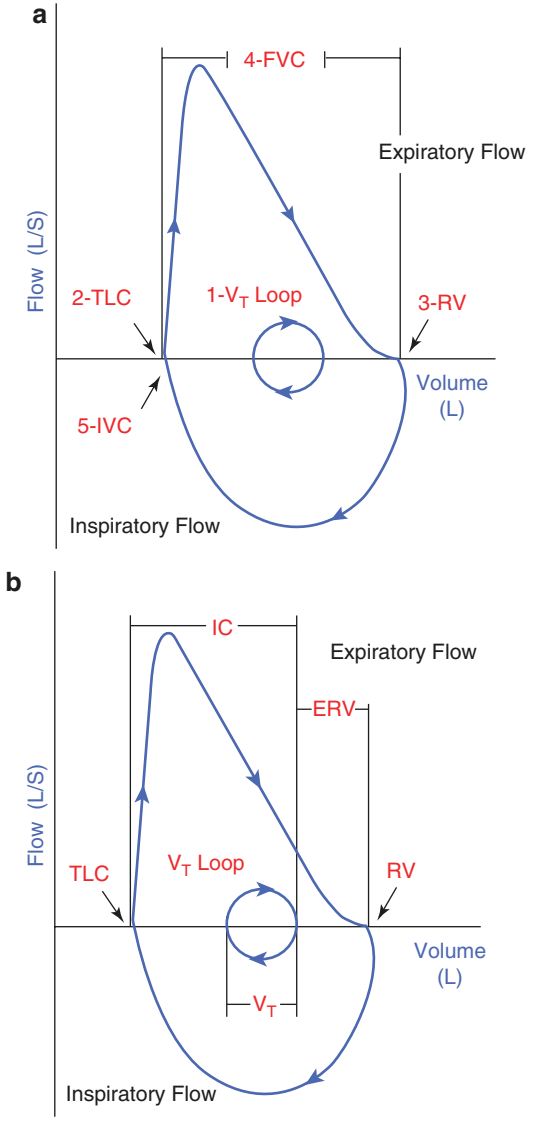


FIGURE 1.4 The flow-volume loop. (**a**) Represents the steps in data measurement during spirometry. (**b**) Demonstrates the ERV and IC in relation to the tidal flow–volume loop (V_T stands for tidal volume)

- The patient must be clinically stable, should sit upright, head erect, nose clip in place and holding the mouth-piece tightly between the lips. Initially, he or she should breathe in and out (Figure 1.4a, No. 1). Then, when the patient is ready, the technician instructs him/her to inhale maximally to TLC (Figure 1.4, No. 2), then exhale as fast and as completely as possible to record the FVC (Figure 1.4, No. 4). The point at which no more air can be exhaled is the RV (Figure 1.4, No. 3). The patient is then instructed to inhale fully to TLC again in order to record the IVC (Figure 1.4, No. 5). This test is then repeated to ensure reproducibility in order to meet quality control criteria (American Thoracic Society or ATS criteria); see next section.
- If a bronchodilator study is needed, the test is repeated in the same way 10 minutes after giving the patient a short acting β_2 agonist (usually 2–4 puffs of salbutamol through a spacer). The ATS criteria should be met in the post-bronchodilator study as well.
- The spirometer will record the volume as absolute numbers and also display volume-time and flow-volume curves.
- The technician should make a note for the interpreter of any technical difficulty that may have influenced the quality of the study. In the final report, the technician's comments are important as well as whether the ATS criteria are met.

THE AMERICAN THORACIC SOCIETY (ATS) GUIDELINES [1, 2]

The ATS criteria are important to consider. They include both acceptability and reproducibility criteria. This means that each individual study should meet certain criteria to be accepted, and the accepted studies should not vary more than predefined limits to ensure reproducibility. If either of the criteria are not met, then the study is rejected as it may give a false impression of either normal or abnormal lung function. Bedside tests or field testing e.g. in the Emergency Department don't, in many instances, meet the ATS criteria that are required for measures in an accredited laboratory. This must be factored into any interpretation.

Acceptability [1, 2]

The ATS mandates 3 acceptable maneuvers. The number of trials that can be performed in an individual shouldn't exceed 8. An acceptable trial should have a good start, a good end, and absence of artifacts.

1. **Good Start of the Test:**
   - The back extrapolation volume shouldn't exceed 5% of FVC or 150 ml, whichever is larger. See Figure 1.5 [1, 2, 15–19].

   Note: Back extrapolation applies to the VT curve and provides the start of test time by back extrapolation to the start axis from the linear portion of the VT curve. To simplify this, consider that a patient's FVC is 2 liters and the study requires a back extrapolation correction, 5% of the FVC (2 liters) is 100 ml. Because 150 ml is larger than the 5% of the patient's FVC (100 ml), 150 ml should be used as the upper limit of extrapolated volume. Then, if the measured extrapolated volume is greater than the 150 mls the result can't be accepted.

   Note: A good start of the study can be identified qualitatively on the FV curve as a rapid rise of flow to PEF from the baseline (0 point), with the PEF being sharp and rounded.

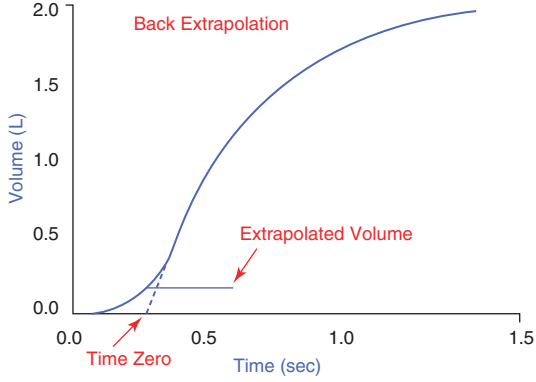


Figure 1.5 Extrapolation volume of 150 ml or 5% of FVC (whichever is larger) (with permission from American Thoracic Society [2])

The FEV_1 can be over- or under- estimated with sub-maximal effort, which may mimic lung disorders such as due to airway obstruction or lung restriction, see later [2, 20].

2. Smooth Flow-Volume (FV) curve, free of artifacts [1, 2]

These artifacts will show in both VT and FV curves, but will be more pronounced in the FV curve. These artifacts include:

(a) *Cough during the first second of exhalation* may significantly affect FEV_1.The FV curve is sensitive in detecting this artifact; Figure 1.6. Coughing after the first second is less likely to make a significant difference in the FVC and so it is accepted provided that it doesn't distort the shape of the FV curve (judged by the technician) [1].
(b) *Variable effort*; Figure 1.7.
(c) *Glottis closure*; Figure 1.8.
(d) *Early termination of effort*.
(e) *Obstructed mouthpiece,* by applying the tongue through the mouthpiece or biting it with the teeth.
(f) *Air leak* [1, 2, 16, 21]

- The air leak source could be loose tube connections or, more commonly, the patient does not get an adequate seal around the mouthpiece. Air leak can often be detected from the FV loop; Figure 1.11e.

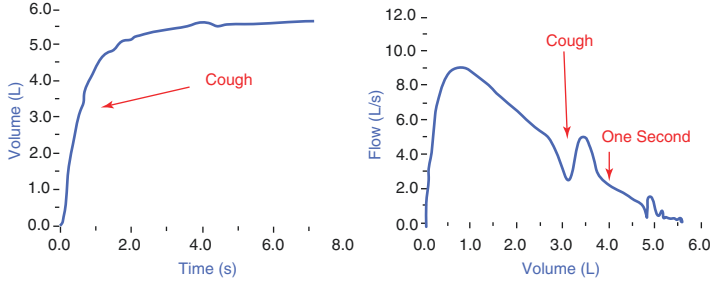


FIGURE 1.6 Cough in the first second. It is much clearer in the FV curve than in the VT curve as indicated by the *arrows* (with permission from American Thoracic Society [2])

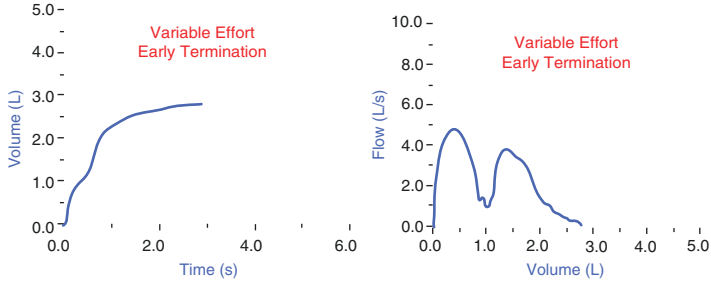


FIGURE 1.7 Variable effort: any study with a variable effort is rejected (with permission from American Thoracic Society [2])

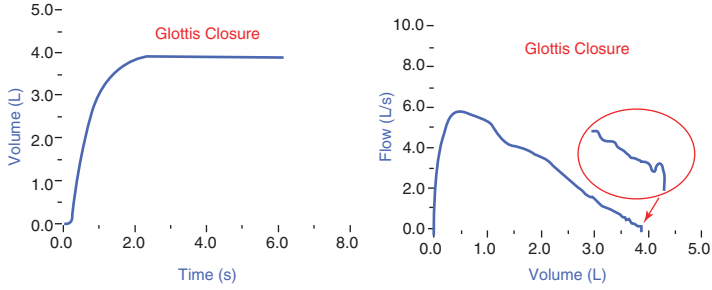


FIGURE 1.8 Glottis closure (with permission from American Thoracic Society [2])

3. ***Good end of the test*** (demonstrated in the VT curve):

(a) Plateau of VT curve of at least 1 second, i.e. volume is not changing with time indicating that the patient is approaching or has reached the residual volume (RV) [1, 2]
OR

(b) Reasonable duration of effort (Forced Expiratory Time, FET) [1, 2]:
- 6 seconds is the minimum accepted duration (3 seconds for children [1]).
- 10 seconds is the optimal.
- FET of >15 seconds is unlikely to change the clinical decision, and may result in the patient's exhaustion [1]. Patients with severe obstructive disorders can exhale for more than 40 seconds before reaching their RV, i.e. before reaching a pla-

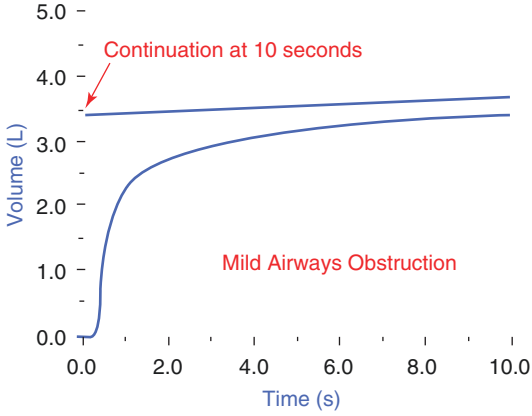


FIGURE 1.9 Mild airway obstruction, with prolonged duration of exhalation (20 seconds). Notice that, when the curve exceeds the limit of the time axis, the continuation of the curve will be plotted from the beginning of the time axis (with permission from American Thoracic Society [2])

teau in the VT curve; Figure 1.9. Normal individuals, however, can empty their lung (i.e. reach a plateau) within 4 seconds.

OR

(c) The patient can't or shouldn't continue to exhale [1, 2].

Note: A good end of the study can be shown in FV curve as an upward concavity at the end of the curve. A downward concavity, however, indicates that the patient either stopped exhaling (prematurely) or started inhaling before reaching the RV; Figure 1.10. This poor technique may result in underestimation of the FVC [10].

- Figure 1.11, shows the morphology of FV curve in acceptable and non-acceptable maneuvers.

Reproducibility [1, 2]

- After obtaining 3 acceptable maneuvers, the following reproducibility criteria should be applied:
  - The 2 largest values of FVC must be within 150 mls of each other.

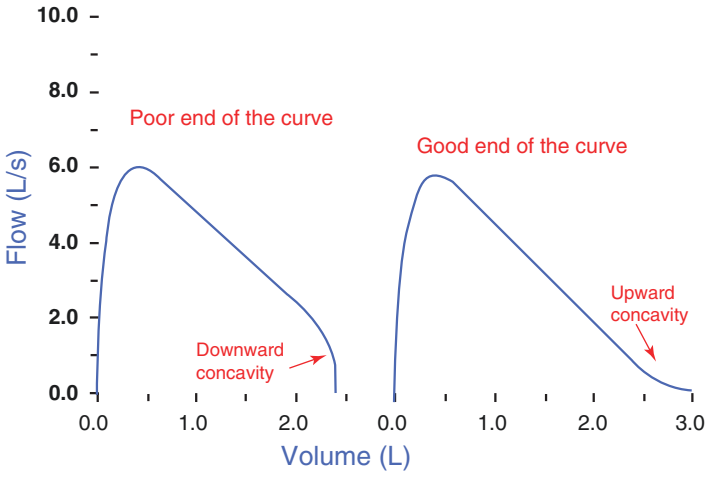


FIGURE 1.10 Poor end in comparison to good end (small upward concavity) of FV curve. A poor end (downward concavity) indicates premature termination of exhalation (before 0 flow)

  - The 2 largest values of FEV_1 must be within 150 mls of each other.
- If the studies are not reproducible, then the studies should be repeated until the ATS criteria are met OR a total of 8 trials are completed OR the patient either can't or shouldn't continue testing [1, 2].
- The final values should be chosen based on the following [1, 2]:
  - FEV_1 and FVC should be reported as the highest values from any acceptable/reproducible trial (not necessarily from the same trial)
  - The other flow parameters should be taken from the *best test curve* (which is the curve with the highest sum of FVC + FEV_1)
  - If reproducibility cannot be achieved after 8 trials, the best test curve (the highest acceptable trial) should be reported. The technician should comment on this deviation from protocol so that the interpreting physician understands the results may not be accurate.

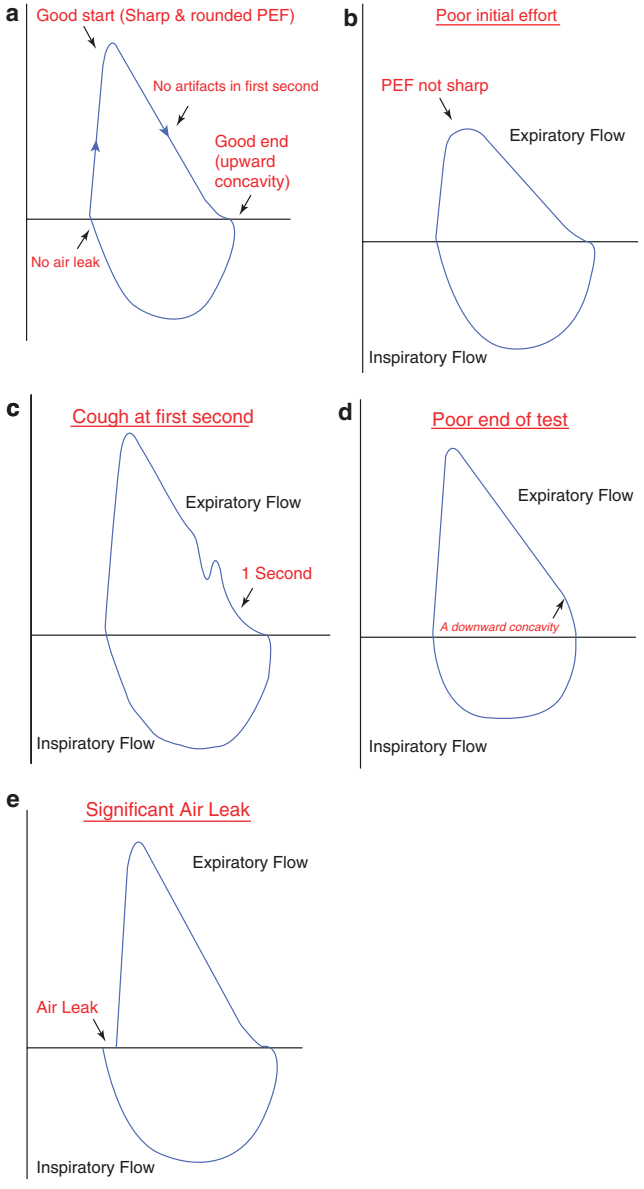


FIGURE 1.11 (**a**) An acceptable FV curve, with good start, good end, and free from artifacts. (**b**) Shows a poor start. (**c**) Shows a cough in the first second. (**d**) Shows a poor end. (**e**) Shows air leak

- Finally, acceptable trials are not necessarily reproducible, because the patient may not produce maximum effort in all trials. Figures 1.12 and 1.13 give some useful examples [2].
- Now, by looking at any FV curve, you should be able to tell whether it reflects an acceptable study. Table 1.2 summarizes

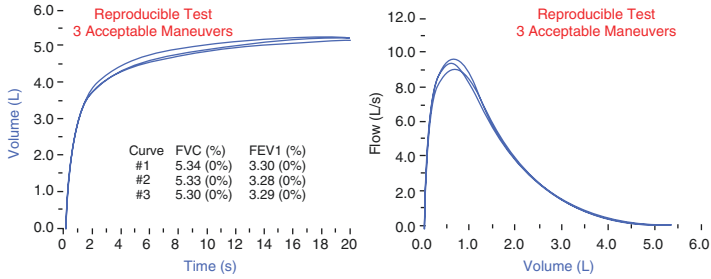


Figure 1.12 Acceptable and reproducible trials (with permission from American Thoracic Society [2])

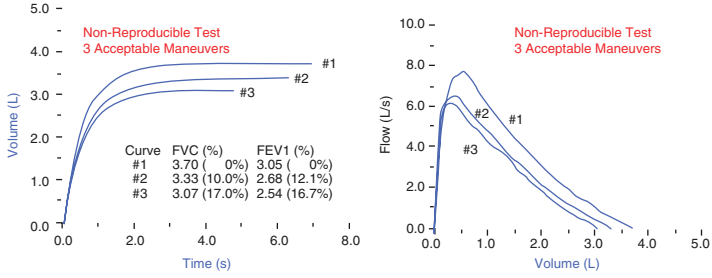


Figure 1.13 Acceptable but not reproducible trials (With permission from: American Thoracic Society [2])

Table 1.2 Features of the ideal FV and VT curves

The ideal FV curve should have the following features; Figure 1.11a:
Good start with sharp and rounded PEF
Smooth continuous decline free from artifacts
Good termination with a small upward concavity at or near the 0 flow
The ideal VT curve should either have a plateau for 1 second OR show an effort of at least 6 seconds

the features of the ideal FV and VT curves. Keep in mind that the lack of any of these features may indicate a lung disorder rather than a poor study.

REFERENCE VALUES [10, 22–27]

- The values for spirometric measurements have a wide range of normal in the normal subjects. These values depend on certain variables:
  - Sex (Men have bigger lungs than women)
  - Age (The spirometric values drop with age)
  - Height (Tall people have bigger lungs. If it is difficult to measure the height, as in kyphoscoliosis, then the arm span can be measured instead [14, 28]).
  - A fourth important variable is race (Caucasians have relatively bigger lungs than those of African and Asian descent), related to differing body proportions (legs to torso)
- Spirometric measurements from a group of healthy subjects with a given sex, age, height and race usually exhibit a normal distribution curve; Figure 1.14. The 5th percentile (1.65 standard deviations) is then used to define the lower limit of the reference range for that given sex, age, height and race; Figure 1.14 [10, 26].

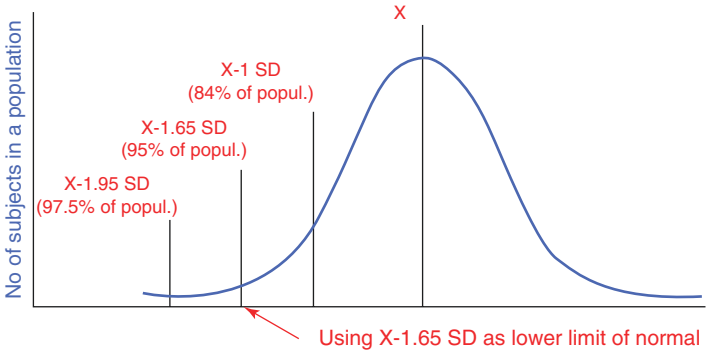


FIGURE 1.14 The predicted values for a group of normal subjects at a given height, age, and sex form a normal distribution curve. Applying 1.65 standard deviations (the 5th percentile) to define the lower limit of normal will include 95% of that population

Table 1.3 Correction factors for the PFT of those of African descent

Variable	Correction factor
FEV_1, FVC, TLC	0.88
RV, DL_{CO}	0.93
FEV_1/FVC ratio	1 (i.e. no correction needed)

Those of African descent have relatively smaller lungs than Caucasians and their lung function values may be adjusted by multiplying these correction factors by the reference values acquired from Caucasian studies [10, 26]

- The available reference values historically apply predominantly to Caucasians. Those of African descent have been well studied too, and they generally have lower predicted values than the Caucasians, although they are usually taller. This is because Africans have higher leg length to torso length ratios, i.e. smaller thoracic cavity. So, while interpreting the lung functions of a person with African descent, you need to make race-specific corrections to the standard predicted values; Table 1.3 [10, 26, 27].
- South East Asians also have lower values than the standard Caucasian predicted. An adjustment factor of 0.94 is recommended [29, 30].
- In 2012 the Global Lung Function Initiative (GLI) published spirometric data from 26 countries, including over 74,000 subjects, ages 3–95, and a wide variety of ethnic groups. This is currently the gold standard spirometric reference and includes normal values for the different races [27].
- The standard normal values roughly range from 80 to 120% of the predicted values.[3] When you interpret a PFT, you should always look at the patient's results as percentage of the predicted values for that particular patient (written in the report as % Pred.). If the patient is normal, then his/her values should roughly lie within 80–120% of predicted values. Current standards call for the interpretation of normal/abnormal to be based on the lower limit of normal from confidence intervals from normal reference values.[4]

[3] Using a fixed value of the lower limit of normal (80%) may be accepted in children but may lead to some errors in adults.

[4] As can be seen in Fig. 1.14 the 95% confidence limit may be used for normality as well. Values outside this range are then below the limit of normal (LLN). Many software programs for lung function testing can display the LLN and interpreting physicians may use this to determine normality. The predicted values used (reference equations) should be representative of the population being tested.

GRADING OF SEVERITY

- Different variables and values have been used to grade severity of different pulmonary disorders [10, 26, 31–34].
- FEV_1 has been selected to grade severity of *any* spirometric abnormality (obstructive, restrictive or mixed); Table 1.4A [10]. (See below for a discussion on COPD vs. Asthma severity grading). The *traditional* way of grading severity of obstructive *and* restrictive disorders involves the following:
  - In obstructive disorders, the FEV_1/FVC ratio should be below the LLN, and the value of FEV_1 is used to determine severity [26]; Table 1.4B.
  - In restrictive disorders however, FEV_1/FVC ratio is normal and the TLC is less than the LLN. The ATS suggested using the TLC to grade the severity of restrictive disorders, which can't be measured in simple spirometry [26]. Where only spirometry is available, FVC may be used to make that grading [26]. The TLC however should be known before confidently diagnosing a restrictive disorder [26, 35, 36]; (Table 1.4B).
- Grading of obstruction in those with a typical COPD PFT pattern has historically used a fixed FEV_1/FVC ratio of <0.7 with fixed FEV_1 cut offs. This grading was described by the Global Initiative for Chronic Obstructive Lung disease (GOLD). However, with the recent and comprehensive databases [27] now available, the calculated lower limit of normal (LLN) of FEV_1/FVC is used instead of the fixed ratio approach. The same FEV_1 cut offs described in the GOLD criteria are still used for severity grading (Table 1.4B).

OFFICE SPIROMETRY AND FEV_6 TO IDENTIFY OBSTRUCTIVE LUNG DISEASE

- Office spirometry has become more widespread with increased availability of, small, portable, and affordable spirometric devices.
- These devices are expected to meet ATS/ERS technical specification, and have the software capable of analyzing ATS/ERS criteria for acceptability and reproducibility [37].

Table 1.4 Methods of grading the severity of obstructive and restrictive disorders

(A) ATS grading of severity of any spirometric abnormality based on FEV_1 [10]	
After determining the pattern to be obstructive, restrictive or mixed, FEV_1 is used to grade severity:	
Mild	FEV_1 > 70 (% pred.)
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35
(B) Grading the severity of obstructive and restrictive disorders* [32]	
GOLD—COPD (based on fixed FEV_1)—*Ratio < 0.7*	
May be a physiologic variant	$FEV_1 \geq 100$ (% pred.)
Mild	80–100
Moderate	50–79
Severe	30–49
Very severe	<30
Asthma (ATS grading used; section "A" of this table)	
Restrictive disorder (based on TLC, preferred)	
Mild	80 > TLC >70 (% pred.)
Moderate	60–69
Severe	<60
Restrictive disorder (based on FVC, in case no lung volume study is available)	
Mild	80 > FVC >70 (% pred.)
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

*This is a widely used grading system but different organizations use different systems

- Spirometry in the office setting must also be conducted by trained and qualified individuals with basic life-support training [37].
- With the wide variety of variables to report, a concise list should be displayed including FEV_1, FVC, FEV_1/FVC ratio, PEF, and forced expiratory time (FET).
- Alternatively the forced expiratory volume in 6 seconds (FEV_6) was proposed as a surrogate to the FVC to simplify

spirometry to enable more widespread spirometric testing, especially in the primary care setting [38].

- When identifying obstruction in an office setting there is evidence to support the use of an FEV_1/FEV_6 ratio of <0.73. It showed a sensitivity of 0.92 and specificity of 0.97 [39]. A meta-analysis in 2009 showed that a FEV_1/FEV_6 cut off of <0.7 or <LLN as a sensitive (0.89) and specific (0.98) surrogate to FEV_1/FVC to identify obstruction [40].

BRONCHODILATOR RESPONSE

- An improvement in spirometric parameters with bronchodilators suggests asthma, but subjects with other obstructive lung disorders can respond to bronchodilators as well, i.e. Chronic Obstructive Pulmonary Disease (COPD). Normal subjects can also respond to bronchodilators by as much as 8% increase in FVC and FEV_1 [36, 41]. The bronchodilator of choice is salbutamol delivered by metered dose inhaler (MDI), through a spacer [42–49].[5]
- For the test to be accurate, patients are advised to stop taking any short acting β_2 agonists or anticholinergic agents within 4 hours of testing [1]. Long acting β_2 agonists (like formoterol and salmeterol) and oral aminophylline should be stopped at least 12 hours before the test [1]. Smoking should be avoided for ≥1 hour prior to testing and throughout the procedure [1, 14]. Inhaled or systemic steroids don't necessarily interfere with the test results, and so, it is up to the discretion of the ordering physician if they should be stopped [8]. The technicians' comments should indicate if a patient has used a bronchodilator prior to the study and provide the timing
- The definition of a significant response to bronchodilators according to ATS and ERS (European Respiratory Society) is an increase in FEV_1 or FVC by >12% AND > 200 ml in the post-bronchodilator study [4, 10].[6]

[5] A spacer is an attachment to the MDI, which optimizes the delivery of salbutamol.

[6] Increments of as high as 8% or 150 mL in FEV_1 or FVC are likely to be within the variability of the measurement.

COMPONENTS OF SPIROMETRY

- Table 1.5 summarizes the causes of abnormal spirometric values. In any spirometry report, you may see multiple other parameters that are not discussed here. We believe these to have little or no clinical usefulness. For completeness, these components are also shown in this table.
- Table 1.6 summarizes the effects of different lung disorders on every component of spirometry.

SPIROMETRIC PATTERN OF COMMON DISORDERS

In this section, we will discuss the PFT pattern of some common disorders.

Obstructive Disorders

- The two major obstructive disorders are Asthma and Chronic Obstructive Pulmonary Disease (COPD); (Table 1.7). The key to the diagnosis of these disorders is the reduction in the FEV_1/FVC ratio [10]. FEV_1 is usually reduced too and is used to define the severity of obstruction; see Table 1.4. FVC may be reduced in obstructive disorders, but usually not to the same degree as FEV_1.
- The features of obstructive disorders are summarized in Table 1.6.
- The flow-volume curve can be used to suggest an obstructive disorder, as it has a distinct shape in such disorders; Figure 1.15. These features include:
  - The height of the curve (PEF) is less than predicted.
  - The descending limb is concave (scooped), with the concavity being more pronounced with more severe obstruction. The slope of the descending limb which represents MMEF and FEFs is reduced due to airflow limitation at low lung volumes.
  - Decreased FEV_1 and FEV_1/FVC ratio is noted by identifying the 1 second mark (FEV_1) and where it lies in relation to the FVC.

TABLE 1.5 Causes of abnormal spirometric components

FVC

Increased in acromegaly [8]

Decreased in restrictive disorders (most important) and obstructive disorders; Table 1.6

FEV_1

Decreased in obstructive and, to a lesser extent, restrictive disorders

FEV_1/FVC ratio

Increased in some restrictive disorders eg interstitial lung diseases (ILD) (because of increased elastic recoil that results in a relatively preserved FEV_1)

Decreased in obstructive disorders (asthma and COPD)

PEF

May be increased in pulmonary fibrosis (because of increased elastic recoil)

Decreased in:

Obstructive disorders (COPD, asthma)

Variable intra-thoracic or fixed upper airway obstruction [10, 50] (associated with flattening of the expiratory curve of the flow-volume loop)

Restrictive disorders

$FEF_{(25, 50, 75, 25–75)}$

Decreased in obstructive and restrictive disorders

Decreased also in variable intra-thoracic or fixed upper airway obstruction

Reduction in FEF_{75} and/or $FEF_{25–75}$ may be the earliest sign of airflow obstruction [10, 51, 52] and is not specific for small airway disease [11]

FET (forced expiratory time)

May be increased in obstructive disorders

PIF (peak inspiratory flow)

Decreased in variable extra-thoracic or fixed upper airway obstruction

FIF50% (forced inspiratory flow at 50% of FIVC)

Decreased in variable extra-thoracic or fixed upper airway obstruction

FIVC (forced inspiratory vital capacity)

Its main use is to check for the quality of the study (for air leak)

FIF/FEF50% (FIF at 50%/FEF at 50% ratio)

Increased in variable intra-thoracic upper airway obstruction (>1) [10]

Decreased in variable extra-thoracic upper airway obstruction (<1), see also Table 1.2 [10]

Table 1.6 Features of obstructive and restrictive disorders

Features of obstructive disorders:
Diagnostic features: ↓ FEV_1/FVC ratio
Other features:
↓ FEV_1
↓ or normal FVC
↓ FEFs and MMEF (FEF_{25}, FEF_{50}, FEF_{75}, $FEF_{25–75}$)
↓ PEF
↑ FET
Possible significant bronchodilator response
Scooped (concave) descending limb of FV curve
Features of restrictive disorders:
Most important features: ↓ FVC and normal or ↑ FEV_1/FVC ratio
Other features:
↓ FEV_1 (proportional to FVC), but it can be normal
↓ MMEF
PEF: Normal, increased or decreased
Steep descending limb of FV curve

Table 1.7 Causes of obstructive and restrictive disorders

Causes of obstructive disorders
Asthma (usually responsive to bronchodilators)
COPD
Bronchiectasis
Bronchiolitis
Causes of restrictive disorders
Parenchymal disease as pulmonary fibrosis and other interstitial lung diseases (ILD)
Pleural disease (effusions or pleural fibrosis)
Chest wall restriction:
Musculoskeletal disorders (MSD), (severe kyphoscoliosis)
Neuromuscular disorders (NMD), (muscular dystrophy, amyotrophic lateral sclerosis (ALS), old poliomyelitis, paralyzed diaphragm); see Table 5.1 for more detail
Diaphragmatic distention (pregnancy, ascites, obesity)
Obesity (restricting chest wall movement)
Other lung parenchymal causes:
Resection (lobectomy, pneumonectomy)
Atelectasis
Tumors (filling or compressing alveolar spaces)
Pulmonary edema (alveolar spaces become filled with fluid)
Pleural cavity disease (pleural effusion, extensive cardiomegaly, large pleural tumor)

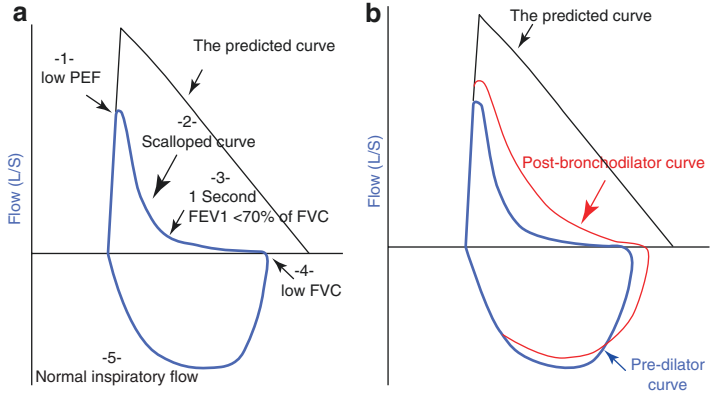


FIGURE 1.15 Obstructive disorders (FV curve): (**a**) The FV curve looks technically acceptable, with good start and end, and absence of artifacts in the first second. There are five features that make the diagnosis of a significant airway obstruction definite, based on this curve alone. (1) Decreased PEF when compared to the predicted curve. (2) Scooping of the curve after PEF, indicating airflow limitation. (3) The first second mark is almost in the middle of the curve indicating that the FEV_1 and FEV_1/FVC ratio are significantly decreased. (4) FVC is decreased when compared to the predicted curve. (5) The inspiratory component of the curve is normal, excluding a central airway obstruction. (**b**) There is a clear response to bronchodilators indicating reversibility and supporting the diagnosis of an obstructive disorder, most likely bronchial asthma

  - The width of the curve (FVC) as seen in the volume axis may be decreased compared to that of the predicted curve.
  - A post-bronchodilator study, represented by the red curve typically, that demonstrates an appreciable improvement in all of the above variables (PEF, the curve's outward concavity (FEF), FEV_1, FEV_1/FVC ratio and FVC); Figure 1.15b suggests a specific obstructive disorder, ***namely asthma***. Lack of bronchodilator response doesn't exclude asthma as responsiveness can vary over time.
- The VT curve similarly has its distinct features in obstructive disorders; Figure 1.16.
- Special Conditions
  - In mild (or early) airway disease, the classic reduction in FEV_1 may not be seen. The morphology of the FV curve can give a clue, as the distal upward concavity may show to be more pronounced and prolonged; Figure 1.17

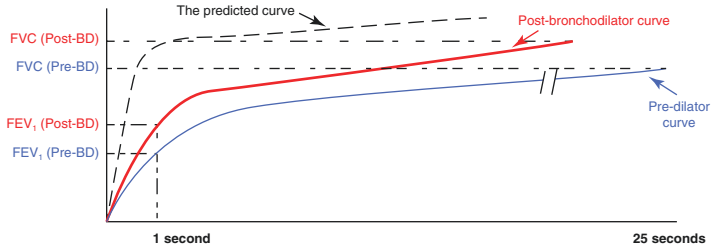


FIGURE 1.16 Feature of obstructive disorders in VT curve: (1) The blue curve (prebronchodilator study) is less steep compared with the dashed curve (the predicted). (2) FEV_1 and the FEV_1/FVC ratio are decreased in the blue curve. (3) The FVC is also decreased. (4) A prolonged FET (length of the curve) suggests airway obstruction. (5) MMEF is also decreased, indicated by the slope of the curve. (6) The curve morphology improves following bronchodilator therapy (the red curve), with subsequent improvement of FEV_1, FVC, and FEV_1/FVC ratio

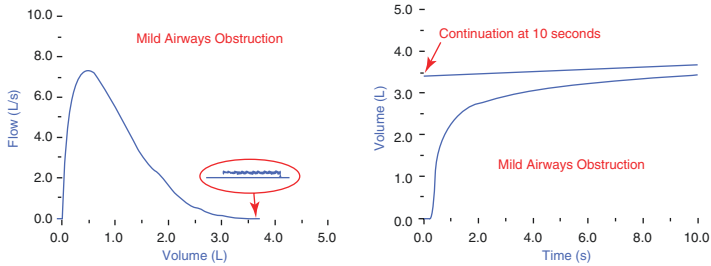


FIGURE 1.17 Mild airway obstruction (with permission from American Thoracic Society [2])

[51–53]. Another clue is the prolonged FET evident in the VT curve; Figure 1.17. However, the clinical significance of these mild changes is unknown if the FEV_1/FVC ratio is in the normal range.

- In emphysema and because of loss of supportive tissues, the airways tend to collapse significantly at low lung volumes, giving a characteristic "dog-leg" appearance in FV curve; Figure 1.18 [9].

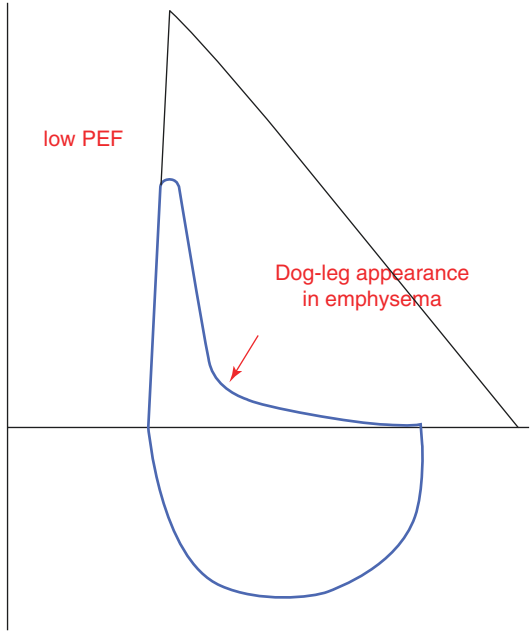


FIGURE 1.18 *Dog-leg* appearance typical of emphysema

Restrictive Disorders

- In restrictive disorders, like pulmonary fibrosis, the key to the diagnosis is the decline in FVC. The lung compliance decreases and the elasticity increases. The FEV_1/FVC ratio is preserved or increased [10]. In order to make a confident diagnosis of a restrictive disorder, the TLC should be measured, and should be low [10, 26, 35, 54]. So, based on spirometry alone, the above features are reported as suggestive (not diagnostic) of a restrictive disorder. Remember that normal FVC or VC excludes lung restriction [35, 54].
- Table 1.6 summarizes the features of a restrictive disorder in spirometry and Table 1.7 summarizes the etiology.
- FV curve features of restrictive disorders are described as follows:
  - For parenchymal lung disease (e.g. pulmonary fibrosis); Figure 1.19a:

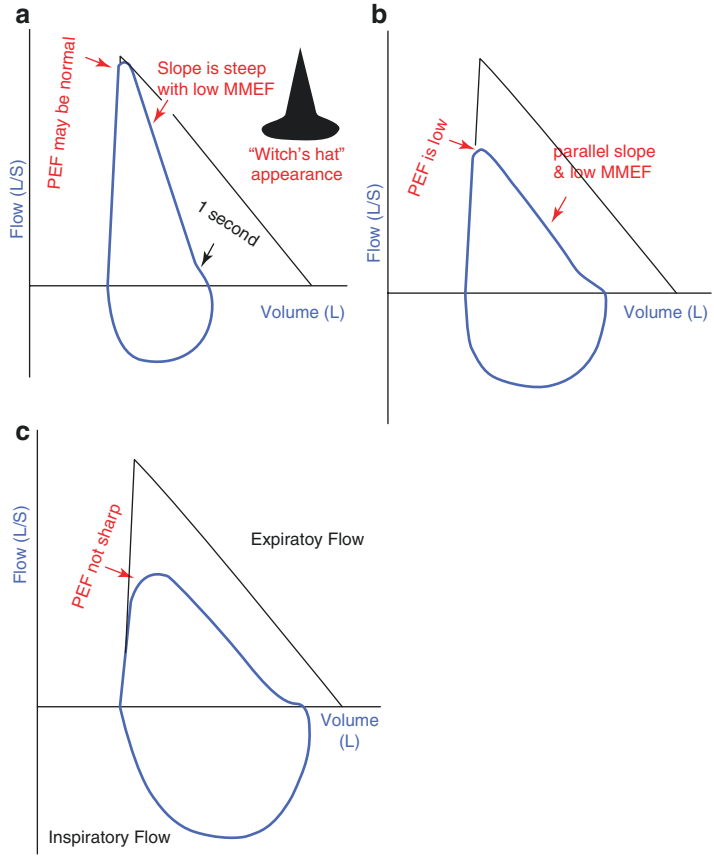


FIGURE 1.19 FV curve features of different forms of restriction: (**a**) ILD with witch's hat appearance; (**b**) chest wall restriction (excluding NMD); (**c**) NMD (or poor effort study) producing a convex curve

(a) The PEF can be normal or high because of the increased elastic recoil that increases the initial flow of exhaled air. However, PEF may be low as the disease progresses due to the reduced volumes exhaled, i.e. fewer liters per second.
(b) The width of the curve (FVC) is decreased and the 1 second mark (FEV_1) on the descending limb of the

curve is close to the residual volume indicating a normal or high FEV_1/FVC ratio.

(c) The slope of the descending limb of the curve is steeper than usual due to high lung recoil or elastance (i.e. low MMEF). The reduction in MMEF, in this case, does not indicate airflow obstruction and is related to the reduced volumes.

(d) The steep descending limb and the narrow width of the FV curve together with the relatively preserved PEF may produce a distinct shape of the curve typical for parenchymal lung fibrosis referred to as the *"witch's hat" appearance*.

– For chest wall restriction (including musculoskeletal disorders, diaphragmatic distention and obesity); Figure 1.19b:

(a) PEF is decreased as the elastic recoil of the lung is not increased here.

(b) The slope of the curve is parallel to the predicted curve, making the whole curve looking like the predicted curve but smaller. The MMEF is similarly decreased.

– For neuromuscular disorders (this pattern is also seen in poor effort study); Figure 1.19c:

(a) The PEF is low and not sharp (the curve is convex in shape).

(b) The MMEF is low.

(c) There may be a rapid decline in flows at the end of expiration on the FV curve

- The volume-time (VT) curve will maintain the normal morphology but will be smaller than the predicted curve in restrictive disorders.

Upper Airway Obstruction [55–59]

The morphology of the flow volume curve is very useful in identifying upper airway disorders. However, these disorders must be advanced to allow detection by this technique. There are 3 types of upper airway obstruction recognizable in the FV curve:

1. *Variable extra-thoracic obstruction* (above the level of sternal notch)
   (a) The word variable means that the obstruction predominates in either inspiration or expiration during a maximal effort, unlike a fixed obstruction that is manifested clearly in both. In variable extra-thoracic obstruction, airway obstruction takes place during inspiration. This is because the pressure inside the airways (larynx, pharynx and extra-thoracic portion of trachea) is relatively negative during inspiration compared to the pressure outside the airways (atmospheric pressure, P_{atm}) and hence flow is reduced (flattened curve) during the inspiratory limb of the FV loop; Figure 1.20a. The obstruction must be mobile or dynamic to follow this pattern. Patients with such lesions often develop stridor, i.e. a wheezy sound during inspiration.
2. *Variable intra-thoracic obstruction* (below the sternal notch)
   (a) In this case, the obstruction will be more pronounced during expiration. The central intra-thoracic airways (intra-thoracic trachea and main bronchi) narrow when they are compressed by the increased intra-thoracic pressure which occurs during expiration; Figure 1.20b. A variable lesion, e.g. tracheomalacia, in the upper airways will compress easily when the pressure outside exceeds the pressure inside the airways. Central tumors can also preferentially reduce expiratory flow. In these cases you may hear expiratory wheezes with the stethoscope placed in the midline over the upper chest.
   (b) Unlike the obstruction in the lower airways (as in asthma and COPD), the expiratory component of the FV loop in intra-thoracic upper airway obstruction is deformed throughout its entire length, starting right from the PEF, which is significantly reduced; Figure 1.20b.
   (c) To remember which part of the FV loop is affected by a variable upper airway obstruction, think of the upper airways oriented upside-down beside the FV loop with the horizontal (volume) axis at the level of the sternal notch; Figure 1.21. Flattening of the lower part of the

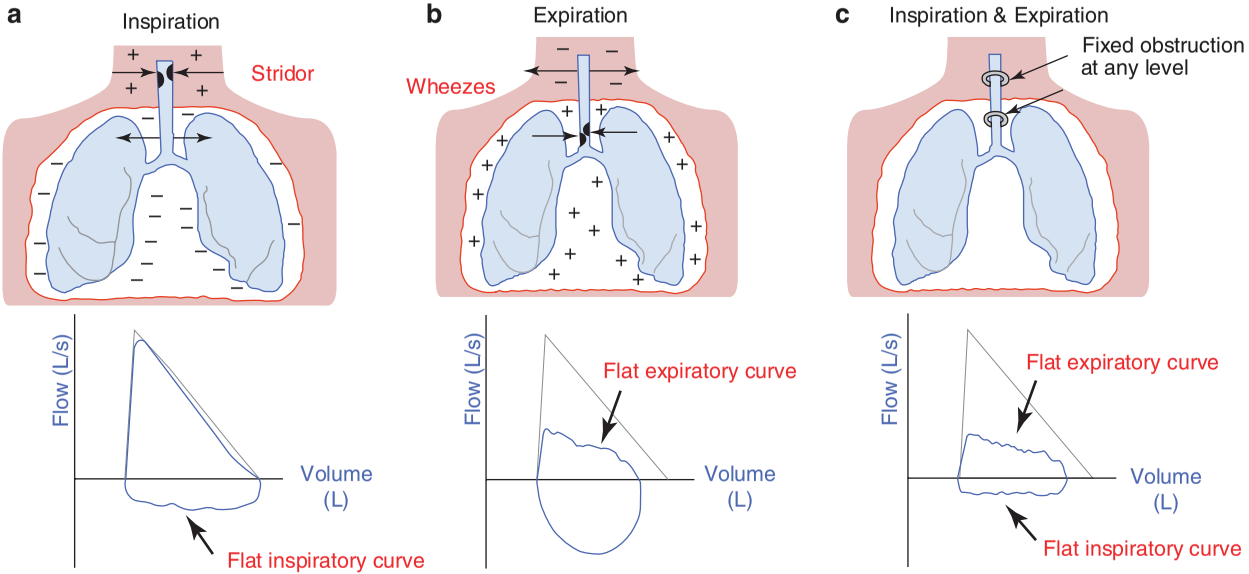


FIGURE 1.20 Upper airway obstruction: (**a**) variable extrathoracic obstruction; (**b**) Variable intrathoracic obstruction; (**c**) Fixed upper airway obstruction

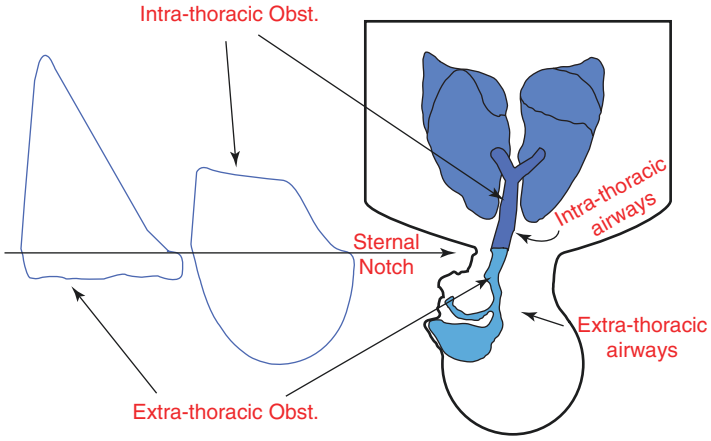


FIGURE 1.21 A way to remember which part of the curve is deformed in either forms of variable upper airway obstruction

loop will then indicate a variable extra-thoracic lesion and vice versa; Figure 1.21.[7]

3. *Fixed upper airway obstruction* (above or below the sternal notch)
   (a) This type of obstruction doesn't change with inspiration or expiration (not dynamic), and hence, it will not matter whether it is in the intra- or extra- thoracic compartment of the upper airways.
   (b) As a result, both the inspiratory and the expiratory components of the FV loop are flattened; Figure 1.20c.
   (c) See Table 1.8 for causes of upper airway obstruction.

Note: In the absence of FV loop, you can still identify the different types of upper airway obstruction numerically using PEF, PEF/FEV_1 ratio, MIF_{50} and MIF_{50}/MEF_{50} ratio; see Table 1.9.[8]

[7] Another way is to think of the intrathoracic obstruction taking place during the ex-piration, while the extrathoracic during the in-spiration. So, intra- will take ex-, while extra- will take in-.

[8] MIF_{50} & MEF_{50} are sometimes used to describe FIF_{50}& FEF_{50}, respectively & they stand for the maximal inspiratory flow at 50% of FIVC and the maximal expiratory flow at 50% of FVC, respectively.

TABLE 1.8 Causes of upper airway obstruction [8]

Variable extra-thoracic lesions (lesions above the sternal notch)
Dynamic tumors of hypopharynx or upper trachea
Vocal cord paralysis
Dynamic subglottic stenosis
External compression of upper trachea (e.g. by goiter)
Variable intra-thoracic lesions (lesions below the sternal notch)
Dynamic tumors of the lower trachea
Tracheomalacia
Dynamic tracheal strictures
Chronic inflammatory disorders of the upper airways (e.g. Wegener granulomatosis with polyangitis, relapsing polychondritis)
External compression of lower trachea (e.g. by retrosternal goiter)
Fixed lesions (lesions at any level in the major airways)
Non-dynamic tumors at any level of upper airways
Fibrotic stricture of upper airways

TABLE 1.9 Differentiating types of upper airway obstruction numerically [10]

	Fixed UAO	Variable extrathoracic	Variable intrathoracic
PEF	Reduced	↓ or normal	Reduced
PEF/FEV_1	Not applicable	<8 [47, 51]	Not applicable
MIF_{50}	Reduced	Reduced	↓ or normal
MIF_{50}/MEF_{50}	~1	<1	>1

A normal variant that mimics a variable intra-thoracic upper airway obstruction; Figure 1.22.

- The key to differentiating this normal variant from a variable intra-thoracic upper airway obstruction is the preserved PEF. Although the peak of the FV curve in this condition is flattened suggesting upper airway obstruction, the PEF is preserved compared to the predicted curve. In variable intra-thoracic upper airway obstruction, PEF is reduced.
- Acceptability criteria may be questioned here (suggesting a poor start), however when this curve is highly reproducible, it is recognized as a normal variant. This variant is very common and is sometimes referred to as the "***knee***" variant [8].

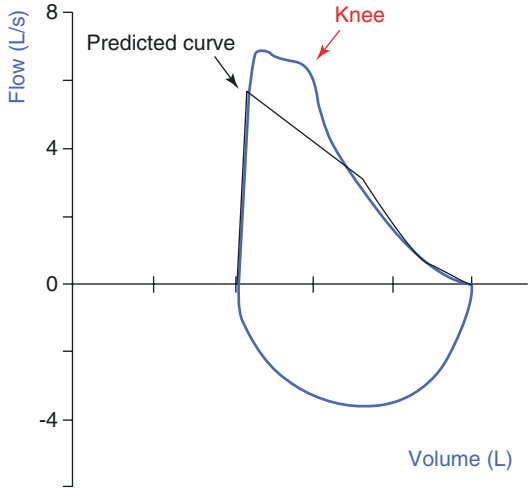


FIGURE 1.22 Normal variant, *knee*. Note that the PEF is normal

References

1. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
2. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.
3. Paoletti P, Pistelli G, Fazzi P. Reference values for vital capacity and flow-volume curves from a general population study. Bull Eur Physiopathol Respir. 1986;22:451–9.
4. Brusasco V, Pellegrino R, Rodarte JR. Vital capacities in acute and chronic airway obstruction: dependence on flow and volume histories. Eur Respir J. 1997;10:1316–20.
5. Hansen LM, Pedersen OF, Lyager S, Naeraa N. Method related differences in vital capacity. Ugeskr Laeger. 1983;145:2752–6.
6. Swanney MP, Jensen RL, Crichton DA, Beckert LE, Cardno LA, Crapo RO. FEV(6) is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med. 2000;162:917–9.
7. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Mørkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. Eur Respir J. 2002;20:1117–22.
8. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of pulmonary function tests, a practical guide. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.

9. Hancox B, Whyte K. Bob pocket guide to lung function tests. 1st ed. Sydney: McGraw-Hill; 2001.
10. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
11. Flenley DC. Chronic obstructive pulmonary disease. Dis Mon. 1988;34:537–99.
12. Gardner RM, Clausen JL, Crapo RO, Epler GR, Hankinson JL, Johnson JL, Plummer AL. Quality assurance in pulmonary function laboratories. Am Rev Respir Dis. 1986;134:625–7.
13. Association for the Advancement of Medical Instrumentation, Standard for spirometers (draft), October 1980. AAMI Suite 602, 1901 N. Ft. Myer Drive, Arlington, VA 22209–1699.
14. Miller MR, Crapo R, Hankinson J, et al. General considerations for lung function testing. Eur Respir J. 2005;26:153–61.
15. Renzetti AD Jr. Standardization of spirometry. Am Rev Respir Dis. 1979;119:831–8.
16. Morris A, Kanner R, Crapo R, Gardner R. Clinical pulmonary function testing: a manual of uniform laboratory procedures title. 2nd ed. Salt Lake City, UT: Intermountain Thoracic Society; 1984.
17. Smith A, Gaensler R. Timing of forced expiratory volume in one second. Am Rev Respir Dis. 1982;126:362–4.
18. Hankinson JL, Gardner RM. Standard waveforms for spirometer testing. Am Rev Respir Dis. 1982;126:362–4.
19. Horvath EJ. Manual of spirometry in occupational medicine. Cincinnati, OH: Division of Training and Manpower Development, National Institutes for Occupational Safety and Health; 1981.
20. Stoller JK, Basheda S, Laskowski D, Goormastic M, McCarthy K. Trial of standard versus modified expiration to achieve end-of-test spirometry criteria. Am Rev Respir Dis. 1993;148:275–80.
21. Townsend MC. The effects of leaks in spirometers on measurements of pulmonary function. The implications for epidemiologic studies. J Occup Med. 1984;26:835–41.
22. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of The European Respiratory Society. Eur Respir J. 1995;8:492–506.
23. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5–40.
24. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J. 1993;6(Suppl 16):41–52.
25. Solberg HE, Gräsbeck R. Reference values. Adv Clin Chem. 1989;27:1–79.
26. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991;144:1202–18.

27. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. Eur Respir J. 2012;40:1324–43.
28. Parker JM, Dillard TA, Phillips YY. Arm span-height relationships in patients referred for spirometry. Am J Respir Crit Care Med. 1996;154:533–6.
29. Korotzer B, Ong S, Hansen JE. Ethnic differences in pulmonary function in healthy nonsmoking Asian-Americans and European-Americans. Am J Respir Crit Care Med. 2000;161:1101–8.
30. Sharp DS, Enright PL, Chiu D, Burchfiel CM, Rodriguez BL, Curb JD. Reference values for pulmonary function tests of Japanese-American men aged 71 to 90 years. Am J Respir Crit Care Med. 1996;153:805–11.
31. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS. GOLD Scientific Committee Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop Summary. Am J Respir Crit Care Med. 2001;163:1256–76.
32. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease Updated; 2015.
33. American Thoracic Society. Evaluation of impairment/disability secondary to respiratory disorders. Am Rev Respir Dis. 1986;133:1205–9.
34. American Medical Association. Guides to the evaluation of permanent impairment. 4th ed. Chicago, IL: American Medical Association; 1995.
35. Glady CA, Aaron SD, Lunau M, Clinch J, Dales RE. A spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. Chest. 2003;123:1939–46.
36. Guyatt GH, Townsend M, Nogradi S, Pugsley SO, Keller JL, Newhouse MT. Acute response to bronchodilator. An imperfect guide for bronchodilator therapy in chronic airflow limitation. Arch Intern Med. 1988;148:1949–52.
37. D'Urzo A. Spirometry in primary care practices. CMAJ. 2009;180:429–30; author reply 430.
38. Ferguson GT, Enright PL, Buist S, Higgins MW. Office Spirometry for Lung Health Assessment in Adults *A Consensus Statement from the National Lung Health Education Program. Chest J. 2000;117:1146–61.
39. Bhatt SP, Kim Y-I, Wells JM, et al. FEV(1)/FEV(6) to diagnose airflow obstruction. Comparisons with computed tomography and morbidity indices. Ann Am Thorac Soc. 2014;11:335–41.
40. Jing J. Should FEV_1/FEV_6 replace FEV_1/FVC ratio to detect airway obstruction? Chest J. 2009;135:991.

41. Brand PL, Quanjer PH, Postma DS, Kerstjens HA, Koëter GH, Dekhuijzen PN, Sluiter HJ. Interpretation of bronchodilator response in patients with obstructive airways disease. The Dutch Chronic Non-Specific Lung Disease (CNSLD) Study Group. Thorax. 1992;47:429–36.
42. Coates AL, Allen PD, MacNeish CF, Ho SL, Lands LC. Effect of size and disease on estimated deposition of drugs administered using jet nebulization in children with cystic fibrosis. Chest. 2001;119:1123–30.
43. Coates AL, Ho SL. Drug administration by jet nebulization. Pediatr Pulmonol. 1998;26:412–23.
44. Newman SP, Clark AR, Talaee N, Clarke SW. Pressurised aerosol deposition in the human lung with and without an "open" spacer device. Thorax. 1989;44:706–10.
45. Tal A, Golan H, Grauer N, Aviram M, Albin D, Quastel ME. Deposition pattern of radiolabeled salbutamol inhaled from a metered-dose inhaler by means of a spacer with mask in young children with airway obstruction. J Pediatr. 1996;128:479–84.
46. Newhouse MT. Asthma therapy with aerosols: are nebulizers obsolete? A continuing controversy. J Pediatr. 1999;135:5–8.
47. Coates AL, MacNeish CF, Lands LC, Meisner D, Kelemen S, Vadas EB. A comparison of the availability of tobramycin for inhalation from vented vs unvented nebulizers. Chest. 1998;113:951–6.
48. Devadason SG, Everard ML, Linto JM, Le Souëf PN. Comparison of drug delivery from conventional versus "Venturi" nebulizers. Eur Respir J. 1997;10:2479–83.
49. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone: a cross-over study in healthy volunteers. Chest. 2002;122:510–6.
50. Cerveri I, Pellegrino R, Dore R, Corsico A, Fulgoni P, van de Woestijne KP, Brusasco V. Mechanisms for isolated volume response to a bronchodilator in patients with COPD. J Appl Physiol. 2000;88:1989–95.
51. Bates JH, Brown KA, Kochi T. Respiratory mechanics in the normal dog determined by expiratory flow interruption. J Appl Physiol. 1989;67:2276–85.
52. Wilson AF, editor. Pulmonary function testing, indications and interpretations. Orlando, FL: Grune & Stratton; 1985.
53. Pride NB, Macklem PT. Lung mechanics in disease. In: Macklem PT, Mead J, editors. Handbook of physiology. The respiratory system. Mechanics of breathing. Section 3, vol. 3, Part 2. Bethesda, MD: American Physiological Society; 1986. p. 659–92.
54. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest. 1999;115:869–73.

55. Miller MR, Pincock AC, Oates GD, Wilkinson R, Skene-Smith H. Upper airway obstruction due to goitre: detection, prevalence and results of surgical management. Q J Med. 1990;74:177–88.
56. Miller RD, Hyatt RE. Obstructing lesions of the larynx and trachea: clinical and physiologic characteristics. Mayo Clin Proc. 1969;44:145–61.
57. Pedersen OF, Ingram RH. Configuration of maximum expiratory flow-volume curve: model experiments with physiological implications. J Appl Physiol. 1985;58:1305–13.
58. Miller MR, Pedersen OF. Peak flowmeter resistance decreases peak expiratory flow in subjects with COPD. J Appl Physiol. 2000;89:283–90.
59. Gibson GJ. Clinical tests of respiratory function. 2nd ed. New York, NY: Taylor & Francis; 1998.

Chapter 2
Lung Volumes

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract Measuring the subsegments of lung volume helps characterize certain disease states. These volumes are termed the static lung volumes, while spirometry measures the dynamic volumes. This chapter will discuss the static lung volumes, how they are measured and their clinical implications.

Keywords Total Lung Capacity (TLC) · Vital Capacity (VC) · Residual Volume (RV)

DEFINITIONS; SEE FIGURE 2.1

Total Lung Capacity (TLC)

- Is the volume of air (in liters) that a subject's lungs contain at the end of a maximal inspiration [1].

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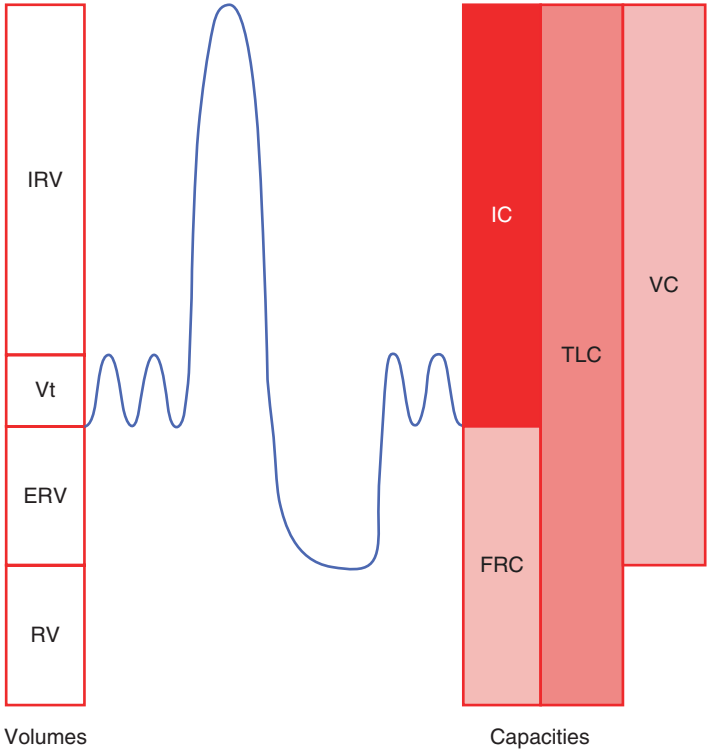

FIGURE 2.1 A volume spirogram showing the different lung volumes (*on the left*) and capacities (*on the right*)

Residual Volume (RV)

- Is the volume of air that remains in the lungs at the end of a maximal exhalation [1]. An abnormal increase in RV is called *air trapping*. The techniques used to measure lung volumes are primarily designed to measure the Residual Volume, as this volume can't be exhaled to be measured. The rest of the lung volumes can then be measured by simple spirometry, using the SVC maneuver rather than the FVC maneuver. The TLC can then be calculated by adding RV to VC or *functional residual capacity (FRC)* to *inspiratory capacity (IC)*; (Figure 2.1).

- So, spirometry is an essential part of any lung volume study.

Functional Residual Capacity (FRC)

- Is the volume of air that remains in the lungs at the end of a tidal exhalation, i.e. when the respiratory muscles are at rest [1]. This means that at FRC, the resting negative intrathoracic pressure produced by the chest wall (rib cage and diaphragm) wanting to expand is balanced by the elastic recoil force of the lungs which naturally want to contract. Therefore, when the elastic recoil of the lungs decreases, as in emphysema, the FRC increases (hyperinflation), while when the elastic recoil increases as in pulmonary fibrosis, the FRC decreases.
- The FRC is the sum of the *expiratory reserve volume (ERV)* and the RV and is ~50% of TLC.
- FRC measured using body plethysmography (discussed below) is sometimes referred to as the *thoracic gas volume (TGV or V_{TG}) at FRC or V_{FRC}* [1]. Indeed, FRC is the volume measured by all the volume measuring techniques and RV is then determined by subtracting ERV.
- FRC has important functions:
  - It aids mixed venous blood oxygenation during expiration and before the next inspiration.
  - Decreases the energy required to re-inflate the lungs during inspiration. If for example each time the patient exhaled, the lungs fully collapsed, a large effort would be needed to re-inflate them. Such effort would soon result in exhaustion and respiratory failure [2].

Expiratory Reserve Volume (ERV)

- Is the maximum volume of air that can be exhaled at the end of a tidal exhalation and can be measured by simple spirometry [1].

Inspiratory Reserve Volume (IRV)

- Is similarly defined as the maximum volume of air that can be inhaled following a tidal inhalation [1].

Inspiratory Capacity (IC)

- Is the maximum volume of air that can be inhaled after a normal tidal exhalation [1]. Accordingly, IC equals the IRV + Tidal volume (V_T).

Tidal Volume (V_T)

- Is the volume of air that we normally inhale or exhale while at rest, and equals roughly 0.5 liter in an average adult and increases with exercise.

SVC or VC

- Was discussed in Chapter 1. See Figure 2.6.

The Terms: "Volume" and "Capacity"; (Figure 2.1) [3]

- The term "volume" refers to the lung volumes that can't be broken down into smaller components (RV, ERV, V_T and IRV).
- While, the term "capacity" refers to the lung volumes that can be broken down into other smaller components (IC, FVC, TLC and VC)
  - IC = IRV + V_T
  - FRC = ERV + RV
  - VC = IC + ERV
  - TLC = VC + RV

Correlation with the FV Curve

- FV curve can be used as a volume spirogram (seen in Figure 2.1), in addition to its other uses; (Figure 2.2). The only three lung volumes that spirometry can't measure are RV, FRC and TLC.

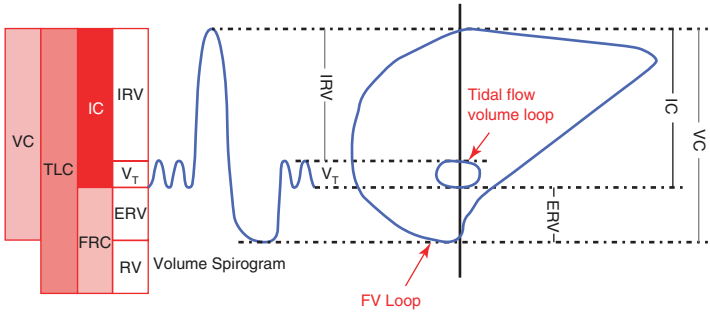

FIGURE 2.2 To aid in understanding lung volumes as they relate to the FV curve, the FV curve may be rotated 90° clockwise and placed beside the volume spirogram

METHODS FOR MEASURING THE STATIC LUNG VOLUMES

- There are different ways of measuring the lung volumes, the most accurate and widely used of which is the body box or body Plethysmography. The other, less widely used, methods are the nitrogen washout method, the inert gas dilution technique and the radiographic method.
- This section will discuss the principles, the advantages and the disadvantages of each method.

Body Plethysmography (Body Box)

- This is an ingenious way of measuring the lung volumes. The primary goal is to measure the FRC by the body box, in addition to allowing measures of the ERV and the SVC. The RV and TLC can then be calculated from these 3 variables, (RV = FRC – ERV; TLC = RV + SVC); see Figure 2.1.
- The principle of body plethysmography depends on *Boyle's law* which states that the product of pressure and volume of a gas is constant at a constant temperature [4, 5]. For the details of how this law is applied in the body box to get the FRC, see Table 2.1.

Table 2.1 Principle of Body Plethesmography
Figure 2.3

Body Plethysmography, Principle: [1, 4, 5]

The principle of body plethysmography depends on Boyle's law which states that the product of pressure and volume ($P \times V$) of a gas is constant under constant temperature conditions (which is the case in the lungs):

Therefore: $P_1 \times V_1 = P_2 \times V_2$

The patient is put in the plethysmograph (an airtight box with a known volume), with a clip placed on the nose, and the mouth tightly applied around a mouth-piece. The patient is then instructed to breathe at the resting tidal volume (V_T). The first part of the equation, above (Boyle's law) can then be applied at the patient's FRC (the end of a normal exhalation), where:

- P_1 is the pressure of the air in the lungs at FRC (the beginning of the test), which equals the barometric pressure (760 cmH_2O, at sea level)
- V_1 is the FRC (V_{FRC}) that is the volume of air in the lungs at the beginning of the test

At FRC, a valve (shutter) will close and the patient will perform a panting maneuver through an occluded airway where the change in pressure will be measured (ΔP)

The air in the lungs will get compressed and decompressed as a result of the change in pressure, resulting in a change in lung volume, i.e. a change in FRC (ΔV). We can now apply the new pressure and volume on the second part of the same equation, above, where:

- P_2 (the pressure of air in the lungs when the air gets decompressed as a result of the negative pressure produced by the inspiratory muscles during the panting maneuver, after the valve closure) will equal the initial pressure (P_1) minus the change in pressure (ΔP), i.e. $P_2 = (P_1 - \Delta P)$.
- Similarly, V_2 (the volume of air in the lungs after it gets decompressed) will equal the sum of the initial volume of the lung (V_1 or V_{FRC}) plus the change in volume (ΔV). So, $V_2 = (V_1 + \Delta V)$
- By substituting these values in the original equation ($P_1 \times V_1 = P_2 \times V_2$), we will get:
  - $P_1 \times V_1 = (P_1 - \Delta P) \times (V_1 + \Delta V)$; multiplying ($P_1 - \Delta P$) by ($V_1 + \Delta V$):
  - $P_1 \times V_1 = (P_1 \times V_1) + (P_1 \times \Delta V) - (\Delta P \times V_1) - (\Delta P \times \Delta V)$; subtracting ($P_1 \times V_1$) from both sides:

TABLE 2.1 (continued)

- $0 = (P_1 \times \Delta V) - (\Delta P \times V_1) - (\Delta P \times \Delta V)$; adding $(\Delta P \times V_1)$ to both sides:
- $(\Delta P \times V_1) = (P_1 \times \Delta V) - (\Delta P \times \Delta V)$; dividing by ΔP
- $(\Delta P \times V_1)/\Delta P = [(P_1 \times \Delta V) - (\Delta P \times \Delta V)]/\Delta P$ **OR** $V_1 = [\Delta V \times (P_1 - \Delta P)]/\Delta P$
- As ΔP is too small compared to P_1 (20 cmH_2O compared a barometric pressure of 760 cmH_2O), then we can accept: $P_1 - \Delta P = P_1$. Then, the final equation can be simplified as follows: $V_1 = (\Delta V \times P_1)/\Delta P$ **OR** $V_{FRC} = (\Delta V \times P_1)/\Delta P$; as P_1 is the barometric pressure; each of ΔP and ΔV are measured by the plethysmograph
- After determining the FRC, the RV and TLC can be calculated, as discussed earlier. You don't need to worry about all of this, as a computer does all the measurements and calculations, but it is still good to know the calculation
- In plethysmography, the FRC is sometimes referred to as the thoracic gas volume (TGV or V_{TG})

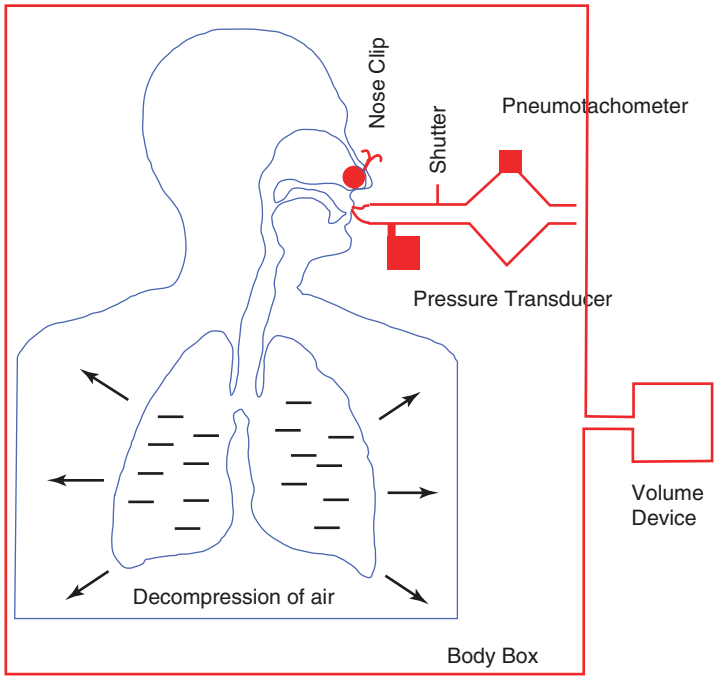

FIGURE 2.3 Principle of body plethesmography (the body box)

- The plethysmograph is the most popular way of measuring the lung volumes, as it is the fastest and probably the most accurate, but it is the most expensive, too. A comparison between the methods for measuring the lung volumes is shown in Table 2.4 [5, 6].

Nitrogen Washout Method [1, 7]

- This is another way of determining FRC. This technique is less accurate and more time consuming (at least 7 minutes [8]). Its principle is related to the concentration of nitrogen in the lungs (which is the concentration of the atmospheric nitrogen, 80%), which then can be washed out to determine the FRC volume. See Table 2.2 for details.

Table 2.2 Nitrogen washout method [1, 7]

Figure 2.4
At FRC (the end of a normal exhalation), the patient will breathe into a closed system. He/she will inhale 100% O_2 and exhale into a separate container with a known volume. The patient will continue this process, until almost all the nitrogen in the lungs is exhaled into that container. The nitrogen concentration in the container is then determined
The equation of the concentration (C) and volume (V) can then be applied: $C_1 \times V_1 = C_2 \times V_2$, where: ○ C_1 is the N_2 concentration in the lungs at FRC (80%) ○ V_1 is the FRC (unknown) ○ C_2 is the N_2 concentration in the container (known) ○ V_2 is the volume of air in the collecting container (known)
The FRC can then be determined. Keep in mind that two correction factors are used for accurate results. One is to account for the N_2 that remains in the lungs at the end of the test and the second is to account for the N_2 that is continuously released from the circulation into the lungs during the test
In obstructive disorders, more time (20 minutes) than usual is needed to washout N_2 from the poorly ventilated areas, resulting in under-estimation of the lung volumes. The test is normally terminated after 7 minutes [8], while body plethysmography is usually carried out over less than a minute. A significant increase in TLC measured by plethysmography compared to N_2 washout method suggests air trapping commonly seen in obstructive disorders (COPD)

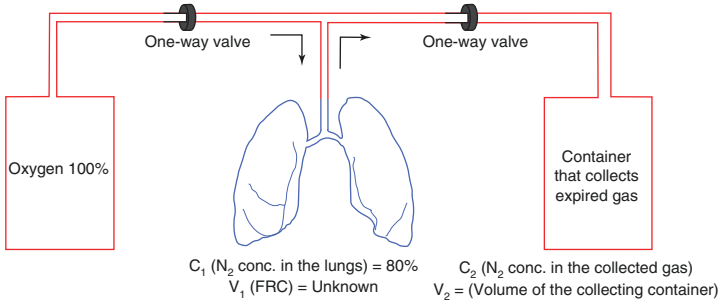

FIGURE 2.4 Principle of Nitrogen washout method

TABLE 2.3 Inert gas dilution technique [1, 9, 10]

Figure 2.5

At FRC (the end of a normal exhalation), the patient will breathe into a closed system with a known volume (V_1) and concentration (C_1) of an inert gas (Helium, He). The patient will continue breathing the Helium until concentration equilibrium is reached and measured by a Helium analyzer (C_2). V_2 will be the sum of the original volume of Helium (V_1) and the initial lung volume (FRC)

The equation of the concentration (C) and volume (V) can be applied to get the FRC as follows:

- $C_1 \times V_1 = C_2 \times V_2$, where $V_2 = (V_1 + \text{FRC})$, therefore:
  $C_1 \times V_1 = C_2 \times (V_1 + \text{FRC})$

$$\text{FRC} = [(C_1 \times V_1)/C_2] - (V_1)$$
$$= V_1 \times [(C_1/C_2) - 1] = V_1 \times [(C_1/C_2) - (C_2/C_2)]$$
$$= V_1 \times (C_1 - C_2)/C_2$$

Inert Gas Dilution Technique [1, 9, 10]

- An inert gas is a gas that is not absorbable in the air-spaces. As in N_2 washout method, the inert gas technique is less accurate (under-estimates lung volumes in airway obstruction) and is more time consuming. See Table 2.3 for details.

Radiographic Method (Planimetry or Geometry)

- The TLC and RV are estimated by doing PA and lateral chest radiographs during full inspiration (TLC) and full expiration

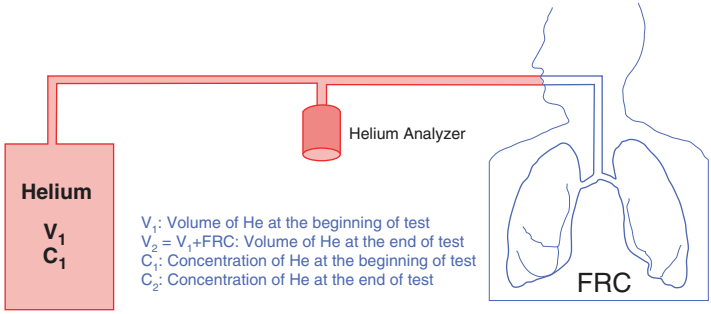

FIGURE 2.5 Principle of Inert Gas (Helium) Dilution Technique

TABLE 2.4 Comparison between the common methods for measuring lung volumes [5, 6]

Plethysmography	N_2 washout method/Inert gas dilution technique
Fast	Time consuming
Readily repeatable for reproducibility	Difficult to repeat [1, 10]. The test is too long [1]; (more time is required for the lungs to equilibrate and to clear inert gas in the dilution technique)
More accurate	Less accurate
Slightly over-estimates FRC in obstructive disorders [5]	Under-estimates FRC in obstructive disorders
Difficult to test patients on wheel chairs or stretchers or patients attached to i.v. pumps	Possible to test patients on wheel chairs or stretchers
Expensive, large size and complex	Cheaper equipment

(RV). It is a method that is not used routinely, due to the unnecessary exposure to radiation. This method may yield a lower TLC by >10% compared to plethysmography [11–13]. CT scan and MRI are more accurate than radiography in determining TLC but they are more costly [14–16].

- In a normal subject, all the above mentioned methods should give similar values for the lung volumes, if done properly [1]. It is only in disease states, that the values will vary to any significant degree between the different methods; Table 2.4.

TECHNIQUE FOR BODY PLETHYSMOGRAPHY

- The plethysmograph should be calibrated daily to ensure accuracy [1, 17–19]. The temperature and barometric pressure should be entered every morning.
- The patient sits comfortably inside the body box, with the door closed, a nose clip applied and the mouth tightly applied to a mouth-piece.
- The patient should breathe normally until 3 or 4 stable tidal breaths are achieved; (Figure 2.6). Then, (Step 1) at the end of the last tidal exhalation (FRC), the patient is instructed to pant fast and shallowly [20] against a closed valve (shutter), where the plethysmograph measures the FRC, as explained earlier.
- Step 2: the patient is then instructed to take a full inspiration (IC) then (step 3) deep, slow expiration (SVC or VC) for at least 6 seconds, which is spirometry but an unforced maneuver. The subsets of lung volume can then be calculated, as shown in Figure 2.6.[1]
- The test is then repeated for reproducibility as ATS criteria should also be met in the measurements. The difference between the two measurements of FRC and TLC should be within 10% and RV within 20% [1].
- Physical and biological calibrations are also needed.
  - The physical calibration is done every morning and includes calibrating the mouth pressure transducer and the volume signal of the plethysmograph. The volume calibration is carried out using a container with a known volume (a 3-liter syringe) where the container's gas volume measurements should be within 50 ml or 3% of each other, whichever is larger [1, 5].
  - Biological calibration should be done once a month on two reference subjects [1]. Measurements shouldn't be significantly different from the previously acquired measurements in the same subjects (<10% for TLC and FRC and <20% for RV) [1].

[1] In some labs, the patient is instructed to exhale fully after the panting maneuver to measure ERV then to inhale fully to measure VC.

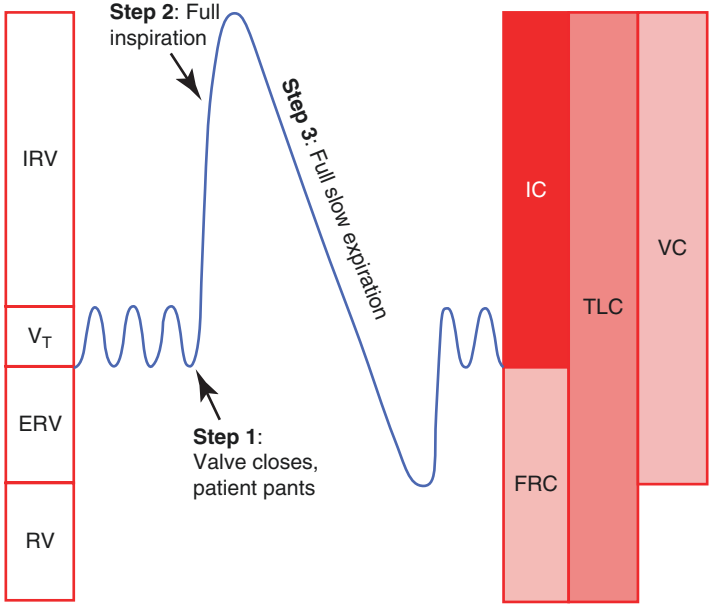

FIGURE 2.6 Technique for plethysmography. Notice that SVC is used instead of FVC

CORRELATING THE FLOW VOLUME CURVE WITH LUNG VOLUMES

- When the FV curve is done while the patient is inside the body box, at the same time as the lung volume study, the TLC and RV can be accurately plotted on the curve too. As discussed in Chapter 1, TLC is represented by the left-most point of the curve and RV by the right-most point of the curve. Comparing these points with their equivalents in the predicted curve, will indicate whether these lung volumes are decreased, normal or increased.
- In restrictive disorders, the TLC and RV are low, which means that the curve will shift to the right compared to predicted (remember, *r*ight = *r*estrictive). The opposite is true in obstructive disorders where lung recoil is reduced i.e. emphysema, see Figure 2.7.

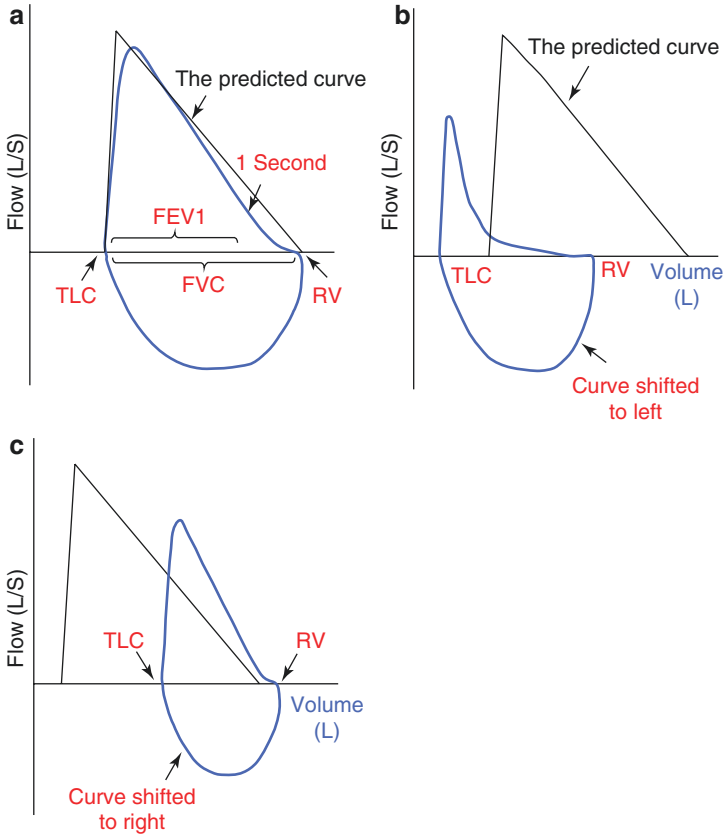

FIGURE 2.7 (**a**) Represents the ideal curve; (**b**) represents an obstructive disorder with increased TLC and RV and shift of FV curve to the left; (**c**) represents a restrictive disorder with decreased TLC and RV and shift of FV curve to the right

REFERENCE VALUES [1, 6, 18, 21–24]

- As with older spirometry databases, lung volume reference values were derived from Caucasian studies [25], and there remains a paucity of lung volume for other ethnic groups and therefore corrections need to be made for ethnic variability. These reference values are related to body size, with

the height being the most important factor. Values above the fifth percentile are considered normal.

COMPONENTS OF A LUNG VOLUME STUDY

- The simple rule for lung volumes is that they increase in obstructive disorders and decrease in restrictive disorders. TLC and RV are the most important for interpreting PTFs. The RV/TLC ratio is similarly useful in interpreting lung volume studies. Table 2.5 discusses the causes for abnormal lung volumes. IC and IRV are not discussed as they have little diagnostic role.

CLINICAL SIGNIFICANCE OF FRC

- A high FRC (as in emphysema) means, the lungs contain more air than normal at rest. Breathing at that high lung volume helps prevent collapse of the airways and air trapping in emphysematous lungs, but at the same time, increases the effort of breathing. This can be very uncomfortable and lead to dyspnea. By way of example take a deep breath and try to talk and breathe at that lung volume and see for yourself. The increased effort noticed when breathing at high lung volumes is caused by two consequences of a high lung volume. Firstly, the breathing muscles are shortened and contract at a mechanical disadvantage. As a result, more muscular activity is required to produce the pressure gradient that leads to airflow and tidal volume. Secondly, the lungs are less compliant as lung volume increases above FRC (more elastic recoil) and so more force is required to produce airflow.
- When patients with emphysema exercise, their respiratory rate increases and the expiratory time decreases. The reduced expiratory time impairs lung emptying and leads to air trapping. The air trapping results in a progressive increase in the FRC with each respiratory cycle. This new volume is called End-Expiratory Lung Volume. This process continues until this volume approaches a critical point, at which time, the patient can't continue exercising. This phenomenon is called "*dynamic hyperinflation*" and is

TABLE 2.5 Causes of abnormal lung volumes

TLC

Increased in:

- COPD, mainly emphysema
- Acromegaly patients may have a high TLC [2], which can be differentiated from emphysema by RV/TLC ratio (normal in acromegaly and high in emphysema [26])
- TLC may be high in normal subjects with big lungs e.g. swimmers
- TLC is usually normal in asthma, as lung elastic recoil is normal [27]

Decreased in restrictive disorders [28] (see Table 1.7 for classification)

RV

Increased (air trapping) in obstructive disorders:

- COPD
- Asthma, although the TLC is normal, but the RV is high because of air trapping

Decreased in parenchymal restriction

RV/TLC ratio

Normal in parenchymal restriction [2]

Increased

- Mainly in obstructive disorders (very high in emphysema) [27, 28]
- Can be increased in chest wall restriction (because of normal RV and low TLC)

ERV

Decreased in

- Restrictive disorders, similar to TLC
- Obstructive disorders (because of the increased RV due to air trapping that occurs in these conditions)
- An isolated reduction in ERV is characteristic for obesity

FRC

Increased (hyperinflation) in

- Obstructive disorders, mainly emphysema due to loss of lung elastic recoil
- FRC increases slightly with aging

Decreased in

- Restrictive disorders, mainly lung fibrosis
- Obesity
- Supine position (abdominal organs push the diaphragm against the lungs)

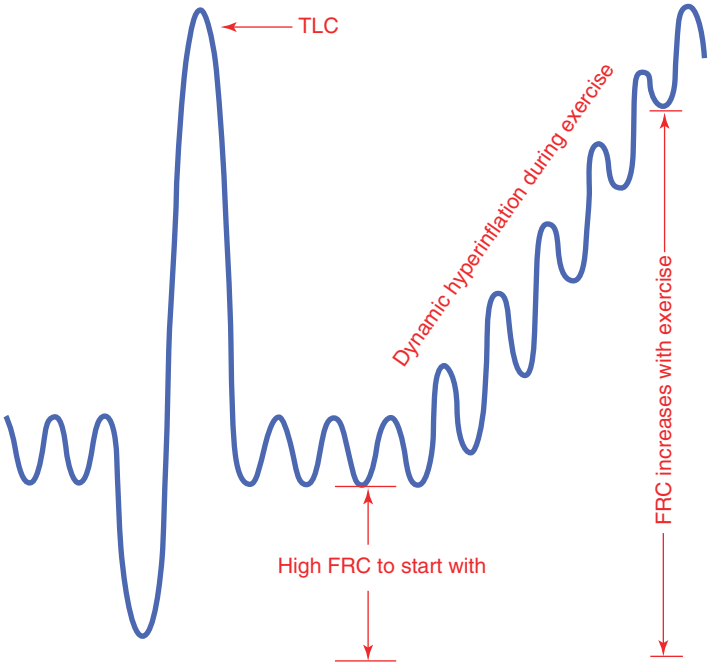

FIGURE 2.8 Dynamic hyperinflation in patients with emphysema during exercise. Note that V_T increases with exercise. Note also that the expiratory phase decreases progressively with continued exercise indicating progressive air trapping

characteristic of patients with emphysema and is responsible for much of their exercise limitation; Figure 2.8.

- Breathing at a low FRC, as in pulmonary fibrosis and obesity, can also increase the work of breathing. In restrictive lung disorders, the lung compliance is reduced which means more effort is needed to inflate the lungs.

DISEASE PATTERNS

The lung volumes are diagnostically useful in many ways. Table 2.6 summarizes their usefulness, which is discussed in more detail in this section:

TABLE 2.6 Additional information acquired by a lung volume study compared to spirometry

Differentiates the subtypes of obstructive disorders
Confirms the diagnosis of a restrictive disorder and separates its subtypes
Separates restrictive from obstructive disorders
Helps in detecting combined, obstructive and restrictive disorders

Defining Air Trapping and Hyperinflation in Obstructive Disorders

- Current guidelines do not specify a fixed cut off for TLC when defining hyperinflation however, a value greater than 120% predicted is generally considered to be indicative of hyperinflation
- Similarly, air trapping is identified by taking the upper limit of normal for RV in combination with an elevated percent predicted RV/TLC ratio. For example, if the measured RV is above the upper limit of normal and the ratio of RV over TLC is greater than 1.2 or 120%, then we have identified air trapping.
- *Differentiate subtypes of obstructive disorders*
  - Generally, obstructive disorders (emphysema and asthma) result in increased RV (air trapping) due to airway narrowing while TLC is increased only in emphysema due to loss of elastic recoil. In asthma, however, the lung has normal elastic recoil and, therefore a normal TLC [21].
  - The RV/TLC ratio may be increased in both emphysema and asthma. The RV/TLC ratio can be used also to differentiate an obstructive from a non-obstructive increase in TLC, like acromegaly (where the RV is increased but the RV/TLC ratio is normal) [2].
  - If lung volumes are measured pre- and post- bronchodilator, much can be learned from looking at the behavior of TLC and RV before and after the bronchodilator. TLC and RV may be shown to decrease following bronchodilator, even in the absence of a significant response in FEV_1 and FVC. Furthermore, IC may increase as FRC may decrease more than TLC in response to bronchodilators. In this case, an increase in IC gives patients with emphysema more room or time to breathe before they

develop dynamic hyperinflation to the point of stopping exercise. These volume changes indicate that the bronchodilators are clinically useful to such patients even though there is no change in FEV_1; (Figure 2.9) [17, 21, 29].

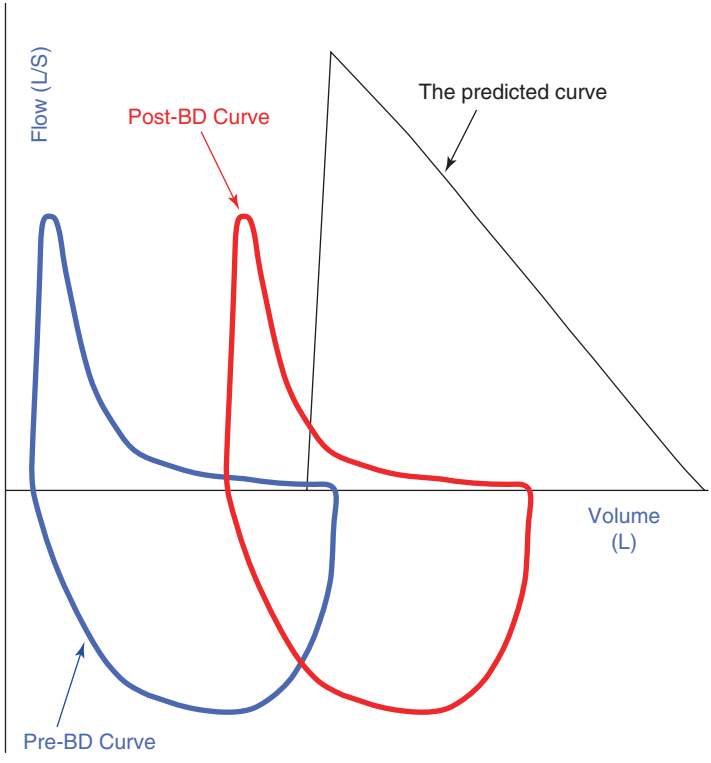

Figure 2.9 Post-BD curve is closer to predicted curve indicating significant reduction in TLC and RV compared to that in the pre-BD curve. The morphology of the curve has not changed indicating no improvement in FEV_1 or FVC. Despite that BD can be of help to such patients because of the lung volume change. Note that the change in TLC in this diagram is exaggerated

- *Confirm the diagnosis of a restrictive disorder and differentiate its subtypes*
  - A decreased TLC is essential to make the diagnosis of a restrictive disorder with confidence [21]. The RV and RV/TLC ratio, however, may be used to differentiate the subtypes of restriction:
    (a) In a parenchymal restriction (lung fibrosis), where there is increased elastic recoil and loss of air space, the RV and TLC are reduced with a normal RV/TLC ratio (both RV and TLC decrease proportionately) [2].
    (b) In chest wall restriction (NMD, musculoskeletal disease, paralyzed diaphragms and obesity), where the lung parenchyma is normal, the RV is usually normal (or increased) with an increased RV/TLC ratio (remember that TLC is low). In NMD, RV may be increased because the ERV can be very low due to weakness of the expiratory muscles.
    (c) The diffusing capacity for Carbon monoxide (DL_{CO}) is a more reliable way of differentiation between parenchymal and chest wall restriction, as will be discussed in next chapter. *Maximal Voluntary Ventilation (MVV)* and *maximal respiratory pressures* are measures to help differentiate the different types of chest wall restriction.
      - Obesity and mild asthma can show a spirometric pattern consistent with mild restriction (decreased FVC and normal FEV_1/FVC ratio), the so called pseudorestriction. The way to differentiate parenchymal restriction from this pseudorestriction (caused by obesity or mild asthma) is by the IC/ERV ratio. This ratio is normally 2–3:1. This ratio decreases in parenchymal restriction to <2:1 and increases in pseudorestriction to >6:1. The maximal FV curve, combined with a FV curve during quiet breathing, can be used to make that distinction as in the Figure 2.10 [31].
      - Poor patient effort during spirometry may mimic a restrictive disorder, with low FVC and FEV_1 and a normal FEV_1/FVC ratio. In this case a normal TLC

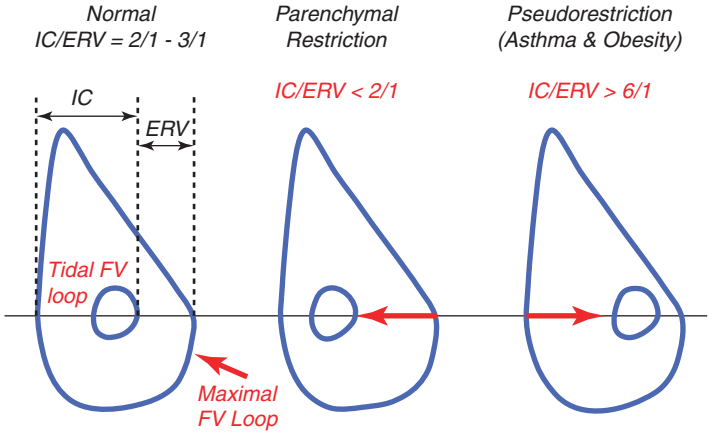

FIGURE 2.10 IC/ERV ratio is used to differentiate parenchymal restriction from pseudorestriction [30]

can exclude restrictive disorders, as body plethysmography doesn't need much patient effort to perform. The shape of the FV curve, can also easily exclude a poor effort study (PEF is not sharp and rounded in a poor effort study). In addition, the study is unlikely to be reproducible with a poor effort. The technicians usually indicate in their comments if a poor effort is apparent.

- *Separating obstructive from restrictive disorders*
  - Obstructive and restrictive disorders are sometimes hard to separate based on spirometry alone. Lung volumes may provide additional clues as they are generally increased with obstructive and decreased with restrictive disorders.
  - As an example, when the FEV_1 and FVC are at the lower limit of the normal range, with a normal FEV_1/FVC ratio, a lung volume study may be of value:
    (a) If the TLC and RV are high, then an obstructive disorder is most likely (RV/TLC ratio is usually high).
    (b) If the TLC is normal and RV is mildly increased, then mild asthma and air trapping could be responsible (RV/TLC ratio is high) [2]. In this case, the airway obstruction is not severe enough to cause a significant drop in

FEV_1 or their ratio. A bronchodilator study may show a significant response.

(c) If the TLC is low, then a restrictive defect is likely to be the cause, provided that FVC is below the fifth percentile (a normal FVC rules out restriction [32, 33]). Before you make such a conclusion, have a quick look at the FV curve and the rest of the PFT values. If all the values are decreased proportionately with a normal FV curve make sure a correction for ethnic background is not required.

(d) If the TLC and RV are normal, then the study is most likely normal.

- *Detection of combined disorders*
  - Combined disorders are hard to diagnose based on spirometry alone. Spirometry coupled with a lung volume study is very useful:
    (a) An obstructive disorder should be clear in spirometry, with low FEV_1/FVC ratio. If this airflow obstruction is seen with a reduced TLC, then the reduced TLC suggests an additional restrictive disorder [21, 28]. The RV could be low, normal or high as airway obstruction may result in air trapping and increased RV [1]. Combined defects can be seen in conditions like sarcoidosis or co-existing COPD and lung fibrosis.
  - Keep in mind that an obstructive disorder (like emphysema) with pulmonary resection (lobectomy or pneumonectomy) can give a similar pattern.
- Chapter 6 discusses the approach to such PFTs in detail.

REFERENCES

1. Wanger J, Clausen JL, Coates A, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005;26:511–22.
2. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of pulmonary function tests, a practical guide. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
3. Steve H. Pulmonary function testing. In: ACCP Pulmonary Board Review Course; 2005. p. 297–320.
4. DuBois AB, Botelho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measur-

ing functional residual capacity in normal subjects. J Clin Invest. 1956;35:322–6.
5. Coates AL, Peslin R, Rodenstein D, Stocks J. Measurement of lung volumes by plethysmography. Eur Respir J. 1997;10:1415–27.
6. Stocks J, Quanjer PH. Reference values for residual volume, functional residual capacity and total lung capacity. ATS Workshop on Lung Volume Measurements. Official Statement of the European Respiratory Society. Eur Respir J. 1995;8:492–506.
7. Newth CJ, Enright P, Johnson RL. Multiple-breath nitrogen washout techniques: including measurements with patients on ventilators. Eur Respir J. 1997;10:2174–85.
8. Cournand A, Baldwin ED, Darling RC, Richards DWJ. Studies on intrapulmonary mixture of gases. IV. The significance of the pulmonary emptying rate and a simplified open circuit measurement of residual air. J Clin Invest. 1941;20:681–9.
9. Meneely GR, Kaltreider NL. The volume of the lung determined by helium dilution. Description of the method and comparison with other. J Clin Invest. 1948;28:129–39.
10. Corbeel LJ. International symposium on body plethysmography. Comparison between measurements of functional residual capacity and thoracic gas volume in chronic obstructive pulmonary disease. Prog Respir Res. 1969;4:194–204.
11. Clausen JL. Estimation of lung volumes from chest radiographs; 1982.
12. Crapo RO, Montague T, Armstrong J. Inspiratory lung volume achieved on routine chest films. Investig Radiol. 1979;14:137–40.
13. Kilburn KH, Warshaw RH, Thornton JC, Thornton K, Miller A. Predictive equations for total lung capacity and residual volume calculated from radiographs in a random sample of the Michigan population. Thorax. 1992;47:519–23.
14. Coxson HO, Hogg JC, Mayo JR, Behzad H, Whittall KP, Schwartz DA, Hartley PG, Galvin JR, Wilson JS, Hunninghake GW. Quantification of idiopathic pulmonary fibrosis using computed tomography and histology. Am J Respir Crit Care Med. 1997;155:1649–56.
15. Johnson RL, Cassidy SS, Grover R, et al. Effect of pneumonectomy on the remaining lung in dogs. J Appl Physiol. 1991;70:849–58.
16. Archer DC, Coblentz CL, deKemp RA, Nahmias C, Norman G. Automated in vivo quantification of emphysema. Radiology. 1993;188:835–8.
17. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
18. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Eur Respir J. 1993;6(Suppl 16):5–40.
19. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med. 1995;152:1107–36.

20. Shore SA, Huk O, Mannix S, Martin JG. Effect of panting frequency on the plethysmographic determination of thoracic gas volume in chronic obstructive pulmonary disease. Am Rev Respir Dis. 1983;128:54–9.
21. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
22. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J. 1993;6(Suppl 16):41–52.
23. Solberg HE, Gräsbeck R. Reference values. Adv Clin Chem. 1989;27:1–79.
24. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991;144:1202–18.
25. Tan WC, Bourbeau J, Hernandez P, et al. Canadian prediction equations of spirometric lung function for Caucasian adults 20 to 90 years of age: results from the Canadian Obstructive Lung Disease (COLD) study and the Lung Health Canadian Environment (LHCE) study. Can Respir J. 2011;18:321–6.
26. Pride NB, Macklem PT. Lung mechanics in disease. In: Macklem PT, Mead J, editors. Handbook of physiology. The respiratory system. mechanics of breathing, Sect. 3, Vol. III, Part 2. Bethesda: American Physiological Society; 1986. p. 659–92.
27. Pride NB. Physiology. In: Clark TJH, Godfrey S, Lee TH, editors. Asthma. 3rd ed. London: Chapman and Hall; 1992. p. 14–72.
28. Dykstra BJ, Scanlon PD, Kester MM, Beck KC, Enright PL. Lung volumes in 4,774 patients with obstructive lung disease. Chest. 1999;115:68–74.
29. Pellegrino R, Rodarte JR, Brusasco V. Assessing the reversibility of airway obstruction. Chest. 1998;114:1607–12.
30. Salzman S. Pulmonary function testing. Tips on how to interpret the results. J Respir Dis. 1999;20:809–22.
31. Salzman J. Pulmonary function testing. Tips on how to interpret the results. J Respir Dis. 1999;20:809–22.
32. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest. 1999;115:869–73.
33. Glady CA, Aaron SD, Lunau M, Clinch J, Dales RE. A spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. Chest. 2003;123:1939–46.

Chapter 3
Gas Transfer

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract Testing for gas transfer abnormalities is often the final invaluable step in our diagnostic decision tree. Here we discuss techniques for measuring DL_{CO} and how to utilize these measurements for accurate classification of pulmonary function abnormalities. We also review the various correction techniques to obtain accurate DL_{CO} values.

Keywords Carobon monoxide (CO) · Hemogobin (Hgb) · Diffusing Capacity for Carbon Monoxide (DL_{CO}) · Alveolar Volume (V_A) · DL_{CO}/V_A ratio

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DEFINITIONS

Diffusing Capacity for Carbon Monoxide (DL_{CO})

- Reflects the ability of Carbon Monoxide (CO) to diffuse into the blood through the alveolar capillary membrane. More accurately this value is a transfer factor of carbon monoxide as diffusion of a gas is not the only mechanism that can hinder alveolar gas from reaching and binding to red blood cell hemoglobin (Hgb). DL_{CO} is used to estimate gas transfer which is impaired in many disorders. DL_{CO} stands for *Lung Diffusing capacity for Carbon Monoxide* and its traditional unit is ml/min/mmHg[1] [1].
- CO is diffusion-limited as it is highly soluble and strongly binds to Hgb (CO affinity for Hgb is >200 times that for O_2). This feature makes the capillary back pressure for CO very low (almost zero) which allows the gas to diffuse freely to the capillary blood (and means that the mixed venous CO does not need to be measured). Therefore, DL_{CO} measurement reflects the diffusing ability of the alveolar-capillary membrane of the lung. A perfusion-limited gas such as acetylene, on the other hand, is so insoluble that if a small fraction of it diffuses to the capillary blood, no more diffusion will take place (no gradient for diffusion) until the capillary blood is replaced by fresh blood (perfusion-limited). This property makes this gas useful in measuring the total pulmonary capillary blood flow (generally reflects the cardiac output) but not diffusion. Oxygen is both diffusion and perfusion limited, therefore it is not suitable to measure the diffusing capacity [2].
- DL_{CO} measurement is very reliable and sensitive. As an example, in interstitial lung disorders (ILD), the DL_{CO} level usually decreases before any drop in lung volume. Therefore, DL_{CO} may drop before the disease is obvious clinically or even radiologically. This ability makes it of great value in the diagnosis and follow-up of such conditions.
- DL_{CO} is determined by the amount of blood recruited in the alveolar capillary bed (Hgb levels) and the alveolar-capillary surface area available for diffusion.

[1] In UK & Europe, TL_{CO} is used instead of DL_{CO} and stands for Lung Transfer factor for Carbon Monoxide and is expressed in SI units (mmol/min/Kilopascal).

Alveolar Volume (V_A)

- Represents an estimate of the TLC using a single-breath inert gas dilution technique, discussed in the previous chapter. V_A is measured simultaneously with the DL_{CO} measurement using a single breath technique, which makes it less accurate in estimating the TLC than the standard test [3, 4], (The standard inert gas dilution technique is performed over several minutes that are required for equilibration of the test gas). The result is expressed as "alveolar volume" (V_A) rather than TLC. V_A is usually less than TLC, because in this technique, there is less time for equilibration, so TLC is underestimated, more so with lung diseases. Substantial discrepancies imply more variability in the measurement of DL_{CO} and clearly limit any applicability of the DL_{CO}/V_A ratio; see below.
- The inert (non-absorbable) gas used in this test is usually Helium (He), which serves three important roles:[2]
  - Helium is used as an inert gas to calculate the initial alveolar CO concentration prior to diffusion of CO from the alveolar gas.
  - V_A calculated by He dilution corrects DL_{CO} to the actual alveolar volume available for diffusion, a ratio represented as DL_{CO}/V_A.
  - A third indirect use of V_A is to provide a crude estimate of the poorly ventilated volume of the lungs by subtracting V_A from TLC (measured by body plethysmography).

SINGLE BREATH DL_{CO} TECHNIQUE [1, 5]

- The most popular method of measuring DL_{CO} is the single-breath technique, which is discussed here.[3] Other methods may be used to measure DL_{CO} but they are less popular (e.g. steady-state, intra-breath and rebreathing techniques).

[2] Newer equipment use methane (CH_4) instead of helium as it can be continuously analyzed together with CO using rapidly responding infrared gas analyzers.

[3] The three-equation method is a widely used way of calculating DL_{CO} in the single-breath technique. It is available in some of the newer DL_{CO} measuring devices and probably provides a more accurate measurement [5].

- Most modern systems use rapid gas analyzers (RGA) to measure CO and inert gas concentrations. This obviates the need to collect a gas volume (~200 ml) during the expiration manoeuvre for gas analysis. Instead the integrated analyzer processes and calculates gas concentration measurements actively during the study. Therefore, ensure up-to-date equipment specifications for maximum accuracy and reproducibility. (See ERS/ATS Technical Standards) [5].
- Volume calibration checks should be calibrated every morning, and biologic controls should be tested weekly. Prior to each test the flow analyzer and gas analyzer should be zeroed. A leak test should be performed monthly with a 3 liters calibration syringe. Furthermore, if problems with the equipment are suspected repeat calibration should take place [5–7].
- The patient should hold supplemental oxygen for 10 minutes prior to the study (if clinically acceptable), and he/she should refrain from smoking for 24 hours as the CO contained in the smoke can artificially reduce the DL_{CO} value [5].
- Technique: after a full exhalation, the patient inhales a mixture of CO, He, O_2 & N_2, each with a known concentration. The patient has to inhale to at least 90% of the previously measured VC, and this will be recorded in the study as IVC (Inspiratory Vital Capacity) [8].[4] Then, the patient should hold his/her breath for 10 seconds to allow for diffusion [9]. This step is critical, as the patient is instructed to keep a neutral pressure on a closed glottis. Blowing out (*Valsalva manoeuvre*) or sucking in (*Muller's manoeuvre*) during this phase interferes with the results by altering pulmonary blood volume. After the 10-s breath hold, the patient exhales into a collection chamber. A mid-exhalation (representing the alveolar gas) sample is analyzed for the concentration of both, CO and He, Figure 3.1. Discarding an early portion is required to avoid sampling the dead space gas. The washout volume should be 0.75–1.0 liter (BTPS). If the patient has a vital capacity of <2 liters the washout volume can be reduced to 0.5 liters [5].
- The actual duration of breath-hold is recorded in the final report as BHT (*Breath-Hold Time*), in seconds.
- The test is repeated once more, after 4 minutes in a classical system, however in RGA systems, measurement of end expi-

[4] For most DL_{CO} measuring devices, a VC of at least 1 L is required to produce an accurate measurement of DL_{CO}.

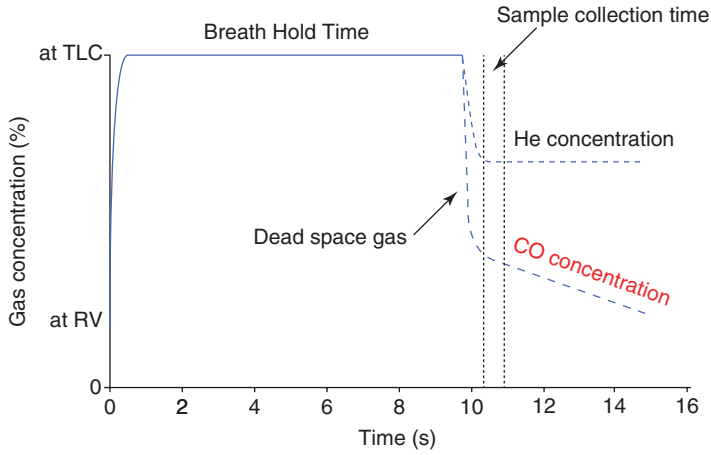

FIGURE 3.1 Schematic of gas concentration during single-breath DL_{CO} measurement. Notice that sample collection takes place after dead-space gas is exhaled (modified from MacIntyre [1]. With permission)

ratory gas concentrations can allow the test to be repeated sooner [1, 5].

- For repeatability collect at least two results that lie within 2 ml/min/mmHg of each other [1, 5, 10].
- For acceptability [5]:
  - Inspiratory volume should be ≥90% of the largest VC in the same session.
  - During the inspiratory manoeuvre, 85% of inspiratory volume should be inspired within 4 seconds.
  - A breath hold of 10 ± 2 seconds with no evidence of Valsalva or Mueller manoeuvres during this time.
- The maximum number of trials is 5, as following that, the retained CO in the blood from the previous trials will significantly interfere with test results [1].[5] Don't worry about CO toxicity, as the amount used for the test is very small, only 0.3% of the gas mixture.
- For details of DL_{CO} calculation using single-breath technique; see Table 3.1 [1].

[5] Five consecutive DL_{CO} measurements may increase CO-Hgb by ~3.5% (i.e., 0.7% per test), which will decrease the measured DL_{CO} by ~3–3.5% [45].

TABLE 3.1 Calculating DL_{CO} using single-breath technique [1]

The diffusing capacity for CO (DL_{CO}) equals the rate of CO uptake (Vco) divided by its transfer pressure gradient ($P_ACO - P_cCO$), as P_ACO is the partial pressure of alveolar CO and P_cCO is the mean capillary partial pressure of CO. This relation can be written as follows:

$$DL_{CO} = Vco/(P_ACO - P_cCO)$$

Because P_cCO is negligible as CO almost completely binds to Hgb, the equation can be simplified as follows:

$$DL_{CO} = Vco/P_ACO$$

Vco can be calculated from the difference between the initial and the final CO concentration. Dividing by the logarithmic mean of P_ACO, results in the following equation:

$$DL_{CO} = V_A/[T \times (P_B - 47)] \times Ln\ (F_ACO_I/F_ACO_F)$$

As F_ACO_I is the initial alveolar CO concentration (before diffusion), F_ACO_F is the final alveolar CO concentration (after diffusion), T is the breath-hold time (BHT) in minutes, P_B is the barometric pressure, 47 is the partial pressure of water vapor at body temperature. V_A is the alveolar volume measured by the single-breath helium dilution

F_ACO_F is measured directly from the mid-exhalation breath sample (alveolar sample after discarding the dead space washout, 0.7–1.0 liters), while F_ACO_I is calculated using the inert gas (He) measurements as follows:

$$F_ACO_I = F_iCO \times (F_AHe/F_iHe)$$

As F_iCO is the inspired CO concentration, F_iHe is the inspired He concentration and F_AHe is the expired alveolar He concentration which are all known.

P_ACO is measured using the single breath helium dilution results to calculate the initial PCO and the final PCO directly measured from the exhaled gas

REFERENCE VALUES [11–14]

- Are derived from population studies. Abnormal values are less than or greater than the lower and upper limits of normal based on reference equations. Practically this usually is in the range of 75–120% of the predicted value for DL_{CO}.[6]

[6] LLN can be applied to appropriate reference equations to determine an abnormal result.

DL_{CO} ADJUSTMENTS

- Adjustment for Alveolar Volume (V_A) [1, 8, 15]
  - As discussed earlier, DL_{CO} can be adjusted for V_A (DL_{CO}/V_A ratio). In simple terms, DL_{CO}/V_A represents the diffusing capacity in the available alveolar spaces. In other words, DL_{CO}/V_A determines whether the currently available alveolar spaces are functioning normally.
  - As an example, in patients who had lobectomy or pneumonectomy with otherwise normal remaining lung tissue, the absolute value for DL_{CO} is expected to be reduced compared to the predicted values. If DL_{CO} is then corrected for V_A (i.e. DL_{CO}/V_A), it will be normal or even high [1]. Therefore, a normal or high DL_{CO}/V_A indicates that the remaining lung tissue is functioning normally. Elevated DL_{CO}/V_A in these patients is due to the increased blood flow in the remaining lung tissue [1].
  - DL_{CO} is usually reduced in ILD, but, at the same time, V_A is likely to be reduced too in such conditions (due to loss of lung tissue because of fibrosis) which may result in a normal DL_{CO}/V_A. Accordingly, a normal DL_{CO}/V_A cannot exclude ILD. A decreased DL_{CO}/V_A, however, strongly suggests parenchymal lung disease (ILD, emphysema) or pulmonary vascular disease (pulmonary hypertension). Unfortunately extrapulmonary restrictive disorders can have a normal DL_{CO}/V_A, possibly because of concomitant pulmonary abnormalities. A decreased DL_{CO}/V_A is also seen in patients with anemia, as is discussed below. See Chapter 6 for more detail in the interpretation of abnormal DL_{CO} measurements.
  - Given the variability discussed, DL_{CO}/V_A has limited utility in interpretation.
- Adjustment to Hgb [1, 16–20]
  - Anemia results in under-estimation of DL_{CO} because of the decreased Hgb available to uptake CO in the pulmonary capillary bed. If the Hgb is not known, anemia should be considered as a possible cause of any isolated or unexplained reduction in DL_{CO}. Similarly, polycythemia will then over-estimate DL_{CO}.
  - Correcting DL_{CO} for Hgb is then essential for patients with anemia. The relation between Hgb level and DL_{CO} value is not a linear relation. For example, if the Hgb is

Table 3.2 DL_{CO} adjustment to Hgb [1]

Men (adjust to a Hgb value of 146 g/L)
DL_{CO} Adj = measured $DL_{CO} \times [(10.22 + Hgb)/(1.7 \times Hgb)]$
Women and children <15 years of age (adjust to a Hgb value of 134 g/L)
DL_{CO} Adj = measured $DL_{CO} \times [(9.38 + Hgb)/(1.7 \times Hgb)]$

30 g/L less than normal, the DL_{CO} drops by ~10%, while if Hgb is 60 g/L less than normal, the DL_{CO} drops by ~30% [21]. Luckily, there are equations to correct DL_{CO} for Hgb, and in fact, a computer program does all the calculations if the Hgb value is entered. These equations are summarized in Table 3.2.

  - A rough way of quickly correcting DL_{CO} for Hgb is by increasing the measured DL_{CO} value by 4% for each 10 g/L drop from the average (~145 g/L for men and ~135 g/L for women), and decreasing the measured DL_{CO} by 2% for each 10 g/L increase in Hgb from the reference (normal) levels [22].

- Adjustments for Alveolar oxygen tension
  - The value of DL_{CO} will increase by ~0.35% for every 1 mmHg increase in P_AO_2
  - DL_{CO} [predicted for elevated P_AO_2] ≈ DL_{CO}[predicted]/$(1.0 + 0.0035(P_AO_2 - 100))$
- Adjustment to Carboxy-Hgb (CO-Hgb)
  - Increased CO-Hgb level tends to under-estimate the DL_{CO} because of (1) back pressure exerted by the CO-Hgb on the alveolar CO and (2) occupying Hgb binding sites producing an 'anemia effect" which results in a reduction in the amount of CO diffusing to the blood [17, 23, 24]. Patients who are suspected of smoking prior to the test can have their CO-Hgb levels measured (but this is rarely ever done). Once the CO-Hgb level is known the DL_{CO} can be estimated by decreasing the predicted DL_{CO} by 1% for each 1% increase in the CO-Hgb level above 2% [1, 25, 26]. Other more complicated equations may be used.[7]
  - In healthy non-smokers, CO-Hgb level is ~1–2% which is acquired from metabolic and environmental sources [1].

[7] Alveolar [CO] = (CO-Hgb/O_2Hgb) × [(alveolar [O_2])/210] [28]; DL_{CO} predicted for CO-Hgb = DL_{CO} predicted × (102% – CO-Hgb%) [1].

– Average smokers have a CO-Hgb level of ~ 4 or 5%, but this can be as high as 10% in heavy smokers [21]. This is why smokers are advised to refrain from smoking for at least 8–10 hours and preferably 24 hours before the test, but will they comply? Some laboratories do measure the serum CO-Hgb level before DL_{CO} measurement to be certain about the level.

CAUSES OF ABNORMAL DL_{CO}

- Anything that increases the blood flow or volume in the pulmonary capillary bed will result in elevation of DL_{CO}. A decreased DL_{CO}, however, could be related to either reduced surface area of the lung available for diffusion or disease of the alveolar-capillary membrane. Table 3.3 summarizes the most important causes of abnormal DL_{CO}.
- Grading of severity for a reduced DL_{CO} is shown in Table 3.4.

TABLE 3.3 Causes of abnormal DL_{CO}

Causes of high DL_{CO}
Recruitment of blood in the alveolar capillary bed:
Supine position [1, 27–29].
Hyperdynamic circulation (exercise, [27, 29, 30] fever)
Asthma
Muller's maneuver (inhaling against a closed glottis) [31–33]
Cardiac causes
Left to right cardiac shunting
Early congestive heart failure
Miscellaneous conditions
Polycythemia
Alveolar haemorrhage (blood in alveolar space will take up CO) [34]
Obesity (uncertain mechanism)
High altitude (due to a lower P_IO_2 at altitude increasing the CO binding to Hgb)
Following bronchodilators in obstructive disorders (up to 6% increase) [35, 36]
Incorrect reference values

(continued)

Table 3.3 (continued)

Causes of low DL_{CO}
Decreased surface area available for diffusion
Pulmonary resection (remaining lung tissue will have more blood supply (i.e. high DL_{CO}/V_A but the overall DL_{CO} will be low)
Emphysema [37–40] (actual functional alveolar capillary surface area is reduced)
VQ mismatch (e.g. significant bronchial obstruction)
Alveolo-capillary membrane disease
ILD [41, 42] (eg IPF, connective tissue disease, sarcoidosis, hypersensitivity pneumonitis, drugs)
Pulmonary vascular disease, e.g. pulmonary hypertension or pulmonary embolism [1]
Diffuse alveolar congestion [43]
CHF (pulmonary edema fluid impairs gas transfer)
Diffuse consolidation
Alveolar proteinosis
Miscellaneous
Anemia [16–20]
Elevated CO-Hgb [23–26, 44]
Pregnancy (unknown mechanism, ~15% drop) [22, 45]
Valsalva manoeuvre [31, 32] (exhaling against closed glottis, opposite to Muller's manoeuvre, reduces amount of blood at the capillary bed available for diffusion)
Extrapulmonary reduction in lung inflation (as low effort, NMD or skeletal deformity as in kyphoscoliosis)
Incorrect reference values
Others (diurnal variation: lower DL_{CO} by evening; during menstrual cycle; [46] ingestion of ethanol [47])

Table 3.4 Degree of severity of the reduction in diffusing capacity of CO [13]

Degree of severity	DL_{CO} (% pred.)
Mild	60–75%
Moderate	40–60%
Severe	<40%

References

1. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35.
2. West JB. Respiratory physiology: the essentials. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.
3. Rodenstein DO, Stănescu DC. Reassessment of lung volume measurement by helium dilution and by body plethysmography in chronic air-flow obstruction 1–3. Am Rev Respir Dis. 1982;126:1040–4.
4. Ferris BG. Epidemiology Standardization Project (American Thoracic Society). Am Rev Respir Dis. 1978;118:1–120.
5. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, Macintyre NR, Thompson BR, Wanger J. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49:1600016. https://doi.org/10.1183/13993003.00016-2016.
6. Renzetti AD Jr. Standardization of spirometry. Am Rev Respir Dis. 1979;119:831–8.
7. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
8. Johnson DC. Importance of adjusting carbon monoxide diffusing capacity (DLCO) and carbon monoxide transfer coefficient (KCO) for alveolar volume. Respir Med. 2000;94:28–37.
9. Welle I, Eide GE, Bakke P, Gulsvik A. Applicability of the single-breath carbon monoxide diffusing capacity in a Norwegian Community Study. Am J Respir Crit Care Med. 1998;158:1745–50.
10. Punjabi NM, Shade D, Patel AM, Wise RA. Measurement variability in single-breath diffusing capacity of the lung. Chest. 2003;123:1082–9.
11. Cotes JE, Chinn DJ, Quanjer PH, Roca J, Yernault JC. Standardization of the measurement of transfer factor (diffusing capacity). Eur Respir J. 1993;6(Suppl 16):41–52.
12. American Thoracic Society. Lung function testing: selection of reference values and interpretative strategies. Am Rev Respir Dis. 1991;144:1202–18.
13. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
14. Solberg HE, Gräsbeck R. Reference values. Adv Clin Chem. 1989;27:1–79.
15. Stam H, Versprille A, Bogaard JM. The components of the carbon monoxide diffusing capacity in man dependent on alveolar volume. Bull Eur Physiopathol Respir. 1983;19:17–22.
16. Viegi G, Baldi S, Begliomini E, Ferdeghini EM, Pistelli F. Single breath diffusing capacity for carbon monoxide: effects of adjust-

ment for inspired volume dead space, carbon dioxide, hemoglobin and carboxyhemoglobin. Respiration. 1998;65:56–62.
17. Mohsenifar Z, Brown HV, Schnitzer B, Prause JA, Koerner SK. The effect of abnormal levels of hematocrit on the single breath diffusing capacity. Lung. 1982;160:325–30.
18. Clark EH, Woods RL, Hughes JM. Effect of blood transfusion on the carbon monoxide transfer factor of the lung in man. Clin Sci Mol Med. 1978;54:627–31.
19. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron-deficiency anaemia: its effect on transfer factor for the lung (diffusiong capacity) and ventilation and cardiac frequency during sub-maximal exercise. Clin Sci. 1972;42:325–35.
20. Marrades RM, Diaz O, Roca J, Campistol JM, Torregrosa JV, Barberà JA, Cobos A, Félez MA, Rodriguez-Roisin R. Adjustment of DLCO for hemoglobin concentration. Am J Respir Crit Care Med. 1997;155:236–41.
21. Steve H. Pulmonary function testing. In: ACCP Pulmonary Board Review Course; 2005. p. 297–320.
22. Hancox B, Whyte K. Bob pocket guide to lung function tests. 1st ed. Sydney: McGraw-Hill; 2001.
23. Coburn RF, Forster RE, Kane PB. Considerations of the physiological variables that determine the blood carboxyhemoglobin concentration in man. J Clin Invest. 1965;44:1899–910.
24. Viegi G, Paoletti P, Carrozzi L, Baldacci S, Modena P, Pedreschi M, Di Pede F, Mammini U, Giuntini C. CO diffusing capacity in a general population sample: relationships with cigarette smoking and airflow obstruction. Respiration. 1993;60:155–61.
25. Roughton FJW, Forster RE. Relative importance of diffusion and chemical reaction rates in determining rate of exchange of gases in the human lung, with special reference to true diffusing capacity of pulmonary membrane and volume of blood in the lung capillaries. J Appl Physiol. 1957;11:290–302.
26. Comroe JJ. Pulmonary diffusing capacity for carbon monoxide (DLCO). Am Rev Respir Dis. 1975;111:225–40.
27. Huang YC, Helms MJ, MacIntyre NR. Normal values for single exhalation diffusing capacity and pulmonary capillary blood flow in sitting, supine positions, and during mild exercise. Chest. 1994;105:501–8.
28. Stam H, Kreuzer FJ, Versprille A. Effect of lung volume and positional changes on pulmonary diffusing capacity and its components. J Appl Physiol. 1991;71:1477–88.
29. Stokes DL, MacIntyre NR, Nadel JA. Nonlinear increases in diffusing capacity during exercise by seated and supine subjects. J Appl Physiol. 1981;51:858–63.
30. Johnson RL, Spicer WS, Bishop JM, Forster RE. Pulmonary capillary blood volume, flow and diffusing capacity during exercise. J Appl Physiol. 1960;15:893–902.

31. Smith TC, Rankin J. Pulmonary diffusing capacity and the capillary bed during Valsalva and Müller maneuvers. J Appl Physiol. 1969;27:826–33.
32. Cotes JE, Snidal DP, Shepard RH. Effect of negative intraalveolar pressure on pulmonary diffusing capacity. J Appl Physiol. 1960;15:372–6.
33. Cotton DJ, Mink JT, Graham BL. Effect of high negative inspiratory pressure on single breath CO diffusing capacity. Respir Physiol. 1983;54:19–29.
34. Greening AP, Hughes JM. Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage. Clin Sci (Lond). 1981;60:507–12.
35. Iversen ET, Sørensen T, Heckscher T, Jensen JI. Effect of terbutaline on exercise capacity and pulmonary function in patients with chronic obstructive pulmonary disease. Lung. 1999;177:263–71.
36. Chinn DJ, Askew J, Rowley L, Cotes JE. Measurement technique influences the response of transfer factor (TICO) to salbutamol in patients with airflow limitation. Eur Respir J. 1988;1:15–21.
37. Cotton DJ, Prabhu MB, Mink JT, Graham BL. Effects of ventilation inhomogeneity on DLcoSB-3EQ in normal subjects. J Appl Physiol. 1992;73:2623–30.
38. Cotton DJ, Prabhu MB, Mink JT, Graham BL. Effect of ventilation inhomogeneity on "intrabreath" measurements of diffusing capacity in normal subjects. J Appl Physiol. 1993;75:927–32.
39. Gelb AF, Gold WM, Wright RR, Bruch HR, Nadel JA. Physiologic diagnosis of subclinical emphysema. Am Rev Respir Dis. 1973;107:50–63.
40. Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, Nelems B, Müller NL. Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. Am Rev Respir Dis. 1989;139:1179–87.
41. Epler GR, Saber FA, Gaensler EA. Determination of severe impairment (disability) in interstitial lung disease. Am Rev Respir Dis. 1980;121:647–59.
42. Nordenfelt I, Svensson G. The transfer factor (diffusing capacity) as a predictor of hypoxaemia during exercise in restrictive and chronic obstructive pulmonary disease. Clin Physiol. 1987;7:423–30.
43. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of pulmonary function tests, a practical guide. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
44. Mohsenifar Z, Tashkin DP. Effect of carboxyhemoglobin on the single breath diffusing capacity: derivation of an empirical correction factor. Respiration. 1979;37:185–91.
45. Frey TM, Crapo RO, Jensen RL, Elliott CG. Diurnal variation of the diffusing capacity of the lung: is it real? Am Rev Respir Dis. 1987;136:1381–4.

46. Sansores RH, Abboud RT, Kennell C, Haynes N. The effect of menstruation on the pulmonary carbon monoxide diffusing capacity. Am J Respir Crit Care Med. 1995;152:381–4.
47. Peavy HH, Summer WR, Gurtner G. The effects of acute ethanol ingestion on pulmonary diffusing capacity. Chest. 1980;77:488–92.

Chapter 4

Airway Dysfunction, Challenge Testing and Occupational Asthma

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract Testing for airways dysfunction is a crucial part of pulmonary function testing. In this chapter we review the classification of reactive airways disease as well as the variety of challenge testing available to us. This variation reflects the heterogeneity of patient manifestation of airways dysfunction. We include testing for asthma, occupational airways disease, and exercise induced bronchoconstriction.

Keywords Methacholine Challenge · Exercise induced bronchoconstriction · Asthma · Occupational asthma · Eucapnic voluntary hyperventilation · PD_{20}

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DEFINITIONS

Airway Dysfunction

- This broad term includes a range of clinically distinct airway diseases that includes asthma, airway hyperresponsiveness (AHR), exercise induced asthma (EIA), and exercise induced bronchoconstriction (EIB) [1].

Exercise Induced Asthma

- Signs and symptoms of asthma developing after physical exercise [2].

Exercise Induced Bronchoconstriction

- Exercise induced bronchoconstriction (EIB) can be defined as a reduction in lung function (FEV_1) measured during objective testing and manifesting during exercise [2]. This is the preferred term over 'exercise induced asthma' since this does not imply a pathophysiologic mechanism. However, those with asthma usually have EIB, yet those with EIB do not always have asthma [2].

Occupational Asthma

- Occupational asthma is a disease characterized by variable airflow limitation and/or hyperresponsiveness due to causes and conditions attributable to an occupational environment and not to stimuli encountered outside the workplace.

Bronchial Challenge

- This is a test used in diagnosing or excluding asthma by provoking a bronchoconstriction response to a controlled external stimulus. This exploits the abnormal airway sensitivity inherent in asthma. Different external stimuli can be

employed, by convention either a drug like methacholine or a physical stimulus like exercise or cold air is used.

Methacholine

- Is the most common drug used in bronchial challenge testing (i.e. methacholine challenge). It leads to bronchial smooth muscle contraction via a cholinergic stimulus. The augmented cholinergic sensitivity will cause bronchoconstriction at lower methacholine concentrations in asthmatics than normal subjects.
- A significant bronchoconstrictive response is defined as a drop in FEV_1 by ≥20% of its baseline value. The degree of airway reactivity is defined by the dose or concentration (PD_{20} or PC_{20}) of methacholine resulting in bronchoconstriction.

PD_{20} or PC_{20}

- Stands for *"provocative dose"* or *"provocative concentration"* respectively; that is the dose or concentration of the drug at which a 20% decrease in FEV_1 occurs. If the provocative test is positive, PD_{20} or PC_{20} is used to grade the severity of the provocative response [3]. The lower the PD_{20} (i.e. the lower the methacholine dose) or PC_{20} (i.e. the lower the concentration of methacholine in mg/ml), the more severe the hyperresponsiveness is.
- The 2-minute tidal breathing methacholine concentration (PC_{20}) method using the English-Wright (EW) nebulizer although historically broadly used, has been shown to be less reliable in identifying and stratifying bronchial hyperresponsiveness when compared to the dosimeter technique (PD_{20}) [4, 5]. This is partly due to underestimation and inconsistency of drug delivery during inhalation.
- The 2-minute tidal breathing and PC_{20} scoring has in many labs been replaced by the 5 breath dosimeter technique with PD_{20} scoring which allows for more reproducible and consistent drug delivery to the patient.
- The cumulative dose dependence on bronchoconstriction has been validated and is the new standard [4, 5]. The 2017 technical standards recommendations made by the European

Respiratory Society replaces the provocative concentration approach with the more reliable provocative dose as the preferred technique for methacholine testing [6].

BACKGROUND: ASTHMATIC BRONCHOCONSTRICTION

- In asthmatics, the bronchial response to an allergen consists of two phases:
  - *Immediate response*, which occurs within few minutes of the exposure and is due to bronchial smooth muscle contraction (bronchospasm). This response can be blocked by bronchodilators.
  - *Delayed response*, which occurs 6–12 hours following exposure and is due to airway inflammation. This can be attenuated by corticosteroids.
- Different allergens may produce either one or both responses. Methacholine triggers the immediate response but it is a good predictor as well of the late response caused by any allergen.
- Because methacholine responsiveness can be blocked by bronchodilators, the patient should be off these drugs prior to testing to achieve the most meaningful results; Table 4.1.

Table 4.1 Minimum time interval for drugs that may influence methacholine test result

Inhaled bronchodilators:	
Short-acting agents (e.g. salbutamol) [7, 8]	8 hours
Medium-acting agents (e.g. ipratropium) [9, 10]	24 hours
Long-acting agents (e.g. salmeterol, formoterol) [11–13]	48 hours
Long-acting oral theophyllines [14, 15]	48 hours
Cromolyn sodium [3]	8 hours
Leukotriene antagonists [3]	24 hours
Caffeine-containing foods [16]	Avoid on the study day
Inhaled or systemic steroids [3, 17]	Don't need to be stopped (although may reduce response)

TECHNIQUE

- The patient should be clinically stable, and the technician should be trained in how to deal with any unwanted response, like severe bronchospasm or systemic reactions [3]. This test is done routinely in any standard pulmonary function laboratory or in specialized respiratory clinics and is generally safe [18–25]. Medical help should be readily available, however, in the rare instance of a severe reaction.
- The test and the possible side effects should be explained to the patient.
- The test is started by doing a baseline spirometry to record the initial FEV_1. The baseline spirometry tests need to be reproducible to allow comparison with later tests.
- If the spirometry reveals that the FEV_1 is less than 1 liter or < 50% of predicted, the test should be abandoned because of the risk relating to further bronchoconstriction [19]. Also the significance of a "positive" test in the setting of appreciable pre-existing airflow obstruction is to be questioned given that small further changes in airway radius can markedly decrease flow.
- After baseline spirometry, the patient inhales nebulized normal saline. Some patients are so hyper-responsive that saline can precipitate a bronchospastic reaction. These patients shouldn't be tested with methacholine. The technician will report this observation for the interpreter.

2-Minute Tidal Breathing Test Using the EW Nebulizer

- A methacholine starting concentration is selected according to different dosing protocols [3] (usually 2 ml of 1–2 mg/ml solution) and delivered to the patient via a nebulizer over 2 minutes [26–34]. FEV_1 is then measured at 30 seconds and 3 minutes after nebulization [3, 18, 35]. In order to protect the PFT laboratory staff from exposure, nebulization is preferably performed in a properly ventilated room.
- The concentration of methacholine is then doubled, and the test is repeated in a stepwise fashion until the patient reaches the maximum concentration of methacholine allowed (8–16 mg/ml) or the test becomes positive. Table 4.2 lists indications for study termination.

Table 4.2 Indication for study termination

Reaching the maximum dose or concentration allowed without a 20% or greater drop in FEV_1
A positive test is achieved (drop in FEV_1 by ≥20% of baseline)
Patient becomes unstable clinically (e.g. dyspnea, wheezing, cough)
Patient develops systemic reaction (e.g. flushing, headache, hypotension, arrhythmia)

5-Breath Dosimeter Test [3]

- The patient is prepared in the same manner described above. The starting dosimeter methacholine solution concentration is 0.025 mg/ml with a step wise increasing protocol to 0.25, 2.5, 10, and finally to 25 mg/ml
- At each dosing level the patient takes 5 breaths from the dosimeter, each approximately 50% of TLC with a 5 seconds breath hold at end of inspiration.
- Again the test is repeated until the maximum dose or the test becomes positive.
- A short acting β_2-agonist (2–4 puffs of salbutamol through a spacing device) is then given to subjects who develop bronchoconstriction and the spirometry is repeated 15 minutes later. The results are plotted graphically; Figure 4.1. The patient should be observed until clinically stable and FEV_1 is back to or near baseline.
- Patients should be instructed to NOT inhale deeply during the dosimeter technique. Historically during the 5 breath dosimeter studies patients were instructed to inhale to TLC. However, this is no longer recommended as there is evidence showing higher rates of false-negative studies. This is due to deep inspiration causing smooth muscle relaxation and bronchodilation [36, 37].
- Challenge testing can be done using other stimuli [3]:
  - Other drugs like histamine
  - Exercise—in suspected exercise-induced asthma
  - Exposure to cold air—in cold air-induced asthma
  - Spirometry before and after work or work compound exposure, in suspected occupational asthma.

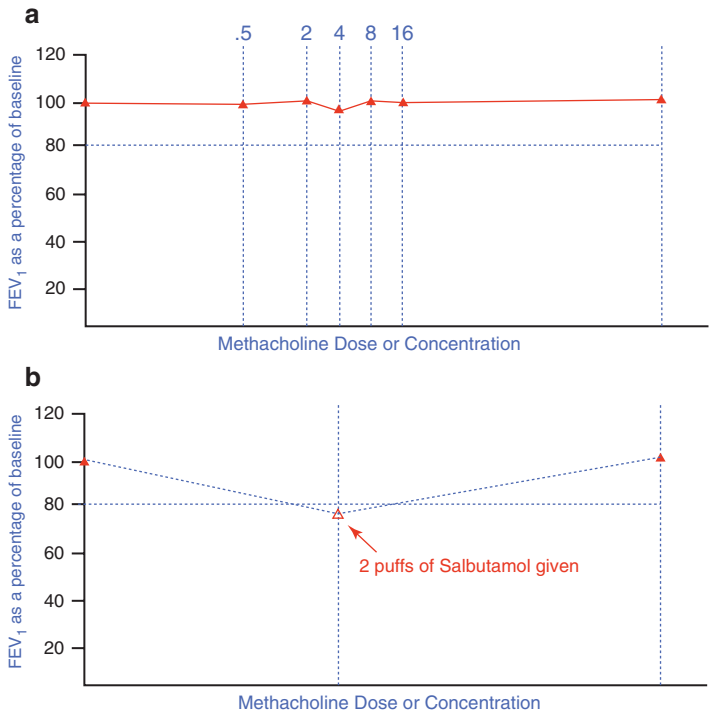

FIGURE 4.1 (**a**) A negative bronchial challenge test; the *y*-axis represents the patient FEV_1 as a percentage of the baseline FEV_1 (before giving methacholine) and the *x*-axis represents the dose or concentration of methacholine. The maximum dose was reached without a significant reduction in FEV_1, indicating a negative test. (**b**) A positive bronchial challenge test, as 2 mg/ml of methacholine resulted in a significant drop in FEV_1 indicating a positive test. Two puffs of salbutamol resulted in restoration of FEV_1

INDICATIONS AND CONTRAINDICATIONS FOR METHACHOLINE BRONCHIAL CHALLENGE

- The test is indicated when asthma is suspected but not obvious clinically or not obvious through pre and post bronchodilator spirometry. In most instances a positive response to bronchodilator negates the need for a methacholine challenge test [3]. Table 4.3 summarizes the indications and contraindications for bronchial challenge testing.

Table 4.3 Indications and contraindications for bronchial challenge

Indications for methacholine bronchial challenge
Unexplained dyspnea, cough or episodic chest tightness
Unexplained dyspnea with exercise or cold air exposure
Normal spirometry and a negative bronchodilator response in a patient with a clinical picture suggestive of asthma
Mild airflow obstruction without a bronchodilator response with a moderate to high pre test probability of asthma
Absolute contraindications
Severe airflow limitation (FEV_1 < 1 liter or < 50% predicted) [19]
A recent MI or CVA (within 3 months)
Arterial aneurysm especially if advanced
Hypertension (systolic >200 or diastolic >100)
Relative contraindications
Moderate airflow limitation (FEV_1 < 1.5 liters or < 60% predicted) [20, 38]
Clinical instability including a recent respiratory tract infection (test may be positive)
Inability to perform acceptable-quality spirometry
Pregnancy or nursing mothers
Current use of cholinesterase inhibitors (for myasthenia gravis)
Epilepsy

INTERPRETATION

- This test is very sensitive but non-specific in the assessment of asthma. If negative, it essentially excludes active asthma [39, 40], except if the patient took a bronchodilator prior to the test. It is also possible that the test may be normal if asthma is in remission. A positive test can be seen in a variety of conditions; summarized in Table 4.4 [41–43]. Therefore, a positive test should be reported as supportive of asthma, and a negative test makes asthma very unlikely [3]. Severe bronchial reactivity, however, may be generally considered diagnostic for asthma.
- Bronchial reactivity alone cannot be used to diagnose concomitant asthma in patients with COPD. There are several clinical criteria available to diagnose the relatively new entity of Asthma/COPD Overlap (ACO).
- Grading of severity of bronchial hyper-responsiveness based on PC_{20} is summarized in Table 4.5 [3].
- Figure 4.1 gives examples of a negative and a positive methacholine challenge test (Table 4.6).

TABLE 4.4 Conditions associated with an increase in bronchial reactivity [41–43]

Asthma
Allergic rhinitis
Sarcoidosis (up to 50% can have a positive test)
COPD
Cystic fibrosis
Recent respiratory tract infection [44–47]

TABLE 4.5 Grading of severity of bronchial hyper-responsiveness (based on PC_{20}) [3]

Normal	PC_{20} > 16 mg/ml
Borderline	4–16
Mild	1–4
Moderate-severe	<1

TABLE 4.6 Comparison of PC20 concentration and PD20 dosing [3, 6]

PC20 (mg/ml)	PD20 µmol (µg) Equivalent	Interpretation
<0.25	<0.03 (<6)	Marked AHR
0.25–1	0.03–0.13 (6–25)	Moderate AHR
1–4	0.13–0.5 (25–100)	Mild AHR
4–16	0.5–2 (100–400)	Borderline AHR
<16	>2 (>400)	Normal

PC20 provocative concentration of methacholine causing a 20% drop in FEV1; *PD20* provocative dose of methacholine causing a 20% drop in FEV_1; *AHR* airway hyperresponsiveness

EXERCISE INDUCED BRONCHOCONSTRICTION

Background

- Patients presenting with symptoms of EIB often, but not always, have a concurrent diagnosis of chronic asthma. Rates of EIB are higher in elite athletes (30–75%) than the general population (20%) [44, 48]. Accurate and reliable testing and diagnosis of EIB often determines if an athlete is allowed to use short acting bronchodilators prior to competing, therefore misdiagnosis can impact these patients professionally [49, 61].

- Environmental factors appear to play a large role in the airway injury and triggering of EIB, including trichloramines and ozone inhaled by competitive swimmers, as well as cold dry air inhaled by skiers and ice rink athletes [47, 50].
- Hyperpnea during exercise appears to play a role, causing osmotic and thermal stress to the respiratory epithelium triggering bronchoconstriction [51].
- Bronchoconstriction following EIB can last 30–90 minutes without treatment [52].
- Absence or presence of symptoms during exercise does not correlate well with objective measurement of airway narrowing, therefore limiting the utility of a purely clinical diagnosis [53, 54].

Exercise Induced Bronchoconstriction Testing

- First, rule out underlying asthma with spirometry (pre and post bronchodilator testing).
- If no underlying obstruction and reversibility is seen, then proceed to methacholine challenge testing.
- If patient is non-reactive to methacholine challenge testing, the gold standard for EIB testing is eucapnic voluntary hyperventilation (EVH) [55].
- Inhaled mannitol challenge can also be considered as a second line and/or confirmatory test [56].
- Exercise specific bronchoconstriction testing (on a treadmill or stationary bicycle) can be employed but has been shown to have lower sensitivity and specificity than the tests mentioned above [57, 58].
- Testing should be done during a period of continuing training/exercise as symptoms may improve with discontinuation of training [56].

Technique: Eucapnic Voluntary Hyperventilation

- The patient should be clinically stable, and the technician should be trained in how to deal with any unwanted response, like severe bronchospasm [3]. This test is done routinely in many standard pulmonary function laboratories

or in specialized respiratory clinics and is generally safe [18–25]. Medical help should be readily available in rare case of hemodynamic compromise such as cardiac arrest or severe bronchoconstriction.

- Inhaled bronchodilators should be discontinued as described in Table 4.1. For the greatest sensitivity inhaled corticosteroids should also be held if clinically appropriate.
- As with a methacholine challenge, testing begins with baseline spirometry. This is followed by a hyperventilation challenge. The patient is asked to breath a specific gas mixture at a minute ventilation (VE) of 30 × FEV_1 for no less than 6 minutes [58]. This ventilation rate is only a target and asthmatic subjects may only require a VE of 21 × FEV_1 to react.
- The gas mixture contains 21% oxygen, 4.9–5.1% carbon dioxide, and the remaining fraction nitrogen. This is typically provided from a gas canister/container with the partial pressures described above [58].
- This can also be done with cold inspired air, however, this is not typically available due to cost and complexity of the system.
- The inspired gas mixture is typically delivered to a 120 liters reservoir that is initially filled with approximately 90 liters to avoid the increased resistance that is associate with a demand valve. Once the study begins the flow into the balloon should approximate the patient's minute ventilation [58].
- After the ventilatory challenge the airway response is measured by collecting FEV_1 measurements at 5, 10, 15, and 20 minutes with the lowest value used to calculate the percentage drop of FEV_1. The lowest post-challenge FEV_1 is used to assess for response and severity of response [2].
- Spirometric values should meet ATS criteria for reproducibility and quality (at least two maneuvers) within and between maneuvers.
- %FEV_1 Drop = (pre-challenge FEV_1 – post-challenge FEV_1)/Pre-Challenge FEV_1
- A drop of 10% or more supports the diagnosis of EIB [2, 57, 58].
- Inhaled short acting bronchodilator therapy should be available for those who develop bronchoconstriction (Table 4.7).
- For interpretation of EVH, refer to Table 4.8.

Table 4.7 Indications and contraindications for EVH testing

Indications
Asthma symptoms during high intensity exercise including cough, wheeze, chest tightness, and shortness of breath with normal spirometry and/or negative methacholine challenge testing
Absolute contraindications
Severe airflow limitation (FEV_1 < 1 liter or < 50% predicted) [19]
A recent MI or CVA (within 3 months)
Arterial aneurysm especially if advanced
Hypertension (systolic >200 or diastolic >100)
Relative contraindications
Moderate airflow limitation (FEV_1 < 1.5 liters or < 60% predicted) [20, 38]
Clinical instability including a recent respiratory tract infection (test may be positive)
Inability to perform acceptable-quality spirometry
Pregnancy or nursing mothers
Epilepsy

Table 4.8 Grading of Severity of EIB (based on drop of FEV_1 post-EVH) [2]

Normal	<10%
Mild	10–24%
Moderate	25–49%
Severe	≥50%

OCCUPATIONAL ASTHMA (OA) TESTING

Background

- Those with bronchoconstriction in the workplace include (1) asthma caused by the workplace specific exposures (occupational asthma) and (2) existing asthma that is exacerbated by the workplace.
- It is estimated that one in six cases of adult asthma are caused by occupational factors and therefore any worker suspected have having occupational asthma should be evaluated formally [59].
- Testing includes longitudinal pulmonary function testing, immunologic testing as well as both non-specific (methacholine) and specific (e.g. plicatic acid) broncho-provocation testing.

- Serial peak expiratory flow (PEF) measurements (discussed below) with computer statistical analysis has shown a moderate-at-best sensitivity and specificity of 64% and 77% respectively [60] for the diagnosis of OA. However, it is more widely available than the gold standard *specific inhalational challenges* (SIC) (not discussed here).
- Patterns of serial peak flows can vary depending on the patient's shift times since airway diameter fluctuates diurnally at baseline. Typically AM peak flows will be lower with readings improving as the day progresses.

Technique [59, 60]

- The patient is provided with a peak flow meter (or portable spirometer) to be used at standardized regular intervals while at work and at home (including work days and full days off).
- Serial PEF's should be taken at least 4 times per day at 2–4 hours intervals (every 2 hours ideally).
- At each time point the peak flow measurement is repeated three times and the highest value is recorded.
- The recording period should last 4 weeks with at least 1 week of recordings during time off work.
- This data can be analysed with validated computer scoring systems (e.g. Oasys) or the plotted data can be visually assessed for patterns of worsening pulmonary function during periods at work.
- Patterns can include:
  - Diurnal worsening throughout the work day, with average readings not worsening during the week with improvement during days off work (Figure 4.2).
  - Diurnal worsening of peak flows during the work day with the daily pre-work reading steadily dropping as the week progresses with improvement with days off work (Figure 4.3)
  - Alternatively, a diagnosis of OA can be made with daily variation in maximum and minimum readings being greater than 20%. Then the ratio of work days to days off work with PEF variation >20% can be compared.

Considering the potential implications of a diagnosis of work related asthma, the above assessment should only be made by those with expertise in making such a diagnosis.

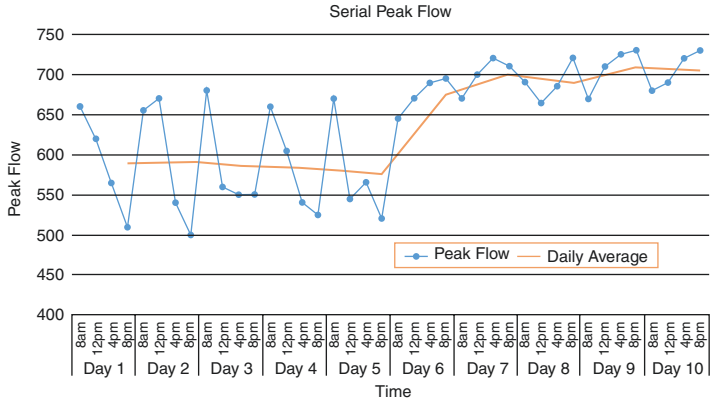

FIGURE 4.2 Idealized chart of serial peak flow measurements over a 5-day work period followed by a 5-day rest period. Daily averages during the work week remain stable

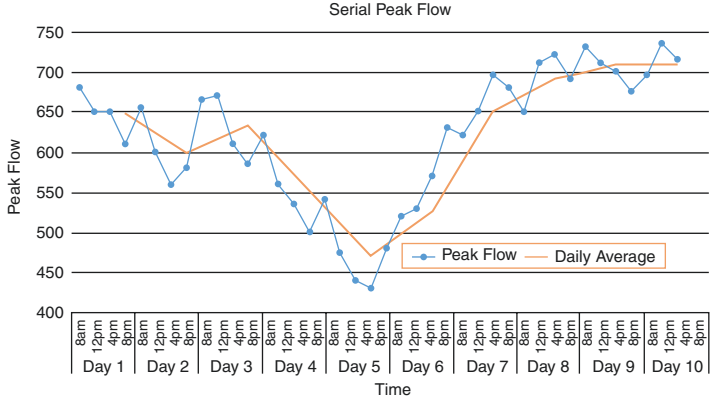

FIGURE 4.3 Idealized example of serial peak flow measurements over a 5-day work period followed by a 5-day rest period. Daily averages during the work week steadily decrease and begin recover during the rest period

References

1. Price OJ, Ansley L, Menzies-Gow a, Cullinan P, Hull JH. Airway dysfunction in elite athletes—an occupational lung disease? Allergy Eur J Allergy Clin Immunol. 2013;68:1343–52.
2. Parsons JP, Hallstrand TS, Mastronarde JG, et al. An Official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. Am J Respir Crit Care Med. 2013;187:1016–27.
3. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. Official statement of the American Thoracic Society. Am J Respir Crit Care Med. 2000;161:309–29.
4. Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: comparison of two methods. Chest. 2005;127:839–44.
5. Dell SD, Bola SS, Foty RG, Marshall LC, Nelligan KA, Coates AL. Provocative dose of methacholine causing a 20% drop in FEV1 should be used to interpret methacholine challenge tests with modern nebulizers. Ann Am Thorac Soc. 2015;12:357–63.
6. Coates AL, Wanger J, Cockcroft DW, et al. ERS technical standard on bronchial challenge testing: general considerations and performance of methacholine challenge tests. Eur Respir J. 2017;49:1–17.
7. Greenspon LW, Morrissey WL. Factors that contribute to inhibition of methacholine-induced bronchoconstriction. Am Rev Respir Dis. 1986;133:735–9.
8. Ahrens RC, Bonham AC, Maxwell GA, Weinberger MM. A method for comparing the peak intensity and duration of action of aerosolized bronchodilators using bronchoprovocation with methacholine. Am Rev Respir Dis. 1984;129:903–6.
9. Crimi N, Palermo F, Oliveri R, Polosa R, Settinieri I, Mistretta A. Protective effects of inhaled ipratropium bromide on bronchoconstriction induced by adenosine and methacholine in asthma. Eur Respir J. 1992;5:560–5.
10. Wilson NM, Green S, Coe C, Barnes PJ. Duration of protection by oxitropium bromide against cholinergic challenge. Eur J Respir Dis. 1987;71:455–8.
11. Rabe KF, Jörres R, Nowak D, Behr N, Magnussen H. Comparison of the effects of salmeterol and formoterol on airway tone and responsiveness over 24 hours in bronchial asthma. Am Rev Respir Dis. 1993;147:1436–41.
12. Cockcroft DW, Swystun VA, Bhagat R. Interaction of inhaled beta 2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. Am J Respir Crit Care Med. 1995;152:1485–9.

13. Derom EY, Pauwels RA, Van der Straeten ME. The effect of inhaled salmeterol on methacholine responsiveness in subjects with asthma up to 12 hours. J Allergy Clin Immunol. 1992;89:811–5.
14. McWilliams BC, Menendez R, Kelly HW, Howick J. Effects of theophylline on inhaled methacholine and histamine in asthmatic children. Am Rev Respir Dis. 1984;130:193–7.
15. Magnussen H, Reuss G, Jörres R. Theophylline has a dose-related effect on the airway response to inhaled histamine and methacholine in asthmatics. Am Rev Respir Dis. 1987;136:1163–7.
16. Henderson JC, O'Connell F, Fuller RW. Decrease of histamine induced bronchoconstriction by caffeine in mild asthma. Thorax. 1993;48:824–6.
17. Prieto L, Bertó JM, Gutiérrez V, Tornero C. Effect of inhaled budesonide on seasonal changes in sensitivity and maximal response to methacholine in pollen-sensitive asthmatic subjects. Eur Respir J. 1994;7:1845–51.
18. Shapiro GG, Simon RA, Sinon RA. Bronchoprovocation committee report. American Academy of allergy and immunology. J Allergy Clin Immunol. 1992;89:775–8.
19. Martin RJ, Wanger JS, Irvin CG, Bucher Bartelson B, Cherniack RM. Methacholine challenge testing: safety of low starting FEV1. Asthma Clinical Research Network (ACRN). Chest. 1997;112:53–6.
20. Tashkin DP, Altose MD, Bleecker ER, Connett JE, Kanner RE, Lee WW, Wise R. The lung health study: airway responsiveness to inhaled methacholine in smokers with mild to moderate airflow limitation. The Lung Health Study Research Group. Am Rev Respir Dis. 1992;145:301–10.
21. Scott GC, Braun SR. A survey of the current use and methods of analysis of bronchoprovocational challenges. Chest. 1991;100:322–8.
22. Rijcken B, Schouten JP, Weiss ST, Speizer FE, van der Lende R. The relationship between airway responsiveness to histamine and pulmonary function level in a random population sample. Am Rev Respir Dis. 1988;137:826–32.
23. Bakke PS, Baste V, Gulsvik A. Bronchial responsiveness in a Norwegian community. Am Rev Respir Dis. 1991;143:317–22.
24. Peat JK, Salome CM, Xuan W. On adjusting measurements of airway responsiveness for lung size and airway caliber. Am J Respir Crit Care Med. 1996;154:870–5.
25. Weiss ST, Tager IB, Weiss JW, Munoz A, Speizer FE, Ingram RH. Airways responsiveness in a population sample of adults and children. Am Rev Respir Dis. 1984;129:898–902.
26. Juniper EF, Cockcroft DW, Hargreave FE. Tidal breathing method. In: Juniper EF, Cockcroft DW, Hargreave FE, editors. Histamine and methacholine inhalation tests: laboratory procedure and standardization. 2nd ed. Lund: Astra Draco AB; 1994.

27. Cockcroft DW, Killian DN, Mellon JJ, Hargreave FE. Bronchial reactivity to inhaled histamine: a method and clinical survey. Clin Allergy. 1977;7:235–43.
28. Toelle BG, Peat JK, Salome CM, Crane J, McMillan D, Dermand J, D'Souza W, Woolcock AJ. Comparison of two epidemiological protocols for measuring airway responsiveness and allergic sensitivity in adults. Eur Respir J. 1994;7:1798–804.
29. Ryan G, Dolovich MB, Roberts RS, Frith PA, Juniper EF, Hargreave FE, Newhouse MT. Standardization of inhalation provocation tests: two techniques of aerosol generation and inhalation compared. Am Rev Respir Dis. 1981;123:195–9.
30. Beaupré AMJ. Comparison of histamine bronchial challenges with the Wright nebulizer and the dosimeter. Clin Allergy. 1979;9:575–83.
31. Britton J, Mortagy A, Tattersfield A. Histamine challenge testing: comparison of three methods. Thorax. 1986;41:128–32.
32. Knox AJ, Wisniewski A, Cooper S, Tattersfield AE. A comparison of the Yan and a dosimeter method for methacholine challenge in experienced and inexperienced subjects. Eur Respir J. 1991;4:497–502.
33. Peat JK, Salome CM, Bauman A, Toelle BG, Wachinger SL, Woolcock AJ. Repeatability of histamine bronchial challenge and comparability with methacholine bronchial challenge in a population of Australian schoolchildren. Am Rev Respir Dis. 1991;144:338–43.
34. Bennett JB, Davies RJ. A comparison of histamine and methacholine bronchial challenges using the DeVilbiss 646 nebulizer and the Rosenthal-French dosimeter. Br J Dis Chest. 1987;81:252–9.
35. Lundgren R, Söderberg M, Rosenhall L, Norrman E. Development of increased airway responsiveness in two nurses performing methacholine and histamine challenge tests. Allergy. 1992;47:188–9.
36. Todd DC, Davis BE, Hurst TS, Cockcroft DW. Dosimeter methacholine challenge: comparison of maximal versus submaximal inhalations. J Allergy Clin Immunol. 2004;114:517–9.
37. Allen ND, Davis BE, Hurst TS, Donald W. Difference between dosimeter and tidal breathing methacholine challenge. Chest J. 2005;128:4018–23.
38. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, Juniper EF, Malo JL. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J. 1993;6 Suppl 16:53–83.
39. Gilbert R, Auchincloss JH. Post-test probability of asthma following methacholine challenge. Chest. 1990;97:562–5.
40. Cockcroft DW, Murdock KY, Berscheid BA, Gore BP. Sensitivity and specificity of histamine PC20 determination in a random selection of young college students. J Allergy Clin Immunol. 1992;89:23–30.

41. Ramsdell JW, Nachtwey FJ, Moser KM. Bronchial hyperreactivity in chronic obstructive bronchitis. Am Rev Respir Dis. 1982;126:829–32.
42. Du Toit JI, Woolcock AJ, Salome CM, Sundrum R, Black JL. Characteristics of bronchial hyperresponsiveness in smokers with chronic air-flow limitation. Am Rev Respir Dis. 1986;134:498–501.
43. Yan K, Salome CM, Woolcock AJ. Prevalence and nature of bronchial hyperresponsiveness in subjects with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1985;132:25–9.
44. Cheung D, Dick EC, Timmers MC, de Klerk EP, Spaan WJ, Sterk PJ. Rhinovirus inhalation causes long-lasting excessive airway narrowing in response to methacholine in asthmatic subjects in vivo. Am J Respir Crit Care Med. 1995;152:1490–6.
45. Little JW, Hall WJ, Douglas RG, Mudholkar GS, Speers DM, Patel K. Airway hyperreactivity and peripheral airway dysfunction in influenza A infection. Am Rev Respir Dis. 1978;118:295–303.
46. Annesi I, Oryszczyn MP, Neukirch F, Orvoen-Frija E, Korobaeff M, Kauffmann F. Relationship of upper airways disorders to FEV1 and bronchial hyperresponsiveness in an epidemiological study. Eur Respir J. 1992;5:1104–10.
47. Prieto JL, Gutiérrez V, Bertó JM, Camps B. Sensitivity and maximal response to methacholine in perennial and seasonal allergic rhinitis. Clin Exp Allergy. 1996;26:61–7.
48. Ansley L, Rae G, Hull JH. Practical approach to exercise-induced bronchoconstriction in athletes. Prim Care Respir J. 2013;22:122–5.
49. Price OJ, Hull JH, Backer V, Hostrup M, Ansley L. The impact of exercise-induced bronchoconstriction on athletic performance: a systematic review. Sport Med. 2014;44:1749–61.
50. Hull JH, Hull PJ, Parsons JP, Dickinson JW, Ansley L. Approach to the diagnosis and management of suspected exercise-induced bronchoconstriction by primary care physicians. BMC Pulm Med. 2009;9:29.
51. Carlsen K-H. Sports in extreme conditions: the impact of exercise in cold temperatures on asthma and bronchial hyper-responsiveness in athletes. Br J Sports Med. 2012;46:796–9.
52. Dickinson JW, Whyte GP, McConnell a K, Harries MG. Screening elite winter athletes for exercise induced asthma: a comparison of three challenge methods. Br J Sports Med. 2006;40:179–82.
53. Hull JHK, Ansley L, Garrod R, Dickinson JW. Exercise-induced bronchoconstriction in athletes—should we screen? Med Sci Sports Exerc. 2007;39:2117–24.
54. Shephard RJ. Misdiagnosis of exercise-induced bronchoconstriction in professional soccer players. Yearb Sport Med. 2012;2012:268–70.
55. Price OJ, Ansley L, Hull JH. Diagnosing exercise-induced bronchoconstriction with Eucapnic voluntary hyperpnea: is one test enough? J Allergy Clin Immunol Pract. 2015;3:243–9.

56. Boulet L-P, O'Byrne PM. Asthma and exercise-induced bronchoconstriction in athletes. N Engl J Med. 2015;372:641–8.
57. Eliasson LWAH, Ec C, Phillips LWYY, Rajagopal LKR, Howard RS. Sensitivityand specificity of bronchial ProvocationTesting—an evaluation of four techniques in exercise induced bronchospasm. Chest J. 1992;102:347–55.
58. Argyros GJ, Roach JM, Hurwitz KM, Eliasson AH, Phillips YY. Eucapnic voluntary hyperventilation as a bronchoprovocation technique: development of a standardized dosing schedule in asthmatics. Chest J. 1996;105:667–72.
59. Fishwick D, Barber CM, Bradshaw LM, et al. Standards of care for occupational asthma: an update. Thorax. 2012;67:278–80. https://doi.org/10.1136/thoraxjnl-2011-200755.
60. Tarlo SM. Diagnosis and management of work-related asthma. Chest J. 2008;134:1S.
61. Price OJ, Hull JH, Ansley L. Advances in the diagnosis of exercise-induced bronchoconstriction. Expert Rev Respir Med. 2014;8:209–20.

Chapter 5

Respiratory Muscle Function and Other Pulmonary Function Studies

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Abstract This chapter reviews testing for respiratory muscle dysfunction and other miscellaneous pulmonary function studies including airways resistance, lung compliance, and shunt testing. This includes maximal inspiratory and expiratory pressure. We also review upright and supine spirometry assessing for diaphragmatic weakness. A new addition to this chapter discusses ultrasonographic assessment of diaphragmatic function.

Keywords Maximal Inspiratory Pressure (MIP) · Maximal Expiratory Pressure (MEP) · Ultrasound · Sniff Nasal Inspiratory Pressure (SNIP, sniff P_{nas}) · Maximum Voluntary Ventilation (MVV) · Airway Resistance (R_{AW}) · Airway Conductance (G_{AW}) · Lung Compliance (C_L) · Forced Oscillation Technique (Oscillometry) · Intrapulmonary Shunt

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RESPIRATORY MUSCLE FUNCTION

Maximal Respiratory Pressures

The 2 tests most used to assess the respiratory pressures are the *Maximal Inspiratory Pressure (MIP)*[1] and the *Maximal Expiratory Pressure (MEP)*. These pressures are largely generated by the respiratory muscles during a forceful inspiration and expiration, respectively.

Indications

- Assessment of respiratory muscle function:
  - In patients with known neuromuscular disorders (NMD)
  - In patients with suspected early NMD (unexplained dyspnea or unexplained restrictive pattern in PFT)
- Particularly helpful when lung mechanics are abnormal, i.e. coexistent interstitial lung disease.

Technique

- To measure MIP, the patient is instructed to exhale fully (to RV) then inhale against a closed valve as hard as possible. The resulting pressure should be sustained for 1 second. The test is repeated for reproducibility and the highest reproducible pressure (i.e. within 20%) is reported [1]. A rubber tube may be used instead of the regular (flanged) mouth piece to prevent air leak during the test [2]. Most laboratories, however, use the flanged mouth piece because its easier to use and the degree of leak associated with its use is not clinically significant [3]. A small leak is introduced (a 2-mm hole in the tubing) to prevent glottic closure during MIP maneuver and use of the buccal muscles (cheeks). For both MIP and MEP the maximum average pressure sustained for 1 second is recorded to avoid recording a peak, which is considered a pressure transient.

[1] MIP and MEP are sometimes referred to as PI_{max} and PE_{max}, respectively.

- To measure MEP, the patient inhales to TLC then exhales against a closed valve as hard as possible. Similarly, the pressure has to be sustained for 1 second and the highest reproducible pressure is reported.

Interpretation

- The MIP is considered normal if it is below −70 cm H_2O and MEP above +90 cm H_2O in young adult males (lower values are reported in females and elderly) [4].[2] Low MIP and MEP are seen in NMD even in early stages, when physical weakness is not clinically apparent [1]. For causes of NMD, see Table 5.1.
- Values tend to be higher in men and decrease with age, see Table 5.2 [5].
- Because the diaphragm is the major inspiratory muscle, in bilateral diaphragmatic paralysis, the MIP is usually low with a preserved MEP. On the other hand, in quadriparesis due to cord injury (below C3–5 where phrenic nerve originates), the MEP is low due to reduced expiratory muscle function with less of a reduction in MIP, as the diaphragm is not affected.
- MIP and MEP can also be decreased in a poor effort study and in patients with significant hyperinflation and air trapping (like emphysema) [1]. The degree of air-trapping and hyperinflation is directly proportional to the degree of the impairment of the respiratory pressures. This effect is a result of the reduction in diaphragm muscle length that occurs when lung volume increases. Shorter length leads to less ability to shorten and produce a pressure.
- Conventionally MIP is measured at RV and MEP at TLC to foster consistency and to allow the muscles to contract at or near their optimal lengths although this does lead to more contribution of thoracic and lung elastic recoil to the pressures.
- MEP of <40 cm H_2O is predictive of an ineffective cough [6, 7].

[2] There is a wide range of normal values in the same age and sex; the normal values vary significantly with age and sex. For more details refer to [2].

Table 5.1 Causes of NMD

Neurogenic causes
Motor neuron disease or amyotrophic lateral sclerosis (ALS)
Guillain-Barre syndrome
Poliomyelitis
Multiple sclerosis
High spinal cord injury (quadriplegia)
Phrenic nerve injury
Neuromuscular junction causes
Myasthenia gravis
Lambert-Eaton Myasthenic syndrome
Muscular causes
Muscular dystrophy
Myopathies (e.g. polymyositis, thyroid-related, inflammatory, steroid-induced, biochemical)
Malnutrition

Table 5.2 Normative MIP values in men and women in different age groups [5]

	Men	Women
Age group (years)	**Mean MIP (cm H_2O)**	**Mean MIP (cm H_2O)**
18–29	128	97
30–39	128.5	89
40–49	117.1	92.9
50–59	108.1	79.7
60–69	92.7	75.1
70–83	76.2	65.3

Limitations

- There is a wide range of normal, making it sometimes difficult to separate normal from abnormal results. Although lower limits of normal have been published for both MIP and MEP as well as SNIP (Sniff Nasal Inspiratory Pressure)(see below) and this has offset this difficulty.
- The test is effort dependent and poor effort may mimic disease.

Sniff Tests

- Are designed to assess the strength of the diaphragm and the other inspiratory muscles. A sniff is a short, sharp voluntary

inspiratory maneuver performed through one or both unoccluded nostrils. To be useful as a test of respiratory muscle strength, sniffs need to be maximal, which is relatively easy for most willing subjects, but may require some practice. Most subjects achieve reproducible values within 5–10 attempts [1].

- 3 sniff tests are available for clinical and research use:
  (a) *Sniff Nasal Inspiratory Pressure (SNIP, sniff P_{nas}):* is the least invasive among the other sniff tests and most practical in the clinical setting. It is measured by placing a plug in one nostril and measuring the pressure in the nose via a pressure catheter passed through the plug. Sniffing with the unoccluded nostril and with mouth closed will generate a negative pressure in the nose which represents a reasonable approximation of the esophageal pressure (P_{es}, used to reflect intra-thoracic pressure) [8, 9]. A negative pressure of >60 cm H_2O excludes significant inspiratory muscle weakness [10]. In COPD, sniff P_{nas} tends to under-estimate the esophageal pressure but can complement MIP in excluding significant inspiratory muscle weakness [11]. A SNIP of ≤18 cm H_2O in ALS patients is associated with an increased risk of death or tracheostomy in 1 year [12].
  (b) *Sniff Esophageal Pressure (Sniff P_{es}):* is similar in principle to the above but is measured by an esophageal balloon catheter system (a pressure sensing device on the end of a thin hollow tube) during maximal sniffs, and is indicated when the sniff P_{nas} is inconclusive. Sniff P_{es}, again, assesses the global inspiratory muscles strength including the diaphragm [13]. A negative pressure of >80 cm H_2O in men and >70 cm H_2O in women excludes significant inspiratory muscle weakness [14].
  (c) *Sniff Transdiaphragmatic Pressure (Sniff P_{di}):* is performed by passing esophageal and gastric balloons and measures the pressure difference on both sides of the diaphragm (transdiaphragmatic pressure) during maximal sniffs. Sniff P_{di} specifically measures diaphragmatic strength. A sniff P_{di} of >100 cm H_2O in men and >70 cm H_2O in women excludes significant diaphragmatic weakness [14]. A sniff P_{di} of <30 cm H_2O is associated with orthopnea, paradoxical abdominal motion and a supine fall in VC, all are highly diagnostic for diaphragmatic paralysis [15].

Transcutaneous Electrical Phrenic Nerve Stimulation

- Diaphragmatic function can be assessed non-volitionally by stimulating the phrenic nerve(s), transcutaneously at FRC usually using an electrode placed over the skin at the posterior border of the sternocledomastoid [1]. This test is particularly useful in identifying muscle weakness when lack of effort is an issue. Supramaximal stimulation can be performed resulting in maximal diaphragmatic contraction that can be measured as a transdiaphragmatic pressure (Twitch P_{di}) using gastric and esophageal balloons.
- One or both hemi-diaphragms may be stimulated at once (single pulse). A resultant twitch P_{di} pressure of >10 cm H_2O (unilateral) or >20 cm H_2O (bilateral) excludes significant diaphragmatic weakness [14].
- Although this test is effort-independent, the electrical stimulation can be uncomfortable and doesn't always produce a supramaximal stimulation which can make it difficult to interpret subnormal results.
- Magnetic stimulation of phrenic nerve may be used instead of the electrical stimulation. Magnetic stimulation is less uncomfortable but is less widely used because of high equipment costs and limited availability [1, 14].
- The continuity of the phrenic nerve is assessed as the EMG of the diaphragm and is recorded using an esophageal electrode or, more commonly, a surface electrode placed in the 7th intercostal space at the mid-axillary line (normal phrenic nerve conduction time is <9.5 ms)[3] [14]. This test can substantiate diaphragmatic paralysis.

Cough Test

- Is used to assess the expiratory muscle strength as cough is a natural maneuver that can produce maximal expiratory pressure. This pressure is measured using a gastric balloon catheter and is referred to as cough gastric pressure (cough P_{ga}). Patients with low MEP can have a nor-

[3] Bilateral tetanic stimulation can give maximal P_{di} but is uncomfortable and only used for research.

mal cough P_{ga} which indicates that this test may be more reliable than MEP, however, is also more invasive [1, 14].

Supine vs Upright Spirometry

- Is indicated when diaphragmatic weakness is suspected. The FVC is significantly reduced in the supine position in such conditions because of displacement upward by abdominal contents that cannot be countered when there is diaphragmatic weakness.
- A drop in FVC of <10% of the sitting value is considered normal [16]. Bilateral diaphragmatic paralysis (or marked weakness) is considered when FVC drops by >30% of the sitting value [17].
- A drop of >30% of the upright/sitting FVC is considered specific for diaphragmatic weakness when differentiating from other neuromuscular deficits.

Other Less Widely Used Tests to Assess Respiratory Muscle Function

- Maximum mouth pressure.
- Maximal static transdiaphragmatic pressure.
- Abdominal muscle stimulation test.
- Peak Cough Flow Rates (although not adopted by Lung Function Laboratories this test can be a very effective field test of effectiveness of the cough in airway clearance. A value of less than 270 L/min indicates the need for strategies to augment cough).

Ultrasonographic Assessment of the Diaphragm Function

- Diaphragmatic dysfunction can either be related to NMD of the diaphragm (Table 5.1) or mechanical dysfunction resulting from abnormalities of the adjacent structures (such as pleural disease (large pleural effusion and severe pleural thickening), subdiaphragmatic inflammatory or infectious processes, large diaphragmatic hernias, extensive ascites or large adjacent masses) [18]. Diaphragm weakness can also

result from conditions that adversely affect its length/tension such as hyperinflation (e.g. COPD).
  - Traditional methods used to evaluate diaphragmatic activity (e.g. fluoroscopy, nerve conduction studies (NCS), electromyography (EMG)) have important limitations. Ultrasonography of the diaphragm is a non-invasive, bedside and relatively easily learned technique that can be used as a substitute for or to complement the above tests. In this section we will briefly touch on some ultrasonographic techniques that can help in the evaluation of the diaphragmatic function. Other techniques such as "Diaphragmatic Velocity" and "Side-to-side Variation" are outside the scope of this chapter. This section is predicated on a basic knowledge of point-of-care ultrasound.
- Diaphragmatic Movement
  - Unilateral or bilateral diaphragmatic paralysis can be diagnosed via ultrasonography in spontaneously breathing, preferably, supine patients [18–20].
  - A crude way of assessing diaphragmatic movement is by using the curvilinear transducer placed over an area corresponding to the costophrenic angle (upper abdomen and lower chest) somewhere between the anterior and posterior axillary lines with the index mark pointing towards the patient's head, Figure 5.1a. The diaphragm can usually be identified as a hyperechoic (bright) curved line above the liver in the right side or the spleen in the left side, Figure 5.1b. It should be noted that confident diaphragm identification cannot always be achieved even in expert hands. Note as well that with marked weakness or paralysis, the diaphragm position can be much higher than typically would be expected.
  - The patient is then instructed to breath normally and the diaphragm movement is observed. If the diaphragm moves downwards during inspiration (the lung usually appears also moving downwards in the form of white air artefact termed the "*curtain sign*"), then there is no unilateral diaphragmatic paralysis, Figure 5.1c. If, on the other hand, the diaphragm moves upwards during inspiration, paradoxical diaphragmatic movement (which takes place when there is diaphragmatic paralysis) is diagnosed.
  - Alternatively, the linear transducer may be placed at the 7th, 8th or 9th intercostal spaces at the anterior or midaxillary lines with the index mark oriented cranially,

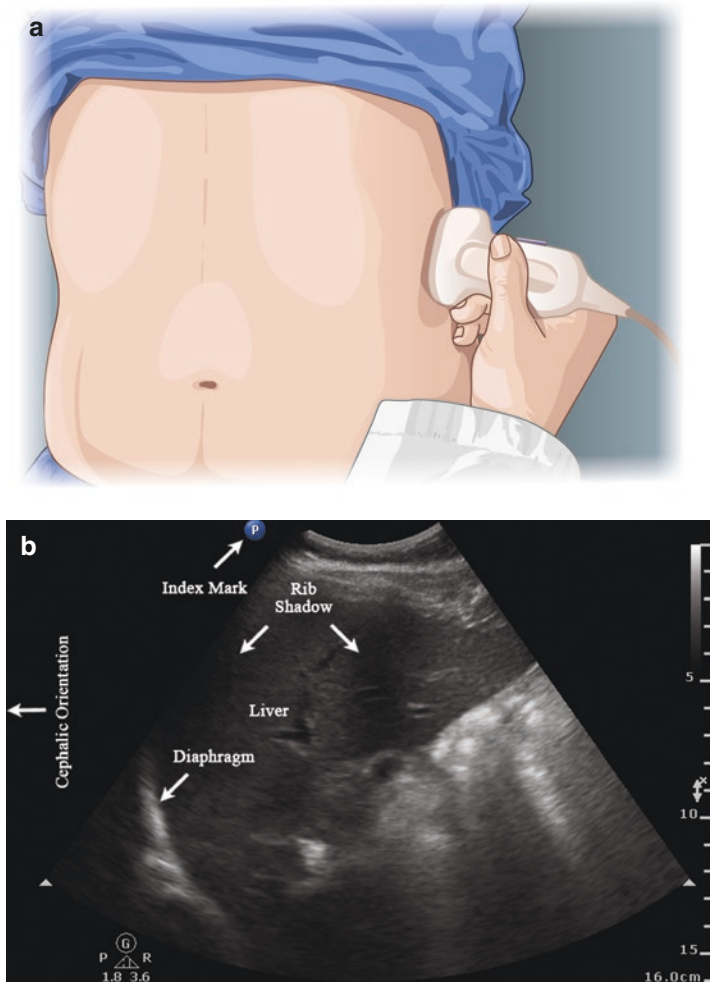

FIGURE 5.1 (**a**) The Curvilinear transducer orientation during the evaluation of diaphragmatic movement, in this case, evaluating the left hemidiaphragm. (**b**) The position of the right hemidiaphragm in relation to adjacent structures at the end of quite expiration. (**c**) The normal downward movement of the right hemidiaphragm and the appearance of the lung shadow (the curtain sign) during deep inspiration

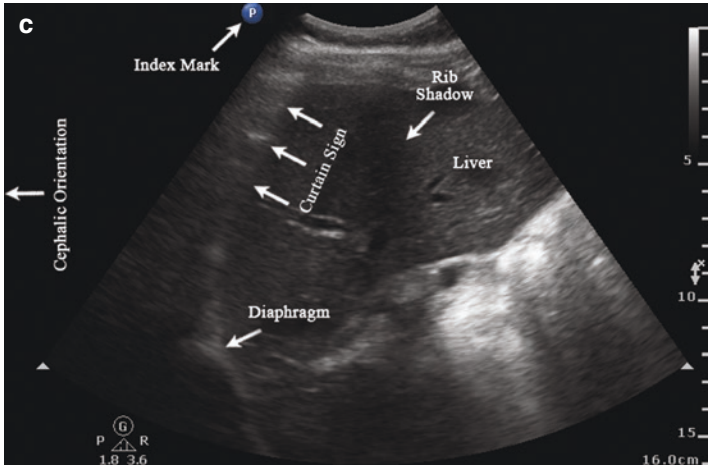

FIGURE 5.1 (continued)

Figure 5.2a [21]. The diaphragm is identified, and the patient is instucted to breath quietly to demonstrate the downward movement of the lung shadow (the curtain sign) and the downward and inward movement of the diaphragm during inspiration, Figure 5.2b, c. This can be more obvious with deeper tidal breathing or particularly with sniff manoeuvres. If these findings are absent or there is paradoxical movement of the diaphragm during inspiration, then diaphragmatic paralysis is likely [21].

  - The interpreter should be aware that with bilateral diaphragm paralysis there can be a falsely reassuring descent of the diaphragm on inspiration that relates to relaxation of the abdominal expiratory muscles (used as a compensation mechanism).

- Diaphragm Thickness
  - Using the linear transducer, as described above (Figure 5.2a), the diaphragm thickness is measured at the end of a quite expiration at the portion of the diaphragm adjacent to the chest wall "Zone of Apposition", Figure 5.2b. This measurement was found to correlate with direct diaphragm thickness in cadavers [22].

  - Normal thickness range in an adult is 0.22–0.28 cm [22] and any endexpiratory measurement of less than 0.2 cm is considered low and indicates diaphragm atrophy [23, 24].
- Diaphragm Excursion
  - The easiest way to measure diaphragm excursion is by using the subcostal approach via applying the curvilinear transducer vertically and subcostally at the midclavicular line with the transducer index mark oriented cranially, Figure 5.3a.

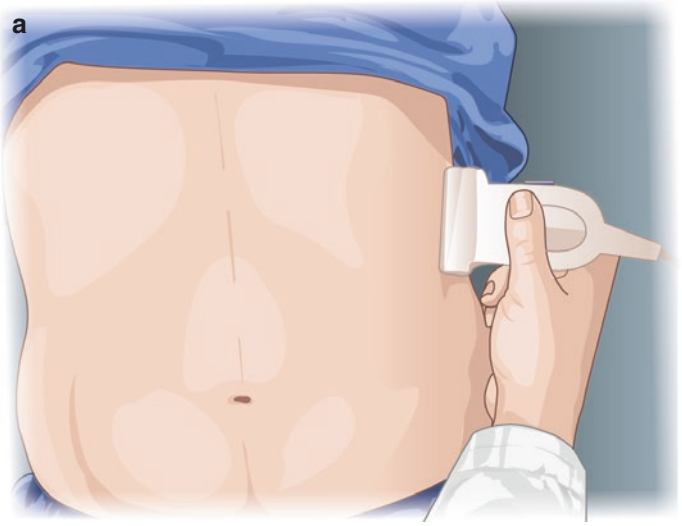

FIGURE 5.2 (**a**) The linear transducer orientation at the ninth intercostal space at the anterior axillary line while evaluating the diaphragmatic movement and thickness. (**b**) Ultrasound image of the diaphragm using the linear transducer placed at the costophrenic angle at the anterior axillary line showing the diaphragm during quite expiration. The thickness of the diaphragm is measured in this view at the zone of apposition. Note: the left side of the image represents the cephalic orientation. (**c**) The diaphragm peeling during inspiration indicating normal diaphragmtic movement. The lung shadow (the curtain sign) is noted to appear during inspiration moving from right (cephalic) to left

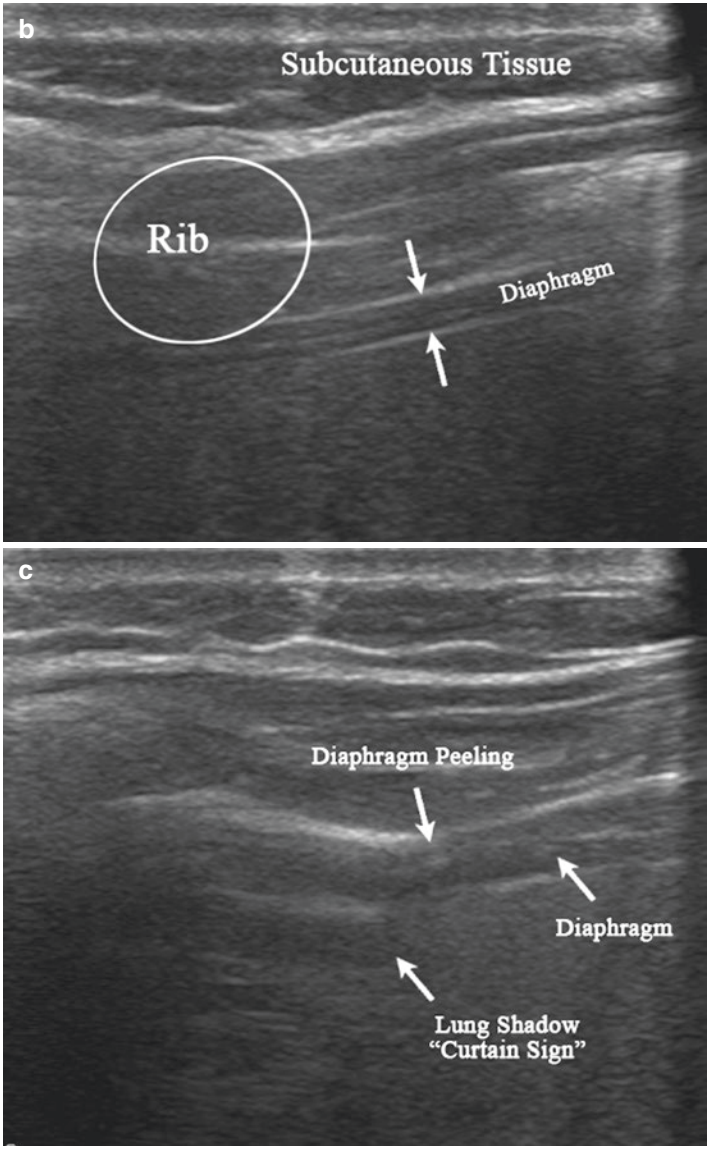

FIGURE 5.2 (continued)

– By applying M-mode as in Figure 5.3b, the diaphragm movement is recorded during deep breathing and/or sniffing. Normally, the diaphragm signal moves upwards (towards the transducer) during inspiration or sniffing, Figure 5.3b [18, 25]. Diaphragmatic paralysis is indicated if excursion is absent or there is paradoxical movement with the above manoeuvres.

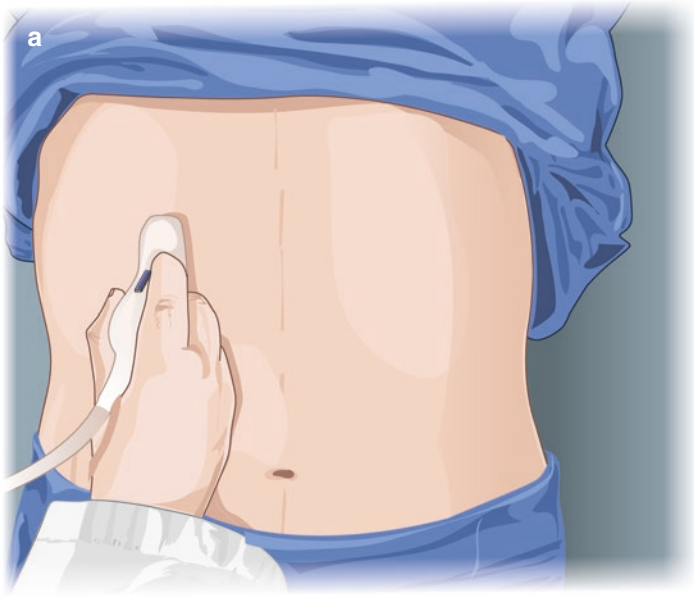

FIGURE 5.3 (**a**) The curvilinear transducer orientation when evaluating diaphragm excursion and amplitude. (**b**) This diagram illustrates the diaphragm excursion and the excursion amplitude. Right: 2D image of the liver with the curvilinear transducer placed vertically and subcostally at the midclavicular line. The doted line represents the curser where M-mode image is obtained. Left: M-mode of the diaphragm during sniffing showing normal upward movement of the diaphragm. "*A*" represents the distance between the bottom and peak of the wave which is equivalent to the excursion amplitude

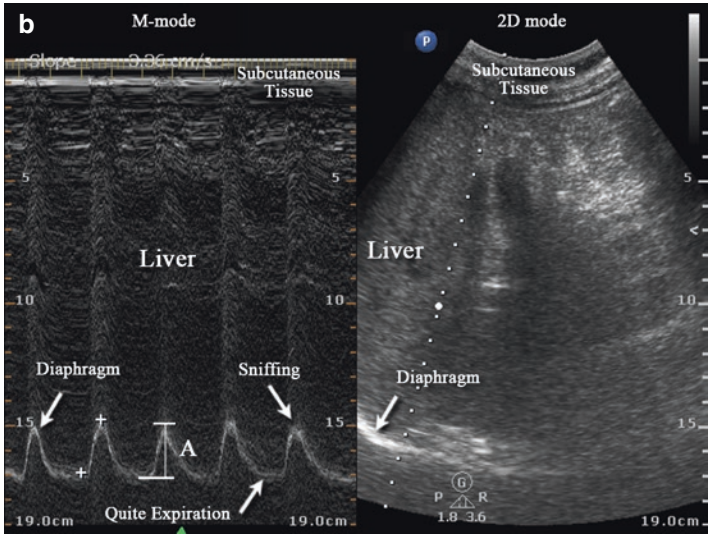

FIGURE 5.3 (continued)

– Additionally, measuring the "amplitude of excursion" (distance between the bottom and peak of the M-mode wave of the diaphragm during sniffing) may be used to quantify the diaphragmatic function, Figure 5.3b [23]. The amplitude of excursion can reach up to 9 cm in healthy adults during deep breathing or sniffing [19, 26–30]. Excursion of more than 2.5 cm rules out significant diaphragmatic dysfunction [31, 32]. On the other hand, excursion of less than or equal to 2.4 cm suggests diaphragmatic weakness and correlates with a vital capacity of less than 50% of the predicted [33].

OTHER PULMONARY FUNCTION STUDIES

Maximum Voluntary Ventilation (MVV)

- Is the maximum volume of air that can be breathed in and out over 1 minute (liters/minute).

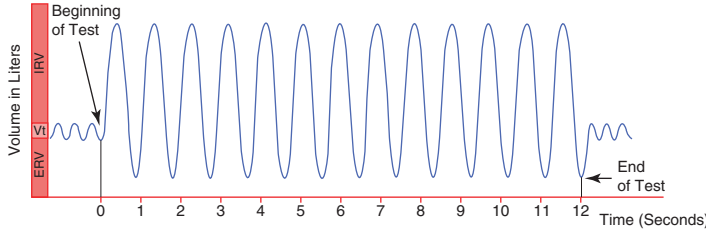

FIGURE 5.4 Measuring MVV in the laboratory. The test is done over 12 seconds and the result is extrapolated to 60 seconds by multiplying by 5

- It is measured in the laboratory by asking the patient to breathe as fast and as hard as possible for 12 seconds, then the result is extrapolated to 1 minute by multiplying that by 5, see Figure 5.4.
- MVV correlates very well with FEV_1, and it can also be estimated by multiplying the patient's FEV_1 by 40 (some prefer 35) [34–39]. If the measured MVV is significantly lower than the calculated one, then this may suggest a poor effort.
- MVV is a very nonspecific test and is usually reduced with any pulmonary disorder (obstructive or restrictive disorders including NMD), being more significantly lower in obstructive disorders. MVV is also reduced in poor effort test and in cardiac disease.
- MVV has, however, an important role in assessing the ventilatory function during exercise, as it correlates well with the maximal exercise capacity (see Chapter 9 for details).

Airway Resistance (R_{AW}) and Conductance (G_{AW})

- R_{AW} (L/sec/cm H_2O) is the amount of pressure (alveolar pressure over the mouth pressure or the transpulmonary pressure) required to generate a given airflow, while G_{AW} (cm H_2O/L/sec) is the reciprocal of that, i.e. the amount of airflow generated by a given alveolar pressure.
- R_{AW} is analogous to Ohm's law of resistance in an electrical circuit. R_{AW} is calculated by dividing difference between alveolar and mouth pressures (driving pressure) by the flow measured at the mouth. This is done by asking the patient to

perform panting maneuvers against a valve while inside the body box. Lung volumes are also measured during these maneuvers.

- These tests are not effort dependent and are used in patients with suspected obstructive disorders who can't produce good effort in spirometry [40, 41]. They are however, prone to measurement and calculation errors which limit their use.
- The reciprocal of R_{AW} is G_{AW}. Because the lung volume at which the flow is measured will influence the airway resistance, the results are corrected to that lung volume to generate the *specific airway resistance* and *conductance* (SR_{AW}, SG_{AW}).
- An increased R_{AW} is likely to be due to an obstructive disorder.

Lung Compliance (C_L)

- Is the change in lung volume for a given change in pressure or simply, the ability of the lung to expand. It is measured by simultaneous measurements of the lung volume and the elastic recoil pressure by an esophageal balloon (P_{es}).
- C_L can be expressed in 2 ways, static or dynamic lung compliance (C_{Lstat} and C_{Ldyn}):
  - C_{Lstat} is calculated by measuring the pressure when there is no flow at 2 different lung volumes. It is decreased in lung fibrosis (decreased ability of the lung to expand) and increased in emphysema.
  - C_{Ldyn} is measured during tidal breathing (V_T) by continuously measuring pressure and volume (C_{Ldyn} is represented as $\Delta P/\Delta V$). C_{Ldyn} is lower than C_{Lstat} in patients with airway obstruction. In these patients, C_{Ldyn} decreases further as frequency of breathing increases [14].[4]
- *Total thoracic compliance* is the compliance of both the lungs and chest wall together. It can only be reliably measured in ventilated and paralyzed patients where activity of the chest

[4] This reduction is caused by the effect of the increasing frequency of breathing on the lung units that are recruited. As the frequency of breathing increases, the lung units with more rapid frequency response, i.e., shorter time constant, are recruited and these units are less compliant.

wall muscles is eliminated. It is decreased in disease of either the chest wall (Ankylosing Spondylitis) or the lungs (Acute Respiratory Distress Syndrome, ARDS).

Forced Oscillation Technique (Oscillometry)

- Is the determination of the total pulmonary resistance by imposing known variations in flow at the mouth and measuring the resultant pressure changes.
- Because it measures the total resistance, it is hard to separate the upper from the lower airway resistance which limits its clinical usefulness.
- Its main use is in younger children who can't generally perform spirometric maneuvers.

Intrapulmonary Shunt Testing

- Normal individuals have a shunt fraction that is up to 5% of cardiac output. This can increase with pulmonary arteriovenous malformations (PAVM), congenital heart disease, and hepatopulmonary syndromes.
- Patients undergoing shunt testing are asked to breathe in 100% oxygen for 20 minutes from a 200 liters reservoir bag to allow for equilibration and complete washout. An arterial blood gas sample and oxygen saturation are then collected and the values are used to calculate the shunt fraction (Q_S/Q_T).
- Q_S = amount of blood flow shunted, Q_T = Total cardiac output/flow
- Shunt Formula → $Q_S/Q_T = (P_AO_2 - P_aO_2)/[(P_AO_2 - PaO_2) + 1670]$ [42]
  - Units of pressure = mmHg
- Simplified Shunt Formula → $Q_S/Q_T = (C_{c'O2} - C_{aO2})/(C_{c'O2} - C_{\bar{v}O2})$
  - C_{aO2}, oxygen content of arterial blood; $C_{c'O2}$, oxygen content of pulmonary end-capillary blood; $C_{\bar{v}O2}$, oxygen content of mixed venous blood.
- A shunt fraction above 5% is generally considered abnormal, and should be investigated further.

References

1. Malcolm ATS, Gary C. Respiratory muscle testing: tests of respiratory muscle strength. Am J Respir Crit Care Med. 2002;166:518–624.
2. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99:696–702.
3. Koulouris N, Mulvey DA, Laroche CM, Green M, Moxham J. Comparison of two different mouthpieces for the measurement of Pimax and Pemax in normal and weak subjects. Eur Respir J. 1988;1:863–7.
4. Enright PL, Kronmal RA, Manolio TA, Schenker MB, Hyatt RE. Respiratory muscle strength in the elderly. Correlates and reference values. Cardiovascular Health Study Research Group. Am J Respir Crit Care Med. 1994;149:430–8.
5. Sclauser Pessoa IMB, Parreira VF, Fregonezi GAF, Sheel AW, Chung F, Reid WD. Reference values for maximal inspiratory pressure: a systematic review. Can Respir J. 2014;21:43–50.
6. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of pulmonary function tests, a practical guide. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
7. Hancox B, Whyte K. Bob pocket guide to lung function tests. 1st ed. Sydney: McGraw-Hill; 2001.
8. Clanton TL, Ameredes BT. Fatigue of the inspiratory muscle pump in humans: an isoflow approach. J Appl Physiol. 1988;64:1693–9.
9. Mador MJ, Rodis A, Magalang UJ, Ameen K. Comparison of cervical magnetic and transcutaneous phrenic nerve stimulation before and after threshold loading. Am J Respir Crit Care Med. 1996;154:448–53.
10. Heritier F, Rahm F, Pasche P, Fitting J. W. Sniff nasal pressure. Anon ivasive assess inspiratory muscle strength. Am J Respir Crit Care Med. 1994;150:1678–83.
11. Bellemare F, Grassino A. Evaluation of human diaphragm fatigue. J Appl Physiol. 1982;53:1196–206.
12. Capozzo R, Quaranta VN, Pellegrini F, et al. Sniff nasal inspiratory pressure as a prognostic factor of tracheostomy or death in amyotrophic lateral sclerosis. J Neurol. 2015;262:593. https://doi.org/10.1007/s00415-014-7613-3.
13. Laaroche CM, Mier AK, Moxham J, Green M. The value of sniff esophageal pressure in the assessment of global inspiratory muscle strength. Am Rev Respir Dis. 1988;138:598.
14. Hughes JM, Pride NB. Lung function tests: physiological principles and clinical applications. Philadelphia, PA: W. B. Saunders; 2000.
15. Mier-Jedrzejowicz A, Brophy C, Moxham J, Green M. Assessment of diaphragm weakness. Am Rev Respir Dis. 1988;137:877–83.
16. Allen SM, Hunt B, Green M. Fall in vital capacity with posture. Br J Dis Chest. 1995;79:267–71.

17. Green M. Respiratory muscle testing. Bull Eur Physiopathol Respir. 1984;20:433–5.
18. Gerscovich EO, Cronan M, McGahan JP, Jain K, Jones CD, McDonald C, Kiran J. Ultrasonographic evaluation of diaphragmatic motion. J Ultrasound Med. 2001;20(6):597–604.
19. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135(2):391–400.
20. Houston JG, Angus RM, Cowan MD, McMillan NC, Thomson NC. Ultrasound assessment of normal hemidiaphragmatic movement: relation to inspiratory volume. Thorax. 1994;49(5):500–3.
21. Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. Muscle Nerve. 2013;47:319–29.
22. Wait JL, Nahormek PA, Yost WT, Rochester DP. Diaphragmatic thickness-lung volume relationship in vivo. J Appl Physiol. 1989;67(4):1560–8.
23. Mccool FD, Tzelepis GE. Dysfunction of the diaphragm. N Engl J Med. 2012;366:932–42.
24. Gottesman E, McCool FD. Ultrasound evaluation of the paralyzed diaphragm. Am J Respir Crit Care Med. 1997;155(5):1570–4.
25. Zifko U, Hartmann M, Girsch W, Zoder G, Rokitansky A, Grisold W, Lischka A. Diaphragmatic paresis in newborns due to phrenic nerve injury. Neuropediatrics. 1995;26(5):281–4.
26. Ayoub J, Cohendy R, Dauzat M, Targhetta R, Coussaye JE, Bourgeois JM, Ramonatxo M, Prefaut C, Pourcelot L. Non-invasive quantification of diaphragm kinetics using m-mode sonography. Can J Anaesth. 1997;44(7):739–44.
27. Kantarci F, Mihmanli I, Demirel MK, Harmanci K, Akman C, Aydogan F, Mihmanli A, Uysal O. Normal diaphragmatic motion and the effects of body composition: determination with M-mode sonography. J Ultrasound Med. 2004;23(2):255–60.
28. Cohen E, Mier A, Heywood P, Murphy K, Boultbee J, Guz A. Excursion-volume relation of the right hemidiaphragm measured by ultrasonography and respiratory airflow measurements. Thorax. 1994;49(9):885–9.
29. Targhetta R, Chavagneux R, Ayoub J, Lemerre C, Prefaut C, Bourgeois JM, Balmes P. Right diaphragmatic kinetics measured by TM-mode ultrasonography with concomitant spirometry in normal subjects and asthmatic patients. Rev Med Interne. 1995;16(11):819–26.
30. Scott S, Fuld JP, Carter R, McEntegart M, MacFarlane NG. Diaphragm ultrasonography as an alternative to whole-body plethysmography in pulmonary function testing. J Ultrasound Med. 2006;25(2):225–32.
31. Alexander C. Diaphragm movements and the diagnosis of diaphragmatic paralysis. Clin Radiol. 1966;17:79–83.

32. Sanchez de Toledo J, Munoz R, Landsittel D, Shiderly D, Yoshida M, Komarlu R, Wearden P, Morell VO, Chrysostomou C. Diagnosis of abnormal diaphragm motion after cardiothoracic surgery: ultrasound performed by a cardiac intensivist vs. fluoroscopy. Congenit Heart Dis. 2010;5:565–72.
33. Kim SH, Na S, Choi JS, Na SH, Shin S, Koh SO. An evaluation of diaphragmatic movement by M-mode sonography as a predictor of pulmonary dysfunction after upper abdominal surgery. Anesth Analg. 2010;110(5):1349–54.
34. Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. Chest. 1991;100:618–23.
35. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol. 1981;47:33–9.
36. Weber KT, Janicki JS. Cardiopulmonary exercise testing: physiologic principles and clinical applications. Philadelphia: W B Saunders; 1986.
37. Szlachcic J, Massie BM, Kramer BL, Topic N, Tubau J. Correlates and prognostic implication of exercise capacity in chronic congestive heart failure. Am J Cardiol. 1985;55:1037–42.
38. Dillard TA, Hnatiuk OW, McCumber TR. Maximum voluntary ventilation. Spirometric determinants in chronic obstructive pulmonary disease patients and normal subjects. Am Rev Respir Dis. 1993;147:870–5.
39. Dillard TA, Piantadosi S, Rajagopal KR. Prediction of ventilation at maximal exercise in chronic air-flow obstruction. Am Rev Respir Dis. 1985;132:230–5.
40. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
41. Pride NB, Macklem PT. Lung mechanics in disease. In: Macklem PT, Mead J, editors. Handbook of physiology. The respiratory system. Mechanics of breathing. Section 3, vol. 3, Part 2. Bethesda, MD: American Physiological Society; 1986. p. 659–92.
42. Chiang ST. A nomogram for venous shunt (Qs/Qt) calculation. Thorax. 1968;23:563–5.

Chapter 6
Approach to PFT Interpretation

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract This chapter provides a structured approach to analyzing and interpreting the many data points necessary to provide an accurate assessment of normal and abnormal pulmonary function tests. Spirometry provides the foundation of all PFT assessments followed by lung volume and gas transfer interpretation. By the end of this chapter we hope to provide a reproducible and reliable framework for PFT interpretation.

Keywords Volume-Time curve · Flow-volume curve · Flow-volume loop · Spirometry · Lung volume study · Gas transfer

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APPROACH OUTLINE

1. Review: clinical history provided, patient's demographics and technician's comments
2. Examine the volume-time curve
   (a) Technical quality of the curve
   (b) Size and shape
   (c) Components
   (d) Post-bronchodilator curve
3. Examine the flow-volume curve/loop
   (a) Technical quality of the curve
   (b) Size and shape
   (c) Components
   (d) Location
   (e) Its relation to the tidal FV loop
   (f) Post-bronchodilator curve
4. Spirometry
   (a) Examine FVC, FEV_1 and FEV_1/FVC ratio
   (b) Examine the post-bronchodilator value of FVC, FEV_1 and FEV_1/FVC ratio
   (c) Examine MMEF and FEFs
   (d) Examine the rest of the spirometry
   (e) Consider some special situations
5. Lung volumes
   (a) Examine TLC, RV and RV/TLC ratio
   (b) Examine the rest of the lung volumes (FRC, ERV, IC)
   (c) Consider some special situations
6. Gas transfer study
   (a) Examine DL_{CO} and DL_{CO}/V_A ratio
   (b) Examine DL_{CO}/Hgb correction
   (c) Examine the rest of the variables
7. Examine any additional test provided
   (a) Methacholine challenge
   (b) Maximum respiratory pressures
   (c) Supine spirometry
   (d) MVV, ABG and other tests provided
8. Compare the current study with previous ones, if available

See also Table 6.1. The following is an abbreviated version of what we have reviewed in the previous chapters.

TABLE 6.1 Approach to PFT interpretation

Approach outline
Review: clinical history provided, patient's demographics, and technician's comments
Examine the volume–time curve
Examine the flow–volume curve/loop, if available
Examine the spirometry
Examine the lung volumes
Examine the gas transfer study
Examine any additional test provided
Compare the current study with previous ones, if available
Reaching a useful conclusion (based on a comparison of spirometry and lung volume studies)
Both are obstructive
Both are restrictive
Both are normal
One is restrictive and the other is obstructive
One is normal and the other is abnormal

REVIEW THE CLINICAL HISTORY PROVIDED, PATIENT'S DEMOGRAPHICS AND TECHNICIAN'S COMMENTS

- *Clinical data* should be provided in the requisition form including a diagnosis (if known) and the rationale for the test. Clinical data are extremely useful in helping formulate your interpretation specifically to address the ordering physician's clinical question.
- The *patient's demographics* (age, gender, height and weight, ethnicity) also provide useful information, e.g. the patient's weight (obesity can lead to a restrictive pattern).
- *Technicians' comments* provide important information about the quality of the study, consistency with the ATS guidelines and patient's effort. Technicians also comment about the patient's condition, for example the presence of kyphoscoliosis, wheezing or stridor while testing. They should record medications used and timing relevant to the test that might impact on results. This information may not be provided in the clinical data.

APPROACH TO VOLUME-TIME (VT) CURVE

- Examine the volume-time (VT) curve by observing:
  - *The duration of the curve:* which should be at least 6 seconds to meet the ATS criteria, and in the laboratory this is usually achievable.
  - *The size and shape of the curve compared to the predicted curve*:
    (a) In obstructive disorder: the curve is less steep than predicted curve.
    (b) In restrictive disorder: the curve has a normal shape but with a reduced total volume than the predicted curve.
  - *The components of the curve* to help distinguish restrictive from obstructive abnormalities:
    (a) FVC (the height of the curve)
    (b) FEV_1 (the volume corresponding to 1 second)
  - *Post bronchodilator curve, if applicable*
    (a) In patients with a suspected obstructive disorder, a post bronchodilator spirometry with VT curve should be performed and reported. Improvement in the shape and slope of this curve compared to the original may indicate a response to bronchodilators. Comparing the absolute values for (FVC) and the volume corresponding to 1 second (FEV_1) from both curves is used to judge the response to bronchodilators more accurately; Figure 1.16.

APPROACH TO THE FLOW-VOLUME (FV) CURVE/LOOP

- *Assess the technical quality of the study based on FV curve*
  - An acceptable curve should have the following; Figure 1.11a: [1, 2]
    (a) Good start (rapid climb to PEF, which should be sharp and rounded)
    (b) Smooth curve free from artefacts (mainly in the 1st second)

(c) Good end (slight upward concavity at the end of the curve)
* A rapid stop to the end of the FV curve suggests a submaximal effort and hence an underestimate of the FVC.

– The inability to meet any of these criteria affects the study quality. The results should then be interpreted with caution. If no acceptable curves are obtained the study should be reported as uninterpretable. The technician's comments also address the patient's technique (if poor) and the study acceptability and reproducibility (which are impaired with a poor technique).
– A morphologically poor start of the study shouldn't prompt you to reject the study right away, as the same curve may be seen in NMD and in children; Figure 6.1f.
– The issue of reproducibility of the FV curves has been discussed previously. To meet quality criteria, the FEV_1 and FVC from 2 acceptable curves have to be within 150 mls of each other and the highest FEV_1 and FVC from either curve is then reported

• *Examine the size and shape of the FV curve/loop*
– The size and shape of the curve (after excluding poor quality curves) should fit one of the following; Figure 6.1:
(a) *Normal size and shape*; Figure 6.1a: indicate a normal study, including the normal variants like the "knee" variant; Figure 1.22.
(b) *Small and concave or scooped expiratory limb*: suggests obstructive disorder; Figure 6.1b, c
(c) *Small and steep slope* with a "*Witch's hat*" shape: suggests parenchymal restriction; Figure 6.1d
(d) *Small and parallel slope to the predicted curve*: is seen in chest wall restriction (musculoskeletal disease, diaphragmatic dysfunction and obesity) or normal patients with small lungs—racial variations; Figure 6.1e
(e) *Small and convex shape* (mimicking poor start, i.e. delayed and decreased PEF which is not sharp): is seen in a study with a poor effort, NMD and in some children; Figure 6.1f
(f) *Small and flattened* (suggests central airway obstruction):
* Only the expiratory component is flat (variable intrathoracic obstruction); Figure 6.1g

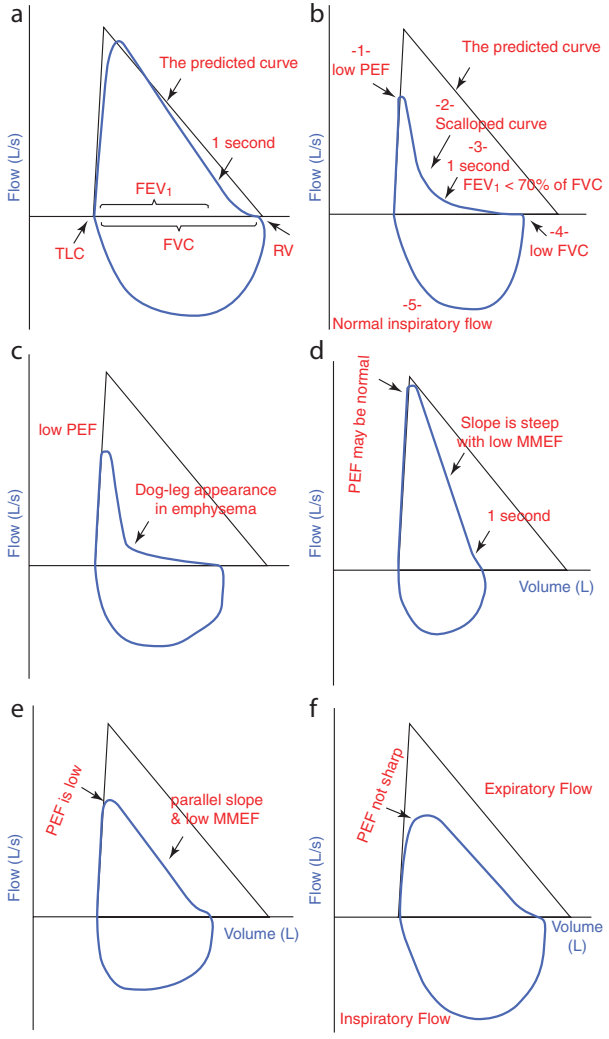

FIGURE 6.1 Normal and most abnormal FV loops: (**a**) Normal. (**b**) Obstructive loop. (**c**) Dog-leg obstructive curve, typical for emphysema. (**d**) Parenchymal restriction with a *witch's hat* appearance. (**e**) Chest wall restriction (consider racial variations). (**f**) NMD or poor initial effort (can also be seen in children). (**g**) Variable intrathoracic upper airway obstruction. (**h**) Variable extrathoracic upper airway obstruction. (**i**) Fixed upper airway obstruction

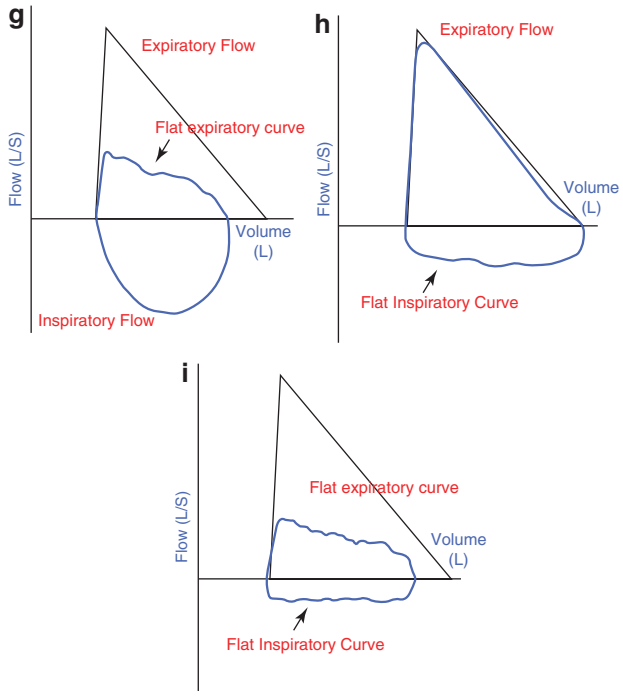

FIGURE 6.1 (continued)

    * Only the inspiratory component is flat (variable extrathoracic obstruction); Figure 6.1h
    * Both components are flat (fixed obstruction); Figure 6.1i
  - This step is important in formulating an initial impression about the underlying disorder but, apart from upper airway obstruction, it requires review of the absolute values
- *Examine the components of the curve*
  - *Height* (PEF) *and slope* (FEF_{25-75})—if low, they may suggest an obstructive disorder.
  - *Width* (FVC)—if smaller than the predicted curve, suggests restrictive (mainly) or obstructive defect (to a lesser extent).

  - *The 1 second mark* (FEV_1)—check how it compares to the whole width of the curve (FVC) to visually estimate the FEV_1/FVC ratio. If low, it suggests obstruction; Figure 6.1b.
- *Examine the location of the curve compared to the predicted:*
  - This is only possible if spirometry is done in the body box while measuring lung volumes. If so, then we can apply the following; Figure 2.7:
    (a) If the curve runs along the predicted one, then TLC and RV are normal.
    (b) If the curve is shifted to the right (↓TLC, ↓RV), this suggests a restrictive defect (remember: shift to the right → restriction)
    (c) If the curve is shifted to the left (↑TLC, ↑RV), this suggests obstruction. (If, in addition, FVC is ↓, then RV/TLC ratio should be ↑, supporting obstruction; think about that for a minute!)
- *Examine post-bronchodilator curve, if applicable*
  - As mentioned earlier, a pre-bronchodilator curve is often coloured in blue, while the post-bronchodilator curve is in red.
  - Quickly, examine the technical quality of the post curve.
  - Then examine its shape, size and location compared to the pre curve. If the post curve shows improvement in the shape, size and/or location compared to the pre curve, it indicates a response to bronchodilators which may be significant; Figure 1.15.

APPROACH TO SPIROMETRY

- *Examine FVC, FEV_1 and FEV_1/FVC ratio*
  - There are 4 possibilities:
    (a) Normal—when all of these values are normal.
    (b) Clearly obstructive—defined by a ↓ FEV_1/FVC ratio (FEV_1 is usually ↓ and FVC is usually normal or relatively preserved; FEV_1 level (% pred.) determines severity; Table 1.4)
      * Historically a ratio of 0.7 has been used as the threshold for an obstructive study, however with more robust normative data sets, the lower limit of normal is now preferred to determine if there is obstruction or not as this ratio decreases with increased age of the subject.
    (c) Restrictive—with ↓ FVC and a normal or ↑ FEV_1/FVC ratio (optimally confirm the restrictive nature of the dis-

order by measuring TLC which should be low; if TLC is not done, termed a non specific restrictive pattern and should be reported as "suggests a lung restrictive disorder". FVC is used to grade severity; Table 1.4). Also, remember that spirometry with a poor effort may look restrictive due to an underestimate of FVC.

(d) Combined obstructive and restrictive disorder—may be suggested if the reduction in FVC is out of proportion to the reduction in the FEV_1/FVC ratio, (e.g. the FEV_1/FVC ratio is 65% and FVC is only 40% pred.) [3]. A normal FVC, however rules out restriction [4, 5]. To be definite about the presence of a combined disorder, the lung volumes need to be examined.

- *Examine the post-bronchodilator value of FVC, FEV_1 and FEV_1/FVC ratio, if available*
  - The response to bronchodilators can be: [6, 7]
    (a) Significant response—12% and 200 ml ↑ in FEV_1 or FVC.
    (b) Insignificant or no response—if it is less than that.
    (c) If there is a significant response, one should comment on whether there is correction into the normal range i.e. complete bronchodilator reversibility which can be seen in asthma but not generally in COPD.
- *Examine $FEF_{25,\ 50,\ 75,\ 50–75}$*
  - Historically, these flows have been considered to reflect more distal early airflow obstruction than the FEV_1. It was thought that, if low, these flows would be a more sensitive test for obstruction, however they can also be low in restrictive disorders, upper airway obstruction or due to loss of lung elastic recoil.
  - These measurements have considerably more variation. Generally they are below the LLN when the FEV_1 is also reduced.
  - These measurements therefore are not specific for early airway disease [6, 8] and overall are of little diagnostic value.
- *Have a QUICK look at the rest of the spirometry:*
  - PEF decreases with
    (a) Poor effort (as it is effort dependent)
    (b) Obstruction (mainly)
    (c) May decrease with restriction (like NMD); It is usually preserved in parenchymal restriction.
  - PIF and PIF_{50}—drop with poor effort or with variable extra-thoracic obstruction (don't worry about the abso-

lute values, as it will be obvious in the FV loop). You need keep in mind that the inspiratory limb of the FV loop does not have acceptability criteria around it so that poor effort may not always commented on by the technician.
  - FET—helps knowing the appropriate duration of exhalation (should be ≥6 seconds). If excessively prolonged, it may suggest airway obstruction.
- *Special Situations*
  - An isolated significant response to bronchodilators with normal flows at baseline suggests asthma [6].

APPROACH TO LUNG VOLUME STUDY

- *Examine TLC, RV and RV/TLC ratio* (these are the most important lung volume variables)
  - They usually change in the same direction, i.e. the direction of obstruction or restriction. The following are the possibilities:
    (a) Normal, when all are normal.
    (b) High volumes, suggesting obstruction; remember:
      * ↑ TLC usually indicates hyperinflation (physiologically, hyperinflation is more accurately defined by FRC)
      * ↑ RV indicates air-trapping (if RV is elevated and RV/TLC is above 120%)
      * ↑ RV/TLC ratio reflects the degree of air-trapping [6].
    (c) Low, in restrictive disorders (↓TLC is essential to make a confident diagnosis of restriction [6]; TLC should be used to grade severity, if available; Table 1.4).
- *Examine the rest of the lung volumes (FRC, ERV, IC):*
  - They usually follow the TLC and RV, so they are high in obstructive and low in restrictive disorders.
- *Special situations*
  - Isolated reduction in ERV indicates obesity, check the patient's weight/BMI.
  - When the lung volumes are incompatible with spirometry, consider combined disorders; see next sections.

APPROACH TO GAS TRANSFER STUDY

- *Examine DL_{CO} and DL_{CO}/V_A ratio*
  - For simplicity, consider 4 possibilities:
    (a) Both are normal (above LLN)—this indicates that there is no gas exchange abnormality.
    (b) Both are high—seen in a variety of pulmonary and systemic disorders, review Table 3.3.
    (c) DL_{CO} is low—this indicates a gas exchange abnormality. Remember the causes of low DL_{CO} (Table 3.3) and consider the most important ones:
      * Parenchymal lung disease
      * Pulmonary vascular disease
      * Anemia
      * Active Smoker
    (d) DL_{CO} is low with a normal or high DL_{CO}/V_A (i.e. it normalizes if corrected to V_A as the loss in V_A is the predominant abnormality)—unfortunately, you can't conclude much from this. Consider the following:
      * This could be an extraparenchymal disease (loss of alveolar spaces) like lung resection or chest wall restriction (e.g., NMD) [9].
      * Remember that gas exchange abnormality like lung fibrosis can't be excluded.
      * Normal subjects who fail to take a deep enough breath or long enough breath-hold can show similar abnormalities; however this should have been noted by the technician and the data are rejected as not meeting quality control criteria, see next.
- *Examine DL_{CO}/Hgb correction, if Hgb is available* [10–14]
  - If a low DL_{CO} corrects to normal, it indicates that anemia is responsible for the reduction in DL_{CO}.
  - If it doesn't correct to normal, then a gas exchange abnormality rather than anemia is present.
- *Examine the rest of the variables*
  - V_A should roughly equal TLC. In an obstructive disorder, the difference between the 2 increases and roughly estimates the volume of the poorly ventilated air spaces; see also Table 6.2.

- Breath-hold time (BHT) and inspired vital capacity (IVC) help in determining the accuracy of DL_{CO} study:
  (a) BHT should equal 10 seconds. If less, DL_{CO} is underestimated and vice versa.
  (b) IVC should be at least 90% of the patient's VC. If less, DL_{CO} is underestimated.

REACHING A CONCLUSION WHEN FULL PFT'S AVAILABLE

Combining spirometry, lung volumes and DL_{CO} measurements help reach an accurate conclusion. Start by determining whether spirometry and lung volumes support the same diagnosis:

If both (spirometry and lung volumes) support an obstructive defect:

- The final diagnosis is then a "*pure obstructive disorder*"
- You will need then to differentiate (if possible) between the 2 major obstructive disorders, asthma and COPD:
  - *FV curve*: a "dog-leg" appearance is more suggestive of emphysema [15].
  - *Spirometry*: a significant bronchodilator response is more suggestive of asthma but can be seen in a significant proportion of other obstructive disorders such as COPD.
  - *Lung volume study:*
    (a) TLC is usually normal in asthma and may be ↑ in emphysema
    (b) RV/TLC ratio is typically more elevated in emphysema than in asthma [6, 16].
  - DL_{CO}: ↓ in emphysema and normal or ↑ in asthma [17–21].
    (a) If you can estimate the degree of *air-trapping*, see Table 6.2: it is much higher in emphysema than in asthma.
  - *Bronchodilator Reversibility*: is more likely to be positive in asthma than in COPD
- Remember that other obstructive disorders (like bronchiectasis, obstructive bronchiolitis, chronic bronchitis) could be responsible.
  - In most cases we advise that (in the conclusion) the presence of obstruction should be stated with the avoidance of a specific

diagnosis. The statement of obstruction could then be followed by a statement such as supportive of a certain condition in the appropriate clinical context particularly if the referring physician has a specific question.

Both support a restrictive defect:

- The final diagnosis is then a *"pure restrictive disorder"*.
- The 2 major groups of disorder involved are:
  - Parenchymal restriction, like ILD
  - Extrapulmonary restriction, like chest wall restriction (NMD, MSD, diaphragmatic paralysis, pleural disease, lung resection and Morbid obesity)
- The following may help in the distinction:
  - *FV curve:*
    (a) A truncated curve with a steep slope suggests a parenchymal restriction
    (b) A small curve with a parallel slope to the predicted curve suggests extrapulmonary restriction other than NMD.
    (c) A convex curve (Figure 6.1f) suggests NMD or poor effort study
  - *Lung volumes:*
    (a) Although the TLC is ↓ in both disorders, RV is usually normal or ↑ in extrapulmonary restriction and ↓ in parenchymal restriction. The RV/TLC ratio is usually ↑ in extrapulmonary restriction (it is mostly normal with parenchymal restriction) [22].
    (b) The degree of the reduction in FVC compared to TLC:
      * If FVC and TLC are proportionally reduced, then this supports parenchymal restriction
      * If the reduction in FVC is out of proportion to the reduction in TLC (i.e. TLC is relatively preserved), this supports extrapulmonary restriction.
  - DL_{CO} [9]
    (a) If low (DL_{CO}/V_A)—it supports parenchymal restriction but cannot rule out extrapulmonary restriction
    (b) If DL_{CO} is ↓ but DL_{CO}/V_A is normal or high—it supports extrapulmonary restriction but can't exclude a parenchymal restriction.

Table 6.2 Methods to identify the presence of air trapping and estimate its volume

From spirometry: a significant difference between SVC and FVC indicates air trapping (SVC being larger than FVC)
From lung volume study: a high RV indicates air trapping; the difference between the measured and the predicted RV roughly estimates the volume of the trapped air
From gas transfer study: a significantly higher TLC compared with VA indicates air trapping
N_2 washout or gas dilution methods vs. plethysmography: if TLC is estimated with plethysmography and either N_2 washout or gas dilution methods, then the difference between the two TLC measurements can estimate the volume of trapped air

- To differentiate some of the types of extrapulmonary restriction:
  - Obesity:
    (a) You can calculate the BMI; a BMI of >35 is suggestive of obesity causing a restrictive pattern.
    (b) ERV is usually very low in obesity
    (c) Usually normal MIP and MEP (if measured).
  - NMD (e.g. ALS)
    (a) Expiratory limb of the FV curve is usually convex in shape with lack of a sharp peak flow.
    (b) MIP, MEP and SNIP are ↓ [23].
    (c) FRC preserved with reduced TLC
    (d) RV may be increased with expiratory muscle weakness
  - Diaphragmatic paralysis
    (a) MIP is ↓ with a normal MEP (normal expiratory muscles)
    (b) FVC is markedly reduced in supine position (drops by >30% from sitting FVC) [24].
    (c) Other tests (transdiaphragmatic pressure is reduced)

If both are normal:

- Consider the "isolated abnormalities" before reporting the study as normal:
  - *Isolated reduction in ERV*: is usually associated with obesity.
  - *Isolated reduction in DL_{CO}*: indicates a gas exchange abnormality. So, consider: early parenchymal lung disease (like

emphysema or ILD), pulmonary vascular disease or anemia [9]. An isolated reduction in DL_{CO} with a normal DL_{CO}/V_A should be reported as abnormal and similar causes explored.
– *Isolated significant response to bronchodilators* (with a normal pre-bronchodilator study): strongly suggests a reversible airway disorder [6] (e.g. asthma).

If the results of spirometry and lung volumes are discordant:

- An obstructive spirometry (↓ FEV_1/FVC ratio) with low lung volumes (↓ TLC):
  – The 2 major possibilities are:
    (a) A combined disorder [3, 6].
    (b) An obstructive disorder with pulmonary resection (history required).
- A restrictive spirometry with high lung volumes
  – May represent a combined abnormality.
  – An obstructive disorder with severe air trapping or poor effort (incomplete exhalation) [6].

If one study (spirometry or lung volume study) is normal and the other is abnormal

- *Normal spirometry with abnormal lung volume study*
  – *Normal spirometry with low lung volumes*
    (a) This is uncommon, and may represent a technical error. Although by definition a normal VC from spirometry essentially excludes a restrictive abnormality [3, 4]. In early ILD, TLC may be reduced but VC preserved due to a concomitant reduction in RV.
  – *Normal spirometry with high lung volumes*
    (a) Obstructive disorder:
      * Emphysema with minimal airway disease.
      * Mild asthma (if TLC is normal and RV is increased) [22]
    (b) Another possibility is acromegaly; a normal RV/TLC ratio is more likely with acromegaly than with obstruction. Another clue is ↑ FVC [22]. Patients with large lungs e.g. swimmer may have similar values.
    (c) Error in lung volume measurements

- *Normal lung volume study with abnormal spirometry*
  - *Normal lung volumes with an obstructive spirometry*
    (a) A combined disorder
    (b) Obstructive disorder with pulmonary resection (review the history).
    (c) Pure obstructive disorder (e.g. asthma without air trapping)
  - *Normal lung volumes with a restrictive spirometry*
    (a) Pure lung restriction is excluded because of a normal TLC. Four possibilities could be considered:
      * Poor effort (examine the FV curve morphology and review technician's comments)
      * Mild obstructive disorder, e.g. mild asthma, sometimes called pseudorestriction (grade according to FEV_1) [25, 26]; the following tests may be supportive:
        (1) ↑ airway resistance
        (2) Significant bronchodilator response
        (3) Positive bronchial challenge
        (4) Increased RV
      * If not a poor effort study and there is no evidence of obstruction, report it as *"non-specific ventilatory limitation"* which simply means, we don't know! [22]
      * Consider a mild combined disorder.

References

1. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. Eur Respir J. 2005;26:319–38.
2. American Thoracic Society. Standardization of spirometry update. Am J Respir Crit Care Med. 1995;152:1107–36.
3. Dykstra BJ, Scanlon PD, Kester MM, Beck KC, Enright PL. Lung volumes in 4,774 patients with obstructive lung disease. Chest. 1999;115:68–74.
4. Aaron SD, Dales RE, Cardinal P. How accurate is spirometry at predicting restrictive pulmonary impairment? Chest. 1999;115:869–73.
5. Glady CA, Aaron SD, Lunau M, Clinch J, Dales RE. A spirometry-based algorithm to direct lung function testing in the pulmonary function laboratory. Chest. 2003;123:1939–46.
6. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26:948–68.
7. Cerveri I, Pellegrino R, Dore R, Corsico A, Fulgoni P, van de Woestijne KP, Brusasco V. Mechanisms for isolated volume

response to a bronchodilator in patients with COPD. J Appl Physiol. 2000;88:1989–95.
8. Flenley DC. Chronic obstructive pulmonary disease. Dis Mon. 1988;34:537–99.
9. MacIntyre N, Crapo RO, Viegi G, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung. Eur Respir J. 2005;26:720–35.
10. Viegi G, Baldi S, Begliomini E, Ferdeghini EM, Pistelli F. Single breath diffusing capacity for carbon monoxide: effects of adjustment for inspired volume dead space, carbon dioxide, hemoglobin and carboxyhemoglobin. Respiration. 1998;65:56–62.
11. Mohsenifar Z, Brown HV, Schnitzer B, Prause JA, Koerner SK. The effect of abnormal levels of hematocrit on the single breath diffusing capacity. Lung. 1982;160:325–30.
12. Clark EH, Woods RL, Hughes JM. Effect of blood transfusion on the carbon monoxide transfer factor of the lung in man. Clin Sci Mol Med. 1978;54:627–31.
13. Cotes JE, Dabbs JM, Elwood PC, Hall AM, McDonald A, Saunders MJ. Iron-deficiency anaemia: its effect on transfer factor for the lung (diffusiong capacity) and ventilation and cardiac frequency during sub-maximal exercise. Clin Sci. 1972;42:325–35.
14. Marrades RM, Diaz O, Roca J, Campistol JM, Torregrosa JV, Barberà JA, Cobos A, Félez MA, Rodriguez-Roisin R. Adjustment of DLCO for hemoglobin concentration. Am J Respir Crit Care Med. 1997;155:236–41.
15. Hancox B, Whyte K. Bob pocket guide to lung function tests. 1st ed. Sydney: McGraw-Hill; 2001.
16. Pride NB, Macklem PT. Lung mechanics in disease. In: Macklem PT, Mead J, editors. Handbook of physiology. The respiratory system. Mechanics of breathing. Section 3, vol. 3, Part 2. Bethesda, MD: American Physiological Society; 1986. p. 659–92.
17. Henderson JC, O'Connell F, Fuller RW. Decrease of histamine induced bronchoconstriction by caffeine in mild asthma. Thorax. 1993;48:824–6.
18. Cotton DJ, Prabhu MB, Mink JT, Graham BL. Effects of ventilation inhomogeneity on DLcoSB-3EQ in normal subjects. J Appl Physiol. 1992;73:2623–30.
19. Cotton DJ, Prabhu MB, Mink JT, Graham BL. Effect of ventilation inhomogeneity on "intrabreath" measurements of diffusing capacity in normal subjects. J Appl Physiol. 1993;75:927–32.
20. Gelb AF, Gold WM, Wright RR, Bruch HR, Nadel JA. Physiologic diagnosis of subclinical emphysema. Am Rev Respir Dis. 1973;107:50–63.
21. Morrison NJ, Abboud RT, Ramadan F, Miller RR, Gibson NN, Evans KG, Nelems B, Müller NL. Comparison of single breath carbon monoxide diffusing capacity and pressure-volume curves in detecting emphysema. Am Rev Respir Dis. 1989;139:1179–87.

22. Hyatt RE, Scanlon PD, Nakamura M. Interpretation of pulmonary function tests, a practical guide. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.
23. Malcolm ATS, Gary C. Respiratory muscle testing: tests of respiratory muscle strength. Am J Respir Crit Care Med. 2002;166:518–624.
24. Green M. Respiratory muscle testing. Bull Eur Physiopathol Respir. 1984;20:433–5.
25. Salzman J. Pulmonary function testing. Tips on how to interpret the results. J Respir Dis. 1999;20:809–22.
26. Gilbert R, Auchincloss JH. What is a "restrictive" defect? Arch Intern Med. 1986;146:1779–81.

Chapter 7
Illustrative Cases on PFT

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Abstract These 15 illustrated cases offer an opportunity to test your PFT interpretation skills and implement the lessons learned in previous chapters.

Keywords Spirometry · FVC · FEV_1 · FEV_1/FVC ratio · Lung volumes · TLC · RV · Diffusing capacity · DL_{CO} · Technician's comments · Interpretation

Table 7.1 lists the normal values for the most important PFTs and their grading of severity.

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CASE 1

A 52-year-old female, Caucasian. Heavy smoker. History of chronic dyspnea.

1. Spirometry (Figure 7.1)

	Pred.	Pre	% Pred.	LLN	Post	%Chg
FVC	3.34	1.53	46	2.54	2.31	50
FEV_1	2.70	0.41	15	2.02	0.53	30
FEV_1/FVC		0.27		0.69	0.23	
$FEF_{25–75}$	2.82	0.11	4	1.41	0.17	

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	5.14	7.15	139	4.07
RV	1.86	5.20	280	1.8
RV/TLC	36%	73%		32%

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	22.9	3.4	15	15.6
DL_{CO}/V_A	4.52	1.47	32	3.3
V_A	5.23	2.31	44	3.8

Technician's Comments: Data acceptable and reproducible. Four puffs of salbutamol inhaler given.

Q1: Interpret this PFT.

Q2: What are the most likely diagnoses?

Q3: How can you estimate the volume of trapped air?

Interpretation (Case 1)

- Spirometry is obstructive:
  - VT curve:
    (a) Is flattened, suggesting obstructive defect. Notice that the FET (16 seconds) is prolonged which supports the obstructive nature of the disorder.

TABLE 7.1 PFT normal values and grading of severity scale[a]

Normal values (ATS)—apply mainly to young and middle ages (only use when lower limit of normal not available)	
FVC	80–120 (% pred.)
FEV_1	80–120
FEV_1/FVC ratio	80–120
$FEF_{25–75}$	>65% pred. but can be as low as 55%
$FEF_{25–75}$/FVC ratio	>0.66 (more accurate)
TLC	80–120
FRC	75–120
RV	75–120
DL_{CO}	80–120
MEP	>90 cmH_2O
MIP	<–70 cmH_2O
Supine FVC	Within 10% of the sitting value; >30% drop suggests diaphragmatic paralysis
Traditional method for grading the severity of obstructive and restrictive disorders	
GOLD—COPD (based on fixed FEV_1)—*Ratio < 0.7*	
May be a physiologic variant	$FEV_1 \geq 100$ (%pred.)
Mild	80–100
Moderate	50–79
Severe	30–49
Very severe	<30
Restrictive disorder (based on TLC, preferred)	
Mild	TLC 70–79 (% pred.)
Moderate	60–69
Severe	<60
Restrictive disorder (based on FVC, in case no lung volume study is available)	
Mild	FVC 70–79 (% pred.)
Moderate	60–69
Moderately severe	50–59
Severe	35–49
Very severe	<35

[a]LLN can be applied to appropriate reference equations to determine an abnormal result

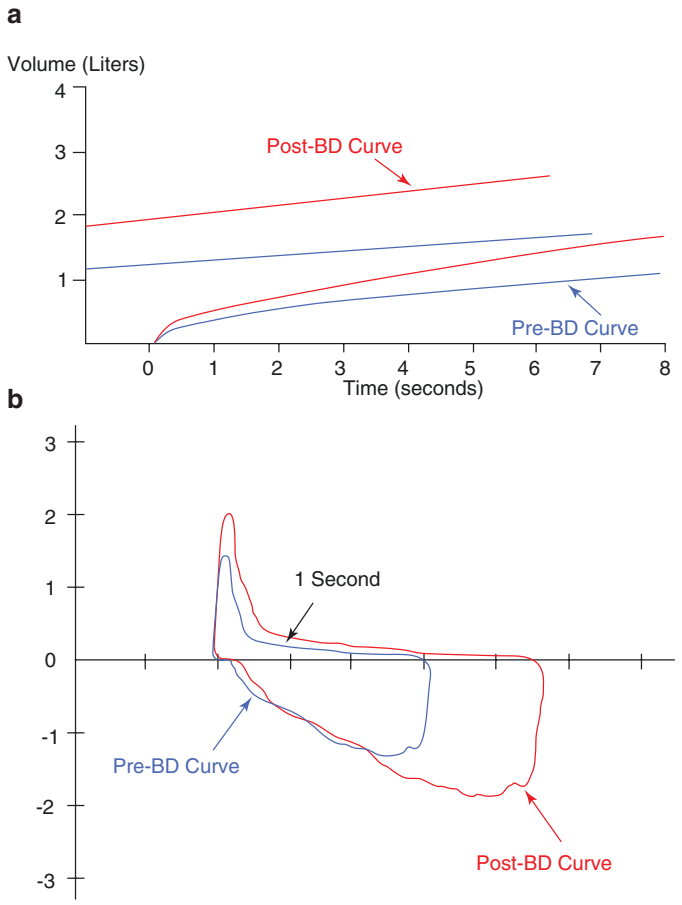

FIGURE 7.1 (**a**) VT curve; (**b**) FV loop

(b) The post bronchodilator curve shows a better morphology indicating a degree of bronchodilator response that needs to be defined numerically.

- FV loop:
  (a) Is of a reasonable quality, although patient didn't take full inspiration during the IVC.
  (b) It is scooped out, with a "dog-leg appearance" (suggesting an obstructive disorder).
  (c) The 1 second mark is closer to the left-most end of the curve indicating a very low FEV_1 and FEV_1/FVC ratio, suggesting severe obstruction.
  (d) Post-BD curve has a higher peak and is less scalloped (suggesting some response to BD).
- Spirometric data:
  (a) Severe obstructive disorder (↓ FEV_1 of a very severe range and ↓ FEV_1/FVC ratio)
  (b) ↓ FEF_{25-75} supporting obstruction
  (c) Partial but significant response to BD in FVC (780 ml and 50%). It didn't reach significance in FEV_1 (120 ml and 30%).

(Based on spirometry alone, the patient has a very severe obstructive defect with a significant response to bronchodilators. Given his smoking history and the dog-leg appearance in the FV curve, COPD is the most likely but bronchial asthma or asthma/COPD overlap can't be excluded which is supported by the significant response to BDs)

- Lung volume study is obstructive
  - TLC and RV are ↑ with a very ↑ RV/TLC ratio suggesting emphysema with hyperinflation and air-trapping (in asthma TLC is usually normal)

(Based on spirometry and lung volumes, both support obstruction, but COPD (emphysema) is the most likely as in asthma TLC is usually normal. DL_{CO} will be of help)

- DL_{CO}
  - DL_{CO} is extremely low suggesting a gas exchange abnormality, favoring emphysema.
- Conclusion: very severe obstructive disorder with significant reversibility and impaired gas exchange suggesting emphysema.

- Air-trapping can be estimated in 2 ways:
  (a) TLC – V_A = 4.84 liters
  (b) RV (Pred) – RV (measured) = 3.34 liters
- This patient has severe COPD (emphysema) clinically and radiologically.

CASE 2

A 74-year-old female, Caucasian.

1. Spirometry (Figure 7.2)

	Pred.	Pre	% Pred.	LLN
FVC	3.21	3.17	99	1.87
FEV_1	2.38	2.57	108	1.44
FEV_1/FVC		81		64
$FEF_{25–75}$	1.91	2.65	139	0.74

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this spirometry.
Q2: How would you describe the FV curve?

Interpretation (Case 2)

- Spirometry is normal:
  - VT curve looks normal. FET is ~ 12 seconds.
  - FV loop:
    (a) Is normal, with a knee. This is reproducible and considered as a normal variant. Notice that PEF is normal.
  - Spirometric data:
    (b) Normal FEV_1, FVC and ratio.
    (c) Normal $FEF_{25–75}$.
- Conclusion: Normal study (the knee variant).

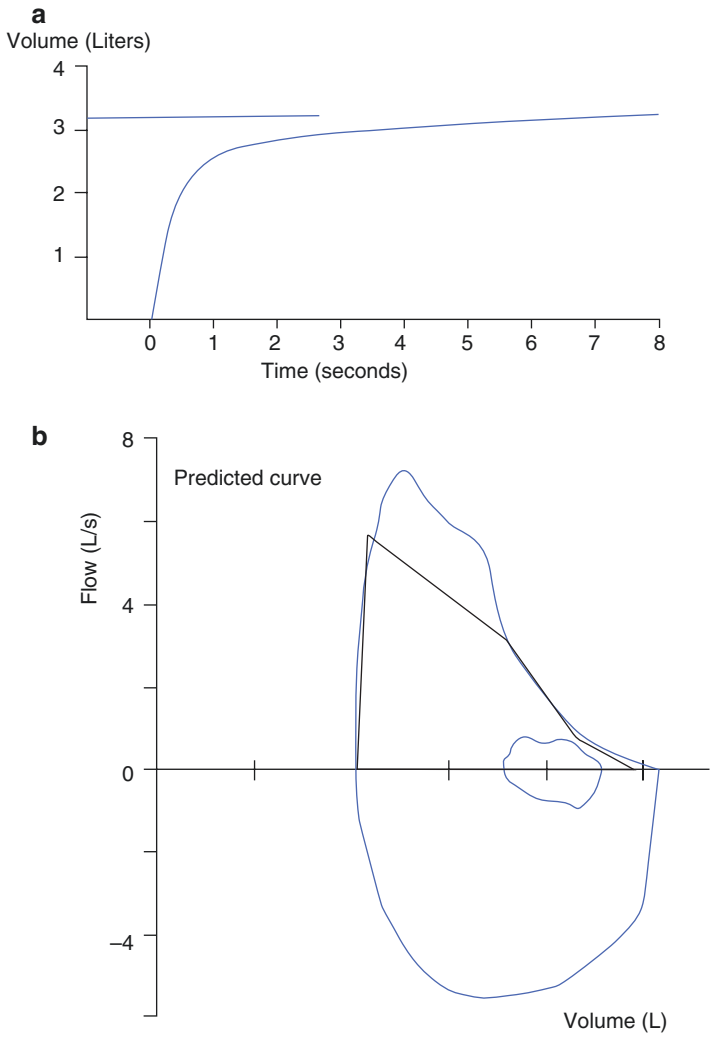

FIGURE 7.2 (**a**) VT curve; (**b**) FV loop

CASE 3

A 65-year-old female, Caucasian. History of progressive dyspnea.

1. Spirometry (Figure 7.3)

	Pred.	Pre	% Pred.	LLN
FVC	4.56	2.43	53	3.65
FEV_1	3.55	1.91	54	2.84
FEV_1/FVC		0.79		0.66
$FEF_{25–75}$	3.27	1.55	47	1.97

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this spirometry.
Q2: What is the most likely diagnosis?

Interpretation (Case 3)

- Spirometry is restrictive:
  - VT curve looks normal morphologically. There is no predicted curve to compare with.
  - FV loop:
    (a) Is small with a steep slope (witch's hat appearance). Its width (FVC) is clearly reduced with a preserved ratio.
    (b) PEF is preserved suggesting a parenchymal restriction.
    (c) The tidal FV loop is closer to the TLC, suggesting a true restriction (IC:ERV ratio is clearly <2:1).
  - Spirometric data:
    (a) Moderate restrictive disorder (Moderately reduced FVC with a normal ratio); ↓ $FEF_{25–75}$ can be seen in restriction.
- Conclusion: spirometry is suggestive of a moderately severe restriction possibly due to an interstitial lung disease. A lung volume study is indicated to confirm the restrictive nature of the disease (low TLC).
- This patient has lung fibrosis secondary to IPF.

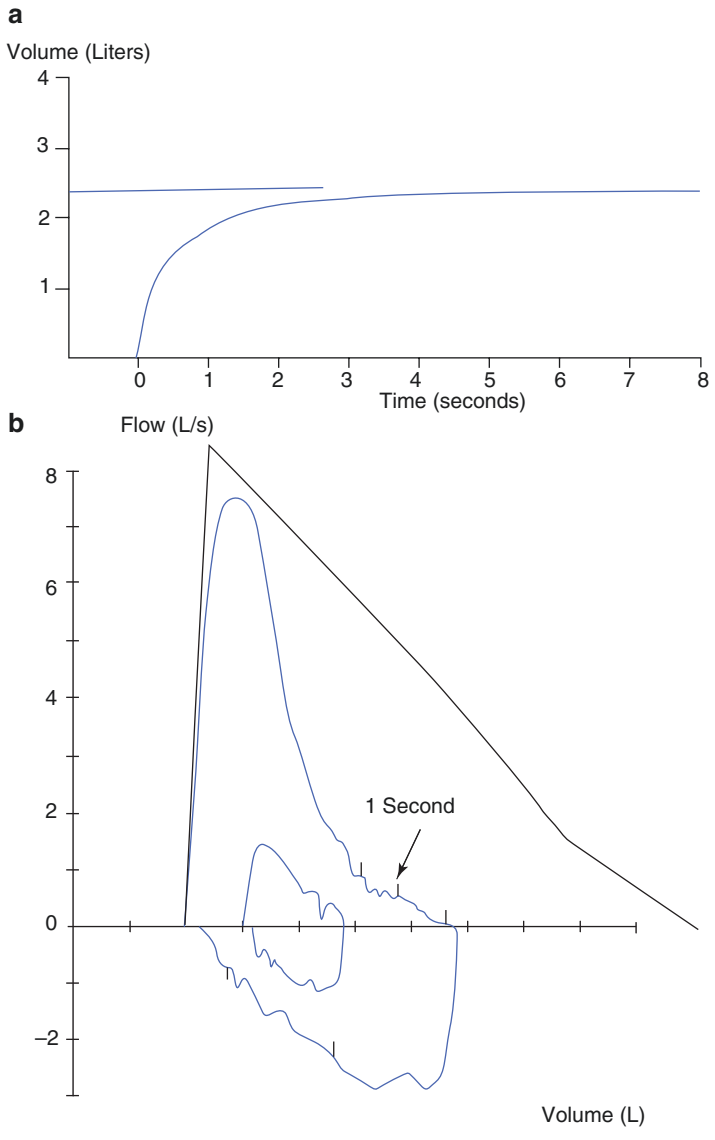

FIGURE 7.3 (**a**) VT curve; (**b**) FV loop

CASE 4

A 79-year-old male, Asian. History of dyspnea.

1. Spirometry (Figure 7.4)

	Pred.	Pre	% Pred.	LLN
FVC	3.02	1.37	45	2.48
FEV_1	2.34	0.61	26	1.82
FEV_1/FVC		48		64
FEF_{25-75}	1.65	0.23	14	0.87

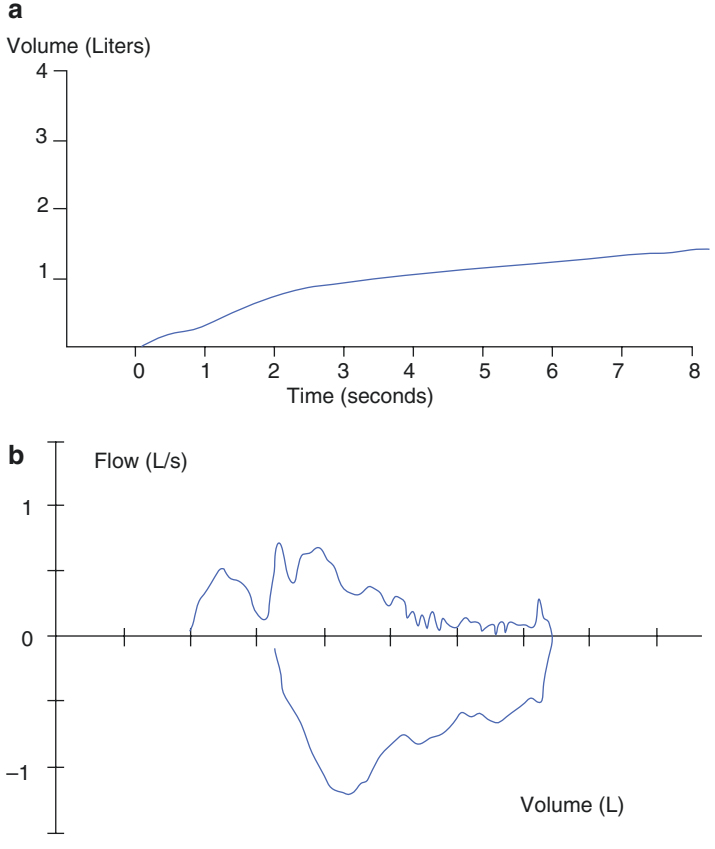

FIGURE 7.4 (**a**) VT curve; (**b**) FV loop

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this spirometry.

Interpretation (Case 4)

- VT curve is very flat suggesting an obstructive disorder.
- FV loop is small and flat. It has flat inspiratory and expiratory components suggesting a fixed upper airway obstruction. Submaximal effort is unlikely based on the technician's comments.
- This patient has a fibrotic tracheal stricture related to a previous tracheostomy.

CASE 5

A 54-year-old male, Caucasian.

1. Spirometry (Figure 7.5)

	Pred.	Pre	% Pred.	LLN	Post	% Chg.
FVC	5.11	4.70	90	3.76	4.61	–2
FEV_1	4.03	3.64	89	2.92	3.58	–1
FEV_1/FVC		78		67	77	
$FEF_{25–75}$	1.92	0.94	49	1.73		

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	7.31	7.63	104	6.06
RV	2.21	2.58	117	1.48
RV/TLC	31	34	110	29
ERV	1.58	0.78	50	0.87

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	30.50	27.99	92	21.9
DL_{CO}/V_A	4.34	4.19	96	3.23
V_A	7.02	6.68	95	5.5

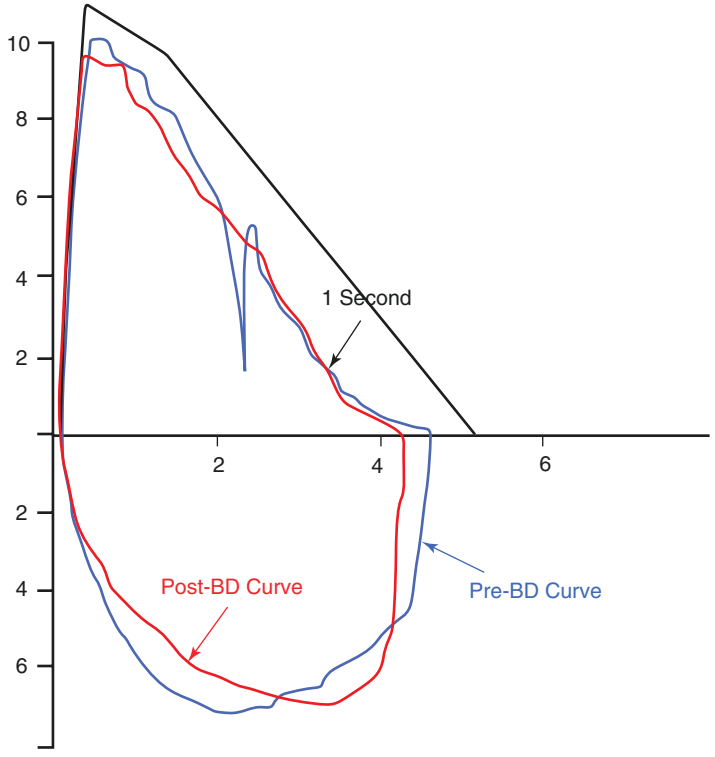

FIGURE 7.5 FV loop

Technician's Comments: Data not reproducible. Best values reported. Four puffs of salbutamol inhaler given.

Q1: Interpret this PFT.

Q2: What is the most likely diagnosis?

Interpretation (Case 5)

- Spirometry is normal:
  - FV loop:
    (a) The pre-BD curve is interrupted by a cough in its 1st second. The study is not reproducible.

(b) The curve looks normal and slightly smaller than the predicted one. FVC and the ratio look normal.
(c) Post-BD curve is smaller than the pre-BD curve indicating lack of response to BDs.

– Spirometric data:
(a) FVC, FEV_1 and the ratio are normal with no response to BD.
(b) ↓ FEF_{75} (nonspecific and may be seen in obesity)

(Based on spirometry alone, the patient has no significant obstructive or restrictive disorder despite the study quality).

- Lung volume study is normal except for an isolated reduction in ERV suggesting obesity.
- DL_{CO}
  – DL_{CO} and DL_{CO}/V_A are normal indicating that there is no gas exchange abnormality.
- Conclusion: Normal PFT with isolated reduction in ERV suggestive of obesity. The patient's weight at the time of the test was 108 kg with a BMI of 33.

CASE 6

A 48-year-old female with chronic dyspnea. Spirometry (shown in Figure 7.6) was done in body box.

Technician's Comments: Data acceptable and reproducible.

Q1: Interpret this FV loop

Interpretation (Case 6)

- FV loop morphology looks acceptable.
- It is small and has a steep slope (witch's hat)
- Its width (FVC) is low with normal ratio suggesting restriction.
- It is shifted to the right compared to the predicted indicating decreased TLC and RV which is consistent with a restrictive defect secondary to a lung disease with reduced compliance such as interstitial lung disease.
- This patient was found to have interstitial fibrosis secondary to sarcoidosis.

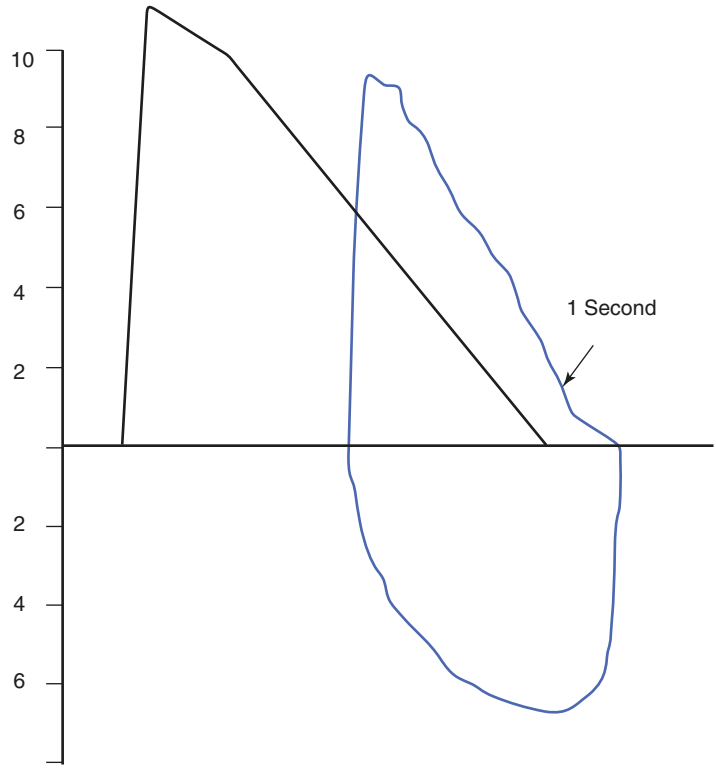

Figure 7.6 FV loop

CASE 7

An 84-year-old male, Caucasian.

1. Spirometry (Figure 7.7)

	Pred.	Pre	% Pred.	LLN	Post	%Chg.
FVC	2.94	1.90	64	2.68	2.07	9
FEV_1	2.09	0.77	37	1.67	0.89	15
FEV_1/FVC		41		59	43	
$FEF_{25–75}$	1.44	0.22	15	0.67		

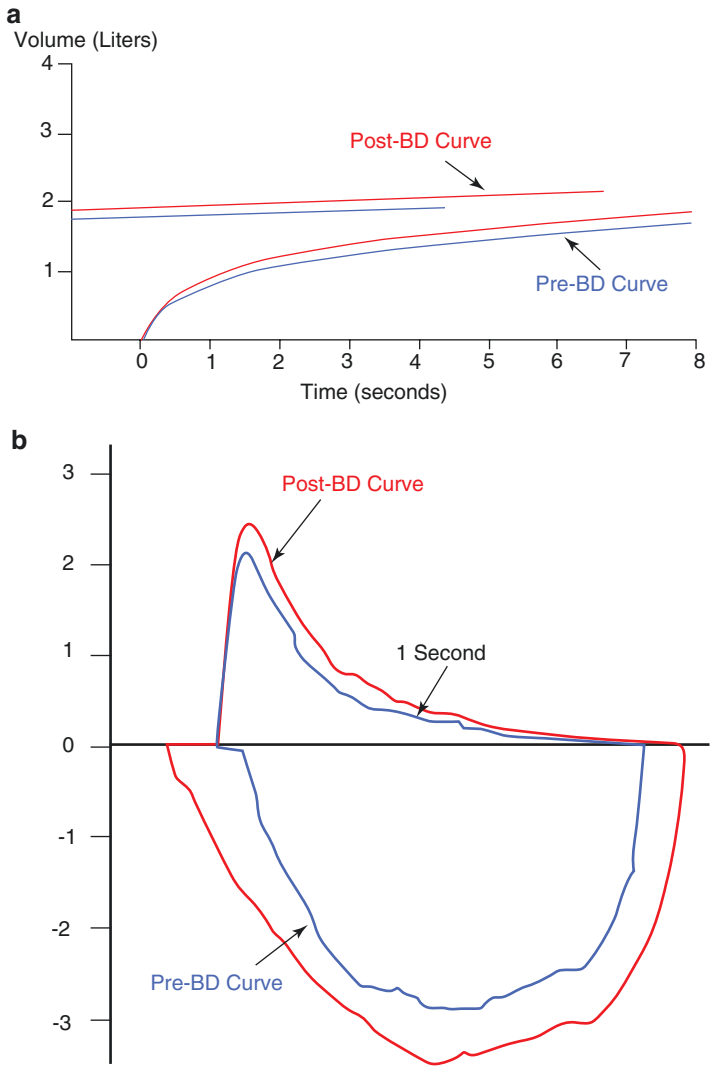

FIGURE 7.7 (**a**) VT curve; (**b**) FV loop

Technician's Comments: Data acceptable and reproducible. Four puffs of salbutamol inhaler given.

Q1: Interpret this spirometry.

Interpretation (Case 7)

- VT curve is flat with increased FET suggesting obstruction. The post BD study indicates some improvement.
- FV loop:
  - Curve quality indicates either air leak or poor initial breath in the post-BD study.
  - Curve is small and scalloped indicating obstruction. The 1 second mark is very proximal indicating that FEV_1 and its ratio are very low.
  - Some improvement in the curve morphology following bronchodilators.
- Spirometric data:
  - FEV_1 and the ratio are severely decreased indicating a severe obstructive defect.
  - ↓ FEF_{75} is very low supporting obstruction
  - There is 15% improvement in FEV_1 but it is less than 200 ml (only 120 ml) indicating some response to BD that didn't reach significance.
- Conclusion: Severe obstructive disorder with no significant response to BD.

CASE 8

A 61-year-old female, Caucasian. Unexplained SOB.

1. Spirometry

	Pred.	Pre	% Pred.	LLN	Post	%Chg
FVC	2.85	2.47	87	2.27	2.55	3
FEV_1	2.27	2.13	94	1.79	2.17	2
FEV_1/FVC		86		67	85	
$FEF_{25–75}$	2.31	2.23	140	1.1	3.06	–5

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	4.78	4.18	87	4.01
RV	1.92	1.71	89	1.18
RV/TLC	40	41		36

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	20.7	10.1	48.8	14.6
DL_{CO}/V_A	4.52	2.42	53.5	3.2
V_A	4.52	4.17	88	3.8

Technician's Comments: Data acceptable and reproducible. Four puffs of salbutamol inhaler given.

Q1: Interpret this PFT.

Q2: What are the most likely diagnoses?

Interpretation (Case 8)

- Spirometry is normal with no response to bronchodilators.
- Lung volume study is normal.
- DL_{CO} is extremely low suggesting a gas exchange abnormality.
- Conclusion: Isolated reduction in the diffusing capacity indicating an early parenchymal lung disease, pulmonary vascular disease or anemia.
- This patient has a pulmonary artery systolic pressure of 74 mmHg i.e. pulmonary hypertension.

CASE 9

A 61-year-old female, Caucasian.

1. Spirometry

	Pred.	Pre	% Pred.	LLN	Post	%Chg
FVC	4.30	3.02	70	3.3	3.10	2
FEV_1	3.72	2.66	72	2.9	2.93	10
FEV_1/FVC		88		67	94	
$FEF_{25–75}$	4.41	2.65	60	2.02	3.46	31

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	5.43	5.49	101	4.13
RV	1.29	2.06	160	0.96
RV/TLC	22.25	37.55	169	31

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	27.17	21.42	79	20.6
DL_{CO}/V_A	4.97	5.37	108	3.68
V_A	5.46	3.99	73	3.98

Technician's Comments: Data acceptable and reproducible. Four puffs of salbutamol inhaler given.

Q1: Interpret this PFT.

Interpretation (Case 9)

- Spirometry is suggestive of mild restriction with some but insignificant response to bronchodilators.
- Lung volume study shows a normal TLC (excluding pure restriction) and evidence of air trapping (↑ RV).
- Diffusing capacity is normal.
- Conclusion: The spirometry is restrictive and the lung volume study shows gas trapping and a normal TLC. The possibilities are either a combined defect (most likely) or an obstructive disorder with a suboptimal spirometry (unlikely as data are reproducible).
- This patient has COPD and interstitial fibrosis.

CASE 10

A 55-year-old male, Caucasian, weight 84 kg; history of shortness of breath.

1. Spirometry (Figure 7.8)

	Pred.	Pre	% Pred.	LLN
FVC	4.73	5.00	106	3.72
FEV_1	3.75	3.25	87	2.88
FEV_1/FVC		79		67
$FEF_{25–75}$	4.35	1.80	41	1.88
FIF_{50}		0.58		–
FEF_{50}		2.42		–

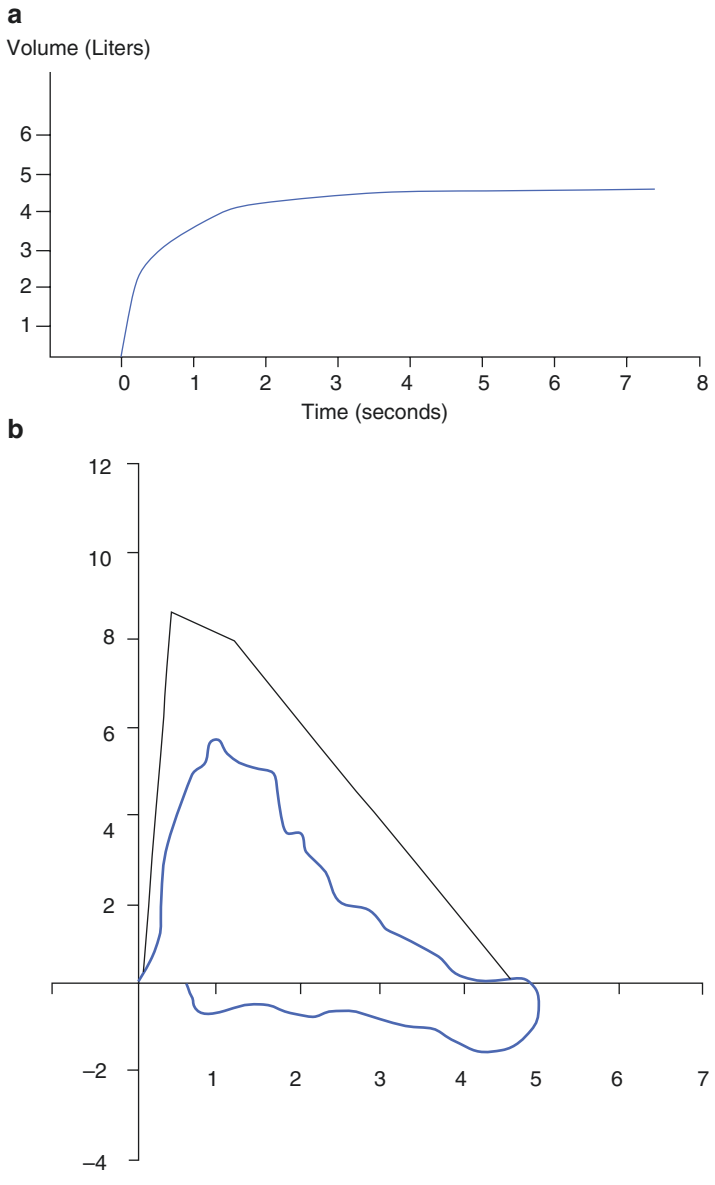

FIGURE 7.8 (**a**) VT curve; (**b**) FV loop

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.91	6.73	97	6.06
RV	2.19	1.44	66	1.50
RV/TLC	0.31	0.21	68	0.29

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	24.79	26.42	107	21.6
DL_{CO}/V_A	3.72	3.73	100	3.2

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 10)

- VT curve looks normal (no predicted curve to compare with).
- FV loop:
  - Curve quality looks suboptimal which could be due to a disease state.
  - Curve is small with a flat inspiratory component. This suggests a variable extrathoracic upper airway obstruction.
  - The expiratory component of the curve is not significantly abnormal.
- Spirometric data:
  - Normal FVC, FEV_1 and FEV_1/FVC ratio.
  - ↓ $FEF_{25–75}$ is nonspecific.
  - FIF_{50}/FEF_{50} is much less than 1 indicating a variable extrathoracic upper airway obstruction.
- Lung volume study:
  - Normal TLC with low RV.
- DL_{CO} and DL_{CO}/V_A are normal.
- Conclusion: The only significant abnormality is the flattened inspiratory component of FV loop and a very low FIF_{50}/FEF_{50} ratio indicating a variable extrathoracic upper airway obstruction. This patient has laryngeal stenosis.

CASE 11

A 67-year-old male, Caucasian, weight 105 kg.

1. Spirometry (Figure 7.9)

	Pred.	Pre	% Pred.	LLN
FVC	4.36	2.66	61	3.26
FEV_1	3.38	2.05	61	2.42
FEV_1/FVC		77		63
$FEF_{25–75}$	3.98	1.82	47	1.16

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.79	4.82	71	6.0
RV	2.40	1.54	64	1.75
RV/TLC	0.35	0.32	92	0.33

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	24.75	14.78	60	18.9
DL_{CO}/V_A	3.37	2.57	76	2.82

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 11)

- VT curve looks normal (no predicted curve to compare with).
- FV loop:
  - Curve quality looks suboptimal with multiple oscillations.
  - The height (PEF) and width (FVC) of the curve are reduced.
- Spirometric data:
  - Reduced FVC and FEV_1 with a normal FEV_1/FVC ratio suggesting a possible restriction.
  - ↓ $FEF_{25–75}$ is nonspecific.

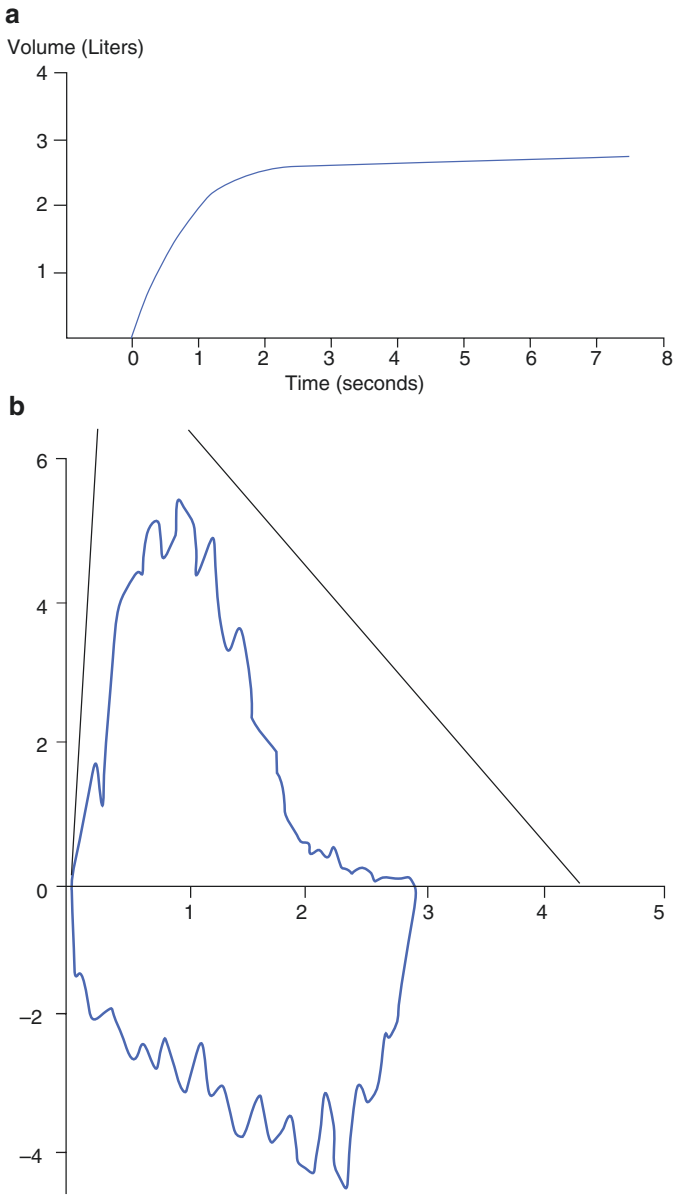

FIGURE 7.9 (**a**) VT curve; (**b**) FV loop

- Lung volume study:
  - Slightly reduced TLC with low RV confirming a mild restrictive pattern.
- DL_{CO} is low which corrects partially when V_A is taken into consideration, which still can't exclude a gas exchange abnormality.
- Conclusion: Mild restrictive disorder. This patient has Parkinson's disease which explains the oscillations noticed in the FV loop. The restrictive disorder noted is probably unrelated to Parkinson's disease.

CASE 12

A 64-year-old male, Caucasian, weight 120 kg; history of shortness of breath.

1. Spirometry

	Pred.	Pre	% Pred.	LLN
FVC	4.36	1.53	35	3.37
FEV_1	3.41	1.15	34	2.54
FEV_1/FVC		78		64
FEF_{25-75}	3.95	0.87	22	1.28

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.70	3.38	50	6.06
RV	2.40	1.54	1.69	0.81
RV/TLC	33	20	61	32

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	26.73	16.04	60	19.6
DL_{CO}/V_A	4.23	4.72	112	2.9

Supine FVC: 0.97 liter
MIP: - 27 cm water
MEP: 229 cm water.

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 12)

- Spirometric data:
  - Reduced FVC and FEV_1 with a normal FEV_1/FVC ratio suggesting a possible restriction.
  - ↓ $FEF_{25–75}$ is nonspecific.
- Lung volume study:
  - Significantly reduced TLC with a low RV confirming the restrictive nature of this disorder.
- DL_{CO} is low which corrects when V_A is taken into consideration, which still can't exclude a gas exchange abnormality.
- Conclusion: Severe restrictive disorder with a relatively preserved DL_{CO} suggesting a non-parenchymal cause of restriction.
- Further tests to be done include MEP and MIP, which showed a low MIP and normal MEP indicating inspiratory muscle (diaphragmatic) weakness. Supine FVC dropped significantly compared to the sitting value (>30% drop). This patient has paralyzed diaphragms.

CASE 13

A 22-year-old male, Caucasian, weight 81 kg; history of shortness of breath.

1. Spirometry (Figure 7.10)

	Pred.	Pre	% Pred.	LLN
FVC	5.38	1.97	36	4.50
FEV_1	4.52	1.37	30	3.79
FEV_1/FVC		72		71
$FEF_{25–75}$	4.99	1.14	23	3.20
PEF	9.24	1.68	18	4.90
$FEF_{50\%}$	5.73	1.51	26	–
$FIF_{50\%}$	5.38	1.80	33	–

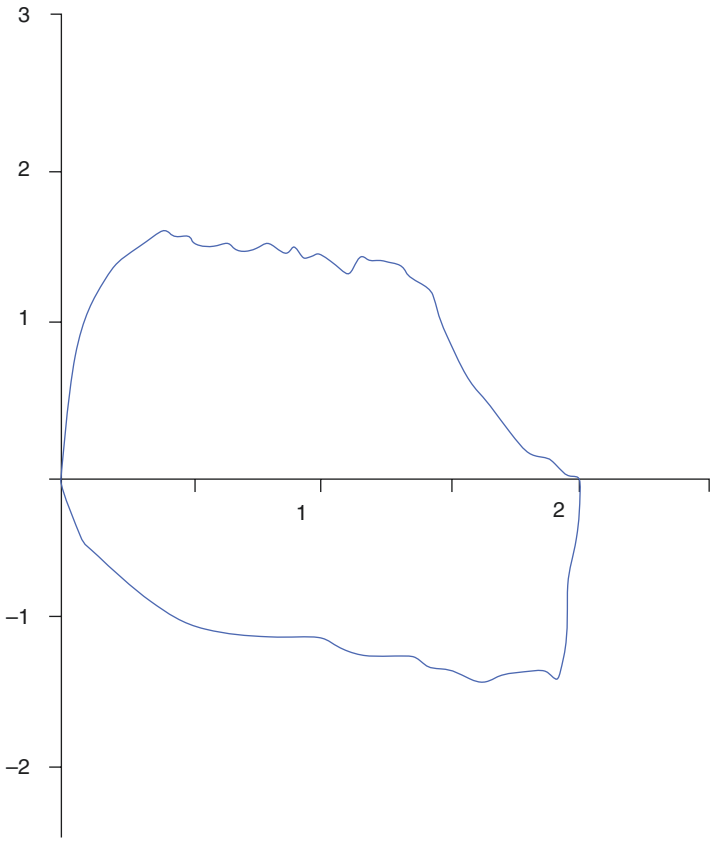

FIGURE 7.10 FV loop

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.73	2.44	36	6.06
RV	1.47	0.23	16	0.81
RV/TLC	0.21	0.09	43	0.20

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	36.67	20.34	55	29.2
DL_{CO}/V_A	5.46	7.82	143	4.21

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 13)

- FV loop:
  - Is small and flat at both inspiratory and expiratory components, suggesting fixed upper airway obstruction.
- Spirometric data:
  - Reduced FVC and FEV_1 with a normal FEV_1/FVC ratio suggesting a restrictive disease.
  - Reduced PEF, FEF_{50} and FIF_{50}. FIF_{50}/FEF_{50} ratio is around 1 which is indicating a fixed upper airway obstruction.
- Lung volume study:
  - Lung volumes are all significantly reduced confirming severe restriction.
- DL_{CO} is also low which overcorrects when V_A is taken into consideration, which possibly indicates that there is no significant parenchymal abnormality.
- Conclusion: fixed upper airway obstruction with severe restiction. This patient has lumphoma with significant paratracheal lymphadenopathy compressing the trachea. He was also found to have significant bilateral pleural effusions related to his lymphoma causing this significant restriction.

CASE 14

A 54-year-old male, Caucasian, weight 89 kg; history of shortness of breath.

1. Spirometry (Figure 7.11)

	Pred.	Pre	% Pred.	LLN
FVC	4.27	2.74	64	3.66
FEV_1	3.45	1.98	58	2.74
FEV_1/FVC		72		67
$FEF_{25–75}$	3.51	1.33	38	1.02
PEF	7.91	11.19	141	4.9

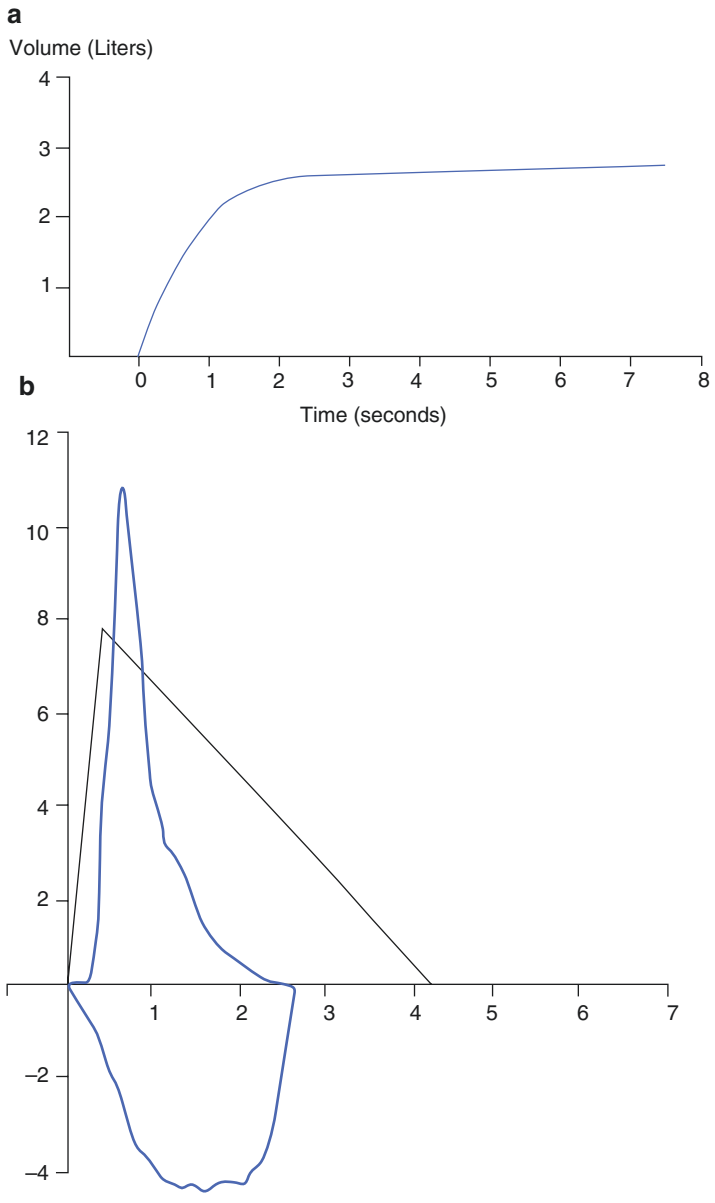

FIGURE 7.11 (**a**) VT curve; (**b**) FV loop

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.28	4.07	65	5.84
RV	2.01	1.24	62	1.88
RV/TLC	32	30		30

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	28.19	18.26	65	21.9
DL_{CO}/V_A	6.28	3.97	63	3.99

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 14)

- Spirometry is restrictive:
  - VT curve looks normal morphologically. There is no predicted curve to compare with.
  - FV loop:
    (a) Is small with a steep slope (witch's hat appearance). Its width (FVC) is clearly reduced.
    (b) PEF is increased suggesting a parenchymal restriction.
- Spirometric data:
  - Reduced FVC and FEV_1 with a normal FEV_1/FVC ratio suggesting a restrictive disease.
- Lung volumes:
  - Moderately reduced TLC and RV with a preserved RV/TLC ratio confirming moderately severe restriction.
- DL_{CO} is reduced also going with a parenchymal restriction.
- Conclusion: Moderately severe restrictive disorder most likely due to a parenchymal disease.

CASE 15

A 78-year-old male, Caucasian, weight 80 kg.

1. Spirometry (Figure 7.12)

	Pred.	Pre	% Pred.	LLN
FVC	4.06	2.46	61	2.86
FEV_1	3.07	1.33	43	2.05
FEV_1/FVC		54		60
$FEF_{25–75}$	2.70	0.44	16	0.81
PEF	7.54	4.88	65	4.13

2. Lung Volumes

	Pred.	Pre	% Pred.	LLN
TLC	6.67	5.00	75	6.06
RV	2.51	2.42	97	1.98
RV/TLC	38	48	127	36

3. Diffusing Capacity

	Pred.	Pre	% Pred.	LLN
DL_{CO}	23.52	10.82	46	16.4
DL_{CO}/V_A	3.80	2.64	69	2.5

Technician's Comments: Data acceptable and reproducible.
Q1: Interpret this PFT.

Interpretation (Case 15)

- Spirometry is obstructive:
  - VT curve looks flat. FET is 9 seconds.
  - FV loop:
    (a) The expiratory curve is small and scooped out, suggesting an obstructive disorder.
- Spirometric data:
  - Reduced FVC and FEV_1 with a reduced FEV_1/FVC ratio suggesting a severe obstructive disorder. $FEF_{25–75}$ is reduced going with an obstructive disorder.

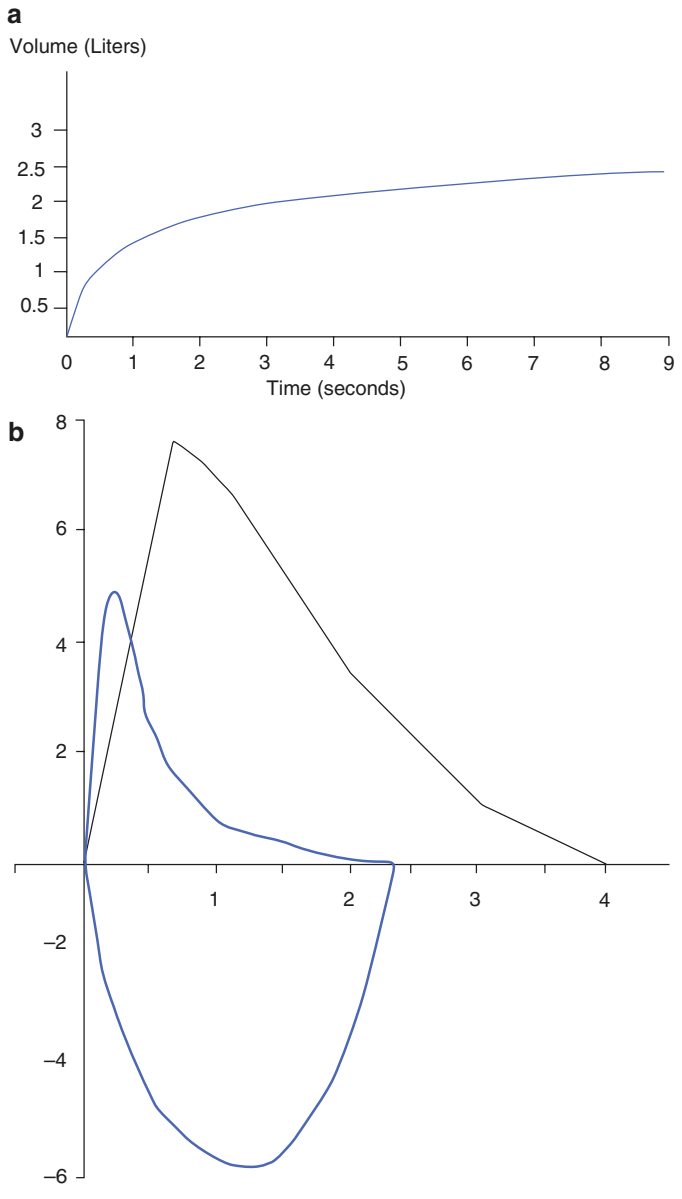

FIGURE 7.12 (**a**) VT curve; (**b**) FV loop

- Lung volume study is restrictive:
  - Mildly reduced TLC with a normal RV and increased RV/TLC ratio. The reduced TLC indicates a restrictive disorder.
- DL_{CO} is reduced which may be seen in restrictive or pulmonary vascular disorders.
- Conclusion: Severe obstructive disorder with a mild restriction. This patient has COPD (emphysema) and lung resection.

Chapter 8
Arterial Blood Gas (ABG) Interpretation

Ali Altalag, Jeremy Road, Pearce Wilcox and Kewan Aboulhosn

Abstract This chapter reviews the fundamentals in acid-base interpretation and the differential diagnosis for each acid-base pattern. We also discuss oxygen transfer physiology and pathophysiology with a final case based illustration of the topic.

Keywords Arterial blood gas (ABG) · Alkalosis · Acidosis · A-a gradient · Hypoxemia · Hypercapnea

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INTRODUCTION

- If you are given this ABG: pH (7.38); $PaCO_2$ (41 mmHg); PaO_2 (95 mmHg); HCO_3 (23 mmol/L); Na^+ (143 mg/dl); Cl^- (98 mg/dl), how would you interpret it?
- These values are all normal but the patient has significant acid base disturbances that may be fatal, if untreated. This chapter tries to introduce a simple approach to help solving any acid-base problem including the hidden ones, such as the one given above.
- The above ABG is discussed in case number 4, below.

DEFINITIONS [1]

- *Acidosis*: is a disturbance that lowers the extra-cellular fluid pH.
- *Alkalosis*: is a disturbance that raises the extra-cellular fluid pH.
- *Acidemia*: is a reduction of the extra-cellular fluid pH of the blood. Accordingly an acidemia may result from a combination of different types of acidosis or a combination of acidosis and alkalosis.
- *Alkalemia*: is an elevation of the extra-cellular fluid pH of the blood.
- *Base Excess (BE)*: is the amount of acid (+) or base (−) (in mEq/liter) required to restore the pH of a liter of blood to the normal range at a $PaCO_2$ of 40 mmHg. Table 8.1 shows the normal values of the ABG components.

Table 8.1 ABG normal values

pH	7.35–7.45
$PaCO_2$	35–45 mmHg
PaO_2	>80 mmHg
HCO_3	21–26 mmol/L (average: ~24)
BE	0 to −2 mmol/L
SaO_2	>95%
Anion Gap (AG)	10 ± 4 (average: ~12)
$P_{(A\text{-}a)}O_2$	<15

To convert from KPa (Kilo-Pascal) to mmHg, multiply by 7.5

HENDERSON EQUATION [2]

- This equation represents the relationship between the components of the ABG and may be written in different ways:
  - A simple way is:

$$\left[H^+\right] = K \times \frac{\left[H_2CO_3\right]}{\left[HCO_3\right]}, \quad \text{where} \quad K = 24$$

  - By substituting $PaCO_2$ for $[H_2CO_3]$ that is measured from ABG, the equation can be written in a more practical way [2]:

$$\left[H^+\right] = K \times \frac{PaCO_2}{\left[HCO_3\right]}, \quad \text{where} \quad K = 24$$

  - $[H^+]$ is the Hydrogen ion (proton) concentration, and it can be easily calculated from pH, see Table 8.2.
  - The rest of the variables can be acquired directly from the ABG.
- The purpose of this equation is:
  - To ensure that the ABG values are accurately recorded. Solving the equation should result in equalization of its two sides.
  - If one of the ABG values is missing, the equation can be solved to determine that missing value. Indeed this is usually done for ABG results. The pH and $PaCO_2$ are actually measured in the blood sample and the HCO_3 is calculated using this equation.

    e.g.: pH 7.3 ($[H^+] = 50$); $PaCO_2$ = 50 mmHg; HCO_3 = unknown

  - By applying Henderson equation:

$$[H^+] = K \times (P_aCO_2/[HCO_3])$$

$$50 = 24 \times (50/[HCO_3])$$

Therefore: $[HCO_3] = 24$.

Table 8.2 Calculating [H+] from pH [2]

When pH is within: (7.30–7.50)

pH of 7.40 ↔ [H+] = 40 nmol/L

Then increasing or decreasing pH by 0.01 is equivalent to decreasing or increasing [H+] by 1 nmol/L, respectively (remember that [H+] changes in the opposite direction of pH; for instance: Acidosis decreases pH but increases [H+])

So if pH is 7.35, then [H+] will equal 40 + 5 = 45 nmol/L

When pH is outside the range 7.3–7.5, the following applies (Note, this technique can be applied when pH is within the above range too):

pH of 7.00 ↔ [H+] = 100 nmol/L

Then every increase or decrease of pH by 0.10 is equivalent to multiplying or dividing [H+] by 0.8

So if pH is 7.10, then [H+] will equal 100 × 0.8 = 80 nmol/L

If pH is 7.20, then [H+] will equal 100 × 0.8 × 0.8 = 64 nmol/L

If pH is 7.40, then [H+] = 100 × 0.8^4 = 40

If pH is 6.80, then [H+] = 100 / (0.8 × 0.8) = 156

If you don't want to bother yourself with these calculations, the following table can be of help:

pH	[H+]	pH	[H+]
7.00	100	7.35	45
7.05	89	7.40	40
7.10	79	7.45	35
7.15	71	7.50	32
7.20	63	7.55	28
7.25	56	7.60	25
7.30	50	7.65	22

METABOLIC ACIDOSIS

Causes

Metabolic acidosis can be classified into anion gap (AG) and non-anion gap (NAG) metabolic acidosis [3, 4]. The NAG metabolic acidosis is also called *hyperchloremic metabolic acidosis*, because it is associated with high serum chloride. Table 8.3 summarizes these causes.

TABLE 8.3 Causes of metabolic acidosis

Anion gap metabolic acidosis
Uremia
Ketoacidosis
Diabetes
Alcohol-induced
Starvation
Lactic acidosis
Toxin ingestion
Salicylates
Methanol
Ethylene glycol
Paraldehyde
Non-anion gap (hyperchloremic) metabolic acidosis
GI loss of HCO_3
Diarrhea
Ileostomy or colostomy
Uretero-segmoid fistula
Pancreatic fistula
Renal loss of HCO_3
Renal tubular acidosis
Proximal (type II)
Distal (types I and IV)
Carbonic anhydrase inhibitors / deficiency
Hypoaldosteronism, aldosterone inhibitors
Hyperkalemia
Renal tubular disease
Acute tubular necrosis (ATN)
Chronic tubulointerstitial disease
Iatrogenic
Ammonium chloride (NH4Cl)
Hydrochloric acid (HCl) therapy
Hyperalimentation (with TPN lacking citrate buffer)
Dilutional acidosis (caused by excessive isotonic saline infusion)

Approach to Metabolic Acidosis

- In both types of metabolic acidosis, the primary disturbance is a drop in bicarbonate. Because the respiratory system is fast in its compensation, there is a rapid drop in $PaCO_2$

Table 8.4 Approach to ABG interpretation

Determine whether the ABG data are accurate by quickly applying Henderson equation
Look at the pH and determine whether it is normal, acidemic or alkalemic
Determine the most likely primary disturbance (by looking at HCO_3 and $PaCO_2$ and determining which one is largely responsible)
If the primary disturbance is respiratory, determine whether it is acute or chronic
If the primary disturbance is metabolic, determine whether an appropriate respiratory compensation is present
Calculate the AG
Calculate the corrected HCO_3, if applicable

which should always accompany a pure metabolic acidosis (remember that $PaCO_2$ changes in the same direction as HCO_3 in a pure metabolic disturbance). Don't forget that normal bicarbonate doesn't exclude a metabolic disturbance as metabolic acidosis may coexist with metabolic alkalosis.

- We suggest using one of the many available protocols in interpreting the ABG. Table 8.4 summarizes a usefull one.
- The first step is to determine the type of disturbance (acidemia or alkalemia) by looking at the pH.
- Then determine the most likely primary disturbance. So, if a reduction in HCO_3 is the predominant abnormality in the setting of acidemia, then the primary disturbance is a metabolic acidosis.
- Determine the type of metabolic acidosis you are dealing with (AG or NAG) by calculating the AG [5]:

$$\mathbf{AG = Na^+ - (Cl^- + HCO_3^-)}$$

  - If normal (≤12), then this is a non-anion gap metabolic acidosis (NAGMA). Go to the next step.
  - If high (>12), then this is an anion gap metabolic acidosis (AGMA). In AGMA, you need to determine then whether another metabolic disturbance is present, by calculating the corrected HCO_3:

Corrected HCO_3 = ΔG + measured HCO_3; as **ΔG = AG−12**

(a) If the corrected HCO_3 is *within* the normal range of HCO_3 (21–26), then there is no other metabolic disturbance, so go to the next step.
(b) If the corrected HCO_3 is *higher* than the normal range, then there is an additional metabolic alkalosis (corrected HCO_3 is higher than it should)
(c) If the corrected HCO_3 is *lower* than the range, then there is an additional NAG metabolic acidosis (NAGMA)

- Determine whether there is a primary respiratory disturbance by initially looking at the $PaCO_2$
  - If $PaCO_2$ is normal or high (opposite direction to HCO_3), then there is a primary respiratory acidosis. Go to the next step.
  - If $PaCO_2$ is low (same direction as HCO_3), then calculate the expected $PaCO_2$ range [4, 6]:

$$\textbf{Expected } PaCO_2 \textbf{ Range} = 1.5 \times HCO_3 + (8 \pm 2)$$

(a) If the patient's $PaCO_2$ is *within* this range, then the patient has no respiratory disturbance (this is an appropriate compensation)
(b) If patient's $PaCO_2$ is *above* the range, then there is a primary respiratory acidosis (inadequate compensation).
(c) If patient's $PaCO_2$ is *below* the range, then there is a primary respiratory alkalosis (overcompensation). The lowest level $PaCO_2$ can reach as a compensation for metabolic acidosis is 10–12 mmHg [7].

- In non-anion gap metabolic acidosis, determine whether the cause is of renal or non-renal origin by calculating the urine anion gap (also called Urine Net Charge or UNC) [8]:

$$\textbf{Urine Gap} = (U_{Na} + U_K) - U_{Cl}$$

  - If urine gap is *negative*, then the kidney is appropriately compensating by secreting H^+ in the form of ammonia (NH_4^+) which neutralizes this negative urine anion gap. An extra-renal cause of metabolic acidosis is the most likely.
  - If urine gap is *positive (or zero)*, then the kidneys are not secreting H^+ appropriately, indicating a renal cause of the metabolic acidosis (Renal tubular acidosis, RTA).
- These steps are summarized in Table 8.5.

Table 8.5 Approach to metabolic acidosis

Quickly apply the Henderson equation
Look at the pH (normal, acidemia or alkalemia).
If the reduction in HCO_3 is the predominant abnormality → primary metabolic acidosis
Calculate the AG (AG = $Na^+ - (Cl^- + HCO_3)$)
  If normal (~ 12) → non-anion gap metabolic acidosis (NAGMA)
  If high (>12) → anion gap metabolic acidosis (AGMA). Calculate the corrected HCO_3, (corrected HCO_3 = ΔG + measured HCO_3; as ΔG = AG − 12):
    – If within normal range of HOC_3 (21–26) → no other metabolic disturbance
    – If >26 → primary metabolic alkalosis
    – If <21 → primary non-anion gap metabolic acidosis
Look at $PaCO_2$:
  If normal or high → primary respiratory acidosis. If in doubt, calculate expected $PaCO_2$ range
  If low → calculate the (expected $PaCO_2$ range) which equals $1.5 \times HCO_3 + (8 \pm 2)$
    – If the patient's $PaCO_2$ is within this range → no respiratory disturbance
    – If patient's $PaCO_2$ is above the range → primary respiratory acidosis
    – If patient's $PaCO_2$ is below the range → primary respiratory alkalosis
In NAGMA, calculate urine anion gap (Urine Gap = $(U_{Na} + U_K) - U_{Cl}$):
  If negative → extra-renal cause of metabolic acidosis
  If positive → a renal cause of the metabolic acidosis (RTA)

METABOLIC ALKALOSIS

Causes

- Are classified into *Cl^- responsive* and *Cl^- resistant alkaloses*, which are summarized in Table 8.6.

Approach to Metabolic Alkalosis

- Opposite to metabolic acidosis, metabolic alkalosis presents as a high HCO_3 which is compensated for by an increase in $PaCO_2$ [9, 10] (which rarely exceeds a level of 60 mmHg [7]). A normal or a low $PaCO_2$ indicates a respiratory alkalosis, in this setting.

TABLE 8.6 Causes of metabolic alkalosis

Cl responsive:
GI loss of H^+
Vomiting, nasogastric suctioning
Cl^- rich diarrhea
Villous adenoma
Renal loss of H^+
Diuretics
Hypovolemia
Post-hypercapnia
High-dose carbenicillin
Cl resistant:
Renal loss of H^+
Primary hyperaldosteronism
Increased corticosteroid activity
Primary hypercortisolism
Adrenocorticotropic hormone (ACTH) excess
Drug-induced
Licorice ingestion
Hypokalemia
Increased rinin activity (e.g. renin-secreting tumor)
Iatrogenic
Excessive $NaHCO_3$ infusion
Excessive citrate infusion (massive blood transfusion)
Excessive acetate infusion (hyperalimentation with acetate-containing TPN)
Excessive lactate infusion (Ringer's Lactate)
Milk–alkali syndrome

- Determine the type of disturbance (acidemia or alkalemia) by looking at the pH.
- Then determine the most likely primary disturbance. So if the increase in HCO_3 is the predominant abnormality rather than a decrease in $PaCO_2$, then the primary disturbance is metabolic alkalosis.
- Determine whether a primary metabolic acidosis is present as well by calculating AG:
  - If *normal* (~12), then there is no primary metabolic acidosis. Go to next step.
  - If *high* (>12), then there is an addition primary anion gap metabolic acidosis (AGMA).
- Determine whether there is a primary respiratory disturbance by initially looking at the $PaCO_2$

- If $PaCO_2$ is *normal* or low (opposite direction to HCO_3), then there is a primary respiratory alkalosis. Go to next step.
- If $PaCO_2$ is *high* (same direction as HCO_3), calculate the expected $PaCO_2$ range [11–13]:

$$\textbf{Expected } PaCO_2 \textbf{ Range} = 0.9 \times HCO_3 + (9 \text{ to } 16)$$

(a) If the patient's $PaCO_2$ is *within* this range, then the patient has no additional respiratory disturbance (this is an appropriate compensation).
(b) If patient's $PaCO_2$ is *above* the range, then there is a primary respiratory acidosis (overcompensation).
(c) If patient's $PaCO_2$ is *below* the range, then there is a primary respiratory alkalosis (inadequate compensation).

- Determine the type of metabolic alkalosis (Cl^- responsive or Cl^- resistant) by measuring the urinary Cl^- (U_{Cl}) [1]:
  - If U_{Cl} is <20 mmol/L, then this is Cl^- responsive (depleted) metabolic alkalosis. Think of it as the body is trying to conserve Cl^-.
  - If U_{Cl} is >20 mmol/L, then this is Cl^- resistant (expanded) metabolic alkalosis.
- Table 8.7 summarizes these steps.

Table 8.7 Approach to metabolic alkalosis

Quickly apply the Henderson equation
Look at the pH (normal, acidemia or alkalemia)
The increase in HCO_3 is the predominant abnormality → primary metabolic alkalosis
Calculate the AG ($AG = Na^+ - (Cl^- + HCO_3)$)
If normal (~12) → no primary metabolic acidosis
If high (>12) → primary anion gap metabolic acidosis (AGMA)
Look at $PaCO_2$:
If normal or low → primary respiratory alkalosis. If in doubt, calculate expected $PaCO_2$ range
If high → calculate the (expected $PaCO_2$ range = $0.9 \times HCO_3 + (9$ to $16)$):
– If patient's $PaCO_2$ is within this range → no respiratory disturbance
– If patient's $PaCO_2$ is above the range → primary respiratory acidosis
– If patient's $PaCO_2$ is below the range → primary respiratory alkalosis
Check the urinary Cl^- (U_{Cl}):
If <20 mmol/L → Cl^- responsive metabolic alkalosis
If >20 mmol/L → Cl^- resistant metabolic alkalosis

RESPIRATORY ACIDOSIS

Types of Respiratory Acidosis

- Because the body compensates slowly for a primary respiratory disturbance, the later is then classified into acute and chronic forms. The following will highlight these forms.
- In acute respiratory acidosis, for every 10 mmHg rise in $PaCO_2$ [14]:
  - pH drops by 0.08; that is:

$$\text{pH} = 0.08 \times \frac{\text{PaCO}_2 - 40}{10}$$

  - HCO_3 increases by 1 mmol/L; maximum level of HCO_3 is ~32 mmol/L.
- In chronic respiratory acidosis, for every 10 mmHg rise in $PaCO_2$ [15]:
  - pH drops by 0.03; that is:

$$\text{pH} = 0.03 \times \frac{\text{PaCO}_2 - 40}{10}$$

  - HCO_3 increases by 3 mmol/L; maximum level of HCO_3 is ~45 mmol/L.
- Tables 8.8 and 8.9 summarize the causes and steps of interpretation of respiratory acidosis, respectively.

Table 8.8 Causes of respiratory acidosis

Obstructive disorders
Upper airway obstruction
Foreign body
Laryngospasm
Obstructed endotracheal tube
Obstructive sleep apnea
Lower airway obstruction
Severe bronchospasm due to bronchial asthma or COPD
Restrictive disorders (see Table 1.7)
ILD
Chest wall restriction
Loss of air spaces (pleural effusion, pneumothorax)
Pleural disease

(continued)

TABLE 8.8 (continued)

Hypoventilation
Central (e.g. secondary to sedative and narcotic drugs)
Obesity-hypoventilation syndrome
Neuromuscular disease (Table 5.1)
Parenchymal lung disease (like ARDS)
Increased CO_2 production
Fever, shivering
Hypermetabolism,
High carbohydrate diet
Others
Inappropriate ventilator settings
Compensatory

TABLE 8.9 Approach to respiratory acidosis

Quickly apply the Henderson equation.
Look at the pH (normal, acidemia or alkalemia)
The increase in $PaCO_2$ is the predominant abnormality → primary respiratory acidosis
Determine whether acute or chronic
Acute: pH ↓ by 0.08 for every 10 mmHg ↑ in $PaCO_2$. HCO_3 ↑ by 1 mmol/L (max ~32)
Chronic: pH ↓ by 0.03 for every 10 mmHg ↑ in $PaCO_2$. HCO_3 ↑ by 3 mmol/L (max ~45)
Calculate the AG ($AG = Na^+ - (Cl^- + HCO_3)$)
If high (>12) → primary anion gap metabolic acidosis (AGMA)
If applicable, calculate the corrected HCO_3, as in metabolic acidosis
If normal (~ 12) → look at HCO_3
If ↓ or N → primary non-anion gap metabolic acidosis
If ↑ → look at HCO_3 and determine the type of respiratory acidosis: (HCO_3 ↑ by 1 (acute) OR 3 (chronic) for each 10 mmol/L ↑ in $PaCO_2$)
If within the expected → no primary metabolic disturbance
If lower → non-anion gap metabolic acidosis
If higher → metabolic alkalosis

RESPIRATORY ALKALOSIS

Types of Respiratory Alkalosis

- In acute respiratory alkalosis, for every 10 mmHg drop in $PaCO_2$ [16]:
  - pH rises by 0.08; that is:

$$pH = 0.08 \times \frac{40 - PaCO_2}{10}$$

  - HCO_3 drops by 2 mmol/L.
- In chronic respiratory alkalosis, for every 10 mmHg drop in $PaCO_2$ [17, 18]:
  - pH increases by 0.03; that is:

$$pH = 0.03 \times \frac{40 - PaCO_2}{10}$$

  - HCO_3 drops by 5–7 mmol/L.
- Tables 8.10 and 8.11 summarize the causes and steps of interpretation of respiratory alkalosis, respectively.

TABLE 8.10 Causes of respiratory alkalosis

Increased hypoxemic drive
Right-to-left shunt
High altitude
Pulmonary disease
Pulmonary embolism (leading to dyspnea then hyperventilation)
Pulmonary interstitial edema (leading to dyspnea then hyperventilation)
Stimulation of respiratory center
Anxiety, pain, psychogenic
Liver failure with encephalopathy
Fever, Sepsis, infection
Respiratory stimulants (e.g. salicylates, progesterone)
Pregnancy
Others
Inappropriate ventilator settings
Compensatory

Table 8.11 Approach to respiratory alkalosis

Quickly apply the Henderson equation
Look at the pH (normal, acidemia or alkalemia)
The drop in $PaCO_2$ is the predominant abnormality → primary respiratory alkalosis
Determine whether acute or chronic
Acute: pH ↑ by 0.08 (and HCO_3 ↓ by 2 mmol/L) for every 10 mmHg ↓ in $PaCO_2$
Chronic: pH ↑ by 0.03 (and HCO_3 ↓ by 5–7 mmol/L) for every 10 mmHg ↓ in $PaCO_2$
Calculate the AG (AG = $Na^+ - (Cl^- + HCO_3)$)
If high (>12) → primary anion gap metabolic acidosis (AGMA)
If applicable, calculate the corrected HCO_3, as in metabolic acidosis
If normal (~ 12) → look at HCO_3
If ↑ or N → primary metabolic alkalosis
If ↓ → look at HCO_3 and determine the type of respiratory alkalosis (HCO_3 ↓ by 2 (acute) OR 5–7 (chronic) for each 10 mmol/L ↓ in $PaCO_2$)
If within the expected → no primary metabolic disturbance
If lower → non-anion gap metabolic acidosis
If higher → metabolic alkalosis

EFFECT OF A LOW ALBUMIN LEVEL ON AG

- Because albumin is one of the unmeasured anions in the blood, a drop in its level (e.g. secondary to a critical illness or liver disease) will influence the AG level. In this case, the calculated AG should be adjusted for albumin:

Adjusted AG = Calculated AG + [2.5 × (4.5 – alb in g/dl)]

- If this adjustment is ignored with a low albumin, the calculated anion gap will be underestimated and a significant AGMA may be missed.

ACID BASE NOMOGRAM

- The nomogram shown in Figure 8.1 is one of many acid-base nomograms developed to assisst in solving difficult acid base disturbances and involves plotting pH, HCO_3 and $PaCO_2$ [19]. These are commonly referred to as Flenley's acid base nomograms.

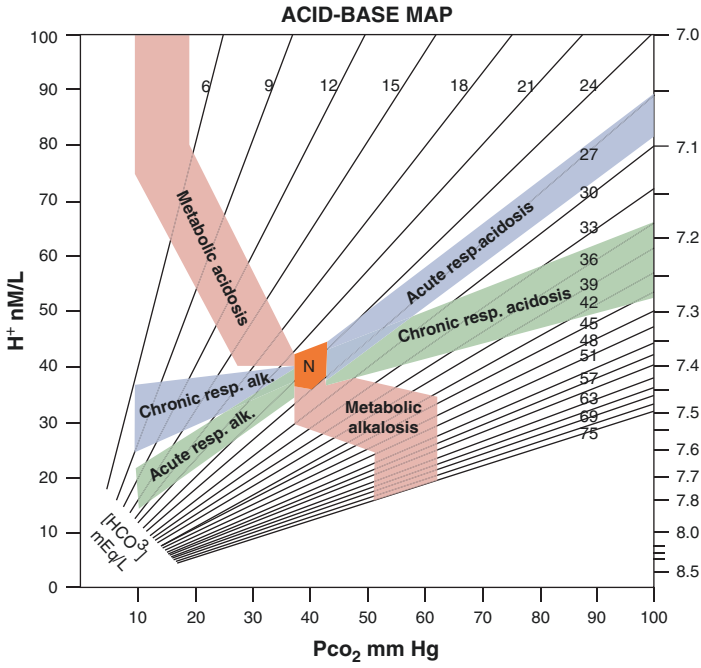

FIGURE 8.1 An acid–base nomogram, used to interpret ABG by directly plotting HCO_3, $PaCO_2$, and pH (With permission from Goldberg et al. [20])

THE ALVEOLAR—ARTERIAL (A-a) GRADIENT AND ALVEOLAR GAS EQUATION [21]

Alveolar Gas Equation

- This equation allows us to estimate the O_2 tension in the alveoli (P_AO_2):

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{RQ}; \quad \text{where} \quad P_IO_2 = F_IO_2\left(P_{atm} - P_{H_2O}\right)$$

- To understand this equation it is good to go through certain definitions:
  - ***$P_{atm}O_2$***: is the atmospheric O_2 tension or partial pressure of O_2. It is calculated by multiplying the atmospheric pres-

sure (760 mmHg at sea level) by the percentage of O_2 in the atmosphere (21%):

$$P_{atm}O_2 = 0.21 \times P_{atm} = 0.21 \times 760 = 160 \text{ mmHg, } \textit{(at sea level)}$$

– ***P_IO_2***: is the O_2 tension of inspired air. Because the inspired air contains water vapor, it doesn't equal $P_{atm}O_2$. The water vapor tension (P_{H2O}) should then be extracted from the atmospheric pressure before applying the above equation:

$$P_IO_2 = F_IO_2 \times (P_{atm} - P_{H2O}) = 0.21 \times (760 - 47) = 0.21 \times 713 = 150 \text{ mmHg}$$

(if breathing room air, at sea level)

– ***P_AO_2***: the alveolar O_2 tension. CO_2 diffuses from the circulation into the alveoli and hence reduces the P_AO_2. Accordingly, P_ACO_2 has to be subtracted from P_IO_2 to get P_AO_2. P_aCO_2 can be substituted for P_ACO_2 (when taking the Respiratory Quotient (RQ) into consideration, which is assumed to be 0.8 while at rest):

$$P_AO_2 = P_IO_2 - \frac{P_aCO_2}{RQ}; \quad \text{as} \quad RQ = 0.8$$

$$= 150 - \frac{P_aCO_2}{0.8} \quad \text{OR} \quad 150 - \left(P_aCO_2 \times 1.25\right)$$

$$= 150 - (40 \times 1.25) = 100 \text{ mmHg}$$

(if breathing room air, at see level)

– ***PaO_2***: is the arterial O_2 tension that is measured in the ABG.

– ***F_IO_2***: is the *Fractional Inspired O_2*, i.e. the percentage of O_2 in the inspired air. If breathing room air at sea level, it equals 0.21. This value changes if the patient is breathing through a nasal cannula or a face mask.

– ***RQ***: is the *Respiratory Quotient* and represents the amount of CO_2 produced for a given amount of O_2 consumed by our bodies. It equals 0.8 at rest, in a normal individual (because we produce 0.8 mole of CO_2 for each mole of O_2 we consume while at rest). The RQ increases with exercise however. Next chapter discusses this in more detail.

A-a Gradient ($P_{(A-a)}O_2$)

- It is the difference between the alveolar and the arterial O_2 tension. Its calculation is now easy; see Figure 8.2:

$$P_{(A-a)}O_2 = P_AO_2 - P_aO_2; \quad \text{where} \quad P_AO_2 = P_IO_2 - \frac{P_aCO_2}{RQ}$$

$$\text{OR} \quad P_{(A-a)}O_2 = \left[P_IO_2 - \frac{P_aCO_2}{RQ}\right] - P_aO_2$$

- If at see level and breathing room air (F_IO_2 of 0.21), then the equation can be simply written as follows:

$$P_{(A-a)}O_2 = \left[150 - \frac{P_aCO_2}{0.8}\right] - P_aO_2$$

$$\text{OR} \quad P_{(A-a)}O_2 = [150 - (1.25 \times P_aCO_2)] - P_aO_2$$

- $P_{(A-a)}O_2$ is normally ≤15 mmHg and increases with age. Different formulas are used to determine the normal $P_{(A-a)}O_2$ in relation to age, the following is a popular one [20]:

$$\text{Normal } P_{(A-a)}O_2 = 2.5 + (0.21 \times \text{age in years})$$

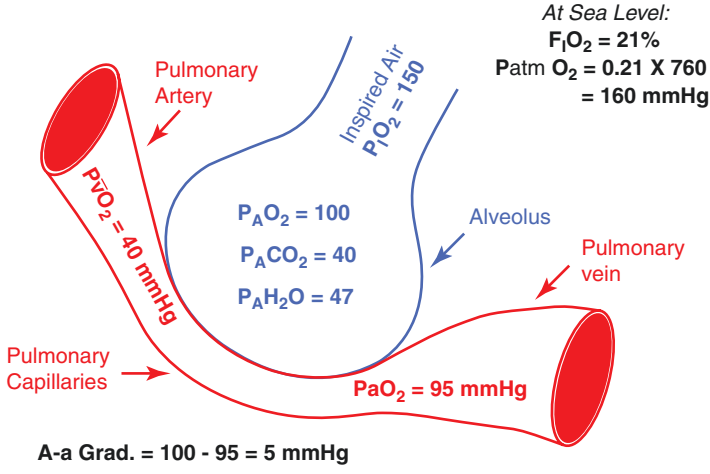

FIGURE 8.2 This diagram summarizes the alveolar gas principles. Breathing RA at sea level in a normal person

MECHANISMS OF HYPOXEMIA [21]

These mechanisms can be classified into hypoxemia with a wide A-a gradient and hypoxemia with a normal A-a gradient:

- Hypoxemia with a wide A-a gradient ($P_{(A-a)}O_2 > 15$)
  - Shunting, like intra-cardiac shunts or pulmonary AV malformation.
  - VQ mismatch, as in atelectasis
  - Decreased mixed venous O_2 tension $\left(P\bar{v}O_2\right)$.
  - Diffusion limitation (reduced gas tranfer) (seen in severe ILD).
- Hypoxemia with a normal A-a gradient ($P_{(A-a)}O_2 \leq 15$)
  - Low inspired O_2 ($\downarrow F_IO_2$), as in case of high altitude.
  - Hypoventilation, as in *obesity hypoventilation syndrome*.
    (a) Hypoventilation causes primarily hypercapnia because of impaired washout of CO_2. As the alveolar CO_2 equals the arterial CO_2, both PaCO2 and P_ACO_2 will be equally elevated.
    (b) Hypoventilation causes hypoxemia, as well, if the patient is breathing room air. In this case, the degree of hypoxemia can be predicted from the level of $PaCO_2$ using the alveolar gas equation. In general, if P_aCO_2 increases by 20 mmHg, P_AO_2 drops by 25 mmHg, even if the lungs are normal; Figure 8.3.

TYPES OF RESPIRATORY FAILURE [21]

- *Type I respiratory failure* (hypoxemic respiratory failure) is characterized by hypoxia and defined as an isolated reduction of PaO_2 to <60 mmHg (the point at which the SaO_2 drops steeply as shown in the O_2 dissociation curve); Figure 8.4. This type of respiratory failure is associated with an increased A-a gradient.
- *Type II respiratory failure* (ventilatory failure) is characterized by hypoxia and hypercapnia and defined as a $PaCO_2$ of >50 mmHg. The A-a gradient is normal.

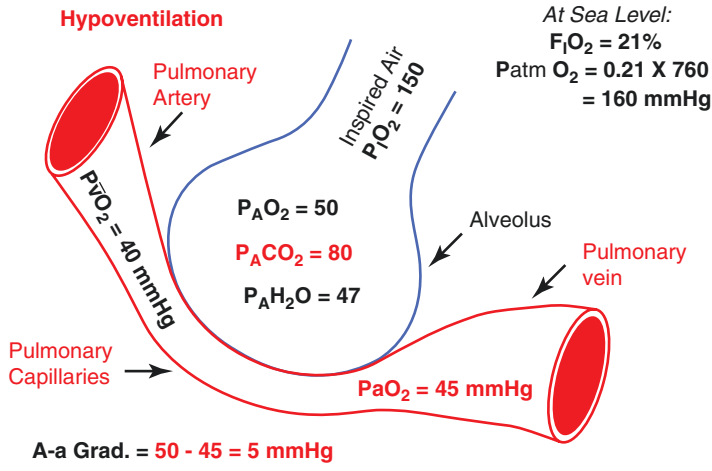

FIGURE 8.3 Effects of hypoventilation on alveolar and arterial O_2 and CO_2 tension: This patient is breathing room air at sea level and has a normal A – a gradient but still has a severe hypoxemia (P_aO_2 of 45). The reason for this hypoxemia is the elevated P_ACO_2 (secondary to hypoventilation). The P_ACO_2 has increased by 40 mmHg resulting in a reduction in P_AO_2 by 50 mmHg, which resulted in this degree of hypoxemia: $P_AO_2 = 150 - (1.25 \times 80) = 150–100 = 50$ mmHg

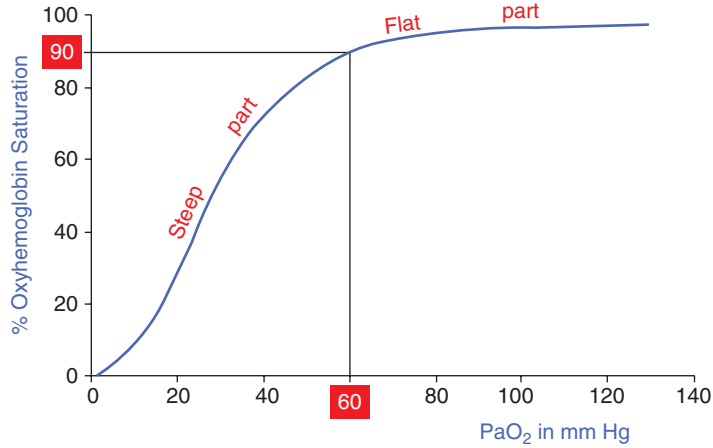

FIGURE 8.4 O_2 dissociation curve: when $P_aO_2 > 60$ mmHg, SaO_2 changes slightly with any given change in P_aO_2. When $P_aO_2 < 60$ mmHg, SaO_2 changes significantly with any given change in P_aO_2

ILLUSTRATIVE CASES

Case 1

- *A 63-year-old man presents with generalized malaise. His ABG shows: pH (7.32); $PaCO_2$ (24); HCO_3 (12); Na^+ (135); K^- (5.4); Cl^- (101). What type of acid base disturbance does this patient have?*
- Interpretation:
  - Applying the Henderson equation:

    $$[H^+] = K \times (PaCO_2 / [HCO_3]) \leftrightarrow 48 = 24 \times (24/12) = 48$$

  - So, the equation proves that the values are accurate.
  - pH is ↓, so this is an acidemia.
  - The predominant abnormality is the ↓ HCO_3 → so this is primary metabolic acidosis.
  - By calculating the AG = $Na^+ - (Cl^- + HCO_3)$ = 22 (↑). It is >12 → so this is an ***anion gap metabolic acidosis*** (AGMA).
  - Corrected HCO_3 = ΔG + measured HCO_3 (as ΔG = AG – 12 = 10).
    = 10 + 12 = 22; it is within the normal range of HCO_3 (21–26), so there is no other metabolic disturbance.
  - $PaCO_2$: is low, so we should calculate the expected $PaCO_2$ range:
  - Expected $PaCO_2$ Range = 1.5 × HCO_3 + (8 ± 2)= 24–28; the patient's $PaCO_2$ lies within this range, so there is no primary respiratory disturbance.
  - Conclusion: This patient has a pure anion gap metabolic acidosis. This patient was found to have a creatinine of 500 mg/dl and so the unmeasured anions producing the gap were related to renal failure.

Case 2

- *Interpret the following ABG: pH (7.11); $PaCO_2$ (16); HCO_3 (5); Na^+ (133); Cl^- (118).*
- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - ↓ pH → so this is an acidemia.
  - ↓ HCO_3 → so this is a primary metabolic acidosis.

  - AG = $Na^+ - (Cl^- + HCO_3) = 10$ (normal) → so this is a ***non-anion gap metabolic acidosis*** (NAGMA).
  - Expected $PaCO_2$ Range = $1.5 \times HCO_3 + (8 \pm 2) = 13.5–17.5$ → the patient's $PaCO_2$ lies within this range, so there is no primary respiratory disturbance.
  - Conclusion: the patient has a simple non-anion gap metabolic acidosis. This patient is a 74-year-old very anxious lady who presented with severe gastroenteritis (diarrhea).

Case 3

- *Interpret the following ABG: pH (6.88); $PaCO_2$ (40); HCO_3 (7); Na^+ (135); Cl^- (118).*
- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - ↓ pH → so this is acidemia.
  - ↓ HCO_3 → so this is primary metabolic acidosis.
  - AG = $Na^+ - (Cl^- + HCO_3) = 10$ (normal) → so this is a ***non-anion gap metabolic acidosis*** (NAGMA).
  - $PaCO_2$ is normal (it should be low in the face of a very low pH) → so, there is a ***primary respiratory acidosis***. Although unnecessary, you can still apply the Expected $PaCO_2$ Range = $1.5 \times HCO_3 + (8 \pm 2) = 16.5–20.5$ → the patient's $PaCO_2$ is higher than this range so there is primary respiratory acidosis.
  - Conclusion: A combined non-anion gap metabolic acidosis and respiratory acidosis. This is the same patient described in case 2 after she was sedated with a benzodiazepine that suppressed her respiratory centre. Sedation can be harmful in elderly patients.

Case 4

- *A 23-year-old man presented with generalized malaise and vomiting. His ABG showed: pH (7.38); $PaCO_2$ (41);PaO_2 (95); HCO_3 (23); Na^+ (143); Cl^- (98). What type of acid base disturbance this patient has?*
- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - Normal pH → so no acidemia or alkalemia.
  - Normal HCO_3 → so no obvious metabolic abnormality.

- AG = $Na^+ - (Cl^- + HCO_3)$ = 22 (↑) → so there is an ***anion gap metabolic acidosis***.
- Corrected HCO_3 = ΔG + measured HCO_3 (ΔG = 22–12 = 10). = 10 + 23 = 33; So, the corrected HCO_3 = 33 → it is higher the normal range of HCO_3 (21–26) → so there is an additional ***metabolic alkalosis***.
- $PaCO_2$ is normal (so does the pH and HCO_3, so this is appropriate. If in doubt, apply expected $PaCO_2$ range).
- Expected $PaCO_2$ Range = 1.5 × HCO_3 + (8 ± 2) = 41–45 → the patient's $PaCO_2$ (41) lies within this range → so, there is no primary respiratory disturbance.
- Conclusion: Although this ABG looked normal, a combined disturbance is present, anion gap metabolic acidosis and metabolic alkalosis. This patient was found to have a blood sugar of 28 mmol/L and he had ketones in the urine. He had diabetic ketoacidosis causing his AGMA and vomiting caused his metabolic alkalosis.

Case 5

- *Interpret this ABG: pH (7.55); $PaCO_2$ (49); HCO_3 (42); Na^+ (148); Cl^- (84).*
- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - ↑ pH → so there is an alkalemia.
  - ↑ HCO_3 → so there is a ***metabolic alkalosis***.
  - AG = $Na^+ - (Cl^- + HCO_3)$ = 22 (↑) → so there is an ***anion gap metabolic acidosis***.
  - ↑ $PaCO_2$ (same direction as HCO_3) → Expected $PaCO_2$ Range = 0.9 × HCO_3 + (9-to-16) = 47–54 → the patient's $PaCO_2$ (49) lies within this range → so, there is no primary respiratory disturbance.
  - Conclusion: a combined anion gap metabolic acidosis and metabolic alkalosis with an alkalemic pH.

Case 6

- *A 58-year-old man (heavy smoker) admitted to the ICU with sepsis. He is not intubated yet but has an NG tube. His ABG*

showed: pH (6.88); $PaCO_2$ (40); HCO_3 (7); Na^+ (142); Cl^- (100). What type of acid base disturbance does this patient have?

- Interpretation:
  - Applying the Henderson equation indicates accurate results.
  - ↓ pH → so this is an acidemia.
  - ↓ HCO_3 → so this is a ***primary metabolic acidosis***.
  - AG = $Na^+ - (Cl^- + HCO_3)$ = 35 (↑) → so this is an ***anion gap metabolic acidosis***.
  - Corrected HCO_3 = 30; it is higher than the normal range of HCO_3 (21–26), so there is an additional ***primary metabolic alkalosis***.
  - $PaCO_2$ is normal (it should be low) → there is a ***primary respiratory acidosis***.
  - Conclusion: A combined anion gap metabolic acidosis, metabolic alkalosis and respiratory acidosis. This patient's metabolic acidosis is most likely related to sepsis. His respiratory acidosis is likely due to respiratory failure (COPD) and the metabolic alkalosis due to gastric suction.

Case 7

- *Interpret the following ABG: pH (7.55); $PaCO_2$ (44); HCO_3 (45); Na^+ (144); Cl^- (112).*
- Interpretation:
  - Applying Henderson equation:

    $[H^+] = K \times (PaCO_2/[HCO_3]) \leftrightarrow 28 \neq 24 \times (44/45) = 21$

    So, the equation indicates that the values are incorrect. Repeat ABG sampling is advised or check with the lab to ensure accurate calculation of HCO_3 and recording of results.

Case 8

- *A 68-year-old man known to have COPD presented to the emergency department with increasing cough. His ABG showed: pH (7.34); $PaCO_2$ (60); PaO_2 (60); HCO_3 (31); AG (11). What is the*

acid base disturbance? What is the A-a gradient provided that the patient was on room air, at sea level?.

- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - pH is slightly low indicating a mild acidemia.
  - ↑ $PaCO_2$, so this is a ***primary respiratory acidosis***.
  - Metabolic compensation indicates a chronic respiratory acidosis: $PaCO_2$ increased by 20 mmHg which corresponds to a drop in pH by ~ 0.6 (0.3/10 mmHg of $PaCO_2$) and an increase in HCO_3 by ~ 6 (3/10 mmHg of $PaCO_2$).
  - AG is normal and HCO_3 is adequately increased, therefore no metabolic disturbances.
  - The A-a gradient = (150 – $PaCO_2$ × 1.25) – PaO_2 = 11 (normal)
  - Conclusion: Chronic primary respiratory acidosis related to COPD.

Case 9

- *The patient in case 8 became drowsy and unresponsive 4 hours after presentation. A repeated ABG showed: pH (7.15); $PaCO_2$ (96); PaO_2 (169) HCO_3 (33); AG (10)*.
- Interpretation:
  - Applying Henderson equation indicates accurate results.
  - ↓ pH → acidemia.
  - ↑ $PaCO_2$ → so this is ***primary respiratory acidosis***.
  - Metabolic compensation indicates an acute respiratory acidosis in addition to the chronic respiratory acidosis.
  - AG is normal and HCO_3 is adequately increased, therefore no metabolic disturbances.
  - Conclusion: Acute primary respiratory acidosis and a chronic respiratory acidosis. This COPD patient was given a high flow O_2 (indicated by the high PaO_2) unnecessarily resulting in CO_2 elevation (the pathophysiology behind this is multifactorial) and severe acute respiratory acidosis. The acute increase in $PaCO_2$ resulted in mental deterioration and unresponsiveness.

Case 10

- *The patient in the previous case was intubated and mechanically ventilated to protect his airways. A repeat ABG showed: pH (7.55); $PaCO_2$ (39); PaO_2 (198); HCO_3 (33); AG (10).*
- Interpretation:
  - Applying the Henderson equation indicates accurate results.
  - ↑ pH, therefore alkalemia.
  - The elevated HCO_3 indicates a metabolic alkalosis resulting from overcorrecting the chronic respiratory acidosis. The elevated HCO_3 was primarily a compensatory mechanism for the respiratory acidosis. The resulting metabolic alkalosis is sometimes called *"post-hypercapnic metabolic alkalosis"*. The ventilator should have been set to target a normal pH rather than a normal HCO_3.

REFERENCES

1. Bear RA, Dyck RF. Clinical approach to the diagnosis of acid-base disorders. Can Med Assoc J. 1979;120:173–82.
2. Kassirer J, Bleich H. Rapid estimation of plasma carbon dioxide tension from pH and total carbon dioxide content. N Engl J Med. 1965;272:1067.
3. Emmett M, Narins RG. Clinical use of the anion gap. Medicine (Baltimore). 1977;56:38–54.
4. Lennon E, Lemann JJ. Defense of hydrogen ion concentration in chronic metabolic acidosis. A new evaluation of an old approach. Ann Intern Med. 1966;65:265.
5. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. Medicine (Baltimore). 1980;59:161–87.
6. Albert MS, Dell RB, Winters RW. Quantitative displacement of acid-base equilibrium in metabolic acidosis. Ann Intern Med. 1967;66:312–22.
7. Dubose TD. Acid–base disorders. In: Brenner BM, editor. Brenner and Rector's The Kidney. 6th ed. Philadelphia, PA: WB Saunders; 2000. p. 925–97.
8. Batlle DC, Hizon M, Cohen E, Gutterman C, Gupta R. The use of the urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. N Engl J Med. 1988;318:594–9.
9. Oliva P. Severe alveolar hypoventilation in a patient with metabolic alkalosis. Am J Med. 1972;52:817.

10. Cuomo A, Lifshitz M, Brasch R, Al E. Marked hypercapnia secondary to severe metabolic alkalosis. Ann Intern Med. 1972;177:405.
11. Javaheri S, Kazemi H. Metabolic alkalosis and hypoventilation in humans. Am Rev Respir Dis. 1987;136:1011–6.
12. Fulop M. Hypercapnia in metabolic alkalosis. NY State J Med. 1976;76:19.
13. de Strihou VY, Frans A. The respiratory response to chronic metabolic alkalosis and acidosis in disease. Clin Sci Mol Med. 1973;45:439–48.
14. NCJ B, Cohen JJ, Schwartz WB. Carbon dioxide titration curve of normal man. Effect of increasing degrees of acute hypercapnia on acid-base equilibrium. N Engl J Med. 1965;272:6–12.
15. Schwartz WB, NCJ B, Cohen JJ. The response of extracellular hydrogen ion concentration to graded degrees of chronic hypercapnia: the physiologic limits of the defense of pH. J Clin Invest. 1965;44:291–301.
16. Arbus GS, Herbert LA, Levesque PR, Etsten BE, Schwartz WB. Characterization and clinical application of the "significance band" for acute respiratory alkalosis. N Engl J Med. 1969;280:117–23.
17. Gennari FJ, Goldstein MB, Schwartz WB. The nature of the renal adaptation to chronic hypocapnia. J Clin Invest. 1972;51:1722–30.
18. Weil JV. Ventilatory control at high altitude. In: Fishman AP, editor. Handbook of physiology. Section 3: the respiratory system. Bethesda, MD: American Physiological Society; 1986. p. 703–27.
19. Goldberg M, Green SB, Moss ML, et al. Computer-based instruction and diagnosis of acid-base disorders: a systematic approach. JAMA. 1973;223:266–75.
20. Mellemgaard K. The alveolar-arterial oxygen difference: its size and components in normal man. Acta Physiol Scand. 1966;67:10–20.
21. West JB. Respiratory physiology: the essentials. Philadelphia, PA: Lippincott Williams & Wilkins; 2012.

Chapter 9
Exercise Testing

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Abstract Exercise tests are often used to develop an accurate profile of an individual's functional exercise capacity. The results of exercise tests form the basis of exercise prescription and assist in identifying underlying physiological factors limiting exercise tolerance. Certain measures taken during exercise tests may be used to indicate disease severity and prognosis as well as to evaluate treatment responses in disease populations.

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Exercise tests are subdivided into laboratory and field tests as well as submaximal and maximal tests. This chapter will discuss the technical features and interpretation of the six minute walk test and cardiopulmonary exercise test.

Keywords Cardiopulmonary exercise testing · Exercise test interpretation · Walking tests

SIX MINUTE WALK TEST

- The Six Minute Walk Test (6MWT) is a self-paced submaximal field test of walking capacity that measures the distance in meters walked by the patient along a flat corridor in 6 minutes [1].
- The 6MWT is similar to the 12 Minute Walk Test, but the 6MWT is preferred because it is faster, better tolerated and more standardized [1, 2].
- The 6MWT is a useful tool for both the clinical and research fields. Its main indication is to assess the response of patients with pulmonary or cardiac disorders to certain interventions (e.g. pulmonary rehabilitation) [1]. This test can also be used to assess functional status and predict mortality and morbidity in such patients. Table 9.1 summarizes the indications and contraindications to the 6MWT. The 6MWT is generally safe [3–9]. The test should be immediately terminated, however, if the patient develops chest pain, intolerable dyspnea, leg cramps, unstable balance, marked diaphoresis or a pale or ashen appearance [1].
- The Incremental Shuttle Walk Test is another field test of walking capacity that measures the distance walked by the patient along a fixed track. Unlike the 6MWT, this test is externally-paced by the assessor whereby the walking speed is increased until test termination. Details of this test are provided in recently published guidelines [10].

Technique

- The technique and methodology of 6MWT used for prognostic studies must follow a standardized protocol.
- The 6MWT is best performed in a building with unobstructed level corridors. A distance of 30 meters (~100 ft) is considered suitable and the laps are then counted [1, 9, 11, 12]. Prior to the start of the test, the patient should rest quietly in a chair

TABLE 9.1 Indications & contraindications for the 6MWT

Indications for 6MWT
To assess outcome of therapy (test is done before and after therapy)
- Lung transplantation [2, 86]
- Lung resection [87]
- Lung volume reduction surgery [88, 89]
- Pulmonary rehabilitation [90, 91]
- Drug therapy for COPD [92, 93] and heart failure (CHF) [94]

To assess functional status in patients with:
- Lung disease (COPD [95, 96], CF [97, 98], pulmonary hypertension [99])
- Heart disease (CHF) [100–102]

To predict mortality and morbidity in patients with CHF [3, 103], COPD [104, 105] and pulmonary hypertension [86, 106]
To assess outcome parameters for research studies

Contraindications [10]
Absolute
- Active endocarditis
- Acute myocardial infarction (3–5 days)
- Acute myocarditis or pericarditis
- Acute noncardiopulmonary disorder that may affect exercise performance or be aggravated by exercise
- Acute pulmonary embolus or pulmonary infarction
- Acute respiratory failure
- Mental impairment leading to inability to cooperate
- Pulmonary oedema
- Room air arterial oxygen saturation at rest ≤85%
- Suspected dissecting aneurysm
- Symptomatic severe aortic stenosis
- Syncope
- Thrombosis of lower extremities
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Uncontrolled asthma
- Uncontrolled heart failure
- Unstable angina

Relative
- Advanced or complicated pregnancy
- Electrolyte abnormalities
- High-degree atrioventricular block
- Hypertrophic cardiomyopathy
- Left main coronary stenosis or its equivalent
- Moderate stenotic valvular heart disease
- Orthopaedic impairment that prevents walking
- Severe untreated arterial hypertension at rest (200 mmHg systolic, 120 mmHg diastolic)
- Significant pulmonary hypertension
- Tachyarrhythmias or bradyarrhythmias

placed by the starting position. During this time, the following resting measurements should be obtained: oxygen saturation (S_PO_2), heart rate, baseline dyspnea and fatigue, and systemic blood pressure [1]. The assessor should start the timer as soon as the patient starts walking. Under the supervision of the respiratory therapist, physical therapist, clinical exercise physiologist, or other assessor with training and experience in a related healthcare field, the patient should walk normally, unassisted in carrying a portable O_2 cylinder if used [1, 13]. The patient is allowed, however, to use any kind of assistance that he/she normally uses for daily activities (e.g. walker). Every 60 seconds during the test, the patient may be encouraged only by standardized phrases [10]. The patient is allowed to rest whenever needed. While resting, the patient may be encouraged by standardized phrases every 30 seconds once S_PO_2 is ≥85% [10]. A portable pulse oximeter may be used during the test but more importantly, is the reporting of S_PO_2 at the start and the end of the test [1, 14, 15]. The 6MWT should be stopped by the assessor when S_PO_2 falls below 80%, however, the patient may be asked to continue if the S_PO_2 returns to ≥85% [10]. Since the 6MWT and other walking tests have been shown to result in peak $\dot{V}O_2$ measures similar to values elicited by cardiopulmonary exercise testing [16], contraindications and safety considerations for field-based exercise tests should be in accordance with those recommended in maximal exercise test guidelines [17].

- The 6MWT is repeated after a sufficient resting period. It is usually reproducible and the largest achieved distance is reported [1]. Given the strong evidence supporting a learning effect for the distance measured during the 6MWT [16], repeat testing should be completed. Current standards suggest that the rest period between tests repeated on the same day should be at least 30 minutes and S_PO_2 and heart rate must return to baseline levels before initiating the second test [10]. However, this amount of recovery time may not be sufficient in those that experience significant fatigue following the first trial.

Interpretation

- Three measurements can be obtained from the 6MWT: the 6 minute walk distance (6MWD), the degree of dyspnea and fatigue, and the S_PO_2 [1, 13].

- The most important measurement is the 6MWD which is normally 585 meters on average in men and 555 meters on average in women [18]. A low 6MWD is nonspecific and nondiagnostic. A low 6MWD may be seen in patients with lung disease, heart disease, musculoskeletal disease (arthritis) or even in normal subjects who perform a submaximal effort. A significant reduction in the 6MWD may be useful to grade exercise capacity, evaluate response to therapy, and to predict overall outcome. An unexplained reduction of the 6MWD should prompt a search for a possible cause. In adult patients with chronic respiratory diseases, the minimal clinically important difference for the 6MWD is approximately 30 meters [16], however, this may vary in other clinical populations.
- The 6MWD varies significantly among normal individuals. Factors like age, weight, sex and height independently influence the 6MWD in healthy adults [1]. Serial measurements of 6MWD in the same patient, to assess disease progression or the effect of therapy, given the low intra-subject variability, make the test more useful.
- Several reference equations have been developed to calculate predicted 6MWD values in groups of normal individuals with varying age ranges and degrees of test familiarization [5, 11, 19]. The following predicted equation may be used in healthy adults over the age of 50 years old who perform repeated 6MWTs:

$$\begin{aligned} 6\text{MWD}_{\text{in meters}} &= 218 + \left(5.14 \times \text{Height}_{\text{cm}} - 5.32 \times \text{Age}_{\text{years}}\right) \\ &- \left(1.80 \times \text{Weight}_{\text{kg}}\right) + \left(51.31 \times \text{Sex}_{\text{male=1,female=0}}\right) \quad [11] \end{aligned}$$

  In younger healthy adults, the following reference equation may be more appropriate:

$$\begin{aligned} 6\text{MWD}_{\text{in meters}} &= 868.8 - \left(2.99 \times \text{Age}_{\text{years}}\right) \\ &- \left(74.7 \times \text{Sex}_{\text{male=0,female=1}}\right) \quad [19] \end{aligned}$$

- *The modified Borg scale,* which is a 0–10 category ratio scale ranging from "no discomfort" to "maximal discomfort"; Figure 9.1, may be used to grade the degree of dys-

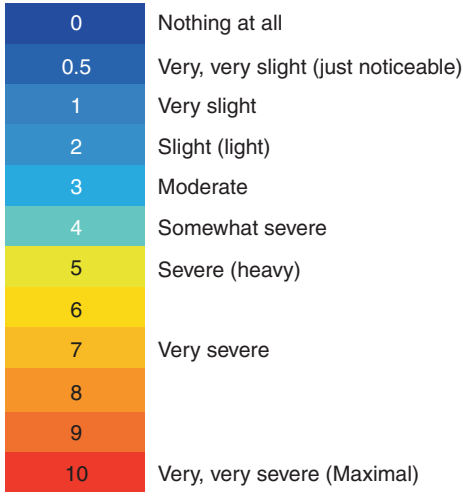

FIGURE 9.1 The modified Borg scale

pnea that the patient experiences during and at the end of the test [20].

- S_pO_2 is normally unchanged with exercise. Any drop of >5% usually indicates a respiratory or possibly a cardiac disorder. Artifacts related to signal recording during walking, however, may influence the accuracy of the S_pO_2 [1, 14, 15].
- Sometimes a walking (exercise) oximetry is done (without measuring the 6MWD) to assess S_pO_2 to determine the need for, or to titrate the level of, supplemental O_2 during exertion. This is often referred to as exercise oximetry and has nothing to do with the 6MWT.

CARDIOPULMONARY EXERCISE TEST

Introduction

- The cardiopulmonary exercise test (CPET) is aimed at assessing the ability of the body organ systems to respond normally during exercise. Exercise normally prompts the delivery of the appropriate amount of O_2 from the external environment to the red blood cells (the function of the pulmonary system).

O_2 is then transported to the muscle cells (the function of the cardiovascular system and blood) where oxidative phosphorylation takes place to produce energy (adenosine triphosphate or ATP) (the function of the mitochondria).

- CO_2 should then flow in the opposite direction through the same organ systems until it is exhaled to the external environment. So, these organ systems interact and coordinate their functions together to achieve one goal, the production of energy needed for function, as is illustrated by the so-called Wasserman's gears; Figure 9.2. Therefore, disorders of any of these organ systems results in exercise limitation, i.e. inability to achieve the predicted maximum exercise capacity for a given individual.

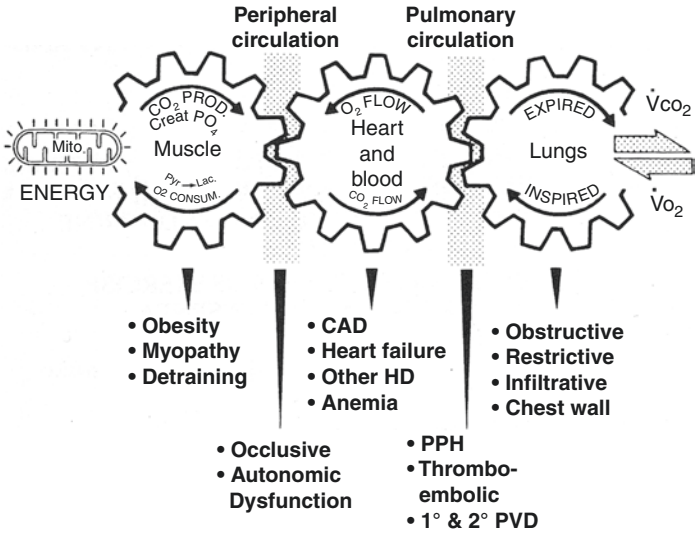

FIGURE 9.2 The Wassermann's gears resemble the interaction and coordination of the body organ systems to produce energy. Failure of any of the organ systems results in failure of energy production. (With permission from: Karlman Wasserman, James E Hansen, Darryl Y Sue, William W Stringer, Brian J Whipp. Principles of Exercise Testing and Interpretation, Fourth edition, Philadelphia, Pa, Lippincott Williams and Wilkins, 2004)

- In exercise testing, where subjects are encouraged to achieve their maximum exercise capacity, we aim to achieve two goals: detecting any exercise limitation and identifying the organ system(s) responsible for that limitation.
- The indications and contraindications for exercise testing are listed in Table 9.2.

Table 9.2 Indications and contraindications for CPET

Major Indications
To determine exercise capacity/impairment [17]
To identify the cause of exercise limitation [43, 64, 107–113]:
If the patient has both cardiac and pulmonary diseases and unsure which is most responsible for the exercise limitation
If no cause is apparent for exercise limitation after full evaluation
Assessment of exercise capacity if resting data do not explain symptoms [17, 64]
Assessment of therapy selection and response (pulmonary rehabilitation [114–116], lung resection [117–119], lung transplantation [120, 121], cardiac transplantation [43, 122, 123], medical therapy for lung diseases like COPD [124, 125], pulmonary hypertension [126–128], ILD [129] and CF [130])
Evaluation for impairment/disability [131–136]
Other Indications
Diagnosis of exercise-induced asthma [137–141]
Identification of gas exchange abnormalities [17, 43]
Titration of supplemental O_2 rate during exercise [47, 51, 124, 142–145]
Absolute Contraindications [51, 80, 146]
Active cardiac disease (acute MI, unstable angina, active arrhythmias, uncontrolled CHF, severe aortic stenosis, aortic dissection, endocarditis, myocarditis, pericarditis)
Active pulmonary disease (uncontrolled asthma, respiratory failure, pulmonary edema, acute PE or DVT)
Hemodynamic instability or acute noncardiopulmonary disease affecting exercise performance (infection, thyroid disease)
Relative Contraindications [17, 147]
Uncontrolled systemic (systolic >200 mmHg; diastolic >120 mmHg) or pulmonary hypertension
Hypertrophic obstructive cardiomyopathy
Significant left main coronary artery stenosis (without acute symptoms)
Others (moderate stenotic valvular heart disease, advanced pregnancy, electrolyte abnormalities, orthopedic impairment)

Equipment

- A *cycle ergometer* or a treadmill:
  - Represents a way to apply a controlled quantifiable workload that can be steadily increased.
  - A cycle ergometer is generally preferred over a treadmill because:
    (a) Cycling is associated with less body movements which produce fewer artifacts in the recorded data.
    (b) A more linear and quantifiable workload can be achieved by the cycle ergometer.
    (c) Cycle ergometer is less expensive and occupies less space.
    (d) Cycle ergometer elicits less stress on the organ systems involved during exercise and less hypoxaemia [21–23].
    (e) Cycle ergometer may be safer as there is a lower risk of falling compared to the treadmill.
  - Cycle ergometer is limited as the high quadriceps loading from cycling exercise may result in exercise termination predominately due to local muscle fatigue before peak cardiovascular capacity is reached [23].
  - Since most activities of daily living incorporate walking modalities, treadmill exercise testing may provide a more accurate reflection of the functional exercise capacity for daily physical activities [17].
- Respiratory system monitors:
  - *Gas analyzers*: measure the amounts of the exhaled O_2 and CO_2 throughout exercise, and from which many exercise parameters are derived. There are several commercially available systems capable of measuring gas exchange, using either gas-mixing chamber methods [24, 25] or breath-by-breath analyses [26, 27] to compute O_2 uptake and CO_2 production.
  - *Airflow or volume recording device:* is used to measure ventilation during exercise and from which other useful data can be derived.
  - *Pulse oximeter:* is used to record S_PO_2 throughout exercise (its function is different from the gas analyzer that measures the amount of exhaled O_2) [28].
  - More invasive methods can be used *(arterial line)* to monitor the arterial blood gases (ABG for PaO_2 and bicarbon-

ate) and lactate. These measurements are not routinely needed [29].
  - *The modified Borg scale:* can be used to grade the degree of discomfort the patient experiences in terms of breathlessness and leg fatigue during different stages of exercise; Figure 9.1 [20]. Breathlessness and leg fatigue are the two major symptoms that limit exercise [30–32].
- Cardiovascular monitors:
  - Include baseline and continuous *ECG monitoring* throughout exercise which monitors the heart rate (HR) and aids in detecting arrhythmias and ischemia.
  - Continuous (through an arterial line) [17, 33, 34] or, more commonly, intermittent (cuff system) *blood pressure (BP) monitoring* is also done.

Technique

- The cardiopulmonary exercise testing equipment must be calibrated before use to meet strict quality control parameters in order to ensure accurate measurements.
- The technique involves asking the patient to pedal the cycle ergometer at a fixed speed with a progressive increase in the resistance to pedaling (Work Rate or WR). The patient is connected, throughout the test, to a number of instruments namely, a mouthpiece for gas collection and flow and volume measurements, ECG monitor, pulse oximeter and a blood pressure cuff. These instruments will feed data to a computer with software that can present the results in both a graphic and numeric format. The test is terminated once any of the factors listed in Table 9.3 arises. ABG may then be withdrawn (if arterial line is placed) and a recovery period starts.
- Continuous supervision by a properly trained technologist is required throughout exercise. In addition, a physician at his/her own discretion should either be present in the laboratory or available nearby to be able to respond in emergency situations [17].

O_2 Uptake, Major Concepts

- Understanding O_2 uptake is the window to understanding the body's physiological changes in response to exercise. This section discusses the major concepts of $\dot{V}O_2$.

TABLE 9.3 Indications for termination of exercise testing [17, 39, 43, 64, 146, 148, 149]

Severe symptomatic desaturation (SpO_2 ≤80%)
Significant ECG changes (ischemia, arrhythmias, high grade AV blocks, complex ectopy)
BP instability (Systolic BP of >250 mmHg or dropping by >20 mmHg from the highest value during CPET; diastolic BP of >120 mmHg)
Signs and symptoms of cardiovascular, respiratory or CNS instability (sudden pallor, loss of coordination, mental confusion, dizziness or faintness, syncope, respiratory failure, chest pain suggestive of ischemia)

Definitions

- $\dot{V}O_2$ (O_2 uptake):
  - Is the amount of O_2 in liters that the body consumes per minute (L/min).
  - $\dot{V}O_2$ (in L/min) represents the internal metabolic work and is directly proportional to the external WR (in watts) applied through the cycle ergometer or treadmill [35]; that is why $\dot{V}O_2$ is considered equivalent to WR under most circumstances. Therefore, whenever you encounter "$\dot{V}O_2$", remember that it closely reflects WR used during the test.
- Maximum $\dot{V}O_2$ ($\dot{V}O_2$ max) (L/min):
  - Is the maximum achievable $\dot{V}O_2$. $\dot{V}O_2$ max can be detected when the $\dot{V}O_2$ plateaus in relation to the external workload (WR), indicating that no further increase in $\dot{V}O_2$ can be achieved despite increasing WR. $\dot{V}O_2$ max represents the maximum exercise capacity for a given subject and is the gold standard indicator of the subject's cardiorespiratory fitness.
- Measured peak $\dot{V}O_2$ (L/min):
  - Is the highest $\dot{V}O_2$ that a subject actually achieves during CPET. Evidence for plateauing of $\dot{V}O_2$ despite an increasing WR is not required for the determination of $\dot{V}O_2$ peak.
- Predicted peak $\dot{V}O_2$ (L/min):
  - Is the highest $\dot{V}O_2$ that a subject is expected to achieve.
  - Is determined by the patient's age, sex and body size.

  - In normal subjects, the measured peak $\dot{V}O_2$ usually equals or exceeds predicted peak $\dot{V}O_2$, while in patients with heart or lung disease, the measured peak $\dot{V}O_2$ is often less than predicted peak $\dot{V}O_2$.

- $\dot{V}O_2$ / kg (mL/kg/min):
  - Is the amount of O_2 in milliliters that the body consumes per minute corrected for the body weight in kg. Since adipose tissue is metabolically inactive, fat mass is not a significant contributer to maximal or peak $\dot{V}O_2$. Studies show an elevated metabolic cost of activities in obese individuals [36, 37]. As a result, normalizing $\dot{V}O_2$ by body weight may underestimate fitness in obese individuals. Therefore, maximal or peak $\dot{V}O_2$ measures are better expressed as absolute and percentage of predicted values [17].

Factors Determining $\dot{V}O_2$

- These factors can be acquired from the *Fick Equation* [38], which can be written as follows (for details see Table 9.4):

$$\dot{V}O_2 = SV \times HR \times (1.34) \times Hgb \times (CaO_2 - CvO_2)$$

  From this equation, the factors that determine $\dot{V}O_2$ are: HR, SV, Hgb and the difference between the arterial and mixed venous O_2 content (i.e. the ability of muscle cells to extract O_2 from the blood). During exercise, these factors progressively increase in response to the increased WR, with the exception of Hgb. As an example, at peak exercise, the amount of O_2 extracted from the blood (CaO_2–CvO_2) is three fold higher than at the start of exercise [39]. Similarly, C.O. can increase by up to four fold at peak exercise by increasing HR and SV [40]. The increases in O_2 extraction and C.O. can be even greater in well trained endurance athletes [41].

- Conditions that affect any of these factors will necessarily affect $\dot{V}O_2$ and hence the exercise capacity:
  - Patients with a cardiac disease (like cardiomyopathy) cannot increase their SV appropriately in response to exercise resulting in exercise limitation [42]. In highly trained

TABLE 9.4 Fick Equation [38]

It states that the cardiac output equals the rate of O_2 uptake divided by the difference in the arterial and mixed venous O_2 content:

$$C.O. = \dot{V}O_2 / (CaO_2 - CvO_2)$$

Therefore: $\dot{V}O_2 = C.O. \times (CaO_2 - CvO_2)$

Because C.O. = SV × HR, then:

$$\dot{V}O_2 = SV \times HR \times (CaO_2 - CvO_2)$$

Because:

$$(CaO_2 - CvO_2) = (1.34) \times Hgb \times (SaO_2 - S_{\bar{v}}O_2) + \left[(0.003) \times (PaO_2 - P_{\bar{v}}O_2)\right]$$

and because: $\left[(0.003) \times (PaO_2 - P_{\bar{v}}O_2)\right]$ is negligible, then the final equation can be written as:

$$\dot{V}O_2 = SV \times HR \times (1.34) \times Hgb \times (SaO_2 - S_{\bar{v}}O_2)$$

where SV is the stroke volume; HR is the heart rate; Hgb is the hemoglobin; SaO_2 is the arterial O_2 saturation; $S_{\bar{v}}O_2$ is the mixed venous O_2 saturation.

athletes, however, there is an augmented increase in SV in response to exercise resulting in a supranormal exercise capacity.

- Patients with chronotropic disorders (e.g. pacemaker patients with fixed HR or patients on β-blockers) can't increase their HR appropriately with exercise, hence, they are exercise limited.
- Patients with anemia (or carboxy-hemoglobinemia) may have low exercise capacity because of low O_2 carrying capacity.
- Patients with muscle disease that impairs O_2 extraction and utilization (e.g. mitochondrial disease) will have exercise limitation.

Assessing the Cardiovascular System

$\dot{V}O_2$ *Relationship with the Cardiac Output Components*

- As discussed previously, the two components determining C.O. are HR and SV; (C.O. = SV × HR).
- During exercise, there is a near linear increase in C.O. with increasing WR ($\dot{V}O_2$), initially accomplished by increases in

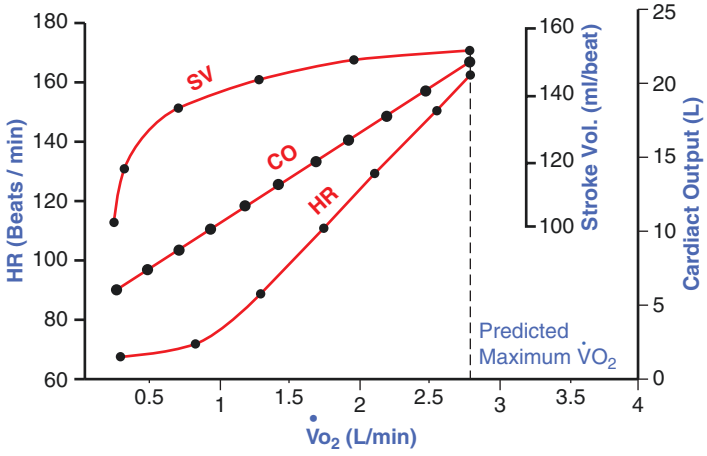

FIGURE 9.3 The relationship between $\dot{V}O_2$ and C.O. components. SV increases first then when it plateaus, HR increases more rapidly. This maintains a linear increase in C.O

both SV and HR (to a lesser extent). Then, SV plateaus, at which time HR increases more rapidly; Figure 9.3 [43].

- Normally we are exercise-limited by our heart, that is, we stop exercising when we achieve our maximum HR [44–46]. So, it is important to determine the predicted maximum HR so that we can define our cardiac limits to exercise.
- The predicted maximum HR depends on age and can be derived from different formulae:

$$\max \mathrm{HR} = 220 - \mathrm{age} \quad [47] \quad \underline{\mathbf{OR}}$$
$$\max \mathrm{HR} = 210 - (0.65 \times \mathrm{age}) \quad [48]$$

- Both formulae give similar values for individuals under the age of 40 years [17], however, the first formula underestimates maximal HR in the elderly and overestimates in young adults [49].
- Certain medications such as β-blockers reduce peak $\dot{V}O_2$ by decreasing maximal HR [50]. Therefore, although HR reserve may be high in patients using these medications due to the large difference between HR at maximal exercise and predicted maximum HR, possible cardiac limitations to

exercise may still be considered if the other variables suggest such a pattern.

- The HR can be easily measured during exercise, while the SV generally requires a more invasive method (e.g. cardiac catheterization). A search for a non-invasive method to estimate SV resulted in the concept of the "O_2 Pulse".

O_2 *Pulse* ($\dot{V}O_2$ / HR)

- Is defined as the O_2 uptake or consumption for each cardiac cycle, i.e. $\dot{V}O_2$ divided by the HR. The Fick equation can then be rearranged to calculate O_2 pulse:

$$O_2 \text{ Pulse } \underline{\textbf{OR}} \ \dot{V}O_2 / HR = SV \times 1.34 \times Hgb \times \left(CaO_2 - CvO_2\right)$$

- The O_2 pulse reflects the SV and O_2 extraction and normally increases with incremental exercise due to increases in both of these variables [17]. Assuming that the variables in the right side of this equation are constant (Hgb and (CaO_2–CvO_2)), then O_2 pulse becomes equivalent to SV. During maximal or near-maximal exercise, CaO_2–CvO_2 is assumed to be relatively constant and any changes in O_2 pulse are reflective of concomitant changes in SV [17]. That is why, O_2 pulse is used by some investigators as a non-invasive surrogate marker for SV in exercise test interpretation [47, 51]. In patients with mitochondrial myopathy, O_2 pulse may reflect both SV and oxygen extraction as these patients show a blunted ability to increase CaO_2–CvO_2 with exercise [52]. When O_2 pulse is plotted against $\dot{V}O_2$, it produces a curve comparable to a SV curve, Figure 9.3. The assumption that the CaO_2–CvO_2 is constant is not always true. The O_2 pulse is a more qualitative assessment of SV and must be viewed in this context for interpretation.
- When O_2 pulse (SV) fails to increase appropriately with exercise, it may indicate cardiac disease e.g. cardiomyopathy, as discussed earlier. As a result, the body will compensate by increasing HR to maintain an appropriate increase in C.O. which is required to continue exercising. The patient will end up reaching the maximum HR much earlier than expected, resulting in premature termination of exercise (i.e. a low peak $\dot{V}O_2$); see Figures 9.4 and 9.5 [42]. A low O_2 pulse can also be seen in deconditioning [17].

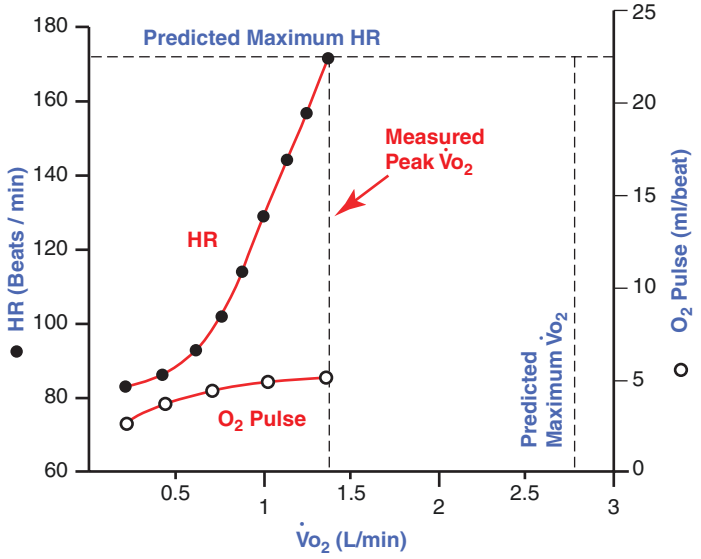

FIGURE 9.4 Heart disease, steep increase in HR with a flat O_2 pulse (SV); peak $\dot{V}O_2$ is not reduced

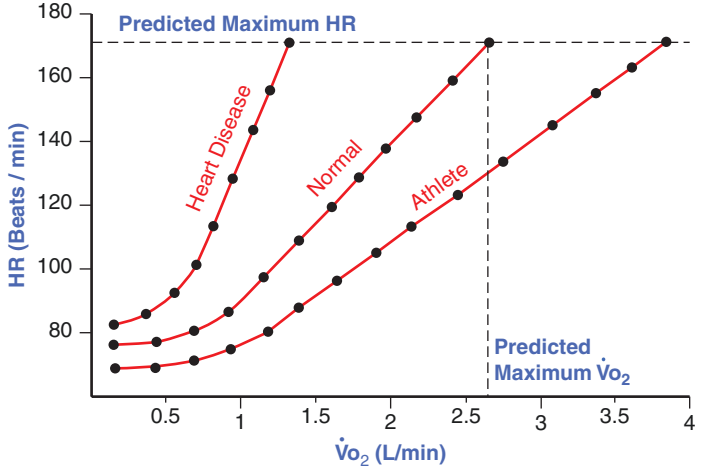

FIGURE 9.5 HR reaches its peak early in heart disease and late in aerobic training resulting in a significant difference in peak $\dot{V}O_2$ in the two conditions

- By looking at the curves in Figure 9.4, we can make three comments:
  - There is a significant reduction in peak $\dot{V}O_2$ (i.e. exercise limitation).
  - The steep increase in HR with minimal increase in O_2 pulse (SV) indicates a cardiovascular origin of exercise limitation.
  - The low peak O_2 pulse relative to the predicted maximum value (predicted maximum $\dot{V}O_2$ / predicted maximum HR) may reflect cardiac limitations if the patient has normal CaO_2–CvO_2 response with exercise.
- Aerobic training, however, results in a reduced HR during rest and submaximal exercise which increases SV. SV at maximal exercise is increased with aerobic training, resulting in increased C.O. at maximal workloads. Oxygen extraction is also improved with aerobic training. A higher $\dot{V}O_2$ therefore can be achieved at maximal exercise as a result of a combination of improved C.O. and CaO_2–CvO_2.
- If peak exercise is reached before reaching the maximum HR, this is referred to as HR reserve:

$$\text{HR reserve} = \text{Pred. HR max} - \text{achieved HR at peak } \dot{V}O_2$$

- HR reserve is increased in patients with pulmonary disease and those who can't reach their peak exercise for other reasons (e.g. volitional muscle fatigue).

Definition of Other Exercise Parameters

- $\dot{V}CO_2$: is the amount of CO_2 produced by the body per minute (L/min).
- *Respiratory Quotient (RQ)*: is the amount of CO_2 the body produces for each liter (mole) of O_2 it consumes, at the tissue level. Normally, at rest, we produce ~0.8 mole of CO_2 for each mole of O_2 we consume (RQ = 0.8), but this increases with exercise as will be discussed.
- *Respiratory Exchange Ratio (RER)*: is the amount of CO_2 produced per liter of O_2 consumed as measured from the exhaled air at the mouth $(\dot{V}CO_2 / \dot{V}O_2)$. At steady state, RER equals RQ allowing RER to be used as a rough index of RQ given the difficulty of measuring the latter [17].

- $\dot{V}_E$ *(Minute Ventilation)*: is the volume of air we breathe per minute. $\dot{V}_E$ is the product of Tidal Volume (V_T) and Respiratory Rate (RR):

$$\dot{V}_E = V_T \times RR$$

- $P_{ET}O_2$: is the end-tidal O_2 tension as measured from the exhaled air.
- $P_{ET}CO_2$: is the end-tidal CO_2 tension as measured from the exhaled air.
- *Ventilatory Equivalent for* $\dot{V}O_2 (\dot{V}_E / \dot{V}O_2)$: is the amount of $\dot{V}_E$ for a given level of $\dot{V}O_2$.
- *Ventilatory Equivalent for* $\dot{V}CO_2 (\dot{V}_E / \dot{V}CO_2)$: is the amount of $\dot{V}_E$ at a given level of $\dot{V}CO_2$.

Anaerobic Threshold (AT)

- Is defined as the $\dot{V}O_2$ (in L/min) at which there is substantial transition to anaerobic metabolism to produce extra energy (ATP). This is aimed at supplementing aerobic metabolism, which becomes insufficient at higher levels of exercise (in healthy subjects AT typically takes place at ~45–60% of predicted peak $\dot{V}O_2$, although this could be highly variable [17]).
- AT is called anaerobic because this process is O_2-independent. At the same time, it results in the production of lactic acid, which when accumulating, contributes to muscle fatigue leading to termination of exercise. This is why AT is sometimes called ***Lactate Threshold***. The body buffers the rising levels of lactic acid in the blood with bicarbonate to stabilize the pH:

$$\text{Lactate} + H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow H_2O + CO_2$$

- As a result, extra CO_2 is produced, unrelated to O_2 consumed ($\dot{V}O_2$) resulting in the rise of RER during exercise which often exceeds 1 (i.e. more CO_2 is produced than the O_2 consumed). Because of this accelerated rise in CO_2 ($\dot{V}CO_2$) at the AT, the respiratory system responds by eliminating the

extra CO_2, resulting in a rise in $\dot{V}_E$ out of proportion to $\dot{V}O_2$ if they are plotted against each other; Figure 9.6. The point at which the slope of the $\dot{V}_E$ curve changes is called the inflection point and corresponds to AT; Figure 9.6a.

- Methods to identify AT include:
  - $\dot{V}_E$ vs. $\dot{V}O_2$ curve, as discussed above; Figure 9.6a.
  - $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve; (Figure 9.6b), at AT $\dot{V}CO_2$ rises faster because of the increased CO_2 production, this is called the ***V-slope*** [53].
  - Ventilatory Equivalents for $\dot{V}O_2$ and $\dot{V}CO_2$ ($\dot{V}_E / \dot{V}O_2$ and $\dot{V}_E / \dot{V}CO_2$) vs. $\dot{V}O_2$ curve; Figure 9.6c [17]:
    (a) With exercise, $(\dot{V}_E / \dot{V}O_2)$ drops steadily as the increase in $\dot{V}O_2$ (denominator) exceeds the increase in $\dot{V}_E$ (numerator), until AT is reached when the $(\dot{V}_E / \dot{V}O_2)$ inflects upwards due to the disproportionate increase in $\dot{V}_E$ compared to $\dot{V}O_2$.
    (b) This inflection point may be clearer in this curve than in the $\dot{V}_E$ vs. $\dot{V}O_2$ curve, as the $\dot{V}_E / \dot{V}O_2$ vs. $\dot{V}O_2$ plot changes direction from downward to upward.
    (c) On the other hand, the ventilatory equivalent for $\dot{V}CO_2 (\dot{V}_E / \dot{V}CO_2)$ continues to decrease after the $\dot{V}_E / \dot{V}O_2$ inflection point (AT) is reached, as, at AT, both the denominator $(\dot{V}CO_2)$ and numerator $(\dot{V}_E)$ increase proportionately initially. This downward slope of $\dot{V}_E / \dot{V}CO_2$ vs. $\dot{V}O_2$ curve continues beyond AT until $\dot{V}_E$ disproportionately increases as a compensation when a frank metabolic acidosis develops, at which point the curve changes direction upward; Figure 9.6c [17].
  - $P_{ET}O_2$ and $P_{ET}CO_2$ vs. $\dot{V}O_2$ curve; Figure 9.6d:
    (a) The expired O_2 tension remains stable during exercise but inflects upward at AT in response to the increased $\dot{V}_E$.
    (b) $P_{ET}CO_2$, similarly remains stable at and beyond AT for some time before deflecting downward in response to the disproportionate increase in $\dot{V}_E$ when a frank metabolic acidosis develops [17].
  - AT can also be determined invasively by serial measurements of lactate or bicarbonate (ABG) during exercise. At AT, lactate rises and bicarbonate drops (to buffer the lactic

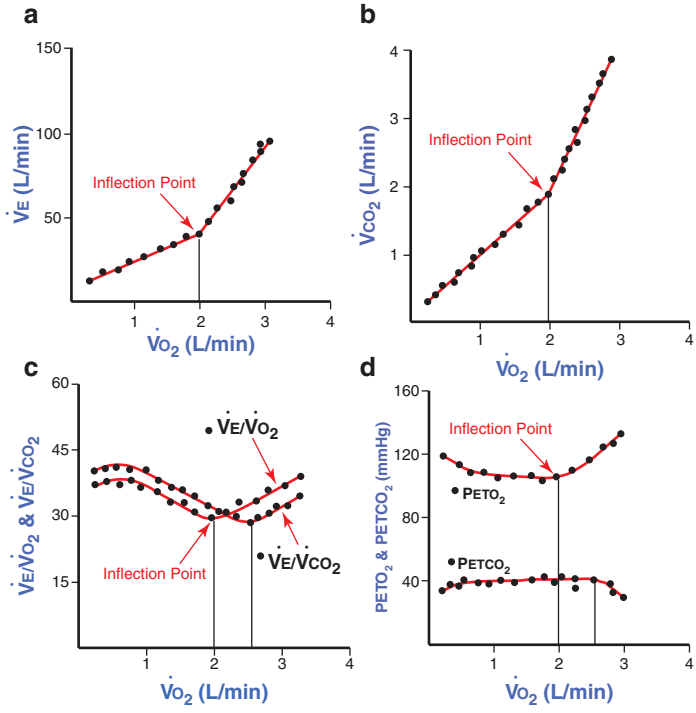

FIGURE 9.6 (**a**) $\dot{V}_E$ vs. $\dot{V}O_2$ curve showing a steady increase in $\dot{V}_E$, then at AT it inflects upward. (**b**) $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve. (**c**) $\dot{V}_E / \dot{V}O_2$ vs. $\dot{V}O_2$ curve and $\dot{V}_E / \dot{V}CO_2$ vs. $\dot{V}O_2$ curve. (**d**) $P_{ET}O_2$ vs. $\dot{V}O_2$ curve and $P_{ET}CO_2$ vs. $\dot{V}O_2$ curve

acid) in the same ratio (they are equimolar) [54, 55]. So, if lactate or HCO_3^- is plotted against $\dot{V}O_2$, then the point at which the lactate starts rising or HCO_3^- starts dropping, corresponds to the AT; Figure 9.7 [17, 56, 57].

- The AT is determined predominantly by the cardiovascular system. If C.O. doesn't increase appropriately during exercise, it will result in impaired O_2 delivery to the muscles and a faster transition to anaerobic metabolism. This means that in cardio-

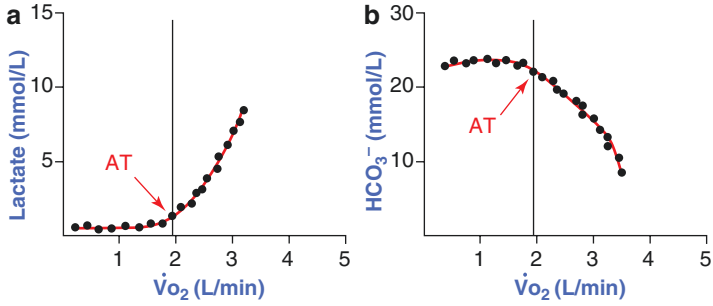

FIGURE 9.7 At AT HCO_3^- starts to drop and Lactate starts to rise

vascular disease, the AT is generally low (<40% of peak $\dot{V}O_2$) and contributes to exercise limitation because of muscle fatigue (accumulation of lactate). Other causes of reduced AT include deconditioning, reduction in O_2 carrying capacity and muscle oxidative disorders [17]. In respiratory disease, the AT is either normal, not reached [58, 59] or indeterminate [17] as the patient is usually limited by ventilatory constraints.

Blood Pressure Response [17, 60]

- BP is another parameter used to assess cardiovascular function. Normally, the systolic BP increases with exercise because of increased C.O., and the diastolic BP remains unchanged or drops slightly because of decreased systemic vascular resistance in response to vasodilatation in the exercising muscles.
- An excessive rise in BP (e.g. systolic >220 mmHg; diastolic >100 mmHg) during exercise suggests abnormal sympathetic BP control, but may also be seen in patients with known resting hypertension.
- Failure of BP to rise with exercise suggests a cardiac disorder or abnormal sympathetic control of BP.
- A drop of BP with exercise should prompt exercise termination as it indicates either a serious cardiac disorder (CHF, aortic

stenosis, or ischemia) or circulatory disorder (pulmonary vascular disease or central pulmonary venous obstruction).

Assessing the Respiratory System

The respiratory system is assessed as two components: the ventilatory component and the gas exchange component.

Ventilatory Component

Definitions

- *Maximal Voluntary Ventilation (MVV)*
  - Is the maximum minute ventilation that a subject can achieve. It is used as an estimation of the maximum ventilatory capacity. It can be assessed as follows:
    (a) *Measured MVV* is determined in the lab by measuring the patient's ventilation over 12- or 15-seconds during a maximal effort, and then extrapolating the results to 1 minute. If both measured and calculated MVV (*see below*) are determined (which is unusual), the higher of the 2 is reported. However, MVV is not routinely measured directly in the clinical setting.
    (b) *Calculated MVV* is derived from the patient's forced expiratory volume in one second (FEV_1) [61–63] which is the technique used by most clinical exercise laboratories:

$$MVV = FEV_1(L) \times 40 \ \textbf{OR}$$

$$MVV = FEV_1(L) \times 35$$

    (c) *Predicted MVV* is calculated from the patient's height, sex and age by multiplying the predicted (not measured) FEV_1 by 40 (or 35). Therefore, in respiratory disease, the calculated MVV will often be less than the patient's predicted MVV.

- $\dot{V}_E$ *max*: is the maximum $\dot{V}_E$ that the patient achieves during CPET.
- *Ventilatory Reserve* = Predicted – measured $\dot{V}_E$ max, i.e. $= MVV - \dot{V}_E \max$ [43, 47, 64].

- *Breathing Reserve (Another way of expressing ventilatory reserve)*[1]

  $= \text{measured / predicted } \dot{V}_E \text{ max, i.e.}$

  $= \dot{V}_E \text{ max/ MVV} \times 100 \quad [43, 47, 64]$

$\dot{V}_E$, Major Concepts

- The components of $\dot{V}_E$ are RR and V_T:

$$\dot{V}_E = RR \times V_T$$

- During exercise, the V_T increases linearly, then plateaus at approximately 50–60% of vital capacity [17], at which point the RR increases maintaining a continuous increase in $\dot{V}_E$; Figure 9.8 [65–67].
- The respiratory system is overbuilt for exercise in healthy untrained individuals resulting in a large ventilatory reserve at maximal exercise [68]. In contrast, elite endurance athletes may achieve their MVV during exercise, but they reach

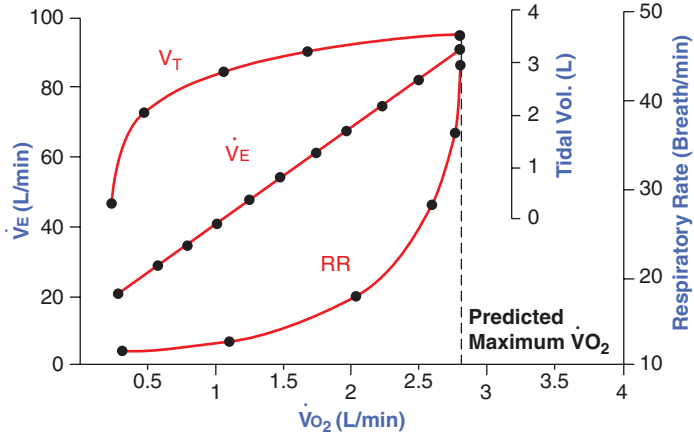

FIGURE 9.8 Behavior of V_T and RR during exercise is similar to SV and HR. Note that $\dot{V}_E$ and $\dot{V}O_2$ maintain a linear relationship

[1] Although this is the conventional formula typically used to express "breathing reserve", the actual reserve is calculated as $100 - (\dot{V}_E \text{ max/ MVV} \times 100)$.

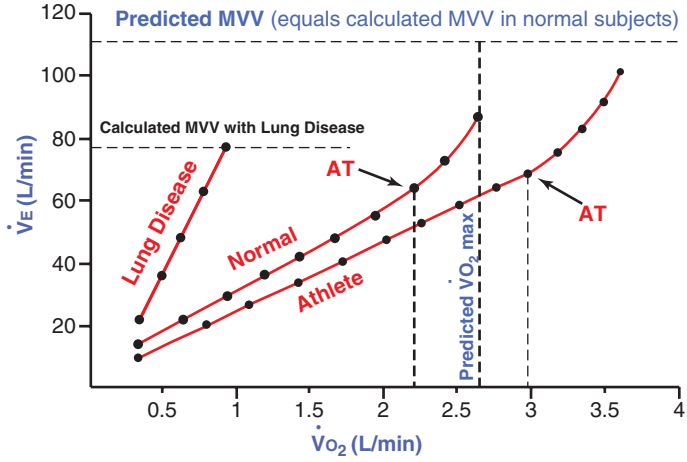

FIGURE 9.9 Patients with lung disease reach their predicted MVV early which is less than their ideal one. Elite athletes may approach their predicted MVV with a supranormal $\dot{V}O_2$

their MVV at a higher than predicted $\dot{V}O_2$; Figure 9.9. Unlike the muscular, cardiovascular and hematological systems, the lungs and airways do not adapt to exercise training [69]. Therefore, elite endurance athletes have a fixed ventilatory capacity (MVV) but have very high ventilatory requirements ($\dot{V}_E$ max) resulting in a small ventilatory reserve at maximal exercise. This may indicate that elite athletes have such well conditioned oxygen delivery from the lungs to the working muscle that they reach their MVV and may thus be exercise limited by their respiratory system.

- A ventilatory Reserve <11 L/min or breathing reserve >85% suggests that exercise is limited by ventilatory factors [17, 40, 70]. However, the MVV may not provide an accurate representation of sustained $\dot{V}_E$ max as the breathing strategy, lung volumes, respiratory muscle activity, and respiratory sensation differ between voluntary hyperpnea and exercise hyperpnea [71]. Despite these limitations, the ventilatory/breathing reserve method remains the most widely used method for identifying ventilatory limitations during exercise.
- Ventilatory limitation may also occur when dynamic hyperinflation is recognized in the tidal flow volume loops recorded during exercise. Dynamic hyperinflation

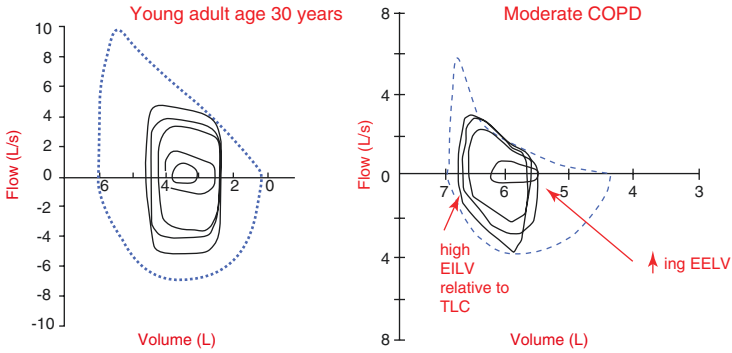

FIGURE 9.10 Normally, tidal flow volume loops expand from both directions during exercise. In emphysema, the decreased expiratory time (because of increased RR during exercise) results in more air-trapping and increases the FRC, shifting the tidal FV curves to the left, a phenomenon called "dynamic hyperinflation"

is defined as the variable and temporary increase in end-expiratory lung volume (or decrease in inspiratory capacity) relative to its baseline value when $\dot{V}_E$ is acutely increased [72]. This is identified on the tidal flow volume loops as a leftward shift in the exercise loop relative to the resting loop; Figure 9.10. Dynamic hyperinflation forces individuals to breathe close to their total lung capacity (i.e., small inspiratory reserve volume) and can contribute to dyspnea and exercise intolerance in patients with COPD [73].

- The flow-volume loop analysis technique is advantageous because it allows several important variables to be determined during exercise including the presence and magnitude of expiratory flow limitation, degree of dynamic hyperinflation, end-inspiratory lung volume relative to total lung capacity, inspiratory reserve volume, and both inspiratory and expiratory flow reserves [74].
- $P\text{aCO}_2$ and $P_{ET}\text{CO}_2$ normally remain stable until AT is reached, when they start to decrease due to the increased $\dot{V}_E$. In some ventilatory disorders, however, both $P\text{aCO}_2$ and $P_{ET}\text{CO}_2$ can increase due to a relative hypoventilation. Although $P\text{aCO}_2$ and $P_{ET}\text{CO}_2$ may be used to assess ventilatory function, they are considered also useful in assessing gas-exchange function as will be explained later.

Gas Exchange Component

This is assessed by three ways: dead space fraction, ABG and RQ.

Dead Space Fraction

- At rest, V_T is normally ~450 ml, 1/3 of which (150 ml) is wasted in the anatomic and physiologic dead spaces (dead space volume, V_D). The other 2/3 reach the gas exchange units and are referred to as the alveolar volume (V_A), so:

$$V_T = V_D + V_A$$

- Similarly, this equation can be applied to the $\dot{V}_E$:

$$\dot{V}_E = \dot{V}_D + \dot{V}_A$$

- Dead space fraction (V_D/V_T) is then, the dead space volume expressed as a fraction of V_T. It similarly equals $\dot{V}_D / \dot{V}_E$.
- At rest, dead space fraction is approximately 150 ml/450 ml which equals 1/3, as discussed. During exercise, however, V_T increases with a relatively constant dead space volume[2], resulting in a reduction of dead space fraction, which improves gas exchange [64].
- At rest, the upper lobes are not as well perfused as the bases but with exercise, perfusion improves to the upper lobes (because of increased blood flow) resulting in a more even $\dot{V}/Q$ distribution and hence better gas exchange [64].
- In summary, we normally improve our gas exchange during exercise by increasing alveolar ventilation more than dead space and improving overall $\dot{V}/Q$ matching.
- On the other hand, diseases that interfere with dead space fraction during exercise result in an inefficient gas exchange process and can contribute to premature termination of exercise. Lung fibrosis is an example, where the stiff small lungs are incapable of increasing the V_T appropriately in response to exercise. So, V_D/V_T remains unchanged or doesn't decrease as

[2] In reality V_D doesn't remain constant with exercise; it increases slightly and may reach 200 mL. This is due to a number of factors including, exercise-induced bronchodilatation and distention of airways related to the increased lung volumes [75].

expected with exercise as the excessive increase in RR at a low V_T increases the volume of wasted ventilation (dead space).

- Estimating V_D/V_T allows for detection of such diseases. This may be done in two ways:
  - V_D/V_T can be measured from *the dead space equation* [76]:[3]

$$V_D / V_T = \left(PaCO_2 - P_ECO_2\right) / PaCO_2$$

  - P_ECO_2 is the mixed expired CO_2 measured in exhaled samples. The smaller the difference between P_aCO_2 and P_ECO_2 (i.e. the higher the P_ECO_2), the lower the V_D/V_T, that is, the more efficient the ventilation is. To measure this parameter non-invasively $P_{ET}CO_2$ is substituted for P_aCO_2.
  - The other way is using *the mass balance equation* that can be rearranged as follows [64]:

$$\frac{\dot{V}_E}{\dot{V}CO_2} = K \times \frac{1}{PaCO_2\left[1-\left(V_D / V_T\right)\right]}$$

  - From this equation, the ventilatory equivalent for $\dot{V}CO_2$ ($\dot{V}_E / \dot{V}CO_2$) can be used as a non-invasive surrogate marker for the dead space fraction (V_D/V_T) if $PaCO_2$ remains constant. This assumption can be applied near or at the AT, but not beyond that, when $PaCO_2$ drops in response to increased $\dot{V}_E$ (to compensate for the lactic acidosis).

Other Methods for Assessing Gas Exchange

- A-a gradient ($P_{(A\text{-}a)}O_2$)
  - At rest, $P_{(A\text{-}a)}O_2$ is normally <10 mmHg and increases with exercise to >20 mmHg, as P_AO_2 normally increases with exercise and P_aO_2 remains constant. However, any increase in $P_{(A\text{-}a)}O_2$ of >35 mmHg with exercise is considered abnormal and indicates a gas exchange abnormality [68, 77].

[3] This equation is derived from Bohr's Law which states that the product of volume and concentration is the same under constant temperature.

  - $P_{(A\text{-}a)}O_2$ can be calculated from *the alveolar gas equation* as follows (see Chapter 8 for details):

$$P(A-a)O_2 = \left[P_IO_2 - \frac{P_aCO_2}{RQ}\right] - P_aO_2$$

  - RQ is substituted for RER that is measured simultaneously with P_aO_2 and P_aCO_2 during and at the end of exercise.

- S_PO_2 (pulse oximetry) or S_aO_2 (ABG)
  - S_PO_2 is the standard measure of oxygenation used during exercise testing. It may be less accurate than SaO_2 particularly at low levels and can be prone to artifact [78, 79]. Both S_PO_2 and S_aO_2 should remain normal and stable with exercise. Any drop of ≥5%, indicates a gas exchange abnormality [80, 81]. A significant symptomatic desaturation (<80%) during exercise indicates a significant gas exchange disorder and should prompt exercise cessation; see Table 9.3.
- P_aO_2
  - Remains stable or increases slightly with exercise. A drop in P_aO_2 indicates a gas exchange abnormality.
- P_aCO_2 and $P_{ET}CO_2$ are increased in gas exchange disorders.

APPROACH TO EXERCISE TEST INTERPRETATION

In interpreting any cardiopulmonary exercise study, you have to apply a structured approach (Table 9.5 shows one suggestion). The following are the major steps in interpreting such studies:

Maximal Effort

Determine whether a truly maximal effort was achieved. A maximal effort is achieved if one or more of the factors listed in Table 9.6 is (are) present. Lack of these factors indicates a submaximal effort which may limit the usefulness of the CPET.

TABLE 9.5 Suggested steps in reading exercise testing

Determine:
- The indication for CPET
- Determine the type of exercise modality used (usually cycle ergometer)
- Report the reason for exercise termination (dyspnea, leg discomfort, fatigue)
- Report the Borg scoring for dyspnea and leg discomfort at exercise termination

Examine the baseline spirometry and maximal flow volume loop

Determine whether a truly maximal effort was achieved; Table 9.6

Determine whether exercise capacity is normal:
- Determine the peak $\dot{V}O_2$ (should be >84% predicted), this can be done numerically or through $\dot{V}O_2$ vs. WR curve
- Determine the maximum WR achieved (>80% predicted)
- Determine the severity of exercise limitation which can be graded according to $\dot{V}O_2$ max. as mild (60–84% pred.), moderate (40–60% pred.) and severe (<40% pred.)

Examine the cardiovascular response:
- Examine HR response (remember that max HR should be achieved at peak exercise)
  - HR max (should be >90% of predicted)
  - Calculate HR reserve = predicted − achieved HR (normal is ±15)
  - HR curve (should be along the predicted curve)
- Examine O_2 pulse at peak $\dot{V}O_2$
  - Determine the value of O_2 pulse at peak exercise (>80% predicted)
  - O_2 pulse curve should run along the predicted curve
- Determine AT (>40% predicted $\dot{V}O_2$ max); graphically identify AT from: $\dot{V}_E$, $\dot{V}CO_2$, $\dot{V}_E / \dot{V}O_2$ and $P_{ET}O_2$ curves
- Examine $\dot{V}O_2$ vs. WR curve; it should run along the predicted curve
- Report the BP (normally: 205 ± 25 over 100 ± 10; i.e. ↑systolic and pulse pressures)
- Examine the ECG for arrhythmia and/or ischemia

Examine the ventilatory response:
- Determine $\dot{V}_E$ max
- Compare the calculated MVV to the predicted MVV
  - Examine $\dot{V}_E$ curve (should be along the predicted curve and shouldn't reach MVV)
  - Determine $\dot{V}_E$ (ventilatory) reserve = calculated MVV − $\dot{V}_E$ max (should be >11 L/min)
  - Determine the breathing reserve = $\dot{V}_E$ max/calculated MVV × 100 (should be <85%)
- RR max (<60 breaths/min)
- Examine tidal FV loops for dynamic hyperinflation, expiratory flow limitation, end-inspiratory lung volume relative to TLC and inspiratory reserve volume

Examine the gas exchange response:
- Examine the dead space fraction:
  - V_D/V_T normally decreases with exercise
  - Determine $\dot{V}_E / \dot{V}CO_2$ at AT (<34)—a surrogate marker for V_D fraction
  - Determine $\dot{V}_E / \dot{V}O_2$ at AT (<31)
- Check $P_{ET}CO_2$ (and $PaCO_2$) at peak exercise (it normally decreases)
- Determine RER at peak $\dot{V}O_2$ (1.1–1.3)
- Determine SpO_2 (more accurately SaO_2) at peak $\dot{V}O_2$ (it shouldn't drop by >5%)
- ABG at the end of exercise
  - P_aO_2 is unchanged normally with exercise
  - $P_{(A\text{-}a)}O_2$ increases slightly but shouldn't exceed 35 mmHg

Finally, the conclusion

Table 9.6 Factors suggesting a maximal effort [17, 48, 149]

Achieving predicted peak $\dot{V}O_2$ and/or a plateau is observed in $\dot{V}O_2$ vs. WR curve
Achieving predicted maximum WR
Achieving predicted maximum HR
$\dot{V}_E$ max approaching or exceeding the calculated MVV
RER of ≥1.15
Patient exhaustion with a Borg scale rating of 9–10

Exercise Capacity

Determine whether the exercise capacity is normal by checking the peak $\dot{V}O_2$, WR and their relationship:

- Peak $\dot{V}O_2$ should be more than 84% of the predicted peak $\dot{V}O_2$ ($\dot{V}O_2$ max). If peak $\dot{V}O_2$ is normal, then you are likely to be dealing with a normal subject. If peak $\dot{V}O_2$ is reduced, then you need to determine the cause, which could be cardiac disease, pulmonary disease, neuromuscular disease, deconditioning, reduced oxygen carrying capacity or submaximal effort. The degree of impairment of exercise capacity is graded into mild, moderate and severe depending on peak $\dot{V}O_2$ (e.g. peak $\dot{V}O_2$ of 60–84% pred. is mild; 40–60% pred. is moderate; <40% pred. is severe).
- Achieving the predicted WR (in watts) also indicates a normal exercise capacity, while failure to achieve the predicted WR indicates a decreased exercise capacity.[4]

Cardiovascular System

Determine whether the cardiovascular response to exercise is normal by looking at the HR max, O_2 pulse, the onset of AT, $\dot{V}O_2$ vs. WR curve, BP and ECG.

- The predicted HR max is reached at the predicted peak $\dot{V}O_2$ in normal subjects (Figure 9.12a), but is reached prematurely

[4] Graphically, looking at $\dot{V}O_2$ vs. WR curve serves the same target. If the curve reaches the predicted peak $\dot{V}O_2$, then the exercise capacity is normal; Figure 9.11a. A subnormal exercise capacity is indicated when the curve doesn't reach the predicted peak $\dot{V}O_2$, with or without an early plateau; Figure 9.11b,c.

in patients with heart disease. This is because these patients can't increase their SV appropriately in response to exercise. The HR vs. $\dot{V}O_2$ curve will generally have a steeper slope (left shift) compared to controls; Figure 9.12b. In patients with lung disease, the predicted HR max is usually not reached and their HR reserve is then increased; Figure 9.12c. Patients with chronotropic incompetence (i.e. can't increase HR appropriately) such as patients with pacemakers, those on β-blockers or patients with severe HF [61, 82], may have a

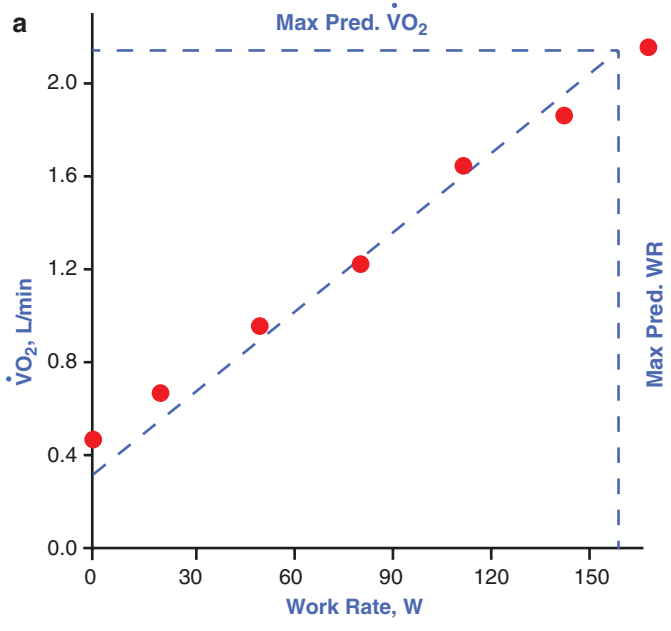

FIGURE 9.11 $\dot{V}O_2$ vs. WR curve; (**a**) Patient achieved predicted max $\dot{V}O_2$; (**b**) Patient didn't achieve the predicted max $\dot{V}O_2$, indicating exercise limitation; (**c**) Patient didn't achieve the predicted max $\dot{V}O_2$ with an early plateau, indicating reaching $\dot{V}O_2$ max and exercise limitation most likely related to a cardiovascular disease. (With permission from: ATS/ACCP Statement on Cardiopulmonary Exercise Testing; Am J Respir Crit Care Med Vol 167. pp 211–277, 2003)

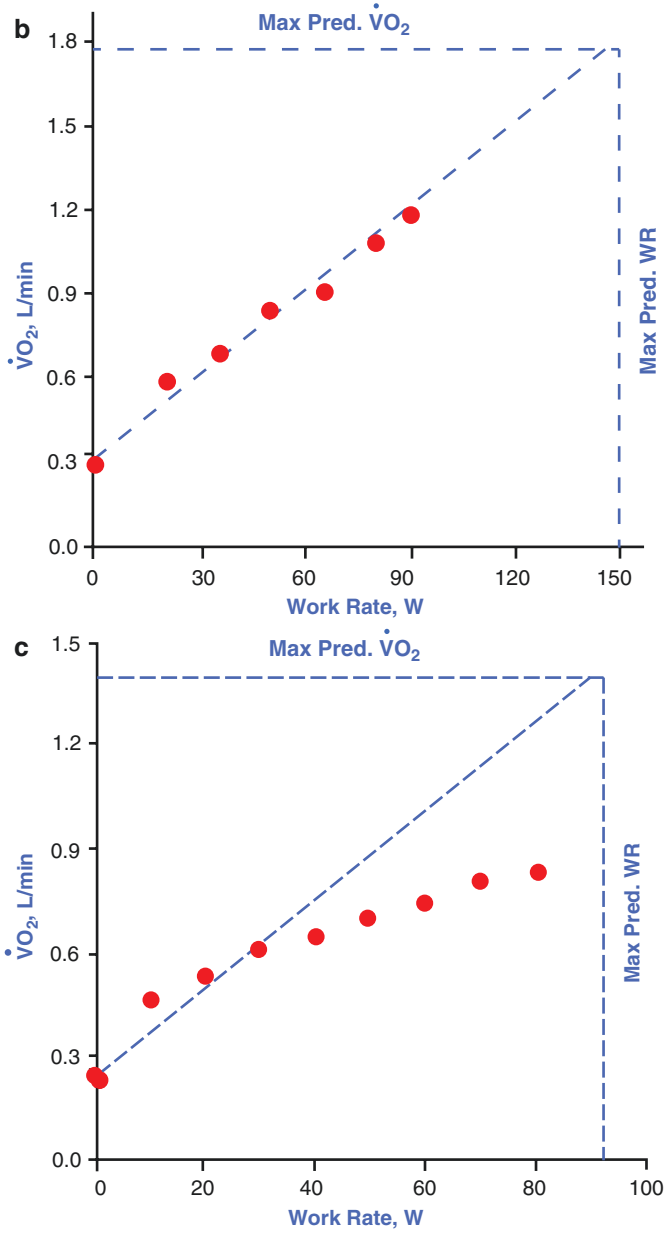

FIGURE 9.11 (continued)

high HR reserve but are still limited by their cardiovascular system.

- The O_2 pulse, which is representative of the SV, is generally decreased at peak exercise in patients with heart disease and its curve shows an early plateau; Figure 9.12b. In normal patients and in patients with lung disease, however, the O_2 pulse is usually normal; Figure 9.12a, c.
- The AT is typically reached earlier than predicted in patients with heart disease. In patients with lung disease, however, it is normal, indeterminate or not reached as the patient may stop prematurely due to ventilatory limitation. AT can be

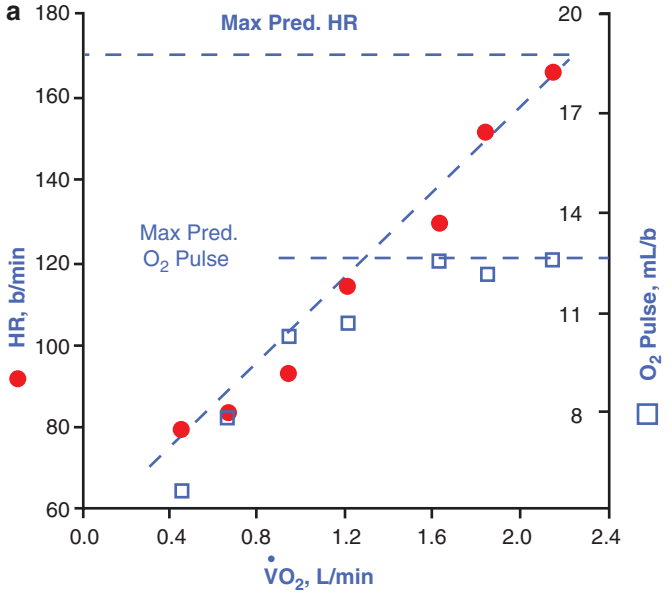

FIGURE 9.12 HR and O_2 Pulse vs. $\dot{V}O_2$ curves; (**a**) HR and O_2 Pulse curves along the predicted curves, indicating normal response to exercise; (**b**) HR curve shifted to the left with steep slope; O_2 Pulse curve has an early plateau indicating a cardiac disease limiting exercise; (**c**) HR and O_2 Pulse curves along the predicted curves but with increased HR reserve. This pattern can be seen in submaximal effort and in respiratory disease. (With permission from: ATS/ACCP Statement on Cardiopulmonary Exercise Testing; Am J Respir Crit Care Med Vol 167. pp 211–277, 2003)

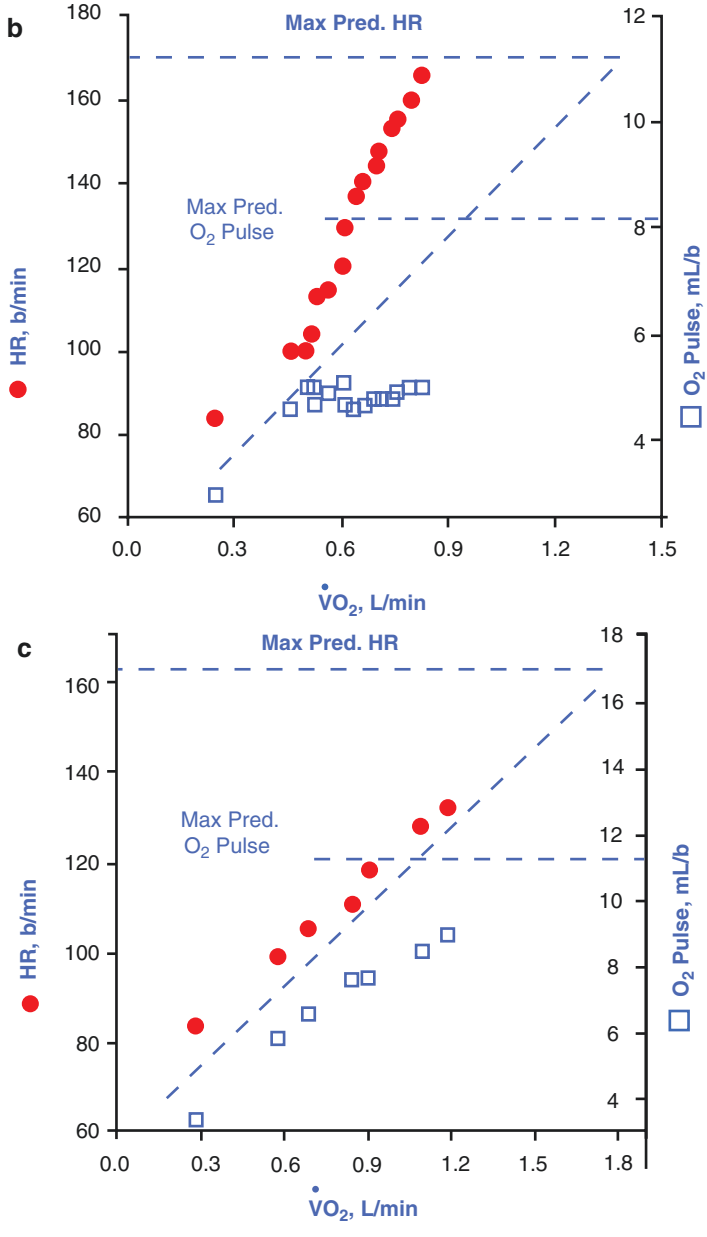

Figure 9.12 (continued)

determined from $\dot{V}_E$, $\dot{V}CO_2$, $\dot{V}_E / \dot{V}O_2$ or $P_{ET}O_2$ curves; Figure 9.6.
- An early plateau of the $\dot{V}O_2$ vs. WR curve (i.e. $\downarrow \Delta\dot{V}O_2 / \Delta WR$ ratio) also suggests a cardiovascular limitation to exercise; Figure 9.11c [83, 84].
- An abnormal BP response (excessive rise, failure to rise or drop in BP) suggests a cardiovascular abnormality.
- Exercise-related significant ECG changes (arrhythmia or ischemia) suggest a cardiac disease.

Respiratory System

- *Ventilatory Response:*
  Determine whether the ventilatory response is normal by looking at $\dot{V}_E$ max, breathing (and/or ventilatory) reserve, RR and tidal FV loops:
  - The measured $\dot{V}_E$ max is normally much less than the measured or calculated MVV (the calculated MVV should equal or be close to the predicted MVV in normal subjects); Figure 9.13a. In disease, however, $\dot{V}_E$ max approaches or even exceeds the calculated MVV which is shown as a shift to the left in $\dot{V}_E$ curve; Figure 9.13b. The calculated MVV itself is significantly reduced compared to the predicted MVV in these patients.
  - The breathing reserve ($\dot{V}_E$ max/Calculated MVV × 100) is usually >85% in patients with ventilatory disease and is much lower in normal subjects and in patients with a pure cardiac disease. There is normally a significant ventilatory reserve (Calculated $MVV - \dot{V}_E$ max), which is reduced in ventilatory disease.
  - RR often increases excessively in ventilatory disease.
  - In COPD, evidence of dynamic hyperinflation in the tidal FV loops indicates a ventilatory limitation to exercise; Figure 9.10. This is not seen normally or in patients with isolated heart disease.
- *Gas Exchange Response:*
  Determine whether the gas exchange response is normal by looking at V_D/V_T, $P_{ET}CO_2$ (and P_aCO_2), S_pO_2 and the ABG at exercise termination (if measured).
  - V_D/V_T fails to drop as expected or even increases in patients with a gas exchange abnormality in response to exercise, while it decreases in normal subjects. It may behave abnor-

mally with exercise in patients with a significant cardiac disease because of impaired lung perfusion.

– A gas exchange disorder can result in an abnormal increase in P_aCO_2 and $P_{ET}CO_2$ at peak exercise, while they normally decrease. Similarly, these variables increase with a ventilatory disease.

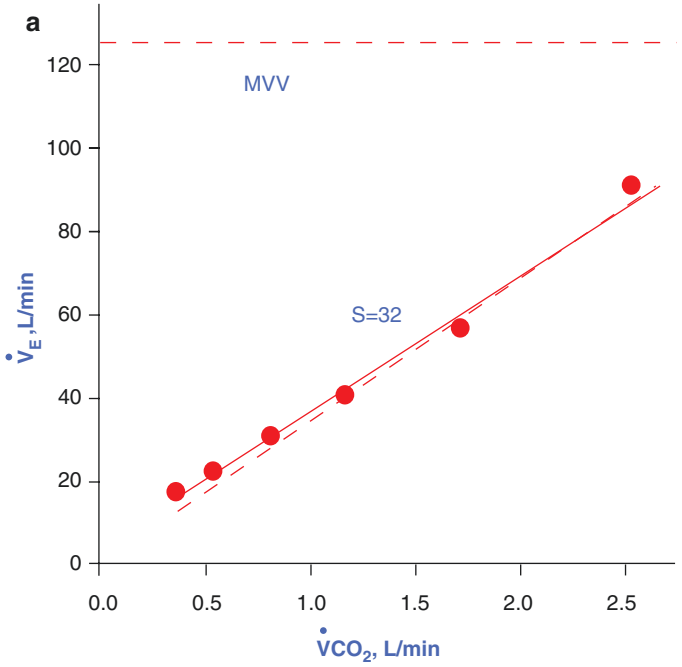

FIGURE 9.13 $\dot{V}_E$ vs. $\dot{V}CO_2$ curve; (**a**) a normal patient with normal curve (solid curve), along the predicted (dashed) curve. The calculated MVV (dashed horizontal line) here equals the predicted MVV. Note the significant ventilatory reserve; (**b**) a patient with ventilatory limitation with a left shift of the curve compared to the predicted (dashed) curve. The calculated MVV (dashed horizontal line) is much lower than the predicted MVV (not shown in this figure), and there is no ventilatory reserve. (With permission from: ATS/ACCP Statement on Cardiopulmonary Exercise Testing; Am J Respir Crit Care Med Vol 167. pp 211–277, 2003)

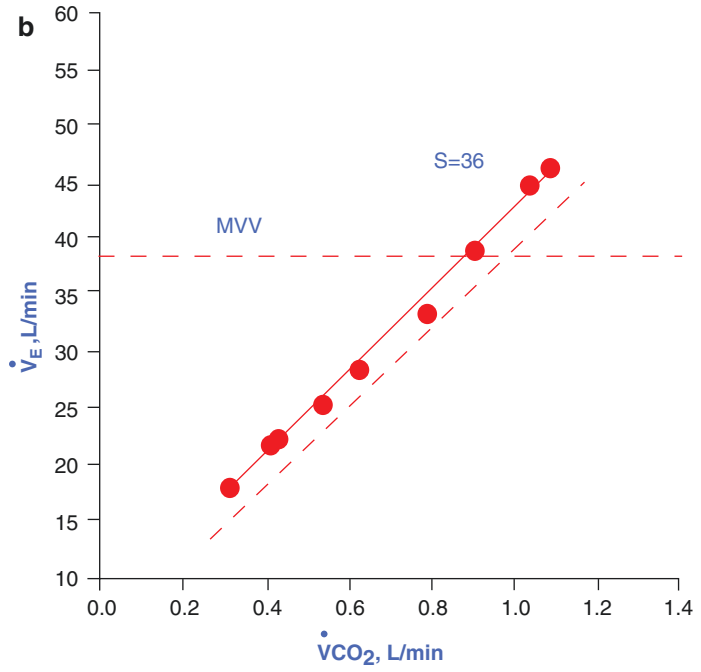

FIGURE 9.13 (continued)

- In patients with a gas exchange abnormality, PaO_2 is reduced and $P_{(A\text{-}a)}O_2$ is increased (>35 mmHg) because of impaired gas exchange and $\dot{V}/Q$ mismatch, while PaO_2 remains stable normally during exercise. $P_{(A\text{-}a)}O_2$ may show a slight increase in normal subjects as a result of $\dot{V}/Q$ mismatching, O_2 diffusion limitation and low mixed venous O_2 [85].
- Similarly, S_PO_2 (and SaO_2) is unchanged in most normal subjects during exercise but may drop in gas exchange disturbances.

- Tables 9.7 and 9.8 show the classic findings in pure cardiac and pulmonary disease in a step-wise approach. Table 9.9 summarizes the exercise patterns of other common conditions.

TABLE 9.7 Pattern in pure Cardiac Disease like cardiomyopathy

The baseline spirometry and maximal flow volume loop are usually normal
Exercise capacity is reduced:
↓ peak $\dot{V}O_2$ (<84% predicted)
Maximum WR is usually ↓
The reason for exercise termination is usually fatigue because of early AT, but it could be dyspnea related to left ventricular failure
The cardiovascular response is abnormal:
HR response
HR max is usually achieved early (>90% predicted)
No HR reserve (<15 bpm)
HR curve is steep (left shifted)
O_2 pulse at peak $\dot{V}O_2$
The value of O_2 pulse is decreased (<80% predicted)
O_2 pulse curve shows an early plateau
AT has an early onset (<40% predicted)
$\dot{V}O_2$ vs. WR curve may show an early plateau
The BP may show abnormal response to exercise (abnormally low)
ECG may show arrhythmia or ischemia
The ventilatory response is normal (under-stressed):
$\dot{V}_E$ max is normal
The calculated MVV is usually equal to or close to the predicted MVV
$\dot{V}_E$ curve is normal (along the predicted curve)
Ventilatory reserve is normal (>11 L/min)
Breathing reserve is normal or even low because $\dot{V}_E$ max is decreased (the patient stopped prematurely)
RR max is normal (<60 breaths/min)
Tidal FV loops show no evidence of dynamic hyperinflation
The gas exchange response is normal:
Dead space fraction:
V_D/V_T decreases with exercise (which is normal) OR is slightly elevated because of impaired lung perfusion
$P_{ET}CO_2$ (and $PaCO_2$) decrease at peak exercise which is normal
RER at peak $\dot{V}O_2$ is normal (1.1–1.3)
SpO_2 (and SaO_2) at peak $\dot{V}O_2$ is normal
P_aO_2 and $P_{(A-a)}O_2$ at the end of exercise are usually normal
Conclusion: reduced exercise capacity with impaired cardiovascular response indicating a cardiac origin of exercise limitation

TABLE 9.8 Pattern in pure Pulmonary Disease like COPD and ILD

The baseline spirometry and flow volume loop are abnormal
Exercise capacity is reduced:
- ↓ peak $\dot{V}O_2$ (<84% predicted); reduced WR
- The reason for exercise termination is usually dyspnea with ↑ Borg scale for dyspnea
- V_E max approaching the calculated MVV (mainly with a ventilatory disease)

The cardiovascular response is normal (under-stressed):
- HR response
  - HR max is not achieved (<90% predicted)
  - Large HR reserve (>15 bpm)
  - HR curve is normal (along the predicted curve)
- O_2 pulse at peak $\dot{V}O_2$
  - The value of O_2 pulse is normal (>80% predicted)
  - O_2 pulse curve is normal (along the predicted curve)
- AT is normal (>40% predicted) or indeterminate if patient stops before reaching AT because of severe ventilatory limitation
- The BP response is normal
- ECG is usually normal

The ventilatory response is abnormal (typically in a ventilatory disease such as COPD):
- $\dot{V}_E$ max/MVV is high
  - The calculated MVV is much less than the predicted MVV
  - $\dot{V}_E$ curve is shifted upwards and to the left
  - No ventilatory reserve (<11 L/min)
  - Breathing reserve ($\dot{V}_E$ max/MVV) is increased, can be >100%
- RR max is ↑ (Typically very high in patients with ILD because of ↓ V_T)
- In COPD, tidal FV loops may show evidence of dynamic hyperinflation

The gas exchange response is abnormal (typically in a gas exchange disorder as ILD):
- Dead space fraction:
  - V_D/V_T is ↑ at rest and only drops slightly with exercise. It may even increase
  - $\dot{V}_E / \dot{V}CO_2$ at AT is increased (>34)
- $P_{ET}CO_2$ and $PaCO_2$ are increased at peak exercise
- RER at peak $\dot{V}O_2$ may be increased
- SpO_2 (and SaO_2) at peak $\dot{V}O_2$ may be reduced (≥5%)
- ABG at peak $\dot{V}O_2$ may show ↓PaO_2 and ↑$P_{(A-a)}O_2$ (>35 mmHg)

Conclusion: reduced exercise capacity with impaired ventilatory, gas exchange or both responses to exercise indicating a pulmonary origin of exercise limitation

TABLE 9.9 Exercise test pattern in other common conditions

Pulmonary hypertension
Exercise capacity is ↓
The cardiovascular response is abnormal (similar to pure cardiac disease)
Ventilatory response may be normal (lung parenchyma is normal)
Gas exchange response is abnormal: ↑ resting V_D/V_T with minor drop or even increase with exercise; $P_{(A\text{-}a)}O_2$ increases and PaO_2 drops with exercise
Myopathy
Exercise capacity is ↓
The cardiovascular response is abnormal (similar to pure cardiac disease)
Ventilatory response is abnormal (similar to pure lung disease but without complete ventilatory limitation based on $\dot{V}_E$ / MVV)
Gas exchange response is normal
Obesity
Exercise capacity is ↓ in mL/kg/min but normal in L/min. The $\dot{V}O_2$ vs. WR curve is shifted upwards relative to normal
The cardiovascular response is normal
Ventilatory response is normal
Gas exchange response is normal
Deconditioning
Exercise capacity is ↓
The cardiovascular response is borderline—abnormal (HR max is reached earlier than normal and O_2 pulse is not profoundly reduced and may course along the predicted curve, except that it doesn't reach its peak because of early exercise termination)
Ventilatory response is normal
Gas exchange response is normal
Malingering
Exercise capacity is ↓ with no obvious reason
The cardiovascular response is normal
Ventilatory response is normal
Gas exchange response is normal

Illustrative Examples

Case 1

A 37 year-old male, Caucasian, presented with shortness of breath. The history and the physical examination were unremark-

able. The initial investigations, including a chest X ray, ECG and a detailed lung function study were normal. A cardiopulmonary exercise test was performed to determine the cause of the patient's shortness of breath. Weight 70 kg; height 184 cm.

- Test details
  - *Instrument*: Cycle erogometer
  - *Technique*: Incremental
  - *Reason for exercise termination*: leg fatigue
  - *Modified Borg scale*: for dyspnea (8); for leg discomfort (9)
  - *ECG*: normal throughout exercise
- *Spirometry*

	Pred.	Measured	% pred.
FVC (Liters)	5.60	4.84	86
FEV_1 (Liters)	4.52	4.30	95
FEV_1/FVC ratio (%)		89	
MVV[a] (L/min)	158	150 (Calculated)	

[a]*The conversion factor used in these cases is 35 (not 40)*

- *Resting data*

HR (bpm)	80
BP (mmHg)	116/76
S_PO_2 (%)	99
V_D/V_T	0.24

- *Cardiovascular Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}O_2$ / kg (ml/kg/min)	39.6	44.0	111
$\dot{V}O_2$ (L/min)	3.0	3.1	101
WR (Watts)	254	250	98
HR (bpm)	176	181	103
O_2 pulse (ml/beat)	17.1	16.9	99
$\dot{V}O_2$ @ AT (L/min)		1.9	63[a]

	Pred.	Measured	% pred.
$\dot{V}CO_2$ (L/min)		3.20	
BP (mmHg)		180/90	

[a]As a percentage of predicted $\dot{V}O_2$ max

- *Ventilatory Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}_E$ (L/min)		92	
$\dot{V}_E$ / MVV × 100 (%)		61	
V_T (Liters)	2.27	2.19	96
RR (breaths/min)		42	
Tidal FV loops:	Normal throughout exercise		

- *Gas-exchange Response @ peak exercise*

	Pred.	Measured	% pred.
$P_{ET}CO_2$ (mmHg)		35	
V_D/V_T	0.18	0.13	72
$\dot{V}_E$ / $\dot{V}O_2$ @ AT		27	
$\dot{V}_E$ / $\dot{V}CO_2$ @ AT		25	
S_PO_2 (%)		99	
RER		1.05	

- For the graphic representation of the patient's data, see Figure 9.14

Interpretation

- The test was performed because the resting data couldn't explain the patient's symptoms. The instrument used was a cycle ergometer with an incremental increase in WR. Exercise was terminated because of leg discomfort that scored 9/10 on the modified Borg scale, while dyspnea scored 8/10.

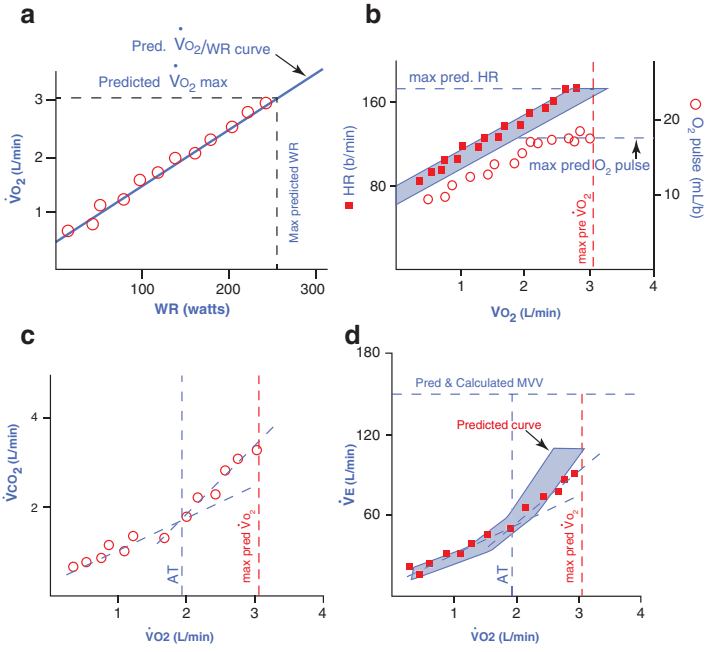

FIGURE 9.14 (**a**) $\dot{V}O_2$ vs. WR curve; (**b**) HR and O_2 pulse vs. $\dot{V}O_2$ curves; (**c**) $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve; (**d**) $\dot{V}_E$ vs. $\dot{V}O_2$ curve

- Baseline spirometry was normal.
- The patient achieved a maximal effort as evident by:
  - Achieving predicted $\dot{V}O_2$ max (101% pred.), see also Figure 9.14a.
  - Achieving predicted maximum WR (98% pred.); Figure 9.14a.
  - Achieving predicted maximum HR (103% pred.), see also Figure 9.14b.
  - Patient's exhaustion; scoring 9/10 for leg discomfort on modified Borg scale at peak exercise.
- The exercise capacity was normal as:
  - Peak $\dot{V}O_2$ was >84% of the predicted $\dot{V}O_2$ max. Peak $\dot{V}O_2$ even exceeded the predicted value of $\dot{V}O_2$ max (101%). This

fact can also be shown in $\dot{V}O_2$ vs. WR curve, Figure 9.14a, as the peak $\dot{V}O_2$ approached the predicted $\dot{V}O_2$ max.
  - Similarly, the predicted maximum WR had been achieved (98% pred.); Figure 9.14a.
- Cardiovascular response:
  - The HR response was normal as:
    (a) HR max was 103% pred. (normal is >90% pred.).
    (b) There was no HR reserve (176 – 181 = –5 which is normal).
    (c) HR curve is along the predicted curve; Figure 9.14b.
  - O_2 pulse at peak exercise was normal (99% pred.) and its curve is along the predicted one; Figure 9.14b.
  - AT as determined from $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve (V-slope) and $\dot{V}_E$ vs. $\dot{V}O_2$ curve, equaled 1.9 L/min (63% of predicted $\dot{V}O_2$ max) which is normal (>40%); Figure 9.14c, d.
  - $\dot{V}O_2$ vs. WR curve is along the predicted curve; Figure 9.14a.
  - ECG and BP responses were normal.
  - Therefore, the cardiovascular response was normal.
- Ventilatory response:
  - The ventilatory response was normal:
    (a) The calculated and predicted MVV are almost identical (150 and 158 L/min, respectively).
    (b) The $\dot{V}_E$ vs. $\dot{V}O_2$ curve is along the predicted one; Figure 9.14d.
    (c) The ventilatory reserve was normal (150 – 92 = 58 L/min, which is >11 L/min).
    (d) The breathing reserve was also normal (92/150 × 100 = 61%, which is <85%).
  - RR at peak exercise was normal (42 breaths/min).
  - Tidal FV loops were normal with no evidence of dynamic hyperinflation (not shown).
  - Therefore, the ventilatory response was normal.
- Gas-exchange response:
  - Dead space fraction @ peak exercise was normal:
    (a) V_D/V_T dropped from 0.24 (at rest) to 0.13 (at peak exercise) which is a normal response.
    (b) $\dot{V}_E / \dot{V}CO_2$ and $\dot{V}_E / \dot{V}O_2$ @ AT were normal (25 and 27, respectively).
  - $P_{ET}CO_2$ @ peak exercise was normal.
  - RER @ peak exercise was 1.05 which is normal.

  - S_PO_2 had remained normal throughout exercise (99%).[5]
  - Therefore, the gas-exchange response was normal.
- Conclusion
  (a) There was no evidence of exercise limitation. The study is normal.

Case 2

A 31 year-old male, Caucasian, a known case of pulmonary hypertension secondary to pulmonary thromboembolism has recently undergone thromboendarterectomy. A cardiopulmonary exercise test was performed to evaluate the results of this intervention. The patient is also known to have significant emphysema secondary to alpha-1-anti-trypsin deficiency. Weight 121 kg; height 190 cm.

- *Test details*
  - *Instrument*: Cycle erogometer
  - *Technique*: Incremental
  - *Reason for exercise termination*: dyspnea
  - *Modified Borg scale*: for dyspnea (9); for leg discomfort (9)
  - *ECG*: normal throughout exercise
- *Spirometry*

	Pred.	Measured	% pred.
FVC (Liters)	6.09	4.29	70
FEV_1 (Liters)	4.92	2.23	45
FEV_1/FVC ratio (%)		52	
MVV (L/min)	172	78 (Calculated)	

- *Resting data*

HR (bpm)	95
BP (mmHg)	117/75
S_PO_2 (%)	100
V_D/V_T	0.39

[5] Comment on the ABG result before and after exercise especially PaO_2, $PaCO_2$ & $P_{(A\text{-}a)}O_2$ if ABG is available.

- *Cardiovascular Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}O_2$ / kg (ml/kg/min)	43	15.7	37
$\dot{V}O_2$ (L/min)	4.5	1.9	42
WR (Watts)	287	132	46
HR (bpm)	181	148	82
O_2 pulse (ml/beat)	21.0	12.8	61
$\dot{V}O_2$ @ AT (L/min)		1.4	31[a]
$\dot{V}CO_2$ (L/min)		2.3	
BP (mmHg)		180/90	

[a]As a percentage of predicted $\dot{V}O_2$ max

- *Ventilatory Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}_E$ (L/min)		95	
$\dot{V}_E$ / MVV × 100 (%)		122	
V_T (Liters)	2.2	2.0	91
RR (breaths/min)		48	

- *Gas-exchange Response @ peak exercise*

	Pred.	Measured	% pred.
$P_{ET}CO_2$ (mmHg)		26.4	
V_D/V_T	0.18	0.13	72
$\dot{V}_E$ / $\dot{V}O_2$ @ AT		31	
$\dot{V}_E$ / $\dot{V}CO_2$ @ AT		32	
S_PO_2 (%)		99	
RER		1.21	

- For the graphic representation of the patient's data, see Figure 9.15

Interpretation

- Incremental cardiopulmonary exercise testing using a cycle ergometer was performed to assess the response to endarterectomy. Exercise was terminated because of dyspnea that scored 9/10 on the modified Borg scale; leg discomfort similarly scored 9/10.
- Baseline spirometry shows severe obstructive defect indicating that the patient's emphysema is severe.
- The patient achieved a maximal effort as evident by:
  - Patient's exhaustion; scoring 9 for dyspnea and leg discomfort on the modified Borg scale.
  - Exceeding the calculated MVV; see Figure 9.15d.
  - Achieving an RER of 1.21.
- The exercise capacity was moderately-to-severely reduced as:
  - Peak $\dot{V}O_2$ was only 42% of the predicted $\dot{V}O_2$ max and the achieved WR at peak exercise was only 46% of the predicted maximum WR. These features are also noticed in the $\dot{V}O_2$ vs. WR curve; Figure 9.15a.
- Cardiovascular response:
  - The HR response was normal although the patient did not achieve his maximum predicted HR as he needed to terminate exercise prematurely because of ventilatory limitation:
    (a) HR max was 82% pred. which is abnormally low (normal >90% pred.).
    (b) Increased HR reserve (181 – 148 = 33 bpm).
    (c) HR curve is along the predicted curve; Figure 9.15b.
  - O_2 pulse at peak exercise was low (61% pred.); Figure 9.15b. The decreased stroke volume response could be due to deconditioning or reduced O_2 carrying capacity.
  - AT was low (1.4 L/min or 31% of predicted $\dot{V}O_2$ max) as determined from $\dot{V}CO_2$ vs. $\dot{V}O_2$ and $\dot{V}_E$ vs. $\dot{V}O_2$ curves; Figure 9.15c, d. The early onset of AT could similarly be related to deconditioning or reduced O_2 carrying capacity.
  - $\dot{V}O_2$ vs. WR curve is parallel to the predicted curve but $\dot{V}O_2$ is slightly lower than expected for any given WR; Figure 9.15a. The curve didn't reach a plateau.
  - ECG and BP responses were normal.
  - Therefore, cardiovascular response was normal.

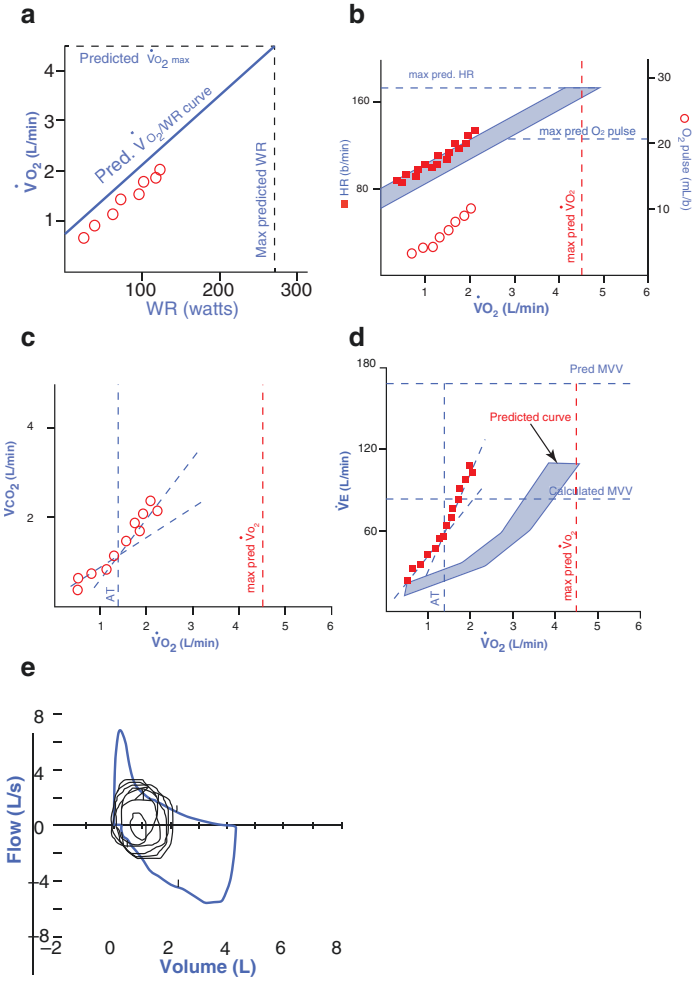

FIGURE 9.15 (**a**) $\dot{V}O_2$ vs. WR curve; (**b**) HR and O_2 pulse vs. $\dot{V}O_2$ curves; (**c**) $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve; (**d**) $\dot{V}_E$ vs. $\dot{V}O_2$ curve; (**e**) Tidal FV loops during exercise within the maximal FV loop

- Ventilatory response:
  - The ventilatory response was abnormal:
    (a) The calculated MVV was much lower than the predicted MVV indicating the patient had a ventilatory abnormality.
    (b) The $\dot{V}_E$ vs. $\dot{V}O_2$ curve is shifted to the left indicating an abnormally increased ventilatory response; Figure 9.15d.
    (c) There was no ventilatory reserve (78 – 95 = –27 L/min; normal >11 L/min).
    (d) The breathing reserve was also abnormally high (95/78 × 100 = 122%; normal <85%).
  - Tidal FV loops showed evidence of expiratory flow limitation and no inspiratory reserve volume during exercise (Figure 9.15e).
  - Therefore, there was an abnormal ventilatory response to exercise.
- Gas-exchange response:
  - Dead space fraction @ peak exercise was normal:
    (a) V_D/V_T dropped from 0.39 (at rest) to 0.13 (at peak exercise) which is a normal response.
    (b) $\dot{V}_E / \dot{V}CO_2$ (32) and $\dot{V}_E / \dot{V}O_2$ (31) @ AT were at the upper limit of normal.
  - $P_{ET}CO_2$ @ peak exercise was normal.
  - RER @ peak exercise was 1.21 which is normal.
  - SpO_2 remained normal throughout exercise (99–100%).
  - No ABG was done.
  - Therefore, there was no significant gas-exchange abnormality.
- Conclusion
  - Findings suggest moderate-to-severe exercise limitation associated with an abnormal venitilatory response which could be attributed to the significant obstructive disorder (COPD). There was no significant gas-exchange abnormality as dead space fraction behaved normally with exercise as did the SpO_2. The patient had a normal HR response to exercise but the reduced O_2 pulse and AT suggests deconditioning or reduced O_2 carrying capacity. Lack of an appropriate increase in HR response to compensate for the decreased stroke volume may indicate that the patient was on a β-blocking agent.

Case 3

A 25 year-old female, Caucasian, who is known to have an idiopathic cardiomyopathy, underwent cardiopulmonary exercise testing to assess the need for a cardiac transplant. Weight 68 kg; height 171 cm.

- *Test details*
  - *Instrument*: Cycle erogometer
  - *Technique*: Incremental
  - *Reason for exercise termination*: fatigue
  - *Modified Borg scale*: for dyspnea (9); for leg discomfort (9)
  - *ECG*: normal throughout exercise
- *Spirometry*

	Pred.	Measured	% pred.
FVC (Liters)	4.27	3.39	79
FEV_1 (Liters)	3.41	2.93	86
FEV_1/FVC ratio (%)		86	
MVV (L/min)	119	103 (Calculated)	

- *Resting data*

HR (bpm)	94
BP (mmHg)	123/78
S_PO_2 (%)	96
V_D/V_T	0.36

- *Cardiovascular Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}O_2$ / kg (ml/kg/min)	39	21	54
$\dot{V}O_2$ (L/min)	3.4	1.4	41
WR (Watts)	170	96	56
HR (bpm)	182	189	104
O_2 pulse (ml/beat)	11.9	7.4	62

	Pred.	Measured	% pred.
$\dot{V}O_2$ @ AT (L/min)		0.74	22[a]
$\dot{V}CO_2$ (L/min)		1.7	
BP (mmHg)		137/88	

[a]As a percentage of predicted $\dot{V}O_2$ max

- *Ventilatory Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}_E$ (L/min)		65	
$\dot{V}_E$ / MVV×100 (%)		63	
V_T (Liters)	1.5	1.9	127
RR (breaths/min)		34	

- *Gas-exchange Response @ peak exercise*

	Pred.	Measured	% pred.
$P_{ET}CO_2$ (mmHg)		31.5	
V_D/V_T	0.18	0.13	72
$\dot{V}_E$ / $\dot{V}O_2$ @ AT		36	
$\dot{V}_E$ / $\dot{V}CO_2$ @ AT		36	
S_PO_2 (%)		95	
RER		1.2	

- For the graphic representation of the patient's data, see Figure 9.16

Interpretation

- An incremental cardiopulmonary exercise test using a cycle ergometer was performed to assess the need for a cardiac transplant. Exercise was terminated because of fatigue. The modified Borg score for dyspnea and leg discomfort was 9/10.
- Baseline spirometry was normal.

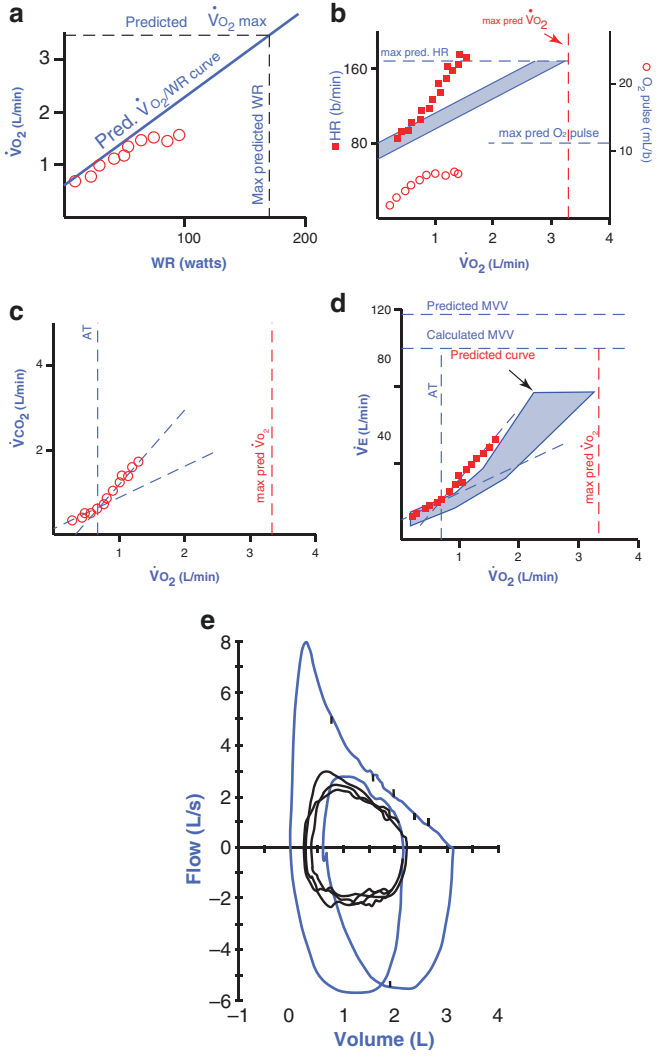

FIGURE 9.16 (**a**) $\dot{V}O_2$ vs. WR curve; (**b**) HR and O_2 pulse vs. $\dot{V}O_2$ curves; (**c**) $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve; (**d**) $\dot{V}_E$ vs. $\dot{V}O_2$ curve; (**e**) Tidal FV loops during exercise within the maximal FV loop

- The patient achieved a maximal effort as evident by:
  - Patient's exhaustion, scoring 9/10 for both dyspnea and leg discomfort on the modified Borg scale at peak exercise.
  - Reaching a plateau in the $\dot{V}O_2$ vs. WR curve; Figure 9.16a.
  - Achieving predicted maximum HR (104%); see also Figure 9.16b.
  - Achieving an RER of 1.2.
- The exercise capacity was moderately-to-severely reduced as:
  - Peak $\dot{V}O_2$ was 41% of the predicted $\dot{V}O_2$ max, see also $\dot{V}O_2$ vs. WR curve; Figure 9.16a.
  - Similarly, the WR achieved was low (56% pred.); see Figure 9.16a.
- Cardiovascular response:
  - The HR response was abnormally increased as:
    (a) The resting HR was increased (94 bpm).
    (b) The maximum predicted HR was achieved prematurely. HR max was 104% pred. with no HR reserve (189 – 182 = –7 bpm).
    (c) HR curve is steep and shifted to the left; Figure 9.16b.
  - O_2 pulse at peak exercise was reduced (62% pred.) and its curve shows an early plateau, Figure 9.16b.
  - AT was achieved prematurely (0.74 L/min, 22% of predicted $\dot{V}O_2$ max); Figure 9.16c, d. An early AT suggests a cardiovascular compromise.
  - $\dot{V}O_2$ vs. WR curve demonstrates an early plateau; Figure 9.16a.
  - BP response to exercise was abnormally low. The ECG was normal throughout exercise.
  - These findings suggest that a cardiac disease is responsible for exercise limitation.
- Ventilatory response:
  - Ventilatory response was normal:
    (a) The calculated and predicted MVV were within the acceptable range of normal (103 and 119 L/min, respectively).
    (b) The $\dot{V}_E$ vs. $\dot{V}O_2$ curve was along the predicted one with a small shift to the left; Figure 9.16d.
    (c) The ventilatory reserve was normal (103 – 65 = 48 L/min; normal >11 L/min).

(d) The breathing reserve was also normal (65/103 × 100 = 63%; normal <85%).
- RR @ peak exercise was 34 breaths/min.
- The tidal FV loops did not meet or exceed the maximal FV loop suggesting significant ventilatory reserve (i.e., no expiratory flow limitation); Figure 9.16e.
- The above findings suggest that the ventilatory system was under-stressed and its response to exercise was generally normal.

- Gas-exchange response:
  - Dead space fraction @ peak exercise was normal:
    (a) V_D/V_T dropped from 0.36 (at rest) to 0.13 (at peak exercise) which is a normal response.
    (b) $\dot{V}_E / \dot{V}CO_2$ and $\dot{V}_E / \dot{V}O_2$ @ AT were elevated (36 and 36, respectively).
  - $P_{ET}CO_2$ @ peak exercise was normal.
  - RER @ peak exercise was normal (1.2).
  - S_PO_2 remained normal throughout exercise (95%).
  - The slightly impaired gas exchange may suggest impaired lung perfusion secondary to cardiomyopathy.
- Conclusion
  - There was moderate-to-severe exercise limitation associated with an abnormal cardiovascular response. Findings also suggest some degree of gas-exchange abnormality which may be explained by impaired pulmonary perfusion.

Case 4

A 62 year-old male, Caucasian, with known idiopathic pulmonary fibrosis (IPF) undergoing cardiopulmonary exercise testing as part of lung transplant workup. The patient is on 24-hour O_2 therapy at 5 L/min through nasal prongs. Weight 79 kg; height 168 cm.

- *Test details*
  - *Instrument*: Cycle erogometer
  - *Technique*: Incremental
  - *Reason for exercise termination*: dyspnea
  - *Modified Borg scale*: for dyspnea (10); for leg discomfort (5)
  - *ECG*: normal throughout exercise

- *Spirometry*

	Pred.	Measured	% pred.
FVC (Liters)	4.10	1.97	48
FEV_1 (Liters)	3.25	1.35	42
FEV_1/FVC ratio (%)		69	
MVV (L/min)	114	47 (Calculated)	

- *Resting data*

HR (bpm)	92
BP (mmHg)	120/78
S_PO_2 (%)	98 (on 45% FIO_2)
V_D/V_T	0.34

- *Cardiovascular Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}O_2$ / kg (ml/kg/min)	25.9	15.2	59
$\dot{V}O_2$ (L/min)	2.2	1.2	55
WR (Watts)	151	70	46
HR (bpm)	156	114	73
O_2 pulse (ml/beat)	13.5	11.1	82
$\dot{V}O_2$ @ AT (L/min)		Indeterminate	
$\dot{V}CO_2$ (L/min)		1.4	
BP (mmHg)		177/98	

- *Ventilatory Response @ peak exercise*

	Pred.	Measured	% pred.
$\dot{V}_E$ (L/min)		37	
$\dot{V}_E$ / MVV × 100 (%)		79	
V_T (Liters)	2.1	0.77	37
RR (breaths/min)		48	

- *Gas-exchange Response @ peak exercise*

	Pred.	Measured	% pred.
$P_{ET}CO_2$ (mmHg)		44.3	
V_D/V_T	0.18	0.32	178
S_pO_2 (%)		91	
RER		1.17	

- For the graphic representation of the patient's data, see Figure 9.17

Interpretation

- An incremental cardiopulmonary exercise test using a cycle ergometer was performed as part of lung transplant workup. Exercise was terminated because of dyspnea. The modified Borg score for dyspnea was 10/10 and for leg discomfort was 5/10.
- Baseline spirometry showed severe restriction with a mild obstructive component.
- The patient achieved a maximal effort as evident by:
  - Patient's exhaustion, scoring 10/10 for dyspnea on the modified Borg scale at peak exercise.
  - $\dot{V}_E$ max approaching the calculated MVV (>70% of calculated MVV).
  - Achieving an RER of 1.17.
- The exercise capacity was moderately reduced as:
  - Peak $\dot{V}O_2$ was 55% of the predicted $\dot{V}O_2$ max, see also Figure 9.17a.
  - Similarly, the WR achieved was reduced (46% pred.); see Figure 9.17a.
- Cardiovascular response:
  - The HR response was normal:
    (a) Although the resting HR was high (92 bpm), the maximum predicted HR hadn't been achieved at peak exercise (73% pred). Therefore, the HR reserve was high (156 – 114 = 42 bpm).
    (b) HR curve is running along the predicted curve; Figure 9.17b.
  - O_2 pulse response was normal (82% pred.); Figure 9.17b.

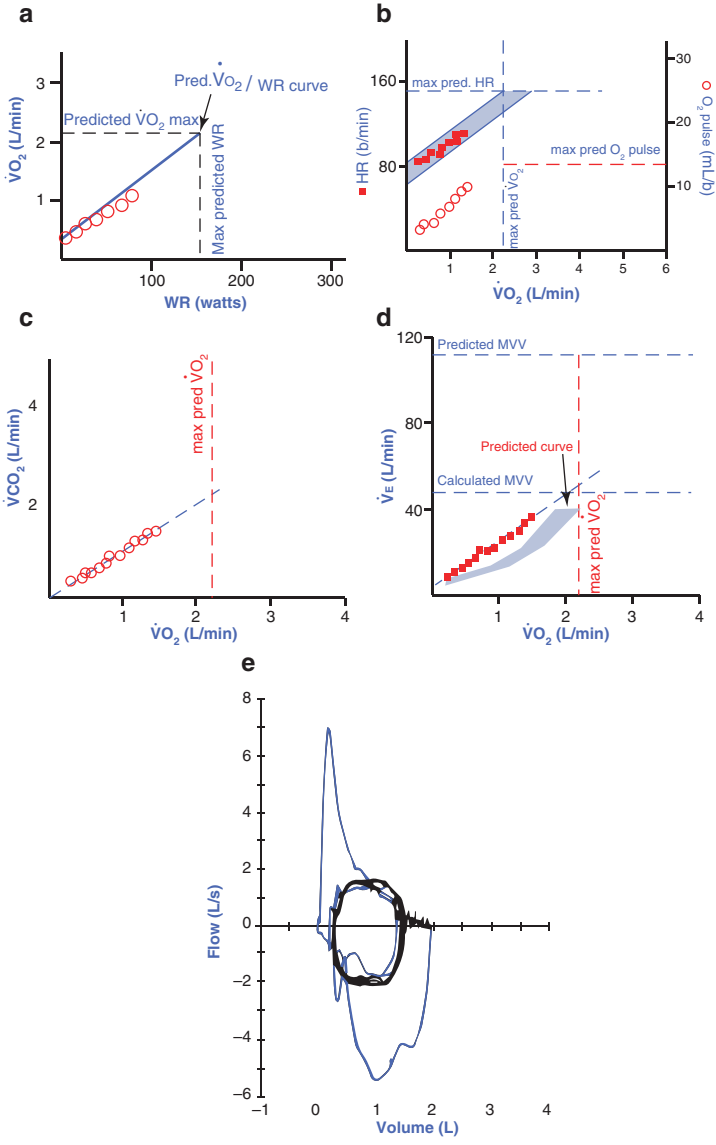

FIGURE 9.17 (**a**) $\dot{V}O_2$ vs. WR curve; (**b**) HR and O_2 pulse vs. $\dot{V}O_2$ curves; (**c**) $\dot{V}CO_2$ vs. $\dot{V}O_2$ curve; (**d**) $\dot{V}_E$ vs. $\dot{V}O_2$ curve; (**e**) Tidal FV loops during exercise within the maximal FV loop

  - AT couldn't be determined which may indicate that it hadn't been achieved as the cardiovascular system hadn't been stressed enough before exercise termination; Figure 9.17c. This strongly supports a non-cardiac cause for exercise limitation.
  - $\dot{V}O_2$ vs. WR curve was normal; Figure 9.17a.
  - BP and ECG responses to exercise were normal.
  - Therefore, the cardiovascular response to exercise was normal.
- Ventilatory response:
  - The ventilatory response was abnormal:
    (a) The calculated MVV was significantly reduced compared to the predicted one, suggesting a ventilatory disturbance, (47 and 114 liters, respectively).
    (b) The $\dot{V}_E$ vs. $\dot{V}O_2$ curve is slightly shifted to the left; Figure 9.17d.
    (c) Ventilatory reserve was reduced (47 – 37 = 10 L/min; normal >11 L/min), while the breathing reserve was normal (37/47 × 100 = 79%; normal <85%).
  - V_T @ peak exercise was significantly reduced (37% pred.).
  - Expiratory flow limitation was present based on the overlap between the tidal breaths and the maximal FV loop. The end-inspiratory lung volume is close to TLC (i.e., small inspiratory reserve volume). This pattern is compatible with the mechanical disturbance seen in patients with interstitial lung disease.
  - Therefore, there was an abnormal ventilatory response to exercise as evident by the reduced calculated MVV, reduced ventilatory reserve, constrained V_T (shallow breathing), expiratory flow limitation, small inspiratory reserve volume and left-shifted $\dot{V}_E$ curve. This ventilatory response is in keeping with a restrictive disorder as seen in IPF.
- Gas-exchange response:
  - Dead space fraction @ peak exercise was abnormally high:
    (a) V_D/V_T was high (at rest, 0.34) and remained elevated throughout exercise (0.32) indicating a gas-exchange abnormality.
  - $P_{ET}CO_2$ @ peak exercise was high.
  - SpO_2 dropped by >5% despite the supplemental O_2 (from 98 to 91%).

  - ABG was not performed.
  - These finding suggest a significant gas-exchange abnormality.
- Conclusion
  - There was moderate exercise limitation associated with an abnormal gas-exchange and ventilatory responses to exercise. Both abnormalities likely played a part in the exercise limitation.

REFERENCES

1. American Thoracic Society. ATS statement: guidelines for the six-minute walk test. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. Am J Respir Crit Care Med. 2002;166(1):111–7.
2. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest. 2001;119(1):256–70.
3. Bittner V, Weiner DH, Yusuf S, et al. Prediction of mortality and morbidity with a 6-minute walk test in patients with left ventricular dysfunction. SOLVD Investigators. JAMA. 1993;270(14):1702–7.
4. Enright PL, McBurnie MA, Bittner V, et al. The 6-min walk test: a quick measure of functional status in elderly adults. Chest. 2003;123(2):387–98.
5. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1384–7.
6. Barst RJ, Rubin LJ, McGoon MD, Caldwell EJ, Long WA, Levy PS. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. Ann Intern Med. 1994;121(6):409–15.
7. Miyamoto S, Nagaya N, Satoh T, et al. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2000;161(2 Pt 1):487–92.
8. Guyatt GH, Sullivan MJ, Thompson PJ, et al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. CMAJ. 1985;132(8):919–23.

9. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. Br Med J (Clin Res Ed). 1986;292(6521):653.
10. Holland AE, Spruit MA, Troosters T, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428–46.
11. Troosters T, Gosselink R, Decramer M. Six minute walking distance in healthy elderly subjects. Eur Respir J. 1999;14(2):270–4.
12. Stevens D, Elpern E, Sharma K, Szidon P, Ankin M, Kesten S. Comparison of hallway and treadmill six-minute walk tests. Am J Respir Crit Care Med. 1999;160(5):1540–3.
13. Enright PL. The six-minute walk test. Respir Care. 2003;48(8):783–5.
14. Jensen LA, Onyskiw JE, Prasad NG. Meta-analysis of arterial oxygen saturation monitoring by pulse oximetry in adults. Heart Lung. 1998;27(6):387–408.
15. Barthelemy JC, Geyssant A, Riffat J, Antoniadis A, Berruyer J, Lacour JR. Accuracy of pulse oximetry during moderate exercise: a comparative study. Scand J Clin Lab Invest. 1990;50(5):533–9.
16. Singh SJ, Puhan MA, Andrianopoulos V, et al. An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1447–78.
17. American Thoracic Society, American College of Chest Physicians. ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med. 2003;167(2):211–77.
18. Casanova C, Celli BR, Barria P, et al. The 6-min walk distance in healthy subjects: reference standards from seven countries. Eur Respir J. 2011;37(1):150–6.
19. Gibbons WJ, Fruchter N, Sloan S, Levy RD. Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years. J Cardiopulm Rehabil. 2001;21(2):87–93.
20. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377–81.
21. Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jenkins SC. Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. Chest. 2004;126(3):766–73.

22. Palange P, Forte S, Onorati P, Manfredi F, Serra P, Carlone S. Ventilatory and metabolic adaptations to walking and cycling in patients with COPD. J Appl Physiol (1985). 2000;88(5):1715–20.
23. Man WD, Soliman MG, Gearing J, et al. Symptoms and quadriceps fatigability after walking and cycling in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2003;168(5):562–7.
24. Poole GW, Maskell RC. Validation of continuous determination of respired gases during steady-state exercise. J Appl Physiol. 1975;38(4):736–8.
25. Spiro SG, Juniper E, Bowman P, Edwards RH. An increasing work rate test for assessing the physiological strain of submaximal exercise. Clin Sci Mol Med. 1974;46(2):191–206.
26. Hughson RL, Kowalchuk JM, Prime WM, Green HJ. Open-circuit gas exchange analysis in the non-steady-state. Can J Appl Sport Sci. 1980;5(1):15–8.
27. Beaver WL, Wasserman K, Whipp BJ. On-line computer analysis and breath-by-breath graphical display of exercise function tests. J Appl Physiol. 1973;34(1):128–32.
28. Clark JS, Votteri B, Ariagno RL, et al. Noninvasive assessment of blood gases. Am Rev Respir Dis. 1992;145(1):220–32.
29. Zeballos RJ, Weisman IM. Behind the scenes of cardiopulmonary exercise testing. Clin Chest Med. 1994;15(2):193–213.
30. Killian KJ, Leblanc P, Martin DH, Summers E, Jones NL, Campbell EJ. Exercise capacity and ventilatory, circulatory, and symptom limitation in patients with chronic airflow limitation. Am Rev Respir Dis. 1992;146(4):935–40.
31. Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med. 1995;152(6):2021–31.
32. Jones NL, Killian KJ. Exercise limitation in health and disease. N Engl J Med. 2000;343(9):632–41.
33. Hansen JE, Sue DY, Wasserman K. Predicted values for clinical exercise testing. Am Rev Respir Dis. 1984;129(2 Pt 2):S49–55.
34. Robinson TE, Sue DY, Huszczuk A, Weiler-Ravell D, Hansen JE. Intra-arterial and cuff blood pressure responses during incremental cycle ergometry. Med Sci Sports Exerc. 1988;20(2):142–9.
35. Wasserman K, Whipp BJ. Exercise physiology in health and disease. Am Rev Respir Dis. 1975;112(2):219–49.

36. Whipp BJ, Davis JA. The ventilatory stress of exercise in obesity. Am Rev Respir Dis. 1984;129(2 Pt 2):S90–2.
37. Dempsey JA, Reddan W, Balke B, Rankin J. Work capacity determinants and physiologic cost of weight-supported work in obesity. J Appl Physiol. 1966;21(6):1815–20.
38. West JB. Respiratory physiology: the essentials. 7th ed. Baltimore: Lippincott Williams & Wilkins; 2005.
39. Jones NL. Clinical exercise testing. 4th ed. Philadelphia: W. B. Saunders; 1997.
40. Wasserman K, Hansen JE, Sue DY, et al. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2012.
41. Ekblom B, Astrand PO, Saltin B, Stenberg J, Wallstrom B. Effect of training on circulatory response to exercise. J Appl Physiol. 1968;24(4):518–28.
42. Weber KT, Wilson JR, Janicki JS, Likoff MJ. Exercise testing in the evaluation of the patient with chronic cardiac failure. Am Rev Respir Dis. 1984;129(2P2):S60–2.
43. Committee on Exercise Testing. ACC/AHA Guidelines for exercise testing. A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol. 1997;30(1):260–311.
44. Saltin B. Hemodynamic adaptations to exercise. Am J Cardiol. 1985;55(10):D42–7.
45. Janicki JS, Sheriff DD, Robotham JL, Wise RA. Cardiac output during exercise: contributions of the cardiac, circulatory and respiratory systems. In: Rowell LB, Shepard JT, editors. Handbook of physiology. Section 12. Exercise: regulation and integration of multiple systems. New York: Oxford University Press; 1996. p. 649–704.
46. Dempsey JA, Babcock MA. An integrative view of limitations to muscular performance. Adv Exp Med Biol. 1995;384:393–9.
47. Wasserman K, Hansen JE, Sue DY, Whipp BJ, Casaburi R. Principles of exercise testing and interpretation: including pathophysiology and clinical applications. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 1999.
48. Lange Andersen K, Shephard RJ, Denolin H, Varnauskas E, Masironi R. Fundamentals of exercise testing. Geneva: World Health Organization; 1971.
49. Tanaka H, Monahan KD, Seals DR. Age-predicted maximal heart rate revisited. J Am Coll Cardiol. 2001;37(1):153–6.

50. Tesch PA. Exercise performance and beta-blockade. Sports Med. 1985;2(6):389–412.
51. Jones NL. Clinical exercise testing. 3rd ed. Philadelphia: WB Saunders Company; 1988.
52. Taivassalo T, Jensen TD, Kennaway N, DiMauro S, Vissing J, Haller RG. The spectrum of exercise tolerance in mitochondrial myopathies: a study of 40 patients. Brain. 2003;126(Pt 2):413–23.
53. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol (1985). 1986;60(6):2020–7.
54. Patessio A, Casaburi R, Carone M, Appendini L, Donner CF, Wasserman K. Comparison of gas exchange, lactate, and lactic acidosis thresholds in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis. 1993;148:622–6.
55. Beaver WL, Wasserman K, Whipp BJ. Bicarbonate buffering of lactic acid generated during exercise. J Appl Physiol (1985). 1986;60(2):472–8.
56. Hughson RL, Weisiger KH, Swanson GD. Blood lactate concentration increases as a continuous function in progressive exercise. J Appl Physiol (1985). 1987;62(5):1975–81.
57. Bishop D, Jenkins DG, Mackinnon LT. The relationship between plasma lactate parameters, W_{peak} and 1-h cycling performance in women. Med Sci Sports Exerc. 1998;30(8):1270–5.
58. Casaburi R, Porszasz J, Burns MR, Carithers ER, Chang RS, Cooper CB. Physiologic benefits of exercise training in rehabilitation of patients with severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1997;155(5):1541–51.
59. Belman MJ, Epstein LJ, Doornbos D, Elashoff JD, Koerner SK, Mohsenifar Z. Noninvasive determinations of the anaerobic threshold. Reliability and validity in patients with COPD. Chest. 1992;102(4):1028–34.
60. Perloff D, Grim C, Flack J, et al. Human blood pressure determination by sphygmomanometry. Circulation. 1993;88(5):2460–70.
61. Weber KT, Janicki JS. Cardiopulmonary exercise testing: physiologic principles and clinical applications. Philadelphi: W. B. Saunders; 1986.
62. Dillard TA, Hnatiuk OW, McCumber TR. Maximum voluntary ventilation: spirometric determinants in chronic obstructive pulmonary disease patients and normal subjects. Am Rev Respir Dis. 1993;147(4):870–5.

63. Dillard TA, Piantadosi S, Rajagopal KR. Prediction of ventilation at maximal exercise in chronic air-flow obstruction. Am Rev Respir Dis. 1985;132(2):230–5.
64. Salzman SH. Cardiopulmonary exercise testing. In: American College of Chest Physicians, editor. The ACCP Pulmonary Board Review. Basel: Karger; 2003. p. 363–80.
65. Johnson BD, Saupe KW, Dempsey JA. Mechanical constraints on exercise hyperpnea in endurance athletes. J Appl Physiol (1985). 1992;73(3):874–86.
66. Gallagher CG, Brown E, Younes M. Breathing pattern during maximal exercise and during submaximal exercise with hypercapnia. J Appl Physiol (1985). 1987;63(1):238–44.
67. Hey EN, Lloyd BB, Cunningham DJC, Jukes MGM, Bolton DPG. Effects of various respiratory stimuli on the depth and frequency of breathing in man. Respir Physiol. 1966;1(2):193–205.
68. Dempsey JA. J.B. Wolffe memorial lecture. Is the lung built for exercise? Med Sci Sports Exerc. 1986;18(2):143–55.
69. Dempsey JA, McKenzie DC, Haverkamp HC, Eldridge MW. Update in the understanding of respiratory limitations to exercise performance in fit, active adults. Chest. 2008;134(3):613–22.
70. Stickland MK, Butcher SJ, Marciniuk DD, Bhutani M. Assessing exercise limitation using cardiopulmonary exercise testing. Pulm Med. 2012;2012:824091.
71. Klas JV, Dempsey JA. Voluntary versus reflex regulation of maximal exercise flow: volume loops. Am Rev Respir Dis. 1989;139(1):150–6.
72. Laveneziana P, Guenette JA, Webb KA, O'Donnell DE. New physiological insights into dyspnea and exercise intolerance in chronic obstructive pulmonary disease patients. Expert Rev Respir Med. 2012;6(6):651–62.
73. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(5):770–7.
74. Johnson BD, Weisman IM, Zeballos RJ, Beck KC. Emerging concepts in the evaluation of ventilatory limitation during exercise: the exercise tidal flow-volume loop. Chest. 1999;116(2):488–503.
75. Bouhuys A. Respiratory dead space. In: Fenn WO, Rahn H, editors. Handbook of physiology. Section III, Vol. 1. Respiration. Washington, DC: American Phsyiological Society; 1964. p. 699–714.

76. Bohr C. Ueber die lungenathmung. Skand Arch Physiol. 1891;2:236–68.
77. Johnson BD, Dempsey JA. Demand vs. capacity in the aging pulmonary system. Exerc Sport Sci Rev. 1991;19(1):171–210.
78. Ries AL, Farrow JT, Clausen JL. Accuracy of two ear oximeters at rest and during exercise in pulmonary patients. Am Rev Respir Dis. 1985;132(3):685–9.
79. Severinghaus JW, Naifeh KH, Koh SO. Errors in 14 pulse oximeters during profound hypoxia. J Clin Monit. 1989;5(2):72–81.
80. American Association for Respiratory Care. AARC clinical practice guideline: exercise testing for evaluation of hypoxemia and/or desaturation. Respir Care. 1992;37(8):907–12.
81. American Thoracic Society. Pulmonary function laboratory management and procedure manual. New York: American Thoracic Society; 1998.
82. Francis GS, Goldsmith SR, Ziesche S, Nakajima H, Cohn JN. Relative attenuation of sympathetic drive during exercise in patients with congestive heart failure. J Am Coll Cardiol. 1985;5(4):832–9.
83. Hansen JE, Casaburi R, Cooper DM, Wasserman K. Oxygen uptake as related to work rate increment during cycle ergometer exercise. Eur J Appl Physiol Occup Physiol. 1988;57(2):140–5.
84. Jones S, Elliott PM, Sharma S, McKenna WJ, Whipp BJ. Cardiopulmonary responses to exercise in patients with hypertrophic cardiomyopathy. Heart. 1998;80(1):60–7.
85. West JB. Ventilation/blood flow and gas exchange. 5th ed. Oxford: Blackwell Scientific [distributed by Year Book (Chicago, IL)]; 1990.
86. Kadikar A, Maurer J, Kesten S. The six-minute walk test: a guide to assessment for lung transplantation. J Heart Lung Transplant. 1997;16(3):313–9.
87. Holden DA, Rice TW, Stelmach K, Meeker DP. Exercise testing, 6-min walk, and stair climb in the evaluation of patients at high risk for pulmonary resection. Chest. 1992;102(6):1774–9.
88. Sciurba FC, Rogers RM, Keenan RJ, et al. Improvement in pulmonary function and elastic recoil after lung-reduction surgery for diffuse emphysema. N Engl J Med. 1996;334(17):1095–9.
89. Criner GJ, Cordova FC, Furukawa S, et al. Prospective randomized trial comparing bilateral lung volume reduction surgery to pulmonary rehabilitation in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;160(6):2018–27.

90. Sinclair DJ, Ingram CG. Controlled trial of supervised exercise training in chronic bronchitis. Br Med J. 1980;280(6213):519–21.
91. Roomi J, Johnson MM, Waters K, Yohannes A, Helm A, Connolly MJ. Respiratory rehabilitation, exercise capacity and quality of life in chronic airways disease in old age. Age Ageing. 1996;25(1):12–6.
92. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. International COPD Study Group. Lancet. 1998;351(9105):773–80.
93. Spence DP, Hay JG, Carter J, Pearson MG, Calverley PM. Oxygen desaturation and breathlessness during corridor walking in chronic obstructive pulmonary disease: effect of oxitropium bromide. Thorax. 1993;48(11):1145–50.
94. De Bock V, Mets T, Romagnoli M, Derde MP. Captopril treatment of chronic heart failure in the very old. J Gerontol. 1994;49(3):M148–52.
95. Bernstein ML, Despars JA, Singh NP, Avalos K, Stansbury DW, Light RW. Re-analysis of the 12-minute walk in patients with chronic obstructive pulmonary disease. Chest. 1994;105(1):163–7.
96. Hajiro T, Nishimura K, Tsukino M, Ikeda A, Koyama H, Izumi T. Analysis of clinical methods used to evaluate dyspnea in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1998;158(4):1185–9.
97. Gulmans VA, van Veldhoven NH, de Meer K, Helders PJ. The six-minute walking test in children with cystic fibrosis: reliability and validity. Pediatr Pulmonol. 1996;22(2):85–9.
98. Nixon PA, Joswiak ML, Fricker FJ. A six-minute walk test for assessing exercise tolerance in severely ill children. J Pediatr. 1996;129(3):362–6.
99. Mathai SC, Suber T, Khair RM, Kolb TM, Damico RL, Hassoun PM. Health-related quality of life and survival in pulmonary arterial hypertension. Ann Am Thorac Soc. 2016;13(1):31–9.
100. Bittner V. Six-minute walk test in patients with cardiac dysfunction. Cardiologia. 1997;42(9):897–902.
101. Peeters P, Mets T. The 6-minute walk as an appropriate exercise test in elderly patients with chronic heart failure. J Gerontol A Biol Sci Med Sci. 1996;51(4):M147–51.
102. Zugck C, Kruger C, Durr S, et al. Is the 6-minute walk test a reliable substitute for peak oxygen uptake in patients with dilated cardiomyopathy? Eur Heart J. 2000;21(7):540–9.

103. Cahalin LP, Mathier MA, Semigran MJ, Dec GW, DiSalvo TG. The six-minute walk test predicts peak oxygen uptake and survival in patients with advanced heart failure. Chest. 1996;110(2):325–32.
104. Cote CG, Celli BR. In patients with COPD, the 6 minute walking distance is a better predictor of health care utilization than FEV_1, blood gases, and dyspnea. Eur Respir J. 1998;383.
105. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159(1):158–64.
106. Cahalin L, Pappagianopoulos P, Prevost S, Wain J, Ginns L. The relationship of the 6-min walk test to maximal oxygen consumption in transplant candidates with end-stage lung disease. Chest. 1995;108(2):452–9.
107. Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. Arch Intern Med. 1989;149(10):2277–82.
108. Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest. 1994;105(1):168–74.
109. Weisman IM, Zeballos RJ. Clinical evaluation of unexplained dyspnea. Cardiologia. 1996;41(7):621–34.
110. Sridhar MK, Carter R, Banham SW, Moran F. An evaluation of integrated cardiopulmonary exercise testing in a pulmonary function laboratory. Scott Med J. 1995;40(4):113–6.
111. Gay SE, Weisman IM, Flaherty KR, Martinez FJ. Cardiopulmonary exercise testing in unexplained dyspnea. In: Weisman IM, Zeballos RJ, editors. Clinical exercise testing. Basel: Karger; 2002. p. 81–8.
112. Weisman IM, Zeballos RJ. A step approach to the evaluation of unexplained dyspnea: the role of cardiopulmonary exercise testing. Pulm Perspect. 1998;15:8–11.
113. Zeballos RJ, Weisman IM, Connery SM, Bradley JP. Standard treadmill (STE) vs incremental cycle ergometry (IET) in the evaluation of airway hyperreactivity in unexplained dyspnea. Am J Respir Crit Care Med. 1999;159:A419.
114. Punzal PA, Ries AL, Kaplan RM, Prewitt LM. Maximum intensity exercise training in patients with chronic obstructive pulmonary disease. Chest. 1991;100(3):618–23.

115. Ries AL. The importance of exercise in pulmonary rehabilitation. Clin Chest Med. 1994;15(2):327–37.
116. Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis. 1991;143(1):9–18.
117. Bolliger CT, Jordan P, Solèr M, et al. Exercise capacity as a predictor of postoperative complications in lung resection candidates. Am J Respir Crit Care Med. 1995;151(5):1472–80.
118. Bolliger CT, Perruchoud AP. Functional evaluation of the lung resection candidate. Eur Respir J. 1998;11(1):198–212.
119. Morice RC, Peters EJ, Ryan MB, Putnam JB, Ali MK, Roth JA. Redefining the lowest exercise peak oxygen consumption acceptable for lung resection of high risk patients. Chest. 1996;110:161S.
120. Howard DK, Iademarco EJ, Trulock EP. The role of cardiopulmonary exercise testing in lung and heart-lung transplantation. Clin Chest Med. 1994;15(2):405–20.
121. Williams RJ, Slater WR. Role of cardiopulmonary exercise in lung and heart–lung transplantation. In: Weisman IM, Zeballos RJ, editors. Progress in respiratory research. Clinical exercise testing. Vol 32. Basel: Karger; 2002. p. 254–63.
122. Stelken AM, Younis LT, Jennison SH, et al. Prognostic value of cardiopulmonary exercise testing using percent achieved of predicted peak oxygen uptake for patients with ischemic and dilated cardiomyopathy. J Am Coll Cardiol. 1996;27(2):345–52.
123. Mancini DM, Eisen H, Kussmaul W, Mull R, Edmunds LH, Wilson JR. Value of peak exercise oxygen consumption for optimal timing of cardiac transplantation in ambulatory patients with heart failure. Circulation. 1991;83(3):778–86.
124. Gallagher CG. Exercise limitation and clinical exercise testing in chronic obstructive pulmonary disease. Clin Chest Med. 1994;15(2):305–26.
125. O'Donnell DE, Flüge T, Gerken F, Hamilton A, Webb K, Aguilaniu B, Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD. Eur Respir J. 2004;23(6):832–40.
126. Janicki JS, Weber KT, Likoff MJ, Fishman AP. Exercise testing to evaluate patients with pulmonary vascular disease. Am Rev Respir Dis. 1984;129(2 Pt 2):S93–5.
127. D'Alonzo GE, Gianotti L, Dantzker DR. Noninvasive assessment of hemodynamic improvement during chronic vasodila-

tor therapy in obliterative pulmonary hypertension. Am Rev Respir Dis. 1986;133(3):380–4.
128. Systrom DM, Cockrill BA, Hales CA. Role of cardiopulmonary exercise testing in patients with pulmonary vascular disease. In: Weisman IM, Zeballos RJ, editors. Progress in respiratory research. Vol 32. Basel: Karger; 2002. p. 200–4.
129. Demedts M, Behr J, Buhl R, et al. High-dose acetylcysteine in idiopathic pulmonary fibrosis. N Engl J Med. 2005;353(21):2229–42.
130. Dodd JD, Barry SC, Daly LE, Gallagher CG. Inhaled beta-agonists improve lung function but not maximal exercise capacity in cystic fibrosis. J Cyst Fibros. 2005;4(2):101–5.
131. Cotes JE, Zejda J, King B. Lung function impairment as a guide to exercise limitation in work-related lung disorders. Am Rev Respir Dis. 1988;137:1089–93.
132. Becklake MR, Rodarte JR, Kalica AR. NHLBI workshop summary. Scientific issues in the assessment of respiratory impairment. Am Rev Respir Dis. 1988;137(6):1505–10.
133. Cotes JE. Rating respiratory disability: a report on behalf of a working group of the European Society for Clinical Respiratory Physiology. Eur Respir J. 1990;3(9):1074–7.
134. Cotes JE. Lung function: assessment and application in medicine. 5th ed. London: Blackwell Scientific Publications; 1993.
135. Smith DD. Pulmonary impairment/disability evaluation: controversies and criticisms. Clin Pulm Med. 1995;2(6):334–43.
136. Sue DY. Exercise testing in the evaluation of impairment and disability. Clin Chest Med. 1994;15(2):369–87.
137. Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. Am J Respir Crit Care Med. 2000;161(1):309–29.
138. Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness. Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl. 1993;16:53–83.
139. European Respiratory Society. Clinical exercise testing with reference to lung diseases: indications, standardization and interpretation strategies. ERS Task Force on

Standardization of Clinical Exercise Testing. Eur Respir J. 1997;10(11):2662–89.
140. Roca J, Whipp BJ. European respiratory monograph 6: clinical exercise testing. Lausanne: European Respiratory Society; 1997.
141. Garfinkel SK, Kesten S, Chapman KR, Rebuck AS. Physiologic and nonphysiologic determinants of aerobic fitness in mild to moderate asthma. Am Rev Respir Dis. 1992;145(4 Pt 1):741–5.
142. Weisman IM, Zeballos RJ. An integrated approach to the interpretation of cardiopulmonary exercise testing. Clin Chest Med. 1994;15(2):421–45.
143. Weisman IM, Zeballos RJ. Clinical exercise testing. Clin Chest Med Dec. 2001;22(4):679–701.
144. Carlin BW, Clausen JL, Ries AL. The effects of exercise testing on the prescription of oxygen therapy. Chest. 1994;106(2):361–5.
145. Dean NC, Brown JK, Himelman RB, Doherty JJ, Gold WM, Stulbarg MS. Oxygen may improve dyspnea and endurance in patients with chronic obstructive pulmonary disease and only mild hypoxemia. Am Rev Respir Dis. 1992;146:941–5.
146. American College of Sports Medicine. ACSM's guidelines for exercise testing and prescription. 6th ed. Baltimore: Lippincott Williams & Wilkins; 2000.
147. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2001;104(4):429–35.
148. Löllgen H, Ulmer HV, Crean P. Recommendations and standard guidelines for exercise testing: a report of the task force conference on ergometry. Eur Heart J. 1988;9(Suppl K):1–37.
149. Shephard RJ. Tests of maximum oxygen intake. A critical review. Sports Med. 1984;1(2):99–124.

Chapter 10
Diagnostic Tests for Sleep Disorders

Ali Altalag, Jeremy Road, Pearce Wilcox, and Kewan Aboulhosn

Abstract We are fortunate to have a variety of investigations available when assessing for the large number of sleep breathing disorders, parasomnias, and other sleep abnormalities. In this chapter we review sleep stages and review sleep breathing pathology. We provide a discussion on components of attended and unattended polysomnography and their clinical use.

Keywords Sleep disordered breathing · Multiple sleep latency · Nocturnal oximetry · Sleep apnea · Narcolepsy · Flow-volume loop · Polysomnogram · Polysomnography · Excessive Daytime Sleepiness · Maintenance of Wakefulness Test

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SLEEP-RELATED DISORDERS

The International Classification of Sleep Disorders classifies 84 distinct sleep disorders into four major categories [1];

1. *Dyssomnias:* are characterized by insomnia and excessive daytime sleepiness (hypersomnolence). The respiratory sleep disorders belong to this group.
2. *Parasomnias:* are characterized by abnormal behavioral events occurring during sleep such as sleep walking. Parasomnias typically don't cause insomnia or excessive sleepiness.
3. *Medical-psychiatric sleep disorders:* are directly caused by medical, neurologic or psychiatric (mental) disorders.
4. *Proposed sleep disorders:* are sleep disorders that so far have no known key features to distinguish them from normal variants or other sleep disorders.

Respiratory Sleep Disorders (Sleep-Disordered Breathing)

Represent a group of sleep disorders caused by abnormal breathing patterns during sleep and may result in sleep fragmentation and excessive daytime sleepiness. There are two major respiratory sleep disorders:

1. Obstructive Sleep Apnea/Hypopnea (OSA or OSAH)
   - The most prevalent respiratory sleep disorder. OSA [2], affects ~9% of men and ~4% of women [3]. It is characterized by repeated upper airway obstruction during sleep due to a collapsible upper airway which results in recurrent arousals and often daytime hypersomnolence. Several risk factors for OSA are identified, obesity being the most important.
   - Prevalence of OSA increases with age and plateaus by the seventh decade. Male sex and obesity also increase the risk of OSA. Retrognathia, micrognathia, oropharyngeal tissue hypertrophy as well as other craniofacial abnormalities also increase the risk of developing OSA [4].
   - OSA is a significant cause of morbidity and mortality [5]. OSA is associated with cardiovascular disease (hypertension [6–11], coronary artery disease [12–17] and arrhythmias [18–23]), cerebrovascular disease [13–17, 24], diabetes mellitus [25], lipid abnormalities [25] and

pulmonary vascular disease [26–29]. In addition, the excessive sleepiness caused by OSA is a potential cause of road traffic collisions and industrial accidents which add to the morbidity and mortality of untreated OSA [30–33].

- The gold standard in the diagnosis of OSA is polysomnography (sleep study) but other tests may aid in making this diagnosis, as will be discussed later. The treatment of choice for OSA is Continuous Positive Airway Pressure (CPAP) applied through the nose &/or mouth during sleep. Other modes of therapy include, oral appliances, weight reduction and surgery (especially if there is an obvious cause for airway obstruction such as enlarged tonsils). Tracheostomy to bypass the upper airway is effective but is generally considered a last resort.
- This chapter will mainly deal with tests used to diagnose OSA.

2. Central Sleep Apnea Syndrome (CSA)
   - Is classified into:
     – *CSA with decreased respiratory drive* as in *sleep alveolar hypoventilation syndrome* and neuromuscular disorders.
     – *CSA with periodic breathing pattern* as in *Cheyne-Stokes Respiration* (seen mainly with heart failure [33, 34]), hypoxia of high altitude, & in diffuse neurological disorders. This form of CSA is more common and is characterized by a hyperpneic phase of breathing (because of abnormally increased respiratory drive) followed by an apneic phase (due to respiratory alkalosis), and repetitive cycling. As in OSA, arousals are common in CSA but they take place during the hyperpneic phase rather than the apneic phase. Excessive sleepiness may be a consequence of the arousals [35].

Conditions That May Mimic Respiratory Sleep Disorders

- Patients with other conditions may present to the respiratory sleep disorders' clinic and may even be misdiagnosed with OSA. Excessive sleepiness is a feature that these conditions share with OSA as do all dyssomnias. These conditions may include: narcolepsy, excessive use of sedatives, reduced sleep duration, depression and anxiety. Periodic Limb Movement disorder (PLMD) is another condition that

should be considered. The distinction of these disorders is usually made on clinical grounds but specific testing may be necessary; Table 10.1.

Table 10.1 Conditions that may mimic respiratory sleep disorders

Narcolepsy

Incidence: 1/2000 [36], equal prevalence in men & women; Starts at young age & worsens over few years then persists for life [37]. May coexist with OSA

Etiology: loss of orexin A & B, neurotransmitters responsible for promotion of wakefulness

Major clinical features

Daytime sleepiness: which could be so severe that patient may doze off with little warning *"sleep attacks"*

Hypnagogic hallucinations: are vivid, often frightening hallucinations that occur just as the patient is falling asleep or waking up

Sleep paralysis: is a complete inability to move for 1–2 minutes immediately after awakening. It is usually associated with hypnagogic hallucinations or a feeling of suffocation

Cataplexy: is unilateral or bilateral loss of muscle tone triggered usually by some form of excitement & leads to partial or complete collapse

Diagnosis: clinically & with Multiple Sleep Latency Test (MSLT); treated with stimulants

Periodic Limb Movement Disorder (PLMD)

Repetitive leg jerks (mostly dorsiflexion of the feet) usually accompanied by arousals, sleep fragmentation & excessive sleepiness. PLMD is sometimes called nocturnal or sleep-related myoclonus, which is a misnomer. More common in older age, incidence is unknown and can be caused by medications like antidepressants (e.g. venlafaxine)

Diagnosis: clinical & Polysomnography (PSG). Treatment: similar to Restless Leg Syndrome (RLS)

Restless Leg Syndrome (RLS)

An unpleasant deep, creeping or crawling sensation in the legs while patient is sitting or lying with an irresistible urge to move the legs. RLS commonly causes insomnia. The prevalence of moderate-severe form is 2.7%, male : female ratio is 1:2. Most patients also have PLMD but most patients with PLMD do not have RLS

TABLE 10.1 (continued)

Etiology: Primary (idiopathic) & secondary (e.g. secondary to: iron deficiency anemia, end-stage renal disease, diabetes mellitus, Parkinson's disease, pregnancy, connective tissue disease, venous insufficiency)

Diagnosis: clinical, PSG may be helpful. Treatment: correct the cause if any (e.g. treat iron deficiency anemia), benzodiazepines, dopaminergic agents & opioids (in resistant cases) [38]

Upper Airway Resistance Syndrome (UARS)

Is caused by abnormal narrowing of the upper airways that results in increased resistance to airflow during sleep leading to the "respiratory effort related arousals". UARS is commonly seen in women with certain craniofacial abnormalities. Snoring & excessive daytime sleepiness (due to recurrent arousals) are common features. Some consider this a mild form of sleep disordered breathing

Diagnosis may be missed in the PSG unless attention is paid to an unexplained increase in arousal index. When considered, PSG is diagnostic but detecting high esophageal pressures prior to arousals using the esophageal balloon catheter system is pathognomonic. Treatment is Continuous Positive Airway Pressure (CPAP) similar to OSA

Primary (habitual or continuous) snoring without sleep apnea

Patients are typically asymptomatic and present due to complaints from their bed partners. Primary snoring is very common & PSG may be needed to exclude OSA

Miscellaneous conditions

GI disorders: Gastro-esophageal reflux disease (GERD), swallowing disorders

Respiratory disorders: nocturnal asthma, COPD, pulmonary fibrosis

Psychiatric disorders: panic attacks, anxiety, depression

Neurological disorders: nocturnal seizures

Others: Drugs (hypnotics), excessive alcohol intake, lack of adequate sleep

LEVEL 1: POLYSOMNOGRAPHY (PSG)

Introduction

- Level 1, Attended polysomnography is a comprehensive diagnostic procedure that allows simultaneous recording of a number of physiologic variables during sleep. A minimum of 12 variables are acquired which include:
  - Central & occipital electroencephalography (EEG)
  - Right & left electro-occulography (EOG)
  - Chin electromyography (EMG)
  - Right & left leg EMG
  - Electrocardiography (ECG)
  - Airflow
  - Chest & abdominal movement channels
  - Pulse oximetry (S_pO_2)
- Each of these variables is displayed on channels (computer display) and are evaluated in a process called scoring of the PSG. Scoring converts the data into a meaningful summary that can be readily interpreted. Each group of these variables is used to evaluate different aspects of the PSG:
  1. Sleep stages, arousals & wakefulness are scored using EEG, EOG & chin EMG channels
  2. Respiratory events (apneas or hypopneas) are scored using airflow, chest & abdominal movements S_pO_2 and EMG channels
  3. Periodic limb movements (PLMs) are scored using the leg EMG channel
  4. Miscellaneous channels include: ECG, sleep position & sound (snoring).

SLEEP STAGES, AROUSALS AND WAKEFULNESS

To discuss the scoring of these variables, it is necessary to know the sleep stages. Sleep is classified into:

- *Rapid Eye Movement* (*REM*) Sleep
- *Non-Rapid Eye Movement* (*NREM*) sleep, which is sub-classified into:
  - *Light sleep* (stages 1 & 2)
  - *Deep sleep* (or slow wave sleep) (stages 3) (The 2007 American Academy of Sleep Medicine (AASM) changed

the sleep staging system by combining sleep stages 3 and 4 into what we now describe as stage 3 sleep) [39].

- *Relaxed wakefulness* is the stage that immediately precedes sleep & is referred to as stage wake (W) which is subdivided into:
  - Stage W *with eyes open*
  - *Stage W* with eyes closed

An arousal is a brief awakening that should meet certain criteria, as will be discussed. The variables used to score sleep stages, arousals & wakefulness, namely EEG, EOG & chin EMG are discussed separately in this section [40]. *The information in this section was acquired mainly from the standard scoring manual, see reference No.* [40].

Electroencephalography (EEG)

Used to record the brain electrical signals which vary according to the sleep stage.

EEG Electrodes (Leads)

- Six EEG electrodes are placed over the patient's scalp, three on each side. These electrodes are: Central, Occipital & Auricular electrodes and are abbreviated as C, O & A, respectively. Each of these letters is followed by a number (1–4) to indicate the side of the electrode; odd numbers (1 or 3) refer to the left side & even numbers (2 or 4) refer to the right side, therefore:
  - O_1 & O_2 are the left & right occipital electrodes, respectively,
  - A_1 & A_2 are left & right auricular electrodes, respectively,
  - C_3 & C_4 are left & right central electrodes, respectively.
- To magnify the amplitude (voltage difference) of the EEG signals, the exploring (recording) electrodes are usually referenced to the auricular electrodes of the opposite side (e.g. C_4-A_1 means the right central electrode is the exploring electrode and is referenced to the left auricular electrode; the other electrode pairs will be: C_3-A_2, O_1-A_2 & O_2-A_1).
- The EEG in PSG is recorded only from one side while the leads in the opposite side are kept in place as a back-up for cases of malfunction of the recoding side while the patient is asleep.

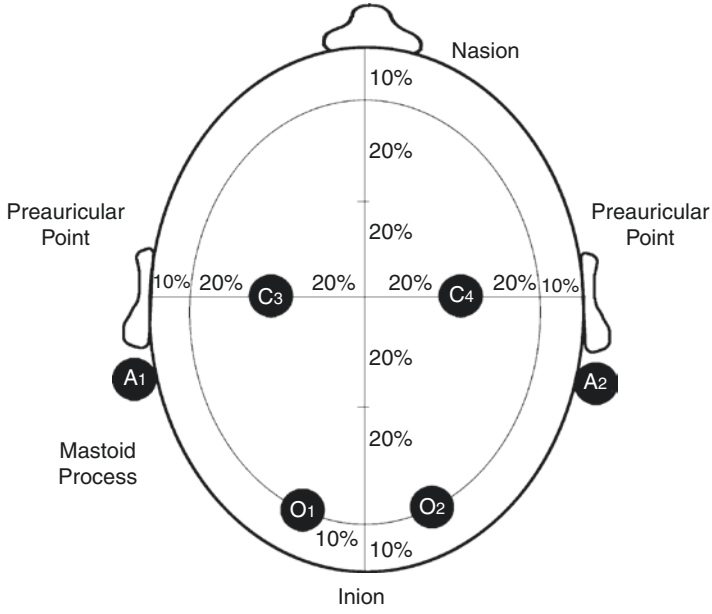


FIGURE 10.1 Schematic of the 10–20 EEG electrode placement system. Landmarks are the nasion (the bridge of the nose), inion (the prominence of the occiput), and the right and left preauricular points. The lines between nasion and inion and between the preauricular points are divided into 10 and 20% segments as shown. The central leads are placed over the preauricular line, 20% from the midline. The occipital leads are placed over an imaginary circle as shown, 10% from the midline. The auricular leads are placed over the mastoid processes

Optimal sleep staging requires two exploring electrodes (C & O) but a minimum of one central exploring electrode is needed for definition of sleep stages [40] (central leads are good in capturing most EEG signals as will be discussed later [37, 41]).

- The placement of the EEG leads is explained in Figure 10.1 [42].

EEG Waves [40]

Distinct EEG waves are present and each is differentiated from one another by its frequency in seconds (Hertz or Hz),[1]

[1] Also referred to as cycles per seconds or cps.

amplitude and/or shape. The following are the wave patterns in human sleep; see Figure 10.2a–i.

- Standard wave patterns:
  - *Beta waves* (>13 Hz): are seen when the patient is awake and alert or excited. Beta waves are not seen during sleep; Figure 10.2a.
  - *Alpha waves* (8–13 Hz): are seen when patient is awake and relaxed. They continue to be seen in stage 1 sleep but with reduced numbers; Figure 10.2b.
  - *Theta waves* (4–7 Hz): are mainly seen in sleep stages 1 & 2; Figure 10.2c).
  - Delta waves (<4 Hz): are seen in sleep stages 3; Figure 10.2d.
- Other EEG patterns:
  - *Slow waves* (<2 Hz): represent a slow form of delta waves with high amplitudes (voltage criteria for slow waves: trough to peak is ≥75 microvolts). They are seen in sleep stages 3; Figure 10.2e.
  - *Sleep spindles:* are oscillations of 12–14 Hz with duration of 0.5–1.5 seconds [43]. They are seen in stage 2 sleep but may persist into stage 3 & 4; Figure 10.2f.
  - *K complexes (Ks):* are high-altitude, biphasic waves of >0.5 second duration with an initial upward (negative) deflection followed by a downward (positive) deflection [40].[2] A cardinal feature of K complexes is that they are clearly distinguishable from background EEG activity.[3] Sleep spindles may be superimposed on K complexes. Ks are seen in stage 2 sleep (may be seen in stages 3 but are then indistinguishable from background EEG [40]); Figure 10.2g.
  - *Vertex sharp waves:* are narrow, high amplitude negative (upward) waves seen in stage 1 & near transition from stage 1 to stage 2 sleep; Figure 10.2h.
- *Saw-tooth waves:* are waves of theta frequency and may be notched. They are seen in stage REM sleep but are not essential for REM definition; Figure 10.2i [44].
- Alpha waves are best recorded by the occipital leads while the rest of EEG waves (including, slow waves, Ks and spindles) are best recorded by the central leads. This is why the central leads are essential for PSG recording [37, 41].

[2] A positive voltage in EEG means a downward deflection and vice versa, a concept that sometimes is referred to as "negative up" rule.
[3] Slow waves may be thought of as a series of two or more K complexes.

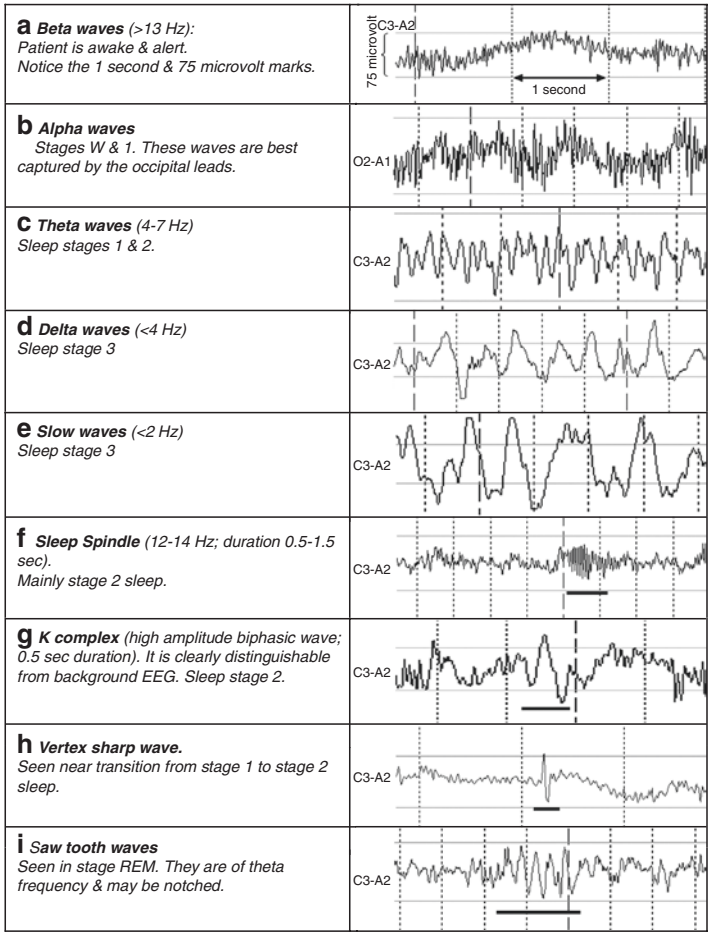


FIGURE 10.2 Wave patterns in EEG. (**a**) **Beta waves** (>13 Hz): Patient is awake & alert; Notice the 1 second & 75 microvolt marks. (**b**) **Alpha waves** (8–13 Hz). Stages W & 1. These waves are best captured by the occipital leads. (**c**) **Theta waves** (4–7 Hz). Sleep stages 1 & 2. (**d**) **Delta waves** (<4 Hz). Sleep stage 3. (**e**) **Slow waves** (<2 Hz). Sleep stage 3. (f) **Sleep Spindle** (12–14 Hz; duration 0.5–1.5 second). Mainly stage 2 sleep. (g) **K complex** (high amplitude biphasic wave; 0.5 second duration). It is clearly distinguishable from background EEG. Sleep stage 2. (h) **Vertex sharp wave.** Seen near transition from stage 1 to stage 2 sleep. (i) **Saw tooth waves**. Seen in stage REM. They are of theta frequency & may be notched

Electro-Occulography (EOG)

- Is used to record the eye movements which are essential to define stage REM sleep. Because the eye has a potential difference (cornea is positive with respect to the retina), then measuring this potential (polarity) difference makes it possible to record eye movements using ocular electrodes; Figure 10.3a. These electrodes are placed at Right Outer Canthus (*ROC*) and Left Outer Canthus (*LOC*).[4]
- Remember that ROC & LOC deflections are out of phase when the eyes move. This phenomenon is used to differentiate true eye movements from artifacts. For example, ocular leads may capture high voltage EEG signals like K complexes or slow waves but the deflections recorded at ROC & LOC will be in-phase (same direction) and shouldn't be mistaken for an eye movement, Figure 10.10c.
- As in EEG, to amplify the signals acquired from ROC & LOC, the ocular leads are usually referenced to the opposite auricular leads and abbreviated as: ROC-A_1 & LOC-A_2 [45].[5]
- Two distinct eye movements can be recorded through the ocular leads:
  - *REMs:* are episodic, sharp waves with a usually flat baseline between movements, Figure 10.3a. REMs are seen typically in stage REM sleep, but similar waves can be seen in stage W with the eyes open representing the normal eye movements. Eye blinks show usually as downward deflections at ROC only; Figure 10.3b.

[4] Right and left ocular electrodes are placed at the right outer canthus (ROC) and left outer canthus (LOC), respectively, with the right electrode placed slightly above and the left slightly below the eye level, in order to record vertical eye movements [40]. Keeping the eyeball polarity in mind, moving the eyes to the right will bring the cornea (relatively positive) of the right eye closer to the right ocular lead and the retina (relatively negative) of the left eye closer to the left ocular lead. This will result in a downward (positive) deflection at ROC and an upward (negative) deflection at LOC, which means that the deflections are out of phase (opposite direction). The same thing will happen if the eyes move upward, as the right ocular lead is at a higher level than the left one. The opposite thing should happen if the eyes move to the left or downward.

[5] Some laboratories reference the ocular leads to the auricular leads in the same side, i.e., ROC-A_2 and LOC-A_1 or to one auricular lead, i.e., ROC-A_2 and LOC A_2 [45].

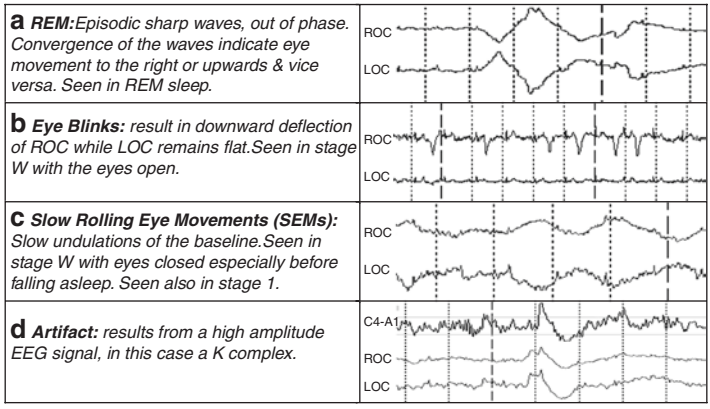


FIGURE 10.3 The different eye movements

– *Slow rolling eye movements* (SEMs): appear as a smooth undulation of the tracing (baseline), Figure 10.3c. These movements are seen in stage W with eyes closed and stage 1 and disappear in stages 2 and 3.

Chin Electromyography (Chin EMG)

- The main implication for chin EMG is to help in identifying REM sleep [40]. Three EMG leads are placed at the mental and submental areas and the voltage between 2 of them is measured. The third lead is reserved for cases of malfunction of any other lead.
- Because the body muscles normally relax during REM sleep, the chin EMG becomes minimal during REM (equal to or lower than the lowest EMG amplitude in NREM sleep). Typically, the chin EMG activity drops with onset of REM sleep. During deep sleep, chin EMG is usually low, but still higher than that of REM sleep. Chin EMG is highest during wakefulness.

Scoring Sleep Stages, Wakefulness and Arousal

Before discussing the scoring technique, it is important to discuss some concepts of PSG recording & scoring:

Concepts of EEG Recording and Scoring

- Before the era of computerized PSG recording, PSG used to be recorded on paper with a standard paper speed of 10 mm/second (Paper speed in recording EEG for detection of seizures is slower, (15–30 mm/s). Currently, computers make PSG recording and scoring easier with the ability to compress or decompress tracings, enlarge or contract scale & change the page or tracing format.
- Each 30 seconds of PSG recording (fit on one screen) represent a distinct time segment termed an *epoch*. Each epoch is divided horizontally into 1-second segments by means of vertical dashed lines to help in distinguishing EEG waves. Longitudinally, because voltage criteria are required to define slow waves, two faint horizontal lines are drawn on the EEG tracing where the distance between them is equivalent to 75 microvolts. Slow waves have to cross these two lines to meet the voltage criteria, see Figure 10.9a.[6]
- In scoring sleep & wakefulness, each epoch is scored independently then the scoring of all epochs is added together and presented in the final report. Because an epoch may show more than one stage of sleep, scoring should be according to the predominant stage.
- Remember that the wave frequency reflects the brain activity. Therefore, the frequency is highest when the patient is awake but slows down as patient gets to sleep and slows down further as he/she goes into deep sleep.

Scoring Sleep Based on EEG, EOG and Chin EMG [40]

- Stage W (eyes open; patient relaxed):
  - EEG in this stage shows low voltage, high frequency waves with attenuated alpha activity. EOG may show REMs and blinks & chin EMG activity is typically increased, Figure 10.4a.
- Stage W (eyes closed; patient drowsy):
  - EEG here consists of low voltage, high frequency waves with >50% alpha waves/epoch (alpha waves are not atten-

[6] In paper recording, a 50-μV stimulus results in a 1-cm longitudinal deflection. This makes 75-μV equivalent to 1.5-cm deflection.

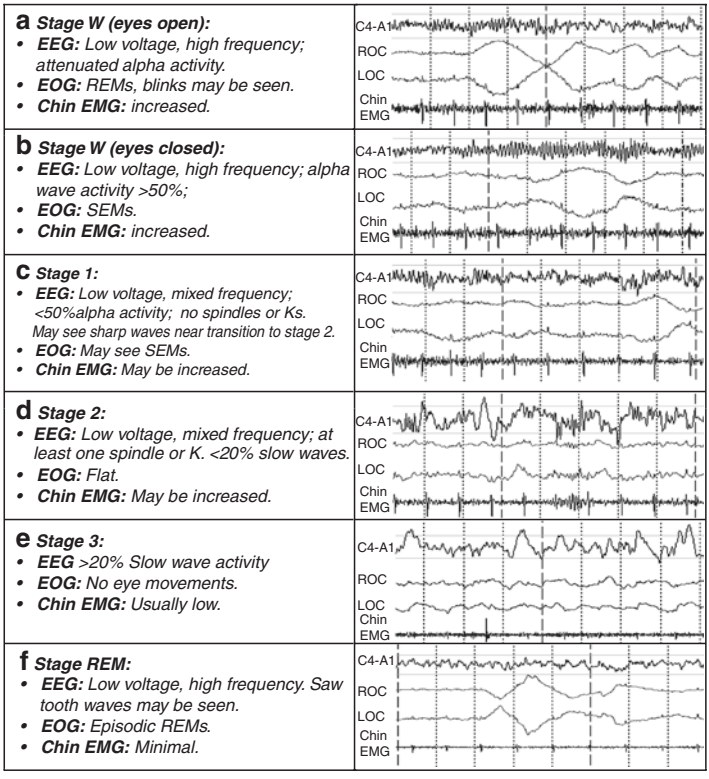


FIGURE 10.4 Sleep stages. (**a**) **Stage W (eyes open): EEG:** Low voltage, high frequency; attenuated alpha activity; **EOG:** REMs, blinks may be seen; **Chin EMG:** increased. (**b**) **Stage W (eyes closed): EEG:** Low voltage, high frequency; alpha wave activity >50%; **EOG:** SEMs; **Chin EMG:** increased. (**c**) **Stage 1: EEG:** Low voltage, mixed frequency; <50% alpha activity; no spindles or Ks. May see sharp waves near transition to stage 2; **EOG:** May see SEMs; **Chin EMG:** May be increased. (**d**) **Stage 2: EEG:** Low voltage, mixed frequency; at least one spindle or K. <20% slow waves; **EOG:** Flat; **Chin EMG:** May be increased. (**e**) **Stage 3: EEG:** >20% slow wave activity; **EOG:** No eye movements; **Chin EMG:** Usually low. (**g**) **Stage REM: EEG:** Low voltage, high frequency. Saw tooth waves may be seen; **EOG:** Episodic REMs; **Chin EMG:** Minimal

uated here). EOG shows slow rolling eye movements and chin EMG is increased, Figure 10.4b.

- Stage 1 sleep:
  - EEG shows low voltage, mixed frequency waves (alpha & theta) with <50% alpha waves/epoch. Sharp waves may be present near transition to stage 2. Typically, stage 1 doesn't have sleep spindles or K complexes. EOG continues to show slow rolling eye movement with increased chin EMG activity, Figure 10.4c.
- Stage 2 sleep:
  - EEG here is similar to stage 1 (low voltage, mixed frequency) but it must show at least one sleep spindle or K complex with <20% slow wave activity/epoch. EOG should record no eye movements and chin EMG activity is still increased, Figure 10.4d.
- Stage 3 sleep:
  - EEG should show >20% slow wave activity/epoch. EOG shows no eye movements & chin EMG activity usually slows down during this stage, Figure 10.4e.
- Stage REM sleep:
  - Is identified mainly by the presence of REMs in EOG & minimal activity in chin EMG. EEG shows low voltage, mixed frequency waves with no spindles or Ks (as in stage 1) & may show saw-tooth waves. The presence of saw-tooth waves supports the definition of REM sleep but their absence doesn't exclude REM, Figure 10.4g.

Additional Rules for Scoring Sleep

- Because sleep spindles & K complexes (in stage 2) and eye movements (in stage REM) are episodic (i.e. are not necessarily seen in every epoch of stage 2 or stage REM, respectively), additional staging rules were introduced concerning these two sleep stages [40]:
  - The 3 minute rule for stage 2:
    (a) *If no arousal is present:* If a period of time between two epochs of unequivocal stage 2 (i.e. containing spindles or Ks) is less than 3 minutes and the intervening sleep would otherwise meet criteria for stage 1 (<50% alpha activity) with no evidence of intervening arousal, then this period of sleep is scored as stage 2. If that period is ≥3 minutes, then this period of sleep is scored as stage 1; Figure 10.5a, b.

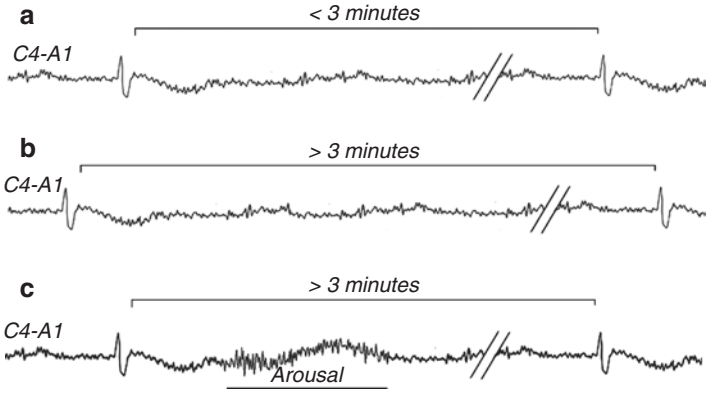


FIGURE 10.5 The 3-minute rule for stage 2. (**a**) Two Ks separated by <3 minutes without arousal; epochs between the two Ks are staged as stage 2; (**b**) Two Ks separated by >3 minutes, so epochs between the two Ks are staged as stage 1; (**c**) Two Ks separated by <3 minutes but with an arousal; epochs following arousal are staged according to their nature, in this case stage 1

(b) *If arousal is present:* If there is an arousal within the intervening sleep (<3 minutes), then the epochs following the arousal are scored according to their nature while the epochs before the arousal will still be scored as stage 2; Figure 10.5c.

– The REM rule:
  (a) *If no arousal is present:* If any section of the record is contiguous with an unequivocal stage REM and has a chin EMG & EEG consistent with stage REM, then that section should be scored as stage REM regardless of whether eye movements are present.[7]
  (b) If arousal is present, then the distinction is between stage 1 & REM: If the arousal is very brief and/or sawtooth waves are present following the arousal, then that section is scored as stage REM. If the arousal is prolonged &/or slow rolling eye movements or sharp

[7] Once a REM sleep is identified, scorer scrolls backward and restudy the previous segment of sleep and rescore it according to this rule.

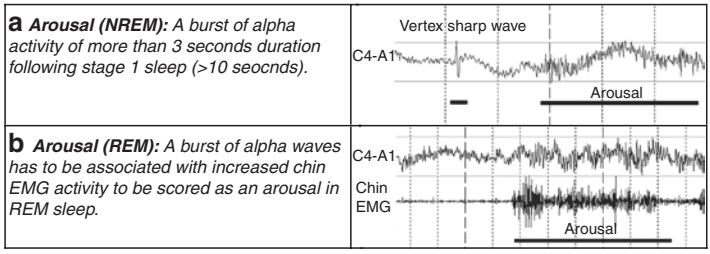


FIGURE 10.6 Arousals

waves are present following arousal, then that section is scored as stage 1.

(c) In stage REM sleep, epochs that exhibit REMs are sometimes referred to as *phasic REM* while those that don't exhibit REMs are referred to as *tonic REM*.

Scoring Arousals

- An arousal in NREM sleep is defined as a brief awakening characterized by abrupt shift in EEG frequency which may include theta, alpha and/or frequencies >16 Hz (usually bursts of alpha waves), lasting 3 seconds or longer, Figure 10.6a [46].
- In REM sleep, there must be a concurrent increase in chin EMG activity in addition, Figure 10.6b. This is because bursts of alpha activity are seen normally in REM sleep [47].
- To be scored as an arousal, such frequency change should be preceded by at least 10 continuous seconds of any stage of sleep. Usually there is a rapid return to a pattern consistent with sleep after an arousal, which is mostly the same sleep stage prior to arousal. An awakening, however, is complete change from any stage of sleep to wakefulness (at least an epoch of stage W). The sleep stage following an awakening can be different from that prior to the awakening.
- The number of arousals per hour of sleep is termed the *arousal index* which is normally ≤20/hour and increases with age [48]. An elevated arousal index is associated with daytime sleepiness [49].

RESPIRATORY EVENTS

Respiratory events including apnea and hypopnea are scored using airflow, oximetric recording, abdominal and chest movement.

Airflow

- Is measured during PSG in order to detect apneas and hypopneas. Different techniques are used to measure airflow. :
  - *Temperature-sensitive devices:* placed close to the nose and mouth to sense the change in temperature of the exhaled air which is translated into a flow signal in the PSG record. This method is a qualitative method that can't accurately detect the amount of flow and, therefore, makes detection of hypopnea problematic. It may also falsely record airflow during apneic episodes if the transducer touches the body. Two types of such devices are available:
    (a) Thermistor: Δ in temperature results in Δ in resistance of transducer [50, 51].
      * *The Thermistor is the most commonly used device for measuring and scoring apneas*
    (b) Thermocouple: Δ in temperature results in Δ in voltage of transducer.
  - *Exhaled CO_2 measurement:* by continuously sampling the exhaled air (rich in CO_2) through a nasal/oral cannula connected to a CO_2 analyzer. A time-delay is expected for the transfer and analysis of the sampled air. Small expiratory puffs (again rich in CO_2) that may take place during inspiratory apneas may be misinterpreted as airflow by the CO_2 analyzer which limits the use of this method.
  - *Pneumotachography:* is an accurate method of measuring airflow but is less comfortable and less practical as a mask covering the nose and mouth is needed to measure the pressure difference created by airflow.
  - *Nasal pressure:* can be measured by a pressure transducer connected to a nasal cannula. This method is convenient and is semiquantitative which makes it a popular method. *This method is potentially a more accurate way to measure and score hypopneas.*

– *V-sum signal:* is derived from chest & abdominal movement, see next session. It is semiquantitative & is sometimes called *Effort Sum* [52].

Chest and Abdominal Movements

- Are measured using bands with coils applied around the chest and abdomen. Changes in the inductance (inductance plethysmography) of these coils due to chest and abdominal expansion during inspiration are recorded as deflections in the PSG traces. A computerized summation of the chest and abdominal movement signals is reported as V-sum. This can be a quantitative measurement of tidal volume (airflow) if calibrated for volume displacement, Figure 10.13b. Calibration, however, is not usually performed and thus this is also a qualitative evaluation of airflow.
- Tracings corresponding to airflow, V-sum, chest & abdominal movement are adjusted in such a way that an upward deflection indicates inspiration & a downward deflection indicates expiration.

Pulse Oximetry

- Is used to measure O_2 saturation (S_pO_2) during sleep using a finger or ear probe. Nadir saturation is delayed by 6–8 seconds due to circulatory & instrumental delay. A desaturation is defined as a drop of S_pO_2 by ≥4% from the baseline.

Scoring Respiratory Events (Apnea and Hyponea)

- Apnea is defined arbitrarily as absence of airflow (or flattening V-sum tracing) at the nose and mouth for 10 seconds or more. Apnea is divided into:
  – *Obstructive apnea:* is when chest and abdomen move paradoxically (out of phase tracing (Figure 10.7a)
  – *Central apnea:* is when no chest or abdominal movements are detected; Figure 10.7b.
  – *Mixed apnea:* is when no chest or abdominal movements are detected initially followed by effort but no airflow and paradoxical movements of the chest & abdomen; Figure 10.7c.

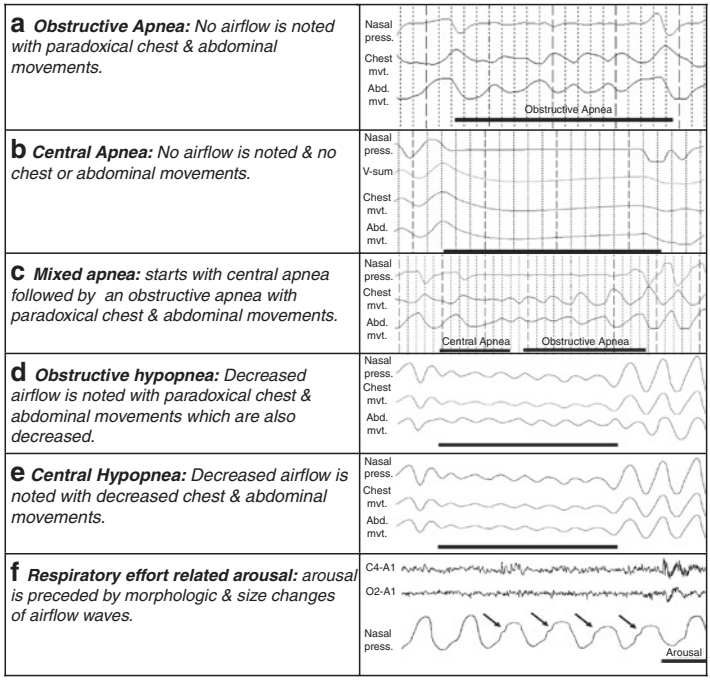


FIGURE 10.7 Respiratory events

  - *Hypopnea* is defined as a reduction in airflow (or V-sum) by a half [51–53] or two thirds [54] from baseline for 10 seconds or more. Hypopneas are more difficult to detect and some experts mandate the presence of arterial desaturation (a drop S_pO_2 by ≥4%) [55] together with the reduction in airflow to define hypopnea. Hypopneas can be obstructive or central:
  - *Obstructive hypopnea:* is a reduction of flow (see above) with ongoing effort. Chest & abdomen generally move paradoxically; Figure 10.7d.
  - *Central hypopnea:* is a reduction in airflow (see above) with waning effort. Chest & abdominal movements continue to be in-phase but with a lower amplitude; Figure 10.7e.
- Apnea & hypopnea are usually followed by an arousal that helps in their identification.

- *Apnea hypopnea Index* (AHI): is the average number of apneas & hypopneas per hour of sleep. It is sometimes called, the *Respiratory disturbance index*. *Apnea Index* (AI) & *Hypopnea Index* (HI) are similarly defined. By consensus, AHI is used to define the severity of sleep apnea (obstructive & central) as follows:
  - <5/hour is normal
  - 5–15/hour is mild
  - 15–30/hour is moderate
  - >30/hour is severe.
- *Respiratory effort-related arousal (RERA)* [56–58] is seen in the upper airway resistance syndrome (UARS) and is not associated with apnea or hypopnea (UARS has a normal AHI of <5). RERA is characterized by change in shape & progressive increase in size (width) of the airflow inspiratory waves prior to the, otherwise, unexplained arousals; Figure 10.7f. These changes are typically not associated with a decrease in S_pO_2. The arousals (in the form of bursts of alpha waves) usually last for 3–14 seconds in UARS. Progressive inversed negative swings in esophageal pressure (using esophageal balloon system during PSG) prior to arousal is considered diagnostic, but is rarely employed clinically.

SCORING PERIODIC LIMB MOVEMENT OF SLEEP

PLMs may be a cause for sleep fragmentation and daytime sleepiness (Periodic Limb Movement Disorder or PLMD). It may also take place before sleep onset resulting in sleep onset insomnia as in Restless Leg Syndrome (RLS). PLMs are scored using leg EMG electrodes.

Leg Electromyography (Leg EMG)

- Right & left EMG leads are placed over the right & left tibialis anterior muscles and the signals acquired are fed to a single recording channel. A leg movement will be recorded as a sudden increase in the leg EMG activity. For leg movements to be part of PLM of sleep, a sequence of four or more leg movements should be present and each leg movement should be separated from the adjacent leg movements by 5–90 seconds (1/2 epoch–3 epochs) [59]. *The duration of each leg movement should be 0.5–5 seconds*. The number of PLMs per hour of

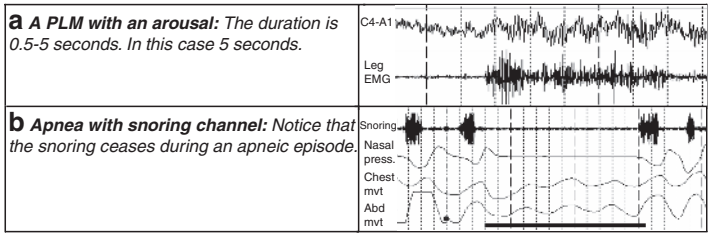


FIGURE 10.8 A PLM arousal, snoring

sleep is the *PLM index* (PLM-I). A PLM-I of <5 is considered normal, 5–25 is mild, 25–50 is moderate and >50 is severe [60].

- In PLMD, leg movements may result in arousals which can be seen in EEG as a burst of alpha waves, Figure 10.14. These arousals can result in sleep fragmentation and excessive daytime hypersomnolence associated with PLMD. On the other hand, arousals may trigger leg movements which, in this case, follow the arousals & should not be counted as PLMs. *PLM arousal Index* (PLM-AI) refers to PLMs accompanied by arousal per hour of sleep. This index is better in defining PLMD than PLM-I as it takes into consideration the arousals caused by PLMs. Severe insomnia and/or excessive daytime sleepiness have been associated with a PLM-AI of >25/hour. PLMs usually take place in NREM sleep (Figure 10.8).

MISCELLANEOUS PSG CHANNELS

Electrocardiography (ECG)

- Is used to detect arrhythmias during sleep especially during periods of obstructive apneas/hypopneas. The most important arrhythmias encountered include: bradycardias & ventricular asystole lasting longer than 10 seconds [18, 19, 21, 22, 62]; non-sustained SVT and VT; and atrial fibrillation [23, 63]. Sinus arrhythmias are commonly observed with apneas and hypopneas but are usually clinically non important.

Sleep Position

- Is determined manually (using a video monitor) or using posture detecting devices. Respiratory events related to OSA preferentially take place while in the supine position.

Snoring

- A microphone may be used to record the snoring as a separate channel. This may help to identify sleep onset (when the patient starts snoring at the beginning of the study) and the apneic episodes (snoring tracing disappears when there is no airflow), see Figure 10.14b.

Visual and Auditory Monitoring

- Visual monitoring is done through a low-light video camera to monitor sleep position (as discussed) and to check for parasomnias, which can be easily synchronized with the PSG. Auditory monitoring is required to provide assistance to the patient if needed.

BIOCALIBRATION

- Is an essential procedure that should be performed prior to any sleep study (PSG). Its role is to ensure appropriate technical function of the components of the polysomnograph in response to different biological stimuli.
  - *Checking eye movements and blinking:* by asking the patient to keep the head still and look to the left, right, up & down and then to blink, Figure 10.9a.
  - *Checking EEG:* first with the eyes closed looking for alpha activity (and slow rolling eye movements in the EOG channels), Figure 10.9b; then with the eyes open looking for attenuation of alpha activity, Figure 10.9c.
  - *Checking chin EMG:* by asking the patient to grit the teeth and observing an appropriate increase in the chin EMG activity, Figure 10.9d.
  - *Checking airflow, chest & abdominal movements:* by asking the patient to inhale and exhale and observing an appropri-

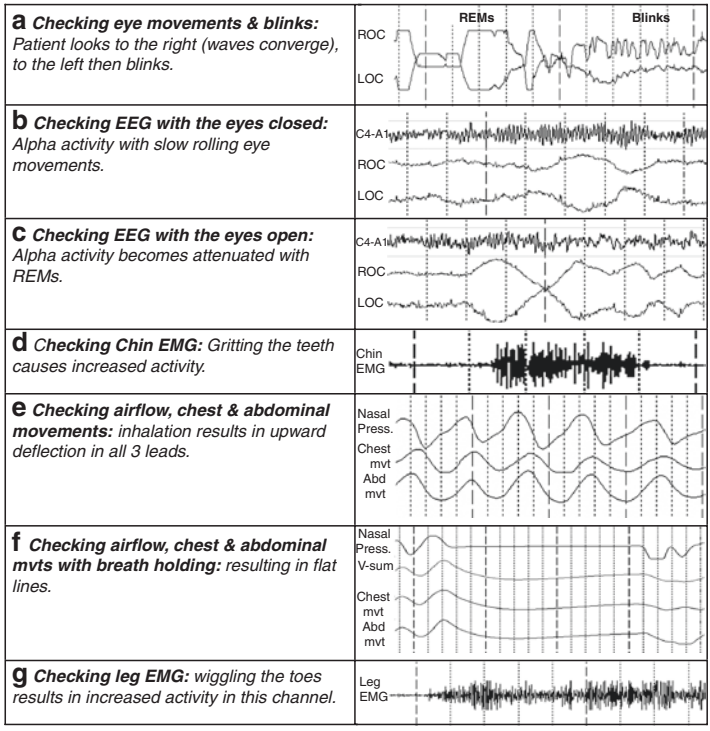


FIGURE 10.9 Biocalibration

ate deflection of all three channels that should be adjusted so that they have the same polarity with an upward deflection during inhalation, as discussed earlier. The patient is then asked to take a deep breath and then hold to simulate apnea that should be translated as flat lines on these three channels, Figure 10.9e, f.[8]

– *Checking leg movements:* by asking the patient to wiggle the right & left toes resulting in appropriately increased leg EMG; Figure 10.9g.

[8] The patient may be asked to breathe through the mouth, which should show movement of chest and abdominal tracing but not the airflow tracing.

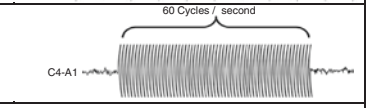
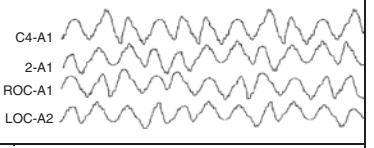
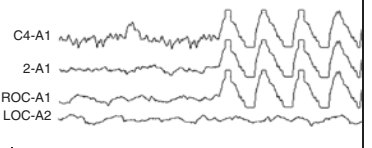
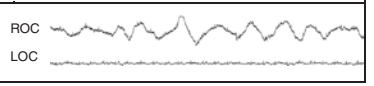
a ***ECG artifact:*** *QRS complexes can be seen clearly in the chin EMG, ROC and LOC tracing.*	
b ***60 cycle artifact:*** *Notice the symmetrical, high frequency signal (60 Hz) of the EEG tracing.*	
c ***Sweat artifact:*** *Undulation of the baseline of most of the tracings. This artifact is also called* ***respiratory artifact*** *because it is synchronous with respiration.*	
d ***Electrode popping artifact:*** *High-amplitude signals corresponding to body movements during respiration. The electrode responsible in this case is A1.*	
e ***Unilateral artificial eye:*** *REMs are seen in the right eye but not in the left(The left eye is an artificial eye).*	

FIGURE 10.10 PSG artifacts

PSG ARTIFACTS

ECG Artifact

- Is a very common and easily recognized artefact. It is made of periodic deflections corresponding to the QRS complexes & resembles them in shape. This artefact is commonly seen in EEG tracings but can be seen in the other tracings too, such as chin EMG & EOG, Figure 10.10a. This artefact is minimized by placing the reference auricular electrode directly over the bone (mastoid process) and avoiding the neck soft tissue, which may conduct the ECG signals. Another way of overcoming this artefact is by referencing the exploring EEG electrode to both auricular electrodes as positive and negative ECG signals going to each auricular electrode will cancel each other out.

Sixty Cycle Artefact

- Occurs when a recording electrode is disconnected or has high impedance which results in recording a 60 Hz AC-electrical activity from the power lines instead, Figure 10.16b. This artifact affects mainly the EEG & EOG leads. It can be minimized by proper placement of electrodes and by using certain filters in the AC amplifiers. Switching to another electrode may be necessary.

Sweat Artifact

- Is caused by sweat getting in contact with a recording electrode altering its potential which results in recording a slow undulation of the baseline activity.[9] If EEG electrodes are affected, the undulated baseline may be mistaken for slow delta waves resulting in overestimation of sleep stages 3 & 4. This artifact may be generalized (if patient is sweating heavily) or confined to the side that the patient is lying on. This artifact may be minimized by lowering room temperature, uncovering the patient or using a fan; Figure 10.10c.

Electrode Popping Artifact

- Is caused by complete loss of signals from one electrode (as complete detachment from the skin or complete dryness of the conducting gel) resulting in high amplitude signals corresponding to body movement during respiration, Figure 10.10d. The offending electrode can be easily identified by looking for a common lead in the affected channels. It is corrected by switching to an alternative electrode.

Unilateral Artificial Eye

- Results in unilateral deflection of EOG during stage REM sleep leading, if un-noticed, to underestimation of REM sleep, Figure 10.10e. This confusion can be avoided by history & a proper biocalibration.

[9] If sweat artifact is synchronous (in-phase) with respiration, it is called respiratory artifact.

APPROACH TO PSG SCORING

Scoring PSG is the most important part of PSG interpretation, as the final report and ultimately the final diagnosis are largely based on the various scores. A computerized scoring program [63–70] is currently available but doesn't replace manual scoring. Different approaches for scoring may be followed by which the scorer goes through the study several rounds, scoring different channels. The following is a suggested approach:

- First round is for scoring sleep stages, arousals & wakefulness: by studying the EEG, EOG & chin EMG. The sleep architecture and the arousal index can then be determined.
- Second round is for scoring respiratory events: by studying airflow, chest and abdominal movements, V-sum, S_PO_2 and snoring. During this round, the scorer should differentiate central from obstructive events and identify events associated with arousals. AI, HI & AHI can then be determined. Apneas and hypopneas become easily identified if tracings are compressed so that the computer screen accommodates three epochs at a time (90 seconds).
- Third round is for scoring leg movements: by studying the leg EMG. The scorer should identify movements that meet the criteria for PLMs & identify those associated with arousals. PLM-I & PLM-AI can then be determined. Consider UARS if arousals are not explained on the bases of respiratory events & PLMs.
- Forth round is for studying the ECG for arrhythmias especially during a respiratory event.

SLEEP ARCHITECTURE

Definitions

- *Time in bed (TIB):* is the monitoring period (from lights-out to lights-on).[10]
- *Movement time:* refers to epochs in which sleep stage is indeterminate due to movement artifacts [71, 72].

[10] Lights-out is the point in time at which lights are turned off to allow the patient to sleep; lights-on is when the patient is awakened in the morning.

- *Total sleep time (TST):* is the total minutes of sleep (stages 1–4 & REM)
- *Wake after sleep onset (WASO):* is the minutes of wakefulness after initial sleep onset and before the final awakening. Increased WASO indicates poor sleep efficiency (i.e. sleep fragmentation) and results in daytime hypersomnolence (e.g. sleep-maintenance insomnia).
- *Sleep period time (SPT):* is TST + WASO. (also called total sleep period (TSP)).
- *Sleep efficiency (SE):* is TST/TIB ratio represented as a percentage.
- *Sleep Onset Latency (SOL or sleep latency):* is the number of minutes from lights-out to the first epoch of sleep. Prolonged sleep latency (sleep-onset insomnia) may be seen in patients with depression.
- *REM latency:* is the number of minutes from sleep onset (not from lights-out) to the first epoch of REM sleep. It is typically reduced in patients with Narcolepsy [73, 74], but can be reduced in many situations such as OSA, circadian rhythm disorder, endogenous depression [74] and withdrawal from REM-suppressing drugs.
- *REM density:* the average number of eye movements (REMs) per unit time.
- *Sleep Architecture:* is the division of TST among the different sleep stages where sleep stages are represented as percentages of TST (or SPT).
- *Hypnogram or Histogram* [72]: is a graphic representation of sleep architecture, Figure 10.11

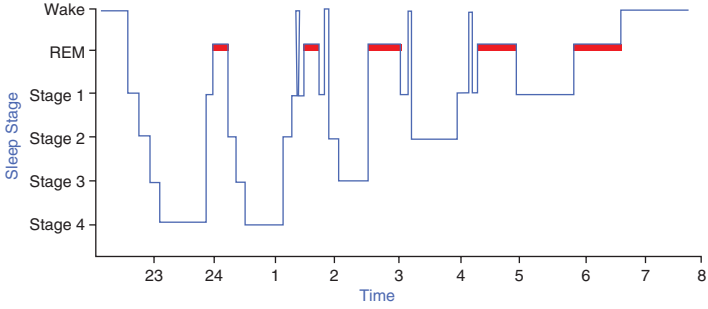


Figure 10.11 A histogram, summarizing the normal sleep architecture in a young adult

TABLE 10.2 Sleep architecture in the young, elder and OSA

	Normal sleep (% SPT)		
	Age 20	Age 60	OSA (% SPT)
Wake	1	8	10
Stage 1	5	10	25
Stage 2	45	57	55
Stage 3	21	2	0
Stage REM	28	23	10

Normal Sleep Architecture

- The proportions of sleep stages vary with age and sex, see Table 10.2 [60]. Normally, sleep stage 2 is the longest in all age groups and in both sexes representing up to 50% of SPT. Sleep stages 1 & 2 and WASO normally increase with age while deep sleep (stages 3) decreases with age.. Age has little influence on REM sleep.
- The human sleep is normally composed of 3–5 cycles of NREM sleep interrupted by 3–5 cycles of REM sleep. The NREM sleep predominates the first ½ of the night while REM sleep predominates the second.
- The first cycle of deep sleep starts early after sleep onset and is the longest, getting shorter as sleep progresses. On the other hand, REM sleep occurs every 90–120 minutes with the first cycle being the shortest. The last cycle is the longest, occurring just before the final awakening. The REM density also increases as sleep progresses [75].
- Because of this composition, parasomnias of deep sleep (such as somnambulism) usually occur during the early hours of sleep while parasomnias of REM sleep (nightmares) are more common in the early morning hours.
- During REM sleep, several unique physiologic changes take place in the body:
  - Most dreams (including nightmares) take place during REM sleep.
  - Skeletal muscle hypotonia: develops during REM sleep to prevent the acting out of dreams. Patients with REM behaviour disorder have abnormalities of this protective mechanism and they may have violent behaviour.
  - Hypotonia of upper airway muscles: results in upper airway obstruction during REM in vulnerable patients. This

is why obstructive apneas take place preferentially during REM [76].
- Ventilatory irregularity: takes place during the phasic REM sleep (REM with eye movements) and results in a reduction in tidal volume (V_T).[11] Additionally, there is reduced ventilatory response to hypoxemia and hypercapnea during REM sleep [77, 78]. Patients with underlying lung disorders experience the most severe O_2 desaturation during the early morning hours that is when phasic REM is most pronounced. All of the ventilatory muscles except the diaphragm become less active in REM and hence the propensity for hypoventilation and arterial oxygen desaturation.
- Nocturnal penile tumescence takes place during REM sleep [79].
- Thermoregulatory mechanisms are attenuated during REM sleep [80].

Final PSG Report

Components of the Final Report

- The final report summarizes the findings of PSG after scoring and can be presented in both numerical and graphic forms. The numerical form contains the following:
  - Sleep architecture: which includes TSP, SPT, SE, SOL, number of REM periods & REM latency. A sleep stage summary is presented in the form of WASO & the different sleep stages are expressed as percentages of TST or SPT.
  - PLM summary: including PLM index & PLM arousal index.
  - Apnea & hypopnea analyses which present AI, HI & AHI, number of central, obstructive and mixed events, number of events during REM & NREM sleep, number of events associated with arousals and number of events in relation to position (supine & non-supine).
  - S_pO_2 summary: showing the different levels of S_pO_2 during stage W, NREM & REM sleep.
- The graphic form is usually composed of five sections with the time represented on the X axis. This form includes a hyp-

[11] Diaphragm becomes the only active inspiratory muscle during phasic REM.

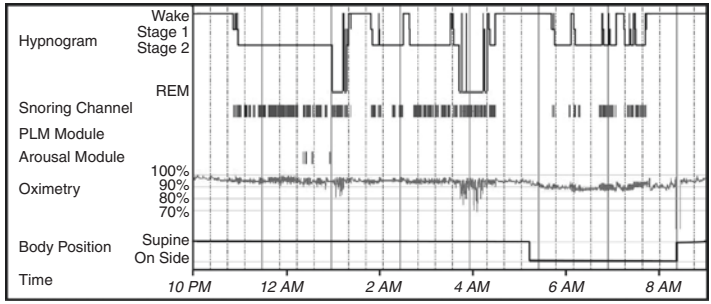


FIGURE 10.12 The final report summarized in this graphic form. Notice that most respiratory events and desaturations occur during REM sleep and while the patient is supine

nogram combined with respiratory events' summary, S_pO_2 tracing, body position and PLMs, Figure 10.12. The presence of a hypnogram allows identifying events in relation to sleep stages.

Interpretation of the Final Report

- The following is a suggested approach:
  - Identify the patient's demographics.
  - Go through the patient's complaints, past history & current medications.
  - Identify the indication for PSG.
  - Examine sleep architecture & sleep stages by checking SE, TST & REM (to make sure that the patient had a period of sleep long enough to make a diagnosis (including enough REM)).[12]
  - Examine the respiratory events during sleep:
    - AHI—to score degree of sleep apnea if present. Check number of events in relation to:

      (a) REM (in OSA, events are more common during REM)
      (b) Position (in OSA, events are more likely to be in supine position)

[12] It is hard to pinpoint a minimum duration of sleep sufficient enough to make a confident diagnosis from a PSG. We suggest a minimum duration (TST) of 3 hours with at least 10% of REM sleep.

(c) Identify if events are predominantly obstructive (OSA) or central (CSA).
- Evaluate the AI & HI in a similar way as AHI.
- Examine S_pO_2 which is best done by looking at the graphic tracing usually showing the typical saw-tooth pattern that is commonly seen during respiratory events.

– Examine ECG monitoring comments (made by the scorer) to report any arrhythmias associated with respiratory events.
– Examine PLM arousal index, a high index (>5/hour) is suggestive of PLMD (a PLM arousal index of >25/hour is consistent with the diagnosis of PLMD). An elevated PLM index with a normal PLM arousal index is suggestive of PLM of sleep which is not associated with sleep fragmentation and, therefore, daytime sleepiness.
– Examine for RERA if no overt OSAH

Other Forms Of Overnight Sleep Studies

C-PAP Titration PSG

- After prescription of C-PAP in patients with confirmed OSA, C-PAP titration PSG is commonly done to detect the appropriate C-PAP pressure and to exclude positive pressure related central events.
- The procedure is similar to the diagnostic PSG except that the patient uses C-PAP machine during the study. Different C-PAP pressures are applied throughout the night & the pressure that best controls the respiratory events is then selected as the appropriate pressure for the patient. The pressure should be adequate to resolve sleep apnea including respiratory events taking place during REM sleep in the supine position.
- A follow up study may be performed to assess the adequacy of initially selected pressure particularly with return of symptoms of OSA (i.e. snoring & daytime sleepiness).

Split Night PSG

- The night is divided into to two parts, a diagnostic PSG is done in the first part & a C-PAP titration PSG is done in the

second. Although less costly, it may influence accuracy of PSG as the duration & quality of the diagnostic PSG are reduced. Additionally, the patient's sleep is interrupted as he/she is awakened for application of C-PAP. Finally, the time reserved for C-PAP titration may be insufficient for adequate results.

Auto C-PAP Titration

- An auto C-PAP machine is capable of automatically changing C-PAP pressure according to patient needs. The PAP data are recoded throughout the night & can be downloaded to a computer. The pressure that the auto C-PAP machine delivered the most during the night (often the pressure to alleviate 90% of the obstructive events) is the pressure that is optimal for the patient. This is often accompanied by an overnight oximetry study to confirm treatment effectiveness.

Limited Channel Sleep Studies (Portable Monitoring Devices) [81]

- Sleep studies can be done with fewer channels than the standard PSG, making these studies less expensive & more portable (can be done in the home). At the same time, these studies are less informative but they can still be useful with appropriate patient selection. For the sake of classification, sleep studies are categorized into four types:
  - Level 1: is the standard PSG with a minimum of 12 channels, as described above. This is not a limited channel study & has to be done under supervision in a sleep laboratory.
  - Level 2: minimum of seven channels, including EEG, EOG, chin EMG, ECG or heart rate, airflow, respiratory effort & S_pO_2. These are typically unattended and could be performed in a patient's home.
  - Level 3 (Ambulatory PSG): minimum of four channels, including ventilation or airflow (at least two channels of respiratory movement, or respiratory movement and airflow), heart rate or ECG & S_pO_2. These have gained broad acceptance and use due to reduced costs and an ability to be conducted in the patients' home with acceptable performance characteristics (See below)

  - Level 4: most monitors of this type measure a single parameter or two parameters, e.g. overnight oximetry, which is the most popular level 4 method.
- These studies can be attended (by a technician) or unattended, full night or split-night or can be of limited duration (<6 hours). Interpretation of type 3 & 4 studies should be done with caution as they can't score sleep. Certain guidelines are currently available to guide the use of these limited sleep studies, see reference [40].

LEVEL 3: UNATTENDED SLEEP STUDIES

Introduction

- With the advent of user friendly and cost effective portable monitors in the setting of limited Level one study availability and higher cost, the use of unattended sleep studies has increased in recent years.
- Joint American Association of Sleep Medicine and Canadian Thoracic Society guidelines published in 2007 and 2010 respectively recommend the use of level 3 polysomnography with patients with a moderate to high pretest probability of OSA [82, 83].
- Patients with comorbid conditions such as cardiac dysfunction or CNS disease are not optimal candidates for home studies.
- Instead of using the AHI to score respiratory events, the respiratory disturbance index (RDI) has been used instead. With AHI which measuring the frequency per hour of apneas and hypopneas during *sleep,* it could not be implemented with an unattended level three device which was not able to accurately identify the sleep period as they do not have EEG capabilities [82]. This may be eventually circumvented by non EEG measures to determine sleep.

Limitations

- Higher false negative rate and lower specificity when compared to monitored laboratory studies, especially with less

severe disease. For example, the specificities of level 3 vs. level 1 studies with AHI/RDI values below 15 events/hour are 0.79–0.92 respectively [84].
- Not recommended if central sleep apnea or non-sleep related breathing disorders are suspected.

Benefits

- Relatively easy to use and applicable to the home setting.
- Reduced cost per study when compared to level 1 studies
- Often shorter wait times to undergo testing.

LEVEL 4: OVERNIGHT OXIMETRY

Introduction

- Overnight oximetry is a widely used tool for screening purposes for sleep disordered breathing. It is simple, inexpensive [85] & readily available as a portable test. It is considered a type 4 sleep study because it monitors two variables: SpO_2 & heart rate.
- Overnight oximetry is usually done in the home as it is simple & can easily be set up by the patient. The data are recorded in a recording card and the results can be downloaded & analyzed electronically. The results are usually presented as numerical & graphic forms.
  - Numerically, the single most important figure is the Oxygen Desaturation Index (ODI) which is defined as the number of desaturation events per hour. A desaturation event in a respiratory sleep disorder is defined as a reduction in SpO_2 by ≥4% from baseline [86–90]. Other numerical data include the highest, the lowest & the mean SpO_2 & heart rate.
  - Graphically, data are plotted as saturation & heart rate vs. time, Figure 10.13

Interpretation

- Oxygen desaturation index (ODI):

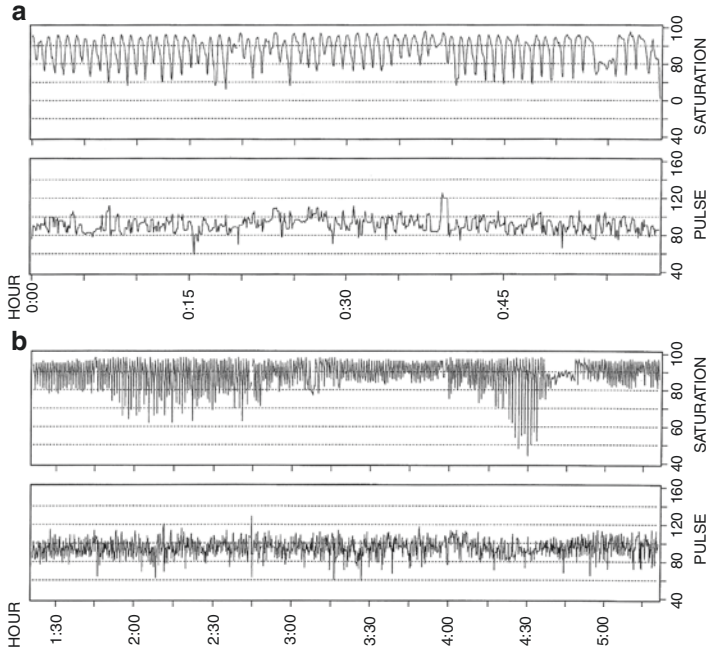


FIGURE 10.13 (**a**) A 1-hour tracing of an overnight oximetry for a patient with severe OSA (ODI: 63/hour). Notice the significant desaturations accompanied by significant variation in heart rate. (**b**) A compressed (4 hours) tracing of the same overnight oximetry shown in (**a**) showing the typical appearance of SPO_2 and heart rate in a positive test. Notice the significant desaturations that reached critical levels (<50%) at 4:30 AM, which may suggest that the patient was in REM sleep during that event

– Is normally less than 5 events/hour [86, 89–92]. ODI cut of point for the diagnosis of OSA is not well defined. Generally, with an ODI of ≥15/hour,[13] the interpreter is more confident to consider a study positive [93–97]. Some laboratories, however, use 5 or 10 events/hour as the threshold and all of these values are supported by evidence [86, 89–92, 98, 99]. ODI alone is not sufficient to make a

[13] An ODI of 10 is widely used as the cutoff point, which, if used, increases the sensitivity but may not significantly change the specificity if compared to an ODI of 15.

definitive conclusion from an overnight oximetric study, as it has to be combined with graphic changes [100, 101].

- Graphically:
  - In OSA, SpO_2 drops gradually during an obstructive event but returns rapidly to the baseline when the obstructive event is terminated (e.g. by arousal). This phenomenon is responsible for the saw-tooth waveform pattern of SpO_2 if plotted against time, Figures 10.5 and 10.7) [102, 103]. This wave pattern combined with a high ODI (>10–15/hour) is considered diagnostic in the presence of the appropriate clinical scenario [92, 103].
  - Hypopneas may be differentiated from apneas by the fact that during hypopneas, the teeth (resaturation peaks) are less sharp than during apneas [102, 103]. This will only be detected by a longer time scale, not usually employed in clinical studies.
  - Central apneas, especially when part of Cheyne-Stokes respiration, produce more symmetrical waveform as the breathing pattern here is more regular (crescendo-decrescendo pattern) compared to that of OSA, Figure 10.6 [102, 103]. Central apneas may produce the saw-tooth pattern as well, especially if not associated with Cheyne-Stokes respiration [102].
  - The overlap syndrome may be differentiated from OSA by the duration of the desaturations, being much longer in the overlap syndrome [104, 105].
  - The heart rate response typically shows reflex bradycardias that develop during obstructive events (apneas or hypopneas) in relation to the nadir negative intrathoracic pressure. The heart rate rapidly increases when an obstructive event is terminated, Figure 10.7. This is also termed sinus arrhythmia. Central apneas are not generally associated with this pattern of heart rate response (Figures 10.14 and 10.15).

Reliability of Overnight Oximetry

- Overnight oximetry is most useful when the clinical index of suspicion for OSA is high. The sensitivity & specificity of overnight oximetry is 100% & 95%, respectively in patients with AHI of ≥25 events/hour, but these values

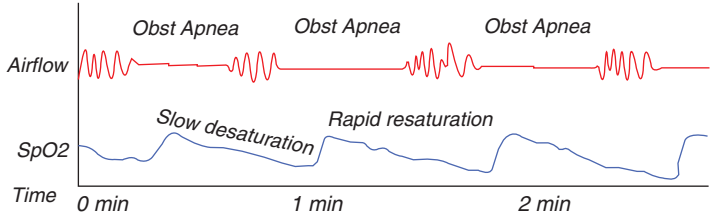


FIGURE 10.14 The characteristic saw-tooth pattern of S_pO_2 in OSA. Notice the slow desaturation and the rapid resaturation. Notice also that there is a delay in the nadir saturation in relation to airflow, which is due to circulatory and instrumental delay (Modified from Netzer et al. [61] with permission)

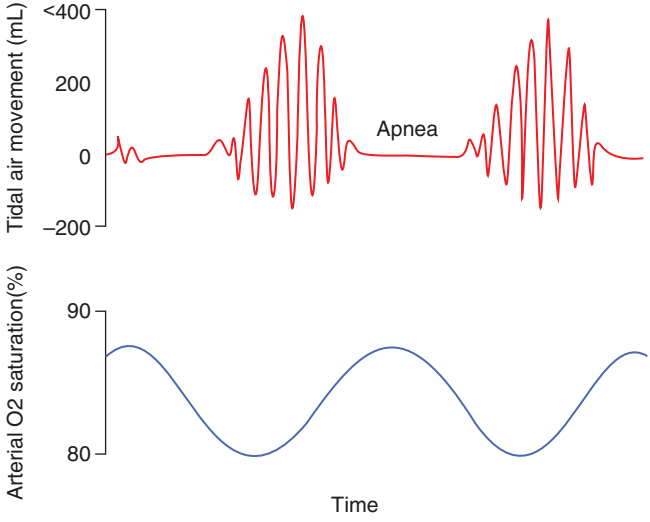


FIGURE 10.15 In CSA (Cheyne-Stokes respiration), S_pO_2 produces more regular and symmetrical waveform due to the regular crescendo–decrescendo pattern of respiration (Modified from Netzer et al. [61] with permission)

decreased to 75% & 86%, respectively in patients with AHI of ≥15 events/hour [92]. This indicates that oximetry is a relatively effective tool for screening patients with moder-

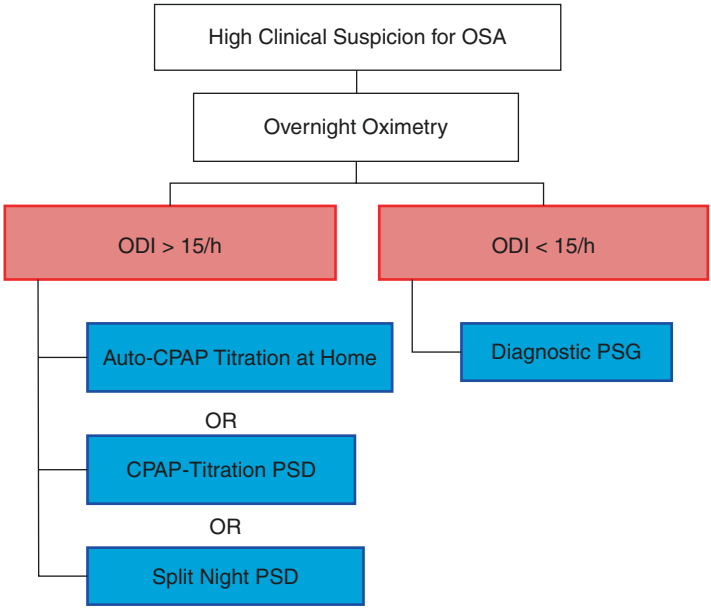


FIGURE 10.16 Approach to patients with strong clinical suspicion for OSA using overnight oximetry as an initial diagnostic study (Modified from Netzer et al. [61] with permission)

ate-to-severe OSA [92]. It is often difficult, however, to differentiate central from obstructive events with oximetry.

- On the other hand, overnight oximetry has less diagnostic value in patients with mild OSA or those who do not desaturate with apneic episodes (often younger patients) or detect RERA, these patients will often require full diagnostic PSG [90]. Figure 10.16 presents a reasonable approach to properly utilize overnight oximetry [102].
- In conclusion, overnight oximetry can be a useful diagnostic test. It is also a very cost-effective test if utilized appropriately.[14]

[14] False negative oximetries occur mostly in nonobese patients or in those with short duration apneas. In the case of thin patients, FRC (O_2 reserve) is preserved and O_2 consumption is reduced compared with obese patients.

ASSESSMENT OF DAYTIME SLEEPINESS[15]

Multiple Sleep Latency Test (MSLT)

Preparation

- MSLT is useful to assess conditions with excessive somnolence, particularly narcolepsy. The aim of this test is to measure the tendency to fall asleep during the day by measuring the sleep & the REM latencies, which are abnormally short in narcolepsy. The following are important points in preparation for MSLT:
  - MSLT should be preceded by a PSG to exclude conditions (e.g. OSA) that may affect sleep architecture & may cause REM-sleep fragmentation. Therefore, the presence of OSA makes the interpretation of the MSLT difficult indicating that sleep apnea should be properly treated first (e.g. with CPAP). A repeat PSG while on CPAP prior to the MSLT is important to ensure that OSA is well controlled before testing. PSG can detect PLMD which may have the same effect on MSLT as OSA. A PSG is also important to ensure that the patient slept adequately the night before.
  - A 1–2 week sleep diary is important to document the sleep pattern as MSLT results may be affected by lack of adequate sleep in any of the preceding seven nights [106–109].
  - Medications that are known to affect sleep or REM latency should be stopped (if possible) at least 2 weeks prior to MSLT.[16] MSLT results are influenced by the chronic or acute usage or acute withdrawal of these drugs. Urine drug screening may be needed in suspected cases.
  - Avoidance of alcohol & caffeine on the day of the test is required. Acute withdrawal from high doses of caffeine is prohibited.

[15] Tests used to assess daytime sleepiness are done during the day as opposed to PSG that is done at night to assess sleep efficiency.

[16] Drugs that affect sleep latency include sedatives, hypnotics, antihistamines and stimulants; drugs that affect REM latency include tricyclic antidepressants, monoamine oxidase inhibitors, lithium, selective serotonin reuptake inhibitors (SSRIs), and amphetamines [110]–[112].

Procedure

- MSLT requires the monitoring of EEG, EOG & chin EMG for sleep staging. The test should be performed in a comfortable, dark & quite room with appropriate temperature. The patient is then allowed to nap 4–5 times throughout the day, 2 hours apart & 1.5–3 hours after a normal PSG.
- The patient is given 20 minutes to fall asleep after lights-out & once asleep an additional 15 minutes to reach REM sleep. Recordings should be monitored closely by an experienced technologist.
- "Naps" are terminated if patient:
  - Fails to initiate sleep in 20 minutes.
  - Fails to reach REM sleep in 15 minutes after first epoch of sleep.
  - Achieved one epoch of unequivocal REM sleep.

Interpretation

- The normal mean sleep latency during MSLT is 10–20 minutes [20, 113–119] which decreases with any dyssomnia, such as OSA. A sleep latency of <5 minutes is pathological [113] & associated with impaired functional performance [75, 107, 108, 120]. A sleep latency of 5–10 minutes is a diagnostic gray area [121] but may be considered mild sleepiness.
- Short sleep latency during the night is considered normal. During the day, sleep latency varies, being shortest near noon or early afternoon (third or fourth nap) & longest during the late afternoon (fifth nap) [115].
- Scoring 0–1 REM periods/5 naps is seen in normal individuals but two or more REM periods is diagnostic for narcolepsy in the right clinical context [20, 114–118]. Sleep-onset REM is seen in 10–15% of patients with narcolepsy [122] but may indicate chronic sleep disturbance [123] or coexistence of OSA & narcolepsy [124, 125]. MSLT should be repeated after the coexisting condition is properly treated.

Maintenance of Wakefulness Test (MWT)

- MWT is used to test the ability to stay awake. It is primarily designed as a measure of safety in occupations dependent on

alertness although this test measures wakefulness, not alertness.
- Unlike MSLT, patients here are encouraged to resist sleep for 40 minutes while seated upright in a bed in a dark, quite room. The patient is monitored by EEG, EOG & chin EMG for detection of sleep. The test is terminated if sleep is detected or after 40 minutes if patient remains awake. This test is then repeated 4–5 times throughout the day.
- The normal MWT latency is 19 minutes which is reduced in case of dyssomnias including OSA & narcolepsy. MWT latency increases significantly when these conditions are treated.
- Patients undergoing this test should provide a 1–2 weeks sleep diary & should be off medications or beverages that influence sleep.

Subjective Tests

Epworth Sleepiness Scale [126]

- Is the most popular subjective score for assessing daytime sleepiness. It represents an 8-statement questionnaire that aims at the detection of the degree of the daytime sleepiness over the last month, Table 10.3. Scoring 3–6/24 is considered normal. Scoring 7–9 indicates mild daytime sleepiness & scoring ≥10/24 is moderate to severe sleepiness. Scoring 24/24 indicates an extraordinary sleepiness while scoring 0/24 suggests a hyper-arousable or insomniac patient.

STOP-BANG Questionnaire

- This sensitive screening questionnaire has been validated in both the sleep clinic as well as the pre-operative surgical population to identify patients at risk for OSA [127], see Table 10.4. It utilizes eight dichotomous, yes/no questions related to clinical features of obstructive sleep apnea. A low score (0–2) indicates a low risk of having moderate to severe OSA, with a high score (5–8) suggesting a high risk for moderate to severe OSA. Also, specificity can be improved when patients with STOP score ≥2 have a BMI > 35, neck circumference >40 cm or have a male gender [128, 129].

TABLE 10.3 Epworth Sleepiness Scale

In the last 30 days, how likely are you to doze off or fall asleep in the following situations (in contrast to feeling just tired)?
This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you

0 = would never doze
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situations:

1. Sitting & reading ( )
2. Watching TV ( )
3. Sitting inactive in a public place ( )
4. As a passenger in a care for an hour without a break ( )
5. Lying down to rest in the afternoon ( )
6. Sitting & talking to someone ( )
7. Sitting quietly after lunch with no alcohol ( )
8. In a car while stopped for a few minutes in traffic ( )

Total score out of 24: ( )

TABLE 10.4 STOP-BANG Questionnaire [127]

Question (Yes/No)	Points
Do you **S**nore Loudly?	1
Do you feel **T**ired, sleepy or fatigued during the daytime?	1
Has anyone ever **O**bserved you stop breathing, choking or gasping in your sleep?	1
Do you have or have you ever been treated for high blood **P**ressure?	1
Body mass index >35?	1
Age older than 50?	1
Neck size large? (Males ≥ 43 cm, Females ≥ 41 cm)	1
Gender male?	1

REFERENCES

1. Diagnostic Classification Steering Committee, Thorpy MJ. International Classification of sleep disorders: diagnostic and coding manual. Rochester: American Sleep Disorders Association; 1990.

2. Pack AI. Obstructive sleep apnea. Adv Intern Med. 1994;39:517–67.
3. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med. 1993;328:1230–5.
4. Young T, Skatrud J, Peppard PE. Risk factors for obstructive sleep apnea in adults. JAMA. 2004;291:2013–6.
5. Parish JM, Somers VK. Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc. 2004;79:1036–46.
6. Hla KM, Young TB, Bidwell T, Palta M, Skatrud JB, Dempsey J. Sleep apnea and hypertension. A population-based study. Ann Intern Med. 1994;120:382–8.
7. Lavie P, Herer P, Hoffstein V. Obstructive sleep apnoea syndrome as a risk factor for hypertension: population study. BMJ. 2000;320:479–82.
8. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. JAMA. 2000;283:1829–36.
9. Young T, Peppard P, Palta M, Hla KM, Finn L, Morgan B, Skatrud J. Population-based study of sleep-disordered breathing as a risk factor for hypertension. Arch Intern Med. 1997;157:1746–52.
10. Grote L, Ploch T, Heitmann J, Knaack L, Penzel T, Peter JH. Sleep-related breathing disorder is an independent risk factor for systemic hypertension. Am J Respir Crit Care Med. 1999;160:1875–82.
11. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Leiby BE, Vela-Bueno A, Kales A. Association of hypertension and sleep-disordered breathing. Arch Intern Med. 1984;160:2289–95.
12. Marin JM, Carrizo SJ, Vicente E, Agusti AGN. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet (London, England). 2005;365:1046–53.
13. Olson LG, King MT, Hensley MJ, Saunders NA. A community study of snoring and sleep-disordered breathing. Health outcomes. Am J Respir Crit Care Med. 1995;152:717–20.
14. Koskenvuo M, Kaprio J, Partinen M, Langinvainio H, Sarna S, Heikkilä K. Snoring as a risk factor for hypertension and angina pectoris. Lancet (London, England). 1985;1:893–6.

15. Schmidt-Nowara WW, Coultas DB, Wiggins C, Skipper BE, Samet JM. Snoring in a Hispanic-American population. Risk factors and association with hypertension and other morbidity. Arch Intern Med. 1990;150:597–601.
16. Hung J, Whitford EG, Parsons RW, Hillman DR. Association of sleep apnoea with myocardial infarction in men. Lancet (London, England). 1990;336:261–4.
17. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med. 2005;172:1447–51.
18. Simantirakis EN, Schiza SI, Marketou ME, Chrysostomakis SI, Chlouverakis GI, Klapsinos NC, Siafakas NS, Vardas PE. Severe bradyarrhythmias in patients with sleep apnoea: the effect of continuous positive airway pressure treatment: a long-term evaluation using an insertable loop recorder. Eur Heart J. 2005;25:1070–6.
19. Tilkian AG, Guilleminault C, Schroeder JS, Lehrman KL, Simmons FB, Dement WC. Sleep-induced apnea syndrome. Prevalence of cardiac arrhythmias and their reversal after tracheostomy. Am J Med. 1977;63:348–58.
20. Carskadon MA, Dement WC. Nocturnal determinants of daytime sleepiness. Sleep. 1982;5(Suppl 2):S73–81.
21. Zwillich C, Devlin T, White D, Douglas N, Weil J, Martin R. Bradycardia during sleep apnea. Characteristics and mechanism. J Clin Invest. 1982;69:1286–92.
22. Alonso-Fernandez A, Garcia-Rio F, Racionero MA. Cardiac rhythm disturbances and ST-segment depression episodes in patients with obstructive sleep apnea-hypopnea syndrome and its mechanisms. Chest. 2005;127:15–22.
23. Gami AS, Friedman PA, Chung MK, Caples SM, Somers VK. Therapy insight: interactions between atrial fibrillation and obstructive sleep apnea. Nat Clin Pract Cardiovasc Med. 2005;2:145–9.
24. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353:2034–41.
25. Reichmuth KJ, Austin D, Skatrud JB, Young T. Association of sleep apnea and type II diabetes: a population-based study. Am J Respir Crit Care Med. 2005;172:1590–5.
26. Bradley TD, Rutherford R, Grossman RF, Lue F, Zamel N, Moldofsky H, Phillipson EA. Role of daytime hypoxemia in

the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis. 1985;131:835–9.
27. Sajkov D, Cowie RJ, Thornton AT, Espinoza HA, McEvoy RD. Pulmonary hypertension and hypoxemia in obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 1994;149:416–22.
28. Guidry UC, Mendes LA, Evans JC, Levy D, O'Connor GT, Larson MG, Gottlieb DJ, Benjamin EJ. Echocardiographic features of the right heart in sleep-disordered breathing: the Framingham Heart Study. Am J Respir Crit Care Med. 2001;164:933–8.
29. Arias MA, García-Río F, Alonso-Fernández A, Martínez I, Villamor J. Pulmonary hypertension in obstructive sleep apnoea: effects of continuous positive airway pressure: a randomized, controlled cross-over study. Eur Heart J. 2006;27:1106–13.
30. Horne JA, Reyner LA. Sleep related vehicle accidents. BMJ. 1995;310:565–7.
31. Masa JF, Rubio M, Findley LJ. Habitually sleepy drivers have a high frequency of automobile crashes associated with respiratory disorders during sleep. Am J Respir Crit Care Med. 2000;162:1407–12.
32. American Thoracic Society. Sleep apnea, sleepiness, and driving risk. Am J Respir Crit Care Med. 1994;150:1463–73.
33. Javaheri S, Parker TJ, Liming JD, Corbett WS, Nishiyama H, Wexler L, Roselle GA. Sleep apnea in 81 ambulatory male patients with stable heart failure. Types and their prevalences, consequences, and presentations. Circulation. 1998;97:2154–9.
34. Javaheri S, Parker TJ, Wexler L, Michaels SE, Stanberry E, Nishyama H, Roselle GA. Occult sleep-disordered breathing in stable congestive heart failure. Ann Intern Med. 1995;122:487–92.
35. Dowdell WT, Javaheri S, McGinnis W. Cheyne-Stokes respiration presenting as sleep apnea syndrome. Clinical and polysomnographic features. Am Rev Respir Dis. 1990;141:871–9.
36. Enright PL. The Six-Minute Walk Test. Arch Phys Med Rehabil. 2012;93:1359–64.
37. Brazier MAB. The electrical fields at the surface of the head during sleep. Electroencephalogr Clin Neurophysiol. 1949;1:195–204.

38. Sun X, Hansen JE, Oudiz R, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. Circulation. 2011;104(4):429–35.
39. Berry RB, Brooks R, Gamaldo C, Harding SM, Lloyd RM, Quan SF, Troester MT, Vaughn BV. AASM Scoring Manual Updates for 2017 (Version 2.4). J Clin Sleep Med. 2017;13:665–6.
40. Rechtschaffen A, Kales A, editors. A manual of standardized terminology: techniques and scoring system for sleep stages of human subjects. Los Angeles: Brain Research Institute; 1968.
41. Blake H, Gerard RW, Kleitman N. Factors influencing brain potentials during sleep. J Neurophysiol. 1939;2:48–60.
42. Jasper HH. The ten twenty electrode system of the International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1958;52:3–6.
43. DiPerri R, Meduri M, DiRosa AE, Simone F. Sleep spindles in healthy people: I) Quantitative, automatic analysis in youngadult subjects. Boll Soc Ital Biol. 1977;53:983–9.
44. Berger RJ, Olley P, Oswald I. The EEG eye movements and dreams of the blind. Psychology. 1962;14:182–6.
45. Keenan S, Hirshkowitz M. Monitoring and staging human sleep. In: Kryger MH, Roth T, Dement WC, editors. Principles and practice of sleep medicine. 5th ed. St. Louis: Elsevier Saunders; 2011. p. 1602–9.
46. American Sleep Disorders Association. The Atlas Task Force: EEG arousals: scoring rules and examples. Sleep. 1992;15:174–84.
47. Johnson LC, Nute C, Austin MT, Lubin A. Spectral analysis of the EEG during waking and sleeping. Electroencephalogr Clin Neurophysiol. 1967;23:80.
48. Mathur R, Douglas NJ. Frequency of EEG arousals from nocturnal sleep in normal subjects. Sleep. 1995;18:330–3.
49. Carskadon MA, Brown ED, Dement WC. Sleep fragmentation in the elderly: relationship to daytime sleep tendency. Neurobiol Aging. 1982;3:321–7.
50. Bliwise D, Bliwise NG, Kraemer HC, Dement W. Measurement error in visually scored electrophysiological data: respiration during sleep. J Neurosci Methods. 1984;12:49–56.
51. Calverley PMA, Shapiro CM, Caterall JR. Breathing and oxygenation during sleep are similar in normal men and normal women. Am Rev Respir Dis. 1985;132:86–8.
52. Bradley TD, Brown IG, Zamel N, Phillipson EA, Hoffstein V. Differences in pharyngeal properties between snorers with

predominantly central sleep apnea and those without sleep apnea. Am Rev Respir Dis. 1987;135:387–91.
53. John, et al. Canadian Thoracic Society guidelines: diagnosis and treatment of sleep disordered breathing in adults. Can Respir. 2007;13:387–92.
54. West P, Kryger MH. Continuous monitoring of respiratory variables during sleep by microcomputer. Methods Inf Med. 1983;22:198–203.
55. Block AJ, Boysen PG, Wynne JW, Hunt LA. Sleep apnea, hypopnea and oxygen desaturation in normal subjects. A strong male predominance. N Engl J Med. 1979;300:513–7.
56. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. Chest. 1993;104:781–7.
57. Guilleminault C, Stoohs R, Kim YD, Chervin R, Black J, Clerk A. Upper airway sleep-disordered breathing in women. Ann Intern Med. 1995;122:493–501.
58. Guilleminault C, Stoohs R, Clerk A, Simmons J, Labanowski M. Excessive daytime somnolence in women with abnormal respiratory efforts during sleep. Sleep. 1993;16:S137–8.
59. The Atlas Task Force of the American Sleep Disorders Association: recording and scoring leg movements. Sleep. 1993;16:749–59.
60. Berry RB. Sleep medicine pearls. 1st ed. Philadelphia: Hanley Belfus; 1999.
61. Netzer N, Eliasson AH, Netzer C, Kristo DA. Overnight pulse 1340 oximetry for sleep-disordered breathing in adults: a review. Chest. 2001;120:625–33.
62. Miller WP. Cardiac arrhythmias and conduction disturbances in the sleep apnea syndrome. Prevalence and significance. Am J Med. 1982;73:317–21.
63. Guilleminault C, Connolly SJ, Winkle RA. Cardiac arrhythmia and conduction disturbances during sleep in 400 patients with sleep apnea syndrome. Am J Cardiol. 1983;52:490–4.
64. Burger D, Catani P, West J. Multidimensional analysis of sleep electrophysiological signals. Biol Cybern. 1977;26:131–9.
65. Gath I, Bar-on E. Computerized method for scoring of polygraphic sleep recordings. Comput Programs Biomed. 1980;11:217–23.
66. Ray SR, Lee WD, Morgan CD, Airth-Kindree W. Computer sleep stage scoring--an expert system approach. Int J Biomed Comput. 1986;19:43–61.

67. Gaillard JM, Tissot R. Principles of automatic analysis of sleep records with a hybrid system. Comput Biomed Res. 1973;6:1–13.
68. Martens WLJ, Declerck AC, Wauquier A, Stefan H, Burr W, Kums DJ, Thm. Considerations on a computerized analysis of long-term polygraphic recordings. 1982. p. 265–74. In: Stefan H, Burr W, editors. Mobile long term: Proceedings of the MLE Symposium. New york: Fischer; 1982. p. 205–17.
69. Agnew HW, Webb WB. Measurement of sleep onset by EEG criteria. Am J EEG Tachnil. 1972;12:127–34.
70. Webb WB. Recording methods and visual scoring criteria of sleep records: comments and recommendations. Percept Mot Skills. 1986;62:664–6.
71. Kryger MH, Thomas R, William CD. Principle and practice of sleep medicine. 2nd ed. Philadelphia: Saunders; 1994.
72. Dement WC, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr Clin Neurophysiol. 1957;9:673–90.
73. Montplaisir J, Billiard M, Takahashi S, Bell IR, Guilleminault C, Dement WC. Twenty-four-hour recording in REM-narcoleptics with special reference to nocturnal sleep disruption. Biol Psychiatry. 1978;13:73–89.
74. Vogel G. Studies in the psychophysiology of dreams ill dreams narcolepsy. Arch Gen Psychiatry. 1960;3:421–8.
75. Dement WC, Carskadon MA, Richardson GS, Guilleminault C. Excessive daytime sleepiness in the sleep apnea syndrome. In: Alan R, editor. Sleep apnea syndrome. New York: Liss Inc.; 1978. p. 23–46.
76. Sackner MA, Landa J, Forrest T, Greeneltch D. Periodic sleep apnea: chronic sleep deprivation related to intermittent upper airway obstruction and central nervous system disturbance. Chest. 1975;67:164–71.
77. Phillipson EA, Sullivan CE, Read DJ, Murphy E, Kozar LF. Ventilatory and waking responses to hypoxia in sleeping dogs. J Appl Physiol. 1978;44:512–20.
78. Phillipson EA, Kozar LF, Rebuck AS, Murphy E. Ventilatory and waking responses to CO2 in sleeping dogs. Am Rev Respir Dis. 1997;115:251–9.
79. Karacan I. The developmental aspect and the effect of certain clinical conditions upon penile erection during sleep. Excerpta Med. 1966;150:2356–9.
80. Parmeggiani PL, Orem J, Barnes CD. Temperature regulation during sleep: a study in homeostasis. In: Orem J, Barnes CD, editors. Physiology in sleep. Research topics in physiology, vol 3. New York: Academic. p. 97–143.

81. Chesson AL, Berry RB, Pack A, American Academy of Sleep Medicine, American Thoracic Society, American College of Chest Physicians. Practice parameters for the use of portable monitoring devices in the investigation of suspected obstructive sleep apnea in adults. Sleep. 2003;26:907–13.
82. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, Hudgel D, Sateia MJ, Schwab RJ. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. J Clin Sleep Med. 2007;3:737–47.
83. Blackman A, McGregor C, Dales R, et al. Canadian Sleep Society/Canadian Thoracic Society position paper on the use of portable monitoring for the diagnosis of obstructive sleep apnea/hypopnea in adults. Can Respir J. 2010;17:229–32.
84. El Shayeb M, Topfer LA, Stafinski T, Pawluk L, Menon D. Diagnostic accuracy of level 3 portable sleep tests versus level 1 polysomnography for sleep-disordered breathing: a systematic review and meta-analysis. CMAJ. 2014;186:25–51.
85. Bennett JA, Kinnear WJ. Sleep on the cheap: the role of overnight oximetry in the diagnosis of sleep apnoea hypopnoea syndrome. Thorax. 1999;54:958–9.
86. Stradling JR, Crosby JH. Predictors and prevalence of obstructive sleep apnoea and snoring in 1001 middle aged men. Thorax. 1991;46:85–90.
87. Rauscher H, Popp W, Zwick H. Computerized detection of respiratory events during sleep from rapid increases in oxyhemoglobin saturation. Lung. 1991;169:335–42.
88. Kripke DF, Ancoli-Israel S, Klauber MR, Wingard DL, Mason WJ, Mullaney DJ. Prevalence of sleep-disordered breathing in ages 40-64 years: a population-based survey. Sleep. 1997;20:65–76.
89. Mooe T, Rabben T, Wiklund U, Franklin KA, Eriksson P. Sleep-disordered breathing in women: occurrence and association with coronary artery disease. Am J Med. 1996;101:251–6.
90. Epstein LJ, Dorlac GR. Cost-effectiveness analysis of nocturnal oximetry as a method of screening for sleep apnea-hypopnea syndrome. Chest. 1998;113:97–103.
91. Loube DI, Andrada TF. Comparison of respiratory polysomnographic parameters in matched cohorts of upper airway resistance and obstructive sleep apnea syndrome patients. Chest. 1999;115:1519–24.
92. Cooper BG, Veale D, Griffiths CJ, Gibson GJ. Value of nocturnal oxygen saturation as a screening test for sleep apnoea. Thorax. 1991;46:586–8.

93. Sano K, Nakano H, Ohnishi Y, Ishii Y, Nakamura T, Matuzawa K, Maekawa J, Narita N [Screening of sleep apnea/hypopnea syndrome by home pulse oximetry]. Nihon Kokyuki Gakkai Zasshi. 1998;36:948–52.
94. Ryan PJ, Hilton MF, Boldy DA, Evans A, Bradbury S, Sapiano S, Prowse K, Cayton RM. Validation of British Thoracic Society guidelines for the diagnosis of the sleep apnoea/hypopnoea syndrome: can polysomnography be avoided? Thorax. 1995;50:972–5.
95. Deegan PC, McNicholas WT. Predictive value of clinical features for the obstructive sleep apnoea syndrome. Eur Respir J. 1996;9:117–24.
96. Levy P, Pepin JL, Deschaux-Blanc C, et al. Accuracy of oximetry for detection of respiratory disturbances in sleep apnea syndrome. Chest. 1996;109:395–9.
97. Vazquez JC, Tsai WH, Flemons WW, et al. Automated analysis of digital oximetry in the diagnosis of obstructive sleep apnea. Thorax. 2000;55:302–7.
98. Williams AJ, Yu G, Santiago S, Stein M. Screening for sleep apnea using pulse oximetry and a clinical score. Chest. 1991;100:631–5.
99. Rauscher H, Popp W, Zwick H. Model for investigating snorers with suspected sleep apnoea. Thorax. 1991;48:275–9.
100. Peck T. Waveforms are needed to interpret figures shown by pulse oximeters [letter]. BMJ. 1999;1353:318.
101. Redline S, Sanders M. Hypopnea, a floating metric: implications for prevalence, morbidity estimates, and case finding. Sleep. 1997;20:1209–17.
102. Arn H, David A. Nikolaus Netzer, and Kristo: Overnight pulse oximetry for sleep-disordered breathing in adults. Chest. 2001;120:625–33.
103. Ullmer E, Strobel WM, Solèr M. Cheyne-stokes respiration or obstructive sleep apnoea: patterns of desaturation. Respiration. 2000;67:203.
104. Calderon-Osuna E, Carmona BC, Arenas GM, et al. A comparative study with chronic obstructive pulmonary disease with and without obstructive sleep apnea syndrome. Arch Bronchoneumol. 1999;35:539–43.
105. Kramer MR, Krivoruk V, Lebzelter J, Liani M, Fink G. Quantitative 15 steps exercise oximetry as a marker of disease severity in patients with chronic obstructive pulmonary disease. Isr Med Assoc J. 1999;1:165–8.
106. Carskadon MA, Dement WC. Cumulative effects of sleep restriction on daytime sleepiness. Psychophysiology. 1981;18:107–13.

107. Carskadon MA, Dement WC. Effects of total sleep loss on sleep tendency. Percept Mot Skills. 1981;48:495–506.
108. Carskadon MA, Harvey K, Dement WC. Sleep loss in young adolescents. Sleep. 1981;4:299–312.
109. Carskadon MA, Dement WC. Sleep loss in elderly volunteers. Sleep. 1985;8:207–21.
110. Dement WC, Seidel W, Carskadon M. Daytime alertness, insomnia, and benzodiazepines. Sleep. 1982;5:528–45.
111. Lumley M, Roehrs T, Asker D, Zorick F, Roth T. Ethanol and caffeine effects on daytime sleepiness/alertness. Sleep. 1987;10:306–12.
112. Roehrs T, Tietz EI, Zorick F, Roth T. Daytime sleepiness and antihistamines. Sleep. 1984;7(2):137–41.
113. Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. Electroencephalogr Clin Neurophysiol. 1978;45:621–7.
114. Mitler MM, Van den Hoed J, Carskadon MA, Richardson G, Park R, Guilleminault C, Dement WC. REM sleep episodes during the Multple Sleep Latency Test in narcoleptic patients. Electroencephalogr Clin Neurophysiol. 1979;46:479–81.
115. Richardson GS, Carskadon MA, Orav EJ, Dement WC. Circadian variation of sleep tendency in elderly and young adult subjects. Sleep. 1982;5(Suppl 2):S82–94.
116. Hartse KM, Roth T, Zorick FJ. Daytime sleepiness and daytime wakefulness: the effect of instruction. Sleep. 1982;5(Suppl 2):S107–18.
117. Carskadon MA. The second decade. In: Guilleminault C, editor. Sleeping and waking disorders: indications and techniques. Menlo Park: Addison Wesley; 1982. p. 99–125.
118. Sullivan SS, Kushida CA. Multiple sleep latency test and maintenance of wakefulness test. Chest. 2008;134(4):854–61. https://doi.org/10.1378/chest.08-0822.
119. Browman CP, Gujavarty KS, Yolles SF, Mitler MM. Forty-eight-hour polysomnographic evaluation of narcolepsy. Sleep. 1986;9:183–8.
120. Carskadon MA, Littell WP, Dement WC. Constant routine: alertness, oral body temperature, and performance. Sleep Res. 1985;14:293.

121. Van den Hoed J, Kraemer H, Guilleminault C, et al. Disorders of excessive daytime somnolence: polygraphic and clinical data for 100 patients. Sleep. 1981;4:23–37.
122. Guilleminault C, Dement WC. 235 Cases of excessive daytime sleepiness. Diagnosis and tentative classification. J Neurol Sci. 1977;31:13–27.
123. Carskadon MA. The role of sleep onset REM periods in narcolepsy. In: Guilleminault C, Dement WC, Passouant P, editors. Narcolepsy. New York: Spectrum; 1976. p. 499–517.
124. Reynolds CF, Coble PA, Kupfer DJ, Holzer BC. Application of the multiple sleep latency test in disorders of excessive sleepiness. Electroencephalogr Clin Neurophysiol. 1982;53:443–52.
125. Zorick F, Roehrs T, Koshorek G, Sicklesteel J, Hartse K, Wittig R, Roth T. Patterns of sleepiness in various disorders of excessive daytime somnolence. Sleep. 1982;5(Suppl 2):S165–74.
126. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14:540–5.
127. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, Khajehdehi A, Shapiro CM. STOP Questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108:812–21.
128. Chung F, Subramanyam R, Liao P, Sasaki E, Shapiro C, Sun Y. High STOP-Bang score indicates a high probability of obstructive sleep apnoea. Br J Anaesth. 2012;108:768–75.
129. Chung F, Abdullah HR, Liao P. STOP-bang questionnaire a practical approach to screen for obstructive sleep apnea. Chest. 2016;149:631–8.

Abbreviations

PFT

ALS	Amyotrophic lateral sclerosis
ARDS	Acute respiratory distress syndrome
ATS	American Thoracic Society
BD	Bronchodilator(s)
BHT	Breath-hold time
BMI	Body mass index
CHF	Congestive heart failure
C_{Ldyn}	Dynamic compliance
C_{Lstat}	Static compliance
CO	Carbon monoxide
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
dl	Deciliter
DL_{CO}	Diffusing capacity of carbon monoxide
ERS	European Respiratory Society
ERV	Expiratory reserve volume
FEF	Forced expiratory flow
FET	Forced expiratory time
FEV_1	Forced expiratory volume in the 1st second
FEV_6	Forced expiratory volume in 6 s
FIF	Forced inspiratory flow
FIVC	Forced inspiratory vital capacity
FRC	Functional residual capacity
FV curve	Flow volume curve

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FV loop	Flow volume loop
FVC	Forced vital capacity
g	Gram
G_{AW}	Airway conductance
H_2O	Water
He	Helium
Hgb	Hemoglobin
IC	Inspiratory capacity
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
IRV	Inspiratory reserve volume
IVC	Inspiratory vital capacity
MDI	Metered dose inhaler
MEP	Maximal expiratory pressure
mg	Milligram
MI	Myocardial infarction
MIP	Maximal inspiratory pressure
MMEF	Maximal med-expiratory flow
ms	Millisecond
MSD	Musculoskeletal disease
MVV	Maximal voluntary ventilation
N_2	Nitrogen
NMD	Neuromuscular disease
O_2	Oxygen
OSA	Obstructive sleep apnea
P_{atm}, P_B	Atmospheric pressure or barometric pressure
P_{di}	Diaphragmatic pressure
PEF	Peak expiratory flow
P_{es}	Esophageal pressure
PFT	Pulmonary function test
P_{ga}	Gastric pressure
PIF	Peak inspiratory flow
P_IO_2	Partial pressure of inspired oxygen
P_{nas}	Nasal pressure
R_{AW}	Airway resistance
RV	Residual volume
SG_{AW}	Specific airway conductance
SOB	Shortness of breath
SR_{AW}	Specific airway resistance
SVC	Slow vital capacity
TGV (V_{TG})	Thoracic gas volume
TLC	Total lung capacity

V_A	Alveolar volume
VC	Vital capacity
VT curve	Volume time curve
V_T	Tidal volume
V_{TG}	(TGV) Thoracic gas volume
% pred.	Percent predicted

ABG

ABG	Arterial blood gas
AG	Anion gap
AGMA	Anion gap metabolic acidosis
AV malf.	Arteriovenous malformation
BE	Base excess
Cl^-	Chloride
COPD	Chronic obstructive pulmonary disease
F_IO_2	Fractional inspired oxygen
H^+	Proton
$[H^+]$	Hydrogen ion concentration
HCl	Hydrochloric acid
HCO_3^+	Bicarbonate
$[HCO_3^+]$	Bicarbonate concentration
ILD	Interstitial King disease
K	Constant
kPa	Kilopascal
Na^+	Sodium
NAG	Nonanion gap
NAGMA	Nonanion gap metabolic acidosis
$NaHCO_3$	Sodium bicarbonate
NH_4^+	Ammonium
NH_4Cl	Ammonium chloride
O_2	Oxygen
$P_{(A\text{-}a)}O_2$	Alveolar arterial oxygen gradient
P_aCO_2	Partial pressure of arterial carbon dioxide
P_ACO_2	Partial pressure of alveolar carbon dioxide
P_aO_2	Partial pressure of arterial oxygen
P_AO_2	Partial pressure of alveolar oxygen
$P_{atm}O_2$	Partial pressure of atmospheric oxygen
P_{H_2O}	Partial pressure of water vapor
P_IO_2	Partial pressure of inspired oxygen
RA	Room air

RQ	Respiratory quotient
RTA	Renal tubular acidosis
S_aO_2	Arterial oxygen saturation
TPN	Total parenteral nutrition
VQ mismatch	Ventilation perfusion mismatch
ΔG	Delta gap

Exercise Test

6MWD	6-min walk distance
6MWT	6-min walk test
12MWT	12-min walk test
AT	Anaerobic threshold
BP	Blood pressure
C.O.	Cardiac output
C_aO_2	Arterial oxygen content
CF	Cystic fibrosis
CHF	Congestive heart failure
$C_{\bar{v}}O_2$	Mixed venous oxygen content
DVT	Deep venous thrombosis
ECG	Electrocardiogram
Ft	Foot (Feet)
HR	Heart rate
LVF	Left ventricular failure
MI	Myocardial infarction
PE	Pulmonary embolism
$P_{ET}CO_2$	End-tidal carbon dioxide tension
$P_{ET}O_2$	End-tidal oxygen tension
RR	Respiratory rate
S_PO_2	Arterial Oxygen saturation with pulse oximetry
SV	Stroke volume
$S_{\bar{v}}O_2$	Mixed venous oxygen saturation
V_A	Alveolar volume
V_D	Dead space volume
V_D/V_T	Dead space fraction
$\dot{V}_A$	Alveolar ventilation per minute
$\dot{V}CO_2$	Carbon dioxide production per minute
$\dot{V}_D$	Dead space ventilation per minute
$\dot{V}_D / \dot{V}_E$	Dead space fraction
$\dot{V}E$	Minute ventilation
$\dot{V}O_2$	Oxygen consumption per minute

Diagnostic Tests for Sleep Disorders

AHI	Apnea hypopnea index
AI	Apnea index
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CSA	Central sleep apnea
ECG	Electrocardiography
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
GERD	Gastroesophageal reflux disease
HI	Hyponea index
Hz	Hertz
LOC	Left outer canthus
MSLT	Multiple sleep latency test
MWT	Maintenance of wakefulness test
NREM	Nonrapid eye movement
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnea
OSAH	Obstructive sleep apnea/hypopnea
PLM-AI	Periodic limb movement arousal index
PLMD	Periodic limb movement disorder
PLM-I	Periodic limb movement index
PSG	Polysomnography
REM	Rapid eye movement
RERA	Respiratory effort-related arousal
RLS	Restless leg syndrome
ROC	Right outer canthus
SE	Sleep efficiency
SEM	Slow rolling eye movement
SOL	Sleep onset latency
S_PO_2	Oxygen saturation by pulse oximetry
SPT	Sleep period time
SSRI	Selective serotonin reuptake inhibitors
SVT	Supraventricular tachycardia
TIB	Time in bed
TST	Total sleep time
UARS	Upper airway resistance syndrome
V_T	Tidal volume
VT	Ventricular tachycardia
WASO	Wake after sleep onset

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